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EDITORIAL

- 3142** Pain management in chronic pancreatitis incorporating safe opioid practices: Challenge accepted
Shah I, Sheth SG, Kothari DJ

EVIDENCE REVIEW

- 3148** Pancreatitis and pancreatic cancer: A case of the chicken or the egg
Umans DS, Hoogenboom SA, Sissingh NJ, Lekkerkerker SJ, Verdonk RC, van Hooft JE

REVIEW

- 3158** Pancreatic adenocarcinoma: A review of recent paradigms and advances in epidemiology, clinical diagnosis and management
Gupta N, Yelamanchi R
- 3182** Silencing hepatitis B virus covalently closed circular DNA: The potential of an epigenetic therapy approach
Singh P, Kairuz D, Arbuthnot P, Bloom K
- 3208** COVID-19-associated diarrhea
Megyeri K, Dernovics Á, Al-Luhaibi ZII, Rosztóczy A
- 3223** Assessment of liver disease in patients with chronic hepatitis C and unhealthy alcohol use
Fuster D, García-Calvo X, Zuluaga P, Bolao F, Muga R

MINIREVIEWS

- 3238** Clinical indicators for progression of nonalcoholic steatohepatitis to cirrhosis
Seen TK, Sayed M, Bilal M, Reyes JV, Bhandari P, Lourdasamy V, Al-khazraji A, Syed U, Sattar Y, Bansal R
- 3249** Update on the management and treatment of viral hepatitis
Almeida PH, Matielo CEL, Curvelo LA, Rocco RA, Felga G, Della Guardia B, Boteon YL
- 3262** Large-duct pattern invasive adenocarcinoma of the pancreas—a variant mimicking pancreatic cystic neoplasms: A minireview
Sato H, Liss AS, Mizukami Y
- 3279** Chronic hepatitis B in pregnant women: Current trends and approaches
Belopolskaya M, Avrutin V, Kalinina O, Dmitriev A, Gusev D
- 3290** Viscoelastic tests in liver disease: where do we stand now?
Buliarca A, Horhat A, Mocan T, Craciun R, Procopet B, Sparchez Z

- 3303** Gastrointestinal involvement in paediatric COVID-19 – from pathogenesis to clinical management: A comprehensive review

Calitri C, Fumi I, Ignaccolo MG, Banino E, Benetti S, Lupica MM, Fantone F, Pace M, Garofalo F

- 3317** Can control of gut microbiota be a future therapeutic option for inflammatory bowel disease?

Nishida A, Nishino K, Sakai K, Owaki Y, Noda Y, Imaeda H

ORIGINAL ARTICLE

Basic Study

- 3327** Oncogenic tuftelin 1 as a potential molecular-targeted for inhibiting hepatocellular carcinoma growth

Wu MN, Zheng WJ, Ye WX, Wang L, Chen Y, Yang J, Yao DF, Yao M

- 3342** Conditioned secretome of adipose-derived stem cells improves dextran sulfate sodium-induced colitis in mice

Lee S, Heo J, Ahn EK, Kim JH, Kim YH, Chang HK, Lee SJ, Kim J, Park SJ

Case Control Study

- 3357** Pancreatic enzymes and abdominal adipose tissue distribution in new-onset prediabetes/diabetes after acute pancreatitis

Ko J, Skudder-Hill L, Cho J, Bharmal SH, Petrov MS

Retrospective Cohort Study

- 3372** Effect of type 2 diabetic mellitus in the prognosis of acute-on-chronic liver failure patients in China

Lai RM, Chen TB, Hu YH, Wu G, Zheng Q

Observational Study

- 3386** Preliminary prospective study of real-time post-gastrectomy glycemic fluctuations during dumping symptoms using continuous glucose monitoring

Ri M, Nunobe S, Ida S, Ishizuka N, Atsumi S, Makuuchi R, Kumagai K, Ohashi M, Sano T

Prospective Study

- 3396** Real-world treatment patterns and disease control over one year in patients with inflammatory bowel disease in Brazil

Sassaki LY, Miszputen SJ, Kaiser Junior RL, Catapani WR, Bafutto M, Scotton AS, Zaltman C, Baima JP, Ramos HS, Faria MAG, Gonçalves CD, Guimaraes IM, Flores C, Amarante HMBS, Nones RB, Parente JML, Lima MM, Chebli JM, Ferrari MLA, Campos JF, Sanna MGP, Ramos O, Parra RS, da Rocha JJR, Feres O, Feitosa MR, Caratin RF, Senra JT, Santana GO

SYSTEMATIC REVIEWS

- 3413** Local ablation of pancreatic tumors: State of the art and future perspectives

Granata V, Grassi R, Fusco R, Belli A, Palaia R, Carrafiello G, Miele V, Grassi R, Petrillo A, Izzo F

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Local ablation of pancreatic tumors: State of the art and future perspectives

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Abstract

BACKGROUND

Currently, the technologies most commonly used to treat locally advanced pancreatic cancer are radiofrequency ablation (RFA), microwave ablation, and irreversible (IRE) or reversible electroporation combined with low doses of chemotherapeutic drugs.

AIM

To report an overview and updates on ablative techniques in pancreatic cancer.

METHODS

Several electronic databases were searched. The search covered the years from January 2000 to January 2021. Moreover, the reference lists of the found papers were analysed for papers not indexed in the electronic databases. All titles and abstracts were analysed.

