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Meta analysis of the efficacy and safety of hyperthermia combined with radiotherapy in the treatment of advanced liver cancer

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ADMINISTRATIVE INFORMATION

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Conflicts of interest - Economic benefits: This study is funded by the Jiande Science and Technology Development Plan, with an amount of RMB 50000. I promise that this funding will not affect the fairness and accuracy of the research. Academic relationship: This study was conducted independently and was not directly influenced by other institutions. Personal relationship: I strictly followed ethical standards during the research process and ensured the objectivity and accuracy of the data. Career benefits: The results of this study may have a positive impact on my career development. However, I will conduct the research with an objective and impartial attitude, and ensure the accuracy and credibility of the research results.

INPLASY registration number: INPLASY202520061

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 11 February 2025 and was last updated on 11 February 2025.

INTRODUCTION

Review question / Objective Review Question: "What is the efficacy and safety of hyperthermia combined with radiotherapy compared to radiotherapy alone in the treatment of advanced liver cancer?" Objective: "To systematically review and meta-analyze published studies assessing the efficacy and safety of hyperthermia combined with radiotherapy for the treatment of advanced liver cancer, and to provide evidence-based insights into the potential benefits and risks associated with this combined therapy."

Condition being studied Advanced Liver Cancer.

METHODS

Participant or population The meta-analysis includes patients with advanced liver cancer who have been treated with hyperthermia combined with radiotherapy. The included studies should specifically focus on this patient population, reporting efficacy and safety outcomes. The patients may have various stages of advanced liver cancer, as defined by clinical guidelines or staging systems, and may have undergone different treatment regimens and doses of hyperthermia and radiotherapy. The analysis will consider the

heterogeneity of the patient population and attempt to identify any subgroups that may respond differently to the combined treatment.

Intervention The meta-analysis will focus on studies evaluating the efficacy and safety of hyperthermia combined with radiotherapy as an intervention for the treatment of advanced liver cancer. The hyperthermia component may involve various techniques such as local, regional, or whole-body hyperthermia, delivered using different methods (e.g., ultrasound-guided hyperthermia). Radiotherapy may include external beam radiotherapy, stereotactic body radiotherapy (SBRT), or other forms of radiation therapy tailored to the specific needs of the patient. Studies must report on the combined use of hyperthermia and radiotherapy, with clear descriptions of the hyperthermia technique, radiotherapy dose, fractionation schedule, and any concurrent systemic therapies or other interventions. Studies evaluating hyperthermia or radiotherapy as monotherapy, or those combining hyperthermia with other non-radiotherapy interventions, will be excluded from the meta-analysis.

Comparator The control group patients received simple radiotherapy, while the experimental group patients received radiotherapy combined with hyperthermia.

Study designs to be included (1) Diagnosed as a patient with advanced liver cancer through typical clinical manifestations, tumor marker test results, tissue cytology biopsy, and imaging examinations such as CT and MRI, age and gender are not required; (2)RCT; (3) The control group patients received simple radiotherapy, while the experimental group patients received radiotherapy combined with hyperthermia. (4) The outcome measures of the study include primary outcome measures [objective response rate (ORR)] or secondary outcome measures (1-year survival rate, adverse reactions).

