

Nonoperative Ablation of Pancreatic Neoplasms



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KEYWORDS

- Pancreatic cancer • Minimally invasive therapies • High-intensity focused ultrasound
- Radiofrequency ablation • Cryotherapy • Irreversible electroporation
- Microwave ablation

KEY POINTS

- The prognosis of pancreatic cancer remains dismal. Although surgical resection is the only curative treatment, almost 80% of patients are diagnosed in advanced unresectable stages.
- The noninvasiveness, high-safety, and multimodal approach suggest high-intensity focused ultrasound as a possible treatment in management of unresectable advanced pancreatic cancer, with promising results in terms of pain palliation and tumor control.
- Radiofrequency ablation, microwave ablation, irreversible electroporation, and cryoablation have been used for the management of unresectable locally advanced pancreatic cancer. There is some experience with their intraoperative use; however, in the future, an important role may be fulfilled by percutaneous approaches to reduce risks and morbidity.
- Minimally invasive therapies are promising for unresectable pancreatic cancers to achieve symptoms palliation and local tumor control.

The prognosis of pancreatic cancer remains dismal.¹ Although surgical resection is thought by many to be the only curative treatment, due to the aggressive nature of the cancer and the nonspecificity of symptoms, almost 80% of patients are diagnosed in advanced unresectable stages.²

For this reason, in the past few years, a strong effort has been made to investigate the application of minimally invasive ablative techniques for unresectable, locally advanced pancreatic cancer. These procedures, associated with lower morbidity and mortality, have demonstrated positive results on local tumor control and palliation

Disclosure Statement: The authors have nothing to disclose.

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Surg Clin N Am 98 (2018) 127–140

<https://doi.org/10.1016/j.suc.2017.09.010>

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of symptoms. The main limitations and challenges of the treatments are the organ location and the risk to develop pancreatitis or to damage the contiguous neurovascular structures. Studies have described the use of high-intensity focused ultrasound (HIFU), radiofrequency ablation (RFA), microwave ablation (MWA), cryotherapy, and irreversible electroporation (IRE). Some experience has accumulated with the intraoperative use of these techniques; however, in the future, an important step may be fulfilled by percutaneous approaches to reduce morbidity and mortality. Although the clinical applications of minimally invasive therapies for pancreatic cancers are still in their infancy, the results are promising.

HIGH-INTENSITY FOCUSED ULTRASOUND

HIFU is a new totally noninvasive technique approved by the US Food and Drug Administration for the treatment of painful bone metastases, uterine fibroids, and essential tremor. Recently, new applications in oncology, including the management of unresectable pancreatic cancer, are undergoing study and are showing promising results.³ HIFU, either ultrasound (US)-guided focused US (FUS) (USgFUS) or MRI-guided FUS (MRgFUS), generates and focuses a beam of high-energy US to a precisely defined region of few millimeters, called the sonication spot. In few seconds the energy accumulates, inducing a steep increase in temperature that causes coagulative necrosis in the targeted tissue. HIFU has considerable advantages over other minimally invasive techniques in that it is totally noninvasive, does not use ionizing radiations, and, if MRI-guided, monitors in real-time the temperature reached in the tissue, ensuring a safe and effective ablation.

PREOPERATIVE PLANNING AND PATIENT PREPARATION

Although some variation may be present among the studies, some steps are universally performed before treatment. The patient should be fasting and procedures to displace the bowel from the US beam, such as drinking degassed water or intestinal cleaning, may be used to decrease the chance of adverse events. The patient is positioned prone on the treatment bed with the region to be treated cleaned, examined to exclude the presence of scars, and aligned with the US transducer. A coupling gel or immersion of the area to be treated in degassed water increases the contact with the transducer eliminating any interposed air. The main precaution to reduce any risk of adverse outcomes is to ensure the patient has neither air nor scars interposed in the beam trajectory because they may reflect or absorb heat, causing collateral damage and decreasing the effective dose delivered. MRgFUS and USgFUS require general anesthesia, whereas in pulsed USgFUS local anesthesia is sufficient and sometimes no anesthesia is necessary. Vital signs are monitored during the procedure. If the patient is conscious, a stop button is provided to interrupt the treatment in case of unpleasant sensations.

TREATMENT

Planning

Before the treatment starts, the patient position is checked and the acoustic window is optimized using the diagnostic probe incorporated in the transducer in USgFUS or acquiring T1-weighted and T2-weighted MRI sequences, with and without fat saturation, at the inspiration phase in MRgFUS.

