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Original Article

Biliary stent with or without ^{125}I seeds for malignant obstructive jaundice: a systematic review and meta-analysis

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Abstract: Aim: The aim of this study was to assess the safety, feasibility, and efficacy of ^{125}I seeds irradiation stents compared with conventional self-expandable metal stents (SEMS) to treat malignant obstructive jaundice (MOJ). Methods: A systematic search of English and Chinese databases, from January 1980 to June 2018, was conducted. All prospective random trials comparing SEMS and the various forms of irradiation stent with ^{125}I seeds to treat MOJ were included. Results: Overall, Nine studies with 697 patients were eligible in the current analysis. Of reported 697 patients, 346 were subjected to irradiation stents and 353 to SEMS. The irradiation stents were associated with a longer survival (hazard ratio (HR) 0.50, IV, random, 95% confidence interval (CI) 0.37-0.67; P<0.001, I^2=0%) and stent patency (HR 0.44, IV, random, 95% CI 0.33-0.60; P=0.27, I^2=20%) than conventional SEMS. There were no differences in total complications rate (relative risk (RR) 0.95, M-H, random, 95% CI 0.65-1.37; P=0.77, I^2=0%), hemobilia (RR 0.94, M-H, random, 95% CI 0.37-2.40; P=0.57, I^2=0%), pain (RR 0.86, M-H, random, 95% CI 0.34-2.18; P=0.89, I^2=0%), and cholangitis (RR 1.08, M-H, random, 95% CI 0.51-2.29; P=0.94, I^2=0%). Also, no differences were observed in all indexes, which included total bilirubin (TBIL) (weighted mean difference (WMD) -7.18, IV, random, 95% CI -18.09-3.73; P=0.94, I^2=23%), direct bilirubin (DBIL) (WMD -0.17, IV, random, 95% CI -10.81-10.46; P=0.49, I^2=0%), alanine aminotransferase (ALT) (WMD -1.50, IV, random, 95% CI -12.52-9.52; P=0.01, I^2=68%), aspartate aminotransferase (AST) (WMD 9.49, IV, random, 95% CI -9.31-28.29; P=0.21, I^2=36%). Conclusions: The current meta-analysis suggest that the irradiation stent is a feasible, safe treatment of MOJ, with longer survival and stent patency. Application of an irradiation stent with anti-tumor effect do not add extra adverse events compared to SEMS stent.

Keywords: ^{125}I, obstructive jaundice, malignancy, meta-analysis

Introduction

Malignant obstructive jaundice (MOJ) is a common clinical disease entity primarily caused by pancreato-biliary malignancies including cholangiocarcinoma, pancreatic cancer, and ampullary cancer [1, 2]. At the time of diagnosis, the majority of patients can not benefit from radical resection due to extensive tumor growth [3, 4]. The median survival of patients with MOJ has been reported as 4.8 months [5]. Alleviation of patients' clinical symptoms and correction of complications are a priority due to the unimproved and limited survival and quality of life [2, 5]. During recent three decades, surgeons and interventional therapists endeavored to perform palliative drainage by means of choledochojejunostomy with conventional or minimal invasive approaches [6]. Biliary stents showed better clinical efficacy and quality of life compared to surgical bypass [7]. Various types of biliary stents with special structure and materials were designed for endoscopy or percutaneous drainage. Previous studies compared different types of stents and claimed that self-expandable metallic stents (SEMS) are superior to plastic stents in terms of patency, morbidity, and re-interventions [8]. In addition, no obvious

advantages were identified in covered self-expandable metal stent (CSEMS) or uncovered self-expandable metal stents (UCSEMS) [9]. However, tumor growth is not controlled and results in a high risk of occlusion, epithelial hyperplasia, sludge formation, and clot accumulation [10, 11]. Efforts have been made to introduce a novel biliary stent with anti-tumor effect. Currently, paclitaxel-eluting stents [12] and irradiation stent loaded with ^{125}I seeds [13-18] are among the mostly used stents in South Korea and China respectively. Permanent radioactive seed implantation in malignancy was firstly suggested by several authors in the early 1900s [19]. Thereafter, this technique has been practiced in different types of cancers. In recent years, a large number of animal experiments, and single arm, and control studies regarding application of ^{125}I stent in patients with MOJ have been published one after the other [20, 21]. However, a systematic review and meta-analysis comparing ^{125}I stents with conventional stents has been lacking. Therefore, we performed a systematic review and meta-analysis by synthesizing present evidence to assess efficacy and safety of the irradiation stents compared with conventional stents.

Methods

Eligibility criteria

We include all human randomized controlled trials (RCTs) and control clinical trials (CCTs). There were no language restrictions. Conference abstracts and theses were ruled out. We included single and multi-center studies, which compared the ^{125}I irradiation stent (various form of combined implantation of ^{125}I seeds and CSEMS or UCSEMS) with CSEMS or UCSEMS. Both endoscopic and percutaneous approaches for stent implantation were included. The study population was without age and gender restrictions. MOJ was caused by any unresectable tumor (distal or proximal).

