Surgical Endoscopy
https://doi.org/10.1007/s00464-020-07689-z

Efficacy and safety of palliative endobiliary radiofrequency ablation using a novel temperature-controlled catheter for malignant biliary stricture: a single-center prospective randomized phase II TRIAL

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Received: 8 February 2020 / Accepted: 27 May 2020

Abstract

Background Endobiliary radiofrequency ablation (EB-RFA) has emerged as a palliative treatment for malignant biliary strictures (MBSs); however, concerns about complications related to thermal injury remain. In this study, we evaluated the efficacy and safety of EB-RFA with a novel catheter for MBS.

Methods Patients with inoperable cancer causing MBS were randomly assigned to either the radiofrequency ablation (RFA) group or the non-RFA group. The RFA group underwent EB-RFA at the stricture site with a temperature-controlled catheter (ELRA™; STARmed Co., Goyang, Korea) followed by deployment of a self-expanding metal stent (SEMS). For the non-RFA group, only SEMS placement was performed. The duration of stent patency, overall survival (OS), and 30-day complication rate were evaluated. This trial was registered at ClinicalTrials.gov (number NCT02646514).

Results A total of 48 patients were enrolled (24 in each group). During a median follow-up period of 135.0 days (RFA group) and 119.5 days (non-RFA group), the 90-day stent patency rate, median duration of stent patency, and median OS were not different between the groups (58.3% vs. 45.8% [$P=0.386$], 132.0 days vs. 116.0 days [$P=0.440$], and 244.0 days vs. 180.0 days [$P=0.281$], respectively). In the RFA group, procedure-related complications including thermal injury-related complications, such as bile duct perforation or hemobilia, were not reported. The early complication (< 7 days) rates were not different between the groups (4.2% vs. 12.5%, $P=0.609$), and there were no late complications (7–30 days) in both groups.

Conclusion EB-RFA with a temperature-controlled catheter followed by SEMS placement for patients with inoperable MBS can be safe and feasible with acceptable biliary patency.

Keywords Biliary stricture · Endobiliary · Radiofrequency ablation · Malignant · Palliative · Metal stent

Malignant biliary strictures (MBSs) are usually diagnosed in patients with advanced pancreatic or biliary cancer, and surgical resection is often not a treatment option. Consequently, endoscopic stenting for biliary decompression has been widely performed to relieve obstructive jaundice, decrease the risk of cholangitis development, and improve the quality of life of patients [1]. Endoscopic retrograde cholangiopancreatography (ERCP)-directed biliary stenting has become a standard procedure. The optimal choice of stents should be carefully individualized based on potential resectability and life expectancy, as each stent has its own advantages and disadvantages [2]. A self-expandable metal stent (SEMS) is considered the first option in the palliation of MBS because of its better patency, lower occlusion rate, lesser need for reintervention, and fewer complications than that associated with a plastic stent [3]. However, it has been reported that an

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Published online: 02 June 2020

uncovered SEMS frequently becomes occluded, especially as a result of epithelial hyperplasia and tumor ingrowth through the metal mesh [4].

Endobiliary radiofrequency ablation (EB-RFA) has emerged as an endoscopic palliative adjunctive therapy for patients with MBS [2, 5–13]. The radiofrequency (RF) energy circuit produced by neighboring bipolar electrodes delivers alternating current and induces frictional heat, resulting in hyperthermia and coagulation necrosis at the site of malignant tissue inside the bile duct [14, 15]. ERCP-directed EB-RFA devices have recently become commercially available. These devices are mainly aimed at palliation, such as prolongation of stent patency or debulking of stent tumor ingrowth [16].

Two types of EB-RFA systems have been developed: one is the power-controlled catheter and the other is the more recently introduced temperature-controlled catheter. Unlike the power-controlled catheter, the temperature-controlled catheter can monitor the temperature of the electrode during RF ablation (RFA). When the temperature reaches the preset target, the system automatically shuts down and reactivates the energy delivery to maintain the target temperature. Theoretically, temperature-controlled EB-RFA can minimize the risk of unintended thermal injury-related complications, such as bleeding or perforation [17]. Previous animal and human studies have evaluated its safety and feasibility for various types of MBSs [5, 17–23]. However, concerns remain even with the temperature-controlled catheter because of the lack of prospective comparative clinical trials. Therefore, we aimed to evaluated the efficacy and safety of temperature-controlled EB-RFA followed by SEMS placement in patients with MBS, compared with SEMS placement alone.

Materials and methods

Study population

The eligibility criteria for inclusion in this study were as follows: age > 19 years, cytologically or histologically proven malignancy that was surgically unresectable or medically unfit for surgery, histologically or radiologically confirmed MBS, life expectancy > 3 months, and voluntary agreement to participate in the study and completion of the consent form. Patients were excluded if they had significant bleeding tendency (international normalized ratio > 1.5 or platelet count < 50,000/mm^3), inaccessible bile ducts, and cardiac pacemaker implantation or were pregnant or breastfeeding, or refused to participate in the study.

Study design

This single-center, randomized, double-arm parallel-group, open-label, phase II trial was conducted at Severance Hospital, Seoul, Korea. Participants were randomized in a 1:1 ratio after achieving biliary access. With the use of sealed opaque envelopes containing computer-generated random numbers created by the investigator (M.J.C.) with a block randomization method with a block size of 4, the participants were assigned to undergo one of two treatment approaches: EB-RFA followed by biliary metal stenting (RFA group) or stenting alone (non-RFA group). The study was performed in accordance with the ethical guidelines of the 1975 Declaration of Helsinki. Written informed consent was obtained from each participant after the possible treatment complications had been fully explained. The institutional review board of Yonsei University Health System approved this study (approval number: 2015-1670-048). This study was registered at ClinicalTrials.gov (number NCT02646514).

