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Efficacy and Safety of Radiofrequency Ablation Plus Stent Versus Stent-alone Treatments for Malignant Biliary Strictures

A Systematic Review and Meta-analysis

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Background/Aims: Malignant biliary strictures (MBS) are very aggressive and cannot be diagnosed in the early stages due to their asymptomatic nature. Stenting the stricture area of the biliary tree is palliative treatment but has poor survival time. Radiofrequency ablation plus stent (RFA+S) have been recently used to improve the survival and stent patency time in patients with MBS. In this systematic review and meta-analysis, we tried to evaluate the efficacy and safety of radiofrequency ablation.

Materials and Methods: Study search up to December 2021 was performed in different medical databases such as PubMed, Web of Science, and Cochrane library, etc. We selected eligible studies reporting survival time, stent patency time, and adverse events in patients with MBS. We compare the outcomes of RFA+S and stent-alone treatment groups.

Results: A total of 15 studies (6 randomized controlled trials and 9 observational studies) with 1815 patients were included for meta-analysis of which 701 patients were in RFA+S group and 1114 patients in the stent-alone group. Pooled mean difference of survival time was 2.88 months (95% CI: 1.78-3.97) and pooled mean difference of stent patency time was 2.11 months (95% CI: 0.91-3.30) and clinical success risk ratio was 1.05 (95% CI: 1.01–1.09). Risk ratios for adverse events are given; Bleeding 0.84 (95% CI: 0.34-2.11), abdominal pain 1.06 (95% CI: 0.79-1.40), pancreatitis 0.93 (95% CI: 0.43-2.01), cholangitis 1.07 (95% CI: 0.72-1.59), and stent dysfunction 0.87 (95% CI: 0.70-1.07).

Conclusions: Radiofrequency ablation is involved in increased survival and stent patency time for MBS patients. With the help of better techniques, adverse events can be limited.

Key Words: malignant biliary strictures, cholangiocarcinoma, bile duct obstruction, biliary strictures, RFA, stent, ERCP, RCTs, review, meta-analysis

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Malignant biliary stricture (MBS) is a narrowing of the biliary tract caused by a blockage in the biliary tract. Cancers such as cholangiocarcinoma (CCA),[1] pancreatic adenocarcinoma, gallbladder carcinoma, hepatocellular carcinoma, and ampullary carcinoma are the most common causes of this blockage. Depending on where it arises, CCA can be divided into intrahepatic CCA and extrahepatic cholangiocarcinoma (eCCA). Because of the difficulty in diagnosing MBS and the fact that it is asymptomatic, the majority of MBS are unresectable at the time of diagnosis.[2] Stent placement and biliary drainage are palliative treatments for such patients to ensure continuous bile flow and prevent obstruction of the bile ducts. Endoscopic retrograde cholangiopancreatography (ERCP), percutaneous transhepatic cholangiodrainage, and endoscopic ultrasound-guided biliary drainage are the most common methods of placing metallic or plastic stents.[3–5]

However, stenting has some disadvantages, including a short stent patency period and stent obstruction due to tumor growth within the mesh of the stent, which are both unwanted outcomes. It is possible to achieve local necrosis of tumor tissues using radiofrequency ablation (RFA), which is a technique that uses thermal energy. To treat bile obstruction, it is used before or after stent placement. Most energy is delivered through the intraductal way achieved by ERCP, percutaneous intraductal, or surgical means (this process has its limitations).[6] Using RFA treatment has yielded impressive outcomes during the past few decades.[7,8] RFA is a locoregional cancer treatment therapy in which thermal energy generated by high-frequency alternating electric current is used. Thermal energy causes burn injuries

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in the stricture area, thus leading to coagulate necrosis, protein denaturation, and cell desiccation.[9] Habib Endo HPB (Boston Scientific; EMcision Ltd) and ELRA (Taewoong Medical) are 2 types of thin probe catheters used for RFA generation and delivery to the stricture area. Despite the fact that this treatment has been around for a long time, the introduction of advanced procedures, as well as careful monitoring, has demonstrated encouraging outcomes in terms of overall survival and stent patency in recent years. So it is necessary to perform a meta-analysis to evaluate a specific result. In this systematic review and meta-analysis, we looked at how well and safely MBS treatment worked.

MATERIALS AND METHODS

We followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines for reporting this systematic review and meta-analysis.[10]

Search Strategy

A search of the medical literature for ideas about MBS and RFA was conducted by 2 independent researchers. "Radiofrequency ablation," "stent," and "malignant biliary strictures" including (Cholangiocarcinoma, Pancreatic Neoplasms, Gallbladder Neoplasms, or Ampullary cancer) were the keywords we used in our search strategies. Searches were conducted in PubMed, Web of Science, and the Cochrane library up to and including December 2021. The results were only available in the English language and as full-text articles. All of the results were gathered, and the titles and abstracts that were eligible were approved (PRISMA, Fig. 1).

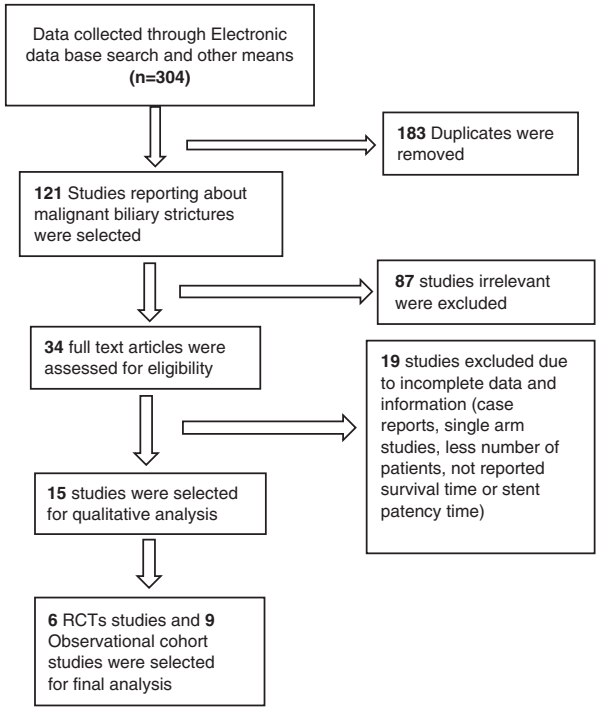

FIGURE 1. PRISMA flowchart of included studies. RCT indicates randomized controlled trial.

