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Minimally invasive image-guided therapy of primary and metastatic pancreatic cancer

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Abstract

Pancreatic cancer is a challenging malignancy with limited treatment options and poor life expectancy. The only curative option is surgical resection, but only 15%-20% of patients are resectable at presentation because more than 50% of patients has distant metastasis at diagnosis and the rest of them has locally advanced pancreatic cancer (LAPC). The standard of care first line treatment for LAPC patients is chemotherapy with or without radiation therapy. Recent developments in minimally invasive ablative techniques may add to the treatment armamentarium of LAPC. There are increasing number of studies evaluating these novel ablative techniques, including radiofrequency ablation, microwave ablation, cryoablation and irreversible electroporation. Most studies which included pancreatic tumor ablation, demonstrated improved overall survival in LAPC patients. However, the exact protocols are yet to set up to which stage of the treatment algorithm ablative techniques can be added and in what kind of treatment combinations. Patients with metastatic pancreatic cancer has dismal prognosis with 5-year survival is only 3%. The most common metastatic site is the liver as 90% of pancreatic cancer patients develop liver metastasis. Chemotherapy is the primary treatment option for patients with metastatic pancreatic cancer. However, when the tumor is not responding to chemotherapy or severe drug toxicity develops, locoregional liver-directed therapies can provide an opportunity to control intrahepatic disease progression and improve survival in selected patients. During the last decade new therapeutic options arose with the advancement of minimally invasive technologies to treat pancreatic cancer patients. These new therapies have been a topic of increasing interest due to the severe prognostic implications of locally advanced and metastatic pancreatic

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cancer and the low comorbid risk of these procedures. This review summarizes new ablative options for patients with LAPC and percutaneous liver-directed therapies for patients with liver-dominant metastatic disease.

Key Words: Pancreatic neoplasms; Interventional radiology; Ablation techniques; Electroporation; Radiofrequency ablation; Therapeutic embolization

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Core Tip: During the last decade new therapeutic options arose with the advancement of minimally invasive technologies to treat pancreatic cancer patients. These new therapies have been a topic of increasing interest due to the severe prognostic implications of pancreatic cancer and the low comorbid risk of these procedures. This review summarizes new ablative options for patients with locally advanced pancreatic cancer and percutaneous liver-directed therapies for patients with liver-dominant metastatic disease.

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INTRODUCTION

Pancreatic cancer carries an extremely poor prognosis with the 5-year survival is around 8% and goes down to 3% in patients with metastatic disease[1]. Although the overall cancer-survival statistics are improving, pancreatic cancer is an exception with no major therapeutic advancement in the last 30 years since the introduction of pancreaticoduodenectomy[2].

As the survival statistics of other malignancies are improving, it is expected that pancreatic cancer becomes the second leading cause of cancer-related death by 2030[3].

The only curative option of pancreatic cancer is complete surgical resection. However, only 15%-20% of patients have potentially resectable disease at presentation [4] approximately 30% patients are unresectable due to locally advanced pancreatic cancer (LAPC)[5] and approximately 50% of patients have stage IV pancreatic cancer with distant metastasis at diagnosis[1]. The most common metastatic site is the liver as 90% of pancreatic cancer patients develop liver metastasis[6].

During the last decade new therapeutic options arose with the advancement of minimally invasive technologies. This review summarizes new ablative options for patients with LAPC and percutaneous liver-directed therapies for patients with liver-dominant metastatic disease. The term pancreatic cancer includes a histologically heterogeneous group. This article focuses only on pancreatic ductal adenocarcinoma, as the most common malignancy of the pancreas, accounting for 85%-95% of cases[4,5].

MINIMALLY INVASIVE TREATMENTS OF LAPC

Non-metastatic LAPC comprises 30% of all newly diagnosed pancreatic cancer cases [7]. Patients with LAPC are not surgical candidates because of unresectable involvement of adjacent vessels like the portal vein, celiac or superior mesenteric artery or their major branches. Current standard-of-care therapy of LAPC is chemotherapy with or without radiation therapy. Adjuvant chemotherapy can downstage 20% of LAPC patients to be potentially resectable. Downstaged, surgically resected patients had a significantly improved survival (35.3 mo) compared to those who did not become surgical candidate after chemotherapy (16.2 mo)[8].

Patients with LAPC who do not become surgical candidate, may benefit from image-guided local ablation therapies, either percutaneously or during intraoperative open approach. The ablation technologies used in patients with LAPC include heat-based ablations, like radiofrequency ablation (RFA), microwave ablation (MWA) and

cryoablation and the new non-thermal ablation technique, irreversible electroporation (IRE).

RFA of LAPC

RFA is the most widely used heat-based ablative method which utilizes high frequency alternating electric current that causes cell death by heating the tissue through rapid electron vibration generating frictional heat[9]. This method of heat generation means that RFA is heavily dependent on conductivity which has close correlation to the water content of the tissue[9,10]. This is one of the disadvantages of RFA because as the tissue adjacent to the electrode heats up, it becomes desiccated and then acts as an “insulating sleeve” around the ablation probe hindering electron flow and further heat generation, thus limiting the ablation zone size[9]. Another major factor which limits the extent of the ablation zone is the cooling effect of flowing blood which works as a “heat sink”[11].

RFA treatment of the primary pancreatic cancer usually performed during open laparotomy. The studies where pancreatic RFA was used during open laparotomy are listed in Table 1. The initial publication by Matsui *et al*[12] included 20 patients and demonstrated that RFA is feasible in pancreatic cancer. This milestone publication was followed by multiple studies using RFA in pancreatic cancer with different endpoints. Wu *et al*[13] studied the pain relief effect of RFA and reported 50% pain reduction after pancreas cancer RFA. Girelli *et al*[14] also reported significantly reduced pain score in 69% of symptomatic patients. Several studies evaluated overall survival following RFA of pancreatic cancer and reported overall survival from 14.7 mo up to 33 mo[15, 16]. The largest study[16] included 107 patients and divided patients into 2 arms: 47 patients underwent RFA as a first-line treatment and 60 patients received neoadjuvant therapy first followed by RFA. All patients received standard of care post-RFA treatment which included systemic chemotherapy and/or radiation and 29 patients also received intra-arterial chemotherapy which consisted of injection of epirubicin and cisplatin into the celiac artery in every 4 wk until disease progression. Median overall survival was 14.7 mo in the RFA group and 25.6 mo in the neoadjuvant treatment + RFA group. They also reported that 32 patients treated with the triple combination of RFA, radiation therapy, and intraarterial chemotherapy had an even longer median survival of 34 mo.

There is only one publication reporting data of percutaneous RFA of the pancreas tumor[17]. The authors analyzed data of 23 patients who underwent ultrasonography (US)-guided percutaneous RFA. There was no severe adverse event reported, which may be explained by the fact that in all patients the tumor located in the pancreatic tail or body and none in the head of the pancreas. Follow-up imaging showed good response to RFA, however, the median overall survival or pancreatic progression-free survival was not reported.

While RFA of pancreatic cancer has proven survival benefit, it also comes with a high morbidity risk of up to 40%[14] and mortality rate of up to 25%[13]. The most frequent major complications are portal vein stenosis (15%) and heat-injury of the duodenum (8%)[14]. The reported most common cause of death is massive gastrointestinal hemorrhage[13]. Girelli *et al*[18] reported that avoiding temperatures to exceed 90 °C during ablation and preserving surrounding tissue from overheating can reduce complications.

