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ORIGINAL ARTICLE – PANCREATIC TUMORS

Induction Chemotherapy Followed by Resection or Irreversible Electroporation in Locally Advanced Pancreatic Cancer (IMPALA): A Prospective Cohort Study

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ABSTRACT

Background. Following induction chemotherapy, both resection or irreversible electroporation (IRE) may further improve survival in patients with locally advanced pancreatic cancer (LAPC). However, prospective studies combining these strategies are currently lacking, and available studies only report on subgroups that completed treatment. This study aimed to determine the applicability and outcomes of resection and IRE in patients with nonprogressive LAPC after induction chemotherapy.

Methods. This was a prospective, single-center cohort study in consecutive patients with LAPC (September 2013 to March 2015). All patients were offered 3 months of induction chemotherapy (FOLFIRINOX or gemcitabine depending on performance status), followed by exploratory laparotomy for resection or IRE in patients with Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 nonprogressive, IRE-eligible tumors.

Results. Of 132 patients with LAPC, 70% ($n = 93$) started with chemotherapy (46% [$n = 61$] FOLFIRINOX). After 3 months, 59 patients (64%) had nonprogressive disease, of whom 36 (27% of the entire cohort) underwent explorative laparotomy, resulting in 14 resections (11% of the entire cohort, 39% of the explored patients) and 15 IREs (11% of the entire cohort, 42% of the explored patients). After laparotomy, 44% ($n = 16$) of patients had Clavien–Dindo grade 3 or higher complications, and 90-day all-cause mortality was 11% ($n = 4$). With a median follow-up of 24 months, median overall survival after resection, IRE, and for all patients with nonprogressive disease without resection/IRE ($n = 30$) was 34, 16, and 15 months, respectively. The resection rate in 61 patients receiving FOLFIRINOX treatment was 20%.

Conclusion. Induction chemotherapy followed by IRE or resection in nonprogressive LAPC led to resection or IRE in 22% of all-comers, with promising survival rates after resection but no apparent benefit of IRE, despite considerable morbidity. Registered at Netherlands Trial Register (NTR4230).

With a global annual incidence of 340,000[1] and a 5-year cumulative survival of 5–10%,[2] pancreatic cancer remains a dreadful disease. Surgical resection offers the best chance for long-term survival but is mostly not feasible in the 30–40% of patients who present with locally advanced pancreatic cancer (LAPC) due to vascular tumor involvement.[3,4] Until recently, gemcitabine-based chemotherapy,

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with or without radiation therapy, was standard treatment, providing only a marginal survival benefit.[4]

Recently, the use of FOLFIRINOX as induction treatment has increased the potential to resect LAPC, with a median overall survival (OS) of 14–24 months.[5,7] Patients in whom resection is not an option might benefit from ablation strategies such as irreversible electroporation (IRE).[8] IRE uses high-voltage, low-frequency, electrical pulses between electrodes placed in and around the tumor. These pulses are thought to cause apoptosis by permeabilizing the cell membrane,[9–14] while leaving the supporting extracellular matrix unaffected,[15] including blood vessels,[16–18] bile ducts,[18–20] and nerves.[21–24] In LAPC, IRE has been associated with a median OS of up to 27 months,[25] with a 51% complication rate.[8,25–31]

Unfortunately, currently available data on IRE and resection in LAPC are heavily influenced by selection and attrition bias. Most studies are retrospective and only report on the subgroup of patients who have stable disease following induction chemotherapy, and thus have better outcomes. Therefore, the true applicability, outcomes, and added value of resection and IRE in LAPC after induction chemotherapy remains unclear.

This prospective study aimed to determine the applicability and outcomes of induction chemotherapy followed by resection or IRE in a cohort of consecutive patients presenting with LAPC.

METHODS

Patients

All consecutive patients presenting with LAPC between September 2013 and March 2015 were discussed at our multidisciplinary pancreatic cancer team meeting, prospectively registered, and treated according to the hereafter described multimodality treatment protocol, which consisted of chemotherapy, restaging, and exploratory laparotomy for resection or IRE.

