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META-ANALYSIS

Percutaneous biliary stent combined with brachytherapy using ^{125}I seeds for treatment of unresectable malignant obstructive jaundice: A meta-analysis

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Abstract

BACKGROUND

Malignant obstructive jaundice (MOJ) is a common pathologic manifestation of malignant biliary obstruction. Recently, several clinical trials have explored the clinical effectiveness of intraluminal ^{125}I seed-based brachytherapy for MOJ patients, and various outcomes have been reported.

AIM

To assess the efficacy and safety of percutaneous biliary stents with ^{125}I seeds compared to conventional metal stents in patients with unresectable MOJ.

METHODS

A systematic search of English-language databases (PubMed, Embase, Cochrane Library, and Web of Science) was performed to identify studies published prior to June 2020 that compared stents with or without ^{125}I seeds in the treatment of unresectable MOJ. The outcomes analyzed included primary outcomes (stent patency and overall survival) and secondary outcomes (complications and liver function parameters).

RESULTS

Six randomized controlled trials and four retrospective studies involving 875 patients were eligible for the analysis. Of the 875 included patients, 404 were treated with ^{125}I seed stents, while 471 were treated with conventional stents. Unadjusted pooled analysis demonstrated that compared to conventional stents,

The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

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I seed stents extended the stent patency time [hazard ratio (HR) = 0.36, 95% confidence interval (CI) = 0.28-0.45, $P < 0.0001$] and overall survival period (HR = 0.52, 95%CI = 0.42–0.64, $P < 0.00001$). Subgroup analyses based on the type of ^{125}I seed stent and type of study design showed consistent results. However, there were no significant differences in the occurrence of total complications [odds ratio (OR) = 1.12, 95%CI = 0.75-1.67, $P = 0.57$], hemobilia (OR = 1.02, 95%CI = 0.45-2.3, $P = 0.96$), pancreatitis (OR = 1.79, 95%CI = 0.42-7.53, $P = 0.43$), cholangitis (OR = 1.13, 95%CI = 0.60-2.13, $P = 0.71$), or pain (OR = 0.67, 95%CI = 0.22-2, $P = 0.47$). In addition, there were no reductions in the levels of serum indices, including total bilirubin [mean difference (MD) = 10.96, 95%CI = -3.56-25.49, $P = 0.14$], direct bilirubin (MD = 7.37, 95%CI = -9.76-24.5, $P = 0.4$), alanine aminotransferase (MD = 7.52, 95%CI = -0.71-15.74, $P = 0.07$), and aspartate aminotransferase (MD = -4.77, 95%CI = -19.98-10.44, $P = 0.54$), after treatment. Publication bias was detected regarding the outcome overall survival; however, the conclusions were not changed after the adjustment.

CONCLUSION
Placement of stents combined with brachytherapy using ^{125}I seeds contributes to a longer stent patency and higher overall survival than placement of conventional stents without extra complications or severe liver damage. Thus, it can be considered an effective and safe treatment for unresectable MOJ.

Key Words: Malignant obstructive jaundice; Brachytherapy; ^{125}I seed; Patency; Survival; Meta-analysis

Core Tip: In recent years, the incidence of malignant obstructive jaundice (MOJ) in Asia has been 40 times higher than that in the Western world, which is a vital issue that requires significant attention. Irradiation stents using ^{125}I seeds have been widely applied in the treatment of unresectable MOJ. However, more convincing evidence-based reviews of the efficacy and safety of ^{125}I seed stents are needed. We used the latest data to further validate the superiority of ^{125}I seed stents, providing strong evidence for clinicians to make correct decisions in clinical practice. Furthermore, we found that ^{125}I seed stents resulted in equivalent complication and serum index outcomes as conventional stents, indicating that ^{125}I seed stents are safe and well tolerated.

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INTRODUCTION

Malignant obstructive jaundice (MOJ) is a common pathologic manifestation of malignant biliary obstruction caused by various adenocarcinomas[1]. Since the disease process is insidious but develops rapidly, only a minority of MOJ patients (< 20%) are suitable for radical operation, leading to a poor overall prognosis[2]. For patients with unresectable MOJ or those who are unwilling to undergo surgery, biliary stent implantation is a mainstay to relieve the biliary obstruction and clinical symptoms caused by progressive neoplasms[3]. Nevertheless, the stent itself has no effect on tumor suppression. The ingrowth or overgrowth of tumors, biliary epithelial cell proliferation, and biliary sludge formation often cause restenosis[4,5]. Thus, extra antitumor therapies are needed to improve the prognosis of patients with unresectable MOJ[6-8].

Intraluminal iodine-125 (^{125}I) seed brachytherapy, due to its antitumor growth function and specificity for destroying target tumors, has been widely applied in local tumor treatment[9-12]. Several studies have demonstrated that intraluminal ^{125}I seed-based brachytherapy has excellent therapeutic effects in the treatment of unresectable MOJ[13-15]. However, most studies are single-center or retrospective with relatively small sample sizes, and the number of randomized controlled trials (RCTs) is still limited.

To provide more convincing clinical evidence, we conducted a meta-analysis to accurately assess the efficacy and safety of percutaneous biliary stents with ^{125}I seeds compared with conventional stents in patients with unresectable MOJ.

MATERIALS AND METHODS

This meta-analysis was conducted according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines[16]. Institutional review board approval was not required for this analysis.

Search strategy and selection criteria

The following electronic databases were searched: PubMed, Embase, Cochrane Library, and Web of Science (before June 2020). The ClinicalTrials.gov website was also searched for randomized trials that were registered as completed but not yet published. Search terms such as "^{125}I seed," "brachytherapy," "biliary stent," "malignant obstructive jaundice," and "malignant biliary obstruction" were included. The detailed search strategy is listed in Supplementary Table 1. In addition, the reference lists of identified studies were screened manually to include other potentially eligible trials. The following inclusion criteria were applied: (1) Studies involving adult patients (aged 18-90 years) with a confirmed diagnosis of MOJ; (2) studies comparing percutaneous biliary stent placement with the placement of ^{125}I seeds and conventional metal stents; and (3) studies published in English. The following exclusion criteria were applied: (1) Abstracts without full texts; (2) studies registered but not completed; (3) studies that included patients whose data was published in multiple papers; and (4) studies with a sample size smaller than 20.

