INPLASY PROTOCOL

To cite: Hou et al. I-125 seeds insertion with transcatheter arterial chemoembolization for advanced hepatocellular carcinoma: a meta-analysis of randomized controlled trials. Inplasy protocol 2020120139. doi: 10.37766/inplasy2020.12.0139

Received: 26 December 2020

Published: 27 December 2020

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**Support:** **None.**

**Review Stage at time of this submission:** **Preliminary searches.**

**Conflicts of interest:**
**None.**

# I-125 seeds insertion with transcatheter arterial chemoembolization for advanced hepatocellular carcinoma: a meta-analysis of randomized controlled trials

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**Review question / Objective:** **To assess the clinical efficacies of I-125 seeds (IS) insertion with transcatheter arterial chemoembolization (TACE) for the treatment of patients with advanced hepatocellular carcinoma (HCC).**
**Condition being studied:** **Hepatocellular carcinoma (HCC) is the most common hepatic malignant tumor. HCC is usually presented with high malignancy and rapid progression. Although surgical resection is the most ideal method for patients with HCC, most HCC patients have lost the chance of operation due to the advanced tumor stage at the time of diagnosis. Transarterial chemoembolization (TACE) has been demonstrated to be an effective treatment in improving survival for patients with advanced HCC. The optimal combination of TACE with anti-tumor agent and adjuvant treatments are still are still evolving. TACE combined with other treatments, such as ablation, systemic therapy, or radiotherapy, have been shown to improve overall survival as compared to TACE alone. At present, I-125 seeds (IS) insertion has been used as an additional treatment after TACE for HCC, as this isotope can deliver prolonged low-dose radiation to the tumor site. IS insertion can strongly stimulate the anti-tumor immune response in HCC patients. The results from the retrospective researches might be influenced by many factors. A meta-analysis of randomized controlled trials (RCTs) is therefore required to better understand the significance of these prior studies and to decrease their potential for bias by increasing the overall statistical power thereof through pooled analyses.**

**INPLASY registration number:** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 27 December 2020 and was last updated on 27 December 2020 (registration number INPLASY2020120139).

## INTRODUCTION

**Review question / Objective:** **To assess the clinical efficacies of I-125 seeds (IS) insertion with transcatheter arterial chemoembolization (TACE) for the treatment of patients with advanced hepatocellular carcinoma (HCC).**

**Rationale:** The clinical effectiveness of TACE with IS insertion will be assessed by evaluating the pooled alpha-fetoprotein (AFP) levels, treatment response, overall survival (OS), OS rates (6-month, 1-year, and 3-year), and treatment-related side effects.

**Condition being studied:** Hepatocellular carcinoma (HCC) is the most common hepatic malignant tumor. HCC is usually presented with high malignancy and rapid progression. Although surgical resection is the most ideal method for patients with HCC, most HCC patients have lost the chance of operation due to the advanced tumor stage at the time of diagnosis. Transarterial chemoembolization (TACE) has been demonstrated to be an effective treatment in improving survival for patients with advanced HCC. The optimal combination of TACE with anti-tumor agent and adjuvant treatments are still are still evolving. TACE combined with other treatments, such as ablation, systemic therapy, or radiotherapy, have been shown to improve overall survival as compared to TACE alone. At present, I-125 seeds (IS) insertion has been used as an additional treatment after TACE for HCC, as this isotope can deliver prolonged low-dose radiation to the tumor site. IS insertion can strongly stimulate the anti-tumor immune response in HCC patients. The results from the retrospective researches might be influenced by many factors. A meta-analysis of randomized controlled trials (RCTs) is therefore required to better understand the significance of these prior studies and to decrease their potential for bias by increasing the overall statistical power thereof through pooled analyses.

## METHODS

**Search strategy:** (((((I[Title/Abstract]) OR (iodine[Title/Abstract])) OR (seed[Title/Abstract])) OR (Brachytherapy[Title/Abstract])) AND ((((hepatocellular carcinoma[Title/Abstract]) OR (HCC[Title/Abstract])) OR (liver cancer[Title/Abstract])) OR (hepatic cancer[Title/Abstract]))) AND ((TACE[Title/Abstract]) OR (transcatheter arterial chemoembolization[Title/Abstract])).

**Participant or population:** Patients with advanced HCC who underwent TACE with or without IS insertion.

**Intervention:** Patients who underwent TACE with IS insertion.

**Comparator:** Patients who underwent TACE alone.

**Study designs to be included:** Studies eligible for inclusion in this analysis were: (a) studies comparing TACE with IS insertion to TACE alone for advanced HCC; (b) inoperable cases; and (c) RCTs. The language of the included articles was not limited. Studies were excluded if they were: (a) non-RCTs; (b) non-human studies; (c) case reports; or (d) reviews.

**Eligibility criteria:** Studies eligible for inclusion in this analysis were: (a) studies comparing TACE with IS insertion to TACE alone for advanced HCC; (b) inoperable cases; and (c) RCTs. The language of the included articles was not limited.

**Information sources:** This meta-analysis was reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement. We searched for relevant studies published through November 2020 in the Pubmed, Embase, and Cochrane Library databases.

**Main outcome(s):** Overall survival.

**Additional outcome(s):** Decrease in alpha-fetoprotein (AFP) levels, treatment response, overall survival rates (6-month, 1-year, and 3-year), and treatment-related side effects.

**Data management:** Two investigators independently extracted relevant data including study baseline data, patient baseline data, and treatment-associated data from all included studies. And discrepancies were resolved by a third author. The endpoints of this study included decrease in alpha-fetoprotein

(AFP) levels, treatment response, overall survival (OS), OS rates (6-month, 1-year, and 3-year), and treatment-related side effects. Among them, OS was the primary endpoint. Treatment response was evaluated by the Response Evaluation Criteria in Solid Tumors, as follows: total response (TR) = complete response (CR) + partial response (PR); disease control (DC) = CR + PR + stable disease (SD).

**Quality assessment / Risk of bias analysis:** Potential biases were assessed using the Cochrane risk of bias tool by 2 investigators independently. Biases were assessed by evaluating the following items: selection, performance, detection, attrition, reporting, and other biases.

**Strategy of data synthesis:** RevMan v5.3 software was used for all data analyses. Dichotomous variables were analyzed based on the odds ratios (ORs) and 95% confidence intervals (CIs), whereas continuous variables were analyzed based on the mean difference (MD) and 95% CIs. Survival times were measured by the hazard ratio (HR) with a 95% CI. X2 and I2 tests were employed to assess heterogeneity among studies. When significant heterogeneity was detected (I2 > 50%), a random-effects model was used, whereas a fixed-effects model was otherwise employed for all analyses. Sources of heterogeneity were examined through sensitivity analyses, while the risk of publication bias was examined using funnel plots.

**Subgroup analysis:** Subgroup analyses were conducted by separately analyzing only assessing RCTs enrolling patients with large HCC.

**Sensibility analysis:** None.

**Language:** Not limited.

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

**Other relevant information:** None

**Keywords:** Hepatocellular carcinoma; I-125 seed; Transcatheter arterial chemoembolization; Meta-analysis

**Dissemination plans:** We plan to publish a meta-analysis in a medical journal.

**Contributions of each author:**
Author 1 - Ju-Pan Hou drafted the manuscript.
Author 2 - Tao Wang provided statistical expertise.
Author 3 - Yi-Bing Shi contributed to the development of the selection criteria, and the risk of bias assessment strategy.
Author 4 - Yu-Fei Fu read, provided feedback and approved the final manuscript.
Author 5 - Hao Li designed this work.