

Radiofrequency Ablation of Pancreatic Ductal Adenocarcinoma: An Evolving Comrade?

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Abstract

Background: Pancreatic ductal adenocarcinoma (PDAC) presents a challenge for the surgeon due to its aggressiveness and to the stagnation of the management options in cases where complete resection is not feasible. Radiofrequency ablation (RFA) in PDAC is described by a few studies as a promising technique. **Methods:** We present our 12 years' experience in locally advanced unresectable PDAC with a series of 19 patients. The mean age was 66.8 years. The mean tumour diameter was 8.1 cm. In all patients, RFA was performed during laparotomy using Cooltip®, in some withIOUS monitoring, followed by palliative bypass procedures. **Results:** The postoperative period was relatively uneventful. A repeat CT showed remarkable changes in the size and morphology of the tumour. We observed significant improvement in pain relief. The mean survival with the RFA was 19.3 months (6 - 30 months). **Conclusions:** Our series suggest that RFA for locally advanced and unresectable PDAC in carefully selected patients (excluding multifocal disease) presents a promising, effective and safe associate for the surgeon. RFA plays a complimentary role to current standard palliative therapy, which may prolong survival and improve quality of life. Whether the laparoscopic approach or other non-invasive methods are feasible, will be a challenge for the following years.

Keywords

Pancreatic Cancer, Radiofrequency Ablation, Locally Advanced, Surgery

1. Introduction

Pancreatic cancer presents a challenge for the clinicians, since the early stages of the disease are relatively symptom-free and therefore usually diagnosed when advanced and non-resectable. This puts pancreatic cancer in the leading 5 most lethal cancers in Europe with more than 104,000 deaths in 2012 (6% of total) and the 7th most common

cause of cancer death worldwide, with more than 330,000 deaths in 2012 (4% of total) [1] [2]. Survival for pancreatic cancer is thus unfortunate, only approximately 20% surviving one year after diagnosis, with 5-year and 10-year survival rates falling to 3% and 1% respectively [3].

Since diagnosed at advanced stage, only the minority of these patients, approximately 20%, will benefit from radical resection [4]. Another 20% of the patients will have locally advanced but unresectable disease [5] [6] [7]. Despite the advancements in therapeutic means, the outcome remains poor. Several palliative techniques have been employed throughout the years in an attempt to control and regress the growth of the tumour, locally control it, relieve its bothersome symptoms, with the ultimate goal of long-term survival. These include palliative chemo-radiation, intraoperative electron beam irradiation/IORT, interstitial or intraluminal brachytherapy [8]-[13].

RFA as a local thermal ablative “debulking” therapy had been used with very good results for the treatment of unresectable hepatic, renal, pulmonary, prostatic, brain and breast cancers [14]. The local destruction of the RFA in these solid tumours deemed an easy and relatively non-demanding approach. When it comes to the “softer” more friable pancreatic tissue, and also due to the close proximity of large vessels and the duodenum that can potentially be lethally damaged, the RFA technique for locally advanced unresectable PDAC becomes more complicated and risky. Therefore, only a few have attempted this palliative technique.

This article presents the experience of a single surgeon over a 12 years period in the treatment of these patients with RFA and our recommendations on the technique.

2. Patients and Methods

This article aims to describe our experience with RFA in locally advanced unresectable PDAC from May 2004 till today. All procedures were performed by the same surgeon. During these 12 years we treated 19 patients with intraoperative RFA using Cooltip®. The male to female ratio was 2.8:1 (14 males and 5 females), aged 45 - 80 years (mean = 66.8). They presented to our departments with various symptoms including anorexia, weight loss, fatigue, pruritus, back pain and in most of the cases painless obstructive jaundice. During workup with abdominal US scan and three-phases CT scan with intravenous contrast revealed suspicious lesion on the pancreas. The size (5 - 15 cm; mean = 8.1 cm) and location of the lesion (head of pancreas:body/tail 17:2) varied. The criteria used to define these lesions as locally advanced unresectable tumours of the pancreas included the absence of distant metastases but the encasement or adherence of adjacent large vessels such as the portal vein and the superior mesenteric vein and artery. In some patients the histologic diagnosis of PDAC was obtained by percutaneous CT guided biopsy, others by biopsy obtained during ERCP and others by endoscopic US and biopsy.

