Chapter 5

# Irreversible Electroporation in Pancreatic Cancer

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Additional information is available at the end of the chapter

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**Abstract**

Pancreatic cancer is the deadliest of the gastrointestinal tract with 5-year survival rates of less than 5%. Given common asymptomatic early disease course, most patients (50%) present with an already metastatic disease, while only 20% can undergo potentially curative resection. The remaining 30% present with locally advanced disease, defined as extended vascular encasement, where the risk of surgical therapy often outweighs its benefits. Traditional thermal local ablative modalities (RFA, MWA, or cryotherapy) have the disadvantage that they are not applicable in proximity to vital vascular structures, which are abundant in the peripancreatic region. Irreversible electroporation (IRE) is an emerging non-thermal alternative that induces apoptosis of tumor cells by the delivery of short repetitive impulses of high-voltage electric current. Given its mostly non-thermal modality, IRE is not hampered by a heat-sink effect and is applicable with little risk around vascular structures, bile and pancreatic ducts. Recent research suggests that local tumor destruction through IRE improves overall survival, progression-free survival and quality of life in patients with locally advanced pancreatic cancer.

**Keywords:** locally advanced pancreatic cancer, borderline resectable pancreatic cancer, irreversible electroporation, local tumor destruction, apoptosis, overall survival

## 1. Introduction

Pancreatic adenocarcinoma is a prevalent disease with 53,760 newly diagnosed patients in the United States in 2017 [1]. Despite the rapidly growing medical progress in the twenty-first century and extensive efforts in cancer research, pancreatic adenocarcinoma remains a highly aggressive malignancy with 5-year survival rate still not exceeding 5% [1, 2]. By extrapolating annual incidence rates, pancreatic adenocarcinoma is estimated to rise to the second leading

cause of cancer-related death in the United States by 2020 [3]. Unfortunately, only a minority of patients presented early during the disease course, and screening programs have been crowned by little success so far [4]. It is globally accepted that early detection of the tumor provides the only chance for cure, given that treatment modalities other than surgical resection are inherently palliative. Several clinical staging systems for patients with pancreatic adenocarcinoma exist, while all of them comply with the only potentially curative treatment option, that is, surgical resection. Thanks to more elaborate imaging techniques now widely available (high-resolution CT, MRI, endoscopic ultrasound), the tumor-vessel relationships can be determined with high precision rendering pretreatment staging increasingly accurate. Among others, one of the largely used and accepted staging definitions has been established by the National Comprehensive Cancer Network (NCCN) [5]. This classification groups pancreatic adenocarcinoma into four categories such as resectable, borderline resectable, locally advanced and metastatic disease [6].

Definition according to the National Comprehensive Cancer Network (NCCN) [6]:

*Resectable tumor*: no distant metastases, no radiographic evidence of superior mesenteric vein (SMV) and/or portal vein (PV) abutment, distortion, tumor thrombus, or venous encasement. Clear fat planes around the celiac axis, hepatic artery and superior mesenteric artery (SMA).

*Borderline resectable*: no distant metastases, encasement of the SMV/PV but without encasement of the nearby arteries or short segment venous occlusion resulting from either tumor thrombus or encasement but with suitable vessel proximal and distal to the area of vessel involvement, allowing for safe resection and reconstruction. Gastroduodenal artery encasement up to the hepatic artery, without extension to the celiac axis. Tumor abutment of the SMA not to exceed >180° of the circumference of the vessel wall (**Figure 1**).

*Locally advanced (unresectable)*: tumor involvement or occlusion of the SMV or PV, which precludes reconstruction of vessels or greater than 180° tumor contact with either SMA, celiac artery or any involvement of first jejunal branch of SMA or Aorta (**Figure 2**).