Study Selection Criteria

The following criteria were used to determine which studies were included and which were excluded.

Inclusion Criteria

Studies that met the following criteria were considered for inclusion in this analysis:

(1) MBS are found in patients under studies (CCA, pancreatic carcinoma, gallbladder carcinoma, and ampullary carcinoma)
(2) Strictures were caused by malignant biliary diseases that were unresectable at the time of the diagnosis.
(3) The study compares the outcome of RFA to stent-alone therapy.
(4) Only randomized controlled trials (RCTs) or observational studies (OS) about MBS.
(5) Only human studies published in English language.

Exclusion Criteria

Studies that met the criteria listed below were considered ineligible:

(1) Strictures result from benign diseases.
(2) Duplicates, case studies, review articles, and letters were not included.
(3) Studies that only have RFA or stent-alone outcomes (single-arm studies).
(4) Studies that do not report results including survival time, stent patency time, and adverse events.
(5) Studies that included <20 patients.
(6) Studies that treated the patients with occluded stents or received RFA for second time.
(7) Animal studies or published in other languages.
(8) Studies performed in pediatric (age less than 18 y).

Data Extraction and Study Selection

Two authors made decisions regarding which studies should be excluded and which studies should be included, and they collected data from the studies that were chosen. We collected information from each study about the publishing year, country, study design, total number of patients, mean age of patients, method of treatment, number of patients who received either a stent-alone or an RFA+stent, procedure approach, type of stricture, final outcome, type of stent used, stent dysfunction, clinical success, the device used for RFA delivery, amount of energy and time, mean survival time, stent patency time, and adverse events. There were some different coefficients (reported survival time and stent patency time) that were all transformed into the same unit [from days to months dividing by 30 (days to months conversion)]. Each study was then subdivided into 2 groups: the RFA group (RFA) and the stent-alone group (S) (Tables 1, 2; summary of the studies that were included).

Outcome and Definitions

Our primary outcomes, which are derived from data extracted from the studies, are the pooled mean difference of survival time (defined as survival time of a patients after receiving the treatment during follow-up time or till death) and pooled mean difference of stent patency time (defined as the time interval between stent placement and stent occlusion or replacement of stent or death). The secondary outcome includes clinical success, stent dysfunction, and risk factors for adverse events such as bleeding, cholangitis, abdominal pain, and pancreatitis. In a subgroup analysis, RCT studies, and OS studies, RFA approaches using

TABLE 1. Characteristics of Included Studies

References, Country	Design	No. Patients	Age (Mean)	RFA Device Stent Type	RFA Energy and Time	Clinical Success	OS Time [Median/Mean (95% CI)] (mo)	SPT (95% CI)
Kallis et al,[11] UK	OS	RFA 23	68.9+	Habib	10 W	NA	9.3 (7.74-10.51)	NA
		Stent 46	69.9+	SEMS	120 s	NA	5.15 (4.4-5.8)	NA
Wang et al,[12] China	OS	RFA 18	56.6+	Habib	10 W	NA	6.1 (4.8-15.2)	5.8 (2.8-11.5)
		Stent 18	58.5+	SEMS	90 s	NA	5.8 (4.2-16.5)	4.5 (2.4-8)
Hu et al,[13] China	RCT	RFA 32	71.9+	Habib	7-10 W	NA	10.4 (8-12.7)	5.73 (4.8-6.6)
		Stent 31	71+	PS	60-90 s	NA	5 (3-7.1)	3.9 (2.6-5.2)
Wu et al,[14] China	OS	RFA 28	58.3+	Habib	10 W	NA	8.1 (7.7-8.6)	8.03 (5.78-10.2)
		Stent 30	57.5+	SEMS	90 s	NA	6.97 (3.22-10.7)	4.50 (4.36-4.73)
Yang et al,[15] China	RCT	RFA 32	62+	Habib	7-10 W	31	13.2 (11.8-14.2)	6.8 (3.6-8.2)
		Stent 33	64+	PS	90 s	27	8.3 (7.3-9.3)	3.4 (2.4-6.5)
Bokemeyer et al,[16] Germany	OS	RFA 20	68+	Habib	NA	NA	11.4+1.9	NA
		Stent 22	66+	PS/MS			7.37+0.87	NA
Kang et al,[17] Korea	RCT	RFA 24	73+	ELAR	7-10 W	21	8.3 (3.9-12.3)	4.4 (3.3-5.5)
		Stent 24	67	MS	120 s	20	6 (0.9-11.1)	3.9 (1.9-5.9)
Uyanik et al,[18] Turkey	OS	RFA 30	67.8+	Habib	10 W	NA	8.2 (2.82-13.52)	7.4 (1.5-13.36)
		Stent 32	65+	MS	120 s	NA	6.6 (2.26-10.9)	5.2 (1.05-9.48)
Yu et al,[19] China	OS	RFA 28	64.5	Habib	10 W	NA	7.2 (6.5-7.9)	6.6 (6.1-7.7)
		Stent 42	64	MS	120 s	NA	5.6 (4.8-6.4)	4.9 (4.2-5.6)
Xia et al,[20] China	OS	RFA 124	68+	Habib	10-12 W	115	9.5 (7.7-11.3)	NA
		Stent 496	67+	MS	60-120 s	440	6.1 (5.6-6.6)	NA
Kong et al,[21] China	OS	RFA 150	62+	Habib	8-10 W	144	12.3 (11.6-13.4)	11.4+3.9
		Stent 127	59+	MS	90-120 s	116	11.8 (11.2-13.1)	7.3+2.6
Gao et al,[22] China	RCT	RFA 87	68.5+	Habib	7-10 W	80	14.3 (11.9-16.7)	3.7 (2.8-4.5)
		Stent 87	67.9+	PS	90 s	79	9.2 (7.1-11.2)	4.1 (3.7-4.5)
Tomas et al,[23] Czech	RCT	RFA 36	65+	Habib	10 W	NA	9.1 (5.4-12.7)	5.2 (0.7-12.8)
		Stent 40	67+	MS	90-120 s	NA	9.8 (6.9-12.7)	4.8 (0.8-18.2)
Gou et al,[24] China	OS	RFA 64	60+	Habib	10 W	NA	13.2 (11.1-16.5)	8.2 (7.1-9.3)
		Stent 71	62+	MS	120 s	NA	8.5 (7.6-9.6)	4.3 (3.6-5.0)
Kang et al,[25] Korea	RCT	RFA 15	76+	ELRA	7 W	15	7.6 (2.56-12.76)	5.9 (3.21-8.6)
		Stent 15	72+	MS	60-120 s	13	4.8 (0-10.76)	4.06 (3.7-4.42)

ELAR indicates ELAR RFA generator; Habib, Endo Habib RFA generator; MS, metal stent; NA, no information available; OS, observational study; OS Time, Overall survival time; PS, plastic stent; RCT, randomized controlled trial; RFA, radiofrequency ablation; SPT, stent patency time.

