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Impact of temperature-controlled endobiliary radiofrequency ablation for inoperable hilar cholangiocarcinoma: A propensity score–matched analysis

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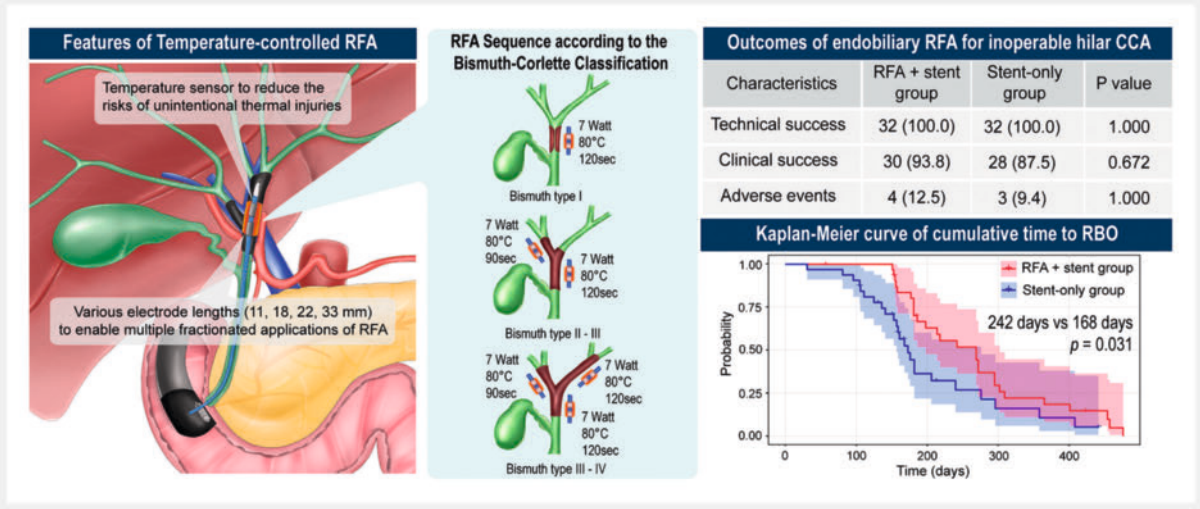
GRAPHICAL ABSTRACT



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ABSTRACT

Background and study aims Endobiliary radiofrequency ablation (RFA) can be an effective palliative treatment, but few studies have evaluated its outcomes for malignant obstruction in the hilar bile duct, which has a thin wall and complex duct–vascular contacts. We evaluated the efficacy and safety of temperature-controlled endobiliary RFA, which can reduce the risk of unintentional thermal injury by maintaining the temperature of the ablation segment, in the treatment of inoperable hilar cholangiocarcinoma (CCA).

Patients and methods After propensity score matching, 64 patients with inoperable hilar CCA were categorized to the RFA + stent group (endobiliary RFA with stenting; n = 32) or stent-only group (stenting only; n = 32). The evaluated outcomes were the median time to recurrent biliary obstruction (RBO), overall survival (OS), and adverse events (AEs).

Results Technical success was achieved in all patients. The clinical success rate was 93.8% in the RFA + stent group and 87.5% in the stent-only group ($P = 0.672$). The median time to RBO was 242 days in the RFA + stent group and 168 days in the stent-only group ($P = 0.031$). The median OS showed a non-significant tendency to be higher in the RFA + stent group (337 versus 296 days; $P = 0.260$). Overall AE rates were comparable between the two groups (12.5% vs 9.4%, $P = 1.000$).

Conclusions Temperature-controlled endobiliary RFA resulted in favorable stent patency without increasing the rate of AEs but it did not significantly increase OS in patients with inoperable hilar CCA (Clinical trial registration number: KCT0008576).

Introduction

To improve stent patency and survival in patients with malignant biliary obstruction, endobiliary radiofrequency ablation (RFA) is an effective local palliative treatment for tumors within the bile duct [1]. It improves bile duct patency by directly delivering ablative thermal energy to the intraductal tumor burden, thus inducing coagulation necrosis [2, 3]. However, there is a potential risk of serious adverse events (AEs) such as bleeding or perforation due to the uncontrolled excessive necrotizing effect of endobiliary RFA [4, 5].

A recently introduced temperature-controlled RFA system could increase the safety and efficacy of RFA [2]. The bipolar electrodes of this system have a temperature sensor, which continuously monitors the temperature of the ablation site to prevent tissue overheating and reduce the risk of unintentional thermal injuries [2, 6, 7]. The system automatically switches off when the electrode reaches a preset target temperature. The catheter is available in lengths of 11, 18, 22, and 33 mm, allowing for a variety of procedures for strictures of different shapes and lengths.

Although endobiliary RFA can prolong stent patency, its efficacy in inoperable hilar cholangiocarcinoma (CCA) is unclear [8, 9]. Because the hilar bile duct has complex duct-vascular contacts and a thin wall, RFA-induced fatal AEs are more likely than in the distal bile duct [8, 9, 10]. We aimed to evaluate the efficacy and safety of temperature-controlled endobiliary RFA in patients with inoperable hilar CCA.

