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Research Article

Iodine-125 Seed Combined with Stent Placement and Transarterial Chemoembolization for Treatment of Hepatocellular Carcinoma with Portal Vein Tumor Thrombosis: A Systematic Review and Meta-Analysis

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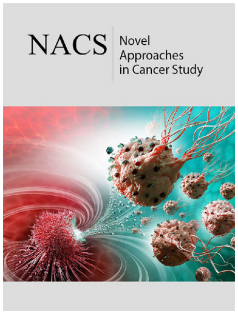
ISSN: 2637-773X



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Submission: October 31, 2022
Published: December 01, 2022

Volume 7 - Issue 3

How to cite this article: Wei Fan Sui. Iodine-125 Seed Combined with Stent Placement and Transarterial Chemoembolization for Treatment of Hepatocellular Carcinoma with Portal Vein Tumor Thrombosis: A Systematic Review and Meta-Analysis. Nov Appro in Can Study. 7(3). NACS. 000665. 2022.
DOI: 10.31031/NACS.2022.07.000665

Abstract

Background: Portal vein tumor thrombus plays an important role in indicating the poor prognosis of hepatocellular carcinoma.

Purpose: To assess the safety and efficiency of iodine-125 seed combined with stent placement and transarterial chemoembolization for treatment of hepatocellular carcinoma with portal vein tumor thrombosis.

Materials and methods: We searched Cochrane library, PubMed, EMBASE, CNKI, Wang fang Data and CQVIP. We assessed the qualities of included studies. We analyzed the characteristic data, tested heterogeneity, explored heterogeneity and tested publication bias by software-Review Manger 3.5.

Result: Totally 7 clinical controlled trials were selected with the inclusion criterion. The results showed that the pressure of main portal vein after stent placement was significantly lower than no stent placement. The cumulative stent patency rates and survival rates in 6 and 12 months of iodine-125 seed combined with stent placement and transarterial chemoembolization were higher than conventional transarterial chemoembolization, transarterial chemoembolization combined with stent and 3-dimensional conformal radiotherapy.

Conclusion: For hepatocellular carcinoma patients with portal vein tumor thrombosis, iodine-125 seed combined with stent placement and transarterial chemoembolization was safety. The efficiency of iodine-125 seed combined with stent placement and transarterial chemoembolization were better than conventional transarterial chemoembolization, transarterial chemoembolization plus stent and transarterial chemoembolization combined with stent and 3-dimensional conformal radiotherapy.

Keywords: Hepatocellular carcinoma; Transarterial chemoembolization; Portal vein tumor thrombus; Stent; Iodine-125; Meta-analysis

Abbreviation: HCC: Hepatocellular Carcinoma; PVTT: Portal Vein Tumor Thrombus; TACE: Transarterial Chemoembolization; 3-DCRT: 3-Dimensional Conformal Radiotherapy; I125: Iodine-125

Introduction

Hepatocellular Carcinoma (HCC) is one of the most common malignancies both in world and China [1] and it is also the third frequent cause of cancer-related deaths in China [2]. Portal Vein Tumor Thrombus (PVTT) plays an important role in indicating the poor prognosis of HCC. PVTT can deteriorate liver function by decreasing blood supply to the normal liver, gastrointestinal bleeding and tumor recurrence [3]. Consequently, HCC with PVTT is regarded as unresectable. The standard first-line therapy in unresectable hepatocellular carcinoma was transarterial chemoembolization (TACE) [4]. However, the effect of conventional TACE in treating HCC with PVTT was limited. Moreover, conventional TACE exacerbated liver function failure in HCC with PVTT. Some research demonstrated that 3-dimensional conformal radiotherapy (3-DCRT) and ^{125}I seeds prolonged the survival time in HCC with PVTT and did not make liver function worse [5,6]. However, 3-DCRT or ^{125}I seed alone could not relieve the obstructed portal vein immediately. Stent placement in portal vein was proved safety

