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**Percutaneous ablation of pancreatic cancer**

D'Onofrio M *et al.* Percutaneous ablation of pancreatic cancer

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**Abstract**

Pancreatic ductal adenocarcinoma is a highly aggressive tumor with an overall 5-year survival rate less than 5%. Prognosis and treatment depend on whether the tumor is resectable or not, which mostly depends on the time of diagnosis. Chemotherapy and radiotherapy can be both used in case of non-resectable pancreatic cancer. In case of pancreatic neoplasm locally advanced, non-resectable but non-metastatic, it is possible to apply percutaneous treatments able to induce a tumor cytoreduction. Nowadays multiple treatment are available, and in this article these techniques will be describe, such as radiofrequency ablation, microwave ablation, cryoablation, and irreversible electroporation, with their possible complications. Furthermore, with literature review, results and complications will be exposed.

**Key words**: Pancreatic cancer; Pancreatic adenocarcinoma; Percutaneous treatment; Ablation treatment; Radiofrequency ablation; Microwave ablation; Cryoablation; Irreversible electroporation

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**Core tip:** Pancreatic ductal adenocarcinoma is a highly aggressive tumor. Prognosis and treatment depend on whether the tumor is resectable or not, which mostly depends on the time of diagnosis. In case of non-metastatic pancreatic neoplasm locally advanced, it is possible to apply percutaneous treatments able to induce a tumor cytoreduction. Nowadays multiple treatment are available. Technical procedure, results and complications will be exposed.

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**INTRODUCTION**

Pancreatic ductal adenocarcinoma is the most common primary malignancy of the pancreas and it is the most frequent exocrine pancreatic neoplasm, representing 80% of malignant pancreatic tumors[1-4].

Treatment of pancreatic ductal adenocarcinoma, and consequently prognosis, depend on tumor resectability, usually linked with the time of diagnosis[5,6]. In almost 95% of cases, pancreatic ductal adenocarcinoma is diagnosed at an advanced stage[1], with locally advanced or metastatic disease in 40% of cases[2,6,7].

The majority of pancreatic tumors treated with percutaneous treatment are ductal adenocarcinomas[8-11].

**CLINICAL INDICATIONS**

The majority percutaneous treatment procedures, both thermal ablative and non-thermal ablative, are dedicated to ductal adenocarcinoma[8-11] if locally advanced un-resectable but not metastatic. Necessary condition for percutaneous treatment indication of ductal adenocarcinoma is therefore a locally advanced un-resectable tumor, without presence of metastases. The tumor resectability is an absolute exclusion criterion since surgical complete resection is the only potentially curative treatment for this tumor, but only about 20% of patients present with resectable disease at the time of diagnosis. Presence of distant metastases is another exclusion criterion, included ascites that can be indirectly a sign of peritoneal carcinomatosis[4]. Before the percutaneous procedures, a pathologically proved diagnosis and correct tumor staging are therefore mandatory.

In un-resectable pancreatic adenocarcinoma, chemotherapy is the therapy of choice. Nowadays new treatments can be considered, together with chemotherapy, in a multimodalities therapeutic approach for un-resectable pancreatic adenocarcinoma, locally advanced without metastases, such as radiofrequency ablation, microwave ablation (MWA), cryoablation, and irreversible electroporation (IRE). The palliative therapeutic effects of these treatments are intuitively linked to the development of intra-lesional necrosis or cytolysis or cells death, with a resulting neoplastic mass cytoreduction[12]; some studies also explain some argumentations on post-ablation amplification of tumor-induced immune response[13]. These treatment can be associated with chemotherapy and could be included in a combined therapeutic plan, tailored for each cases[4].

**TECHNIQUES AND RESULTS**

Nowadays, there are many techniques for treating pancreatic ductal adenocarcinoma locally advanced without metastases. These different techniques can be split in two big groups: the thermal ablative group and the non-thermal ablative one. The first takes advantage from thermal energy, while the second group works by using energy making direct damage to neoplastic cells not mediated by thermal effect. All of these techniques can be performed in surgery room with a laparotomy or a laparoscopy approaches, or they can be applied through a percutaneous or an endoscopic approaches, thus being less invasive.

***Radiofrequency ablation***

Radiofrequency ablation (RFA) causes coagulative necrosis with tissue damage by generation of high local temperatures produced by high frequency alternating current application. Nowadays RFA is used in many solid organs malignancies, such as hepatocellular carcinoma, thyroid neoplasms, breast and prostate tumors, and finally pancreatic neoplasms; it has a very important role in the treatment of hepatocellular carcinoma, all the way it becomes a standard therapy[14,15].

Radiofrequency ablation of pancreatic cancer can be guided by ultrasound, both percutaneously or with endoscopic ultrasound or intraoperative by intraoperative ultrasound (IOUS), this latter usually when it has to be performed also a biliary and gastric bypass for pancreatic head tumors[4,16,17].