Search strategy

English databases (MEDLINE, EMBASE, Cochrane library), Chinese databases (CBM, CNKI, VIP), and Clinicaltrials.gov (from January 1980 to June 2018) were searched. References of systematic review and included studies were also searched. The search strategy was based on MeSH terms combined with text words. The details can be viewed in Table S1.

Choice of outcome

The primary outcomes included patient survival and cumulative stent patency. Cumulative stent patency was the time from stent placement to recurrent biliary obstruction or death of the patient.

Secondary outcomes included (i) complications: total complications, pancreatitis, cholecystitis, cholangitis, hemobila, stent and seed migration, tumor ingrowth, and outgrowth; (ii) postoperative laboratory values: alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), direct bilirubin (DBIL).

Data collection

Two independent reviewers (K.T and L.Y.P) selected the studies by reviewed the title and abstract of every single study. Disagreements were resolved by a third reviewer (A.S). For selected studies, data of trial information (author, year, intervention, center and type of stent), population characteristics (sex, age, classification of the tumor and location of obstruction), and reported outcomes were extracted independently by two investigators (H.Z and K.T). Quality of studies were assessed by the Cochrane Collaboration tool for assessing risk of bias. The assessment was carried out by three independent investigators (H.Z, A.S and K.T).

Statistical analysis

Hazard ratios (HRs) with 95% confidence intervals (CIs) were chosen to measure the effects of stent patency and patient survival, relative ratios (RRs) with 95% CIs to measure the complications, and weighted mean differences (WMDs) to measure laboratory values. HRs can be extracted from the paper directly or obtained by method of Tierney et al. [22] from Kaplan-Meier curves or other data. All comparisons were performed by random-effects models in RevMan software version 5.3. Inconsistency index (I^2) statistics were calculated to measure the heterogeneity. Although size of heterogeneity have no uniform definition, I^2 values more

Table 1. Characteristics of the studies included in meta-analysis

Study	Stent	NO. of patients	Male/female	Age (y)	Patient survival (days)	Stent patency (days)	No. of complications
Hasimu 2017	Irradiation stents	28	11/17	Mean ± sd 70.93±8.58	Mean ± sd 222.6±21.0	Mean ± sd 191±19.8	4
	UCSEMSs	27	14/13	Mean ± sd 70.26±9.71	Mean ± sd 139.1±14.5	Mean ± sd 88.3±16.3	5
Zhu 2012	Irradiation stent	12	7/5	Median 62.50 (21.00)	Median 222	Median 222	1
	UCSEMSs	11	9/2	Median 71.00 (22.00)	Median 75	Median 75	5
Chen 2012	Irradiation stents	17	12/5	Mean ± sd 61.2±14.5	-	Median 300	4
	UCSEMSs	17	10/7	Mean ± sd 63.9±9.3		Median 240	4
Wang 2016	Irradiation stents	24	29/21	Median (range) 57.3 (41-80)	Median 306	Median 295	-
	UCSEMSs	26			Median 162	Median 167	
Fei 2015	Irradiation stents	26	10/16	Mean ± sd 70±12	Mean ± sd 386±47	-	6
	UCSEMSs	26	11/15	Mean ± sd 73±11	Mean ± sd 267±32.4		7
Zhao 2015	Irradiation stents	31	28/34	Mean ± sd (range) 68±3.5 (56-85)	Median 330	-	0
	UCSEMSs	31			Median 300		0
Chen 2018	Irradiation stents	13	8/5	Mean 66	Median 298	Median 243	3
	UCSEMSs	19	12/7	Mean 68	Median 139	Median 117	5
Jiao 2017	Irradiation stents	31	12/17	Mean ± sd 60.4±8.8	Median 355	Median 368	11
	SEMSs	30	16/14	Mean ± sd 60.2±8.1	Median 209	Median 220	9
Zhu 2018	Irradiation stents	164	103/61	Median (IQR) 65 (56-75)	IQR 212-	Median 202	14
	UCSEMSs	164	109/55	Median (IQR) 64 (57-75)	Median 294	Median 104	13

UCSEMSs: Uncovered self-expandable metal stents; Irradiation stents: Conbination of 125I seeds and uncovered self-expandable metal stents.

Table 2. Tumor type of studies included in meta-analysis

Study	Stent	Diagnosis of obstructive jaundice					
		Cholangiocarcinoma	Hepatocellular carcinoma	Pancreatic cancer	Metastases	Gallbladder cancer	Ampullary carcinoma
Hasimu 2017	Irradiation stents	24	-	-	-	4	-
	UCSEMSs	24				3	
Zhu 2012	Irradiation stent	-	-	-	4	-	-
	UCSEMSs				6		
Chen 2012	Irradiation stents	7	2	3	5	-	-
	UCSEMSs	7	4	3	4		
Wang 2016	Irradiation stents	18	-	14	12	-	6
	UCSEMSs						
Fei 2015	Irradiation stents	26	-	-	-	-	-
	UCSEMSs	26					
Zhao 2015	Irradiation stents	39	-	17		3	3
	UCSEMSs						
Chen 2018	Irradiation stents	2	-	7	-	4	0
	UCSEMSs	5		11		2	1
Zhu 2018	Irradiation stents	80	-	46	38	-	-
	SEMSs	74		53	37		
Jiao 2017	Irradiation stents	Primary adenocarcinoma 19, Metastatic adenocarcinoma 13					
	SEMSs	Primary adenocarcinoma 21, Metastatic adenocarcinoma 9					

UCSEMSs: Uncovered self-expandable metal stents; Irradiation stents: Combination of ^{125}I seeds and uncovered self-expandable metal stents.

than 50% indicated significant heterogeneity in current article. Sensitivity analyses were performed, if high heterogeneity was found or the significance of effect size was affect by a single study. For primary outcome, publication bias was assessed using Funnel plot.

