Interventional procedure overview of endoscopic bipolar radiofrequency ablation for malignant biliary obstruction

Contents

Table 1 Abbreviations

Abbreviation	Definition
CCA	Cholangiocarcinoma
CI	Confidence interval
CBD	Common bile duct
ECOG	Eastern cooperative oncology group
ERCP	Endoscopic retrograde cholangiopancreatography
ERFA	Endoscopic radiofrequency ablation
HR	Hazard ratio
IHD	Intrahepatic duct
ITT	Intention-to-treat
IQR	Interquartile range
KPS	Karnofsky performance status
MBO	Malignant biliary obstruction
MBS	Malignant biliary stricture
MHBO	Malignant hilar biliary obstruction
NRS	Numeral rating scale
OS	Overall survival
PTC	Percutaneous transhepatic cholangiogram
PSM	Propensity score matching
RCT	Randomised controlled trial
RFA	Radiofrequency ablation
SD	Standard deviation
SEMS	Self-expanding metal stent
VAS	Visual analogue scale

Indications and current treatment

Biliary obstruction caused by cancers such as CCA or pancreatic adenocarcinoma can lead to symptoms such as jaundice, nausea, bloating and abdominal pain. Surgical resection is often not possible.

Treatment of unresectable CCA or pancreatic cancer includes biliary stenting during ERCP, chemotherapy, radiation therapy, chemoradiation therapy, immunotherapy and photodynamic therapy. Stents often need to be replaced because of blockage by tumour ingrowth.

Unmet need

Biliary obstruction caused by unresectable CCA or pancreatic cancer can be managed with biliary stenting during ERCP. Stent replacement is often needed because of obstruction caused by tumour ingrowth. But repeated intervention exposes people to further procedure-related risks. There is a need for active control of tumour growth to prolong survival and stent patency. Some interventions that have been used include photodynamic therapy and intraductal radiotherapy. But there are drawbacks to these treatments. Also, they are usually delivered in multiple sessions. RFA is an effective local ablative therapy that has been used extensively in many cancers, such as CCA or pancreatic cancer. So, endoscopic bipolar RFA might provide an option for treating a stricture caused by cancer.

What the procedure involves

Endoscopic bipolar RFA uses heat energy to ablate malignant tissue that is obstructing the bile or pancreatic ducts. This procedure is usually done before inserting stents (primary RFA), but can also be done to clear obstructed stents (secondary RFA). The aim is to prolong stent patency, so reducing symptoms and improving survival.

The procedure is usually done under sedation. ERCP with fluoroscopic guidance is used to establish the length, diameter and position of the biliary stricture. Under endoscopic visualisation, a bipolar endoscopic RFA catheter is deployed over a guide wire across the stricture. Controlled pulses of radiofrequency energy are applied to ablate the obstructing tumour tissue to allow stent insertion or to clear the lumen of a previously placed stent. Sequential applications are usually applied throughout the length of the stricture to achieve recanalisation. The treatment can be repeated.

Outcome measures

The main outcomes included clinical success, stent patency, OS, quality of life and adverse events. Some of the measures used are detailed in the following paragraphs.

Clinical success, representing the symptomatic control, was defined as a decrease in total bilirubin level by less than 25% of the initial value, to the upper normal limit (Kang 2021a), or to less than 34.2 micromol/l, without moderate or severe post-procedural cholangitis and necessity for additional endoscopic or percutaneous interventions (Xia 2021).

Stent patency was defined as normal laboratory findings and without evidence of cholestasis in diagnostic imaging or non-occluded stent without intervention. Its duration was the time from the index procedure to stent occlusion needing revision of biliary drainage, or death. If the index procedure was done bilaterally with 2 stents at the same time, at least 1 stent occlusion was considered as event for calculating stent patency.

OS was defined from enrolment or the first RFA, to death or the end of the study.

Quality of life was not measured using a conventional tool but instead using KPS; the lower the Karnofsky score, the worse the likelihood of survival. KPS is

designed to measure physical functional performance from a clinician perspective rather than quality of life from a person's perspective.

Evidence summary

Population and studies description

This interventional procedure overview is based on 1,593 people from 5 RCTs (including a pilot RCT), 1 non-randomised comparative study and 1 systematic review and meta-analysis. Of these 1,593 people, 440 people had the RFA procedure after removing duplications. This is a rapid review of the literature, and a flow chart of the complete selection process is shown in figure 1. This overview presents 7 studies as the key evidence in table 2 and table 3, 1 Health Technology Assessment in the existing assessment, and lists other relevant studies in table 5.

Of the 6 primary studies, 3 studies were done in China, 2 in Korea and 1 in Germany. The follow-up duration ranged from 4 months to 32 months in 5 RCTs, and the longest duration was around 7 years in 1 observational study.

Primary RFA was done in 5 studies (Gao 2021; Albers 2022; Kang 2021a, 2021b; Yang 2018), and both primary and secondary RFAs were carried out in 1 study (Xia 2021). For the systematic review and meta-analysis (Cha 2021), 7 studies involved ERCP-directed RFA and 1 study (n=36) reported percutaneous RFA. Of the 7 studies, 6 studies were for primary RFA and only 1 study (Dutta 2017) reported both primary and secondary RFAs.

In terms of stent types, plastic stents were initially used in 3 RCTs (Gao 2021; Kang 2021b; Yang 2018), SEMS in 2 RCTs (Albers 2022; Kang 2021a), and both plastic and metal stents in 1 observational study (Xia 2021). It is worth noting that Kang (2021b) changed the plastic stents to uncovered SEMS at 3 months after the index procedure or in case of premature plastic stent malfunction. For the

systematic review and meta-analysis (Cha 2021), plastic stents were used in 2 studies and SEMS in 6 studies.

Across all the studies, biliary strictures or obstructions were caused by cancer that was surgically unresectable or unsuitable for surgery. The most common cancer was CCA (mostly hilar and distal CCA), followed by pancreatic cancer, gallbladder cancer and others. In all but 1 primary study (Yang 2018), other anti-tumour treatments (such as chemotherapy) were allowed concomitantly or after the index procedure. Chemotherapy was identified as a key confounding factor for OS.

As part of this review, a meta-analysis was done, combining the results from the 6 primary studies which contained relevant and valid data using the same outcome measures. Data analysis and all pooled results including forest plots are available in the appendix.

Table 2 presents study details.

Figure 1 Flow chart of study selection

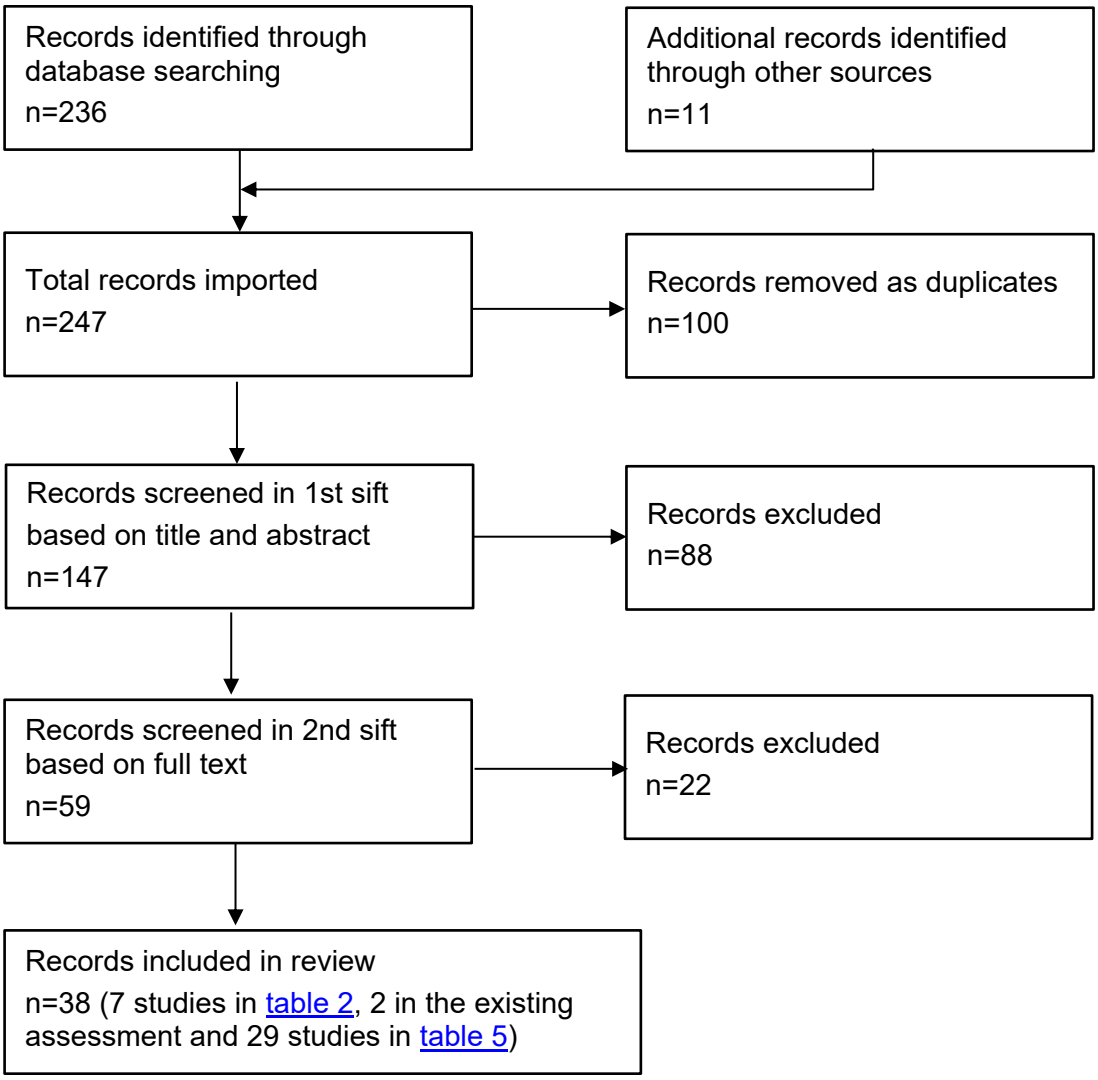

Table 2 Study details

No.	First author, date country	Population characteristics	Study design	Inclusion criteria	Intervention	Follow up
1	Gao (2021) China (3 centres)	174 (men, n=89; women, n=85) •RFA plus plastic stent: n=87 (mean 68 years) •Plastic stent only: n=87 (mean 67.9 years)	RCT (open-label; NCT01844245)	Age 18 years or over, obstructive jaundice caused by pathology-confirmed extrahepatic CCA or ampullary cancer which was unsuitable for surgery.	•ERCP-directed RFA (2-session RFA therapy using; Habib EndoHPB catheter and ESG-100 generator) plus plastic stent •Plastic stent only	Median 31.8 months
2	Albers (2022) Germany (5 centres)	86 (women, n=47; men, n=39; mean 71.6 years) •RFA plus SEMS: n=42 (mean 70.9 years) •SEMS only: n=44 (mean 72.3 years)	RCT (DRKS00018993)	Age over 18 years, obstructive jaundice caused by unresectable malignancy, and malignant tumour causing consequential biliary stenosis with the need for biliary drainage.	•ERCP-directed RFA (Habib EndoHBP RFA catheter and VIO 200D generator) plus SEMS (single stent, n=38; more than 1 stent, n=4) •SEMS only (single stent, n=38; more than 1 stent, n=6)	6 months
3	Kang (2021a) Korea (single centre)	48 (male, n=30; female, n=18) •RFA plus SEMS: n=24 (median 73 years) •SEMS only: n=24 (median 67 years)	RCT (open-label; NCT02646514)	Age over 19 years, malignancy that was surgically unresectable or medically unfit for surgery, MBS, and life expectancy more than 3 months.	•RFA (ELRA™ catheter and VIVA Combo™ generator) and uncovered SEMS placement. •Uncovered SEMS only. Percutaneous RFA was done in 4 people of each group.	•Median 135.0 days •Median 119.5 days
4	Kang (2021b)	30 (male, n=20; female, n=10) •Intraductal RFA plus plastic stent: n=15 (mean 76 years)	Pilot RCT (open-label;	Age over 19 years, a confirmed MHBO because of CCA or gallbladder cancer which was unresectable or	•RFA (ELRA™ catheter and VIVA Combo™ generator) and plastic stent insertion.	12 months •Median 178 days

No.	First author, date country	Population characteristics	Study design	Inclusion criteria	Intervention	Follow up
	South Korea (3 centres)	•Plastic stent only: n=15 (mean 72 years)	KCT0003275)	medically inoperable, life expectancy more than 3 months, and ECOG performance status 0 (fully active) to 1 (restricted in strenuous activity)	•Plastic stent only: bilateral placement. For both groups, plastic stent was changed to uncovered SEMS after 3 months or in case of premature plastic stent malfunction.	•Median 134 days
5	Yang (2018) China (single centre)	65 (male, n=33; female, n=32) •RFA plus plastic stent: n=32 (mean 62 years) •Plastic stent only: n=33 (mean 64.5 years)	RCT (NCT02592538)	Age 18 to 75 years, pathology-confirmed extrahepatic CCA, initial treatment, and KPS of 50 points or higher	•ERCP- guided RFA (Habib EndoHPB catheter and RITA 1500X generator) plus plastic stents (mean 4.7 ERCPs per person) •Plastic stent only (mean 3.8 ERCPs per person) For both groups, stent replaced every 3 months or upon recurrent jaundice or cholangitis symptoms.	21 months
6	Xia (2021) China (2 centres)	883 (male, n=537; female, n=346; mean 65.3 years) •RFA plus stent: n=124 •Stent only: n=759 ([496 in the matched cohort)	Non-randomised comparative study (retrospective)	People with inoperable extrahepatic MBS who had ERCP therapies	•ERCP-guided RFA (Habib catheter and ERBE VIO200D generator) plus stent (plastic or metal stents) •Stent only (plastic or metal)	7 years
7	Cha (2021)	420 (3 RCTs and 5 retrospective observational studies) •RFA plus stent: n=190	Systematic review and	People with unresectable extrahepatic CCA or MBO; studies comparing treatment	ERCP-guided RFA in 7 studies and percutaneous RFA in 1 observational study (n=18);	Not reported

No.	First author, date country	Population characteristics	Study design	Inclusion criteria	Intervention	Follow up
		• Stent only: n=230 Age, not reported	meta-analysis	outcomes between endobiliary RFA with stent and stent only; RCTs and case-control studies with adjustment for confounding variables; and studies reporting the relative risks or odds ratios of survival rate and stent patency duration for both treatments.	plastic stents used in 2 RCTs and SEMS in 1 RCT and 5 observational studies.	

