Irreversible Electroporation of Pancreatic Tumors

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11.1 Introduction

Over 95% of pancreatic cancers are exocrine tumors that bare a dismal prognosis. Although oncological outcome is best for patients presenting with nonmetastatic resectable disease, cure is rarely achieved [1]. Up to 40% of patients present with nonmetastatic disease that is considered unresectable due to vascular encasement (locally advanced pancreatic carcinoma or LAPC) [1, 2]. These patients are nowadays routinely offered systemic chemotherapy with or without radiotherapy. Irreversible electroporation (IRE) represents a promising new method for focal destruction of pancreatic tumors. Evidence to support its effectiveness is gradually surfacing.

Over the last years, image-guided pancreatic tumor ablation has gained increased interest when surgical options are excluded. However, thermal ablation techniques such as radiofrequency ablation (RFA) and microwave ablation (MWA) are associated with substantial morbidity and mortality, due to the proximity of large vessels, the pancreatic and common bile duct, and the gastroduodenal wall [3]. Another major downside of thermal ablation techniques is the so-called "heat-sink" effect, when heat is lost to the flowing blood, which can hinder complete ablation [4].

One of the most promising new tumor ablation techniques, with distinct theoretical advantages over thermal ablative therapies, is irreversible electroporation (IRE). Since

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IRE is thought to leave the integrity of inlaying and adjacent vulnerable structures like large blood vessels, bile ducts, and intestines intact, IRE in theory represents a safe and feasible method to destroy pancreatic tumors that are considered unsuitable for surgical resection. Supporting evidence is gradually surfacing.

11.2 Anatomical and Physiological Considerations

The pancreas lies behind the peritoneum of the posterior abdominal wall and is covered by connective tissue, although it does not have a true capsule [5]. The second and third duodenum curvatures lie around the head of the pancreas. The anterior surface of the head of the pancreas is adjacent to the pylorus, the first part of the duodenum, and the transverse colon. The posterior surface adjoins the hilum and medial border of the right kidney, the inferior caval vein, the renal vasculature, the right gonadal vein, and the right muscular crus of the diaphragm. The uncinate process is an extension of the pancreatic tissue of variable shape off the lower part of the head of the pancreas, extending to the left and upward. The neck of the pancreas is a constricted part of the gland extending from the head of the pancreas toward the left, joining the head with the body of the pancreas. The neck extends to the right as far as the anterior superior pancreaticoduodenal artery from the gastroduodenal artery and lies anterior to the confluence of the superior mesenteric and splenic veins to form the portal vein. It is partly covered by the pylorus and the peritoneum of the minor omentum. The anterior surface of the pancreatic body is covered by the peritoneum of the omental bursa that separates the stomach from the pancreas. The stomach and the transverse mesocolon abut the body anteriorly. Posterior to the body of the pancreas are the aorta, the origin of the superior mesenteric artery, the left crus of the diaphragm, the left kidney and adrenal gland, and the splenic vein. The midline part of the body lies over the lumbar vertebrae, which makes this area of the pancreas most at risk to abdominal trauma. The body passes laterally and merges with the tail of the pancreas without a marked junction point. The relatively mobile tail is located in the anterior pararenal space. Its tip usually reaches the hilum of the spleen. With the splenic artery and vein, the tail is enclosed between the two layers of the splenorenal ligament.

The common bile duct is located in the posterior wall of the duodenum to the right of the gastroduodenal artery. The bile duct passes through the pancreatic head, to join with the main pancreatic duct before reaching the major duodenal papilla. The main pancreatic duct (of Wirsung) is formed by ductules that drain the lobules of the gland. At the level of the major papilla, the duct joins the common bile duct. In adults the length of the common channel averages 5 mm. The accessory pancreatic duct of Santorini, present in more than two thirds of patients, usually communicates with the main duct. The accessory duct lies anterior to the bile duct and usually drains into the minor papilla, which lies proximal to the ampulla of Vater.

The pancreas derives blood from several branches of the celiac and superior mesenteric arteries [6]. The descending part of the duodenum and the head of the pancreas are supplied by two pancreaticoduodenal arterial arcades. They are formed by the anterior and posterior superior pancreaticoduodenal arteries from the

gastroduodenal artery that arises off the common hepatic branch of the celiac artery to join a second pair of anterior and posterior inferior pancreaticoduodenal arteries. The anterior inferior pancreaticoduodenal artery arises from the superior mesenteric artery by the inferior margin of the pancreatic neck. The posterior inferior pancreaticoduodenal artery originates from the gastroduodenal artery. Its course is visible on the posterior surface of the pancreas, and branches may join the dorsal pancreatic artery. The dorsal pancreatic artery frequently arises from the splenic artery at the pancreatic neck. A right branch supplies the head and joins the posterior arcade. One or two left branches pass through the body and tail of the pancreas. The course of the splenic artery is posterior to the body and tail and loops above and below the superior margin of the pancreas. It gives off the great pancreatic artery, which usually joins one of the posterior superior arcades after giving off the inferior pancreatic artery. The caudal pancreatic artery arises from the left gastroepiploic artery or from a splenic branch at the spleen. It joins branches of the splenic and great pancreatic arteries.

In general, the venous drainage of the pancreas parallels the arterial blood supply. It flows into the portal vein, which is formed by the joining of the superior mesenteric and splenic veins at the confluence behind the neck of the pancreas. The portal vein lies behind the pancreas, with the common bile duct to the right and the hepatic artery to the left. The pancreatic veins that drain the neck, body, and tail of the pancreas join the splenic vein. The pancreaticoduodenal veins lie close to their corresponding arteries and empty into the splenic or portal veins. Because of the close anatomic relationship of the portal vein with the pancreas, inflammatory or neoplastic diseases involving the pancreatic body and tail can lead to portal vein occlusion. This in turn can result in retrograde venous drainage toward the splenic hilum and the short gastric and left gastroepiploic veins which may result in gastric varices.

The superior and inferior lymphatic vessels run along the border of the pancreas, respectively, with the splenic blood vessels and the inferior pancreatic artery [7, 8]. Those on the left side of the body and tail empty into nodes in the splenic hilum. Those on the right side of the body and the pancreatic neck empty into nodes near the upper border of the head. Lymphatic vessel drainage of the pancreatic head is composed of an anterior system and a posterior system. These vessels generally occupy the grooves between the head of the pancreas and the duodenum, near the pancreaticoduodenal blood vessels. The lymphatic drainage of the head of the pancreas and duodenum eventually flows into the celiac and superior mesenteric groups of pancreatic nodes and into the cisterna chyli. The lymphatics of the body pass to the pancreaticosplenic nodes lying along the superior border, which drain into celiac nodes. The lymphatics of the tail drain into splenic hilar nodes.

The celiac plexus, the largest of the three sympathetic plexuses, is situated at the level of the upper part of the first lumbar vertebra and is composed of two large ganglia, the celiac ganglia, and a dense network of nerve fibers uniting them together [9]. It surrounds the celiac artery and the root of the superior mesenteric artery. It lies behind the stomach and the omental bursa, in front of the crus of the diaphragm and the commencement of the abdominal aorta, and between the suprarenal glands.

The plexus and the ganglia receive the greater and lesser splanchnic nerves of both sides and some filaments from the right vagus and give off numerous secondary plexuses along the neighboring arteries. The celiac ganglia (semilunar ganglia) are two large irregularly shaped masses having the appearance of lymph glands and placed one on either side of the middle line in front of the crura of the diaphragm close to the suprarenal glands, that on the right side being placed behind the inferior vena cava. The upper part of each ganglion is joined by the greater splanchnic nerve, while the lower part, which is segmented off and named the aorticorenal ganglion, receives the lesser splanchnic nerve and gives off the greater part of the renal plexus. The greater splanchnic nerves modulate the activity of the enteric nervous system of the foregut. They also provide the sympathetic innervation to the adrenal medulla, stimulating catecholamine release. The lesser splanchnic nerves modulate the activity of the enteric nervous system of the midgut. The nerves that enter the pancreas include sympathetic, parasympathetic, and afferent components. The exact relationships of these fibers to the celiac ganglia and their distribution within the gland are not fully understood.

The pancreas is two glands intimately mixed together into one organ. The bulk of the pancreas is composed of exocrine cells that produce digestive enzymes. The endocrine pancreas, composed of small islands of cells (islets of Langerhans), constitutes approximately 4.5% of the pancreas volume and receives 10–15% of its blood flow [10]. It releases hormones such as insulin, glucagon, pancreatic polypeptide, preproinsulin, proglucagon, somatostatin, vasoactive intestinal peptide, growth hormone-releasing hormone, and gastrin. For these reasons, weight loss and new-onset diabetes mellitus often precede the clinical diagnosis of pancreatic carcinoma [11].

11.3 Pancreatic Malignancies

11.3.1 Pancreatic Adenocarcinoma

Pancreatic adenocarcinoma is among the most aggressive of all cancers. The overall 2-year survival rate is less than 10% and has barely improved over the past decades [12]. Tumors are often diagnosed at an advanced stage and as a consequence only 15–20% of patients are eligible for surgical resection. About 30–40% of patients present with locally advanced pancreatic cancer (LAPC, AJCC stage III), for whom median overall survival is approximately 1 year [13].

