Radiofrequency Ablation of Pancreatic Cancer

Alessandro Sarno[1] Alessandro Beleù[1] Riccardo De Robertis[2] Gabriele Giannotti[1] Giorgia Tedesco[1] Salvatore Paiella[3] Mirko D'Onofrio[1]

[1] Department of Radiology, G.B. Rossi Hospital, University of Verona, Verona, Italy
[2] Department of Radiology, Azienda Ospedaliera Universitaria Integrata di Verona, Verona, Italy
[3] Department of Surgery, G.B. Rossi Hospital, University of Verona, Verona, Italy

Address for correspondence Prof. Mirko D'Onofrio, Department of Radiology, G.B. Rossi Hospital, University of Verona, Piazzale L.A. Scuro 10, 37134 Verona, Italy (e-mail: mirko.donofrio@univr.it).

Dig Dis Interv 2019;3:133–137.

Abstract

Radiofrequency ablation (RFA) is emerging as a safe and feasible technique to treat various pancreatic lesions. In particular, pancreatic ductal adenocarcinoma (PDAC) is the most frequent treated lesion. Nowadays, PDAC treatment by means of RFA is limited to locally advanced, non-resectable, but non-metastatic lesions. The aim of this article is to describe the RFA technique, its results and possible complications.

Keywords

- pancreas
- radiofrequency ablation
- pancreatic adenocarcinoma

In the past decades different techniques have been proposed for ablation of locally advanced pancreatic cancer. Those are commonly divided in thermal and nonthermal ablative techniques. Radiofrequency ablation (RFA), High-intensity focused ultrasound (HIFU), and irreversible electroporation (IRE) are currently the most used and most promising techniques in the ablation panorama, each one with its own pros and cons.

Radiofrequency ablation (RFA) of pancreatic cancer gains its roots from the positive experience in liver, kidney, and other organs ablation.[1,2] One of the first pancreatic application in an ex vivo model is dated 1999, in an attempt to ablate a porcine pancreas. The study analyzed technical feasibility, safety, and effect of the RFA providing positive results in obtaining an area of circumscribed necrosis.[3] Later, a lot of studies regarding pancreatic RFA have been published.[4–8] The ablative therapies were then used in different contexts, ranging from intraoperative approaches to mini-invasive ones (endoscopic and percutaneous).

The most frequent pancreatic lesion treated with RFA is the ductal adenocarcinoma[9] which represents about the 90% of pancreatic malignancies.[10] However, ablative treatment of different lesions has been described in literature, from neuroendocrine tumors to pancreatic metastases.[11,12]

Radiofrequency Ablation: Imaging Guidance, Materials and Techniques

RFA is a thermal ablative technique that consists in the application of a high alternating current to generate high temperatures to induce protein denaturation and coagulative necrosis inside tissues.[13] RFA seems also to have a role in systemic immunogenic stimulation which is not completely understood but probably related to activation of tumor-specific T-lymphocytes and release of heat shock proteins that stimulate immunological processes.[14,15]

Approaches

RFA can be performed with different types of guidance (e.g., computed tomography [CT] and ultrasound [US]), but most commonly, it is applicated with US guidance using different approaches: intraoperatively, usually associated with biliary and gastric bypass for pancreatic head tumors, or with mini-invasive approaches, both percutaneously and endoscopically.[4,16,17] The percutaneous approach is preferred for lesions located in the pancreatic body, whereas for pancreatic head tumors the endoscopic intervention is recommended. Thanks to mini-invasive approaches, major concerns regarding impaired immune response and invasiveness due to

received
December 3, 2018
accepted after revision
March 12, 2019
published online
May 10, 2019

Issue Theme Ablation Techniques in Liver and Pancreatic Cancers; Guest Editors, Giovanni Mauri, MD, and Miltiadis Krokidis, MD

DOI https://doi.org/10.1055/s-0039-1688437.
ISSN 2472-8721.

laparotomy are avoided.[9] The procedure is performed under local anesthesia for the mini-invasive approaches and under deep sedation if applied during laparotomy. The endoscopic approach has been widely described and applied to different pancreatic lesions.[18–20] Intraoperative approach has been largely validated,[4,16,21] whereas few studies have investigated the percutaneous approach so far.[22]

The Needle

Every patient is treated with a tailored approach, with different choice of needle and opening degree of the electrodes, mostly based on tumor location, shape, and size.