and efficient in portal vein hypertension, which could delay the time of liver function failure and prolong the survival time in HCC with PVTT [7]. However, within a short period, portal vein might obstruct again because tumor thrombus re-grew into stent through the mesh of stent. With the development of medical technology, ^{125}I seeds combined with stent placement and TACE was demonstrated safety and efficiency (Figure 1). It could prolong the survival time of HCC with PVTT and postponed the restenosis of the portal vein further [8-10]. However current clinical trails lack of large samples to demonstrate the clinical significance of ^{125}I seed combined with stent placement and TACE in HCC with PVTT, and no systematic analysis on the safety and efficiency of ^{125}I seeds combined with stent placement and TACE in HCC with PVTT. Hence, this study was aimed to carry out a meta-analysis to assess the safety and efficiency of ^{125}I seeds combined with stent placement and TACE in HCC with PVTT.

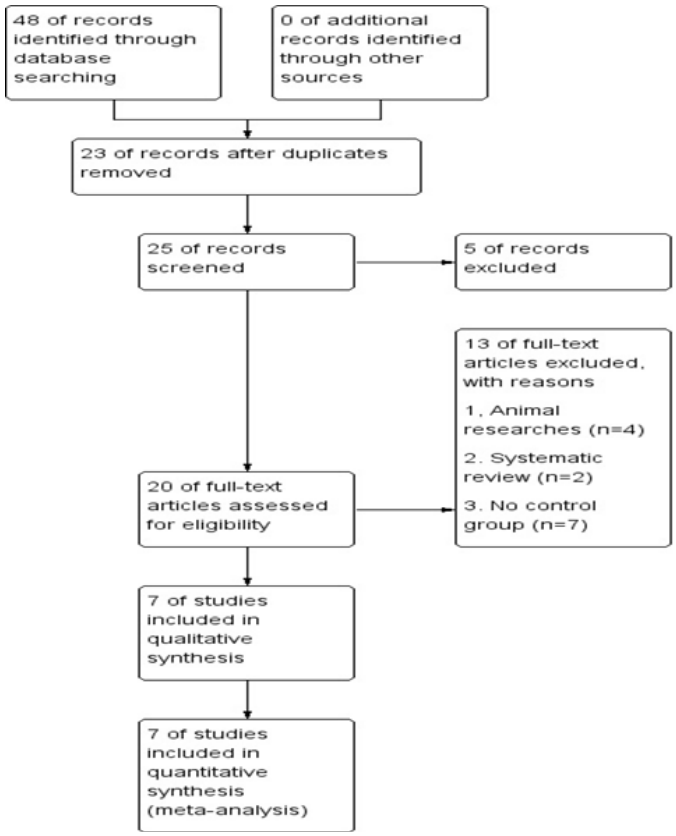

Figure 1: Flowchart shows flow of information through the different phases of systematic review toward a meta-analysis.

Materials and Methods

Search strategy

We conducted a comprehensive literature search both in English database including PubMed, Cochrane Library and Excerpt Medica Database and Chinese database including Chinese national Knowledge Infrastructure (CNKI), Wang fang Data and CQVIP up until 2019. We used the following search terms in the field for Title/Abstract and/or keywords: "hepatocellular carcinoma" and ''transarterial chemoembolization'' or ''TACE'' or "chemoembolization" and "Portal vein tumor thrombus" and "^{125}I" and "stent". All the data was available from published papers.

Study selection

The studies selected were required to meet the following inclusion criteria: 1) The original research. 2) The study participants were human. 3) The study had clinical results, such as, stent patency rates, survival rates, et al. 4) The study showed the clinical value of I^{125} seed combined with stent placement and TACE in HCC with PVTT. 5) The data could be extracted in study.

Data extraction and data quality assessment

Two doctors screened the titles and abstracts of potentially eligible studies independently and examined the full text articles to determine whether they could be included. One doctor independently extracted data, including author, country, publication year, design, treatment, patients' number, et al. Then put the collected data into Review Management 5.3 to conduct meta-analysis. We assessed the quality of all included studies by Cochrane Collaboration's tool [11].