The patients were all informed about the incapability of complete surgical resection and offered the option of palliative surgery and intraoperative RFA. All patients underwent an explorative laparotomy, Kocher mobilisation of the duodenum and the

head of the pancreas and RFA was performed under direct vision of the tumour. We used the latest Cooltip® RFAblation (Radionics) system. The cooltip electrode was a 17-gauge, 15 cm with 3 cm length for rapid tumour destruction (**Figure 1 & Figure 2**). Simultaneous infusion/perfusion with cold normal saline of the areas surrounding tissues was done during the ablation to further avoid burn damage. The duodenum was in direct vision, however, the large vessels were not directly seen during the initial cases, but in the last 8 patients we performed intraoperative US (IOUS) in the attempt to definitely avoid ablating anywhere near these vessels (**Figure 3**), a technique that is advisable. The RFA in all these patients was done for duration of 2 - 5 minutes and in 2 - 3 different sites in the tumour (overlapping technique) at a temperature of 60 - 70 degrees Celsius.

In all the patients the RFA was followed by palliative bypass procedures (loop or Roux-en-Y cholecystojejunostomy/choledochojejunostomy and Braun-type side-to-side enteroenterotomy and/or gastrojejunostomy, according to the individual case) (**Figure 4**).

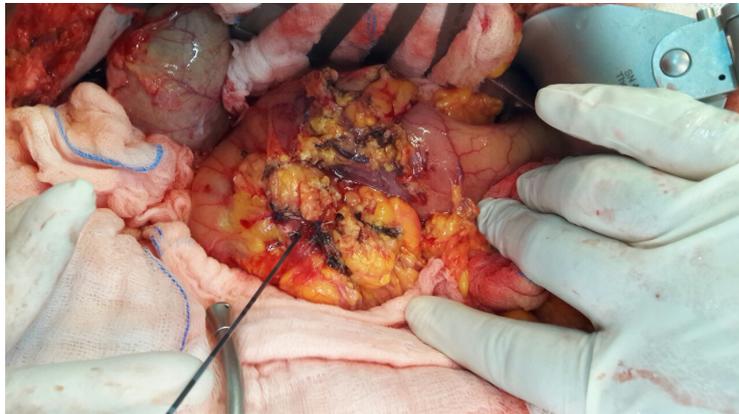


Figure 1. RFA of tumor of the head of pancreas.

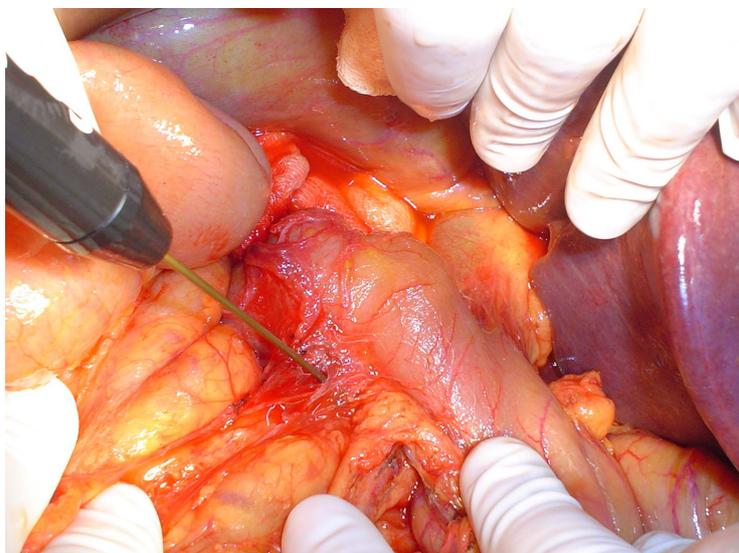


Figure 2. Kocher mobilization and RFA of tumor of the head of pancreas.