Two kinds of needles are currently available: those with multiple expandable electrodes and those with single electrode. The first type is provided of several electrodes opened at the needles' top; in this case, the needle tip should be positioned immediately before the lesion and so the electrodes have to be opened inside the lesion. An advantage of this kind of needle is the possibility to treat small tumors, thanks to the different degrees of needle opening, but difficulties related to electrodes flexibility have to be considered, especially for really hard lesions treatment. A variant of this type of needle is, however, equipped with electrodes that open from the back; in this case, needle has to be positioned inside the lesion for at least 2 cm within the mass before electrodes are opened; those electrodes are stiffer and allow to treat harder lesions, but the necessity to position the main needle inside the lesion for at least 2 cm represent a problem related to tumor location and size. Both types of expandable needles provide an ovoidal necrotic area that ranges from 2 to 6 cm, according to the different grade of opening of electrodes.

The single-electrode needle needs to be positioned inside the lesion and the necrotic area width and length (usually cylindrical, range 1–3 cm) depends on the length of the uncovered electrode and from the time the current is applied. This kind of needle is better indicated for small ovoidal lesions with difficult approaching route, thanks to their lower caliper (e.g., 17G).[9,16]

Parameters Setting

There are two main parameters that have to be settled for the RFA, power (expressed in Watts) and time. Usually, the treatment ranges from 5 to 10 minutes with different power settings that influence directly the temperature reached (that should be kept under 90°C) and indirectly the treated volume. Some systems provide also impedance evaluation, which increases during the procedure with the development of tissue necrosis, and that could help in deciding when to stop the procedure.

Cooling, Thermal Issues and Technical Tips

Since the first application of pancreatic RFA, major concerns were about the pancreatic anatomical position and relationship with other vital structures, with the possibility of a life-threatening thermal injury as a side effect. Many complications have been described during the development of the technique[23] and nowadays, there is still a lack of homogeneity in how the RFA parameters should be settled to diminish complications. On one hand, application of higher temperatures leads to more homogeneous necrotic areas; on the other hand these higher temperatures increase the risk of complications without a true favorable effect. Girelli et al have proposed temperatures of approximately 90°C and to keep a safe distance of approximately 5 mm from vital structures, while ablating the lesion, obtaining a reduction in the complication rate.[4]

For the laparotomic approach, some authors also suggest the use of a cold wet gauze placed over the inferior vena cava to protect it from heating and a continuous duodenal perfusion with cold saline solution through a nasogastric tube placed in the second part of the duodenum to avoid thermal injury.[4,8]

Heat sink effect has been described as a potential limit of the procedure,[24] decreasing treatment efficacy of tumors that surround large vessels due to the cooling effect of blood flow. Considering that the first therapeutic effect of ablative techniques is tumor cytoreduction,[25] heat sink effect could compromise the success of the procedure. Anyway, it can also provide a protective effect against thermal injury to major vessels.

Thanks to the development of internally cooled electrodes for RFA, an increased energy delivery to tissues has been obtained that results in an increased volume of induced coagulative necrosis.[26] Nevertheless, during pancreatic tumor ablation the necrotic area should always be bound inside the lesion borders leaving a viable residue at tumor periphery, unlike procedures performed on other organs, where it is possible to ablate outside the tumor margins to achieve a complete necrosis of the lesion.[27]

Before, during and after the Procedure

Before the procedure an accurate evaluation of CT and magnetic resonance (MR) imaging is essential to evaluate the correct indication and also the feasibility of the procedure. Moreover, a common B-mode US and color-Doppler evaluation is crucial to choose a safe route for the needle to avoid vessels and peripancreatic vital structures. All the ablation procedure is constantly monitored with US while the lesion is replaced by a hyperechoic gas-filled area. Usually the procedure is stopped when a change of impedance is noted on the RFA instrument or when a large gas-filled hyperechoic area is obtained. After the procedure, it is possible to check immediately for complications with US and also to assess if there is an abundant neoplastic remnant passible of an immediate second treatment. Moreover, clinical surveillance, laboratory tests and imaging studies (►**Fig. 1**) should be performed to monitor eventual complications.

