Preprints are preliminary reports that have not undergone peer review. They should not be considered conclusive, used to inform clinical practice, or referenced by the media as validated information.

# Radiofrequency Ablation Combined with Stent Placement versus Stent Placement Alone for Malignant Biliary Obstruction: A Systematic Review and Meta-analysis

### **Hongyang Chen**

Zhejiang University School of Medicine Sir Run Run Shaw Hospital

### Chunxian Zhu

Zhejiang University School of Medicine Sir Run Run Shaw Hospital

Leimin Sun (■ sunlm@zju.edu.cn)

Zhejiang University School of Medicine Sir Run Run Shaw Hospital

### Research article

Keywords: radiofrequency ablation; stent; malignant biliary obstruction; meta-analysis; cholangiocarcinoma;

Posted Date: June 30th, 2020

**DOI:** https://doi.org/10.21203/rs.3.rs-36723/v1

License: @ 1 This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License

# **Abstract**

**Background:** Malignant biliary obstruction was typically diagnosed at an advanced stage due to painless jaundice. Stent placement is the therapy of choice in this set of patients. Radiofrequency ablation is an ablative therapy which has been well recognized for treating malignant biliary strictures. This meta-analysis aims to help to better understand the safety and efficacy of biliary Radiofrequency ablation combined with stent placement.

**Methods:** Five databases (PubMed, Embase, Cochrane Central Register of Controlled Trials, Web of Science, and China National Knowledge Infrastructure) were searched for randomized controlled trials and observational studies up to April 2020.

**Results:** The mean difference in survival time was 54.87 days (95% confidence interval *Cl*, 34.6-75.14), meaning patients performed with radiofrequency ablation benefit more. Reconstructed Kaplan-Meier data showed improved survival in joint intervention with RFA (hazard ratio, 1.39; 95% *Cl*, 1.34-1.75; P < .001). However, no survival benefit was observed in the extrahepatic distal cholangiocarcinoma. With regard to patency time, the mean difference was 42.88 days (95% *Cl*, 34.02-51.37). Reconstructed Kaplan-Meier data showed improved survival in the radiofrequency ablation treated group (hazard ratio, 1.629; 95% *Cl*, 1.35-1.96; P < .001). Concerning postoperative complications such as abdominal pain, cholangitis and pancreatitis, our analysis did not show a significant difference between the radiofrequency ablation treatment group and the controls.

**Conclusion:** Radiofrequency ablation plus stent resulted in improved survival and stent patency, with longer median survival and patency time than stent alone.

# **Background**

Malignant biliary obstruction (MBO) means stenosis and blockage of the bile ducts in the biliary tree, generally caused by local invasion or compression of the extrahepatic biliary tract by advanced stage cholangiocarcinoma, pancreatic adenocarcinoma gallbladder cancer, and metastatic tumors<sup>[1]</sup>. MBO is seriously influencing the quality of life and survival time. Typically, at the time of diagnosis, most patients with MBO are at the advanced stage, only 20% are suitable for curative surgery. [2-4]. Biliary drainage is the therapy of choice in this set of patients, the most highly recommended is the placement of self-expanding metal stents(SEMS)[5]. SEMS is recommended if their life expectancy is at least 3 months. However, stent placement only provides palliation for a limited duration and has no therapeutic effect on tumors. More recently, Radiofrequency ablation (RFA) has been well recognized for treating malignant biliary strictures [6-8]. Although most published studies have shown that the combination of RFA and stent placement can improve survival and stent patency time[9], recent research results suggest the combination has no clinical benefit concerning survival time[10]. Therefore, the goal of this systematic review and meta-analysis is to confirm the benefit of RFA combined with biliary stent placement in providing increased survival time and patency time in patient with malignant biliary obstruction.

# Methods

In accordance with the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses and Meta-Analysis of Observational Studies in Epidemiology[11, 12], We performed this systematic review and meta-analysis. This systematic review and meta-analysis has been registered at International Prospective Register of Systematic Reviews(number CRD42020169605)

### 1. Search Strategy

The search was formulated in PubMed, Embase, Cochrane Central Register of Controlled Trials, Web of Science, and China National Knowledge Infrastructure using the same subject headings and key words. Search terms included (Radiofrequency Ablation OR Ablation Radio-Frequency OR Radio Frequency Ablation) AND (malignant biliary obstruction OR malignant bile

duct obstruction OR malignant extrahepatic biliary obstruction OR obstructive jaundice OR Malignant hilar strictures) AND (stent). Title and abstract were reviewed for all search results, and potentially eligible studies were received a full-text review. Finally, the reference lists of the included studies and literature reviews found in the initial search were manually screened for additional articles meeting the inclusion criteria. All results were downloaded into EndNote X9 and duplicate citations were identified and removed, this procedure was conducted by 2 reviewers independently (Chen and Zhu).

### 2.Inclusion Criteria

The inclusion criteria for clinical articles were (1) publications dates 2010 to April 2020; (2) Published articles in English or Chinese, including thesis and conference literature; (3) Prospective, retrospective studies or random clinical trials comparing the clinical outcomes in biliary stent placement with or without RFA therapy were included, all patients included in the study were inoperable (4) at least including one of patency rate or survival rate; (5) full text of studies available.

### 3. Exclusion Criteria

The exclusion criteria were (1) failure to report statistics on the survival or stent patency time (2) duplicate publications, case reports, and letters were also excluded; (3) the same study of the same author, we selected the latest one; 48 The research included primary tumors that can be treated with surgery.

### 4.Data Extraction and Assessment of Study Quality

Two researchers independently conducted data extraction and analysis using a predetermined data sheet. The relevant information included the following: type of study, country, published date, patient demographics and clinical characteristics, methods of stent implantation, type of stents, etiology, and complications. Two reviewers independently assessed the eligibility and validity of each study by using the Cochrane tool for assessing risk of bias in randomized controlled trials (RCTs) and the Newcastle-Ottawa scale in observational studies. The Newcastle-Ottawa scale measured quality in the three parameters of selection, comparability, and exposure/outcome and allocated a maximum of 4, 2, and 3 points respectively. High quality studies were scored greater than 7, while those scored under 5 represented low-quality studies and score  $5 \sim 7$  were moderate quality studies. The Cochrane review recommended for the inclusion of research bias risk assessment tools consisting of two partial tools, six specific domains, including sequence generation, allocation concealment, blinding, incomplete data outcomes, selective outcome reporting and evaluation of other topics, based on these 6 dimensions. We conducted research bias detection on included articles. The Grading of Recommendations, Assessment, Development and Evaluation framework were used in this systematic review and meta-analysis. Each study was independently assessed by 2 authors, and any disagreement was to be discussed with a third reviewer and resolved in consensus.

