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Efficacy and safety of iodine-125 seed implantations combined with chemotherapy and immunotherapy for patients with non-small cell lung cancer: protocol for a systematic review and meta-analysis

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ABSTRACT

Background Non-small cell lung cancer (NSCLC) is a leading cause of cancer-related mortality worldwide, with conventional treatments often limited by radiation resistance, systemic toxicity and poor outcomes in advanced stages. Iodine-125 (I-125) seed implantation, combined with chemotherapy and immunotherapy, has emerged as a promising therapeutic strategy, but its efficacy and safety compared with conventional external beam radiotherapy combined with systemic therapies remain unclear. This systematic review and meta-analysis aims to synthesise the available evidence to evaluate the comparative benefits and risks of these treatment modalities.

Methods and analysis Two reviewers will independently search seven databases—PubMed, Embase, Web of Science and the Cochrane Library—for randomised controlled trials (RCTs). These RCTs should compare the efficacy and safety of I-125 seed implantations combined with chemotherapy and immunotherapy against chemoradiotherapy combined with immunotherapy in patients with NSCLC. The risk of bias in the included studies will be evaluated using the Revised Cochrane risk-of-bias tool V.2. Data synthesis will be conducted using RevMan software. Trial sequential analysis will be applied to the primary outcomes. Additionally, subgroup and sensitivity analyses will be performed to assess the robustness of the findings.

Ethics and dissemination Ethical approval is not required because this study is a secondary analysis of existing data. We will disseminate the findings through peer-reviewed publications.

PROSPERO registration number CRD42024591684.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This systematic review and meta-analysis employ a rigorous methodology and strict adherence to randomised controlled trial inclusion criteria.
⇒ The use of the Revised Cochrane risk-of-bias tool V.2 ensures a robust evaluation of study quality.
⇒ The credibility of the evidence may be compromised due to the potential for uncertain study quality and limited sample sizes in some included trials.

INTRODUCTION

Non-small cell lung cancer (NSCLC) is a leading cause of cancer-related mortality worldwide, accounting for approximately 85% of all lung cancer cases.[1] Despite advancements in treatment modalities, including chemotherapy, immunotherapy and radiotherapy, the prognosis for patients with advanced NSCLC remains poor.[2–4] Conventional treatments often face challenges such as radiation resistance, systemic toxicity and limited efficacy in controlling metastatic disease. Therefore, there is a pressing need to explore novel therapeutic strategies that can improve patient outcomes while minimising adverse effects.

Radiotherapy is a cornerstone in the management of NSCLC, with conventional external beam radiotherapy (EBRT) being the most commonly employed technique.[5] EBRT delivers radiation from outside the body, targeting the tumour while attempting to spare surrounding healthy tissues. However, this approach is limited by the inherent difficulty in achieving adequate tumour coverage while minimising radiation exposure to critical structures, leading to potential complications such as radiation pneumonitis and oesophagitis.[6–8] Additionally, the systemic nature of EBRT can contribute to overall toxicity, affecting patients' quality of life (QOL) and treatment compliance.

In recent years, intratumoral iodine-125 (I-125) seed implantation, a form of brachytherapy, has emerged as a promising

alternative to conventional EBRT.[9] Brachytherapy involves the placement of radioactive seeds directly into or near the tumour, allowing for highly localised and targeted radiation delivery. This technique offers several advantages over EBRT, including higher radiation dose to the tumour with reduced exposure to surrounding tissues, potential for higher tumour control rates and lower systemic toxicity.[10–13] The use of I-125 seeds, in particular, is advantageous due to their long half-life, precise dosimetry and minimal radiation leakage, making them suitable for treating localised and recurrent NSCLC.

The integration of I-125 seed implantation with systemic therapies such as chemotherapy and immunotherapy represents a novel and synergistic approach to NSCLC treatment.[14 15] Chemotherapy remains a mainstay in the management of NSCLC, targeting rapidly dividing cancer cells.[16] Immunotherapy, on the other hand, harnesses the patient's immune system to recognise and attack cancer cells, offering the potential for durable responses and long-term survival.[17] The combination of these modalities with I-125 seed implantation aims to enhance tumour control by addressing both local and systemic disease components. However, there is a paucity of high-quality evidence comparing its efficacy and safety to conventional EBRT combined with the same systemic therapies. Therefore, this systematic review and meta-analysis aims to synthesise the available evidence to evaluate the comparative benefits and risks of these treatment approaches.