Each study (title and abstract) identified through the search strategy was screened for potential relevance by two authors (Chen WY and Kong CL). The full articles of studies chosen as being relevant were reviewed by the same authors for final inclusion. Differences of opinions were resolved by consensus.

Data extraction

The following data were independently extracted by two authors: Trial information (first author, year of publication, country, design, period of enrollment, intervention, number of included patients, and stent manufacturer and type), baseline patient characteristics (age, sex, causes of MOJ, and obstruction level), and outcomes (clinical effectiveness and complications). The extracted data were documented into a standardized Excel (Microsoft Corp, Redmond, WA, United States) file and were checked by another author. Any disagreement was resolved through discussion and a reassessment and recheck of the data and/or involvement of a senior author.

Quality assessment

All randomized controlled trials were analyzed using Cochrane Collaboration's tool. The risk of bias assessment in trials was based on random sequence generation, allocation concealment, blinding of participants, personnel and outcome assessment, incomplete outcome data, selective reporting, and other factors. Each category was assessed as "yes" (low risk of bias), "no" (high risk of bias), or "unclear". Cohort studies were assessed using the Newcastle–Ottawa Scale (NOS) with three main domains: Study group selection, comparability of cohorts, and ascertainment of outcomes. A study with an NOS score of 7 or higher was considered high quality.

Outcomes and definitions

This meta-analysis analyzed primary outcomes (stent patency and overall survival) and secondary outcomes (complications and liver function parameters). Stent patency was calculated from the date of stent placement to the first episode of stent restenosis. Stent restenosis was defined as the presentation of clinical signs of recurrent jaundice with elevated bilirubin levels along with biliary dilation on imaging study. Overall survival was defined as the interval between initial stenting and patient death or the

last follow-up. Classification of complications was performed according to the Common Terminology Criteria for Adverse Events (CTCAE 4.02) or the guidelines of the Society of Interventional Radiology Standards of Practice Committee[17]. Postoperative procedure-related complications mainly included hemobilia, pancreatitis, cholangitis, and pain. Liver function parameters were evaluated by assessing the change in serum indices before and 1 wk after treatment, including total bilirubin (TBIL), direct bilirubin (DBIL), alanine aminotransferase (ALT), and aspartate aminotransferase (AST).

Three types of ^{125}I seed stents were mentioned in the included studies. Type I stents refer to self-expanded stents with ^{125}I seed strand fixation in a drainage catheter. Type II stents refer to ^{125}I seed-loaded stents. Type III stents refer to self-expanded stents with ^{125}I seed strand fixation between the stent and the bile duct wall. The ^{125}I seed strand is a combination of a 4F catheter and multiple ^{125}I seeds.

Statistical analysis

Statistical analyses were performed using Review Manager (version 5.0) and Stata 15.1. For time-to-event data, the aggregated hazard ratio (HR) and its 95% confidence interval (95%CI) were applied to report the final pooled estimate. HRs and the corresponding 95%CIs were directly obtained if mentioned in the manuscript; however, if not, the HR and lnHR were estimated by the method of Tierney *et al*[18] from Kaplan–Meier curves or the calculated value of the O-E and V. The outcomes of dichotomous and continuous variables are expressed as odds ratios (ORs) and weighted mean differences, respectively. Statistical heterogeneity across the included studies was quantified by the I^2 statistic. When heterogeneity was significant (I^2 > 50%), a random-effects model was applied to calculate the pooled effect sizes; otherwise, a fixed-effects model was used. Sensitivity analysis was performed by excluding one trial in each turn to explore the potential causes of heterogeneity. Subgroup analysis was conducted according to the type of ^{125}I seed stent and study design (RCT and retrospective study). Potential publication bias was appraised using Egger's and Begg's tests. Publication bias was adjusted using the trim and fill method [19]. Two-sided P < 0.05 was considered significant.

RESULTS

Search results and characteristics of the studies

The PRISMA flow diagram for the selection process is presented in Figure 1. The initial database search yielded 244 potentially relevant studies, ten of which were included in this meta-analysis[13-15,20-26]. Of these studies, four were retrospective cohort studies and six were RCTs published between 2012 and 2018[13,14,20,21,25,26]. Five of these RCTs were single-center studies, while one was a multicenter study performed at 20 centers in China[21]. All of them were conducted in China and written in English. These studies included a total of 875 patients, among whom 404 (46.17%) underwent biliary stent placement combined with brachytherapy using ^{125}I seeds, and 471 (53.83%) received conventional metal stents only for treatment. Percutaneous transhepatic biliary drainage was performed before stent placement in all cases. Three studies used type I stents[14,24,25], three used type II[20,21,26], and four used type III [13,15,22,23]. The target population was patients with unresectable MOJ, and the majority of them had cholangiocarcinoma (n = 331, 37.83%) and pancreatic carcinoma (n = 177, 20.23%). The trial information and patients' baseline characteristics are shown in Table 1, while the intervention details for the deployment of ^{125}I seeds and the main outcomes are listed in Table 2, with detailed data shown in Supplementary Tables 2 and 3.

Quality assessment

According to the Cochrane Collaboration's tool, the risk of bias varied among the six RCT studies included in this meta-analysis, ranging from low to high levels (Supplementary Figures 1 and 2). All studies had a high risk of performance bias because it was difficult to conceal the grouping and interventional procedures from the participants, researchers, and outcome measurers. Three RCTs (50%) did not describe the method of allocation concealment in detail. According to the NOS, the retrospective cohort studies had high quality scores, which were measured to be between 7 and 9 (Supplementary Table 4).