The risk of bias (RoB) was assessed using the Cochrane RoB Tool for RCTs, ROBINS-I (RoB in Nonrandomized Studies [NRSs] of Interventions) for NRSs, and ROBIS for systematic reviews. The RoB for RCTs was graded as “low” for low risk, “high” for high risk, and “some concerns”. For NRSs, each domain of the RoB was rated as “low”, “moderate”, “serious”, or “critical” for RoB. For systematic review, each domain of the RoB was judged as ‘‘low,’’ ‘‘high,’’ or ‘‘some concerns.’’. The overall RoB was determined according to the judgment for each domain.

Among the RCTs, 3 studies (Gao 2021; Albers 2022; Yang 2018) were rated as low for all RoB domains, whereas for the other 2 studies (Kang 2021a, 2021b), concerns were raised for 1 domain (deviation from intended intervention as PTC was also allowed [4 people in Kang 2021a and 3 people in Kang 2021b] and no subgroup analysis of people with ERCP-guided RFA only) and they were rated as low for all other domains. So, the overall risk of bias was judged as low for 3 studies (Gao 2021; Albers 2022; Yang 2018) and some concerns for 2 studies (Kang 2021a, 2021b).

For the retrospective, observational study (Xia 2021), it was rated as low for 4 domains (classification of intervention, deviation from intended intervention, missing data and measurement of outcomes) and as moderate for 3 domains (selection bias, (unmeasured) confounding, and reporting). So, the overall risk of bias was judged as moderate.

In terms of the systematic review and meta-analysis (Cha 2021), based on ROBIS, there were some concerns regarding the synthesis (outcomes for ERCP-guided RFA not reported separately and no sensitivity or subgroup analysis), but the levels of concerns for all other domains were judged as low.

Table 3 Study outcomes

First author, date	Efficacy outcomes	Safety outcomes
Gao (2021)	Total sample, n=174 (RFA plus plastic stent, n=87; plastic stent only, n=87) Mortality due to tumour progression during follow up: RFA plus plastic stent, n=67; plastic stent only, n=81, p=0.940 OS: RFA plus plastic stent versus plastic stent only •Median cumulative survival (Kaplan-Meier analysis): 14.3 months (95% CI, 11.9 to 16.7) versus 9.2 months (95% CI, 7.1 to 11.2); HR, 0.488; 95% CI 0.351 to 0.678; p<0.001. •Median OS for people with CCA: 13.3 months (95% CI, 10.2 to 16.3) versus 9.2 months (95% CI 7.2 to 11.1); HR, 0.546; 95% CI, 0.386 to 0.771; p<0.001 •Statistically significant differences in OS were noted in all subgroups, including hilar CCA (HR, 0.414; 95% CI, 0.025 to 0.762; p=0.004), distal CCA (HR, 0.642; 95% CI, 0.421 to 0.981; p=0.038), and ampullary cancer (HR, 0.301; 95% CI, 0.100 to 0.900; p=0.032) RFA treatment (HR, 0.498; 95% CI, 0.352 to 0.703; p<0.001) was an independent predictor of increased OS. Within the RFA group, ampullary cancer (HR, 0.274; 95% CI, 0.092 to 0.817; p=0.020; compared with hilar CCA) was a statistically significant predictor of increased survival, whereas total bilirubin (HR, 1.804; 95% CI, 1.010 to 3.223; p=0.046) was the predictor of decreased survival after RFA. Clinical success for jaundice control: 92.0% (80/87) versus 90.8% (79/87), p>0.99 Stent occlusions before the second scheduled ERCP (mean 90 days after the first procedure): 22% (19/87) versus 18% (16/87), p=0.570	Early adverse events (less than 30 days) - RAF plus plastic stent versus plastic stent only: 27.6% (n=4) versus 19.5% (n=17), p=0.211 •Post-ERCP pancreatitis (mild): 4.6% (n=4) versus 5.7% (n=5), p>0.99 •Bleeding: 1.1% (n=1) versus 3.4% (n=3), p=0.621 •Acute cholangitis: 11.5% (n=10) versus 10.3% (n=9), p=0.808 •Acute cholecystitis, 10.3% (n=9) versus 0; p=0.003; 7 of the 9 people had hilar CCA, 1 had ampullary cancer, and 1 had distal CCA coexisting with gallstones. •Perforation: 0 in both groups Late adverse events: 39.1% (n=34) versus 36.8% (n=32); p>0.99 •Delayed cholangitis (treated with systemic antibiotics): 37.9% (n=33) versus 36.8% (n=32), p=0.875 •Liver abscess: 1.1% (n=1) versus 0, p=0.755 No severe procedure-related adverse events or procedure-related mortality were noted.

First author, date	Efficacy outcomes	Safety outcomes
	After the second procedure the cumulative stent patency duration: 3.7 months (95% CI, 2.8 to 4.5) versus 4.1 months (95% CI, 3.7 to 4.5), p=0.674; HR, 1.069; 95% CI, 0.782 to 0.460 KPS scores: the median KPS scores at baseline were both 80 in the 2 group. After the procedure, KPS scores were statistically significantly higher in the RFA plus plastic stent group than in the plastic stent only group at 1, 3, 6 and 9 months (all p<0.05).	
Albers (2022)	Total sample: n=86 (RFA plus SEMS, n=42; SEMS only, n=44) Technical success of the RFA procedure (defined by passing the malignant stenosis with a guidewire, subsequently with the RFA electrode, and applying the total ablation energy): 100% Technical success for SEMS insertion in the correct position: 98.8% (85/86) Patency rate (RFA plus SEMS versus SEMS only): •After 3 months: 73.1% versus 81.8%; p=1.0 •After 6 months: 33.3% versus 52.4%, p=0.6 The addition of RFA did not impact OS (HR, 0.72; p=0.389 for RFA plus SEMS). The patency rate in the subgroup with extrahepatic strictures indicated no statistically significant difference after 3 and 6 months between groups (SEMS only [n=37], 77.2% and 53.3%, respectively [p=0.51]; RFA plus SEMS [n=37], 75% and 36.4%, respectively [p=0.45]). Accordingly, patency rates in the subgroup with pancreatic cancer showed no statistical difference after 3 and 6 months (SEMS only [n=18], 87.5% and 40%, respectively [p=0.25]; RFA plus SEMS [n=16], 65% and 25%, respectively, [p=0.11]) Overall mortality after 3 and 6 months: •RFA plus SEMS: 24.3% and 41.9%, p=0.56	Adverse events within the first 30 days after the intervention (RFA plus SEMS versus SEMS alone): 4 (10.5%) versus 1 (2.3%), p=0.18 •Minor events: ○ Bleeding: 1 (2.6%) versus 1 (2.3%) ○ Pancreatitis: 1 (2.6%) versus 0 ○ Cholangitis: 1 (2.6%) versus 0 •Major event: ○ Cholecystitis with gallbladder perforation: 1 (2.6%) versus 0

First author, date	Efficacy outcomes	Safety outcomes
	•SEMS only: 26.8% and 50%, p=0.99 Similar results were found in the cohort with extrahepatic strictures (SEMS only [n=37], 22.6% and 53.3%, respectively [p=0.77]; RFA plus SEMS [n=37], 23.5% and 39.3%, respectively [p=0.38]) and in the pancreatic cancer subgroup (SEMS only [n=18], 37.9% and 62.1%, respectively [p=0.23]; RFA plus SEMS [n=16], 20% and 38.9%, respectively [p=0.48]) Subgroup analysis of 74 people with extrahepatic versus 12 with intrahepatic strictures and of 54 people with pancreatic cancer versus 32 with other entities: no statistically significant difference in the patency rate and overall mortality after 3 and 6 months.	
Kang (2021a)	Total sample, n=48 (RFA plus SEMS, n=24; SEMS only, n=24) Comparison of outcomes: RFA plus SEMS versus SEMS only •Technical success: 100% versus 100%, p=1.000 •Clinical success: 87.5% (n=21) versus 83.3% (n=20), p=1.000 •90-day stent patency: 58.3% (n=14) versus 45.8% (n=11), p=0.386 •Duration of stent patency (median): 132.0 days (95% CI, 99.6 to 164.4) versus 116.0 days (95% CI, 52.4 to 179.6), p=0.440 •OS (median): 244.0 days (95% CI, 117.8 to 370.0) versus 180.0 days (95% CI, 27.8 to 332.2), p=0.281 Subgroup analysis of people with MBS at the CBD only: RFA plus SEMS versus SEMS only •90-day stent patency: 70.6% (12/17) versus 42.9% (9/27), p=0.087 •The median duration of stent patency and the median OS were not statistically significantly different in this subgroup analysis (exact data not reported).	Comparison of complications within 30 days: RFA plus SEMS versus SEMS only •Early complications within 7 days: 1 (4.2%) versus 3 (12.5%), p=0.609 •Pancreatitis (all mild): 0 versus 3 (12.5%), p=0.234 •Cholangitis: 1 (4.2%) versus 0, p=1.000 A cholangitis resulting in septic shock and death was reported as unlikely related severe adverse event. •Postprocedure pain (24 hours), VAS: median 6.0 (IQR 2.0 to 6.0) versus 6.0 (IQR 3.3 to 7.0), p=0.163 •Postprocedure pain (24 hours), VAS 7 or more: 3 (12.5%) versus 8 (33.3%), p=0.086 All procedure-related complications were managed conservatively, and the people recovered uneventfully, except the death mentioned above.

First author, date	Efficacy outcomes	Safety outcomes
	Analysis with stratification of people according to the primary site of malignancy did not find any statistically significant differences in outcomes.	No perforation, bleeding and late complications (more than 7 days) in both groups.
Kang (2021b)	Total sample, n=30 (RFA plus plastic stent, n=15; plastic stent only, n=15; per-protocol analysis, n=22 [12 versus 10]) Total event-free stent patency: •ITT analysis: 178 days (95% CI, 96.2 to 259.8) versus 122 days (95% CI, 111.2 to 132.8), p=0.154 •Per-protocol analysis: 175 days (95% CI, 144.4 to 205.6) versus 122 days (95% CI, 111.2 to 132.8), p=0.623 OS: •ITT analysis: 230 days (95% CI, 77.0 to 383.0) versus 144 days (95% CI, 0 to 323.1), p=0.643 •Per-protocol analysis: 178 days (95% CI, 84.6 to 271.4) versus 144 days (95% CI, 0 to 292.2), p=0.593 Technical success: 100% (n=15) versus 93.3% (n=14), p>0.999 Clinical success: 100% (n=15) versus 86.7% (n=13), p=0.483 Among 13 people of each group who had the sequential procedure, more people had scheduled stent exchange after 3 months without PS occlusion in the RFA plus plastic stent group than in the plastic stent only group (69.2% vs 23.1%, p=0.018, power=81.49%). Subgroup analysis – total event-free stent patency: •people with strictures lengths of 11 mm or more on both side IHDs (13 people in each group): 175 days (95% CI, 146.1 to 203.9) versus 121 days (95% CI, 104.5 to 137.5), p=0.028	Early adverse events (within 30 days) (RFA plus plastic stent versus plastic stent alone) •Cholangitis: 3 (20%) versus 5 (33.3%) •Cholecystitis: 1 (6.7%) versus 1 (6.7%) •Fever: 2 (13.3%) versus 3 (20.0%) •Abdominal pain, NRS: 3 (0 to 4) versus 0 (0 to 5) All p>0.05 Pancreatitis, liver abscess and death (because of sudden myocardial infarction, so it was unrelated to the procedure) were reported in the stent alone group only, but no statistically significant difference was found. Late adverse events (more than 30 days) (RFA plus stent versus stent alone) •Cholangitis: 5 (33.3%) versus 5 (33.3%) •Cholecystitis: 1 (6.7%) versus 0 •Liver abscess: 0 versus 2 (13.3%) All p>0.05 All reported adverse events were mild to moderate except for 3 cases of severe late cholangitis related to stent occlusion in the stent only group. All adverse

First author, date	Efficacy outcomes	Safety outcomes
	•no statistically significant difference was found in people with different types of bismuth, in people with hilar CCA only, in people with mass-forming type CCA. No survival difference was shown in any subgroup analyses.	events were medically manageable and procedure-related death was not reported.
Yang (2018)	Total sample: n=65 (RFA plus plastic stent, n=32; plastic stent only, n=33) OS: RFA plus plastic stent versus plastic stent only •6-month survival rate: 96.9% versus 81.8%, p=0.08 •9-month survival rate: 87.5% versus 24.2%, p<0.05 •12-month survival rate: 62.5% versus 12.1%, p<0.05 •15-month survival rate: 28.1% versus 3.0%, p<0.05 •Overall mean survival time: 13.2 months (SD 0.6, 95% CI 11.8 to 14.2) versus 8.3 months (SD 0.5, 95% CI 7.3 to 9.3), p<0.001 •Multivariable Cox regression analysis showed that RFA was the main protective factor affecting survival (HR 0.182; 95% CI, 0.08 to 0.322; p<0.001) •All people died by July 2017. The total follow-up duration of the study was 21 months. Stent patency: 6.8 months (95% CI, 3.6 to 8.2) versus 3.4 months (95% CI, 2.4 to 6.5), p=0.02 No statistically significantly difference in the stent length between groups (8.3 cm versus 9.3 cm, p>0.05) KPA scores: RFA plus plastic stent versus plastic stent only •Preoperation: 82.9 (SD 9.3) versus 79.9 (SD 7.8), p=0.28 •1-month postoperation: 86.1 (SD 6.8) versus 72.4 (SD 8.2), p=0.02 •3-month postoperation: 71.4 (SD 7.1) versus 60.3 (SD 5.4), p=0.04	Postoperative adverse events: •RFA plus plastic stent: 6.3% (2/32) •Plastic stent only: 9.1% (3/33) •p=0.67 RFA plus plastic stent group: •Acute cholangitis: 6.3% (2/32), both people improved after nasobiliary drainage through the bile duct and intravenous antibiotic therapy. Plastic stent only group: •Acute cholangitis: 3.0% (1/33) •Acute pancreatitis: 3.0% (1/33) •Haemorrhage of the incision margin of the papilla: 3.0% (1/33) All people were successfully managed endoscopically. No serious adverse events were found.

