Lightning strikes

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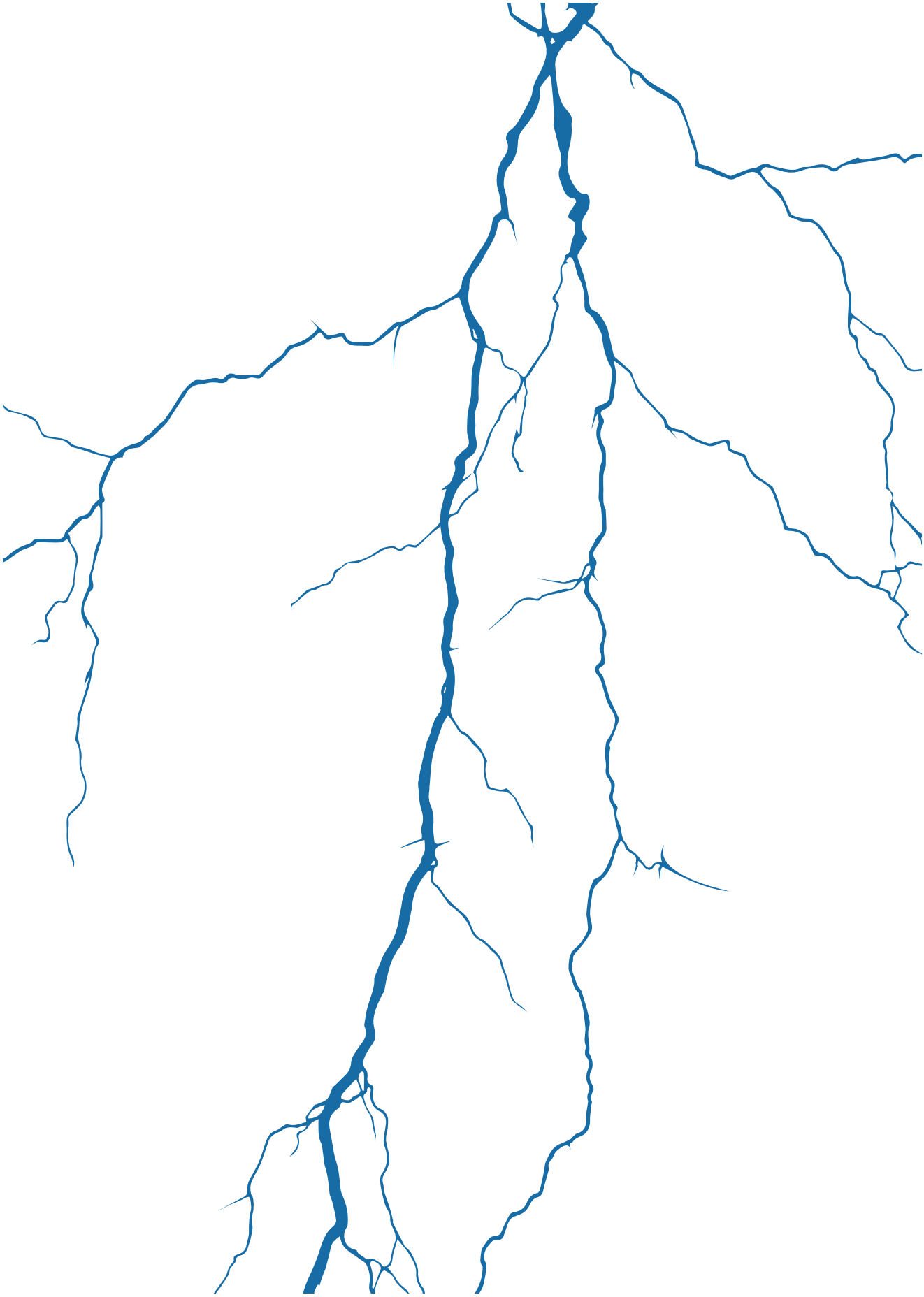

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Ablation of locally advanced pancreatic cancer by percutaneous irreversible electroporation: results of the phase I/II PANFIRE-study

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Abstract

Purpose

The primary aim of the prospective PANFIRE-study (clinicaltrials.gov NCT01939665) was to investigate the safety of percutaneous IRE for LAPC. Secondary objectives were quality of life (QoL), pain perception and efficacy in terms of time to local progression (TLP), event-free survival (EFS) and overall survival (OS).

Materials and Methods

Between January 2014 and June 2015, twenty-five patients with histologically proven LAPC ≤ 5cm (13 women, 12 men; median age, 61 [range, 41-78]) were prospectively included to undergo percutaneous CT-guided IRE. The study was approved by the local review board (NL42888.029.13). All patients signed informed consent for study participation, the ablation procedure and data usage. Patients with a metallic biliary Wallstent, epilepsy or ventricular arrhythmias were excluded. Kaplan-Meier estimates were used to investigate TLP, EFS, and OS. Safety was assessed based on adverse events, which were graded according to the CTCAE v4.0. Pain perception and QoL were evaluated using specific questionnaires.