LAPC was defined according to the Dutch Pancreatic Cancer Group (DPCG) definition (>90° involvement of the hepatic artery [HA], celiac trunk and/or superior mesenteric artery, and/or >270° involvement of the portal vein [PV] and/or superior mesenteric vein, without metastases).[32] Tumor size in three dimensions, involvement of individual blood vessels, and presence of pathologic lymph nodes were recorded.

Our aim was to select patients eligible for IRE, based on an Institutional Review Board-approved protocol. Written informed consent was obtained for patients undergoing surgical exploration with the intention to undergo IRE. The study was registered at the Netherlands Trial Register (identification number: NTR4230).

Chemotherapy

After pathological confirmation of pancreatic ductal adenocarcinoma, patients were offered induction chemotherapy consisting of FOLFIRINOX for patients with World Health Organization (WHO) performance status 0–1, and gemcitabine for others. Patients with elevated bilirubin levels were referred for fully covered metal biliary stent placement prior to chemotherapy; only patients with severe back pain were referred for radiation therapy (3 × 8 Gy).

FOLFIRINOX therapy consisted of a 2-weekly schedule of a 2-h intravenous infusion of oxaliplatin 85 mg/m^2, followed by a 2-h intravenous infusion of leucovorin 400 mg/m^2, concomitantly with 90 min of intravenous infusion of irinotecan 180 mg/m^2, subsequently followed by 5-fluorouracil 400 mg/m^2 as a bolus and 2400 mg/m^2 as a 46-h continuous intravenous infusion. All patients routinely received ondansetron and dexamethasone with each cycle for emesis prophylaxis.

Gemcitabine 1.000 mg/m^2 was given in 500 ml NaCl 0.9% in a 30-min intravenous infusion on days 1, 8, and 15, followed by 1 week of rest. Dose modifications were made at the treating physician's discretion or at the patient's request.

Treatment was discontinued in case of unacceptable toxicity, disease progression, or at the patient's request.

Restaging

All patients were restaged after at least 3 months of induction chemotherapy, according to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria,[33,34] and were again discussed at the multidisciplinary meeting.

Eligibility for Irreversible Electroporation (IRE)

Patients with nonprogressive disease at restaging were evaluated for IRE eligibility by an interventional radiologist (KvL), according to the criteria in Appendix, Table 4. IRE eligibility was confirmed by an external expert (RM), who has performed >200 pancreatic IRE procedures.

Surgical Exploration

After a midline or subcostal incision, visual inspection was performed for metastases. Frozen sections were taken if needed to determine the presence of metastases or local ingrowth prohibiting further resection. Intraoperative ultrasound was performed by an interventional radiologist. Patients with intraoperatively determined resectable disease underwent resection. Patients with intraoperatively confirmed IRE eligibility and unresectable disease (i.e. confirmed by biopsies) were treated with IRE. Metal stents,

when present, were removed intraoperatively prior to IRE and replaced by a surgical biliary bypass after the procedure. Patients with metastatic disease received palliative bypass surgery if indicated.

Irreversible Electroporation

IRE was performed under complete muscle paralysis, using the Nanoknife® system (AngioDynamics, Amsterdam, the Netherlands). Three to six electrodes were placed, typically in a craniocaudal direction through the mesocolon, in and around the tumor, under ultrasound guidance. All IRE procedures were performed by the same interventional radiologist (KvL). Pulses were delivered under cardiac synchronization (Accusync; Medical Research Corporation, Milford, CT, USA) between all electrode pairs with an interelectrode distance <2.5 cm, using a pulse length of 90 μs, 1.5 cm tip exposure (1.0 cm when previously treated with radiation therapy), 90 pulses per electrode pair, and 1500 V/cm (adjusted when current was out of the 25–35 A range). Ablations were aimed at an increase of at least 10 A, and when not achieved after 90 pulses, an additional set of 90 pulses was given.[35] When tumor dimension in the craniocaudal direction exceeded the exposed tip length, electrodes were pulled back and the procedure was repeated to cover the entire tumor.

