Radiofrequency ablation combined with biliary stent placement versus stent placement alone for malignant biliary strictures: a systematic review and meta-analysis

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Background and Aims: Unresectable malignant biliary strictures are generally managed by palliative stent placement for drainage of biliary tree. Recently, radiofrequency ablation (RFA) has been used to improve the patency of biliary stents in these patients. Several studies have evaluated the effectiveness of biliary stent placement with RFA on stent patency and patient survival with variable results. We performed this meta-analysis to evaluate the efficacy and safety of biliary stent placement with RFA compared with stent placement alone in patients with malignant biliary strictures.

Methods: We performed a comprehensive search of electronic databases for all studies comparing RFA with biliary stent placement versus stent placement only. Measured outcomes included patient survival, stent patency, and procedure-related adverse events. An inverse variance method was used to pool data on stent patency into a random-effects model. Cox-regression analysis was used to calculate hazard ratio for survival analysis. We used the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework to interpret our findings.

Results: Nine studies (including 2 abstracts) with a total of 505 patients were included in the meta-analysis. The pooled weighted mean difference in stent patency was 50.6 days (95% confidence interval [CI], 32.83-68.48), favoring patients receiving RFA. Pooled survival analysis of the reconstructed Kaplan-Meier data showed improved survival in patients treated with RFA (hazard ratio, 1.395; 95% CI, 1.145-1.7; $P < .001$). However, RFA was associated with a higher risk of postprocedural abdominal pain (31% vs 20%, $P = .003$). Our analysis did not show significant difference between the RFA and stent placement–only groups with regard to the risk of cholangitis, acute cholecystitis, pancreatitis, and hemobilia.

Conclusions: 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. (Gastrointest Endosc 2018;87:944-51.)

Abbreviations: CI, confidence interval; RFA, radiofrequency ablation; SEMS, self-expanding metal stents.

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Malignant biliary tumors are commonly diagnosed at an advanced stage, and as a result most are unresectable. The primary goal of treatment in these patients is generally palliative, which includes therapies to relieve biliary obstruction. Biliary stent placement provides the least-invasive and cost-effective method of achieving biliary decompression.[1] Self-expanding metal stents (SEMSs) and plastic stents have been used to relieve biliary obstruction secondary to malignant tumors of biliary tract. Although the stent patency of SEMSs is superior to plastic stents, it is still limited to a median duration of 6 to 8 months.[2] Primary causes of stent occlusion include tumor ingrowth or epithelial hyperplasia in addition to biofilm deposition, biliary sludge, and formation of granulation tissue.[3]

