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EUS-guided Radiofrequency Ablation (EUS-RFA) of Solid Pancreatic Neoplasm Using an 18-gauge Needle Electrode: Feasibility, Safety, and Technical Success

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ABSTRACT

Background & Aims: Endoscopic ultrasound-guided radiofrequency ablation (EUS-RFA) is a promising technique for the treatment of pancreatic neoplasm. We evaluated the feasibility, safety, and technical success of pancreatic EUS-RFA performed in a single center.
Methods: 9 consecutive patients (8 with pancreatic adenocarcinoma and 1 with renal cancer metastasis) were referred for EUS-RFA between November 2016 and July 2017. EUS-RFA was performed using 18-gauge internally cooled electrode with a 5 or 10 mm exposed tip. Feasibility, technical success or early and late adverse events were assessed.
Results: One patient was excluded because of a large necrotic portion. EUS-RFA was feasible in all the other 8 (100%) cases. An ablated area inside the tumor was achieved in all treated patients. No early or late major adverse event was observed after a mean follow-up of 6 months. Three patients experienced mild post-procedural abdominal pain.
Conclusions: EUS-RFA seems a feasible, safe, and effective procedure for pancreatic neoplasms. Its role in the treatment and management of pancreatic masses must be further investigated.

Key words: pancreatic ablation – endoscopic ultrasound – pancreatic cancer – pancreatic adenocarcinoma – radiofrequency ablation.

Abbreviations: CECT: contrast-enhanced computed tomography; EUS: endoscopic ultrasound; EUS-RFA: endoscopic ultrasound-guided radiofrequency ablation; PDAC: pancreatic ductal adenocarcinoma; RFA: radiofrequency ablation.

INTRODUCTION

Despite the progress in research, pancreatic cancer (PDAC) remains one of the most aggressive tumors, along with a poor prognosis. It is often diagnosed at a non-resectable stage. Different chemo and/or radiotherapies have had poor results, with the five-year survival rate at around 5–7% [1]. In this setting, combining multimodality therapies might improve the treatment outcome [2]. Radiofrequency ablation (RFA) produces a thermal-induced coagulative necrosis of the tumor [3]. Some studies demonstrate that thermal ablation can induce an immune response towards the tumor, determined by the release of necrotic cell content in the extracellular space that stimulate the host's antitumor immunity [4]. Moreover, a recent study documented increased blood flow around the ablated area [5]. Complete ablation of pancreatic tumors is contraindicated as it increases the risk for major complication (e.g. hemorrhage, pancreatic fistula, duodenum necrosis) [6-9]. However, RFA may be included in a multimodality treatment strategy to improve the efficacy of the standard therapy. Radiofrequency ablation of the pancreatic masses can be performed through laparotomy, laparoscopy, endoscopy or percutaneously, all under ultrasound guidance [5-6, 10-12].

Endoscopic ultrasound (EUS) represents the perfect tool to guide local treatment of pancreatic lesions, as it provides real-time visualization of the procedure with high-resolution images of the pancreas and surrounding structures. This is particularly relevant, because the pancreatic tumors often infiltrate or encase structures that could be damaged during the procedure, leading to severe adverse events.

A specifically designed needle tip electrode for performing EUS-RFA (EUSRA RF Electrode, STARmed, Koyang, Korea)

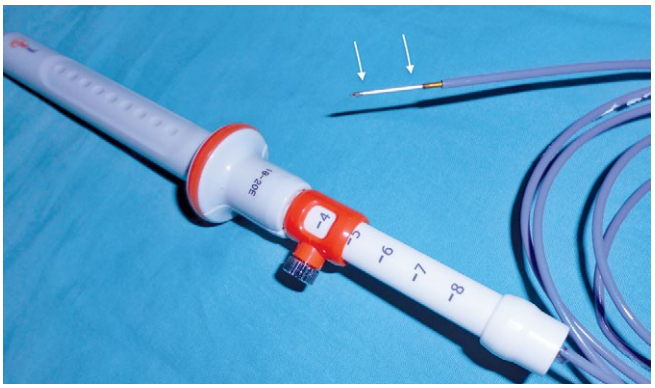

Fig. 1. The EUSRA electrode, handle, and exposed tip (arrows).