The clinical presentation of pancreatic malignancies depends on the size and location of the tumor as well as its metastases. Jaundice, pain, and weight loss are classic symptoms of pancreatic cancer [14]. Nonspecific early symptoms often are unrecognized; therefore, most pancreatic cancers are advanced at diagnosis. More than two thirds of pancreatic cancers occur in the head of the pancreas and usually present as steadily increasing jaundice caused by biliary duct obstruction. Painless obstructive jaundice traditionally is associated with surgically resectable cancers. Obstruction of the bile duct causes jaundice with disproportionately increased levels of conjugated bilirubin and alkaline phosphatase in the blood. The urine is dark

because of the high level of conjugated bilirubin and the absence of urobilinogen. The stool is pale because of the lack of stercobilinogen in the bowel. In addition to jaundice, rising bilirubin levels can cause severe pruritus. Patients with tumors in the body and tail of the pancreas generally present with nonspecific pain and weight loss. Body and tail tumors are much less likely to cause obstructive signs and symptoms. Patients may have pain in the epigastrium or back ranging from a dull ache to a severe pain. Tumors in the body and tail usually do not cause symptoms until they are large, and most present as locally advanced disease extending to the peritoneum and spleen.

11.3.2 Pancreatic Malignant Islet Cell Tumors

Islet cell tumors of the pancreas are rare tumors that are also called pancreatic neuroendocrine tumors. These tumors stem from neuroendocrine cells and tend to be slow-growing lesions that are often well treatable even after they have metastasized. Islet cell tumors can produce symptoms since up to half of these tumors may secrete hormones that produce side effects due to excessive secretion of the hormones such as insulin (insulinoma), gastrin (gastrinoma), glucagon (glucagonoma), VIP (VIPoma), and somatostatin (somatostatinoma).

11.4 Treatment of Pancreatic Malignancies

While surgical resection remains the only curative option, the majority of patients present with unresectable disease [15]. Even among those who undergo resection for AJCC stage I (tumor confined to the pancreas) and II (tumor growing outside the pancreas or pathology proven nodal metastases) disease, the reported median survival is 15–23 months, with a 5-year survival rate of approximately 20% [16]. Disappointingly, over the past decades, only modest improvements in survival have been realized despite improvements in diagnostic imaging, surgical technique, and chemotherapeutic options. Nevertheless, it remains clear that surgical resection is a prerequisite to achieve long-term survival. The prognosis for patients undergoing surgical resection for pancreatic ductal adenocarcinoma is highly dependent on margin status, with total gross excision and histologically negative margins (R0 resection) being associated with the best outcomes. Survival for patients who undergo total gross excision but have histologically positive margins (R1 resection) is reduced according to most series [17]. There is now emerging consensus that a subgroup of patients, previously considered poor candidates for resection because of the relationship of their primary tumor to surrounding vasculature, may benefit from resection, particularly when preceded by neoadjuvant therapy [18]. In these patients, an interface exists between the tumor and the superior mesenteric or portal vein measuring 180° or greater of the vessel wall circumference or between the tumor and the celiac trunc or superior mesenteric artery measuring less than 180° of the vessel wall circumference. Short-segment occlusion of the superior mesenteric/portal vein or hepatic artery is allowed if considered

reconstructable. For patients with unresectable stage III pancreatic cancer, systemic therapy with or without radiation has been the standard of care for decades. Relatively new chemotherapy regimens such as FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan, and oxaliplatin) and the addition of nab-paclitaxel to gemcitabine have recently shown to significantly improve survival for patients with metastatic pancreatic adenocarcinoma. Nevertheless, the prognosis remains dismal [5, 6].

11.4.1 Chemotherapy for LAPC

Several randomized studies have demonstrated a median overall survival of 9.2–11.7 months for patients with LAPC treated with gemcitabine alone [19, 20]. Although newer, potentially more effective, chemotherapy regimens have become available, most of these studies focused on patients with metastatic disease. One major advancement in systemic chemotherapy for pancreatic cancer is FOLFIRINOX (fluorouracil, folinic acid, oxaliplatin, and irinotecan), which resulted in a significant improvement in progression-free and overall survival of patients with metastatic disease in a phase III European study [21]. There is much interest to incorporate FOLFIRINOX into the multimodality treatment of LAPC, as several retrospective observational cohorts also suggest a survival benefit for patients with stage III pancreatic cancer. Nevertheless, no randomized controlled trials have so far evaluated the effect of FOLFIRINOX as a stand-alone therapy for LAPC. Several observational series have reported median overall survival results ranging 11.2–18.4 months for first-line FOLFIRINOX with or without radiotherapy [22–28]. Although complications such as neutropenia, neutropenic fever, anemia, thrombocytopenia, fatigue, anorexia, mucositis, nausea, vomiting, diarrhea, peripheral neuropathy, and alopecia are often encountered, the incorporation of specific dose reductions has decreased the number of patients having to stop treatment prior to having reached progression [29].

11.4.2 Radiotherapy for LAPC

The role of concurrent radiotherapy for LAPC remains controversial as the results of randomized controlled trials are in conflict [30]. Traditionally, trials using radiotherapy include the use of conventional external beam radiation (EBR). This technique uses large radiation fields that inevitably deliver a high percentage of the radiation dose into critical surrounding structures. When irradiating abdominal tumors with conventional external beam radiation, strict adherence to normal structure dose constraints may limit the delivery of the intended radiation dose to the tumor and potentially result in premature local failure and death. Conversely, delivering high doses of radiation to adjacent critical structures without strict dose constraints increases the risk of late radiation-induced complications [31]. A recent advancement in radiation therapy is stereotactic ablative body radiotherapy (SABR). SABR can deliver higher doses of radiation more precisely to the tumor and a small margin (usually 2–3 mm) because of the rapid dose falloff beyond the treated volumes. This limits the dose delivered to normal bowel,

resulting in decreased toxicity and dose escalation to the tumor. Several studies investigated the effects of SABR for patients with LAPC. The reported median overall survival ranges from 6.2 to 24 months [32–35]. Complications include gastroparesis, gastrointestinal (duodenal) bleeding, duodenal or gastric ulcer, anorexia, nausea/vomiting, and thrombosis of the superior mesenteric vein or inferior vena cava.

11.4.3 New Local Ablative Therapies for LAPC

Due to poor efficacy results of currently used treatments, researchers are continuously investigating novel and modified treatment strategies to improve survival. Whereas two decades ago, image-guided tumor ablation techniques were still in its infancy, nowadays many different ablation techniques have substantially improved curative treatment possibilities for numerous types of localized cancer in many different organs. Different nonsurgical thermal ablation techniques (cryoablation, radiofrequency ablation (RFA), high-intensity focused ultrasound (HIFU), laser ablation, and microwave ablation (MWA)) have been investigated in order to improve survival for patients with LAPC. However, ablative therapies are limited due to the risk of thermal damage to nearby vital structures, associated with high complication rate (28–40%) and high mortality rate (7.5%) [36]. Also, the so-called "heat-sink" effect, in which tumor cells near to large vessels are prevented from adequate heating due to flowing blood cooling adjacent tissue, can lead to incomplete ablation. This effect is another drawback in the performance of thermal ablation in LAPC, since the tumor is typically surrounded by major vessels.

Irreversible electroporation (IRE) is a new, image-guided tumor ablation technique that takes advantage of the electric potential gradient that exists across cell membranes. The application of an electric field across a cell alters the cellular transmembrane potential. By reaching a sufficiently high voltage, the phospholipid bilayer structure of the cell membrane is permanently disrupted, inducing apoptosis and cell death [37]. Tumors in contact with vessels can be treated with IRE without compromising the vessels or resulting in heat-sink since its effectiveness relies on electrical energy. Because of its vessel-sparing mechanism of action, IRE is hypothesized to have wider indications than the thermal ablation technologies. This makes IRE a very attractive option in patients with LAPC, as the reason for unresectability is usually vascular encasement.

11.5 Patient Selection, Indications, and Contraindications

Because of the relatively high morbidity involved in the radical ablative treatment of pancreatic tumors, patient selection is fundamental. Patients must be motivated and understand that recovery may be prolonged, and that quality of life and daily functioning may be compromised, even following a successful procedure. Physicians should take patient comorbidities and overall performance status into account. Patients with poor functional reserve at baseline are not good candidates. Patients

should be evaluated with detailed and appropriate pre-procedural workup, including medical, cardiac, and pulmonary clearance, and optimized prior to the intervention. The treatment plan should ideally be made by a multidisciplinary team that includes interventional radiologists, surgeons, medical and radiation oncologists, abdominal diagnostic radiologists, and gastroenterologists.