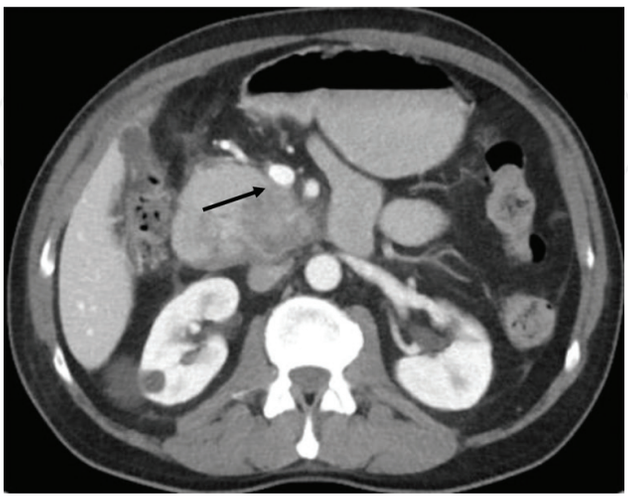

**Figure 1.** Borderline resectable pancreatic cancer. Tumor with contact to the SMV (black arrow).

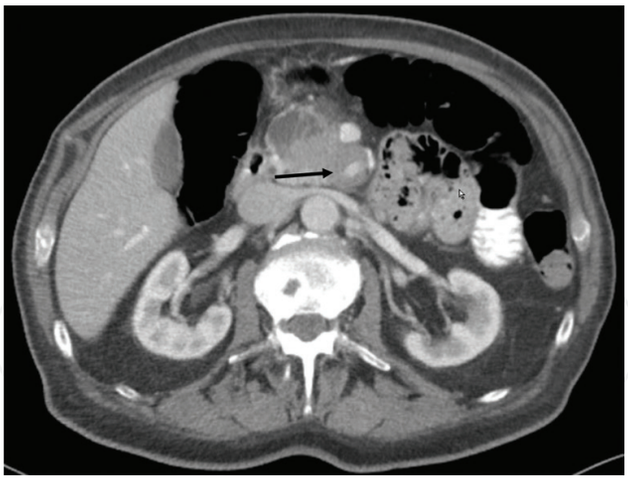

**Figure 2.** Locally advanced pancreatic cancer. Encasement of the superior mesenteric artery (black arrow).

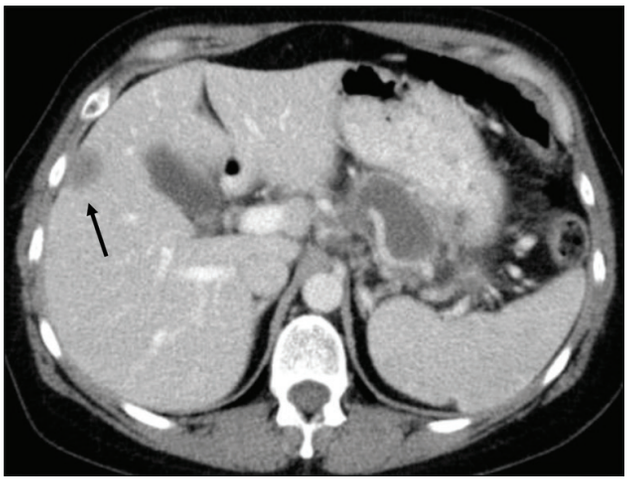

**Figure 3.** Metastatic pancreatic cancer. Liver metastasis (black arrow).

*Metastatic disease*: presence of distant metastases (e.g. hepatic, peritoneal, or other) (**Figure 3**).

At the time of diagnosis, only approximately 20% of patients present with a resectable or borderline resectable disease. If treated by surgical resection with negative histological margins (R0) followed by adjuvant chemotherapy, this patient group can achieve a 5-year survival rate of about 20% [2, 5]. While 50% of patients initially present with metastatic disease, the remnant 30% show a locally advanced stage with involvement of vital adjacent structures as defined earlier. While the diagnosis of resectable and metastatic disease usually is simple, the distinction between borderline resectable and locally advanced disease can be challenging. In patients with borderline resectable disease, the involvement of major vessels is less extensive, and a macroscopic negative resection margin (e.g., with segmental/partial resection of venous structures) is potentially achievable without adding major morbidity [7]. In contrast, patients with locally advanced pancreatic cancer are often characterized by arterial vessel involvement. A resection with negative margins in these cases is technically rarely feasible

and often implies arterial resection associated with high perioperative morbidity and mortality [8–11]. A timely meta-analysis by Mollberg et al. assessed the impact of arterial resection on perioperative outcomes among patients undergoing pancreatic resection. They showed that perioperative morbidity and mortality was, with 53 and 12%, significantly higher for patients with arterial resection compared to around 25–30 and 6% reported for pancreatoduodenectomies, not requiring arterial reconstruction, respectively [12–14]. In summary, given the high perioperative risk and its limited impact on survival, arterial resection can at present not be justified as a standard procedure in the treatment of pancreatic cancer [2, 10]. Accordingly, the current treatment recommendations for patients with locally advanced pancreatic cancer are chemo- and/or radiotherapy, which achieve a median overall survival of 9–13 months on average [2]. There is notably a difference in the standard treatment regimens according to the geographic location; most patients in the USA with locally advanced pancreatic cancer are currently undergoing combined chemoradiotherapy, whereas patients in the Europe are usually treated with chemotherapy alone. Recent advances in chemotherapy allow to downstage certain patients with locally advanced disease, making a surgical resection of some tumors possible [15, 16]. Patients treated with neoadjuvant chemotherapy followed by surgical resection can achieve similar survival rates like patients diagnosed in a resectable or borderline resectable state. It is estimated that in select patient cohorts, up to one-third of patients initially judged as non-resectable can be converted into a resectable state by neoadjuvant chemotherapy. However, the neoadjuvant regimen is still debated and is not internationally accepted yet as standard of care [17, 18].