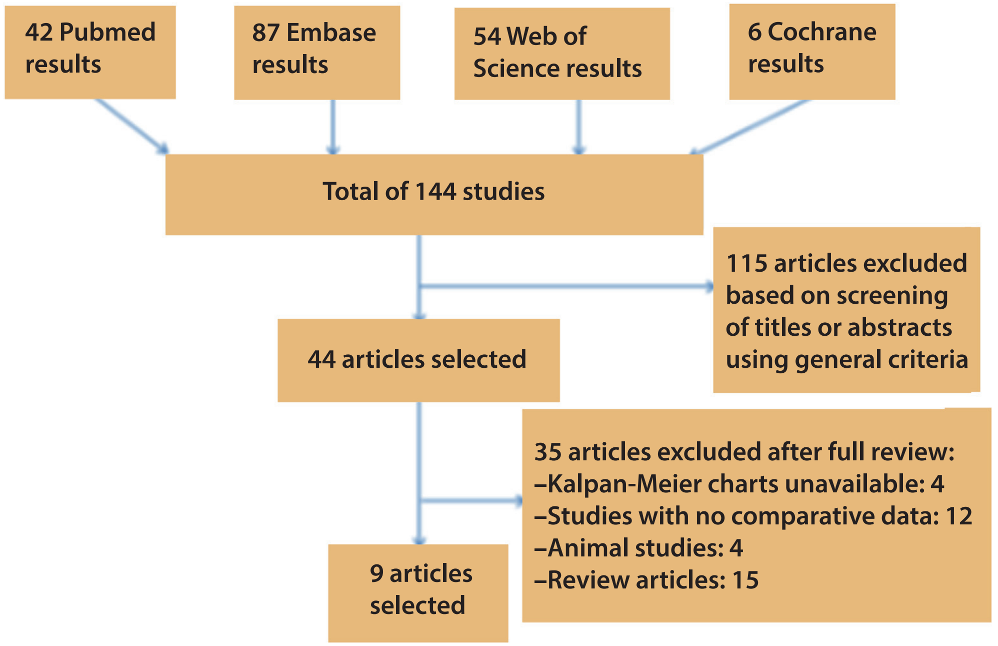

Figure 1. Flowchart summarizing study selection process.

Radiofrequency ablation (RFA) can safely induce tumor necrosis and is successfully used for the treatment of hepatocellular cancers.[4] Recently, intraductal RFA with an endobiliary catheter (Habib EndoHPB; EMcision, London, U.K.) has been used as an adjuvant therapy to potentially improve stent patency and survival. Several studies have evaluated the use of RFA in malignant biliary obstruction with conflicting results. The purpose of this meta-analysis was to compare the efficacy and safety of RFA and biliary stent placement versus stent placement alone in patients with malignant biliary obstruction.

METHODS

A computerized literature search was performed under the supervision of a University of Toledo librarian (W.L.). On March 30, 2017 search strategies and subsequent literature searches were performed by an experienced health sciences reference librarian (W.L.) in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[5] Search strategies that leveraged controlled vocabularies, keyword synonyms, and device brand names were developed for PubMed. This strategy was translated to be used in Embase, the Cochrane Central Register of Controlled Trials, and the Web of Science Core Collection databases on the Clarivate Analytics Web of Science platform. The searches accounted for plurals and variations in spelling with the use of appropriate wildcards.

The searches combined the following concepts: radiofrequency ablation with biliary stents. Within the results for those combined concepts, additional filters, publication types, and keyword strategies were used to identify and exclude the most common articles types that do not report trial results (reviews and case studies). An exhaustive forward search tool was used for Web of Science database to capture all possible studies of interest. The databases were searched for publications dates 2005 to present. No language limits were applied. Appendix 1 (available online at www.giejournal.org) details the exemplar PubMed search.

To identify further articles, references were hand-searched. All results were downloaded into EndNote (Thompson ISI ResearchSoft, Philadelphia, Pa), a bibliographic database manager, and duplicate citations were identified and removed. In addition, abstracts from Digestive Disease Week, annual meetings of American College of Gastroenterology, and United European Gastroenterology Week from the last 5 years were also searched.

Inclusion criteria

Prospective and retrospective studies or abstracts were included that compared the clinical outcome, including patient survival and stent patency, after endoscopic biliary stent placement with or without RFA therapy. Adult human studies published in English were also included.

Exclusion criteria

Studies were excluded when information on the survival or stent patency in the patient groups with and without RFA was not provided. In addition, duplicate publications, animal studies, reviews, case reports, and letters were also excluded.

TABLE 1. Characteristics of studies and patient demographics

References	Country	Design	No. of patients	Mean age (y)		Male (%)	
				RFA	Stent	RFA	Stent
Li et al,[11] 2015	China	OS	26	53	60	58	57
Kallis et al,[6] 2015	UK	OS	69	68	69	52	52
Liang et al,[14] 2015	China	OS	76	67	63	64	62
Wang et al,[9] 2016	China	OS	36	56	58	78	67
Wu et al,[10] 2017	China	OS	71	58	57	74	70
Kadayifci et al,[15] 2016	USA	OS	50	25	25	32	56
Hu et al,[8] 2016	China	RCT	63	72	71	47	52
Sampath et al,[12] 2016	USA	OS	25	73	67	60	60
Cui et al,[13] 2017	China	OS	89	50	39	72	56

RFA, Radiofrequency ablation; *Stent*, stent alone; *OS*, observational study; *USEMS*, uncovered self-expanding metal stent; *CSEMS*, covered self-expanding metal stent; *PTC*, percutaneous transhepatic cholangiography; *RCT*, randomized controlled trial.