Neoadjuvant systemic chemotherapy should be favored for patients with LAPC for several reasons. Firstly, to exclude patients with aggressive subtypes that will progress and/or metastasize during the induction period and who will presumably not benefit from an IRE procedure. Secondly, because a considerable percentage of patients will be downstaged to resectable disease and, given the promising percentage of R0 resections in this specific group, resection should be considered favorable over focal tumor ablation. Lastly, with a decrease in volumetric tumor size, the IRE procedure presumably becomes a safer and more efficacious treatment option.

Adult patients with non-metastasized histopathologically proven pancreatic adenocarcinoma are considered eligible for irreversible electroporation if the tumor is truly unresectable based on at least a dedicated contrast-enhanced pancreatic CT. The authors consider a tumor diameter of 5 cm the upper limit for IRE. In case of biliary obstruction, adequate biliary drainage prior to the procedure should be guaranteed either by placing a (nonmetal) biliary endoprosthesis prior to a percutaneous procedure or by creating a surgical biliodigestive anastomosis prior to an open procedure.

Transmucosal tumor invasion into surrounding intestines or extensive involvement (complete encasement) of the duodenum, a history of ventricular arrhythmias, congestive heart failure (>NYHA class 2), uncontrolled hypertension, and any implanted cardiac stimulation devices are considered absolute contraindications. Coronary artery disease (defined as myocardial infarction within 6 months prior to screening); atrial fibrillation; the presence of metallic foreign objects, such as non-removable self-expanding metal biliary stent (SEMS), in the ablation zone; and having received chemo- or immunotherapy maximum 4 weeks prior to the procedure are considered relative contraindications. Patients with a compromised liver function (e.g., signs of portal hypertension, INR > 1,5 without use of anticoagulants, ascites) or patients suffering uncontrolled infections are not good candidates. If the anatomical location of the tumor would necessitate advancing needles through the small bowel or colon safety-enhancing procedures such as pneumo-, hydro-, or balloon dissections or laparoscopic surgical assistance may be considered as well as a dorsal percutaneous approach [38]. For such procedures, extensive experience with percutaneous image-guided tumor ablation is mandatory.

11.6 Patient Workup and Treatment Planning

Eligible patients should be suitable for general anesthesia by anesthetic review with special attention to cardiac history and include electrocardiography (ECG). Routine blood samples should include electrolyte and creatinine testing, complete

blood count, and coagulation studies. For patients taking anticoagulant or antiplatelet drugs, the risk of stopping the medication must be balanced against the risk of harm if treatment is stopped. For low-risk procedures, aspirin can be continued. Clopidogrel and warfarin should be stopped although this may require bridging anticoagulation with unfractionated or low molecular weight heparin. Consultation with a cardiologist is particularly recommended for patients with coronary artery stents.

Prophylactic biliary protection is recommended for tumors adjacent to the biliary tree in order to prevent biliary obstruction caused by the IRE procedure. Placement of a plastic biliary endoprosthesis is much more challenging in the initial days following IRE due to extensive swelling of the ampullary area.

The treatment plan should be based on a dedicated contrast-enhanced abdominal CT (with the upper abdomen scanned according to a dedicated 3-mm-slice-multiphase-pancreatic tumor protocol). The size and shape of the tumor should determine the number and configuration of the needle electrodes aiming at an interelectrode distance of approximately 2 cm and a tumor-free margin of 0.5 cm.

11.7 Approach, Image Guidance, and Technique

The preferred line of attack for pancreatic IRE will be the topic of widespread debate for many years to come. Although, in general, pancreatic surgeons promote the open approach, most interventional radiologists prefer the percutaneous route. At this moment, advocating superiority of one over the other approach is ungrounded since no direct comparison has ever been performed. Both approaches have distinct advantages and disadvantages. The chapter authors each have their own preferences, which will be debated in the following sections. As there is currently no proof that one method is superior to the other, it can be said that the method of choice is the method that works best for the person about to perform the treatment. Procedures are always performed under general endotracheal anesthesia with deep paralysis, defined as zero twitches before IRE delivery as per a standard anesthesia twitch monitor. Using the only commercially available system currently out there (NanoKnife, AngioDynamics Inc., Queensbury, NY), at least 90 pulses of 1,000–1,500 V/cm with a 90-ms pulse length are delivered for each electrode pair, including 10 or 20 test pulses. An ECG-gating device is connected to a 5-lead ECG to allow IRE pulses to be synchronized with the refractory period of the heart to avoid arrhythmias. When necessary, additional doses to block the neuromuscular cascade can be administered by the anesthesiology team. Prior to the procedure, two defibrillation pads are placed and connected to a defibrillator as a precautionary measure. Given the high conductivity of pancreatic cancerous tissue and hence the higher risk to induce overcurrent, the active working length is routinely set at 1.5 cm by most physicians (Table 11.1).

Table 11.1 The open versus the percutaneous approach for pancreatic IRE

	Open	Percutaneous
Invasiveness		
Length of hospital stay	Long	Short
Impact on quality of life	Major	Moderate
Pain assessment post-IRE	Moderate–high	Low–moderate
Mortality		
Related to IRE	4%	0%
Related to general procedure	2%	0%
	2%	0%
Safety		
Complications related to probe insertion	Less likely due to manual segregation of surrounding structures from the pancreas	Crossing the stomach or liver often inevitable. Traversing major blood vessels, the duodenum or colon should be avoided
Complications related to the delivery of pulsed electrical fields	Collateral damage to surrounding intestines less likely	Collateral damage to surrounding intestines possible
Complications caused by the general procedure	Complications caused by the laparotomy such as infection, bleeding, bile or pancreatic fluid leakage, fistula formation, and pancreatitis are common, as are pneumonia, pleural effusion, and deep vein thrombosis can occur	Complications such as pneumonia and deep vein thrombosis are rare
Outcome		
Progression-free survival	8.0–13.0 months	8.0–11.0 months
Overall survival	16.0–23.2 months	17.0–27.0 months

11.7.1 The Open Approach (R. Martin)

Access for open IRE is performed through a superior midline incision [39]. A superior midline incision is utilized based on the planned needle placement performed most commonly and in a safer manner through a caudal-to-cranial approach. In turn, the caudal-to-cranial approach is more easily facilitated through a midline laparotomy than through a bilateral subcostal laparotomy. The abdomen is thoroughly examined to rule out any type of occult solid organ liver metastases as well as peritoneal or mesenteric metastases. Intraoperative ultrasound of the liver is also performed to rule out any type of non-palpable liver metastases that may have been missed on dynamic CT scan. Only after no evidence of metastatic disease is confirmed is intraoperative ultrasound then turned to the operative assessment of the tumor. Given the lack of definitive accuracy as well as positive predictive value of CT scan alone because of volume averaging, it is important to ensure that the patient truly has greater than 180° encasement of the SMA before deciding on in situ IRE therapy vs. pancreaticoduodenectomy with margin accentuation with IRE along the

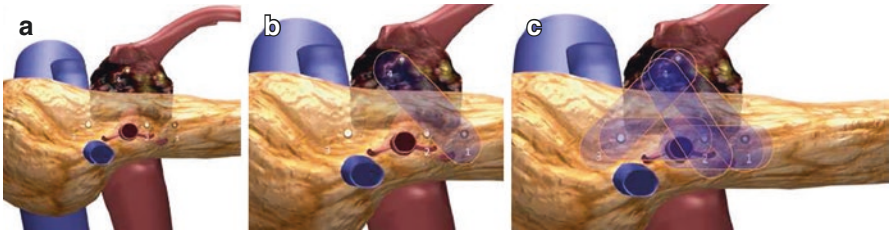

Fig. 11.1 Axial plane with a triangle probe technique for locally advanced pancreatic tumor with a broader base in the axial plane requiring a three-probe posterior placement technique with either one probe (or two probes) on top to create the triangle. The probe pair with the longest distance (maximum 2.3 cm) is then treated first, followed by other probe pairs to ensure a complete irreversible electroporation utilizing all probe pairs that are active. Note – probe pair 1–3 is not active since the distance between them is more than 2.3-cm spacing [39]

SMA. Our optimal ultrasound technique is transgastric and is performed with placing the ultrasound probe on top of the gastric body closer to the pylorus. We recommend imaging with minimal amount of mobilization and avoiding the mobilization into the lesser sac, which further impedes optimal intraoperative imaging since this will disrupt the tissue planes with air and lead to a greater artifact. The reason for performing through a transgastric approach is that the stomach serosa allows for a complete and clean apposition of the ultrasound crystals and provides minimal to no artifact to truly image a pancreatic head lesion and subsequent portal vein as well as superior mesenteric vein. Thus, intraoperative ultrasound imaging has become our gold standard for elucidating whether a patient has a true locally advanced tumor or a borderline resectable tumor. In short, 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, 1,500 V/cm, with 100 μs wavelength. Preoperative narcotic management was normalized to fentanyl dosages because that was the predominant narcotic used, with additional wide ranges of other narcotics being used. A jejunal feeding tube was used at the surgeon's discretion but was placed in most cases secondary to a conservative approach and to avoid a prolongation of hospital stay related to delayed gastric emptying. A prophylactic gastrojejunostomy, J-tube, or hepaticojejunostomy should be considered at surgeon's discretion (Fig. 11.1).