Results

All patients underwent IRE. Median largest tumor diameter was 4.0 cm (range, 3.3-5.0). After a median follow-up period of 12 months (IQR 7-16), median EFS from IRE was 8 months (95%CI 4-12); median TLP from IRE was 12 months (95%CI 8-16). Median OS was 11 months from IRE (95%CI 9-13) and 17 months from diagnosis (95%CI 10-24). Twelve minor (grade-I/II) and eleven major complications (9 grade-III; 2 grade-IV) occurred in 10/25 patients. There were no deaths within 90 days post-IRE.

Conclusions

Percutaneous IRE for LAPC is generally well tolerated, although major adverse events can occur. Preliminary survival data are encouraging and support the setup of larger phase II and III clinical trials to assess the efficacy of IRE plus chemotherapy in the (neo)adjuvant or second-line setting compared to more widely adopted regimens such as chemo(radio)therapy.

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Introduction

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 .[1] 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 one year.[2] For these patients, systemic therapy with or without radiation has been the standard of care.[3,4] Although new chemotherapy regimens such as FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan and oxaliplatin), and the addition of nab-paclitaxel to gemcitabine are showing improved survival, the prognosis for LAPC remains dismal.[5,6]

Given that only a minority of patients with pancreatic cancer is amenable for surgery with curative intent, and that most patients have a limited response to chemoradiation, a number of ablative therapies have been examined as adjunct or stand-alone therapy. Of these, thermal ablation using radiofrequency ablation and microwave ablation are most frequently used. Unfortunately, thermal ablation of lesions close to vital structures like major bile ducts and vessels is associated with a high morbidity (28%-40%) and mortality (7.5%) due to thermal damage.[7,8]

A tumor ablation technique with distinct advantages over the existing ablative therapies is irreversible electroporation (IRE). IRE is based on the pulsatile application of electric energy delivered between two electrodes. The electric pulses change the existing cellular membrane potential, resulting in nanoscale defects in the lipid bilayer of the membrane which disrupts cellular homeostasis and leads to apoptosis.[9] Theoretically, IRE destroys all cells within the ablation zone, but – due to the primarily non-thermal mechanism – leaves supporting extracellular matrix structures unaffected. Therefore, the structural integrity of inlaying and adjacent vulnerable tissue like vessels and bile ducts should remain intact.[10] This allows for the ablation of malignancies that are surrounded by these structures, which is typically the case for LAPC. Several studies have investigated the safety and efficacy of open and percutaneous IRE for LAPC, with an overall complication rate of 10-37% and suggested improved progression-free and overall survival.[11–14] In contrast to the present study, these results are mainly retrospective and derived from surgical rather than percutaneous IRE procedures or originate from small scaled studies. In addition, this study represents data of the largest reported series of patients undergoing percutaneous IRE for LAPC.

The primary aim of the prospective PANFIRE-study was to investigate the safety of percutaneous IRE for LAPC. Secondary objectives were to examine quality of life (QoL), pain perception and efficacy in terms of time to local progression (TLP), event-free survival (EFS) and overall survival (OS).

Materials and Methods

The local medical ethics committee approved this prospective study (NL42888.029.13; registered at clinicaltrials.gov NCT01939665). Study design and conduct were in accordance with Good Clinical Practice and the STROBE statement for observational studies.[15] Participants gave written informed consent for study participation, the ablation procedure, and data usage. The PANFIRE-study was supported by a grant from the National Foundation

Against Cancer (NFtK, Amsterdam, the Netherlands) and the Foundation for Image-Guided Cancer Therapy (SBBvK, Diemen, the Netherlands). The needle electrodes were partially funded by AngioDynamics (Latham, New York). The funding organizations had no involvement in the design or conduct of this study, data management and analysis, or manuscript preparation and review or authorization for submission. Dr. M.R. Meijerink is a paid consultant for AngioDynamics. The other authors declare no conflict of interest. HJS and LGV had full control of inclusion of all study data and information.

Table 1. In- and exclusion criteria

Inclusion criteria	Exclusion criteria
Radiologic confirmation of LAPC stage III	Successful downstaging after (radio)chemotherapy from previous unresectable/borderline tumor to resectable tumor
Maximum tumor diameter ≤ 5 cm	Chemo- or radiotherapy ≤ 6 weeks prior to the procedure
Histological or cytological confirmation of pancreatic adenocarcinoma	Allergy to contrast media
Written informed consent	History of epilepsy
ASA-classification 0 – 3	Any implanted stimulation device
Age ≥ 18 years	Ventricular cardiac arrhytmias
Adequate bone marrow, liver and renal function: - Hemoglobin ≥ 5.6 mmol/L - Absolute neutrophil count (ANC) ≥ 1,500/mm3 - Platelet count ≥ 100*109/l - Total bilirubine ≤ 1.5 x ULN* - ALT and AST ≤ 2.5 x ULN* - Serum creatinine ≤ 1.5 x ULN* or a calculated creatinine clearance ≥ 50 ml/min - Prothrombin time or INR < 1.5 - Activated partial thromboplastin time < 1.25 x ULN*	Successful downstaging after (radio)chemotherapy from previous unresectable/borderline tumor to resectable tumor

