Emerging Ablative and Transarterial Therapies for Pancreatic Cancer

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Abstract

Pancreatic adenocarcinoma is a highly aggressive malignancy with a poor prognosis secondary to late presentation with metastases, challenging resection, and limited alternative therapies. Standard treatment strategies for pancreatic cancer include surgery, chemotherapy, and radiation therapy. These options can extend survival and/or relieve symptoms but are seldom curative. Thermal ablative therapies have been utilized in pancreatic cancer mostly in an open surgical setting. Irreversible electroporation (IRE) is a nonthermal ablative option for pancreatic cancer that uses high voltage, low energy direct current to induce cell death. IRE technology has been shown to spare critical structures such as blood vessels and bile ducts. The safety and efficacy of the percutaneous IRE in Stage 3 pancreas cancer has been studied and there is currently a Food and Drug Administration approved, randomized, controlled trial, and registry enrolling patients in the United States. Recent animal studies have also demonstrated that the advantages of IRE may extend beyond the local tumor effect. In addition to this local ablative option, a phase 3 trial is studying a transarterial option in the management of pancreatic cancer.

Keywords
- pancreas
- IRE
- nanoknife

Pancreatic cancer is the third leading cause of cancer-related deaths in the United States and may soon surpass colorectal cancer, the second leading cause, by the end of 2020.[1] According to the National Cancer Institute Surveillance, Epidemiology, and End Results (NCI SEER) program, pancreatic cancer has one the highest mortality rates and its incidence in the United States has gradually increased by 0.5% annually for more than a decade.[2] Despite advances in understanding potential causative risk factors for pancreatic cancer and implementation of new innovative tools for early diagnosis, it is still characterized by aggressive tumor growth and poor prognosis.[3] Over the past two decades there have only been marginal improvements in overall long-term prognosis. The 5-year survival rate in the United States ranges from 5 to 10% and the estimated global 5-year survival rate is approximately 5%.[4] Pancreatic ductal adenocarcinoma accounts for more than 85% of all pancreatic malignancies.[5] Overall survival (OS), efficacy, and clinical outcomes are significantly affected by the stage of the disease at the time of patient's diagnosis.

Staging

Pancreatic cancer is characterized by silent progression and accelerated growth, which remains undetectable and often precludes an early diagnosis. Because of this, less than 20% of

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the patients present with resectable disease at time of diagnosis. The remaining patients present with Stage 3 locally advanced, unresectable pancreatic cancer (LAPC) typically associated with extensive vascular involvement (30–40%) or Stage 4 metastatic disease (40–50%).[4] Locally advanced disease is broadly defined as major tumor invasion into critical structures, particularly encasement of the hepatic artery, superior mesenteric artery/celiac trunk or extensive involvement of the portomesenteric vein, which is beyond the scope of feasible reconstruction.[6]

Imaging

Imaging plays a vital role in the initial diagnosis, staging, and follow-up of pancreatic cancer. The most common radiologic imaging modality is triple-phase contrast-enhanced thin-slice (multidetector row) helical computed tomography with three-dimensional reconstructions.[7] The advantages of computed tomography (CT) include ready availability, rapid acquisition time, and good spatial resolution. CT has a sensitivity of around 76 to 92% and specificity of 67% in the detection of pancreatic cancer.[8–11] During a pancreatic protocol CT, the arterial phase imaging is usually acquired 30 seconds after contrast injection and portal-venous phase imaging at 60 to 70 seconds after contrast injection. Multiphase acquisition aids with detection of the pancreatic mass, characterization of its enhancement pattern, identification of extent of involvement of vascular structures, and in detecting distant metastases to the liver.[12] Recent advances in CT technology include dual energy scans. Dual energy CT or spectral imaging can simultaneously image the patient utilizing two photon energies of X-rays (typically 80 and 140 kVp) with subsequent post processing, resulting in improved detection of pancreatic tumors.[13]

Magnetic resonance imaging (MRI) with gadolinium is a valuable imaging modality in pancreatic cancer. MRI's superb soft tissue resolution, multiplanar capabilities, and recent advances in diffusion-weighted imaging have proven to be invaluable in detection of even small tumors and subcentimeter metastases. Diffusion-weighted imaging can also be used in patients who are allergic to CT contrast or who have severe renal insufficiency. Compared with CT, MRI does require a much longer acquisition time and is highly dependent on patient cooperation for a quality scan. Patient motion and respiratory artifact significantly degrade image quality and diminish diagnostic capabilities. The quality of the MRI machine also significantly affects image quality, as does the signal strength of the magnet.