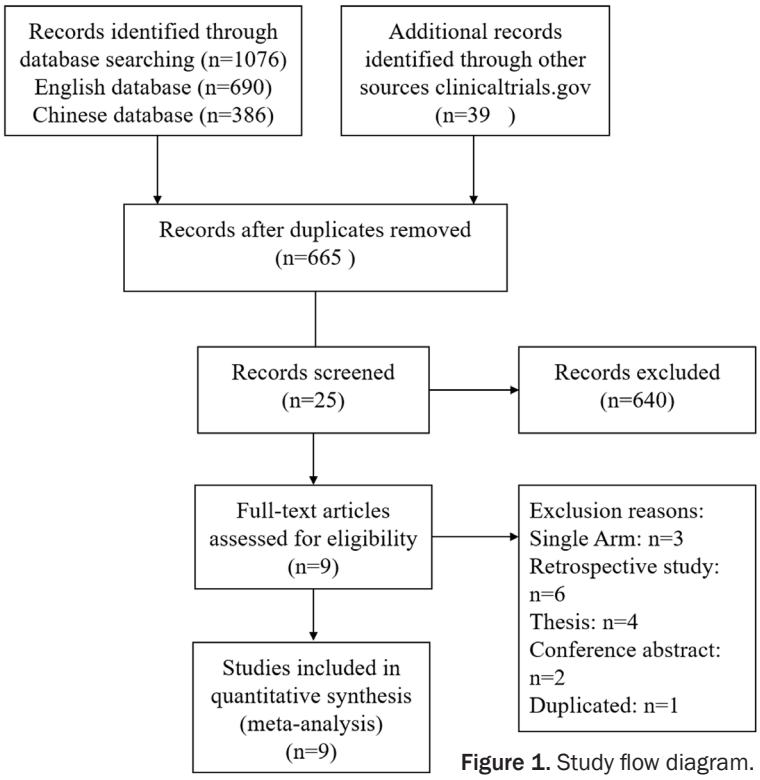

Figure 1. Study flow diagram.

Results

Search results

A total number of 1072 publications were examined in initial systematic search. 1047 duplicates and irrelevant comparisons publications were excluded. Of the remaining 25 trials, seven were single arm studies, six were retrospective studies, two were theses and conference abstracts, one was duplicate publications. Finally, nine studies (**Tables 1**, **2**) were included in the meta-analysis with six English articles [13, 15, 18, 23-25] and three Chinese articles [14, 16, 17]. English abstracts of Chinese articles were searched in PubMed or EMBASE, and one was registered in clinicaltrial.com. The prisma flow data is shown in **Figure 1**.

A total of 697 patients were enrolled, 346 to irradiation stents and 353 to UCSEMS. Cholangiocarcinoma and pancreatic cancer were the main reasons for MOJ. In all studies, stent and ^{125}I seeds implantations was performed by percutaneous insertion and UCSEMS was identified as control group. All studies were carried out by single center in China.

Risk of bias

Six trials included three RCTs and three CCTs. Every study had a qualitative risk assessment conducted by Cochrane Collaboration tool for assessing risk of bias (Figures S1, S2). PRISMA Checklist was shown in Table S2. Performance bias was severe, due to it is difficult to mask radiologists on whether to implant radiation sources. High heterogeneity was observed in comparisons of stent patency and ALT. Sensitivity analyses were carried out, no differences were observed in any comparisons. Heterogeneity of stent patency originates from a CCTs. After excluding the trial, heterogeneity decreased distinctly, but the outcome was the same indicated that irradiation stents exhibited a better stent patency. The Egger and Begg tests were carried out to assess potential publication bias for primary outcomes. No potential publication biases were observed (Figure S3).

Primary outcome

Patient survival: Patient survival data were not provided in one study. The statistical data of five studies revealed significantly favorable to irradiation stents at patient survival (HR 0.50, IV, random, 95% CI 0.33-0.60; P<0.001, I^2=20%) (**Figure 2**).

Stent patency: The meta-analysis from the 4 studies revealed significantly favorable to irradiation stents at stent patency (HR 0.44, IV, random, 95% CI 0.33-0.60; P=0.27, I^2=20%) (**Figure 3**).

