Role of radio-ablative technique for optimizing the survival of patients with locally advanced pancreatic adenocarcinoma (Review)

IOANA IANCU[1,2*], ADRIAN BARTOȘ[1,3*], CRISTIAN LIVIU CIOLTEAN[1*], CAIUS BREAZU[1,4], CORNEL IANCU[1] and DANA BARTOȘ[1,2]

[1]Department of Surgery, Regional Institute of Gastroenterology and Hepatology, 400162 Cluj-Napoca; [2]Anatomy and Embryology Department, 'Iuliu Haţieganu' University of Medicine and Pharmacy, 400006 Cluj-Napoca; [3]Department of Surgery, 'Iuliu Haţieganu' University of Medicine and Pharmacy; [4]Department of Anesthesiology and Intensive Care, Regional Institute of Gastroenterology and Hepatology, 400162 Cluj-Napoca, Romania

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Abstract. Pancreatic ductal adenocarcinoma (PDAC) is one of the most common and frequently diagnosed malignant tumor of the pancreas with few treatment options and poor life expectancy. Despite the advances in the surgical field, 40% of the patients are diagnosed with locally advanced disease which is not suitable for surgery. Radio-frequency ablation (RFA) has been described as a new 'weapon' in the multimodal treatment of PDAC, representing a cytoreductive procedure which must be completed with radiotherapy or chemo-radiotherapy. A systematic research was carried out utilizing the PubMed database in regards to this subject, to evaluate the role of RFA in PDAC management. Abstracts, letters-to-the-editor and non-English language manuscripts were excluded. The literature showed that RFA can be used in open and laparoscopic surgery but it is also feasible for endoscopic ultrasound (EUS-guided RFA) or percutaneous approach. Even though we found optimistic and encouraging reports on overall survival (OS), randomized studies are still required to corroborate these findings. Our review research underline that surgical resection remains the only radical treatment option, RFA being a safe and feasible technique reserved for unresectable, non-metastatic pancreatic tumors. Its combination with oncological treatment can improve the OS of these patients.

Correspondence to: Dr Adrian Bartoș, Department of Surgery, Regional Institute of Gastroenterology and Hepatology, 19-21 Croitorilor Street, 400162 Cluj-Napoca, Romania
E-mail: bartos.adi@gmail.com

*Contributed equally

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Contents

1. Introduction: Rational for radiofrequency ablation of pancreatic tumors

To date, pancreatic ductal adenocarcinoma (PDAC) represents the most frequently diagnosed malignant tumor of the pancreas, with the worst prognosis (1). At the time of diagnosis, only 20% of PDAC cases are resectable due to their aggressive histopathological type and late diagnosis. The overall 5-year survival rate, depending on TNM stage is approximately 7-25% (2,3). Most of the patients are candidates for chemotherapy or chemoradiotherapy according to various protocols. Despite the advances in the imaging field, 40% of the patients are diagnosed intraoperatively with locally advanced disease, which is not suitable for radical surgery, even after neoadjuvant treatments (4-6). Median overall survival (OS) for patients who undergo surgery and adjuvant therapy is about 20-22 months. Patients with locally advanced disease (stage III) who are treated with chemo-radiotherapy exhibit an OS of approximately 9-13 months, while for patients with stage IV the median survival rate is approximately 2-6 months (7-9).

Locally advanced pancreatic carcinoma (LAPC) is characterized by invasion of the nearby vessels, without the

possibility of resection or reconstruction, in the absence of systemic disease (distant metastases) (10-12) (Table I).

Borderline resectability refers to the absence of distant metastases, involvement of superior mesenteric vein (SMV) or portal vein (PV), no encasement of nearby arteries, no extension to the celiac axis, encasement of the superior mesenteric artery (SMA) <180˚, local lymph node metastases (13-17) (Table I).

Unresectable LAPC refers to the absence of distant metastases, involvement of SMV or PV, unreconstructable vein occlusion, encasement of celiac artery >180˚, encasement of SMA >180˚, distant lymph node metastases (13,14,16,18) (Table I).

