Endoscopic ultrasound-guided radiofrequency ablation for pancreatic neuroendocrine tumors and pancreatic cystic neoplasms: a prospective multicenter study

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ABSTRACT

Background Pancreatic neuroendocrine tumors (NETs) and intraductal pancreatic mucinous neoplasia (IPMN) with worrisome features are surgically managed. Endoscopic ultrasound (EUS)-guided radiofrequency ablation (RFA) has recently been developed. The safety of EUS-RFA was the primary end point of this study, its efficacy the secondary end point.

Methods This was a prospective multicenter study that was planned to include 30 patients with a 1-year follow-up with either a NET <2 cm or a pancreatic cystic neoplasm (PCN), either a branch duct IPMN with worrisome features or a mucinous cystadenoma (MCA). EUS-RFA was performed with an 18G RFA cooling needle.

Results 12 patients had 14 NETs (mean size 13.1 mm, range 10–20 mm); 17 patients had cystic tumors (16 IPMNs, 1 MCA; mean size 28 mm, range 9–60 mm). Overall three adverse events occurred (10 %), two of these in the first two patients (one pancreatitis, one small-bowel perforation). After these initial patients, modifications in the protocol resulted in a decrease in complications (3.5 %), with one patient having a pancreatic ductal stenosis. Among the 14 NETs, at 1-year follow-up 12 had completely disappeared (86 % tumor resolution), with three patients having a delayed response. Among the 17 PCNs, at 12 months, there were 11 complete disappearances and one diameter that decreased by >50 % (significant response rate 71 %). All 12 mural nodules showed complete resolution.

Conclusions EUS-RFA of pancreatic NETs or PCNs is safe with a 10 % complication rate, which can be decreased by improved prophylaxis for the procedure.

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Introduction

More and more pancreatic tumors are being discovered, mainly fortuitously because of the advances in conventional imaging (abdominal ultrasound, computed tomography [CT], magnetic resonance imaging [MRI]), resulting in the question of surgical management of asymptomatic pancreatic lesions ("incidentalomas") [1–4]. The lesions detected mostly include pancreatic cystic neoplasms (PCNs) and neuroendocrine tumors (NETs) that are mainly well differentiated [1, 4, 5].

Clinically, NETs are mostly nonfunctional and do not induce any secretory disorder [3]. Once their nature is yielded by diagnostic tests, such as endoscopic ultrasound (EUS)-guided fine-needle aspiration (FNA), incidental nonfunctional NETs currently lead to difficult management decisions when their largest diameter is < 2 cm [3–6]. Therapeutic surgical choices could be challenged by EUS-guided treatment [7–9].

PCNs are mainly discovered fortuitously [1, 2, 10, 11]. Most PCNs have a benign pattern, with few of them becoming malignant, and include intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystadenomas (MCAs). Branch duct IPMN develops into malignancy in about 5 %–10%, requiring imaging follow-up [2]. PCNs that have worrisome features on imaging (presence of mural nodules > 5 mm and cyst size > 3 cm) have been considered to have risk factors for development of malignancy [2, 10, 11]. In patients with PCNs that are inoperable, some teams have proposed EUS-guided antitumor treatment, mainly by washing the content of cystic tumors with pure alcohol under EUS control. At least seven series have included 173 patients, with clinical success rates and morbidity rates of 35 %–79% and 3 %–10 %, respectively [12–14]. An interesting alternative could be their destruction with endoscopic radiofrequency ablation (RFA) [8, 12, 15–17].

Some publications or preliminary reports have described the use of EUS-RFA with a dedicated cooled needle or through a 1-Fr probe introduced in the lumen of a 19G needle (Habib EndoHBP, EMcision) for the treatment of adenocarcinomas or NETs in six series including 1–8 patients, with complete feasibility reported [8, 12]. Experimental studies showed necrosis of 8–10 mm in diameter for powers of 5–20 W and an application time of 60–120 seconds [15–17]. A study on mediastinal lymph nodes from 18 pigs using 10 W bipolar current for 2 minutes also showed a necrosis diameter of 9.8 mm [17]. The efficacy and safety of this treatment remains questionable with there being a risk of damaging surrounding structures.