### 5.Study Outcome

The primary outcome of this study was to evaluate the overall survival time and patency time. Secondary aims included assessing adverse events of the combination with the RFA. Different types of stent implantation, stents and malignancy were also analyzed.

### **6.Statistical Analysis**

We used software Engauge Digitizer (version 12.0) to extract information in the coordinates of the Kaplan-Meier curves from each included graph, the survival analysis data points were extracted simultaneously. All the extracted information was exported into Microsoft Excel 2019, the survival data information was analyzed and extracted again, which imported into the software SPSS (version 22) to obtain the HR (Hazard Ratio), median survival time, median patency time, *P* value and cumulative survival curves that compared with the original text. The extracted information was considered valuable when the difference was less than 5% between the original and the extracted.

Cochrane f and  $\chi^2$  statistics were used to estimate statistical heterogeneity, P < .05 and f > 50% were defined to be high heterogeneous. Random-effects models were used when the f value was >50%, otherwise, fixed-effects models were chosen. Statistical significance was defined at the 5% (F = .05) level. Inverse variance method was used in analyzing subgroups. Odds ratios (F0) was calculated in 95% confidence intervals (F1) by using raw data when analyzing complications. Egger linear regression was conducted to define publication bias. All statistical analysis was performed by the software STATAMversion 14.0Mand RevMan (version 4.2.10).

# **Results**

### 1.Study Selection and Characteristics

The initial literature search obtained 682 total studies. After removal of 287 duplicates, the rest articles were screened based on inclusion and exclusion criteria. Full texts of 376 unique studies were evaluated and assessed for eligibility. Ultimately sixteen articles[10, 13-27] were selected for our meta-analysis, including thirteen observational studies[13-19, 21-25, 27] and three RCTs(Randomized Controlled Trials) studies[10, 20, 26]. The search strategy is presented in Figure.1.

A total of 953 patients were included in this meta-analysis, 447 patients were performed RFA combined stent placement compared with 506 controls only given stent placement. Among those studies, eight studies[10, 14, 16, 17, 20, 24-26] via ERCP (Endoscopic retrograde Cholangiopancreatography), seven studies[13, 15, 18, 19, 21, 22, 27] used percutaneous transhepatic cholangiography (PTC) to implant stent, ERCP and PTC were mixed used in one research[23]. Types of biliary stents were mentioned in 15 of 16 studies. Metal biliary stents placement were performed in 12 studies[10, 13-16, 19-21, 23-25, 27], among those studies, uncovered self-expanding metallic stents (USEMS) were used in 8 studies[10, 13-15, 18, 19, 24, 27], USEMS and covered self-expanding metallic stents (SEMS) were mixed performed in 3 studies[21, 23, 25]. Plastic stents were chosen in 2 studies[20, 26], both of them were RCTs. Metal and plastic stents were mixed used in 2 studies[16, 22]. The details of selected process were presented in Table.1.

Table 1: study characteristics

| Author                              | RCT      |     |                |                    | Male  | Etiology             | Method   |                  |                                     |                 |
|-------------------------------------|----------|-----|----------------|--------------------|-------|----------------------|----------|------------------|-------------------------------------|-----------------|
| Year<br>country                     | Num<br>( |     | A(<br>(Mean    | Age<br>(Mean ± SD) |       |                      |          | Stent            | Prior bilirubin<br>(mean±SD) μmol/L |                 |
|                                     |          |     | RFA            | Control            | -     |                      |          |                  | RFA                                 | Control         |
| Liang<br>2015<br>China              | NO       | 76  | 67.5 ± 2.1     | 63.1± 1.6          | 22:26 | Extrahepatic<br>CCA  | PTC/ERCP | SEMS/USEMS       | 198.4±23.4                          | 212.9±18.9      |
| Li, T. F.<br>2015<br>CHINA          | NO       | 26  | 53*            | 60*                | 7:8   | Mixed                | PTC      | USEMS            | 287.2±<br>123.5                     | 254.2±<br>108.5 |
| Kallis, Y.<br>2015 UK               | NO       | 69  | 68.9± 9.0      | 69.8± 9.9          | 12:24 | Pancreatic<br>Cancer | ERCP     | USEMS            | 244.1±48.4                          | 203.9±149.9     |
| Hu<br>2016<br>China                 | YES      | 63  | 71.9±11.5      | 71.0±10.7          | NA    | Extrahepatic<br>CCA  | ERCP     | Plastic          | 153.8±107.8                         | 174.5±156.2     |
| Wang<br>2016<br>China               | NO       | 36  | 56. 6<br>±12.0 | 58.3<br>±10.7      | 14:12 | Extrahepatic<br>MBO  | PTC      | USEMS            | 93.1±32.4                           | 99.2±38.6       |
| Kadayifci,<br>A.                    | NO       | 50  | 65.4±13.1      | 62.4±11.7          | 8:14  | Mixed                | ERCP     | USEMS            | -                                   | -               |
| 2016 USA<br>Sampath<br>K            | NO       | 25  | 73.3*          | 67.3*              | 6:9   | Hilar CCA            | ERCP     | Plastic/Metal    | -                                   | -               |
| Dutta, A.<br>K.<br>2017 UK          | NO       | 31  | 78*            | 76*                | 7:8   | Mixed                | ERCP     | USEMS/p-<br>SEMS | -                                   | -               |
| Ma<br>2017<br>China                 | NO       | 80  | 58.1±12.6      | 55.1±12.2          | 26:27 | Mixed                | PTC      | USEMS            | 253.7±76.1                          | 246.2±77.2      |
| Wu<br>2017<br>China                 | NO       | 71  | 59.2±7.5       | 56.5±8.75          | 26:25 | Distal MBO           | PTC      | SEMS/USEMS       | 246.7±120.1                         | -               |
| Yang<br>2018<br>China               | YES      | 55  | 62±7.7         | 64.5±3.4           | 15:18 | Extrahepatic<br>MBO  | ERCP     | Plastic          | 266.8±88.5                          | 245.9±76.2      |
| Teoh, A.<br>Y.<br>2018 HK,          | YES      | 47  | 67.2±11.9      | 77.2±10.9          | 15:12 | Distal MBO           | ERCP     | USEMS            | -                                   | -               |
| China Bokemeye A 2019               | NO       | 42  | 68±2.0         | 66                 | -     | Hilar MBO            | PTC      | Plastic/ SEMS    | -                                   | -               |
| Germany<br>Cui W<br>2019<br>China   | NO       | 163 | -              | -                  | -     | Mixed                | PTC      | USEMS            | -                                   | -               |
| Buerlein<br>R                       | NO       | 49  | -              | -                  | -     | Hilar MBO            | ERCP     | -                | 218.88*                             | 123.12*         |
| 2019 USA<br>Yu, T.<br>2020<br>CHINA | No       | 70  | 64.5*          | 64*                | 15:25 | Mixed                | PTC      | USEMS            | 247.7±90.9                          | 241.6±81.3      |

