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Review Article

A review of the recent advances in endoscopic retrograde cholangiography-guided intraductal radiofrequency ablation for malignant biliary strictures

Min Young Do, Jae Hee Cho*, Sung Ill Jang, and Dong Ki Lee

A B S T R A C T

Pancreatobiliary malignancy is relatively rare; however, it remains one of the most lethal malignancies and has a dismal prognosis. Endoscopic retrograde cholangiopancreatography (ERCP)-guided intraductal radiofrequency ablation (ID-RFA) is a promising, minimally invasive treatment for unresectable malignant biliary strictures by delivering high-frequency alternating current to the target tissue, leading to coagulative necrosis. Recent studies have provided evidence that ERCP-guided ID-RFA is a safe, well-tolerated, and effective adjunctive treatment in terms of stent patency as well as overall survival. Compared with other local treatments, such as photodynamic therapy, ERCP-guided ID-RFA has advantages, including ease of delivery, controlled application of thermal energy, low cost, and fewer systemic side effects, with an acceptable safety profile. ERCP-guided ID-RFA has been proposed as an attractive endobiliary ablative therapy and is regarded to be an adjuvant method for the palliative care of patients with unresectable malignant biliary strictures. However, due to the ongoing lack of comparative studies, the choice of local ablative therapy remains, in each case, an individual decision by the multidisciplinary team.

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Keywords: Biliary tract neoplasms; Endoscopic retrograde cholangiopancreatography; Intraductal; Radiofrequency ablation

Introduction

Radiofrequency ablation (RFA) is a technique that causes coagulation necrosis in tissues by generating thermal energy using a high-frequency alternating current. Currently, RFA is an established modality for treating solid tumours in individuals with hepatocellular carcinoma, lung cancer, and renal cell carcinoma.[1] Pancreatobiliary malignancy is relatively rare; however, it remains one of the most lethal malignancies and has a dismal prognosis. Most patients are diagnosed with locally advanced or metastatic disease and, even in those with resectable disease, a multidisciplinary approach is required to treat symptomatic biliary obstruction or impaired liver function.[2] Of the various therapeutic modalities, there has been increasing interest in the use of local thermal ablation techniques including photodynamic therapy, cryoablation, and RFA in this patient population. The most commonly used local thermal ablation technique is RFA,[3] which can be performed using different approaches including intraoperative and percutaneous approaches under ultrasound or radiological imaging guidance, an endoscopic approach using endoscopic ultrasound, or endoscopic retrograde cholangiopancreatography (ERCP).[4] The present review describes ERCP-guided intraductal RFA (ID-RFA), which has been widely used for many years and has been in the spotlight recently for the treatment of malignant biliary strictures.

Principles of RFA

RFA is an effective, minimally invasive therapeutic modality involving tumour cytoreduction through various mechanisms including coagulative necrosis, protein denaturation, and activation of anticancer immunity.[2] During RFA, a high-frequency alternating current is applied directly to the target lesion, resulting in coagulative necrosis. A perturbation of positive and negatively charged ions within the tissue produces friction heat[5] that is proportional to the voltage of the high-frequency current and the

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irradiation time, and is inversely proportional to the distance from the electrode. At temperatures ≥ 50°C, cells undergo coagulation necrosis, which is reversible and damages cytosolic and mitochondrial enzymes. On the other hand, at temperatures > 100°C, a coagulum is created in the tissue around the RFA catheter tip. Because contiguous areas around the coagulum are exposed to the highest current and heat shock due to reduced electrical conductivity, which reduces the efficiency of RFA, the recommended safe temperature range for RFA 50°C–100°C.[6]

ERCP-guided ID-RFA

ERCP-guided ID-RFA is being implemented in many medical centers around the world based on specific protocols and the individual experiences of clinicians over many years. Currently, there are two commercialised RFA catheters, Habib EndoHBP® (Boston Scientific, Marlborough MA, USA) and the Endoluminal Radiofrequency Ablation (ELRA) RFA catheter® (Starmed, Goyang, Korea). These are bipolar RFA devices that can be placed on the target lesion through ERCP channels for endoluminal delivery of RFA along the guidewire (Fig. 1). The bipolar Habib EndoHBP catheter is an 8 Fr (2.6 mm), 1.8 m long RFA catheter consisting of two stainless steel ring electrodes spaced 8 mm apart.[7] Itoi et al[8] reported that a suitable RFA setting was 7–10 W power for 2 minutes in *ex vivo* pig livers, while the manufacturer recommends 7–10 W for 90 seconds RFA settings in clinical human applications. The ELRA catheter is a bipolar device 175-cm long and 7 Fr in diameter, with four types: 11, 18, 22, and 33 mm. A special feature of the ELRA catheter is a temperature sensing system used to maintain RFA tip temperature. The optimal ID-RFA settings determined in our studies were 7–10 W for 120 seconds at a target temperature of 80°C.[9] More specifically, according to site in the biliary tract, 7–10 W, 80°C, 120 seconds of ID-RFA is recommended for distal malignant biliary strictures, while 7 W (preferably the short ELRA catheter), 80°C, and 60–120 seconds ID-RFA is advantageous for perihilar malignant biliary strictures.[10,11]