Data analysis

We analyzed the data by Rev Man Manger 5.3. For all analyses, $P<0.05$ was considered statistically significant. Heterogeneity was assessed by using chi-square testing and I^2 statistics [12,13]. When $25\% \leq I^2 \leq 50\%$, it indicated low heterogeneity. When $50\% < I^2 \leq 75\%$,

it indicated moderate heterogeneity. When $I^2 \geq 75\%$, it indicated significant heterogeneity. Subgroup analyses were performed to explore the source of heterogeneity when $I^2 \geq 50\%$ in our meta-analysis. Publication bias was evaluated through funnel plots [13]. When a funnel plot was asymmetrical, interpretation of the results should be assessed critically. Otherwise, no publication bias existed.

Result

Search strategy

We selected 7 studies in this meta-analysis based on the criteria. Three studies were English [8-10] and four studies were Chinese [14-17].

Data extraction and data quality assessment

The extracted data contained information including the author, publication year, nation, study design, number of patients and therapies of experimental, control group. The characteristics of selected studies were induced in Table 1. Based on Cochrane collaboration's tool including random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias, the results of selected studies were showed in Figure 2.

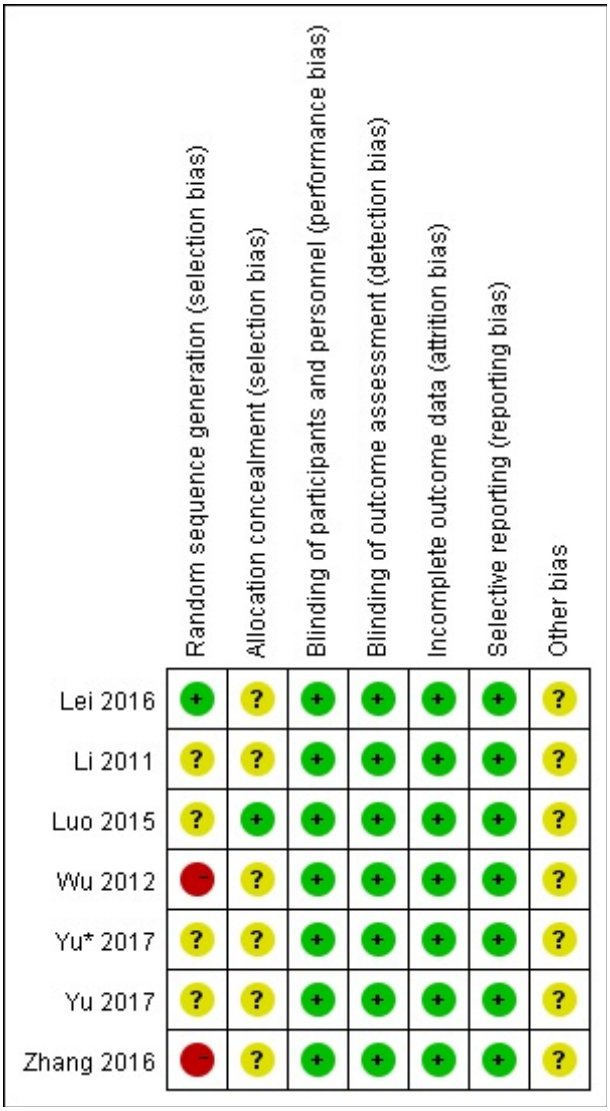

Figure 2: Risk of bias summary: review authors' judgements about each risk of bias item for each included study. −high risk, +: low risk,?: unclear risk.

Table 1: The characteristics of included studies; NG: not given.

Author	Nation	Design	Number of Patients(M/F)	Therapy
			Experimental Group; Control Group	Experimental Group; Control Group
Li 2011	China	NG	17/9; 23/7	TACE+Stent+^{125}I; TACE+Stent
Wu 2012	China	Retrospective study	51/5; 43/7	TACE+Stent+^{125}I; TACE+Stent

Yu 2017	China	Retrospective study	113/10;46/7	TACE+Stent+^{125}I; TACE+Stent+3-DCRT
Yu 2017	China	Retrospective study	113/10;46/7	TACE+Stent+^{125}I; TACE+Stent+3-DCRT
Luo 2009	China	Retrospective study	167/15; 82/12	TACE+Stent+^{125}I; TACE+Stent
Leu 2016	China	Prospective study	20/23;20/23	TACE+Stent+^{125}I; TACE
Zhang 2016	China	Retrospective study	178/16;83/12	TACE+Stent+^{125}I; TACE+Stent

