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Safety of radiofrequency ablation in patients with locally advanced, unresectable pancreatic cancer: A phase II study

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ABSTRACT

Introduction: Radiofrequency ablation (RFA) has been proposed as a new treatment option for locally advanced, unresectable pancreatic cancer (LAPC). In preparation of a randomized controlled trial (RCT), the aim of this phase II study was to assess the safety of RFA for patients with LAPC.
Materials and methods: Patients diagnosed with LAPC confirmed during surgical exploration between November 2012 and April 2014 were eligible for inclusion. RFA probes were placed under ultrasound guidance with a safety margin of at least 10 mm from the duodenum and 15 mm from the portomesenteric vessels. During RFA, the duodenum was continuously perfused with cold saline to reduce risk for thermal damage. Primary outcome was defined as the amount of major complications (Clavien-Dindo grade ≥III). RFA-related complications were predefined as: pancreatic fistula, pancreatitis, thermal damage to the portomesenteric vessels and duodenal perforation.
Results: In total, 17 patients underwent RFA. Delayed gastric emptying (DGE) requiring endoscopic feeding tube placement occurred in 4 patients (24%) as only major complication. Five patients (29%) had a major complication other than DGE. One (6%) RFA-related major complications occurred. One patient (6%) died due to complications from a biliary leak following hepaticojejunostomy. After evaluation of the first 5 patients, gastrojejunostomy was no longer performed routinely. Since then severe DGE seemed to occur less (3/5 vs. 3/12 grade C DGE).
Conclusion: RFA is a major, but safe procedure for patients with LAPC if performed with strict predefined safety criteria. A RCT is currently investigating the true effectiveness of RFA in patients with LAPC.

Introduction

Pancreatic cancer is among the most aggressive cancers and estimated to become the number two leading cause of cancer related death in the near future [1]. Overall survival hardly improved over the last decades [2]. Surgical resection combined with (neo-)adjuvant chemotherapy provides the best chances of long-term survival but is only feasible in a minority of patients. About 30–40% of patients present without distant metastases, but with unresectable disease at the time of diagnosis due to involvement of important vascular structures [3]. Currently, standard treatment for these patients with locally advanced, unresectable pancreatic cancer (LAPC) is palliative systemic chemotherapy.

Interestingly, several new treatment strategies for LAPC have become available. Radiofrequency ablation (RFA) is one of those

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techniques aiming for local tumor destruction through application of a high frequency alternating current. With this thermal-based technique one or more electrodes are implanted centrally into the tumor to induce cell death by frictional heating [4]. It has recently been shown that RFA may also induce a systemic immune response in pancreatic cancer, different from normal surgical stress, possibly due to a transitional zone of apoptosis-undergoing tumor tissue exposing tumor-specific antigens [5]. It is hypothesized that this can result in a systemic anti-tumor immune response that can improve overall survival. Non-randomized studies showed promising overall survival up to 25.6 months after RFA for LAPC [6]. However, no randomized controlled trials (RCTs) have been performed, so the true effectiveness of RFA combined with systemic chemotherapy regimens remains unknown. Moreover, morbidity rates range from 14% to 28% and seems to depend on RFA temperature settings, preventive duodenal cooling, and safety margins from vital structures [6–8]. In preparation for an international multicenter RCT, this prospective single-center observational phase II study aims to assess the safety of RFA for patients with LAPC.

Methods

Study population and study design

Patients diagnosed with histologically proven borderline resectable pancreatic cancer and LAPC underwent an explorative laparotomy with the intention for resection. If the tumor turned out to be unresectable during surgical exploration without metastases, patients were eligible for inclusion. Exclusion criteria were: portal vein thrombosis, inability to achieve predefined safety margins to vital structures, age below 18 years and pregnancy. Pre-operative staging was based on a multiphasic contrast-enhanced computed tomography (CT) scan, discussed at the multidisciplinary meeting and defined according to the consensus criteria of the Dutch Pancreatic Cancer Group [9]. Intraoperative resectability was determined by surgical expertise and based on the vascular tumor encasement: >180° of arterial contact or venous unreconstructable disease were defined unresectable. Both patients with and without preoperative chemotherapy treatment were eligible for inclusion.