Table 1 Study information and patient characteristics of this Meta-analysis

Ref.	Design	Country	Period of enrolment	Groups	Number of patients	Age (yr)	Sex (male/female)	Obstruction levels	Causes of MOJ
Chen *et al* [25], 2012	Single-centre, RCT	China	Mar. 2009-Jan. 2010	^{125}I + stent	17	61.2 ± 14.5	12/5	Hilar and distal	Cholangiocarcinoma (*n* = 7), hepatocellular carcinoma (*n* = 2), pancreatic cancer (*n* = 3), hepatic metastases from the stomach or colorectum (*n* = 5)
				Stent	17	63.9 ± 9.3	10/7		Cholangiocarcinoma (*n* = 6), hepatocellular carcinoma (*n* = 4), pancreatic cancer (*n* = 3), hepatic metastases from the stomach or colorectum (*n* = 4)
Hasimu *et al* [13], 2017	Single-centre, RCT	China	July 2011-June 2014	^{125}I + stent	28	70.93 ± 8.58	11/17	Hilar and distal	Cholangiocarcinoma (*n* = 48), gallbladder cancer (*n* = 7)
				Stent	27	70.26 ± 9.71	14/13		
Chen *et al* [26], 2018	Single-centre, RCT	China	Sep. 2014-Nov. 2016	^{125}I + stent	13	66 (49, 88)	8/5	Lower	Pancreatic head carcinoma (*n* = 7), gallbladder carcinoma (*n* = 4), bile duct carcinoma (*n* = 2)
				Stent	19	68 (48, 86)	12/7		Pancreatic head carcinoma (*n* = 11), bile duct carcinoma (*n* = 5), gallbladder carcinoma (*n* = 2), ampullary carcinoma (*n* = 1)
Jiao *et al* [14], 2017	Single-centre, RCT	China	Jan. 2013- Jan. 2015	^{125}I + stent	31	60.4 ± 8.8	12/17	Hilar and distal	Primary adenocarcinoma (*n* = 19), metastatic adenocarcinoma (*n* = 12)
				Stent	30	60.2 ± 8.1	16/14		Primary adenocarcinoma (*n* = 21), metastatic adenocarcinoma (*n* = 9)
Zhu *et al* [20], 2012	Single-centre, RCT	China	Nov. 2008-Oct. 2010	^{125}I + stent	12	62.5 ± 21.0	7/5	Hilar and distal	Primary adenocarcinoma (*n* = 8), metastatic adenocarcinoma (*n* = 4)
				Stent	11	71.0 ± 22.0	9/2		Primary adenocarcinoma (*n* = 5), metastatic adenocarcinoma (*n* = 6)
Zhu *et al* [21], 2018	Multicentre, RCT	China	Oct. 2013-Mar. 2016	^{125}I + stent	164	65.0 (56.0, 75.0)	103/61	Hilar and distal	Biliary tract cancer (*n* = 80), pancreatic carcinoma (*n* = 46), lymph node metastases (*n* = 38)
				Stent	164	64.0 (57.0, 75.0)	109/55		Biliary tract cancer (*n* = 74), pancreatic carcinoma (*n* = 53), lymph node metastases (*n* = 37)
Pan *et al* [15], 2020	Retrospective cohort study	China	Mar. 2014-Dec. 2017	^{125}I + stent	30	56.53 ± 12.24	23/7	Hilar and distal	NR
				Stent	54	60.44 ± 11.83	35/19		
Wang *et al* [24], 2017	Retrospective cohort study	China	Sep. 2010-Feb. 2013	^{125}I + stent	24	57.3 (41, 80)	29/21	Hilar and distal	Holangiocarcinoma (*n* = 18), pancreatic head carcinoma (n = 14), hilar lymph node metastasis (*n* = 12), ampullary carcinoma (*n* = 6)
				Stent	26				

Zhou *et al* [22], 2019	Retrospective cohort study	China	Nov. 2015-Oct. 2017	^{125}I + stent	45	61.7 (32, 87)	31/14	Hilar, middle and distal	Cholangiocarcinoma (n = 18), gallbladder carcinoma (n = 6), pancreatic carcinoma (n = 4), hepatocellular carcinoma (n = 7), gastric cancer (n = 7), ampullary cancer (n = 0), hilar node metastases from other solid malignancies (n = 3)
				Stent	87	64.4 (35, 92)	59/28		Cholangiocarcinoma (n = 32), gallbladder carcinoma (n = 9), pancreatic carcinoma (n = 17), hepatocellular carcinoma (n = 9), gastric cancer (n = 11), ampullary cancer (n = 1), hilar node metastases from other solid malignancies (n = 8)
Zhou *et al* [23], 2020	Retrospectively cohort study	China	Jan. 2017-June 2018	^{125}I + stent	40	70.2 ± 13.8	21/19	Hilar	Cholangiocarcinoma (n = 22), pancreatic cancer (n = 10), gallbladder cancer (n = 2), duodenal cancer (n = 2), metastatic cancer (n = 4)
				stent	36	68.1 ± 12.2	21/15		Cholangiocarcinoma (n = 19), pancreatic cancer (n = 8), gallbladder cancer (n = 3), duodenal cancer (n = 1), metastatic cancer (n = 5)

MOJ: Malignant obstructive jaundice; RCT: randomized controlled trial.

Egger's and Begg's tests were carried out to evaluate the potential publication bias for primary endpoints. There was no evidence that publication bias occurred in the outcome of stent patency (Egger's test P = 0.705), whereas it was observed in the outcome of overall survival (Egger's test P = 0.027). The conclusions were not changed after adjustment for publication bias by using the trim-and-fill method.

Primary endpoints

Stent patency: HR data for stent patency were extracted from seven studies[13,14,21,22,24-26]. The utilization of ^{125}I seed stents resulted in a better stent patency than the use of conventional stents (HR = 0.36, 95%CI = 0.28-0.45, P < 0.0001; Figure 2A). There was no significant heterogeneity among these studies (I^2 = 0%, P = 0.48). The test for subgroup analyses revealed no significant difference in heterogeneity based on the type of ^{125}I seed stent and type of study design. The results showed that compared with conventional stents, three ^{125}I seed stent types were all associated with a significantly prolonged stent patency (Figure 3). Both RCTs and retrospective studies demonstrated that the ^{125}I seed stent group was superior to the conventional stent group in patency (RCTs: HR = 0.42, 95%CI = 0.31-0.58, P < 0.00001; retrospective studies: HR = 0.28, 95%CI = 0.20-0.41, P < 0.00001; Figure 4A and B).

Overall survival: HR data for overall survival were extracted from eight studies[13-15,20-23,26]. In comparison with the use of conventional stents, the application of ^{125}I seed stents resulted in a better overall survival (HR = 0.52, 95%CI = 0.42-0.64, P < 0.00001, Figure 2B). Heterogeneity among these studies was not significant (I^2 = 7%, P = 0.37). The test for subgroup analysis demonstrated no significant difference in heterogeneity according to the type of study design (P = 0.904). The results of a stratified analysis of RCTs and retrospective studies showed that the ^{125}I seed stent group had a better overall survival than the conventional stent group (RCTs: HR = 0.42, 95%CI = 0.31-0.58, P < 0.00001; retrospective studies: HR = 0.60, 95%CI = 0.46-0.79, P = 0.0003; Figure 4C and D).