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RESULTS

We found 30 studies (14 studies for RFA, 3 for microwave therapy, 10 for IRE, and 3 for electrochemotherapy), comprising 1047 patients, which were analysed further. Two randomized trials were found for IRE. Percutaneous and laparotomy approaches were performed. In the assessed patients, the median maximal diameter of the lesions was in the range of 2.8 to 4.5 cm. All series included patients unfit for surgical treatment, but Martin *et al* assessed a subgroup of patients with borderline resectable tumours who underwent resection with margin attenuation with IRE. Most studies administered chemotherapy prior to ablative therapies. However, several studies suggest that the key determinant of improved survival is attributable to ablative treatment alone. Nevertheless, the authors suggested chemotherapy before local therapies for several reasons. This strategy may not only downstage a subgroup of patients to curative-intent surgery but also support to recognize patients with biologically unfavourable tumours who would likely not benefit from ablation treatments. Ablation therapies seem safe based on the 1047 patients assessed in this review. The mortality rate ranged from 1.8% to 2%. However, despite the low mortality, the reported rates of severe post procedural complications ranged from 0%-42%. Most reported complications have been self-limiting and manageable. Median overall survival varied between 6.0 and 33 mo. Regarding the technical success rate, assessed papers reported an estimated rate in the range of 85% to 100%. However, the authors reported early recurrence after treatment. A distinct consideration should be made on whether local treatments induce an immune response in the ablated area. Preclinical and clinical studies have shown that RFA is a promising mechanism for inducing antigen-presenting cell infiltration and enhancing the systemic antitumour T-cell immune response and tumour regression.

CONCLUSION

In the management of patients with pancreatic cancer, the possibility of a multimodal approach should be considered, and conceptually, the combination of RFA with immunotherapy represents a novel angle of attack against this tumour.

Key Words: Pancreatic cancer; Ablation treatment; Radiofrequency ablation; Microwave ablation; Irreversible; Electrochemotherapy

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Core Tip: In the current state of knowledge, the most commonly used technologies in locally advanced pancreatic cancer are radiofrequency ablation, microwave ablation, and irreversible or reversible electroporation combined with low doses of chemotherapeutic drugs. Our purpose is to report an updated overview of these techniques, highlighting the advantages and limitations of each technology.

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INTRODUCTION

Worldwide, an estimated 19.3 million new cancer cases and almost 10.0 million cancer deaths occurred in 2020[1]. Pancreatic cancer accounts for almost as many deaths (466000) as cases (496000) because of its poor prognosis, and it is the seventh leading cause of cancer death in both sexes. Both incidence and mortality rates have been stable or slightly increased in many countries, likely reflecting the increasing prevalence of obesity, diabetes, and alcohol consumption, although improvements in diagnostic and cancer registration practices may also be factors in some countries.

Given that the rates of this disease are rather stable relative to the declining rates of breast cancer, it has been projected in a study of 28 European countries that pancreatic cancer will surpass breast cancer as the third leading cause of cancer death by 2025[1].

The only curative treatment is surgery; however, many patients have locally advanced or metastatic disease at diagnosis, and systemic chemotherapy is usually the main treatment[2-6]. The median survival of patients with metastatic disease treated with FOLFIRINOX therapy is only 3 mo[2,5]. FOLFIRINOX or modified FOLFIRINOX and gemcitabine/albumin-bound nab-paclitaxel remain the first-line treatment regimens, and for patients with *BRCA1/2* and *PALB2* mutations, FOLFIRINOX or modified FOLFIRINOX and gemcitabine/cisplatin are a second option[2,3]. Despite the recent introduction of novel chemotherapeutic schemes, these treatments still correlate with inadequate survival and significant systemic complications. Additionally, only one-third of patients are responsive to chemotherapy[6,7].

Local ablation treatment is considered in some centres for patients with persistent locally advanced disease after chemotherapy. Although randomized trials to establish the role of ablation treatments in addition to chemotherapy alone are absent and there are no concluded trials that have compared various ablative modalities[8], patients with persistent locally advanced disease who are in good clinical condition (World Health Organization performance status 0-1) and Response Evaluation Criteria in Solid Tumours (RECIST) stable disease after 2-4 mo of chemotherapy can be treated by local ablation therapies. Moreover, there is a growing interest in these techniques related to the fact that they can encourage a systemic antitumour response. Therefore, it is proposed to combine ablative treatments with immunotherapy to improve disease control[8]. Nonetheless, ablative treatments should be employed in pancreatic cancers that show a local growth pattern without systemic involvement and should be chosen as consolidative treatments in a multimodal approach. The superior technique between the two remains unknown; therefore, the choice to employ one or the other should be reserved for a multidisciplinary team, considering the patients' comorbidities, the tumour characteristics and, particularly, the response to medical therapies[9-19].

In the current state of knowledge, the most commonly used technologies in locally advanced pancreatic cancer (LAPC) are radiofrequency ablation (RFA), microwave ablation (MWA), and irreversible electroporation (IRE) or reversible electroporation combined with low-dose chemotherapeutic drugs (ECT).

We report an overview and an update of these procedures, highlighting the advantages and limitations of each technology.

MATERIALS AND METHODS

This study is an autonomous study with no protocol or registration number.

Search criteria

The following electronic databases were used for search: PubMed (United States National Library of Medicine, <http://www.ncbi.nlm.nih.gov/pubmed>), Scopus (Elsevier, <http://www.scopus.com/>), Web of Science (Thomson Reuters, <http://apps.webofknowledge.com/>), and Google Scholar (<https://scholar.google.it/>). The following search criteria were used: "Pancreatic Cancer" AND "Ablative Therapies"; "Pancreatic Cancer" AND "RFA"; "Pancreatic Cancer" AND "MWA"; "Pancreatic Cancer" AND "IRE"; "Pancreatic Cancer" AND "ECT".