<sup>\*</sup>mean the median. RCT, Randomized Controlled Trials. RFA, Radiofrequency ablation combined with stent placement. Control, only stent placement. CCA, Cholangiocarcinoma. MBO: malignant biliary obstruction. Mixed, the etiology includes more than 2 tumor types. PTC, percutaneous transhepatic cholangial drainage. ERCP, Endoscopic retrograde cholangiopancreatography. SEMS: self-expanding metal stents. USEMS, uncovered SEMS. p- SEMS, partially covered SEMS

### 2. Methodologic Quality and Risk of Bias Assessment

Seven observational studies[14, 15, 19, 22-25] were of high quality and six[13, 16-18, 20, 27] were judged as moderate quality in Newcastle-Ottawa Scale assessment. In three RCTs: two studies[10, 20] could not be assessed bias risk for no mention of experimental methodology, one study[26] was confined as low risk by the Cochrane tool. The overall heterogeneity was P = .12 and P = .12 and considered to be low. *Egger's* test showed P = .166, meaning there's no public bias. Risk of bias assessment was provided in Figure.2.

### 3. Baseline Characteristics for Patients

The baseline characteristics and patient demographics were showed in Table 2. There was no statistical significance between the RFA-treated and stent alone group in gender proportion, age, adjuvant chemotherapy or radiotherapy, types of stent, preoperative bilirubin level and primary stenosis length.

Table 20baseline characteristics in RFA + Stent group and Stent alone

|                             | RFA+ Stent      | Stent           | P value |
|-----------------------------|-----------------|-----------------|---------|
| Gender (male%)              | 59.43           | 57.8            | .61     |
| Age(y)                      | 64.58±10.726    | 3.75±10.74      | .73     |
| Chemotherapy (%)            | 44.30           | 47.25           | 0.32    |
| Cholangiocarcinomal%        | 72.56           | 69.69           | 0.45    |
| Metastases (%)              | 36.97           | 38.89           | .75     |
| Metal stent (%)             | 55.80           | 60.97           | .14     |
| Uncovered Stent (%)         | 87.5            | 87.12           | .87     |
| Complications               |                 |                 | .75     |
| Abdominal pain (%)          | 43.83           | 47.42           | .70     |
| Pancreatitis (%)            | 4.94            | 1.86            | .34     |
| Cholangitis (%)             | 29.01           | 29.81           | .36     |
| Pro-Bilirubin(μmol/L)       | 241.57<br>±79.0 | 235.60<br>±83.3 | .88     |
| Initial stenosis length(cm) | 3.48            | 3.45            | .58     |

### 4. Survival Analysis

The pooled median survival time was significantly longer in the intervention groups with RFA (255 days, 95%  $\it Cl$ , 237-272) compared with control groups (178 days, 95%  $\it Cl$ ,168-188,  $\it P$ <0.01). The reconstructed Kaplan-Meier analyses showed improved survival in the intervention groups with RFA (hazard ratio, 1.53; 95%  $\it Cl$ , 1.34-1.75,  $\it P$ <.001) (Figure.3). The mean difference between the RFA-treated group and the controls was 54.87 days (95%  $\it Cl$ ,34.6-75.14,  $\it P$ <.001), favoring patients receiving RFA.

The median time of RFA-treated groups intervened by ERCP was 292 days (95% Cl,248-336) Mexhibiting a prolonged survival than PTC groups (213 days, 95% Cl,189-237, P<.001). The reconstructed Kaplan-Meier analyses showed improved survival in the intervention groups with ERCP groups (HR= 1.39; 95% Cl, 1.15-1.7). Subgroup analysis revealed the mean difference of the ERCP groups was 87.15 days (95% Cl,37.2-137.28, P<.001, Cochran Q test P =35%, P=.17), the PTC groups was 43.14 days (95% Cl,18.73-67.55, P<.001 Cochran Q test P =49%, P=.08), but there was no significant difference between the two groups, P=0.12. (Figure 4). Since most of the included studies cause MBO as extrahepatic factors, another subgroup analysis was grouped according to different extrahepatic obstruction sites. The result showed that the survival benefit of the hilar cholangiocarcinoma was 129.84 days (95%Cl: 59.76-199.92, p<.001), however, there was no survival benefit observed in the distal cholangiocarcinoma group(p=.53) Figure 5.

### 5.Stent patency

In the studies mentioning stent patency time, the overall heterogeneity was low (Cochran Q test P =43.0%, P =.12), and there was no publication bias in the Egger's (P =.9).

Overall patency time was 216 days (95% *Cl*, 197-235) in the RFA groups compared to 156 days (95% *Cl*, 144-168; *P*<.001) in the controls, showing a great improvement in the RFA combining with stent implantation. The pooled overall patency time from reconstructed Kaplan-Meier analyses showed improved time in patients receiving RFA compared with patients undergoing biliary stent placement alone (hazard ratio, 1.63; 95% *Cl*, 1.35-1.96, *P*<.001) (Figure.6). The mean difference of patency time between the RFA and control groups was 42.88 days (95% *Cl*,34.02-51.37).

Subgroup analysis was conducted based on the approaches of stent implantation and etiology. Among the subgroup of procedures used for biliary drainage, the mean difference in the PTC was 54.81 days (95% CI 39.89-69.73, P<.001, Cochran Q test P =0%, P =.42). In the ERCP group, the mean difference was 39.88 days (95% CI 21.51-58.24 $\mathbb{Z}$ p<.001, Cochran Q test P =16%, P =.30). There was no statistical difference between the two groups (P =.22) $\mathbb{Z}$ Figure P. Another subgroup analysis was based on different types of stents. The overall benefit of patency time in the uncovered SEMS was 53.81 days (95% P CI 39.76-67.87, P <.001, Cochran P test P = 0) was longer than that of the plastic stent group 33.00 days (P = .03).

We divided the studies into 3 groups according to the different etiology of MBO. The three groups were the Cholangiocarcinoma studies, the pancreatic cancer studies, and the mixed studies (Figure 8). Subgroup analysis showed the mean difference of pure- Cholangiocarcinoma groups was 51.09 days (95% Cl,24.53-77.66, Cochran Q test P=.05), the pure pancreatic cancer groups were 90.16 days (95% Cl,43.19-137.12, Cochran Q test P=10%, P=.33), the group of the mixed etiology of MBO was 51.77 days (95% P0.35.66-67.87, Cochran P0 test P0.