Patents and methods

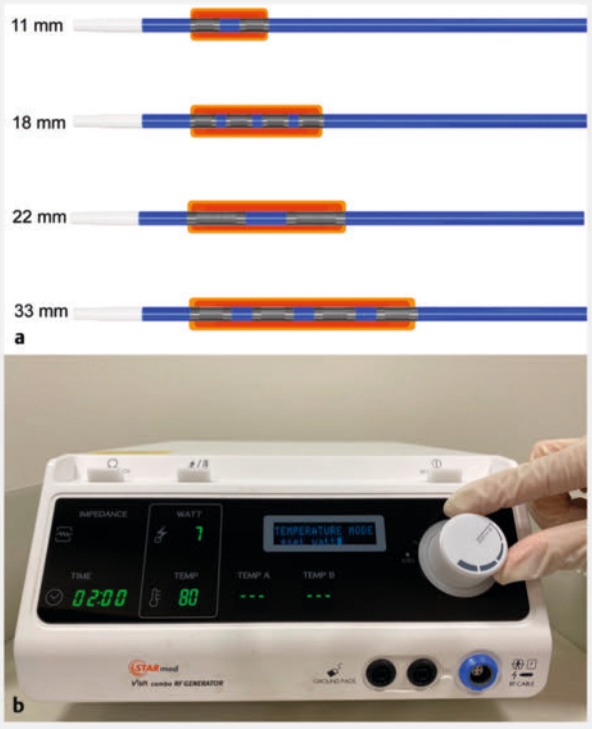
Study design and patients

We reviewed an endoscopic database from one tertiary referral center to retrieve information on consecutive patients with inoperable CCA between August 2020 and November 2022. The inclusion criteria were age >19 years; histologically confirmed hilar CCA; ineligibility for surgery because of advanced tumor stage or operative risks; Eastern Cooperative Oncology Group (ECOG) performance status ≤3; and no previous treatment. The exclusion criteria were technical failure of a transpapillary approach due to gastric-outlet obstruction or surgically altered anatomy; presence of other malignancy; severe renal or hepatic dysfunction (creatinine clearance rate <10 mL/min or prothrombin time activity ≤40%); bleeding tendency (platelet count <50,000 mm^3 or international normalized ratio >1.5); and contraindications for endoscopic retrograde cholangiopancreatography (ERCP).

All included patients with definite stricture on cholangiogram and intraductal ultrasound (IDUS) were offered the opportunity to receive endobiliary RFA. Because endobiliary RFA may be associated with longer procedure time and additional medical costs, some patients did not receive endobiliary RFA and were studied as part of the stent-only group. This study was approved by our Institutional Review Board (SCHBC 2020–05–015–007) and was conducted in accordance with the Declaration of Helsinki. The participants provided written informed consent before undergoing procedures. This trial was registered at https://cris.nih.go.kr (KCT0008576).

Temperature-controlled RFA system

The ELRA (STARmed, Goyang, South Korea) 7F RF catheter of 175 cm length has a bipolar electrode (11, 18, 22, and 33 mm in length) with a temperature sensor at the distal end, and can be connected to an RF generator (VIVA combo; STARmed) to deliver energy in temperature-control mode (▶ **Fig. 1**). The RF generator prevents excessive heating at the ablation site by automatically switching heating on and off based on the predetermined target temperature. The RF catheter can be inserted into the bile duct over a 0.025- or 0.035-inch guidewire and generates thermal energy at an appropriate temperature to induce coagulation necrosis of the obstructive lesion.



▶ **Fig. 1** Endobiliary radiofrequency (RF) catheter (ELRA; STARmed, Goyang, South Korea) and power generator (VIVA Combo; STARmed). **a** Four types of RF catheter with ablation lengths of 11, 18, 22, and 33 mm. **b** The RF power generator and its settings. Temperature was continuously monitored during the procedure.

Procedures

All procedures (including endobiliary RFA and stent placement) were performed by two experienced endoscopists (J.H.M. and Y.N.L.). After being administered prophylactic antibiotics, patients were placed in prone position with electrocardiogram monitoring and supplied with oxygen. During ERCP procedures using a side-viewing duodenoscope (TJF-260V; Olympus Medical Systems, Tokyo, Japan), carbon dioxide (Colosense CO-3000; Mirae Medics Co., Seoul, South Korea) was used for insufflation to prevent AEs. After successful selective bile duct cannulation and bilateral guidewire placement, a cholangiogram was obtained under fluoroscopic guidance to identify the location and length of the hilar stricture. IDUS using an ultrasonic probe (20 MHz/6F, transducer, UM G20 ± 29R; Olympus Medical Systems) was performed to assess the stricture and the maximum thickness of the corresponding bile duct wall. Balloon sweeping was conducted to confirm the length of the stricture and remove any biliary sludge or stones that might interfere with the RFA procedure.