Ablation procedure is done under local anesthesia with patients sedation, both with percutaneous or endoscopic approaches. Before the procedure is mandatory to confirm the malignant nature of the lesion by pathological analysis and it is extremely important to do a precise staging of the tumor.

The percutaneous approach can more safely considered for the ablation of pancreatic tumor located in the body, because the complicated anatomy of pancreatic head region makes more difficult and dangerous the percutaneous RFA procedure in this region. However the pancreatic head can be treated with RFA with the endoscopic approach. RFA is done with a needle that has to be inserted completely inside the lesion. The more correct approach, the choice of the needles and the opening degree of the electrodes are usually influenced by tumor shape and size.

Nowadays there are two main types of needle: needles with expandable electrodes (Figure 1) and needle with single electrode (Figure 2). In the first case, the expandable electrodes can be opened from the top (Figure 1A) or from the back of the needle (Figure 1B): these two needle types have to be used in different way. In case of electrodes opened from the top, the needle tip has to be stopped immediately before the lesion and electrodes (up to nine) have to be opened up and widened into the lesion. This type of needle can treat small tumors because it can be opened at different degrees in relation to the size of the requested ablation area; but unfortunately, the flexibility of electrodes can be a disadvantage in the treatment of very hard lesions. In case of needle with electrodes opened from back, the electrodes, usually four, are opened up at about 2 cm behind the tip and moved towards the outside; so the needle, for a correct positioning, has to pass completely through the tumor (presence of central needle for at least 2 cm within the mass assures that the electrodes are inside the neoplastic tissue). On the contrary of the previous described needle, this one, crossing throughout the mass, and with stiffer electrodes, guarantees excellent stability inside the tumor, even in the presence of hard one. But, contrary to the first, this last needle, requiring the introduction of it throughout the lesion for at least 2 cm, can have disadvantages related to dimensions and tumors location.

These needles are used to produce a spherical/ovoid necrotic area, with a mean diameter ranging from 2 to 5-6 cm, depending on the needle and on the electrode degree opening.

On the other hand, using needle with a single electrode incorporated, the length of the area to be treated depends on the uncovered portion of the electrode; the measure of the treated area depends on both the length of the uncovered portion and the time of ablation. This type of needle usually produces a cylindrical necrotic area ranging from 1 to 3 cm, depending on the extension of needle uncovered metallic portion.

As previously stated, the choice of the needles and the opening degree of the electrodes are usually influenced by tumor shape and size. In example, if there is a rounded lesions that has to be treated it is better to do with the first needle type described; whereas in case of ovoid lesion the second type has to be preferred. The last one is also preferable in case of very small lesions with particularly difficult access (better choosing needle with a lower caliper)[4].

Then with ultrasound it is possible to guide the ablation technique, both during the orientation of needle and both during the opening of the electrodes inside the tumor, that are both echoic. Usually, the needle tip and the electrodes must be kept at almost 5 mm from the sensitive structures such as peri-pancreatic vessels, as previously reported[4,18-20].

The correct needle positioning and electrode opening are followed by procedure parameters setting, that are different depending on the system used. Usually the procedure lasts from 5 to 10 min.

The power provided to the system influence directly the temperature reached and indirectly the treated volume of the lesion. In some cases, with some systems, it is possible to evaluate the tissue impedance, that increased with necrosis growth during the procedure. The system shows the temperature at the electrode tip, also in case of needle with multiple electrode, assuring in this way a more uniform distribution of the temperature in the treated lesion. The choose of the correct temperature is very important for the treatment aims and to prevent irreparable damages. As a result of the protein denaturation starts at the temperature of 50-60 °C, higher temperatures reached during RFA lead to achieve more homogeneous coagulative necrosis, but the use of very high temperatures (usually more than 105 °C) expands complications risk, without a favorable effect. For this reason, during RFA ablation of a pancreatic mass is better to apply middle range temperatures (mean 90 °C) to avoid complications. Several studies confirmed that reducing RFA temperature to about 90°C lead to have minimal complications related to the procedure[14,16,21].

The RFA capacity to successfully treat a tumor is in part limited by two primary characteristics linked to this heating mechanism. The heating of the tissue with the electric current used in this process is a self-limiting process because the desiccation, water vapor, and charring created during RFA process gradually increase the tissue impedance that limits additional current application and limits temperatures that can be reached in the ablation area. Secondly, the heat transfer is moderately slow in most tissues and can be differ according to the local tissue environment, perfusion and ventilation[22-24].