### 6.Adverse Events

Total procedure-related complications referred from each study included abdominal pain, cholecystitis, pancreatitis and hemobilia[20, 23, 28-31] Mabdominal pain was the most common complications (range from  $10\% \sim 77.14\%$ ), but it did not reach statistical significance between RFA+ stent group and stent alone group (P=.75), the same with the acute cholecystitis (P=.36) and pancreatitis (P=.34). All postoperative pancreatitis only existed in the ERCP-related groups. Cholangitis existed in ERCP group and PTC group.

# **Discussion**

Radiofrequency ablation is a minimally invasive treatment technology for solid tumors developed in recent years, mainly based on that tumor cells are less resistant to heat than normal cells [32-35]. By raising the effective local temperature to 90-120°C, RFA could heat the tumor area, resulting in coagulation, degeneration and necrosis, therefore, it can reduce tumor burden and the risk of stent restenosis. Many experiments in vivo and in vitro proved its effectiveness and safety [28, 36-38]. For malignant biliary obstruction, biliary stent implantation is performed to relieve clinical symptoms and reduce complications such as cholangitis or pain. Recent studies have shown that the combined use of RFA and stent has no clinical benefit, contrary to the previous experience[10], hence, we conducted this update meta-analysis.

Our meta-analysis reported that radiofrequency ablation combined with stent implantation can obtain survival benefits. The survival benefit of RFA is mainly related to its ability to cause necrosis of the local tumor issue, cut off the blood supply of the tumor, reduce tumor burden, and stimulate the body's immune response to the tumor, prevent the spread of malignant tumors to the bile duct tree, and control disease progression. One of the main factors affecting survival is etiology. Traditionally, MBO can be divided into intrahepatic MBO and extrahepatic MBO according to different obstructive sites. Patients with extrahepatic MBO had generally a better outcome if compared to patients with intrahepatic MBO. The etiology of MBO in the literature we included mainly included hilar cholangiocarcinoma, pancreatic cancer, ampullary cancer, and gallbladder cancer. Extra-hepatic malignancies were the main etiology of the included studies. Intrahepatic MBO, such as

hepatocellular carcinoma, occupied only a small part of the etiology in two included studies[14, 15], and at the same time, there is no research solely based on intrahepatic MBO. Therefore, we cannot compare the efficacy of radiofrequency ablation in MBO intrahepatic and extrahepatic malignant obstruction. We further chose to discuss the survival benefits based on the location of extrahepatic MBO such as hilar cholangiocarcinoma and distal cholangiocarcinoma. Results showed the hilar cholangiocarcinoma group benefited from RFA combined with stents, while the distal cholangiocarcinoma group showed no survival benefit. The reason may be that in patients with advanced distal cholangiocarcinoma who were inoperable, the local tumor volume reduction caused by RFA was not enough to prevent the in-stent restenosis and improve the survival rate. At the same time, Wu *et al.* analyzed the functional status and quality of life of the patients. The results suggested that only patients in good condition, without cachexia, and patients with an expected life span of more than 6 months could obtain significant benefits from RFA[21]. Meanwhile patients with inoperable distal cholangiocarcinoma often have lymph nodes and distant metastases, and these two usually indicate a poorer prognosis and shorter life span [39, 40]. Therefore, for advanced distal cholangiocarcinoma, RFA may not have survival benefit.

When referring to methods of stent implantation such as ERCP and PTC, both procedures of operation had definite clinical benefits. Due to the different types of malignancy and obstruction sites, ERCP and PTC have their scope of application. ERCP was recommended for malignant extrahepatic biliary obstruction and Bismuth types I and II in malignant hilar strictures. The overall mean difference of the ERCP group is greater than that of the PTC group, but there is no statistically significant difference. It is worth noting that the plastic stents were all implanted through ERCP, plastic stents are usually used for short life expectancy patients, this may have an impact on the experimental results. And most studies did not adjust the implantation method according to the obstruction site. In general, ERCP seems to have better clinical benefit, but the long-term efficacy of the two needs to be further studied.

The improved stent patency caused by RFA can also be observed. Total patency time of the RFA-treated group was longer than the controls, the total mean difference was 42.88 days. RFA can reduce tumor thickness, slow the growth of cancer, and reduce the risk of stenosis. The enlarged bile duct resulting from RFA enhanced the drainage effect of the stent, causing an increase in patency time and an improvement in the quality of life. Different types of stents influence on patency time, our study confirmed that the patency time of uncovered SEMS was better than that of plastic stents, which was consistent with previous experience[41]. However, only a small amount of covered and partially covered SEMS was used in some of the included studies [23, 25], so we cannot compare the patency time of these two types of stents. Subgroup analysis shows that the PTC groups showed better stent patency, this is inconsistent with the overall survival time results, which may be related to the small number of studies included in the ERCP group, and the use of plastic stents also had an impact on the results. In some observational studies, the median patency time of the pancreatic cancer subgroup was higher than the overall[14]. Subgroup analysis based on specific tumor types showed that the pancreatic cancer subgroup had the largest mean difference, and the cholangiocarcinoma subgroup had the least. There was no statistical difference between the three groups P=.24. When only pancreatic cancer and cholangiocarcinoma subgroups were compared, the results suggest that there was a statistical difference between the two (P = .03), meaning that patients with pancreatic cancer combined with RFA indeed had a higher patency time, This may be related to the lower site of obstruction caused by pancreatic cancer and low rate of restenosis.

Our meta-analysis revealed the combination of RFA therapy and stent implantation was superior to the stent drainage in the overall survival and patency time, and we found first that distal cholangiocarcinoma did not benefit from additional RFA. In terms of postoperative complications, there was no difference between the experimental group and the control group in all studies. Overall, common complications were postoperative abdominal pain, pancreatitis, and cholangitis. In the study of a high incidence of abdominal pain, the medication of analgesic was effective, and abdominal pain may be a transient reaction after the RFA. In the operation of RFA, most of the research used the Habib™ EndoHPB catheter, only one study used Habib™ VesOpen catheter, Habib™ VesOpen catheters were considered to be safer and with fewer complications[15]. Given only one study based on the Habib™ VesOpen catheter, we could not compare the effectiveness and safety between them. In general, RFA is safe and does not improve related complications.