Safety and Efficacy Assessment

All postoperative complications within 90 days were recorded prospectively and graded according to the Clavien–Dindo classification.[36,37] Length of hospital stay was recorded and readmission within 30 days after surgery was added to the initial hospital stay. Data on survival were extracted from the Dutch municipal personal records database. Overall survival (OS) was defined as the time between the date of the radiologic diagnosis of LAPC and death.

Study Outcomes

Primary outcomes were the resection and IRE rate after chemotherapy in a cohort of consecutive LAPC patients (including those not receiving chemotherapy), whereas secondary outcomes were R0 resection rate (1 mm margin[38,39]), the rate of clinically relevant complications, defined by Clavien–Dindo score ≥3, 90-day mortality, median OS, and 1-year cumulative survival.

Statistical Analysis

Normally distributed data were presented as mean and standard deviation (SD), while non-normally distributed data were presented as median and interquartile range (IQR). During follow-up, patients alive at last follow-up were censored. Median OS was estimated using Kaplan–Meier curves, and compared between subgroups using a log-rank test. SPSS version 23.0 (IBM SPSS Statistics for Windows; IBM Corporation, Armonk, NY, USA) was used for statistical analyses, and a two-tailed p value <0.05 was considered statistically significant. A sensitivity analysis for median OS, and resection and IRE rate was performed for patients who received FOLFIRINOX chemotherapy.

RESULTS

A total of 132 patients with LAPC were registered (Fig. 1). Patient and tumor characteristics at baseline are presented in Table 1. Median follow-up of all patients was 24 months (IQR 21–28).

Chemotherapy

Of all 132 patients, 93 (70%) started chemotherapy; the remaining patients either refused chemotherapy and/or had a WHO performance status of 3–4. FOLFIRINOX was administered to 61 (46%) patients, and gemcitabine was administered to 26 (20%) patients. Six patients received alternative regimens.

Restaging

Restaging was performed in 82 (62%) of all 132 patients (88% of patients who started with chemotherapy) after a median of 5.5 (IQR 4–7) cycles of FOLFIRINOX, and 3 (IQR 2–4) cycles of gemcitabine. RECIST 1.1 nonprogressive disease was observed in 59 (45%) of all 132 patients. Of these patients, 44 (75%) had been treated with FOLFIRINOX, 12 (20%) with gemcitabine, and 3 (5%) with other regimens. The Pearson Chi square value for nonprogressive disease for patients receiving FOLFIRINOX versus patients receiving gemcitabine was 4.89 ($p = 0.027$).

Forty-four of the nonprogressive patients were eligible for IRE, of whom 36 (27%) ultimately underwent surgical exploration (of whom 15 underwent IRE).

Resection

Of all 132 patients, 14 (11% of the entire cohort, 39% of the explored patients), underwent resection (10 pancreatoduodenectomies [PD; seven pylorus-preserving PDs, three standard Whipple procedures], two total pancreatectomies, one modified Appleby procedure [distal pancreatosplenectomy with celiac axis resection], and one distal pancreatectomy). A radical (R0) resection was achieved in 8 of 14 resected patients (57%).