In a recent published paper by our Institute[8], percutaneous approaches and single tip needle with a single electrode incorporated and exposable uncovered portion of the electrode of 17 Gauge is used. In this paper a relatively short explosion of the needle is used with power set at low values (30 W) at the beginning of the procedure to obtain a progressive low development of coagulative necrosis allowing intratumoral heat propagation. In respect to uncovered portion of the needle double necrotic volume can be obtain with this techniques thanks to intra-lesional passive conduction, in example with exposure of 1.5 cm a necrosis of more than 3 cm can be obtained. And this is reported to be particularly safe because the heat is conducted inside the neoplastic mass and not outside lacking conductive neoplastic tissue. This effect, that is strictly related to heat neoplastic conductibility and can be called “thermal diffusivity effect”, lead to a necrotic area morphology quite perfectly modelled inside each single treated lesion (Figure 1). In this study we applied registered a mean radiofrequency application time for every single passage of 3 min 13 s (range: from 30 s to 10 min). In our experience 18 patients, with proved pancreatic ductal adenocarcinoma not resectable, locally advanced without metastases, were treated with percutaneous RFA. In 16 (93%) on 18 patients were obtained technical success of the procedure, proved by a CT study. Furthermore, one month after the treatment, a decreased blood value in Ca19.9 marker has been observed in 40% of treated patients.

Ultrasound makes possible to monitor the procedure in real-time, watching the lesion progressively becomes hyperechoic owing to the gas produced inside, confirming the thermal effect obtained in the tumor and monitoring the integrity of the sensitive surrounding structures[4,25].

Carrafiello *et al*[26] treated with percutaneous RFA a patient with pancreatic metastasis from renal cell carcinoma localized in the body-tail, using percutaneous approach under fluoro-CT guidance in a patient treated under deep sedation. They utilized a 19-G needle electrode (Invatec Miras RC, Brescia, Italy) that usually generates up to 3-cm diameter predetermined zone of necrosis. The RFA procedure lasted 8 min and 35 s and it reached a temperature between 80 and 100 °C. As complications patients had abdominal pain, amylase serum increase and a little peri-pancreatic fluid collection, with the result that he was free of symptoms without recurrence in the follow-up of 12 mo.

Limmer *et al*[27] with a CT-guided RFA ablated an insulinoma localized in the body-tail under general anesthesia. A 16 G-cooled tip single RFA needle with 3-cm active tip was stepwise advanced into the tumor until the needle tip had reached the center of the tumor. The ablation cycle last 18 min (last 3 min without cooling) with a maximum energy delivery ranged from 70 to 130 W. Patient had a minimal peri-pancreatic inflammatory reaction and then he was free of symptoms in 1,5 months of follow-up.

Wu *et al*[28] treated a gastrinoma in the pancreatic tail with a percutaneous transplenic radiofrequency ablation combined with radioactive 125I seed implantation, without complications. Patient was free of symptoms without recurrence in 20 mo follow-up.

Singh *et al*[29] treated a patient with ductal adenocarcinoma with a percutaneous approach CT guided (the other 10 patients included in the study were treated with the surgical approach), putting the needle in the center of the tumor and applying approximately 4200 W of energy to the tumor using saline perfused needle with the aim of producing a necrosis of 3 cm. Partial necrosis (up to 3 cm) of the tumor was achieved in all cases, both intraoperative than the one percutaneous. One patient died 1 mo after RFA due to a massive myocardial infarction. Survival of other 10 patients ranged between 9 to 36 mo and 8 patients had post RFA chemotherapy. He concluded that RFA is a safe and feasible technique of tumor cytoreduction, but he did not specify if this treated patient developed complications and if yes which one among mild abdominal pain, transient ascites, self-limiting pleural effusion or an asymptomatic pseudocyst. Furthermore he did not specify the follow-up length and medial survival.

Rossi *et al*[30] treated under local anesthesia 8 patients (7 with percutaneous RFA and 1 with endoscopic RFA) with neuroendocrine tumors (6 in the head and 2 in the body-tail; 5 with non-functional neuroendocrine tumors, 2 with insulinomas and 1 with gastrinoma). The 19G single-spiral electrode was used and it was inserted under US guidance, with the tip in the center of the tumor. The RF generator was activated to deliver 20 to 50 W for 6 to 12 min. Depending on the tumor size, this maneuver was repeated 1 to 4 times. The same technique was used with the 17-gauge triple-spiral electrodes, but in this case, a single 60- degree rotation of the shaft was sufficient to ensure full circumference ablation of the tumor. Three patients of them developed acute pancreatitis with fluid collections. After a median follow-up of 34 mo all treated patients are alive and in good conditions. He conclude that RFA is a feasible, safe, and effective option for patients with small pancreatic neuroendocrine tumors who cannot or do not want to undergo surgical resection. A short summery about these studies in Table 1.

***MWA***

Microwave radiation indicate the electromagnetic spectrum region with frequencies from 900 to 2450 MHz, laying between infrared radiation and radio waves. Electromagnetic microwaves heat material by agitating water particles in the surrounding tissue, producing friction and heat, and inducing cellular death due by coagulation necrosis[31], nearly identical to that observed in radiofrequency ablation[22]. In some cases, the mechanism of microwave heating may have advantages. Polar molecules (primarily water) continuously realign with the oscillating microwave field, effectively increasing kinetic energy and tissue temperature. Unlike electric currents, microwaves spread through all biological tissues, also in those with high impedance to electric current[22,32], allowing that microwaves incessantly generate heat in a larger volume of tissue around the antenna[22,33]. Therefore microwave energy can produce faster, hotter, and larger ablation areas in multiple tissues than radiofrequency current, with the need of fewer applicators and effective abla­tive margins easier to be obtained.