11.7.2 The Percutaneous US-Guided Approach (A. Nilsson)

When using ultrasound guidance, it is strongly recommended to plan the procedure by doing a contrast-enhanced ultrasound on the day before the ablation taking note of tumor delineation, projected needle paths, and possible vascular occlusions. Ultrasound, as in all types of image-guided intervention, has the advantage of being cheap and readily available in most departments. It offers a real-time image with a good delineation of vascular structures and spatial resolution, these traits being

important when a needle is to be placed very close to critical structures, which is most often the case with IRE. On the other hand, when using ultrasound, compared to CT, it is more difficult to measure the distance between the needles with absolute accuracy and also to know that the needles are parallel. To overcome these shortcomings, it is important to take special care about the positions of the needle insertions making the distances between the needles correct on the skin, maybe even with the use of a spacing device (image). Also, as we may not know the exact distance between needles, starting the treatment with ten pulses of a slightly lower V/cm than recommended enables the user to deliver some pulses (typically 10–20), check the resulting current (graph produced by the machine), and then adjust the V/cm according to the initial resulting amperes. Another drawback, it has to be admitted, is that needle placement under ultrasound guidance is not possible in all patients due to factors like obesity and/or overlying bowel gas so that the pancreas cannot be visualized. In most cases, though, the pancreas can be seen and the tip of the IRE needle is clearly visible on ultrasound. Another slightly weaker echo is also seen at the beginning of the active needle. This makes it easier to estimate if a pullback is needed or not. When the needles are in place the treatment, of course, follows the same guidelines as with CT guidance, see below.

11.7.3 The Percutaneous CT-Guided Approach (M. Meijerink)

For optimal CT image quality, the arms should be elevated above the patient's head. To define the three-dimensional measurements of the tumor and its vicinity to vital structures, a contrast-enhanced (ce)CT or cone-beam CT scan should be performed prior to the ablation, preferably using multiplanar image reconstruction to verify and if necessary adjust the treatment plan. Needle electrodes will be advanced in and around the tumor under CT fluoroscopy guidance, aiming at an interelectrode distance of 15–24 mm. For spherical tumors <3 cm, placing three to five needles in the edge of the tumor should allow for a complete ablation. For lesions ≥3 cm, it is recommended to place one needle electrode in the center of the tumor and, depending on lesion size, at least four additional needles aiming at the outer margins. To avoid having to traverse the colon or other crucial structures, it is often necessary to use an angulated approach. For this reason, either gantry tilt, virtual gantry tilt, or CT to ultrasound real-time image registration and fusion software is crucial. Similar to percutaneous CT-guided thermal ablation, we advise to use pneumo- or hydrodissections whenever considered necessary. The order in which the electrodes are placed depends on the position of the patient with regard to the gantry (feet or head first) and the position of the physician (right or left side of the patient). To avoid blocking your view and to preserve all degrees of freedom with respect to the needle trajectory, we advise to begin with the electrode furthest away from the operator within the gantry. For larger tumors that need pullback ablations for complete coverage, we advise to start with the deep (dorsal) part of the tumor and work your way upward to the more superficial part. After having placed all electrodes, a ceCT scan is made to verify the exact needle locations and the interelectrode distances in a plane perpendicular to the needle electrodes, again

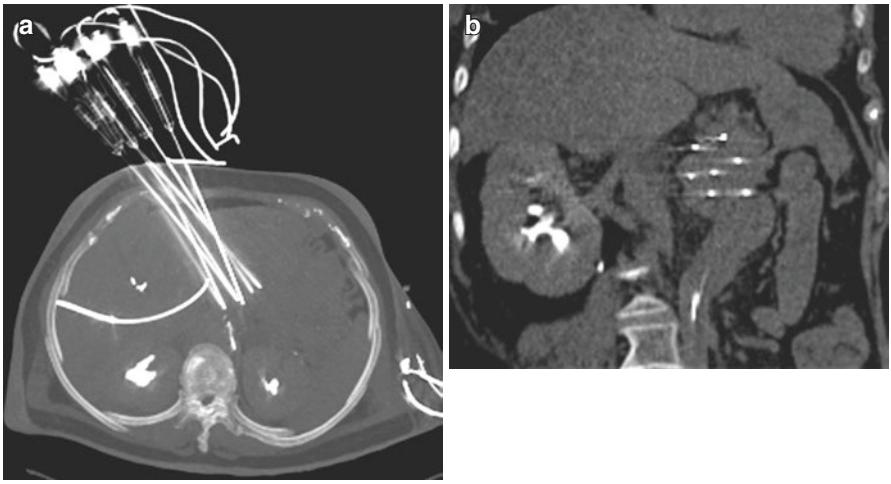

Fig. 11.2 Example of a percutaneous CT-guided IRE procedure of the pancreas. Using transcatheter aortography (with a catheter in the aorta, we can repeatedly visualize the arteries and veins, while advancing the needles, with just 20 cc of contrast material [diluted 1:1 with saline])-guided CT fluoroscopy, one needle is placed in the center and six in the margins of the lesion. In this case, a total number of 12 electrode pairs (six connecting the outer electrodes and six connecting the central electrode with the outer electrodes)

using multiplanar image reconstruction. Immediately after the procedure, a third ceCT scan will assess the ablation zone and detect crucial early complications such as an active perilesional hemorrhage and/or iatrogenic vascular occlusions such as acute portal vein thrombosis (Fig. 11.2).

11.8 Complications

IRE-related hazards can be divided into three types: (1) risks associated with the general procedure, (2) risks associated with probe insertion, and (3) risks associated with exposing patients to pulsed electrical fields. Although an early systematic review describes a low overall complication rate for pancreatic IRE of 19% (8–42) and a major complication rate of 7% (3–42) [37], in the more recently published prospective PANFIRE trial, 10 out of 25 patients developed 23 adverse events (40%) [40].

Expected adverse events associated with the delivery of strong electric pulses are cardiac arrhythmias and severe muscle contractions. To prevent these events, pulses are generally delivered in the refractory period of the heart and with deep muscle paralysis. Scheffer et al. reported eight arrhythmias (CTCAE grade I–II), corresponding to a total incidence of 4% (8–194) [37]. Without synchronized pulsing, ventricular arrhythmias occurred four times (transient ventricular tachycardia) and immediately resolved after pulse delivery was aborted. With the use of cardiac synchronization, only atrial arrhythmias occurred, which resolved spontaneously or within 24 h after therapy. With the administration of muscle relaxants, no uncontrolled muscle contractions were reported. Only Thomson et al. reported a

transient increase in systolic blood pressure in all patients directly after IRE (20–30 mmHg), which normalized spontaneously [41].

Complications associated with probe insertion were spontaneous pneumothorax during anesthesia requiring chest drainage and small subcutaneous hematoma [37, 42].

On follow-up, five site-specific complications occurred. Two were portal vein thrombosis after open IRE; one required paracentesis and aldactone, and one was fatal [37, 43]. Two cases of bile leak (CTCAE grade III–IV) were reported after open IRE [44]. One patient had undergone concurrent duodenal stent removal via duodenotomy; in the other patient, the electrodes were placed transduodenally. Both complications required percutaneous drainage after which they resolved. Scheffer et al. reported pancreatitis only once in 42 procedures which resolved spontaneously (CTCAE grade II) [37]. Martin et al. reported elevated amylase and lipase in all 27 patients, without clinical signs of pancreatitis [45]. Abdominal pain grade I was reported in all patients (15 of 15) after percutaneous pancreatic ablation [42]. Pain was always easily manageable with oral or intravenous analgesics and did not lead to prolonged hospitalization. In the recently published prospective PANFIRE trial (percutaneous IRE), 10 out of 25 patients (40%) developed 23 adverse events (two CTCAE grade IV) [40]. One patient developed an edematous pancreatitis (Balthazar E; CT severity index [CTSI] 4) with bile leakage and hemodynamic instability requiring intravenous antibiotics, fluid resuscitation, and percutaneous drainage. Another patient presented with massive hematemesis 3 days after discharge caused by a duodenal wall ulcer directly adjacent to the ablation zone and was treated with blood transfusion and proton pump inhibitors. Three patients developed de novo biliary obstruction requiring biliary drainage within 90 days post-IRE (grade III). Two out of three endoscopic retrograde cholangiopancreatography (ERCP) revealed swelling of the ampullary area. In these cases, placement of a plastic biliary endoprosthesis was challenging, but eventually successful (Fig. 11.3).