METHODS AND ANALYSIS

Study registration

To ensure the standardisation and rigour of our study, we meticulously reported this protocol in adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Protocols guidelines.[18] The protocol for our systematic review and meta-analysis was preregistered in the PROSPERO database, with the registration ID: CRD42024591684.

Eligible criteria

Study designs

We will include phases II and III randomised controlled trials (RCTs) published as full-text articles. Non-English language studies, reviews, conference abstracts and unpublished studies will be excluded.

Participants

Adult patients (age≥18 years) diagnosed with stage III or stage IV NSCLC.

Intervention

The experimental groups receive I-125 seed implantations combined with chemotherapy and immunotherapy.

Comparison

The control groups receive chemoradiotherapy combined with immunotherapy.

Primary outcome

Primary outcome includes overall mortality.

Secondary outcomes

Secondary outcomes include:

1. Total cost.
2. Adverse reaction.
3. Eastern Cooperative Oncology Group (ECOG) Score.
4. The incidence of pulmonary fibrosis.
5. The incidence of radiation-induced lung injury.
6. Weight change.

Exclusion criteria

The exclusion criteria were as follows: studies that included pregnant or lactating women, studies involving small cell lung cancer or other types of cancer; studies with insufficient data to extract the required outcomes; studies with overlapping patient populations; patients who participated in clinical studies during the 3 months prior, patients who were unwilling to participate in the trial and non-randomised trials, reviews or non-English language studies were excluded from this systematic review and meta-analysis.

Literature sources and retrieval strategy

To minimise errors and ensure comprehensive data retrieval, one reviewer (KW) will construct the literature search strategy, which will then be reviewed by a second reviewer (H-yZ) for completeness prior to execution. This approach ensures a single set of preplanned searches. The following databases will be searched: PubMed, Web of Science, Embase and the Cochrane Library. Only studies published in English were included in our meta-analysis. The detailed retrieval strategy is outlined in table 1.

Literature screening and data extraction

To minimise errors and ensure comprehensive data extraction, two reviewers (KW and H-yZ) will rigorously screen and extract data in accordance with the PRISMA guidelines. Any discrepancies will be discussed and resolved within the team. The flowchart of the study selection process is illustrated in figure 1. The extracted data will include study design, baseline patient information and statistics on overall mortality; total cost; adverse reaction; ECOG Score; the incidence of pulmonary fibrosis; the incidence of radiation-induced lung injury; and weight change.

Assessment of risk of bias

To minimise errors and ensure comprehensive evaluation, two reviewers (KW and H-yZ) will independently assess the risk of bias in the included RCTs. The assessment will be conducted using the Revised Cochrane risk-of-bias tool. RCTs cover five dimensions of bias that can affect quality: bias arising from the randomisation process, deviations from intended interventions, missing outcome data, outcome measurements and selection of the reported result. Any disagreements will be discussed and resolved within the team.