Despite the reported potential survival benefit of RFA, it remains unclear when RFA is best incorporated into the first line standard of care systemic chemotherapy/chemoradiation treatment protocol; should RFA performed before or after the standard of care systemic therapy? Does its potential high complication rates worth its benefit?

MWA of LAPC

MWA is another heat-based ablation technology which appears to have several advantages over RFA. Microwave generates heat using electromagnetic radiation-induced rotation of dipole molecules, such as water[19]. MWA is more powerful than RFA and generates higher temperatures in a shorter time. This leads to larger ablation zones and less heat-sink effect from the adjacent blood vessels[20]. MWA can be effective in tissues with high impedance, such as charred desiccated tissue, what is a weakness of RFA[20].

The available data on the usage of MWA in LAPC is very limited[21-24]; only 4 studies have been published with limited follow-up and survival data included (Table 2). The largest series of 20 patients reported 100% technical success without major complications and only 9.8% minor complications. However, 3-mo follow-up imaging was available in 10 patients (50%) only and no overall survival was reported

Table 1 Studies evaluating intraoperative pancreas radiofrequency ablation

Ref.	Study type	Patients	Outcome measure	Results	Complications
Giardino <i>et al</i> [16], 2013	Retrospective	107	OS	RFA 1 st line: 14.7 mo RFA + adjuvant: 25.6 mo	Mortality: 1.8%; morbidity: 28%
Girelli <i>et al</i> [18], 2013	Prospective	100	OS and DSS	20 and 23 mo	Mortality 3%; morbidity 24%
Girelli <i>et al</i> [14], 2010	Prospective	50	Safety and feasibility	-	Mortality 2%; morbidity 24%
Spiliotis <i>et al</i> [15], 2007	Retrospective	25	OS	OS: 33 mo ¹	Mortality: 0%; morbidity: 23%
Wu <i>et al</i> [13], 2006	Prospective	16	Pain relief	50% pain relief	90-d mortality: 25%;
Matsui <i>et al</i> [12], 2000	Prospective	29	OS	OS: 3 mo	Mortality: 10%

¹Mean value. OS: Overall survival; DFS: Disease-free survival; PFS: Progression-free survival; DSS: Disease-specific survival.

Table 2 Studies evaluating microwave ablation of pancreatic cancer

Ref.	Patients	Survival	Procedure	Guidance	Major adverse events
Lygidakis <i>et al</i> [23], 2007	15	Up to 22 mo	Open	N/A	No
Carrafiello <i>et al</i> [21], 2013	10	80% at 1 yr	5 open, 5 percutaneous	US, US/CT	2
Vogl <i>et al</i> [24], 2018	20	N/A	Percutaneous	CT	No
Ierardi <i>et al</i> [22], 2018	5	N/A	Percutaneous	US	No

US: Ultrasound; CT: Computed tomography.

[24]. In the study of Lygidakis *et al*[23] 15 patients were included with large pancreatic tumors (average tumor size of 6 cm) and only partial ablation was achieved in all patients. No major complications were reported. The longest follow-up was 22 mo; survival data of the group was not published. Carrafiello *et al*[21] reported of 10 patients with LAPC who underwent MWA; 5 during open surgery, and 5 percutaneously. Two major complications were reported, one pancreatic pseudocyst requiring drainage and one arterial pseudoaneurysm. The 1-year survival rate was 80%. Ierardi reported 100% technical success in 5 patients without major complications and 60% partial response and 40% progressive disease at 1 mo follow-up[22].

In our experience of 2 patients with pancreatic tail cancer, MWA was very effective without major complications; in one patient the ablation was complete (Figure 1), in the other patient the tumor recurred in the pancreatic tail 17 mo after ablation. Besides the recurrence, the MWA was also complicated with a development of an asymptomatic pancreatic pseudocyst which required no treatment. The local recurrence was first treated with stereotactic body radiation therapy which provided local control with stable disease for approximately a year, then the patient underwent repeat MWA of the enlarging pancreatic recurrence and a new solitary liver metastasis 32 mo after the initial ablation. There was no evidence of recurrence at the latest follow-up 6 mo after the second MWA.

Cryoablation of LAPC

During cryoablation intra- and extracellular ice crystals causing damage to the cell membrane, that will lead to cell death due to dehydration and osmotic pressure changes[25]. The cooling mechanism of the cryoablation probe based on the Joule-Thomson effect as high pressure argon gas is circulated *via* tiny tubes inside the probe with sudden expansion of the gas in a chamber in the ablation probe tip. The probe tip reaches temperatures as low as -160 C. The major advantage of cryoablation over other ablation technologies is that ice is visible on US, computed tomography (CT) and magnetic resonance imaging, therefore, the size of the iceball can be monitored during the ablation to prevent inadvertent damage to adjacent tissues. The other advantage is the analgesic property of cold during cryoablation which is associated with reduced intra- and postprocedural pain[26,27]. The heat sink effect of adjacent vessels can negatively influence the size of the ablation zone in cryoablation, but this effect is not as pronounced compared to RFA[28]. One of the potential major complications of cryoablation is cryoshock which occur in 0.3 to 2.0% of patients[29,30] and is charac-

