Endoscopically applied radiofrequency ablation appears to be safe in the treatment of malignant biliary obstruction

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Background: In unresectable malignant bile duct obstruction in a patient with a life expectancy longer than 3 months, the use of self-expandable metal stents (SEMSs) is the standard technique to ensure continued biliary drainage. As many as 50% of patients with SEMSs will present with stent occlusion within 6 months. Changes to stent design and composition and concomitant therapy have failed to improve stent patency; therefore, alternative techniques to safely prolong stent patency are required.

Objective: To demonstrate the safety of endobiliary bipolar radiofrequency ablation (RFA) in patients with malignant biliary obstruction and to report the 90-day biliary patency of this novel procedure.

Design: Open-label pilot study.

Setting: Single tertiary care unit.

Patients: A total of 22 patients with unresectable malignant bile duct obstruction.

Interventions: Bipolar RFA within the bile duct.

Main Outcome Measurements: Immediate and 30-day complications and 90-day stent patency.

Results: A total of 22 patients (16 pancreatic, 6 cholangiocarcinoma) were recruited between January 2009 and April 2010. Deployment of an RFA catheter was successful in 21 patients. SEMS placement was achieved in all cases of successful RFA catheter deployment. One patient failed to demonstrate successful biliary decompression after SEMS placement and died within 90 days. All other patients maintained stent patency at 30 days. One patient had asymptomatic biochemical pancreatitis, 2 patients required percutaneous gallbladder drainage, and 1 patient developed rigors. At 90-day follow-up, 1 additional patient had died with a patent stent, and 3 patients had occluded biliary stents.

Limitations: Cohort study.

Conclusions: Endobiliary RFA treatment appears to be safe. Randomized studies with prolonged follow-up are warranted.

Since stainless steel self-expandable metal stents (SEMSs) superseded plastic stents in the 1990s,[1,2] their use in unresectable malignant bile duct obstruction has become the standard technique if the patient's life expectancy is longer than 3 months.[3,4] Tumor in-/overgrowth, epithelial hyperplasia, biofilm deposition, and sludge limits median SEMS patency to 120 days.[5] Ongoing or renewed biliary obstruction leads to significant morbidity and mortality.[1,2,6,7]

Abbreviations: RFA, radiofrequency ablation; SEMS, self-expandable metal stent.

DISCLOSURE: *The following authors disclosed financial relationships relevant to this publication: Ms. Nicholls: stockholder and board member of EMcision Ltd UK; Dr. Habib: stockholder and board member of EMcision Ltd UK. The other authors disclosed no financial relationships relevant to this publication.*

0016-5107/$36.00
doi:10.1016/j.gie.2010.09.031

Received June 16, 2010. Accepted September 15, 2010.

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Use of organic polymers to coat SEMSs, substituting alloys such as nitinol for stainless steel, or delivering endobiliary photodynamic therapy were all heralded as potential solutions to stent failure[6,8-10]; however, subsequent data have not confirmed these findings, while demonstrating increased cholecystitis, pancreatitis, prolonged cholangitis, and hemobilia.[5,11-18]

Radiofrequency ablation (RFA) has been used for percutaneous and intraoperative delivery of heat energy, achieving localized tumor necrosis in primary and secondary hepatic cancers.[19-21]

Endobiliary RFA has not been used in human subjects. This study is the first human use of endoscopically applied radiofrequency treatment. Preliminary animal studies provided the basis for the power and duration of endobiliary therapy delivered.[22,23]

Take-home Message

- Despite many attempts, the most recently reported large-scale trials have demonstrated that there has been little advance in the duration of bile duct patency since the introduction of metal stents in the early 1990s. This study reports safety and early efficacy data and demonstrates that application of heat energy within a malignant bile duct can be safely performed, and thus these data are the basis for conducting the next stage of controlled trials in this field.

METHODS

Patients

Patients with unresectable pancreatic or bile duct cancer were recruited for this pilot study. Exclusion criteria were uncorrected coagulopathy, cardiac pacemaker, failure to insert guidewire across a biliary stricture, Karnofsky score less than 40%,[24] and inability to give informed consent. Prospective data were collected detailing ERCP complications, patient survival, and stent patency as long as 90 days after the procedure. Serial liver function tests (imaging where indicated) determined the presence of biliary obstruction after ERCP. The study was approved by the institutional research ethics committee (08/H0718/46).

Intervention

Study ERCP with an RFA catheter was performed by experienced pancreatobiliary endoscopists (D.W., P.V.). ERCP was performed under standard operating conditions with Olympus TJF-260 duodenoscopes (Olympus, Tokyo, Japan). Previously placed plastic stents were removed before study cholangiography, which then confirmed biliary stricture length, diameter, and position. The RFA catheter was placed under fluoroscopic guidance across the biliary stricture (Fig. 1A).