Secondary outcomes

Complication rate: There were no differences in total complications rate (RR 0.95, M-H, random, 95% CI 0.37-2.40; P=0.57, I^2=0%), hemobilia (RR 0.94, M-H, random, 95% CI 0.37-2.40; P=0.57, I^2=0%), pain (RR 0.86, M-H, random, 95% CI 0.34-2.18; P=0.89, I^2=0%), and cholan-

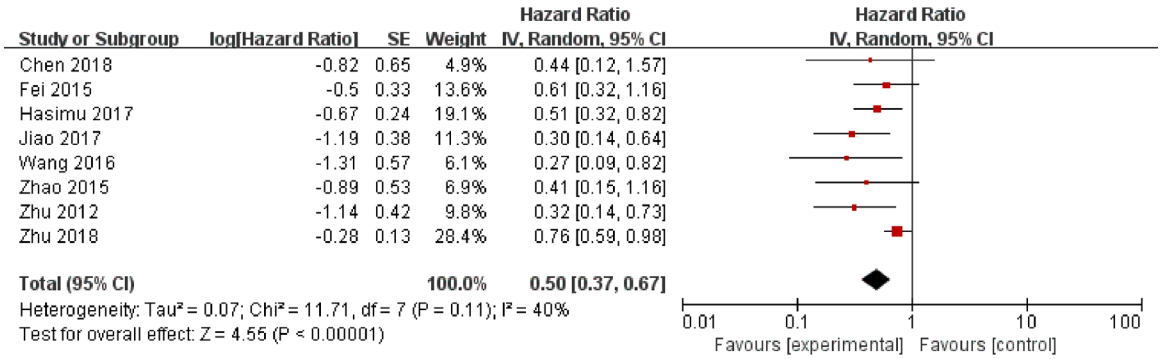

Figure 2. Forest plot of patient survival.

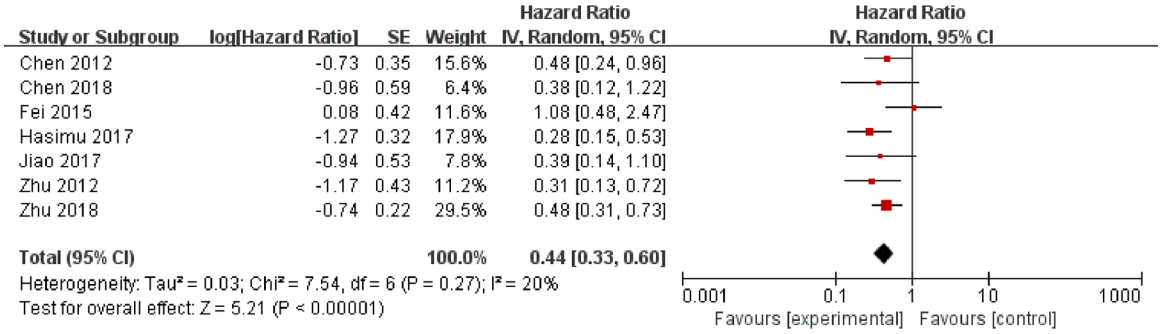

Figure 3. Forest plot of stent patency.

gitis (RR 1.08, M-H, random, 95% CI 0.51-2.29; P=0.94, I^2=0%) (**Figure 4**).

Postoperative laboratory index: No differences were observed in all indexes, which included to TBIL (WMD -7.18, IV, random, 95% CI -18.09-3.73; P=0.25, I^2=23%), DBIL (MMD 0.17, IV, random, 95% CI -10.81-10.46; P=0.49, I^2=0%), ALT (WMD -1.5, IV, random, 95% CI -12.52-9.52; P=0.01, I^2=68%), AST (WMD 9.49, IV, random, 95% CI -9.31-28.29; P=0.21, I^2=36%) (**Figure 5**).

Discussion

Biliary stents have been applied in treatment of patients with MOJ more than 30 years due to its effectiveness and minimal invasiveness. Currently, local chemoradiotherapy in combination with stent drainage is regarded as a classic therapeutic strategy to prolong patient survival and stent patency [6]. Averagely, pancreatic cancer and cholangiocarcinoma presented hypo-vascular feature with limited chemo response rate [26, 27]. Additionally, the existence of radiosensitive organs around the site of obstruction and poor general conditions of patients may lead to adverse events in application of external beam radiation therapy. Intraluminal brachytherapy (ILBT) avoid these problem. Before Iodine-125, Iridium-192 wire as a high dose of irradiation showed promising effects in MOJ treatment [27, 28]. With the development of radioisotope seeds, Iodine-125 seed as a low dose seed has been replacing Iridium-192 in many indications [29], due to the advantage of safety and prolonged exposure which avoid the second operation to take out the seeds and/or repeated interventions in some conditions.

Current study is aiming to assess the safety and efficacy of ^{125}I irradiation stent compared with conventional metal stents. Our results showed that irradiation stent provided significantly longer patient survival and stent patency. Similar results were observed from median or mean of patient survival and stent patency which were not involved the meta-analysis, due to the limited expression of overall survival status.