In patients assigned to the RFA + stent group, the radiopaque electrodes of the RF catheter preselected according to the characteristics of the stricture were advanced over the guidewire and positioned at the stricture under fluoroscopic guidance. Temperature-controlled endobiliary RFA was performed at an RF power of 7 W, a target temperature of 80°C, and for a duration of 90 to 120 seconds [6, 11]. Fluoroscopic views were obtained intermittently during the RFA procedure to ensure that the entire target area received RFA. Two or more fractionated RFA applications were attempted in the proximal-to-distal direction in an effort to ablate all lesions. For instance, one application of RFA was sufficient in Bismuth–Corlette type I patients, whereas two could be required to ablate the common hepatic duct (CHD) and one of the left or right hepatic duct in Bismuth-Corlette type II-III patients. Similarly, some Bismuth-Corlette type III-IV patients required three RFA applications in the CHD and both the left and right hepatic ducts (▶ **Fig. 2**). The duration of RFA was 120 seconds; during RFA for the right hepatic duct, this was adjusted to 90 seconds based on the proximity of the right hepatic duct and right hepatic artery. After RFA procedures, the RF catheter was removed from the bile duct and self-expandable metal stents (SEMSs) (▶ **Fig. 3**) or plastic stents (PSs) (▶ **Fig. 4**; ▶ **Video 1**) were deployed to cover the stricture for palliative biliary drainage. Bilateral stenting was performed for drainage in patients with Bismuth III-IV hilar CCA.

In patients assigned to the stent-only group, procedures including balloon sweeping and stent placement, but not RFA, were performed as in the RFA + stent group. In both groups, the decision about which or how many stents to place was at the discretion of the endoscopist based on patient life expectancy and stricture severity. We used uncovered braided nitinol SEMSs with a cross-wired structure (Bonastent M-hilar; Standard Sci-Tech Inc., Seoul, South Korea), allowing for stent-in-stent deployment, and a 7F PS in a pigtailed configuration (Zimmon; Cook Medical., Winston-Salem, North Carolina, United States) [12].

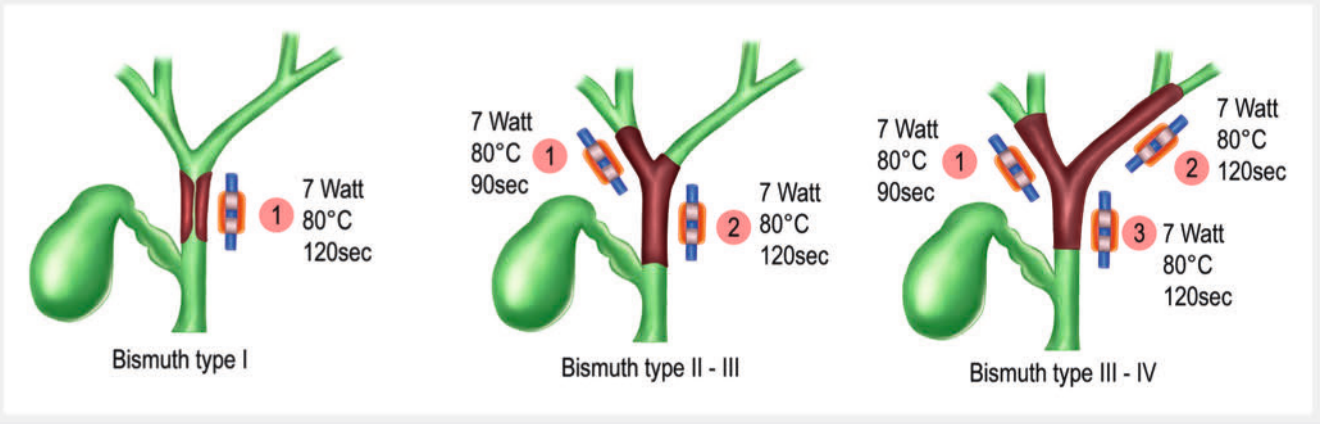
Data collection and follow-up

All patients underwent blood tests and simple abdominal X-rays at 4 hours, 24 hours, and 1 week post-procedure, together with confirmation of clinical symptoms and signs to assess the clinical effectiveness of biliary drainage and the occurrence of AEs after endobiliary RFA. If clinically successful biliary drainage was not achieved, additional drainage procedures, including percutaneous transhepatic biliary drainage, were considered. At 1-month intervals, patients were followed up and subjected to blood tests and simple abdominal X-rays. Computed tomography was performed as needed for suspected recurrent biliary obstruction (RBO) or AEs, or every 2 months to assess disease progression in patients who received chemotherapy. Chemotherapy using gemcitabine and cisplatin was administered according to patient performance status. Scheduled secondary interventions including regular stent exchange or additional RFAs after RBO were not performed for both groups.