Patients

All patients were discussed and evaluated by our multidisciplinary hepato-pancreatico-biliary tumor board prior to inclusion. If patients were excluded for study participation, the reason for non-eligibility was noted. Inclusion criteria were histologically proven LAPC with a maximum axial diameter of 5 cm. Locally advanced disease (stage III) was defined as per the National Comprehensive Cancer Network staging system for pancreatic cancer (NCCN version 1.2013).[16] Previous chemo- or radiotherapy was allowed as long as treatment had been completed six weeks before IRE. The number of patients who received previous chemo- or radiotherapy was monitored, as well as the type of chemotherapy and the number of cycles given. In addition, the presence of a previous biliary bypass or endoprosthesis was noted. American Society of Anesthesiologists [ASA] performance status 0-3, and adequate bone marrow, liver and renal function were required. Exclusion criteria were a metallic biliary Wallstent, a history of ventricular cardiac arrhythmias and epilepsy (**Table 1**). One of the study coordinators (HJS or LGV) noted study-related specifications before, during, and after the procedure.

Intervention

A contrast-enhanced abdominal CT and MRI was performed no more than four weeks before IRE and tumor marker CA 19.9 was obtained within 7 days prior to treatment. Before the procedure, a catheter was placed via the transfemoral route in the proximal abdominal aorta, for the repeated administration of small doses of intra-arterial contrast to enable dynamic and

real-time visualization of the tumor and the surrounding vessels before, during, and after the ablation. The CT arteriography technique was similar to the previously described technique in the liver[17] with the exception that the catheter was placed in the proximal abdominal aorta. All procedures were performed percutaneuously by the same interventional radiologists (MRM) on a 64-slice multidetector CT scanner (SOMATOM Sensation; Siemens, Erlangen, Germany), using CT-fluoroscopy guidance. General anesthesia was induced as described previously.[18] A transcatheter contrast-enhanced CT was made to determine the exact size and shape of the target lesion and its vicinity to surrounding structures. The obtained three-dimensional tumor-measurements, including a 5 mm tumor-free margin and aiming at an inter-electrode distance of 1.5-2.4 cm, determined the required number and configuration of the electrodes (NanoKnife, AngioDynamics, Latham, NY). Needle electrodes with an exposure length of 15 mm were placed within and around the tumor. Correct electrode position and inter-electrode distances were verified using multiplanar image reconstruction. Next, for all electrode-pairs with an inter-electrode distance of 1.5-2.4 cm, pulses were delivered with the objective to achieve complete ablation of the macroscopically visible tumor. First, ten test-pulses of 1,500 V/cm with a duration of 90 μs were delivered via each electrode pair, after which the delivered current – aimed to lie between 20-50 Amperes – was verified. Voltage settings were manually adjusted in case of pending over- or undercurrent. Subsequently, three cycles of 30 pulses were administered sequentially for each electrode pair. For larger tumors, electrodes were repositioned or pulled back to ablate the remaining part of the tumor. Upon completion of the ablation procedure, a transcatheter portal venous phase CT scan was made, using the abovementioned CT arteriography technique, to confirm technical success (the absence of any residual tumor enhancement) and for evaluation of vessel patency and early complications.

Follow up

The following day, routine laboratory tests (amylase and lipase) and contrast-enhanced MRI were performed to detect potential complications. Following discharge, contrast-enhanced CT and laboratory tests (tumor marker CA 19.9, amylase, and lipase) were performed at six weeks and three months post-IRE, and then every three months. All follow-up scans were interpreted independently by two radiologists. The presence of local recurrence and/or metastases was ultimately determined by consensus. Local recurrence (LR) was 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 6 weeks post-IRE.[19] Of all twenty-five patients, qualitative analyses of imaging data were performed by two dedicated abdominal radiologists in order to assess specific imaging characteristics after pancreatic IRE. Discrepancies between the interpreters' findings were solved by consensus. Visual pain scores (VAS) ranging from 0-10 and the amount of administered pain medication were recorded. To assess quality of life (QoL), patients filled in two QoL-questionnaires (QLQ): the EORTC QLQ-C30 and EORTC QLQ-PAN26 [20,21] and a pain registration form at baseline, 6 weeks, and 3 and 6 months after IRE. One of the study coordinators (HJS or LGV) documented all adverse events within 90 days from the procedure, using the CTCAE v4.0 criteria [22] plus the type of treatment (if needed).

Statistical analysis

Continuous variables were summarized with standard descriptive statistics including means, standard deviations (SD), medians and ranges. Categorical variables were summarized

with frequencies. P-values <0.05 were considered statistically significant. The definition of TLP was the time between IRE and LR; in case of death without local progression patients were censored. An event in EFS was defined as local or distant progression, or death of disease. Analysis of TLP, EFS and OS was performed using the Kaplan-Meier method. The log-rank test was used to examine whether patients who showed early LP (≤6 months) had a worse survival outcome. To evaluate the effect of potential confounders (i.e. age, sex, chemotherapy [>2 cycles] before IRE, tumor volume [<15 cm3 versus ≥15 cm3], early LP (< 6 months post-IRE) and CA 19.9 increase [duplication compared to baseline]), we performed univariable Cox regression analysis. Due to the small sample size no multivariable analyses were considered. The Wilcoxon signed-rank test was performed to compare the QoL and pain perception at baseline versus six weeks, three and six months follow-up.[23,24] In addition, the Wilcoxon signed-rank test was also used to compare amylase- and lipase values pre-IRE against values at one day, and two weeks follow-up. All statistical analysis were performed in consultation with an epidemiologist (MCJ).