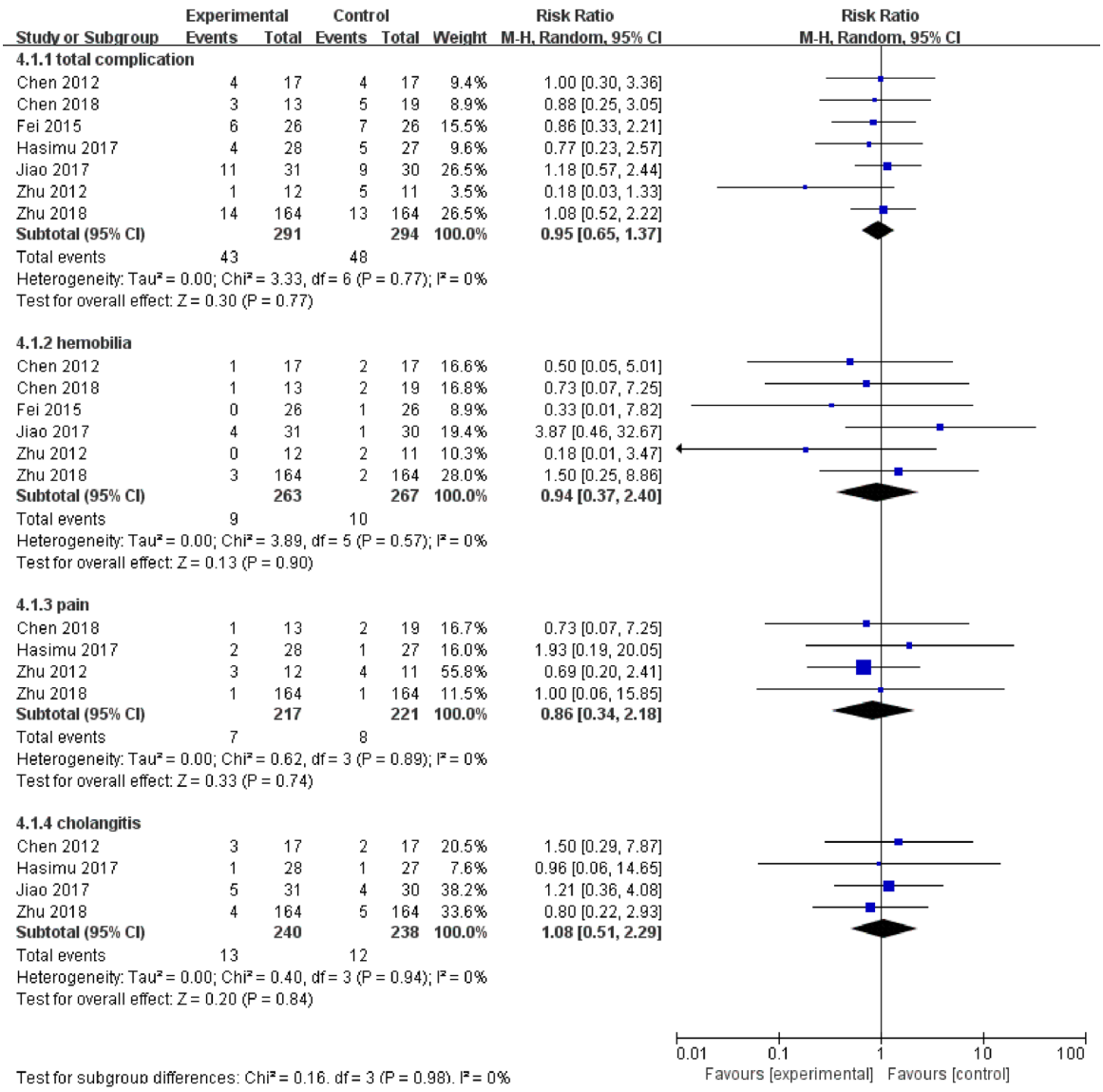

Figure 4. Forest plot of total complication, hemobilia, pain, and cholangitis.

Although there were various inserting ways and type of irradiation stents in different studies, all implanting seeds increased complexity of the operation and narrowed caliber of stent indirectly. However, our analyses showed no significant difference between two groups in complication rates and laboratory values after operation which were analyzed to measure the short-term drainage efficiency and recovery of liver function. Three studies reported Hemobilia, which occurred mainly during hospital stay and were healed before discharge, due to injury of the biliary intima resulted from the interventional operation rather than effect of irradiation. Fecal occult blood test in Chen et al. [13] indicated negative results in both groups during the first month of follow-up. The quantitative records of pain were defined as short-term and severe conditions, which were mainly caused by biliary irritation, operative injury, and infection. Two investigators have reported the incidence of cholangitis, although a pervious study [30] suggested that ILBT correlates with increased risk for cholangitis, especially after percutaneous transhepatic biliary drainage (PTBD) or stent insertion, our analyses showed no significant difference between two group, even carrying drainage catheter with the seeds strand for two months in the experimental group of Chen et al.

