Radiofrequency ablation for pancreatobiliary disease: an updated review

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Abstract	Endoscopic radiofrequency ablation (RFA) has emerged as a minimally invasive treatment option in cases of malignant biliary obstruction, pancreatic cancer, and other pancreatic cystic neoplasms. Intraductal biliary RFA is safe, effective, and confers a survival advantage over stenting alone, where it should be used an adjunct to biliary stenting. Endoscopic ultrasound-guided RFA can also provide pancreatic cyst resolution in patients who are not ideal operative candidates. The aim of this review is to describe the endoscopic applications and associated outcomes of RFA.

Keywords Malignancy, obstruction, stricture, neoplasm, photodynamic therapy

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Introduction

Radiofrequency ablation (RFA) has been used percutaneously and intraoperatively to treat liver malignancy since the early 1990s [1], with additional roles in diseases of the colon and esophagus (especially in instances of Barrett's esophagus) [2,3]. Recently, endoscopic applications of RFA have emerged, where it has been utilized in the palliative treatment of malignant biliary strictures and pancreatic cancer.

RFA can induce direct tissue damage using alternating high frequency currents and electromagnetic energy via a bipolar probe [4]. The probe is inserted into the surrounding tissue prior to applying the current in a radiofrequency range of 450-500 kHz [5]. The high resistance to the current in biological tissue results in the production of heat, which at sufficient levels causes coagulative necrosis and fibrotic changes in a targeted manner [6].

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There is also evidence to suggest that RFA can stimulate a delayed, systematic immune response through the release of intracellular antigens following cell death through hyperthermic injury [7].

Technologic advances in endoscopic imaging and improvements in endoscopic RFA probes have allowed for greater endoscopic access to the biliary tree. Endoscopists can precisely and accurately deliver RFA energy to malignant tissue under visual guidance, reaching locations that were previously less readily accessible. In this context, there is a growing body of evidence supporting the applications of RFA for several pancreatobiliary conditions, including the treatment of intraductal papillary mucinous neoplasms (IPMN), pancreatic neuroendocrine tumors (NET), advanced pancreatic carcinomas, malignant biliary obstructions, and obstructed biliary self-expandable metal stents (SEMS).

Within the bile duct, RFA appears to be safe and may result in decreased epithelial hyperplasia and tumor ingrowth, through specific endobiliary probes that enable more precise delivery of thermal energy in the biliary tree and pancreas [6]. Given that endoscopic decompression of biliary obstruction is limited by stent patency, thus necessitating repeat procedures with stent changes, RFA provides an alternative, as ablative therapy may result in less tissue ingrowth and stent occlusion, thus minimizing procedures for stent changes.

Endobiliary applications

Malignant obstructive jaundice is a common sequela of advanced stage pancreatic adenocarcinoma and cholangiocarcinoma, as well as other malignancies that metastasize to the liver. Over 50% of common bile duct obstructions are due to malignancy, and the majority of neoplasms are unresectable at the time of diagnosis [8,9]. Palliation is the therapy of choice for biliary decompression and symptomatic relief with transpapillary stenting [10]. In patients with a life expectancy greater than 3 months, placement

of a SEMS is a cost-effective and viable option [11]. However, long-term stent patency can become a significant issue, with occlusion rates of up to 50% in the first 6-8 months [12,13]. Stent dysfunction can result from sludge formation, tumor ingrowth, benign epithelial hyperplasia and biofilm deposition within 3 months [12]. Consequently, the use of RFA has emerged as a complimentary tool to enhance stent patency and improve survival outcomes in cases of inoperable malignant obstruction.

RFA technique in hepatobiliary disease

RFA is typically used prior to stenting for endobiliary applications (Fig. 1,2). The RFA probe is loaded on a 0.035" wire. Fluoroscopy is used to target the stricture and a radiofrequency current of 7-10 W is applied for a time period of 90-120 sec, with a 1- to 2-min resting period between each of the RFA applications [6,14,15]. Important parameters to consider in the application of RFA are the number of RFA sessions, the power of the current used, and the duration of the application. In instances of failed endoscopic retrograde cholangiopancreatography (ERCP) or surgically altered anatomy, RFA has also been used via endoscopic ultrasound-guided antegrade stenting and balloon enteroscopy-assisted ERCP [16,17].