Assessment of study quality

Quality of studies included in the analysis was assessed by using the Newcastle-Ottawa Scale for cohort studies and the Cochrane tool for assessing the risk of bias for randomized control trials. The Newcastle-Ottawa Scale uses a tool that assesses quality in 3 parameters of selection, comparability, and exposure/outcome and allocates a maximum of 4, 2, and 3 points, respectively. High-quality studies are scored >7 on this scale and moderate-quality studies between 5 and 7. The Cochrane Collaboration has adopted the principles of the Grading of Recommendations, Assessment, Development and Evaluation system for evaluating the quality of evidence for outcomes reported in systematic reviews. We used the Grading of Recommendations, Assessment, Development and Evaluation framework to interpret our findings relevant to clinical practice.

Data extraction

Data were extracted by 2 authors (A.A.S. and M.A.K.) independently using characteristics of included studies. Parameters were study methodology, year of study, demographics, type of stent, etiology of malignant biliary obstruction, method of stent placement, RFA (endoscopic vs percutaneous), proportion of patients with distant metastasis, length of stricture, percentage of patients who received chemotherapy and radiation therapy, mean stent patency, mean survival, and adverse events in the 2 treatment groups. The kappa coefficient for agreement between the 2 reviewers was .77. In case of discrepancy between reviewers, agreement was reached by consensus after discussion with a third reviewer (A.D.).

Outcomes

The primary outcome of this study was to assess stent patency with the use of RFA in patients with malignant biliary obstruction. Secondary aims included assessing differences in overall survival and adverse events with the use of RFA. Corresponding authors of studies[6] were contacted if data on stent patency and survival were not reported. Authors who shared their data have been acknowledged.

Statistical analysis

The inverse variance method was used to pool data on stent patency into a random-effects model. Cochrane χ^2 and I^2 statistics were used to estimate statistical heterogeneity. Presence of heterogeneity was defined as $P < .1$ and $I^2 > 50\%$.

We expected heterogeneity in our estimate because studies had included patients with various etiologies of malignant biliary strictures and methods of attaining biliary drainage were not uniform (endoscopic and/or percutaneous). Therefore, predetermined subgroup analyses were conducted based on type of procedure used for biliary drainage and etiology of malignant biliary strictures with a focus on studies evaluating cholangiocarcinoma exclusively. Further, to account for such variability, we assumed there would be a range of true effect sizes, and therefore a random-effects model was used for this meta-analysis.

Publication bias was assessed using funnel plots and Egger's test for asymmetry. We used digital software (**DigitizeIt**) to read in the coordinates of the Kaplan-Meier curves from each of the published graphs. The survival analysis data points were extracted from the included articles as a portable document format and imported into the digitizing software (DigitizeIt). The digitized coordinates of time (*x* axis) and survival probability (*y* axis) were exported into Microsoft Excel 2010 (Microsoft, Redmond, Wash).[7] Authors were contacted to obtain survival data if a Kaplan-Meier curve was not provided in their study.

Cox regression analysis was used to calculate hazard ratios for survival analysis. Odds ratios of adverse events were calculated using raw data with 95% confidence intervals (CIs). The statistical analysis was performed using R-statistical software (Foundation for Statistical Computing, Vienna, Austria) and RevMan 4.2.10 (Cochrane Collaboration, Oxford, U.K.).