Given that patients with locally advanced disease have a poor prognosis despite multimodal therapy, additional treatment alternatives are desperately needed. In the group of locally advanced pancreatic cancer, the tumor is confined to the location of origin without evidence of distant spread—rendering local therapy an attractive additional treatment option. As such, loco-regional therapies including radiofrequency ablation (RFA), microwave ablation (MWA) and irreversible electroporation (IRE) have gained increased attention in the treatment of locally advanced pancreatic adenocarcinoma over the last years [19, 20].

## 2. Local ablative strategies

### 2.1. Thermal local ablative strategies

Radiofrequency (RFA) and microwave ablation (MWA) have been used in an attempt to achieve local control among patients with locally advanced pancreatic cancer. Both treatments generate thermal energy by a high-frequency alternating current, which is delivered to the cancerous tissue by one or more needle electrodes. The created high local temperature at the tip of the electrodes leads to cell death by coagulative necrosis and protein denaturation [21, 22]. RFA has been used with success in the setting of unresectable tumors in multiple solid organs (liver, lung, kidney, brain, breast, prostate, bone, adrenal glands, spleen) [22]. Over the last years, it has also been deployed in the palliative setting of locally advanced pancreatic cancer. However, RFA in patients with pancreatic adenocarcinoma has not been widely accepted because of considerable morbidity and mortality rates [19]. The high complication rate was thought to be due to thermal injury to the multiple delicate structures (bile duct, pancreatic duct, duodenum, vital vessels)

surrounding the pancreas. By adjusting the administered temperature from 105 to 90°C for 5 min' length, complications in recent patient cohorts treated by RFA were substantially reduced [20]. Still, gastrointestinal hemorrhages, acute pancreatitis, pancreatic/biliary fistulas, duodenal injury and portal vein thrombosis are regularly reported in the literature [19]. A systematic review from 2014 cited an RFA-related morbidity ranging from 10 to 37% and an RFA-related mortality from 0 to 19% [23]. Another important downside of thermal ablative therapies is the so-called "heat-sink effect." During the ablation process, adjacent blood vessels are "cooling the tissue down" leading to an insufficient temperature in the immediate proximity of the vessels, where therefore efficient cell death cannot be induced [24]. Given the anatomical complexity of the pancreatic region and bearing the abovementioned aspects in mind, it is self-evident that the application of thermal ablative therapy in locally advanced pancreatic cancer is delicate. It is at this state unknown whether RFA should be combined with chemo- and/or radiotherapy as a standard treatment. A retrospective analysis of patients with locally advanced pancreatic cancer with short induction chemotherapy and RFA compared to a patient group with RFA did not show a difference in early disease progression or overall survival [25]. While there is no evidence from randomized controlled trials regarding the oncological outcome of RFA in locally advanced disease, several case series show a significantly increased median overall survival in patients where RFA was part of the treatment concept [26, 27].

MWA is less prone to the heat-sink effect compared to RFA and is therefore more suitable for application closer to large vessels. Similar to RFA, no randomized data using MWA in locally advanced pancreatic cancer are available [28]. Given the heterogeneous reports of MWA and RFA, direct comparisons between the two techniques in regard of long-term survival are currently not available. However, based on published evidence, MWA seems to lead to less postoperative pain and decreased ablation time with similar results in morbidity and mortality compared to RFA [29]. However, at present, MWA is still studied less extensively than RFA [30, 31].

## 2.2. Irreversible electroporation

### *2.2.1. Introduction to IRE*

Irreversible electroporation (IRE) is an emerging ablative modality that gained enormous interest over the last years. In contrast to the abovementioned thermal ablative strategies, IRE leads to cell death mainly through a nonthermal technique. In IRE, high voltage (maximum of 3000 V) electrical pulses of 70–90 μs duration are applied through a minimum of two electrodes positioned next to or into the target neoplastic tissue. The thus created electrical field leads to a disruption of the cell membrane's lipophilic bilayer by formation of nanoscale micropores. This damage to the cell membrane eventually leads to a collapse of intracellular homeostasis and an activation of apoptotic pathways, finally resulting in cell death. The distinct advantage of this technique compared to thermal ablative strategies is the preservation of structural components like collagen and elastin as thermal damage does only occur in the very close proximity to the ablation needles depending on pulse length, exposure of the needle tips, delivered energy, distance between the electrodes and underlying tissue. Another advantage of IRE compared to thermal ablative modalities is its nonexisting "heat sink effect," which means that the efficiency of IRE will not be reduced in proximity to large

vessels [21, 32]. For the above-cited reasons, IRE is a very attractive local ablation method in pancreatic cancer, given the inherent proximity of the pancreas to vital vascular structures as well as the bile and pancreatic duct.