Procedures

All procedures were carried out by fully experienced endoscopists who had each performed > 5000 cases of ERCP and percutaneous transhepatic cholangioscopy (PTCS), with the patients under anesthesiologist-assisted conscious sedation with propofol and fentanyl. Approach to the MBS through either the transpapillary or percutaneous transhepatic route was allowed. Under fluoroscopic guidance, ERCP or PTCS was conducted to diagnose and manage MBS with a large (4.2-mm) accessory channel duodenoscope (TJF-260V; Olympus Optical Co., Ltd., Tokyo, Japan) or cholangioscope (CYF-240A, Olympus Optical Co., Ltd.).

During ERCP, bile duct cannulation was attempted with a conventional cannula (Contour™ ERCP cannula; Boston Scientific, Natick, MA, USA) or a pull-type sphincterotome (Clever-cut [Olympus Optical Co.] or Autotome RX [Boston Scientific]). A precut papillotomy or infundibulotomy was attempted in the case of failure of bile duct cannulation with a pull-type sphincterotome. After performing selective cannulation, an index cholangiogram was taken to evaluate the location and length of the stricture. Thereafter, the guidewire was passed fully across the stricture. Patients with MBS who were not eligible for ERCP, for reasons such as an altered upper gastrointestinal anatomy, underwent PTCS. The guidewire was inserted into the bile duct through the percutaneous transhepatic route, secured, and dilated in advance. After the cholangioscope had entered the biliary tract, the presence and the characteristics of the stricture were evaluated with both cholangioscopy and fluoroscopic cholangiography.

For the RFA group, EB-RFA was first performed with the temperature-controlled RF catheter (ELRA™; STARmed Co., Goyang, Korea) and the RF generator (VIVA Combo™, STARmed Co.) (Fig. 1). The RF catheter type (18 or 22 mm) was selected according to the measured stricture length on endoscopist`s discretion to minimize unnecessary damage of bile duct as possible. After the RF catheter had been advanced over the guidewire and the radio-opaque electrode rings had been placed fully across the stricture, EB-RFA was performed. On the RF generator, the temperature-controlled mode was selected with preset values of temperature, power, and duration. Each RFA procedure was performed at 10 W with the 22-mm catheter or at 7 W with the 18-mm catheter for 120 s at a target temperature of 80 °C. The RF generator was used to monitor energy delivery and electrode temperature. When the temperature of the electrode had increased to