Table 2 Procedure details and outcomes of studies included in the meta-analysis

Ref.	Intervention	Stent manufacturer and type[a]	Outcomes
Chen *et al* [25], 2012	^{125}I seed strands performed after stent insertion	Nitinol self-expendable stent (Luminexx III; BARD); Type I	Laboratory values before and after stent placement, complications, stent patency
	Conventional stent		
Hasimu *et al* [13], 2017	Biliary stent with ^{125}I seed strands	Nitinol self-expandable stent (S.M.A.R.T.; Cordis Corporation, Miami Lakes, FL, United States); Type III	Stent patency, survival, relief of symptoms, technical and clinical success, complications, laboratory values before and after stent placement, radiation safety
	Conventional stent		
Chen *et al* [26], 2018	^{125}I seeds-loaded-biliary stent	Self-expendable stent (produced by Mirco-tech, Nanjing, China); Type II	Laboratory values before and after stent placement, complications, stent patency, survival, CR, PR, SD, PD
	Conventional stent		
Jiao *et al*[14], 2017	SEMS with ^{125}I seed strands	A Nitinol self-expendable stent (Niti-S Biliary stent, Taewoong, Seoul, Korea); Type I	Technical success, laboratory values before and after stent placement, stent patency, overall survival, early or late complications
	Conventional stent		
Zhu *et al*[20], 2012	^{125}I seeds-loaded-biliary stent	Outer self-expandable 125I radioactive seeds-loaded stent and inner conventional self-expanding biliary nitinol alloy stent (Nanjing MicroInvasive Medical Inc., Nanjing, China); Type II	Technical success, jaundice relief, radiation safety, complications (subjective and objective), survival, stent patency, laboratory values before and after stent placement
	Conventional stent		
Zhu *et al*[21], 2018	^{125}I seeds-loaded-biliary stent	Inner conventional uncovered SEMS (Nanjing Micro-Tech Co. Ltd., Nanjing, China) and outer ^{125}I seed-Xloaded stent; Type II	Stent restenosis, patency time, technical success, relief of jaundice, survival, complications
	Conventional stent		
Pan *et al*[15], 2020	Biliary stent with ^{125}I seed strands	Biliary stent (E-Luminexx Biliary Stent; Wachhausstrasse 6D76227, BARD Corporation, Karlsruhe, Germany); Type III	Stent patency, overall survival, complications, laboratory values before and after stent placement, independent factors associated with survival
	Conventional stent		
Wang *et al* [24], 2017	Biliary stent with ^{125}I seed strands	Biliary internal stent (Micro-Tech Co., Ltd. Nanjing, China); Type I	Success rate, laboratory values before and after stent placement, stent patency, survival
	Conventional stent		
Zhou *et al* [22], 2019	UCSEMS with ^{125}I seed strands	Three types of SEMS [E-Luminexx (Bard Peripheral Vascular, Tempe, AZ, United States), S.M.A.R.T (Cordis, Milpitas, CA, United States), and Zilver (Cook Medical, Bloomington, IN, United States)];Type III	Technical success, clinical success, complications, follow-up time, stent patency, survival, laboratory values before and after stent placement
	UCSEMS		
Zhou *et al* [23], 2020	SEMS with ^{125}I seed strands	Self-expandable metallic stent (Cook Medical, Bloomington, IN, United States); Type III	Technical success, clinical success, laboratory values before and after stent placement, complications, overall survival, and stent patency
	Conventional stent		

[a]The ^{125}I seed stents include three types. Type I: Self-expanded stent with ^{125}I seed strand fixation in a drainage catheter; Type II: ^{125}I seed-loaded stent; Type III: Self-expanded stent with ^{125}I seed strand fixation between stent and the bile

duct wall.

Secondary endpoints

Complications: A total of nine studies provided incidence data for all complications or at least one kind of complication. Overall, both groups had low overall complication rates, with slightly worse results being observed in the ^{125}I seed stent group than in the conventional stent group (19.2% *vs* 16.5%). However, this difference was not statistically significant (OR = 1.12, 95%CI = 0.75-1.67, P = 0.57; Figure 5), and there was a low level of heterogeneity among these studies (I^2 = 0%, P = 0.74). There were also no significant differences between the ^{125}I seed stent group and the conventional stent group in the incidence of hemobilia (OR = 1.02, 95%CI = 0.45–2.3, P = 0.96; I^2 = 0%, P = 0.8), pancreatitis (OR = 1.79, 95%CI = 0.42-7.53, P = 0.43; I^2 = 0%, P = 0.65), cholangitis (OR = 1.13, 95%CI = 0.60-2.13, P = 0.71; I^2= 0%, P = 0.83), or pain (OR = 0.67, 95%CI = 0.22-2, P = 0.47; I^2 = 0%, P = 0.97) (Figure 5).

Posttreatment reductions in the levels of serum indices: After the procedure, there was a significant decrease in liver function indices, including TBIL, DBIL, ALT, and AST. The numbers of studies that reported pretreatment and posttreatment TBIL, DBIL, ALT, and AST data were 8, 6, 7, and 4, respectively. We calculated the degree of reduction in each index, and found that there were no significant differences in the posttreatment reductions in the levels of TBIL (MD = 10.96, 95%CI = -3.56-25.49, P = 0.14; I^2 = 0%, P = 0.54), DBIL (MD = 7.37, 95%CI = -9.76-24.5, P = 0.4; I^2 = 33%, P = 0.19), ALT (MD = 7.52, 95%CI = -0.71-15.74, P = 0.07; I^2 = 0%, P = 0.51), and AST (MD = -4.77, 95%CI = -19.98-10.44, P = 0.54; I^2 = 0%, P = 0.77) between the ^{125}I seed stent group and the conventional stent group (Figure 6).