Systems that can create microwave energy are mainly divided into three types: the first-generation systems have not an active antenna cooling and they are limited to low power and short durations; the second-genera­tion systems have antenna cooling but limited generator power; andthe third-generation sys­tems have incorporated antenna cooling and high-power generators. Each of these system is characterized by different combination of diameter of the antenna, numbers of its, frequency, generated power, and power loss between the generator and applicator tip. Due to all of these features, system perfor­mance can change a lot, so it is very important to understand that ablation-zone shapes and sizes are created by different time and power associations with a particular system: microwave ablation areas volume depends on the power applied, design, number and orientation of antennae, and micro­wave frequency.

Microwave antenna type affects size and shape of the abla­tion area, and lots of antennae have been described to control energy transfer[22,34,35]. Some antennae create an elongated ablation area (up to 6 cm), called triaxial antennae, that they can burn skin or other structures adjacent to the treated organ, so nowadays newer antennae let to create a more rounded and forward-weighted heating to treat smaller tumors (modified triaxial antennae or dual slot antennae[22,36,37]. Multiple antennae can be used together to create a larger and confluent ablation area inside the tumor[22,38,39].

Microwaves systems differs also for created frequency. Usually the greatest heating occurs within 1 cm of the antenna. The potential advantages of microwave ablation over radiofrequency ablation include faster ablations (usually 2–8 min with high-powered systems), higher temperatures without disadbantages related to electric impedance, less sensitivity to different tissue type, the ability to create much larger ablation zones if needed[22,32,35,40-42].

This ablation techniques, same as radiofrequency ablation, can be done with different approaches, such as the percutaneous one, the endoscopic, the laparoscopic and the open surgical one. The percutaneous approach ,and the endoscopic one, usually is performed with conscious sedation of the patient, whereas in the other case a general anesthesia is done. The lesion that has to be treated is localized with the computed tomographic guide, or, even better, with the ultrasound guide, and the better approach has to be chosen[31]. Then the tumor is hit with a thin microwave antenna (14-15 Gauge), that it is in turn connected to the microwave generator with a coaxial cable and an electromagnetic microwave is released from the exposed, non-insulated portion of the antenna. Each generator is capable of producing 60 W of power at a frequency of 915 MHz. Temperatures reached inside the tumor can be measured with a separated placed thermocouple. Microwave ablation can be used in different organs, such as liver, kidneys, lung, adrenal glands, pancreas and bone[31,43-46].

In Literature exists only one paper dedicated to percutaneous microwave ablation, where Carrafiello *et al*[47] treated percutaneously 5 patients with ductal adenocarcinoma with 2 cases of mild pancreatitis, 1 pseudocyst and 1 pseudoaneurysm of gastroduodenal artery. In all patients, MW ablation was performed under moderate sedation. The path of the antenna was carefully evaluated on the basis of a preliminary US examination; a path was chosen such that the vessels, stomach, and bowel were far from the antenna. The most important evaluation involves the prediction of the ablation area on the basis of the position of the antenna. In particular, on the end of the antenna is a tip; the use of an antenna with a 37-mm radiating section will result in an ablation zone with a diameter of 37 mm (7 mm on the back of the tip and 30mm ahead of it), the use of an antenna with a 20 mm radiating section will result in an ablation zone with a diameter of 20 mm (ahead of the tip). Technical success rate was 100%, due to the correct position of antennae. An improvement in the quality of life was observed in all patients and in no one it was necessary to repeat treatment in a 9 mo follow-up. He concluded that patients had an improvement of their quality of life and that microwave ablation appears to be feasible in the palliative treatment of cephalic pancreatic tumors, with a precise patient selection for the high risk of visceral injury. A short summery about this study in Table 2.

***Cryoablation***

In the cryoablation technique the cells death is due to cold tempera­tures and the death mechanisms is different from that one with heat, because in the freezing process there will be ice formation both intracellular and both extra­cellular, that can result in cellular death: location of ice formation and mechanism of cell death change with the freezing rate and final tissue temperature. In fact rapid freezing supports formation of intracellular ice crystals, which results in cell death due to the direct damage to cell mem­brane and organelles[22,48]. On the other hand slow freezing favors extracellular ice crystals formation, with a change of osmolality within the extracellular space with consequently cell dehy­dration and cell death[22,49]. In addition, apoptosis induced by freezing contributes to this process, a role that is poorly understood[22,50]. However break of cell membrane with re­lease of intracellular contents causes cell death. The temperature necessary to cause necrosis depends on the cells type and on thermal history of the tissue where the lesion is, but usually the useful temperature estimated is from -35 °C to -20 °C[22,51,52].