Table 1 The retrieval strategy

PubMed	#1 ("randomized controlled trial"[Publication Type]) OR ("randomized"[Title/Abstract] AND "controlled"[Title/Abstract] AND "trial"[Title/Abstract]) OR ("randomised"[Title/Abstract] AND "controlled"[Title/Abstract] AND "trial"[Title/Abstract]) OR ("randomized controlled trial"[Title/Abstract]) OR ("randomised controlled trial"[Title/Abstract]) OR ("RCT"[Title/Abstract]) OR ("randomly"[Title/Abstract]) OR ("randomization"[Title/Abstract]) OR ("randomisation"[Title/Abstract]) #2 ("Carcinoma, Non-Small-Cell Lung"[MeSH Terms]) OR ("non-small cell lung cancer"[Title/Abstract]) OR ("NSCLC"[Title/Abstract]) OR ("non small cell lung cancer"[Title/Abstract]) OR ("non-small-cell lung carcinoma"[Title/Abstract]) OR ("non small cell lung carcinoma"[Title/Abstract]) #3 ("Iodine-125"[MeSH Terms]) OR ("iodine-125"[Title/Abstract]) OR ("125I"[Title/Abstract]) OR ("I-125"[Title/Abstract]) OR ("iodine 125"[Title/Abstract]) #4 (#1) AND (#2) AND (#3)
Embase	#1 'randomized controlled trial'/exp OR ('randomized':ab,ti AND 'controlled':ab,ti AND 'trial':ab,ti) OR ('randomised':ab,ti AND 'controlled':ab,ti AND 'trial':ab,ti) OR 'randomized controlled trial':ab,ti OR 'randomised controlled trial':ab,ti OR 'rct':ab,ti OR 'randomly':ab,ti OR 'randomization':ab,ti OR 'randomisation':ab,ti #2 'non small cell lung cancer'/exp OR 'non-small cell lung cancer':ab,ti OR 'nsclc':ab,ti OR 'non small cell lung cancer':ab,ti OR 'non-small-cell lung carcinoma':ab,ti OR 'non small cell lung carcinoma':ab,ti #3 'iodine 125'/exp OR 'iodine-125':ab,ti OR '125i':ab,ti OR 'i-125':ab,ti OR 'iodine 125':ab,ti #4 (#1) AND (#2) AND (#3)
Web of Science	#1 TS=("randomized controlled trial" OR "randomised controlled trial" OR "RCT" OR "randomly" OR "randomization" OR "randomisation") #2 TS=("non-small cell lung cancer" OR "NSCLC" OR "non small cell lung cancer" OR "non-small-cell lung carcinoma" OR "non small cell lung carcinoma") #3 TS=("iodine-125" OR "125I" OR "I-125" OR "iodine 125") #4 (#1) AND (#2) AND (#3)
Cochrane Library	#1(mh "randomized controlled trial")OR ("randomized":ab,ti AND "controlled":ab,ti AND "trial":ab,ti) OR ("randomised":ab,ti AND "controlled":ab,ti AND "trial":ab,ti) OR "randomized controlled trial":ab,ti OR "randomised controlled trial":ab,ti OR "rct":ab,ti OR "randomly":ab,ti OR "randomization":ab,ti OR "randomisation":ab,ti #2(mh "Carcinoma, Non-Small-Cell Lung")OR "non-small cell lung cancer":ab,ti OR "nsclc":ab,ti OR "non small cell lung cancer":ab,ti OR "non-small-cell lung carcinoma":ab,ti OR "non small cell lung carcinoma":ab,ti #3(mh "Iodine-125")OR "iodine-125":ab,ti OR "125i":ab,ti OR "i-125":ab,ti OR "iodine 125":ab,ti #4 (#1) AND (#2) AND (#3)

Statistical analyses

Statistical analyses are conducted using Review Manager software (V.5.4). Data will be pooled and forest plots will be generated. For dichotomous variables, risk ratios with 95% CI are calculated using the Mantel-Haenszel method. Continuous variables are analysed as mean differences with 95% CI, employing the inverse variance method. The standard α level for statistical tests was set at 0.05. Significant statistical differences are defined as $p<0.05$. High statistical heterogeneity was considered present if I^2 exceeded 50%. Random-effect models are employed for the analyses.

Publication bias

Publication bias will be evaluated when the number of included RCTs exceeds 10, as a limited number of studies can compromise the robustness of the assessment.

Subgroup analysis and sensitivity analysis

Subgroup analyses will be conducted based on varying sample sizes of the included studies. Additionally, a sensitivity analysis will be performed to assess the stability and reliability of the findings.

Trial sequential analysis (TSA)

Random errors can produce misleading results when a meta-analysis is based on a limited number of studies and patients. TSA helps mitigate the risks of random error due to insufficient sample size or repeated testing, and it aids in estimating the required information size for the meta-analysis. We will conduct TSA for the primary outcomes using TSA V.0.9.5.10 Beta software, with type 1 error set at 5% and power at 80%.

Certainty of evidence

The certainty of the evidence will be assessed using GRADEpro, a tool developed by the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group. The assessment criteria for evidence certainty include the initial study design, risk of bias, imprecision, indirectness and inconsistency. Following these guidelines, the certainty of the evidence will ultimately be rated as 'high', 'moderate', 'low' or 'very low'.