The study meets all guidelines of the Dutch responsible governmental agency, was approved by the institutional ethical committee and registered at clinicaltrials.gov (identification number: NCT01628458). All patients provided written informed consent before surgical exploration. An independent data and safety monitoring board (DSMB) conducted a review and evaluation of the safety of the data after every 5 patients.

Radiofrequency ablation procedure

All patients received prophylaxis for surgical site infections (cefazolin 2 g/metronidazole 500 mg), pancreatic fistulas (octreotride) and deep vein thrombosis (low molecular weight heparin). Patients underwent explorative laparotomy under general anesthesia. The peritoneal cavity was explored for possible metastases, and Kocher maneuver performed to expose the pancreatic head. In case of unresectable pancreatic cancer, the surgical team proceeded with RFA. RFA was carried out by an interventional radiologist with the multipolar CelonLab® POWER System generator and CelonProSurge® probes with exposure lengths of 20/30/40 mm (Olympus Surgical Technologies Europe, Teltow, Germany). A total of 15 kJ per probe was delivered with a power setting of 1 W per mm probe length as previously investigated [7,8]. Before ablation a cold wet gauze was placed over the inferior caval vein and the duodenum was continuously perfused with cold saline through 2 nasogastric tubes to reduce the risk for thermal damage. The RFA probe was placed in the center of the tumor under direct ultrasound guidance. A distance of the probe of at least 10 mm from the duodenum and 15 mm from the portomesenteric vessels (i.e. portal vein, superior mesenteric vein, superior mesenteric artery, celiac trunc, common hepatic artery) and surrounding vital structures was remained and the ablation zone was planned to not exceed the tumor in accordance with previously published studies [7,8,10]. In case of pancreatic head cancer in the first 5 patients a biliary and gastric bypass were performed routinely for palliative reasons and to prevent the consequences of possible RFA induced biliary damage. After evaluation of the first 5 procedures with the DSMB, gastrojejunostomy was only performed in case of high risk of gastric obstruction, since a relatively high amount of delayed gastric emptying (DGE) was observed. An abdominal drain was left in the omental bursa.

Outcome measures

The primary endpoint of the study was safety defined as the number of patients with major complications (i.e. Clavien-Dindo grade ≥III) within 30 days or during the initial admission. All complications were scored according to Clavien-Dindo classification [11]. Postoperative pancreatic fistula, DGE, post-operative hemorrhage, bile and chyle leakage were classified according to the definitions of the International Study Group on Pancreatic Surgery (ISGPS) as well, but only grade B/C complications were included [12–15]. For comparability with previous studies, RFA-related complications were predefined as: pancreatic fistula, pancreatitis, thermal damage to the portomesenteric vessels and duodenal perforation[9]. Secondary outcome parameters were late complications, length of hospital stay, CA19-9 response and overall survival. At day 7 after the RFA procedure, a 2-phase pancreatic CT-scan was performed. The study had a follow-up period of 3 months for late complications, afterwards only survival data was collected.

Sample size and statistics

Based upon a systematic review involving 158 patients with pancreatic cancer treated with RFA from 5 studies, the proportion of RFA-related complication Clavien-Dindo grade ≥III was expected to be approximately 12% [16]. Together with an expected complication rate after combined biliary and gastric bypass of 14% [17] a maximum acceptable rate of 25% was defined. As this study was a safety study, a power of 0.50 was chosen to detect any unsafe situation of the treatment as early as possible. Using an expected occurrence of 12% with a fixed undesirable upper reference bound of 25%, in order to have a power of 0.50 with a one-sided α of 0.05, a total of 17 patients were needed and at most 5 were allowed to have a major complication (binomial test for one proportion) [18].