The first evidence that endobiliary RFA prior to stenting provides a survival benefit was published in 2014 [15]. Since then, there have been studies showing that endobiliary RFA (prior to stenting) provides a survival benefit greater than stenting on its own [18,19].

Malignant biliary obstruction

Steel *et al* conducted the first open-label prospective pilot study to demonstrate the safety and efficacy of RFA in the management of malignant biliary obstruction from pancreatic
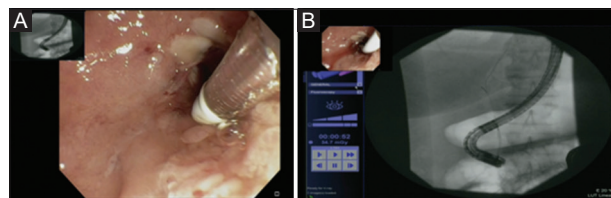

Figure 1 (A) Radiofrequency ablation (RFA) catheter is advanced over a wire into the stricture. (B) After the position is confirmed on fluoroscopy, RFA is performed for 90 sec
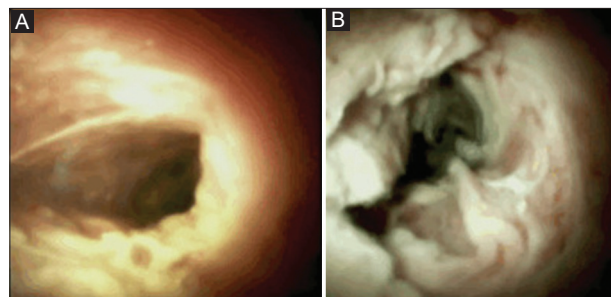

Figure 2 Choledochoscopy demonstrating tissue necrosis before (A) and after (B) radiofrequency ablation of the bile duct

and/or cholangiocarcinoma [6]. The study demonstrated immediate and 30-day safety, as well as 90-day stent patency, in all 21 patients who received RFA, with an improvement in the median bile duct diameter from 0-4 mm. Since then, a handful of studies have shown favorable results when endoscopic RFA and stenting placement are combined, as a means to achieve a significant survival benefit when compared to patients treated with stenting alone [15,18,19]. A single-center, retrospective study by Sharaiha *et al* included 66 patients with malignant strictures and compared stenting alone vs. stenting plus RFA. The investigators found no difference in terms of stent patency, but did show that the use of RFA was an independent predictor of survival [15]. The same first author went on to conduct an additional study using the Surveillance, Epidemiology, and End Results Program Database and found that RFA was associated with better overall survival in cases of pancreatic cancer (5.9 vs. 14.6 months) and cholangiocarcinoma (6.2 vs. 17.7 months, P<0.001) [19]. Of the 69 patients in this study, 1 developed post-ERCP pancreatitis, 2 experienced cholecystitis, 1 had hemobilia and 3 patients suffered from mild abdominal pain that resolved without intervention. There were no procedural-related deaths noted.

Two recent randomized control trials (RCT) were conducted using RFA with or without plastic stents. Yang *et al* reported favorable survival outcomes when comparing RFA (n=32) to stenting alone (n=33) in unresectable cholangiocarcinoma (13.2 vs. 8.3 months, P<0.001) [20]. The trial showed that the RFA group had longer periods of stent patency (6.8 vs. 3.4 months, P=0.02), with no significant differences in adverse events [20]. It should be noted that, in this study, stent exchange occurred every 3 months with a plastic stent. On the other hand, Gao *et al* found that while survival outcomes favored the RFA group (14.3 vs. 9.2 months, P<0.001), there were no apparent differences in jaundice control or stent patency [21]. These 2 RCTs probably produced conflicting results because Gao *et al* only conducted stent exchanges as clinically indicated. There are no current guidelines on whether to change stents at regular intervals, or as clinically indicated, and it is largely left to the endoscopist's discretion.