The response evaluation criteria in solid tumors (RECIST) and RECIST 1.1. are accepted imaging criteria traditionally used to assess response to treatment.[14] Concerns about using change in tumor size, as the only criterion to assess response following locoregional therapy have not been fully addressed, even in RECIST 1.1.

Data on imaging characteristics following locoregional treatment to the pancreas are limited. Vroomen et al studied MR and CT imaging characteristics and ablation zone volumetry of locally advanced pancreatic cancer treated with irreversible electroporation (IRE).[15] The study concluded that the most remarkable signal alterations after pancreatic IRE were shown by diffusion-weighted imaging with a high B-value and by contrast enhanced MRI (DWI-b800 and ceMRI).[15]

Surgery

Surgical resection still remains the most effective treatment modality in improving survival though only a small percentage of patients are surgical candidates at presentation. The standard Whipple procedure (pancreaticoduodenectomy) improves survival to 23 months when a tumor-free margin of 1 mm can be achieved.[16] Survival is increased to 35 months when a greater than 1-mm tumor-free margin (R0 wide) can be achieved. The optimal outcome following successful neoadjuvant treatment is downstaging to borderline-resectable disease or even resectable disease for surgical conversion.[17,18] Only 12 to 35% of LAPC patients are eligible for conversion surgery following neoadjuvant treatment.[19,20] The role of neoadjuvant therapy has been studied extensively. The recently published results of the PREOPANC randomized phase 3 trial found that preoperative chemoradiotherapy was associated with significantly better disease-free survival and locoregional failure free interval with improved survival.[21] Restaging after chemotherapy to determine resectability is evaluated via cross-sectional imaging and assessment of CA 19–9 levels.

Minimally invasive pancreatoduodenectomy is another surgical option, which results in decreased inflammation, morbidity, length of hospital stay, and improved outcomes as compared with an open Whipple surgery. The challenging technique has a steep learning curve, which has had an impact on widespread adoption. Several reviews of laparoscopic MIDP have been published highlighting advantages of this technique compared with open distal pancreatectomy.[22–24]

Medical Oncology

Gemcitabine (GEM) monotherapy has been the standard treatment for pancreatic cancer for over 30 years. It is known to have modest impact, with studies consistently reporting a marginal OS benefit of 5 to 7 months.[25,26] Recent efforts to enhance clinical efficacy have investigated the clinical benefit of GEM-based combination therapies but have failed to significantly improve the dismal prognosis associated with unresectable pancreatic cancer.[25,27–30] In the past decade, FOLFIRINOX has emerged as a treatment in the neoadjuvant setting for LAPC patients with a good performance status. FOLFIRINOX is a four-drug (5-fluorouracil, leucovorin, irinotecan, and oxaliplatin) chemotherapy regimen that has been shown to improve OS, increase patient eligibility for curative-intent surgery, and improve response rate by approximately 30%.[20,26,31,32] The PRODIGE 4/ACCORD 11 trail compared FOLFIRINOX with GEM monotherapy in metastatic pancreatic cancer. This study reported a median overall survival of 11.1 months in the FOLFIRINOX group compared with 6.8 months in the GEM group.[33] Following this study, two regimens, FOLFIRINOX and GEM plus nab-paclitaxel

(GnP) have been reported as effective therapeutic alternatives that provide more favorable outcomes in unresectable pancreatic cancer when compared with GEM alone.[32,34] A meta-analysis on FOLFIRINOX-based neoadjuvant therapy in borderline resectable or unresectable pancreatic cancer by Petrelli et al concluded that downstaging after neoadjuvant FOLFIRINOX-based therapy resulted in a 40% R0 resection rate.[32] FOLFIRINOX therapy is characterized by increased risk for toxicity, and patients who are unable to tolerate such toxicities can either receive a reduced dose to improve tolerability or receive GnP combination therapy.[33,35]

Locoregional Therapies

Despite multimodal treatment, the majority of patients with LAPC remain ineligible for resection. For this reason, patients who respond to neoadjuvant therapy with stable disease, or a partial response, should be considered as potential candidates for locoregional treatment strategies.