Because pancreatic adenocarcinoma is usually a widespread disease, which therefore excludes local treatment, we planned to include only premalignant tumors of the pancreas. We focused on safety because scientific data are lacking with regard to the management of pancreatic tumors with RFA. This prospective, multicenter, open-label, nonrandomized, phase I study planned to include pancreatic NETs or PCNs (IPMN and MCA) in inoperable patients treated with a dedicated cooling RFA needle. The primary objective of this study was to investigate the safety of EUS-guided pancreatic RFA (severe complications or minor complications). The secondary objective was to assess its efficacy based on 1-year follow-up imaging.

Methods

Patients and criteria for inclusion

This study was conducted as a prospective, multicenter, open-label, nonrandomized, phase I study, which planned to include 30 patients presenting with either NETs or PCNs over a 2-year period with a 1-year follow-up. The expected rate of complications according to a previous series reporting EUS-guided tumor treatment was 10 % [12].

The study received the approval of an independent ethics committee (Comité de protection des personnes Sud Méditerranée I; 17 November 2014; reference number 2014-AO1474-43).

The inclusion criteria were: the presence of a pancreatic NET < 2 cm with histological proof and inoperability or refusal of surgery, or a branch duct IPMN with worrisome features, including mural nodes > 5 mm or MCA. All indications for medical or surgical management were discussed in a multidisciplinary meeting.

The patients were 16 men and 14 women (mean age 54.4 years, range 49–84 years), 12 of whom had NETs and 17 with PCNs. One patient who received a final diagnosis of late pancreatic metastasis of renal carcinoma was excluded.

Objectives and end points

The primary objective of this study was to check the safety of the treatment. The safety end points used were: major complications including acute pancreatitis, perforation, bleeding, and injury to adjacent structures; minor complications including pain and fever. An independent safety committee (made up of one surgeon, one clinical researcher, one gastroenterologist who was not involved in the inclusion of patients) was designed to ensure the quality of the data and the management of complications.

The secondary objective was to assess the antitumor efficacy at 1-year follow-up. The efficacy end points at 6 months and 1 year were: complete necrosis, diameter decrease > 50 % and diameter decrease < 50 % assessed by CT scan or MRI. The diagnosis of necrosis in NETs was based on the absence of contrast enhancement in the arterial phase in a low-density lesion. The diagnosis of disappearance was based on the lesion being nonvisible in a comparable cross-section on CT scan or MRI. Results were classified as complete resolution (disappearance or necrosis), significant response (decrease > 50 % or complete resolution), or failure (decrease < 50 % or no effect).

Technique

All endoscopic examinations were performed with an EUS therapeutic scope (EG-3870UTK, HOYA corporation, Pentax life care division, Tokyo, Japan; or GF-UCT180 Olympus, Tokyo, Japan). For NETs, the operative needle was used directly. For PCNs, the operative needle was also used directly in the first two patients before the protocol was modified (see below). In subsequent patients with PCNs, FNA was first performed with a 22G regular needle (chosen to decrease the risk of seeding after two PCN punctures) to suck the fluid content until a thin

layer of fluid remained, thereby allowing targeting of the remaining cystic lesion.

EUS-RFA was performed with an 18G RFA needle (Starmed, Taewoong, South Korea) applying 50 W with the setting of Continuence Mode until reaching 100 Ohms impedance (appearance of white bubbles) but not going beyond 500 Ohms. The operative needle has an associated internal cooling system, which was connected via an external pump with cold saline. The operative needle was used to target the lesion after EUS Doppler assessment to prevent damage to interposed vessels. Where possible, a 2-mm distance was kept between any critical surrounding structures (i.e. common bile duct, duct of Wirsung) and the tip of the active part. RFA was stopped either when the operator saw white bubbles coming alongside the needle and outside the targeted lesions on the ultrasound screen or when the impedance exceeded 100 Ohms.

Prophylaxis for complications

At the onset of the study no prophylaxis was given. On the third patient, because of the occurrence of two complications in the first two patients, prophylaxis was introduced against acute pancreatitis, infection, and perforation. Rectal diclofenac was used as recommended before endoscopic retrograde cholangiopancreatography (ERCP) to prevent post-endoscopic pancreatitis. Antibiotic prophylaxis (2 g of amoxicillin and clavulanic acid intravenously) was used to prevent infection. The main part of the fluid content was sucked out prior to RFA in PCNs in order to avoid excessive application of radiofrequency current into the liquid component.