First author, date	Efficacy outcomes	Safety outcomes
	•6-month postoperation: 61.4 (SD 7.1) versus 48.2 (SD 6.2), p=0.03 •9-month postoperation: 58.2 (SD 11.5) versus 22.5 (SD 8.9), p<0.001 Serum bilirubin (micromol/l): RFA plus plastic stent versus plastic stent only •Total bilirubin at baseline: 266.8 (SD 88.5) versus 245.9 (SD 76.2), p=0.23 •Total bilirubin at 3 months: 39.2 (SD 6.3) versus 46.9 (SD 8.9), p=0.68 •Direct bilirubin at baseline: 188.5 (SD 48.6) versus 169.5 (SD 58.4), p=0.43 •Direct bilirubin at 3 months: 19.3 (SD 5.9) versus 22.6 (SD 7.8), p=0.58	
Xia (2021)	Total sample: n=883 (RFA plus stent [plastic or metal stent], n=124; stent [plastic or metal stent] only, n=759; following PSM, 124 in RFA plus stent and 496 in stent only) Clinical success: RFA plus stent versus stent only •Unmatched: 92.7% (115/124) versus 85.2% (647/759), p=0.024, 95% CI (difference), 0.022 to 0.128 •Matched: 92.7% (115/124) versus 88.7% (440/496), p=0.190, 95% CI (difference), -0.014 to 0.094 Time to recurrent biliary obstruction (median, IQR): RFA plus stent versus stent only •Unmatched: 7.2 months (IQR 5.4 to 11.3) versus 6.0 months (IQR 3.6 to 9.7), p=0.016, 95% CI (difference), -3.636 to -0.576 •Matched: 7.2 months (IQR 5.4 to 11.3) versus 6.4 months (IQR 3.8 to 10.2), p=0.121, 95% CI (difference), -3.203 to 0.130 Total number of intervention (mean): •Unmatched: 1.6 (SD 0.9) versus 1.5 (SD 0.9), p=0.391, 95% CI (difference), -0.097 to 0.247	Adverse events: RFA plus stent versus stent only •Unmatched: 18.5% (23/124) versus 19.5% (148/759), p=0.804, 95% CI (difference) -0.085 to 0.066 •Matched: 18.5% (23/124) versus 15.9% (79/496), p=0.481, 95% CI (difference) -0.047 to 0.099 Post-ERCP pancreatitis: RFA plus stent versus stent only •Unmatched: 8.9% (11/124) versus 5.1% (39/759), p=0.095, 95% CI (difference) -0.016 to 0.090 •Matched: 8.9% (11/124) versus 5.4% (27/496), p=0.155, 95% CI (difference) -0.020 to 0.089 Cholangitis: RFA plus stent versus stent only •Unmatched: 6.5% (8/124) versus 14.2% (108/759), p=0.017, 95% CI (difference) -0.128 to -0.028 •Matched: 6.5% (8/124) versus 10.3% (51/496), p=0.194, 95% CI (difference) -0.090 to 0.013 Cholecystitis: RFA plus stent versus stent only

First author, date	Efficacy outcomes	Safety outcomes
	•Matched: 1.6 (SD 0.9) versus 1.5 (SD 0.9), p=0.163, 95% CI (difference), -0.050 to 0.296 OS (median): RFA plus stent versus stent only •Unmatched: 9.5 months (95% CI, 7.7 to 11.3) versus 5.5 months (95% CI, 5.0 to 5.9), p<0.001, 95% CI (difference), 1.600 to 3.400 •Matched: 9.5 months (95% CI 7.7 to 11.3) versus 6.1 months (95% CI 5.6 to 6.6), p<0.001, 95% CI (difference), 1.288 to 4.936 By the final follow up, 789 (89.4%) people died of disease progression. In multivariable Cox proportional hazard models, RFA plus stent (HR 0.552, 95% CI 0.438 to 0.697, p<0.001), TNM stage IV (HR 1.2073, 95% CI 1.026 to 1.420, p=0.023), re-procedural total bilirubin level more than 200microμmol/l (HR 1.265, 95% CI 1.085 to 1.474, p=0.003), other antitumour therapy (HR 0.908, 95% CI 0.866 to 0.951, p<0.001), and use of metal stent (HR 0.751, 95% CI 0.640 to 0.880, p<0.001) were found to be independent predictors of OS. In stratified analyses, the improved OS was only demonstrated in the subgroup of extrahepatic CCA (n=463 [RFA plus stent in 79 people and stent alone in 384 people], 11.3 months [95% CI, 10.2 to 12.4] versus 6.9 months [95% CI, 6.0 to 7.8], p<0.001), but not in the subgroups of gallbladder cancer, hepatocellular carcinoma, intrahepatic CCA, pancreatic cancer and other metastatic cancers (all p>0.05). The survival benefits were noted only in the people with non-metastatic CCA (11.5 versus 7.4 months, p<0.001).	•Unmatched: 4.8% (6/124) versus 0.1% (1/759), p<0.001, 95% CI (difference) 0.009 to 0.086 •Matched: 4.8% (6/124) versus 0.2% (1/496), p<0.001, 95% CI (difference) 0.008 to 0.085 More acute cholecystitis occurrences in the RFA plus stent group, which might be related to cystic duct injury caused by RFA. All people were cured by enhanced antibiotic therapy or percutaneous gallbladder drainage. Bleeding: RFA plus stent versus stent only •Unmatched: 1.6% (2/124) versus 1.2% (9/759), p=0.691, 95% CI (difference) -0.017 to 0.025 •Matched: 1.6% (2/124) versus 1.2% (6/496), p=0.722, 95% CI (difference) -0.018 to 0.026 Perforation: RFA plus stent versus stent only •Unmatched: 0.8% (1/124) versus 0% (0/759), p=0.140, 95% CI (difference) -0.008 to 0.024 •Matched: 0.8% (1/124) versus 0% (0/496), p=0.200, 95% CI (difference) -0.008 to 0.024 One person in the RFA plus stent group developed minor duodenal perforation induced by a plastic stent and was successfully closed using endoscopic clipping. No RFA-related bleeding, perforation, or mortality occurred.

First author, date	Efficacy outcomes	Safety outcomes
Cha (2021)	420 (3 RCTs and 5 retrospective observational studies; RFA plus stent, n=190; stent only, n=230) Comparative outcomes - RFA plus stent versus stent only: •Pooled HR for OS: 0.47; 95% CI, 0.34 to 0.64; I^2=44% (8 studies) •Pooled HR for stent patency: 0.79; 95% CI, 0.57 to 1.09; I^2=7% (2 RCTs and 2 observational studies) No significant publication bias was noted in the funnel plot for overall survival (Egger's test p=0.2869).	Adverse events: •Abdominal pain: n=3 •Pancreatitis and hyperamylasaemia: n=3 •Cholangitis regardless of symptoms, n=34 •Cholecystitis: n=8 All these complications were treated with antibiotics and conservative therapy, and no procedure-related mortality was reported. One case of intestinal perforation with pneumothorax occurred in 1 study; but the authors commented that it was not related to the RFA procedure but rather to the scope device. No study showed statistically significant differences in terms of adverse events between the RFA plus stent group and the stent only group.

Procedure technique

All 6 primary studies detailed the procedure technique and devices used. The most common catheter used was Habib EndoHPB, followed by ELRA catheter. Four RFA generators were used.

This procedure was done under sedation or monitored anaesthesia. Biliary dilation could be done at the endoscopist's discretion. RFA was usually done with a power of 7 to 10 w for 90 sections with a subsequent cooling period of 60 seconds to reduce adverse events. The ablation was done in a stepwise manner, covering the stricture from the proximal to the distal edge. More than 1 ablation could be done in a single session. After RFA, plastic or metal stents were inserted. Repeated RFA sessions could be done (Gao 2021; Kang 2021b; Yang 2018; Xia 2021).

Efficacy

The meta-analysis of the 6 primary studies was done, and the pooled results of stent patency and OS can be found in the appendix.

Clinical success

Clinical success was reported in 4 studies, with its rate ranging from 88% to 100%. When comparing RFA plus stent with stent only, no statistically significant difference was found in general.

Gao (2021) did not find any statistically significant difference in clinical success for jaundice control between the RFA plus plastic stent group (n=87) and the plastic stent only group (n=87; 92% versus 91%, p>0.99). Similarly, Kang (2021a) reported that the clinical success rate did not have a statistically significant difference between the RFA plus SEMS group (n=24) and the SEMS only group (n=24; 88% versus 83%, p=1.000). Kang (2021b) also did not see any statistically significant difference in clinical success between the RFA plus plastic

stent group (n=15) and the plastic stent only group (n=15; 100% versus 87%, p=0.483).

In a non-randomised comparative study of 883 people, Xia (2021) noted that the rate of clinical success was statistically significantly higher in the RFA plus stent group (n=124) than the stent only group (n=759; 93% versus 85%, p=0.024). But after PSM no statistically significant difference was found between groups (93% of 124 people versus 89% of 496 people, p=0.190).

Stent patency

Stent patency was described in 6 studies. There were conflicting results in the duration of stent patency or the patency rate between RFA plus stent and stent only. But no statistically significant difference was found, except for the Yang (2018) study.

Gao (2021) did not find any statistically significant difference in the cumulative stent patency duration after the second procedure between the RFA plus plastic stent group and the plastic stent group (3.7 months versus 4.1 months, p=0.674; HR, 1.069; 95% CI, 0.782 to 0.460).

Albers (2022) did not report any statistically significant difference in the patency rate between the RFA plus SEMS group (n=42) and the SEMS only group (n=44) after 3 months (73% versus 82%, p=1.0) and 6 months (33% versus 52%, p=0.6). The patency rate in the subgroup with extrahepatic strictures showed no statistically significant difference after 3 and 6 months between groups. So, the patency rate in the subgroup with pancreatic cancer (SEMS only, n=18; RFA plus SEMS, n=16) showed no statistically significant difference after 3 and 6 months.

Kang (2021a) also did not find any statistically significant differences in the median duration of stent patency (132 days versus 116 days, p=0.440) and the

90-day stent patency rate (58% versus 46%, p=0.386) between the RFA plus SEMS group and the SEMS only group.

Kang (2021b) reported that ITT analysis of 30 people (15 in each group) did not show any statistically significant difference in the total event-free stent patency between the RFA plus plastic stent group and the plastic stent only group (178 days versus 122 days, p=0.154). But the authors found that in people with each stricture length of 11 mm or longer on both sides, stent patency was statistically significantly longer in the RFA plus plastic stent group than in the plastic stent only group (175 days versus 121 days, p=0.028). More people had elective exchange to SEMS without plastic stent occlusion in the RFA plus stent group than in the stent only group (69% versus 23%, p=0.018).

Yang (2018) reported that the duration of stent patency was statistically significantly longer in the RFA plus plastic stent group than the plastic stent only group (6.8 months versus 3.4 months, p=0.02), and stent length was comparable between groups.

In a systematic review and meta-analysis of 420 people who had RFA plus stent or stent only (3 RCTs and 5 retrospective observational studies; RFA plus stent, n=190; stent only, n=230), Cha (2021) described that no statistically significant difference was found in the duration of stent patency between groups (HR, 0.79; 95% CI 0.57 to 1.09, I^2=7%; 2 RCTs and 2 observational studies).

OS

OS was reported in all 7 studies and the evidence suggested a trend in favour of RFA plus stent. A statistically significant level was achieved in 3 studies (Gao 2021; Yang 2018; Xia 2021) and in a systematic review and meta-analysis (Cha 2021).

Gao (2021) found that the median OS was statistically significantly higher in the RFA plus plastic stent group than the plastic stent only group (14.3 months versus 9.2 months; HR, 0.488; 95% CI, 0.351 to 0.678; p<0.001). A survival benefit was also shown in people with CCA (13.3 months versus 9.2 months; HR, 0.546; 95% CI, 0.386 to 0.771; p<0.001).

Kang (2021a) did not find any statistically significant difference in median OS between the RFA plus SEMS group and the SEMS only group (244 days versus 180 days, p=0.281).

Albers (2022) described that the overall mortality after 3 and 6 months did not differ statistically significantly in both groups (RFA plus SEMS, 24% and 42%, p=0.56; SEMS, 27% and 50%, p=0.99). Similar results were found in the cohort with extrahepatic strictures (37 people in each group) and in the pancreatic cancer subgroup (SEMS only, n=18; RFA plus SEMS, n=16). The addition of RFA did not impact OS (HR, 0.72; p=0.389 for RFA plus SEMS).

Yang (2018) reported that the mean OS time was statistically significantly longer in the RFA plus plastic stent group than the plastic stent only group (13.2 months versus 8.3 months, p<0.001). The survival rates were statistically higher in the RFA plus plastic stent group than the plastic stent only groups at 9 months (88% versus 24%), 12 months (63% versus 12%) and 15 months (28% versus 3%; all p<0.05) but not at 6 months (97% versus 82%, p=0.08). Multivariable Cox regression analysis showed that RFA was the main protective factor affecting the survival of people (HR 0.182, 95% CI, 0.08 to 0.322; p<0.001).

Kang (2021b) described that ITT analysis of 30 people did not show any statistically significant difference in OS between the RFA plus plastic stent group and the plastic stent only group (230 days versus 144 days, p=0.643).

