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INTERVENTIONAL RADIOLOGY

ORIGINAL ARTICLE

Outcomes of two types of iodine-125 seed delivery with metal stents in treating malignant biliary obstruction: a systematic review and meta-analysis

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PURPOSE

To conduct a meta-analysis comparing the efficacy and safety of two types of iodine-125 (I-125) seed delivery with metal stents (the study group) versus conventional metal stents (the control group) in patients with malignant biliary obstruction (MBO).

METHODS

Our team systematically searched the PubMed, Embase, and Cochrane Library databases for relevant studies published from January 2012 up to July 2021. Survival time and stent dysfunction were the primary measured outcomes. Subgroup analyses were conducted according to the type of I-125 seed delivery.

RESULTS

Eleven studies, including 1057 patients in total, were pooled for stent dysfunction. The study group showed a lower risk of stent dysfunction than the control group [odds ratio (OR): 0.61, 95% confidence interval (CI) 0.46–0.81, $P = 0.001$]. The pooled results of six studies reporting overall survival (OS) showed that the study group had a better survival outcome than the control group [hazard ratio (HR): 0.34, 95% CI: 0.28–0.42, $P < 0.001$]. In the subgroup analyses, the I-125 seed stent group had significantly less stent dysfunction than the control group (OR: 0.49, 95% CI: 0.31–0.76, $P = 0.002$). Meanwhile, the metal stents + I-125 radioactive seed strand group showed significantly more improvement in OS than the control group (HR: 0.33, 95% CI: 0.26–0.42, $P < 0.001$). Moreover, our analysis suggests that using I-125 seeds did not result in increasing related adverse events compared with using metal stents alone (all $P > 0.05$). The study group was significantly superior to the control group, with better survival and decreased stent dysfunction. Meanwhile, the delivery of I-125 seeds did not increase adverse events.

CONCLUSION

The delivery of I-125 with metal stents may be considered a preferable technique for MBO.

KEYWORDS

Malignant biliary obstruction, iodine-125 seed, biliary stent, meta-analysis

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Malignant biliary obstruction (MBO) is the stenosis or obstruction of the hepatic duct and bile duct system.[1] Frequently, clinicians need to treat this condition when managing malignant tumors,[2-7] such as cholangiocarcinoma, gallbladder cancer, pancreatic carcinoma, and metastatic lymph nodes.[8]

Because there are no early clinical indications of these malignant tumors, symptoms only gradually appear until invasion occurs in the hepatic–biliary system. Consequently, MBO is detected at an advanced stage, which leads to obstructive jaundice and low quality of life.[2,4,5,7,9] As 80% of patients diagnosed are no longer surgical candidates,[1,2] MBO can become a com-

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mon refractory complication of these malignant cancers. Only approximately 10%–20% of patients are medically ready for surgical resection of the obstructive lump.[9-11] Sadly, the three- and five-year survival rates after surgical excision remain unsatisfactory at 18%–52% and 5%–31%, respectively.[12]

Metal stent insertion is widely accepted as the preferred palliative treatment to relieve symptoms caused by MBO for inoperable patients.[3-7,9,13-17] Metal stents have no therapeutic action on tumors, and post-stent procedures have high rates of stent dysfunction, which limits the long-term efficacy of palliative treatment.[3] Conventional metal stent insertions are not sufficient for MBO patients, and the current methods of delivering iodine-125 (I-125) seeds have shown a promising future, including radioactive I-125 seed-loaded stent [consisting of a self-expandable metal stent (SEMS) and several I-125 seeds] and metal stents insertion + I-125 radioactive seed strand (IRSS) (IRSS is a thin catheter containing several I-125 seeds). Previously, two meta-analyses compared I-125 seed delivery + stents with stents alone.[18,19] However, the trials did not distinguish between the two different delivery types, namely radioactive stent and IRSS, making their results insufficient. Recently, several randomized controlled trials (RCTs) and retrospective studies on the use of metal stents + IRSS or I-125 seed stents were conducted. As such, we conducted a meta-analysis to compare the efficacy and safety of these two methods of I-125 seed delivery, namely metal stents + IRSS and radioactive I-125 seed stents. We then compared this with conventional metal stents in patients with MBO and reported the outcomes in terms of stent dysfunction, survival, clinical success, and complications.

Methods

Our meta-analysis was guided by the publication "Preferred Reporting Items for Systematic reviews and Meta-Analysis" (PRISMA).[20]

Main points

- Iodine-125 (I-125) played a significant role in inhibiting tumor growth through its unique radioactive function.
- Metal stents + I-125 radioactive seed strand or I-125 seed-loaded stents demonstrated superior survival and decreased stent occlusion compared with conventional metal stents in the treatment of inoperable malignant biliary obstruction.
- The two types of I-125 delivery with metal stents did not increase the risk of procedure-related complications when compared with conventional metal stents.

Inclusion and exclusion criteria

A study had to satisfy particular conditions. The inclusion criteria were as follows: (a) patients who had a confirmed diagnosis of MBO; (b) patients who refused surgical resection or inoperable cases; (c) studies that compared metal stents + IRSS or I-125 seed stents (the study group) versus conventional metal stents alone (the control group) in patients with MBO; and (d) studies published in English.

Exclusion criteria were: (a) case reports; (b) narrative reviews; (c) non-English studies; (d) studies on plastic biliary stents; and (e) animal studies.

Literature search and study selection

The PubMed, Embase, and Cochrane Library databases were systemically searched to find correlating studies from January 2012 to July 2021 using the following search string: (SEMS OR stent) AND (I125 OR 125I OR I-125 OR irradiation OR radioactive OR seed) AND (jaundice OR biliary). We also reviewed the references of identified articles. All studies chosen were in the English language.

Types of studies

We initially included only RCTs, but this produced a small sample size. As this could have reduced the statistical significance of the meta-analysis and led to bias, we decided to include matched retrospective cohort studies also.