Our meta-analysis has low heterogeneity and included as many studies as possible, confirming that RFA combined with stent implantation had overall survival benefits, except for the extra-hepatic distal cholangiocarcinoma. But our research also has some shortcomings. Firstly, this analysis is mainly composed of observational studies and a lack of high-quality randomized controlled studies. Secondly, we did analyze the clinical effects of different stents such as uncovered SEMS and plastic stents, for covered and partially covered SEMS, we were unable to compare the efficacy of the two because the number of covered and partially covered SEMS was small in the included literature and there was no specific patency time description. More clinical data are needed to discuss the advantages between them in the mid-to-long term patency time. Finally, given the few reports on intrahepatic MBO in the included studies, we were unable to compare the benefits of RFA in such patients, and more clinical data are needed in the future.

## Conclusion

This systematic review and meta-analysis showed that radiofrequency ablation plus stent placement resulted in increased survival and stent patency than stent placement alone, with longer median survival and patency time.

# List Of Abbreviations

MBO: Malignant biliary obstruction

SEMS: Self-expanding metal stents

RFA: Radiofrequency ablation

**RCTs: Randomized Controlled Trials** 

Cls: Confidence Intervals

HR: Hazard Ratio

RCP: Endoscopic Retrograde Cholangiopancreatography

PTC: Percutaneous Transhepatic Cholangiography

USEMS: uncovered self-expanding metallic stents

# **Declarations**

Ethics approval and consent to participate Not applicable.

Consent for publication: Not applicable.

**Availability of data and material:** The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

**Funding:** None. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

**Authors' contributions:** CHY put forward ideas, analyzed data entry, and wrote articles. ZCX performed data analysis and reviews articles. SLM put forward ideas, read and revised the manuscript. All authors have read and approved the manuscript, and ensure that this is the case.

Acknowledgements: Not applicable

# References

- 1. Krokidis M, Hatzidakis A: **Percutaneous Minimally Invasive Treatment of Malignant Biliary Strictures: Current Status**. *Cardiovascular and Interventional Radiology* 2014, **37**(2):316-323.
- 2. Ryan DP, Hong TS, Bardeesy N: **Pancreatic Adenocarcinoma**. *New England Journal of Medicine* 2014, **371**(11):1039-1049.
- 3. Dhir V, Itoi T, Khashab MA, Park DH, Yuen Bun Teoh A, Attam R, Messallam A, Varadarajulu S, Maydeo A: **Multicenter** comparative evaluation of endoscopic placement of expandable metal stents for malignant distal common bile duct obstruction by ERCP or EUS-guided approach. *Gastrointest Endosc* 2015, **81**(4):913-923.
- 4. Cheng Tao Pu LZ, Singh R, Loong CK, Hourneaux de Moura EG: **Malignant Biliary Obstruction: Evidence for Best Practice**. *Gastroenterology Research and Practice* 2016.
- 5. Dumonceau JM, Tringali A, Papanikolaou IS, Blero D, Mangiavillano B, Schmidt A, Vanbiervliet G, Costamagna G, Deviere J, Garcia-Cano J et al: Endoscopic biliary stenting: indications, choice of stents, and results: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline Updated October 2017. Endoscopy 2018, 50(9):910-930.
- 6. Rustagi T, Jamidar PA: Intraductal Radiofrequency Ablation for Management of Malignant Biliary Obstruction. *Digestive Diseases and Sciences* 2014, **59**(11):2635-2641.
- 7. Dolak W, Schreiber F, Schwaighofer H, Gschwantler M, Plieschnegger W, Ziachehabi A, Mayer A, Kramer L, Kopecky A, Schrutka-Kolbl C *et al*: **Endoscopic radiofrequency ablation for malignant biliary obstruction: a nationwide retrospective study of 84 consecutive applications**. *Surg Endosc* 2014, **28**(3):854-860.
- 8. Rustagi T, Irani S, Reddy DN, Abu Dayyeh BK, Baron TH, Gostout CJ, Levy MJ, Martin J, Petersen BT, Ross A *et al*: Radiofrequency ablation for intraductal extension of ampullary neoplasms. *Gastrointestinal Endoscopy* 2017, **86**(1):170-176.
- 9. Sofi AA, Khan MA, Das A, Sachdev M, Khuder S, Nawras A, Lee W: **Radiofrequency ablation combined with biliary stent** placement versus stent placement alone for malignant biliary strictures: a systematic review and meta-analysis. *Gastrointest Endosc* 2018, **87**(4):944-951 e941.
- 10. Teoh AY, Cheung SY, Chong C, Lee KF, Ng EK, Lai PB, Lau JY: Endoscopic Biliary Radiofrequency Ablation for Malignant Distal Common Bile Duct Strictures Does Not Improve Survival. A Randomized Controlled Trial. Gastrointestinal Endoscopy 2018, 87(6):AB104-AB105.
- 11. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D: **The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration**. *BMJ* 2009, **339**:b2700.
- 12. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB *et al*: **Meta-analysis of observational studies in epidemiology A proposal for reporting**. *Jama-Journal of the American Medical Association* 2000, **283**(15):2008-2012.
- 13. Li TF, Huang GH, Li Z, Hao CF, Ren JZ, Duan XH, Zhang K, Chen C, Han XW, Jiao DC *et al*: **Percutaneous transhepatic cholangiography and intraductal radiofrequency ablation combined with biliary stent placement for malignant biliary obstruction**. *J Vasc Interv Radiol* 2015, **26**(5):715-721.
- 14. Kadayifci A, Atar M, Forcione DG, Casey BW, Kelsey PB, Brugge WR: **Radiofrequency ablation for the management of occluded biliary metal stents**. *Endoscopy* 2016, **48**(12):1096-1101.
- 15. Yu T, Zhang W, Li C, Wang C, Gong G, Wang L, Li G, Chen Y, Wang X: **Percutaneous intraductal radiofrequency ablation** combined with biliary stent placement for treatment of malignant biliary obstruction. *Abdom Radiol (NY)* 2020.
- 16. Sampath K, Hyder SM, Gardner T, Gordon SR: **The Effect of Endoscopic Radiofrequency Ablation on Survival in Patients with Unresectable Peri-Hilar Cholangiocarcinoma**. *Gastrointestinal Endoscopy* 2016, **83**(5):AB595.