TABLE 1. Continued

Stent type		Method of stenting	Noncholangiocarcinoma etiology (n)		No. of procedures	
RFA	Stent		RFA	Stent		
USEMS	USEMS	PTC	2	1	2	5
USEMS	USEMS	ERCP	23	46	0	0
USEMS/CSEMS	USEMS/CSEMS	PTC/ ERCP	0	0	4	4
USEMS	USEMS	PTC	4	4	3	10
USEMS/CSEMS	USEMS/CSEMS	PTC	0	0	—	—
USEMS	USEMS	ERCP	14	20	—	—
Plastic	Plastic	ERCP	0	0	2	2
USEMS	USEMS	ERCP	0		2.3	5
USEMS	USEMS	PTC	25	25	1	1

RESULTS

The search strategy identified 144 articles after duplicates were removed. A manual search identified an additional 2 studies. One author declined to share data. After exclusion of 135 articles based on exclusion criteria, 9 studies (Fig. 1) were selected for inclusion (7 published studies and 2 abstracts). The baseline characteristics of individual studies are presented in Table 1.

One study presented data as an interim analysis of an ongoing randomized controlled trial,[8] whereas the remaining studies were observational.[6,9-15] A total of 505 patients were included in this meta-analysis, including 239 patients in whom RFA was used in addition to biliary stent placement. Biliary stent placement with or without RFA was performed endoscopically in 4 studies,[6,8,12,15] percutaneously in 4 studies,[9-11,13] and with either method in 1 study.[14] SEMSs were used in 6 studies[6,9-11,13,14] and both SEMSs and plastic stents in 2 studies[8,12] (Table 1). RFA was indicated for primary placement of biliary stents in experimental groups in all but 1 study.[15] In this study RFA was used for management of occluded SEMSs in the experimental group[15] and a plastic stent was placed in occluded SEMSs in control subjects. RFA therapy was used twice in 1 study.[8] In that study therapy was repeated if the stent occluded after initial therapy. Stent exchange was performed in the control group if the stent occluded.[8] In another small study a mean of 3 RFA therapies was administered in the treatment group.[12] RFA therapy was performed only once in all other studies in the treatment group.

Patient demographics and other baseline characteristics in the RFA-treated and control groups were comparable (Table 2). Chemotherapy was used more often in the control group compared with the treatment group in the pooled data analysis ($P = .03$). Also, a significantly greater number of patients in the control group received chemotherapy. Cholangiocarcinoma was the predominant etiology of biliary obstruction in both the treatment and control groups. One study evaluated RFA exclusively in patients with pancreatic cancer.[6] Performance status of patients in the treatment and control groups (reported in 6 of 8 observational studies) was similar between the 2 groups.

RFA technique

The Habib EndoHBP (8F) probe (EMcision) was used for delivering RFA therapy in all studies. The RFA probe was advanced over a guidewire under fluoroscopic guidance to the level of stricture. RFA was applied using a generator (ERBE, Medical UK Ltd, Leeds, United Kingdom), and 10 W of energy was delivered over 1.5 to 2 minutes for each application. The whole length of the stricture was ablated in all studies. Biliary stents were deployed after the application of RFA in all studies.

Methodologic quality and risk of bias assessment

Four observational studies[6,13-15] were of high quality and 4[9-12] of moderate quality per the Newcastle-Ottawa Scale assessment. The study presenting the interim analysis from a randomized control trial[8] could not be evaluated by the Cochrane tool for assessing risk of bias because methodology was not reported (Table 1). Risk of bias assessment is provided in Figure 4.

Stent patency

Stent patency between the treatment and control groups was measured in 5 of 6 studies. The pooled weighted mean difference in stent patency between the treatment and control groups was 50.6 days (95% CI, 32.83-68.48; Cochran Q test $P = .002$, $I^2 = 79\%$ in favor of RFA) (Fig. 3). The funnel plot was asymmetric, but Egger's test failed to detect any publication bias (intercept = 1.34, $P = .19$; Fig. 2).