Follow-up

Patients were kept in hospital for 2 days to ensure the safety of the RFA treatment (risks of pain, acute pancreatitis, fever, perforation, bleeding). Clinical follow-up was planned at 1 month, 6 months, and 1 year, with biological sampling for chromogranin A (CgA) in patients with a NET at 6 months and 1 year. Imaging was performed at 6 months and 1 year with MRI for cystic lesions or CT scanning for NETs. EUS was repeated at 1 year.

Results

Patients

The study group included 12 patients with 14 NETs (7 men [58 %]; mean age 59.9, range 45 – 77). All of the tumors were well-differentiated nonfunctional NETs belonging to WHO grade 1 classification, one of which was associated with multiple endocrine neoplasia (MEN) type 1. The mean size of the NETs was 13.1 mm (range 10 – 20 mm). Their locations were three in the head, six in the body, and five in the tail. The mean serum level of CgA was 344 mg/L (range 84 – 1230 mg/L) (▶ **Table 1**).

The remainder of the study group consisted of 17 patients with a PCN (16 with a branch duct IPMN and one with an MCA; 7 men [41 %]; mean age 65.7, range 65 – 83). The mean tumor diameter was 28 mm (range 9 – 60 mm) and they were located in the head in 10 patients, the body in four patients, and the tail in three patients. Among the 16 patients with a branch duct IPMN, 12 presented with mural nodes (mean size 5.7 mm [range 5 – 10 mm]) and four with increased thickness of the cyst wall (mean size 3.3 mm [range 2 – 7 mm]) (▶ **Table 1**).

▶ **Table 1** Description of the 31 pancreatic lesions in 29 patients that were included in the study.

	Neuroendocrine tumor	Pancreatic cystic neoplasm
Number of lesions	14	16 IPMN 1 MCA
Location		
▪ Head	3	10
▪ Body	6	4
▪ Tail	5	3
Mean size (range), mm	13.1 (10 – 20)	28 (9 – 60)
CgA level (range), U/mL	344 (84 – 1230)	NA
Mural nodes, n (%)	NA	12 (70.6 %)
Thick cystic wall, n (%)	NA	4 (23.5 %)

IPMN, intraductal pancreatic mucinous neoplasm; MCA, mucinous cystic neoplasm; CgA, chromogranin A; NA, not applicable.

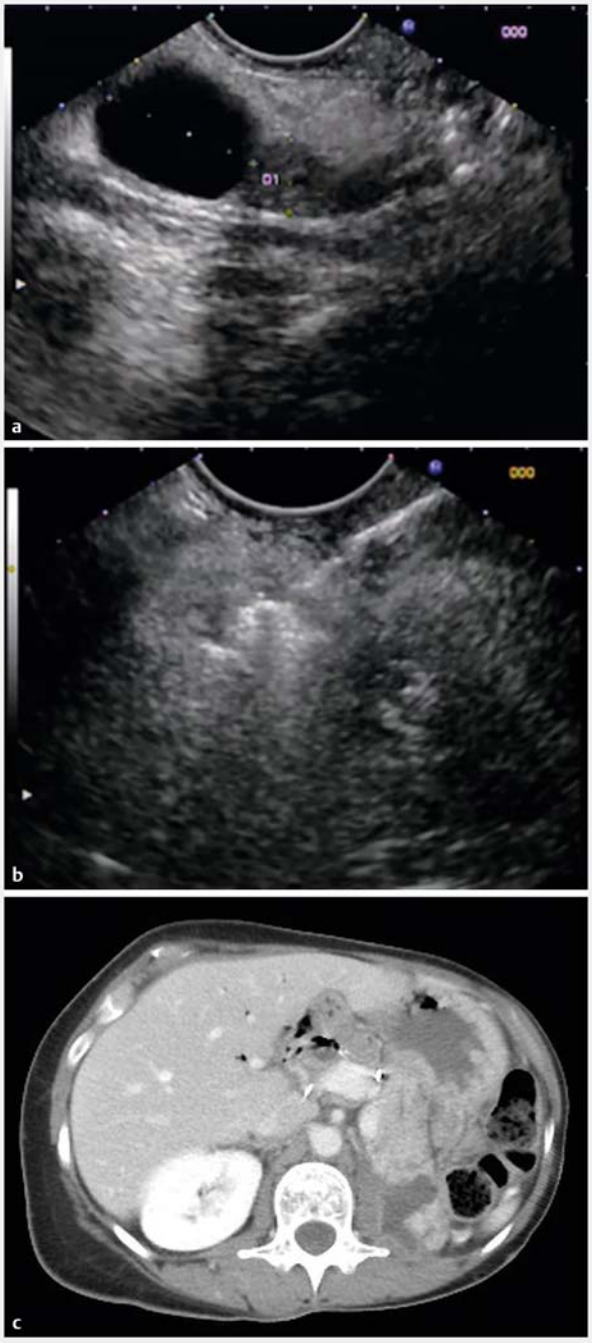
The overall mean duration of hospital stay was 4 days (range 2 – 4 days).