Eligibility criteria 1. Research design: Inclusion: Randomized controlled trials (RCTs) to evaluate the efficacy and safety of hyperthermia combined with radiotherapy in the treatment of advanced liver cancer. Exclusion: Non randomized controlled trials, excluded case series, case reports, expert opinions, comments, and animal studies. Studies without comparative groups or studies comparing interventions with multiple concurrent treatments will also be excluded to avoid the complexity of interpreting the results. Inclusion: Adults with advanced liver cancer confirmed by histology or cytology (aged ≥ 18 years) (usually stage III or IV according to the standard staging system). Exclusion: Studies involving pediatric patients, patients with other concurrent malignant tumors, patients with severe comorbidities that affect treatment tolerance or outcome evaluation, or patients who have previously undergone systemic therapy that may confuse efficacy and safety analysis will be excluded. Intervention: Inclusion: A study in which patients receive hyperthermia combined with radiotherapy as part of their treatment plan. Thermal therapy components may involve various techniques, and radiation therapy may include different modes (e.g. external beam radiation therapy, stereotactic body radiation therapy). Exclusion: Studies that use hyperthermia or radiotherapy as a single therapy, or combine hyperthermia with other non radiotherapy interventions (excluding concurrent systemic treatment as specified in the control criteria), will be excluded. Comparison object: Inclusion: A study comparing combination therapy with radiotherapy alone. Exclusion: Studies comparing combination therapy with multiple concurrent treatments or studies without clear comparison groups will be excluded. Outcome measures: Inclusion: Research reporting the main outcomes, such as objective response rate. Secondary outcomes may include toxicity. Exclusion: Studies without these key outcome measures will be excluded. Publication status and language: Inclusion: Research published in peer-reviewed journals, conference proceedings, and grey literature (e.g. papers, dissertations) will be considered. There are no restrictions on publication date and language. Exclusion: Studies that have not been published in a retrievable format or for which full-text data cannot be obtained will be excluded.

Information sources

1. Databases Searched:

PubMed、Embase、Cochrane Library、Web of Science、China National Knowledge Internet (CNKI)、Wanfang Data and other databases

2. Search Strategy:

A detailed search strategy was developed for each database, using a combination of keywords and MeSH terms related to hyperthermia, radiotherapy, advanced liver cancer, efficacy, and safety.

The search was conducted without restrictions on publication date or language.

Main outcome(s) Objective Response Rate (ORR): The proportion of patients who have a partial or complete response to treatment, as assessed by imaging studies (e.g., CT or MRI scans). This will

indicate the tumor-shrinking effect of the combined therapy.

Quality assessment / Risk of bias analysis
1. Quality Assessment of Included Studies:
Study Design: RCT、Sample Size、Methodological Quality、Follow-Up Duration.
Reporting Quality: Assess the completeness and clarity of reporting, including the description of methods, results, and conclusions.
2. Risk of Bias Analysis:Selection Bias、Performance Bias、Detection Bias、Attrition Bias、Reporting Bias.
3. Strategies to Mitigate Bias:Comprehensive Literature Search、Quality Appraisal Tools、Sensitivity Analysis、Funnel Plot Analysis.

Strategy of data synthesis
1. Data extraction and management:
Data extraction: Extract relevant data from each included study.
Data management: Use Excel and RevMan to manage and organize extracted data.
2. Statistical methods:
Meta analysis: Conduct a meta-analysis using RevMan.
Effect indicator: For binary outcomes such as overall survival rate and response rate, use the hazard ratio or odds ratio with a 95% confidence interval.
Heterogeneity assessment: Use I^2 statistics to quantify heterogeneity between studies.
Publication bias: Use a funnel plot to evaluate publication bias.
3. Data combination and analysis:
Fixed effects model, random effects model, subgroup analysis, sensitivity analysis.
4. Result introduction:
Forest map, summary of research results, limitations and impacts.

Subgroup analysis 1-year survival rate, adverse reactions: leukopenia, liver function damage, nausea and vomiting.

Sensitivity analysis 1. Method:
Research selection: Exclude studies with high risk of bias or significant impact on overall results.
2. Statistical methods:
Fixed and random effects models.
Missing an analysis.
Trimming and filling methods.
Subgroup analysis.
Outcome indicators.
3. Result:
Present the results of sensitivity analysis.
Highlight any studies or subgroups that have a significant impact on the results of the meta-analysis and discuss the potential reasons for these findings.
4. Discussion:
Explain the results of sensitivity analysis in the context of the overall meta-analysis findings.
Discuss the impact of these results on clinical practice and future research.
Recognize any limitations of sensitivity analysis, such as the possibility of residual confounding or selection bias.
5. Conclusion:
Summarize the main findings of sensitivity analysis.

Country(ies) involved China.

Keywords Meta-analysis, hyperthermia, radiotherapy, advanced liver cancer, efficacy, safety, combined therapy, survival rate, adversereactions.

Contributions of each author
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