Xia (2021) reported that the median OS was statistically significantly longer in the RFA plus stent group than the stent only group (9.5 months versus 5.5 months,

p<0.001). After PSM, people who had RFA plus stent also showed statistically significantly longer OS than those who had stent alone (9.5 months versus 6.1 months, p<0.001). In multivariable Cox proportional hazard models, RFA plus stent was found to be an independent predictor of OS (HR, 0.552; 95% CI, 0.438 to 0.697; p<0.001), In stratified analyses, the improved OS was only showed in the subgroup of extrahepatic CCA (11.3 months versus 6.9 months, p<0.001) but not in the subgroups of other cancers (all p>0.05). The survival benefit was noted only in the people with non-metastatic CCA (11.5 months versus 7.4 months, p<0.001).

In the systematic review and meta-analysis by Cha (2021), when comparing RFA plus stent with stent only, the pooled HR for OS was 0.47 (95% CI, 0.34 to 0.64, I^2=44%; 8 studies). No significant publication bias was noted in the funnel plot for overall survival (Egger's test p=0.2869).

Quality of life

Quality of life was measured using KPS in 2 RCTs, suggesting a better quality of life after RFA plus stent than stent only. Gao (2021) reported that the postprocedural KPS scores were statistically significantly higher in the RFA plus plastic stent group than the plastic stent only group until 9 months (all p<0.05). Similarly, Yang (2018) described that the postoperative KPS scores of people in the RFA plus plastic stent group were statistically significantly higher than those of the plastic stent only group after 1 month (86.1 versus 72.4), 3 months (71.4 versus 60.3), 6 months (61.4 versus 48.2), and 9 months (58.2 versus 22.5, all p<0.05). The authors of both RCTs described that the preoperative KPS scores were comparable between groups.

Safety

The pooled results of cholangitis and cholecystitis can be found in the appendix.

Overall postoperative adverse events

In general, the overall postoperative adverse events were comparable between people with RFA plus stent and people with stent only across studies.

Gao (2021) did not find a statistically significant difference in early (within 30 days; 28% versus 20%, p=0.211) or late adverse events (39% versus 37%, p>0.99) between the RFA plus plastic stent group and the plastic stent only group.

Albers (2022) did not report a statistically significant difference in adverse events between the RFA plus SEMS group and the SEMS only group within the first 30 days after the procedure (11% versus 2%, p=0.18).

Kang (2021a) described that the early complication (within 7 days) rates were not statistically significantly different between the RFA plus SEMS group and the SEMS only group (4% versus 13%, p=0.609), and there were no late complications (7 to 30 days) in both groups.

Yang (2018) did not find a statistically significant difference in the incidence of postoperative adverse events between the RFA plus plastic stent group and the plastic stent only group (6% versus 9%, p=0.67).

Xia (2021) found that the overall complication rates were comparable between the RFA plus stent group and the stent only group before and after PSM (unmatched: 19% versus 20%; matched: 19% versus 16%). The authors also found that the total post-ERCP complication rates were comparable between the RFA plus stent group and the stent only group before and after PSM (9% versus 5%).

In the systematic review and meta-analysis (Cha 2021), no study showed any statistically significant difference in adverse events between the RFA plus stent group and the stent only group.

Cholangitis

Cholangitis was described in all studies and its incidence was generally comparable between the RFA plus stent group and the stent only group.

Gao (2021) did not find a statistically significant difference in cholangitis (acute cholangitis: 11.5% versus 10.3%, p=0.808; delayed cholangitis, 38% versus 37%, p=0.875) between the RFA plus plastic stent group and the plastic stent only group within 30 days after the procedure. Kang (2021b) did not report any statistically significant difference in cholangitis between the RFA plus plastic stent group and the plastic stent only group within the first 30 days (20% [n=3] versus 33% [n=5]) and more than 30 days after the procedure (33% [n=5] versus 33% [n=5]).

Albers (2022) reported cholangitis in 1 person in the RFA plus SEMS group but 0 in the SEMS only group within the first 30 days after the procedure. Similarly, Kang (2021a) reported cholangitis in 1 person in the RFA plus SEMS group but 0 in the SEMS only group within 30 days after the procedure. This case resulting in septic shock and death was reported as an unlikely related severe adverse event.

Yang (2018) reported acute cholangitis in 2 people (6.3%) in the RFA plus plastic stent group and 1 (3%) in the plastic stent group only after the procedure.

Xia (2021) reported that the incidence of cholangitis was statistically significantly lower in the RFA plus stent group than the stent only group (6.5% [8/124] versus 14% [108/759], p=0.017) before PSM. But this statistically significant difference was not found after PSM (7% [8/124] versus 10% [51/496], p=0.194).

In the systematic review and meta-analysis, Cha (2021) reported cholangitis regardless of symptoms in 34 people after RFA plus stent insertion.

Cholecystitis

Cholecystitis was reported in 4 studies and in 1 systematic review and meta-analysis. Gao (2021) and Xia (2021) found a statistically significantly higher incidence of acute cholecystitis in the RFA plus stent group than the stent only group. This finding was not supported by Kang (2021b) and Albers (2022).

Gao (2021) reported that the number of people experiencing acute cholecystitis was statistically significantly higher in the RFA plus plastic stent group than the plastic stent only group (10% versus 0%, p=0.003) within 30 days after the procedure. Of the 9 people with acute cholecystitis, 7 had hilar CCA, 1 had ampullary cancer, and 1 had distal CCA coexisting with gallstones. Xia (2021) reported that the incidence of acute cholecystitis was statistically significantly higher in the RFA plus stent group than the stent only group (6 versus 1, p<0.001) before and after PSM.

But Kang (2021b) did not find any statistically significant difference in cholecystitis between the RFA plus plastic stent group and the plastic stent group within the first 30 days (7% [n=1] in each group) and more than 30 days (7% [n=1] versus 0%) after the procedure. Albers (2022) reported cholecystitis with gallbladder perforation in 1 person in the RFA plus SEMS group but not in the SEMS only group within the first 30 days after the procedure.

In the systematic review and meta-analysis, Cha (2021) reported cholecystitis in 8 people after RFA plus stent insertion.

Pancreatitis

Pancreatitis was seen in 2 studies and in 1 systematic review and meta-analysis.

Gao (2021) did not find a statistically significant difference in post-ERCP pancreatitis (mild; 5% versus 6%, p>0.99) between the RFA plus plastic stent group and the plastic stent only group within 30 days after the procedure. Albers

(2022) reported pancreatitis in 1 person in the RFA plus SEMS group but 0 in the SEMS only group within the first 30 days after the procedure. Cha (2021) reported pancreatitis and hyperamylasaemia in 3 people.

Perforation

Perforation was reported in 2 studies, with 1 case in each study after RFA plus stent insertion.

Xia (2021) did not find a statistically significant difference in the incidence of perforation between the RFA plus stent group and the stent only group before and after PSM (1 versus 0). This case was a minor duodenal perforation induced by a plastic stent and was successfully closed using endoscopic clipping. Albers (2022) reported cholecystitis with gallbladder perforation in 1 person in the RFA plus SEMS group but 0 in the SEMS only group within the first 30 days after the procedure.

Liver abscess

Gao (2021) saw 1 person with liver abscess in the RFA plus plastic stent group but not in the plastic stent only group after 30 days following the procedure.

Bleeding

Bleeding was described in 3 studies and its incidence was comparable between the RFA plus stent group and the stent only group.

Gao (2021) did not find a statistically significant difference in bleeding (1% versus 3%, p=0.621) between the RFA plus plastic stent group and the plastic stent only group within 30 days after the procedure. Albers (2022) reported bleeding in 1 person in the RFA plus SEMS group and 1 in the SEMS only group within the first 30 days after the procedure. Xia (2021) reported that the incidence of bleeding was comparable between the RFA plus stent group and the stent only group before and after propensity score matching (2% versus 1%).

Pain

Pain was reported in 2 studies and 1 systematic review and meta-analysis.

Kang (2021a) did not find any statistically significant difference in postprocedural pain between the RFA plus SEMS group and the SEMS only group (median 6.0 in each group; for VAS 7 or more, 13% [n=3] versus 33% [n=8], p=0.086). Kang (2021b) reported the median score of abdominal pain (NRS) 3 (IQR 0 to 4) in the RFA plus plastic stent group and 0 (IQR 0 to 5) in the plastic stent only group within the first 30 days after the procedure. Cha (2021) reported abdominal pain in 3 people.

Anecdotal and theoretical adverse events

Expert advice was sought from consultants who have been nominated or ratified by their professional society or royal college. They were asked if they knew of any other adverse events for this procedure that they had heard about (anecdotal), which were not reported in the literature. They were also asked if they thought there were other adverse events that might possibly occur, even if they had never happened (theoretical).

In addition to the adverse events reported in the literature, they did not list anecdotal or theoretical adverse events.

Three professional expert questionnaires for this procedure were submitted. Find full details of what the professional experts said about the procedure in the specialist advice questionnaires for this procedure.

Validity and generalisability

The key evidence includes 5 RCTs, 1 non-randomised comparative study and 1 systematic review and meta-analysis. All 6 primary studies were conducted outside the UK. Most studies had a follow up of 4 to 32 months, although the

observational study reported the data for 7 years. A mixture of cancer types was included in most studies, but the most common tumour was CCA.

In addition to the RoB assessment detailed in table 2, samples were often not adequately powered for key efficacy outcome measures. Sample size calculation was done in 4 RCTs but for different efficacy outcomes. 2 RCTs (Albers 2022; Kang 2021a) were reasonably powered for stent patency while the other 2 RCTs (Gao 2021; Yang 2018) were reasonably power for OS. Kang (2021b) was a pilot RCT with a small sample size. Therefore, statistical power was generally not desirable for key efficacy outcome measures across studies.

Stent patency was one of the key efficacy outcomes. This outcome was least affected by tumour types, concomitant systemic antitumour therapies or comorbidities (Albers 2022). Although there were conflicting results, in general, the evidence did not show any statistically significant difference in the duration of stent patency or the patency rate between the RFA plus stent group and the stent only group. This indicates no benefit in stent patency after RFA regardless of stent types.

However, the mechanism of stent occlusion differs principally between plastic stents and SEMS. Albers (2022) stated that tumour ingrowth is the main reason for malfunction of SEMS, resulting in stent occlusion. The occlusion of plastic stents is mainly caused by bacterial biofilm formation, biliary sludge, and duodenobiliary reflux. Endoscopic RFA preceding stent insertion aims at reducing tissue overgrowth. Therefore, the effect of RFA on the patency of different stents needs to be explored further.

OS was another key efficacy outcome. Across all the included studies, the evidence suggested a survival benefit in favour of RFA plus stent. It is noted that RFA is more like a local therapy than a systemic therapy and OS could be affected by many factors, such as stent patency, systemic control in combining

with antitumour therapies (especially chemotherapy), cancer types and stages, and repeated RFA sessions.

Other antitumour treatments (such as chemotherapy) were allowed concomitantly or after the index procedure in all but 1 primary study (Yang 2018). However, the proportion of people who actually had antitumour therapies, in particular chemotherapy, was generally low across studies but comparable between the RFA plus stent group and the stent only group within studies. So, the survival benefit may be more presentative of people who were forgoing systemic treatments.

In respect of cancer type, the most common type of cancer was CCA. A survival benefit was generally directed towards people with MBO, mainly caused by extrahepatic CCA (especially in those without metastasis). Extrahepatic CCA mostly grows along the bile duct wall within limited thickness, thus the endoscopic RFA can reduce the maximal tumour load differing disease's progression (Xia 2021). For MOB caused by other cancers (such as pancreatic cancer), the survival benefit was uncertain.

More than 1 RFA session was allowed in 4 studies, and of these, 3 studies reported a statistically significant survival benefit after RFA plus stent compared with stent only (Gao 2021; Yang 2018; Xia 2021). It is noted that 1 study (Kang 2021b) had only 2 of 13 people were clinically eligible for a second RFA session, indicating the difficulty to repeat RFA in MHBO, due to some clinical obstacles such as active cholangitis. Although the results were indicative, the survival benefit after repeated RFA procedures was shown.

In terms of safety outcomes, no statistically significant difference was found in the overall postoperative adverse events, cholangitis and bleeding between people with RFA plus stent and people with stent only across studies. Regarding cholecystitis, 2 studies (Gao 2021; Xia 2021) found that its incidence was

statistically significantly higher in people with RFA plus stent than people with stent only, suggesting extra precaution would be necessary during ablation. The incidences of pancreatitis, perforation and liver abscess were generally low.

In conclusion, most evidence focused on primary RFA, with CCA (mainly hilar and distal CCA) being the most common tumour. The evidence suggested that endoscopic bipolar RFA confers a survival benefit to people with MBO (mainly caused by CCA, particularly in those without metastasis). However, the evidence failed to exhibit a benefit for stent patency which is the primary aim of the procedure. Although endoscopic RFA, in addition to stent insertion, could improve quality of life but this was measured using KPS, so no data on quality of life using a conventional tool. More well-designed studies are warranted to evaluate the effects of endoscopic bipolar RFA in MBO caused by different tumour entities, stages and locations, in different RFA application protocols and in secondary RFA. To date, no ongoing trials specifically for this procedure have been identified.

Existing assessments of this procedure

A Health Technology Assessment was carried out by Beyer et al. (2023). This assessment evaluated the clinical effectiveness, cost-effectiveness and potential risks of endoscopic bipolar RFA for MBO, and the value of future research. In this assessment, 68 studies (1,742 people) were included, with 18 comparative studies and 50 non-comparative studies. The majority (53%) of results were conference abstracts with no peer-reviewed published reports. Of the comparative studies, 2 RCTs (Gao 2021; Yang 2018) were peer-reviewed publications and others were conference abstracts, A total of 8 studies were included in meta-analyses.

