

The Synergistic Role of Ultrasound-Guided Interventions and Radiotherapy in Hepatocellular Carcinoma: A Meta-Analysis of Treatment Outcomes

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ADMINISTRATIVE INFORMATION

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 21 November 2024 and was last updated on 21 November 2024.

INTRODUCTION

Review question / Objective The PCOS framework for this meta-analysis investigates the synergistic role of ultrasound-guided interventions and radiotherapy in treating hepatocellular carcinoma (HCC). The study will focus on patients diagnosed with HCC, regardless of disease stage, who have received a combination of ultrasound-guided interventions (e.g., ablation or biopsy) and radiotherapy. The comparison will involve treatments like ultrasound-guided interventions alone, radiotherapy alone, and conventional therapies. Key outcomes include overall survival, progression-free survival, local recurrence rates, treatment-related complications, tumor response, and quality of life. The meta-analysis will include randomized controlled trials, non-randomized controlled trials, and observational studies reporting relevant treatment outcomes.

Condition being studied Hepatocellular carcinoma (HCC) is the most common primary

malignancy of the liver, often arising in the context of chronic liver diseases such as cirrhosis, chronic hepatitis B or C, and non-alcoholic fatty liver disease. It is characterized by its aggressive nature, high mortality rates, and the challenge it poses for effective treatment. HCC is often diagnosed at advanced stages due to its asymptomatic progression in early phases, limiting treatment options. Current therapeutic strategies for HCC include surgery, liver transplantation, local ablation therapies, and systemic treatments like chemotherapy and targeted therapies. However, the prognosis remains poor, particularly for patients with advanced or unresectable tumors. In recent years, the combination of ultrasound-guided interventions, such as ablation or biopsy, with radiotherapy has emerged as a promising approach for improving treatment outcomes. This combined modality aims to enhance tumor control, reduce recurrence, and potentially improve survival rates, especially in patients who are not candidates for surgery or other curative treatments. Understanding the synergistic role of these

interventions is critical to optimizing treatment protocols and improving patient prognosis in this challenging disease.

METHODS

Participant or population The participants in this meta-analysis will be individuals diagnosed with hepatocellular carcinoma (HCC), including those with early, intermediate, or advanced stages of the disease. These participants will be selected based on the following criteria:

Age and Gender: There are no specific restrictions on age or gender, as the analysis will include all adult patients diagnosed with HCC.

Diagnosis: Participants must have a confirmed diagnosis of HCC, based on imaging studies (e.g., ultrasound, CT, MRI) or biopsy results. They may have varying degrees of liver function, ranging from well-preserved to cirrhotic liver states, but the focus will be on patients with HCC as the primary malignancy.

Treatment Modalities: The key inclusion criterion is that participants have received ultrasound-guided interventions (e.g., ablation, biopsy) combined with radiotherapy (e.g., external beam radiation, stereotactic body radiotherapy). The analysis will consider both single- and multi-modality interventions for HCC treatment.

Exclusion Criteria: Participants with other forms of liver cancer (such as cholangiocarcinoma) or those who have received treatments not involving ultrasound-guided procedures or radiotherapy will be excluded. Additionally, case reports or studies without quantitative survival data or treatment outcomes will not be included.

Intervention Intervention Group - Combination of Ultrasound-Guided Interventions and Radiotherapy: Patients in this group receive a combination of ultrasound-guided interventions (e.g., ultrasound-guided tumour ablation, ultrasound-guided biopsy, etc.) and radiotherapy (including external beam radiotherapy, stereotactic body radiotherapy, etc.). This is the primary intervention group and focuses on the impact of the synergy of the two treatments on the outcome of hepatocellular carcinoma (HCC).

Comparator Comparison Groups - Ultrasound-Guided Interventions Alone: This group of patients will receive only ultrasound-guided interventions, such as tumour ablation or biopsy, without radiotherapy.

Radiotherapy Alone: This group of patients receives only radiotherapy without ultrasound-guided interventions.

Conventional Treatments: This group of patients receives conventional treatments such as hepatectomy, liver transplantation, or chemotherapy, but not ultrasound-guided interventions or radiotherapy.

Placebo or No Treatment: If included in the relevant study, there may be a control group that receives placebo or no treatment as a comparison of outcomes.