Data extraction and quality assessment

Data were extracted from 18 full-text-identified articles by two independent investigators. Discrepancy problems were solved by a third investigator. A data extraction sheet was produced that included baseline study data (authors, publication year, period of enrollment, region of the conducted studies, trial types, interventions); patient baseline data (mean age, sex, sample size, cancer types, type of MBO); and treatment-related data (clinical success, stent dysfunction, complications, survival). The potential bias of RCTs was gauged by applying the Cochrane risk-of-bias tool, where possible bias relating to selection, detection, performance, reporting, attribution, and other issues was assessed. Disagreements were resolved by consensus.

Retrospective studies were scored by the Newcastle–Ottawa scale (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp), and selection methods and comparability were assessed. Studies could be awarded a maximum score of 9 points, with lower scores assigned as follows: <4 = high bias risk; 4–6 = moderate bias risk; and ≥7 = low bias risk.

Publication biases were assessed by visual estimation of funnel plots, while quantitative assessment was carried out by performing Egger's test.[21] We considered a *P* value of less than 0.05 to represent the possibility of small-study effects.

Endpoints and definitions

The original primary study endpoints for the current analysis included stent dysfunction and overall survival (OS), while the secondary study endpoints included procedure-related complications and clinical success. The relief of jaundice was defined as a clinical success if bilirubin levels were a minimum of 30% lower in two weeks or 70% lower in four weeks. Stent dysfunction was defined as the relapsing of jaundice with elevated bilirubin levels or signs related to MBO with evidence of bile duct dilation through imaging techniques. The time between stent insertion and death was defined as the patient survival period. Procedure-related complications mainly included cholangitis, cholecystitis, pancreatitis, and hemobilia. Cholangitis and cholecystitis were defined as having symptoms of abdominal pain and fever (temperature above 38°C) that required antibiotic administration within 24 hours after the procedure, with no indications of any other system being infected. Pancreatitis was diagnosed when serum amylase levels rose to more than three times the normal limit (60–180 U/L), with persistent abdominal pain after the procedure. Hemobilia was defined as the requirement for a blood transfusion or hemostatic surgery.

Statistical analysis

Dichotomous variables and event frequencies were extracted from the identified studies. We calculated the odds ratios (ORs) with 95% confidence intervals (CIs). Hazard ratios (HRs) and 95% CIs were used to assess the OS. The heterogeneity was assessed via χ^2 and I^2 tests. The OR was pooled by using either a fixed-effect or random-effect model. If heterogeneity was not high (I^2 <50%), data were pooled using a fixed-effect model. In contrast, if heterogeneity was present (I^2 >50%), data were appropriately analyzed with a random-effect model. In addition, subgroup analysis was performed to assess the potential causes of heterogeneity, depending on the type of I-125 delivery via metal stents (I-125 seed stents or metal stents + IRSS). The results of this subgroup analysis were reported. Sensitivity analysis was performed by omitting each study from the analysis individually and measuring the impact this had on the results. The potential for publication bias was tested by applying funnel plots. Egger's test was also used to assess each publication's bias for pooled values with 95% CIs ($P < 0.05$ was considered significant bias). The statistical analysis was conducted using RevMan Cochrane Collaboration software, Review Manager (RevMan) version 5.4, and STATA v15.1 (Stata Corp, College Station, Texas, USA).

Results

Study selection and baseline characteristics

We initially gathered 301 potentially relevant articles based on the inclusion and exclusion criteria (Figure 1). Eighteen studies with full texts were selected to conduct the meta-analysis (Table 1). In these studies, seven were RCTs,[22-28] and the remaining 11 were retrospective studies.[29-39] Three RCTs (with 383 total participants) and two retrospective studies (with 114 total participants) compared I-125 seed-loaded stents with conventional metal stents.[23,26,27,31,39] Four RCTs (with 217 total participants) and nine retrospective studies (with 852 total participants) compared metal stents + IRSS with metal stents alone.[22,24,25,28-30,32-38] Details of the baseline features included in these studies are shown in Table 1. Most of the baseline characteristics were comparable, with all studies being conducted in China. The target population was patients with MBO for all studies. The causes of MBO included cholangiocarcinoma, gallbladder carcinoma, pancreatic carcinoma, hepatocellular carcinoma, and cancer metastases, among others. The interventional modality in the study group was the delivery of I-125 seeds via metal stents, while the control group was implanted with conventional metal stents.

In addition, all metal stents in the control groups were SEMS. Stent implantation occurred via endoscopic retrograde cholangiopancreatography or percutaneous transhepatic cholangiography. Five studies used I-125 seed stents, and the remaining 13 used metal stents + IRSS. Two types of I-125 seed delivery were analyzed as subgroups.

Stent dysfunction

In the analysis of stent dysfunction, 11 studies[22,23,25,26,29,30,33,34,37-39] reported data on dysfunction rates, including five RCTs and six retrospective studies. The heterogeneity was low among these 11 studies ($I^2 = 41.7\%$; $P_h = 0.071$). The pooled OR was significant (OR: 0.61, 95% CI: 0.46–0.81, $P = 0.001$), which was demonstrated by using a fixed-effect model (Figure 2a). These results suggest that the study group had a significantly reduced incidence of stent dysfunction.

Overall survival

Six retrospective studies reported the HR of OS.[32,34,35,37-39] These studies included 276 total patients in the study group and 290 total patients in the control group. The study group (patients who underwent surgery to implant metal stents + IRSS or I-125 seed stents) was compared with the control group (patients who underwent implantation of conventional metal stents). We pooled the HRs and revealed a significant extension of OS in the study group (HR: 0.34, 95% CI: 0.28–0.42, $P < 0.001$) ($I^2 = 0.0\%$; $P_h = 0.771$) (Figure 2b).

Clinical success

Eight studies[25,26,30,34-36,38,39] reported data on clinical success (Table 1). There was no significant difference in success rates between the study group and the control group (OR: 1.27, 95% CI: 0.71–2.27, $P = 0.424$) ($I^2 = 0.0\%$; $P_h = 0.469$) (Figure 3).