The Habib EndoHPB (EMcision UK, London, United Kingdom) catheter has U.S. Food and Drug Administration and EU European Conformity approval. It is a bipolar RFA probe that is 8F (2.6 mm), 1.8 m long, compatible with standard (3.2-mm working channel) side-viewing endoscopes, and passes over 0.035-inch guidewires. The catheter has 2 ring electrodes 8 mm apart with the distal electrode 5 mm from the leading edge, providing local coagulative necrosis over a 2.5-cm length (Fig. 2).

Energy was delivered by an RFA generator (1500 RF generator; RITA Medical Systems Inc, Fremont, Calif) delivering electrical energy at 400 kHz at 7 to 10 W for 2 minutes, with a rest period of 1 minute before moving the catheter. Depending on the length of the stricture, sequential applications were applied to ensure RFA treatment throughout the length of the stricture without significant overlap of treated areas. After RFA treatment, uncovered SEMSs (Wallstent; Boston Scientific, Natick, Mass) were deployed per standard protocols.

Study design

The design was a single-center, open-label pilot study to demonstrate safety and biliary patency.

RESULTS

Twenty-two patients were recruited for the study between January 2009 and April 2010. Patient data are shown in Table 1.

In 1 patient, irretrievable proximal migration of a plastic stent resulted in no attempt to deploy the RFA catheter; a SEMS procedure was undertaken.

SEMS placement was achieved in all cases of endobiliary deployment. There were no technical difficulties placing the RFA catheter across the biliary stricture. Six study subjects had evidence of hepatic hilar or intrahepatic involvement; 3 of these subjects underwent balloon dilation of the stricture to facilitate further instrumentation. One patient had 2 SEMSs inserted at a hilar stricture with RFA applied for each stent (Fig. 1B).

Asymptomatic biochemical pancreatitis (amylase 1450 U/L) developed after ERCP in 1 patient. Cholecystitis requiring percutaneous gallbladder drainage developed in 2 patients; both of these patients had tumor encasement of the cystic duct on abdominal CT scan and sepsis before study ERCP. Six other patients had evidence of tumor encasement of the cystic duct. Rigors developed in 1 patient after ERCP that resolved after empirical antibiotic therapy.

One patient did not demonstrate biliary decompression; subsequent review demonstrated significant intrahepatic biliary malignancy precluding successful biliary decompression. Thirty-day patency was maintained in all other patients with no 30-day mortality.

At 90-day follow-up, the patient who failed to demonstrate biliary decompression had died; 1 other patient had

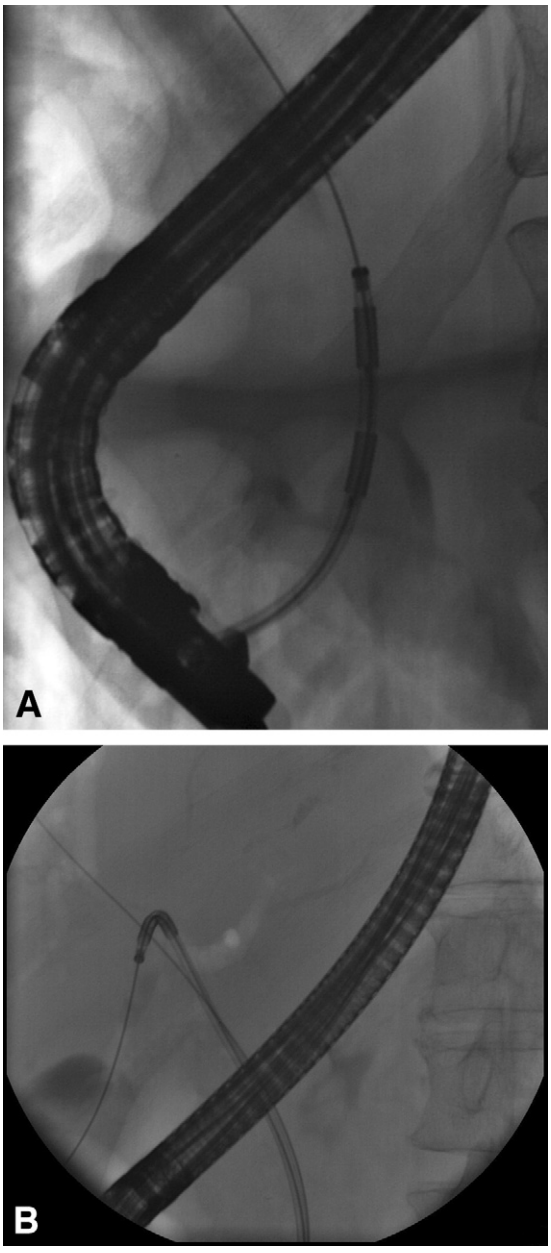

Figure 1. RFA catheter shown within the common bile duct (**A**) and at the hepatic hilum (**B**).