TABLE 2. Characteristics of Included Studies Continued

References, Country	RFA Delivery Route	Stricture Location (RFA+Stent)	Cholangitis	Pancreatitis	Bleeding	Stent Days	Abdominal Pain
Kallis et al,[11] UK	Endo	PC = 23+46	NA	NA	NA	9	NA
			NA	NA	NA	14	NA
Wang et al,[12] China	Percut	CCA = 9+9, PC = 4+4, GC = 3+3	3	NA	NA	3	NA
			0	NA	NA	10	NA
Hu et al,[13] China	Endo	CCA = 32+31	4	2	1	28	NA
			6	2	0	24	NA
Wu et al,[14] China	Percut	CCA = 28+30	0	NA	0	10	20
			2	NA	3	19	18
Yang et al,[15] China	Endo	CCA = 32+33	2	0	0	NA	NA
			1	1	1	NA	NA
Bokemeyer et al,[16] Germany	Endo	CCA = 20+22	6	2	NA	NA	NA
			0	0	NA	NA	NA
Kang et al,[17] Korea	Endo	CCA = 18+12, PC = 4+10, other = 2+2	1	0	NA	14	9
			0	3	NA	11	14
Uyanik et al,[18] Turkey	Percut	CCA = 13+17, PC = 11+12, AC = 1+0, GC = 0+1, GIC = 3+1	2	NA	1	9	11
			4	NA	3	18	16
Yu et al,[19] China	Percut	CCA = 11+16, PC = 9+14, GC = 0+12, AC = 1+1, HCC = 3+5	NA	NA	NA	23	4
			NA	NA	NA	35	8
Xia et al,[20] China	Endo	CCA = 79+256, GC = 12+76, HCC = 16+50, PC = 8+70, ICC = 7+37	NA	NA	NA	NA	NA
			NA	NA	NA	NA	NA
Kong et al,[21] China	Percut	PC = 37+31, GC = 11+8, CCA = 73 +62, ICC = 3+1, HCC = 6+7, LNM = 20+8	23	5	71		76
			16	2	36		47
Gao et al,[22] China	Endo	CCA = 69+78, AC = 18+9	10	4	1	19	6
			9	5	3	16	3
Tomas et al,[23] Czech	Percut	CCA = 22+23, PC = 5+8, GC = 2+5, other = 7+4	NA	NA	NA	6	1
			NA	NA	NA	8	2
Gou et al,[24] China	Endo	CCA = 36+42, ICC = 7+8, GC = 7+7, AC = 14+14	NA	NA	NA	NA	NA
			NA	NA	NA	NA	NA
Kang et al,[25] Korea	Endo	CCA = 13+13, GC = 2+2	3	0	NA	NA	3
			5	1	NA	NA	0

AC indicates adenocarcinoma; AC, ampullary carcinoma; CCA, cholangiocarcinoma; Endo, endoscopic retrograde cholangiopancreatography; GC, gallbladder cancer; GIC, gastrointestinal cancer; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; LNM, lymph node metastasis; NA, no information available; OT, other types; PC, pancreatic adenocarcinoma; Percut, percutaneous cholangiography; S, stent.

endoscopic and percutaneous techniques, Habib RFA generator, and ELRA RFA generator were compared. In addition, the pooled mean difference in survival time only for eCCA patients was also calculated.

Assessment of Risk of Bias

For risk of bias assessment, we applied the tool developed by the Cochrane Collaboration to determine the probability of bias.[26] For RCT studies, a rating of "low" indicated a low risk of bias, "high" signified a high risk, and "some concerns" indicated that the information available was insufficient to make a risk of bias determination.[27] Specifically, we evaluate studies based on the randomization method, missing outcome data, the timeliness of participant identification or recruitment, measuring the outcome, bias due to deviations from intended interventions, and choosing which outcomes to report. While for non-RCT studies we utilized tools and results and judge the studies according to the information given by each study. Most of OS were at moderate risk of bias studies (Risk of bias table, Supplementary Table, Supplemental Digital Content 1, http://links.lww.com/JCG/A935).

Publication Bias and Study Effect

For our meta-analysis, number of included studies is 15 so there was a risk of publication bias. For that we assessed the each outcome by funnel plots and each study effect was judged by removing each study one by one and see its effect on the final outcome.

Statistical Analysis

The continuous variance method was used to calculate pooled standard mean differences. Because some studies reported median survival time, we can use median as a substitute for mean survival time, according to the Cochrane Handbook Guide for Meta-analysis.[28] The pooled mean survival time and pooled mean stent patency time were calculated by using generic inverse variance method with the random-effects model. The dichotomous inverse variance method was used to calculate the risk ratios (RRs) for adverse events for categorical variables in this study.[29] The Cochrane I^2 statistics were used to estimate statistical heterogeneity. Low heterogeneity was represented by 25% to 49%, whereas moderate heterogeneity by 50% to 74%, and high heterogeneity was represented by values of 75% or >75%.[30] P value <0.05 was considered statistically significant ($P < 0.05$). The Review Manager software was used to conduct all of our statistical analysis (Rev Man 5.4, The Cochrane Collaboration).