However, IRE cannot be applied under any circumstances given that several contraindications for its use exist. The presence of metallic material in close proximity to the placed IRE needles (e.g., metallic biliary stent that is not removable) is a relative contraindication for IRE, given that the conductivity of the metal could potentiate the minimal thermal effect of it. Even more importantly, the presence of metal can distract, respectively, and derivate the electrical current used in IRE, rendering prediction of the ablation zone impossible. Hence the effect of IRE is potentially dangerous [33, 34]. Also, a tumor size >5 cm is generally seen as a contraindication, given that the volume of the ablation zone of a tumor exceeding this size is technically difficult to achieve [21]. Additionally, IRE is contraindicated in patients with certain cardiac arrhythmias, and patients with pacemakers should be evaluated by a cardiologist prior to IRE, as the high-voltage electric current applied can itself provocate potentially serious arrhythmias [32]. To avoid such complications in ablations at the level of the pancreas, the electrical pulses are applied during the complete refractory phase of the heart (50 ms after the R wave). To achieve the coordination of the IRE pulses and the heart rhythm of the patient, the IRE device is synchronized with the patient's ECG. Furthermore, application of IRE is not recommended in patients having a history of epilepsy or recent myocardial infarction. No data exist about the use of IRE in pregnancy.

*2.2.2. IRE in locally advanced pancreatic cancer*

IRE has first been established as a complementary local therapy in conjunction with chemotherapy for patients with locally advanced pancreatic cancer, which is not amenable to surgical resection [30]. In situations where surgical resection seems too risky (e.g., a tumor encapsulating the superior mesenteric artery), IRE has shown to be a safe and valuable treatment alternative. Standalone IRE without surgical resection of the primary tumor is called "in situ" IRE. Its primary aim is to achieve maximal local tumor control. As in thermal ablative strategies, there is currently no randomized data available that look at oncological outcomes of (radio-) chemotherapy and IRE compared to (radio-) chemotherapy alone. However, there is encouraging evidence that suggests a relevant improvement of overall survival in patients with in situ IRE after induction chemotherapy/(radio-) chemotherapy [2, 35]. A propensity-matched score analysis by Martin et al. showed a survival benefit of induction chemotherapy and/or radiation followed by IRE compared to (radio-) chemotherapy alone. The additional treatment with IRE showed a prolongation of local progression free survival from 6 to 14 months, distant progression free survival from 9 to 15 months and overall survival from 13 to 20 months [35]. Another study analyzing 200 patients with locally advanced pancreatic cancer, either undergoing in situ IRE or margin accentuation IRE after an induction chemotherapy/(radio-)chemotherapy showed an encouraging median overall survival of 24.9 months and local recurrence rates of only 3% [36]. These results indicate that local tumor control with IRE is achievable and has a significant positive effect on patients with locally advanced pancreatic cancer. However, the interpretation of data on long-term oncological outcomes after IRE is still difficult, given that the studies available are of substantial heterogeneity and mostly lacking direct control groups. Additionally, most studies were not primarily designed to demonstrate oncological efficacy of the procedure but rather aimed to demonstrate safety and efficacy of the IRE procedure itself [2]. Some authors emphasize

the possible impact of neoadjuvant chemotherapy over the direct effect of IRE given that the specific impact of IRE has not yet been demonstrated. However, Gillen et al. found a median overall survival of 22 months in patients with locally advanced pancreatic cancer treated with neoadjuvant chemotherapy and if possible subsequent pancreatic resection [17]. These survival outcomes are still slightly worse than the ones of the 200 patients documented by Martin et al. in his cohort undergoing in situ IRE/margin accentuation IRE with pancreatic resection. IRE thus seems to add some additional benefit that systemic chemotherapy cannot provide, most probably by its local field of action. This observation has led to the hypothesis that the resection margin in pancreatic cancer deserves further investigation, as IRE might contribute to better overall survival by achieving more "true" R0 resections (see Chapter 4) [37]. Additional studies focusing on overall survival are certainly needed to further investigate the potential of IRE in improving the outcomes of patients with locally advanced pancreatic cancer.