The search covered the years from January 2000 to January 2021. Reference lists of the found papers were analysed for papers not indexed in the electronic databases. The included papers were required to be clinical studies (*e.g.*, retrospective analyses, case series, and prospective cohort studies) evaluating the safety and efficacy of ablative therapies in pancreatic adenocarcinoma. Articles published in the English language from January 2000 to January 2021 were included. The exclusion criteria were: Different topics, unavailability of full text, insufficient data, and case reports, reviews, or letters to editors.

RESULTS

The search strategy resulted in 30 studies [14 studies for RFA, 3 for MWA, 10 for IRE, and 3 for electrochemotherapy (ECT)] (Figure 1), including 1047 patients, which were



Figure 1 Included and excluded studies in systematic review.

further assessed. We found two randomized trials for IRE. Percutaneous and laparotomy approaches were performed. In the assessed patients, the median maximal diameter of the lesions was in the range of 2.8-4.5 cm, including patients unfit for surgical treatment. Additionally, Martin *et al*[19] evaluated patients with borderline resectable tumours who underwent resection with margin attenuation with IRE. Most series administered chemotherapy prior to IRE. The specific types of drugs varied between series, but gemcitabine- or 5-FU-based regimens were common.

In **Table 1**, we report the sample size, overall survival (OS), major complication rate, minor complication rate, and mortality rate in pancreatic cancer treated with RFA according to the studies assessed.

In **Table 2**, we report the sample size, OS, major complication rate, minor complication rate, and mortality rate in pancreatic cancer treated with MWA according to the studies assessed.

In **Table 3**, we report the sample size, OS, major complication rate, minor complication rate, and mortality rate in pancreatic cancer treated with IRE according to the studies assessed.

In **Table 4**, we report the sample size, OS, major complication rate, minor complication rate, and mortality rate in pancreatic cancer treated with ECT according to the studies assessed.

DISCUSSION

Ablation techniques-physical principles

RFA and MWA are hyper-thermic techniques that utilize energy to heat the lesions to at least 60°C[16].

RFA produces necrosis due to thermocoagulation. With this treatment, the area of active tissue heating is limited to a few millimetres near the electrode[16]. Consequently, the efficacy is closely correlated to the lesion size, and the maximum result is obtained for targets less than 3.5 cm[16]. Additionally, some tissue features, such as electrical conductivity, thermal conductivity, dielectric permittivity, and blood perfusion rate, have an effect on the efficacy of the RFA procedure. In particular, RFA treatment should be avoided when the target is near large vessels because of the heat sink effect[19]. However, the bipolar system of RFA can reduce the heat sink effect and lower pancreatic injury[10].

MWA uses the dielectric effect, which occurs when an imperfect dielectric material is subjected to an alternating electromagnetic field, to generate a larger area of active heating (up to 2 cm close to the antenna), allowing more homogeneous necrosis in the target zone compared to RFA[16]. Additionally, MWA has several supposed improvements with respect to RFA: The target can be greater given that it generates a larger area of necrosis; the treatment time is quicker; and it is less influenced by the defence of the neighbouring tissues, which is due to vaporization and charring, so the heat-sink effect impacts the efficacy of MWA[16].

In contrast to RFA and MWA, IRE and ECT are non-thermal techniques that cause ablation, changing cell membrane permeability through an induced electric field

Table 1 Sample size, overall survival, major complication rate, minor complication rate, and mortality rate in pancreatic cancer treated with radiofrequency ablation

Ref.	Sample size	Overall survival	Major complication rate	Minor complication rate	Mortality rate
D'Onofrio <i>et al</i> [28], 2016	51	-	-	-	-
D'Onofrio <i>et al</i> [29], 2017	18	Median, 185 d (range, 62-398 d)	0%	0%	0%
Giardino <i>et al</i> [30], 2013	168	34.0 mo	3.70%	17.70%	1.80%
Hadjicostas <i>et al</i> [31], 2006	4	6 mo	0%	25%	0%
Kallis <i>et al</i> [33], 2015	23	226 d (range, 140-526 d)	0%	4.30%	0%
Song <i>et al</i> [37], 2016	6	NR	0%	33.30%	0%
Spiliotis <i>et al</i> [38], 2007	25	33 mo	0%	-	0%
Varshney <i>et al</i> [39], 2006	3	-	0%	66.70%	0%
Zou <i>et al</i> [41], 2010	32	17.5 mo	3.10%	0%	0%
Giardino <i>et al</i> [44], 2017	10	NR	30%	0%	0%
D'Onofrio <i>et al</i> [46], 2020	35	310 (65-718) d	0%	0%	0%
Wang <i>et al</i> [48], 2020	11	12 mo	0%	0%	0%
He <i>et al</i> [50], 2020	18	1-yr 40.5%; 2-yr 27.0%	22.20%	50%	0%
Fegrachi <i>et al</i> [52], 2019	17	9 mo (range, 5-11 mo)	6%	24%	0%

NR: Not reported.

Table 2 Sample size, overall survival, major complication rate, minor complication rates, and mortality rate in pancreatic cancer treated with microwave ablation

Ref.	Sample size	Overall survival	Major complication rate	Minor complication rate	Mortality rate
Carrafiello <i>et al</i> [59], 2013	10	80% at 1 yr	10%	20%	0%
Ierardi <i>et al</i> [60], 2018	5	-	0%	20%	0%
Vogl <i>et al</i> [61], 2017	20	-	0%	9.10%	0%

(electroporation). IRE is considered a direct ablation tool since electroporation is used in an irreversible manner[17-26]. The use of short high-voltage electric current fields (up to 3000 V and 50 A for milliseconds) cause irreversible permeabilization of the lipid bilayer, disruption of cellular homeostasis, and stimulation of apoptotic pathways, causing death of neoplastic cells[9-17,26]. Taking into account its mechanism of action, IRE can protect surrounding structures, such as vessels, and it is a central element if the tumour encases the peripancreatic vessels in which the employment of RFA could be unsafe[22]. ECT conceives of the electroporation of cells and the associated administration of low doses of non-permanent or poorly permanent chemotherapeutic agents[11,13-27]. The application of an electrical field to a cell causes a transient and reversible orientation of its polar membrane molecules, with increased permeability[11-13]. This transient permeability allows the cell to receive a higher dose of chemotherapeutic drugs than would occur otherwise, increasing the cytotoxic effects of the agents. This local potentiation of chemotherapy allows reducing the doses of the drugs, lowering the side effects and increasing the chemotherapy efficacy [11-13].