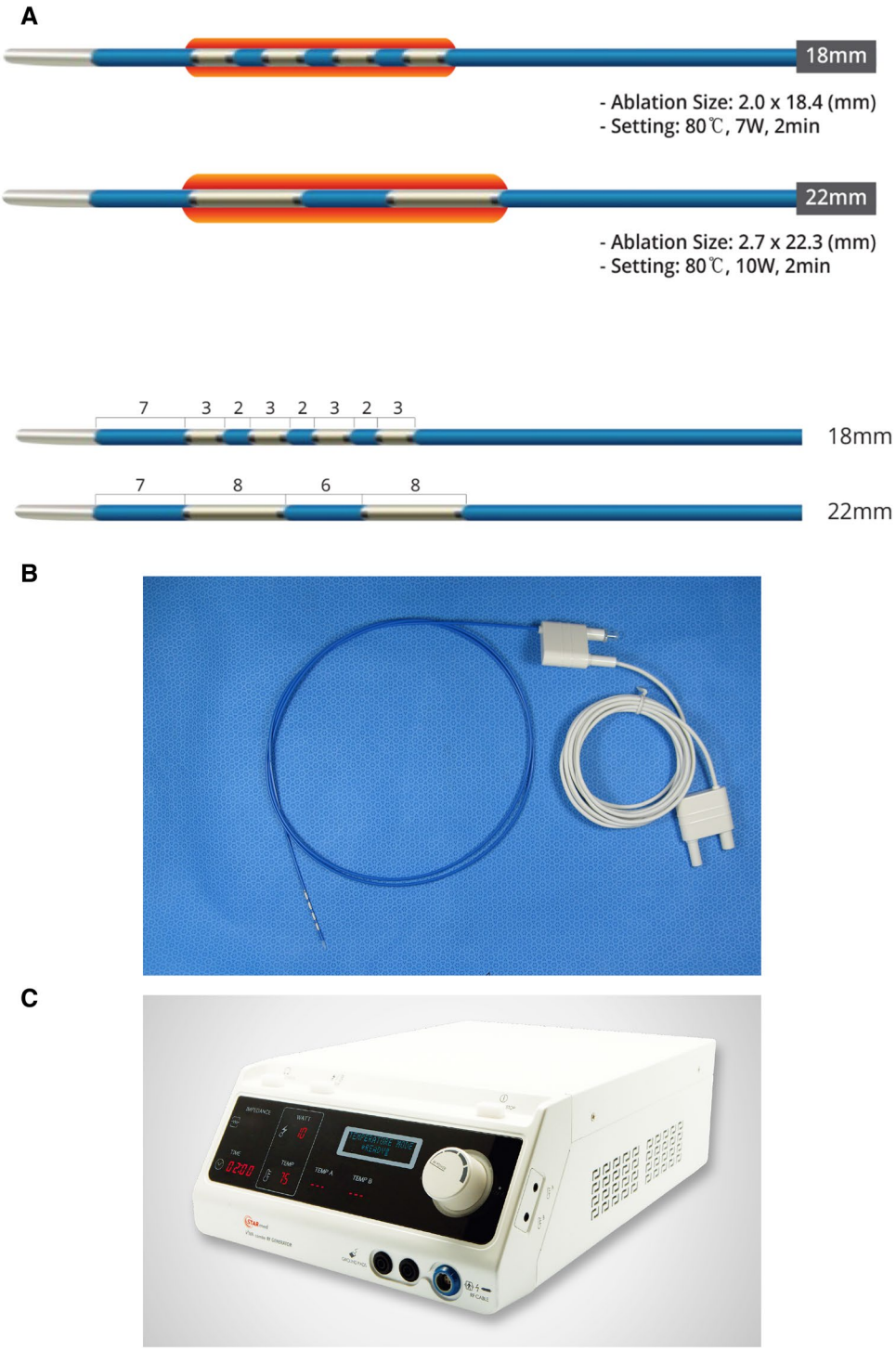

Fig. 1 Novel catheter for endobiliary radiofrequency ablation (ELRA®, Endoluminal Radiofrequency Ablation electrode; STARmed, Korea).The catheter has a 9-mm leading tip, 7 mm proximal to stainless-steel electrodes. **A** The two types of radiofrequency (RF) catheter used in this study and the recommended settings. The 18-mm catheter has four 3-mm electrodes. The 22-mm catheter has two 8-mm electrodes. **B** A 7-Fr, 175-cm-long catheter with a temperature sensor inside and is operated by an RF generator. **C** On the RF generator, the temperature, power, and duration can be preset and monitored

the predetermined target, the generator automatically maintained the target temperature for 120 s by controlling the energy delivery. If the length of the electrode was shorter than the stricture, multiple tandem ablations were allowed. Ablation was performed in a stepwise manner, covering the stricture from the proximal to distal edge, with care taken to ensure minimal overlap in the subsequent ablative steps. The RF catheter was removed after the planned ablation without cooling-down period, and an immediate cholangiogram was obtained to rule out complications such as perforation or bleeding. Thereafter, an uncovered SEMS (Taewoong Medical, Seoul, Korea) was placed for biliary drainage (Fig. 2). For the non-RFA group, SEMS deployment at the MBS site was the sole procedure. The length and diameter of the SEMS was chosen by the endoscopist according to the characteristics of the MBS of each patient.

Data assessment and follow-up

Complete medical history taking; physical examination; performance status assessment; and laboratory tests including complete blood count, blood chemistry, liver function tests,