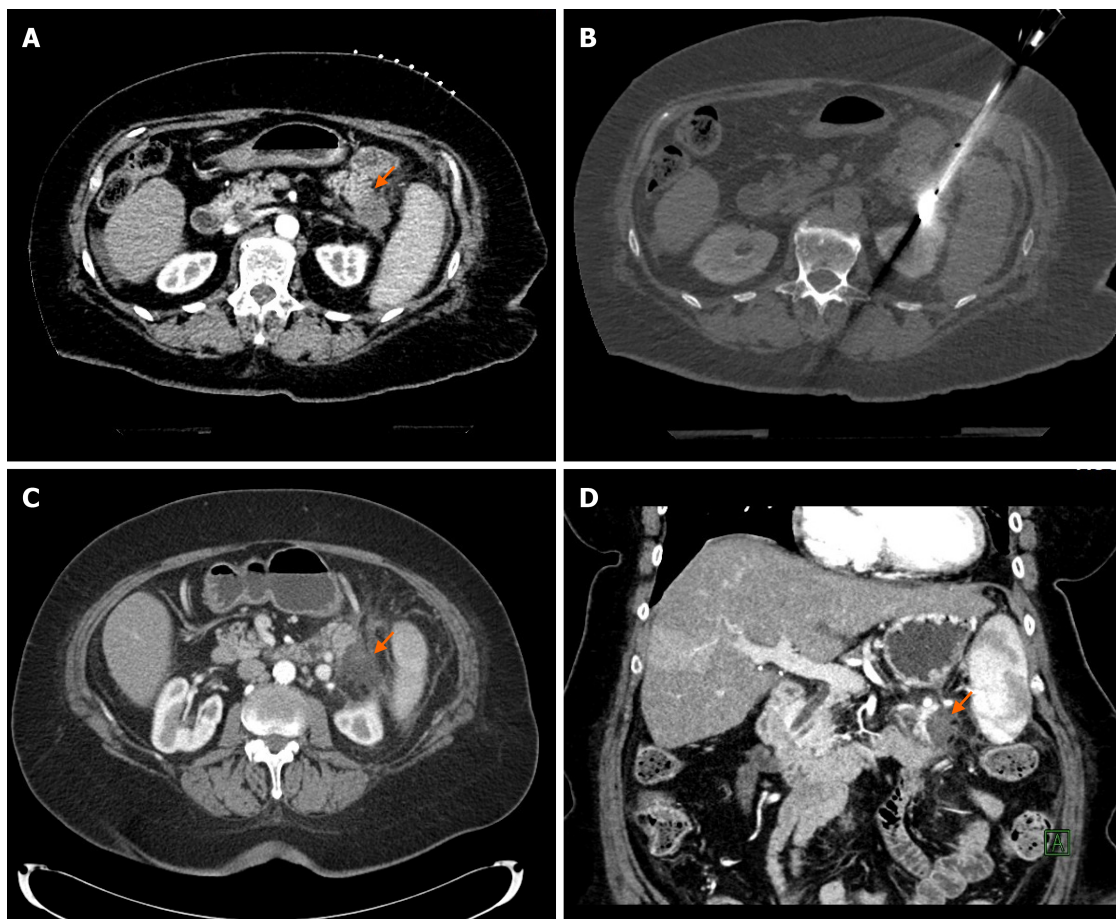


Figure 1 Percutaneous computed tomography-guided microwave ablation of a pancreatic tail adenocarcinoma. A: 72-year-old patient presented with a 1.9 cm biopsy-proven pancreatic adenocarcinoma in the tail of the pancreas as it shown on this contrast-enhanced computed tomography (CT) image (orange arrow); B: The patient was not surgical candidate due to comorbidities and underwent percutaneous CT-guided microwave ablation (MWA) of the pancreatic tumor. CT image shows the microwave antenna in place in the pancreatic tail tumor; C and D: Axial and coronal contrast-enhanced CT images 6 wk after the MWA show good radiological response with an avascular area in the tail of the pancreas corresponding to the ablation zone (orange arrows). Patient developed peritoneal metastases 4 mo later and died 13 mo after the MWA treatment.

terized by multiorgan failure and disseminated intravascular coagulation[31]. Cryoshock was observed most often in large volume liver ablations[32].

Similar to MWA, the available data on cryoablation of pancreatic cancer is very limited. There is no data regarding the effect of cryoablation in patients with LAPC. There are 3 papers which reported pancreatic cryoablation, but two of them included patients with stage 4 pancreatic cancer[33,34] the third study used combination of cryoablation with radioactive iodine-125 treatment[35]. Song *et al*[33] compared gastrojejunal bypass surgery alone *vs* bypass surgery with pancreatic tumor cryoablation in 118 patients with advanced pancreatic cancer. Cryoablation was performed in 42 patients. There were no differences between the patient characteristics and postoperative mortality; however, the 1-year survival rate was superior in the cryoablation group (4.8% *vs* 2.6%). The reason for the poor overall survival rate is the inclusion of patients with distant metastases.

Niu *et al*[34] compared 4 groups of patients with metastatic pancreatic cancer who underwent cryotherapy alone (36 patients), immunotherapy alone (17 patients), chemotherapy alone (22 patients) or cryoimmunotherapy (31 patients). Cryotherapy was used to treat both the primary tumor and the metastatic sites. Median overall survival (OS) was significantly higher in the cryoimmunotherapy (13 mo) group compared to cryotherapy (7 mo), immunotherapy (5 mo) and chemotherapy (3.5 mo) groups. There was no major complication.

Xu *et al*[36] reported outcomes of 49 patients of whom 38 underwent a combination therapy of cryoablation and iodine-125 seed implantation for LAPC. Both laparoscopic and percutaneous approach were used in this study. Complete response was seen in 20.4% of patients, partial response in 38.8%, stable disease in 30.6% and progressive disease in 10.2%. The median OS was 16.2 mo, and the 12-mo and 24-mo survival was 63.1% and 22.8%, respectively. Six patients (12.2%) developed acute pancreatitis, in

one case it was considered as severe.

Given the promising results with cryoablation, further studies are warranted in patients with LAPC.

IRE of LAPC

Irreversible electroporation is a novel ablation technology[36], which, unlike RFA, MWA, and cryoablation, is non-thermal. IRE delivers high-voltage electrical current (1500 to 3000 V) between the IRE ablation probes which creates nanoscale defects in the cell membranes[37-39]. The cells within the ablation zone lose the ability to maintain homeostasis which results in apoptotic cell death with narrow zone of transition[36-38]. Since this is a non-thermal ablation, its efficacy is independent of thermal conductivity of the tissues and not influenced by the “heat-sink” effect of adjacent vessels[36,39]. The ablation zone is very predictable and easy to monitor using US or CT[39]. The high voltage delivered by IRE may cause muscular contraction and cardiac arrhythmia. Therefore, IRE must be performed under general anesthesia with complete neuromuscular blockade and electrocardiogram synchronization. Patients with pacemakers may not be a candidate for IRE[40].

The main advantage of IRE is the controlled apoptosis of the cells without harming the adjacent collagen matrix and proteins, thus saving scaffolds of blood vessels and bile ducts[41-44]. As IRE leads to apoptotic cell death it enhances antigen presentation to immunocompetent cells which may improve immunological response locally and at abscopal metastatic sites. Irreversible nanopore formation at the ablation site and reversible nanopore formation in the vicinity of the ablation zone can lead to higher intracellular concentration of chemotherapeutic agents in the damaged cancer cells[45, 46]. The disadvantage of IRE is that it requires placements of multiple ablation probes because the high electric currents delivered between the probes. The probes have to be parallel to each other and at the same tissue depth which adds complexity to the probe placements and increases procedure time.

IRE most commonly performed intraoperatively during open laparotomy (Table 3, Figure 2). Although, some surgeons use palpation and visual guidance for ablation probe placements, most commonly intraoperative US is used to precise identification of the tumor extent and visualization of major arteries inside the tumor to maximize ablation success and minimize bleeding complications.

Several studies described survival benefit for patients who underwent IRE (Table 3) [47-50]. Huang *et al*[47] found that median OS was significantly extended to 22.6 mo. The authors analyzed data of 70 patients who were treated with IRE for LAPC. All patients received neoadjuvant chemotherapy with either a gemcitabine-based or TS-1 (tegafur, gimeracil, and oteracil) chemotherapy based on the patient's age and performance status. Local recurrence rate was only 8.6% at 28 mo follow-up. Disease progression was noted in 25 patients (36%) at distant sites, mostly in the liver (12 patients). Both median OS (28.7 mo *vs* 19.1 mo) and progression-free survival (PFS, 26.4 mo *vs* 13.2 mo) were significantly longer in patients who received TS-1 adjuvant therapy compared to patients with gemcitabine-based adjuvant therapy. Patient selection bias could play a role in the excellent survival results because patients with larger than 4 cm pancreatic tumor were excluded.

Martin *et al*[48] analyzed data of 200 patients and so far this is the largest study on IRE of the pancreas. All patients received chemo- or chemoradiation therapy before the IRE (the chemotherapy was either gemcitabine- or FOLFIRINOX-based). In 50 patients IRE was used only for surgical margin extension and in 150 patients IRE was used without resection. In the resection + IRE group 75% of patients had body and neck tumors, while in the IRE group most patients (63%) had pancreatic head tumors. There was no significant difference in median OS between the two groups, however, the median OS was slightly longer in patients who received resection + IRE (28.3 mo *vs* 23.2 mo). The median OS and PFS for the entire group were 24.9 mo and 12.4 mo, respectively.