The assessment concluded that primary RFA appears to improve survival and is likely to be cost-effective; however, the evidence for this is mainly in people with

bile duct cancers rather than in people with pancreatic cancers. Only 6 of 18 comparative studies could be included in the meta-analysis looking at survival because of the differences in outcome measures, but none reported a decrease in survival in the RFA group compared with the stent-only group. There was no increased risk of cholangitis or pancreatitis following RFA, but possibly an increased risk of cholecystitis. There was a lack of high-quality data examining similar outcomes in people having secondary RFA. For both primary and secondary RFAs, there were insufficient data to determine the effect of RFA on quality of life. Recommendations for further research include the following:

- Prospective RCTs of primary RFA should be conducted, with a specific focus on quality of life and accurate reporting of AEs in each group. People with pancreatic cancers should be classified separately from people with bile duct cancers, to determine the effects of RFA in each group.
- The mechanism by which primary RFA has a beneficial effect on survival should be explored.
- Consideration should be given to whether or not a repeat application of RFA at a specified interval may further improve outcomes in people with both pancreatic and bile duct cancers.
- High-quality prospective RCTs of secondary RFA should be carried out to determine whether or not there is benefit to survival and quality of life, including accurate reporting of AEs. These RCTs should also incorporate an assessment of cost-effectiveness.
- If benefit is shown in secondary RFA, an exploration of the mechanism should be carried out.

The British Society of Gastroenterology guidelines for the diagnosis and management of cholangiocarcinoma (Rushbrook et al. 2024) endorse the use of fully covered SEMS given the lower rates of stent dysfunction (21.6% vs 46.8%), lower reintervention rates and better survival rates over plastic stents. Furthermore, for distal obstruction one would use fully covered SEMS rather than uncovered SEMS, which is supported by meta-analysis, despite the small risk of cystic duct obstruction.

The guidelines recommend that at present the use of adjunctive endobiliary radiofrequency ablation (RFA) and photodynamic therapy is not considered standard of care for patients with hilar and distal CCA having palliative care (strength of recommendation: STRONG; quality of evidence: HIGH). The guidelines further state that adjunctive biliary treatments to improve long-term stent patency and patient survival are not considered standard of care. The application of RFA via either Habib EndoHPB Bipolar Radiofrequency Catheter or the ELRA are designed to cause cancer necrosis while reducing damage to normal biliary mucosa. Complications of RFA include acute pancreatitis, cholangitis, cholecystitis and haemobilia. Likewise, although photodynamic therapy has been reported to increase stent patency, quality of life and survival, 10% of patients incur systemic photosensitivity.

Related NICE guidance

Interventional procedures

- NICE interventional procedures guidance on irreversible electroporation for treating pancreatic cancer (2017) (Recommendation: research).
- NICE interventional procedures guidance on selective internal radiation therapy for unresectable primary intrahepatic cholangiocarcinoma (2018) (Recommendation: research).

- NICE interventional procedures guidance on photodynamic therapy for bile duct cancer (2005) (Recommendation: special arrangements).

Professional societies

- Association of Upper Gastrointestinal Surgeons of Great Britain and Northern Ireland
- British Society of Gastroenterology
- British Society of Interventional Radiologists
- Royal College of Radiologists
- Royal College of Surgeons of England
- Royal College of Surgeons of Edinburgh
- Royal College of Physicians and Surgeons of Glasgow.

Evidence from patients and patient organisations

NICE received 1 submission from a patient organisation about endoscopic bipolar RFA for MBO.

Company engagement

NICE asked companies who manufacture a device potentially relevant to this procedure for information on it. NICE received a completed submission. This was considered by the IP team and any relevant points have been taken into consideration when preparing this overview.

References

1. Gao DJ, Yang JF, Ma SR et al. (2021) Endoscopic radiofrequency ablation plus plastic stent placement versus stent placement alone for unresectable extrahepatic biliary cancer: a multicenter randomized controlled trial. Gastrointestinal endoscopy 94(1): 91-100e2
2. Albers D, Schmidt A, Schiemer M et al. (2022) Impact of endobiliary radiofrequency ablation on biliary drainage in patients with malignant biliary strictures treated with uncovered self-expandable metal stents: a

randomized controlled multicenter trial. Gastrointestinal endoscopy 96(6): 970-9

3. Kang H, Chung MJ, Cho IR et al. (2021a) Efficacy and safety of palliative endobiliary radiofrequency ablation using a novel temperature-controlled catheter for malignant biliary stricture: a single-center prospective randomized phase II TRIAL. Surgical endoscopy 35(1): 63-73
4. Kang H, Han SY, Cho JH et al. (2021b) Efficacy and safety of temperature-controlled intraductal radiofrequency ablation in advanced malignant hilar biliary obstruction: a pilot multicenter randomized comparative trial. Journal of hepato-biliary-pancreatic sciences
5. Yang J, Wang J, Zhou H et al. (2018) Efficacy and safety of endoscopic radiofrequency ablation for unresectable extrahepatic cholangiocarcinoma: a randomized trial. Endoscopy, 50: 751-60
6. Xia MX, Wang SP, Yuan JG et al. (2022) Effect of endoscopic radiofrequency ablation on the survival of patients with inoperable malignant biliary strictures: A large cohort study. Journal of hepato-biliary-pancreatic sciences 29(6): 693-702
7. Cha BH, Jang MJ and Lee SH (2021) Survival benefit of intraductal radiofrequency ablation for malignant biliary obstruction: A systematic review with meta-analysis. Clinical Endoscopy 54(1): 100-6
8. Beyer F, Rice S, Orozco-Leal G et al. (2023) Clinical and cost effectiveness of endoscopic bipolar radiofrequency ablation for the treatment of malignant biliary obstruction: a systematic review. Health Technology Assessment 27(7): 1-118
9. Rushbrook SM, Kendall TJ, Zen Y et al. (2024) British Society of Gastroenterology guidelines for the diagnosis and management of cholangiocarcinoma. Gut, 73: 16-46

Methods

NICE identified studies and reviews relevant to endoscopic bipolar radiofrequency ablation for malignant biliary obstruction from the medical literature. The following databases were searched between the date they started to 12 December 2023: MEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the internet were also searched (see the literature search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following inclusion criteria were applied to the abstracts identified by the literature search.

- Publication type: clinical studies were included with emphasis on identifying good quality studies. Abstracts were excluded if they did not report clinical outcomes. Reviews, editorials, and laboratory or animal studies, were also excluded and so were conference abstracts, because of the difficulty of appraising study methodology, unless they reported specific adverse events that not available in the published literature.
- People with malignant biliary obstruction or stricture.
- Intervention or test: endoscopic bipolar RFA (ERCP-directed RFA; primary or secondary RFA).
- Outcome: articles were retrieved if the abstract contained information relevant to the safety, efficacy, or both.

If selection criteria could not be determined from the abstracts the full paper was retrieved.

Potentially relevant studies not included in the main evidence summary are listed in the section on other relevant studies.

Find out more about how NICE selects the evidence for the committee.

Table 4 literature search strategy

Databases	Date searched	Version/files
MEDLINE ALL (Ovid)	12/12/2023	MEDLINE ALL 1946 to December 07, 2023
EMBASE (Ovid)	12/12/2023	EMBASE 1974 to 2023 December 11 30
EMBASE Conference (Ovid)	12/12/2023	EMBASE 1974 to 2023 December 11 30

Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	12/12/2023	Issue 11 of 12, November 2023
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	12/12/2023	Issue 12 of 12, December 2023
International HTA database (INAHTA)	12/12/2023	-

Trial sources searched

- Clinicaltrials.gov
- ISRCTN
- WHO International Clinical Trials Registry

Websites searched

- National Institute for Health and Care Excellence (NICE)
- NHS England
- Food and Drug Administration (FDA) - MAUDE database
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- General internet search

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

MEDLINE search strategy

1 *Endoscopy/mt [Methods]
2 *Endoscopes/
3 (endoscop* or scope* or probe*).tw.
4 endobiliary.tw.
5 or/1-4
6 *Radiofrequency Ablation/
7 *Catheter Ablation/
8 ((catheter* or radiofrequen* or radio frequen* or radio-frequen* or rf) adj4 ablat*).tw.
9 (Radio* adj4 frequen* adj4 ablat*).tw.
10 RFA.tw.
11 or/6-10
12 5 and 11

13 Pancreatic Neoplasms/
14 (pancrea* adj4 (Neoplasm* or Cancer* or Carcinom* or Adenocarcinom* or Tumour* or Tumor* or Malignan* or Lump* or Masses* or Sarcom* or Metastas*)).tw.
15 exp Bile Duct Neoplasms/
16 (bile duct adj4 (Neoplasm* or Cancer* or Carcinom* or Adenocarcinom* or Tumour* or Tumor* or Malignan* or Lump* or Masses* or Sarcom* or Metastas* or stricture* or obstruct*)).tw.
17 Biliary Tract Diseases/
18 (Biliary adj4 (Neoplasm* or Cancer* or Carcinom* or Adenocarcinom* or Tumour* or Tumor* or Malignan* or Lump* or Masses* or Sarcom* or Metastas* or stricture* or obstruct*)).tw.
19 Cholangiocarcinoma/
20 Cholangiocarcinom*.tw.
21 CCA.tw.
22 exp Cholestasis/
23 cholestas*.tw.
24 or/13-23
25 12 and 24
26 (EndoHBP or ELRA).tw.
27 25 or 26
28 Animals/ not Humans/
29 27 not 28
30 limit 29 to ed=20230531-20231231
31 limit 30 to english language

Other relevant studies

Other potentially relevant studies to the IP overview that were not included in the main evidence summary (tables 2 and 3) are listed in table 5.

Table 5 additional studies identified

Article	Number of patients and follow up	Direction of conclusions	Reason study was not included in main evidence summary
Bokemeyer A, Matern P, Bettenworth D et al. (2019) Endoscopic Radiofrequency ablation prolongs survival of patients with unresectable hilar cholangiocellular carcinoma - a case-control study. Scientific reports 9(1): 13685	Case control (retrospective) N=42 (RFA plus stent, n=32 [20 included in the case-control analysis]; stent alone, n=22)	ERFA therapy significantly prolonged survival in patients with unresectable Bismuth type III and IV hilar cholangiocellular carcinoma. As an effective and safe method, ERFA should be considered as a palliative treatment for all these people.	Small sample
Buerlein RCD, Strand DS, Uppal DS et al. (2022) Endobiliary ablation improves survival in patients with unresectable perihilar cholangiocarcinoma compared to stenting alone. Techniques and Innovations in Gastrointestinal Endoscopy 24(3): 226-33	Non-randomised comparative study (retrospective) N=59 (ERCP-directed biliary ablation [RFA and/or PDT] and stenting, n=30; biliary stenting alone, n=29)	Endobiliary ablation (with RFA and/or PDT or RFA alone) followed by stenting was associated with significantly improved survival compared to biliary stenting alone in people with unresectable perihilar CCA without an increase in adverse events and should be offered as first-line palliative therapy.	Small sample (ERCP-directed biliary ablation using RFA, n=20)
Dutta AK, Basavaraju U, Sales L et al. (2017) Radiofrequency	Non-randomised comparative study	Biliary RFA is a technically feasible with a low adverse event rate and is	More recent studies with larger samples or better designs included

ablation for management of malignant biliary obstruction: a single-center experience and review of the literature. ExpertRev Gastroenterol Hepatol, 11: 779-84	N=31 (RFA plus stent, n=15; stent only, n=16)	associated with increased survival. Multi-centre RCTs are required.	in the key evidence
Galindo Orozco MC, Hernandez Guerrero A, Alonso Larraga JO et al. (2020) Efficacy and safety of radiofrequency ablation in patients with unresectable malignant biliary strictures. Revista espanola de enfermedades digestivas : organo oficial de la Sociedad Espanola de Patologia Digestiva 112(12): 921-924	Non-randomised comparative study N=40 (RFA plus stent, n=12; stent alone, n=28)	The radiofrequency group had a 3-month increase in survival, which did not reach statistical significance.	Studies with larger samples or better designs included in the key evidence.
Inoue T, Ibusuki M, Kitano R et al. (2023) Long-term disease control by endobiliary radiofrequency ablation in localized extrahepatic cholangiocarcinoma: a first case report. Clinical journal of gastroenterology 16(6): 908-12	Case report N=1	This is the first report of a stent-free status and long-term survival in a patient with localised extrahepatic CCA that was achieved using only endobiliary RFA without any other antitumour treatment. Although several problems and issues associated with endobiliary RFA remain unelucidated, it may be a useful therapeutic option for early and localised extrahepatic cholangiocarcinoma	Small sample

		in poor surgical candidates.	
Inoue T, Ibusuki M, Kitano R et al. (2023) Endoscopic radiofrequency ablation for ingrowth occlusion after bilateral metal stent placement for malignant hilar biliary obstruction: a prospective pilot study. Gastrointestinal endoscopy 97(2): 282-290e1	Case series (retrospective) N=41	The study showed that endobiliary RFA with bilateral SEMS placement achieved good results, but selection of patients with an appropriate stricture length may be needed to obtain a sufficient ablative effect.	Studies with larger samples or better designs included in the key evidence.
Inoue T, Ibusuki M, Kitano R et al. (2023) Endoscopic radiofrequency ablation for ingrowth occlusion after bilateral metal stent placement for malignant hilar biliary obstruction: a prospective pilot study. Gastrointestinal endoscopy 97(2): 282-290e1	Case series N=30 Follow up: median 179 days	Endoscopic biliary RFA elicited promising results, with good long-term stent patency and without the need of any additional stent placement, for the palliation of ingrowth occlusion after bilateral SEMS placement. However, the clinical success rate was insufficient, necessitating improvements in the future.	Studies with larger samples or better designs included in the key evidence.
Inoue T, Ibusuki M, Kitano R et al. (2022) Endobiliary radiofrequency ablation using a short-type balloon enteroscope in patients with surgically altered anatomy. Digestive diseases and sciences 67(8): 4181-4187	Case series N=37	This study demonstrated the technical safety and feasibility as well as good long-term outcomes of endobiliary RFA combined with metal stent placement under balloon enteroscope guidance. This approach may be a	Studies with larger samples or better designs included in the key evidence.