DISCUSSION

This meta-analysis showed that biliary stents irradiated using ^{125}I seeds resulted in a longer stent patency and higher overall survival than conventional stents in the treatment of unresectable MOJ. The same results were observed for the median or mean time of stent patency and overall survival in the included studies. However, due to the different presentations of the main results, this study transformed these original results into HR values rather than conducting a pooled analysis. The risk of restenosis was associated with patient death[21]. The longer stent patency was attributed to the short-distance irradiation effect of radioactive seeds embedded in the stents. Brachytherapy using ^{125}I seed stents was developed to inhibit tumor ingrowth, relieve the obstruction, and finally prolong the survival time of patients with unresectable MOJ. This result further confirms the superior effect of irradiation stents using ^{125}I seeds, which provides strong evidence for clinicians to make correct decisions in clinical

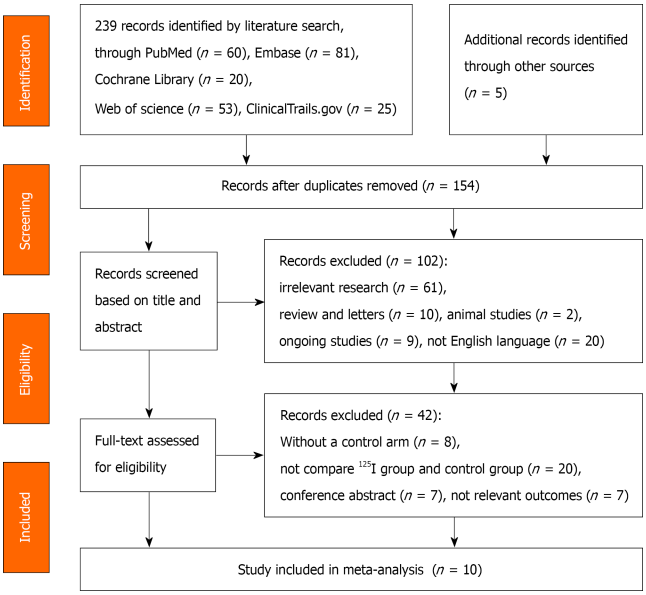

Figure 1 Flow diagram outlining methods of selecting eligible studies.

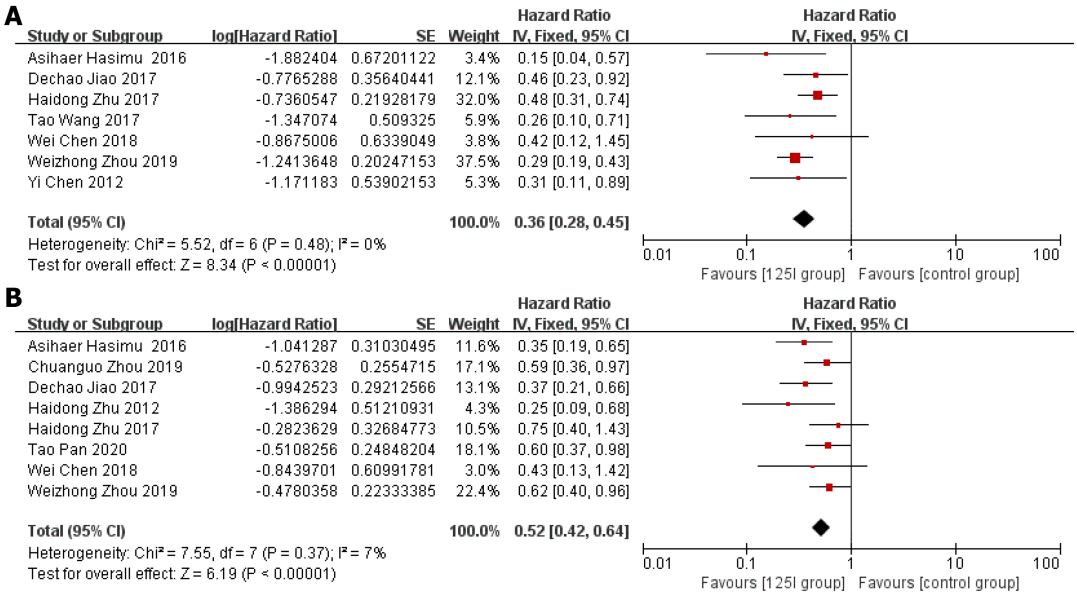

Figure 2 Forest plot (whole studies). A: Hazard ratios for stent patency; B: Hazard ratios for overall survival.

practice.

The implantation of stents irradiated using ^{125}I is safe and well tolerated. All particle stents have some radiation hazards, and they also increase the complexity of the operation, which may cause certain damage to the intima and radiation damage to the gastrointestinal or bile duct during the treatment procedure[27]. However, our analysis showed that the treatment with ^{125}I seed stents did not result in a higher incidence rate of complications than conventional stents. Additionally, none of the studies reported fatal complications, such as biliary or intestinal perforation or massive hemorrhage, and there was no device- or procedure-related mortality. Cholangitis is a more frequent complication associated with irradiated stents, with an incidence of 8.4% in the ^{125}I seed stent group and 6.9% in the conventional stent group in this meta-analysis. However, this difference was not statistically significant. The incidence rates of other complications, such as hemobilia, pancreatitis, and pain, between the two groups were also comparable. Therefore, we concluded that no additional biliary complications occurred due to the use of ^{125}I seed stents in patients with unresectable MOJ.