A large dual-center retrospective study, using propensity score matching to compare RFA and stenting (n=124) to stenting alone (n=759) for inoperable malignant biliary strictures, found that RFA survival benefits were limited only to cases of non-metastatic extrahepatic cholangiocarcinoma [22]. This was probably due to the fact that endobiliary ablation can target the area of disease with limited thickness. The authors also found that acute cholecystitis was associated with RFA, which may reflect cystic duct injury from the ablation, rather than the involvement of the cystic duct itself in the stricture leading to the damage [22]. A recent meta-analysis of 15 studies, comparing RFA plus stenting (n=701) to stenting alone (n=1114), further supported the findings of better survival time and stent patency with RFA and stenting [23].

A multitude of studies have demonstrated that RFA can achieve local tumor control, increase stricture diameter, prolong stent patency, and improve survival outcomes [24]. It has also been suggested that the better survival is associated with targeted tumor necrosis from the thermal injury, which can remove the metastatic burden [2,6,25]. We believe that, with further prospective RCTs, intraductal RFA is set to become

standard of care. For instance, in patients with unresectable cholangiocarcinoma, photodynamic therapy (PDT) has also been shown to improve survival, stent patency and quality of life [26]. However, its use is limited by its exceedingly high cost, restriction to specialized centers, and the phototoxic adverse events related to direct sunlight [27]. A study directly comparing RFA (n=16) to PDT (n=32) found no difference in survival outcomes for unresectable cholangiocarcinoma [28], while another comparative retrospective study demonstrated a short-term effect favoring RFA in terms of biliary drainage, number of stent replacements and adverse events [29]. It is difficult to compare RFA and PDT given the limited number of studies and lack of RCTs; furthermore, there is heterogeneity in the study populations, since PDT involves hilar cholangiocarcinoma while RFA studies have included hilar and distal cholangiocarcinomas [30]. That being said, there are benefits of RFA over PDT, including costs, stent patency and phototoxicity.

Occluded biliary SEMS

Long-term biliary patency continues to pose a challenge for palliative treatment of unresectable malignant biliary obstruction. The cause of recurrent biliary obstruction is associated with the type of stent used, ranging from plastic stents (sludge) to covered SEMS (sludge and migration) and uncovered SEMS (tumor ingrowth) [31]. Some of the early RFA studies did not differentiate their findings based on the type of stent used. As mentioned above, the 2 recent RCTs examining the use of plastic stents produced conflicting results due to differences in their stent exchange protocols [20,21]. There have also been studies looking at SEMS, which can be used in the setting of a longer life expectancy [18,32,33]. An RCT by Kang et al found no survival benefit with RFA and SEMS (244 vs. 180 days, P=0.281) [33], whereas 2 retrospective studies by Dutta [32] and Kallis [18] suggested there may be a survival benefit. The study by Dutta et al used both covered and uncovered SEMS in a cohort of 31 patients, with longer periods of stent patency favoring the RFA cohort (220 vs. 107 days, P=0.025) [32]. In a subset of patients, choledochoscopy demonstrated tissue necrosis following RFA, confirming its effect within the bile duct. A meta-analysis of 9 studies with 505 patients further confirmed these findings, in that RFA and SEMS placement were able to prolong survival compared to stenting alone [34].

There are also new studies and concepts related to improving intraductal RFA delivery. In a study by Yang et al, the indirect effects of RFA-induced cell death leading to a delayed systemic immune response were further studied as a potential synergistic effect in patients also treated with 5-fluorouracil for unresectable cholangiocarcinoma [35]. Their RCT demonstrated longer survival and stent patency in those treated with combination therapy compared to RFA alone. It is also possible that RFA alone may be able to destroy local tumors via coagulative necrosis as monotherapy [36], where a few studies have shown histological confirmation of tumor necrosis and destruction [37,38]. However, the long-term effects from endobiliary RFA may be a limiting factor,

as a swine model found that segmental stricture can develop 1 month after therapy, which would probably necessitate stent placement [39]. In an effort to minimize the risk of thermal damage to the bile duct, an automatic temperature-controlled RFA catheter was recently studied in a small prospective study of 30 patients [40]. The study by Lee et al only reported 3 adverse events (2 mild pancreatitis and 1 cholangitis), which resolved with conservative management. A subsequent RCT of 48 patients compared this new probe to stenting alone, and further confirmed its safety, feasibility and effectiveness for biliary patency [33]. In addition to reducing thermal injury, one study investigated means to reduce restenosis and tissue hyperplasia using a silver nanofunctionalized stent in conjunction with RFA in a rabbit bile duct [41]. Reduced levels of tissue hyperplasia were confirmed with histological and cholangiography views.