The treatment plan is assessed in 4 phases:

1. Calibration: The orientation and position of the transducer in relation to the target lesion is assessed.

2. Segmentation: On acquired 2-dimensional cross-slice images, the operator manually outlines the region of treatment to be ablated, the skin border, and the limited energy density regions that may be damaged by the US beam (nerves, bowel, and bones). Anatomic fiducials are placed to detect any movement of the patient.
3. Planning: The software automatically calculates the optimal ablation coverage of the region of treatment, planning the number and position of sonications, and ensures a safe margin between the beam and neighboring viscera. Manual adjustments of the US beam orientation and the number and location of the sonications ensure a safe complete ablation of the target.
4. Verification: A series of sonications below the ablative threshold are performed to confirm the correct targeting.

Procedure

After the planning, treatment is started by increasing the power and energy of the sonications to reach ablative temperatures between 60°C and 80°C. For pancreatic cancer, the authors use a threshold of 65°C to define successful ablation. The treatment includes a specific number of sonications separated by a cooling time to allow heat dissipation and avoid damage in the near-fields or far-fields. For each sonication, the operator can change sonication parameters: duration, location, size of the spot, power, energy, angulation of the US beam, and cooling time (**Fig. 1**). USgFUS relies on the detection of a hyperechogenic change in the targeted region to assess the ablation status. MRgFUS provides more accurate monitoring using MRI thermometry sequences that detect temperature changes based on heat-induced changes in the hydrogen bonds of water contained within the tissue. It displays a thermal map where

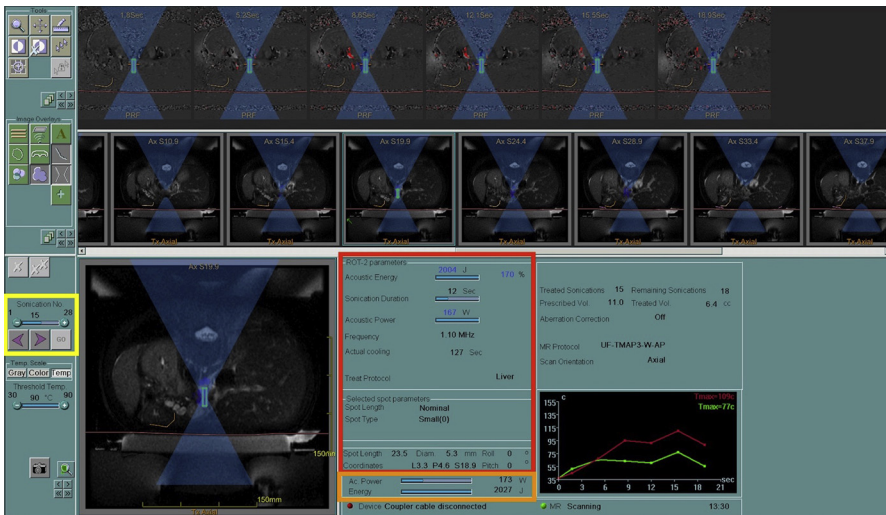


Fig. 1. MRgFUS (ExAblate 2100 type 1.1, InSightec, Haifa, Israel) coupled with a 3T-MRI system (General Electric Health Care, Milwaukee, WI, USA) treatment of pancreatic cancer. This treatment screen illustrates the intraprocedural MRI and parameters of sonication number 15 (yellow outline). On the right, a panel (red outline) displays the sonication parameters with the possibility of manual adjustments of the settings by the operator. The actually delivered energy and power are reported below (orange outline). The temperature reached in the spot can be monitored on the temperature curves at the bottom right. Note in the top row the MRI thermometry sequences.

regions that achieved a sufficient temperature for ablation are colored and easily visualized. The temperature in the surrounding tissues is also monitored (Fig. 2). At the end of the MRgFUS procedure, hypointense regions on gadolinium-enhanced T1-weighted images are considered ablated.