Statistical analysis was performed with SPSS statistical software (SPSS Statistics Version 22.0, Inc., Chicago, Illinois, USA). Patient characteristics and study outcomes were presented with descriptive statistics using mean with standard deviation or median with interquartile range when appropriate for continuous data and number with percentage for categorical data.

Results

Between November 2012 and April 2014, 34 patients underwent an explorative laparotomy and 13/34 patients were treated with a surgical resection. Another 4 patients were excluded from RFA due to absence of a safety margin to vital structures on intraoperative ultrasound (n = 2), concomitant pancreatitis (n = 1), or peritoneal metastases (n = 1). The remaining 17 patients turned out to have LAPC and were included for RFA. Demographics of these patients

Table 1
Patients and tumor characteristics.

Characteristic	All patients n = 17
Age, years (SD)	62 (11)
Male sex, n (%)	7 (41)
Tumor location, n (%)	
Head/uncinate process	13 (76)
Body/tail	4 (24)
Biggest tumor diameter, mm (SD)	48 (11)
Vascular involvement, n (%)	
Superior mesenteric artery	12 (71)
0°– =< 90°	2 (12)
90°– =< 180°	2 (12)
>180°	8 (47)
Celiac trunk	7 (41)
0°– =< 90°	1 (6)
90°– =< 180°	-
>180°	6 (35)
Portal vein	12 (71)
0°– =< 270°	4 (24)
>270°	8 (47)
Superior mesenteric vein	16 (94)
0°– =< 270°	7 (41)
>270°	9 (53)
Significant stenosis/occlusion of portomesenteric vein, n (%)	14 (82)
Pre-treated with chemotherapy, n (%)	3 (18)
FOLFIRINOX	2 (12)
Gemcitabine based	1 (6)

and tumor characteristics are shown in Table 1. Procedural details are given in Table 2 and Fig. 1 shows an image of intra-operative RFA probe placement under direct ultrasound guidance. A pre-operative CT-scan, intra-operative ultrasound during the RFA procedure, and a post-procedural CT-scan within the same patient are shown in Fig. 2 in order to visualize the procedure in more detail.

Overall complications

All major complications that occurred within 30 days are depicted in Table 3. A Clavien-Dindo grade ≥III complication occurred in 9 patients (53%). A common problem was DGE requiring endoscopic tube placement in 8 patients (47%). In 4 of them (24% of all patients) this was the only major complication. After a gastrojejunostomy bypass was no longer performed routinely, DGE complications seemed less frequent and less severe (Table 4). In total, 5 patients (29%) had a Clavien-Dindo grade ≥III complication other than DGE. One patient (6%) died 57 days after the RFA procedure due to an ongoing deterioration after a hepaticojejunostomy leakage with multiple intra-abdominal abscesses, cholangiosepsis

Table 2
Procedural details.

Characteristic	All patients n = 17
Bypass surgery, n (%)	
Hepatico- and gastrojejunostomy	8 (47)
Hepaticojejunostomy only	5 (29)
No bypass[a]	4 (24)
Additional procedures, n (%)	
Small bowel resection[b]	1 (6)
No. of RFA probes used per procedure, n (%)	
1	4 (24)
2	11 (65)
3	1 (6)
4	1 (6)
Ablation time, min:sec, median (IQR)	20:42 (14:34 – 29:02)

[a] One patient underwent a previous exploration elsewhere with a hepatico- and gastrojejunostomy.
[b] Because of adhesion of the small bowel with the tumor, one patient received a small bowel resection with a duodenojejunostomy.