Radio-frequency ablation (RFA) has been described as a new 'weapon' in the multimodal treatment of PDAC, after successful treatment of hepatic, renal, brain and pulmonary tumors (19). RFA is a thermal ablative technique which generates local high temperatures leading to coagulative necrosis, apoptosis and protein denaturation (20-22). The direct effect of RFA is represented by the necrotic area which can be identified immediately after the procedure. At the peripheral cells, RFA may induce an alteration of the metabolic endocellular process that makes them sensitive to further treatments such as chemotherapy or chemoradiotherapy (20,23). In addition, RFA induces antitumor antibodies due to activation of proinflammatory cytokines, T, B and natural killer (NK) lymphocytes (23).

Surgical resection is the only radical treatment for resectable pancreatic cancer; RFA being indicated for unresectable, non-metastatic, locally advanced pancreatic tumors (24) (Table II). The presence of metastases is an exclusion criterion due to the fact that the disease exhibits systemic spread (25).

RFA induce focal hyperthermic injury to ablated cells, which affects the tumor microenvironment and damages cells at the membrane and subcellular levels. Mechanical cell damage that is generated by heat-induced necrosis releases various immunogenic intracellular substrates which lead to the activation of the immune system (26). Pro-inflammatory cytokines are released from the ablated tissue. Levels of serum interleukin-1β (IL-1β), IL-6, IL-8 and tumor necrosis factor-α (TNFα) have all been shown to be increased after RFA. Increasing the level of cytokines by RFA has been shown to have a key role in stimulating the antitumor immune response-'vaccine antitumoral' (26). Increased levels of tumor-specific T cells have been detected in post-RFA cancer patients and confer increased tumor-free survival in certain patients. There is information from the literature which indicate that RFA performed in a neoadjuvant setting could offer clinical benefits that might be superior to conventional neoadjuvant treatments (27). RFA performed as a neoadjuvant treatment can decrease the size of the tumor and increase the possibility of obtaining negative margins at the time of surgery (27). The main purpose for neoadjuvant treatment is to obtain downstaging but this only occurs in 15 to 30% of cases with chemotherapy followed by radiotherapy (3). There are some studies which show that RFA associated with chemoradiotherapy seems to have an important role in downstaging and could lead to radical surgery (3,5,28).

Regarding the value of the CA19-9 tumoral marker, it has been shown that the RFA of pancreatic tumors leads to reduction in the CA19-9 level. One previous study considered that the larger is the ablated area, the more important is the CA19-9 level reduction (29).

Local ablation techniques appear to be a future therapeutic option for patients with stage III pancreatic adenocarcinoma. RFA and irreversible electroporation (IRE) are actually the latest local ablation techniques used for patients with LAPC. Initial clinical trials on the use of these techniques have already shown encouraging results in terms of safety and feasibility (3,22).

To date, the indications for RFA of pancreatic tumors are: Stage III PDAC (3); patients no longer responding to standard system therapy, for local control and immune additive response; patients with stage IV pancreatic adenocarcinoma (with metastatic disease-only some studies, for local control of the disease) (30,31) (Table II).

According to recent studies, the ideal parameters for RFA are actually represented by 90˚ for 5 min, with a distance of 10 mm between the probe and the duodenum and portomesenteric axis (3). In addition, according to the proximity of the tumor with the vital surrounding structure, the ablation of the entire tumor is contraindicated: A peripheral 'security ring' of tissue is left in place, to avoid thermal injuries of the nearby structures. This 'security ring' can be later targeted by the use of chemo/radiotherapy (3,22).

According the proximity of the tumor to vital structures such as the upper mesenteric artery, upper mesenteric vein, duodenum, tumor ablation may be incomplete. Furthermore, tumoral tissue that cannot be subjected to RFA therapy is subject to radiotherapy (32).