Data analysis

We compared pre-operation with post operation in the changes of main portal vein pressure (Figure 3). We found that the main portal vein pressure was decreased after stent placement(P<0.00001). The heterogeneity did not exist in this result (I^2=0%). We did comparison in cumulative stent patency rates in 6 and 12 months between TACE+I125+stent with TACE+stent (Figure 4,5). The cumulative stent patency rates in 6 and 12 months of TACE+I125+stent were higher than TACE+stent and TACE+stent+3-DCRT(P<0.00001). The result indicated that therapies of stent without I^{125} seed and stent with 3-DCRT were easier to be obstructed by PVTT. The low heterogeneity existed in 6 months (I^2=34%) and no heterogeneity existed in 12 months (I^2=0%).

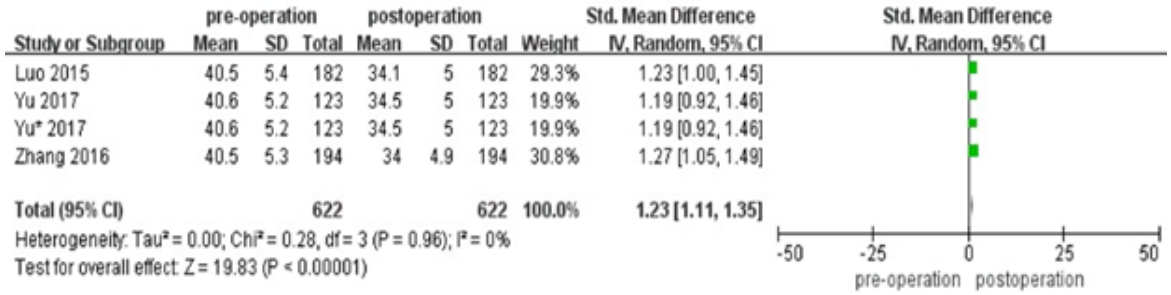

Figure 3: Forest plots of changes of main portal vein pressure.

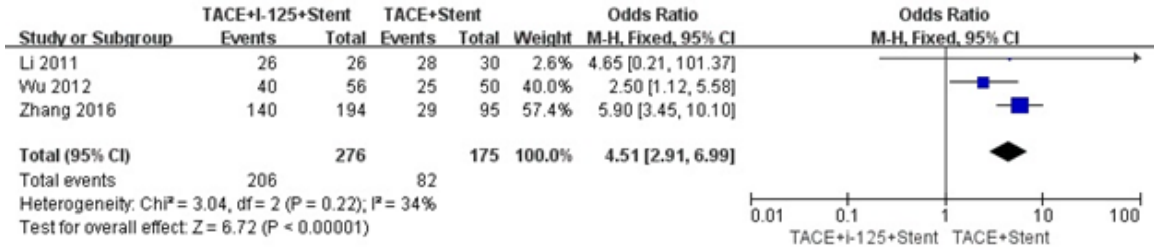

Figure 4: Forest plots of cumulative stent patency rates in 6 and 12 months.