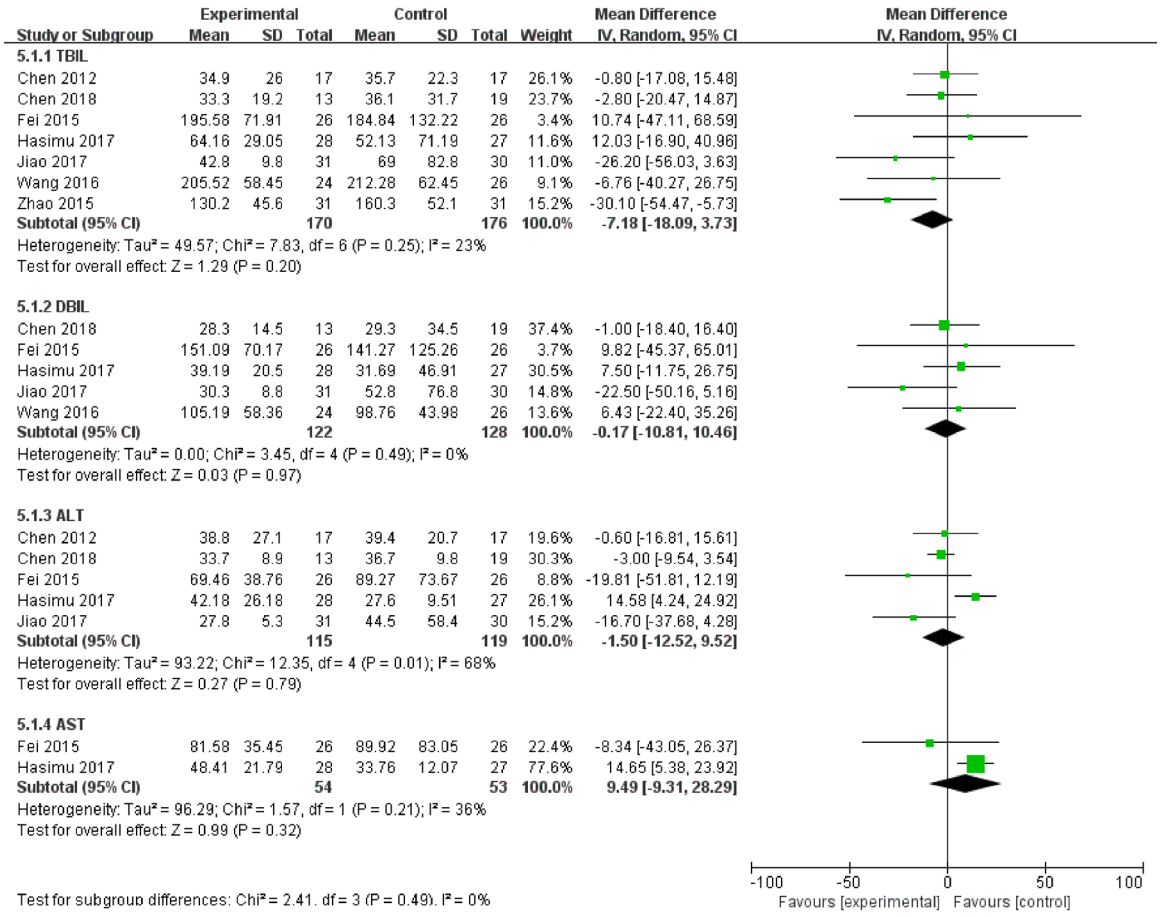

Figure 5. Forest plot of laboratory values.

Three studies reported antitumor effect of irradiation stents. CA19-9 were followed up by two investigators [16, 17] at different time point, the results showed after procedure the marker declined and remained at a lower level in experimental group, while the marker in control group was gradually increased. Fei et al. [14] showed the changed in maximum and minimum tumor size before and six months after operation by CT scan. The results indicated that the seed strand shrank the tumor obviously.

In terms of radiological safety, a minimal average does (0.018±0.009 mSV) were detected in Liu et al. [21] by a personal dosimeter, which was worn on the waist of operator during all procedures. Additionally, the effective radiation radius of ^{125}I seeds was less than 20 mm that results in easy radioprotection for peri-tumor tissue and medical workers [31]. The number and distribution of implanted seeds were determined by the length of the obstructive segment. In seeds strand, Fei et al. [14] identified a 6-10 mm source-to-source distance to adjust radiation dose. However, other studies arranged no spacing in their seed strand. Tight arrangement provided higher dose (80-90 Gy), which has been proven to be safe in the previous experiment [32]. And all studied mentioned no migration or dislodging of ^{125}I seed was observed during the follow-up period, also no radiation-induced enteritis or liver injury were reported.

The irradiation stent displayed better efficiency and has equal safety and stability compared with conventional stent in current study. Although various forms of the irradiation stent with ^{125}I seeds have been used in treatment of MOJ and a number of clinic retrospective studies can be indexed, there are no guidelines for specific applications, uniformly designed stents, and experience of using radioactive source for the most of clinical department.

Considering radioactivity, operators might prefer to other non-radioactive methods. Clearly, the wide application of irradiation stent in MOJ still has a long way to go, and need further promotion and more special stent and auxiliary equipment. Moreover, a recent high quality RCT(12) demonstrated another anti-tumor paclitaxel-eluting stent had no obvious advantage over the conventional covered stent. Nevertheless, maybe we can compose the two stent together to obtain better effectiveness, based on the radiosensitization of paclitaxel in many malignant tumors [33].

Limitations

The most important limitation of the current meta-analysis is only six studies were included into the analyses according to our inclusion criteria, and all studies are from Chinese single center. Owing to the limited number of studies, the power of publication bias tests were also reduced significantly. All studies were performed by percutaneous insertion and only used UCSEMS both in two groups. Sources of heterogeneity include patient populations (different department, other treatments during follow-up or not, proximal or distal), use of antibiotics, definitions of complications, choice of reporting secondary outcomes, and measures of data spread. The Cochrane bias risk scare showed incomplete blind method, which caused by the nature of invasive procedures. Moreover, since most of the patients died during the follow-up period, there was not an appropriate index to measure the stent patency only, which also caused the differently reported form making it difficult to integrate. Finally, no studies involved cost-effective analysis or mentioned the cost of seed strand and seeds-loaded-stent, which may limit the application of the results and choice of finished products or self-made seed strand.