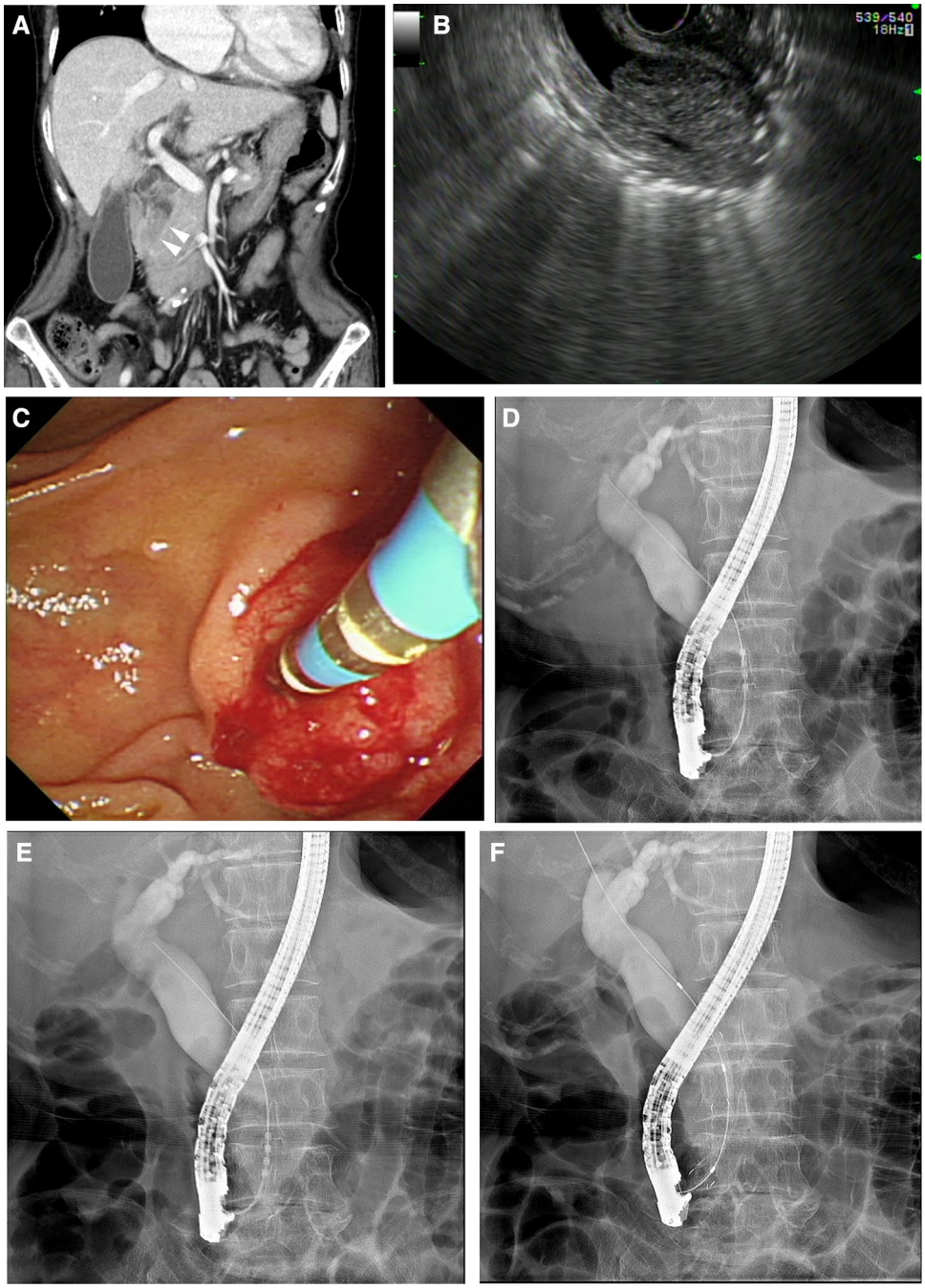

Fig. 2 Procedure for the radiofrequency ablation (RFA) group. An intraductally growing mass in the distal common bile duct causing a malignant biliary stricture (MBS) was noted on **A** computed tomography (arrows) and **B** endoscopic ultrasonography. **C** After biliary cannulation, a temperature-controlled RFA catheter was placed at the MBS site over the guidewire. **D**, **E** RFA was applied multiple times to cover the entire length of the MBS. **F** After RFA, an uncovered biliary self-expandable metal stent was deployed

amylase, and lipase were performed at baseline. Available cross-sectional imaging and histologic records were used for reviewing participant eligibility and for designing the procedures. To evaluate the clinical success and complications, postprocedural examinations, including laboratory tests and simple abdominal radiography, were performed at 4 h, 24 h, 7 days, and 30 days after the index procedure. Thereafter, the participants were followed up monthly with laboratory tests and radiographic evaluations. Scheduled computed tomography scans were obtained at 4, 12, 24, and 36 weeks after the index procedure. Follow-up was continued until stent occlusion, death, dropout from the trial, or 36 weeks after the index procedure. When the laboratory tests or clinical features were suggestive of cholestasis (jaundice or bilirubin elevation) or cholangitis (right upper quadrant pain, fever, leukocytosis, or cholestatic pattern in the liver function tests), stent occlusion was checked using cross-sectional imaging or ERCP. If occlusion was confirmed, reintervention for biliary drainage was performed, unless the patient could not tolerate the procedure.

Definitions and study endpoints

The primary study endpoint was the duration of stent patency, defined as the time from the index procedure to stent occlusion requiring revision of biliary drainage, or death. If the index procedure was performed bilaterally with two stents at the same time in patient with hilar MBS, at least one stent occlusion was considered as event for calculating stent patency. The secondary endpoints were overall survival (OS), defined as the time from the index procedure to death, and rate of 30-day complications, which were divided into early complications (within 7 days) and late complications (7–30 days). Procedure-related complications were defined and graded according to the consensus criteria [24]. Mild post-ERCP pancreatitis was defined as the presence of clinical symptoms (new or worsened abdominal pain) with serum amylase level more than three times the normal limit at more than 24 h after the procedure, requiring admission or prolongation of hospitalization by 2–3 days. Mild cholangitis was defined as a body temperature of > 38 °C for 24–48 h after the procedure. Mild bleeding was defined as clinical (not only endoscopic) evidence of bleeding, hemoglobin level decrease by < 3 g/dL, and no need for transfusion. Mild perforation was defined as a possible or only very slight leak of fluid or contrast, treated medically for < 3 days. The definitions of moderate and severe grades of each complication were also based on the consensus criteria. Postprocedure pain was assessed using Visual Analogue Scale (VAS) for 24 h after the procedure, and the highest VAS was recorded. For calculating OS, survival data were collected at the last cutoff date of follow-up for each participant. Technical success was defined as proper stent positioning and confirmation of immediate bile juice drainage, and clinical success was defined as a decrease in total bilirubin level by < 25% of the initial value or to the upper normal limit. For participants who initially had bilirubin levels within the normal range, clinical success was defined as the maintenance of the normal range value or the resolution of clinical signs and symptoms of cholangitis.

Statistical analysis

Sample size was calculated on the basis of the median SEMS patency for MBS of 177 days (standard deviation 69.1 days) [25]. To demonstrate a 60-day difference in stent patency between the RFA group and the non-RFA group, with a beta error of 0.20 and an alpha error of 0.025, we estimated that 22 participants were required for each group. Considering a 10% dropout rate during the follow-up, we determined a total sample size of 48 participants (24 participants in each group). The differences between the groups were assessed using a two-sided chi-square test or Fisher's exact test for categorical variables. Student's *t* test or the Mann–Whitney test was used to compare continuous variables. Estimations of the duration of stent patency and OS in each group were performed using the Kaplan–Meier method with 95% confidence intervals (CIs), and the log-rank test was used for comparison between groups. In case of loss to follow-up or follow-up being completed without a defined event for the calculation stent patency duration or OS, the participant was censored at the date of the last follow-up. Statistical analysis was performed using an intention-to-treat approach and conducted with IBM SPSS (version 23.0; IBM Corp., Armonk, NY, USA).

Results

Baseline characteristics

Forty-eight patients were enrolled from January 2016 to November 2018 (24 patients in each group) (Fig. 3). The baseline characteristics of the two groups were compared and are shown in Table 1. The demographic characteristics did not differ between the two groups. Further, disease-related characteristics, including the primary cancer site, proportion of metastatic disease, tumor size, predominant site, and stricture length, were not significantly different.