The ID-RFA procedure proceeds in the following manner. The RFA catheter is placed at the target lesion, and ID-RFA is applied using the recommended generator setting. A balloon cholangiogram is performed to confirm the absence of ID-RFA-related complications, and ablated necrotic debris can be removed using balloon removal. Because ID-RFA causes post-RFA biliary stricture, biliary drainage should be performed using plastic stents or self-expandable metal stents (SEMS). Because biliary stricture(s) may temporarily worsen due to edema shortly after the procedure and fibrotic stricture changes may occur in the long term, insertion of stents to maintain biliary flow is recommended after ID-RFA (Fig. 2).[11]

Safety of ID-RFA

Because clinical studies investigating ID-RFA have mostly been small-scale investigations, many concerns in clinical practice remain. Absolute contraindications for RFA include cardiac pacemakers, pregnancy, and coagulation disorders. While ID-RFA has been reported to be relatively safe and well tolerated, the incidence of adverse events have been reported to range from approximately 1% to 20%.[12,13] Common RFA-related adverse events include cholangitis and pancreatitis;[3] however, more serious events have also been reported, including hepatic infarction, hemobilia, liver abscess, sepsis, portal vein thrombosis, and death.[14–16] While it is difficult to provide accurate figures due to the lack of research, recent studies have reported a decrease in the frequency of serious complications.[17–20] This may be attributable to the accumulation of experience with ID-RFA and the use of safer ID-RFA settings. However, RFA always poses a risk for potential lethal adverse events due to the proximity of surrounding vital structures; nevertheless, the ID-RFA procedure requires constant attention. Another safety concern is the actual therapeutic depth and extent of ID-RFA in human bile duct tissue. In our clinicopathological study, which included eight patients with distal extrahepatic cholangiocarcinoma who underwent preoperative temperature controlled ID-RFA, pathological examination revealed that median maximal ablation depth was 4.0 mm (range, 1–6 mm) and median effective ablation length (histological ablation length/fluoroscopic ablation length) was 72.0% (range, 42.1%–95.3%).[21]

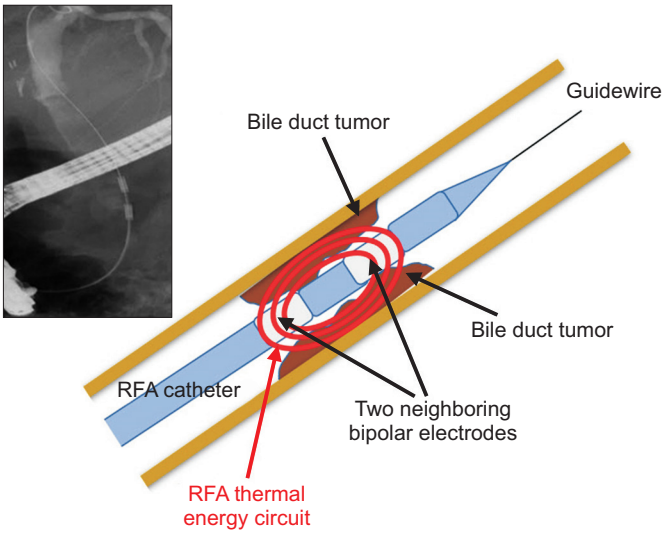

Fig. 1. Scheme for endoscopic retrograde cholangiography-guided intraductal radiofrequency ablation (RFA).