### 2.3. Induction therapy in locally advanced pancreatic cancer before in situ IRE

At present, in situ IRE is mainly recommended in combination with upfront chemotherapy or (radio-) chemotherapy for at least 3 months. This does not only allow a "test for time" to get familiar with the biology of the patients underlying tumor, but also avoids local treatment with in situ IRE among patients with metastatic disease. Several induction treatment regimens have been suggested while so far no specific data are available, which favor one regimen over the other. Gemcitabine-based chemotherapy and/or radiotherapy is an option; however, more recent studies show beneficial results with the more aggressive FOLFIRINOX regimen as initial therapy [38–40]. Given the significant toxicity of FOLFIRINOX, a modified regimen has been suggested, where the 5-FU bolus is left out [15]. An alternative chemotherapy regimen often used in advanced pancreatic cancer and also in the setting of induction therapy before IRE is the combination of gemcitabine and Nab-paclitaxel [41]. Further studies assessing the best inductive treatment before IRE are needed before any general recommendation can be given.

Whatever induction therapy is used, it must be followed by restaging investigations. While there is no standard algorithm recommended, we perform a 3-phase contrast enhanced pancreas protocol computer tomography including the chest, to exclude pulmonary metastases and to plan the IRE procedure in detail. High quality CT-scans allow for sound judgment of tumor vessel relationships. In addition, given that diffusion MRI of the liver has shown to outperform CT-scans in regard of detection of liver metastases, all patients will undergo this imaging tool prior to surgical exploration [42].

## 3. Technique of IRE

### 3.1. General considerations

As mentioned earlier, all eligible patients for in situ IRE with locally advanced pancreatic cancer have to complete at least 3 months of neoadjuvant (radio-) chemotherapy, mainly to avoid local IRE treatment in patients with metastatic disease. This said, restaging after finishing induction treatment is crucial and should be performed with major diligence. Noteworthy is the usually absent "radiographic response" in pancreatic imaging after neoadjuvant

therapy—consensus is therefore to proceed to in situ IRE unless imaging shows local disease progression or newly observed distant metastases [2, 35, 36].

In case restaging confirms the presence of locally advanced pancreatic adenocarcinoma, every patient should be discussed at an interdisciplinary tumor board including medical oncologists, radiation oncologists, radiologists, pathologists and surgical oncologists. If tumor response is achieved and the lesion can be downstaged to borderline resectable disease, patients should be considered for surgical resection with margin-accentuation IRE (see part 4). In cases of stable disease without development of distant metastases and a maximal tumor diameter of <5 cm, patients can be planned for in situ IRE.

### 3.2. Practice of IRE

#### *3.2.1. Open approach*

Technically, there are different ways to apply IRE to a target lesion. Practice in our institution is at the moment the "classical" open abdominal approach. An upper midline or transverse incision is performed followed by a meticulous abdominal exploration looking for occult metastatic disease. IRE needles are then placed under ultrasound guidance covering the suspected tumor area. At least two unipolar probes are needed to deliver the high-voltage current. Parallel orientation of the needles is of utmost importance, with ideally a distance of about 2 cm between each needle pair (**Figures 4** and **5**).

A maximum of six probes can be inserted at the same time [43]. During the IRE procedure itself, full neuromuscular relaxation has to be guaranteed as the high voltages transmitted by the electrodes can produce significant muscular contractions [44]. If successful ablation was performed at one site, needle pull-back can be repeated as many times as needed with performance of the treatment at another level in order to cover the full desired ablation volume. Early imaging documentation of the success of IRE treatment is not possible, given the unspecific postoperative changes. As such, control imaging by CT-scan is not recommended before 3 months after IRE, as the images can be altered by ongoing edema following electroporation [45].

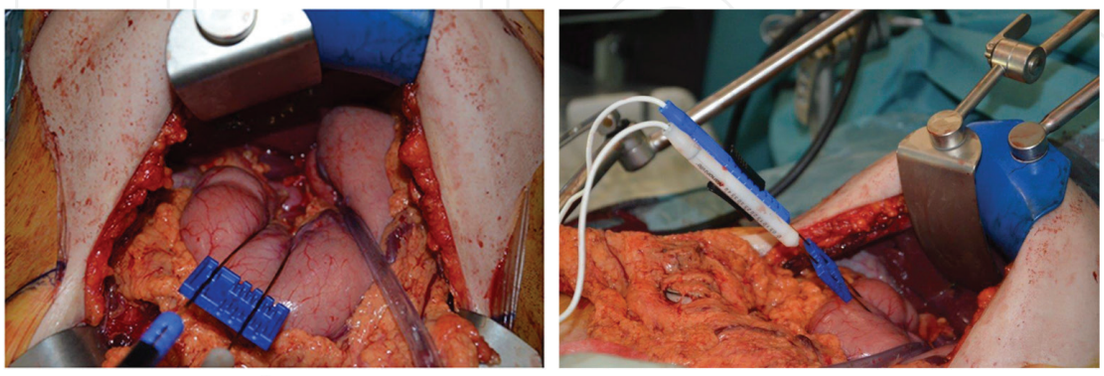


**Figure 4.** (a and b) Parallel placement of two needles at the distance of 2 cm for an IRE treatment around the common hepatic artery.