Table 2. Patient characteristics

Characteristic	Value
Patients (n)	25
Gender (n)	
Male	12
Female	13
Age in years (median, range)	61, 41-78
ASA (n)	
I	1
II	21
III	3
Tumor location (n)	
Head	18
Body	2
Uncinate process	5
Vessel encasement (>180°; n)	
SMA	11
Celiac axis	5
Hepatic artery	10
SMV	12
Portal vein	12
Tumor size in cm (median, range)	
Left-to-right (width)	3.6, 2.2-5.0
Anteroposterior (depth)	2.9, 2.0-4.2
Craniocaudal (length)	3.7, 2.3-5.0
Systemic chemotherapy prior to IRE (n)	
Gemcitabine	2
FOLFIRINOX	10
Gemcitabine + nab-paclitaxel	1
Number of chemotherapy cycles (median, range)	7, 2-12
Time from diagnosis to IRE in months (median, range)	5, 1-16
Surgical bypass prior to IRE (n)	
Gastrojejunostomy	1
Hepaticojejunostomy	3
Double bypass	5
Plastic retrievable endoprosthesis (n)	7

Results

Between January 2014 and June 2015, thirty-eight patients with LAPC were evaluated for inclusion by the multidisciplinary tumor board; thirteen were not eligible due to tumor size >5 cm (n=6), the presence of a metal biliary stent (n=5), or metastatic disease encountered during workup (n=2). Twenty-five patients were included and treated with IRE. Baseline characteristics are summarized in Table 2. Median largest tumor diameter was 4.0 cm (3.3-5.0). None of the patients had undergone previous radiotherapy, whereas 13/25 patients had received previous chemotherapy (10 FOLFIRINOX, 2 gemcitabine, 1 gemcitabine plus nab-paclitaxel) with a median of 7 cycles (range 2-12). The median time from diagnosis to IRE was 5 months (range 1-16 months). No patient was lost during follow-up.

In all patients needle placement and pulse delivery was successful. Electrodes were placed ventrally in all but one patient, in whom a dorsal approach was chosen due to extensive

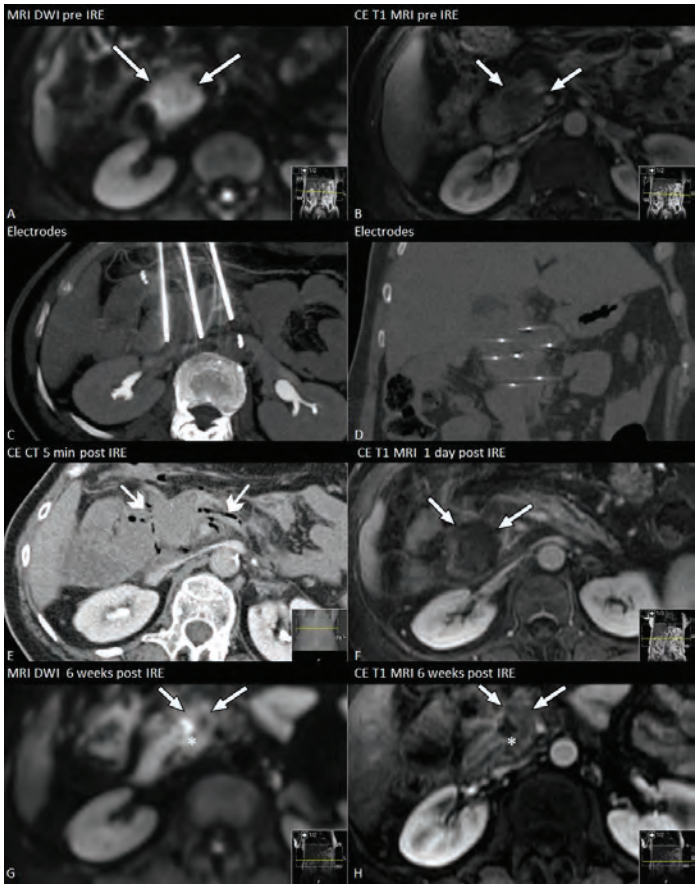

Figure 1: Radiologic appearance of the pancreatic tumor before, during and after IRE. (A) MRI pre-IRE showing hyperintensity of the tumor on diffusion-weighted imaging (DWIb800), and (B) hypoattenuation compared to normal pancreatic tissue on ceMRI (T1-weighted with fat suppression). Electrode configuration in the (C) axial and (D) coronal plane. (E) CeCT showing gas pockets immediately after IRE (arrowhead). (F) T1-weighted CeMRI demonstrating loss of tumor enhancement 1 day post-IRE. (G, H) DWIb800 and T1-ceMRI six weeks after IRE reveal no residual diffusion restriction and involution of the ablation zone. A typical DWIb800 hyperintense area, typical for a fluid collection presumably represents a small abscess (*).