Complications

Most of the complications due to local ablative techniques are the result of thermal injury in the structures surrounding the tumor. The correct positioning of the electrodes and the careful evaluation of a safe route to the lesion are essential to reduce the risk of a direct lesion due to the needle tip. Then, the other most important factor to reduce complication rate is the correct setting of RFA parameters.

The first clinical applications of pancreatic RFA was burdened by a high rate of morbidity (0–40%) and mortality (0–25%) [4,8,23,28–30] and a systematic review by Rombouts et al[31] that

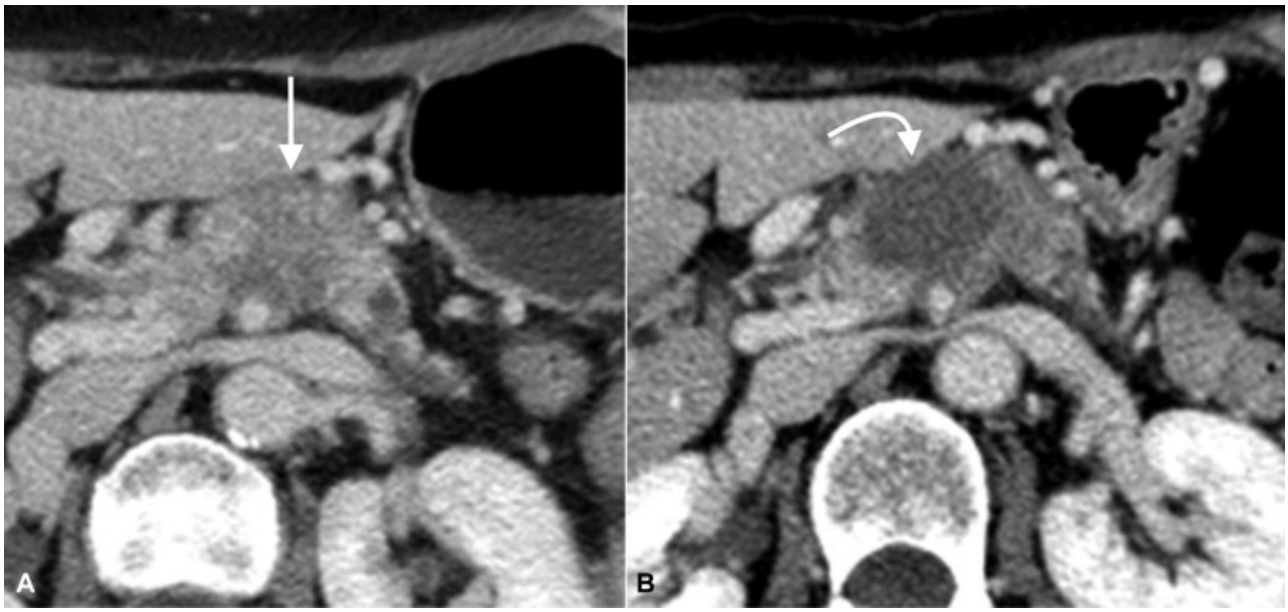

Fig. 1 Contrast enhanced computed tomography scan before (**A**) and after (**B**) the radiofrequency ablation (RFA) procedure. (**A**) Unresectable hypodense pancreatic mass in the venous phase (arrow). (**B**) After the RFA procedure a necrotic area appearing markedly hypodense in the venous phase is well visible within the pancreatic mass (curved arrow).

reported a RFA-related morbidity (range, 4–22%) and an RFA-related mortality (range, 0–11%). Nowadays, a recent application of percutaneous RFA for locally advanced pancreatic adenocarcinoma on 18 patients reported a 0% rate of morbidity and mortality.[22] The main complications that could be encountered are gastrointestinal hemorrhages and minor local bleedings, acute pancreatitis, pancreatic and biliary fistulas, duodenal injury and portal vein thrombosis.[32]

Radiofrequency Ablation of Pancreatic Adenocarcinoma

Pancreatic adenocarcinoma is one of the most aggressive cancers with a 5-year overall survival of approximately 5%.[33,34] It represents the most common malignancy of the pancreas and at the time of diagnosis only in the 20% of cases it is eligible for surgical intervention. The other 80% is represented by metastatic disease and by locally advanced pancreatic cancer (LAPC).[35]

Current management of LAPC is based on a multimodality approach comprehending chemotherapy and radiotherapy.[10] With the advent of new chemotherapeutic regimens (FOLFIRINOX and Gemcitabine/Abraxane), there is an increasing number of patients that will remain with stable LAPC disease for longer time.[17,36,37] In this kind of patients, a tailored approach enriched by a cytoreductive RFA treatment could be considered.