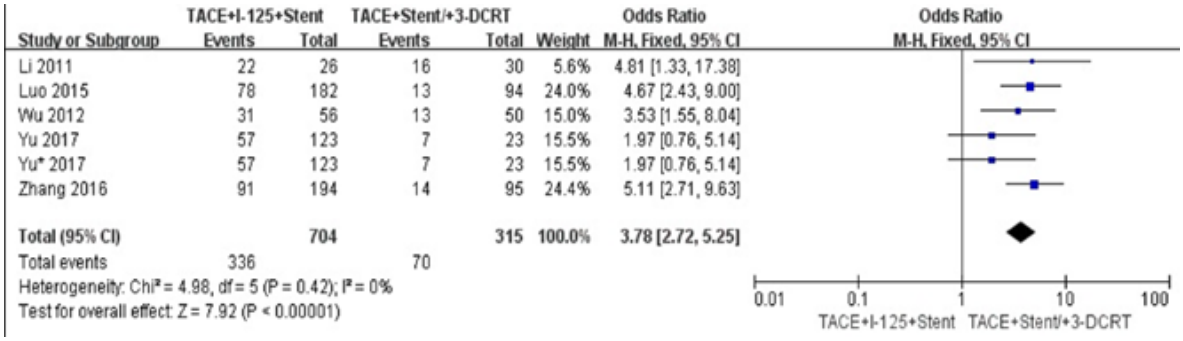

Figure 5: Forest plots of cumulative stent patency rates in 6 and 12 months.

We did comparison in overall survival rate in 6 and 12 months among TACE+^{125}I+stent, TACE+stent and TACE+stent+3-DCRT (Figure 6,7). The overall survival rate of TACE+^{125}I+stent was higher than TACE+stent and TACE+stent+3-DCRT(P<0.00001). The results indicated that TACE+^{125}I+stent could prolonger the survival time in HCC with PVTT than TACE+stent and TACE+stent+3-DCRT. The moderate heterogeneity existed in 6 and 12 months (I^2=60%, I^2=59%). The number of selected studies in overall survival rate in 6 months was not enough to explore the source of heterogeneity. consequently, we did subgroup analysis about the overall survival rates in 12 months (Figure 8). We found the heterogeneity of this meta-analysis was therapy(P<0.00001). The result also demonstrated that TACE+^{125}I+stent in HCC with PVTT was better than TACE+stent and TACE+stent+3-DCRT. To assess publication bias, funnel plots regression was conducted and no publication bias was found in this meta-analysis (Figure 9).

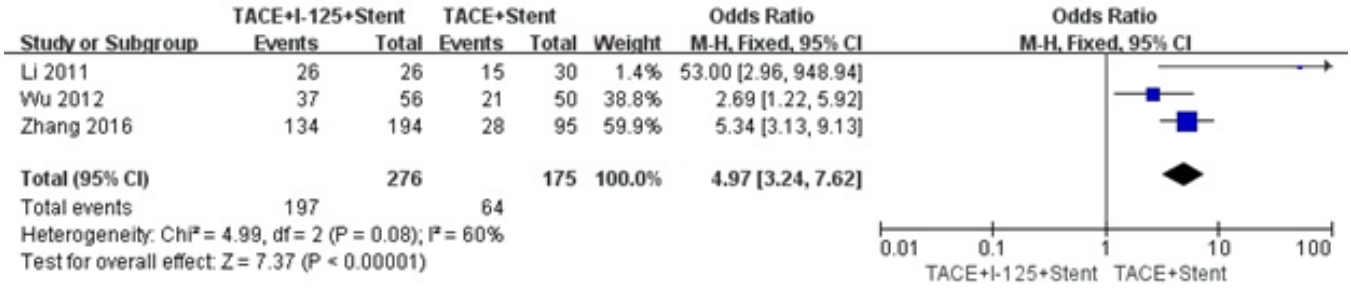

Figure 6: Forest plots of survival rates in 6 and 12 months.