Safety

Overall three adverse events occurred (10 %) in three different centers, of which two occurred in the two initial patients, these being the first patient in each center's experience. These complications were considered as major complications.

The first adverse event, which occurred in the first patient to be included, was acute pancreatitis with an area of early infected necrosis located close to the tail of the pancreas. This patient with MEN 1 underwent treatment for two NETs located in the tail: one a 15-mm cystic NET, the other an 8-mm solid NET (▶ **Fig. 1a**). The solid NET was treated directly with a one-shot RFA. The cystic NET was treated without sucking the fluid content at the first attempt but, because of the lack of increase in impedance, a second attempt was made after sucking out the fluid content and RFA was performed successfully (▶ **Fig. 1b**). The following day, the patient developed mild pain with pancreatitis and fever with bacteremia. A CT scan showed an area of well-delineated parenchymal necrosis in the tail (▶ **Fig. 1c**) and a small area of extrapancreatic necrosis behind the tail of the pancreas. The patient was discharged 10 days later and, at follow-up at 6 months and 1 year, the tumors had completely disappeared.

The second adverse event occurred in the second patient to be included who had an IPMN cyst located in the uncinate process of 18 mm in diameter with high grade dysplasia shown on EUS-FNA. One RFA shot was applied without suction. The patient experienced pain and fever 12 hours later and a CT scan showed pneumoperitoneum with a fluid collection. The patient underwent surgical exploration and a perforation of an adja-



▶ **Fig. 1** Endoscopic ultrasound (EUS)-guided radiofrequency ablation (RFA) for neuroendocrine tumors (NETs) in the first patient treated. **a,b** EUS views showing: **a** a cystic NET and a solid NET located in the tail of the pancreas; **b** RFA with visible white bubbles within the cystic NET after sucking out the fluid content. **c** Computed tomography scan 2 days after RFA showing a necrotic area in the tail of the pancreas and a small extrapancreatic necrotic area close to the tail of the pancreas.

cent jejunal loop was found and surgically treated. The patient was discharged from the hospital 21 days later. Follow-up at 6 months and 1 year showed complete disappearance of the IPMN and no evidence of any clinical sequalae.

After these two initial complications in the first two patients included, the independent safety committee decided to modify the study protocol with an increase in prophylaxis, as mentioned above. These modifications in the protocol resulted in a decrease in complications, with the following 28 patients experiencing no pancreatitis, perforations, or infections, and only one further complication occurring to give a morbidity rate for the modified protocol of 3.5 %.

The one additional complication was a stenosis of the main pancreatic duct (MPD), which was treated with endoscopic stenting. The patient had a 12-mm NET located at the neck of the pancreas, 1 mm from the duct of Wirsung (▶ **Fig. 2a**). The course following RFA was uneventful and the patient was discharged from the hospital at day 2. They re-presented 1 week later with post-prandial pancreatic pain. A CT scan showed a slight dilatation of the MPD upstream to the neck of the pancreas (▶ **Fig. 2b**). ERCP was performed and showed contrast filling of the NET, which was necrotic and fistulized into the MPD (▶ **Fig. 2c**). The patient was successfully treated with pancreatic ductal stenting for 6 months. At 1-year follow-up, no tumor could be demonstrated and the patient had no symptoms, despite the MPD remaining slightly dilated upstream of the postoperative ductal stenosis.

