

## NEW METHODS

## Long-term results of temperature-controlled endobiliary radiofrequency ablation in a normal swine model

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**Background and Aims:** Endobiliary radiofrequency ablation (EB-RFA) is a new adjunctive method for biliary drainage restoration. However, a concern remains about long-term adverse events of this procedure, such as biliary stricture, perforation, and hemorrhage. Therefore, we aimed to assess the long-term effects of in vivo EB-RFA in a swine model.

**Methods:** Six mini-pigs were divided into 2 groups: 10-W/33-mm EB-RFA and 7-W/18-mm EB-RFA. Endoscopic retrograde cholangiography-guided temperature controlled EB-RFA (80°C, 7-10 W, 120 seconds) was performed. After 28 days all mini-pigs underwent follow-up ERC and were killed to assess the long-term effects of EB-RFA.

**Results:** All mini-pigs developed biliary stricture (median length, 10.5 mm; range, 6-15) with jaundice (total bilirubin, 5.84 mg/dL; range, 4.3-9.2) and purulent bile at 1 month after EB-RFA. A significant difference was found in the length of stricture on cholangiogram between the 10 W/33-mm and 7 W/18-mm EB-RFA groups (median, 14 vs 6 mm;  $P = .034$ ); however, no differences were found in the width of the stricture and laboratory findings. Histologic examination revealed marked thickening of bile duct with severe damage of whole layers replaced with reactive myofibroblastic proliferation, dense collagen laydown, chronic and acute inflammation, and fat necrosis. However, long-term adverse events, such as perforation or hemorrhage, were not found.

**Conclusions:** As a long-term result of EB-RFA, segmental biliary stricture with cholangitis develops in proportion to the power/length of the RFA electrode. Therefore, biliary stents should be placed to maintain biliary drainage after EB-RFA.

Endobiliary radiofrequency ablation (EB-RFA) is a new endoscopic palliation and adjunctive method for patients with malignant biliary obstruction. Although EB-RFA has been increasingly performed worldwide, its safety and effectiveness remain major concerns.<sup>1-3</sup> To determine the short-term safety and efficacy of EB-RFA, we previously performed in vivo swine experiments regarding temperature-controlled EB-RFA. Twelve mini-pigs underwent endoscopic retrograde cholangiogram (ERC)-guided EB-RFA and were killed after 24 hours. Post-RFA cholangiogram showed no biliary leakage, and histologic

*Abbreviations:* BD, bile duct; CBD, common bile duct; EB-RFA, endobiliary radiofrequency ablation; ERC, endoscopic retrograde cholangiography.

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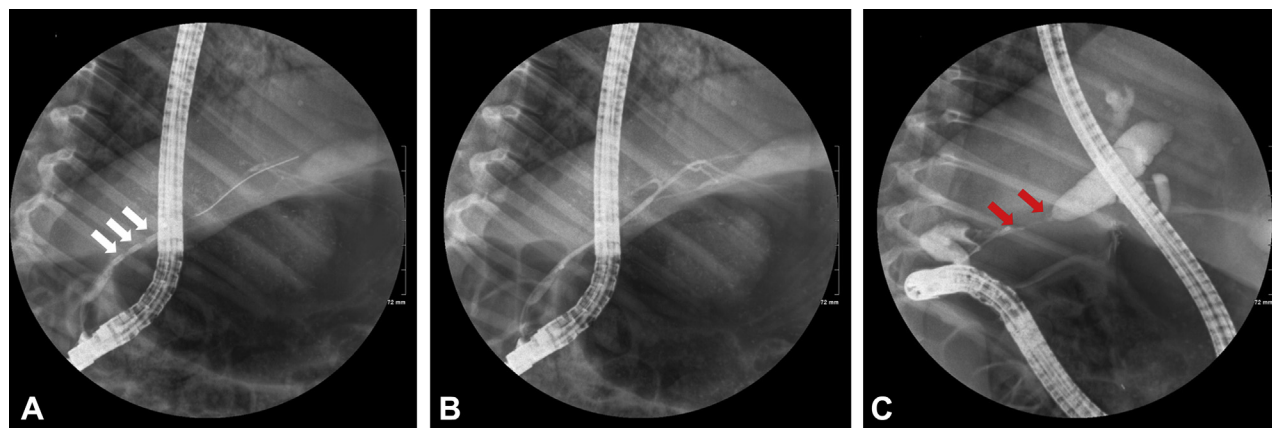
analysis revealed no perforation or bleeding at 24 hours after procedure. Additionally, we provided safe clinical reference values for EB-RFA performed at 80°C target temperature and 7- to 10-W power applied for 120 seconds.<sup>1</sup>

