

Endobiliary radiofrequency ablation for malignant biliary obstruction

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BACKGROUND: The cornerstone of palliative treatment for inoperable extrahepatic cholangiocarcinoma is the relief of malignant biliary obstruction. The most commonly applied method is endoscopic stenting. However, the procedure can be complicated with stent obstruction. In this respect, endobiliary radiofrequency ablation may serve as an adjunctive tool for prolonging the stent patency.

METHODS: Patients who underwent endoscopic retrograde cholangiopancreatography for differential diagnosis and/or palliative treatment after the diagnosis of inoperable extrahepatic cholangiocarcinoma between March 2011 and January 2012 were analyzed. Those in whom endobiliary radiofrequency ablation and endoscopic stenting was successfully performed were included in the study. Technical details of the procedure, duration of stent patency, length of hospital stay, short-term morbidity and mortality rate were documented.

RESULTS: Seventeen patients were analyzed, and 10 patients were included in the study. The morbidity and mortality rate within the first 30 days after the procedure was 20% and 0%, respectively. In 2 patients, mild pancreatitis occurred because of the endobiliary procedure. In 1 patient, endobiliary decompression could not be achieved, and therefore, percutaneous transhepatic biliary drainage was carried out. The median duration of stent patency in 9 patients with successful biliary decompression was 9 months (range 6-15).

CONCLUSION: Endobiliary radiofrequency ablation seems to be safe and feasible as a palliative measure and may prolong the stent patency and overall survival in patients with malignant biliary obstruction due to inoperable extrahepatic cholangiocarcinoma.

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Introduction

The vast majority of patients with extrahepatic cholangiocarcinoma present with malignant biliary obstruction, and most have advanced disease and thus can only be offered palliative treatment. The cornerstone of palliative treatment is the relief of malignant biliary obstruction, which can be achieved surgically, endoscopically, or radiologically.^[2]

Endoscopic retrograde biliary drainage by endoscopic stenting, if possible, is a desirable method for palliation of malignant biliary obstruction.^[3, 4] However, the major drawback of endoscopic stenting is that the patency of endoscopic stent is limited to a median duration of 120 days with plastic stents and 130-217 days with self-expandable metallic stents (SEMSs).^[5-14] This is mainly due to tumor in- or over-growth, biofilm deposition, biliary sludge, or formation of granulation tissue, all of which may result in ongoing or recurrent biliary obstruction that causes significant morbidity and mortality.^[6]

Several methods such as the use of organic polymers to coat SEMSs, substituting alloys like nitinol for stainless steel, or endobiliary photodynamic therapy, have been proposed for increasing the duration of stent patency in malignant biliary obstruction but have not been proven to be effective by sufficient data.^[6]

Radiofrequency (RF) energy produces a high frequency electric current, which leads to coagulation necrosis in the tissue.^[15, 16] RF ablation (RFA) has been increasingly accepted in the last 15 years with promising results for various medical indications, and its use for cancer is approved by the US Food and Drug Administration. Recently, preliminary reports based

on the use of endobiliary RFA in malignant biliary obstruction have emerged.^[6, 17] Two major advantages of RFA in this setting are brought forward. First, it reduces the tumor load, and thus, delays tumor growth, both of which may potentially prolong stent patency.^[6, 17] And second, endobiliary RFA may eventually constitute a form of neoadjuvant therapy in unresectable cholangiocarcinoma.^[6]

In this study, the patients with unresectable extrahepatic cholangiocarcinoma were treated by endoscopic stenting after the application of endobiliary RFA, and the management and the outcome of the patients were described.

Methods

The study was a retrospective analysis. The patients with unresectable extrahepatic cholangiocarcinoma who had undergone endoscopic retrograde cholangiopancreatography (ERCP) for differential diagnosis and/or palliative treatment between March 2011 and January 2012 were recruited, and those who had successfully undergone endobiliary RFA and endoscopic stenting were also included. All of the patients were fully informed about details and complications of the procedure, and were requested to sign an informed consent form.

All patients underwent a detailed clinical and radiological investigation for differential diagnosis. The medical data of all patients were evaluated by a multidisciplinary team including surgeons, radiologists, medical and radiation oncologists, and pathologists. Patients who refused to join the study or to sign the informed consent form, patients with Bismuth type II, III or IV hilar cholangiocarcinoma, patients in whom endoscopic procedure could not be completed, and patients with

benign biliary stricture were excluded from the study.