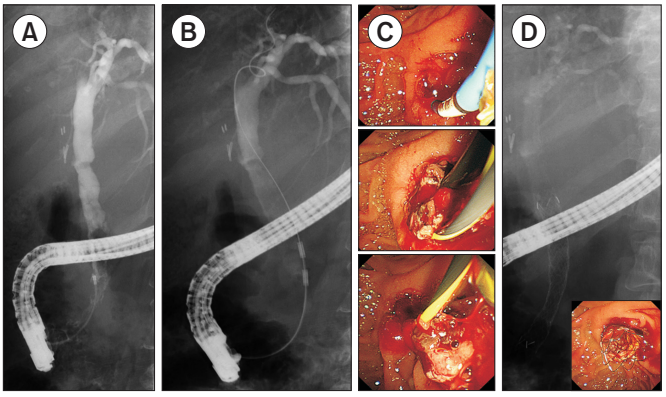

Fig. 2. Endoscopic retrograde cholangiography (ERCP)-guided intraductal radiofrequency ablation (ID-RFA). (A) ERCP revealing intraductal filling defects in the distal common bile duct (CBD). (B) Cholangiography depicting the endoluminal radiofrequency ablation (ELRA) catheter® (Starmed, Goyang, Korea) in the distal CBD stricture along the guidewire. ERCP-guided ID-RFA was applied at 80°C and 10 W for 120 seconds. (C) Endoscopic image showing the ELRA RFA catheter and ablated tumor tissue following balloon retrieval. (D) At the end of the procedure, a biliary self-expanding metal stent was placed in the post-RFA stricture site after ID-RFA.

Clinical Efficacy of ID-RFA

Over the past decade, many studies have validated the technical safety and effectiveness of ID-RFA (Table 1).[14–20,22–33] Most studies used the Habib RFA catheter, and various biliary stents were placed to maintain biliary drainage after ID-RFA. Alis et al[24] reported that endobiliary RFA therapy is feasible and safe for palliative treatment of distal and bismuth type I hilar extrahepatic cholangiocarcinoma. In a nationwide retrospective study, Dolak et al[15] reported that RFA was technically feasible and safe for the palliative treatment of malignant biliary obstruction. In a Korean multicentre study,[19] 30 patients with unresectable or inoperable extrahepatic malignant biliary stricture underwent temperature-controlled ID-RFA and post-RFA SEMS insertion. The cumulative duration of stent patency was 236 days, and adverse events occurred in two patients with pancreatitis and one with cholangitis.

To date, several studies have reported positive therapeutic outcomes for ID-RFA. A meta-analysis by Sofi et al[34] demonstrated that median survival rates were significantly better in ID-RFA with biliary stent placement than in biliary stent placement only (285 days vs 248 days; $P < 0.001$). Yang et al[18] also reported that endoscopic ID-RFA combined with stenting can significantly prolong survival (mean [± standard deviation] survival time, 13.2 ± 0.6 months vs 8.3 ± 0.5 months; $P < 0.001$) and stent patency (6.8 months vs 3.4 months; $P = 0.02$) without increasing the incidence of adverse events in 65 patients with unresectable extrahepatic cholangiocarcinoma. However, caution should be exercised in interpreting the positive results of this research. In the meta-analysis, the authors included two unpublished abstracts with poor-quality data,[34] and could not fully evaluate the efficacy of ID-RFA due to disease heterogeneity and procedural differences such as percutaneous or endoscopic approaches. Moreover, the study by Yang et al[18] had a small sample size and could not explain the theoretical hypothesis of how ID-RFA increases survival. On the other hand, contrasting results of ID-RFA have been published. In a Korean prospective randomised phase II trial, 48 patients with inoperable malignant biliary strictures were randomly assigned to either an RFA (ID-RFA + uncovered SEMS) or non-RFA (uncovered SEMS only) group. Kang et al[9] showed that the median duration of stent patency, and median overall survival were not different between the groups (132.0 days vs 116.0 days; $P = 0.440$ and 244.0 days vs 180.0 days; $P = 0.281$, respectively). To address these conflicting results, additional large-scale randomised studies have recently been conducted. Gao et al[31] compared the efficacy and safety between the RFA + stent group and the stent-only group in patients with unresectable malignant biliary obstruction, such as those with cholangiocarcinoma and ampullary cancer: 174 participants were randomly assigned in a 1 : 1 ratio and completed the two scheduled ERCPs with an interval of approximately 3 months. Median overall survival was significantly higher in the RFA group (14.3 vs 9.2 months; hazard ratio [HR], 0.49; 95% confidence interval [CI], 0.35–0.68; $P < 0.001$). In the subgroup analysis of cholangiocarcinoma, a survival benefit was also demonstrated (13.3 vs 9.2 months; HR, 0.55; 95% CI, 0.39–0.77; $P < 0.001$). As such, recent research has emphasised the positive therapeutic effects of RFA.