Patient and public involvement

Patients and/or the public were not involved.

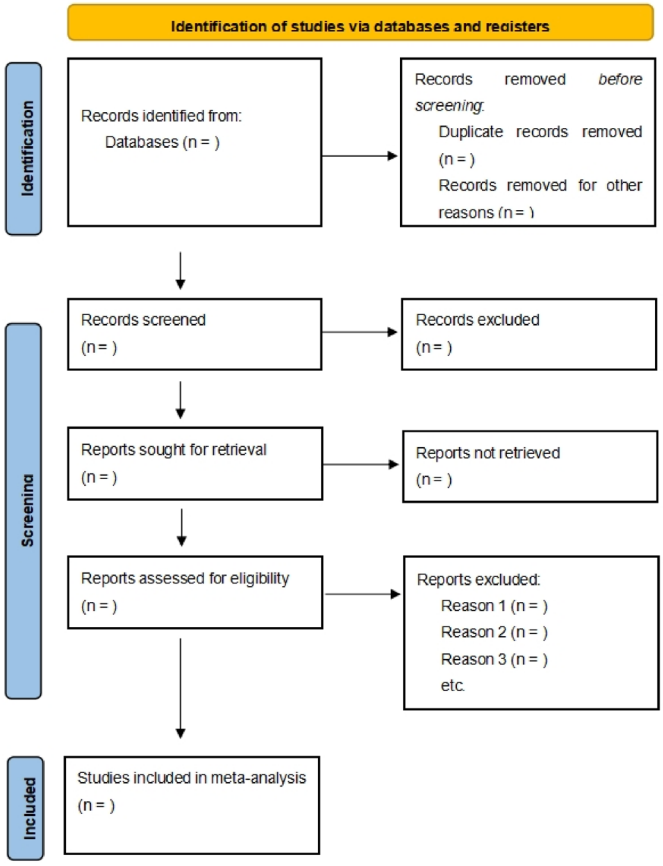

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart of the study inclusion process.

ETHICS AND DISSEMINATION

No ethical approval is required for this review. Our findings will be submitted to peer-reviewed journals.

DISCUSSION

This meta-analysis aims to compare the efficacy and safety of I-125 seed implantation combined with chemotherapy and immunotherapy versus conventional EBRT combined with the same systemic therapies in patients with NSCLC. The study addresses a critical gap in the literature by synthesising existing evidence on these two treatment modalities, which have not been comprehensively compared in prior research.

There are some strengths of this study. This meta-analysis provides a direct comparison between I-125 seed implantation and conventional EBRT, focusing on their combined effects with chemotherapy and immunotherapy. This approach addresses a significant gap in the current evidence base. The study evaluates not only survival outcomes (eg, overall mortality) but also patient-centred outcomes such as QOL (ECOG Score), adverse reactions and cost-effectiveness, which are critical for clinical decision-making. The use of a systematic approach, including a comprehensive search strategy, strict inclusion/exclusion criteria and standardised data extraction, ensures the reliability and validity of the findings.

There are some limitations of this study. Variability in study designs, patient populations and treatment protocols may introduce bias and affect the comparability of results. High-quality data on certain outcomes, such as total cost and weight change, may be limited, potentially restricting the scope of the analysis. The inclusion of only English-language studies and published articles may exclude relevant data from non-English sources or unpublished studies, potentially introducing bias.

The findings of this meta-analysis will provide valuable insights for clinicians in selecting the most effective and safe treatment approach for NSCLC patients. Additionally, the study will highlight areas for future research, such as optimising treatment protocols, reducing adverse effects and improving cost-effectiveness. By addressing these gaps, this analysis aims to contribute to improved patient outcomes and QOL.

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Contributors KW and X-yS conceived and designed the study. KW and H-yZ developed the search strategy and will perform the literature retrieval. KW and H-yZ will independently extract data and assess the risk of bias. KW drafted the manuscript, and X-yS critically revised it for important intellectual content. KW is the guarantor of this work. All authors approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

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Competing interests None declared.

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

Patient consent for publication Not applicable.

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