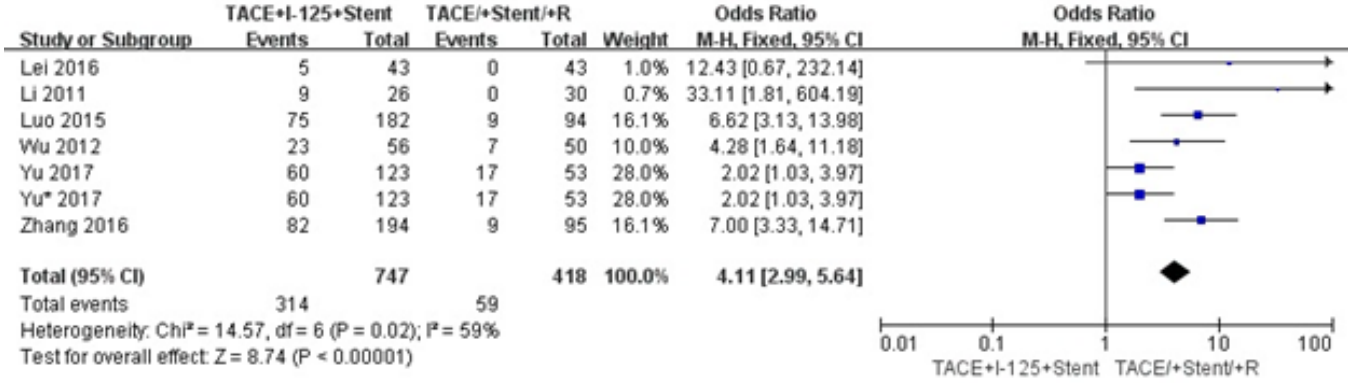

Figure 7: Forest plots of survival rates in 6 and 12 months.

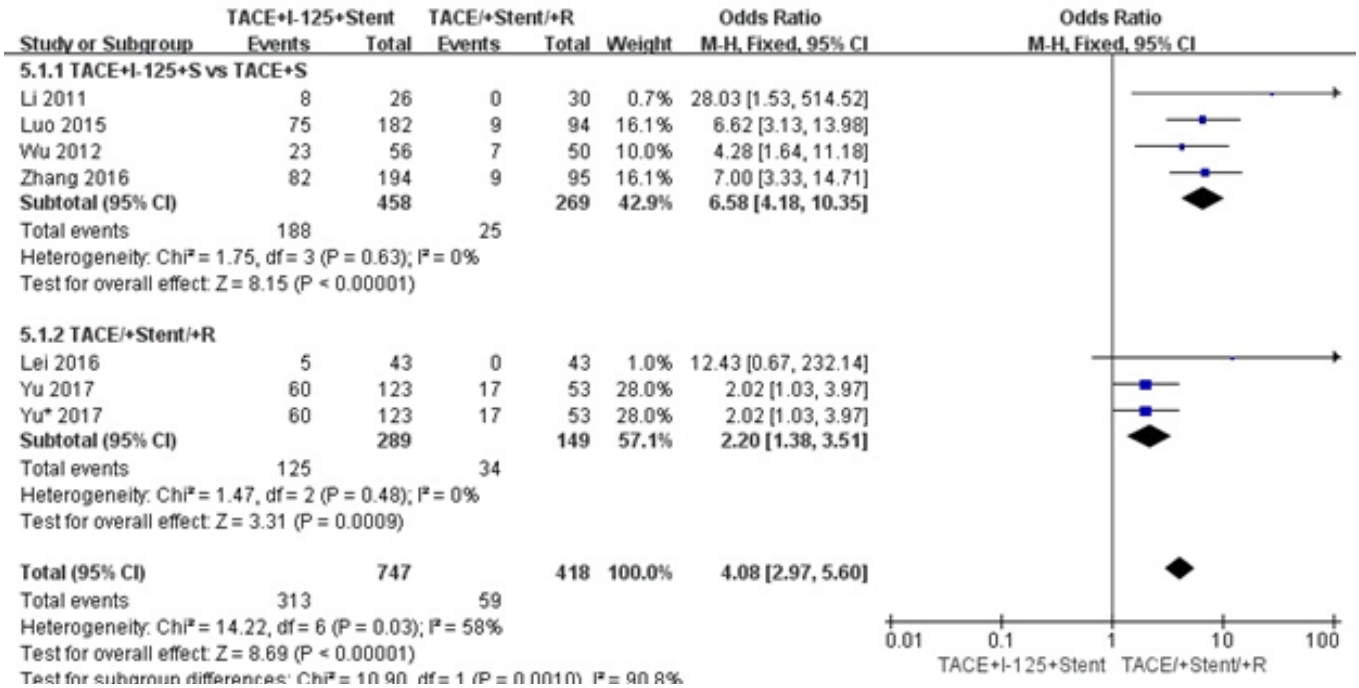

Figure 8: Forest plots of subgroup analysis about survival rates in 12 months.