Thermal Ablation in Pancreas Cancer

Radiofrequency ablation (RFA) is local ablative modality that uses needle electrodes to apply high frequency alternating current to solid tumors. This process generates high temperatures, resulting in thermal coagulation, necrosis, and protein denaturation in the target lesion. Early studies investigating the clinical efficacy and safety of RFA in the setting of LAPC reported high rates of morbidity (4–37%) and mortality (0–25%).[33,35–38] Complications have been attributed to thermal injury to critical structures such as bile ducts, pancreatic duct, duodenum, vital vessels, and heat-sink resulting in incomplete ablation of the target lesion.[39] More recent RFA studies have reported improved OS by optimizing ideal parameters for temperature range (<90 degrees), treatment time, and probe placement.[40] More importantly, RFA requires a safety margin of at least 5 mm from the ablation zone to avoid thermal damage to vital structures.[39] Given the intricate anatomical location of pancreatic cancer, RFA is primarily used for large tumor debulking (i.e., cytoreductive treatment) to avoid potential damage to critical vasculature.[40]

Cryoablation induces rapid argon-gas-based freezing and thawing of target lesions based on the Joule-Thompson effect.[41] The freeze thaw cycles lead to cellular destruction by vascular-mediated cytotoxicity, endothelial damage, and cell death. Ablation of pancreatic cancer using cryoablation with and without immunotherapy was studied in a retrospective study along with patients who received chemotherapy or immunotherapy alone.[42] Median OS was higher in the cryoimmunotherapy (13 months) and cryotherapy groups (7 months) than in the chemotherapy group (3.5 months; both $p < 0.001$) and was higher in the cryoimmunotherapy group than in the cryotherapy ($p < 0.05$) and immunotherapy groups (5 months; $p < 0.001$).

Microwave ablation (MWA) is a heat-based thermal ablation modality that promotes tissue coagulation by the oscillation of water molecules, ultimately generating tissue necrosis.[43] Microwave has advantages over RFA in the ease of setup, active heating, and larger ablation zones in a shorter period of time. Published experience on the use of MW ablation in pancreatic cancer with survival data is very limited. A series of 15 patients treated with MWA, reported a median survival of 22 months.[44] Minor complications were seen in 40% of the patients, including mild pancreatitis, and minor bleeding.

Irreversible Electroporation

IRE is a nonthermal tumor-ablation technique that uses ultrashort high voltage direct current pulses to create an electric field across the cell membrane. This process disrupts membrane homeostasis and irreversibly alters transmembrane potential, which activates the apoptotic pathway and leads to cell death. Unlike thermal ablation modalities that can cause unwanted collateral damage, IRE has the unique ability to preserve the extracellular matrix, critical vasculature and minimize heat-sink effects.[45] The technology is commercially available as the NanoKnife (Angiodynamics Latham, NY) and has 510(k) clearance by the Food and Drug Administration (FDA) for ablation for soft tissue tumors.

Percutaneous IRE in Pancreas Cancer

There have been a growing number of clinical studies documenting the safety profile and efficacy of percutaneous IRE in the treatment of pancreatic cancer. Narayanan et al first described the percutaneous technique using IRE in 14 patients who underwent 15 treatments and two were downstaged to R0 resection.[46] A larger retrospective review of 50 patients with LAPC treated with percutaneous IRE reported a median OS of 27 months (95% confidence interval [CI], 22.7–32.5 months) from the time of diagnosis and 14.2 months (95% CI, 9.7–16.2 months) from the time of IRE.[47] On multivariate analysis, OS was significantly longer in tumors ≤3 cm than those >3 cm (33.8 vs. 22.7 months from the time of diagnosis and 16.2 vs. 9.9 months from IRE, respectively). A retrospective review of 75 patients with unresectable pancreatic carcinoma who underwent percutaneous IRE after chemotherapy between 2011 and 2016 reported a median OS and progression free survival post-IRE for LAPC of 27 and 15 months, respectively.[48] Four patients with LAPC were downstaged to surgery post-IRE ablation, with complete R0 resections in three cases.