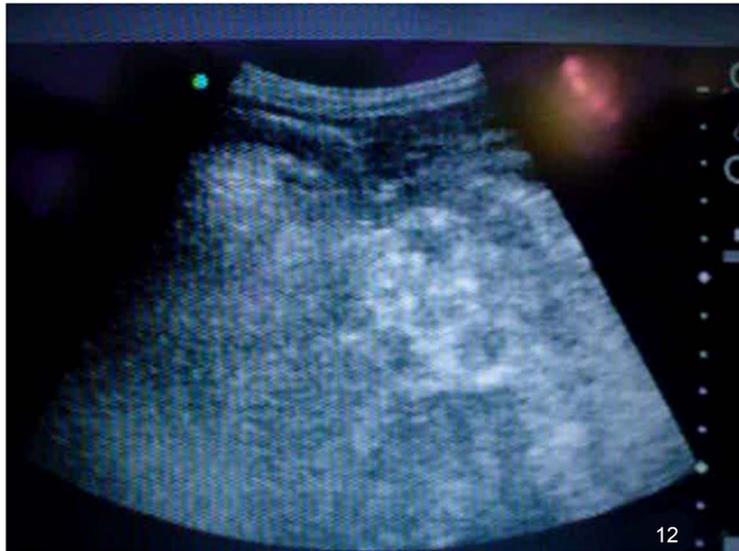


Figure 3. The use of IOUS during RFA.



Figure 4. Palliative cholecystojejunostomy bypass procedure.

These palliative bypass procedures were done for the obvious two reasons of biliary or duodenal obstruction but also as a precaution measure in case of duodenal thermal damage because of the RFA. A drainage tube was placed by the ablated area. The post-operative serum and peritoneal fluid amylase was measured for 5 days. Furthermore, the patients were administered prophylactically subcutaneous octreotide (Sandostatin) for 3 - 5 days.

3. Results

The technique for RFA was time and cost efficient and deemed no procedural difficulties. All of our patients had an uneventful and uncomplicated postoperative period. None of the patients was complicated with pancreatitis; however, 3 of them had asymptomatic hyperamylasaemia which resolved spontaneously. A repeat abdominal CT scan with intravenous contrast was performed in all patients one month and six months after the operation, which showed remarkable changes in the morphology of the tumour in almost of the patients (in one month), and also in the size of the tumour (in 6 months) (**Figure 5 & Figure 6**). The intention to control and regress the growth of the tumour and locally control extending was achieved. In one patient the tumour was undetectable in a repeat CT scan 6 months later. We also observed significant improvement in pain relief especially in the two cases where the tumour was found at the body of pancreas. The ultimate goal of longer-term survival was also attained. The mean survival of our patients post the RFA was 19.3 months (6 - 30 months).

4. Discussion

Pancreatic cancer is one of the most lethal neoplasms acquired by mankind. Due to its natural history and aggressiveness, it has a dismal prognosis at diagnosis. About 40% of pancreatic cancers are unresectable at diagnosis, condemning the patient to certain



Figure 5. Tumour of the head of the pancreas before RFA.



Figure 6. Changes in the morphology of the tumour one month after the RFA.

death within only a few months [15]. While oncologists still have no magical answers, the surgeons may offer ‘solutions’ with a new tool in their toolbox, RFA.