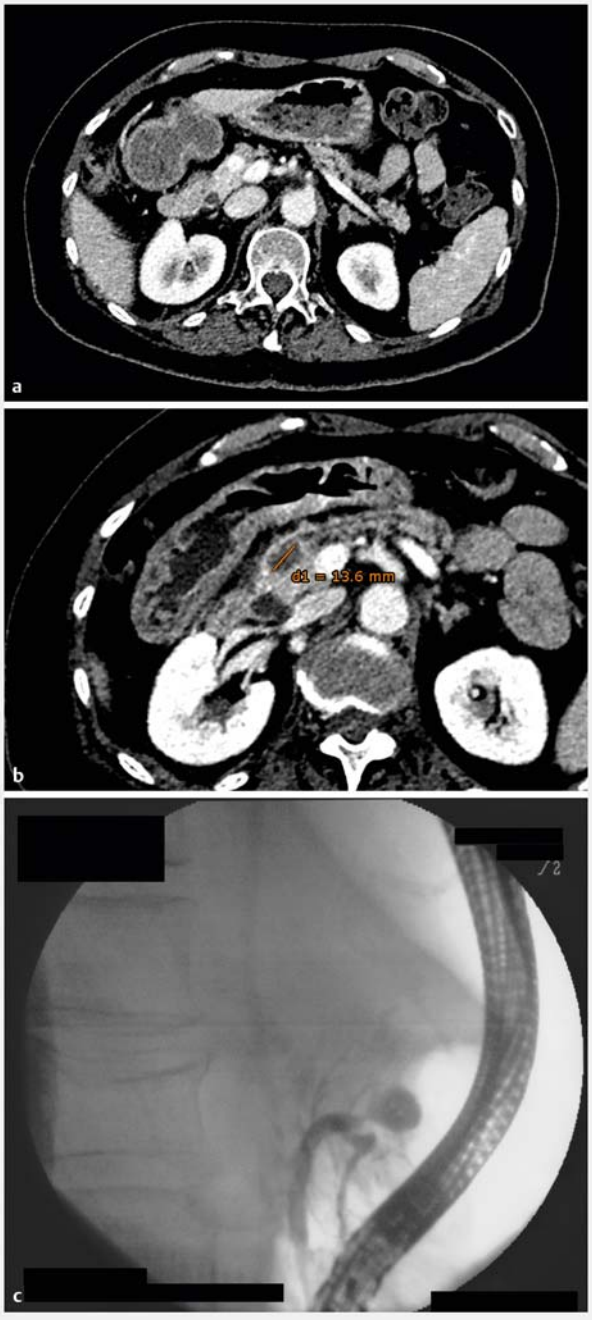
No patients had bleeding and only one experienced fever (the first patient who developed pancreatitis). The only other minor complications were pain, which occurred in six patients (20 %) who had mild pain on postoperative day 1 requiring level 1 analgesic treatment (paracetamol) for 2 days.

Efficacy in neuroendocrine tumors

Technical success (ability to target the RFA needle) was achieved in all tumors.

At 6-month follow-up, nine of the NETs had disappeared or showed complete necrosis, and one had decreased in diameter by > 50 %. Therefore, responses were considered to have been significant in 71 % of the tumors. Four patients were considered to have failed treatments (decrease in diameter < 50 % in three patients, no change in one). The mean serum level of CgA decreased from 344 U/mL (range 84 – 1230 U/mL) to 253.3 U/mL (range 72 – 616 U/mL).

At 1-year follow-up, 12 of the NETs had completely disappeared or undergone necrosis (86 %). Two treatments were considered to have been failures: a 20-mm tumor in the tail of the pancreas, which showed an increase in size by 3 mm, and a 16-mm lesion located in the body of the pancreas, which remained unchanged in size but no longer displayed a Doppler signal on EUS examination. The mean serum level of CgA was 257.5 U/ml (range 64 – 648 U/mL) (▶ **Table 2**).