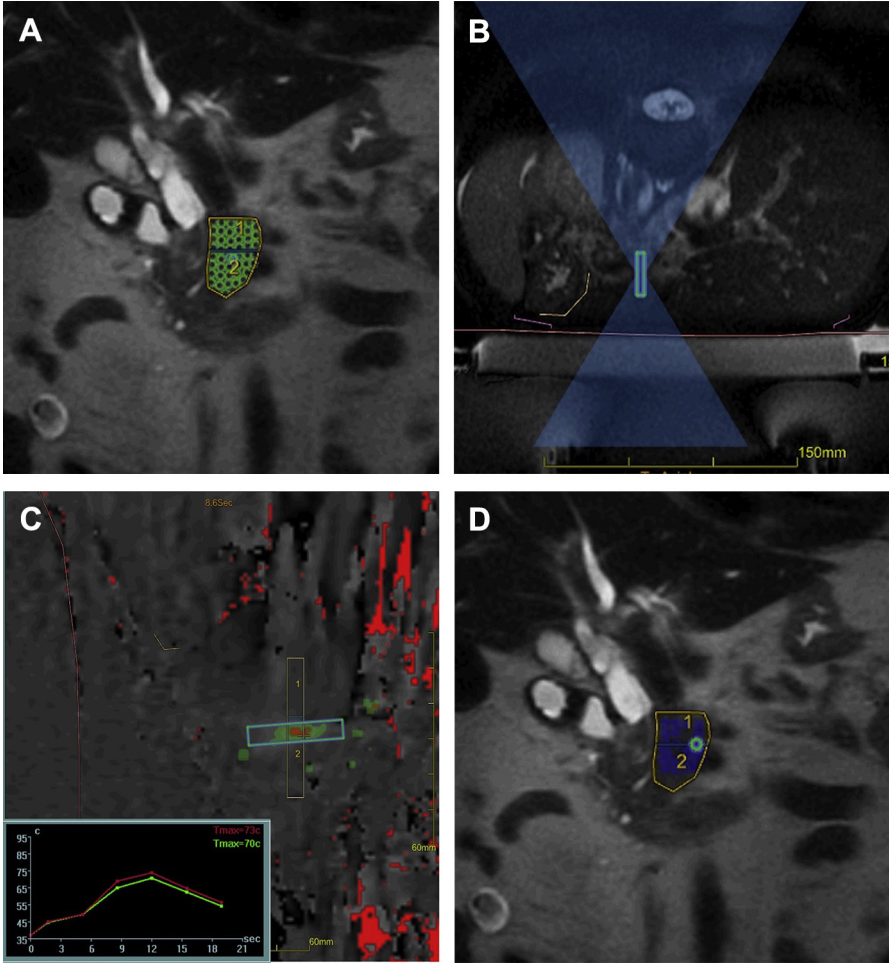


Fig. 2. (A) MRI reformatted on the coronal plane showing the region of treatment (yellow line) delineated during the segmentation phase of the procedure. The green circles are the sonication spots computed by the software; the operator is free to change and adjust them based on tumor features. (B) MRI reformatted on the axial plane displaying the sonication spot (blue rectangular box) with the acoustic window highlighted as a blue cone. It is important to exclude air and scar tissue from the acoustic window because they can interact with the US beam, causing adverse events. (C) MRI thermometry sequence that allows visualization in real-time of the deposition of energy and the increase in tissue temperature during the treatment. The sonicated area is indicated by the blue rectangular box; inside, the region that reached the ablative temperature threshold is colored. A cursor allows monitoring of the temperature in the surrounding tissue. The temperature graph below provides quantitative information of tissue heating. (D) MRI reformatted on the coronal plane shows the ablated area (blue) inside the region of treatment (yellow) and the next sonication spot (light blue circle) that is going to be targeted.

Postanesthesia, the vital signs and pancreatic function are monitored, and the skin is monitored for burns. Analgesics or antiemetics are administered as needed. We hospitalize all patients for 24 hours and all receive intravenous steroids (40 mg methylprednisolone) to avoid vascular compression from edema of the lesion or surrounding tissue.

REVIEW OF THE LITERATURE

The 2 main imaging guidance methods for HIFU are US or MRI. For pancreatic cancer most use USgFUS, whereas MRI guidance has been used only in the authors' center. USgFUS is less expensive, more accessible and allows easier control of respiratory displacement of the target and easy visualization of interfering interphase in the US beam.⁴ Two different devices have been used. The first involves the application of continuous high-intensity US, which requires general anesthesia and hospitalization, but potentially treats the entire lesion in a single session. The second uses pulsed lower energy sonications, which permits treatment with conscious sedation or, at times, without anesthesia and hospitalization but requires multiple sessions per patient.⁵ Both result in reasonably successful treatments.⁶ The largest clinical trials published are from China and are not available in English language. In Western countries, the application of HIFU to pancreatic cancer is quite recent and the publications are mostly retrospective. Prospective randomized clinical trials are expected in the future.

In the literature, the inclusion criteria vary. The most selective treat only body and tail lesions of the pancreas and exclude pancreatic head lesions to avoid posttreatment edema. Most patients had stage III or IV pancreatic adenocarcinoma.