The phase 1/2 PANFIRE study was the first prospective trial to analyze the safety of percutaneous IRE for locally advanced pancreatic cancer. There were no reported patient deaths within 90 days of the IRE procedure. Out of the 25 patients included in the study, 11 and nine patients developed grade I/II and grade III adverse events (AEs), respectively.[49]

Another small prospective series, that included both percutaneous and intraoperative IRE showed no significant difference between the safety profiles of either procedure and reported no mortalities within 90 days of the procedure.[50] There were two grade IV AEs, one hematemesis and epigastric pain, a second patient with a pseudoaneurysm in the first jejunal artery.[50] The median time to local

progression after IRE was 12.0 months, and the median OS was 17.5 months from IRE and 24.0 months from the diagnosis, with no significant differences between the approaches.

The PANFIRE II, a multicenter prospective single-arm phase 2 study, included 50 patients with locally advanced and recurrent pancreatic cancer. The median OS was 17 months from the time of diagnosis, with a median local tumor PFS of 10 months and 46% local progression after IRE.[19] However, in this study the authors do note that because IRE was performed percutaneously without precursory laparoscopy, some patients with disseminated disease were possibly included in the study.

Although the amount of available retrospective and prospective data are growing, there is still a need for a randomized controlled clinical trial to conclusively compare both the safety and efficacy of IRE and its role in standard of care regimens. This would add to the body of available evidence, which is currently complicated by the heterogeneity of systemic treatment regimens before and after IRE, which may make it difficult to clearly isolate the effect of IRE on survival.

The DIRECT Study for Stage 3 Pancreatic Cancer

In 2018, the FDA approved the Nanoknife system for Breakthrough Device Designation and subsequently approved an investigational device exemption application for the Nanoknife to study the role in pancreatic cancer. This enabled the DIRECT study, a randomized control trial (RCT) and a real-world evidence registry, which will also have a control arm.

This multicenter trial will involve 264 patients receiving IRE and 264 patients receiving standard of care treatment. The primary end points will be OS and safety. Other end points will include PFS and pain scores. Following induction chemotherapy with FOLFIRINOX, patients with inoperable biopsy proven Stage 3 pancreatic carcinoma will be randomized to IRE plus institutional standard of care treatment and follow-up versus institutional standard of care treatment and follow-up. The IRE treatment can be offered by either a percutaneous or open surgical approach. The registry will provide insight into the clinical utility of IRE and capture evidence of multimodal treatment regimens in a real-world setting. Both studies are currently enrolling patients in the United States.

Transarterial Option

The inability of chemotherapeutic agents to effectively penetrate pancreatic cancer cells has been one of the limiting factors. The FDA-cleared RenovoCath (RenovoRx, Inc) provides the ability to deliver highly concentrated therapeutic and/or chemotherapeutic materials to specific vasculature safely via a dual-balloon catheter without perfusion overlap to other regions.

This catheter has the potential to deliver much higher concentrations of drug to the tumor, as well as limit systemic exposure. In the first-in-human, phase 1, multicenter safety study in patients with LAPC 20 participants were enrolled in a dose escalation study of intra-arterial, locally delivered GEM with doses up to 1,000 mg/m^2.[51] Fifteen patients completed the study with more than two treatments. This study results reported a 58% reduction of cancer antigen 19–9 tumor marker, three patients had tumor progression, one had a partial response, and 11 showed stable disease. The survival rate for this cohort was 60% at 1 year and 43% at 2 years.[51] A phase 2, multicenter, registry of 22 patients reported a median OS from diagnosis of 18.8 months with the greatest benefit in those who had previous chemoradiation. The TIGeR-PaC is a phase 3, multicenter RCT that is currently enrolling patients and is evaluating transarterial GEM versus systemic chemotherapy with GEM and nab-paclitaxel following initial chemoradiation for patients with LAPC. The primary objective is OS from the time of randomization. Secondary objectives include progression-free survival, response rates, quality of life, tolerability, and safety. The outcome of this trial will help to better understand the role of transarterial therapy in the management of LAPC.