With emerging data and ongoing prospective multicenter trials, the application of RFA in malignant obstruction is rapidly expanding and is proving to be an effective treatment option for biliary decompression. Further data are needed to evaluate the cost-effectiveness of this strategy, as well as the impact on patient quality of life.

Pancreatic applications

Since Goldberg et al first described results of the procedure in a porcine model, several studies have examined the use of RFA in pancreatic tissue [42]. Reports in the surgical literature describe patients with locally advanced pancreatic cancer who have received RFA as a component of a multimodal approach [43,44]. However, studies utilizing endoscopically delivered RFA for pancreatic cancer in humans have been very limited until recently [45,46]. Continued research efforts have brought us closer to determining safe and effective methods for the endoscopic delivery of RFA to the pancreas (Table 1). Silviu et al described the effects of RFA of the head of the pancreas in an in vivo porcine model [47]. The investigators utilized a Habib™ RF DUO 13 probe through an endoscopic ultrasound fine-needle aspiration (EUS-FNA) needle to perform EUS-guided RFA (EUS-RFA). The RFA energy was delivered for 120 sec during 4 cycles, beginning at 5 W and with each subsequent cycle increasing by 5 W. The pigs tolerated the procedure, with no immediate or short-term mortality or morbidity noted prior to autopsy 1-week post-ablation. Histopathology showed focal necrosis, with an area of central coagulative necrosis and a surrounding inflammatory response limited to only 2-3 cm from the lesion. On autopsy, it was noted that 2 pigs displayed evidence of complications that the authors attributed to iatrogenic causes.

Pancreatic cystic neoplasms

EUS-RFA has recently emerged as a novel and minimally invasive method to treat pancreatic cyst lesions (Fig. 3,4). Managing lesions with malignant potential (i.e., mucinous

Table 1 Studies involving endoscopic ultrasound-guided radiofrequency ablation for pancreatic cystic neoplasms

Author (year) [ref.]	Study design	Number of pancreatic neoplasms	Mean size of PCL and NET (mm)	Follow up (months)	Complete resolution	Partial resolution	Adverse events, (n=#)
Pai (2015) [46]	Prospective, multicenter	8 (4 MCN, 1 IPMN, 1 microcystic adenoma, 2 NET)	36.5 and 27.5	3-6	2	3 (48.4% reduction)	Mild abdominal pain (2)
Barthet (2019) [49]	Prospective, multicenter, open-label	31 (14 NET, 16 IPMNS, 1 MCN)	28 and 13.1	12	12/17 for PCL and 12/14 for NET	1 (71% reduction)	*Acute pancreatitis (1), jejunal perforation (1), main pancreatic ductal stenosis (1), mild abdominal pain (6)
Oleinikov (2019) [50]	Retrospective, multicenter	18 (11 insulinomas and 7 non-functional NETs)	14.3	8.7	15**	1	Mild pancreatitis (2)
Rossi (2022) [63]	Case Report	3 insulinomas (mean age 83.3 years old)	9-14	24	All 3 patients exhibited resolution in symptoms	N/A	Immediate bleeding (1)
Marx (2022) [52]	Retrospective, single center	7 insulinomas	13.3	21	6	1	Retrogastric collection (1)
Marx (2022) [53]	Retrospective, single center	27 non-functional pancreatic NETs	14	15.7	25	N/A	Acute pancreatitis (4)
Younis (2023) [51]	Prospective, single center	12 (4 IPMNs, 1 MCN, 7 NET)	36 and 8.9	7	3/5 for PCL and 4/6 NETs	1 for PCL	Mild acute pancreatitis (1), abdominal pain (2)

*Following the first 2 consecutive major adverse events, the study protocol was modified to include rectal diclofenac, antibiotic prophylaxis (2 g of amoxicillin and clavulanic acid) and fine-needle aspiration prior to radiofrequency ablation

**All 7 insulinomas exhibited immediate resolution in glucose levels after the procedure

MCN, mucinous cystic neoplasm; IPMN, intraductal papillary mucinous neoplasm; NET, neuroendocrine tumors; PCL, pancreatic cystic lesions

cystic neoplasm [MCN], IPMN, and NET) can be challenging in patients who are not ideal operative candidates or may decline surgical intervention [48]. In this context, EUS-guided ablation techniques have been well studied; however, only a handful of EUS-studies have been investigated in humans [46,49-53].