The surgical approach to RFA for pancreatic tumors is performed under general anesthesia and involves access to the abdominal cavity by laparotomy (medial or bi-subcostal incision). The next step refers to the inspection of the peritoneal cavity, liver surface palpation for the detection of eventual metastases and liver/pancreas intra-operative ultrasound (31). Surgery continues with the Kocher maneuver. The pancreatic head must be fully mobilized from the inferior vena cava to the level where the left renal vein intersects the aorta, so the pancreatic head and the uncinate process may be throbbed between the left hand fingers. The purpose of this maneuver is to appreciate the relationship of the pancreatic head to the large vessels (eventual invasion). The entry into the omental bursa is performed by cutting the gastro-colic ligament. The pancreatic tumor is biopsied if there is no preoperative examination to confirm malignancy (extemporaneous exam). For ablation time, a RITA device is used as a (AngioDynamics) generator (33). The ablation needle is inserted into the tumor under the ultrasound guidance (33). The number of ablations must be done according to the size of the tumor and the relationships with the adjacent structures. The duration of the sessions will be 5 min and an ablation temperature of 90˚; the distance between the ablation needle, the duodenum and the portomesenteric axis will be at least 10 mm (3). During ablation, a naso-gastric catheter will be mounted and cold saline solution will be administered to prevent thermal injury to the stomach or duodenum (32,34). Drains are placed at the level of the omental bursa and Douglas space.

Even if the temperature of the ablation technique has been validated to be safe at 90˚, there are no general agreements on the most appropriate RFA parameters and standardization

Table I. Resectability criteria for LAPC.

Locally advanced pancreatic carcinoma		
Localized and resectable	Borderline resectable	Unresectable
Absence of distant metastases		
No radiologic evidence of SMV or PV distortion	Involvement of SMV or PV with reconstruction possible	Involvement of SMV or PV
	No encasement of nearby arteries Proximal and distally free vessel	Unreconstructable vein occlusion
Clear fat planes around celiac axis, hepatic artery and SMA	Gastroduodenal artery encasement. No extension to the celiac axis	Encasement of celiac axis >180°
-	Encasement of SMA <180°	Encasement of SMA >180°
-	Local lymph node metastases	Distant lymph node metastases

LAPC, locally advanced pancreatic carcinoma; SMV, superior mesenteric vein; PV, portal vein; SMA, superior mesenteric artery.

of the operative technique. Fegrachi *et al* recommended in a porcine experiment that the needle used for the RFA procedure must be at least 10 mm from the first part of the small bowel (duodenum) and portomesenteric vessels (35-37). It is also recommended that cold saline solutions must be administered through the naso-gastric tube to prevent the thermal injury of the duodenum (100 ml/min saline at 5˚) (35-37). By reducing the temperature, they registered lower complication rates. The temperature between 60˚ and 100˚ induced immediate coagulation of the tissue with irreversible damage to the inner structure of the cells, while using 100˚-110˚ induced tissue vaporization and carbonization (35-37).

The ablation procedure is in most of the cases associated with palliative surgery such as biliary or digestive bypass or both of them. Siriwardena recommended that no patients should undergo surgery only for ablation (21).

2. Methods

A systematic research was carried out in PubMed using the keywords 'radio-frequency ablation' or 'RFA' of 'pancreatic tumors' for papers published in English up to April 2019. All papers identified in our first search were reviewed to indicate those studies that were carried out on patients with unresectable pancreatic tumors undergoing ablation. We identified a number of 11 articles. Case reports were also included (Table III).

The primary endpoint was to investigate the safety and complications of these techniques, while the secondary endpoint included patient survival and quality of life in terms of the control of symptoms.

3. Results

In the present review, we analyzed 11 studies: 2 case reports, 5 retrospective studies and 4 prospective papers.