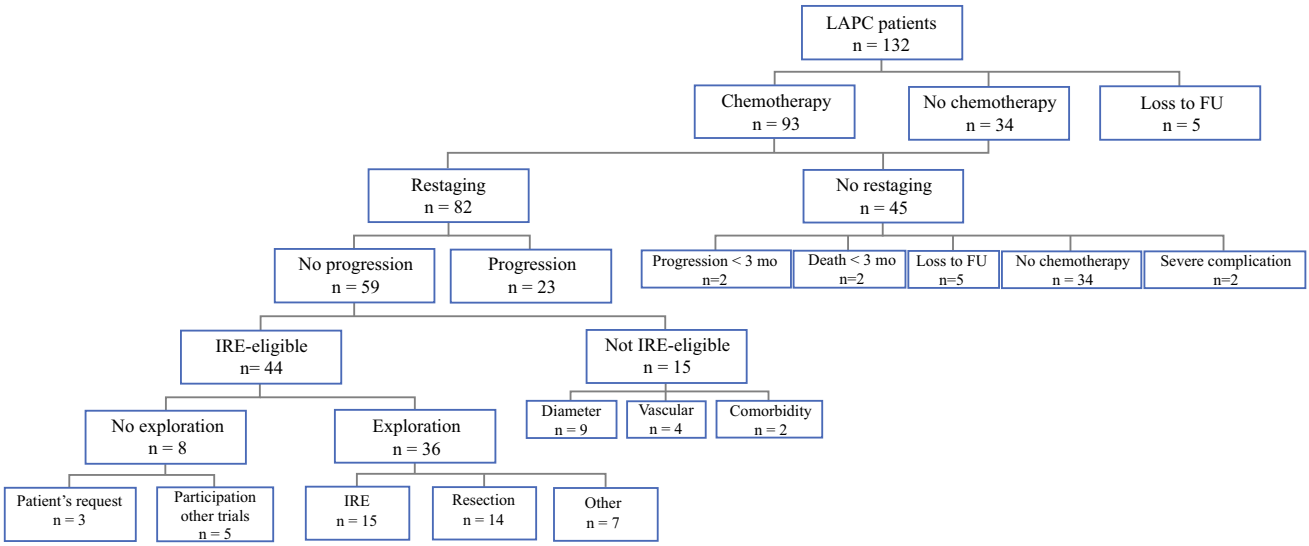

FIG. 1 Flowchart of 132 patients with LAPC. *LAPC* locally advanced pancreatic cancer, *mo* months, *FU* follow-up, *IRE* irreversible electroporation, *diameter* tumor diameter >5 cm in at least two directions, *vascular* significant narrowing of both hepatic artery and portal vein or a partial thrombosis

Irreversible Electroporation

Fifteen patients (11% of the entire cohort, 42% of the explored patients) received IRE. Eleven patients received additional palliative bypass surgery, of whom four patients had their metal bile duct stents removed intraoperatively. Four patients had extensive dissection before the start of the electrode placement. The reason for unresectability was extensive arterial involvement in 10 patients and extensive venous involvement in five patients.

Explorative Laparotomy without Resection or IRE

During surgical exploration, four patients were found to have metastases and two patients had IRE ineligible tumors. Three received palliative bypass surgery. One patient with portal hypertension due to PV occlusion had a venous retroperitoneal bleeding at the start of laparotomy, precluding IRE or resection.

Safety and Efficacy Assessment

Clavien–Dindo grade 3 or higher complications after explorative laparotomy occurred in 16/36 patients (44%): 5/14 resected patients (36%), 8/15 IRE patients (53%), and 3/7 patients (43%) who underwent explorative laparotomy without resection/IRE. Of the eight patients with complications after IRE, two had extensive dissection prior to IRE, and two had metal stent removal prior to IRE. For a full list of all complications, see Appendix, Table 5.

Four patients (11%) died within 90 days after laparotomy: one after resection (leakage of hepaticojejunostomy and pancreatojejunostomy), two after IRE (one liver failure, one hemorrhagic gastric ulcer for which the patient refused treatment), and one after palliative exploration (progression of disease).

Adjuvant Treatment

Twenty-one patients received adjuvant treatment—11 after resection (FOLFIRINOX $n = 8$, median of five cycles [IQR 3–6]; gemcitabine $n = 2$, two and seven cycles; other regimen $n = 1$), seven after IRE (FOLFIRINOX $n = 3$, median of five cycles; gemcitabine $n = 4$, median of six cycles), and three after palliative exploration (FOLFIRINOX $n = 2$, four and nine cycles; gemcitabine $n = 1$, six cycles).

Survival

Median OS and 1-year cumulative survival are presented in Tables 2 and 3 and Fig. 2.