There were several studies which could not demonstrate survival benefit of IRE over standard of care chemotherapy with reported 9.3 mo median OS[51-54]. However, these are relatively early studies with potential biases (patient selection, different chemotherapeutic protocols, lack of experience) that may have influenced the outcomes. Although survival benefit of IRE was not proved compared to a matching control group, Lambert *et al*[54] recommended IRE in cases where unresectability was noted during laparotomy.

IRE can also be performed with laparoscopic approach using endoscopic or laparoscopic US guidance, but there are only 9 cases reported when laparoscopic technique was used[47,55,56]. In the study of Huang *et al*[47] 5 out of the 70 patients underwent laparoscopic ablation and their survival and complication results were not

Table 3 Studies evaluating intraoperative irreversible electroporation of pancreatic cancer

Author	Patients	Median OS(mo)	Guidancemodality	Major adverse events
Paiella <i>et al</i> [53], 2015	10	7.5	US	20%
Martin <i>et al</i> [48], 2015	200	24.9	US	22%
Kluger <i>et al</i> [52], 2015	50	7.7	Not reported	38%
Lambert <i>et al</i> [54], 2015	21	10.2	Not reported	24%
Yan <i>et al</i> [57], 2016	25	Not reported	US	16%
Vogel <i>et al</i> [50], 2017	15	16	US	53%
Huang <i>et al</i> [47], 2018	70	22.6	US	4%
Yang <i>et al</i> [105], 2020	74	53% (3 yr) ¹	US	12%
He <i>et al</i> [106], 2020	36	53.5% (2 yr) ²	US	5%
He <i>et al</i> [49], 2020	167	16	US	N/A

¹Survival probability at 3-year.²Survival probability at 2-year. US: Ultrasound.

significantly different compared to the laparotomy group. Stillström *et al*[56] used an advanced stereotactic navigation system to perform laparoscopic IRE in 3 patients. The technical success rate was 100% and a prospective, randomized trial is planned. Tartaglia *et al*[55] reported a single case of laparoscopic IRE, where operators used laparoscopic ultrasound for guidance. The procedure was uneventful, and the 6-mo follow-up positron emission tomography-CT showed no fluorodeoxyglucose-uptake in the treated region.

In our experience probe placement-related bleeding is almost always seen due to the requirements of multiple probe placements and due to the rich blood supply of the upper gastrointestinal tract and porta hepatis. The IRE probe placements often performed *via* transgastric or transduodenal approach. During the open procedure the bleeding complications can be easily managed; in case of arterial bleed most of the times 5-10 min of manual compression is sufficient. Surgical vascular ligation is also readily available if needed. The other major advantage of open IRE over percutaneous IRE is the ability to sample and analyze suspicious lymph nodes with frozen section during the surgery and to detect obscure peritoneal metastases which are not seen on prior imaging. This reduces the chance to perform IRE on patients who have stage IV disease and unlikely would have benefit from the pancreatic ablation. Laparotomy is unavoidable anyway in a large number of LAPC patients since pancreatic head and neck tumors often cause gastric outlet obstruction. In these cases, IRE can be performed at the same time as the gastrojejunal bypass procedure.

Major adverse events of open IRE were reported in a wide range, from 4% to 53%. These can be laparotomy-related or IRE-related complications. Kluger *et al*[52] evaluated IRE-related and surgery related adverse events and found that 44% of grade 3-4 adverse events were IRE-related and 56% related to the surgical procedure. Authors concluded that IRE should not be considered as a minimally invasive treatment due to its high adverse event rate. Several authors did not describe whether they used imaging guidance during the IRE for probe placement and to monitor the ablation zone. Lack of imaging guidance may explain the high morbidity rates. Lambert *et al*[54] also included patients who underwent percutaneous IRE, but the percutaneous arm was closed after two patients due to high complication rate; one patient developed cholangitis, liver abscess, and biliary peritonitis resulting in surgical revision and antibiotic treatment, the other patient developed pancreatic fistula treated with stoma bag and antibiotics.

The most common IRE-related serious adverse events are pancreatic abscess formation, pancreatic fistula, gastrointestinal bleeding, and duodenal ulceration[47,48,57].

Percutaneous IRE is most commonly performed with CT guidance. CT-guided IRE requires administration of intravenous contrast to best visualize the tumor and its relationship to adjacent major vessels. US-guided percutaneous IRE has been reported [58-60] and US-guidance may be feasible in patients with low body mass index and without overlying gas-filled stomach and bowel loops, but in most patients