RFA-related characteristics (RFA group)

All patients of the RFA group underwent the assigned procedure as intended. Forced bile duct dilation before RFA was avoided to allow maximal contact of the stricture and the RF catheter electrode. In all patients, placement of the

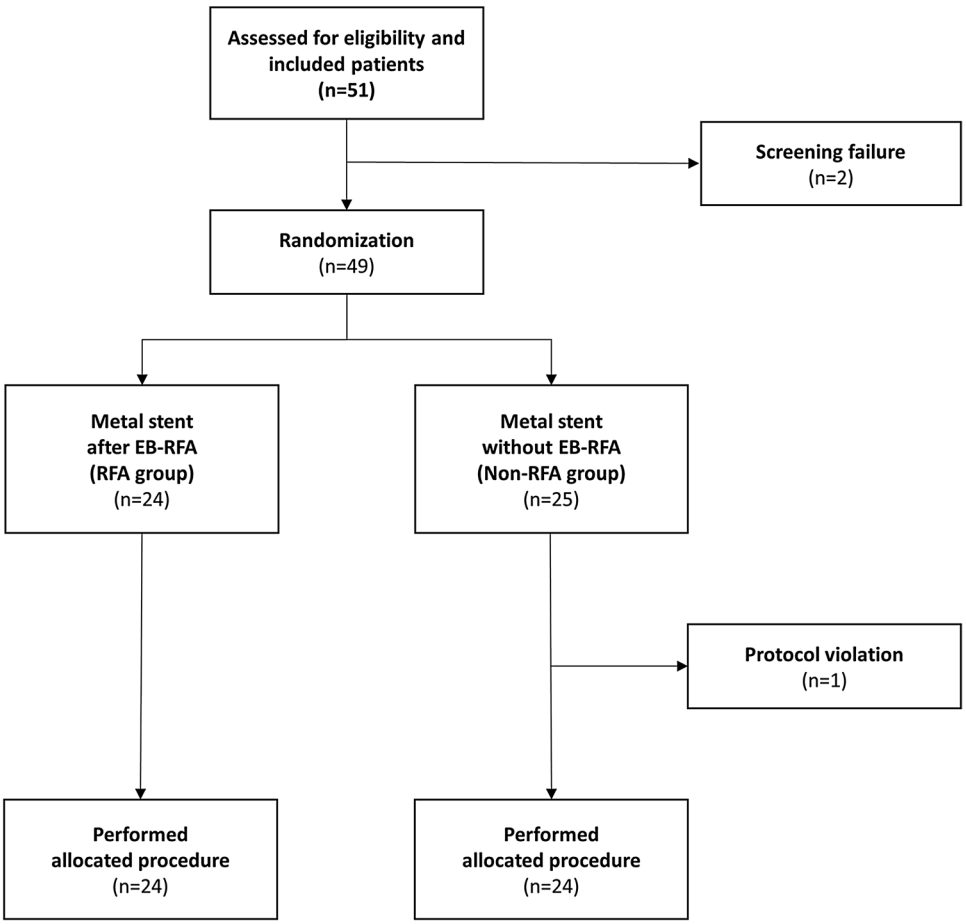

Fig. 3 Patient inclusion flowchart

RF catheter to the predominant MBS site was successful without any resistance, regardless of the site (distal, hilar, or intrahepatic bile duct). Table 2 shows the characteristics of the RFA procedure. The distal common bile duct (CBD) was the most common site of RFA application (58.3%), and the 22-mm RF catheter (66.7%) was more frequently used than the 18-mm catheter (33.3%). Most of the patients underwent RFA twice to cover the whole length of the MBS (54.2%).

Outcome comparison

The treatment outcomes are compared in Table 3. Both groups achieved a 100% technical success rate, and the clinical success rate did not differ between the two groups (RFA group 87.5% vs. non-RFA group 83.3%, $P=1.000$). In the RFA group, the median duration of stent patency and the 90-day stent patency rate were 132 days (95% CI 99.6–164.4) and 58.3%, respectively, which were not different from those in the non-RFA group (116 days [95% CI 52.4–179.6], $P=0.440$ and 45.8%, $P=0.386$, respectively) (Fig. 4a). Moreover, the median OS did not differ between the two groups (244 days [95% CI 117.8–370.0] vs. 180 days [95% CI 27.8–332.2], $P=0.281$) (Fig. 4b).

Complications

Table 4 shows the comparison of 30-day complications. The early complication rate did not statistically differ between the groups (RFA group: 4.2% vs. non-RFA group: 12.5%, $P=0.609$). All reported complications were mild pancreatitis in the non-RFA group. In the RFA group, an 80-year-old woman with preprocedural cholangitis due to MBS from CBD cancer died on day-3 after the index ERCP. In this patient, hypotension and metabolic acidosis developed on the same day that ERCP was performed, and multiorgan failure rapidly progressed to death. Two days after the ERCP, *Citrobacter freundii* was identified in the blood culture samples that were obtained before the index ERCP, which indicated that bacterial sepsis was preexisted. Therefore, a cholangitis resulting in septic shock and death was reported as unlikely related severe adverse event. There were no unintended thermal injury-related complications, such as bile duct perforation or hemobilia, in the RFA group. All procedure-related complications were managed conservatively, and the patients recovered uneventfully, except the death mentioned above. No late complications were reported in both groups (7–30 days).