RFA as a novel local therapy has shown encouraging results in terms of safety and feasibility and has been shown to improve survival, reduce morbidity and improve Quality of Life (QoL) in these patients where diagnosis of pancreatic cancer was late. This technique therefore can be used for PDAC that is locally advanced (stage III) [16]-[21], even though it has also been shown to have positive results in selected patients with systemic involvement (stage IV) [22] [23] [24] but also importantly in patients who cannot tolerate a major pancreatic resection. Patient selection is very important before applying RFA and topics that need to be considered include patient comorbidities, QoL expected after the RFA, patient preferences and response to neo-adjuvant medical oncological treatment if any. Tumour size is not a contraindication [15], however, these tumours require more extensive ablation (Figure 7 & Figure 8).

RFA as a local thermal technique aims to ultimately destroy the tumour at a cellular level inducing coagulative necrosis and protein denaturation, acting as a “salvage” local cytoreductive therapy. RFA can be done during laparotomy (our preferred method), percutaneously (76% of our liver RFA series) or more recently endoscopically. The technique proposed by us is with the use of Cooltip© RF Ablation (Radionics) system, 17-gauge, 15 cm with 3 cm length electrode for rapid tumour destruction and simultaneous infusion/perfusion with cold normal saline of the surrounding tissues during the ablation in order to avoid burn damage, during laparotomy. The duration of the ablation ranges from 2 - 5 minutes in 2 - 3 different sites in the tumour at a temperature of 60 - 70 degrees Celsius. We advise an IOUS during the procedure in order to avoid ablating 5 - 10 mm near the portomesenteric vessels and the duodenum. Some authors also advise cooling the duodenum during the procedure with cold normal saline through a nasogastric tube in order to avoid thermal damage, a procedure that we did

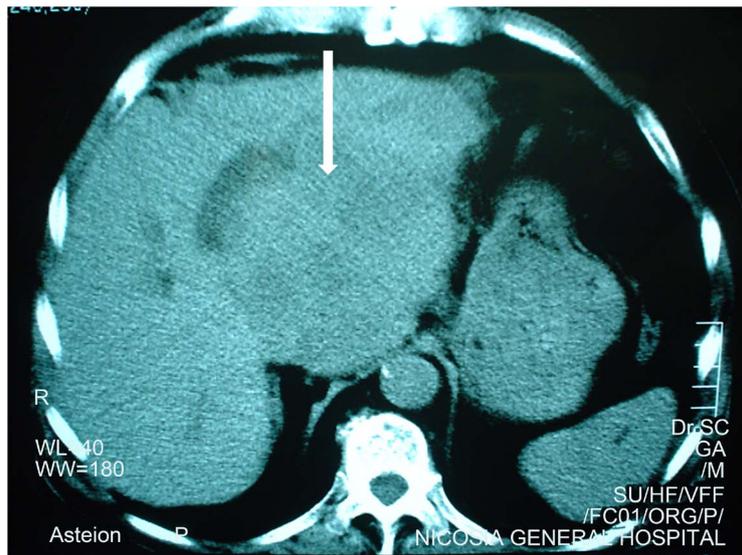


Figure 7. A huge pancreatic tumour before RFA.

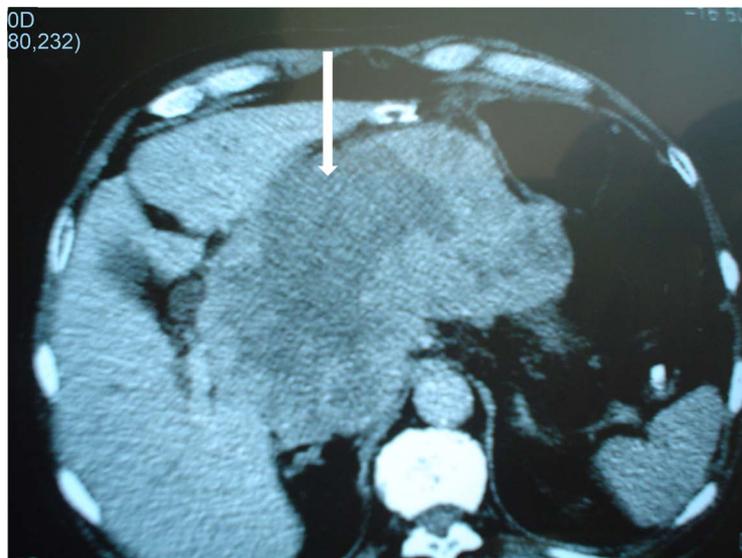


Figure 8. Changes in the morphology of the tumour one month post RFA.