IRE beyond Local Ablation in Pancreas Cancer

One of the most promising areas of therapeutic development in cancer management has been immuno-oncology. In this approach tumors cells are targeted by various approaches that aim to strengthen the body's natural immune response. This approach, although promising has been met with mixed response and varies greatly depending on the tumor type. The most success thus far has been seen in what are referred to as "hot tumors." These are tumors in which there is already an existing antitumor immune response within the local tumor microenvironment. However, there are many tumors such as pancreatic cancer, where there is little to no local antitumor response and where the local microenvironment and response is overwhelmingly immunosuppressive.[52] To overcome these "cold" tumors different strategies are needed that work to convert the immune-suppressive microenvironment to one that is more amendable to a more robust antitumor immune response. Other factors that influence the responsiveness of tumors to immunotherapies include microsatellite instability and tumor mutational burden. These factors have been shown to affect the tumors visibility and sensitivity to the immune system.[52]

In preclinical studies comparing the local immune response to focal therapies in pancreatic cancer, IRE induced a greater infiltration of critical antitumor immune cell population such as macrophages and T cells within 24 hours after the ablation.[53] The study also observed a potential abscopal effect after IRE, in which there is both an increased local and systemic immune response, which offers increased antitumor immunity.[53]

In pancreas cancer the local tumor environment is composed of a highly fibrotic stroma that promotes tumor growth while excluding and suppressing a local immune response.[54] Promising preclinical studies suggest that IRE may work in concert with established immune checkpoint

blockades such as anti-PD1 in an orthotopic murine pancreatic cancer model.[55] This study suggests that IRE increases the immunogenicity of pancreatic cancer by releasing tumor antigens and other immune signals that alter the local stroma collectively improving the efficacy of antitumor immune modulation within the tumor.[55]

In a clinical study of 10 patients with LAPC, the safety, feasibility, and efficacy of percutaneous image-guided IRE were explored. Using flow cytometry, the authors evaluated the frequency and activation state of lymphocytic and myeloid subsets in pre- and post-treatment peripheral blood samples.[56] Tumor-specific systemic T-cell responses to the pancreatic cancer-associated antigen Wilms Tumor were determined after in vitro stimulation in an interferon-y enzyme-linked immune spot assay, at baseline and at 2 weeks and 3 months after IRE. The data showed a transient decrease in systemic regulatory T cells (Treg) and a simultaneous transient increase in activated PD-1 + T cells, consistent with the temporary reduction of tumor-related immune suppression after the IRE procedure. Post-IRE boosting of a preexisting WT1 specific T-cell response was seen in two out of three patients as well as the de novo induction of these responses in another two patients. There was a trend for these WT1 T-cell responses to be related to longer OS ($p = 0.055$). The findings were consistent with a systemic and tumor-specific immune stimulatory effect of IRE and support the combination of percutaneous IRE with therapeutic immune modulation. The data regarding the immunomodulatory effect of IRE, though preliminary, is very promising and should be an area of active investigation especially given the increase in combinatorial approaches in oncology clinical treatment algorithms.

Conclusion

The presentation of pancreatic cancer allows only a very small percentage of patients qualifying for surgery. Conventional treatment of pancreatic cancer, with chemotherapy, and chemoradiotherapy has not made a significant impact on the OS of these patients. Focal therapies, especially when delivered percutaneously, provide a safe and efficacious option for local tumor control. Current studies investigating IRE in the setting of LAPC have demonstrated the advantage of its clinical versatility in combination with multimodal treatment strategies. There is a growing amount of evidence that supports the clinical utility of IRE and other nonthermal modalities as a method of local and systemic control. The studies presented highlight additional opportunities to better understand how local treatments like IRE and transarterial treatment with RenovoCath can be further developed to improve tumor response, OS, and quality of life. Locoregional treatments in combination with other therapeutic strategies hold promise for the enhancement of clinical outcomes in the setting of LAPC.

Conflict of Interest
A.U. reports grants from Renovo Rx, during the conduct of the study. G.N. reports personal fees from Angiodynamics, outside the submitted work. Dr. R.T.G. reports grants from Renovo Rx, during the conduct of the study. All the other authors report no conflict of interest.