After resection, IRE, and laparotomy without resection/IRE, median OS was 34, 16, and 22 months, respectively. For all patients with nonprogressive disease, receiving chemotherapy but no resection/IRE, median OS was 15 months.

Sensitivity Analysis

A sensitivity analysis, addressing only the 61 patients who received at least one cycle of FOLFIRINOX, showed that 44 (72%) had RECIST 1.1 nonprogressive disease at

TABLE 1 Baseline and tumor characteristics of 132 consecutive patients with LAPC

Baseline characteristics	$n = 132$
Sex, no. (%)	
Male	71 (54)
Female	61 (46)
Age, years [mean (SD)]	64 (11)
WHO score	
0	56 (42)
1	49 (37)
2	12 (9)
3	5 (4)
4	1 (1)
Comorbidity	
Cardiac	22 (17)
Second malignancy	22 (17)
Active or < 5 years since cure	8 (6)
>5 years since cure	14 (11)
Vascular	28 (21)
Psychiatric	12 (9)
Endocrine	35 (27)
Diabetes mellitus	29 (22)
Neurologic	3 (2)
Pulmonary	5 (4)
Autoimmune	3 (2)
None	59 (45)
Tumor characteristics	**$n = 132$**
Size, mm [median (IQR)]	
Cranial—caudal	41 (33–53)
Anterior—posterior	33 (28–39)
Transverse	40 (33–48)
Pathologic lymph nodes no (%)	
Yes	41 (31)
No	88 (67)
Unknown	3 (2)
Vascular involvement, no (%)	
Arterial (>90°)	
Celiac axis	41 (33)
Superior mesenteric artery	57 (45)
Hepatic artery	44 (35)
Venous (>270°)	
Portal vein	41 (33)
Superior mesenteric vein	48 (38)
Biliary drainage prior to treatment, no (%)	
Yes	66 (50)
No	66 (50)
Previous surgery, no (%)	
Exploration	12 (9)
Palliative bypass	9 (7)
No previous surgery	120 (91)
Pathology confirmation PDAC, no (%)	
Yes	110 (83)
Suspected PDAC	22 (17)
Radiation therapy, no (%)	13 (10)

LAPC locally advanced pancreatic cancer, *SD* standard deviation, *WHO* World Health Organization, *IQR* interquartile range, *PDAC* pancreatic ductal adenocarcinoma

restaging, leading to 12 (20%) resections (R0 in 7/12 [58%]), and 9 (15%) IREs. Surival data are presented in Appendix, Table 6.

DISCUSSION

This is the first prospective study that reports on consecutive patients initially classified as LAPC, treated with at least 3 months of induction chemotherapy, followed by exploratory laparotomy for resection or IRE in patients with RECIST nonprogressive disease. Outcomes were especially promising for the 11% of patients undergoing surgical resection (median OS 34 months) after induction chemotherapy but no apparent survival benefit of IRE, despite considerable morbidity.

The resection rate of 39% ($n = 14$) in patients undergoing surgical exploration after induction chemotherapy in this study reflects the current inability to determine resectability on imaging after treatment with FOLFIRINOX.[40] The necessity of surgical exploration of LAPC patients after FOLFIRINOX treatment was shown by Ferrone et al.[40] by demonstrating an R0 resection rate of 92% in 40 explored patients, who were initially assessed as being unresectable based on CT imaging. This finding, and the outcomes of the current study, justify the policy to surgically explore selected patients with LAPC who remained (at least) stable during induction chemotherapy. Notably, at the time of this study, surgical exploration in patients with LAPC after treatment with FOLFIRINOX was not routine practice in The Netherlands, but only conducted in clinical trials.