Conclusion

Our meta-analysis suggested that various kinds of ^{125}I seeds irradiation stent are a potent tool for MOJ. The patients treated with the irradiation stent do not experience extra adverse events (pain, hemobilia, and cholangitis) and have a longer survival, stent patency, compared with UCSEMS. Furthermore, the unique anti-tumor effect of irradiation stent was noted by CA19-9 and CT scan during the follow up period.

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Disclosure of conflict of interest

None.

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Table S1. From January 1980 to April 2017

PUBMED
#1 jaundice[mesh]
#2 cholestasis[mesh]
#3 ((bile) OR biliary)
#4 ((obstruct*) OR stricture*) OR stenosis
#5 #3 AND #4
#6 #1 OR #2 OR #5
#7 Stents[Mesh]
#8 (stent*) OR endoprosthesis
#9 #7 OR #8
#10 Radiotherapy[Mesh]
#11 ((((Brachytherapy*) OR Radiotherapy*) OR seed*) OR irradiati*)
#12 #10 OR #11
#13 #6 AND #9 AND #12
result: 195 items

Cochrane library
#1 MeSH descriptor: [Jaundice] explode all trees
#2 MeSH descriptor: [Cholestasis] explode all trees
#3 ((bile) or biliary) and (((obstruct*) or stricture*) or stenosis)
#4 #1 or #2 or #3
#5 MeSH descriptor: [Stents] explode all trees
#6 (stent*) OR endoprosthesis
#7 #5OR #6
#8 MeSH descriptor: [Radiotherapy] explode all trees
#9 ((((Brachytherapy*) OR Radiotherapy*) OR seed*) OR irradiati*)
#10 #8 OR #9
#11 #4 AND #7 AND #10
result: 41 items

embase
#1 'jaundice'/exp
#2 'cholestasis'/exp
#3 bile OR biliary
#4 obstruct* OR stricture* OR stenosis
#5 #3 AND #4
#6 #1 OR #2 OR #5
#7 'stent'/exp
#8 stent* OR endoprosthesis
#9 #7 OR #8
#10 'radiotherapy'/exp
#11 brachytherapy* OR radiotherapy* OR seed* OR irradiati*
#12 #10 OR #11
#13 [humans]/lim
#14 [clinical study]/lim
#15 #6 AND #9 AND #12 AND #13 AND #14
result: 460 items

CNKI
(SU = iodine OR SU =I OR SU =seed) AND (SU = jaundice)
limit: Journal articles
result: 96 items

VIP
(abstract= jaundice AND range= all the journals) AND (abstract =iodine OR abstract =I seed AND range= all the journals)
result: 104 items

CBM
(((“iodine “[Full field: intelligent]) OR “Iseed”[Full field: intelligent])) AND “ jaundice “[Full field: intelligent]
result: 186 items

clinicaltrials.gov
Conditions: malignant or cancer or carcinoma or neoplasm or adenocarcinoma
Intervention: Brachytherapy OR Radiotherapy OR seed OR irradiation
result: 39 items

Table S2. PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Introduction
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Introduction
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Eligibility criteria
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Search strategy
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Table S1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Eligibility criteria
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Data collection
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Choice of outcome
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Figure S2
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Figure S1
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Statistical analysis
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Statistical analysis
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Statistical analysis
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	**Figure 1**
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	**Table 1**
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Figure S2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	**Figures 2-5**
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	**Figures 2-5**
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Figure S3

DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Discuss
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Limitations
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Conclusion
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Professional consultation

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097.