Complications which were reported to occur were related to the associated surgery or to the RFA procedure. RFA-related complications included: Severe acute pancreatitis, pancreatic fistula, duodenal perforation, and vascular damage (PV thrombosis, hemorrhage) (Table III). Complications related to palliative surgery referred to postoperative bleeding, biliary fistulas, digestive fistulas, and abdominal fluid collection. Adjustment of the RFA temperature (reducing from 105˚ to 90˚) was found to lead to a significant decrease in postoperative complications. Girelli *et al* reported in a recent study of 100 cases using RFA of the pancreas that the overall morbidity was approximately 26% with a 24% incidence of abdominal complications, but not all related to the RFA (Table III) (3). The first 25 patients had a complication rate of 40% due to the high temperature used (105˚), while the rest of the patients had a reduced complication rate due to the adjustment of the temperature (3). Girelli *et al* reported an OS at 1 year of 41% (3). Date *et al* reported in a porcine model that reducing the temperature from 105˚ to 90˚ and an ablation time of 5 min was safer and no mesenteric or portal thrombosis was recorded (38). Concerning the same idea, Girelli *et al* reported that when using the right temperature, the mortality rate was about 2% (22), while Wu *et al* reported that the mortality rate could rise to 25% due to postoperative bleeding (34). Wu *et al*

Table II. Indications for RFA of pancreatic tumors.

Main indications	Relative indications
Stage III ductal adenocarcinoma without distant metastasis-pancreatic head	Patients no longer responding to standard system therapy
Stage III ductal adenocarcinoma without distant metastasis-pancreatic body and tail	Patients with stage IV pancreatic adenocarcinoma-patients with metastatic disease (only some studies, for local control of the disease)
	Borderline tumors, before neoadjuvant treatment

RFA, radio-frequency ablation.

also reported a morbidity of 18.8% (34). Girelli *et al* reported a morbidity of 28%, while the mortality rate was 1.8% (3). From the literature reports we observed an OS of 14.7 months for patients which undergo only RFA, while the patients who benefit from RFA and them chemoradiotherapy have an OS of 25.6 months (3,6,33). Matsui *et al* considered that the method is relatively safe and is feasible to treat unresectable tumors without metastasis; the authors showed that the mortality rate was about 10% and the OS median was 3 months (Table III) (30).

In contast, Spiliotis *et al* reported their experience with zero mortality and an OS of 33 months (31). In addition, Frigerio *et al* reported in his paper 0% mortality and a median OS of 19 months (33).

Date and Siriwardena reported one case of unresectable pancreatic adenocarcinoma which was suitable for radiofrequency ablation with a survival of only 3 months after the procedure (39). Furthermore, Hadjicostas *et al* reported no complication after the procedure, but all of the patients died at 3 months after the procedure (40). In addition, Casadei *et al* reported that all of the patients developed complications after the procedure and the OS at 5 months was 0% (41). Figueroa-Barojas *et al* studied 20 patients and reported a median OS of 19 months (42). Varshney *et al* reported in their study 3 patients who were suitable for pancreatic ablation; one patient died at 1 month (Table III) (43).

4. Discussion

RFA of pancreatic tumors is not a radical procedure, being a cytoreductive treatment which must be completed with radiotherapy or chemo-radiotherapy.

As described above, RFA of the pancreas is a technique which can improve the survival of patients with unresectable LAPC. There are still discussions related to the role of neoadjuvant treatment for LAPC. Using systemic chemotherapy as an up-front treatment has been thought to benefit the survival rate due to the early dissemination risk of pancreatic carcinoma. For the chemotherapy of pancreatic carcinoma, gemcitabine and FOLFIRINOX combination have been used. Gemcitabine offers an OS of 9.2-11.7 months while patients who undergo FOLFIRINOX chemotherapy have an OS of 11.7 months (44). FOLFIRINOX treatment includes administration of leucovorin, 5-fluorouracil, irinotecan and oxaliplatin (45,46). Giardino *et al* reports a median OS of 25.6 months for patients who benefit from neoadjuvant treatment and RFA while patients who undergo RFA plus radiochemotherapy and intra-arterial chemotherapy have a median OS of about 34 months (24). From a report made by Fegrachi *et al*, we found a median survival of 25.6 months for these patients (36), while Matsui *et al* reported a median survival of only 5 months (30). For other authors, patients with advanced pancreatic carcinoma who benefit from RFA as an up-front treatment and then adjuvant chemotherapy have a poorer OS (24). On the other hand, there are some papers which report that using RFA as an up-front treatment could lead to the modulation of the immune system (20,27,47).