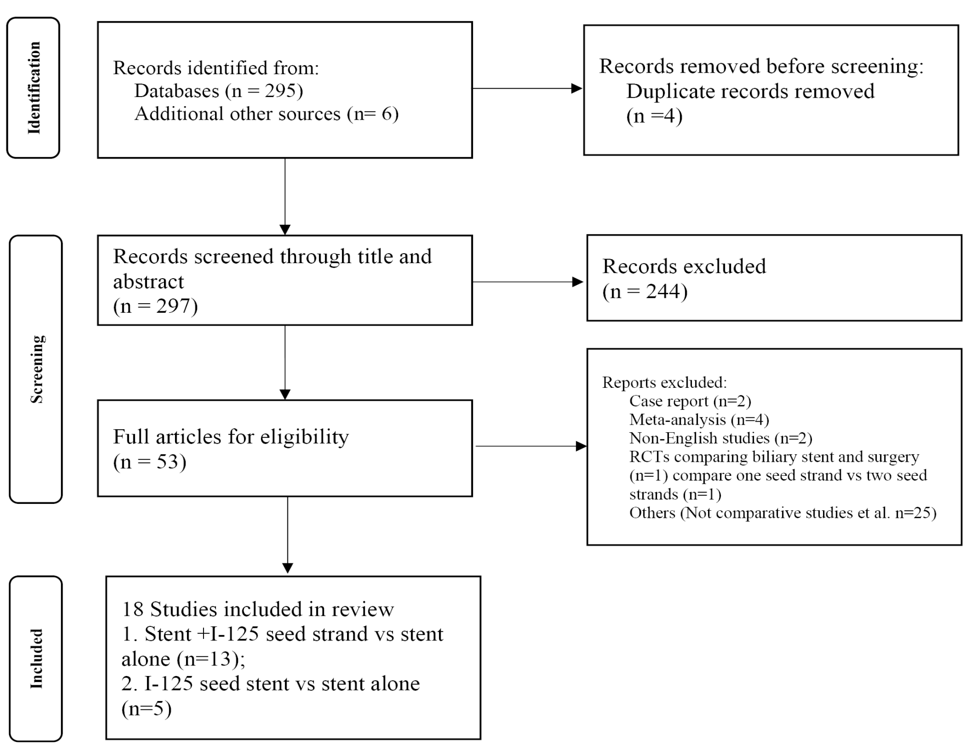

Figure 1. The process of article identification, inclusion, and exclusion according to the preferred reporting items for systematic reviews, meta-analyses guidelines and above criteria.

Table 1. Characteristics of the studies included

Studies	Intervention	Sample size (M/F)	Country	Study type	Cause of MBO	MBO site	Age (mean/ median, years)	Follow-up (mean/ median, months)	Mean seed number	Clinical success	Stent dysfunction (%)	OS (median, days)	NOS
Chen et al.[22] 2012	Sent + I-125 seed strand	17 (12/5)	China	RCT	Cholangiocarcinoma, hepatocellular carcinoma, pancreatic carcinoma, metastases	Hilar and distal	61	10.2	10.9	NG	6/17 (35.3%)	NG	-
	Stent	17 (10/7)					64	7.2			8/17 (47.1%)		
Zhu et al.[23] 2012	I-125 seed stent	12 (7/5)	China	RCT	Primary adenocarcinoma, metastatic adenocarcinoma	Hilar and distal	63	4.5 for all	NG	NG	0/12 (0)	222	-
	Stent	11 (9/2)					71				3/11 (27.3%)	75	
Hasimu et al.[24] 2017	Stent + I-125 seed strand	28 (11/17)	China	RCT	Cholangiocarcinoma, gallbladder carcinoma	Hilar and distal	71	7.4	15.5	NG	NG	241	-
	Stent	27 (14/13)					70	4.6				142	
Jiao et al.[25] 2017	Stent + I-125 seed strand	29 (12/17)	China	RCT	Primary adenocarcinoma, metastatic adenocarcinoma	Hilar and distal	63	9.1 for all	10.5	31/31 (100%)	16/31 (51.6%)	355	-
	Stent	30 (16/14)					64			28/30 (93.3%)	15/30 (50%)	271	
Zhu et al.[26] 2018	I-125 seed stent	164 (103/61)	China	RCT	Biliary tract cancer, pancreatic carcinoma, lymph node metastases	Hilar and distal	65	5.6 for all	NG	152/164 (93%)	34/164 (20.7%)	202	-
	Stent	164 (109/55)					64			155/164 (95%)	56/164 (34.1%)	140	
Chen et al.[27] 2018	I-125 seed stent	13 (8/5)	China	RCT	Cholangiocarcinoma, gallbladder carcinoma, pancreatic carcinoma, ampullary carcinoma	Distal	66	9.9	NG	NG	NG	298	-
	Stent	19 (12/7)					68	4.6				139	
Wang et al.[28] 2021	Stent + I-125 seed strand	32 (16/16)	China	RCT	pancreatic carcinoma, gallbladder carcinoma, cholangiocarcinoma, lymph node metastasis from digestive malignant tumors	Hilar and distal	63	NG	NG	NG	18/32 (56.3%)	330	-
	Stent	35 (15/20)					63				19/35 (54.2%)	210	
Wang et al.[29] 2017	Stent + I-125 seed strand	24	China	Retrospective	Cholangiocarcinoma, hilar lymph node metastases, pancreatic carcinoma, ampullary carcinoma	Hilar and distal	57 for all	NG	18.8	NG	NG	306	6
	Stent	26										262	
Zhou et al.[30] 2018	Stent + I-125 seed strand	45 (31/14)	China	Retrospective	Cholangiocarcinoma, gallbladder carcinoma, pancreatic carcinoma, hepatocellular carcinoma, gastric cancer, ampullary carcinoma, metastases	Hilar and distal	61	7.5	14	42/45 (93.3%)	5/45 (11.1%)	196	8
	Stent	87 (59/28)					64	4.5		83/87 (95.4%)	4/87 (4.6%)	96	