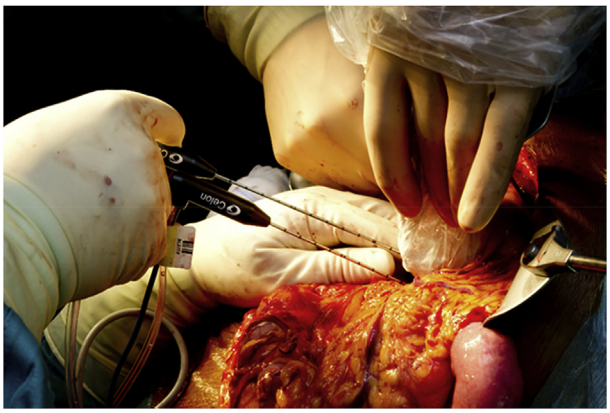

Fig. 1. Intra-operative placement of RFA probe under direct ultrasound guidance.

with liver abscesses and respiratory failure. One patient (6%) had a bleed from a pseudoaneurysm of the gastroduodenal artery after RFA of a tumor in the uncinate process. The aneurysm was successfully coiled during angiography. Three weeks after coiling, this patient had melena due to a bleeding ulcer at the gastrojejunostomy that could be treated endoscopically. One patient (6%) required a percutaneous hepatic biliary drainage under general anesthesia, because of a biliary leak from the hepaticojejunostomy. This patient developed a pneumosepsis requiring admission to the medium care without the need for invasive ventilation. Other major complications were: ultrasound guided drainage of ascites in a patient with a pre-existing portomesenteric vein (PMV) occlusion (n = 1, 6%) and pneumosepsis with medium care admission without the need for invasive ventilation (n = 1, 6%). According to ISGPS definitions 4 patients (24%) had a grade B chyle leakage, but this did not require a re-intervention.

RFA-related complications

No major pancreatic fistulas, pancreatitis or duodenal perforations occurred. The described pseudoaneurysm in 1 patient (6%) was probably related to thermal damage to the gastroduodenal artery. Other thermal effects to the PMV only resulted in minor complications (Clavien-Dindo grade II): 4 patients (24%) were diagnosed with a new thrombus of the PMV one week after RFA (Fig. 2c). All 4 had a significant stenosis of the PMV caused by tumor encasement in advance of the RFA procedure. These patients had no clinical symptoms and were treated with low molecular weight heparine. One of them was readmitted 44 days after the procedure with abdominal pain and ascites, which was drained under ultrasound guidance. One patient had a thrombus in the left renal vein, without any clinical symptoms.

Secondary outcomes

During 3 months follow-up, 2 patients had additional major complications. One patient had a retrogastric fluid collection that was transgastrically drained 58 days after the RFA procedure. The second patient developed hematemesis 73 days after the procedure based on an arterial bleed at the gastrojejunostomy that could be clipped endoscopically. Two other patients showed a peripancreatic fluid collection on CT-scan during follow-up, but without any clinical signs, so no drainage or intervention was performed. The median postoperative hospital stay was 15 days (IQR 8–23). The postoperative CA19-9 value decreased from a median preoperative value of 315 (IQR 123–1205) to a median of 180 (IQR 70–500) and