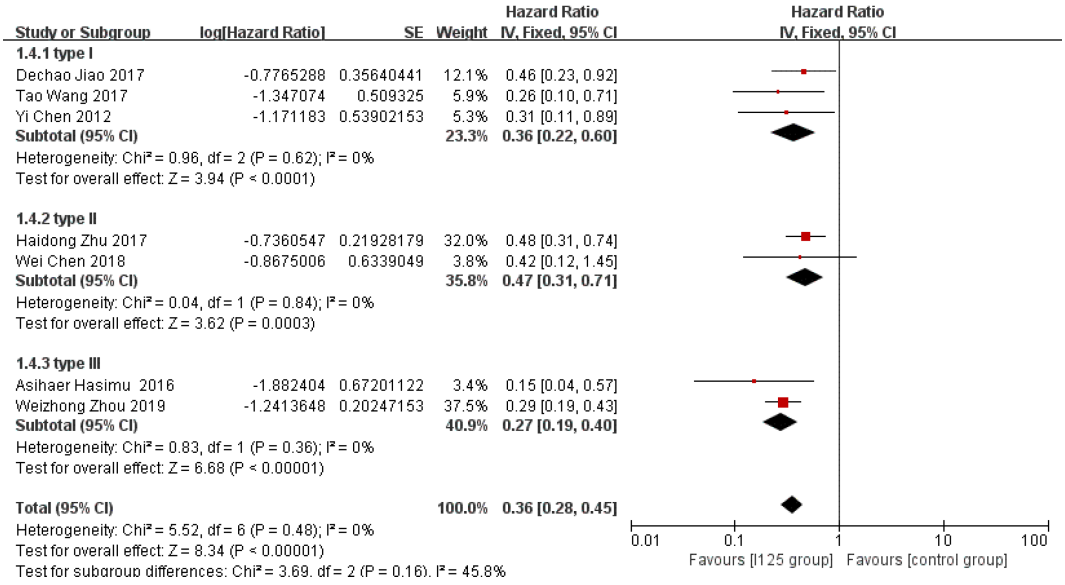

Figure 3 Subgroup analysis of stent patency based on irradiation stent type.

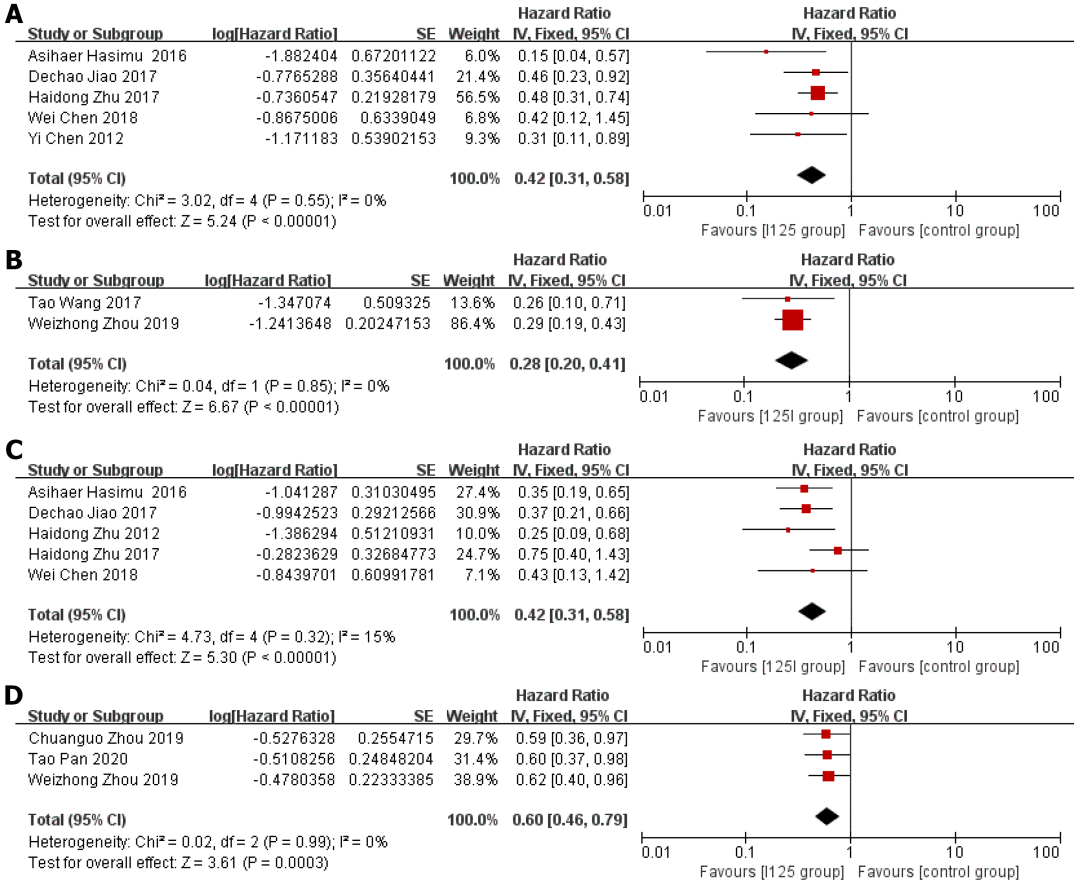

Figure 4 Forest plot (subgroup, divided by randomized controlled trials and retrospective studies). A: Randomized controlled trial (RCT)-stent patency; B: Retrospective study-stent patency; C: RCT-overall survival; D: Retrospective study-overall survival.

After implantation of the stents, the reductions in the serum indices of patients indicated improved therapeutic efficacy. Part of the biliary system is intrahepatic. Theoretically, irradiation biliary stent implantation may induce damage to the liver parenchyma. However, the reductions in the levels of serum indices (TBIL, DBIL, ALT, and AST) after treatment were not significantly different between the two groups, which demonstrated that the [125]I seed stents were as effective as the conventional stents