The application of pancreatic RFA is not comprehended in current guidelines because of the lack of a clinical randomized trial that confirms a survival benefits due to RFA.[10,38] Nowadays, this procedure is limited to nonmetastatic locally advanced pancreatic cancer.[6,22,25,39] Most of the literature is focused on the surgical and endoscopic approach, but, more recently, also the percutaneous mini-invasive approach has been validated.[22]

The effects obtained by this technique are several: a cytoreductive action with a decrease in CA 19.9 values,[4,25] a systemic effect due to the activation of the immune system,[14,15] and a pain relief.[4,28,30]

About the survival, many papers reported their experience. Cantore et al[21] reported a median overall survival (OS) of 25.6 months in a cohort treated with multitreatment modality including RFA alone or in conjunction with radiochemotherapy, and/or systemic chemotherapy, and/or intra-arterial chemotherapy combined with systemic chemotherapy. Frigerio et al reported an overall survival of 9 months,[40] while Girelli et al[39] and Paiella et al[6] reported an OS of 20 months and 19 months, respectively. As previously reported, we still lack randomized controlled trials confirming the additional value of local ablative therapies over systemic palliative chemotherapy alone.

Pancreatic adenocarcinoma is the most frequent pancreatic lesion treated with RFA. Many groups have reported application of this treatment to other types of lesions as described by Keane et al.[33] Carrafiello et al[11] treated a pancreatic metastasis from renal cell carcinoma with percutaneous RFA with fluoro-CT guidance in a patient that refused surgical intervention. The procedure was followed by minor complications (diffuse abdominal pain, slight increase of serum amylase and small peripancreatic fluid collection) and the 1 year follow-up showed no disease recurrence. Pai et al[18] treated with endoscopic-RFA eight patients, two with a neuroendocrine tumor and six with a cystic pancreatic lesion, with good safety results. Wu et al[41] treated a gastrinoma located in the pancreatic tail with multiple liver metastases; they performed a CT-guided transplenic RFA with radioactive 125-Iodine seed implantation, without major complications and reducing clinical symptoms, with no recurrence in 20 months of follow-up.

Conclusions

RFA of pancreatic tumors, in particular of pancreatic adenocarcinoma, could now be considered a safe and feasible technique. Mini-invasive approaches should be preferred and preferably performed in high volume centers for pancreatic pathology. The indication to perform this kind of treatment should always be evaluated and decided by a multidisciplinary team after all the validated therapies have been proposed. As this treatment represent a cytoreductive technique and not a curative one, we should always consider the possibility of further treatments following RFA and it is mandatory to apply the treatment modality in combination with all other palliative therapies. Among the ablative techniques, a consideration could be made as a matter of discussion, whether using RFA just to obtain a tumor debulking and cytoreduction or whether to use IRE that could ablate larger areas, thanks to the preservation of critical anatomical structures. RFA of pancreatic cancer, compared with other ablative methods, considering the single-needle insertion technique, remains easily applicable and available with low costs and complications.

Conflict of Interest
None declared.