The 11% overall resection rate supports the need for a 'back-up' therapy, such as IRE, which may be used in case of unresectability. Although a median OS of 34 months after resection is highly promising, the 16 months median OS after IRE was actually not that different from the 15 months in patients with nonprogressive disease without resection/IRE. Therefore, while the availability of palliative ablative strategies may seem alluring, the value remains unclear, especially given the IRE-associated morbidity. Moreover, pancreatectomy with arterial

TABLE 2 Survival from diagnosis in 59 patients with nonprogressive LAPC after 3 months of chemotherapy

	n	Median OS (months)	1-year OS (%)
IRE	15	16	75
Resection	14	34	93
Laparotomy without resection or IRE	7	22	72
RECIST 1.1 nonprogressive without resection or IRE	30	15	75
Log-rank[a]	$p = 0.003$		

LAPC locally advanced pancreatic cancer, *OS* overall survival, *IRE* irreversible electroporation, *RECIST* Response Evaluation Criteria in Solid Tumors

[a] Log-rank test for median OS, with groups defined as resection, IRE, and RECIST nonprogressive disease without resection or IRE

TABLE 3 Survival from diagnosis in 132 patients with LAPC according to chemotherapy response

	n	Median OS (months)	1-year OS (%)
All patients	132	11	50
Patients receiving chemotherapy	93	13	58
Patients not receiving chemotherapy	34	6	15
Patients with nonprogressive disease after 3 months	54	20	77
Patients with progressive disease within 3 months	28	11	40

LAPC locally advanced pancreatic cancer, *OS* overall survival

resection is increasingly utilized as a treatment approach to increase resection rates.[41] However, these arterial resections lead to comparable morbidity and mortality outcomes, as with IRE. It would be of interest to prospectively compare overall (short- and long-term) outcomes of IRE and surgery with arterial resection.[42]

Since this is the first study describing outcomes of all consecutive patients diagnosed with LAPC, we can only compare our outcomes in 61 patients who received FOLFIRINOX, of whom 20% underwent a subsequent resection (58% R0), with previous studies. Our outcomes are within the range of 13–43% resection (50–100% R0), as reported by two recent systematic reviews.[5,6] Our resection rate after gemcitabine treatment is lower than the resection rate of 31–33% (19–26% R0) after gemcitabine combined with radiation therapy reported by two systematic reviews.[43,44] However, these results were based on different selection criteria and definitions of LAPC.

Regarding survival, median OS in all patients receiving at least one cycle of FOLFIRINOX in this study was 13 months. Only three previous studies solely included patients with LAPC.[6,7] Of these, one study reported a median OS of 15.7 months after treatment with FOLFIRINOX (without radiation therapy).[45] FOLFIRINOX (including radiation therapy) in LAPC followed by resection was reported in 12 studies, with a pooled resection rate of 26%.[6] One study reported a median OS of 24.9 months after treatment with FOLFIRINOX followed by resection in LAPC,[46] where we reported a 34-month median OS.

A recent large study by Martin et al. demonstrated a median OS of 23 months after IRE for LAPC.[27] Our study and others,[25] could not reproduce these results. It is unclear whether the higher resection rate in our study (39% [$n = 14/36$] vs. 25% [$n = 50/200$][47]) influenced these findings.

The rates of morbidity (53%) and mortality (7%) after IRE in our study were substantial. A recent systematic review reported a comparable morbidity of 51%, and a mortality of 2% after IRE.[8] After one death due to liver failure with PV thrombosis, we changed the IRE eligibility criteria and excluded patients with narrowing (>50%) of both the hepatic arterial and venous blood supply, after which this complication was no longer observed. These outcomes are comparable with morbidity and mortality rates after pancreatectomy with arterial resection.[42]

This study has some limitations. First, LAPC was defined according to the DPCG guideline, which is more conservative than the National Comprehensive Cancer Network (NCCN) guidelines.[48] The NCCN defines LAPC as arterial involvement beyond 180° and unreconstructable venous involvement. Therefore, our study may give a more positive representation of the actual survival rates. Second, although this study describes a relatively large cohort of patients, subgroups are still small and therefore data should be interpreted with caution. However, previous studies also included small numbers of patients in the subgroups. According to a recent systematic review, only two previous studies reported on more than 15