Table 1 Patient characteristics

Variables	RFA group ($n=24$)	Non-RFA group ($n=24$)	*P*
Age, years	73.0 (58.5–76.0)	67.0 (59.0–72.8)	0.227
Male	16 (66.7)	14 (58.3)	0.551
ECOG-PS			
0–1	22 (91.7)	22 (91.7)	1.000
2	2 (8.3)	2 (8.3)	
BMI, kg/m^2	22.2 (19.2–24.5)	21.4 (19.9–24.4)	0.893
Primary site of malignancy			
Bile duct	18 (75.0)	12 (50.0)	0.152
CBD	10 (41.7)	7 (29.2)	
GB	3 (12.5)	2 (8.3)	
Hilar	3 (12.5)	3 (12.5)	
Intrahepatic	2 (8.3)	0 (0.0)	
Pancreas	4 (16.7)	10 (41.7)	
Others[a]	2 (8.3)	2 (8.3)	
Metastatic disease	16 (66.7)	15 (62.5)	0.763
Resectable (medically inoperable)	3 (12.5)	3 (12.5)	1.000
CA 19–9, IU/mL	120.7 (31.3–779.2)	402.7 (94.2–1215.0)	0.370
Tumor size, mm	37.5 (30.2–49.5)	36.0 (26.3–46.8)	0.403
Predominant site of stricture			
CBD	17 (70.8)	21 (87.5)	0.155
Hilum/IHD	7 (29.2)	3 (12.5)	
Stricture length, mm	25 (20.5–34.3)	20.0 (18.0–35.0)	0.383
Hyperbilirubinemia (≥ 2 mg/dL)	14 (58.3)	19 (79.2)	0.119
Presence of biliary drainage	21 (87.5)	18 (75.0)	0.461
CTx after index procedure	14 (58.3)	19 (79.2)	0.119

All categorical variables are presented as *n* (%). All continuous variables are presented as median (interquartile range)

RFA radiofrequency ablation, *ECOG-PS* Eastern Cooperative Oncology Group performance status, *BMI* body-mass index, *CBD* common bile duct, *GB* gallbladder, *IHD* intrahepatic duct, *CTx* chemotherapy

[a]Others included gastric, rectal and duodenal cancer

The median scale of post-procedure pain for 24 h after the procedure, and the proportion of patient with pain ≥ VAS 7 did not differ between two groups.

Subgroup analysis

Subgroup analysis was performed according to the site of MBS. Among patients with MBS at the CBD only, although there was no significant difference between the two groups, the RFA group showed a tendency toward having a higher rate of 90-day stent patency than the non-RFA group (12/17 [70.6%] vs. 9/27 [42.9%], $P=0.087$). The median duration of stent patency and the median OS were not different in this subgroup analysis.

We also performed an analysis with stratification of patients according to the primary site of malignancy; however, no significant differences in outcomes were observed.

Discussion

Biliary SEMS placement and photodynamic therapy (PDT) have been widely used to treat obstructive jaundice in patients with MBS. SEMS placement has been recognized as a safe palliative option entailing fewer serious adverse events and less invasiveness. Nevertheless, placement of a SEMS alone may require repeating the procedure because of stent obstruction or migration [26]. PDT requires expensive photosensitizers and equipment. Moreover, it is a time-consuming procedure with certain risks of complications, including cholangitis, hemobilia, and photosensitivity (12.5–30%) [27, 28]. The photosensitizer may cause dermal phototoxicity. Thus, patients who undergo PDT are required to avoid exposure to light for 2 weeks after treatment. On the contrary, EB-RFA allows earlier recovery of patients and is relatively less expensive than PDT. EB-RFA has another advantage that it can be easily performed by ERCP experts,

Table 2 RFA-related characteristics (RFA group)

Variables	RFA group ($n=24$)
RFA site	
Hilum/IHD	7 (29.2)
Proximal CBD	3 (12.5)
Distal CBD	14 (58.3)
RFA energy, J	540.0 (383.0–663.5)
RFA power and electrode length	
7 W, 18 mm	8 (33.3)
10 W, 22 mm	16 (66.7)
Number of application at RFA site	
1	6 (25.0)
2	13 (54.2)
3	5 (20.8)

RFA target temperature: 80 °C, Duration: 120 s for each application

All categorical variables are presented as *n* (%). All continuous variables are presented as median (interquartile range)

RFA radiofrequency ablation, *IHD* intrahepatic duct, *CBD* common bile duct

because it is not very different from handling other devices over the guidewire.

Previous studies have shown the efficacy of EB-RFA for MBS. The first experience of EB-RFA in patients with MBS was published in 2011, in which a power-controlled RFA catheter (Habib; EMcision UK, London, UK) was used [6]. To date, most of the EB-RFA-related studies have used this power-controlled RFA catheter, and most of them were retrospective studies or case series with a small number of patients. These studies reported a median stent patency of 4–9 months and demonstrated the acceptable safety of the procedure [6–10, 12, 13, 28–31]. However, there remain concerns about potential thermal damage of the bile duct due to uncontrolled high-temperature delivery during EB-RFA. This type of damage may induce considerable injury to the bile duct wall and adjacent vessels, which can lead to severe complications. Tal et al. reported on complications such as hemobilia and mortality [29]. The Austrian Biliary RFA Study Group reported various complications including liver infarction, hemobilia, and hepatic coma [7]. Thus, the novel temperature-controlled EB-RFA system had an important advantage of being able to avoid unintended hyperthermic damage of the bile duct when compared with the previous power-controlled EB-RFA system.