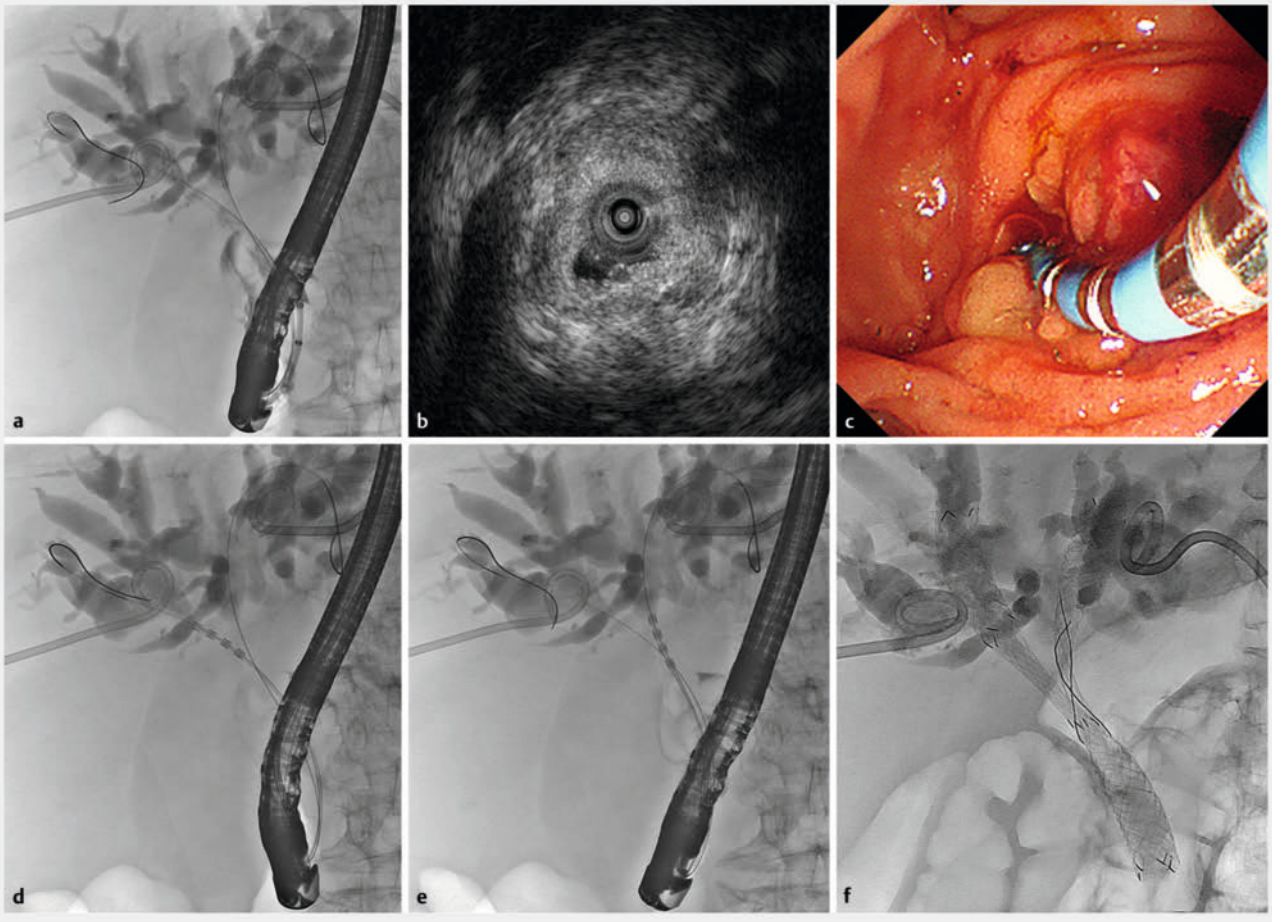
Definitions and outcome measurements

The primary outcome was the cumulative time to RBO and secondary outcomes were the technical success rate, clinical success rate, AE rate, overall survival (OS), and factors affecting time to RBO.

RBO was defined as a composite outcome of stent occlusion or migration, which was confirmed by clinical signs such as