▶ **Fig. 2** Endoscopic ultrasound (EUS)-guided radiofrequency ablation (RFA) for a neuroendocrine tumor (NET). **a,b** Computed tomography scan images showing: **a** a NET (12 mm in size, hyperenhancing in the arterial phase) located at the neck of the pancreas; **b** the appearance 1 week after RFA with complete necrosis of the tumor and a dilatation of the upstream duct of Wirsung. **c** Endoscopic retrograde cholangiopancreatography image showing the necrotic NET filled with contrast and fistulized with the duct of Wirsung.

▶ **Table 2** Results of endoscopic ultrasound-guided radiofrequency ablation in the 31 pancreatic lesions.

	6 months follow-up	12 months follow-up
Neuroendocrine tumors (n = 14), n (%)		
Significant response	10 (71.4)	12 (85.7)
▪ Disappearance or necrosis	9 (64.3)	12 (85.7)
▪ Decrease in diameter > 50 %	1 (7.1)	0 (0)
Failure*	4 (28.6)	2 (14.3)
Pancreatic cystic neoplasms (n = 17), n (%)		
Significant response	11 (64.7)	12 (70.6)
▪ Disappearance or necrosis	8 (47.1)	11 (64.7)
▪ Decrease in diameter > 50 %	3 (17.6)	1 (5.9)
Failure*	6 (35.3)	5 (29.4)

* No change in size or decrease in diameter < 50 %.

Efficacy in pancreatic cystic neoplasms

Technical success (sucking of the fluid content and targeting the RFA needle) was achieved in all tumors.

At 6 months, eight tumors had completely disappeared (47 %) and three had a diameter that had decreased by > 50 %. The significant response rate was 65 %. Five patients presented with a diameter decrease < 50 % and one with an unchanged tumor. Mural nodes had disappeared at EUS follow-up in 11/12 patients (92 %).

At 1 year, 11 tumors had completely disappeared (65 %) and one had decreased in diameter by > 50 %. The significant response rate was 71 %. Four patients continued to have a diameter decrease < 50 % and one still had an unchanged tumor. Mural nodes had all disappeared at EUS follow-up in 12/12 patients (100 %) (▶ **Table 2**).

Discussion

This prospective, multicenter, open-label, phase I study was planned as its first objective to assess the safety of EUS-guided RFA for pancreatic premalignant tumors because no data were available in prospective series. EUS-guided treatments for pancreatic tumors have been developed for many years for adenocarcinoma, NETs, or PCNs, the most popular being ethanol ablation, which carries the risk of uncontrolled diffusion of ethanol [8, 12 – 14, 18 – 20].

EUS-RFA has been developed to try to ensure a better controlled EUS-guided antitumor treatment combining both tumor necrosis and enhancement of the immune response [20 – 22]. A recent review of endoscopic RFA reported only early data on EUS-guided RFA in pancreatic tumors and the largest study included only eight patients [20, 22]. They concluded that more data about safety, long-term durability, and clinical indications were needed [20].

The primary objective of our study was to assess the safety of the treatment including 30 patients with a follow-up duration at least 1 year. We used a dedicated needle-RFA device (Starmed; Taewoong, Seoul, Korea) connected to an external generator and a water pump for cooling the needle in order to try to decrease damage to the surrounding structures and any carbonization effect. The needle diameter was 18 G at the time of the study, although it has since become available with a 19 G diameter, which could improve maneuverability. In this series, the number of NETs located in the head was three and there were 10 IPMNs, with passes made through the duodenum with complete feasibility.

Most EUS-guided RFA treatments have been reported in the management of adenocarcinoma of the pancreas [12, 22 – 24]. We focused on premalignant pancreatic tumors such as NETs or PCNs to assess the safety of this procedure as no procedure should be further developed if it is not safe for the patient. An assessment of its efficacy was only the secondary objective.