Table 1. continued

Studies	Intervention	Sample size (M/F)	Country	Study type	Cause of MBO	MBO site	Age (mean/ median, years)	Follow-up (mean/ median, months)	Mean seed number	Clinical success	Stent dysfunction (%)	OS (median, days)	NOS
Wang et al.[31] 2019	I-125 seed stent	17 (7/10)	China	Retrospective	Pancreatic carcinoma	Distal	59	NG	16	NG	NG	312	6
	Stent	15 (6/9)					60					291	
Pang et al.[32] 2019	Stent + I-125 seed strand	113 (75/38)	China	Retrospective	Cholangiocarcinoma	Hilar and distal	68	NG	NG	NG	NG	390	6
	Stent	71 (43/28)					68					240	
Li et al.[33] 2020	Stent + I-125 seed strand	48 (33/15)	China	Retrospective	Pancreatic carcinoma	Distal	66	NG	NG	NG	9/48 (18.8%)	209	8
	Stent	62 (37/25)					65				34/62 (54.8%)	202	
Chen et al.[34] 2020	Stent + I-125 seed strand	35 (20/15)	China	Retrospective	Cholangiocarcinoma, gallbladder carcinoma	Hilar	66	NG	NG	35/35 (100%)	7/36 (19.4%)	250	8
	Stent	45 (26/19)					65			42/45 (93.3)	11/48 (22.9)	188	
Pan et al.[35] 2020	Stent + I-125 seed strand	30 (23/7)	China	Retrospective	NG	Hilar and distal	59 for all	NG	NG	27/30 (90%)	NG	311	6
	Stent	54 (35/19)								48/54 (88.9)		173	
Zhou et al.[36] 2020	Stent + I-125 seed strand	40 (21/19)	China	Retrospective	Cholangiocarcinoma, pancreatic carcinoma, gallbladder carcinoma, duodenal carcinoma, metastatic carcinoma.	Hilar	70	NG	15.2	38/40 (95%)	NG	177	8
	Stent	36 (21/15)					68			35/36 (97.2)		123	
Yang et al.[37] 2021	Stent + I-125 seed strand	31 (18/13)	China	Retrospective	Cholangiocarcinoma	Distal	65	NG	9.9	NG	6/31 (19.4%)	242	8
	Stent	40 (24/16)					67				11/40 (27.5%)	182	
Lin et al.[38] 2021	Stent + I-125 seed strand	30 (18/12)	China	Retrospective	Cholangiocarcinoma	Hilar	67	NG	11	30/30 (100%)	7/30 (23.3%)	256	8
	Stent	35 (21/14)					66			33/35 (86.8)	9/35 (25.7%)	198	
Zhu et al.[39] 2021	I-125 seed stent	37 (20/17)	China	Retrospective	Cholangiocarcinoma, secondary biliary adenocarcinoma	Distal	68	NG	NG	37/37 (100%)	7/37 (18.9%)	250	8
	Stent	45 (27/18)					66			41/45 (91.1)	13/45 (28.9%)	176	

RCT, randomized controlled trial; MBO, malignant biliary obstruction; M, male; F, female; OS, overall survival; NOS, Newcastle–Ottawa scale; NG, not given.

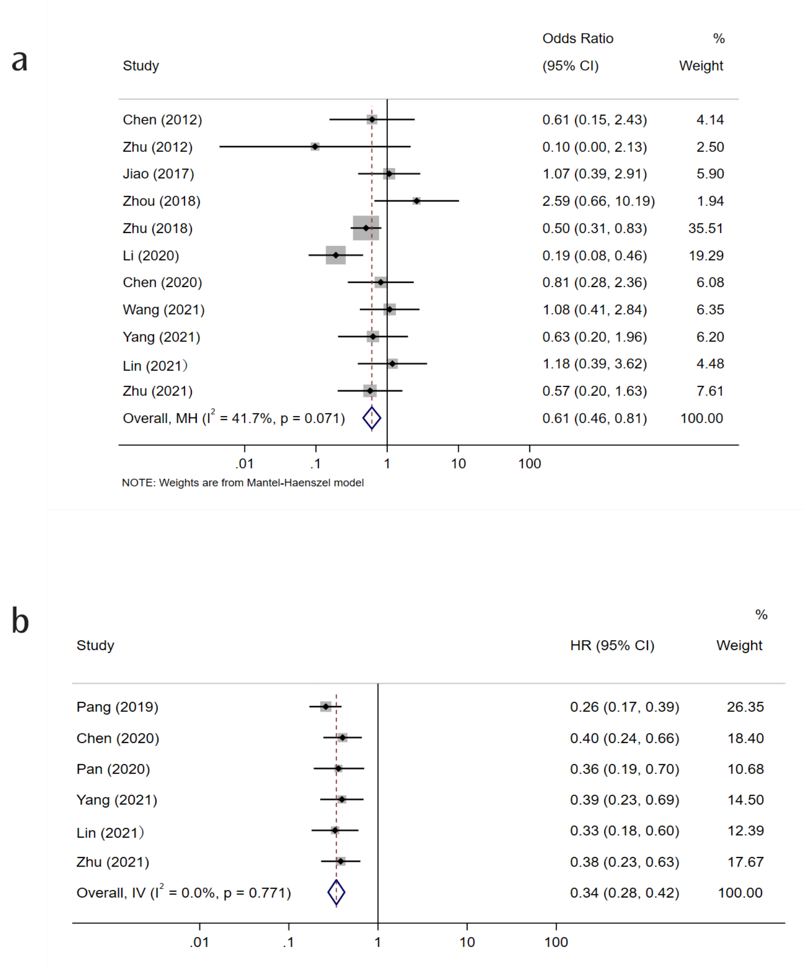

Figure 2. (a) Group analysis results of stent dysfunction rate; **(b)** group analysis of overall survival.