Subgroup analysis was conducted based on the etiology of the malignant biliary strictures (Fig. 5). Among studies evaluating cholangiocarcinoma exclusively, the pooled

TABLE 2. Pooled baseline characteristics of RFA study group and control group

	RFA + biliary stent placement (n = 239)	Biliary stent placement only (n = 266)	*P* value
Mean age, y	64.0 (7.0)	63.37 (4.8)	.633
Male, %	62.7 (10.5)	57.8 (8.4)	.17
Pancreatic cancer, n	14.5 (13.52)	25.5 (26.66)	.196
Distant metastases, %	19.8 (15.1)	29.2 (14.3)	.092
Local infiltration, %	57.3 (32.8)	50.7 (34.5)	.118
Adjuvant chemotherapy, %	17.5 (12.5)	21.0 (14.8)	.033
Plastic stent, %	19 (15.5)	18.5 (12)	.874
Mean length of stricture, mm	27.0 (9.49)	26.9 (9.08)	.936

Values in parentheses are standard deviations.
RFA, Radiofrequency ablation.

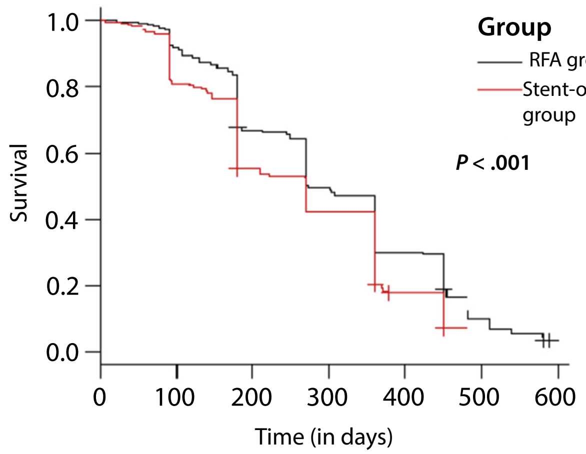

Figure 2. Pooled Kaplan-Meier survival analysis of radiofrequency ablation (RFA) treatment and control groups.

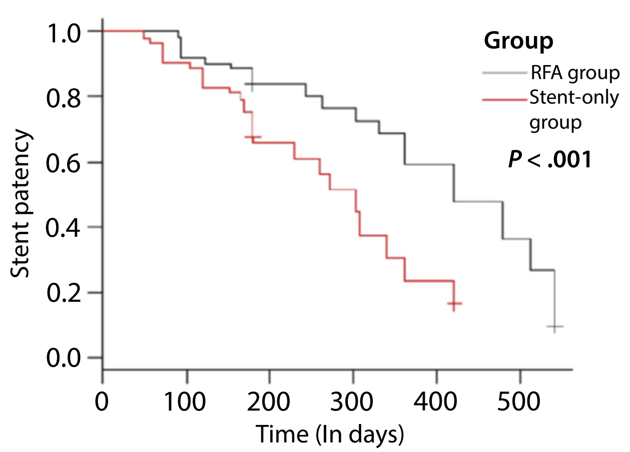

Figure 3. Pooled Kaplan-Meier analysis of stent patency in radiofrequency ablation (RFA) treatment and control groups.

mean difference for stent patency was 42.7 days (95% CI, 17.19-68.19; Cochran Q test $P = .11$, $I^2 = 55\%$). The pooled mean difference for stent patency among studies evaluating various etiologies of malignant biliary strictures

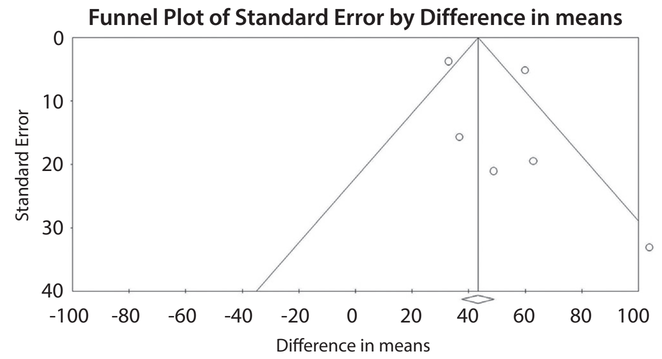

Figure 4. Contour-Funnel plot assessing publication bias.

was 59.6 days (95% CI, 58.64-68.65; Cochran Q test $P = .87$, $I^2 = 0\%$).