ERCP was performed under standard operating conditions with a Fujinon EVE 200 duodenoscope (Fujinon, Tokyo, Japan). Prophylactic antibiotherapy with ceftriaxone (1 g, intravenous) (Rocephin®, Roche, Istanbul, Turkey) was done prior to the procedure. Conscious anesthesia was induced with intravenous propofol (2 mg/kg) and fentanyl (2 mg/kg). The patient was placed in a left lateral decubitus position. After the cannulation of the common bile duct, a cholangiogram was obtained to assess the length, diameter, and location of the biliary stricture. Habib EndoHPB (Emcision®, London, UK) was used for RFA. An RF catheter was placed through the biliary stricture under fluoroscopic guidance (Fig.). The catheter had a bipolar RF probe, which was 8F (2.6 mm), 1.8 m long, compatible with standard (3.2-mm working channel) side-viewing endoscopes, and could be passed over 0.035-inch guidewires. The catheter has two 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. An RF generator (1500 RF generator; RITA Medical Systems Inc., California, USA) producing electrical energy at 400 kHz at 10 W was utilized. Total duration of an RFA session was two minutes with two 40-second periods and a final 10-second period of RFA separated with 15-second breaks. At the end of RFA session, a control cholangiogram was obtained to rule out skipped areas of biliary stricture, which would necessitate an additional RFA session, after a 60-second rest period without removing the catheter (Fig.). Thereafter, the RF catheter was withdrawn without removing the guidewire. A 10F silicone-covered SEMS (Niti-S™ Biliary Stent, Taewoong Medical Co., Ltd., Gyeonggi-Do, Korea) was introduced over the previously placed guidewire. Endoscopic stent was



Fig. The view after the placement of endobiliary RFA catheter (A); the filling of the entire biliary tree with contrast media after the application of endobiliary RFA (B); the confirmation of patency of the entire biliary tree after the application of self-expandable metallic stent (C).

Endobiliary radiofrequency ablation

placed according to the findings of index cholangiogram. After the placement of the stent, a cholangiogram was obtained to confirm the correct position of endoscopic stent and whether the patency of entire biliary tree could be achieved (Fig.).

Physical examination, measurement of complete blood count, and measurement of serum amylase levels were carried out in all patients. Those who had no positive clinical signs or biochemical results were discharged at the end of 48 hours after the procedure. The patients who were suspected to have any complications were promptly evaluated and treated in the in-hospital setting.

The patients were referred to medical oncologist for adjuvant chemotherapy. All patients, except one who was found to be a poor candidate for systemic chemotherapy, had a combined chemotherapy with gemcitabine and cisplatin.

All of the patients were followed regularly after the procedure, and no patients were lost to follow-up. Demographics, inoperability criteria, the location of malignant stricture, details of previous interventions, technical details of the procedure, the duration of stent patency, length of hospital stay, short-term morbidity and mortality rate were documented.

Results

Seventeen patients with inoperable extrahepatic cholangiocarcinoma were recruited for the study. ERCP or endobiliary RFA was not attempted or not successful in 7 patients. Therefore, 10 patients who had successful ERCP with endobiliary RFA and endoscopic stenting were included in the study.

Inoperability criteria in 17 patients were as follows: unresectability (9 patients); extremely high-risk for surgery due to preexisting comorbidities (6); and refusal to undergo surgery (2). Three of 7 patients in whom ERCP or endobiliary RFA was not attempted or not successful were found to have Bismuth type II or III hilar cholangiocarcinoma, both of which were not suitable for placement of RFA probe. The other two patients developed severe respiratory distress due to significant comorbidities during the procedure. In the last 2 patients, the common bile duct could not be cannulated due to severe fibrosis of major duodenal papilla, which was found to be benign after histopathological examination of endoscopic biopsy materials.

The mean age and female-to-male ratio was 62.3±8.7 years (48-74) and 3/7, respectively. The indications for palliative treatment were unresectable tumor due

Table. Technical details, and the results of outcome variables

Variables	Data
Number of applications	3 (3-4)
Total duration of the procedure (min)	35.4±8.5 (20-45)
Length of stricture (mm)	20 (20-35)
Diameter of stricture before the procedure (mm)	1.5 (1.5-2)
Diameter of stricture after the procedure (mm)	5 (4-7)
Total amount of energy delivered (W)	10
Length of hospital stay (d)	2 (1-5)
Thirty-day morbidity	20% (2/10)
Thirty-day mortality	0

to locally advanced disease (6 patients), metastatic disease (2), and considerably high-risk for surgery due to comorbidities (2). Bismuth type I hilar and distal cholangiocarcinoma was present in 4 and 6 patients, respectively. None of the patients had undergone any surgical or endoscopic intervention before the procedure.

The procedure was uneventful in all patients. In spite of a successful session of endobiliary RFA and endoscopic stent application, biliary decompression could not be achieved in one patient at the end of 10 days after the endoscopic procedure. Therefore, the patient was referred to the interventional radiologist for the application of percutaneous transhepatic biliary drainage. Two patients developed abdominal pain and 8 to 10-fold elevation in serum amylase levels within the first 12 hours after the procedure, and thus, were considered to have post-ERCP pancreatitis. Post-ERCP pancreatitis in both patients had a mild course, and had subsided with conservative treatment without any complications.