References

1 Goldberg SN, Grassi CJ, Cardella JF, et al; Society of Interventional Radiology Technology Assessment Committee and the International Working Group on Image-guided Tumor Ablation. Image-guided tumor ablation: standardization of terminology and reporting criteria. J Vasc Interv Radiol 2009;20(7, Suppl):S377–S390
2 McWilliams JP, Lee EW, Yamamoto S, Loh CT, Kee ST. Image-guided tumor ablation: emerging technologies and future directions. Semin Intervent Radiol 2010;27(03):302–313
3 Goldberg SN, Mallery S, Gazelle GS, Brugge WR. EUS-guided radiofrequency ablation in the pancreas: results in a porcine model. Gastrointest Endosc 1999;50(03):392–401
4 Girelli R, Frigerio I, Salvia R, Barbi E, Tinazzi Martini P, Bassi C. Feasibility and safety of radiofrequency ablation for locally advanced pancreatic cancer. Br J Surg 2010;97(02):220–225
5 Giardino A, Girelli R, Frigerio I, et al. Triple approach strategy for patients with locally advanced pancreatic carcinoma. HPB (Oxford) 2013;15(08):623–627
6 Paiella S, Malleo G, Cataldo I, et al. Radiofrequency ablation for locally advanced pancreatic cancer: SMAD4 analysis segregates a responsive subgroup of patients. Langenbecks Arch Surg 2018; 403(02):213–220
7 Choi JH, Seo DW, Song TJ, et al. Endoscopic ultrasound-guided radiofrequency ablation for management of benign solid pancreatic tumors. Endoscopy 2018;50(11):1099–1104
8 Spiliotis JD, Datsis AC, Michalopoulos NV, et al. Radiofrequency ablation combined with palliative surgery may prolong survival of patients with advanced cancer of the pancreas. Langenbecks Arch Surg 2007;392(01):55–60
9 D'Onofrio M, Ciaravino V, De Robertis R, et al. Percutaneous ablation of pancreatic cancer. World J Gastroenterol 2016;22 (44):9661–9673
10 Tempero MA, Malafa MP, Al-Hawary M, et al. Pancreatic adenocarcinoma, version 2.2017, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 2017;15(08):1028–1061
11 Carrafiello G, Laganà D, Recaldini C, et al. Radiofrequency ablation of a pancreatic metastasis from renal cell carcinoma: case report. Surg Laparosc Endosc Percutan Tech 2008;18(01):64–66
12 Rossi S, Viera FT, Ghittoni G, et al. Radiofrequency ablation of pancreatic neuroendocrine tumors: a pilot study of feasibility, efficacy, and safety. Pancreas 2014;43(06):938–945
13 Kim YS, Rhim H, Lim HK, Choi D, Lee MW, Park MJ. Coagulation necrosis induced by radiofrequency ablation in the liver: histopathologic and radiologic review of usual to extremely rare changes. Radiographics 2011;31(02):377–390
14 Dromi SA, Walsh MP, Herby S, et al. Radiofrequency ablation induces antigen-presenting cell infiltration and amplification of weak tumor-induced immunity. Radiology 2009;251(01):58–66
15 Teng LS, Jin KT, Han N, Cao J. Radiofrequency ablation, heat shock protein 70 and potential anti-tumor immunity in hepatic and pancreatic cancers: a minireview. Hepatobiliary Pancreat Dis Int 2010;9(04):361–365
16 D'Onofrio M, Barbi E, Girelli R, et al. Radiofrequency ablation of locally advanced pancreatic adenocarcinoma: an overview. World J Gastroenterol 2010;16(28):3478–3483
17 Shah R, Ostapoff KT, Kuvshinoff B, Hochwald SN. Ablative therapies for locally advanced pancreatic cancer. Pancreas 2018;47(01):6–11
18 Pai M, Habib N, Senturk H, et al. Endoscopic ultrasound guided radiofrequency ablation, for pancreatic cystic neoplasms and neuroendocrine tumors. World J Gastrointest Surg 2015;7(04): 52–59
19 Arcidiacono PG, Carrara S, Reni M, et al. Feasibility and safety of EUS-guided cryothermal ablation in patients with locally advanced pancreatic cancer. Gastrointest Endosc 2012;76(06): 1142–1151
20 Pai M, Yang J, Zhang X, et al. PWE-055 endoscopic ultrasound guided radiofrequency ablation (EUS-RFA) for pancreatic ductal adenocarcinoma. Gut 2013;62(Suppl 1):A153
21 Cantore M, Girelli R, Mambrini A, et al. Combined modality treatment for patients with locally advanced pancreatic adenocarcinoma. Br J Surg 2012;99(08):1083–1088
22 D'Onofrio M, Crosara S, De Robertis R, et al. Percutaneous radiofrequency ablation of unresectable locally advanced pancreatic cancer: preliminary results. Technol Cancer Res Treat 2017;16 (03):285–294
23 Elias D, Baton O, Sideris L, Lasser P, Pocard M. Necrotizing pancreatitis after radiofrequency destruction of pancreatic tumours. Eur J Surg Oncol 2004;30(01):85–87
24 Ruarus A, Vroomen L, Puijk R, Scheffer H, Meijerink M. Locally advanced pancreatic cancer: a review of local ablative therapies. Cancers (Basel) 2018;10(01):E16
25 D'Onofrio M, Barbi E, Girelli R, et al. Variation of tumoral marker after radiofrequency ablation of pancreatic adenocarcinoma. J Gastrointest Oncol 2016;7(02):213–220
26 Lorentzen T. A cooled needle electrode for radiofrequency tissue ablation: thermodynamic aspects of improved performance compared with conventional needle design. Acad Radiol 1996;3(07): 556–563
27 McDermott S, Gervais DA. Radiofrequency ablation of liver tumors. Semin Intervent Radiol 2013;30(01):49–55
28 Wu Y, Tang Z, Fang H, et al. High operative risk of cool-tip radiofrequency ablation for unresectable pancreatic head cancer. J Surg Oncol 2006;94(05):392–395
29 Matsui Y, Nakagawa A, Kamiyama Y, Yamamoto K, Kubo N, Nakase Y. Selective thermocoagulation of unresectable pancreatic cancers by using radiofrequency capacitive heating. Pancreas 2000; 20(01):14–20
30 Hadjicostas P, Malakounides N, Varianos C, Kitiris E, Lerni F, Symeonides P. Radiofrequency ablation in pancreatic cancer. HPB (Oxford) 2006;8(01):61–64
31 Rombouts SJ, Vogel JA, van Santvoort HC, et al. Systematic review of innovative ablative therapies for the treatment of locally advanced pancreatic cancer. Br J Surg 2015;102(03):182–193