While the direct effect of RFA is clearly represented by the necrotic area immediately identifiable after the procedure, on the other hand, the indirect effects are on the viable zone adjacent to this area (transition or peripheral zone). The cells populating the peripheral zone are affected by RFA in terms of the alteration of metabolic endocellular processes that makes them quite sensitive to further cytolytic therapies, such as chemotherapy or chemoradiotherapy.

Even if an article written by Fegrachi *et al* states that the survival rate is 25.6 months for patients who undergo chemotherapy followed by RFA, there are some results which underlines that the rate of early progression (12.3 and 16%) and the survival rate (19 months) are the same with or without chemotherapy before the procedure (33,36). An increasing number of studies have been published regarding the role of thermal ablation for stimulating and modulating the immune system and the immune response against the tumor. Dromi *et al* demonstrated using laboratory animals an increase in the infiltration of dendritic cells, which are the most powerful antigen-presenting cells, following the ablation; subtotal RFA treatment results in systemic antitumor T cell immune responses and tumor regression (23).

Over the last decades, new approaches of using RFA for pancreatic tumors have been cited (48). RFA can be used in open surgery, laparoscopic surgery but also by endoscopic (EUS-guided RFA) (48) or percutaneous approach (49,50). There are previous studies which have shown that RFA is a safe and feasible technique for patients with unresectable pancreatic cancer, no matter the approach (51,52). Open approach is the most commonly used technique due to the anatomical location of the pancreas (53,54). By this approach, the main advantage is that the surgeon can be very accurate with the RFA technique, by exposing the anatomical landmarks. In the same idea, the intraoperative incidents (hemorrhage) can be easily controlled. The laparoscopic approach is a good alternative,

Table III. RFA for LAPC outcome and technique (temperature/length of RF).

Year	Authors (Refs.)	Study	N	Morbidity (%)	Mortality (%)	OS-median	Complication			Time (min)	Temperature (ºC)
							Pancreatic fistula (%)	Duodenal injury (%)	Acute pancreatitis		
2013	Giardino *et al* (24)	Retrospective	107	28%	2%	RFA: 14.7 months RFA+CRT: 25.6 months	6%	3%	3%	10	105°C for the first 25 patients, then 90°C
2013	Girelli *et al* (3)	Prospective	100	24%	3%	OS at 1 year: 41%	3%	1%	3%	NA	90°C
2007	Spiliotis *et al* (31)	Retrospective	16	16%	0%	33 months	NA	NA	NA	5	90°C
2013	Frigerio *et al* (33)	Prospective	57	14%	0%	19 months	2%	2%	NA	NA	NA
2006	Wu *et al* (34)	Retrospective	16	43%	25%	NA	19%	NA	NA	12	30°C
2000	Matsui *et al* (30)	Retrospective	9	22%	10%	3 months	NA	NA	NA	15	50°C
2005	Date and Siriwardena (39)	Case report	1	NA	NA	3 months	NA	NA	NA	10	90°C
2006	Hadjicostas *et al* (40)	Prospective	4	0%	0%	OS at 3 months: 0%	0%	0%	0%	2	NA
2010	Casadei *et al* (41)	Prospective	3	100%	NA	OS at 5 months: 0%	NA	NA	NA	5	90°C
2013	Figueroa-Barojas *et al* (42)	Retrospective	20	4%	0%	19 months	NA	NA	NA	NA	NA
2006	Varshney *et al* (43)	Case report	3	NA	1 patient died at 1 month	NA	NA	NA	NA	NA	NA

RFA, radio-frequency ablation; LAPC, locally advanced pancreatic carcinoma; OS, overall survival; CRT, chemoradiation therapy; NA, not assessed.

with the advantages of minimally invasive approach, together with the safety of surgical maneuvers.