collateral vessels on the anterior side.[25] The median number of electrodes used was 6 (range 3-9). In 21 patients an electrode pullback was performed. Figure 1 shows an example of typical imaging characteristics of the pancreatic tumor before, during, immediately after, and 6 weeks after IRE. The median length of hospital stay was 3 days, including the treatment day (range 2-20). On immediate postprocedural CT, irregular vessel narrowing of the SMA (n =

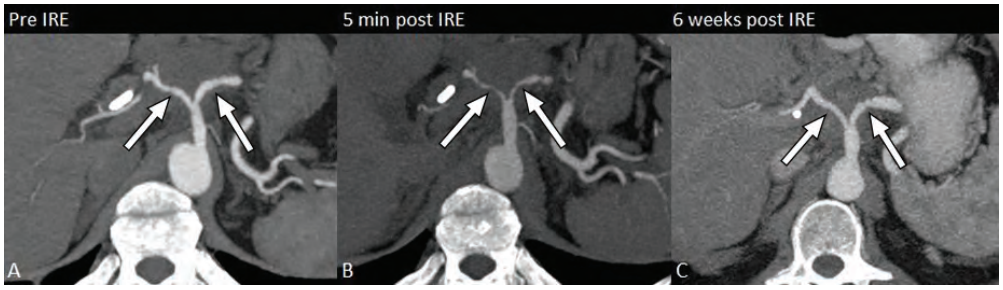

Figure A1: (A) Arterial phase ceCT pre-IRE showing an irregular celiac, splenic and common hepatic artery without stenosis. (B) CeCT immediately after IRE demonstrating diffuse irregular narrowing of the splenic and common hepatic artery presumably caused by spasm. (C) CeCT 1 month post-IRE showing recovery of vascular patency.

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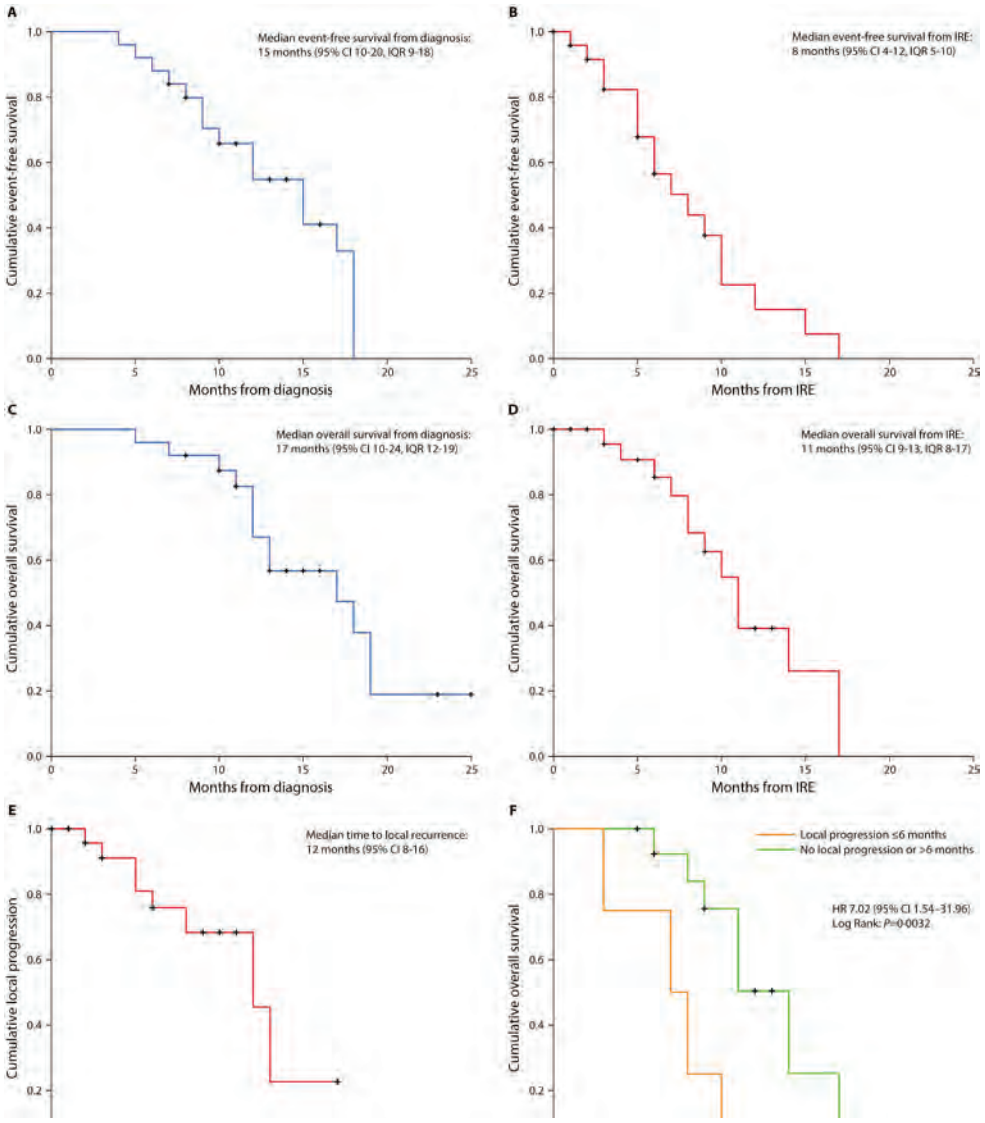