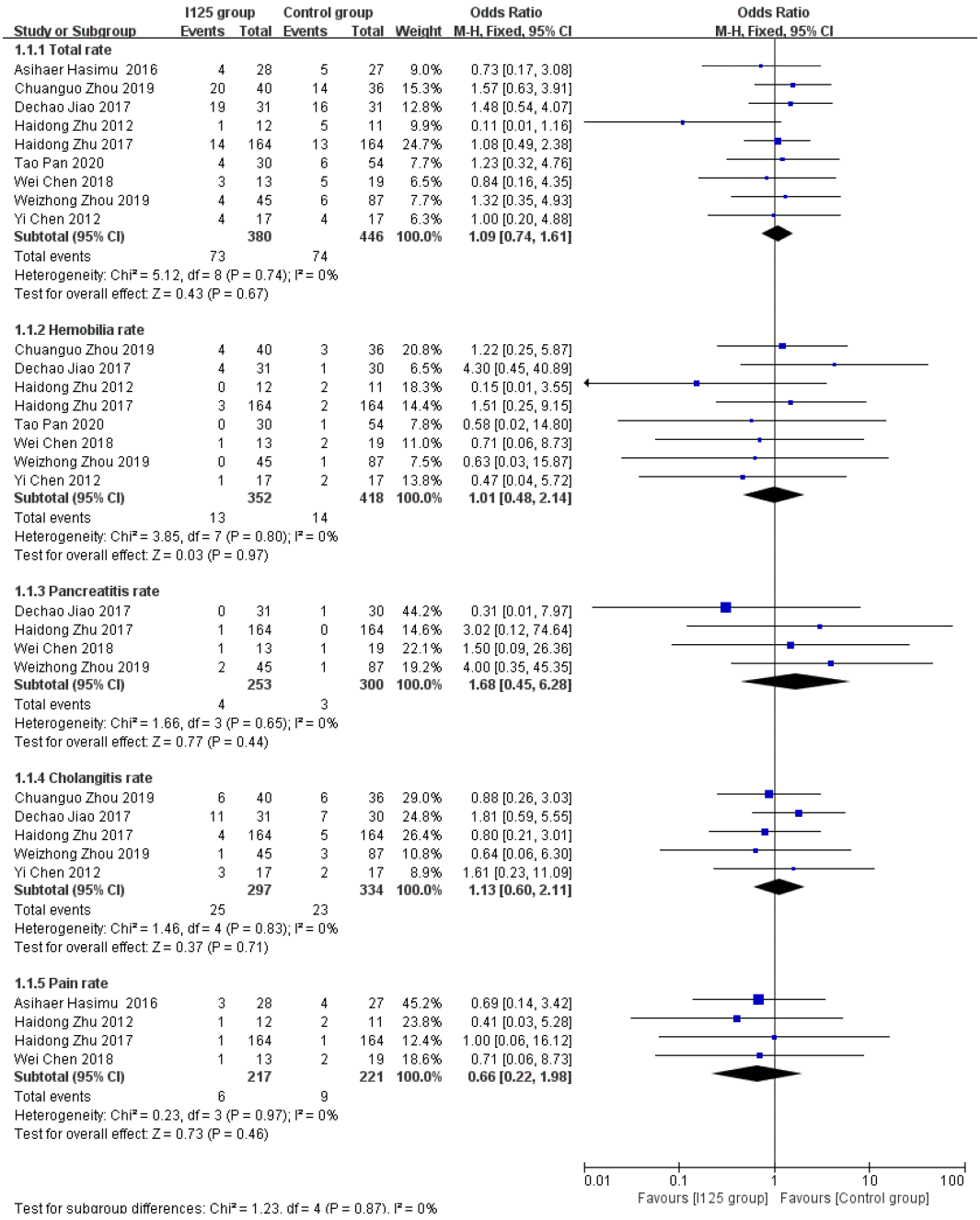

Figure 5 Forest plot comparing rate of complications.

in improving liver function in patients with unresectable MOJ. Nevertheless, ^{125}I seed stents have obvious advantages in inhibiting tumor growth. An investigation by Wang *et al*[24] showed that the levels of tumor markers (CA-199 and CA-242) in the ^{125}I seed stent group were significantly reduced after stent implantation, while no significant change was observed in the conventional stent group. This might be the reason why patients with unresectable MOJ treated with irradiated stents show amelioration of obstructive jaundice and a delayed disease process.

In terms of radiation safety, irradiation dose is the focus of brachytherapy[28]. The amount of ^{125}I embedded in the stents is based on the tumor size and relevant recommendations of the Treatment Planning System (TPS, FTT Technology Ltd. Co., Beijing, China). The radiation doses used in all studies met the minimum threshold for effective brachytherapy treatment of adenocarcinoma (7.87 cGy and 30 Gy), while some of the studies used a higher dose (80–990 Gy) within the safety limits established through animal experiments and clinical trials[25]. A suitable dose has the optimal capacity to kill the primary tumor effectively. Although several previous reports indicated that a decrease in white blood cell count and immunoglobulin (IgA, IgG, and IgM) levels is associated with long-term and low-dose radiotherapy with ^{125}I-based

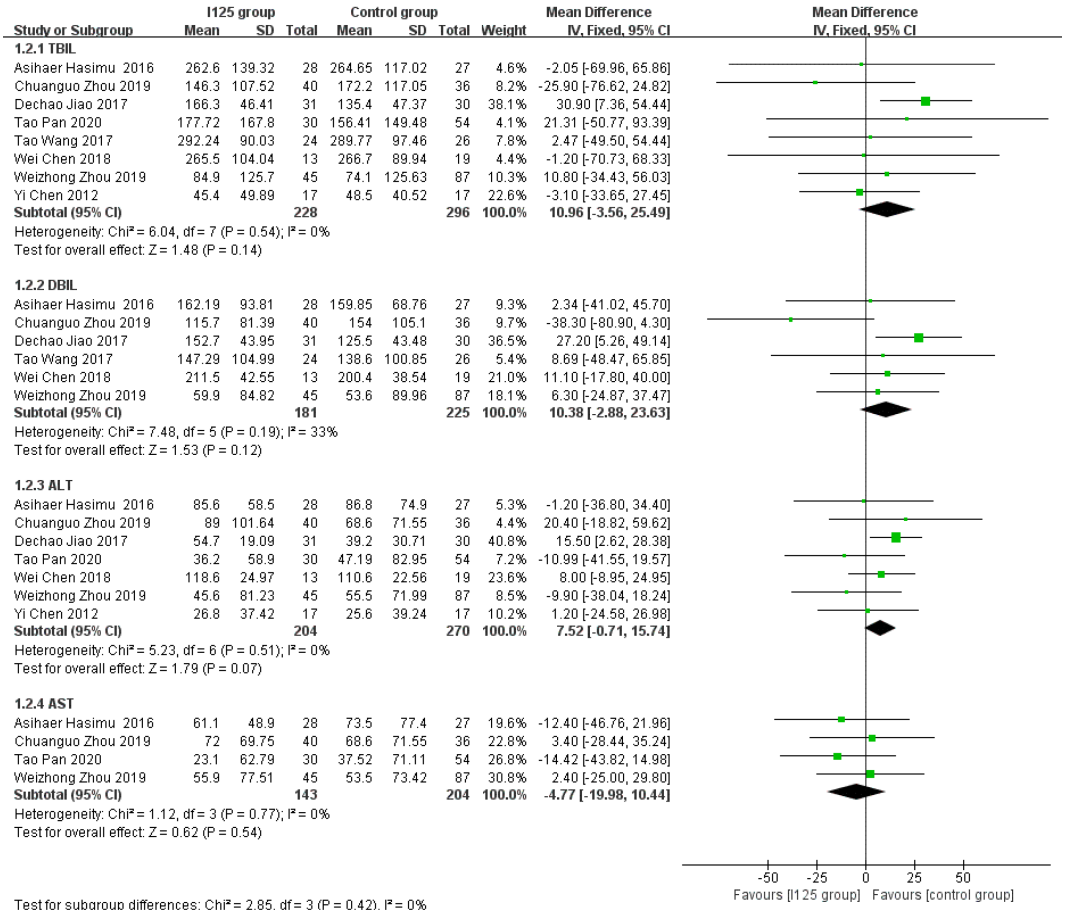

Figure 6 Forest plot comparing mean difference in posttreatment reductions in serum indices.

particles[29,30], the results of two included studies showed no significant differences between the pre- and post-procedure irradiated stent groups[20,26]. This again proved the safety of the radiation dose and ^{125}I seed stents.