Partial tumor responses range from 14% to 100%.⁶ Debate exists on assessing effective ablation in USgFUS because the hyperechogenic change of lesions may differ with the postablation computed tomography (CT) scan. CT or contrast-enhanced MRI are preferred postablation. Recently, PET-CT is being evaluated to determine the metabolic tumor changes.⁶

Importantly, some investigators have reported downstaging of unresectable lesions to resectable ones after HIFU therapy.^{7,8} HIFU has been used to treat liver and other metastases, to gain better tumor control.^{9,10} HIFU treatment of the liver can be challenging but was successful in all reported cases.

A greater tumor response and longer survival has been obtained when HIFU is combined with concurrent chemotherapy or radiotherapy.¹¹ Because the overall survival has not been rigorously addressed and randomized controlled studies are lacking, it is not possible to compare survival with HIFU and other therapies. Vidal-Jove and colleagues¹² evaluated retrospectively 48 pancreatic cancers after HIFU with chemotherapy. The overall median survival was 16 months, with 14 patients alive at the time of the report. The study identified patients with stage III cancers and minimal vascular invasion who were not candidates for surgical resection as a subpopulation that could benefit from HIFU for a long-term disease-free survival. In a retrospective analysis on 689 patients with unresectable pancreatic cancer, 436 were treated with HIFU alone or HIFU combined with other therapies. A stratified analysis found a survival benefit after HIFU combined with other therapies compared with only HIFU, and for repeated HIFU for tumor recurrence compared with single HIFU. The major survival advantage was found in stage IV pancreatic cancers.¹³

HIFU has a high safety profile. No deaths were reported in the published reports. Mild complications occurred, mostly skin burns of first and second degree, skin redness, edema and pain in the treated region, induration of subcutaneous tissue, transient edema, and low-grade fever.¹⁴ A pancreatic pseudocyst has been

observed.^{7,15} These events can be minimized by adopting the necessary precautions in the treatment preparation. Jaundice has also been reported secondary to HIFU ablation.¹⁶ The transient amylase and lipase increase detected in some patients is usually asymptomatic and clinical pancreatitis is rarely encountered.¹⁶ This may be explained by the mechanism of cell death induced by HIFU: when the cell's temperature reaches the ablative threshold, there is a degradation of pancreatic enzymes followed by cell death (thermal fixation).¹⁷ The feared complication is bowel perforation due to the interposition of intestinal loops along the US beam. The literature reports a few cases of pancreaticoduodenal fistula.⁹ One case of portal vein thrombosis requiring hospitalization occurred. The pancreatic cancer was compressing the vessel and the edema after the procedure may have increased the impingement.¹⁸

Other Pancreatic Lesions

Although most of the studies use HIFU for pancreatic adenocarcinoma, there are case reports of HIFU and other pancreatic lesions.

Currently, there is no standard management for patients with unresectable pancreatic neuroendocrine tumors.¹⁹ In these cases, HIFU may palliate symptoms and ameliorate survival and quality of life. In a case report by Chen and colleagues,¹⁹ an 80-year-old patient diagnosed with a very large lesion (10.1–9.4 cm) on CT scan was experiencing significant clinical symptoms. Because other treatment modalities were not feasible because of comorbidities or refusal, HIFU was used to palliate the pain and achieve local tumor control. After 3 cycles of pulsed FUS, pain decreased from a baseline numeric rating scale (NRS) of 8 out of 10 to a posttreatment NRS of 1 out of 10. The patient was still alive at article writing, with stable disease according to World Health Organization Criteria for Response.

Orgera and colleagues²⁰ described the palliative treatment of 3 patients with unresectable insulinomas with lung and liver metastases. These patients were suffering severe episodes of nocturnal hypoglycemia, uncontrolled by medical therapy. After undergoing a combined regiment of HIFU, chemotherapy, and radiotherapy, the tumors were successfully ablated with no occurrence of side effects and resolution of the episodes of nocturnal hypoglycemia.

Orsi and colleagues¹⁸ described HIFU combined with radiotherapy and chemotherapy for 1 unresectable neuroendocrine pancreatic tumor. A complete response was observed on posttreatment images with no side effects. The same group treated a metastatic anaplastic pancreatic carcinoma infiltrating the splenic artery and superior mesenteric vein. After 5 cycles of systemic chemotherapy, the patient underwent HIFU and other 5 more cycles of chemotherapy. After HIFU, a large necrosis was present in the center of the tumor with a reduction in the mass and paraaortic lymph nodes size. Dyspepsia and dorsal pain were resolved.²¹

Orgera and colleagues²² described the treatment of a pancreatic metastatic lesion from a renal cell carcinoma. After resection of the primary renal cell carcinoma, staged as T3bN0M0 according to the TNM classification of Malignant Tumours, a nodule was detected in the pancreatic head by CT scan at a 3-month follow-up. The patient was not considered a suitable candidate for surgery due to the short disease-free interval. During follow-up, further progression was seen and the patient underwent HIFU. After the treatment, there was a complete lack of enhancement without any injury to the surrounding organs. At 9-month follow-up after HIFU, the decreased size of the mass and lack of enhancement were confirmed, without evidences of recurrence.