Clinical study

RFA: RFA is the typical treatment worldwide for the treatment of LAPC if further benefit from chemotherapy is expected. Several studies have evaluated the role of RFA in metastatic pancreatic cancer[9]. To the best of our knowledge, 14 studies assessed the safety and efficacy of RFA in pancreatic cancer[28-52]. In several studies, the use of RFA was limited to patients with locally advanced cancer and/or metastatic cancer. Only in cases where the patients were unfit for surgery was RFA used in resectable

Table 3 Sample size, overall survival, major complication rate, minor complication rate, and mortality rate in pancreatic cancer treated with irreversible electroporation

Ref.	Sample size	Overall survival	Major complication rate	Minor complication rate	Mortality rate
Vroomen <i>et al</i> [14], 2017	25	-	8%	20%	0%
Martin <i>et al</i> [19], 2015	200	24.9 mo (range, 4.9–85 mo)	18.50%	50,5%	2%
Martin <i>et al</i> [20], 2013	54	20 mo	24%	55,5%	2%
Lambert <i>et al</i> [23], 2016	21	10.2 mo	23.80%	-	0%
Yan <i>et al</i> [24], 2016	25	-	36%	16%	0%
Scheffer <i>et al</i> [26], 2017	25	11 mo	40%	40%	0%
Ruarus <i>et al</i> [65], 2020	50	11.6 mo (no induction chemotherapy or gemcitabine-based induction chemotherapy) and 14.9 mo (FOLFIRINOX)	42%	28%	2%
van Veldhuisen <i>et al</i> [66], 2020	30	17.0 (range, 5-35 mo)	20%	23%	0%
Narayanan <i>et al</i> [67], 2017	50	27 mo	20%	-	0%
Liu <i>et al</i> [68], 2019	54	16.2 and 20.3 mo in the IRE and IRE + chemo groups	7.40%	81%	0%

IRE: Irreversible electroporation.

Table 4 Sample size, overall survival, major complication rates, minor complication rate, and mortality rate in pancreatic cancer treated with Electrochemotherapy

Ref.	Sample size	Overall survival	Major complication rate	Minor complication rate	Mortality rate
Granata <i>et al</i> [11], 2015	13	-	0%	23%	0%
Granata <i>et al</i> [12], 2017	19	-	-	-	-
Granata <i>et al</i> [71], 2020	25	In fixed geometry, treated patients 6 mo (range, 1-74 mo); in variable geometry treated patients 12 mo (range, 2-50 mo)	0%	23%	0%

cancer[25-52]. Recently, RFA has been used as an upfront option at the time of diagnosis[9], justified based on immunological antitumoral stimulation[43,44].

The results of the assessed studies in terms of OS, major and minor complication rates, and mortality rates are reported in Table 1.

In the treatment of pancreatic adenocarcinoma, RFA has been mainly applied during laparotomy or with an endoscopic approach. The percutaneous approach has rarely been described in the literature, and worldwide experience is still limited[46]. However, the percutaneous approach should be favoured to avoid the invasiveness of the intraoperative approach. If percutaneous RFA is feasible, it could avoid unnecessary laparotomy, thus reducing the risk of surgical complications as well as the time and costs of the treatment[46]. Moreover, while surgery involves an impaired immune response, enhanced immune system stimulation and immune response against the tumour have been described in a percutaneously treated patient[43,47].

Nonrandomized studies showed a promising OS up to 25.6 mo after RFA for LAPC [53]. However, no randomized controlled trials have been performed, so the true effectiveness of RFA combined with systemic chemotherapy regimens remains unknown. Several studies[9] reported an excellent outcome with a median OS of 30 mo for patients subjected to RFA and a median OS of 25.6 mo in the patients subjected to primary treatments plus RFA plus further systemic treatments. Few studies have assessed the efficacy of RFA compared to other treatments[50]. He *et al*[50] compared

the efficacy of IRE with RFA in patients with LAPC, showing that IRE after induction chemotherapy is superior to RFA after induction chemotherapy for treating LAPC, while these two therapies have comparable efficacy for tumours that were larger than 4 cm. However, the study was not a randomized controlled trial but a retrospective study.

Morbidity rates range from 14% to 28% and seem to depend on RFA temperature settings, preventive duodenal cooling, and safety margins from vital structures[52]. Since pancreatic tissue is sensitive to heat and rich in blood vessels and since the anatomical position is close to arteries and bile ducts, the application of thermotherapy techniques carries a high risk. However, as RFA application becomes increasingly mature, the incidence of postoperative complications has decreased significantly[52]. Complications related to RFA included pancreatic fistulae, portal vein thrombosis, gastrointestinal bleeding, and acute pancreatitis. The rates of RFA-related mortality ranged from 0% to 19%[51]. The RFA-related complications that resulted in patient deaths included gastrointestinal bleeding and sepsis. The rates of overall complications ranged from 10% to 43%[51]. The types of complications reported varied widely and included pneumonia, peritoneal cavity abscess, acute renal failure, transient ascites, hepatic insufficiency, pseudomembrane colitis, hemoperitoneum, abdominal fluid collection, gastric bypass fistula, gastric ulcer, and choledocholithiasis.