		useful option for treating MBO in people with surgically altered anatomy.	
Inoue T, Naitoh I, Kitano R et al. (2022) Endobiliary radiofrequency ablation combined with gemcitabine and cisplatin in patients with unresectable extrahepatic cholangiocarcinoma. Current oncology (Toronto, Ont.) 29(4): 2240-51	Non-randomised comparative study (retrospective) N=50 (gemcitabine plus cisplatin therapy with RFA, n=25; gemcitabine plus cisplatin therapy only, n=25)	Endobiliary RFA prolonged the patency period of uncovered SEMS combined with gemcitabine plus cisplatin therapy in patients with extrahepatic CCA. Although RFA also yielded survival benefits, its effect was restricted to locally advanced tumours.	Studies with larger samples or better designs included in the key evidence.
Kadayifci A, Atar M, Forcione DG et al. (2016) Radiofrequency ablation for the management of occluded biliary metal stents. Endoscopy, 48(12): 1096-101	Non-randomised comparative study (retrospective) N=50 (RFA, n=25; plastic stent, n=25)	The application of RFA for occluded SEMS improves stent patency. RFA is an alternative treatment of tissue ingrowth in malignant biliary obstruction.	More recent studies with larger samples or better designs included in the key evidence
Kim EJ, Cho JH, Kim YJ et al. (2019) Intraductal temperature-controlled radiofrequency ablation in malignant hilar obstruction: A preliminary study in animals and initial human experience. Endoscopy International Open 7(10): e1293-e1300	Case series N=11	This study suggests that ID-RFA performed using a short-length probe with settings of 80 °C, 7W and 60 – 120 s is a safe and feasible palliative treatment for malignant hilar obstruction.	Small sample
Kim EJ, Chung DH, Kim YJ et al. (2018) Endobiliary radiofrequency ablation for distal	Case series (retrospective) N=8	Endobiliary RFA partially ablated human cancer tissue and preoperative endobiliary RFA	Small sample

extrahepatic cholangiocarcinoma: A clinicopathological study. PloS one 13(11): e0206694		might be a safe and feasible in patients with distal extrahepatic CCA who require a delayed operation. Ablation of the target lesion longer than the estimated length by fluoroscopy may improve the efficacy of endobiliary RFA.	
Laleman W, van der Merwe, Schalk, Verbeke L et al. (2017) A new intraductal radiofrequency ablation device for inoperable biliopancreatic tumors complicated by obstructive jaundice: the IGNITE-1 study. Endoscopy 49(10): 977-82	Case series N=18 Follow up: mean 213 days	Intraductal RFA using a new device in patients with inoperable biliopancreatic cancer complicated by jaundice appeared feasible and safe with acceptable biliary patency. Randomised trials with prolonged follow-up are warranted.	Small sample; more recent studies included in the key evidence.
Liang H, Peng Z, Cao L et al. (2015) Metal stenting with or without endobiliary radiofrequency ablation for unrespectable extrahepatic cholangiocarcinoma. Journal of cancer therapy, 6: 981-92	Non-randomised comparative study N=76 (RFA plus SEMS, n=34; SEMS only, n=42)	ERFA is effective for unresectable extrahepatic CCA and may improve metal stent patency and patient survival for unresectable extrahepatic CCA with biliary obstruction. RCTs will be needed to confirm these findings.	Mixed approaches (ERCP and PTC); more recent studies with larger samples or better designs included in the key evidence.
Lee YN, Jeong S, C HJ et al. (2019) The safety of newly developed automatic temperature-controlled endobiliary radiofrequency ablation system for malignant biliary	Case series N=30 Follow up: mean 208 days	Automatic temperature-controlled endobiliary RFA using a newly developed catheter was safely applied in patents with extrahepatic malignant biliary	Small sample

strictures: A prospective multicenter study. Journal of gastroenterology and hepatology 34(8): 1454-1459		stricture. Further prospective studies are needed to confirm the efficacy of endobiliary RFA for MBS.	
Marti Romero L, Martinez Escapa V, Castello Miralles I et al. (2019) Intraductal ablation by radiofrequency for inoperable biliopancreatic neoplasms with jaundice: experience at a regional hospital. Revista espanola de enfermedades digestivas: organo oficial de la Sociedad Espanola de Patologia Digestiva 111(6): 485-7	Case reports N=3 Follow up: 10 months	Preliminarily data suggest that the application of intraductal biliary RFA in people with non-resectable or inoperable neoplasia that causes bile duct stenosis apparently does not increase technical difficulty. However, it does extend the duration of the examination. Thus, the evidence suggests that it is feasible and safe due to the absence of immediate complications. However, more cases and long-term monitoring are pending. This previously non-existent treatment option provides people with metal biliary stents that improve the quality of life and prevent repeated admissions due to obstructive jaundice or cholangitis.	Small sample
Mohring C, Khan O, Zhou T et al. (2023) Comparison between regular additional endobiliary	Non-randomised comparative study (retrospective)	Additional endobiliary ablative therapies in combination with systemic chemotherapy were	Studies with larger sample or better designs included in the key evidence.

radiofrequency ablation and photodynamic therapy in patients with advanced extrahepatic cholangiocarcinoma under systemic chemotherapy. Frontiers in Oncology 13: 1227036	N=63 (systemic chemotherapy and endobiliary RFA, n=28; systemic chemotherapy and endobiliary PDT, n=22; systemic chemotherapy and endobiliary RFA and PDT, n=13)	feasible. Both modalities, endobiliary RFA and endobiliary PDT, showed a similar benefit in terms of survival. Interestingly, patients receiving both regimes showed the best overall survival indicating a possible synergism between both ablative therapeutic techniques.	
Nair P, Rao HB, Koshy AK et al. (2021) Safety and efficacy of endobiliary radio frequency ablation in hilar cholangiocarcinoma. Journal of Gastroenterology and Hepatology Research 11(1): 3658-3664	Non-randomised comparative study (retrospective) N=49 (endobiliary RFA plus stenting, n=22; stenting alone, n=27) Follow up: 236 days	Patients who underwent endobiliary RFA were found to have a significant survival advantage as compared to standard treatment options. Endobiliary RFA was found to be technically feasible, safe and can be a useful adjunct to endoscopic palliation in patients with hilar cholangiocarcinoma.	Studies with larger samples or better designs included in the key evidence.
Nayar MK, Oppong KW, Bekkali NLH et al. (2018) Novel temperature-controlled RFA probe for treatment of blocked metal biliary stents in patients with pancreaticobiliary cancers: Initial experience. Endoscopy International Open 6(5): e513-e517	Case series N=7 Follow up: mean 194 days	These are the first reported data on use of a RFA catheter in humans to treat blocked metal biliary stents. The device is safe but further randomised trials are required to establish the efficacy and survival benefits of this probe.	Small sample
Oh D, Chong J, Song TJ et al. (2022) The	Non-randomised comparative	SEMS placement after endobiliary RFA	Studies with larger sample or better

usefulness of endobiliary radiofrequency ablation before metal stent placement in unresectable malignant hilar obstruction. Journal of gastroenterology and hepatology 37(11): 2083-2090	study (retrospective) N=79 (RFA plus SEMS, n=28; SEMS only, n=51)	in malignant hilar obstruction was not associated with improvement in the stent patency or patient survival. Further prospective randomized studies are necessary to establish the effectiveness of EB-RFA with stents in malignant hilar obstruction.	designs included in the key evidence.
Ogura T, Onda S, Sano T et al. (2017) Evaluation of the safety of endoscopic radiofrequency ablation for malignant biliary stricture using a digital peroral cholangioscope (with videos). Digestive endoscopy: official journal of the Japan Gastroenterological Endoscopy Society 29(6): 712-7	Case series (retrospective) N=12 Follow up: median 107 days	RFA for malignant biliary stricture may be safe. To confirm the feasibility and efficacy of RFA, additional cases, prospective studies, and a comparison study between with and without endobiliary RFA are needed.	Small sample; more recent studies included in the key evidence.
Park N, Jung M Kyu, Kim EJ et al. (2023) In-stent radiofrequency ablation with uncovered metal stent placement for tumor ingrowth/overgrowth causing self-expandable metal stent occlusion in distal malignant biliary obstruction: multicenter propensity score-matched study. Gastrointestinal	Propensity score-matched study N=48 (in-stent RFA plus SEMS, n=14; SEMS only, n=34)	In-stent RFA followed by an uncovered SEMS is safe and feasible and may improve time to recurrent biliary obstruction as a stent revision for occluded SEMSs in pancreatobiliary cancer.	Studies with larger samples or better designs included in the key evidence.

endoscopy 97(4): 694-703e2			
Rebhun J, Shin CM, Siddiqui UD et al. (2023) Endoscopic biliary treatment of unresectable cholangiocarcinoma: a meta-analysis of survival outcomes and systematic review	Systematic review and meta-analysis N=307 (6 studies: endoscopic RFA, 4 studies; percutaneous RFA, 2 studies	While further prospective, randomised studies are needed to assess efficacy of ERFA, meta-analysis showed that this technique offers endoscopists a reasonable palliative method by which to treat unresectable CCA that results in longer survival as compared to biliary stenting alone, percutaneous RFA with biliary stenting and photodynamic therapy with biliary stenting as well as an acceptable adverse event profile based on available data.	Of the 4 relevant studies, 3 were included in Cha (2021) and 1 case-control study with a small sample (n=25).
Sandru V, Ungureanu BS, Stan-Ilie M et al. (2022) Efficacy of endobiliary radiofrequency ablation in preserving survival, performance status and chemotherapy eligibility of patients with unresectable distal cholangiocarcinoma: a case-control study. Diagnostics 12(8): 1804	Case control N=25 (RFA plus stenting, n=8; stenting alone, n=17) Follow up: 6 months	Given the isolated adverse events and the impact on the patient survival, performance, and laboratory profile, RFA can be considered safe and efficient in the management of patients with unresectable distal cholangiocarcinomas.	Small sample
Sharaiha RZ, Natov N, Glockenberg KS et al. (2014) Comparison of metal stenting with	Non-randomised comparative study	RFA appears to improve survival in people with end-stage CCA and pancreatic cancer. In	More recent studies with larger samples or better designs included

radiofrequency ablation versus stenting alone for treating malignant biliary strictures: is there an added benefit? Digestive Diseases & Sciences 59: 3099–102	N=66 (RFA plus SEMS, n=26; SEMS only, n=40 Follow up: median 29 months	a disease with limited treatment options, this modality may prove to be beneficial compared to stenting alone. RCTs and evaluation of quality-of-life measures should be performed to confirm these findings.	in the key evidence
Sofi AA, Khan MA, Das A et al. (2018) Radiofrequency ablation combined with biliary stent placement versus stent placement alone for malignant biliary strictures: a systematic review and meta-analysis. Gastrointestinal endoscopy, 87: 944-51	Systematic review and meta-analysis N=505 (9 studies [ERCP-guided RFA in 4 studies, PTC-guided RFA in 4 studies, both approaches in 1 study])	In the light of this limited data based on observational studies, RFA was found to be safe and was associated with improved stent patency in patients with malignant biliary strictures. In addition, RFA may be associated with improved survival in these patients.	Mixed approaches (ERCP and PTC), limited outcomes relating to ERCP-guided RFA reported; more recent studies and systematic review and meta-analysis included in the key evidence.
Tarar ZI, Farooq U, Gandhi M et al. (2023) Effect of radiofrequency ablation in addition to biliary stent on overall survival and stent patency in malignant biliary obstruction: an updated systematic review and meta-analysis. European journal of gastroenterology & hepatology 35(6): 646-53	Systematic review and meta-analysis N=1766 (14 observational studies and 3 RCTs; ERCP for RFA in 12 studies and PTC for RFA in 5 studies)	RFA treatment, in addition to stent placement in MBO, potentially improves OS and stent patency duration.	Of the 12 relevant studies, 3 RCTs and 4 observational studies included in Cha (2021) and 1 observational study (Xia 2021) included in the key evidence. Subgroup analysis was done to determine the effect of the procedure used to deliver RFA (ERCP versus PTC) on stent patency so no other outcomes of interest relating to the ERCP

			approach only were reported.
Yang J, Wang J, Zhou Hb et al. (2020) Endoscopic radiofrequency ablation plus a novel oral 5-fluorouracil compound versus radiofrequency ablation alone for unresectable extrahepatic cholangiocarcinoma. Gastrointestinal endoscopy 92(6): 1204-1212e1	RCT N=75 (RFA plus S-1, n=37; RFA, n=38)	For the treatment of locally advanced extrahepatic CCA, endoscopic RFA combined with S-1 is associated with longer survival and stent patency and improved functional status than RFA alone.	This study focused on the effect of S-1.
Yang J, Han S, Zhou H et al. (2022) The efficacy and safety of endoscopic papillectomy combined with endobiliary radiofrequency ablation for ampullary neoplasms with intraductal biliary extension. Techniques and Innovations in Gastrointestinal Endoscopy 24(3): 240-5	Case series (retrospective) N=8 Follow up: mean 28.5 months	Endoscopic papillectomy combined with intraductal RFA may be an effective and safe treatment for ampullary neoplasms with intraductal extension, particularly for patients who are poor surgical candidates. Given the risk of recurrence, indefinite surveillance is recommended.	Small sample

Appendix Meta-analysis

The 6 primary studies in the key evidence (tables 2 and 3) were included in the meta-analysis.

Data analysis

The effects of treatments (RFA plus stent versus stent only) on OS and stent patency were examined using pooled HR and weighted mean difference[1], respectively, with 95% CI. Data on OS and stent patency was analysed using the random-effects generic inverse variance model. Sensitivity analyses were carried out to explore the influence of different factors on the effect size for OS and stent patency (including study design, approaches to RFA, repeated RFA sessions, the use of other antitumour treatments, and stent types). Adverse events were analysed using an exploratory approach, and data was pooled in a fixed-effect meta-analysis using the Mantel-Haenszel model.

Heterogeneity was assessed using Chi^2 and I^2 statistics. I^2 values of 25%, 50%, and 75% were considered as low, medium, and high levels of heterogeneity. Forest plots were used to display the meta-analysis results. All analyses were performed using Cochrane Review Manager V5.

Results

OS

All 6 studies (n=1,023) reported a measure of survival, with 4 studies presenting HRs and 2 studies describing median OSs. When comparing RFA plus stent with stent only, the pooled HR for OS from 6 studies (n=1,040) was 0.50 (95% CI, 0.36 to 0.69; figure 1a), favouring RFA plus stent insertion. This effect was statistically significant ($p<0.0001$), with moderate heterogeneity ($I^2=56\%$). This

[1] Medians were used when means were not reported.

direction of effect on survival is consistent across all individual studies as shown in figure 1a.