These preliminary reports support the efficacy of HIFU in the treatment of numerous types of pancreatic lesions. Further clinical trials are needed to evaluate the efficacy, safety, and long-term results.

THE AUTHORS EXPERIENCE WITH MRI-GUIDED FOCUSED US

At the authors' center, the HIFU clinic was established in 2010 with the acquisition of a MRgFUS machine (ExAblate, Insightec, Haifa, Israel) mounted on a 3T-MRI guiding device. The first applications were limited to uterine fibroids and bone metastases, but expansion of the program included pancreas, liver, prostate, breast, and osteoid osteoma.^{3,23–28}

The authors' interest in the HIFU therapy arose from its noninvasive features, safety, and low morbidity, with multiple applications to palliate patients with cancer. The high degree of safety and precise targeting are particularly useful for pancreatic cancer, a lesion surrounding or involving major vessels and contiguous organs. HIFU is unique among minimally invasive procedures because it avoids insertion of needles or probes, and allows uniform heating. An additional benefit in recurrent tumors is that it can easily be repeated because ionizing radiations are not used and there is no concern with chemotherapy use.

The effect of HIFU on the disease includes a thermally induced ablation of the tumor mass, plus additional therapeutic benefits to improve quality of life. Pancreatic cancer-associated pain can be debilitating and difficult to control. As many as 81% of patients experience pain relief after HIFU, with sustained response reported even 17 months after therapy.²⁹ Other cancer-related symptoms also improve, such as fatigue and loss of appetite, with an improvement in the Karnofsky Performance Scale.³⁰

HIFU, similar to other minimally invasive techniques, such as cryoablation and RFA, seems to increase the tumor-specific immunity, which contributes to the control of micrometastases and helps maintain a disease-free survival.³¹ The level of CD4+ and the CD4+ to CD8+ ratio increases after HIFU. The probable underlying mechanism is the localized inflammation and lysis of tumor cells that leads to the exposure of previously sequestered cancer antigens. Immune components, such as dendritic cells and macrophages, also increase.³²

A third effect of HIFU therapy is potentiation of concomitant treatments. HIFU increases the radiosensitivity of cancer cells, and increases the sensitivity and permeability of the tumor to chemotherapy.¹¹ The relative lack of perfusion and the anatomic composition of pancreatic cancer generally limits the entry of chemotherapy particles. HIFU favors the entrance of drugs by a transient increase in permeability of blood vessels and cellular membranes (sonoporation), a result of the mechanical effect of US energy on the tissue.^{33,34}

MRI guidance favors a better contrast resolution, with detailed morphologic depiction of the complicated neurovascular anatomy, and a monitoring of the temperature reached within the lesion.⁴

For all these reasons, we began to treat patients with unresectable pancreatic cancer with MRgFUS. A preliminary study on 2 patients with unresectable adenocarcinoma of the pancreatic neck showed that 80% and 85% of the tumor volumes were nonperfused, indicating successful ablation. Pain palliation was achieved with reduction in the visual analog scale (VAS) score from a mean of 7 out of 10 to 3 out of 10. No complications occurred.²⁷ We confirmed these results in 6 patients with unresectable pancreatic adenocarcinoma in the body or neck.³⁵ Although successful USgFUS treatments for lesions in the head of the pancreas have been reported without complications, some fear an increased risk of posttreatment duodenal or vascular obstruction, and we have excluded these lesions.

The main difficulty in treating abdominal organs with HIFU is targeting the lesion while taking into account the organs' displacement secondary to respiratory or peristaltic movements. Although promising automatic respiratory gating devices are being

developed, they are not available for clinical practice.³⁶ This limit is even more relevant in MRgFUS because it relies on scanner images acquired before or during treatment, without the continuous US probe assessment of the organs possible in USgFUS. In our experience, all patients were treated under general anesthesia with controlled respiration and images were acquired at the inspiration phase with a fixed amount of inhaled airflow and duration of apnea, to confirm an identical organ shift and lesion positioning. A recovery period of 2 minutes between apneas was established for blood oxygen saturation.