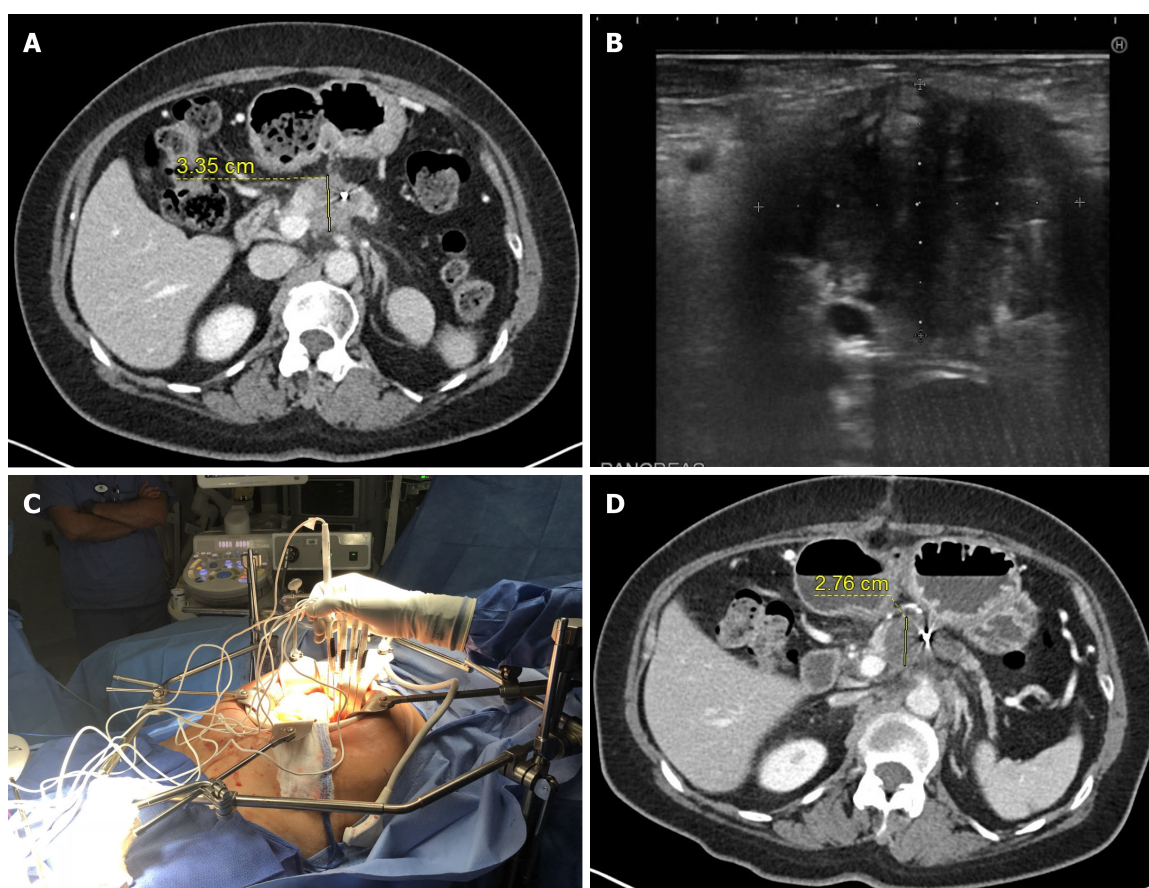


Figure 2 Intraoperative irreversible electroporation of a pancreatic adenocarcinoma. A: Pre-operative contrast-enhanced computed tomography image shows a hypodense mass in the head of the pancreas. A hyperdense fiducial marker, which was placed for prior radiation therapy, is also visible in the mass; B: Intraoperative ultrasound image shows a 3.2 cm hypoechoic mass in the pancreas; C: Intraoperative photo shows the patient with upper median laparotomy with ablation probes are placed directly into the pancreatic tumor, using ultrasound guidance; D: Follow-up imaging 1 mo after the irreversible electroporation (IRE) showed an avascular ablation zone covering the previously seen pancreatic tumor. The CA19-9 tumor marker decreased from 959 U/mL to 76 U/mL 1 mo after the ablation. The patient is still alive 31 mo after the IRE ablation.

percutaneous US is not suitable to guide pancreatic IRE ablation. The percutaneous approach is less invasive, and the hospital stay is shorter compared to open IRE, however, the management of procedural bleeding complications can be challenging and there are limitations to detect peritoneal and nodal metastases. The median OS of the percutaneous IRE studies is ranging from 10 to 19.8 mo. The longest overall survival was recently reported by Ma *et al*[51]. The authors evaluated LAPC patients treated with gemcitabine plus IRE (33 patients) and gemcitabine alone (35 patients). The median OS of 19.8 mo in the combination therapy group indicates that including IRE into the treatment protocol provides significant survival benefit over gemcitabine alone (9.3 mo).

Narayanan *et al*[61] performed CT-guided percutaneous IRE in 50 LAPC patients. Nine of the 50 patients underwent a second IRE due to evidence of residual tumor. Three patients were downstaged and underwent surgical resection: pathologic examination showed negative margins in all the 3 patients with complete (1 patient) or partial (2 patients) tumor necrosis. Median OS was 14.2 mo. Most common major adverse event was abdominal pain in 7 patients. Ruars *et al*[62] also published outcome of 50 patients who underwent CT-guided percutaneous IRE. This study included 16 patients who did not receive neoadjuvant chemotherapy (FOLFIRINOX, gemcitabine, or capecitabine and oxaliplatin combination). For all patients, the median OS from IRE was 10 mo. Interestingly, the median OS was slightly longer in the patient group that received no chemotherapy, compared to those who did (11 mo *vs* 9 mo). Uni- and multivariate analysis revealed large tumor size, baseline CA19-9 level higher than 2000 U/mL, and less than 50% reduction of CA19-9 at 3 mo follow-up as prognostic factors for poor survival.

A recent systematic review[63] compared open and percutaneous IRE. The mortality and morbidity rates were significantly higher in the open IRE group, meanwhile the median OS was found to be superior compared to the percutaneous approach. The

authors concluded that the treatment plan needs to be tailored individually.

There is a big difference between major centers in the rate of reported major adverse events ranging from 0% to 42% [58,62,64,65]. Belfiore *et al* [64] and Zhang *et al* [58] treated 20 and 21 patients, respectively, without any serious adverse events. On the other hand, most studies reported 20% or higher major adverse events after percutaneous IRE (Table 4).

Some patients may require special attention before IRE. Patients with pacemakers may not be a candidate for IRE. Metal stents and surgical clips may also contraindicate IRE. Månsson *et al* [66] reported a case of a patient with implanted metallic biliary stent who underwent IRE for the tumor in the head of the pancreas and developed severe late complications (persistent pain, abscess formation, diarrhea, peritonitis) within 8 wk of the procedure, that ended in emergency laparotomy and subsequent right hemicolectomy (for severe diarrhea). Martin *et al* [67] strongly recommends removal of metal biliary stents before IRE procedures. The metal stent can be removed endoscopically and replaced with a plastic stent or can be removed surgically with hepaticojejunostomy creation at the same laparotomy for open IRE. Dunki-Jacobs *et al* [68] demonstrated significant energy deflection during IRE in the presence of a metal stent which can lead to high current conditions, incomplete ablation, and possible thermal injury to adjacent organs. On the other hand, Melenhorst *et al* [69] successfully used IRE to treat a patient with hilar cholangiocarcinoma who had metallic stent in place. In our practice we haven't experience increased rate of complications of IRE in patients with metal stent in place (Kis *et al* unpublished data). At this point, the relationships between metal stent and IRE complications are not fully understood.

The non-thermal nature of IRE and its ability to preserve the structural integrity of blood vessels and bile ducts made IRE the preferred ablation modality in the pancreas. There are several ongoing clinical studies investigating the role of IRE in pancreatic cancer patients and to identify potential combination treatments which could improve survival (Table 5).

MINIMALLY INVASIVE TREATMENTS OF PANCREATIC CANCER LIVER METASTASES

At the time of diagnosis 53% of patients have distant metastases from pancreatic cancer and the 5-year survival of patients with metastatic disease is only 3% [1]. Liver is the most common site of metastasis with approximately 90% of patients develop hepatic metastasis [6]. In very selected cases of oligometastatic liver disease surgery can be considered [70-72], but the majority of patients are unresectable [73]. Chemotherapy is the only treatment option for most patients with metastatic pancreatic cancer [74]. The ACCORD11 trial reported 11.1 mo survival in metastatic pancreatic cancer patients treated with FOLFIRINOX, but the treatment had significant grade 3 and 4 toxicities including neutropenia (45.7%), thrombocytopenia (9.1%), diarrhea (12.7%), sensory neuropathies (9.0%), and fever (5.4%) [6]. For unresectable patients with liver-dominant metastatic disease liver-directed therapies may offer survival benefit and can provide chemotherapy holiday.

Percutaneous liver ablation

Percutaneous liver ablation is a widely used technique to treat primary and secondary malignancies in the liver [75]. The results of thermal ablations that covers the entire metastatic lesion is comparable to the results of surgical resection [76]. Studies evaluating percutaneous liver ablation in metastatic pancreatic cancer are summarized in Table 6.

Park *et al* [77] published a retrospective study of 34 patients who underwent liver RFA for metastatic pancreatic cancer. Median OS was 14 mo. Tumor size of less than 2 cm and well differentiated histology were predictive factors of longer survival. Second ablation due to new or recurrent metastasis was performed in 18 patients (58.1%), and in 16 of them the hepatic disease was controlled with the repeated ablation. Nine and one patient underwent a third and fourth ablation session, respectively.