Computed tomography (CT) is the diagnostic tool most often employed to evaluate treatment in terms of efficacy and safety. Although CT is best known for its role in the evaluation of abdominal emergencies, it is also an excellent tool in the evaluation of posttreatment complications[54-58]. However, CT has significant limitations in assessing treatment effectiveness[6]. RFA produces side effects such as interstitial oedema, haemorrhage, carbonization, necrosis, and fibrosis. These are responsible for heterogeneous appearances on imaging. The assessment of the treatment response in terms of dimensional criteria, according to RECIST 1.1[15] criteria, is not applicable because effectiveness is not always correlated to a size decrease[6]. Nevertheless, the assessed studies evaluated short- and long-term RFA efficacy according to dimensional criteria[15]. The assessment time was between 7 and 34 mo considering only dimensional criteria. According to Paiella *et al*[9] for RFA the technique to choose is CT, and the effectiveness is related to a post treatment hypodense zone. However, pancreatic tumours are also hypodense, so a “qualitative evaluation” based on a visual assessment could cause misdiagnosis. A quantitative evaluation founded on functional analysis allows a more objective assessment and a more correct diagnosis[6].

Distinct consideration should be made regarding whether RFA induces an immune response in the ablated area. Preclinical and clinical studies have shown that RFA is a favourable tool to induce antigen-presenting cell infiltration and to enhance the systemic antitumour T-cell immune response and tumour regression. The treatment is followed by a significant inflammatory response with intense T-cell infiltration[43,45].

Therefore, in the management of patients with pancreatic cancer, the possibility of a multimodal approach should be considered, and theoretically, the association of RFA with immunotherapy is a novel strategy against this tumour.

Microwave ablation

The results of the assessed studies in terms of OS, major and minor complication rates, and mortality rates are reported in Table 2.

Carrafiello *et al*[59] evaluated the efficacy of MWA in ten unresectable pancreatic head adenocarcinomas. The mean follow-up was 9.2 mo (range, 3 to 16 mo). The rate of MWA-related morbidity was 30% (3 patients). The authors found pancreatitis in two patients and gastroduodenal artery pseudoaneurysm in one patient. CT was executed up to 15 mo after the procedure. At the first follow-up, the researchers found one case with partial response (PR), eight with stable disease (SD), and one with progressive disease.

Ierardi *et al*[60] evaluated the feasibility and safety of MWA in five head pancreatic locally advanced cancer patients using a new technology with a high power and frequency of 2450 MH. CT was performed after 1, 3, 6, and 12 mo. No major complications were reported with a safe treatment in all patients (100%). Minor complications resolved during hospitalization (median, 4 d)[60].

Vogl *et al*[61] cured 22 lesions: In 17 (77.3%) patients, the tumour was in the pancreatic head and in 5 (22.7%) in the pancreatic tail. The rate of MWA efficacy was 100%. No major complications were reported; however, in two (9.1%) cases, minor complications were found because of severe local pain post-MWA treatment. Only ten patients underwent follow-up magnetic resonance imaging (MRI) examinations (median, 3 mo); local tumour progression was reported in one (10%) case.

Unlike RFA, the percutaneous approach was the most commonly used during MWA treatment, probably explaining the lower complication and death rates. However, the complication rates of MWA varied among the assessed studies. This finding might be due to the heterogeneity and the sample size of the studies assessed. In fact, Carrafiello *et al*[59] treated ten unresectable head pancreatic adenocarcinomas, Ierardi *et al*[60] treated five locally advanced head pancreatic cancers, and Vogl *et al* [61] treated 22 patients: In 17 (77.3%) patients, the tumour was in the pancreatic head and in five (22.7%) in the pancreatic tail.

CT is the diagnostic tool most often employed to evaluate the treatment, for either efficacy and/or safety. However, an assessment centred only on dimensional criteria is inappropriate to evaluate this procedure.

No data on MWA and immune response in the ablated area are described in the literature.

Although MWA is a promising treatment for LAPC, further studies are needed to increase the data about its safety and efficacy as well as the oncological outcome.

Irreversible electroporation

Currently, IRE is applied in stage III LAPC[17,26], even if several studies have reported three cases of IRE in stage IV with liver metastases[62] and the option to employ IRE as a technique to reduce the rate of R1 resections[19,21,63]. According to the reported data[17-26,62,64], IRE works better on target areas not larger than 3-3.5 cm; in addition, IRE should be more suitable than thermal tools when the tumour encapsulates the superior mesenteric artery. However, IRE has the disadvantage of necessitating general anaesthesia.

The results of the assessed studies in terms of OS, major and minor complication rates, and mortality rates are reported in Table 3.

