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World Journal of Gastrointestinal Oncology (*World J Gastrointest Oncol*, *WJGO*, online ISSN 1948-5204, DOI: 10.4251) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJGO covers topics concerning carcinogenesis, tumorigenesis, metastasis, diagnosis, prevention, prognosis, clinical manifestations, nutritional support, molecular mechanisms, and therapy of benign and malignant tumors of the digestive tract. The current columns of *WJGO* include editorial, frontier, diagnostic advances, therapeutics advances, field of vision, mini-reviews, review, topic highlight, medical ethics, original articles, case report, clinical case conference (Clinicopathological conference), and autobiography. Priority publication will be given to articles concerning diagnosis and treatment of gastrointestinal oncology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

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MINIREVIEWS

Radiofrequency ablation of pancreatic ductal adenocarcinoma: The past, the present and the future

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Abstract

Pancreatic ductal adenocarcinoma (PDAC) is one of the most aggressive cancers with a grim overall 5-year survival rate of 5%. Advances in surgical techniques, critical care, molecular diagnosis, diagnostic imaging, endosonology and adjuvant therapy have improved outcomes; but still more needs to be achieved. There is an urgent need to discover new avenues that may impact survival. Radiofrequency ablation (RFA) has attracted attention as an adjunctive treatment in PDAC. A review of English literature in PubMed was done using the MESH terms for PDAC and RFA. All the articles were reviewed and core information was tabulated for reference. After a comprehensive review of all articles the data was evaluated to discover the role of RFA in PDAC management. Indications, contraindications, feasibility, success rate, safety, complications and impact on survival were reviewed and are discussed further. RFA appears to be an attractive option for non-metastatic locally advanced PDAC. RFA is feasible but has a significant morbidity. At the present time the integration of RFA into the management of pancreatic ductal adenocarcinoma is evolving. It should be considered as having a complimentary role to current standard therapy in the multimodal management care model. It is likely that indications and patient selection for pancreatic RFA will expand.

Key words: Pancreatic cancer; Radiofrequency ablation

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Core tip: Radiofrequency ablation of pancreatic cancer is rapidly emerging as an attractive adjunct in locally advanced inoperable disease and is a part of modern multimodal hepatobiliary teams. Due to technological advances, refinements in thermokinetic principles and ongoing advances in medicinal oncology; it is likely that the role of radiofrequency in management of pancreatic cancer is going to increase in future. In this article we summarize the current evidence of application of radiofrequency ablation in pancreatic cancer.

Pandya GJ, Shelat VG. Radiofrequency ablation of pancreatic ductal adenocarcinoma: The past, the present and the future. *World J Gastrointest Oncol* 2015; 7(2): 6-11 Available from: URL: http://www.wjgnet.com/1948-5204/full/v7/i2/6.htm DOI: http://dx.doi.org/10.4251/wjgo.v7.i2.6

INTRODUCTION

Pancreatic ductal adenocarcinoma is the commonest form of pancreatic cancer and is characterized by delayed diagnosis, aggressive tumour biology and dismal survival. At presentation, only 10% of the tumours are potentially curable[1]. Currently, surgery is the only curative treatment which provides long-term survival benefit for patients with pancreatic cancer[2,3]. The median survival of untreated patients is 3-4 mo and less than 5% of patients are alive one year after diagnosis[4]. The 5 years survival rate after a combination of resection and adjuvant therapy does not exceed 30%. Patients with locally advanced and inoperable disease have limited options[5]. Stagnation in surgical and oncological advances has challenged the medical community to explore alternative avenues. While molecular and genetic advances may have a future impact, thermal ablative techniques are increasingly being explored since last decade.

RADIOFREQUENCY ABLATION OF PANCREAS

Principles

Radiofrequency ablation (RFA) is the commonest thermal ablative technique used to treat solid abdominal organ tumours. Apart from the thermal destructive effect of RFA, secondary anticancer immunity due to activation of tumour-specific T lymphocytes appears to play a role[6]. Increasing evidence suggests that RFA might stimulate anti-tumour immunity through an alternative pathway by inducing expression of heat shock protein 70[7].

The past

First animal application of pancreas RFA was done in 1999[8]. However, due to retroperitoneal location, distal bile duct traversing head of pancreas, proximity to major vascular structures and close relation to duodenum and stomach were the major hurdles which curtailed the widespread acceptance of RFA. The increased risk of thermal injury during RFA of pancreatic ductal adenocarcinoma also relates to its diffuse nature and vessel encasement[9]. Earlier reports of RFA of pancreatic adenocarcinoma quoted severe complications with unacceptable mortality[10]. Some serious complications of RFA of pancreas include gastro-intestinal haemorrhage, pancreatic fistula, biliary leak, portal vein thrombosis, pancreatic pseudocyst and sepsis[11,12].