RESULTS

Search Outcome, Characteristic, and Assessment of Studies

After removing duplicates and unrelated studies from our search, we were able to identify 121 studies. Only 34 studies were selected for the full-text evaluation. The final analysis included 15 studies, 6 of which were RCTs[13,15,17,22,23,25] and 9 of which were prospective OS.[11,12,14,16,18–21,24] The remaining 19 articles were eliminated because they were review articles, missing required outcome, animal studies, and single-arm studies (Fig. 2). A total of 1815 patients were included in the analysis, among whom 701 underwent RFA with a stent and 1114 underwent stent-alone therapy procedures. Fourteen studies were published as complete articles, and one study was published as an abstract. Six RCT studies were included, with 3 being multicenter RCTs, 3 being single-center RCTs, and 9 being the prospective OS. Self-expanding metal stents were used in 12 studies, whereas the other 3 studies used plastic stents. Radiofrequency ablation) generation was carried out in 2 trials using the ELRA STAR Korean device, with energy levels ranging from 7 to 10W for 60 to 120 seconds, while the other studies used the HABIB Endo HBP UK/USA device, with energy levels ranging from 7 to 10 W for 90 to 120 seconds. There were 1105 patients with CCA, 296 patients with pancreatic cancer, 151 patients with gallbladder cancer, 58 patients with ampullury carcinoma, and 205 patients with other cancers in the group. Every study, with the exception of Kallis and colleagues, Xia and colleagues, and Yu and colleagues, describes specific adverse events. Some studies distinguish between early and late adverse events, but we only consider early adverse events for the purposes of our calculations. Only 6 studies reported clinical success percentage. There were 3 studies that did not report stent patency time and 5 studies that did not provide the number of patients who had stent occlusions/dysfunction. The median duration of follow-up ranged from 3 to 31.8 months, or till the patient's death. In RCT trials, there was no evidence of a high risk of bias. They were all low, and one of them was concerned with the possibility of bias in reporting, selection, attrition, and calculation of the results of experiments. The fact that Hu and colleagues was published as an abstract reduced the amount of materials and methods details available. In contrast, the risk of bias in OS research was examined and a report was produced. The risk of bias in the results is shown in the risk of bias table (Supplementary risk of bias Tables 1, 2, Supplemental Digital Content 1, http://links.lww.com/JCG/A935).

Primary Outcomes

Pooled Mean Survival Time

The difference in mean survival time between the RFA +S and S-alone groups in 1815 patients was 2.88 months (95% CI: 1.78-3.97), $I^2 = 77\%$, $P < 0.0001$. Subgroup analysis shows that RCTs comparing data from 456 patients shows a pooled mean difference for mean survival time of 4.20 months (95% CI: 2.64-5.77), $I^2 = 23\%$, $P < 0.0000$. Only OS studies produced data from 1359 patients, with a pooled mean survival time difference of 2.44 months (95% CI: 1.16-3.71), $I^2 = 82\%$. $P = 0.0002$. This indicates a statistically significant increase in survival time in the RFA+S group when compared with the S-alone group (Fig. 2A).

Pooled Mean Stent Patency

The mean difference in stent patency time between the RFA and S-only groups was 2.11 months (95% CI: 0.91-3.30), $I^2 = 84\%$ $P = 0.0005$. Whereas for subgroup analysis between RCT and OS showed the results of pooled mean difference for stent patency time of 1.04 months (95% CI: −0.22 to 2.30), $I^2 = 55\%$, $P = 0.11$) and 3.04 months (95% CI: 1.79-4.29), $I^2 = 75\%$, $P < 0.00001$, respectively (Fig. 2B). Stent patency time data shows that there is a greater difference in patency time for OS studies compared with RCT studies.

Secondary Outcomes

Only eCCA

For eCCA, we calculated the pooled mean difference in overall survival in 859 patients, which was 4.19 months (95% CI: 3.57-4.82), $I^2 = 0\%$, $P < 0.00001$. For RCT studies, the mean difference in survival time was 4.64 months (95% CI: 3.35-5.94), $I^2 = 0\%$, $P < 0.00001$, and for OS studies, it was 4.06 months (95% CI: 3.35-4.77), $I^2 = 0\%$, $P < 0.00001$, showing that the mean survival time difference is significantly higher for eCCA patients undergoing RFA than stenting alone. eCCA patient's shows relatively higher survival time compared with other types of strictures (Fig. 3A).

Clinical Success

The RR for clinical success was 1.05 (95% CI: 1.01-1.09), $I^2 = 0\%$, $P = 0.009$, indicating that stent dysfunction was almost the same for RFA+S group compared with S-alone group, whereas in subgroup analysis shows that RR for RCT studies was 1.06 (95% CI: 0.98-1.14), $I^2 = 1\%$, $P = 13$, and for OS studies was 1.05 (95% CI: 1.0-1.09), $I^2 = 0\%$, $P = 0.03$ (Supplementary Fig. 3, Supplemental Digital Content 1, http://links.lww.com/JCG/A935).

Stent Dysfunction

The RR for stent dysfunction was 0.87 (95% CI: 0.70-1.07), $I^2 = 41\%$, $P = 0.33$, indicating that stent obstruction/dysfunction incidents have no significant difference for RFA +S group compared with S-alone group. Subgroup analysis between RCT and OS showed RR of 0.91 (0.75-1.11), $I^2 = 0\%$, $P = 0.35$ and 0.73 (95% CI: 0.48-1.09), $I^2 = 62\%$, $P = 0.13$, respectively (Supplementary Fig. 4, Supplemental Digital Content 1, http://links.lww.com/JCG/A935).

Adverse Events

Bleeding. The bleeding RR was 0.84 (95% CI: 0.34-2.11), $I^2 = 30\%$, $P = 0.71$ indicating that the number of cases of bleeding have no difference for the RFA group and the S-alone group. RCT showed RR of 0.58 (95% CI: 0.12-2.82), $I^2 = 0\%$, $P = 0.50$, while OS showed RR of 0.74 (95% CI: 0.17-3.22), $I^2 = 54\%$, $P = 0.69$ Thus subgroup also show the same results (Fig. 3B).

Abdominal Pain. The RR for abdominal pain was 1.06 (95% CI: 0.79-1.40), $I^2 = 32\%$, $P = 0.71$ indicating that the number of abdominal pain occurrences is the same for both groups. While in subgroup analysis RCT and OS showed RR of 1.04 (95% CI: 0.43-2.52), $I^2 = 33\%$, $P = 0.93$ and 1.13 (95% CI: 0.86-1.49), $I^2 = 30\%$, $P = 0.36$, respectively (Fig. 4).

