Stereotactic body radiotherapy vs radiofrequency ablation for the treatment of hepatocellular carcinoma: a systematic review and meta-analysis

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Review question / Objective: Hepatocellular carcinoma (HCC) represents the fifth most common kind of cancer and the most important cause of mortality in cirrhotic subjects. RFA is a first-line treatment for HCC. Stereotactic body radiation (SBRT) has been pioneered by several centres worldwide as an alternative local ablative therapy for HCC. There are limited and discordant results on the comparison between stereotactic body radiotherapy (SBRT) and radiofrequency ablation (RFA) for the treatment of hepatocellular carcinoma (HCC). Therefore, it is necessary to compare the efficacy and safety of these two treatments.

Study designs to be included: Randomized controlled trials (RCTs), non-randomized clinical trials, observational studies, cohort studies and retrospective studies from original research.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 07 June 2022 and was last updated on 07 June 2022 (registration number INPLASY202260029).

INTRODUCTION

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it is necessary to compare the efficacy and safety of these two treatments.

**Condition being studied:** Hepatocellular carcinoma (HCC) represents the fifth most common kind of cancer and the most important cause of mortality in cirrhotic subjects. Although an increasing number of HCC patients in the developed countries are currently amenable of curative therapies at the time of diagnosis, tumor recurrence and long-term survival still remain an unsolved issue. A recent meta-analysis compared the two treatments in several kinds of liver malignancies showing discordant results, in particular better local control with SBRT but higher survival rates in patients treated with RFA; therefore, given the publication of several recent studies in this field, we decided to conduct an updated meta-analysis focused on HCC patients.

**METHODS**

**Participant or population:** Hepatocellular carcinoma (HCC).

**Intervention:** Stereotactic body radiation (SBRT).

**Comparator:** Radiofrequency Ablation (RFA).

**Study designs to be included:** Randomized controlled trials (RCTs), non-randomized clinical trials, observational studies, cohort studies and retrospective studies from original research.

**Eligibility criteria:** Inclusion criteria:(1) HCC patients, residual HCC or intrahepatic metastases.(2) Treatment with only SBRT or RFA;(3) Reported relevant outcomes such as overall survival (OS), freedom from local progression (FFLP), progression-free survival (PFS) and complications;(4) Randomized controlled trials (RCTs), non-randomized clinical trials, observational studies, cohort studies and retrospective studies from original research./Exclusion criteria:(1) The sample size is too small.(2) The intervention measures are inconsistent or combined with multiple treatment methods.(3) The outcome indicators are inconsistent.(4) The research method is not clear.

**Information sources:** PubMed, Embase, Cochrane Library, Web of Science, Scopus database and the China Biomedical Literature Database (CBM).

**Main outcome(s):** The primary outcomes were overall survival (OS), local progression-free survival (FFLP), progression-free survival (PFS), and treatment-related complications.

**Additional outcome(s):** Adverse Events.

**Data management:** Data management: A systemic search was performed by two independent researchers by using PubMed, Embase, Web of Science, Cochrane Library, Scopus database and the China Biomedical Literature Database (CBM) for those from inception to June 2022 without any other limits. The following medical subject headings (MeSH) terms include “Hepatocellular carcinoma”, “Stereotactic body radiation therapy”, “Radiofrequency ablation”. The MeSH terms and free text terms were utilized to locate articles, combined with the boolean operators AND/ OR to made an appropriate search strategy. The results generated by the retrieval were export as bibliography import into EndNote(X9) for further comment, and the disagreement was decided by the third researcher. Then we extracted all the effect quantities of interest and made an Excel sheet.

**Quality assessment / Risk of bias analysis:** We will assess: methodological quality, or risk of bias, for each individual study based on the Cochrane Risk of Bias tools for RCTs, non-randomized clinical trials, observational studies, cohort studies. (low risk) These studies had the least bias, and the results were considered valid. These studies adhered to the commonly held concepts of high quality, including the following: a clear description of the population, setting, approaches, and comparison groups; appropriate.
measurement of outcomes; appropriate statistical and analytical methods and reporting; no reporting errors; a low dropout rate; and clear reporting of dropouts. (moderate risk) These studies were susceptible to some bias, but not enough to invalidate the results. They did not meet all the criteria required for a rating of good quality because they had some deficiencies, but no flaw was likely to cause major bias. The study may have been missing information, making it difficult to assess limitations and potential problems. (high risk) These studies had significant flaws that might have invalidated the results. They had serious errors in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting.

**Strategy of data synthesis:** STATA 15.1 was used to analyse the data. OR (95% CI) was used to evaluate the difference in OS rate, FFLP rate, and PFS rate between SBRT and RFA. \( I^2 \) is used to evaluate heterogeneity. If the heterogeneity test is \( P \geq 0.1 \) and \( I^2 \leq 50\% \), it indicates that there is homogeneity between studies, and the fixed effects model is used for combined analysis; Otherwise, it indicates that the study has heterogeneity, use sensitivity analysis to find the source of heterogeneity. If the heterogeneity is still large, use the random effects model or give up the combination of results and use descriptive analysis. Funnel plot and Egger's test was used to analyze publication bias.

**Subgroup analysis:** Subgroup analysis: (a) Whether the number of tumors is single. (b) Tumor size. (c) Race.

**Sensitivity analysis:** After deleting any one of them, the combined results of the remaining documents are not much different from those when they were not deleted, which means that the sensitivity analysis has passed.

**Country(ies) involved:** China.

**Keywords:** Hepatocellular carcinoma (HCC); stereotactic body radiation therapy (SBRT); radiofrequency ablation (RFA); meta-analysis.

**Contributions of each author:**
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