References

1 Zhu H, Li T, Du Y, Li M. Pancreatic cancer: challenges and opportunities. BMC Med 2018;16(01):214
2 Landman A, Feetham L, Stuckey D. Working together to reduce the burden of pancreatic cancer. Lancet Oncol 2020;21(03):334–335
3 Orth M, Metzger P, Gerum S, et al. Pancreatic ductal adenocarcinoma: biological hallmarks, current status, and future perspectives of combined modality treatment approaches. Radiat Oncol 2019;14(01):141
4 Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020;70(01):7–30
5 Kleeff J, Korc M, Apte M, et al. Pancreatic cancer. Nat Rev Dis Primers 2016;2:16022
6 Tempero MA, Malafa MP, Chiorean EG, et al. Pancreatic adenocarcinoma, version 1.2019. J Natl Compr Canc Netw 2019;17(03): 202–210
7 Ferrone CR, Marchegiani G, Hong TS, et al. Radiological and surgical implications of neoadjuvant treatment with FOLFIRINOX for locally advanced and borderline resectable pancreatic cancer. Ann Surg 2015;261(01):12–17
8 Ahn SS, Kim MJ, Choi JY, Hong HS, Chung YE, Lim JS. Indicative findings of pancreatic cancer in prediagnostic CT. Eur Radiol 2009;19(10):2448–2455
9 Amin Z, Theis B, Russell RC, House C, Novelli M, Lees WR. Diagnosing pancreatic cancer: the role of percutaneous biopsy and CT. Clin Radiol 2006;61(12):996–1002
10 Palazzo L, Roseau G, Ruskone-Fourmestraux A, et al. Endoscopic ultrasonography in the local staging of primary gastric lymphoma. Endoscopy 1993;25(08):502–508
11 Sheridan MB, Ward J, Guthrie JA, et al. Dynamic contrast-enhanced MR imaging and dual-phase helical CT in the preoperative assessment of suspected pancreatic cancer: a comparative study with receiver operating characteristic analysis. AJR Am J Roentgenol 1999;173(03):583–590
12 McNulty NJ, Francis IR, Platt JF, Cohan RH, Korobkin M, Gebremariam A. Multi–detector row helical CT of the pancreas: effect of contrast-enhanced multiphasic imaging on enhancement of the pancreas, peripancreatic vasculature, and pancreatic adenocarcinoma. Radiology 2001;220(01):97–102
13 George E, Wortman JR, Fulwadhva UP, Uyeda JW, Sodickson AD. Dual energy CT applications in pancreatic pathologies. Br J Radiol 2017;90(1080):20170411
14 Ohorodnyk P, Eisenhauer EA, Booth CM. Clinical benefit in oncology trials: is this a patient-centred or tumour-centred end-point? Eur J Cancer 2009;45(13):2249–2252
15 Vroomen LGPH, Scheffer HJ, Melenhorst MCAM, et al. MR and CT imaging characteristics and ablation zone volumetry of locally advanced pancreatic cancer treated with irreversible electroporation. Eur Radiol 2017;27(06):2521–2531
16 Andriulli A, Festa V, Botteri E, et al. Neoadjuvant/preoperative gemcitabine for patients with localized pancreatic cancer: a meta-analysis of prospective studies. Ann Surg Oncol 2012;19 (05):1644–1662
17 Flak RV, Stender MT, Jensen TM, et al. Treatment of locally advanced pancreatic cancer with irreversible electroporation—a Danish single center study of safety and feasibility. Scand J Gastroenterol 2019;54(02):252–258
18 Hank T, Strobel O. Conversion surgery for advanced pancreatic cancer. J Clin Med 2019;8(11):E1945
19 Ruarus AH, Vroomen LGPH, Geboers B, et al. Percutaneous irreversible electroporation in locally advanced and recurrent pancreatic cancer (PANFIRE-2): a multicenter, prospective, single-arm, phase II study. Radiology 2020;294(01):212–220

20 Rombouts SJ, Mungroop TH, Heilmann MN, et al. FOLFIRINOX in locally advanced and metastatic pancreatic cancer: a single centre cohort study. J Cancer 2016;7(13):1861–1866