Perihilar Application and Combination Therapy of ID-RFA

ID-RFA is an attractive therapy for unresectable malignant biliary obstruction(s); however, research investigating whether it can be used safely in perihilar lesions remains lacking. Because the perihilar bile duct is located closer to the hepatic artery and portal vein, the potential risk for ID-RFA-related complications appears to be higher. For this reason, recent research investigating the safety and utility of ID-RFA in the perihilar area, where treatment methods are more limited than those for distal malignant biliary strictures, are being conducted. In our animal study, because we found a higher risk for peribiliary bile duct perforation after using conventional settings for ID-RFA for distal malignant biliary obstruction (i.e. 10 W, 2 minutes), we could recommend that the use of the lower power shortest type of ID-RFA (7W, 11 mm ELRA) was preferred for hilar ID-RFA.[20] In particular, because ELRA has four different lengths—the shortest being 11 mm—it is expected to be safer for hilar ID-RFA compared with the 24-mm Habib RFA catheter. Although various treatment results for ID-RFA have been reported for perihilar lesions,[30,31] because sufficient evidence has not yet been accumulated, more well-designed clinical studies are needed to clarify whether ID-RFA could extend stent patency and improve survival in those with malignant perihilar biliary strictures.

Another interesting topic is the combined effect of anticancer drugs. Considering the local effect of ID-RFA, an enhanced therapeutic outcome can be anticipated when ID-RFA is combined with anticancer treatment, which is the current standard treatment for biliary cancer. A prospective randomised controlled study[32] reported that ID-RFA combined with S-1 for locally advanced extrahepatic cholangiocarcinoma was associated with longer survival and stent patency and improved functional status than RFA alone (16.0 months vs 11.0 months; $P < 0.001$ and 6.6 ± 1.5 months vs 5.6 ± 0.1 months; $P = 0.014$, respectively). Although S-1 is not the primary choice of anticancer agent for biliary tract cancer, it is necessary to evaluate the combined effects of various systemic anticancer therapies to improve the therapeutic outcomes of ID-RFA.

Expansion of New Indications for ID-RFA

Therapeutic indications for ERCP-guided ID-RFA have been expanded to the ampulla of Vater and *in-stent* revision of occluded SEMS beyond classical ID-RFA application to unresectable malignant biliary obstruction. Several studies have reported successful ablation of residual/recurrent intraductal adenomas after endoscopic papillectomy.[35–38] Given that the alternative to endoscopic treatment—more specifically, pancreaticoduodenectomy—has increased morbidity and mortality, the opportunity to offer ERCP-guided ID-RFA is very attractive to patients. Interestingly, a pilot study demonstrated that ERCP-guided ID-RFA is safe and can reduce tumour volume and reinterventions in patients with inoperable ampullary cancer.[33] In addition, *in-stent* ID-RFA, as a rescue therapy for occluded SEMS due to tumour ingrowth, has been introduced by several studies. For treating blocked biliary SEMS, *in-stent* ID-RFA appeared to be safe and useful in selected patients.[39,40]

Conclusions and Future Directions

With recent changes in the medical environment, such as preferences for non-invasive treatments, increased need for better quality of life, and increasing cancer rates among the elderly, interest in various local treatments, such as RFA and photodynamic therapy, has increased, especially in pancreatobiliary cancer. ERCP-guided ID-RFA is regarded to be an effective, minimally invasive treatment for unresectable malignant biliary strictures, and is mainly used for adjunctive and palliative treatment and can efficiently restore biliary drainage; moreover, recent studies have

Table 1 Results of Endoscopic Retrograde Cholangiopancreatography-Guided Intraductal Radiofrequency Ablation in Pancreatobiliary Tumor