(Fig. 1) was used for the first time in 2012 [13]. However, few data about the feasibility, safety, and technical success of EUS-RFA performed with this special needle for pancreatic masses are available. This study aimed to evaluate the feasibility, safety, and technical success of pancreatic EUS-RFA performed in a single center.

METHODS

The local Ethics Committee approved this study (no. 51824). At the Pancreatic Care Center of Verona, data of all patients referred to undergo EUS-RFA of a pancreatic mass were prospectively collected between November 2016 and August 2017, and retrospectively analyzed. The procedures were performed with the patient hospitalized and all patients gave written informed consent before the procedure.

Indications for EUS-RFA include: a) a cyto/histological diagnosis of PDAC, which was non-resectable and had no metastases after first line chemotherapy and/or radiotherapy (stage III); b) a solid pancreatic lesion that was resectable but not suitable for surgery or chemotherapy due to the patient's comorbidities. Contraindications were poor performance status, extension of necrosis into the tumor, coagulation disorders, and no informed consent given.

EUS-RFA technique

EUS-RFA was performed by two expert endosonographers, with the patients placed on the left lateral position under deep sedation, employing a linear-array echoendoscope (EG-3870UTK, Pentax Medical, Tokyo, Japan). An 18-gauge EUSRA electrode needle connected to a radiofrequency generator (VIVA RF generator; STARmed, Seoul, S. Korea) was used in all patients. The electrode was internally cooled with iced saline solution. A 5 or 10 mm exposed tip was chosen according to the size of the tumor. The 5 and 10 mm exposed tip electrode can produce, with one application, a maximum ablation area of about 15 and 25 mm, respectively [13], depending on wattage and application time.

After the standard EUS scanning, the electrode needle was inserted into the lesion under direct EUS guidance, avoiding interposed vessels. The procedure was considered feasible if it was possible to insert the electrode into the targeted point and to apply the radiofrequency energy for a sufficient time. All procedures were started with a preset radiofrequency power of 30W. The slowly increasing hyperechoic zone was easily visualized during EUS examination (Fig. 2). The radiofrequency generator was stopped if the hyperechoic area sufficiently covered the tumor, or a few seconds after there was an increase in the value of the impedance indicated by the generator (Fig. 3). If necessary, the procedure was repeated by reinserting the needle in another part of the lesion until obtaining the largest possible ablation of the tumor. In particular, if a not ablated, a large (>3cm) portion of tumor was clearly visible after the first RFA application, the needle was reinserted specifically targeting that area to perform a second ablation. Procedures were performed leaving a "security ring" of at least 5mm at the periphery of the tumor in order to avoid thermal injuries of the nearby structures [14].

Post-procedural follow-up

Clinical evaluation and laboratory tests (complete blood count, liver function tests, and serum amylase/lipase levels) were performed at 6 and 24 h after the procedure. A contrast-enhanced computed tomography (CECT) scan was performed one day and one month after the procedure to check the treatment outcome and exclude early and late adverse events. A radiologist expert in pancreatic diseases evaluated all the CECTs. Technical success was defined by achieving tumor ablation (i.e., the presence of a markedly hypodense area inside the tumor that was detectable at the day after CECT scan) (Figs. 4 and 5). The size of the thermo-lesion was assessed in three axes (anteroposterior, transverse, and longitudinal). The volume of the ablated area (and its percentage in respect to the original tumor volume) was calculated [15].