Our preliminary results are encouraging. All 6 patients who underwent MRgFUS experienced pain palliation with a mean VAS score decrease from 7 out of 10 to 3 out of 10 in the week after treatment. Pain medications were stopped after 2 days, except 1 patient who continued paracetamol as needed for 1 month and 2 patients who continued paracetamol as needed for the entire follow-up. The results were long-lasting with continued palliation at 6 months. All patients had a technically successful treatment, with a mean devascularization of 80% (SD of 5%) of the tumor volume without regrowth in 5 patients at 6-month follow-up. One patient had a cluster of solid enhancing tissues at the periphery of the ablated area at 6 months, but it was negligible and did not extend beyond the outer borders of the originally ablated lesion. Except for 1 patient who had a significant shrinkage of the mass, the volume of the tumor remained essentially stable over time. This is a common finding after HIFU, with the volume of the mass sometimes increasing because of edema. Indeed, the reduction of mass size is not considered reliable in evaluating treatment success. All treatments were successful, even in case of vascular encasement by the tumor (Fig. 3). We addressed the areas close to large vessels with a mildly increased amount of energy to avoid any heat dissipation from the circulating blood. The noninvasiveness and accurate planning ensured safety without bowel perforation or skin burns in our patients.

MINIMALLY INVASIVE ABLATIVE THERAPIES

The image-guided minimally invasive procedures can be roughly divided into 2 groups: thermal ablative techniques (RFA, MWA, cryoablation) and nonthermal ablative techniques (IRE).¹⁴ The main challenges with these therapeutic approaches are the anatomic and histologic features of the pancreas that entail a significant risk to the close sensitive structures with thermal energy and to pancreatitis. Improvements in imaging and energy monitoring would improve the efficacy and safety of the procedures.

Radiofrequency Ablation

RFA uses high-frequency alternating current, conveyed by 1 or more needle electrodes inserted in the neoplastic tissue. The local increase in temperature leads to coagulative necrosis and protein denaturation inside the neoplastic tissue.³¹ The treatment is performed under US or CT guidance and the ablation is achieved by increasing the local tissue temperature for a short time interval. Several studies suggest reaching 90°C to ensure ablation without complications.³⁷ The tissue echogenicity change is the main parameter for the assessment of the efficacy; the tissue impedance can also be used because it increases when necrosis occurs. The temperature reached within the tissue can be directly detected by the electrode tip, which can be multiple or single, depending on the needle used.³⁷

The dimension of the mass does not represent an absolute limit for this technique because it is applicable for tumor masses of 5 cm or more.³¹ RFA can be performed at laparotomy, percutaneously, or during laparoscopy. The approach most commonly

