INPLASY PROTOCOL

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None declared.

Can Stereotactic Body Radiotherapy Provide Long Term Efficacy for Small Hepatocellular Carcinoma? — A Network Meta-analysis

Li, LQ[1]; Wu, QY[2]; Su, TS[3]; Lin, ZT[4]; Liang, SX[5].

Review question / Objective: **We included studies based on the following PICOS criteria: (P) Patients: patients with small liver-confined HCC ≤3 lesions and the longest diameter≤5 cm (if the main population of an article did not meet the inclusion criteria but subpopulations did, said article was included and data from the subgroup analysis were used for NMA); (I) Intervention: SR, RFA, and/or SBRT; (C) Comparator: studies comparing SR and RFA, SBRT and RFA, or SR and SBRT; (O) Outcomes: studies with sufficient data for at least one endpoint. (S) Study design: RCT, prospective cohort study, and retrospective cohort study. In addition, reference lists of eligible studies were also examined to select further studies for inclusion.**
Condition being studied: **Hepatocellular carcinoma (HCC) is the fifth most common cancer in men and the seventh in women, worldwide. Outcomes remain disappointing, despite recent progress in the techniques of diagnosis and therapy.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 13 November 2022 and was last updated on 13 November 2022 (registration number INPLASY2022110060).

INTRODUCTION

Review question / Objective: **We included studies based on the following PICOS criteria: (P) Patients: patients with small liver-confined HCC ≤3 lesions and the longest diameter≤5 cm (if the main population of an article did not meet the inclusion criteria but subpopulations did, said article was included and data from the subgroup analysis were used for NMA); (I) Intervention: SR, RFA, and/or SBRT; (C) Comparator: studies comparing SR and RFA, SBRT and RFA, or SR and SBRT; (O) Outcomes: studies with sufficient data for at least one endpoint. (S) Study design: RCT, prospective cohort study, and retrospective cohort study. In addition,**

reference lists of eligible studies were also examined to select further studies for inclusion.

Rationale: Clinically, SBRT is typically administered to patients with HCC who do not undergo surgery or RFA. However, there have been limited head-to-head comparisons between SBRT and other local modalities, particularly between SBRT and SR. Conducting intensive randomized controlled trial (RCT) can be challenging because it is difficult to identify patients who are candidates for both interventions. Is SBRT an effective and safe option compared with SR and RFA for patients with small HCC? In the absence of RCTs, we conducted a NMA based on clinical considerations of tumor size to address this question by interpreting a wider picture of available evidence.

Condition being studied: Hepatocellular carcinoma (HCC) is the fifth most common cancer in men and the seventh in women, worldwide. Outcomes remain disappointing, despite recent progress in the techniques of diagnosis and therapy.

METHODS

Search strategy: Full search terms: (RFA OR Radiofrequency Ablation OR Radiofrequency) OR (Surgery OR SR OR Hepatectomy OR Resection) OR (Stereotactic Ablative Radiotherapy OR Stereotactic body radiotherapy OR Stereotactic radiotherapy OR Stereotactic radiation therapy OR Stereotactic body radiation therapy OR Stereotactic Ablative radiation therapy OR SBRT) AND ("Carcinoma, Hepatocellular"[Mesh] OR HCC OR liver cancer).

Participant or population: Patients with small liver-confined HCC (≤3 lesions with longest diameter ≤5cm).

Intervention: Stereotactic body radiotherapy (SBRT).

Comparator: Surgical resection (SR) and radiofrequency ablation (RFA).

Study designs to be included: RCT, prospective cohort study, and retrospective cohort study.

Eligibility criteria: In addition, reference lists of eligible studies were also examined to select further studies for inclusion. Studies that met the following criteria were excluded: (1) locoregional treatments exclusively used for liver metastases or as a bridge to liver transplantation for HCC; (2) studies with insufficient information; (3) duplicate reports; (4) studies with sample sizes less than 50; and (5) non-English articles. For studies involving data that overlapped with other studies, only one study was selected based on better applicability of the data or a larger sample size.