In animal studies on temperature-controlled EB-RFA, procedure-related short-term complications were not observed [17]. However, with respect to long-term effects, all animals developed suppurative cholangitis with stricture at 4 weeks after EB-RFA. With these results, the authors suggested that biliary stent placement after EB-RFA is necessary [5]. In an early clinical study evaluating the safety of temperature-controlled EB-RFA, no serious complications were reported after RFA with settings of 75 °C, 10 W, and 120 s [23]. Thus far, in combination with EB-RFA and biliary stent placement, no study using the temperature-controlled EB-RFA system has reported thermal injury-related complications such as bile duct perforation, hemobilia, or liver infarction [19–23], which were reported in other studies using the power-controlled EB-RFA system [7, 9, 29]. These types of complications were not reported in the RFA group of the present study, and the total complication rates did not differ between the two groups. In conjunction with previous studies, our results demonstrated that temperature-controlled EB-RFA in the setting of 7 W with an 18-mm catheter or 10 W with a 22-mm catheter at 80 °C for 120 s can be conducted safely. While a patient in the RFA group died due to aggravation of cholangitis and septic shock, whether the EB-RFA was

Table 3 Comparison of outcomes

Variables	RFA group ($n=24$)	Non-RFA group ($n=24$)	*P*
Technical success	24 (100)	24 (100)	1.000
Clinical success	21 (87.5)	20 (83.3)	1.000
Stent diameter (mm)	10 (10–10)	10 (10–10)	0.301
Stent length (cm)	7 (6–8)	7 (6–7)	0.806
Via percutaneous transhepatic route	4 (16.7)	4 (16.7)	1.000
Follow-up period (days)	135.0 (80.3–190.8)	119.5 (85.5–255.0)	0.621
90-day stent patency	14 (58.3)	11 (45.8)	0.386
Duration of stent patency, median (95% CI) (days)	132.0 (99.6–164.4)	116.0 (52.4–179.6)	0.440
OS, median (95% CI) (days)	244.0 (117.8–370.0)	180.0 (27.8–332.2)	0.281

All categorical variables are presented as *n* (%). All continuous variables are presented as median (interquartile range)

RFA radiofrequency ablation, *OS* overall survival, *CI* confidence interval

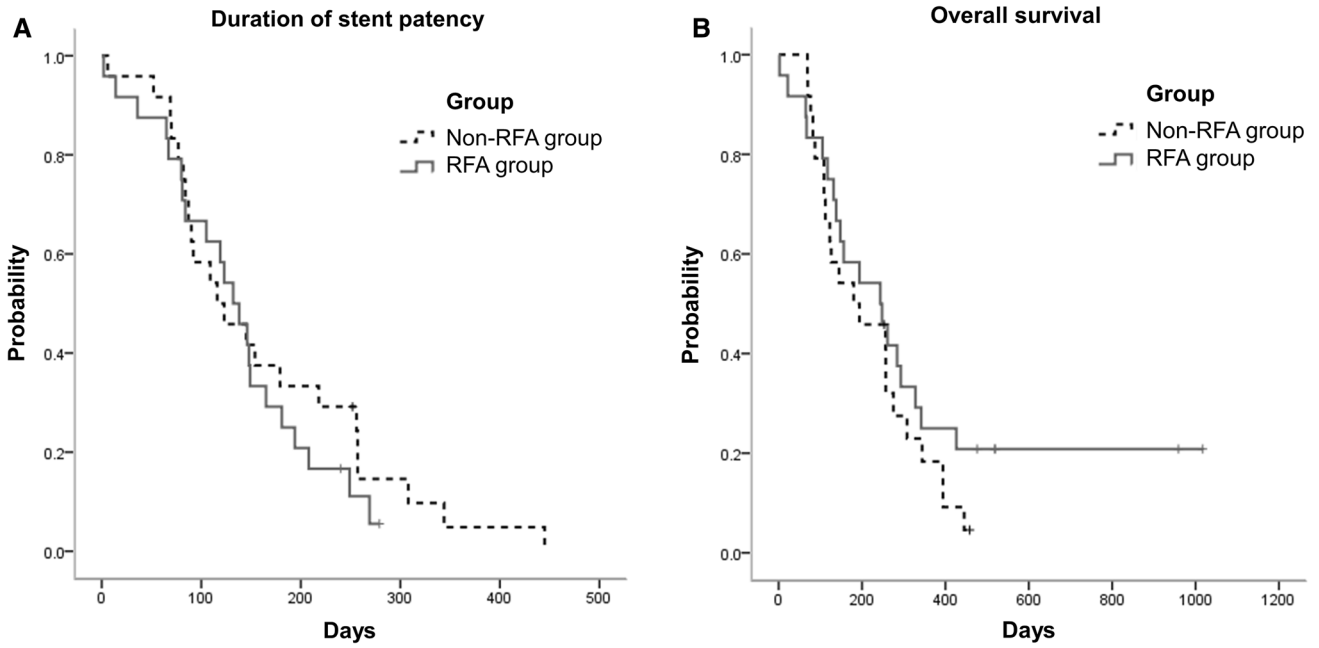

Fig. 4 Survival comparison with Kaplan–Meier plots. **A** Duration of stent patency and **B** overall survival according to the treatment group

Table 4 Comparison of complications in 30 days

Complications	RFA group ($n=24$)	Non-RFA group ($n=24$)	*P*
Early complications (≤7 days)	1 (4.2)	3 (12.5)	0.609
Pancreatitis (all mild)	0	3 (12.5)	0.234
Cholangitis	1[a] (4.2)	0	1.000
Perforation	0	0	–
Bleeding	0	0	–
Late complications (> 7 days)	0	0	–
Post-procedure pain, VAS	6.0 (2.0–6.0)	6.0 (3.3–7.0)	0.163
Post-procedure pain ≥ VAS 7	3 (12.5)	8 (33.3)	0.086