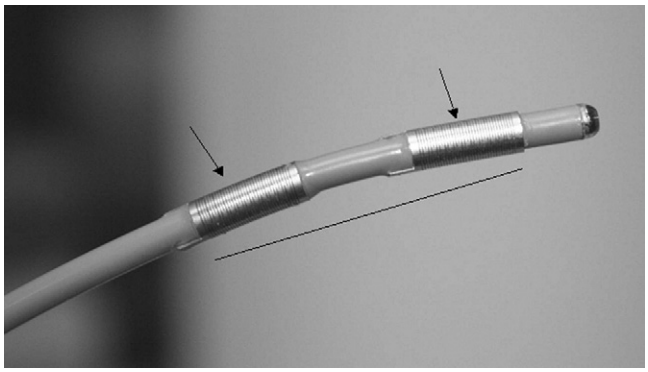

Figure 2. Habib EndoHPB catheter. Electrodes shown by *arrows*; the *solid line* indicates the 25-mm length of coagulative necrosis after catheter activation.

TABLE 1. Demographics (N = 22)

Sex: male	11
Age, y, mean (range)	70 (56-84)
Pancreatic/cholangiocarcinoma, no.	16/6
Metastatic, no.	10
Locally advanced, no.	17
Metastatic and locally advanced, no.	7
Declining surgery, no.	2
Hilar strictures, no.	6
Plastic stent before SEMS, no.	16
Sepsis at RFA ERCP, no.	7
Bilirubin, μmol/L, median (range)	26 (4-286)
Karnofsky score, median (range)	55 (40-100)

RFA, Radiofrequency ablation; *SEMS*, self-expandable metal stent.

died of disease progression with a patent stent. Biliary obstruction developed in 3 other patients. Further RFA procedure data are shown in Table 2.

DISCUSSION

This phase 1 study of endobiliary RFA treatment of malignant biliary obstruction demonstrates immediate and 30-day safety and 90-day biliary patency.

Potential complications identified in the preclinical pig model were extension of the RFA burn into local structures and difficulty reintroducing catheters into the bile duct after RFA treatment.[22,23] Furthermore, hemorrhage and abscess formation at the site of RFA are recognized complications of hepatic RFA.[20,21] These complications were not apparent in our patients. Blood tests demonstrating systemic inflammatory response to RFA were not measured.

This is the first reported use of endobiliary RFA, and our reported complications are in keeping with literature-reported type and incidence for biliary SEMSs.[5,18,25]

Application of RFA within the bile duct induces local coagulative necrosis; unlike the superficial (700 μm) burn induced with esophageal RFA in the treatment of Barrett's esophagus, it is likely that the energy delivered in this study resulted in a deeper level of tissue damage.[26,27] RFA coagulative necrosis within a malignant biliary stricture will likely result in some damage to an adjacent healthy bile duct. Our use of 2 electrodes means that the heating pattern is substantially cylindrical, stretched between the 2 electrodes, ensuring that the energy is spread over a larger

TABLE 2. Radiofrequency ablation procedure details (N = 21)

Procedure time, min, mean (range)	43 (22-68)
Fluoroscopic screening time, min, median (range)	5 (3-36)
No. of applications, median (range)	2 (1-4)
Total energy delivered, J, mean (range)	2474 (1200-3600)
Stricture diameter before RFA, mm, median (range)	0 (0-1)
Stricture diameter after RFA, mm, median (range)	4 (3-6)
Length of stricture, mm, mean (range)	37 (20-60)
After ERCP day stay, d, median (range)	1 (1-24)
Patients alive with biliary patency at 90 days	16/21
Median stent patency at day 90 of final subject, d, median (range)	114 (0-498)

RFA, Radiofrequency ablation.

volume than with a single electrode, and the spatial variation of energy deposition is less. Additionally, because the RFA burn was immediately followed by insertion of SEMSs, any biliary injury was empirically treated. Prospective data to determine the best treatment of bile duct injury in this situation are lacking; however, with traumatic or surgical bile duct injuries, endoscopic biliary stent placement is considered the best form of therapy.[28-31] There were no complications that could be attributed to full-thickness bile duct RFA, nor was there any evidence of biliary leak or local fibrotic reactions during follow-up.

An increased risk of sepsis could result from bacterial translocation at the time of RFA.[19,32] Bacterial colonization of the bile duct after the initial ERCP and plastic stent insertion may increase the risk of bacterial translocation at the time of RFA ERCP. This was not apparent in our data. Subjects underwent previous ERCP and plastic stent insertion according to local practice (hyperbilirubinemia, biliary sepsis, biliary drainage pending definitive staging procedures or while awaiting referral to this institution). Previously placed plastic biliary stents were typically 7F or 10F; however, all cases had a biliary stricture diameter less than that of the 8F RFA catheter at study ERCP (Table 2), ensuring tight contact between the RFA probe and the malignant stricture.

Despite the limitations described, this study demonstrates 30-day safety and 90-day biliary patency. Randomized studies to determine the effect of endoscopically applied RFA therapy on long-term biliary stent patency are warranted.

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