During the process of cryoablation it will be create an “ice ball”, that is predictive of the ablation area, inside the treated area and one of the biggest advantage of this technique is that this expanding ball is really well visualized at ultrasound, CT, and MRI, allowing a more precise monitoring of the ablation area than during heat-based techniques[22].

Systems that generate cryoablation take advantages from the Joule-Thomson theory of expanding gases within a needle like cryoprobe: argon moves from an internal feed line into an internal expansion chamber, producing a heat sink near antenna tip that cools the probe to tempera­tures of -160 °C or more. Then the heat transfer from the tissue into the cryoprobe is governed by pas­sive thermal diffusion, so cryoablation devices provide no zone of direct or active cooling, differing from RFA or microwave ablation devices, with the result that the surface area of the cryoprobe limits cooling efficiency: smaller diameters of cryoprobe are usually linked with lower cooling capacity and, then, smaller ablation zones, making indispensable the use of several cryoprobes to treat majority of the tumors in the clinical practice, with large ablation times (usually mean 25–30 min), longer than the average times of microwave or RFA procedures[22].

Furthermore, after the procedure there is a rapid release of cellular debris into systemic circulation, due to the ablation area reperfusion, causing sometimes any systemic complications, such as cryochock, rare with heat-based ablation[22,53].

Cryoablation technique can be done percutaneously with ultrasound or computed tomography guide or most commonly it is performed intraoperatively under ultrasound guidance. As previously said, lesions small than 3 cm can be treated with a single, centrally placed probe, instead larger tumors require multiple probes or sequential treatments. At 160 °C the tumor is cooled and ultrasound guide can monitor the created ice ball that it has to be inside the entire lesion without compromise local structures. After ice ball creation, the tissue has to slowly thaw to 0° C and then a second cycle of freezing is performed after any necessary repositioning of the cryoprobes. As the radiofrequency ablation technique, it is better to have at least 5 mm of safety margins from major structures[14].

Xu *et al*[9] enrolled in their paper 49 patients with locally advanced pancreatic cancer (12 with liver metastases) that underwent cryosurgery, or 36 percutaneously and 13 intraoperative, combined with 125I seed implantation. The procedure was performed under local anesthesia and under guidance of ultrasound or CT. Based on the location of the tumor, cryoprobe insertion was often carried out *via* the retroperitoneal approach. Generally, 2 or 3 mm cryoprobes were used. For tumors greater than 3 cm in size (mean tumor size ranged from 2.2-7.1 cm), 2 to 3 probes were used. For liver metastases, simultaneous cryosurgery was performed using additional cryoprobes which were inserted through the right intercostal space. The procedure consisted of a double cycle of freeze/thaw procedure was used with an argon gas-based cryosurgical unit (EndoCare, Inc., CA, USA). Each cryoprobe was cooled to -160 °C and the resulting ice-ball was monitored with ultrasound until the frozen region encompassed the entire mass of the tumor with at least a “0.5-cm safe border”. The tissue was then allowed to slowly thaw to 0°C. A second cycle of freezing/thawing was performed after repositioning of the cryoprobes. The cryoprobes were then removed. Among 36 patients, 17 received a second course of cryosurgery and 3 a third one. The conclusions were that cryosurgery, which is far less invasive than conventional pancreatic resection, and it is associated with a low rate of adverse effects, should be the treatment of choice for patients with locally advanced pancreatic cancer. Furthermore 125I seed implantation can destroy the residual surviving cancer cells after cryosurgery with complementary effect combining both modalities. A complete response was observed in 20,4%; a partial response in 38,8%; a stable disease in 30.6% and progression disease in 10.2% (5/49), during a median follow-up of 18 mo (range of 5-40 mo), with a median duration of survival of 16.2 mo.

Li *et al*[54] treated with percutaneous cryosurgeries 2 neuroendocrine tumors in 2 patients with MEN 1 syndrome. The first insulinoma was treated under CT guidance, where three 1.7 mm diameter cryoprobes were inserted into the tumor localized in the pancreatic tail, and 100% argon was applied for 10 min. The target zone was covered by an ice-ball and the cycle was repeated. The second lesion was in the pancreatic head and it was preventively treated with trans-arterial embolization due to its dimensions and after was performed cryosurgery under ultrasound guidance. Four 2 mm diameter cryoprobes were placed into the pancreatic head tumor, frozen for 15 min and then rewarmed; all probes were extracted by 3 cm and frozen for a further 15 min. Glucose levels blood reduction and necrosis at CT studies were found, with a quality of life improvement in the 3 mo follow-up.

Niu *et al*[55] treated 67 patients (31 with cryoimmunotherapy and 36 with cryotherapy) with ductal adenocarcinoma and complications as abdominal distension and nausea, increased amylase serum, ascites, abdominal bleeding, fever, mild decrease in platelet and increase of fasting blood glucose levels. The obtained results were a pain score decreased and a median overall survival higher after multiple cryoablations than after a single cryoablation. A short summery about these studies in Table 3.