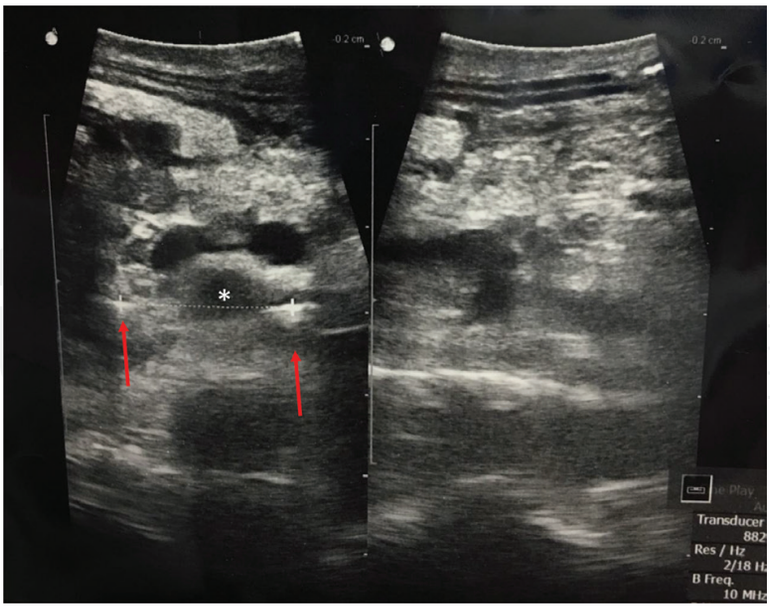


**Figure 5.** Intraoperative needle positioning under ultrasound guidance. In this example the two needle tips (red arrows) are placed to the left and right of the superior mesenteric artery (*).

### *3.2.2. Minimal-invasive approach*

IRE may also be applied in the setting of minimally invasive surgery under laparoscopic ultrasound guidance [46].

Additionally, surgical interventions like hepaticojejunostomy or gastroenterostomy, which have the potential to improve the quality of life in patients suffering from locally advanced pancreatic adenocarcinoma, can be performed during the same intervention in patients receiving IRE by either an open or a laparoscopic approach.

### *3.2.3. Percutaneous approach*

Several groups have gained experience in the percutaneous application of IRE supported by different imaging modalities. Narayanan et al. reported a series of 50 patients with CT-guided percutaneous IRE. The procedure was technically feasible in all patients. A median overall survival of 27 months from the time of diagnosis and 14 months from the time of IRE was reported, which is comparable to the oncological outcomes observed in open IRE [47]. Another group around Mansson performed IRE under ultrasound guidance. Of the 24 patients, all treatments were completed using ultrasound guidance only [48]. The case series presented are small, but the data suggest that the percutaneous approach is technically feasible and generally safe [47, 48]. A potential drawback of the percutaneous approach is the lack of visual assessment of the peritoneal cavity. Small liver/peritoneal lesions can be missed and patients with potential metastatic disease might be "locally overtreated," given that at present no data for application of IRE in metastatic settings exist.

### 3.3. Potential complications of IRE

Despite its nonthermal technique, also IRE is associated with potential complications. In the so far largest population from Martin et al. consisting of 200 patients treated with IRE, a total rate of 37% adverse events were recorded along with a mortality rate of 2%. The most common adverse events reported were pancreatic leak, pancreatitis and duodenal ulcer formation. Also, less frequently vascular complications (such as hepatic arterial thrombosis or mesenteric/portal vein thrombosis) and liver dysfunction/failure have been observed [36]. A group from Scandinavia analyzed the so-far gained IRE experience in a recent review including 10 studies comprising 446 patients in total (304 patients treated with open IRE and 142 patients treated percutaneously). A total of nine fatalities (2%) were recorded, while overall complication rate was summarized to be 35% [37]. It has to be kept in mind that complications after open IRE are challenging to interpret, as in many cases, patients had major gastrointestinal surgery in addition to their IRE treatment. However, whereas most complications seemed self-limited, there have been several reports on severe complications in open IRE such as portal vein thrombosis, pancreatic fistula and pancreatitis. Overall complications following percutaneous IRE vary from 0 to 20% in the different study groups. In the abovementioned population of 50 patients from Narayanan et al., most patients described postinterventional abdominal pain, 10 patients (20%) were reported to have a severe complication, but no IRE-related deaths occurred [47].