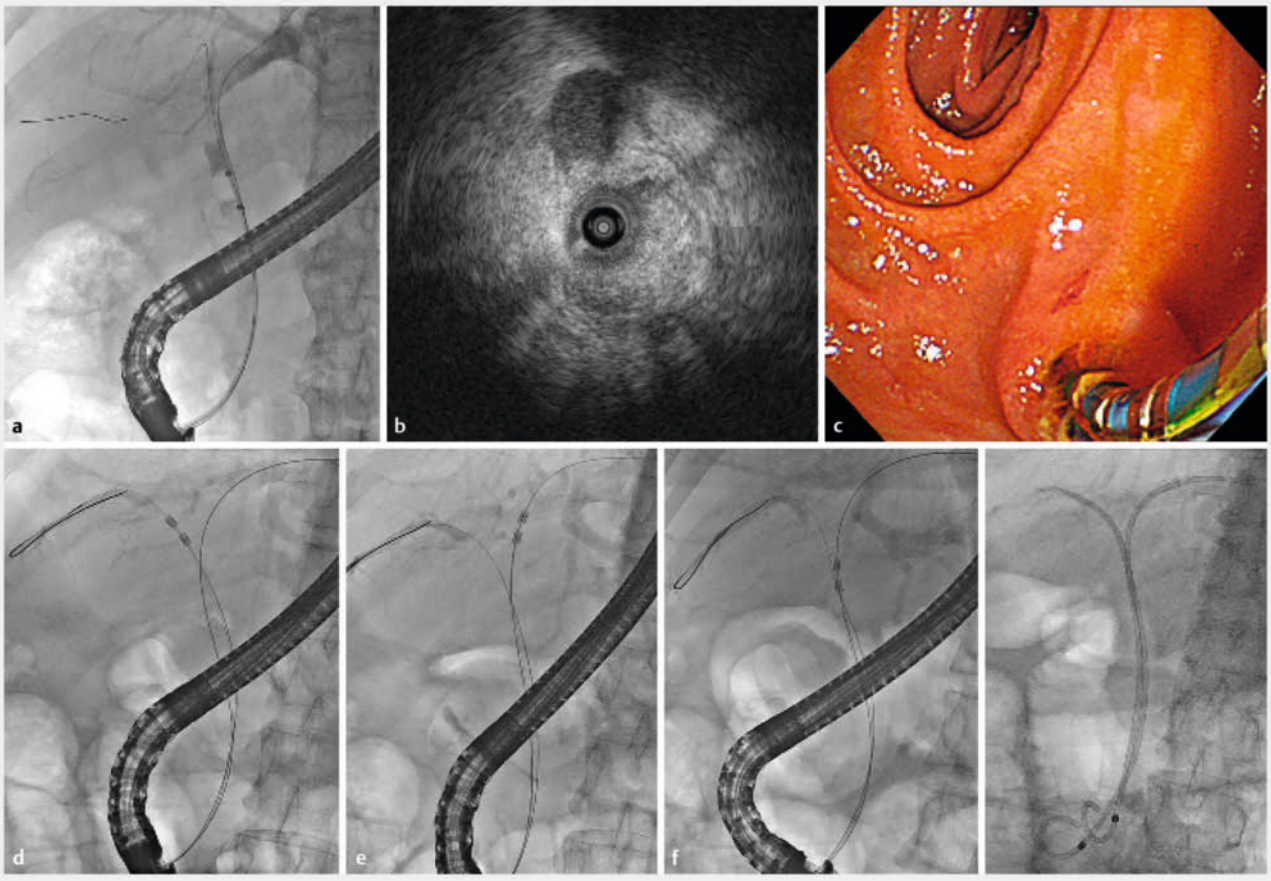


▶ **Fig. 2** Schema of radiofrequency ablation (RFA) application for hilar cholangiocarcinoma according to the Bismuth classification.



▶ **Fig. 3** **a** Cholangiogram and **b** intraductal ultrasound to assess stricture. **c** Endoscopic view showing a radiofrequency ablation (RFA) catheter entering the bile duct. **d,e** Fluoroscopic view showing bilateral endobiliary RFA using 18-mm RF catheters for 120 seconds at a power of 7 W and temperature of 80°C. **f** Successful deployment of metal stents after RFA.

jaundice and/or cholangitis and imaging findings. [13] The cumulative time to RBO was defined as the time from the date of stent placement until the date of RBO, death, loss to follow-up, or survival at the end of the study with no occlusion. Technical success was defined as successful completion of stent placement after endobiliary RFA or successful completion of stenting only. The RFA session was considered successful if the ablative energy was delivered for the scheduled time (90 to 120 sec-



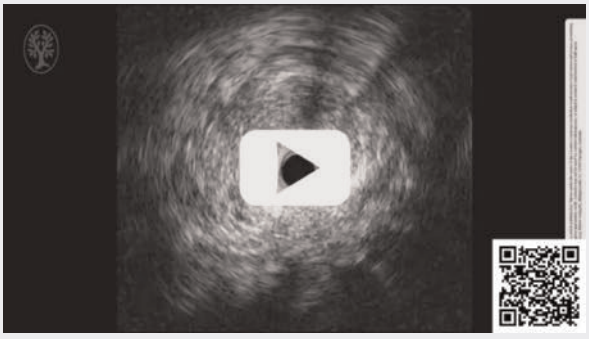
▶ **Fig. 4** **a** Cholangiogram and **b** intraductal ultrasound to assess stricture. **c** Endoscopic view showing a radiofrequency ablation (RFA) catheter entering the bile duct. Fluoroscopic view showing endobiliary RFA procedures using 11 mm RF catheters in the **d** right intrahepatic duct (IHD) for 90 seconds, **e** left IHD for 120 seconds, and **f** common hepatic duct for 120 seconds at a power of 7 W and temperature of 80°C. **g** Successful deployment of a plastic stent after RFA.

onds) with coverage of all tumor lesions. Clinical success was defined as resolution of symptoms, including obstructive jaundice and cholangitis, without further interventions within 1 week [14, 15]. AEs were assessed during follow-up after the initial intervention, with the exception of RBO, and were evaluated according to the grading system of the American Society for Gastrointestinal Endoscopy [16]. OS was defined as the time from initial stenting to death or the day of the last follow-up. Factors affecting time to RBO—including baseline characteristics, RFA treatment, stent type, and chemotherapy status—were evaluated.

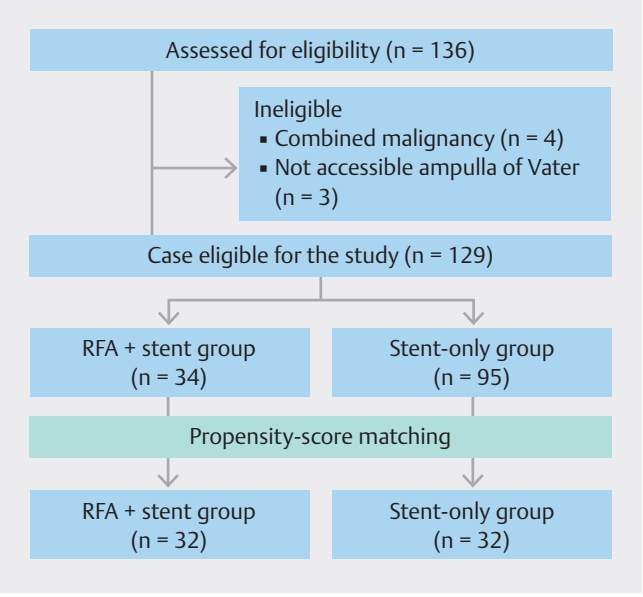
Statistical analysis

Propensity score matching was performed to reduce the effects of potential confounding bias on measured outcomes because of differences between the groups in patient baseline characteristics. Bismuth classification, ECOG performance status, tumor stage, and stent type were selected as the observed covariates. The aforementioned variables were selected based on analysis of previous literature [17, 18]. Propensity scores were estimated using logistic regression models based on this set of

VIDEO



▶ **Video 1** Fractionated endobiliary radiofrequency ablation at a power of 7 W and temperature of 80°C with subsequent deployment of plastic stents.