***IRE***

Irreversible electroporation is a non-thermal technique that can be used in the treatment of locally advanced non metastatic pancreatic adenocarcinoma, inducing cells death. The ablative effect, with consequently cells death, is based on sending short high-voltage electric current. Application of these short high-voltage electric pulses, guided by one or more monopolar electrodes put within the lesion, causes irreversible permeabilization of lipid membranes, with consequently the disruption of cellular homeostasis, and the switching on apoptotic pathways, resulting then in cell death of neoplastic cells[56-63].

So this is an emerging non-thermal ablative technique which uses electrodes, put within the lesion that has to be treat, to deliver up to 3 kV of direct current, inducing formation of nanoscale pores within the cell membrane, which irreversibly damages cell homeostatic mechanism, causing subsequently apoptosis[14].

One of the positive features of IRE, differently from RFA, is the ability to preserve surrounding structures, such as the underlying tissue, the vital surrounding structures such as nerves or vessels[56,64-66]. This IRE proper ability of IRE of preserve vessels could be a very important aspect to evaluate in case of tumor encases major peri-pancreatic vessels.

This treatment is not a “pure” non-thermal technique, because it could be cause partially cellular damage in a thermal way, because in some conditions of high intensity, the current applied can produce a coagulative necrosis, similar to those one produced by the thermal techniques, such as RFA, or MWA[56,67]. Other studies then concluded that IRE does not produce significant thermal energy, at least using settings most commonly applied in clinical treatment, but they showed that the presence of a metallic stent could rise the risk of producing thermal injuries, due to the metal conductivity[56,68]. Of course this aspect is fundamental to kept in mind in case of treatment in patients carrying a biliary metallic stent for jaundice palliation.

The planning of the IRE treatment has extremely importance. Several tool can be used to choose the best planning and in some papers were also accurately described the procedure with the ideal settings in case of pancreatic tumor treatment pancreas[56,69,70].

Irreversible electroporation can be perform both during surgery and both percutaneously.

One of the bigger restriction of IRE is the need of a general anesthesia with a complete muscular paralysis[71].

Bagla *et al*[72] described in a case report the percutaneous ablation of a pancreatic cancer in the body-tail, planned and performed as two ablative sessions to avoid the need for more than six probes to be placed at once. The treatment was done with four 15 cm monopolar probes (Na- noknife; AngioDynamics, Latham, New York) placed into the central and lateral aspect of the tumor under ultrasound guidance in a square configuration, with average spacing of 1.8 cm. Then CT imaging with contrast medium was performed to evaluate needle position relative to vessels and measure inter-probe distance. A 22-gauge spinal needle (Becton Dickinson, Franklin Lakes, New Jersey) was placed under US guidance into the gastro-hepatic space to perform hydro-dissection with sterile water. The treatment had no complications and patients had no recurrence at a 6 mo follow-up. He concluded that percutaneous IRE showed promise as a feasible and potentially safe method for local tumor control in patients with surgically un-resectable disease.

Martin II *et al*[73] described 27 pancreatic cancer (15 in the head and 12 in the body-tail), 26 treated with surgical IRE and 1 with percutaneous IRE. IRE was performed *via* the Nanoknife system (Angiodynamics, Lanthan). Two monopolar probes with 2 cm spacing will deliver an electroporation defect of approximately axial 3.5 cm, anterior-posterior 2.5 cm, and cranial-caudal of 2.5 cm. This electroporation defect is achieved through a maximum of 1, 5-cm exposure, 1500 volts/cm, and with 100 microsec wavelength. No specific complications occurred to the patient percutaneously treated among hematologic disorders, ileus, bile leak, portail vein thrombosis, deep venous thrombosis, pulmonary infections, renal failure, ascites and wound infection. He concluded that IRE ablation of locally advanced pancreatic adenocarcinoma is safe and feasible as a primary local treatment in un-resectable locally advanced disease.

Narayanan *et al*[10] in a 2012 paper treated 14 ductal adenocarcinoma (6 in the head, 1 in uncinated process, 7 in body-tail), using the NanoKnife IRE device (AngioDynamics, Queensbury, New York). The IRE was set up to produce 70-microsecond high-voltage (1500–3000 V) direct current (25–45 A) electrical pulses. Unipolar electrodes were more commonly used, and the maximum separation between the electrodes was 2.2 cm. No tissue separation maneuvers were used to protect structures adjacent to the IRE electrodes. The electrodes were advanced percutaneously under CT guidance. Bipolar probes were positioned within and around the tumor, and current was applied when CT had confirmed adequate position. The generator was programmed to stop delivery and recharge if the current flow exceeded 48 A. Pull-back was performed if the target treatment zone was greater than 2 cm, and treatment was repeated to cover the entire target. He had as complications 1 pancreatitis and 1 pneumothorax during anesthesia, concluding that percutaneous IRE for pancreatic adenocarcinoma is feasible and safe. 1 patients were re-treated because he had local progression of disease after 7 mo. In two patients could be possible go to surgery after IRE, due to downstaging reached. The median event-free survival after the IRE procedure was 6,7. The the 6-month overall survival was 70%.