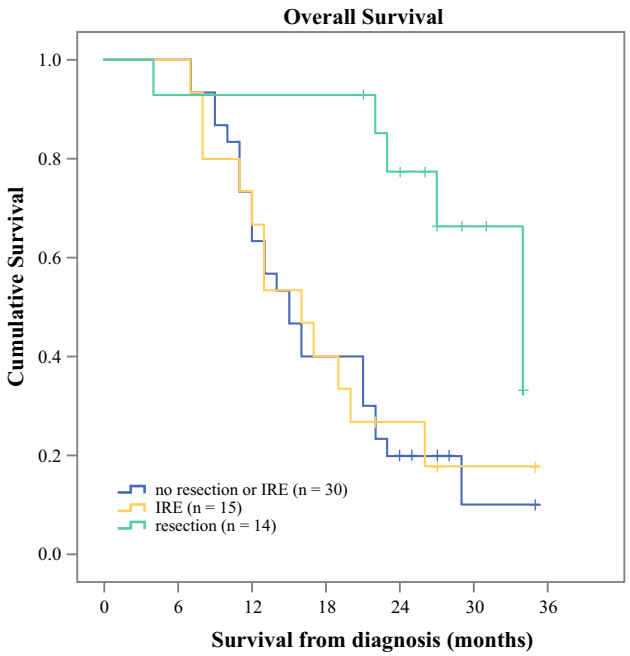

FIG. 2 Median overall survival from diagnosis for patients with RECIST nonprogressive disease after 3 months of chemotherapy per treatment category. The 'no resection or IRE group' represents all patients with nonprogressive disease (of whom some underwent exploratory laparotomy) after 3 months of chemotherapy. *IRE* irreversible electroporation, *RECIST* Response Evaluation Criteria in Solid Tumors

resected patients.[7] Third, a learning curve effect for both resections after FOLFIRINOX chemotherapy and IRE in LAPC cannot be excluded. The strengths of this study are the prospective study design with a cohort of consecutive LAPC patients. Hereby, resection rates and survival are less influenced by selection bias in contrast to previous studies.

Ideally, randomized studies should establish the added benefit of resection or ablative therapies such as IRE after treatment with FOLFIRINOX in LAPC. Currently, three randomized controlled trials on this topic are ongoing. First, the PRODIGE 29-NEOPAN trial (NCT02539537) randomizes between FOLFIRINOX and gemcitabine in patients with LAPC to compare progression-free survival. Second, in The Netherlands, the PELICAN trial (NTR5517) randomizes between radiofrequency ablation with chemotherapy versus chemotherapy alone in patients with nonprogressive LAPC after 2 months of induction chemotherapy. Third, the CROSSFIRE trial (NCT02791503) randomizes between IRE and stereotactic body radiation therapy in patients with LAPC to compare safety and efficacy. Future studies should also focus on optimizing imaging modalities to better determine resectability of LAPC after treatment with FOLFIRINOX.[40]

CONCLUSIONS

This is the first prospective study on consecutive patients initially identified with LAPC, analogous to an intention-to-treat analysis. An important finding is that resection seems to be associated with the best survival (median OS of 34 months) after induction chemotherapy, albeit only in the small subgroup (11%) of all patients initially identified as LAPC. No apparent survival benefit could be demonstrated for IRE, despite considerable morbidity.

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CONFLICT OF INTEREST Steffi J. Rombouts, Thijs de Rooij, Otto M. van Delden, Marcel G. Dijkgraaf, Thomas M. van Gulik, Jeanin E. van Hooft, Hanneke W. van Laarhoven, Annuska Schoorlemmer, Johanna W. Wilmink, and Olivier R. Busch declare no conflicts of interest.

APPENDIX 1

Tables 4, 5, and 6.