Study designs to be included This meta-analysis will include randomized controlled trials (RCTs), non-randomized controlled trials, and observational studies that report on the use of ultrasound-guided interventions combined with radiotherapy for the treatment of hepatocellular carcinoma (HCC). Eligible studies must provide quantitative data on key outcomes such as overall survival, progression-free survival, tumor response, recurrence rates, and treatment-related adverse events. Both prospective and retrospective studies will be considered, provided they meet the inclusion criteria and report relevant treatment effects.

Eligibility criteria Inclusion criteria: Studies that report on the combination of ultrasound-guided interventions and radiotherapy for HCC.

Studies that provide quantitative data for survival outcomes, tumor response, or other key treatment outcomes.

Exclusion criteria:

Studies that only report on one of the treatment modalities (ultrasound-guided interventions or radiotherapy alone).

Case reports, letters, and non-peer-reviewed publications.

Information sources The information for this meta-analysis will be sourced from several key databases, including PubMed, Embase, Cochrane Library, and Web of Science, which are comprehensive resources for medical and clinical research. Additionally, trial registries such as ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) will be searched for relevant unpublished or ongoing studies. Grey literature will be explored by reviewing sources like conference abstracts, dissertations, and government reports. Authors of relevant studies will also be contacted to request unpublished data or clarifications when necessary.

Main outcome(s) CR\PR\NC\PD, and 1-year survival rate.

Quality assessment / Risk of bias analysis The quality of the included studies will be assessed

using standardized tools tailored to the study design. For randomized controlled trials (RCTs), the Cochrane Risk of Bias Tool will be used, evaluating domains such as random sequence generation, allocation concealment, blinding, incomplete data handling, and selective reporting.

Strategy of data synthesis Data analysis in this meta-analysis will be conducted using random-effects models to account for potential heterogeneity across studies. The primary outcomes, including overall survival, progression-free survival, and local recurrence rates, will be pooled using hazard ratios (HRs) or odds ratios (ORs) with corresponding 95% confidence intervals (CIs). For continuous outcomes, such as tumor response rates or quality of life measures, mean differences (MDs) or standardized mean differences (SMDs) will be calculated. Statistical heterogeneity between studies will be assessed using the I^2 statistic, with values greater than 50% indicating significant heterogeneity. If substantial heterogeneity is found, potential sources will be explored through subgroup analyses based on factors like study design, treatment regimens, or patient characteristics. Sensitivity analyses will be performed to assess the robustness of the findings by excluding studies with high risk of bias or by using different statistical models. All statistical analyses will be performed using R software or Stata, with a significance level set at $p < 0.05$.

Subgroup analysis Subgroup analyses will be conducted to explore potential sources of heterogeneity and to assess whether treatment effects vary based on specific patient or study characteristics. Key subgroups will include:
 Tumor Stage: Patients with early-stage versus advanced-stage hepatocellular carcinoma (HCC) to determine if treatment efficacy differs by disease stage.
 Type of Ultrasound-Guided Intervention: Subgroups will be based on the specific ultrasound-guided procedure used, such as ultrasound-guided ablation versus biopsy, to assess if the type of intervention influences outcomes.
 Radiotherapy Type: Different forms of radiotherapy (e.g., external beam radiotherapy versus stereotactic body radiotherapy) will be examined to assess whether treatment response varies according to the radiation technique.
 Liver Function: The analysis will compare outcomes in patients with preserved liver function versus those with cirrhosis or compromised liver function, to determine if liver health affects the success of combined treatments.

Study Quality: The impact of study quality (based on risk of bias) on treatment outcomes will be explored by comparing studies with low, moderate, or high risk of bias.

Sensitivity analysis Sensitivity analysis will be performed to assess the robustness of the meta-analysis results. This will involve systematically excluding studies with high risk of bias or outliers to determine whether the findings are consistent across different study qualities. Additionally, we will test the impact of using different statistical models (e.g., fixed-effects vs. random-effects models) on the pooled effect sizes. If significant changes in results occur after excluding specific studies or altering model assumptions, it will indicate potential vulnerabilities in the conclusions. Sensitivity analysis ensures the reliability and generalizability of the meta-analysis findings.

Country(ies) involved China.

Keywords Hepatocellular Carcinoma (HCC), Ultrasound-Guided Interventions, Radiotherapy, Synergistic Treatment, Meta-Analysis.

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