Mansson *et al*[11] included 24 patients with locally advanced pancreatic cancer (19 in the head and 5 in the body-tail), that had prior chemotherapy and/or radiochemotherapy, and they underwent to percutaneous IRE procedure. The NanoKnife IRE equipment from Angiodynamics System (Queensbury, NY, USA) was used. In all patients, the ultrasound guided needle placement outlined the tumor, with a needle also placed in the center of the tumor when tumor diameter exceeded 2.0 cm. The electrical parameters are calculated by the machine in order to compensate for any error in the assessment of the needle distance. Six needles were used in 20 patients, four needles in two patients, and three needles in the remaining two patients. Active needle length was 1.5 cm in all cases. A minimum of 90 pulses was delivered between each adequate needle pair, defined as a distance between the needles not exceeding 2.5 cm. After completion of the treatment cycles in the deep portions of the tumors, the needles were pulled back 1.5 cm and another treatment with the same parameters was performed in the superficial portion of the tumor. In 11 patients were observed IRE related complications (infections and thrombosis), three of which were serious. There was no IRE related mortality. In 9 patients there was a recurrence. The overall survival of 17.9 mo. He concluded that percutaneous IRE of after chemo-/radio-chemotherapy appears reasonably safe and shows promising results for efficacy. A short summery about these studies in Table 4.

**POSTOPERATIVE IMAGING AND** **COMPLICATIONS**

The goal of all these treatment is to reduce the tumor volume with cytoreduction. In case of pancreatic treatment, being ductal adenocarcinoma significantly hypovascular, the detection of the created necrotic area in respect to residual viable tumor tissue can be very difficult. A very important difference between radiofrequency ablation of the pancreas and the one on the liver is that in the treatment of pancreatic tumors the presence of residual viable tumor at the periphery of the treated area is quite always an intrinsic aspect of the procedure because the necrotic area must be included in the tumor. Also in the other thermal ablative procedure, such as microwave ablation and cryoablation, the ablated area has to be kept inside the tumor, in order to avoid complications due to thermal energy outside the pancreatic parenchyma. The most important difference among all the thermal procedures and irreversible electroporation is that with IRE is possible to create necrosis in all the tumor and not only inside it, hypothetically destroying all the cells within the lesion, so it has to not see a tissue viable border outside the necrosis induced.

To evaluate the ablated resulted area, dynamic examinations after contrast agents injection are usually done from one month after the procedure because they are able to detect the intratumoral necrotic area produced by the thermal ablation treatments. In our experience, patients treated with percutaneous RFA for pancreatic adenocarcinoma, undergo a CT study one day after the procedure, in order to completely exclude the presence of some complications; if complications are not present, patients will do a CT one month after, according to the routine follow-up. The ablated area at dynamic CT results slightly hyperdense at basal scan then obviously avascular during all the dynamic phases, so maintaining quite the same basal density. In particular, while the arterial and venous phases are very important to highlight vascular complications, such as pseudo-aneurysms and venous thrombosis, the late phase is the most important to show the ablated area better delineated from the enhancement of the adjacent tissue (Figure 3). Therefore the late phase is the best one for the ablated area measurement.

With this tumor reduction the possibility to improve life quality and life expectancy is high, both because is possible to reduce pain caused by pancreatic tumor, causing necrosis within it, both because causing a cytoreduction is possible to reduce the possibility that the disease goes on in less time[4,14,54,74-78]. Furthermore, these procedures, creating necrosis inside the tumor, can reduce tumor marker and can induce an immune response towards the tumor, releasing factors from the tumor able to stimulate the immune response: they can activate a host antitumor immunity to control micro-metastases and generate tumor resistance[8,12]. But about this last point more studies are necessary to assess the ability of these treatment to improve life expectancy, because still now these are few in Literature.

Percutaneous pancreatic cancer treatment minor complications include abdominal pain, nausea, fever, skin burn, and fluid collection; whereas major complications comprise splenic vein or portal vein thrombosis, digestive or abdominal bleeding, duodenal perforation, pancreatic fistula, infection, severe pancreatitis, and death.

In our experience, on 18 cases of pancreatic adenocarcinoma treated with percutaneous RFA, none of the patients developed intra- or post-procedural complications[8].

**CONCLUSION**

In last years ablation procedures have been combined with chemotherapy for the treatment of pancreatic cancer. Percutaneous approach is one of the possible reported route to guarantee mini-invasiveness.

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**Figure 1 Needle with expandable electrodes.** Electrodes can be opened within the lesion from the top (A) or from the back (B) of the needle.

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**Figure 2 Needle with single electrode.** Single electrode of the needle within the lesion.