A sensitivity analysis for 5 RCTs versus 1 observational study showed statistically significant effects for both subgroups (RCTs: HR, 0.48 [95% CI 0.29 to 0.78], I^2=63%; observational study, HR, 0.55 [95% CI, 0.44 to 0.70]) and there was no detectable subgroup difference (I^2=0%, p=0.61; figure 1b).

It is noted that 2 studies (Kang 2021a, 2021b) included a small proportion of people undergoing RFA via PTC (≤20%). Also, these 2 studies reported median OSs which were then used to calculate HRs. In contrast, the other 4 studies included people undergoing ERCP-directed RFA and reported HRs. Proportional hazards were assumed, even though proportionality was untested. Visual observation of the Kaplan-Meier curves suggested that this assumption was considered reasonable, except for Albers (2022). Although the Kaplan-Meier curves in the Albers study crossed during the first 3 months, after which the curves diverged and then showed parallel curves until the end of follow up; so, its impact on the overall result would likely to be small. A sensitivity analysis of studies with endoscopic RFA versus mixed approaches to RFA was carried out. The analysis showed a statistically significant effect on survival after endoscopic RFA (HR, 0.46; 95% CI, 0.31 to 0.67; I^2=69%; p<0.0001) but not after mixed approaches to RFA (HR, 0.72; 95% CI, 0.42 to 1.25; I^2=0%; p=0.24). There was no statistically significantly subgroup difference, but with moderate heterogeneity (I^2=43.8%; figure 1c).

When considering studies with versus without repeated RFA sessions, a sensitivity analysis indicated a statistically significant effect of RFA on OS for the use of repeated RFA sessions (HR, 0.43; 95% CI, 0.28 to 0.64; I^2=66%; p<0.0001) but not for single RFA session (HR, 0.73; 95% CI, 0.46 to 1.14; I^2=0%; p=0.17; figure 1d). There was no statistically significantly subgroup difference, but moderate heterogeneity presented (I^2=65.6%, p=0.09).

For the use of other antitumour treatments, especially chemotherapy as a key confounding factor, a sensitivity analysis of studies with versus without the use of other antitumour treatments was conducted. The effects of RFA on survival for both subgroups were statistically significant (studies with the use of other antitumour treatments: HR, 0.56 [95% CI, 0.47 to 0.66]; studies without the use of other antitumour treatments: HR, 0.18 [95% CI, 0.09 to 0.37]), but there was a subgroup difference with significant heterogeneity (I^2=89.2%, p=0.002; figure 1e).

Noticeably, only Yang (2018) excluded people who underwent systemic therapies. After separating this study, the analysis for studies with other antitumour treatments showed no observed heterogeneity, indicating a substantial reduction in the level of heterogeneity. One possible explanation would be due to a different RFA application protocol used. People in the Yang study received more RFA sessions (half of the people had 3 or more sessions of RFA) and had their stent replaced more frequently (every 3 months) than people in other studies. This difference could also contribute to the large effect of RFA on survival and prolong stent patency duration (as described in the 'stent patency' section).

Across the 5 studies that involved the use of other antitumour treatments, the proportions of people who received other treatments were generally low (18% versus 17% across studies) but comparable between the RFA plus stent group and the stent only group within studies. This suggests that the results from this subgroup may be more representative of people who were forgoing systemic treatments. In fact, such treatments (e.g. chemotherapy) might have limited efficacy, because MBO is usually diagnosed in people with advanced CCA or pancreatic cancer (Kang 2021a). In addition, due to strict eligibility criteria, systemic treatments may not be suitable for many people with advanced cancer. Nevertheless, careful interpretation of the results is warranted and further

exploration of repeated RFAs (such as its application frequency) would be valuable.

When considering different types of stents used, a sensitivity analysis was conducted. Evidence suggested statistically significant effects of RFA on OS for the subgroups using plastic stents (HR, 0.31; 95% CI, 0.12 to 0.82; I^2=84%; p=0.02) or both types of stents (HR, 0.55; 95% CI, 0.44 to 0.70; I^2=0%; p<0.0001), but not for the SEMS subgroup (HR, 0.73; 95% CI, 0.46 to 1.14; I^2=0%; p=0.17; figure 1f). Despite that, there was no statistically significant subgroup difference with low heterogeneity. It is noted that Kang (2021b) inserted plastic stents and then exchanged to SEMS after 3 months. The stent patency was measured from enrollment to at least 1 SEMS occlusion or death. Thus, this study was included in the subgroup with the use of both types of stents.

Stent patency

In term of stent patency, its duration was reported in 4 RCTs (n=317). The pooled weighted mean difference in patency duration between RFA plus stent and stent only was 0.97 months (95% CI, -0.67 to 2.62; I^2=61%; p=0.25; figure 2a), but this effect was not statistically significant, with significant heterogeneity. This non-significant effect was also consistent with the finding from each individual RCT except for Yang 2018. Given the difference in the RFA application protocol used, the results need to be interpreted with caution.

In terms of stent types, a sensitivity analysis of studies using different stents was conducted. No evidence suggested that RFA statistically significantly prolonged patency duration in all 3 subgroups (figure 2b), and there was no detectable subgroup difference (I^2=0%, p=0.93).

Stent patency is one of the factors that affect survival. The mechanism of the survival benefit of RFA may be explained by its ability to relieve biliary obstruction and prevent recurrent cholangitis. Interestingly, in this meta-analysis, although

RFA fails to show a prolonged effect on stent patency, it is proven to have a survival benefit. One possible explanation would be that mechanisms other than stent patency improve survival outcomes: 1) RFA reduces the maximal tumour load differing the disease's progression (Xia 2021); 2) in situ tumour destruction provided a useful antigen source for the induction of antitumor immunity; 3) RFA may play a role through indirect antitumour effects (Cha 2021).

Cholangitis and cholecystitis

Cholangitis is typically inflammation of the biliary tract, commonly caused by infection. Cholangitis influences morbidity and mortality. Based on 6 studies (n=1,023), the pooled risk ratio of cholangitis between groups was 0.94 (95% CI, 0.72 to 1.22; I^2=0%; p=0.64; figure 3a). A sensitivity analysis for acute cholangitis (within 30 days) was conducted. The pooled risk ratio reduced slightly to 0.86 (95% CI, 0.53 to 1.36), but also no evidence of a statistically significant difference between groups (p=0.49; figure 3b).

For cholecystitis, which is an inflammation of the gallbladder, commonly caused by a blockage, the pooled risk ratio from 4 studies (n=910) was 9.48 (95% CI, 2.96 to 30.31; I^2=7%; p=0.0002; figure 4) between groups. This indicates that RFA carries a higher risk of cholecystitis than stent insertion alone, although the estimates are very imprecise. One possible explanation for this imprecision is that RCTs are not powered for safety outcomes. Nevertheless, most individual studies favour stent only and extra precaution would be necessary during ablation. It is noted that all cases were acute cholecystitis (within 30 days) except for 1 delayed cholecystitis after RFA plus stent; so, the impact of this delayed case on the overall outcome is likely to be minimal.

Figure 1a Pooled HR for OS between RFA plus stent and stent only

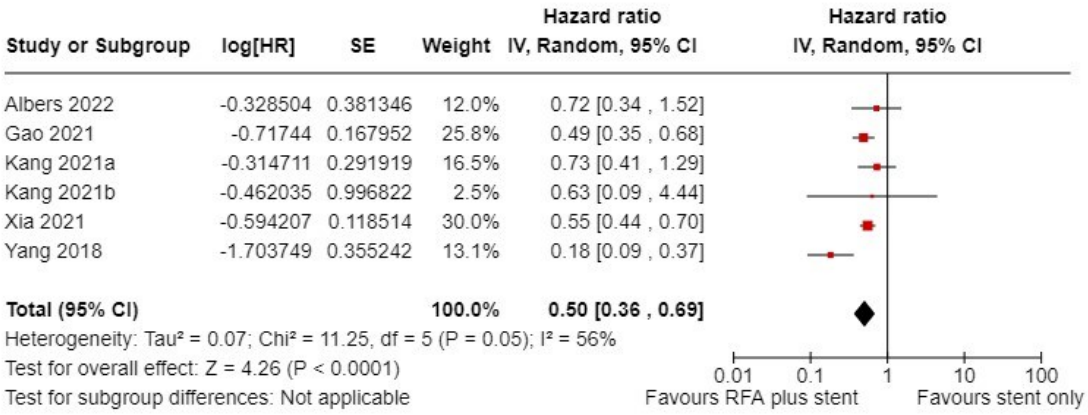

Figure 1b Sensitivity analysis of OS between RFA plus stent and stent only for RCTs or observational study

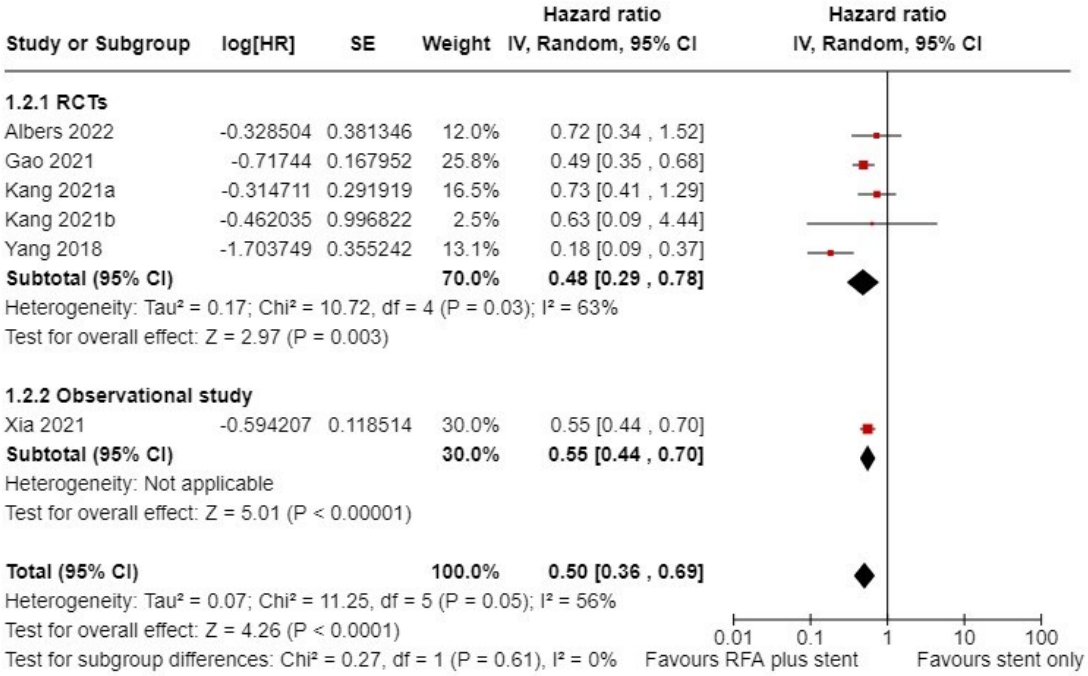

Figure 1c Sensitivity analysis of OS between RFA plus stent and stent only for endoscopic RFA or mixed approaches to RFA

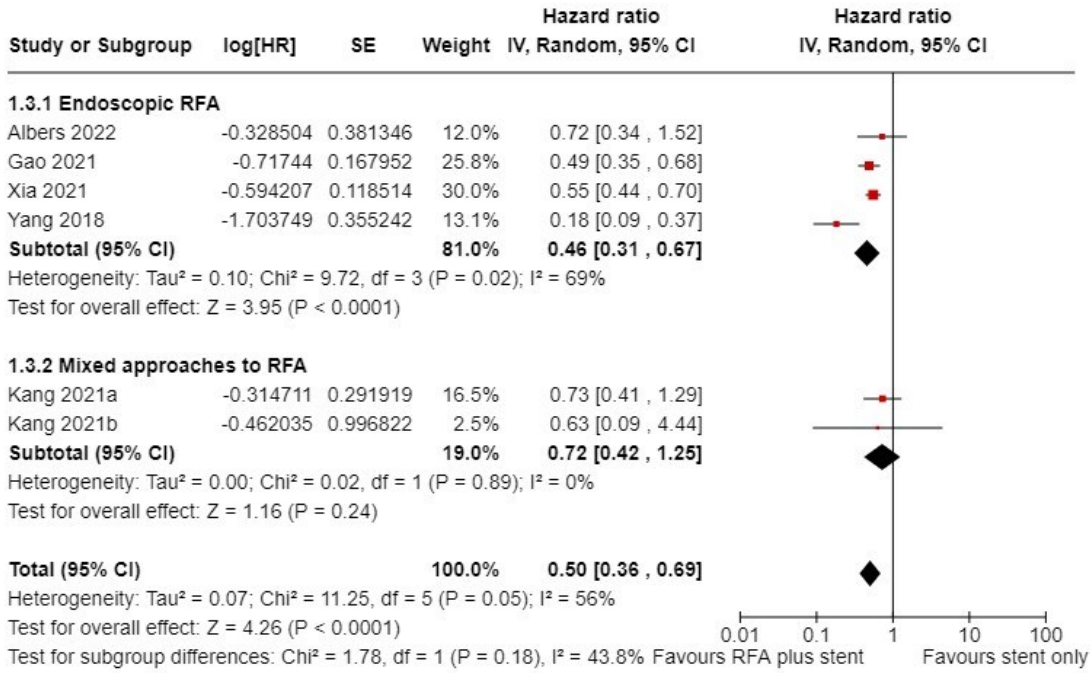

Figure 1d Sensitivity analysis of OS between RFA plus stent and stent only for studies with or without repeated RFA sessions