The present

Thermokinetic principles: It was the systematic efforts of Manchester group that helped define and validate the thermokinetic principles[13]. Although the ideal temperature for optimal thermal ablation of the pancreatic adenocarcinoma has been validated in experimental model there is still lack of consensus on the optimal RFA parameters and standardization of operative technique[13]. In a porcine experiment, Fegrachi *et al*[14] has recommended a probe distance of 10 mm from duodenum and portomesenteric vessels along with continuous duodenal cooling with 100 mL/min saline at 5 ℃[14]. Using these settings in six animals, they did not encounter major morbidity and there was no mortality at two weeks. The same group has also demonstrated that duodenal cooling does not affect the ablation efficacy[15]. Performing concomitant biliary and gastric bypass procedures can reduce some complications[9]. RFA of the distal pancreas cancer may be performed without duodenal cooling as the bile duct and duodenum are some distance away. Figure 1 shows general principles underlying the application of RFA in pancreatic lesions.

Technical approaches: The pancreas can be accessed directly by an open laparotomy, endoscopically *via* transgastric or transduodenal approach and percutaneously by a posterior retroperitoneal approach. Endoscopic ultrasound guided RFA (EUS-RFA) appears attractive as it avoids surgery. In a study involving ten adult mini pigs, Kim *et al*[16] has demonstrated safety, feasibility and efficacy for pancreatic body and tail EUS-RFA. In a study involving five Yucatan pigs, Gaidhane *et al*[17] have demonstrated that EUS-RFA of pancreatic head was well tolerated with minimal pancreatitis. Pai *et al*[18] has reported EUS-RFA on eight patients with pancreatic cystic or neuroendocrine tumours with good results and acceptable safety profile. At the 2010 annual conference of International Hepatopancreaticobiliary Association, we presented a report of percutaneous RFA in a patient with local recurrence following a Whipple's operation for a lower bile duct cholangiocarcinoma[19]. We performed duodenal cooling *via* a nasogastric tube and splenomesenteric occlusion to reduce heat sink effect. This patient survived for nine months after RFA.

Multimodal cancer care: RFA is increasingly recognized as an attractive adjunct treatment modality in reducing tumour burden and compliments other adjuvant therapies with potential for improved palliation. Although the effectiveness of RFA have been estimated by reductions in carbohydrate antigen 19-9, improvement of abdominal/back pain and/or non-progression of tumour on repeat interval imaging, such end points are surrogate measurements only. The desired endpoint is ultimately improvement in survival. RFA has shown to improve survival in patients with locally advanced inoperable pancreatic cancer[20,21]. Concomitant octreotide, antiproteases and chemotherapy (systemic or transarterial liver directed) or local