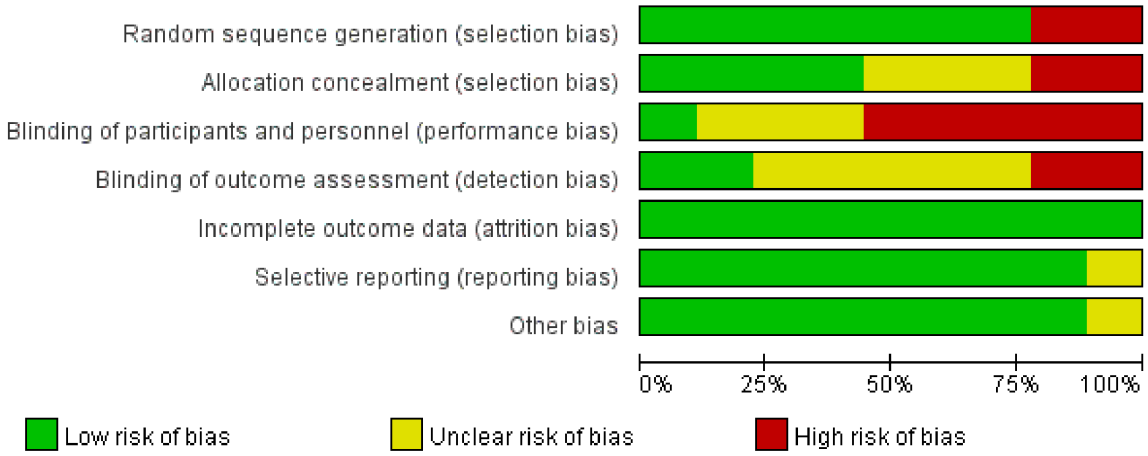

Figure S1. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

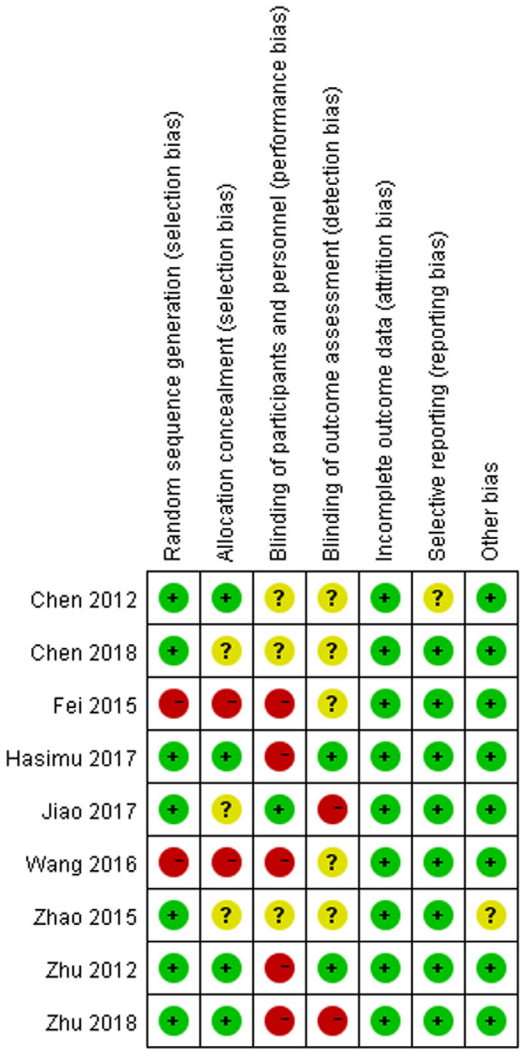

Figure S2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

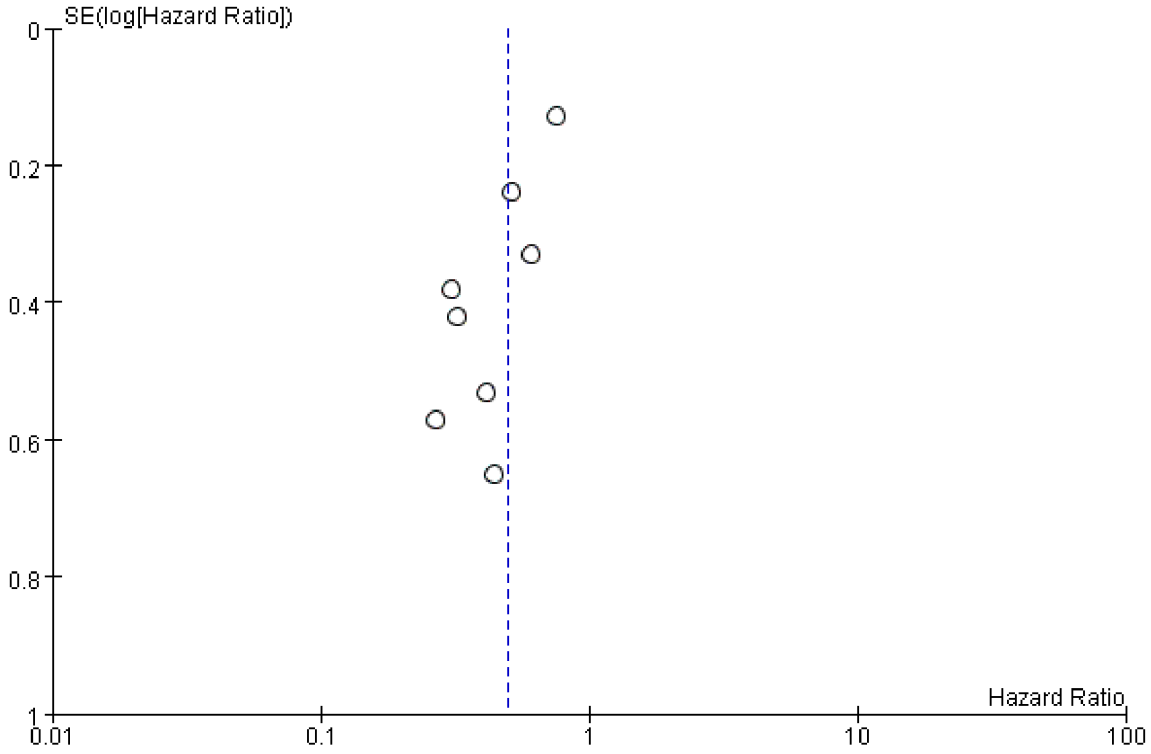

Figure S3. Publication bias for primary outcomes.