Author (year)	Patients (*n*)	Diagnosis (*n*)	Type of stents (*n*)	Median stent patency (day)	Median survival (mo)	Median no. of RFA	No. of adverse events (%)
Steel et al (2011)[22]	22	BDC 6 PDAC 16	Uncovered SEMS 21	114	NA	2	4/21 (19.0) Cholecystitis 2 Pancreatitis 1 Rigor 1
Figueroa-Barojas et al (2013)[23]	20	BDC 11 PDAC 7 Others 2	Uncovered SEMS 1 Partially/fully covered SEMS 13 Plastic stent 6	NA	NA	NA	5/20 (25.0) Pancreatitis 1 Cholecystitis 1 Pain 5
Alis et al (2013)[24]	17	BDC	Fully covered SEMS 10	270	NA	3	2/10 (20.0) Pancreatitis 2
Dolak et al (2014)[15]	58	BDC (Klatskin 45) Others 13	SEMS 35 Plastic stent 19	171	10.6	1.4	11/58 (19.0) Liver infarction 1 Hemobilia 3 GB empyema 1 Cholangitis 5 Sepsis 2 Hepatic coma 1 Left bundle branch block 1
Tal et al (2014)[14]	12	BDC (Klatskin 9) Others 3	Plastic stent 12	NA	6.4	1.5	6/12 (50.0) Hemobilia 4 Mortality 2
Sharaiha et al (2014)[29]	26	BDC 18 PDAC 8	Uncovered SEMS 7 Covered SEMS 8 Plastic stent 11	NA	5.9	NA	5/26 (19.2) Pancreatitis 1 Cholangitis 1 Pain 3
Sharaiha et al (2015)[16]	69	BDC 45 PDAC 19 GBC 2 Others 4	SEMS 49 Plastic stent 20	NA	11.5	1.4	7/69 (10.1) Pancreatitis 1 Cholecystitis 2 Hemobilia 1 Pain 3
Kallis et al (2015)[25]	23	Unresectable PDAC	Uncovered SEMS 23	324	7.5	NA	2/23 (8.7) Hyperamylasemia 1 Cholangitis 1
Laquière et al (2016)[26]	12	BDC (Klatskin 12)	SEMS or plastic stent	NA	12.3	1.6	2/12 (16.7) Cholangitis 1 Sepsis 1
Wang et al (2016)[27]	12	BDC 9 Others 3	SEMS or plastic stent	125	7.7	1.67	1/12 (8.3) Pancreatitis 1
Schmidt et al (2016)[28]	14	BDC 14 Others 2	SEMS or Plastic stent	NA	NA	2.2	4/14 (28.6) Cholangitis 2 Liver abscess 2

Table 1 Continued

Author (year)	Patients (*n*)	Diagnosis (*n*)	Type of stents (*n*)	Median stent patency (day)	Median survival (mo)	Median no. of RFA	No. of adverse events (%)
Laleman et al (2017)[17]	18	PDAC 7 BDC (Klatskin 11)	SEMS or Plastic stent	110	7.6	1	6/18 (33.3) Cholangitis 4 Pancreatitis 2
Yang et al (2018)[18]	32	BDC (distal 22, Klatskin 10)	Plastic stent	195	13.2	NA	2/32 (6.3) Cholangitis 2
Lee et al (2019)[19]	30	BDC 19 PDAC 9 GBC 2	Uncovered SEMS 10 Covered SEMS 20	236	12.8	NA	3/30 (10.0) Pancreatitis 2 Cholangitis 1
Kim et al (2019)[20]	11	BDC (Klatskin 8) GBC 2 Others 1	Uncovered SEMS 10 Plastic stent 1	91	NA	4 (2-8)	6/12 (50.0) Pancreatitis 1 Post-procedural fever 5
Bokemeyer et al (2019)[30]	32	BDC (distal 1, Klatskin 23) PDAC 2 GBC 2 Others 4	SEMS or Plastic stent	NA	11.4	1.68	10 (31.3) Cholangitis 6 Pancreatitis 2 Intestinal perforation 1 Pneumothorax 1
Hu et al (2020)[33]	23	Ampullary cancer 23	SEMS or Plastic stent	NA	36.0	2.26	4 (7.7) Mild pancreatitis 1 Bleeding 1 Late distal biliary stenosis 2
Gao et al (2020)[31]	87	BDC (Klatskin 69) Ampullary cancer 18	Plastic stent	NA	14.3	1	24 (27.6) Pancreatitis 4 Bleeding 1 Cholangitis 10 Cholecystitis 9
Yang et al (2020)[32]	38	BDC (distal 26, Klatskin 12)	Plastic stent	168	11.0	1	4 (10.5) Cholangitis 2 Pancreatitis 1 Bleeding 1

RFA, radiofrequency ablation; BDC, bile duct cancer; PDAC, pancreatic ductal adenocarcinoma; GBC, gallbladder cancer; SEMS, self-expandable metallic stent.

suggested a survival benefit with ID-RFA. Nevertheless, the utility and long-term therapeutic outcomes of ID-RFA according to various sites in the biliary tree remain lacking, and we believe that further prospective large-scale multicentre studies are required to confirm the clinical benefits of these techniques for the management of malignant biliary strictures.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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