Hua *et al* [78] performed a retrospective analysis of 102 pancreatic cancer patients who underwent RFA of liver metastases. Median OS was 11.4 mo. Univariate analysis showed that tumors in the head of the pancreas, tumor size between 3 and 5 cm and neutrophil-lymphocyte ratio > 2.5 were associated with worse prognosis. Recently Lee *et al* [79] published a retrospective study of 60 patients who underwent liver RFA for metachronous pancreatic cancer metastases and compared survival to a group of 66 patients who received systemic therapy. The median OS was significantly longer in the

Table 4 Studies evaluating percutaneous IRE in pancreatic cancer

Ref.	Patients	Median OS from IRE	Guidance	Major adverse events
Belfiore <i>et al</i> [64], 2015	20	13.95 ¹ mo	CT	0%
Narayanan <i>et al</i> [61], 2017	50	14.2 mo	CT	20%
Zhang <i>et al</i> [58], 2017	21	N/A	CT/US	0%
Scheffer <i>et al</i> [65], 2017	25	11 mo	CT	40%
Månsson <i>et al</i> [59], 2019	24	13.3 mo	US	25%
Flak <i>et al</i> [60], 2019	33	10.7 mo	US	20%
Ruarius <i>et al</i> [62], 2020	50	10 mo	CT	42%
Ma <i>et al</i> [51], 2020	33	19.8 mo	CT	9%

¹Mean value. CT: Computed tomography; US: Ultrasound.

RFA group (12 mo) compared to the systemic therapy group (9.1 mo).

Although MWA and cryoablation is widely used in liver malignancies, there are no dedicated reports to date on pancreatic cancer metastases. Since MWA has several advantages over RFA it can be assumed that MWA is at least as effective as RFA ablating pancreatic cancer liver metastases. Bailey *et al*[80] published a study which included 20 metastatic pancreatic cancer patients who underwent any kind of liver directed treatment. In this study 10 patients had MWA of liver metastasis, but no survival or complication data was reported. During last 10 years we performed MWA of pancreatic liver metastasis in only 2 patients despite we are a high-volume ablation center and using almost exclusively MWA for liver metastases (Figure 3). Our practice reflects the recommendations of Ghidini *et al*[81] who reviewed the available data of surgical hepatic metastasectomy and ablative techniques for metastatic pancreatic cancer. They concluded that despite the advancements in both fields, neither surgery nor ablation improved overall survival significantly during the last decade. Therefore, metastasectomy and ablation of liver metastasis are not recommended routinely for stage IV pancreatic cancer patients.

Transarterial chemoembolization of pancreatic cancer liver metastases

All trans-arterial embolization therapies for liver tumors are predicated upon the fact that the liver has dual blood supply and while the normal liver receives approximately 80% of the blood from the portal vein and 20% from the hepatic artery, the blood supply of tumors are almost exclusively is from the hepatic artery. Therefore, by embolizing the tumor feeding hepatic arteries, tumor ischemia can be achieved with minimal hypoxic damage to the normal liver parenchyma.

During transarterial chemoembolization (TACE) the embolic agent is delivered simultaneously with a chemotherapeutic agent. Direct intra-arterial administration of chemotherapy increases concentration in the target area and decreases systemic toxicities of the drug. Embolization reduces intra-tumoral blood flow, therefore prolongs the dwell time of chemotherapy within the tumor and further decreases the systemic side effects of the drug.

TACE is a well-studied intraarterial therapy in the management of hepatocellular carcinoma and colon cancer, but there is limited data on TACE in metastatic pancreatic cancer (Table 7). In the largest series Vogl *et al*[82] analyzed the data of 112 patients with metastatic pancreatic cancer who underwent TACE using a combination of mitomycin C, cisplatin, and gemcitabine, followed by iodized oil and 50 μ m embolization microspheres until stasis. Median OS was 19.2 mo with an impressive 5-year survival rate of 50%. Azizi *et al*[83] retrospectively analyzed the data of 32 patients who were treated with TACE, using the same technique as Vogl *et al*[82]. The median OS was 16 mo. Sun *et al*[84] reported a very promising 23 mo median OS of the 27 patients who underwent TACE for metastatic pancreatic cancer. The authors found that TACE prolongs survival and improves quality of life.

Transarterial radioembolization of pancreatic cancer liver metastases

During transarterial radioembolization (TARE) treatment Yttrium-90 (Y90) containing microspheres are delivered into the arteries feeding the liver metastases (Figure 4). Y90 is a pure β -emitting isotope with a physical half-life of 64.2 h[85]. It has a high energy

Table 5 Active pancreas irreversible electroporation clinical trials (source: ClinicalTrials.gov)

Title	Location	Hyperlink	Patients	Estimated completion
An open-label, multicenter, prospective study of IRE (Nano Knife) combined with radiotherapy and chemotherapy in patients with LAPC	Shanghai, China	https://clinicaltrials.gov/ct2/show/NCT04310553	40	December, 2020
Ablation of unresectable LAPC with IRE system	Teaneck, New Jersey, United States	https://clinicaltrials.gov/ct2/show/NCT03614910	30	May, 2023
Chemotherapy followed by irreversible electroporation in patients with unresectable LAPC	Aalborg, Denmark	https://clinicaltrials.gov/ct2/show/NCT04093141	30	May, 2024
Chemotherapy and IRE in the treatment of advanced pancreatic adenocarcinoma	Louisville, Kentucky, United States	https://clinicaltrials.gov/ct2/show/NCT03484299	20	December, 2023
PANFIRE-3 trial: Assessing safety and efficacy of IRE + Nivolumab + CpG for metastatic pancreatic cancer	Amsterdam, North-Holland, Netherlands	https://clinicaltrials.gov/ct2/show/NCT04612530	18	October, 2022
Outcomes of ablation of unresectable pancreatic cancer using the nanoknife IRE system	Baltimore, Maryland, United States	https://clinicaltrials.gov/ct2/show/NCT02041936	12	December, 2021
Immunotherapy and IRE in the treatment of advanced pancreatic adenocarcinoma	Louisville, Kentucky, United States	https://clinicaltrials.gov/ct2/show/NCT03080974	10	April, 2022
A study of the use of IRE in pancreatic ductal cancer	Toronto, Ontario, Canada	https://clinicaltrials.gov/ct2/show/NCT03257150	47	September, 2021
Safety and efficacy of IRE for LAPC	Seoul, Korea, Republic of	https://clinicaltrials.gov/ct2/show/NCT02898649	100	August, 2019
IRE (Nano Knife) for the treatment of pancreatic adenocarcinoma	Poitiers, France	https://clinicaltrials.gov/ct2/show/NCT03105921	20	June, 2020
IRE for inoperable hepatic and pancreatic malignancy	Hong Kong	https://clinicaltrials.gov/ct2/show/NCT02822716	35	December, 2021
Phase II/III of randomized controlled clinical research on IRE synchronous chemotherapy for LAPC	Guangzhou, Guangdong, China	https://clinicaltrials.gov/ct2/show/NCT03673137	120	November, 2021
Anti-tumor immunity induced by IRE of unresectable pancreatic cancer	Guangzhou, Guangdong, China	https://clinicaltrials.gov/ct2/show/NCT02343835	20	January, 2025
A pivotal study of safety and effectiveness of Nano Knife IRE for stage 3 pancreatic cancer	USA, Multicentre	https://clinicaltrials.gov/ct2/show/NCT03899636	528	December, 2023
Immunologic signatures following surgery for pancreatic cancer	Durham, North Carolina, United States	https://clinicaltrials.gov/ct2/show/NCT03001518	30	April, 2027

IRE: Irreversible electroporation; LAPC: Locally advanced pancreatic cancer.

radiation with average β -emission is 0.9367 MeV, with a mean tissue penetration of 2.5 mm and maximum tissue penetration of 11 mm[86,87], allowing delivery of high radiation doses to hepatic tumors with a “cross-fire” mechanism between the Y90 microspheres, while limiting the radiation dose to the surrounding liver parenchyma [88]. The antitumoral effect of Y90 is thought to be secondary to irreversible damage to tumor epithelial, stromal, and endothelial cells[89]. The absorbed dose of Y90 microspheres in the liver may be heterogeneous as it depends on hemodynamics and intratumoral vessel density[90]. The injected microspheres implant mostly in the terminal arterioles of tumors[88] in a 3: 1 to 20: 1 ratio compared to normal liver, with a preferential deposition in the tumor periphery[91]. There are currently two type of Food and Drug Administration-approved microspheres on the market: a glass (TeraSphere, Boston Scientific, Marlborough, MA) and a resin (SIR-Spheres, Sirtex Medical Pty. Ltd, St Leonards, Australia) based microspheres. The two types of Y90 microspheres differ in several physical parameters. The most important difference is the approximately 50 times higher radioactivity/beads in glass microspheres compared to resin.