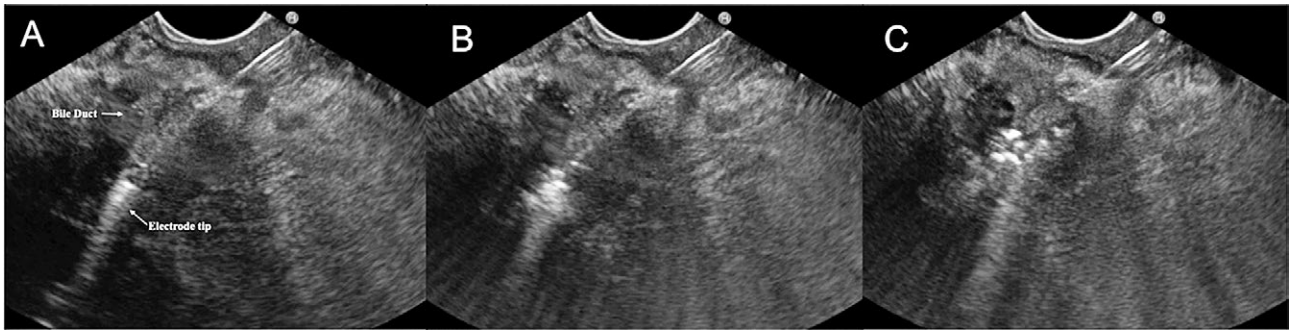

Fig. 2 (A, B, and C). A session of endoscopic ultrasound-guided radiofrequency ablation (EUS-RFA) of a pancreatic head cancer. The hyperechoic area slowly spread from the electrode tip and is clearly visualized at EUS scan. The bile duct is easily recognized and remains under direct visualization during the whole procedure.

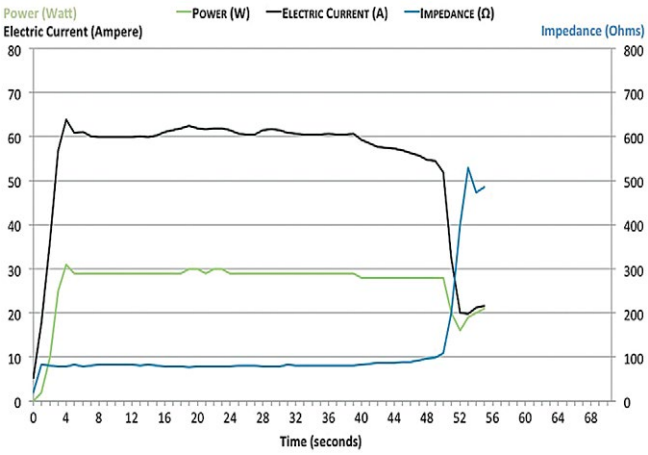

Fig. 3. A graph of the radiofrequency power (Watt, green), electric current (Ampere, black), and impedance (Ohms, blue) vs. time during a session of EUS-guided radiofrequency ablation.

RESULTS

Data from 9 consecutive patients (6 males, mean age 67 years) with a diagnosis of locally advanced PDAC in 8 cases, and pancreatic head metastasis from renal clear cell carcinoma in 1 patient (not suitable for resection or chemotherapy due to chronic renal failure) were collected (Table I). One PDAC patient was excluded because of the presence of a large necrotic area inside the tumor, which was detected during EUS as a fluid portion with avascular pattern after contrast injection (Sonovue, Bracco, Milan, Italy).

EUS-RFA was feasible in all the 8 remaining patients. Tumors were located in the pancreas head (3), body (3), and uncinate process (2). One patient with pancreatic head cancer underwent EUS-RFA with a previously placed plastic biliary stent. Mean tumor size was 36 mm (range 22 - 67 mm). Procedures were performed from the stomach, the duodenal bulb, and the second portion of the duodenum in 4, 2, and 2 patients, respectively. No technical difficulty in inserting the needle was recorded even for those lesions ablated with the scope in a torque position. The mean time of a single RFA application was 58 seconds, with a mean number of applications of 1.5 (range 1-3). An ablated area in the tumor was obtained in all patients. At post-procedure CECT (both at one day and one month) the mean volume of thermo-lesions was 3.75 cm^3 (range 0.72-12.6 cm^3), corresponding to a mean of 30% tumor mass (range 5.8-73.5 %) (Table II).

Three patients experienced mild abdominal pain after the procedure, which was managed conservatively with NSAIDs administration. No major adverse events such as pancreatitis, bleeding, duodenal or biliary injury, infection or perforation, or procedure-related mortality was observed in a mean follow-up of 4.3 months (range 1-8 months). Post-procedural serum amylase or lipase levels were normal in all but one case: in one asymptomatic patient, we recorded a significant (more than