Pancreatic cystic lesions

When risk stratifying a pancreatic cystic lesion, evaluating the lesion's malignant potential and the patient's surgical candidacy are crucial [54]. EUS-RFA is a non-surgical option that is garnering interest because of its safe and minimally invasive profile. The first preliminary study by Pai *et al* in 2015 examined the effects of RFA in 6 patients with pancreatic cystic neoplasms (4 mucinous cysts, 1 IPMN, and 1 microcystic adenoma). They reported complete resolution in 2 patients, while 3 others had a 48.4% size reduction over a 3-6-month follow-up period [46]. Reassuringly, there were no procedure-related adverse events, and only 2 patients experienced mild abdominal discomfort, which resolved 3 days after the procedure. A recent prospective, multicenter study by Barthet *et al* demonstrated favorable results from treating 17 pancreatic cystic neoplasms (16 IPMN, 1 MCN) over a 1-year follow-up period [49]. Complete resolution was achieved in 47% and 64.7% of individuals at 6- and 12-month
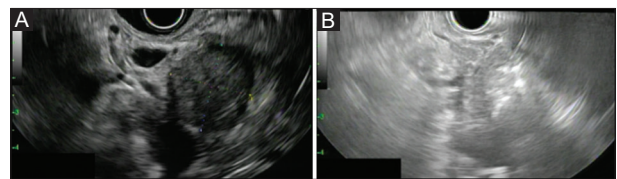

Figure 3 Endoscopic ultrasound images showing a pancreatic neuroendocrine tumor before (A) and after (B) radiofrequency ablation

follow up, respectively. It is important to highlight that in this study there was only a 10% adverse event rate, which improved to 3.5% after the study protocol was changed in the beginning to include antibiotics, rectal indomethacin and cyst fluid aspiration prior to RFA [49].

Pancreatic neuroendocrine tumors

Pancreatic NETs exhibit a wide array of biological activity. The majority are often sporadic, nonfunctional and malignant at the time of diagnosis [55]. Nevertheless, 15% are functional, and can be classified based on their hormone section. For functional NETs, surgical resection is curative, regardless of the size. Management of non-functional NETs is typically based on the size, location, and presence of symptoms [56].
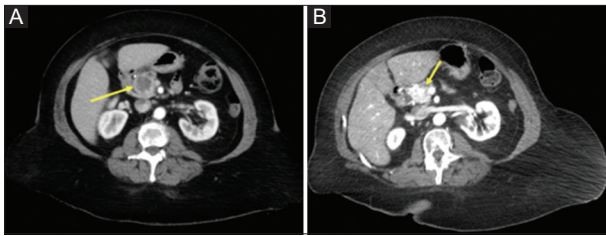
Figure 4 Computed tomography of the abdomen with views of a pancreatic neuroendocrine tumor before (A) and after (B) application of radiofrequency ablation

Shared decision making is important, especially since surgical resection is associated with a high postoperative complication rate [57]. In this context, EUS-RFA has been investigated as an alternative minimally invasive treatment option. When selecting individuals for EUS-RFA therapy, it is important to factor in the patient's comorbidities, life expectancy, risk of postoperative complications (i.e., fistula) and long-term pancreatic insufficiency [58]. To help answer these questions, a large prospective study across 11 centers is underway [59].

A recent comparative study by Crinò *et al*, utilizing propensity score matching (89 patients with insulinomas), showed that EUS-RFA was safer than surgery (18% vs. 61.8% adverse event rates respectively, P<0.001) and equally as effective (95.5% vs. 100%, P=0.160) [60]. Similar findings by Ferriera *et al* were seen in a prospective cohort with 13 pancreatic insulinomas, where there was an immediate and sustained clinical response [61]. A meta-analysis of 19 studies with 196 lesions (101 functional and 95 non-functional) also showed that the EUS-RFA has a well-tolerated safety profile, especially in non-surgical candidates [62]. The overall adverse events for functional and non-functional pancreatic NETs were 17.8% and 24.6%, respectively. As operator experience with EUS-RFA continues to grow, more data regarding its effectiveness and relatively safe profile will continue to emerge. Given recent clinical data, it is likely to be the best indication for symptomatic insulinomas.