Figure 2: Kaplan-Meier survival curves

1), splenic artery (n = 1), hepatic artery (n = 2), SMV (n = 2) or portal vein (n = 4) was noted in seven cases (**Figure A1**). CT at six weeks post-IRE showed full recovery of vessel patency, suggesting the immediate vessel narrowing was caused by reactive spasm.

Survival

After a median follow-up period of 12 months (IQR 7-16), median OS from diagnosis was 17 months (95%CI 10-24), median OS from IRE was 11 months (95%CI 9-13; **figure 2**). Median EFS from diagnosis was 15 months (95%CI 10-20); median EFS from IRE was 8 months

Table 3. Univariable Cox regression analysis of overall survival after IRE

Variable	Category†	Hazard ratio (95% CI)	P-value
Local progression:	>6 months or no local progression	reference	..
	≤6 months	7.71 (1.69–35.14)	0.0083
Age:	continuous, years	0.99 (0.93–1.06)	0.83
Sex:	male	reference	..
	female	0.43 (0.12–1.54)	0.20
Tumor volume at time of IRE*:	≤15 cm3	reference	..
	>15 cm3	1.83 (0.57–5.84)	0.31
Chemotherapy before IRE:	no	reference	..
	yes	0.99 (0.24–4.02)	0.95
Chemotherapy before IRE:	none or ≤2 cycles	reference	..
	>2 cycles	0.74 (0.15–3.57)	0.71
CA 19.9 change 3 months after IRE:	no change or decrease	reference	..
	increase	4.41 (0.81–23.99)	0.086

CI = confidence interval

†Reference categories: HR=1

*Based on the median tumor volume of 15.5 cm^3

(95%CI 4-12). Median TLP from IRE was 12 months (95%CI 8-16). Patients who showed early LP (≤6 months and unsuitable for retreatment: n = 4) had significantly worse survival after IRE (log-rank test: p=0.0032), and in univariable Cox regression analysis this was the only significant predictor of OS (univariable HR 7.02; 95%CI 1.54-31.96; **table 3**).

Postprocedural pain and quality of life

All patients completed the QoL and pain questionnaires pre-IRE, 80% (20/25) at six weeks, 88% (22/25) at three months and 85% (17/20) at six months follow-up.

One day post-IRE, the reported pain was moderate with a median VAS score of 2 (range 0–5); pain control was managed with acetaminophen combined with an NSAID and an opioid if needed. Compared to baseline, 3/13 pain-items (23%) had deteriorated six weeks post-IRE: the impact of pain on 1) gait (p=0.016), 2) normal work (p=0.039), and 3) patients' daily activities (p=0.023). Pain increased after six months and was more difficult to treat with analgesics (p=0.039).

The QLQs revealed that post-IRE, patients experienced diminished general functioning compared to baseline at three and six months follow-up (p=0.040, p=0.028). Compared to baseline, at six weeks follow-up reduced appetite was reported (p=0.048); at six months an increased feeling of weak arms and/or legs (p=0.031), and indigestion problems (p=0.007) were reported. The remaining twenty-seven QLQ-items did not significantly change post-IRE.

Safety/complications

No patients died within 90 days post-IRE. Overall, 10/25 patients developed 23 adverse events (**Table 4**). Individual patients experienced one (n=2), two (n=6), or three (n=2) complications.

Two CTCAE grade-IV complications occurred. 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.

Table 4. Adverse events observed in 10/25 patients

Adverse Event	Grade I/II (n, %)	Grade III (n, %)	Grade IV (n, %)	Treatment
Infection				
Pancreatitis		2	1	Antibiotics + drainage
Abscess	1			Antibiotics
Pneumonia	1			Antibiotics
Biliary				
Biliary obstruction		3		ERCP + stent
Cholangitis + biloma		1		PTCD
Vascular				
Bleeding from duodenal ulcer			1	Endoscopy + blood transfusion
High-grade SMA stenosis		1		Balloon-expandable stent
Gastrointestinal				
Nausea	1			Antiemetics
Vomiting	2	1		Antiemetics, gastric drainage, nasojejunal tube feeding
Diarrhoea	2			Pancreatic enzyme suppletion, loperamide
Gastroparesis	2			Conservative
Abdominal pain	3			Oral analgesics
Loss of appetite/ reduced intake		1		Nasojejunal tube feeding
Total	12	9	2	

Another patient presented with massive hematemesis three 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 out of ten patients without a biliary bypass or endoprosthesis pre-IRE developed new-onset biliary obstruction requiring drainage within 90 days post-IRE (grade-III). In 2/3 patients, endoscopic retrograde cholangiopancreaticography (ERCP) revealed swelling of the ampullary area, but placement of a plastic biliary endoprosthesis was successfully performed (**Figure 3**). The third 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 contrast enhanced CT six weeks post-IRE, with no other signs for local site recurrence. Because this patient also experienced post-prandial abdominal cramps, a vascular stent was placed for symptom relief and to prevent mesenteric ischemia (**Figure 4**).