Rombouts *et al*[53] described an IRE-related complication rate of 13%, with a mortality of 2%. The complication rate increases with the percutaneous treatment (29% vs 13%)[53]. Martin *et al*[19], evaluating 200 cured lesions, reported an overall rate of adverse events of 37% and a mortality rate of 2%. The most common complications reported are abdominal pain as a minor complication and pancreatitis, bile leakage, pancreatic leakage, duodenal leakage, duodenal ulcer, pneumothorax, haematoma, and deep vein thrombosis as major complications[6]. Several studies have confirmed the safety profile of IRE, with encouraging survival outcomes. Most studies, however, were retrospective, had limited sample sizes, and had a relatively short follow-up time. The aim of the PANFIRE study was to evaluate the efficacy and safety of percutaneous IRE for LAPC and isolated local recurrence following surgical resection of pancreatic cancer[65]. In this prospective single-arm phase II study, 40 patients with LAPC and 10 with local recurrence after resection were treated. The primary endpoint was the median survival times with primary LAPC (median OS, 17 mo) and with local recurrence (median OS, 16 mo), which exceeded the target median survival times based on chemotherapy alone. These results show a survival benefit compared with the current standard of care[65]. The reported overall complication rate was of 58%, including 21 major adverse events and two deaths within 90 d of the treatment. In addition, 13 (33%) patients were treated upfront with IRE. No survival benefit was demonstrated for patients receiving a 5-FU-based regimen. This finding suggests that the key determinant of improved survival is attributable to IRE treatment alone. Nevertheless, the authors recommend at least four cycles of a 5-FU-based regimen before IRE for several reasons. First, a 5-FU-based regimen enables the identification of patients with aggressive tumour biologic features, allowing the exclusion of those who would not benefit from IRE. Second, a 5-FU-based regimen can result in downstaging, potentially rendering 15%–25% of patients with resectable disease. Last, an upfront 5-FU-based regimen has the potential to result in a longer OS[65]. The combination of systemic chemotherapy and cytoreductive ablation using IRE may prove synergistic for several reasons[66]. Induction chemotherapy may not only downstage a subgroup of lesions to curative-intent surgery but also identify biologically unfavourable tumours with rapid progression that would likely not benefit from ablative treatment [66]. As systemic chemotherapy remains the only treatment for LAPC proven to be beneficial, patients should first receive systemic chemotherapy followed by experimental treatment in the setting of a clinical trial[66-69].

IRE can be implemented successfully as an adjunctive measure for attempting to achieve negative microscopic operative margins in selected patients[21]. This treatment is limited to patients who have generally stable disease at the time of resection. To date, there are few options for effective therapy to facilitate microscopically negative margin resections outside of patient selection and meticulous operative dissection. Accepting that true margin-positive rates are significantly high (> 75%) in

resected pancreatic cancers, intraoperative IRE could accentuate negative-margin dissection of the retroperitoneal margin and its surrounding perivascular soft tissue, primarily the perineural and mesenteric tissue adjacent to critical vascular structures [21].

MRI and CT are the diagnostic tools mostly used to assess IRE.

IRE produces the formation of nanoscale pores within the cell membrane, changing the transmembrane potential and causing cell death. Experimental models showed that diffusion-weighted imaging (DWI) could be used to assess therapeutic effects [14, 70]. Vroomen *et al* [14] evaluated specific imaging parameters with contrast-enhanced (ce) MRI and ce-CT. The authors evaluated pre- and post-treatment, for MRI, the signal intensity (SI) on T2-weighted (W) images, on T1-W images before and after contrast medium, on DWI, and on apparent coefficient of diffusion (ADC) maps and for CT attenuation in the arterial and portal-venous phases. These authors showed that the most significant features to evaluate efficacy and outcome were SI on images with $b = 800\text{s/mm}^2$ and contrast-enhanced MRI.

Only two studies [19, 67] reported an outstanding median OS of 24.9 and 27 mo, respectively. Consequently, there is a need for a greater number of studies that assess efficacy in terms of oncological outcomes.

Electrochemotherapy

Today, few studies have evaluated the role of ECT in LAPC [11-13, 71]. In our previous study, we assessed 13 patients with LAPC. In seven (53.8%) patients, the tumour was localized in the head, and in six (46.2%), it was localized in the body tail (Figure 2). The treatment was safe in all patients without major complications. The types of minor complications reported varied widely and included transient ascites, transient pleural effusion, and gastric emptying documented by radiological studies, without clinically significant signs. The mean duration of hospitalization was 12 d. CT and MR were utilized for the follow-up [11]. In an ongoing study, we found that the median OS was 11.5 mo with a range in values of 73 mo. At 1 mo after ECT, 76.0% of patients were in PR, and 20.0% were in SD. Moreover, we found that the use of pre-treatment planning (Figure 3), which optimizes the multiple insertions of single electrodes, increases the local disease control rate (LDCR) and the OS compared with the use of fixed-geometry electrodes (hexagonal or linear). The patients treated with fixed geometry had an LDCR of 46.1%, whereas the group treated with variable geometry (Figure 4) had an LDCR of 66.7%. For the 13 patients treated with fixed geometry, the median OS was 6 mo (range, 1-74 mo), whereas for the 12 patients treated with variable geometry, the median OS was 12 mo (range, 2 to 50 mo) [71].

Although ECT is a promising tool for cancer treatment, how to assess tumour treatment response is still a problem. In fact, as highlighted in our preliminary experience, the RECIST 1.1 criterion, using the variation of the largest diameter on both CT and MRI images, does not provide appropriate patient stratification in responders or non-responders [12, 13]. It is clear that when considering therapeutic effects on tumours, imaging observations are sometimes difficult to interpret, so functional imaging should resolve this problem. We evaluated several functional features as follows: for MRI, wash-in slope and wash-out slope by dynamic contrast-enhanced MRI, pseudo-diffusivity, perfusion fraction, and tissue diffusivity by the intravoxel incoherent motion model, ADC by the conventional mono-exponential approach, and the mean of the diffusion coefficient and the mean of diffusional kurtosis by diffusion kurtosis imaging. In addition, for positron emission tomography, maximum standardized uptake value was assessed and for CT, lesion density was evaluated. We found that conventional morphologic criteria were not able to differentiate partial, complete, or incomplete responses after ECT, while changes in functional parameters could be more suitable to assess ECT responses [11, 13].

Today, ECT is recommended during clinical trials in dedicated centres [11-13].