not follow since we performed extensive and direct simultaneous cooling of the surrounding ablated area during the procedure with cold normal saline. Apart from thermal damage and injury to the duodenum and the portomesenteric vessels, other complications reported include gastrointestinal haemorrhages, minor local bleeding, acute pancreatitis (mild or severe), asymptomatic hyperamylasaemia and pancreatic and biliary fistulas. Since the RFA approach in these patients has a palliative intention, we completing the operation with palliative biliary and enteric bypass procedures such as cholecystojejunostomy and gastrojejunostomy are considered obligatory by us. Bearing this in mind then, the internal cooling of the common bile duct, as suggested by some authors is futile. We further suggest the use of subcutaneous octreotide (Sandostatin)

prophylactically and also the monitoring of the serum and peritoneal amylase level postoperatively.

RFA has also been shown to act as an 'endogenous vaccine' against the neoplastic effects. This interesting observation of the RFA's strong positive anti-tumoral effect on the immune system has been described extensively by Chu and Dupuy [25]. Several authors proved the direct effect that RFA has on adjacent tissues causing an alteration of metabolic endocellular processes which makes them more sensitive to adjuvant cytolytic therapies such as chemo-radiotherapy. Furthermore, several studies demonstrated how RFA can boost the systemic immune response against the tumour by releasing proinflammatory cytokines [26] [27] [28], lymphocytes (T-, B-, and NK-types) [29] [30] [31] [32], and antibodies [33] that are responsible for acquired anti-tumoral antigen-specific immunity [34] [35] with ultimate goal the improved survival in the patients.

The use of RFA in locally advanced PDAC, even though not proven by large randomised controlled studies, has been shown to have very encouraging oncological outcomes. Spiliotis *et al.* compared RFA only with systemic treatment only in stage III PDAC and showed excellent results with RFA only with an increase in mean survival to the amazing of 30 months compared to only 13 months in patients receiving only systemic treatment ($p = 0.0048$) [18]. Furthermore, a previous article by the author P. Hadjicostas *et al.* observed a significant effect in pain relief in these patients, which played an important role in the palliative approach of the procedure [19]. Also, Giardino *et al.* suggested the so called "triple approach strategy" where RFA is also combined with systemic chemo-radiotherapy and intra-arterial chemotherapy, with even better results and overall survival reaching 34 months [36].

In the current study we incorporated the use of RFA during laparotomy combined with palliative bilioenteric and enteroenteric bypass procedures which yielded promising results in terms of tumour reduction, pain relief and overall survival. We suggest the use of the Cooltip® RFAblation (Radionics) system intraoperatively (under direct vision) with the use of IOUS and local cooling with cold normal saline of the surrounding tissues in order to minimise the risk of direct thermal damage to the portomesenteric vessels, the extrahepatic biliary system or the duodenum.

5. Conclusion

In the hostile situation of pancreatic cancer that is unfortunately locally advanced and therefore unresectable, there is growing evidence that RFA can be a comrade for the surgeon. Our series suggest that the use of RFA for locally advanced and unresectable PDAC in carefully selected patients (excluding multifocal disease) presents a promising, effective and safe associate for the surgeon. Given the fact that is applicable to these high risk patients with relatively low cost, morbidity and time, its proven anti-tumoral effect, we believe that RFA can be used with confidence as part of the multimodal treatment of locally advanced PDAC. RFA can play a complimentary role to current standard palliative therapy, which may prolong survival and improve quality of life.

Whether the laparoscopic approach for ablation or other non-invasive ablative methods are feasible, will be a challenge for the following years.

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