Pancreatitis. Pancreatitis RR was 0.93 (95% CI: 0.43-2.01), $I^2 = 0\%$, $P = 86$ that mean the incidents of pancreatitis are almost same for RFA group and S-alone group. Whereas subgroup analysis showed the data of 0.61 (95% CI: 0.25-1.52), $I^2 = 0\%$, $P = 0.29$ for RCT and 2.63 (95% CI: 0.63-10.94),

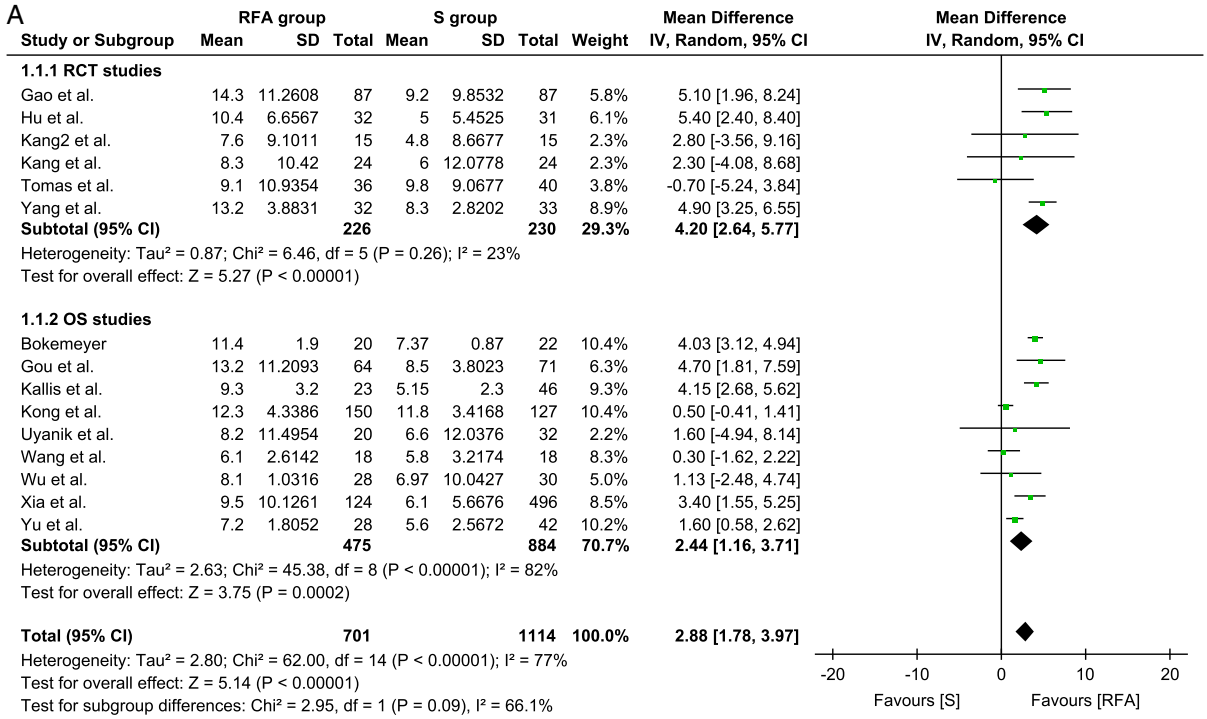

FIGURE 2. A, Forest plot of pooled mean difference of overall survival. B, Forest plot of pooled mean difference of stent patency. OS indicates observational study; RCT, randomized controlled trial; RFA, radiofrequency ablation; S, stent-alone.

$I^2 = 0\%$, $P = 0.18$ for OS. This mean pancreatitis is higher in OS studies compared with RCT studies but this difference is not significantly statistical (Supplementary Fig. 1, Supplemental Digital Content 1, http://links.lww.com/JCG/A935).

Cholangitis. RR for cholangitis was 1.07 (95% CI: 0.72-1.59), $I^2 = 2\%$, $P = 0.75$, that mean the number of cases of cholangitis for S-alone also same with the RFA+S group. Subgroups of RCT and OS studies showed data of 0.92 (95% CI: 0.52-1.62), $I^2 = 0\%$, $P = 0.76$ and 1.33 (95% CI: 0.72-1.59), $I^2 = 40\%$, $P = 0.59$, respectively. Statistically, there is no difference of RR between the groups (Supplementary Fig. 2, Supplemental Digital Content 1, http://links.lww.com/JCG/A935).