## 4. Navigated IRE

An additional, novel technology is the so-called navigated IRE. One of the most critical and difficult steps of IRE is the correct positioning of the needles in accurate depth and perfect parallelism. If IRE is performed in an open fashion, the placement of the needles is normally controlled under ultrasound guidance. However, given the complex anatomical situation around the pancreas, 3D reconstructions based on preoperative imaging can provide the surgeon with a better topologic understanding of the patient's specific anatomy. Those reconstructions can nowadays be transferred to planning tools and even be used intraoperatively as navigational help. It has been shown that the ability to plan procedures on these image data and visualize them during the surgery holds significant value as different surgical strategies can be evaluated on the 3D models preoperatively and can be used as additional patient-specific information throughout the surgery (**Figure 6**) [49, 50].

In 2005, Grenacher et al. discussed the role of computer-assisted surgery (CAS) in the field of liver and pancreas surgery [51]. Up to then, CAS was well established in surgical procedures related to orthopedics and neurosurgery, but the advantage of transferring the knowledge to soft tissue applications was insufficiently studied. However, advances in computer science nowadays enable intraoperative navigation in hepato-pancreato-biliary surgery. Using the CAScination® system, the real world can be linked to tThe virtual scene, either by using landmarks on the surface of the organs or by using ultrasound to mark internal structures like

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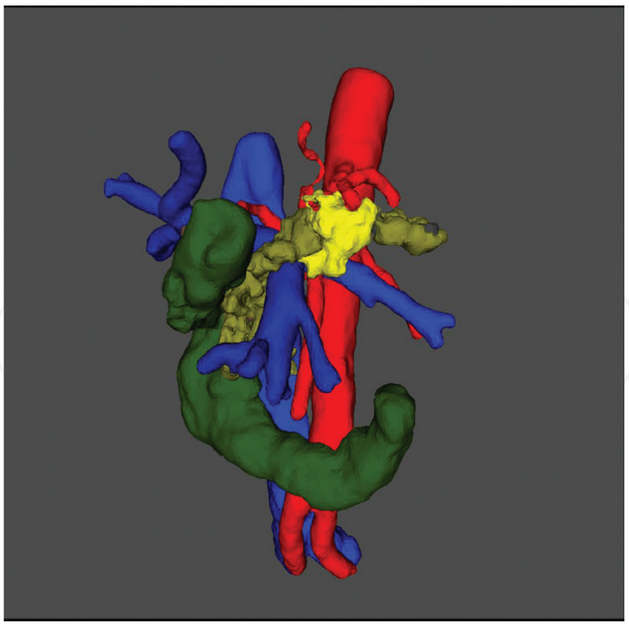

**Figure 6.** 3D reconstruction showing the arteries (red), veins (blue), tumor of the pancreatic body (yellow), duodenum (green) and the pancreas (light green).

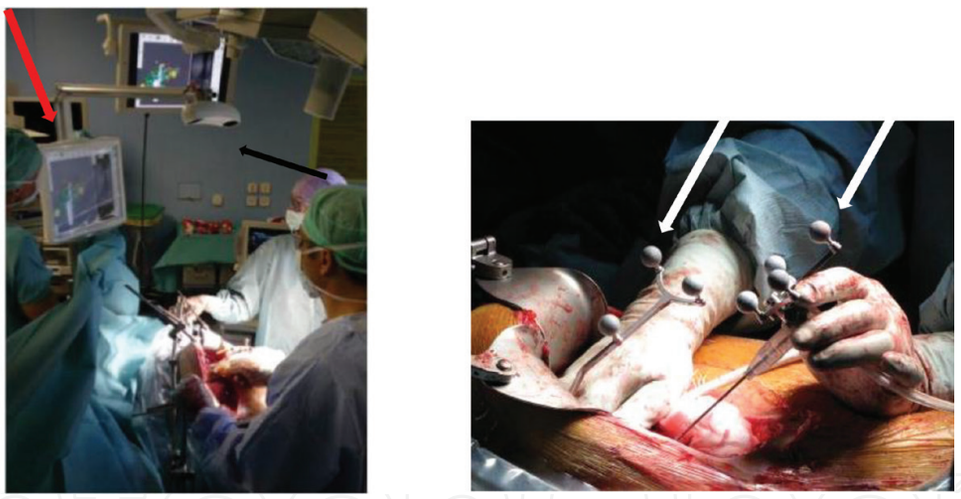

**Figure 7.** Demonstration of equipment for navigated IRE: touch screen (red arrow); infra red detection device (black arrow); metal spheres required for real-time instrument tracking consisting of instrument and ultrasound (white arrow).

tumors or bifurcations of vessels [52]. The surgical instruments are then equipped with markers, which can be detected by an optical tracking system in real time (**Figure 7**).