All categorical variables are presented as *n* (%). All continuous variables are presented as median (interquartile range)

RFA radiofrequency ablation, *VAS* visual analogue scale

[a]Reported as unlikely related severe adverse event resulting in death

related to death is uncertain because preprocedural sepsis was identified after the ERCP. Nevertheless, a relationship between the EB-RFA and the worsening of sepsis cannot be excluded. Previous studies have been reported that RFA can induce cytokine production or bacterial translocation [32, 33]. On the contrary, Schell et al. demonstrated that cytokine and cytokine-receptor production were not notably altered by RFA [34]. These previous studies, however, only evaluated RFA of liver or pancreas. It needs to be demonstrated more clearly in a future animal or human study evaluating the effect of EB-RFA on alteration of systemic inflammatory response.

As severe complications after power-controlled EB-RFA have been associated with perihilar obstruction [7, 29], there were certain concerns for patients with perihilar MBS when applying EB-RFA. Perihilar MBS is considered to have a high risk of complications because the perihilar duct has a more complicated duct-vascular anatomy and thinner bile duct wall than the extrahepatic duct. A recent study of 11 patients with hilar MBS reported the good safety profile of temperature-controlled EB-RFA, and the authors suggested that RFA using an 11-mm probe at 7 W, 80 °C for 60–120 s is safe [20]. Seven patients in the RFA group in our study had perihilar MBS, and EB-RFA was safely performed in these patients mostly with the 22-mm probe. Our result also demonstrated the safety of temperature-controlled EB-RFA for perihilar MBS. Considering the differences in tumor burden and anatomic structures between individual patients, a tailored approach in selecting the RFA probe and the preset values after a careful pretreatment assessment of perihilar MBS can make the procedure safer [31].

Whether EB-RFA followed by SEMS placement can increase stent patency or survival remains controversial owing to a lack of comparative prospective studies. A recent randomized controlled study using power-controlled EB-RFA and plastic stenting for unresectable extrahepatic cholangiocarcinoma concluded that EB-RFA can increase the survival and stent patency rates [31]. On the contrary, another randomized controlled study with a similar design although using SEMS reported no benefit in survival or

patency [35]. In our first randomized controlled study using temperature-controlled EB-RFA, SEMS placement after EB-RFA did not prolong survival or patency when compared with SEMS placement alone. Although the treatment efficacy in the RFA group was comparable to that reported in previous EB-RFA studies, it needs to be considered that the patients in our study had various sites of MBS. A subgroup analysis of patients with MBS at the CBD showed a trend of a higher rate of 90-day stent patency in the RFA group. This may indicate that the specific indications for EB-RFA should be defined. In a recent study in 18 patients who underwent temperature-controlled EB-RFA, the distal MBS group showed a longer median patency than the hilar MBS group (110 vs. 187 days); however, they were not compared statistically [23]. Moreover, several comparative studies in patients with extrahepatic MBS showed a survival or patency benefit of EB-RFA over stenting alone [11, 30, 31]. Considering the long-term post-RFA inflammatory reaction reported in an animal study, and the relatively narrow diameter and complex anatomy of the perihilar duct, patients with perihilar MBS might be prone to restenosis. Taking the results together, it is reasonable to speculate that patients with extrahepatic MBS may be better candidates for EB-RFA in terms of treatment efficacy. Further, as EB-RFA is a local palliative therapy, accompanying chemotherapy is an important factor related to survival. The optimal indication of EB-RFA needs to be defined in future large-volume prospective studies with more specific inclusion criteria.

Our study had several limitations. First, this was a single-center study with a small sample size. Second, the study participants had various types of primary cancers, predominant sites of MBS, and disease stages. This heterogeneity might make the results difficult to interpret. Third, the median follow-up period was relatively short in both groups (135.0 days in the RFA group and 119.5 days in the non-RFA group). This is because the majority of the enrolled patients had unresectable pancreatobiliary malignancy with metastasis who had a short life expectancy and higher chance of follow-up loss with the progression of disease. Despite these limitations, our study is the first prospective randomized study to establish the safety and feasibility of temperature controlled EB-RFA with SEMS for MBS, compared with SEMS placement alone. Future large, multicenter studies with a more homogeneous study population are warranted to overcome these limitations.

In conclusion, we demonstrated that EB-RFA with a temperature-controlled catheter followed by SEMS placement can be a safe and feasible procedure with acceptable biliary patency for patients with inoperable MBS.

Author contributions MJC and SB led the study design. The study was managed by SB. HK and MJC performed the data analysis. All authors interpreted the data. MJC and HK wrote the draft and revised versions of the manuscript. All versions of the manuscript were reviewed by all authors. All authors provided final approval of the manuscript.

Funding All device used for the radiofrequency ablation (RF generator and catheters) were provided by STARmed Co., Ltd. (Goyang-si, Republic of Korea). However, this study was initiated and carried out by the investigators, independently from the company.

Compliance with ethical standards

Disclosures Study devices including radiofrequency ablation catheters and the radiofrequency generator were provided by STARmed Co., Ltd. (Goyang-si, Republic of Korea). However, the design of the study protocol, study management, and data analysis were conducted by the investigators independently from the company. Drs. Huapyong Kang, Moon Jae Chung, In Rae Cho, Jung Hyun Jo, Hee Seung Lee, Jeong Youp Park, Seung Woo Park, Si Young Song, and Seungmin Bang have no conflicts of interest or financial ties to disclose.

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