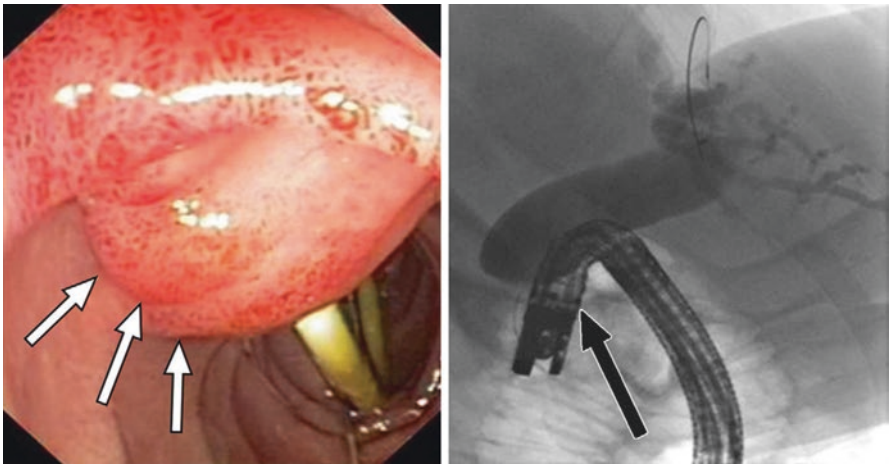

Fig. 11.3 Adapted from Scheffer et al. (**a**) Image from endoscopic retrograde cholangiopancreatography performed 6 weeks after IRE shows erythematous swelling of the ampullary area, with major papilla turned backward. (**b**) Fluoroscopy image shows cannulation of major papilla by positioning duodenoscope in "long position" [40]

Another patient presented with cholangitis and an infected biloma, requiring percutaneous drainage and placement of a percutaneous transhepatic cholangiography drain (PTCD). In one patient, a near occlusion of the – previously slightly narrowed – superior mesenteric artery (SMA) was visible on ceCT 6 weeks post-IRE, with no other signs for local site recurrence. Because she also experienced postprandial abdominal cramps, a vascular stent was placed for symptom relief and to prevent mesenteric ischemia. Further, 12 gastrointestinal complications such as nausea, vomiting, diarrhea, delayed gastric emptying, abdominal pain, loss of appetite, and reduced intake were observed ($n = 6$). Two patients required temporary nasogastric drainage and placement of a nasojejunal feeding tube. Diarrhea and abdominal pain were treated with loperamide and by adjusting the amount of pancreatic enzyme suppletion. There was a significant increase in amylase and lipase 1 day post-IRE compared to pre-IRE values ($p = 0.009$ and $p = 0.001$. After 2 weeks, amylase and lipase had returned to pre-IRE values ($p = 0.26$ and $p = 0.12$). Three patients developed clinical signs of pancreatitis (Table 11.2 and Fig. 11.4).

Table 11.2 Adverse events of pancreatic IRE

Risks associated with the general procedure	Risks associated with probe insertion	Site-specific complications
Cardiac arrhythmias	Hemorrhage	Portal vein thrombosis, arterial stenosis
Transient hypertension	Pancreatic fistula	Pancreatitis, abdominal pain
		Hemorrhagic duodenal wall ulcer
		Biliary obstruction, pancreatitis
		Nausea, vomiting, diarrhea
		Delayed gastric emptying, loss of appetite, and reduced intake

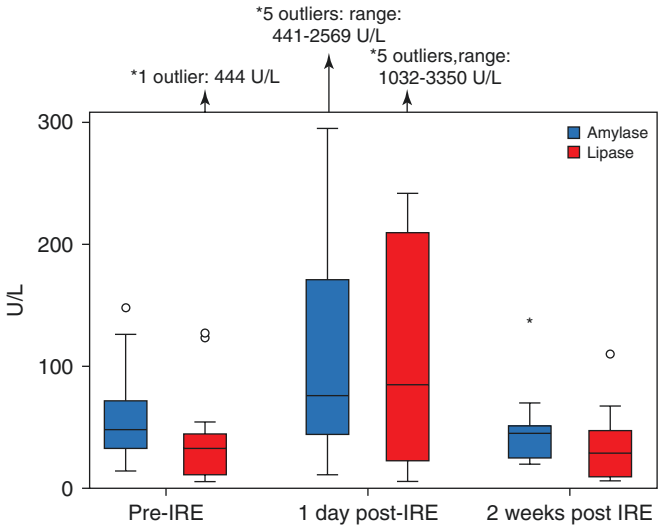

Fig. 11.4 Adapted from Scheffer et al. Box-and-whisker plot shows amylase and lipase values before and after IRE [40]

11.9 Follow-Up and Response Evaluation

Knowledge of postinterventional MR and CT findings is essential for accurate interpretation of the ablated area [46]. Familiarity with these characteristics prevents confusion between normal or less typical postablational changes and residual or recurrent disease. In addition, timely recognition of IRE-related complications and vital tumor allows for expedited management and possible retreatment. The World Health Organization (WHO) and RECIST criteria depend on decrease in tumor size. However, decrease in viable cell mass is not always reflected by changes in tumor size. Exclusive reliance on tumor size does therefore not provide a complete assessment of tumor response and may lead to inaccurate conclusions. A preferable method of post-IRE treatment evaluation is to combine tumor and ablation zone sizes with functional information such as alterations in enhancement and diffusion.

Since little healthy pancreatic parenchyma surrounds the pancreatic tumor, the ablation zone is often ill-defined on MRI and especially on CT. Also, the presence of edema within the ablation zone impedes precise ablation zone delineation. A reasonable explanation for the observed hyperintense rim surrounding the ablation zone post-IRE is reactive hyperemia of edematous inflammatory origin. However, it cannot be excluded that this rim still contains residual disease and longer follow-up is needed to explore the exact significance. The remarkable hypointense rim that we found on T2 at 2 weeks suggests hemosiderin deposition resulting from degradation of the extravagated erythrocytes in the periphery of the ablation zone [46]. Post-IRE, arterial and portal venous phase CT attenuation decreased in nearly all patients. This decline in enhancement is in line with the observed postcontrast MRI findings which may be indicative for accurate tumor therapy response. The observed intralesional gas pockets may be caused by electrolysis of water into hydrogen and oxygen caused by the electric pulses or by vaporization due to heat development or by a combination of these mechanisms.

Initial post-IRE examinations reveal a notable volume increase on ceCT and ceMRI, followed by a decrease during follow-up. The calculated volumes varied widely between the two modalities, which is caused by the difficult ablation zone delineation from surrounding structures. Studies investigating the size and shape of the IRE ablation zone have predominantly correlated imaging findings to histology in animal studies. Overall, the radiological ablation zone size as measured on CT and MRI-DWI correlates well with the histologic ablation zone. In addition, studies suggested that ablation zone size and shape depend on the IRE parameters used and on the type of tissue ablated. There is clear concordance between our findings and preclinical and early clinical studies that describe a reduction of the size of the ablated area over several weeks, resulting from the clearance of cellular debris aided by the preservation of larger vessels.

Vroomen et al. all describe DWI-b800 hyperintensity and low ADC values at 6 weeks to predict tumor residue or early recurrence [46]. Hence, DWI-b800 and ADC may be useful to predict early recurrence or incomplete ablation, similar to imaging after hepatic ablation. This may allow for earlier retreatment. 18F-fluorodeoxyglucose positron emission tomography (18F-FDG PET) CT has demonstrated better diagnostic accuracy compared with ceCT and even MRI (without DWI-b800) in the diagnosis of pancreatic cancer. Also, 18F-FDG PET is increasingly used to assess tissue response to

chemoradiation for LAPC. One recent study showed the difference in maximum standardized uptake value (SUVmax) pre- and post-chemoradiation for LAPC was an independent predictor of clinical outcome [46] (Figs. 11.5 and 11.6).