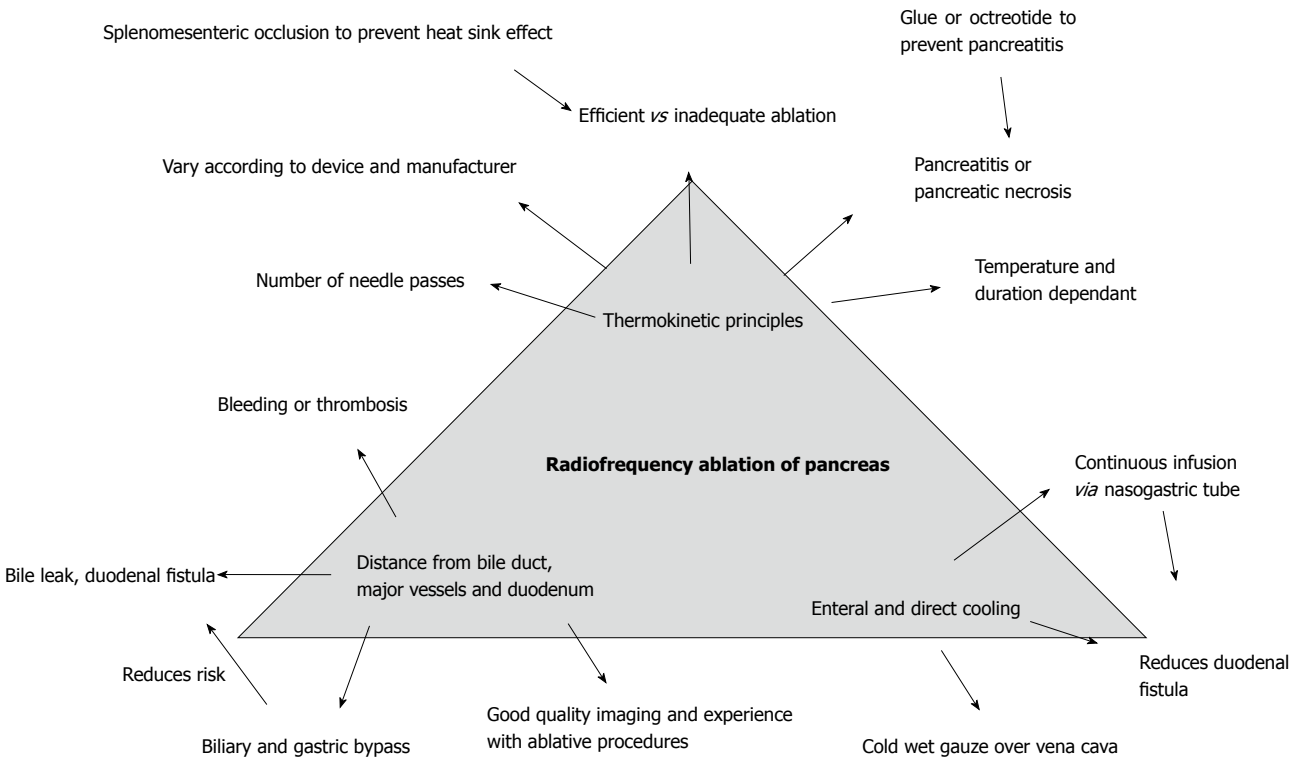

Figure 1 Principles of pancreatic radiofrequency ablation.

Table 1 Case series on radiofrequency ablation of pancreatic ductal adenocarcinoma-themokinetic principles

Ref.	*n*	Age (yr)	Tumour size (cm)	Thermokinetics
Matsui *et al*[24]	20	59	5.3	15 min at 50 ℃ in 2 × 2 × 2 cc field
Date *et al*[25]	1	58	3	RITA probe, 90 ℃ for 10 min each
Hadjicostas *et al*[26]	4	70	8.5 (3-12)	Cooltip© RFA for shorter duration of 2-8 min with 17-gauge electrode
Varshney *et al*[27]	3	58	6.5	4200 W of energy was delivered using a saline perfused needle with the aim of producing a 3 cm diameter necrosis
Wu *et al*[28]	16	67	5[1]	Cooltip© RFA probe with up to 200 W energy, 12 min and tip temperature < 30 ℃. A 5 mm safe distance between probe and major vessel
Spiliotis *et al*[20]	12	67	3.5	Cooltip© 17-gauge RFA electrode which achieved 80-90 ℃. Cooltip© at < 10 min each
Casadei *et al*[29]	3	66	4.7	Cooltip© ablation at 90 ℃ for 5 min each
Girelli *et al*[11]	50	65	4	RITA system was used. Initial temperature of 105 ℃ (first 25 patients) was reduced to 90 ℃ after interim review
Zou[3] *et al*[30]	32	68	4-12[2]	17 gauge electrode at 100-150 W energy with tip temperature of 90-100 ℃ for 12 min each After RFA, ^{125}Iodine seed was implanted
Ikuta *et al*[31]	1	60	4	Cooltip© 17-gauge RFA electrode for 3-4 min each and a temperature of 99 ℃

[1]82% tumors were > 5 cm; [2]Mean/median size not mentioned; [3]Simultaneous ^{125}I seed implantation. RFA: Radiofrequency ablation.

application of radioactive seeds could also modify the clinical response. It is evident from the current reports that RFA should not be done in an obviously resectable pancreatic cancer or a metastatic disease. While RFA of pancreas cancer may not be worthwhile in this clinical context, RFA of liver metastases from pancreatic cancer have been attempted in the setting of multimodal approach. Park *et al*[22] have reported a retrospective review of RFA ablation for liver metastases from pancreatic ductal adenocarcinoma. They performed RFA on 34 patients over a period of seven years including patients with less than six liver lesions and size ≤ 3 cm and excluding patients with extrahepatic metastatic disease. Median survival time was 14 mo. Patients with oligometastatic disease showed improved survival after RFA compared to patients without liver metastases and no treatment. Huang *et al*[23] reported a median survival of 11 mo with transarterial chemoembolization plus RFA and/or ^{125}I radioactive seed implantation on unresectable pancreatic cancer in a series of 71 patients. In this study the one-year survival was 32.4% for all patients and 25.5% for patients with liver metastases. Multiple case series of RFA application have been published and they generally testify its safety and feasibility. Table 1 provides details of

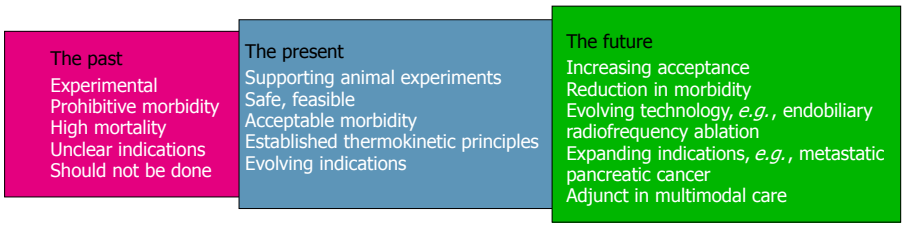

Figure 2 The past, the present and the future of pancreatic radiofrequency ablation.