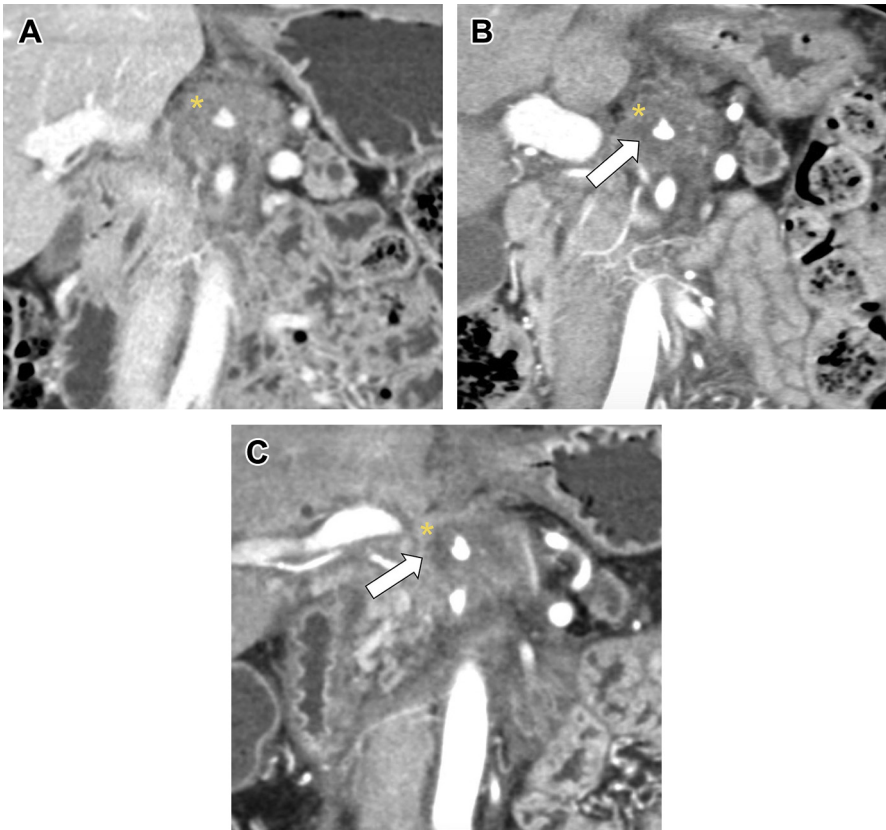


Fig. 3. CT multiplanar reformatted image on the coronal plane obtained before MRgFUS treatment (A), immediately posttreatment (B), and at 1-year follow-up (C). (A) The tumor (yellow asterisk) with encasement of both the celiac axis and the superior mesenteric artery. Immediately posttreatment (B) there is devascularization and necrosis (arrow) of the ablated area associated with clinical reduction in pain. At 1-year follow-up (C), the tumor still presents devascularized area with no symptoms recurrence.

described is to use RFA via laparotomy with US-guidance. Nevertheless, its use in locally advanced pancreatic cancer has been questioned for the invasiveness of the procedure and an often incomplete ablation. The ring of neoplastic tissue that is not ablated to ensure safety of close structures is often targeted with chemotherapy or radiotherapy because the tissue becomes more vulnerable and sensitive after RFA.³¹

A few studies have described percutaneous RFA and most are case reports of various pancreatic tumors (functional and nonfunctional neuroendocrine tumors, metastases, and ductal adenocarcinomas).¹⁴ D'Onofrio and colleagues³⁸ treated 18 patients who had locally advanced adenocarcinoma in the pancreatic body and tail with vascular encasement unsuitable for surgery after chemotherapy. The verification of the needle path and its insertion into the center of the mass was carefully monitored through US and the efficacy assessed with hyperechoic changes in the ablated tissue. Technical success, defined as the ablation of 50% or more of the targeted mass, was obtained in 93% of the patients without complications.

The capacity of RFA to successfully ablate a pancreatic tumor, in addition to the difficult location, is limited by the increased impedance linked to the necrotic tissue

change, which self-limits the ablation.^{37,39} Moreover, although new needle technology is improving heat deposition, this is still heterogeneous due to the intrinsic tissue features and it cannot currently be monitored in real-time during the procedure. Safety is nevertheless ensured because the heat conduction occurs mainly inside the neoplastic mass due to the specific tissue conductivity (thermal diffusivity effect).³⁷

The main adverse events reported with percutaneous RFA are abdominal pain, the self-limiting form of pancreatitis, minimal peripancreatic inflammatory reaction with little fluid collection, and slight and transient increase in serum amylase and lipase.¹⁴

Microwave Ablation

MWA uses microwave radiations to locally increase the temperature by agitating the water molecules contained in the tissue, causing cellular death via coagulation necrosis. The procedure can be done openly, endoscopically, or percutaneously. US or CT image guidance is used to verify the correct and safe position of the probe (antenna).³⁷

Even if further studies are needed to assess its efficacy, this technique has some advantages compared with RFA. It can treat larger areas and reach local higher temperatures, measured with a thermocouple probe. The effect of microwaves does not depend on tissue type, is not limited by tissue impedance, and pancreatic regions close to vascular structures can be treated with no heat-sink effect experienced.⁴⁰ The procedure is faster and more than 1 applicator can be used, avoiding multiple procedures. The pain experienced is less than with RFA and generally occurs after percutaneous and endoscopic MWA, during which the patient is under conscious sedation.^{14,41} On the other hand, the ablation area is very sensitive to the type of antenna, its position and frequency. A study reporting percutaneous MWA for the treatment of 5 subjects with pancreatic ductal adenocarcinoma concluded that this procedure may increase the patients' quality of life and seems to be a feasible palliative treatment of pancreatic head tumors.⁴²

Cryoablation

Cryoablation is a thermal technique that uses low temperature to induce tumor ablation. The cold local environment causes tissue necrosis and apoptosis through both intracellular and extracellular ice formation. The technique consists in the insertion of a cryoprobe into the tumor, with multiple probes often necessary for the ablation of lesions larger than 3 cm.³⁷ It can be performed percutaneously or surgically, under CT or US guidance. Cryoablation is based on a freezing-thawing cycle, usually repeated twice, although more cycles are necessary for larger lesions. First, the temperature decreases to -160°C with the formation of an ice ball, which is predictive of the ablated area and can be easily visualized with US.⁴³ Then, the temperature slowly thaws to zero and another cycle is repeated. As for RFA, the maintenance of a safety margin to close sensitive structures is advised, with 5 mm distance ensuring safe ablation.³⁷