21 Versteijne E, Suker M, Groothuis K, et al; Dutch Pancreatic Cancer Group. Preoperative chemoradiotherapy versus immediate surgery for resectable and borderline resectable pancreatic cancer: results of the Dutch randomized phase III PREOPANC trial. J Clin Oncol 2020;38(16):1763–1773

22 Shi S, Hua J, Yu XJ. Oncologic outcomes of minimally invasive versus open distal pancreatectomy for pancreatic neuroendocrine tumors: randomized controlled trials are needed. J Surg Oncol 2019;120(07):1284–1285

23 van Hilst J, de Rooij T, Klompmaker S, et al; European Consortium on Minimally Invasive Pancreatic Surgery (E-MIPS). Minimally invasive versus open distal pancreatectomy for ductal adenocarcinoma (DIPLOMA): a pan-European propensity score matched study. Ann Surg 2019;269(01):10–17

24 Yang DJ, Xiong JJ, Lu HM, et al. The oncological safety in minimally invasive versus open distal pancreatectomy for pancreatic ductal adenocarcinoma: a systematic review and meta-analysis. Sci Rep 2019;9(01):1159

25 Cunningham D, Chau I, Stocken DD, et al. Phase III randomized comparison of gemcitabine versus gemcitabine plus capecitabine in patients with advanced pancreatic cancer. J Clin Oncol 2009;27 (33):5513–5518

26 Moris D, Machairas N, Tsilimigras DI, et al. Systematic review of surgical and percutaneous irreversible electroporation in the treatment of locally advanced pancreatic cancer. Ann Surg Oncol 2019;26(06):1657–1668

27 Berlin JD, Catalano P, Thomas JP, Kugler JW, Haller DG, Benson AB III. Phase III study of gemcitabine in combination with fluorouracil versus gemcitabine alone in patients with advanced pancreatic carcinoma: Eastern Cooperative Oncology Group Trial E2297. J Clin Oncol 2002;20(15):3270–3275

28 Bramhall SR, Schulz J, Nemunaitis J, Brown PD, Baillet M, Buckels JA. A double-blind placebo-controlled, randomised study comparing gemcitabine and Marimastat with gemcitabine and placebo as first line therapy in patients with advanced pancreatic cancer. Br J Cancer 2002;87(02):161–167

29 Burris H, Storniolo AM. Assessing clinical benefit in the treatment of pancreas cancer: gemcitabine compared to 5-fluorouracil. Eur J Cancer 1997;33(Suppl 1):S18–S22

30 Hu J, Zhao G, Wang HX, et al. A meta-analysis of gemcitabine containing chemotherapy for locally advanced and metastatic pancreatic adenocarcinoma. J Hematol Oncol 2011;4:11

31 Dhir M, Zenati MS, Hamad A, et al. FOLFIRINOX versus gemcitabine/nab-paclitaxel for neoadjuvant treatment of resectable and borderline resectable pancreatic head adenocarcinoma. Ann Surg Oncol 2018;25(07):1896–1903

32 Petrelli F, Coinu A, Borgonovo K, et al; Gruppo Italiano per lo Studio dei Carcinomi dell'Apparato Digerente (GISCAD). FOLFIRINOX-based neoadjuvant therapy in borderline resectable or unresectable pancreatic cancer: a meta-analytical review of published studies. Pancreas 2015;44(04):515–521

33 Conroy T, Desseigne F, Ychou M, et al; Groupe Tumeurs Digestives of Unicancer PRODIGE Intergroup. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011;364(19): 1817–1825

34 Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med 2013;369(18):1691–1703

35 Tong H, Fan Z, Liu B, Lu T. The benefits of modified FOLFIRINOX for advanced pancreatic cancer and its induced adverse events: a systematic review and meta-analysis. Sci Rep 2018;8(01):8666

36 Fegrachi S, Besselink MG, van Santvoort HC, van Hillegersberg R, Molenaar IQ. Radiofrequency ablation for unresectable locally advanced pancreatic cancer: a systematic review. HPB (Oxford) 2014;16(02):119–123

37 Pandya GJ, Shelat VG. Radiofrequency ablation of pancreatic ductal adenocarcinoma: the past, the present and the future. World J Gastrointest Oncol 2015;7(02):6–11