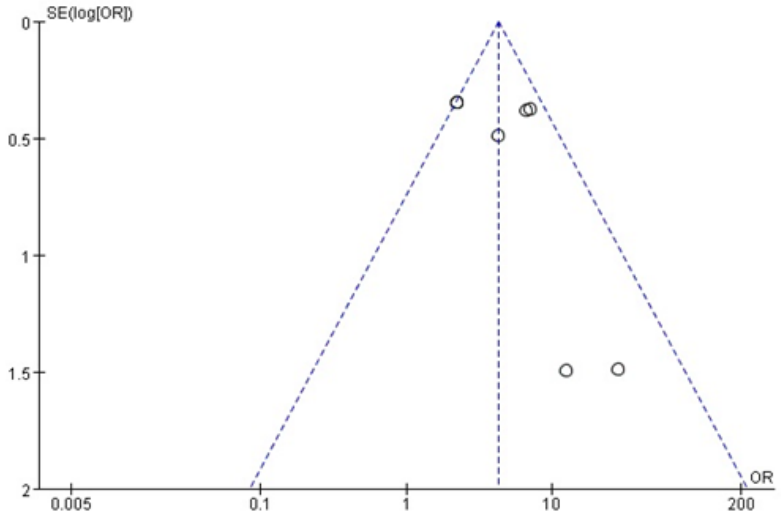

Figure 9: Funnel polt of included studies.

Discussion

Portal vein is nutrient vessel for liver, In HCC patients, the portal vein can be invaded by tumor metastasis and be obstructed by tumor thrombus. The drawbacks of portal vein occlusion are liver function failure and increased pressure of esophageal gastrointestinal bleeding, which are lethal for HCC patients. Hence, PVTT is recognized as one of the most significant signs for HCC. The effect of conventional TACE for HCC with PVTT was restricted because of indirect chemoembolization for PVTT. The effect of 3-DCRT alone was also restricted, because a radiation dose for PVTT was harmful to liver body [18]. Stent placement in portal vein was proved effective in decreasing portal vein pressure obviously [7]. However, the stent was obstructed easily by tumor thrombus re-grow through the mesh of stent. ^{125}I seeds got close to tumor to delivery continuous low does irradiation, which restrained the ability to proliferate of tumor and induced apoptosis through damaging the DNA in the nuclei of the tumor cells. ^{125}I seeds have been widely used in treating solid tumors like head and neck tumors, lung cancer, pancreatic cancer and prostate cancer [19-21]. In our meta-analysis, the therapy of TACE+^{125}I+stent for HCC with PVTT was proved safety and efficient. To explore the heterogeneity, we found that the therapy of TACE+^{125}I+stent significantly maintained the stent patency, extended the survival time and improved the prognosis of patients with HCC and PVTT. Compared with conventional TACE, stent in portal vein relieved the pressure of portal vein, which reduced the probability of lethal esophageal gastrointestinal bleeding and liver function failure. Furthermore, stent placement provided patients with opportunities for follow-up therapies. Compared with 3-DCRT, 125I seeds had a short radiation distance and highly accumulated radiation within tumor thrombus without serious damage to the surrounding tissue. Moreover, curative effect of ^{125}I seeds was not affected by respiration motion. Some researchers showed that the combination of stent and ^{125}I seeds was a good method for HCC with PVTT [22,23]. ^{125}I seeds were prevented from loss and displacement by fixed in the site of tumor thrombus. It achieved fully covered radiation of tumor thrombus. Also, some researchers found that neointimal hyperplasia restenosis after stent placement could be counteracted by ^{125}I seeds [24,25].

We should acknowledge the limitations of this meta-analysis. First, there were not enough prospective and high-qualities studies in selected studies that might uncover the clinical significance of TACE+^{125}I+stent for HCC patients with PVTT. Second, with the limited number of selected studies, we cannot find more sources of heterogeneity. Third, the potential publication bias could not be ignored, although our result showed no significant publication bias. In summary, the therapy of TACE+^{125}I+stent was better than conventional TACE, TACE+stent, and TACE+stent+3-DCRT in prolonging the survival time and improving long-term portal vein stent patency in HCC patients with PVTT.

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