A second subgroup analysis was conducted based on type of procedure used for attaining biliary drainage (Fig. 5). Among studies using percutaneous transhepatic cholangiography, the pooled mean difference was 60.3 (95% CI, 51.14-69.49; Cochran Q test $P = .37$, $I^2 = 0\%$), whereas the pooled mean difference for stent patency with ERCP was 41.9 (95% CI, 15.04-68.74; Cochran Q test $P = .13$, $I^2 = 56\%$). There was no significant difference ($P = .20$) in stent patency based on type of procedure used for attaining biliary drainage.

Pooled survival rates

The pooled median survival rates were significantly better in treatment groups (285 days; 95% CI, 270-309) compared with control groups (248 days; 95% CI, 188-272; $P < .001$). The pooled overall survival from reconstructed Kaplan-Meier analyses showed improved survival in patients receiving RFA compared with patients undergoing biliary stent placement alone (hazard ratio, 1.39; 95% CI, 1.145-1.7) (Fig. 2).

Adverse events

Details of adverse events in either treatment group were reported in all studies. Serious adverse events were rare in

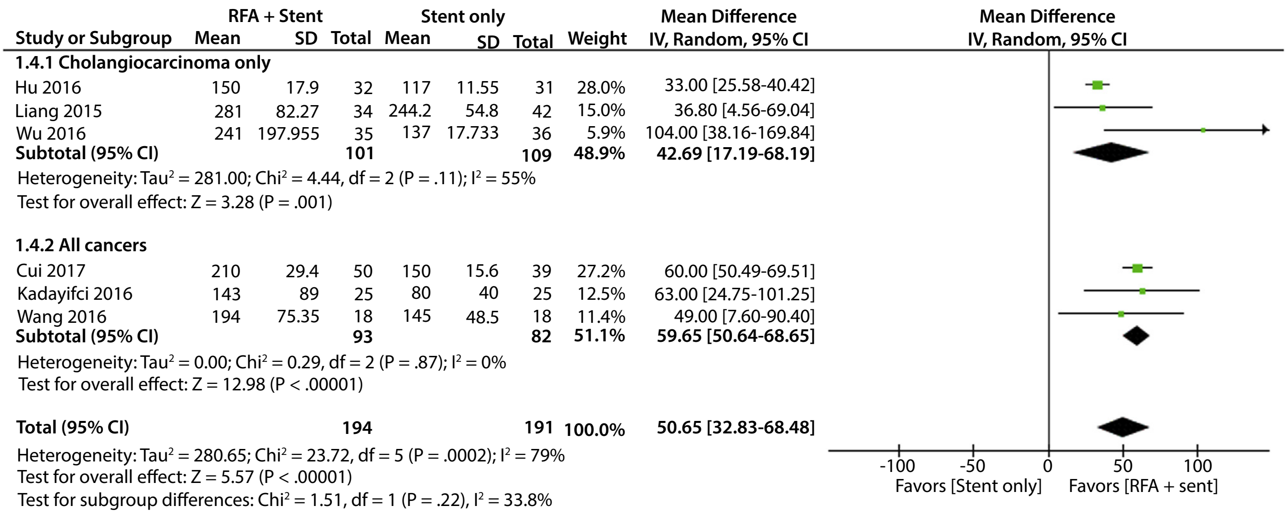

Figure 5. Forest plot to compare stent patency based on the etiology of malignant biliary strictures. *CI*, Confidence interval; *RFA*, radiofrequency ablation.