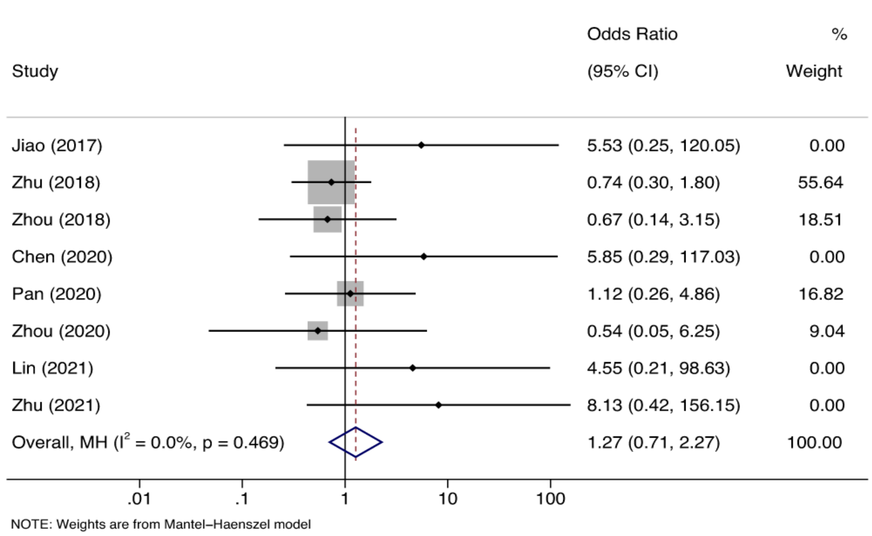

Figure 3. Group analysis results of clinical success rate.

Complications

All adverse events from studies, including cholangitis, pancreatitis, hemophilia, and cholecystitis, were reported. However, the differences between the study and the control group were not statistically significant. Heterogeneity among the studies was not significant when compared with the control group (all I^2 = 0.0%, all P_h > 0.05), including for cholangitis (OR: 1.00, 95% CI: 0.66–1.53, P = 0.992) (Figure 4a), cholecystitis (OR: 1.82, 95% CI: 0.55–6.0, P = 0.326) (Figure 4b), pancreatitis (OR: 1.79, 95% CI: 0.48–6.70, P = 0.390) (Figure 4c), and hemobilia (OR: 1.11, 95% CI: 0.47–2.65, P = 0.813) (Figure 4d).

Subgroup analysis

Subgroup analyses were conducted to analyze the dysfunction rates for the two different methods of I-125 seed deployment. The I-125 seed stents significantly decreased stent occlusion rates compared with metal stents alone (I^2 = 0; P_h = 0.560) (OR: 0.49, 95% CI: 0.31–0.76, P = 0.002) (Figure 5a). However, only three studies[23,26,39] reported this data. The heterogeneity was high for the metal stents + IRSS groups versus the metal stents group (I^2 = 51.2%; P_h = 0.045). Using a random-effect model to pool ORs, the analysis demonstrated no obvious reduction in stent dysfunction between the two groups (OR: 0.78, 95% CI: 0.45–1.36, P = 0.378) (Figure 5b). In the subgroup analysis of survival, five studies were included.[32,34,35,37,38] Survival was obviously improved in patients who received the metal stents + IRSS compared with patients who received conventional metal stents (HR: 0.33, 95% CI: 0.26–0.42, P < 0.001) (I^2 = 0.0%; P_h = 0.680) (Figure 5c).

Sensitivity analysis

In our sensitivity analysis, 11 studies reported that stent dysfunction ranged from a low of 0.58 (95% CI: 0.44–0.78, I^2 = 30.2%; P_h = 0.177), after omitting the 2018 report by Zhou et al.[30], to a high of 0.73 (95% CI: 0.54–0.99; I^2 = 0.0%; P_h = 0.464), after omitting the 2020 report by Li et al.[33], and results were generally similar. Six studies reported specific HRs for OS, from a low of 0.38 (95% CI: 0.26–0.42, I^2 = 47.2%; P_h = 0.048), after omitting the 2020 report by Chen et al.[34], to a high of 0.38 (95% CI: 0.29–0.42; I^2 = 0.0%; P_h = 0.996), after omitting the 2019 report by Pang et al.[32] Again, results were similar without great fluctuation. Our sensitivity analysis indicates that there were no significant variations in the combined effect sizes after excluding any one of the studies, which confirms the stability of the overall results.

Study quality assessment

In total, 18 studies were conducted in China. Although these authors described the use of proper randomization methods, some studies did not provide details of patient allocation; as such, the validity of seven RCTs was assessed in detail (Figure 6). The scores of 11 retrospective studies were 6–8 (Table 1).

Publication bias

No publication bias was found in this meta-analysis. A funnel plot analysis showed no asymmetry. Additionally, Egger's test was used to assess the stent dysfunction results (P = 0.227 for OS; P = 0.167 for stent dysfunction) (Supplementary Figures 1, 2). The included studies indicated no evident publication bias.

Discussion

Principle findings

The main palliative treatment for MBO is stent insertion, with relief of stenosis being its main purpose. However, stent dysfunction remains a severe challenge for clinical practitioners and directly leads to patient mortality. Therefore, we conducted this meta-analysis to provide evidence of the advantages of metal stents + IRSS or I-125 seed stents. I-125 seed deployment resulted in lower stent dysfunction rates than conventional metal stent implantation. Moreover, the OS of patients who suffered MBO and received the I-125 seed stents had obvious improvement. Aligning with our results, Xiang et al.[19] also found that I-125 seeds did not increase procedure-related complications, which demonstrates that the treatment is generally safe.

Tumors can easily grow into the lumen via the stent mesh. This can lead to the recurrent occlusion of the stent and to symptoms such as jaundice.[18,40] In addition, the formation of granulation tissue and epithelial hyperplasia may also contribute to stent failure.[11,41] Radioactive stents may help to avoid this stent dysfunction. First, I-125 seeds serve as the sustained radiation source. I-125 plays an important role in damaging the DNA of malignant cells, which triggers apoptosis.[42] Second, the I-125 insertion may trigger the activation of CD3+ and CD4+ cells and cause an anticancer immune response.[43] Conventional metal stents lack this unique radioactive function, which limits their longer-term benefits. These characteristics may explain why metal stents + IRSS and I-125 seed stents demonstrate a lower rate of restenosis and longer OS than conventional metal stents.