- 17. Buerlein R, Strand DS, Patrie JT, Sauer BG, Shami VM, Scheiman JM, Zaydfudim VM, Bauer TW, Adams RB, Wang AY: Ercp-Directed Biliary Ablation Prolongs Survival in Patients with Unresectable Perihilar Cholangiocarcinoma Compared to Stenting Alone. *Gastrointestinal Endoscopy* 2019, **89**(6):AB91-AB92.
- 18. Wang J, Zhao L, Zhou C, Gao K, Huang Q, Wei B, Gao J: **Percutaneous Intraductal Radiofrequency Ablation Combined with Biliary Stent Placement for Nonresectable Malignant Biliary Obstruction Improves Stent Patency but not Survival.** *Medicine (Baltimore)* 2016, **95**(15):e3329.
- 19. Yemo M: Percutaneous intraluminal radiofrequency ablation associated with biliary stent placement for malignant biliary obstruction. Guangxi Medical University; 2017.
- 20. Hu B, Gao D-j, Zhang X, Zhang Y-c: **Endobiliary Radiofrequency Ablation Improve Overall Survival of Cholangiocarcinoma: A Multi-Center Randomized Control Study**. *Gastrointestinal Endoscopy* 2016, **83**(5).
- 21. Wu TT, Li WM, Li HC, Ao GK, Zheng F, Lin H: Percutaneous Intraductal Radiofrequency Ablation for Extrahepatic Distal Cholangiocarcinoma: A Method for Prolonging Stent Patency and Achieving Better Functional Status and Quality of Life. Cardiovasc Intervent Radiol 2017, 40(2):260-269.
- 22. Bokemeyer A, Matern P, Bettenworth D, Cordes F, Nowacki TM, Heinzow H, Kabar I, Schmidt H, Ullerich H, Lenze F: Endoscopic Radiofrequency Ablation Prolongs Survival of Patients with Unresectable Hilar Cholangiocellular Carcinoma A Case-Control Study. *Sci Rep* 2019, **9**(1):13685.
- 23. Liang H, Peng Z, Cao L, Qian S, Shao Z: **Metal Stenting with or without Endobiliary Radiofrequency Ablation for Unresectable Extrahepatic Cholangiocarcinoma**. *Journal of Cancer Therapy* 2015, **06**(11):981-992.
- 24. Kallis Y, Phillips N, Steel A, Kaltsidis H, Vlavianos P, Habib N, Westaby D: **Analysis of Endoscopic Radiofrequency Ablation of Biliary Malignant Strictures in Pancreatic Cancer Suggests Potential Survival Benefit.** *Dig Dis Sci* 2015, **60**(11):3449-3455.
- 25. Dutta AK, Basavaraju U, Sales L, Leeds JS: Radiofrequency ablation for management of malignant biliary obstruction: a single-center experience and review of the literature. *Expert Rev Gastroenterol Hepatol* 2017, **11**(8):779-784.
- 26. Yang J, Wang J, Zhou H, Zhou Y, Wang Y, Jin H, Lou Q, Zhang X: **Efficacy and safety of endoscopic radiofrequency ablation for unresectable extrahepatic cholangiocarcinoma: a randomized trial**. *Endoscopy* 2018, **50**(8):751-760.
- 27. Cui W, Li J: PERCUTANEOUS ENDOBILIARY RADIOFREQUENCY ABLATION AND SELF-EXPANDABLE METAL STENT PLACEMENT VERSUS STENT PLACEMENT ALONE FOR MALIGNANT BILIARY OBSTRUCTION. *Gut* 2019, **68**:A129-A130.
- 28. Sampath K, Hyder SM, Gardner T, Gordon SR: **The Effect of Endoscopic Radiofrequency Ablation on Survival in Patients with Unresectable Peri-Hilar Cholangiocarcinoma**. *Gastrointestinal Endoscopy* 2016, **83**(5).
- 29. Kallis Y, Phillips N, Steel A, Kaltsidis H, Vlavianos P, Habib N, Westaby D: **Analysis of Endoscopic Radiofrequency Ablation of Biliary Malignant Strictures in Pancreatic Cancer Suggests Potential Survival Benefit**. *Digestive Diseases and Sciences* 2015, **60**(11):3449-3455.
- 30. Laquiere A, Boustiere C, Leblanc S, Penaranda G, Desilets E, Prat F: **Safety and feasibility of endoscopic biliary** radiofrequency ablation treatment of extrahepatic cholangiocarcinoma. *Surgical Endoscopy and Other Interventional Techniques* 2016, **30**(3):1242-1248.
- 31. Tal AO, Vermehren J, Friedrich-Rust M, Bojunga J, Sarrazin C, Zeuzem S, Trojan J, Albert JG: **Intraductal endoscopic radiofrequency ablation for the treatment of hilar non-resectable malignant bile duct obstruction**. *World journal of gastrointestinal endoscopy* 2014, **6**(1):13-19.
- 32. Rustagi T, Jamidar PA: Intraductal radiofrequency ablation for management of malignant biliary obstruction. *Dig Dis Sci* 2014, **59**(11):2635-2641.
- 33. Slakey DP: Radiofrequency ablation of recurrent cholangiocarcinoma. American Surgeon 2002, 68(4):395-397.
- 34. Curley SA, Izzo F, Ellis LM, Vauthey JN, Vallone P: **Radiofrequency ablation of hepatocellular cancer in 110 patients with cirrhosis**. *Annals of Surgery* 2000, **232**(3):381-389.

- 35. Yevich S, Calandri M, Gravel G, Fresneau B, Brugieres L, Valteau-Couanet D, Branchereau S, Chardot C, Aerts I, de Baere T et al. Reiterative Radiofrequency Ablation in the Management of Pediatric Patients with Hepatoblastoma Metastases to the Lung, Liver, or Bone. Cardiovascular and Interventional Radiology 2019, **42**(1):41-47.
- 36. Sharaiha RZ, Sethi A, Weaver KR, Gonda TA, Shah RJ, Fukami N, Kedia P, Kumta NA, Clavo CMR, Saunders MD *et al*: Impact of Radiofrequency Ablation on Malignant Biliary Strictures: Results of a Collaborative Registry. *Digestive Diseases and Sciences* 2015, **60**(7):2164-2169.
- 37. Itoi T, Isayama H, Sofuni A, Itokawa F, Tamura M, Watanabe Y, Moriyasu F, Kahaleh M, Habib N, Nagao T *et al*: **Evaluation** of effects of a novel endoscopically applied radiofrequency ablation biliary catheter using an ex-vivo pig liver. *Journal of Hepato-Biliary-Pancreatic Sciences* 2012, **19**(5):543-547.
- 38. Steel AW, Postgate AJ, Khorsandi S, Nicholls J, Jiao L, Vlavianos P, Habib N, Westaby D: **Endoscopically applied** radiofrequency ablation appears to be safe in the treatment of malignant biliary obstruction. *Gastrointestinal Endoscopy* 2011, **73**(1):149-153.
- 39. Murakami Y, Uemura K, Hayashidani Y, Sudo T, Ohge H, Sueda T: **Pancreatoduodenectomy for distal cholangiocarcinoma: prognostic impact of lymph node metastasis**. *World journal of surgery* 2007, **31**(2):337-342; discussion 343-334.
- 40. Kiriyama M, Ebata T, Aoba T, Kaneoka Y, Arai T, Shimizu Y, Nagino M: **Prognostic impact of lymph node metastasis in distal cholangiocarcinoma**. *The British journal of surgery* 2015, **102**(4):399-406.
- 41. Almadi MA, Barkun A, Martel M: **Plastic vs. Self-Expandable Metal Stents for Palliation in Malignant Biliary Obstruction: A Series of Meta-Analyses**. *American Journal of Gastroenterology* 2017, **112**(2):260-273.