A

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B

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C

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**Figure 3 Radiofrequency ablation of pancreatic cancer.** Computed tomography (CT) study in the portal phase (A, B) shows the markedly hypodense necrotic avascular area modelled within the tumor. CT study in the late phase (C) show the ablated area better delineated from the enhancement of the adjacent tissue.

**Table 1 Summery of studies about radiofrequency ablation**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Authors** | **Patients number** | **Lesion** | **Location** | **Type of treatment** | **Approach** | **Needle** | **Mean treatment duration** | **Conclusion** |
| D’Onofrio *et al*[8] | 18 | Pancreatic ductal adenocracinoma | Head | Radiofrequency ablation | Percutaneous with US | 17 G | 3 min and 13 s | High rate success with 40% cases with Ca19.9 reduction |
| Carrafiello *et al*[26] | 1 | Pancreatic metastases from renal cell | Body-tail | Radiofrequency ablation | Percutaneous with CT | 19 G | 8 min and 35 s | RFA is feasible for  metastatic lesion at body-tail |
| Limmer *et al*[27] | 1 | Insulinoma | Body-tail | Radiofrequency ablation | Percutaneous with CT | 16 G | 18 min | RFA proved to be a clinically successful  procedure |
| Wu *et al*[28] | 1 | Gastrinoma | Tail | Radiofrequency ablation | Percutaneous transplenic with CT | - | - | Percutaneous transplenic RFA is feasible |
| Singh *et al*[29] | 11 | Pancreatic ductal adenocracinoma | - | Radiofrequency ablation | 1 percutaneous with CT + 10 laparoscopic | - | - | RFA is a safe and feasible technique of tumor cytoreduction |
| Rossi *et al*[30**]** | 8 | Pancreatic neuroendocrine tumors | Head and body-tail | Radiofrequency ablation | Percutaneous with CT | 17 and 19 G | 9 min | RFA is a feasible, safe, and effective option |

US: Ultrosound; CT: Computed tomography; RFA: Radiofrequency ablation.

**Table 2 Summery of the study about microwave ablation**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Authors** | **Patients number** | **Lesion** | **Location** | **Type of treatment** | **Approach** | **Needle** | **Mean treatment duration** | **Conclusion** |
| Carrafiello *et al*[47] | 5 | Pancreatic ductal adenocarcinoma | Head | Microwave ablation | Percutaneous with US | - | - | Microwave ablation appears to be feasible in palliative treatment |

**Table 3 Summery of studies about cryosurgery**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Authors** | **Patients number** | **Lesion** | **Location** | **Type of treatment** | **Approach** | **Needle** | **Mean treatment duration** | **Conclusion** |
| Xu *et al*[9] | 49 | Pancreatic ductal adenocarcinoma | - | Cryosurgery | 36 percutaneous with US or CT + 13 intraoperative | 2 or 3 mm | - | Cryosurgery is associated with a low rate of adverse effects |
| Li *et al*[54] | 2 | Neuroendocrine tumors | Head and tail | Cryosurgery | Percutaneous with US and CT | 1.7 mm and 2 mm | 10 and 15 min | Percutaneous cryosurgery is minimal invasive and  has advantages compared with conventional surgery |
| Niu *et al*[55] | 67 | Pancreatic ductal adenocarcinoma | - | Cryosurgery | Percutaneous with US and CT | 1.7 mm | - | Cryoimmunotherapy significantly increased overall survivall in metastatic  pancreatic cancer |

US: Ultrosound; CT: Computed tomography.

**Table 4 Summery of studies about irreversible ablation**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Authors** | **Patients number** | **Lesion** | **Location** | **Type of treatment** | **Approach** | **Needle** | **Mean treatment duration** | **Conclusion** |
| Bagla *et al*[72] | 1 | Pancreatic ductal adenocarcinoma | Body-tail | Irreversible electroporation | Percutaneous with US and CT | 22 G | - | Percutaneous IRE showed promise as a feasible and potentially safe method for un-resectable tumor |
| Martin II *et al*[73] | 27 | Pancreatic ductal adenocarcinoma | 15 head + 12 body-tail | Irreversible electroporation | 1 percutaneous + 26 surgical | - | - | IRE ablation is safe and feasible as a primary local treatment in un-resectable locally advanced disease |
| Narayanan *et al*[10] | 14 | Pancreatic ductal adenocarcinoma | 6 head + 1 uncinated process + 7 body-tail | Irreversible electroporation | Percutaneous with CT | - | - | Percutaneous IRE in pancreatic adenocarcinoma is feasible and safe |
| Mansson *et al*[11] | 24 | Pancreatic ductal adenocarcinoma | 19 head + 5 body-tail | Irreversible electroporation | Percutaneous with US | - | - | Percutaneous IRE reasonably safe and shows promising results for efficacy |

US: Ultrosound; CT: Computed tomography; IRE: Irreversible electroporation.