A prospective study by Barthet *et al* included 14 pancreatic NETs over a 1-year follow up, where complete resolution occurred in 12 of 14 patients [49]. The other 2 lesions failed to respond at all (in fact one grew by 3 mm). Another retrospective study involving 18 pancreatic NETs (7 insulinomas and 11 non-functional lesions) reported no post-procedure complications or clinically significant recurrences over a mean follow up of 8.7 months [50]. Furthermore, all insulinomas displayed normalization of glucose levels 24 h after treatment [50]. Another case series showed adequate treatment responses to RFA in 3 elderly patients with insulinomas over a 24-month period, without the need for any further medical therapy [63].

A recent single-center prospective study of 12 patients (4 IPMNs, 1 MCN, 7 pancreatic NETs) were treated with RFA and followed for a median of 7 months [51]. Failure of pancreatic cysts and pancreatic NET resolution were seen in 20% (1/5) and 33.3% (2/6), respectively. These studies are indeed promising, though larger, long-term data will be needed to determine the number of RFA treatments and the interval of follow up required. Since there is a delayed response to treatment, it is likely that patients should be followed for at least 1 year to achieve the full effects of treatment [4]. Interestingly, a long-term study by Barthet *et al* found that the effects of RFA were stable over up to 42 months of follow up [64]. A recent systematic review pooling the available data of EUS-RFA from 100 patients with 112 pancreatic NETs found that technical success was seen in all patients; complete resolution was approximately 90%, while adverse events were experienced in 21.9% of patients, the majority being mild or moderate [65]. There was 1 fatal adverse event reported in a study by Marx *et al* in an elderly patient (age 97) who developed a retrogastric collection and declined drainage [53].

Advanced pancreatic cancer

EUS-RFA has also been investigated in cases of non-resectable pancreatic neoplasms. The first feasibility study conducted by Arcidiacono *et al* in 2012 failed to show a clear survival benefit or effect on tumor size [45]. All patients received gemcitabine chemotherapy; the technical success was 72.7% and the adverse event rate was 36.4% (with the majority considered as mild). In 6 cases, there was failure to penetrate the tumor and gastric wall. In 2016, Song *et al* published data collected from a feasibility study examining EUS-RFA in a set of 6 patients with unresectable pancreatic cancer [66]. The investigators used 20-50 W of power for 10 sec at one given site, and repeated until the hyperechoic region around the electrode was extended beyond the tumor. The mean follow-up time was just over 4 months, and the only procedure-related adverse events were mild abdominal pain in 2 patients. There were no major adverse events or procedure-related mortality observed in this study. Since then, additional studies have reported promising results [67-71]. However, there is no clear protocol for wattage and duration of treatment in this setting [72]. One study by Crinò *et al* used a low energy (30 W) setting over a longer period of time (15-95 sec), and reported no instance of early or late adverse events in 8 patients [67]. A recent prospective observational study by Oh *et al* found that EUS-RFA in combination with systemic chemotherapy may improve survival outcomes, using a median number of 5 RFA session with resumption of chemotherapy within 2 days in all patients [71]. Only 4 adverse events (3 abdominal pain, 1 peritonitis) were encountered [71]. In addition to RFA, other ablative treatments, such as irreversible electroporation, microwave ablation or cryoablation, are being studied [73].

Concluding remarks

The endoscopic therapeutic armamentarium for pancreatobiliary disease continues to evolve. RFA is proving to be a reliable and safe minimally invasive option for malignant strictures and neoplasms. As a complimentary tool, it has proven to prolong stent patency and survival outcomes. EUS-RFA may also prove to play an important role for patients who are intolerant to chemotherapy. Larger prospective RCTs are

needed to improve the safety and efficacy of RFA for pancreatic malignancy and define its role as a non-surgical option for pancreatic neoplasms.

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