Comparison with other studies

A previous meta-analysis by Huang et al.[44] compared IRSS+ stents with stents alone in MBO treatment. However, the inclusion of only three RCTs did not provide sufficient evidence. In addition, Huang et al.[44] did not include patients who used I-125 seed stents. In our meta-analysis, we included I-125 seed stents and conducted subgroup analyses on survival and stent dysfunction for the two different deployments of I-125 seeds.

Another similar meta-analysis conducted by Xiang et al.[19] compared two different methods of deploying I-125 seeds and found no significant difference in survival between the brachytherapy group and the control group. The brachytherapy group had decreased stent occlusion rates regardless of the method of I-125 deployment. This evidence is consistent with our results.

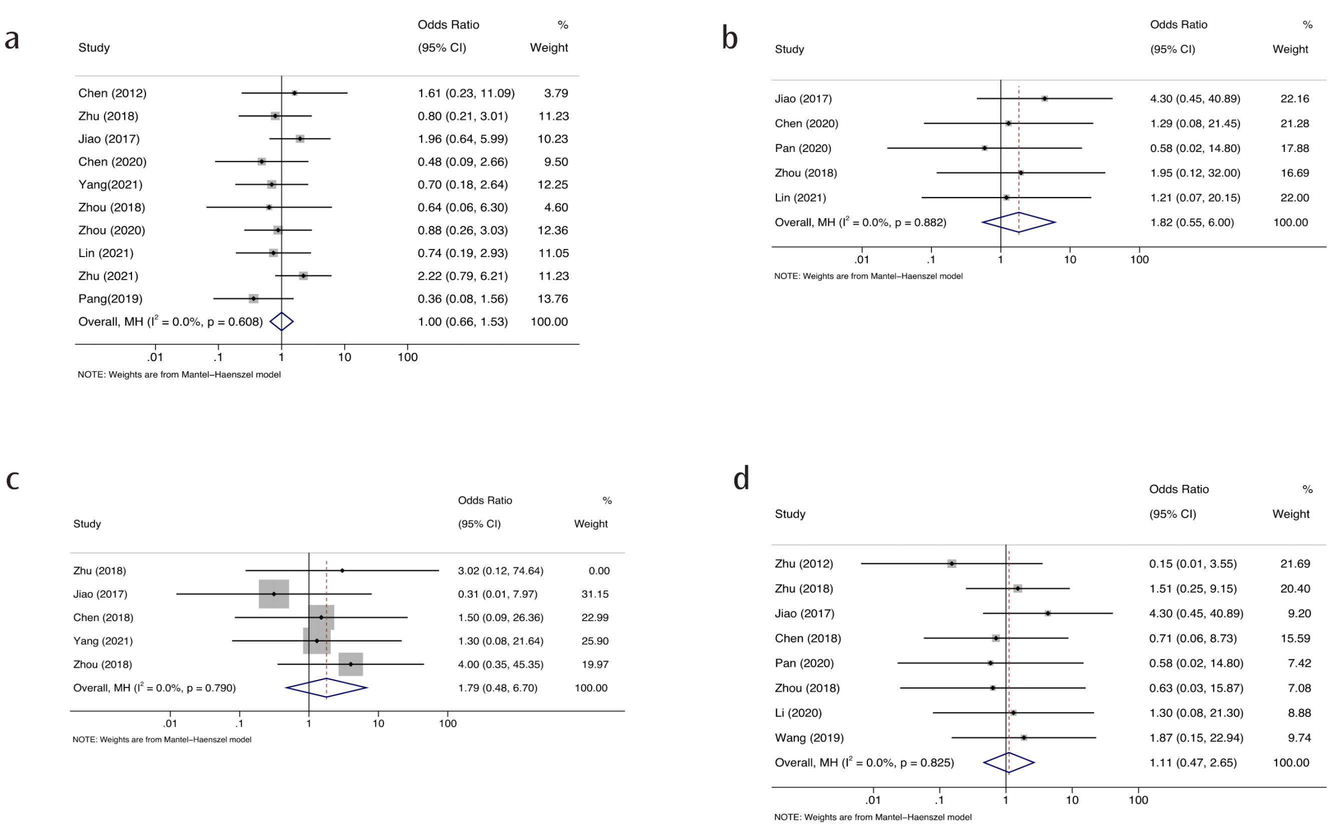

Figure 4. (a) Group analysis result of cholangitis; **(b)** group analysis result of cholecystitis; **(c)** group analysis result of pancreatitis; **(d)** group analysis result of hemobilia.

Two studies associated with high-dose-rate 192 iridium (Ir) intraluminal brachytherapy for MBO patients demonstrated a survival time of 9.2–9.4 months.[45,46] In our included studies, the median survival period was longer than that of the control group (Table 1). Nevertheless, there are several shortcomings of HDR-192 Ir. First, it cannot provide the sustained radiation associated with I-125 seeds.[24] Second, it increases biliary infection through the procedure.[25] Third, for a few patients who suffer from MBO, the tissue of the biliary tract is relatively thin, which makes it difficult to complete the procedure.[25] Environmental requirements are also demanding, necessitating an isolated, well-shielded room.[47]