Table 2 Case series on radiofrequency ablation of pancreatic ductal adenocarcinoma-outcomes and comments

Ref.	Survival	Morbidity and mortality	Comments
Matsui *et al*[24]	3 mo (median)	Morbidity (10%)-septic shock and gastrointestinal bleeding Mortality (5%)-patient with septic shock	All patients had a laparotomy
Date *et al*[25]	3 mo (overall)	Patient developed polyuria. No major complication	Single patient
Hadjicostas *et al*[26]	7 mo (median)	No major complications occurred	Sandostatin was administered prophylactically. Palliative bypass procedures were performed. One patient had significant pain relief
Varshney *et al*[27]	7 mo (mean)	Self-limiting complications occurred in two patients	One patient had percutaneous CT guided RFA. All patients had endobiliary stenting All patients received 7 d of antibiotics
Later this group has updated their results in 10 patients with 10% morbidity and no mortality. Eight patients received post RFA chemotherapy. One patient developed a 2 cm pseudocyst. Overall survival range was 9-36 mo[32]			
Wu *et al*[28]	Not reported	Pancreatic fistula 18.8% (3/16). Overall morbidity 43%. Mortality 25% Massive and mortal gastrointestinal bleeding occurred in 3 patients	Initially performed only for body and tail lesions. Later expanded for head of pancreas lesions, but had 50% mortality in this group 50% patients had relief of back pain 5 patients had liver metastases 5 mm distance to portal vein may not be safe
Spiliotis *et al*[20]	33 mo (mean)	Overall morbidity 25% and nil mortality	Mean survival without RFA was 13 mo RFA in parallel to palliative therapy provided survival benefit for patients with unresectable pancreatic cancer
Casadei *et al*[29]	4 mo (mean)	3 patients developed ascites 1 patient developed biliary fistula	Prospective study. Included 3 patients Complete necrosis achieved in all patients All patients had a laparotomy and double bypass. Study was stopped at interim analysis
Girelli *et al*[11]	Not reported	Abdominal complications occurred in 24%. 30 d mortality 2%. Three patients with surgery related complicated required reoperation	Prospective study RFA was the only treatment in 19 patients All patients received antibiotics, octreotide and gabexate mesilate. Reduction of RFA temperature from 105 ℃ to 900 ℃ resulted in significant reduction in complications
Later this group has updated their experience of 107 patients (Cantore *et al*[21]). They performed a group wise comparison between upfront RFA *vs* RFA following primary therapy and concluded that RFA following primary treatment improves survival (14.7 mo *vs* 25.6 mo)			
Zou[1] *et al*[30]	17.6 mo (mean)	Three patients experienced complications, but no mortality	Somatostatin analogues were used post-operatively The overall 12 mo survival was 65.6%
Ikuta *et al*[31]	Alive at 18 mo	No complications	Laparotomy with bypass procedure followed by chemoradiotherapy to induce pancreatic fibrosis. This was followed by second laparotomy and RFA

[1]Simultaneous ^{125}I seed implantation. CT: Computerized tomography; RFA: Radiofrequency ablation.

thermokinetic principles applied by various authors and Table 2 summarizes outcomes with reference to survival and morbidity/mortality. RFA appears to have a role in treating locally advanced disease; however heterogeneity in the current reports makes it difficult to draw any robust recommendation about RFA applicability. RFA is being explored for improved palliation in malignant obstructive jaundice. Endobiliary RFA along with self-expanding metal stents is reported to be safe, feasible and associated with improved stent patency rates in patients with malignant biliary obstruction[33]. In the first *in vivo* study involving 22 patients with locally advanced pancreatic cancer, Arcidiacono *et al*[34] demonstrated feasibility and safety of endoscopic ultrasound guided cryothermal ablation with technical success in 16 patients (72.8%) and median post-ablation survival of 6 mo. They described late complications of jaundice, duodenal stricture and cystic fluid collection in four patients. Keane *et al*[35]

conducted a systematic review on novel ablative methods in locally advanced pancreatic cancer and concluded that despite proven safety, feasibility and reproducibility; the benefit of ablative techniques on long term survival remains to be confirmed in large prospective randomized studies. Figure 2 shows the past, the present and the future of RFA application in pancreatic cancer.

The future

At the present time the integration of RFA into the management of pancreatic ductal adenocarcinoma is evolving. It should be considered as having a complimentary role to current standard therapy in the multimodal management care model. It is likely that indications and patient selection for pancreatic RFA will expand.

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