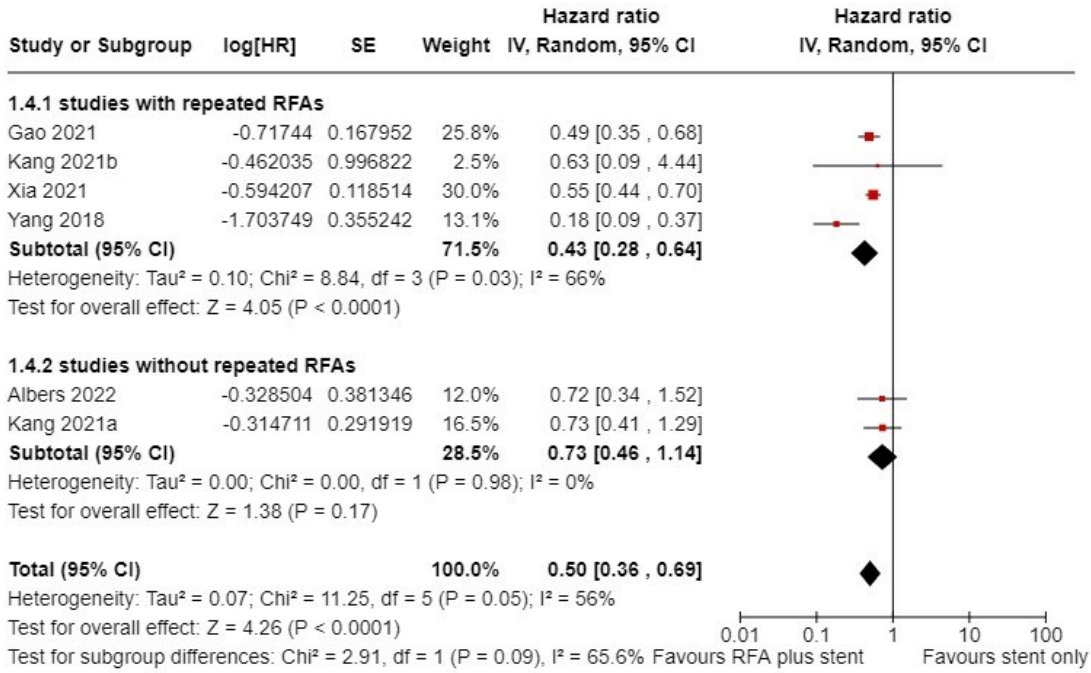

Figure 1e Sensitivity analysis of OS between RFA plus stent and stent only for studies with or without antitumour therapies

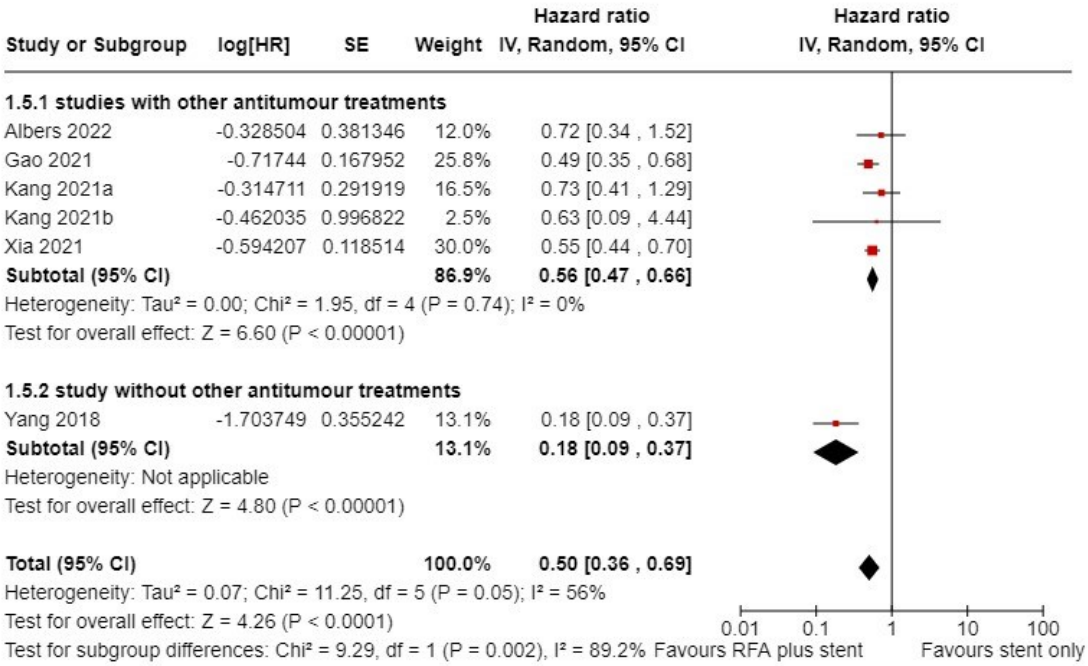

Figure 1f Sensitivity analysis of OS for studies with different stents

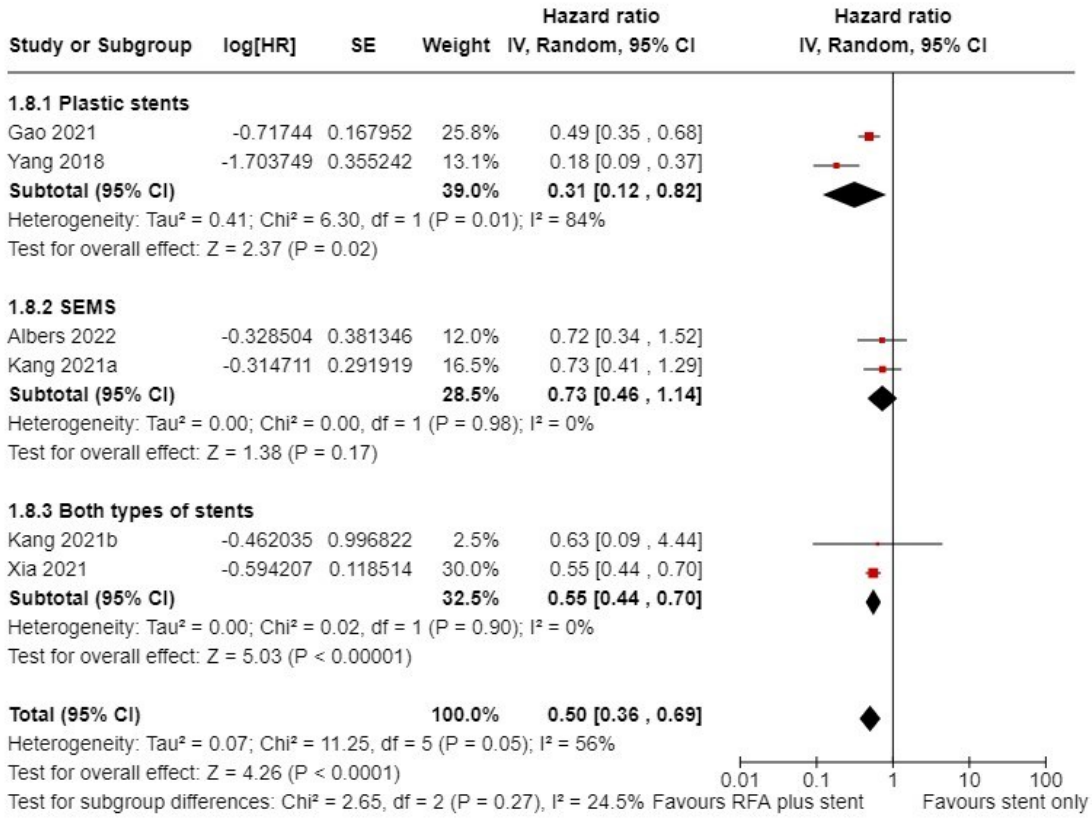

Figure 2a Pooled mean difference in stent patency duration between RFA plus stent and stent only

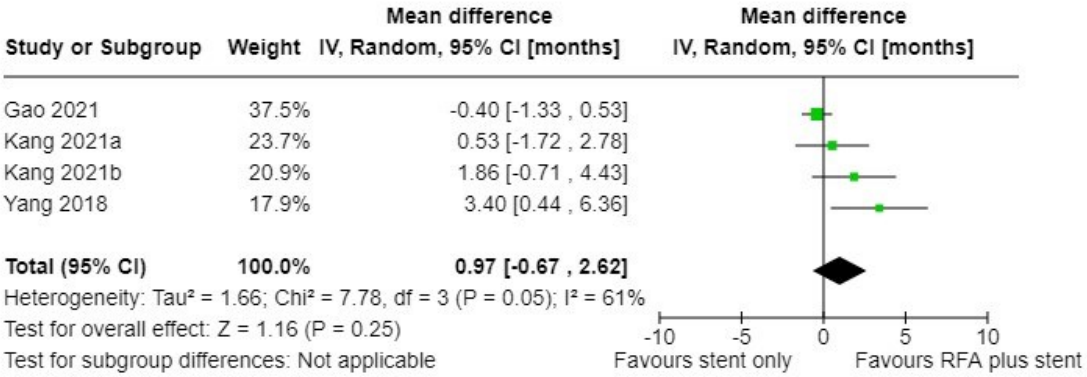

Figure 2b Sensitivity analysis of stent patency for different stents

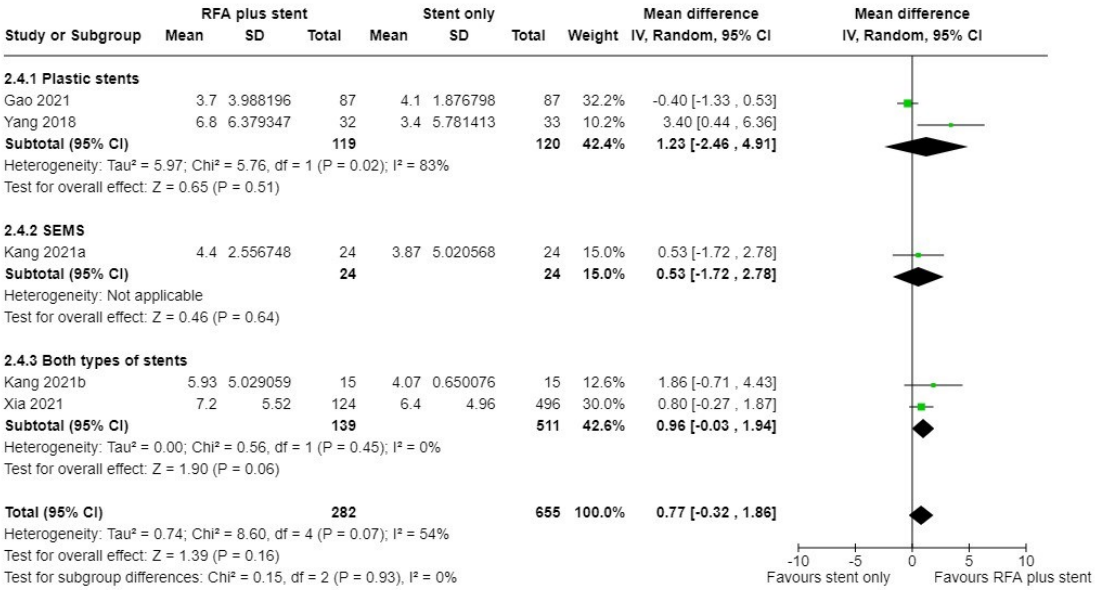

Figure 3a Pooled risk ratio of cholangitis between RFA plus stent and stent only

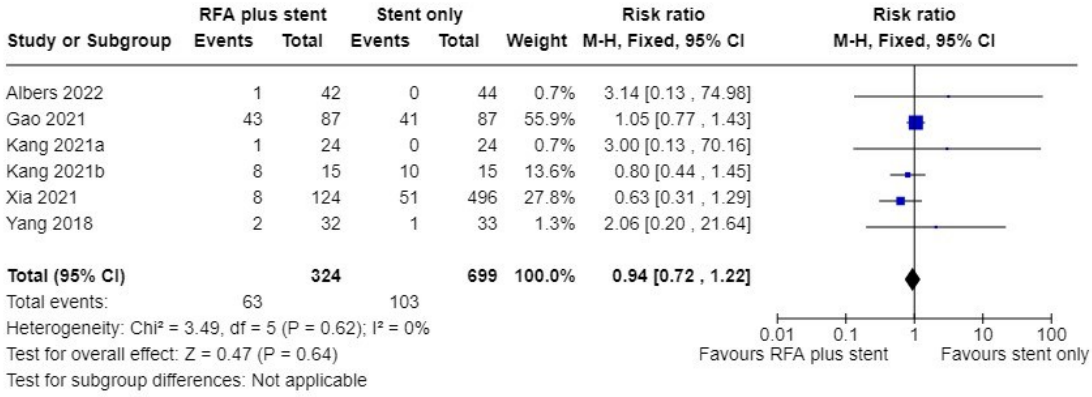

Figure 3b Sensitivity analysis of risk ratio for acute cholangitis between RFA plus stent and stent only

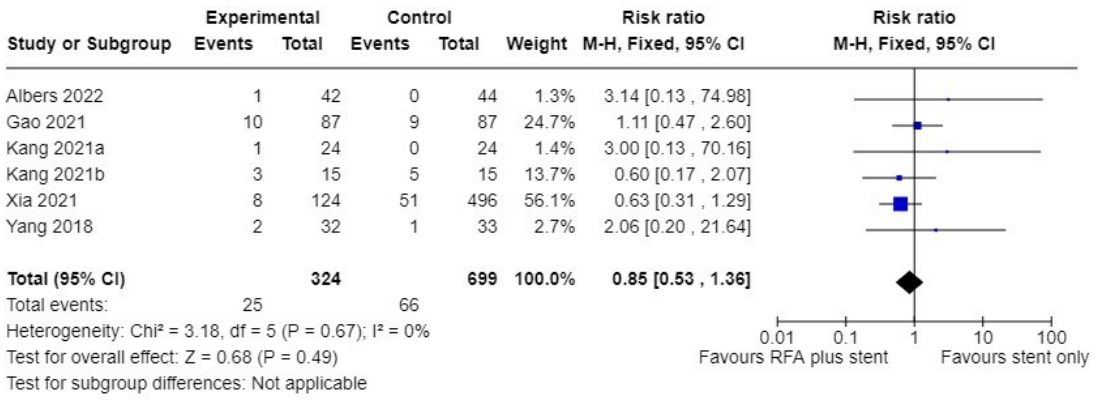

Figure 4 Pooled risk ratio of cholecystitis between RFA plus stent and stent only