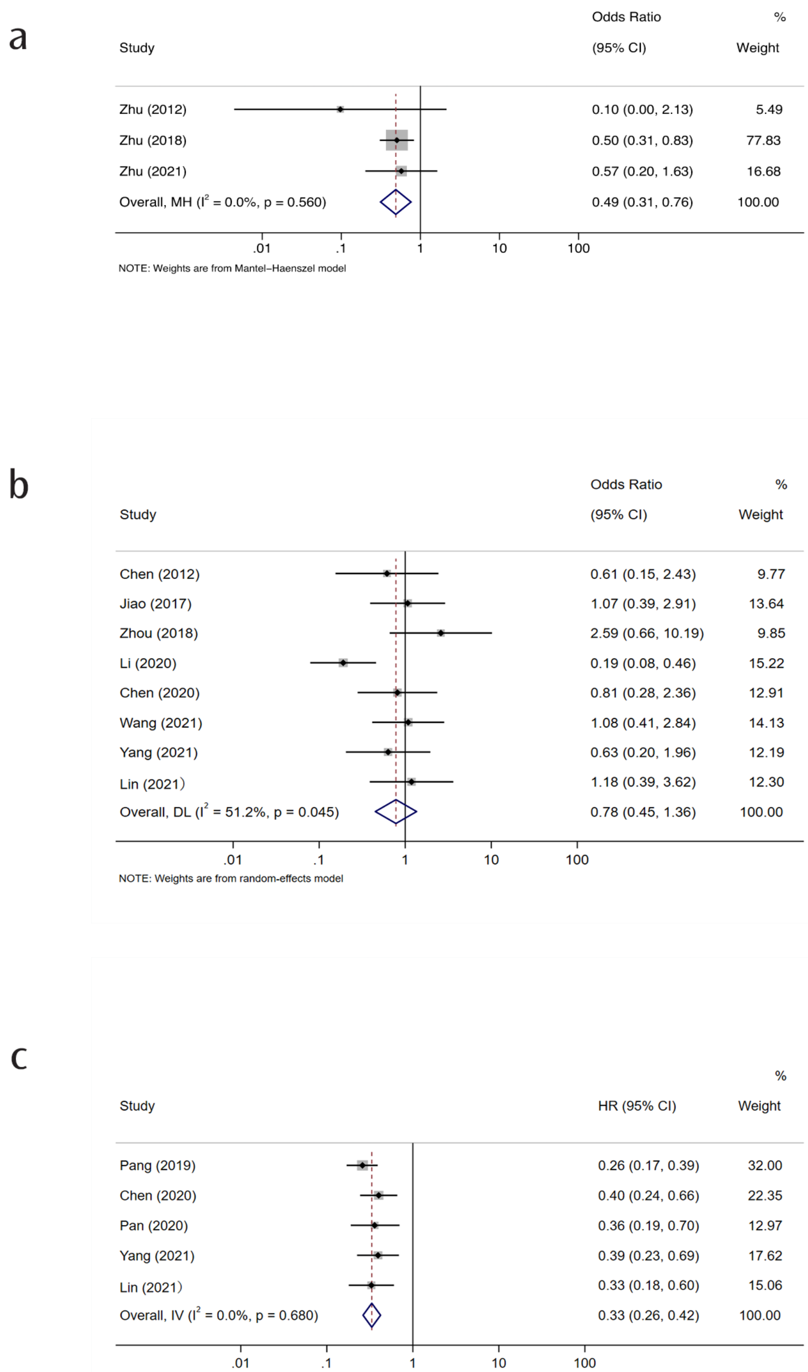

Figure 5. (a) Subgroup analysis results of the dysfunction rate (I-125 seed stents group versus control group); **(b)** subgroup analysis results of the dysfunction rate (metal stents + IRSS group versus control group); **(c)** subgroup analysis results of overall survival (metal stents + IRSS group versus control group).

Frequently, I-125 seeds are deployed via either IRSS or the use of I-125 seed stents. To fully cover the stent surface, the manufacturing process of I-125 seed stents is rigorous. The existing meta-analysis tends to emphasize the IRSS approach. However, theoretically, the latter method may be more suitable for luminal diseases such as MBO. Hopefully, more studies will be designed to compare the efficacy rates of these different deployment methods in MBO patients.

Strengths and limitations

In our meta-analysis, we included seven RCTs and 11 retrospective studies. Compared with previous meta-analyses,[19,44] we provided relatively useful evidence. In addition, we conducted subgroup analysis between two different types of I-125 delivery with metal stents, which may provide more individualized treatment options for patients experiencing MBO. Moreover, our publication bias and sensitivity analyses indicate the reliability and stability of the results.

However, some RCTs lacked blinding procedures, which could possibly result in selection bias, with only Zhu et al.[26] employing a multi-center randomized research approach. Eleven studies were not RCTs in design; as such, these studies may be prone to bias,

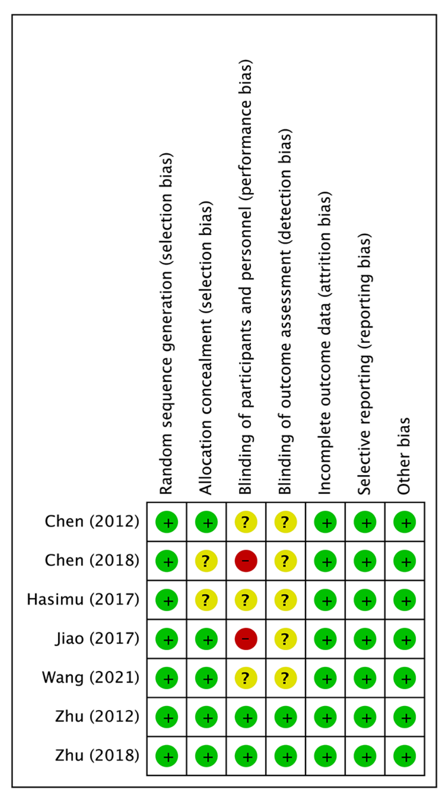

Figure 6. Quality assessment of randomized controlled trials.

which could affect the reliability of the data. All studies but four[32,33,37,38] included participants with MBO who suffered from different malignant tumors. In addition, the obstruction sites were not well distinguished. Subgroup analysis based on the anatomic levels and cancer types could not be conducted. Future studies are necessary to evaluate related study endpoints in single-type cancers. Additionally, different sites of obstruction of MBO should be further explored for treatment.