Comments and future perspectives

Several studies have suggested that the key determinant of improved survival is attributable to ablative treatment alone [72-75]. Nevertheless, the authors recommend at least four cycles of a 5-FU-based regimen before local therapy for several reasons. Induction chemotherapy may not only downstage a subgroup of lesions to curative-intent surgery but also identify biologically unfavourable tumours with rapid progression that would likely suffer from ablation treatment [66, 76-80]. As systemic chemotherapy remains the only treatment for LAPC proven to be beneficial, patients should first receive systemic chemotherapy followed by experimental treatment in the setting of a clinical trial [66].

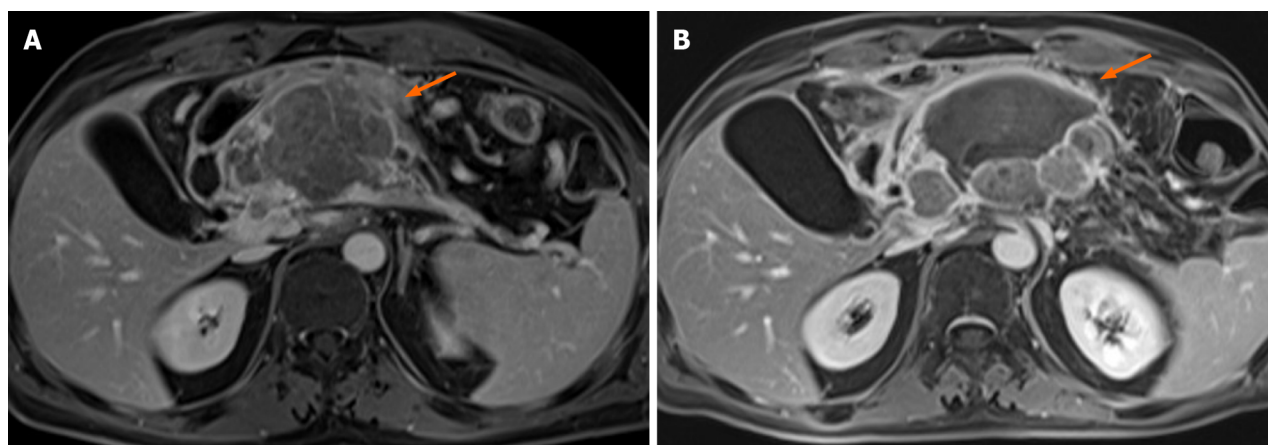


Figure 2 A patient with body pancreatic cancer. A: Volume-interpolated breath-hold examination (VIBE) T1-W post contrast sequence during the portal phase in axial plane for pretreatment evaluation of the lesion (arrow); B: VIBE T1-W post contrast sequence during the portal phase in axial plane showing the ablated area (arrow). According to qualitative assessment (significant differences in signal intensity in pre and post treatment sequences), the lesion was in partial response.

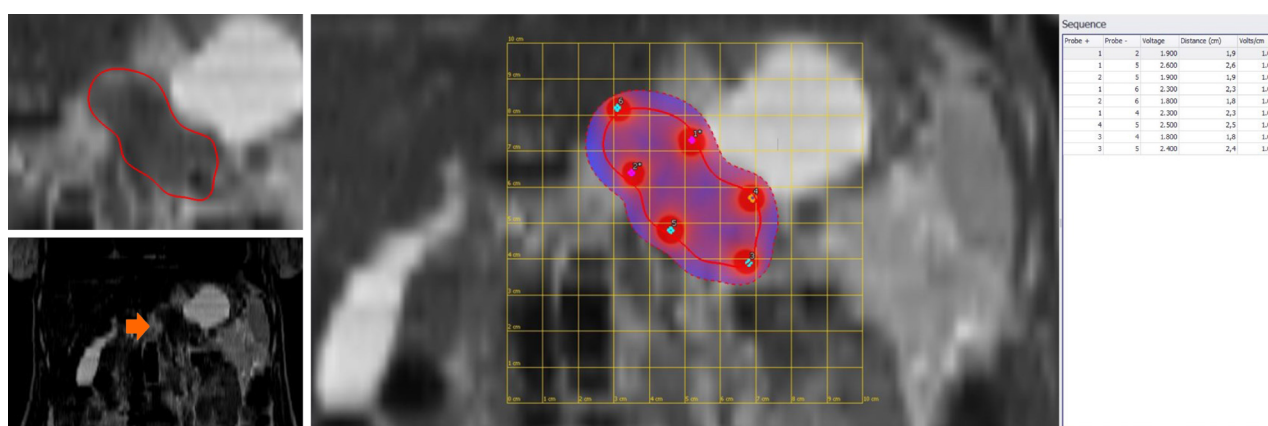


Figure 3 Preoperative planning for electrochemotherapy treatment with multiple single needles in a variable geometry for locally advanced pancreatic cancer.

Ablation therapies seem to be safe in 1047 patients assessed in this study. The mortality rate ranged from 1.8% to 2%. However, despite the low mortality, the reported rates of severe post procedural complications ranged from 0%–42%. Additionally, for laparotomy, the series reported by Martin *et al*[19] had more severe complications, including procedure-related deaths. The major drawback inherent to all thermal ablation techniques is the fact that these therapies comprise the risk of the heat-sink effect[69]. This issue is particularly important, as the pancreas is an organ with a peculiar position that is closely related to the duodenum, bile duct, and major vessels. This feature turned IRE into an attractive tool for LAPC ablation[69]. Taken together, pathological studies revealed that one-third of patients died of PC as a result of local tumour infiltration, without evidence of metastatic disease. This population appears to be ideal for IRE to increase patient survival and, importantly, quality of life [69]. A registry-based study showed a high rate of complications (42%) post-IRE. An important point demonstrated in this study is the correlation of the learning curve to the rate of complications, which seems to drop after a cumulative experience of a minimal of five IRE cases in PC[69].

Median OS varied between 6.0 and 33 mo. However, these data are very problematic to understand because of the heterogeneity between the series.