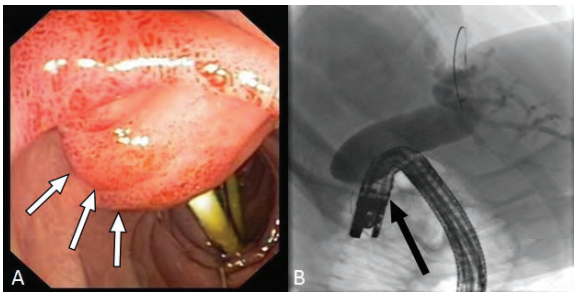

Figure 3: (A) ERCP six weeks after IRE showing erythematous swelling of the ampullary area, with the major papilla turned backwards. (B) Cannulation of the major papilla by positioning the duodenoscope in 'long position'.

Twelve gastro-intestinal complications such as nausea, vomiting, diarrhea, delayed gastric emptying, abdominal pain, loss of appetite and reduced

Figure 4: (A) CeCT pre-IRE showing pre-existent slight narrowing of SMA lumen. (B) CeCT immediately post-IRE showing increased narrowing of the SMA lumen. (C) Six weeks post-IRE ceCT shows a near occlusion (D) Digital subtraction angiography (DSA) confirming the high-grade stenosis. (E) The insertion of a balloon expandable stent restored patency. It remains unclear whether the stenosis was caused by IRE or by tumor progression.

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 one day post-IRE compared to pre-IRE values (p=0.009 and p=0.001, Figure 5). After two weeks, amylase and lipase had returned to pre-IRE values (p=0.26 and p=0.12). Remarkably, only three patients developed the clinical signs of pancreatitis.

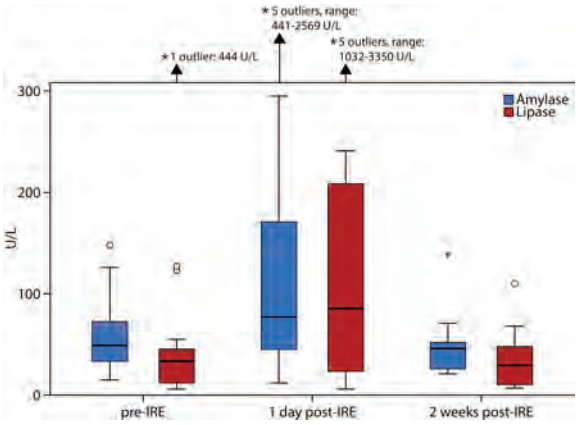

Figure 5: Box- and whisker plot showing amylase and lipase values.

Discussion

The main results of our study indicate that percutaneous IRE for LAPC should be considered as a relatively high-risk procedure. This finding is in contrast to previously published complication rates for percutaneous and open IRE for LAPC.[14,26–28] The higher complication rate of the present study may be explained by the fact that we counted all complications separately. Also, the CTCAE registration is stricter than the surgical Clavien-Dindo scale, which in our study would have led to downgrading eight grade-II and three grade-III adverse events. Additionally, frequently encountered complications such as nausea and mild or moderate abdominal pain may not have been reported in the other studies. Nevertheless, the complication rate remains substantial. Considering the theoretical working mechanism of IRE, the bowel and vessel wall should remain intact due to the sparing of collagenous structures. However, one duodenal ulcer led to life-threatening hemorrhage. Although the causality between IRE and the origination of the duodenal ulcer could not be established, this complication should be kept in mind for patients who undergo IRE close to the

duodenum. Similarly, a stenosis of the SMA was observed in one patients, which suggest IRE induced vessel injury. Kluger et al investigated the perioperative morbidity and mortality of IRE for LAPC stage IV using the Clavien-Dindo scale, and reported 10 grade III or IV complications (20%); six patients died within 90 days after the procedure (12%; grade V).[29] A relation between the disease stage (stage IV) and the high mortality rate could not be firmly confirmed, however it strongly suggests inappropriate patient selection, which is essential for treatment success.[30]

Post-IRE, ERCP with placement of a plastic biliary endoprosthesis or PTCD for biliary obstruction was necessary in three patients without previous biliary protection. This procedure was notably challenging because of extensive swelling of the ampullary area. Additionally, IRE may distort the normal anatomy through fibrosis and remodeling, impeding endoscopic stent placement for patients who develop local recurrent disease at a later stage. To avoid this, we advise prophylactic biliary protection through ERCP and biliary endoprosthesis placement or PTCD for pancreatic head tumors, even in the absence of pre-existing or imminent biliary obstruction.