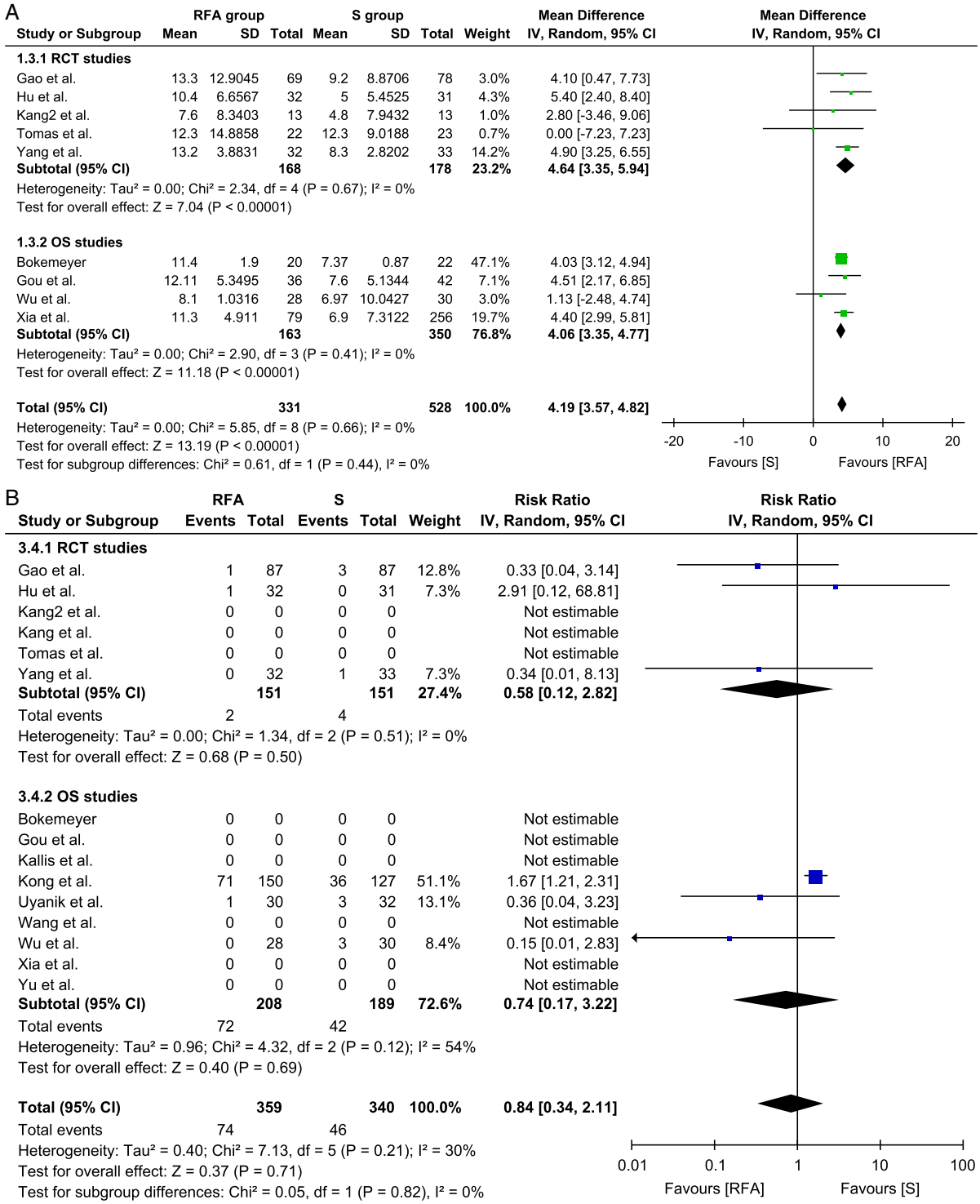

FIGURE 3. A, Forest plot of pooled mean difference of survival time for cholangiocarcinoma. B, Forest plot of risk ratio for bleeding. OS indicates observational study; RCT, randomized controlled trial; RFA, radiofrequency ablation; S, stent-alone.

Endoscopic Versus Percutaneous Approach

The subgroup analysis between endoscopic and percutaneous approaches for RFA delivery reveals that the endoscopic approach has a pooled mean difference of survival time of 4.18 months (95% CI: 3.55-4.80), $I^2 = 0\%$, $P < 0.00001$. Whereas the percutaneous RFA approach has a mean difference survival time of 1.37 months (95% CI: 0.22-2.53), $I^2 = 56\%$, $P = 0.02$. This mean endoscopic approach has a longer mean survival duration than the percutaneous technique (Fig. 5A). Patients who received RFA through the Habib device had a survival difference of 4.21 months (95% CI: 3.58-4.83), $I^2 = 0\%$, $P < 0.00001$,

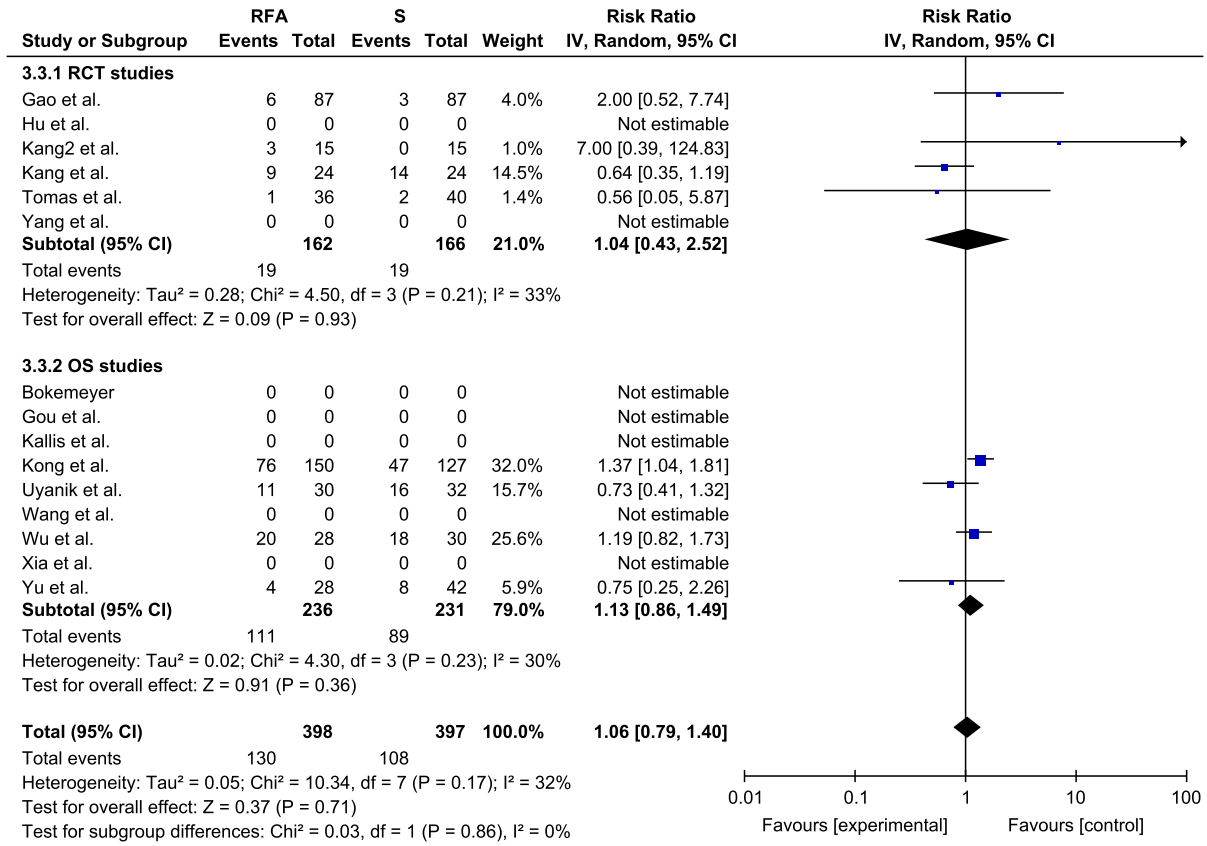

FIGURE 4. Forest plot of risk ratio of abdominal pain. OS indicates observational study; RCT, randomized controlled trial; RFA, radiofrequency ablation; S, stent-alone.

whereas patients who received RFA through the ELAR RFA device had a survival difference of 2.55 months (95% CI: −1.95 to 7.06), $I^2 = 0\%$, $P = 0.27$ according to the comparison of the Habib RFA device and the ELRA RFA device. That mean the patients using Habib RFA device has a significantly longer mean survival time than the ELRA device (Fig. 5).