A specific solution for IRE treatment of the pancreas has been implemented, which provides the surgeon with the possibility to preoperatively verify the needle placement based on given constraints like parallelism and spacing between the needles [53]. The aim of this novel technique in IRE would be the placement of the needles under live CAS-guidance according to the preoperatively defined plan. Nevertheless, further improvements of the intraoperative navigation

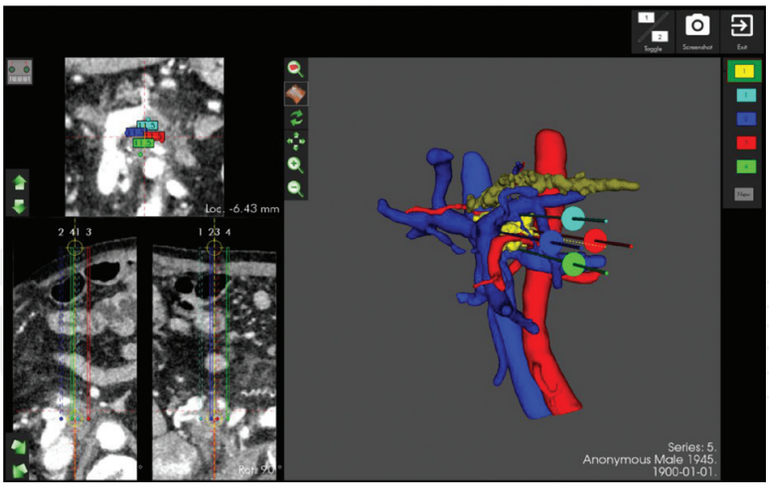


**Figure 8.** Preoperative 3D planning of an in situ IRE with 4 needles in a patient with locally advanced pancreatic cancer.

tools are required before they can be implemented to clinical routine and will be tackled by our team in the near future (**Figure 8**).

## 5. Additional indications: margin accentuation IRE

In recent years, the indications of IRE have been expanded to the so-called "margin accentuation" IRE, typically in patients with borderline resectable pancreatic cancer. In this patient group, IRE is used as an adjunct to surgery intraoperatively, aiming to achieve a higher percentage of negative margin resections [32]. It is well known that margin-negative resection is a strong indicator for better overall survival in pancreatic cancer. However, isolated local recurrences are observed in 35–80% of patients after intended R0 resection, raising the hypothesis that R1 resections are underestimated [54, 55]. A comprehensive work-up done by Esposito et al. confirmed that almost 80% of the patients had a true R1 resection, if a thorough examination is performed by the pathologist [56]. It is commonly accepted that R1 resections are associated with worse outcome as compared to R0 resections. In addition, there are different R0 definitions used in the current literature: no microscopic tumor at the or within 1 mm of the resection margin [57]. Hence, the role of R1 resections is not yet entirely clear—some advocate that R1 margins have a negative impact on the overall survival, whereas others state that R1 margins do influence local recurrence rates, without having a significant effect on survival [58–61]. Margin-accentuation IRE has been implemented in multiple pancreatic centers aiming to achieve a higher "true" R0 percentage and to therefore potentially increase overall survival and decrease local recurrences. At the present time, there are no clear recommendations of when margin accentuation IRE should be performed, because there are no clear radiological signs of when a microscopic positive resection margin has to be expected. Given the true R1-resection rate of up to 80%, one might argue that every patient with suspected or proven pancreatic cancer should have a margin accentuation IRE, if the additional procedure risk is limited and operation time is not significantly prolonged. However, as long as no data are published on the benefit of margin accentuation IRE over surgical resection only, the indication remains somewhat arbitrary. Further

research is definitely needed to assess the independent effect of margin accentuation IRE on local recurrence rates and overall survival.

## 6. Conclusions

Pancreatic cancer remains a highly lethal disease. Especially patients with locally advanced pancreatic cancer usually face a discouraging prognosis with limited treatment options. The local ablative therapy with IRE is a valuable additional treatment modality, which, looking at present evidence, seems to have the potential to improve disease-specific and overall survival among patients with this dreadful disease. IRE is technically feasible and generally safe in its open and minimal-invasive access. It can either be applied as in situ IRE in unresectable cases or as a complementary treatment to surgery in borderline resectable patients in order to improve the percentage of true R0 resections. Despite being now an accepted and increasingly applied therapy, there are still a lot of open questions regarding the use of IRE. Future efforts should aim toward the establishment of standard treatment protocols for IRE, in order to make its potential benefit available to more patients suffering from pancreatic adenocarcinoma.

## Conflict of interest

The authors declare no conflict of interest.

## Notes/thanks/other declarations

None.

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