▶ **Fig. 5** Study flow chart. RFA, radiofrequency ablation.

covariates. The groups were matched by using 1:1 optimal matching without replacement and a caliper of width of 0.2 [19].

Continuous variables are presented as the median and interquartile range (IQR), and categorical variables are presented as the frequency and percentage. Continuous variables were compared using Student's *t*-test or the Wilcoxon rank-sum test, and categorical variables were compared using the Pearson chi-squared test or Fisher's exact test. The median cumulative time to RBO and OS with 95% confidence intervals (CIs) were estimated using the Kaplan-Meier method and compared with the log-rank test. Data were censored for patients who died, were lost to follow-up, or did not develop RBO by the end of the study period. A Cox proportional hazard model was used to identify factors affecting the time to RBO. Statistical analysis was conducted using SPSS version 21.0 for Windows software (IBM Corp., Armonk, New York, United States), and P <0.05 was considered indicative of statistical significance.

Results

One hundred twenty-nine patients with inoperable hilar CCA were included in the analysis; 34 patients received RFA and 95 patients did not receive RFA. After 1:1 propensity score matching, 32 patients each were categorized in RFA + stent and stent-only groups (▶ **Fig. 5**). No significant differences in Bismuth classification, ECOG status, tumor stage, or stent type were detected between the two groups (▶ **Table 1**).

▶ **Table 2** lists the outcomes of both groups after propensity score matching. Technical success was achieved in all patients. The clinical success rate was 93.8% (30 of 32) in the RFA + stent group and 87.5% (28 of 32) in the stent-only group (P = 0.672). The RBO rate was 75.0% (24 of 32) in the RFA + stent group and 84.4% (27 of 32) in the stent-only group (P = 0.351). The overall AE rates in the RFA + stent and stent-only groups were 12.5% and 9.4% (P = 1.000), respectively. In both groups, cholangitis (RFA + stent group, n = 3; stent-only group, n = 2) and cholecystitis (stent-only group, n = 1) occurred within 30 days of the RFA procedure and were graded as mild and treated conservatively without additional interventions. In the RFA + stent group, one patient experienced hemobilia after PS removal 182 days after RFA, which was successfully controlled without transfusion by immediate insertion of a SEMS into the bile duct.

In the RFA + stent group, the number of RFA applications required to ablate all lesions was one in 21.9% (7 of 32), two in 31.3% (10 of 32), and three in 46.9% (15 of 32) of the patients. The median total ablation length was 33 mm (IQR, 22–40) and the median total ablation time was 240 seconds (IQR, 120–330). The lengths of the electrodes used were 11 mm (55.6%), 18 mm (31.9%), and 22 mm (12.5%) (▶ **Table 3**).

The median cumulative time to RBO was 242 days (95% CI 181–309 days) in the RFA + stent group and 168 days (95% CI 159–281 days) in the stent-only group (P = 0.031). The median OS was 337 days (95% CI 252–404 days) in the RFA + stent group and 296 days (95% CI 289–383 days) in the stent-only group (P = 0.260) (▶ **Fig. 6**).

Discussion

Few studies have evaluated endobiliary RFA for hilar CCA due to the complexity of the hilar strictures and reports of severe AEs such as hemobilia, pseudoaneurysm, and hepatic infarction due to arterial thrombosis [4, 5, 20]. Compared with the distal bile duct, the curved structures with side branches of the hilar bile duct can reduce the uniformity of the therapeutic effect of RFA, and its thin fibromuscular/serosal layers and location adjacent to the hepatic artery and portal vein increase the risk of severe AEs [21, 22].

A new RFA system that can maintain a target temperature has been introduced to improve efficacy and reduce serious AEs [6, 17, 23]. Temperatures >100°C not only increase the risk of AEs but also cause the formation of a "coagulum," which increases resistance to alternating current and reduces RFA effectiveness. The new RFA system is safe for use in the hilar bile duct because it monitors the temperature at the catheter tip and maintains a preset temperature by means of an automatic on-and-off function [6, 7].

In this study, we evaluated the effectiveness and safety of temperature-controlled endobiliary RFA followed by stent placement compared with stent placement only for the palliative treatment of inoperable hilar CCA. In contrast to the recent RCTs by Albers et al. [24] and Jarosova et al. [25], our results showed a significant improvement in cumulative time to RBO in the RFA + stent group compared with the stent-only group (242 days vs 168 days, P = 0.031). We speculate that the benefit of RFA on the median time to RBO is likely due to the study design; unlike the aforementioned study in which the majority of patients had pancreatic cancer, we recruited and evaluated only patients with pathologically confirmed CCA. Given that the primary mechanism of obstruction by pancreatic cancer is compression rather than wall infiltration, ablation treatment

▶ **Table 1** Baseline characteristics.