Regarding the technical success rate, several studies reported an estimated technical success rate in the range of 85%–100%. However, the authors reported early recurrence after treatment, indicating the limitations of the radiological assessment post-treatment [16]. In addition, none of these studies assessed the relationship between the technical success rate and tumour size.

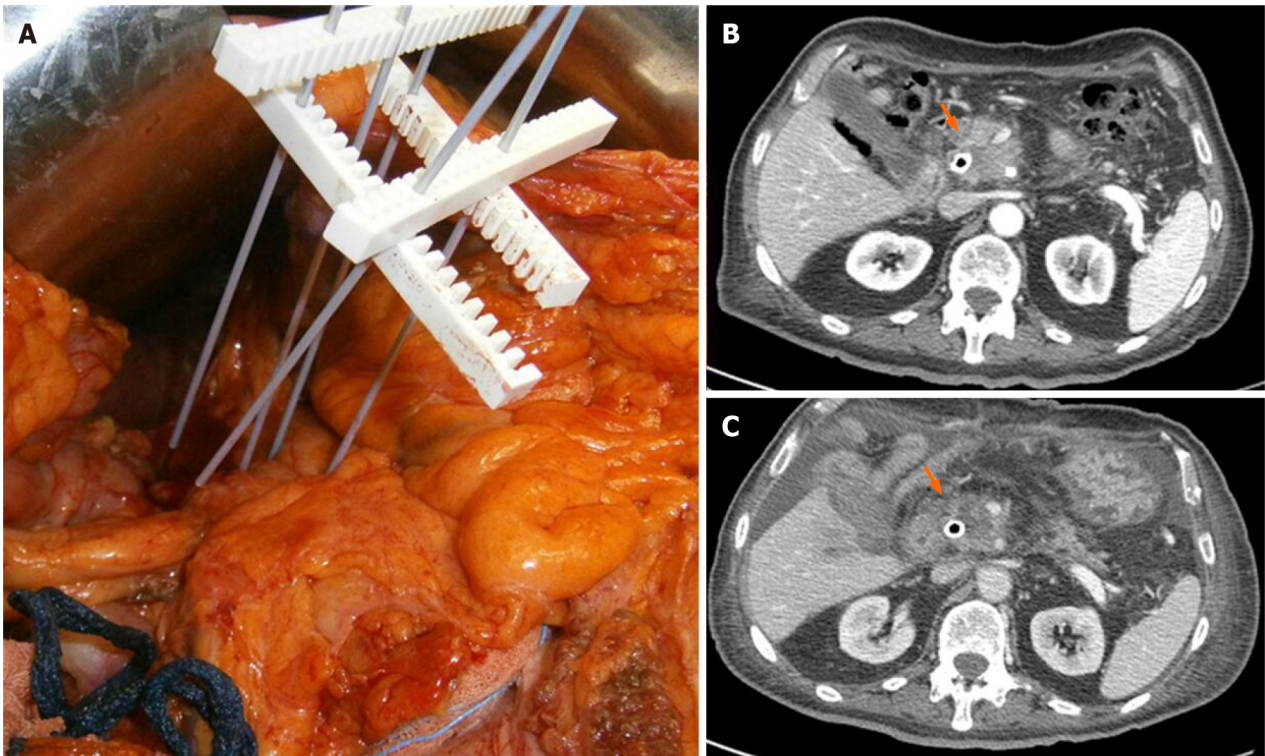


Figure 4 Electrochemotherapy with variable geometry and computed tomography pre-treatment and 6 mo post-treatment. A: Electrochemotherapy treatment with variable geometry; B: Computed tomography pre-treatment; C: Computed tomography 6 mo post-treatment. Computed tomography density showed a reduction as a positive response to treatment.

A distinct consideration should be made on whether local treatments induce an immune response in the ablated area. Preclinical and clinical studies have shown that RFA is an interesting tool to induce antigen-presenting cell infiltration and to enhance the systemic antitumour response. To the best of our knowledge, no data on other local treatments are available; therefore, studies that also evaluate this aspect for the other methods would be interesting.

Therefore, in the management of patients with pancreatic cancer, the possibility of a multimodal approach should be considered, and theoretically, the association of RFA with immunotherapy is a novel strategy against this tumour.

CONCLUSION

In conclusion, ablation therapies seem effective and safe with low post-treatment mortality. Although complications are mostly self-limiting, severe complications do occur. The technical success rate is high at 85%–100%, but this feature may be an over-estimation. Further efforts are also needed to address patient selection, as well as the use of IRE for “margin accentuation” during surgical resection, so the combination of RFA with immunotherapy represents a novel strategy against this tumour.

ARTICLE HIGHLIGHTS

Research background

In the current state of knowledge, the most commonly used technologies in locally advanced pancreatic cancer (LAPC) are radiofrequency ablation (RFA), microwave ablation, and irreversible electroporation (IRE) or reversible electroporation combined with low doses of chemotherapeutic drugs.

Research motivation

In the management of patients with pancreatic cancer, the possibility of a multimodal approach should be considered.

Research objectives

The research purpose was to report an overview and an update on ablation techniques, highlighting the advantages and limitations of each technology.

Research methods

The search covered the years from January 2000 to January 2021 and was performed using data from several electronic databases.

Research results

Ablation therapies seem effective and safe with low post-treatment mortality. Although complications are mostly self-limiting, severe complications do occur.

Research conclusions

Overall survival varies widely between different studies, and the additional value of ablation treatments for LAPC needs to be further explored.

Research perspectives

Further efforts are also needed to address patient selection, as well as the use of IRE for “margin accentuation” during surgical resection, so the combination of RFA with immunotherapy represents a novel angle of attack against this tumour type.

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