The median duration of stent patency in 9 patients with successful biliary decompression was 9 months (range 6-15). Of these 9 patients, 1 patient died in the 8th month after the endoscopic procedure because of preexisting comorbidities. The details of the procedure and the results of the study are illustrated in Table.

Discussion

Steel and his coworkers^[6] recently published a clinical study including 22 patients with malignant biliary obstruction who were palliated by endobiliary RFA and stenting. They reported that the technique was safe and effective for the palliation of such patients. In this series, we observed the safety and the feasibility of this procedure in a similar group of patients as it could be carried out with minor complications and no mortality.

The median duration of stent patency in the present study is within the normal ranges given for endoscopic

SEMS application alone. However, 9 of the 10 patients in this study have not experienced any episode of obstructive jaundice within the follow-up period. Therefore, we can only speculate that endobiliary RFA is at least as effective as endoscopic stenting alone.

The main concern about endobiliary RFA is the likelihood of an iatrogenic thermal injury to adjacent structures, which might lead to perforation in involved or intact bile ducts or vessel injury.^[6] This may occur because of inappropriate placement of an RF catheter or a stricture shorter than 2.5 cm, which is the exact distance between two RF electrodes. The use of a bipolar system instead of a single electrode, which delivers a greater energy radially from a focus, significantly decreases the risk of thermal injury. In the bipolar system, energy travels between the 2 electrodes, and thus, the heat spreads to a larger field.^[11] Furthermore, if the RF catheter is in a correct position, the bulk of tumor avoids the radial spread of heat energy. One can never be sure about whether the RF catheter is placed in an optimal position by a cholangiogram under fluoroscopic guidance. The only way to place the RF catheter in an optimal position, as well as to explore the bile ducts for possible thermal injury, is performing the procedure under direct vision using a babyscope. Nevertheless, if an inadvertent bile duct injury occurs, it can still be managed by combined endoscopic and percutaneous approach in most cases.

Fortunately, we did not experience any iatrogenic bile duct injuries of clinical significance in this series. Because covered SEMSs may lead to inadvertent obstruction of intrahepatic side branches when applied for hilar strictures, they are generally not preferred for palliation of hilar cholangiocarcinomas.^[5] The only reason of our preference for covered SEMS was the fear of an iatrogenic thermal injury to involved or intact bile ducts, which may eventually result in biliary sepsis. Moreover, we already excluded the patients with Bismuth type II, III and IV hilar cholangiocarcinoma. In those who had Bismuth type I hilar cholangiocarcinoma, we did not find any problem, which was confirmed by final cholangiogram showing the patency of both hepatic ducts. This may be partially due to remodeling effect of RFA therapy on tumoral mass.

The use of endobiliary RFA, which is expected to increase the duration of stent patency, along with covered SEMS seems paradoxical at first sight because biliary covered SEMSs are much more durable when compared to plastic stents and uncovered SEMSs and usually keep their patencies as long as the expected survival of such patients. If the median diameter of biliary strictures in this study (range 1.5-2.0 mm) was

considered, however, we could not apply a SEMS in any size without reducing the bulk of tumor mass in most of the cases. In this respect, endobiliary RFA served as an adjunctive tool for the application of large caliber SEMSs, which not only facilitates biliary flow but also improves patency rates.^[5]

In other words, we performed endobiliary RFA to reduce the size of tumor mass, and thus, to enable the placement of a SEMS, preferentially a large caliber one, through a biliary stricture that did not allow the placement of a SEMS of any size initially. And we used covered SEMSs because of the fear of an inadvertent bile duct injury. Moreover, endobiliary RFA therapy can be repeated in patients who admit for recurrent biliary obstruction due to tumor in- or over-growth.

From an optimistic perspective, single or multiple sessions of endobiliary RFA can result in an increase in overall survival in patients with locally advanced disease. In this series, 2 patients with locally advanced disease did well without any recurrent episodes for 13 and 15 months, respectively, which are beyond the median survival estimated for such patients.

The present study has important weakness with its retrospective nature. Second, the presence of a control group composed of either endoscopic stenting alone or photodynamic therapy plus endoscopic stenting would be of a great value. Third, long-term outcomes, which would show the actual impact of RFA on both stent patency and overall survival, are lacking. Therefore, it is yet impossible to claim that endobiliary RFA is superior to other methods. However, the study has already been designed as a pilot study aiming to investigate the safety and the feasibility of endobiliary RFA.

In conclusion, endobiliary RFA therapy is feasible and safe for palliative treatment of malignant biliary obstruction due to distal and Bismuth type I hilar extrahepatic cholangiocarcinoma, and may have a positive impact on stent patency and overall survival. However, large-volume randomized controlled clinical trials are necessary to assess its exact place in palliative treatment of extrahepatic cholangiocarcinomas.

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