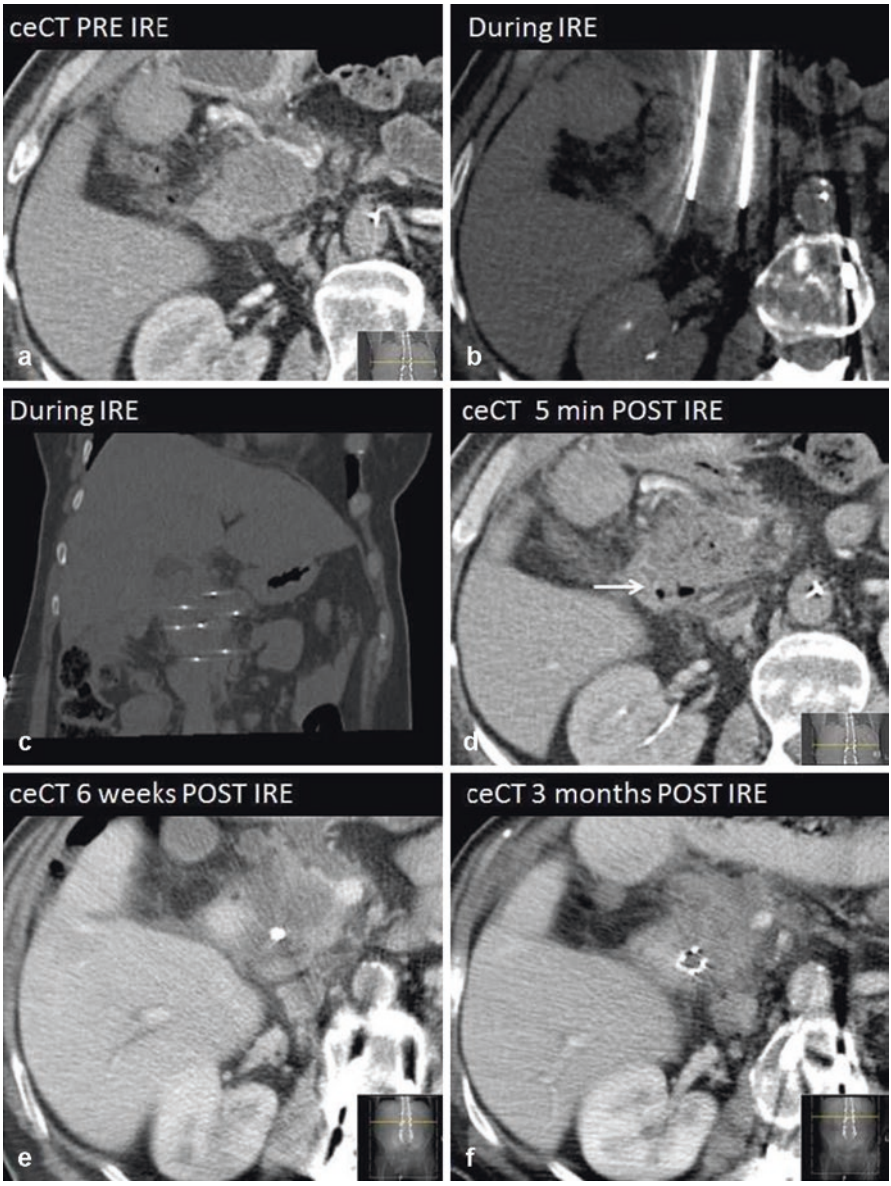

Fig. 11.5 Adapted from Vroomen et al. Imaging findings during follow-up on ceCT (**a**) Isoattenuating tumor on ceCT pre-IRE (**b**) CT-guided placement of electrodes around the outer border of the tumor (**c**) Confirmation of correct electrode configuration according to the treatment plan with a nonenhanced CT scan (**d**) Hypoattenuating IRE ablation zone with intralesional gas pockets immediately after IRE (**e**) Hypoattenuating IRE ablation zone at 6 weeks follow-up (**f**) Hypoattenuating IRE ablation zone at 3 months follow-up [46]

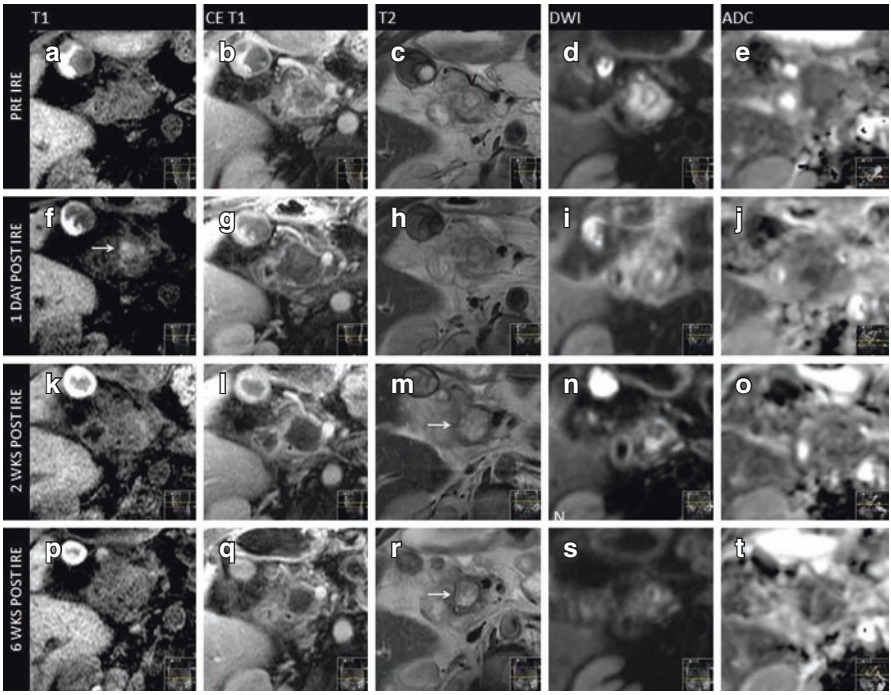

Fig. 11.6 Adapted from Vroomen et al. Prior to IRE: (**a**) Isointense tumor on T1 sequence (**b**) Hypointense tumor on T1 sequence (portal venous phase) (**c**) Hyperintense tumor on T2 sequence (**d**) Hyperintense tumor on DWI-b800 sequence (**e**) Hypointense tumor on ADC map. 1 day post-IRE: (**f**) Isointense IRE ablation zone with small hyperintense blood residues on T1 sequence (**g**) Hypointense IRE ablation zone plus rim enhancement surrounding the treated area on T1 sequence (portal venous phase) (**h**) Hyperintense (+) IRE ablation zone on T2 sequence (**i**) Hyperintense (+) IRE ablation zone on DWI-b800 sequence (**j**) Isointense IRE ablation zone on ADC map. 2 weeks post-IRE: (**k**) Isointense IRE ablation zone on T1 sequence (**l**) Hypointense IRE ablation zone plus rim-enhancement surrounding the treated area on T1 sequence (portal venous phase) (**m**) Hyperintense (+) IRE ablation zone plus hypointense rim enhancement surrounding the treated area on T2 sequence (**n**) Hyperintense (+) IRE ablation zone on DWI-b800 sequence (**o**) Isointense IRE ablation zone on ADC map. 6 weeks post-IRE: (**p**) Isointense IRE ablation zone on T1 sequence (**q**) Hypointense IRE ablation zone on T1 sequence (portal venous phase) (**r**) Hyperintense (+) IRE ablation zone plus hypointense rim enhancement surrounding the treated area on T2 sequence (**s**) Hyperintense (+) IRE ablation zone on DWI-b800 (**t**) Isointense IRE ablation zone on ADC map [46]

11.10 Disease Recurrence

11.10.1 Local Recurrence After Pancreaticoduodenectomy

Regarding the role of repeat surgery after pancreaticoduodenectomy for pancreatic ductal adenocarcinoma, there is conflicting data in the literature. Kleef et al. included 30 patients with recurrent disease, 15 underwent repeat curative intent surgery and 15 did not [47]. The median survival was 17 months in the group that was resected versus 9.4 months in those who were not, with statistically significant survival improvement

in those patients who were resected after a disease-free interval of greater than 9 months. A second, larger study evaluated a series of 97 patients with pancreatic cancer recurrence. Of these, 57 had an isolated local recurrence and 41 were found to be resectable [48]. Again there was a significant survival advantage in those undergoing repeat resection with a median survival of 16.4 versus 9.4 months in those that were resectable or unresectable, respectively. The most recent study by Miyazaki et al. examined 170 patients with recurrent pancreatic cancer [49]. Sixty-seven of these had isolated recurrences within the pancreatic remnant and 11 ultimately underwent re-resection. Consistent with the previous reports, they found improved median survival of 25 months with repeat resection versus 9.3 months in those not resected. Although these three studies show similar results, with improved median survival in resectable cases of recurrent pancreatic cancer, a study from MD Anderson Cancer Center looked at the results of selective operation for locally recurrent or metastatic pancreatic cancer [50]. This study showed little benefit in resecting local recurrences in the pancreas even after a disease-free interval on over 20 months. Given the advances of systemic chemotherapy and stereotactic body radiation therapy, controversy regarding the specific sequencing of therapy for patients who develop recurrent disease within the pancreatic gland remnant remains. No clear guidelines regarding retreatment of pancreatic remnant carcinoma exist. Although feasible, the exact role for IRE to treat local site recurrences after resection remains unclear.

11.10.2 Local Recurrence After IRE

Although patients with local tumor residue after IRE should be considered suitable for retreatment, it may prove difficult to differentiate vital tumor tissue from fibrotic scar tissue based on early cross-sectional imaging findings. However, local site recurrence, detected at least 6 months after the initial procedure, in the absence of distant disease progression retreatment should be considered. Local recurrence (LR) is defined as a focal or diffuse growing mass (>20% solid lesion increase in longest diameter on the axial plane) within 1 cm of the ablated region compared to the new baseline scan at 4–12 weeks post-IRE. Although the median time to local progression was 13 months in the PANFIRE trial (percutaneous IRE) and 14 months in Martin's registry (open IRE), the number of patients eventually suitable for repeat ablation was low (3/25 in the PANFIRE trial), primarily because of coexisting extra-pancreatic disease or a multidirectional growth pattern of the recurring tumor tissue [40, 44] (Fig. 11.7).

11.11 Results from Literature

11.11.1 Quality of Life

The most relevant and attainable goal in management of LAPC is good symptom palliation. Therefore, quality of life (QoL) outcomes should be carefully weighed against survival benefit and treatment-related complications. In the PANFIRE trial, no significant decrease in QoL or pain perception was described in the early months after IRE, and the deterioration hereafter conceivably reflects disease progression [40].