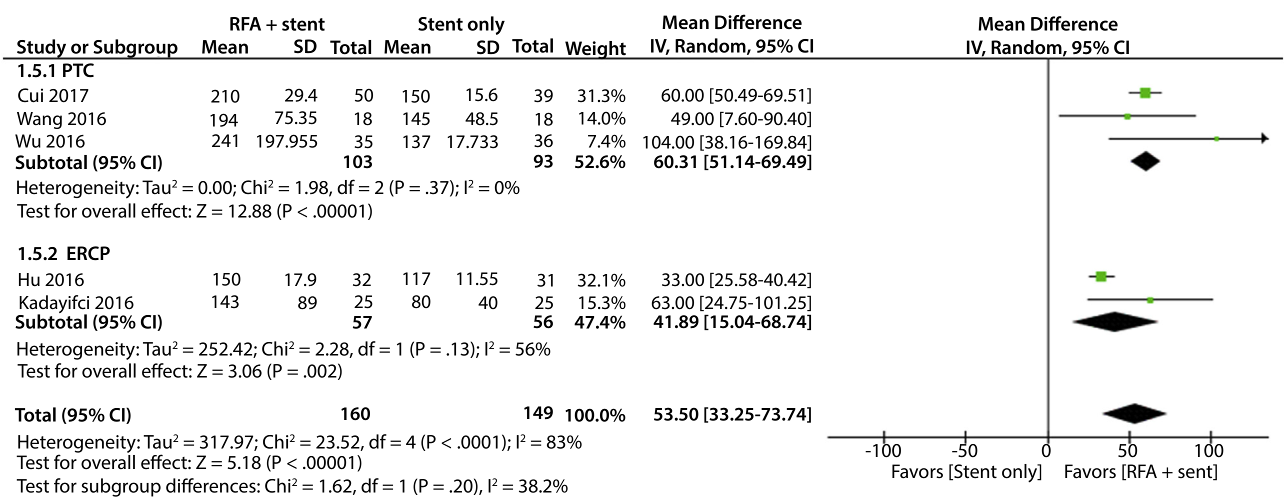

Figure 6. Forest plot to compare stent patency based on the type of procedures.

either treatment group. Acute cholecystitis in the RFA group was almost exclusively reported in a single study, although it did not reach statistical significance. All patients with acute cholecystitis in the treatment group were reported in patients with hilar tumors. Abdominal pain was reported more often in patients undergoing RFA compared with control subjects (Table 3).

DISCUSSION

This meta-analysis of mostly observational studies provides very low quality evidence in favor of RFA therapy for management of malignant biliary strictures. It is associated with improved survival in patients with malignant biliary obstruction compared with patients who undergo biliary stent placement alone. Additionally, RFA therapy is associated with superior stent patency. Therefore, RFA can be considered as an effective adjuvant therapy in patients with unresectable biliary and pancreatic malignancy. Moreover, RFA is generally safe in the treatment of patients with malignant biliary obstruction.

An overall improved stent patency was noted with the use of RFA in this meta-analysis. All except 1 study[6] showed better stent patency in the treatment group. The authors of that study suggested that failure to show the difference in stent patency could be because of high rates of censorship from high death rates at early time points in control group. Stent occlusion can be associated with jaundice with or without cholangitis, which can delay chemotherapy or radiation therapy in these patients. Improved stent patency will potentially improve the quality of life in patients with malignant biliary obstruction and decrease the need for subsequent

TABLE 3. Adverse events in RFA study group and control group

	RFA + biliary stent placement (n = 239)	Biliary stent placement only (n = 266)	*P* value
Abdominal pain	31	20	.003
Cholangitis	6.2	5.2	.87
Acute cholecystitis	3.3	0	.4
Acute pancreatitis	2.09	1.5	.2
Hemobilia	3.76	1.88	.19

Values are percents.
RFA, Radiofrequency ablation.

intervention. The mechanism of superior stent patency with the use of RFA is likely secondary to the putative tumor suppressive effects induced by RFA, as described below. In addition, RFA also decreases the intimal hyperplasia.

Survival benefit with the use of RFA was not observed in 2 of 6 included studies.[9,10] Few individual studies in this meta-analysis showed early survival benefit with the use of RFA. Pooled analysis of the survival data showed very low-quality evidence for both early and delayed survival benefit with the use of RFA. This observation in our meta-analysis could potentially be because of a larger sample size in the pooled data. It is notable that this difference in survival was observed even though the number of patients on systemic chemotherapy was significantly higher in the control group compared with the treatment group.