Information sources: We searched the PubMed/MEDLINE, EMBASE, Cochrane Library, and ClinicalTrials.gov electronic databases. PubMed/MEDLINE, EMBASE, Cochrane Library, and ClinicalTrials.gov electronic databases.

Main outcome(s): Main outcome indices of efficacy were short-term (1 year) and long-term (3 and 5 year) efficacy. The primary endpoints of the present study were pooled odds ratios (OR) for 1-, 3-, 5-year overall survival (OS) rates. If original data or exact numbers of OS were not available, the studies were not included in further analysis. Since the endpoints regarding relapse varied by study, progression/recurrence/disease-free survival was combined and redefined as recurrence-free survival* (RFS*).Major complications and grade ≥3 adverse events defined according to specific criteria (including the Clavien–Dindo classification, Common Terminology Criteria for Adverse Events, or National Institutes of Health-defined Common Terminology Criteria for Adverse Events) were combined and redefined as severe complications.

Quality assessment / Risk of bias analysis: Methodological quality was assessed using the Cochrane Risk of Bias Tool [26] for RCT and the Newcastle-Ottawa Scale (NOS) criteria[27] for non-randomized studies.

The rating criteria for NOS were as follows: low quality=0–5; medium quality=6–7; and high quality=8–9. Studies with fewer than 7 points on the NOS score were excluded. Discrepancies were resolved by repeated examinations and joint discussions of the studies to reach a consensus. We interpreted the I^2 statistic based on the Cochrane Handbook for Systematic Reviews of Interventions as follows[10]1: 0% to 40% represented low heterogeneity, 30% to 60% represented moderate heterogeneity, 50% to 90% represented substantial heterogeneity, and 75% to 100% represented considerable heterogeneity. If heterogeneity was tested, subgroup and sensitivity analyses were conducted for further dissection. Regarding consistency of NMAs, we used the node-splitting model[29] to assess inconsistencies between direct and indirect treatment effects, in which $P > 0.05$, indicating good agreement within treatment loops. If the interventions showed no statistically significant differences, we used a ranking plot to explore the best possible measure.

Strategy of data synthesis: Two assessors (Li-LQ and Wu-QY) independently reviewed the full manuscripts of eligible studies, and conflicts were adjudicated by a third investigator (Su-TS). The extracted data included author names, year of publication, study type, patient characteristics, inclusion criteria, treatment protocols, follow-up time, and study endpoints. For studies in which statistical matching was performed, both original (unadjusted) and adjusted treatment outcomes were extracted. If the results were represented only in the form of graphs, we used Engauge Digitizer software, version 4.1 (http://markummitchell.github.io/engauge-digitizer/) to extract numerical survival data from the published Kaplan-Meier survival curves.

Subgroup analysis: We conducted subgroup analysis in studies with a retrospective study design and studies consisting of a high proportion of patients with hepatitis B virus (HBV) infection.

Sensitivity analysis: Sensitivity analyses were also performed to assess the sources of heterogeneity among the comparisons of RFA and SR, but these did not obviously alter heterogeneity.

Language restriction: English articles.

Country(ies) involved: China (Guangxi Medical University Cancer Hospital).

Keywords: hepatocellular carcinoma; surgical resection; radiofrequency ablation; stereotactic body radiotherapy.

Contributions of each author:
Author 1 - Liqing Li - Li-LQ reviewed the literature and extracted data.
Author 2 - Qiaoyuan Wu - Wu-QY reviewed the literature and extracted data.
Author 3 - Tingshi Su - Su-TS conceived and designed the study.
Author 4 - Zhitao Lin - Lin-ZT performed statistical analyses and wrote the manuscript.
Author 5 - Shixiong Liang - Liang-SX provided administrative support and reviewed the final draft before submission.