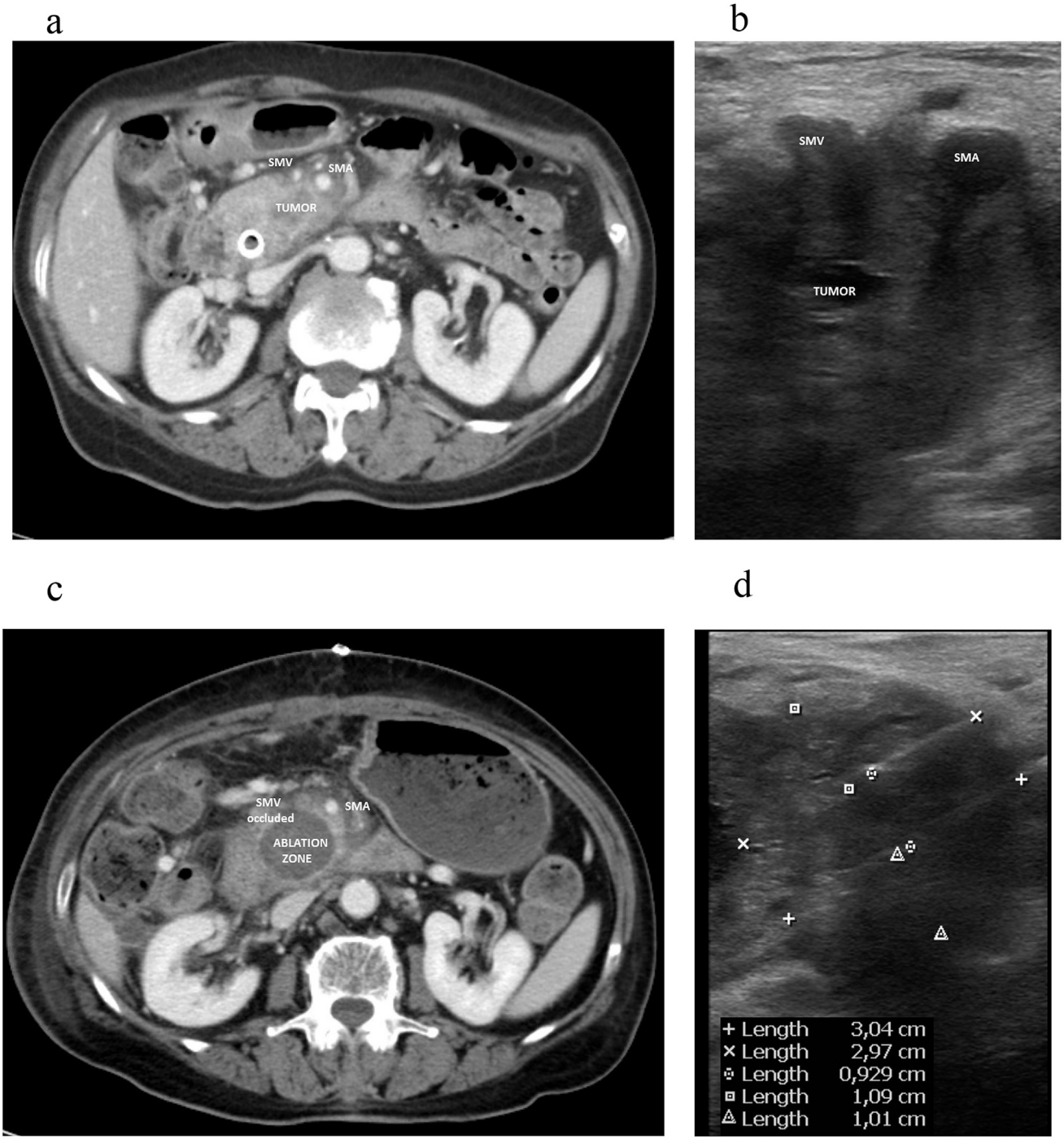

Fig. 2. Pre-operative CT-scan, intra-operative ultrasound and post-operative CT-scan in a patient with LAPC treated with RFA.
2a: preoperative CT-scan with >270° contact with superior mesenteric artery (SMA) and superior mesenteric vein (SMV); 2b: intraoperative ultrasound showing the same configuration as the CT-scan; 2c: postoperative CT-scan one week after RFA pancreas shows a distinct ablation area and an occluded superior mesenteric vein without further complications; 2d: example of intra-operative ultrasound measurements with two 3 cm RFA probes (between plus signs and multiplication signs respectively) placed 1 cm width apart.

180 (IQR 63–588) on day 7 and 3 months after the operation respectively. Median overall survival was 9 months (IQR 5–11 months).