In theory, radioactive stenting is more effective, as it loads the I-125 seeds around the implanted stent. Unsatisfactorily, five studies mention only one type of radioactive stent made from a SEMS with radioactive I-125 seeds.[23,26,27,31,39] Moreover, studies on different radioactive stents (I-125 seed stents or other sources of radioactive material) are very rare, and more studies are urgently required.

Moreover, all included studies were conducted in China because the I-125 seed strand was developed by Chinese researchers.[26] A series of studies could be performed in the future when the application of I-125 seed stents becomes more accepted in other countries.

Implications

MBO is caused by various cancers, and only approximately 10%–20% of patients who suffer from MBO are eligible for surgical resection.[9-11,14,48] Even after successful surgery, the three- and five-year survival rates remain at 18%–52% and 5%–31%, respectively.[12,49,50] Metal stent insertion is widely used in MBO patients to relieve stenosis. I-125 seeds have a radioactive half-life of approximately 59.6 days and can persistently suppress tumorous cells.[27] Moreover, I-125 seeds can reliably inhibit the growth of neoplasm into the mesh of the stent, which greatly avoids stent dysfunction. This meta-analysis proves this method's advantages. Using I-125 seed strand or radioactive stents can provide a better prognosis than conventional metal stents without increasing complications, which provides clinical practitioners with an optimal choice for handling this difficult medical condition. When the symptoms were relieved, the quality of life of patients greatly improved. Indeed, according to our results, the study group had a longer survival rate than the conventional metal stent group. Large RCTs are required to verify these results.

In conclusion, the study group (using metal stents + IRSS or I-125 seed stents) was significantly superior to the conventional metal stent group, with a superior survival rate and decreased stent occlusion. In addition, the two types of I-125 seed delivery did not increase the risk of procedure-related complications when compared with conventional metal stents. More strictly designed, multiple-center RCTs are required to confirm these findings.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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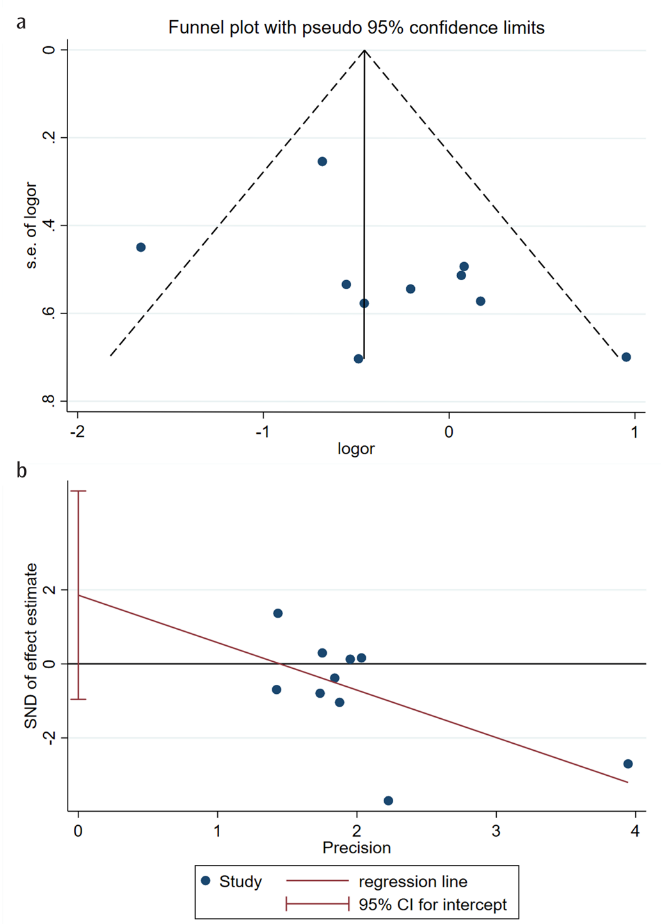
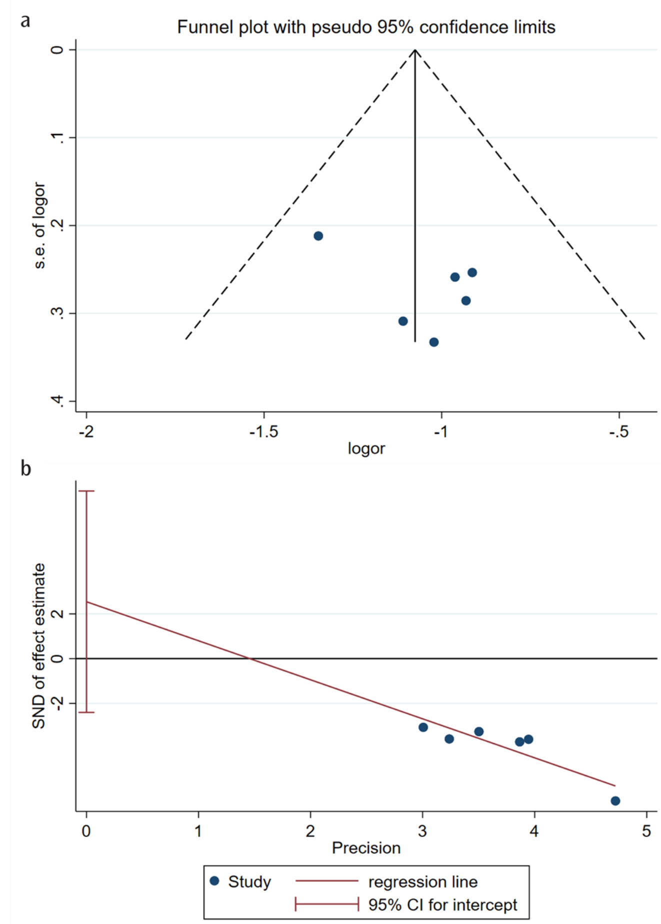


Supplementary Figure 1. (a, b) Funnel plot and Egger's test on stent dysfunction. CI, confidence interval.



Supplementary Figure 2. (a, b) Funnel plot and Egger's test on overall survival. CI, confidence interval.