Characteristics	Before propensity score matching			After propensity score matching		
	RFA + stent group (n = 34)	Stent-only group (n = 95)	SMD	RFA + stent group (n = 32)	Stent-only group (n = 32)	SMD
Age, years	76 (68–78)	73 (65–80)		75 (67–78)	74 (69–79)	
Sex, female	22 (64.7)	44 (50.6)		20 (62.5)	17 (53.1)	
Bismuth classification			0.298			0.025
▪ I–II	12 (35.3)	53 (55.8)		11 (34.4)	12 (37.5)	
▪ III–IV	22 (64.7)	42 (44.2)		21 (65.6)	20 (62.5)	
ECOG performance status			0.271			< 0.001
▪ 0–1	24 (70.6)	48 (50.5)		25 (78.1)	22 (68.8)	
▪ 2–3	10 (29.4)	47 (49.5)		7 (21.9)	10 (31.3)	
Stage			0.129			< 0.001
▪ Locally advanced	21 (61.8)	51 (53.7)		21 (65.6)	19 (59.4)	
▪ Metastatic	13 (38.2)	49 (51.6)		11 (34.4)	13 (40.6)	
Types of deployed stent			0.317			0.066
▪ Plastic stent	15 (44.1)	52 (54.7)		15 (47.3)	16 (50.0)	
▪ Metal stent	19 (55.9)	43 (45.3)		17 (53.1)	16 (50.0)	
Total bilirubin, mg/dL	6.3 (4.4–11.4)	6.3 (4.3–9.3)		6.3 (4.5–13.0)	6.4 (6.1–8.3)	
Chemotherapy, *n* (%)	18 (52.9)	36 (37.9)		17 (53.1)	15 (46.9)	

Values are n (%) or median (interquartile range).
ECOG, Eastern Cooperative Oncology Group; RFA, radiofrequency ablation; SMD, standardized mean difference.

▶ **Table 2** Comparison of outcomes between both groups.

Characteristics	RFA + stent group (n = 32)	Stent-only group (n = 32)	*P* value
Technical success	32 (100.0)	32 (100.0)	1.000
Clinical success	30 (93.8)	28 (87.5)	0.672
Recurrent biliary obstruction	24 (75.0)	27 (84.4)	0.351
Overall AEs, *n* (%)	4 (12.5)	3 (9.4)	1.000
▪ Pancreatitis	0 (0.0)	0 (0.0)	1.000
▪ Cholangitis	3 (9.4)	2 (6.3)	1.000
▪ Cholecystitis	0 (0.0)	1 (3.1)	1.000
▪ Hemobilia	1 (3.1)	0 (0.0)	1.000
Perforation	0 (0.0)	0 (0.0)	1.000

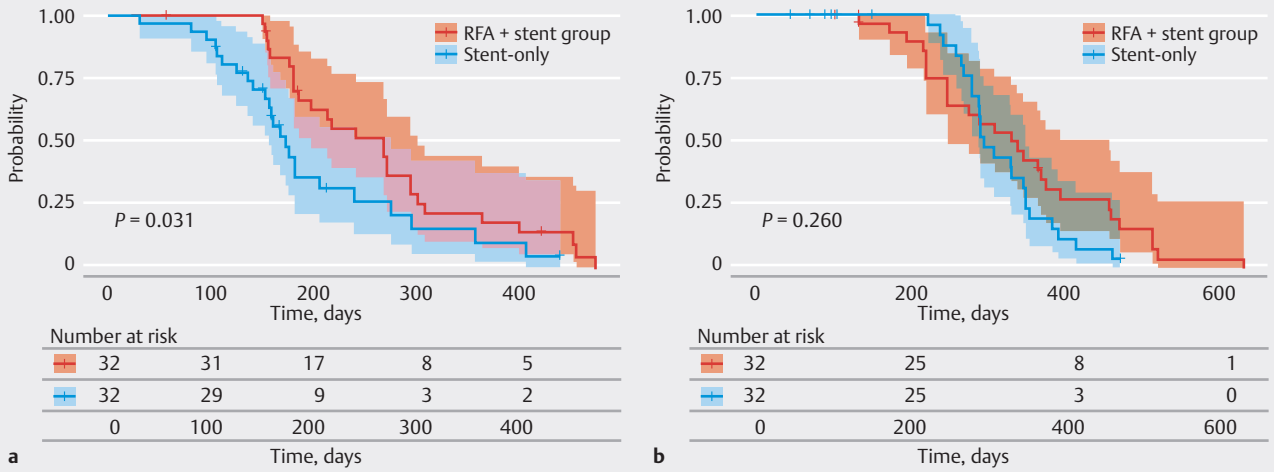
Values are n (%).
AE, adverse event.

▶ **Table 3** Outcomes of endobiliary RFA.

Characteristics	n = 32
Total number of RFA applications	
▪ 1	7 (21.9)
▪ 2	10 (31.3)
▪ 3	15 (46.9)
Total ablation length, mm	33 (22–40)
Total ablation time, sec	240 (120–330)
Electrode lengths used, mm	
▪ 11	40/72 (55.6)
▪ 18	23/72 (31.9)
▪ 22	9/72 (12.5)

Values are n (%), n/N (%), or median (interquartile range).
RFA, radiofrequency ablation

may be more effective in reducing the tumor load in CCA because the latter typically grows along the bile duct wall and is of limited thickness [26].