EUS-guided RFA. EUS-guided RFA is a minimally invasive technique, with a success rate of 100% in human studies, being a good alternative to surgery (55,56). The pancreas can be accessed endoscopically via transgastric or transduodenal approach (48,57). In a paper by Pai *et al* we found that they reported that the technique is safe and well tolerated by patients and also has an important role in decreasing the tumor size and CA19-9 levels (58). Pai *et al* described abdominal pain in 25 to 33% of the patients, but with no major complication reported in human studies (58).

Percutaneous RFA. Percutaneous RFA is limited by the anatomical topography, quality of imaging guidance and access to the tumor. This is a minimally invasive technique which permits the treatment of patients with important comorbidities and with contraindication for general anesthesia (50,59). There are some recent studies which report no deaths related to this procedure (51). Regarding complications, Rossi *et al* described diffuse abdominal pain, pancreatitis associated with thermal injury and peripancreatic collection, but no major complications (53). Rossi *et al* sustained that only doctors with substantial experience in interventional US-guided procedures must perform the percutaneous approach due to the proximity of the pancreas with the celiac trunk, superior mesenteric vein, PV and duodenum (53). Carrafiello *et al* reported that this is a safe and feasible technique for tumors located in the body-tail of the pancreas (49,60).

5. Perspectives

In addition to RFA, there are new techniques which have been developed to optimize the management of locally advanced pancreatic tumors: Microwave ablation, cryoablation, high intensity focused ultrasound (HIFU) and IRE.

Microwave ablation. Microwave ablation is a technique which induces tissue heating in the area of interest. The main difference between microwave ablation and RFA refers to the frequency range of the electromagnetic waves which leads to a better ablation volume. This procedure is associated with fewer complications than RFA and it takes a shorter operative time (49,54).

Cryoablation. Cryoablation is a procedure which freezes tumoral tissue leading to necrosis of the tumor. Complication rates range from 0 to 40%, the most important being severe bleeding and pancreatitis. The mortality rate of this procedure is low. Li *et al* reported that cryoablation of pancreatic tumors associated with bypass surgery can improve the quality of life in these patients (61).

High intensity focused ultrasound (HIFU). High intensity focused ultrasound (HIFU) leads to thermal tissue damage due to the boiling bubbles which disrupt the tissue mechanically. This technique needs to be guided by high resolution imaging techniques such as MRI. It is a safe, effective and feasible technique for patients with LAPC. The median survival of patients which benefits from HIFU ranges from 10 to 12.6 months according to some studies. Also, there are no complications reported (62-65).

IRE. IRE is a non-thermal ablation procedure which was developed in the last few years for the treatment of LAPC. This procedure induces cell death due to the delivery of short high-voltage electric current fields. Complications are reported in about 13% of patients, while the IRE-related mortality is 2%. The main complications appear to be duodenal perforation, bile leakage and pancreatic fistula (66). Martin *et al* reported in a study that IRE prolonged OS by 9 months (67).

6. Conclusions

Although surgical resection remains the only radical treatment for LAPC, palliative management has been improved in the last few decades. RFA is a safe and feasible technique which can be performed by open, laparoscopic, endoscopic or by percutaneous approach and can be associated with low complications rates if a standardized technique is used. Most important is that in combination with chemotherapy and chemoradiotherapy, RFA leads to prolonged OS of LAPC patients. However, RFA together with the new ablative procedures mentioned above must be re-evaluated by a prospective multicentric approach and a protocol of selection and conduit must be standardized.

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Authors' contributions

II, AB, and DB designed and performed the review. II, AB and CLC wrote the paper. CI and CB reviewed the literature and revised the manuscript accordingly. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declared no potential competing interests with respect to the research, authorship, and/or publication of this article.

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