Table 6 Studies evaluating percutaneous liver ablation in metastatic pancreatic cancer

Ref.	Modality	Patients	Median OS from ablation	Guidance	Major adverse events
Park <i>et al</i> [77], 2012	RFA	34	14 mo	US	Not reported
Hua <i>et al</i> [78], 2017	RFA	102	11.4 mo	US	9.8%
Lee <i>et al</i> [79], 2020	RFA	94	12 mo	US (<i>n</i> = 91), CT (<i>n</i> = 3)	8.5%
Bailey <i>et al</i> [80], 2019	Mixed	20	9.7 mo	Mixed	N/A

US: Ultrasound; CT: Computed tomography.

Table 7 Transarterial chemoembolization in liver-metastatic pancreatic cancer

Ref.	Patients	Median OS from TACE	Technique
Vogl <i>et al</i> [82], 2015	112	19.2 mo	cTACE after mitomycin C, cisplatin, and gemcitabine chemoperfusion
Azizi <i>et al</i> [83], 2011	32	16 mo	cTACE after mitomycin C, cisplatin, and gemcitabine chemoperfusion
Sun <i>et al</i> [84], 2017	27	23 mo	Chemoperfusion with gemcitabine, oxaplatin, and irinotecan plus embolization with Lipiodol + pirarubicin or DEB with pirarubicin

OS: Overall survival; TACE: Transarterial chemoembolization; cTACE: Conventional transarterial chemoembolization.

TARE is generally better tolerated by patients than TACE. TARE was associated with better quality-of-life scores compared to TACE in patients with hepatocellular carcinoma[92]. Similarly, fewer side effects were reported after TARE compared to TACE in patients with intrahepatic cholangiocarcinoma and liver-dominant metastatic breast cancer patients[93-95].

Three workgroups published studies that evaluated the safety and efficacy of TARE in liver-dominant metastatic pancreatic cancer (Table 8)[96-100]. Michl *et al*[96] published a retrospective study of 19 patients treated with Y90-labelled resin microspheres. Six (31%) grade 3 or higher toxicity was reported. Overall survival was 9 mo. Kim *et al*[98] also used Y90-labelled resin microspheres in 33 patients and reported 8.1 mo median OS. Grade 3 adverse events were noted in 2 patients. Very recently we reported our experience of Y90 TARE using Y90-labelled glass microspheres in 26 patients with liver dominant metastatic pancreatic cancer[100]. Median OS was 7 mo and 3 patients (11.5%) had grade 3 clinical toxicity in this study. We found that longer hepatic progression free survival was associated with younger age (< 65 years) and decreased or stable CA19-9 tumor marker level following TARE treatment.

There was no head-to-head comparison between TACE and TARE, but it appears that TACE resulted in better OS in patients with metastatic pancreatic cancer. The reason for this difference is unknown.

CONCLUSION

The introduction of minimally invasive technologies in cancer care opened new therapeutic options for patients with malignancies beyond surgery, chemotherapy and radiation treatment. Interventional oncology is becoming the fourth pillar of cancer care besides the classic trio of medical oncology, surgery and radiation oncology. The data presented above demonstrates only modest improvement in overall survival of patients with LAPC and patients with metastatic pancreatic cancer, but still this is a significant step forward in the treatment of a disease which has dismal prognosis. In the current medical practice these new minimally invasive treatments are used mostly as salvage therapies, when a patient has no other option. This approach introduces a selection bias into the studies and may mask the real potential of these novel treatment modalities. Despite the selection bias, they have one obvious advantage, the low mortality and morbidity rates of image guided-procedures compared to surgery,

Table 8 Transarterial radioembolization in liver-metastatic pancreatic cancer

Ref.	Patients	Median OS from TARE	Technique
Michl <i>et al</i> [96], 2014	19	9 mo	Resin microspheres
Kim <i>et al</i> [97], 2016 ¹	16	12.5 mo	Resin microspheres
Kim <i>et al</i> [99], 2017 ¹	24	6 mo	Resin microspheres
Kim <i>et al</i> [98], 2019 ¹	33	8.1 mo	Resin microspheres
Kayaleh <i>et al</i> [100], 2020	26	7 mo	Glass microspheres

¹Patient cohort in studies by Kim *et al* may overlap. OS: Overall survival; TACE: Transarterial chemoembolization.