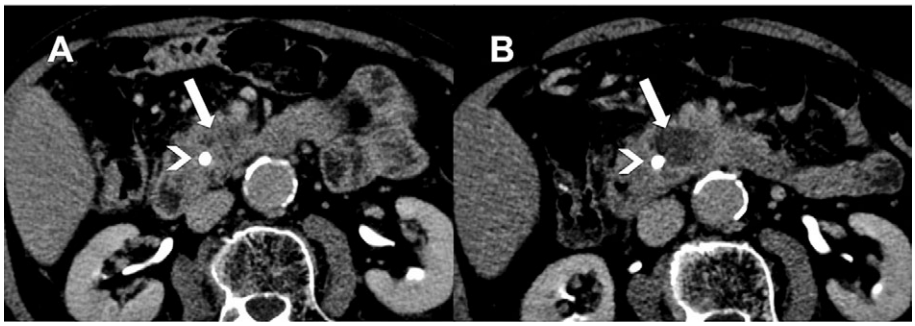

Fig. 4. Contrast-enhanced computed tomography (late phase) scans before (A) and after (B) endoscopic ultrasound-guided radiofrequency ablation (EUS-RFA), in a patient with pancreatic head cancer (arrows). A plastic stent is visible in the bile duct (arrowheads).

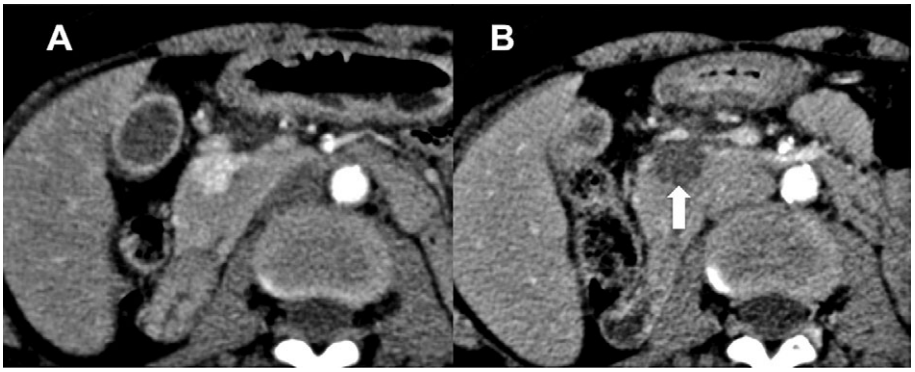

Fig. 5. (A) A case of pancreatic head hypervascular metastasis from renal cell carcinoma. (B) After endoscopic ultrasound-guided radiofrequency ablation, a markedly hypodence area is detectable instead of the tumor (arrow).

Table I. The clinical features of treated patients.

Case	Sex, age (years)	Diagnosis	Previous treatment	Tumor location	Tumor size: diameters*, cm; volume¶, cm^3
1	F, 65	LA PDAC	Folfirinox + Radiotherapy	Body	1.8x2.5x1.8; 3.7
2	M, 64	LA PDAC	Folfirinox + Radiotherapy	Uncinate process	2x2.3x2; 4.7
3	M, 85	LA PDAC	Gemcitabine	Body	4.2x4.5x3; 29.4
4	F, 68	LA PDAC	Folfirinox	Body	3.4x4.3x3; 22.8
5	M, 62	LA PDAC	Gemcitabine	Head	3.8x6.7x4.1; 54.3
6	M, 82	LA PDAC	Radiotherapy	Head	3x3.5x2.9; 15.8
7	F, 48	Renal metastasis	None	Head	1.7x2.1x2.2; 4.08
8	M, 68	LA PDAC	Folfirinox + Radiotherapy	Uncinate process	2.8x2.4x2.8; 9.8

LA PDAC: locally advanced pancreatic cancer; * anteroposterior x transverse x longitudinal; ¶ anteroposterior x transverse x longitudinal x 0.523

3 times the upper normal limits) elevation of amylase and lipase the day after procedure, returning to the normal range on the second day.

The mean hospitalization time was 3 days (range 1-6 days). However, the longer (more than 3 days) hospitalization time was not related to the RFA procedure.

DISCUSSION

Pancreatic RFA was initially performed during palliative surgery and showed encouraging results in terms of feasibility, safety and survival [6, 16]. Several severe adverse events (e.g., thermal-induced pancreatitis, and duodenal or biliary injury) have been previously reported after intraoperative and percutaneous pancreatic RFA [6, 17]. However, after an adjustment of both temperature and length of the dispensed energy, better outcomes with fewer complications were achieved [6, 12, 14]. Moreover, using percutaneous or EUS guidance, a safe mini-invasive approach can be obtained avoiding laparotomy. To the best of our knowledge, 10 patients underwent pancreatic EUS-RFA with the EUSRA electrode without severe adverse events and with high technical success [5, 18-20]. The results of our series confirm the feasibility, safety and local thermal effect of the procedure.