Discussion

The present observational phase II study showed that after RFA of the pancreas major morbidity could mainly be attributed to DGE with the need for endoscopic tube placement (8 patients; 46%). DGE seemed to occur mostly as a result of the surgical gastro-jejunostomy that were performed routinely in case of pancreatic head cancer in the first 5 patients of the study. After a gastro-jejunostomy was performed only when indicated, DGE occurred less often and was less severe. In 5 patients (29%) a major complication other than DGE occurred, 1 patient (6%) developed a major RFA-related complication and 1 patient (6%) died 57 days

Table 3
Major complications during hospital stay or within 30-days after RFA pancreas defined by Clavien-Dindo classification ≥III and ISGPS.

	All patients n = 17
Overall complications, n (%)[a]	9 (53)
Overall RFA-related complications, n (%)	1 (6)
Clavien Dindo classification	
Clavien-Dindo grade IIIa, n (%)[a]	9 (53)
DGE with endoscopic tube placement	8
Ascites drained under ultrasound guidance	1
Melaena (bleeding ulcer at GJ)	1
Clavien-Dindo grade IIIb, n (%)	1 (6)
Biliary leak from HJ	1
Clavien-Dindo grade IVa, n (%)	3 (18)
Pneumosepsis (medium care admission)	2
Hemorrhage with coiling pseudoaneurysm from gastroduodenal artery	1
Clavien-Dindo grade IVb, n (%)	-
Clavien-Dindo grade V, n (%)	1 (6)
Biliary leak from HJ with cholangiosepsis, intra-abdominal abscesses and respiratory failure	1
ISGPS classification	
Pancreatic fistula	-
Bile leakage, n (%)	2 (12)
Grade B	1
Grade C	1
Postoperative hemorrhage, n (%)	1 (6)
Grade B	1
Delayed gastric emptying, n (%)	8 (47)
Grade B	2
Grade C	6
Chyle leakage, n (%)	4 (24)
Grade B	4

DGE: delayed gastric emptying, GJ: gastrojejunostomy, HJ: hepaticojejunostomy, ISGPS: International Study Group on Pancreatic Surgery.
[a] Since some patients had more than one major complication, all separate complications do not sum up to total number of complications.

Table 4
Relationship between gastrojejunostomy and DGE.

	Gastrojejunostomy	DGE Grade B/C	DGE Grade C
Period 1 (n = 5)	3 (60%)	3 (60%)	3 (60%)
Period 2 (n = 12)	5 (42%)	5 (42%)	3 (25%)

after the procedure due to leakage of the hepaticojejunostomy.

One of the first studies reporting on RFA of the pancreas in 16 patients with LAPC described a relatively high amount of complications, with a mortality rate of 25%. This study ablated with a probe tip temperature exceeding 90 °C at a 5-mm safety distance from the probe to vital structure and each patient underwent 2–5 sessions of ablations [19]. The Verona group optimized the safety of the procedure by lowering ablation temperature to a maximum of 90 °C and performing a more prudent ablation, aiming to leave an undefined peripheral rim of tumor as a safety margin to surrounding tissues [10]. With these measures, they were able to lower morbidity rates from 40% to an overall complication rate of 26% in 100 patients treated with RFA. A RFA-related complication occurred in 15% of patients. In the present study the minimum distance of the RFA probe to vital structures was further defined as at least 10 mm from the duodenum and 15 mm from the portomesenteric vessels. With this more specific safety criteria, RFA-related complications as defined in previous studies occurred in only 1 patient (6%). Although hepaticojejunostomy leakage occurred in a notable high proportion of patients (n = 2, 12%), it is unlikely to be a direct thermal effect of the RFA procedure since the hepaticojejunostomy was performed after the RFA procedure and at a reasonable distance from the ablated area. Future studies with larger sample sizes should pay attention to this specific complication and might investigate the possibility of omitting a hepaticojejunostomy in the presence of a metal stent.