# **Figures**

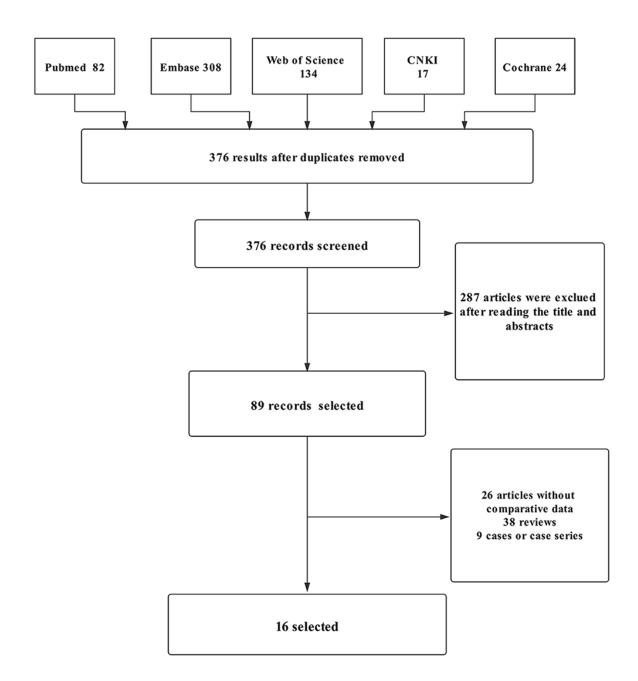
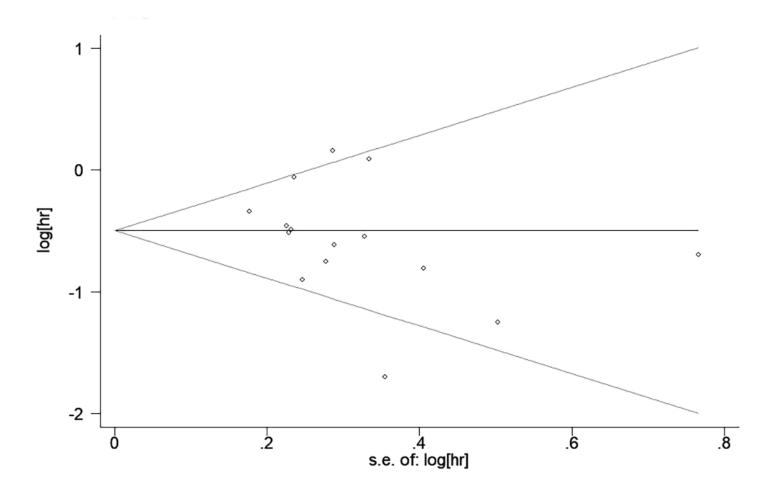


Figure 1

Detailed flow diagram of study selection process.



**Figure 2**Begg' s Funnel plot assessing publication bias.

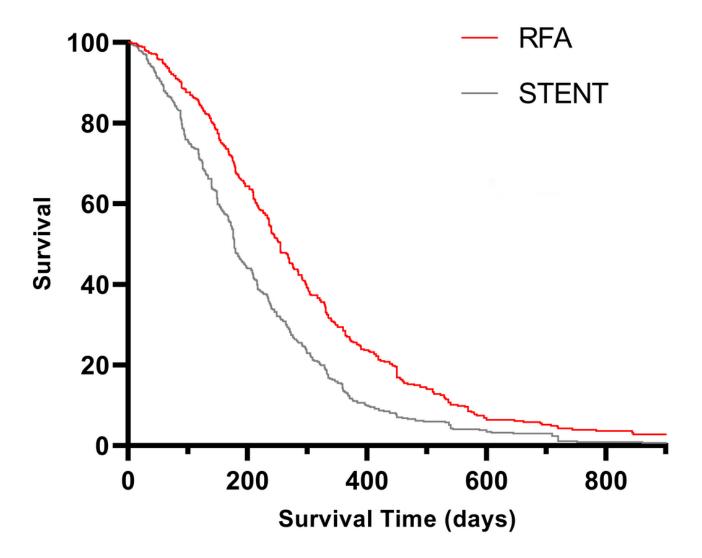


Figure 3

Kaplan-Meier analysis of total survival time between radiofrequency ablation treatment and control groups. Hazard Ratio =1.39, P<.001.

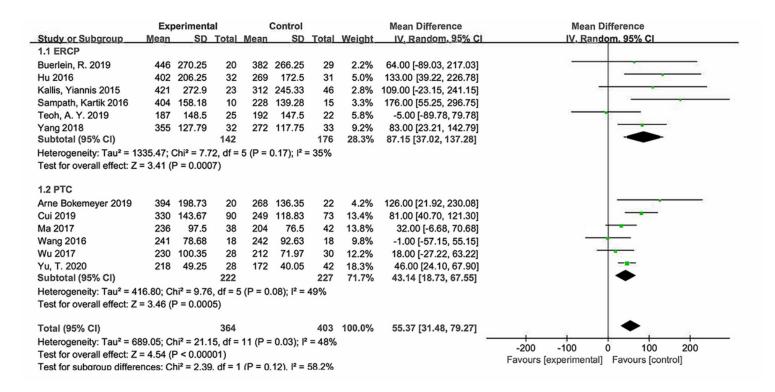


Figure 4

Forest plot to compare survival based on the types of procedures.