38 Pezzilli R, Casadei R, Calculli L, Santini D, Morselli-Labate AMNeoPan Study Group. Serum determination of CA 19-9 in diagnosing pancreatic cancer: an obituary. Dig Liver Dis 2010;42(01):73–74

39 D'Onofrio M, Barbi E, Girelli R, et al. Radiofrequency ablation of locally advanced pancreatic adenocarcinoma: an overview. World J Gastroenterol 2010;16(28):3478–3483

40 Girelli R, Frigerio I, Giardino A, et al. Results of 100 pancreatic radiofrequency ablations in the context of a multimodal strategy for stage III ductal adenocarcinoma. Langenbecks Arch Surg 2013; 398(01):63–69

41 Cazzato RL, Garnon J, Ramamurthy N, et al. Percutaneous image-guided cryoablation: current applications and results in the oncologic field. Med Oncol 2016;33(12):140

42 Niu L, Chen J, He L, et al. Combination treatment with comprehensive cryoablation and immunotherapy in metastatic pancreatic cancer. Pancreas 2013;42(07):1143–1149

43 Ahmed M, Brace CL, Lee FT Jr, Goldberg SN. Principles of and advances in percutaneous ablation. Radiology 2011;258(02): 351–369

44 Lygidakis NJ, Sharma SK, Papastratis P, et al. Microwave ablation in locally advanced pancreatic carcinoma—a new look. Hepatogastroenterology 2007;54(77):1305–1310

45 Maor E, Ivorra A, Leor J, Rubinsky B. The effect of irreversible electroporation on blood vessels. Technol Cancer Res Treat 2007;6 (04):307–312

46 Narayanan G, Hosein PJ, Arora G, et al. Percutaneous irreversible electroporation for downstaging and control of unresectable pancreatic adenocarcinoma. J Vasc Interv Radiol 2012;23(12): 1613–1621

47 Narayanan G, Hosein PJ, Beulaygue IC, et al. Percutaneous image-guided irreversible electroporation for the treatment of unresectable, locally advanced pancreatic adenocarcinoma. J Vasc Interv Radiol 2017;28(03):342–348

48 Leen E, Picard J, Stebbing J, Abel M, Dhillon T, Wasan H. Percutaneous irreversible electroporation with systemic treatment for locally advanced pancreatic adenocarcinoma. J Gastrointest Oncol 2018;9(02):275–281

49 Scheffer HJ, Vogel JA, van den Bos W, et al. The influence of a metal stent on the distribution of thermal energy during irreversible electroporation. PLoS One 2016;11(02):e0148457

50 Sugimoto K, Moriyasu F, Tsuchiya T, et al. Irreversible electroporation for nonthermal tumor ablation in patients with locally advanced pancreatic cancer: initial clinical experience in Japan. Intern Med 2018;57(22):3225–3231

51 Rosemurgy AS, Ross SB, Vitulli PL, Malek R, Li J, Agah R. Safety study of targeted and localized intra-arterial delivery of gemcitabine in patients with locally advanced pancreatic adenocarcinoma. J Pancreat Cancer 2017;3(01):58–65

52 Bonaventura P, Shekarian T, Alcazer V, et al. Cold tumors: a therapeutic challenge for immunotherapy. Front Immunol 2019;10:168–168

53 White SB, Zhang Z, Chen J, Gogineni VR, Larson AC. Early immunologic response of irreversible electroporation versus cryoablation in a rodent model of pancreatic cancer. J Vasc Interv Radiol 2018;29(12):1764–1769

54 Feig C, Gopinathan A, Neesse A, Chan DS, Cook N, Tuveson DA. The pancreas cancer microenvironment. Clin Cancer Res 2012;18(16): 4266–4276

55 Zhao J, Wen X, Tian L, et al. Irreversible electroporation reverses resistance to immune checkpoint blockade in pancreatic cancer. Nat Commun 2019;10(01):899

56 Scheffer HJ, Stam AGM, Geboers B, et al. Irreversible electroporation of locally advanced pancreatic cancer transiently alleviates immune suppression and creates a window for antitumor T cell activation. OncoImmunology 2019;8(11):1652532