Severe complications occurred in three patients (10 %), including the initial two patients (acute pancreatitis with early infection and perforation of adjacent jejunum). The study protocol was therefore modified: (i) to try to reduce the risk of pancreatitis by adapting the prophylactic guidelines for ERCP (rectal diclofenac) to this procedure also; (ii) to try to reduce infection of the necrosis by giving antibiotic prophylaxis; (iii) to try to reduce damage to adjacent organs in cystic lesions due to excessive application of RFA in the presence of fluid content. Out of the remaining 28 patients who received the revised prophylactic protocol, only one experienced a complication (3.5 %), this being obstructive pancreatitis due to fistulization of a NET within the MPD. This patient was successfully treated by ERCP, including pancreatic sphincterotomy and stenting (▶ **Fig. 2**). At the 1-year follow-up, all of these three patients were doing perfectly well with no further evidence of tumor. Very few data about the safety of EUS-guided RFA can be found in the articles about EUS-guided RFA in PCNs [25 – 28]. Pai et al. [28] applied EUS-guided RFA with the Habib probe in six PCNs (4 MCAs, 1 IPMN, 1 cystic NET) and two patients experienced transient mild pain, which resolved within 3 days. In this series, six patients (20 %) experienced mild pain with complete resolution within 2 days.

The secondary objective of this study was to evaluate the efficacy of this therapy in premalignant pancreatic tumors (NETs and PCNs) (▶ **Table 2**). Very few data are available for EUS-guided RFA in NETs from short series including a total of seven patients [8, 25 – 28]. The outcome showed complete ablation in two patients, central necrosis in one patient, and reduced size in three patients [25 – 28]. A recent series including only three insulinomas showed quick symptomatic and biological improvement within 2 days following the procedure, with sustained results at 2 years of follow-up [25]. In this series, the final efficacy for NETs reached a complete resolution rate in 86 % of the tumors after 1 year of follow-up, despite an incomplete significant response of 71 % at 6 months of follow-up (▶ **Table 2**). These results appear to be close to those previously reported [25 – 28].

One could wonder about the spontaneous improvement of efficacy between 6 and 12 months after RFA. EUS-guided RFA acts not only by tumor necrosis but also by triggering immunostimulation owing to the release of intracellular antigens that lead to systemic antitumor activity [21]. Even if EUS-guided RFA has the main objective of inducing necrosis of solid tumors or of the epithelial layer of PCNs, it has been demonstrated in animal models that RFA not only induces necrosis but also triggers immunomodulation, mainly stimulating the immune response with local and systemic antitumor activity [21]. RFA induces direct cell death and coagulative necrosis, the dead cells then release intracellular antigens that can be picked up by dendritic cells and stimulate a systemic immune response [21]. This could be responsible for the delayed response after RFA as shown for NETs in this series: 6-month significant response rate of 71 %, but 86 % complete resolution at 1 year. This could change follow-up, with patients requiring at least 1 year of follow-up to be sure of the final efficacy of RFA.

This series also included PCNs as premalignant tumors. Very few data can be found in the literature for RFA efficacy in PCNs, despite it being the most frequent premalignant pancreatic tumor [1, 2]. Pai et al. [28] in their study included six PCNs (4 MCAs, 1 IPMN, 1 cystic NET); two complete resolutions occurred and three underwent size reduction. In this series, we included 17 patients with branch duct IPMN and worrisome features (n = 16) or MCA (n = 1). At 12 months, among 17 PCNs, complete disappearance was shown in 11 patients and a diameter decrease > 50 % in one patient (significant response rate of 71 %) (▶ **Table 2**). All 12 mural nodules showed complete resolution.

The limitations of this prospective study are: (i) the limited number of patients, requiring cautious analysis of the morbidity rate; (ii) the absence of histological control of the efficacy; (iii) the limited follow-up, which was restricted to 1 year because the primary objective of the study was to assess complications related to EUS-RFA in the pancreas. Other large studies with longer follow-up are required to confirm the exact place of EUS-guided RFA in NETs and PCNs. Randomized series comparing EUS-guided management with surgery should be performed.

In conclusion, EUS-RFA management of pancreatic NETs or PCNs using a dedicated operative cooling needle is associated with a 10 % morbidity rate. This complication rate should be decreased by an improved prophylactic protocol. The efficacy for the management of NETs reached 86 % (all complete disappearances) although this sometimes did not occur until the 1-year follow-up, while the efficacy for PCNs appears to be lower with a 71 % significant response rate. Further studies with more patients and a longer follow-up are required.

Competing interests

Marc Barthet received a research grant from Boston Scientific (Endoscopic gastrojejunal anastomosis). Bertrand Napoleon is a consultant for Boston Scientific. All other authors have no financial disclosures or conflicts of interest to declare.

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