Plastic Stent Versus Metal Stent

Plastic stents was used in 3 studies showed pooled mean stent patency time of 1.24 months (95% CI: −0.87 to 3.36), $I^2 = 80\%$, $P = 0.25$ that is statistically insignificant. While metal stent used in 9 studies showed stent patency of 2.54 months (95% CI: 1.44-3.65), $I^2 = 70\%$, $P < 0.00001$. This means metal stents shows more stent patency time compared with plastic stent (Supplementary Fig. 5, Supplemental Digital Content 1, http://links.lww.com/JCG/A935).

Survival Rate

The 9-month survival rate for the RFA group was 87.5%, compared with 24.2% for the S-alone group, according to Yang and colleagues, while Thomas and colleagues have reported survival rates of 52.5% and 57.5%, and Gou and colleagues, have reported survival rates of 81.3% and 47.9% for the RFA and S-only groups, respectively. Other studies did not report the survival rate.

Publication Bias and Study Effect

Publication bias for our meta-analysis was performed by funnel plot and data Egger test. Funnel plot distribution shows that there was no risk of publication bias as all funnel plots were symmetrical. We judged every study's effect on final outcome by removing each study one by one but the final outcome was almost similar. Thus we concluded that no study has special effect on the final outcome that may lead to publication bias (Supplementary funnel plots 1–11, Supplemental Digital Content 1, http://links.lww.com/JCG/A935).

DISCUSSION

MBS are rare diseases that show poor clinical outcomes and a high mortality rate. This is due to the fact that the diagnosis is made at an advanced stage. Because of the asymptomatic character of the disease, we are unable to diagnose it at an early stage. Surgical resection of the stricture area is the most effective curative therapy available for this condition. However, the majority of MBS patients are unable to undergo surgical resection because they are either unresectable or have poor health conditions (elderly patients cannot be operated on). Stents of various types, compositions, designs, and sizes have been developed, but stenting does not appear to improve survival time; however, stenting may result in slightly longer stent patency, particularly for large-diameter stents.[31] Researchers have developed new treatment options for advanced MBS, including

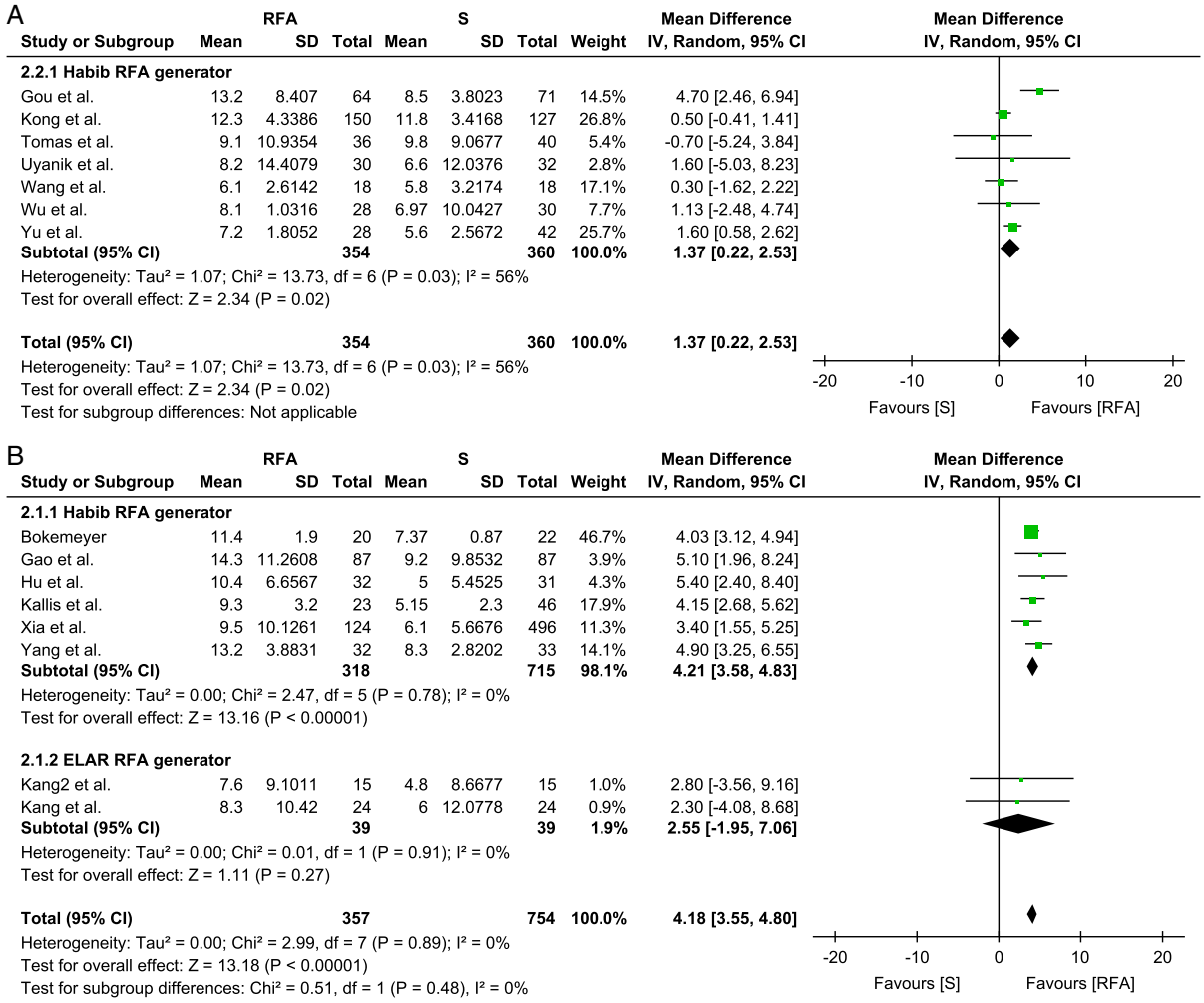

FIGURE 5. Forest plot of pooled mean difference of overall survival for endoscopic approach (A) and percutaneous approach (B). RFA indicates radiofrequency ablation; S, stent-alone.

photodynamic therapy and RFA, to provide palliative care. But efficacy and safety of RFA for MBS is not clear yet.