The mechanism of putative benefit in survival with the use of RFA is unclear. One study demonstrated significant tumor-specific cytotoxic T cell stimulation with an intensely increased tumor-specific cytolytic activity of CD(+) T cells after RFA in patients with hepatocellular carcinoma and liver metastasis from colorectal malignancies.[16] Another study in a mouse model demonstrated a weak but detectable immune response against tumor cells after the application of RFA.[17] RFA-induced immune activation could potentially enhance tumor suppression by the same mechanism in patients with biliary and pancreatic malignant tumors. However, it remains unclear if improved survival in the RFA therapy group is secondary to superior stent patency or independent of its effect on stent patency. It is also unclear if repeated sessions would offer any benefit over single-session RFA therapy. The only randomized control trial included in this meta-analysis used RFA twice, which was compared with stent placement twice in control group.[8] Finally, caution is warranted in interpreting survival benefits in the real world because our analysis is mostly based on observational studies, and we could not adjust for presence of metastasis.

Our study shows that RFA is generally safe in the treatment of patients with malignant biliary obstruction. Postprocedural abdominal pain was relatively more frequent in patients treated with RFA compared with those who received a stent alone. All these episodes were managed with administration of analgesic medications. Acute cholecystitis was reported exclusively in the treatment group. Similar reports were found in several other case series that were not included in this meta-analysis. Hu et al[8] reported that all cases of acute cholecystitis in the treatment group occurred in patients with hilar cholangiocarcinoma. Ablation of the segment of the bile duct at the junction with the cystic duct may lead to obstruction of cystic duct drainage, resulting in acute cholecystitis. Currently, ongoing prospective studies may provide more evidence on the safety of the procedure.

This is the first systematic review and meta-analysis to evaluate the use of RFA as an adjuvant therapy with biliary stents in malignant biliary obstruction. We used a comprehensive search strategy and included the largest number of relevant studies. Limitations of our work include weaknesses inherent to meta-analyses and retrospective design of 7 of 8 included studies. We found significant heterogeneity in the estimate of stent patency, but we conducted a subgroup analysis to dissect heterogeneity based on type of procedure and malignant etiologies of biliary obstruction. Further, different types of stents were used in different studies, although the proportion of patients receiving SEMSs or plastic stents was similar between the 2 treatment groups. We could not evaluate the difference between covered and uncovered metal stents because such data were not provided uniformly. Finally, not all survival analyses were adjusted based on tumor burden and presence of metastases, which could be a further limitation of this study.

In conclusion, RFA may be a promising adjuvant therapy in patients with malignant biliary obstruction who otherwise have dismal outcomes with the current standard of therapy. In addition, it improves stent patency and is safe and well tolerated in patients with malignant biliary obstruction. The results of currently ongoing controlled studies examining the role of RFA in malignant biliary obstruction are keenly awaited.

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APPENDIX 1. PubMed search strategy

Search	Query	Items found
1	Search (Biliary-stent OR biliary-stenting OR (Aurora AND stent) OR bile-duct-stent OR BONASTENT OR ComVi OR Cotton-Leung OR IntraStent-Maxi OR IntraStent-Mega OR stent-biliary OR Valeo OR Visi-Pro OR ZEOSTENT OR (stent* AND bile) OR (stent* AND biliary))[all]	6695
2	Search (Radiofrequency-ablat* OR radio-frequency-ablat* OR RFA OR (radiofrequency AND catheter-ablation) OR BarrxFLEX OR Coblator OR Cool-tip OR InCircle OR LeVeen-CoAccess OR NovaSure OR OPES-Ablator OR Prostiva OR PVAC-catheter OR Starburst-XL OR Surgitron OR Visitrax OR ClosureFAST)	19,891
3	Search 1 AND 2	79
4	Search 3 NOT ((“case reports”[Publication Type] OR “review”[Publication Type]))	45
5	Search 4 Filters: Publication date from 2005/01/01	44