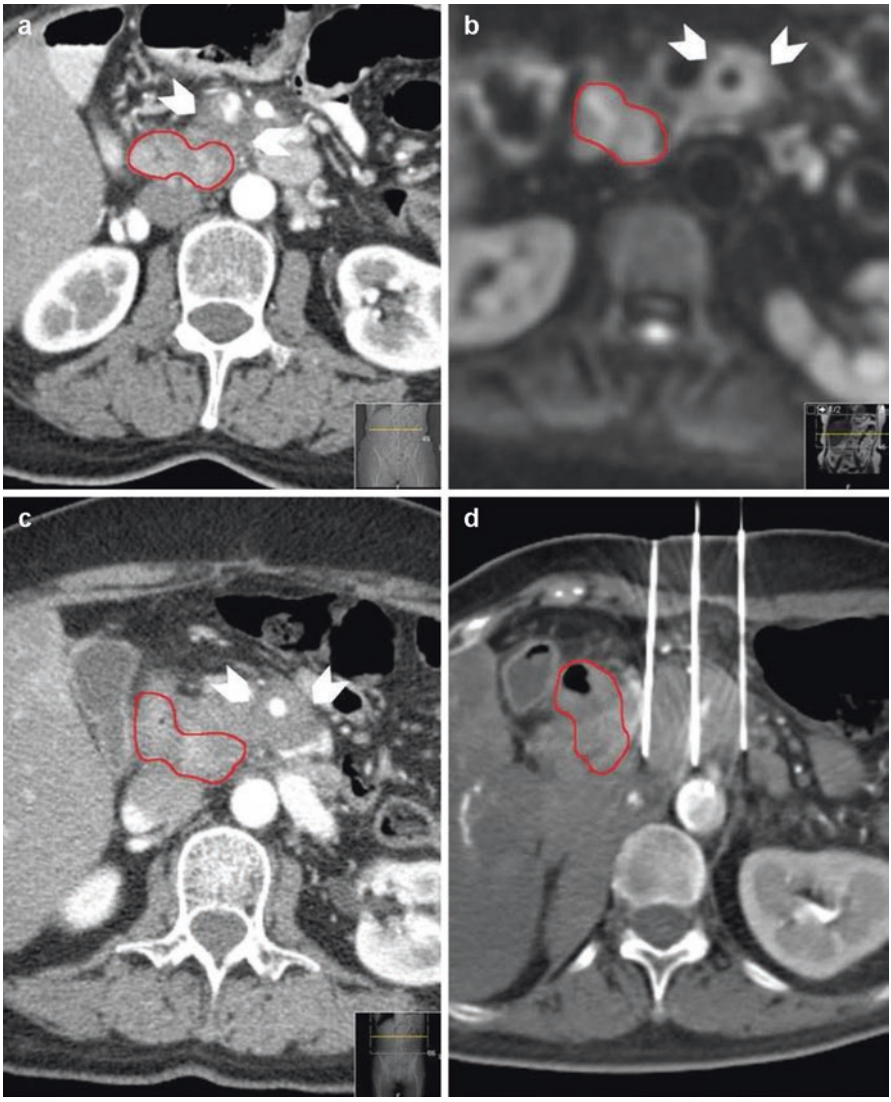

Fig. 11.7 Adapted from Scheffer et al. and Vroomen et al. The development of a local recurrence. *Red line*, duodenum. (**a**) CeCT pre-IRE showing the initial tumor (*white arrowheads*) that was treated with IRE (**b**) MR DWI-b800 6 weeks post-IRE showing new hyperintensity around the superior mesenteric artery (*white arrowheads*) (**c**) CeCT 4 months post-IRE showing evident local recurrence (*white arrowhead*) (**d**) re-IRE of the local recurrence [40, 46]

11.11.2 Overall and Progression-Free Survival

Ten studies (excluding case reports) reported survival results: six retrospective series, two prospective cohorts, and two prospective controlled clinical trials [40, 42, 44, 51–56]. The chemotherapeutic regimens in these series were heterogeneous

(Table 11.1). Chemotherapy was administered as palliative therapy, as neoadjuvant or induction therapy prior to IRE, or as adjuvant regimen after IRE, which makes overall survival results from IRE difficult to interpret. For the open approach, we could extract 281 patients with a mean median OS of 15.2 months from IRE and 22.9 months from date of diagnosis (range 16–23.2 months). For the percutaneous group, we included 138 patients with a mean median OS from date of diagnosis of 22.3 months from the date of diagnosis (range 17–27 months). These heterogeneous results are probably caused by differences in selection criteria and referral bias, and hence it remains erratic to compare these results and jump to conclusions regarding the superior approach or the best (neo)adjuvant chemotherapeutic regimen.

11.12 Ongoing and Future Clinical Trials

There is no standard of care for patients with locally advanced pancreatic cancer. Extrapolating results from patients with metastatic pancreatic cancer, most centers nowadays offer eligible patients FOLFIRINOX with or without radiotherapy (preferably SABR). Whether FOLFIRINOX plus SABR is superior to FOLFIRINOX alone will hopefully be answered by the PANCRS trial from Stanford, USA (NCT01926197), which has been recruiting patients for several years now. If adding SABR proves superior, the standard of care probably becomes FOLFIRINOX plus SABR for eligible patients.

Anticipating on these results the prospective, multicenter, multinational, phase III, randomized controlled trial called the CROSSFIRE trial (NCT02791503) compares the efficacy of chemotherapy (preferably FOLFIRINOX) plus IRE (experimental arm) to the efficacy of chemotherapy plus stereotactic ablative radiotherapy or SABR (control arm) in patients with locally advanced, non-resectable, non-metastasized, pancreatic cancer in terms of overall survival from randomization. Primary participating centers are the VU University Medical Center (Amsterdam, the Netherlands) and the Miami Miller School of Medicine (University of Miami, Miami, Florida, USA). The trial started including patients in July of 2016.

There is an increasing evidence that margin accentuation for borderline resectable pancreatic cancer, performing open IRE of the resection margin prior to resection, is effective with an increase in local progression-free survival, distant progression-free survival, and overall survival compared to historic controls [44]. One group from Berne is focusing on the impact of margin accentuation as compared to a historic control group (NCT02952859).

IRE enhances delivery of gemcitabine to pancreatic adenocarcinoma [57]. Investigators from Texas will examine how well electrochemotherapy works at treating people with stage III pancreatic adenocarcinoma (NCT02592395). Electrochemotherapy is a treatment that combines electroporation and chemotherapy administration. Electroporation uses an electric current to produce holes in pancreatic tumor, which causes the tumor cells to die or take up a higher concentration of administered chemotherapy agent. This study will test the safety and look at the effect of electrochemotherapy in the treatment of stage III pancreatic adenocarcinoma.

Another group from Guangzhou will study the impact of IRE on immune response in patients diagnosed with unresectable pancreatic cancers smaller than 5.0 cm (NCT02343835). It will profile the immune response to IRE of unresectable pancreatic cancers. The intra-tumoral and systemic immune response to IRE will be determined and compared to pre-ablated pancreatic cancer specimens and historical control specimens.

A probe with two electrodes on a single needle (single insertion device) is currently being developed by AngioDynamics. The advantage of only having to place a single needle in the middle of a tumor seems self-evident for many pancreatic and other tumors. A group from Utrecht, the Netherlands, is evaluating IRE with two parallel plate electrodes (paddles, personal communication). This would theoretically lead to less needle-based complications such as pancreatic fistula, bile or pancreatic fluid leakage, and hemorrhage and result in a more homogenous energy delivery for open procedures.

References

1. Bilimoria KY, et al. Validation of the 6th edition AJCC pancreatic cancer staging system – report from the National Cancer Database. Cancer. 2007;110(4):738–44.
2. Callery MP, et al. Pretreatment assessment of resectable and borderline resectable pancreatic cancer: expert consensus statement. Ann Surg Oncol. 2009;16(7):1727–33.
3. Pandya GJ, Shelat VG. Radiofrequency ablation of pancreatic ductal adenocarcinoma: the past, the present and the future. World J Gastrointest Oncol. 2015;7(2):6–11.
4. Pezzilli R, et al. Radiofrequency ablation for advanced ductal pancreatic carcinoma is this approach beneficial for our patients? A systematic review. Pancreas. 2011;40(1):163–5.
5. Pansky B. Anatomy of the pancreas – emphasis on blood-supply and lymphatic drainage. Int J Pancreatol. 1990;7(1–3):101–8.
6. Ibukuro K. Vascular anatomy of the pancreas and clinical applications. J Gastrointest Cancer. 2001;30(1–2):87–104.
7. Cesmebasi A, et al. The surgical anatomy of the lymphatic system of the pancreas. Clin Anat. 2015;28(4):527–37.
8. OMorchoe CCC. Lymphatic system of the pancreas. Microsc Res Tech. 1997;37(5–6):456–77.
9. Bilina C. Dorland's electronic medical dictionary, 28th ed. Lab Med. 2000;31(1):51.
10. Ionescu-Tirgoviste C, et al. A 3D map of the islet routes throughout the healthy human pancreas. Sci Rep. 2015;5:14634.
11. Olson SH, et al. Weight loss, diabetes, fatigue, and depression preceding pancreatic cancer. Pancreas. 2016;45(7):986–91.
12. Worni M, et al. Modest improvement in overall survival for patients with metastatic pancreatic cancer: a trend analysis using the surveillance, epidemiology, and end results registry from 1988 to 2008. Pancreas. 2013;42(7):1157–63.
13. Maisonneuve P. Epidemiology and risk factors of pancreatic cancer. Eur J Cancer. 2016;57:S4.
14. Freelove R, Walling AD. Pancreatic cancer: diagnosis and management. Am Fam Physician. 2006;73(3):485–92.
15. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin. 2013;63(1):11–30.
16. Neoptolemos JP, et al. Adjuvant chemotherapy with fluorouracil plus Folinic acid vs gemcitabine following pancreatic cancer resection a randomized controlled trial. J Am Med Assoc. 2010;304(10):1073–81.
17. Howard TJ, et al. A margin-negative R0 resection accomplished with minimal postoperative complications is the surgeon's contribution to long-term survival in pancreatic cancer. J Gastrointest Surg. 2006;10(10):1338–45. discussion 1345–6.