TABLE 4 Eligibility criteria for explorative laparotomy with potential IRE or resection

Inclusion criteria	Exclusion criteria
Age ≥ 18 years	Presence of metastatic disease
Capable of providing written and oral informed consent	Histological diagnosis of cholangiocarcinoma
	History of cardiac arrhythmia's (sinus tachycardia (BPM > 100), sick sinus syndrome, sinoatrial exit block, atrioventricular block, sinus node re-entry, presence of a pacemaker or defibrillator)
Physically fit enough to undergo explorative laparotomy	
Histologically confirmed pancreatic cancer	

TABLE 4 continued

Inclusion criteria	Exclusion criteria
Locally advanced disease	
Maximum tumor diameter in transverse and anteroposterior dimension of 5 cm	
	History of myocardial infarction within 6 months
Potentially resectable disease	History of epilepsy
Non-progressive disease on restaging after at least 3 months of chemotherapy	Partial portal vein thrombosis
	Both narrowing (sclerosis) of the portal vein and a reduced diameter of either the common hepatic artery, celiac trunk or superior mesenteric artery of ≥50%[a]

[a] This criterion was added to the exclusion criteria after the occurrence of fatal liver failure in the second treated patient, due to thrombosis of the PV and occlusion of the HA

TABLE 5 Complications according Clavien–Dindo grade ≥3 per treatment strategy

	Resection	IRE	Palliative exploration
Thrombosis PV/SMV	1	2	
Bile leakage	2	3	
Fluid collection	3		
DGE	1	3	
Abdominal bleeding			2
CBD obstruction		1	
Chyle leakage	1		
GI bleeding		1	
Pancreatic fistula	1	1	
Perforation			1

IRE irreversible electroporation, *PV* portal vein, *SMV* superior mesenteric vein, *DGE* delayed gastric emptying, *CBD* common bile duct, *GI* gastrointestinal

TABLE 6 Survival from diagnosis of patients with non-progressive disease after 3 months FOLFIRINOX chemotherapy

	No	mOS (mo)	1-year OS (%)
Resection	12	34	92
Irreversible electroporation	9	16	78
Laparotomy without resection or IRE	6	22	83
RECIST 1.1 non-progressive LAPC without resection or IRE	23	13	70
Log-rank*	$p = 0{\cdot}006$		

1-year OS one year survival, *mOS* median overall survival, *mo* months, *RECIST* Response Evaluation Criteria in Solid Tumors

APPENDIX 2

Specification of adverse events per treatment category

Resection

Pt. 1 Thrombosis SMV → re-laparotomy (thrombectomy, PV reconstruction) (grade IIIb) + fluid collection → drainage (grade IIIa).

Pt. 2 GDE grade C → duodenal tube, total parenteral feeding (TPF) (grade IIIa).

Pt. 3 Pancreas fistula grade B → drain (grade IIIa) + chyle leakage → TPF (grade IIIa).

Pt. 4 Leakage hepaticojejunostomy (HJ) and gastrojejunostomy → death (grade V).

Pt. 5 Fluid collection → drain (grade IIIa).

Nb. No intra-procedural complications occurred.

IRE

Pt. 1 Pancreatic fistula/bile leak → drain (grade IIIa).
Pt. 2 Thrombosis PV leading to liver failure → death (grade V).
Pt. 3 Nausea → duodenal tube (grade IIIa).
Pt. 4 DGE grade C → duodenal tube, parental feeding (TPF) (grade IIIa).
Pt. 5 Bleeding gastric ulcer → wanted no treatment, death (grade V).
Pt. 6 Bile leakage → drain (grade IIIa) and bleeding GDA → coil (grade IIIa).
Pt. 7 Thrombosis PV with ascites → drain (grade IIIa) + Nausea → duodenal tube (grade IIIa).
Pt. 8 Bile obstruction → ERCP (stent) (grade IIIa).
Nb. No intra-procedural complications occurred.

Palliative

Pt. 1 Perforation → drain (grade IIIa).
Pt. 2 Bleeding HJ → gastroscopy with clip placement (grade IIIa).
Pt. 3 Intra-operative retroperitoneal bleeding → intraoperative management (grade IIIb).

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