Considering the immediate histologic changes of coagulation necrosis on the RFA site, there is a high probability of post-RFA stricture development; therefore, when EB-RFA is performed in patients with malignant biliary obstruction, additional stent placement with either a plastic stent or self-expandable metal stent could be necessary for biliary tract restoration. However, there is a paucity of

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**Figure 1.** Endoscopic retrograde cholangiograms of mini-pigs obtained during endobiliary radiofrequency ablation (RFA). **A**, Endobiliary RFA was performed in the mid common bile duct (*white arrows*). **B**, Immediate post-RFA cholangiogram showed no contrast leakage. **C**, Follow-up cholangiogram at 4 weeks showed post-RFA stricture and proximal duct dilation (*red arrows*).

clinical and preclinical studies regarding late effects of EB-RFA. We aimed to assess the long-term effects of ERC-guided EB-RFA in a normal swine bile duct (BD) under the setting used in clinical practice for humans (80°C, 7-10 W, 120 seconds).

## METHODS

### Subjects

Six healthy, 14-month-old, female miniature pigs (*Sus scrofa*) were used in this in vivo experimental study. All mini-pigs were fed only with water for 24 hours before the endoscopic procedures and fasted overnight before the procedures. The Animal Care and Use Committee of the sponsoring institution approved this study (MK-IACUC: 150713-002).

### Endobiliary radiofrequency ablation

Under general anesthesia, six mini-pigs underwent ERC-guided EB-RFA using a temperature-sensing RFA catheter (ELRA RF catheter; STARmed, Goyang, Korea). After catheterization of the common BD (CBD), an initial cholangiogram was obtained, and a narrow segment of the BD was chosen as the site for the EB-RFA with a close contact between the RFA electrode and the BD wall. All mini-pigs were divided into 2 groups according to the 2 types of used RFA catheters: 10-W/33-mm electrode and 7-W/18-mm electrode. Radiofrequency energy was delivered by a VIVA combo radiofrequency generator (VCS10; STARmed) with a target temperature-controlled mode (80°C, 7-10 W for 120 seconds), which could automatically terminate ablation if a certain presetting temperature was exceeded.

### Post-RFA follow-up and pathology assessment

Biochemical test results of liver function were evaluated at baseline and twice weekly to assess the development of cholestasis. At 4 weeks after the EB-RFA, ERC was repeated

to measure the fluoroscopic stricture width and length, and all mini-pigs were killed to access the long-term results. An experienced pathologist (J.M.K.) performed gross and histologic analysis of post-RFA resected specimens.

### Primary and secondary outcomes

Primary outcome of interest was development of gross and microscopic long-term adverse events after temperature-controlled EB-RFA in normal swine BD. Secondary outcomes assessed were laboratory and clinical findings such as jaundice (yellow skin discoloration and icteric sclera) and purulent bile discharge on duodenoscopic images.

### Statistical analysis

Statistical analysis was performed using SPSS software, version 21.0 for Windows (SPSS Inc, Chicago, Ill). Laboratory findings and measurable experimental parameters were compared using Mann-Whitney U tests. Values are shown as medians and ranges.  $P < .05$  was considered significant.

## RESULTS

The experimental procedure of ERC-guided EB-RFA was successfully performed in all mini-pigs at the level of the CBD (2 distal CBD, 4 mid CBD). At 2 weeks after EB-RFA all animals developed clinical signs of jaundice and poor oral intake. Median values of the liver profiles were as follows: total bilirubin 8.6 mg/dL (range, 7.5-9.7), aspartate aminotransferase 403 IU/L (range, 310-1663). At 4 weeks after the procedure the follow-up ERC showed segmental biliary strictures with proximal BD dilation and large amounts of pus gushing out of the biliary orifice in all animals. The median length of stricture was 10.5 mm (range, 6-15), and the microscopic width of the stricture segment was 3.5 mm (range, 1-6) (Fig. 1). Laboratory test abnormalities were indicative of cholestasis that

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