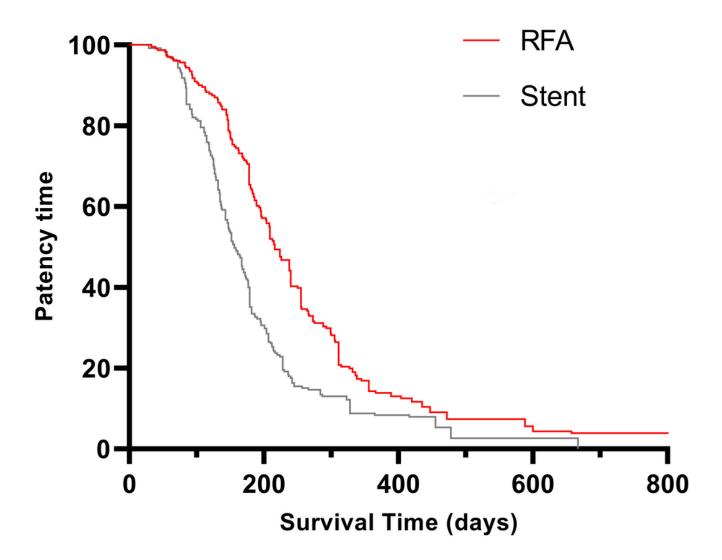


Figure 5

Forest plot to compare survival based on the location of extrahepatic Malignant Biliary Obstruction.

|   | Experimental |           |       | Control |        |       | Mean Difference |                        | Mean Difference    |  |
|---|--------------|-----------|-------|---------|--------|-------|-----------------|------------------------|--------------------|--|
| Study or Subgroup   | Mean         | SD        | Total | Mean    | SD     | Total | Weight          | IV, Random, 95% CI     | IV, Random, 95% CI |  |
| 2.11.1 PTC  |              |           |       |         |        |       |                 |                        |                    |  |
| Cui 2019  | 265          | 103.98    | 90    | 202     | 64.33  | 73    | 16.7%           | 63.00 [36.94, 89.06]   |                    |  |
| Ma 2017   | 203          | 95.04     | 38    | 170     | 77.63  | 42    | 9.6%            | 33.00 [-5.27, 71.27]   | <del></del>        |  |
| Wang 2016   | 194          | 71.4      | 18    | 146     | 46.2   | 18    | 9.2%            | 48.00 [8.71, 87.29]    | <del></del>        |  |
| Wu 2017   | 241          | 197.955   | 35    | 137     | 17.733 | 36    | 3.7%            | 104.00 [38.16, 169.84] |                    |  |
| Yu, T. 2020   | 217          | 60.25     | 28    | 165     | 45.16  | 42    | 16.6%           | 52.00 [25.84, 78.16]   |                    |  |
| Subtotal (95% CI)   |              |           | 209   |         |        | 211   | 55.8%           | 54.81 [39.89, 69.73]   | •                  |  |
| Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 3.93, df = 4 (P = 0.42); l <sup>2</sup> = 0%   |              |           |       |         |        |       |                 |                        |                    |  |
| Test for overall effect:  | Z = 7.20     | (P < 0.00 | 001)  |         |        |       |                 |                        |                    |  |
| 2.11.2 ERCP   |              |           |       |         |        |       |                 |                        |                    |  |
| Hu 2016   | 150          | 31.3      | 32    | 117     | 19.7   | 31    | 32.7%           | 33.00 [20.13, 45.87]   | <del></del>        |  |
| Kadayifci, A. 2016  | 143          | 89        | 25    | 80      | 40     | 25    | 9.6%            | 63.00 [24.75, 101.25]  | <del></del>        |  |
| Kallis, Yiannis 2015  | 449          | 202.16    | 23    | 388     | 151.55 | 46    | 1.9%            | 61.00 [-32.51, 154.51] |                    |  |
| Subtotal (95% CI)   |              |           | 80    |         |        | 102   | 44.2%           | 39.88 [21.51, 58.24]   | •                  |  |
| Heterogeneity: Tau <sup>2</sup> = 71.18; Chi <sup>2</sup> = 2.39, df = 2 (P = 0.30); l <sup>2</sup> = 16% |              |           |       |         |        |       |                 |                        |                    |  |
| Test for overall effect: Z = 4.26 (P < 0.0001)  |              |           |       |         |        |       |                 |                        |                    |  |
| Total (95% CI)  |              |           | 289   |         |        | 313   | 100.0%          | 48.61 [35.36, 61.86]   | •                  |  |
| Heterogeneity: Tau <sup>2</sup> = 96.70; Chi <sup>2</sup> = 9.83, df = 7 (P = 0.20); l <sup>2</sup> = 29% |              |           |       |         |        |       |                 |                        |                    |  |
| Test for overall effect: Z = 7.19 (P < 0.00001)   |              |           |       |         |        |       |                 |                        |                    |  |
| Test for subgroup differences: Chi <sup>2</sup> = 1.53, df = 1 (P = 0.22), l <sup>2</sup> = 34.6%         |              |           |       |         |        |       |                 |                        |                    |  |

# Figure 6

Kaplan-Meier analysis of total patency time between radiofrequency ablation treatment and control groups. Hazard Ratio =1.629, P<.001.

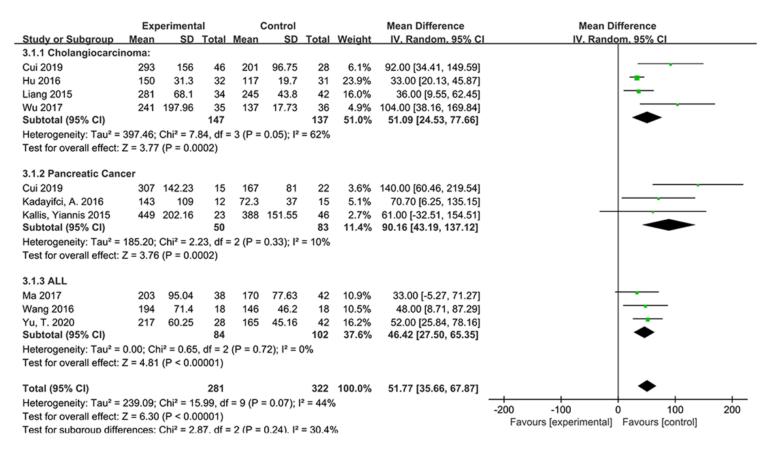
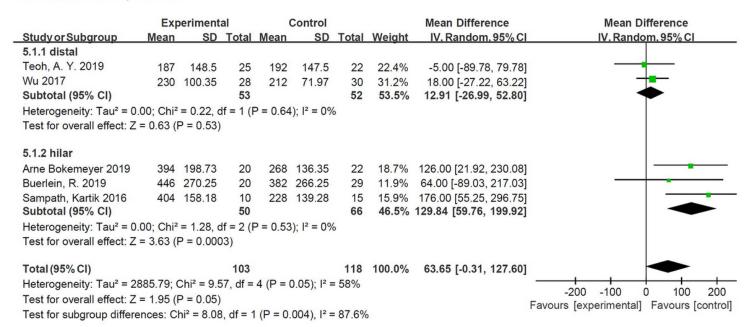


Figure 7

Forest plot to compare stent patency based on the types of procedures.

5 survival time

### 5.1 location of extrahepatic MBO



### Figure 8

Forest plot to compare stent patency based on the different tumors.

# **Supplementary Files**

This is a list of supplementary files associated with this preprint. Click to download.

- PRISMA2009checklist.pdf
- searchstrategy.pdf