The curative effect of irradiated stents varies in patients with unresectable MOJ with different tumor etiologies and obstruction levels. However, due to the small sample size of enrolled patients, most studies did not explore the differences in the efficacy of irradiated stents for different pathological tumors, except for the study by Zhu *et al* [21]. In Zhu's multicenter study, subgroup analysis of tumor etiology was performed, and the researchers first proposed that patients with biliary tract cancer could benefit more from irradiated stents using ^{125}I seeds than those with pancreatic carcinoma and lymph node metastases. These results suggest that ^{125}I seed stents provide better tumor control for localized malignant obstruction from the biliary tract. Nevertheless, obstruction can occur at any level within the biliary tract, most often in hilar and distal bile ducts. Zhou *et al*[23] and Chen *et al*[26] focused on the role of ^{125}I seed stents in malignant hilar and lower biliary tract obstruction, respectively. The conclusions of these two studies are consistent with those of other studies, suggesting that ^{125}I seed stents can serve as a safe, feasible, and effective method with minimal invasiveness for the treatment of obstruction at different levels within the biliary tract.

As mentioned in this analysis, there are three main types of ^{125}I seed stents currently applied in the bile duct. Subgroup analysis based on the type of stent demonstrated that all three types of ^{125}I seed stents were equally effective in prolonging stent patency. ^{125}I seed strands have the advantages of replaceability and sustained radiation[31]. However, the use of a bile duct drainage tube as a carrier has certain limitations for invasive tumor growth along the bile duct wall. The radiation dose can be evenly distributed by using seed-loaded stents, but this type of stent is composed of two-layer stents and a large diameter sheath, which is not suitable for patients with hilar strictures. A self-expanded stent with ^{125}I seed strand fixation between the stent and the bile duct wall is widely adopted in current studies due to its simple process and broader applicability. However, nonintegrated radiation stents still have many internal radiation stent-related issues that need to be solved.

This meta-analysis included RCTs and retrospective studies. In the subgroup analysis, a disparity between the results of RCTs and retrospective studies was not observed in stent patency and overall survival. Although RCTs provide a higher level of clinical evidence, retrospective studies have their own strengths as well, such as a potentially wider range of patients and therefore probably more real-world data. There was no significant heterogeneity in the test for subgroup differences, which indicated that the potential bias caused by the type of study design was small.

This meta-analysis still has several limitations: (1) There was a lack of stratified randomization and strict control of blinding in some research centers, which could influence the quality of this study to some extent; (2) the analysis had publication bias, which could be the result of the inclusion of studies concerning small sample sizes and only those that were written in English; (3) no studies involved in-depth comparative investigations of the applicable conditions and cost-effectiveness of three types of irradiated stents, which could limit the application of the results to some extent; and (4) all the studies were conducted in China, which could have had a potential impact on the generalizability of the results.

CONCLUSION

In conclusion, percutaneous biliary stents combined with brachytherapy using ^{125}I seeds offers a longer stent patency and higher overall survival than conventional stents for patients with unresectable MOJ, resulting in equivalent complication and serum index outcomes. High-quality multicenter prospective randomized studies are needed to further assess the long-term therapeutic outcomes and safety of irradiated stents using ^{125}I seeds and to define the selection criteria for stent type.

ARTICLE HIGHLIGHTS

Research background

Malignant obstructive jaundice (MOJ) is a common condition caused by various adenocarcinomas. Less than 20% of patients are suitable for radical surgery, leading to a poor overall prognosis. Recently, several clinical studies have raised concern regarding the clinical effectiveness of intraluminal ^{125}I seed-based brachytherapy for patients with unresectable MOJ; hence, we analyzed evidence from randomized controlled trials (RCTs) and cohort studies comparing ^{25}I seed stents and conventional stents.

Research motivation

Recently, there has been growing concern regarding the efficacy and safety of intraluminal ^{125}I seed-based brachytherapy in the treatment of unresectable MOJ. However, most studies are single-center or retrospective with relatively small sample sizes and thus provide less convincing clinical evidence. The purpose of our study was to conduct a rigorous meta-analysis of RCTs and cohort studies on irradiated stents.

Research objectives

To investigate the clinical efficacy and safety of percutaneous biliary stents with ^{125}I seeds compared with conventional metal stents in patients with unresectable MOJ.

Research methods

We performed a meta-analysis of RCTs and cohort studies. Four English-language databases (PubMed, Embase, Cochrane Library, and Web of Science) were searched up to June 2020 for studies comparing stents with and without ^{125}I seeds in the treatment of unresectable MOJ.

Research results

A total of ten studies were included (6 RCTs and 4 cohort studies), involving a total of 875 patients. Our study revealed that compared with conventional stents, ^{125}I seed stents extended the stent patency time and overall survival period. No extra complications or severe liver damage was caused by ^{125}I seed stents. This topic remains to be studied, and more research is needed to further assess the long-term therapeutic outcomes and safety of stents irradiated using ^{125}I seeds.

Research conclusions

Percutaneous biliary stents combined with brachytherapy using ^{125}I seeds offers a longer stent patency and higher overall survival than conventional stents for patients with unresectable MOJ, resulting in equivalent complications and serum index outcomes.

Research perspectives

To promote the clinical application of ^{125}I seed stents for the treatment of MOJ, future studies are needed to conduct in-depth comparative studies on the applicable conditions and cost-effectiveness of the three types of irradiated stents. In addition, it is necessary to compare the efficacy of irradiation stents using ^{125}I seeds for MOJ caused by different adenocarcinomas.

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