Through this meta-analysis and systematic review, we attempted to investigate the clinical results of RFA therapy and compare them to those of stenting alone. The findings are encouraging, pooled mean difference survival time significantly is longer in the RFA group when compared with the S-alone group in the study. In addition, the RFA+S group had a longer stent patency time. The survival benefits of the RFA treatment group can be demonstrated by its ability to relieve biliary obstruction and prevent recurrent cholangitis, the 2 leading causes of mortality. Interestingly, the stent patency duration in Gao and colleagues was longer in the S-alone group than in the RFA+S group, while the overall survival time in the RFA+S group was longer than in the S-alone group. In contrast, other studies reported comparatively longer mean survival time and stent patency time for the RFA+S group than the S-alone group. Thomas and colleagues reported no significant difference in mean survival and stent patency time. Yang and colleagues, Gou and colleagues, and Kong and colleagues reported a stent patency time difference of >3.4 months, comparatively much higher than other studies. In the same way in OS, Kong and colleagues, Gou and colleagues, and Wu and colleagues reported comparatively higher mean difference in stent patency time that have significantly contributed to final outcome.

In other meta-analyses, the outcome of RFA+S treatment for MBS patients is compared with that of S-alone treatment. According to the findings of a meta-analysis published by Zheng et al,[32] RFA is both safe and effective for the treatment of malignant biliary obstruction (MBO). However, there were significant concerns regarding the reliability of the included study. Another meta-analysis, conducted by Sofi et al,[33] evaluated the results of 9 different studies and found that RFA is associated with increased survival as well as stent patency time. Mohan et al[34] revealed the findings of a network analysis that included 55 studies on photodynamic therapy, RFA, and S-alone for the treatment of MBS. The results suggest that RFA combined with a stent is preferable to a stent alone. Another meta-analysis by Cha et al,[35] which consisted of 8 studies and included 420 patients, demonstrated that RFA therapy is involved in the advantages to survival, but it showed no influence on the stent patency time. It is possible that this is because some of the studies that were included in the

meta-analysis did not describe the patency time for RFA. A recent meta-analysis that included 19 studies (3 RCT and 16 OS) suggests that RFA is associated with the improved survival and stent patency time of patients with MBO.[36] Another meta-analysis conducted by de Jong et al,[37] which included 9 articles and included a total of 511 patients with unresectable perihilar CCA, found that RFA treatment showed promising outcomes to improve patients' survival times. In their study, Song et al[38] showed the results of a Bayesian network meta-analysis of 33 trials with a total of 2974 patients. The results showed that RFA combined biliary stent is an effective and safe local palliative therapy for patients with unresectable MBO.

A large number of additional prospective and retrospective trials have also demonstrated the advantages of RFA therapy for stent patency. According to Sharaiha and colleagues,[39,40] the RFA+S group had a longer overall survival time and a longer stent patency duration than the S-only group, based on their reported data of 64 patients. In another study, Cui et al[41] found that while survival time was nearly the same between the RFA+S and S-only groups, stent patency time was considerably longer in the RFA+S group.

There were 1105 patients with CCA (extrahepatic distal/hiliar CCA) who participated in this study. According to our subgroup analysis, the survival time for eCCA is much longer than the survival time for other kinds of carcinomas. As a result, it is possible that this is the most important factor influencing total survival time in the studies we assessed. On the list, there were 296 with pancreatic cancer, 151 with gallbladder cancer, 58 patients with ampullary carcinoma, and 205 with various malignancies combined. These people, who had various forms of cancer, may have had an impact on the results of their respective research. Stent patency time was not considerably higher in these trials since patients were returned for stent replacement after a defined time interval of ~3 to 6 months. So, from all the data, we can conclude that RFA had a significant impact on improving survival time and enhancing stent patency time. Different studies for other types of tumors treated by the RFA therapy process also supported this theory. Hansler et al[42] described the method by which the RFA group's survival time was prolonged. A significant increase in the tumor-specific catalytic activity of CD8 (+) T cells was seen after treatment with RFA, suggesting that RFA may have a role in antitumor effects, since CD8 (+) T cells are engaged in the cytotoxicity of malignant cells in the condition of hepatocellular carcinoma. den Brok et al[43] reported that the generation of antitumor immunity during in situ tumor elimination results in the activation of the immunity antigen.[32] Gao and colleagues a maximum median depth of 4 mm in the bile duct has been shown to be useful in decreasing tumor volume, resulting in the proliferation of malignant cells being delayed. Immune suppression is reduced by the modulation of the circulatory system, immune cells, and cytokines, which may result in enhanced patient survival.

For the adverse events of the procedures, there were no perioperative severe or postoperative adverse events in any of the enrolled studies except Kang and colleagues reported a case of cholangitis related to septic shock resulting in death, and Gao and colleagues reported a case of liver abscess. Cholangitis, pancreatitis, cholecystitis, hemorrhage, and abdominal pain are some of the other mild to moderate side effects that might occur. Gao and colleagues found that 7 of 9 instances of cholecystitis in their study were in individuals with hilar CCA. All of these adverse occurrences were addressed in a timely and effective manner. In their study, Tal et al[44] found that 2 people died as a result of hemobilia. It recommended the use of self-expanding metal stents rather than plastic stents following the delivery of RFA. Our analysis, on the other hand, did not uncover any instances of hemobilia.

To overcome and reduce the severity of these adverse events, excellent specialist skills are necessary. According to Yang and colleagues, rectal indomethacin (100 mg) was administered before ERCP to avoid pancreatitis, and antibiotics such as quinolones or cephalosporins were administered to all patients 1 hour before RFA to prevent bacterial infection. To avoid post-ERCP pancreatitis, Gao and colleagues applied a prophylactic pancreatic duct stent to block the pancreatic duct. There have been several studies that have demonstrated the significant impact of RFA therapy for CCA. Our study has certain limitations, such as the fact that only 15 articles were included in our systematic review and meta-analysis. Only 6 RCTs involving a total of 456 patients were reported. These investigations were carried out with a high level of proficiency. With the exception of Thomas and colleagues, Wang and colleagues, and Kong and colleagues, all investigations revealed that RFA had nearly the same impact. According to stent types, Yang and colleagues, Gao and colleagues, and Hu and colleagues used PS, but other investigations used MS; it is possible that this had an impact on the final conclusion. With the exception of Bokemeyer and colleagues, Kallis and colleagues, and Xia and colleagues, who did not provide stent patency time, all research reported pooled survival and stent patency time.

CONCLUSIONS

All of the data we evaluated from 6 RCTs and 9 prospective studies demonstrated that RFA results in a marked improvement in both survival and stent patency. When combined with sound expertise, this has the potential to produce even greater outcomes.

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