The optimal thermal kinetic characteristics of the pancreas are not yet determined, so there is no standardized protocol for pancreatic RFA. The needle temperature is affected by the energy used, which determines the ablation volume reached. In previous studies, 50 W was employed for 10/15 seconds, and the procedure was repeated by reinserting the electrode in different zones until the hyperechoic area sufficiently covered the tumor [5, 18]. In this study, a slightly different technical approach was used: the electrode was positioned in the middle of the tumor and a lower radiofrequency power (30 W) was applied. The time of the procedure was not determined in advance and the procedure was stopped after noting the rise in impedance and its stabilization (Fig. 3). The sudden increase of impedance expresses the dehydration of the tissue when the thermal diffusion reaches the largest area. We believe that a lower wattage, applied for a longer time can result in a greater but slower diffusion of

Table II. Procedural features and patient outcomes.

Case	Site of puncture	Active tip, mm	Thermo-kinetics (per application)	RFA applications, N	Ablation size: - diameters*, cm;- volume¶, cm^3	Percent of tumor ablation, %	Adverse events	Hospitalization time, days	Follow-up, months
1	Stomach	5	30 Watt, 60 s	2	14x12x10; 0.86	24.3	Abdominal pain	2	11
2	Bulb	5	30 Watt, 15 s	2	14x10x10; 0.72	15.3	None	2	8
3	Stomach	10	30 Watt, 50 s	3	2.7x2.9x3.1; 12.6	42.9	None	2	10
4	Stomach	10	30 Watt, 56 s	1	1.7x1.4x1.4; 1.7	7.5	None	1	7
5	Second part of duodenum	10	30 Watt, 60 s	1	1.6x1.6x14; 1.86	5.8	None	5	6
6	Bulb	10	30 Watt, 95 s	1	2.2x2.4x2; 5.49	34.8	Abdominal pain	6	3
7	Stomach	10	30 Watt, 55 s	1	1.6x1.9x1.9; 3	73.5	Abdominal pain	4	3
8	Second part of duodenum	10	30 Watt, 75 s	1	2x1.9x1.8; 3.55	36.2	None	2	1

RFA: radiofrequency ablation; * anteroposterior x transverse x longitudina;. ¶ anteroposterior x transverse x longitudinal x 0.523

thermal damage. This should result in longer applications of radiofrequency energy (on average, 50 s/application), which could reduce the number of applications (in our series, 1.5 on average), and avoid the need to relocate the electrode several times inside the tumor. This technique is based on the so-called "thermal diffusivity effect" [3], which is related to thermal neoplastic conductibility: heat spreads inside the neoplastic mass, and not outside of it, making the procedure safer. Moreover, the slower thermal diffusion, which can be visualized real-time during EUS, should make the procedure easier to control for endosonographers.

EUS-RFA offers at least two major indications for the treatment of pancreatic neoplasms. First, EUS-RFA can be included in multimodality treatment protocols for locally advanced PDAC. Second, EUS-RFA could represent a possible treatment for pancreatic solid lesions in patients unfit for surgery due to comorbidities, or for patients who refuse surgery [19].

EUS-RFA of pancreatic neoplasms aims to reduce the mass [15], to improve the vascularity in the residual mass [5] and to stimulate a systemic immune response that acts against the tumor [21], thus facilitating the efficacy of chemo(radio) therapy. The timing of EUS-RFA during the multimodality treatment approach remains to be established [22].

CONCLUSION

Our series confirmed that EUS-RFA is feasible and safe with a different generator setting, demonstrating its ability to produce substantial necrosis at the ablation site. The role of EUS-RFA in PDAC management must be further assessed in properly designed studies.

Conflicts of interest: The authors declare no conflict of interest.

Authors' contributions: S.F.C. designed the study and wrote the first draft. S.F.C. and L.B. performed the EUS-RFA procedures. M.D.O. and M.I. performed the CT scans before and after RFA. G.M. and S.P. collected data and took care of patients before and after the procedure. L.F., A.L., and A.G. revised the manuscript for important intellectual content. All authors approved the final version of the manuscript.

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