18. Lopez NE, Prendergast C, Lowy AM. Borderline resectable pancreatic cancer: definitions and management. World J Gastroenterol. 2014;20(31):10740–51.
19. Poplin E, et al. Phase III, randomized study of gemcitabine and oxaliplatin versus gemcitabine (fixed-dose rate infusion) compared with gemcitabine (30-minute infusion) in patients with pancreatic carcinoma E6201: a trial of the Eastern Cooperative Oncology Group. J Clin Oncol. 2009;27(23):3778–85.
20. Louvet C, et al. Gemcitabine in combination with oxaliplatin compared with gemcitabine alone in locally advanced or metastatic pancreatic cancer: results of a GERCOR and GISCAD phase III trial. J Clin Oncol. 2005;23(15):3509–16.
21. Conroy T, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med. 2011;364(19):1817–25.
22. Faris JE, et al. FOLFIRINOX in locally advanced pancreatic cancer: the Massachusetts General Hospital Cancer Center experience. Oncologist. 2013;18(5):543–8.
23. Gunturu KS, et al. FOLFIRINOX for locally advanced and metastatic pancreatic cancer: single institution retrospective review of efficacy and toxicity. Med Oncol. 2013;30(1):361.
24. Metges JP, et al. Efficacy and safety of FOLFIRINOX in patients with pancreatic metastatic cancer. J Clin Oncol. 2013;31(4):248–248.
25. Moorcraft SY, et al. FOLFIRINOX for locally advanced or metastatic pancreatic ductal adenocarcinoma: the royal Marsden experience. Clin Colorectal Cancer. 2014;13(4):232–8.
26. Neha C, et al. The impact of Folfirinox chemotherapy on the treatment pattern of patients with pancreas cancer seen at a tertiary referral Centre in the UK. Ann Oncol. 2014;25:75.
27. Sadot E, et al. FOLFIRINOX induction therapy for stage 3 pancreatic adenocarcinoma. Ann Surg Oncol. 2015;22(11):3512–21.
28. Walsh EMA, et al. FOLFIRINOX in pancreatic cancer: can results be reproduced outside the clinical trial setting? J Clin Oncol. 2014;32(15):e15236.
29. Hosein PJ, et al. A retrospective study of neoadjuvant FOLFIRINOX in unresectable or borderline-resectable locally advanced pancreatic adenocarcinoma. BMC Cancer. 2012;12:199.
30. Johung K, Saif MW, Chang BW. Treatment of locally advanced pancreatic cancer: the role of radiation therapy. Int J Radiat Oncol Biol Phys. 2012;82(2):508–18.
31. Gurka MK, et al. Stereotactic body radiation therapy with concurrent full-dose gemcitabine for locally advanced pancreatic cancer: a pilot trial demonstrating safety. Radiat Oncol. 2013;8:44.
32. Chuong MD, et al. Stereotactic body radiation therapy for locally advanced and borderline resectable pancreatic cancer is effective and well tolerated. Int J Radiat Oncol Biol Phys. 2013;86(3):516–22.
33. Schellenberg D, et al. Single-fraction stereotactic body radiation therapy and sequential gemcitabine for the treatment of locally advanced pancreatic cancer. Int J Radiat Oncol Biol Phys. 2011;81(1):181–8.
34. Seo Y, et al. Stereotactic body radiation therapy boost in locally advanced pancreatic cancer. Int J Radiat Oncol Biol Phys. 2009;75(5):1456–61.
35. Macchia G, et al. Quality of life and toxicity of stereotactic radiotherapy in pancreatic tumors: a case series. Cancer Investig. 2012;30(2):149–55.
36. Rombouts SJ, et al. Systematic review of innovative ablative therapies for the treatment of locally advanced pancreatic cancer. Br J Surg. 2015;102(3):182–93.
37. Scheffer HJ, et al. Irreversible electroporation for nonthermal tumor ablation in the clinical setting: a systematic review of safety and efficacy. J Vasc Interv Radiol. 2014;25(7):997–1011. quiz 1011.
38. Scheffer HJ, et al. Percutaneous irreversible electroporation of locally advanced pancreatic carcinoma using the dorsal approach: a case report. Cardiovasc Intervent Radiol. 2015;38(3):760–5.
39. Martin RC. Irreversible electroporation of stage 3 locally advanced pancreatic cancer: optimal technique and outcomes. J Vis Surg. 2015;1(4):1–9.
40. Scheffer HJ, et al. Ablation of locally advanced pancreatic cancer with percutaneous irreversible electroporation: results of the phase I/II PANFIRE study. Radiology. 2017;282(2):585–97.
41. Thomson KR, et al. Investigation of the safety of irreversible electroporation in humans. J Vasc Interv Radiol. 2011;22(5):611–21.

42. Narayanan G, et al. Percutaneous irreversible electroporation for downstaging and control of unresectable pancreatic adenocarcinoma. J Vasc Interv Radiol. 2012;23(12):1613–21.
43. Martin RC, et al. Irreversible electroporation of unresectable soft tissue tumors with vascular invasion: effective palliation. BMC Cancer. 2014;14:540.
44. Martin RC 2nd, et al. Treatment of 200 locally advanced (stage III) pancreatic adenocarcinoma patients with irreversible electroporation: safety and efficacy. Ann Surg. 2015;262(3):486–94. discussion 492–4.
45. Martin RC 2nd, et al. Irreversible electroporation in locally advanced pancreatic cancer: potential improved overall survival. Ann Surg Oncol. 2013;20(Suppl 3):S443–9.
46. Vroomen LG, et al. MR and CT imaging characteristics and ablation zone volumetry of locally advanced pancreatic cancer treated with irreversible electroporation. Eur Radiol. 2016; 27:2521–31.
47. Kleeff J, et al. Surgery for recurrent pancreatic ductal adenocarcinoma. Ann Surg. 2007;245(4):566–72.
48. Lavu H, et al. Reoperative completion pancreatectomy for suspected malignant disease of the pancreas. J Surg Res. 2011;170(1):89–95.
49. Miyazaki M, et al. Repeat pancreatectomy for pancreatic ductal cancer recurrence in the remnant pancreas after initial pancreatectomy: is it worthwhile? Surgery. 2014;155(1):58–66.
50. Thomas RM, et al. Selective reoperation for locally recurrent or metastatic pancreatic ductal adenocarcinoma following primary pancreatic resection. J Gastrointest Surg. 2012;16(9):1696–704.
51. Paiella S, et al. Safety and feasibility of Irreversible Electroporation (IRE) in patients with locally advanced pancreatic cancer: results of a prospective study. Dig Surg. 2015;32(2):90–7.
52. Kluger MD, et al. Single-institution experience with irreversible electroporation for T4 pancreatic cancer: first 50 patients. Ann Surg Oncol. 2016;23(5):1736–43.
53. Lambert L, et al. Treatment of locally advanced pancreatic cancer by percutaneous and intraoperative irreversible electroporation: general hospital cancer center experience. Neoplasma. 2016;63(2):269–73.
54. Mansson C, et al. Percutaneous irreversible electroporation for treatment of locally advanced pancreatic cancer following chemotherapy or radiochemotherapy. Eur J Surg Oncol. 2016;42(9):1401–6.
55. Mansson C, et al. Safety and preliminary efficacy of ultrasound-guided percutaneous irreversible electroporation for treatment of localized pancreatic cancer. Anticancer Res. 2014;34(1):289–93.
56. Belfiore MP, et al. Percutaneous CT-guided irreversible electroporation followed by chemotherapy as a novel neoadjuvant protocol in locally advanced pancreatic cancer: our preliminary experience. Int J Surg. 2015;21(Suppl 1):S34–9.
57. Bhutiani N, et al. Irreversible electroporation enhances delivery of gemcitabine to pancreatic adenocarcinoma. J Surg Oncol. 2016;114(2):181–6.