A relatively large number of gastrointestinal complications resulted in prolonged hospital stay, temporary nasojejunal tube feeding and weight loss. Transitory reactive edema probably compressed the – often already narrowed – postpyloric duodenal lumen. Passage of gastric content past the reactively inflamed duodenal wall may explain delayed gastric emptying, nausea and vomiting. Indeed, patients who had undergone previous gastrojejunostomy did not experience these complications. Furthermore, the sympathetic celiac ganglia and splanchnic nerves, and the parasympathetic gastric branches of the vagal nerve are located near the pancreas and innervate the stomach. Damage to these structures may also cause gastric emptying or secretion dysfunction. Last, destruction of healthy pancreatic tissue distorts the endocrine function of the pancreatic gland, causing or aggravating diarrhea and malabsorption.

The most relevant and attainable goal in management of LAPC is good symptom palliation. Therefore, QLQ outcomes should be carefully weighed against survival benefit and treatment-related complications. Up to six months post-IRE overall pain perception and QoL were unaffected (pain perception: 10/13 items [77%] six weeks post-IRE; QLQ: 28/30 [93%], and 27/30 [90%] items, respectively, 6 weeks and 6 months follow-up). However, after six months several items deteriorated. This conceivably reflects disease progression rather than IRE effect. Paiella et al evaluated QoL, using the EORTC QLQ C30 and PAN26 questionnaires, after open IRE in patients with unresectable pancreatic adenocarcinoma and reported a decrease in the median QoL-score of 36% and 43%, respectively, two weeks and three months post-IRE.[12] In respect of these results, patients might tolerate percutaneous IRE for pancreatic carcinoma better in comparison with open IRE, however more research is needed.

Martin et al retrospectively examined the efficacy of IRE for LAPC (stage III) and reported a TLP of 14 months which is in line with our results, however, they found a better OS from diagnosis (24 months versus 17 months).[13] The difference in survival may be partly explained by the fact that a third of Martin's patients showed less extensive disease during laparotomy and underwent a subtotal pancreatectomy or pancreatoduodenectomy with IRE for margin accentuation. Also, Martin's patient group had remained stable under (often numerous cycles of) chemotherapy, with or without additional chemoradiation - thereby filtering out

the patients with rapid disease progression - as opposed to only 13/25 patients that received chemotherapy in our group.

Although we did not find a survival difference between patients based on neoadjuvant chemotherapy, retrospective data showed that induction chemotherapy prior to local treatment with chemoradiation can identify patients with early metastatic progression. This group, representing roughly 30% of the LAPC population, would not benefit from initial local treatment.[31,32] Accordingly, a previous study on RFA for LAPC showed a higher incidence of early progression in patients who received RFA as initial treatment, compared to patients who received RFA as secondary treatment after neoadjuvant chemotherapy followed by.[33] These data emphasize the importance of induction chemotherapy prior to ablative treatment.[16,32]

There are inherent limitations of our study. Specifically, in this phase-I study the neoadjuvant chemotherapy regimen was highly variable, which may confound the survival analysis. Over the past few years recommendations from the medical oncology community shifted from (1) no chemotherapy for asymptomatic patients to (2) gemcitabin with or without radiation to (3) FOLFIRINOX for eligible patients or to (4) gemcitabin plus nab-paclitaxel in the more recent era. Although neoadjuvant gemcitabin was recommended by the PANFIRE protocol, patients and their referring oncologists could opt for other strategies given the cumbersome survival benefit of gemcitabin monotherapy. The time at which IRE was performed depended on the time of referral and varied greatly. When comparing survival data of IRE with conventional chemo(radio)therapy another confounder may be the upper size limit of 5 cm to perform IRE, since a larger tumor size is likely to be associated with a worse a priori outcome. Additionally, the relatively small number of patients and the lack of an untreated control group inevitably introduce doubt that the fairly promising survival data we observed may have resulted from chance or selection.

In a disease with so many systemic manifestations, it is hard to see the impact of localized therapy on the natural history of the disease without obtaining some control of metastastic spread with systemic therapy. A multimodal approach combining systemic chemotherapy with focal ablation offers great promise to improve the survival of this disease. IRE may represent a useful adjunct to slow down disease progression whilst preserving quality of life.[6] Moreover, immunological studies suggest that besides inducing local tumor destruction, IRE may also induce a systemic immune response that might result in the destruction of micrometastases, which could further improve survival.10,34,35 This hypothesis is currently being investigated. In conclusion, percutaneous IRE for LAPC is generally well tolerated, although major adverse events can occur. Preliminary survival data are encouraging and support the setup of larger phase II and III clinical trials to assess the efficacy of IRE plus chemotherapy in the neoadjuvant or second-line setting compared to more widely adopted regimens such as chemo(radio)therapy. To validate our findings, we have recently started a multicenter phase-III trial comparing IRE with stereotactic ablative body radiotherapy after neoadjuvant FOLFIRINOX (CROSSFIRE-study, NCT02791503).

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