32 Paiella S, Salvia R, Ramera M, et al. Local ablative strategies for ductal pancreatic cancer (radiofrequency ablation, irreversible electroporation): a review. Gastroenterol Res Pract 2016; 2016:4508376
33 Keane MG, Bramis K, Pereira SP, Fusai GK. Systematic review of novel ablative methods in locally advanced pancreatic cancer. World J Gastroenterol 2014;20(09):2267–2278
34 Pandya GJ, Shelat VG. Radiofrequency ablation of pancreatic ductal adenocarcinoma: The past, the present and the future. World J Gastrointest Oncol 2015;7(02):6–11
35 Verslype C, Van Cutsem E, Dicato M, et al. The management of pancreatic cancer. Current expert opinion and recommendations derived from the 8th World Congress on gastrointestinal cancer, Barcelona, 2006. Ann Oncol 2007;18(Suppl 7):vii1–vii10
36 Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med 2013;369(18):1691–1703
37 Conroy T, Desseigne F, Ychou M, et al; Groupe Tumeurs Digestives of Unicancer; PRODIGE Intergroup. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011;364(19): 1817–1825
38 Takaori K, Bassi C, Biankin A, et al; IAP/EPC study group on the clinical managements of pancreatic cancer. International Association of Pancreatology (IAP)/European Pancreatic Club (EPC) consensus review of guidelines for the treatment of pancreatic cancer. Pancreatology 2016;16(01):14–27
39 Girelli R, Frigerio I, Giardino A, et al. Results of 100 pancreatic radiofrequency ablations in the context of a multimodal strategy for stage III ductal adenocarcinoma. Langenbecks Arch Surg 2013; 398(01):63–69
40 Frigerio I, Girelli R, Giardino A, Regi P, Salvia R, Bassi C. Short term chemotherapy followed by radiofrequency ablation in stage III pancreatic cancer: results from a single center. J Hepatobiliary Pancreat Sci 2013;20(06):574–577
41 Wu PH, Pan CC, Huang ZL, Li W, Zhao M, Zhou ZW. Percutaneous radiofrequency ablation approach through the spleen: initial case report for pancreatic tail gastrinoma. Chin J Cancer 2010;29(09): 836–841