Results with percutaneous cryoablation for pancreatic cancer and neuroendocrine pancreatic tumor are promising in terms of pain palliation, increased overall survival, and improved performance status.⁴⁴ The largest retrospective study of 67 subjects observed an increase in the overall survival of metastatic pancreatic cancer following US-guided and CT-guided percutaneous or open cryoablation.⁴⁵ The median overall survival of the cryotherapy group was 7 months compared with 3,5 months in the chemotherapy group. Multiple sessions of cryoablation associated with immunotherapy are linked to better results, with a median overall survival of 13 months. Combinations of cryotherapy and iodine seed implantation has also been studied in 38 subjects by Xu and colleagues.⁴⁶ Of the subjects, 23.6% had a total response,

42.1% had partial response, 26.3% had stable disease, and 7.9% experienced disease progression with a median overall survival of 12 months.

Cryotherapy is a feasible and potentially safe therapeutic option for locally advanced and unresectable pancreatic cancer even in the presence of metastases.⁴⁷ Also, neuroendocrine tumors in multiple endocrine neoplasia type 1 have been treated achieving good symptoms control.⁴⁴

The rate of complications following cryoablation is not high, with the main adverse events being mild abdominal pain and delayed gastric emptying. Major adverse events reported include bleeding, pancreatic and biliary leak, acute pancreatitis, and cryoprobe needle metastasis.^{37,42,48} Also, cryoshock may occur following the rapid release of cellular debris in the systemic circulation after the reperfusion of the ablated area. This phenomenon is rare with heat-based ablation.³⁷

Irreversible Electroporation

IRE is a nonthermal technique delivering short high-voltage electric current pulses that trigger apoptotic pathways through disruption of the cellular homeostasis with induction of irreversible permeabilization of lipid membranes. The innovation of this ablative technique is the preservation of the supporting connective extracellular structures, which allows a fast recovery; and of the close surrounding structures, such as vital tissues, nerves, and vessels, which allows the treatment of tumors encasing major peripancreatic vessels.³¹

Electrodes, from 2 to 6 needles, are introduced into the pancreatic tumor mass through a percutaneous or surgical approach.⁴⁹ US or CT can be used for image guidance and the treatment protocol is computed based on tissue conductivity and needle position. As a general rule, it is preferred to treat lesion sizes of 3 to 3.5 cm.³¹ The patient is under general anesthesia with complete muscular paralysis and the electric pulses are electrocardiogram-synchronized to avoid triggering arrhythmias. Indeed, the electric fields applied can cause cardiac muscle contraction.³⁷ Therefore, IRE is not indicated for patients with history of cardiac arrhythmia, congestive heart failure, or symptomatic coronary artery disease. Biliary metallic stents must be removed for concern of thermal injuries.³¹ These limitations of IRE may decrease the number of patients who could benefit from the treatment. Immediately after the procedure, treatment efficacy is assessed with hyperechogenic changes and is confirmed after an hour as a hypodense lesion on CT.⁴⁹

A recent prospective study investigated the safety of percutaneous IRE and evaluated the quality of life, pain perception, and efficacy in terms of local tumor progression and survival. The median size of the tumors treated was 4 cm. The pain control was moderate, with recurrence of a pain difficult to control with analgesics 6 months after the procedure. The patients experienced a decrease in general functioning at 3-month and 6-month follow-up on quality of life scores. The median overall survival after IRE was 11 months.⁵⁰ Minor adverse events reported were nausea, vomiting, diarrhea, delayed gastric emptying, abdominal pain, and loss of appetite. Edematous pancreatitis, massive hematemesis caused by duodenal wall ulcer, and new onset biliary obstruction were observed among the major adverse events.⁵⁰

IRE is a relatively new technique that is still performed only in few centers and more studies are needed to assess its efficacy. The main factors limiting its wider application are the need of general anesthesia with muscular block and the exclusion of patients with cardiac problems and/or biliary stents. For now, IRE is limited to stage III and IV pancreatic cancer with centimetric liver metastases, and is often offered as a bridge therapy before radical surgical resection.⁴⁹

SUMMARY

Minimally invasive techniques are promising for local tumor control and palliation of symptoms from unresectable pancreatic cancer to improve the quality of life and to reduce the tumor burden. Further studies are needed to standardize the clinical indications and the technical parameters to maximize the results minimizing morbidity and mortality. Considering all the advantages of HIFU and the future expected technological improvements, this technique has the potential to have a dominant role in the management of unresectable locally advanced pancreatic cancer.

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