▶ **Fig. 6** **a** Kaplan-Meier curves of cumulative time to recurrent biliary obstruction (RBO). The median time to RBO was significantly longer in the radiofrequency ablation (RFA) + stent group than in the stent-only group (242 days vs 168 days, $P = 0.031$). **b** Kaplan-Meier curves of overall survival (OS). There was no significant difference in median OS (337 days vs 296 days, $P = 0.260$) between the two groups.

Findings about the correlation between endobiliary RFA and increased survival are conflicting [3, 8, 27]. In this study, there was a marginal trend toward increased OS in the RFA + stent group compared with the stent-only group (337 days vs 296 days, $P = 0.260$). Because endobiliary RFA is a local ablative treatment that delivers thermal energy to accessible tissues, it would have been difficult to demonstrate a significant OS improvement in our population, which included a large number of CCA patients with distant metastasis (34.4% in the RFA + stent group and 40.6% in the stent-only group). Although the trend toward an improved OS in the RFA + stent group suggests systemic effects of RFA on tumor-specific cytotoxic T-cell responses, modulation of circulating immune cells and cytokines, and amelioration of immunosuppression, further research is needed [28].

In the meta-analysis by Sofi et al. [29], two deaths as well as mild-to-moderate cholangitis and acute cholecystitis were reported among 239 patients who underwent endobiliary RFA; severe AEs were associated with injury to the major vessels adjacent to the bile ducts, which may have been caused by excessive heat during RFA [30]. In this study, all AEs were mild to moderate, and no severe AE was attributed to endobiliary RFA. In the RFA + stent group, cholangitis (n = 3), which was probably caused by poor drainage of the bile duct due to tumor necrosis after RFA, improved after conservative treatment. Although there was one case of hemobilia caused by the separation of deep necrosis from the perihilar tissue after PS removal in the RFA + stent group, it was stopped by immediate insertion of a SEMS into the bile duct. The comparable rates of AEs in the RFA + stent and stent-only groups (12.5% vs 9.4%; $P = 1.000$) indicate the safety of temperature-controlled RFA in patients with hilar CCA.

The favorable results of this study may be due to the variety of electrode types used and the temperature-control function of the RFA system [31]. The most widely used Habib EndoHBP (Boston Scientific, Marlborough, Massachusetts, United States) is a 180-cm-long 8F bipolar catheter with two 8-mm electrodes spaced 8 mm apart for an expected ablation length of 24 mm; it has a long ablation zone, which may not be suitable for use in the hilar bile duct. The RF catheter used in this study (ELRA; STARmed) allows the use of short electrodes (11 or 18 mm), thereby promoting effective RFA in the hilar bile duct. This system allows continuous maintenance of the selected electrode temperature during RFA, ensuring safe and effective RFA procedures even in the presence of complex hilar bile duct structures.

We aimed to improve the clinical outcomes of RFA. First, we measured stricture thickness using IDUS to reduce the risk of AEs in all patients. Second, we attempted to ablate all lesions using a short catheter (11 mm, 55.6%; 18 mm, 31.9%) by dividing strictures into several sections rather than ablating a single long segment. Of the patients, 46.9% (15 of 32) underwent three RFA procedures. Fractionated applications of RFA with a short catheter may have maximized intimate contact with the target tumor burden even in the angulated hilar bile duct. Third, we adjusted the ablation time of the right hepatic duct to 90 seconds, based on the risk of severe bleeding due to complex duct–vascular contact of the right hepatic duct and the right hepatic artery. Because the right hepatic artery typically crosses the posterior aspect of the CHD and then runs along the right hepatic duct, RFA of the right hepatic duct requires caution. Finally, subsequent stent placement for biliary drainage was performed immediately following endobiliary RFA to maintain bile duct patency. Ablation using a short RF catheter (11 or 18 mm) for 90 to 120 seconds at 7 W of power and a temperature of 80°C was effective and safe in patients with hilar CCA.

This study had several limitations. First, although propensity score matching was adjusted for background characteristics, the small sample size reduced the reliability of the statistical a-

nalysis and hampered subgroup analyses. Second, the type of deployed stent was not controlled for, although the types were distributed similarly between the groups. It was difficult to use the same type of stent for drainage due to differences in patient life expectancy. Third, there was no direct comparison of available RFA systems, so our results do not confirm that temperature-controlled RFA has better outcomes than power-controlled RFA. Further studies of the clinical outcomes of such systems are needed. Fourth, because RFA was performed in a single session, we could not determine the optimal frequency and interval. Fifth, biologic tests of antitumor cells and immunity were not performed, so no conclusions could be drawn about the systemic effects of RFA. The effect of endobiliary RFA on the systemic inflammatory response needs to be evaluated. Finally, the procedures were performed by highly skilled endoscopists, so the results may not be directly applicable to low-volume centers.

Conclusions

In conclusion, temperature-controlled endobiliary RFA is an effective and safe palliative treatment that provides sufficient destruction of local tumor without increasing the risks of severe AEs, thereby improving the effectiveness of subsequent treatments in patients with inoperable hilar CCA.

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Conflict of Interest

All the authors disclose no financial relationship relevant to this article. This study was supported in part by the SoonChunHyang University Research Fund (J.H.M.).

Funding Information

SoonChunHyang University Research Fund

Clinical trial

Clinical Research Information Service, Republic of Korea (https://cris.nih.go.kr)
Registration number (trial ID): KCT0008576
Type of Study: Retrospective propensity-mached study

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