Compared to the study of Girelli et al. [10], the overall major complication rate was higher (53% compared to 26%). This might be explained by the use and interpretation of the Clavien-Dindo classification. In the present study, endoscopic feeding tube placement caused all DGEs to be classified as a grade 3a complication, while other centers might place tubes intraoperatively, without endoscopy, or simply not interpret tube placement as a major complication. For example, although a gastrojejunostomy was performed in 43/100 patients, no cases of DGE were described in the study of Girelli et al. [10,20]. This, while other studies describe up to 30% DGE after palliative doubly bypass surgery for pancreatic adenocarcinoma [21,22]. When DGE is not considered as major complication, the complication rate is within the predefined acceptable amount (5 patients, 29%) and comparable to the Verona group (29% versus 26%). Together with less RFA-related complications this supports that despite the high rate of DGE and the possibility of thermal damage, the current study establishes the safety of RFA pancreas in patients with LAPC.

Regarding overall survival, the present study is not comparable to other studies because RFA was given as upfront therapy in the majority of patients. This was deliberately chosen, since the aim of the study was to investigate the safety rather than efficacy. Moreover, the standard treatment at the time of this study was primary surgery and in case of inoperability gemcitabine monotherapy. This chemotherapeutic regimen only demonstrated an improvement of symptoms and benefit concerning survival is very limited [23]. In the current era, where new chemotherapeutic regimens like FOLFIRINOX have proven their superiority and where neoadjuvant treatment has become standard treatment, local ablative therapies should be used in the context of a multimodal treatment strategy [24,25].

This study provides unique data as the effects of only RFA treatment could be evaluated, without interference of other treatments. Strengths of this study include the strict and predefined

safety measures. First, a systematic literature review was performed [16]. Second, the Verona hospital was visited in order to be trained by longstanding and highly regarded international experts in the field. To further specify optimal RFA settings, animal studies were performed upon which safety distances from the probes in the current study were based [7,8]. The optimization of these criteria introduces a safe RFA pancreas procedure. Because of the pilot nature of the study and the monitoring of complications after every 5 patients, it was possible to optimize the procedure along the way and the possible influence of gastrojejunostomy could be clarified during the study. Some aspects of the study should be interpreted with care. Since this study was not designed to investigate efficacy of RFA, overall survival might not be representative. Moreover, the current study investigated RFA in the open setting while more recent studies also reported the feasibility of minimal invasive ablation [26,27]. This can reduce laparotomy related morbidity, but probe placement is performed in a less controlled setting. Therefore safety of endoscopic-ultrasound guided or percutaneous RFA should be a subject of further investigation synchronously along with the current efficacy studies in the open setting.

Non-randomized studies report a survival of 25.6 months in patients pre-treated with systemic therapy followed by ablative control of the primary tumor [25]. However, more recently FOLFIRINOX has become the preferred chemotherapeutic regimen and promising overall survival of up to 25 months have been described for patients treated with FOLFIRINOX without ablative therapy [28,29]. Therefore, the true effectiveness of RFA in addition to the current chemotherapy regimens remains unclear. Based on the current observational phase II study an international multicenter RCT was designed: the PELICAN trial. This study compares overall survival in patients with non-progressive LAPC after 2 months of induction chemotherapy who are either treated with RFA plus chemotherapy versus chemotherapy alone. PELICAN is currently the only ongoing RCT investigating ablative therapy in combination with induction chemotherapy for this patient population, and the results will be of great relevance. At this moment, inclusion in the PELICAN trial is halfway (114/228).

Conclusion

In conclusion, RFA pancreas should be considered as a major procedure with the risk of thermal damage to nearby vital structures. However, when strict safety measures are taken it can be considered safe with approximately 25% major morbidity. A gastrojejunostomy should not be performed routinely since this might contribute to severe gastric delayed emptying. Considering the current dismal prognosis of patients with LAPC the possible survival benefit of RFA combined with current improving chemotherapeutic regimens should be investigated within a RCT. This trial is currently ongoing [30].

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Declaration of interest

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