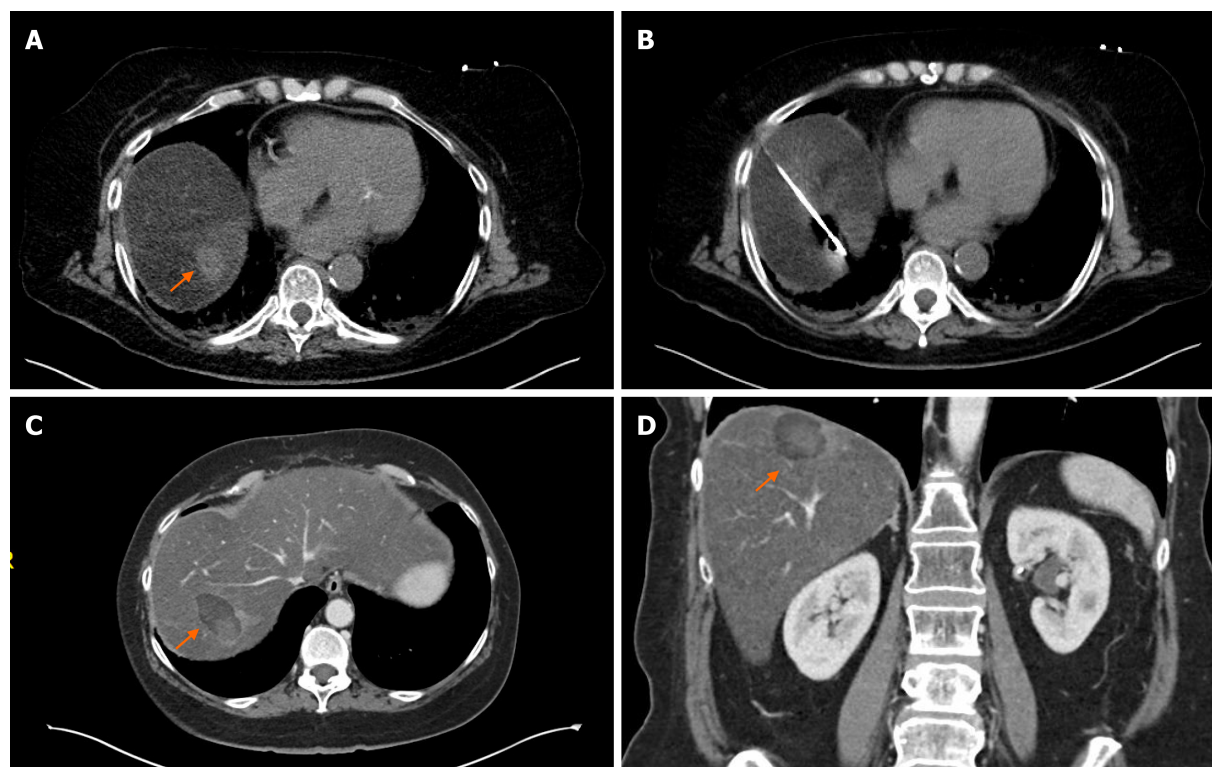


Figure 3 Percutaneous computed tomography-guided microwave ablation of a solitary pancreatic adenocarcinoma liver metastasis. A: 62-year-old female presented with a 2 cm solitary liver metastasis (orange arrow), 9 mo after the surgical resection of the primary tumor from the pancreatic head; B: Intraprocedural image shows the microwave antenna in the liver metastasis; C and D: Axial and coronal contrast-enhanced computed tomography images 1 mo after the ablation demonstrates a 4.3 × 2.7 cm hypodense ablation zone (orange arrows). There was no evidence of residual or new metastases in the liver. Patient is currently on systemic therapy 2 mo after the ablation without evidence of disease.

radiation therapy and even to chemotherapy. Interventional oncology has many tools in its armamentarium to manage patients with primary and secondary pancreatic cancer; however, most of the new treatment options are in the experimental phase and only performed by large-volume centers.

We are in an era of a paradigm shift from conventional oncology to immunoncology which could promote the concurrent use of ablative technologies together with immune therapies[45,101-104]. It has been found that ablation of solid tumors triggers a tumor-specific immune response which can be beneficial in combination with immune checkpoint inhibitors or other immune modulator agents. Future studies are needed to define the specific role of interventional oncology in every stages of pancreatic cancer with special attention on the immunological effect of ablative techniques.

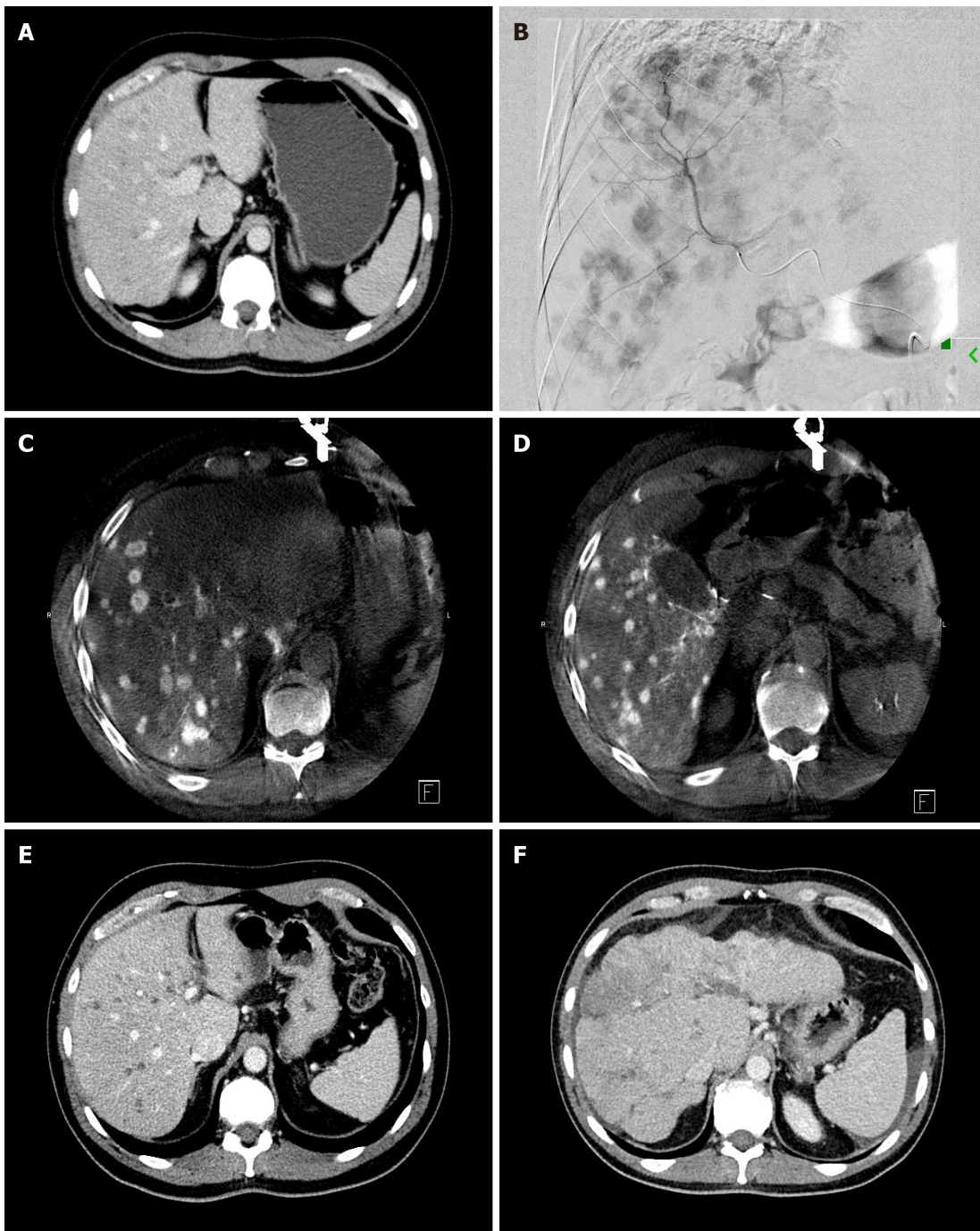


Figure 4 Transarterial radioembolization of pancreatic adenocarcinoma liver metastases. A: Pre-treatment contrast-enhanced computed tomography (CT) image of a 45-year-old man with pancreatic cancer demonstrates bilobar multifocal mildly hypodense liver metastases; B: Hepatic angiogram with contrast injection into the anterior division of the right hepatic artery shows multifocal arterially enhancing liver metastases; C and D: Intra-procedural cone-beam CT images of the liver during selective contrast injection into right hepatic artery shows multifocal arterially enhancing liver metastases; E: Contrast-enhanced CT image 1 mo after bilobar transarterial radioembolization (TARE) shows hypodense, "burnt out" liver metastases. The patient CA19-9 Level decreased from 882 U/mL pre-procedure to 56 U/mL. One year after the initial TARE new liver lesions appeared and his CA19-9 increased to 530 U/mL. He underwent a second round of bilobar TARE, and his CA19-9 Level decreased to 233 U/mL; F: Contrast-enhanced CT image 18 mo after the initial TARE shows shrunken liver with lobulated, nodular borders consistent with TARE-induced pseudocirrhosis. The patient died 22 mo after the initial TARE due to extrahepatic and hepatic progression of his disease.

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