



# Intraoperative electrochemotherapy of the posterior resection surface after pancreaticoduodenectomy: Preliminary results of a hybrid approach treatment of pancreatic cancer

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## ABSTRACT

**Background:** Despite extensive research in recent decades, pancreatic cancer continues to be among the most lethal forms of cancer, with no substantial increase in survival rates. Local recurrences account for approximately 30 per cent of all disease recurrences. With the intent to improve survival, we designed a novel, hybrid treatment strategy consisting of surgical resection and additional intraoperative electrochemotherapy of the posterior resection surface. We present the study protocols and preliminary findings of a prospective pilot study investigating this treatment approach.

**Methods:** Consenting patients with resectable pancreatic head ductal adenocarcinoma who met the inclusion criteria were enrolled in the study. After surgical resection, electrochemotherapy with bleomycin was performed using plate electrodes to cover the area between anatomical landmarks.

**Results:** Electrochemotherapy of the posterior resection surface was feasible in all 7 patients. We observed pancreatic fistula grade B in only one patient; all other noted complications were Clavien-Dindo grade 2 or less. The hospital mortality was 0%.

**Conclusions:** Our preliminary results suggest that a hybrid approach combining surgery with intraoperative electrochemotherapy is safe and feasible.

## 1. Introduction

Pancreatic cancer remains among the most lethal forms of cancer, with no significant improvement in survival rates despite extensive research in recent decades [1–3]. Radical surgical resection is the only curative option, which is feasible in only about one-fifth of patients due to late diagnosis [3,4]. However, even after radical surgical resection, the disease prognosis remains dismal, with 10–25% 5-year survival [5–8]. Thus, early diagnosis and more efficient treatment methods are needed to improve survival.

The classical surgical procedure for pancreatic head adenocarcinoma

is the Whipple procedure, which was introduced in 1940 as a one-stage procedure [9,10]. During the resection phase of the procedure, the pancreatic head, gallbladder, common bile duct, duodenum and distal stomach are removed en-block, together with lymphadenectomy of the common and true hepatic arteries [10]. However, considering the vital importance of the remaining blood vessels and organs, surgical treatment alone appears insufficient. Furthermore, the literature shows that extended lymphadenectomy or even more radical resections do not influence oncological outcomes [11,12].

In the event of a disease recurrence, a local recurrence occurs in approximately 30% of cases [5–8]. The posterior and medial resection

**Abbreviations:** DFS, disease-free survival; ECG, electrocardiogram; ECT, electrochemotherapy; HPB, hepato-pancreato-biliary; ICU, intensive care unit; MDT, multidisciplinary team; OS, overall survival; PDAC, pancreatic ductal adenocarcinoma; PPPD, pancreaticoduodenectomy with preserved pylorus; US, ultrasound.

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surfaces account for up to 90% of all local recurrences because achieving a tumor-free margin at these sites is the most difficult and technically challenging [13].

In recent years, the neoadjuvant systemic chemotherapy is gaining popularity in pancreatic cancer and it has been investigated intensively; however, it seems that the overall results are not statistically superior in the case of a resectable disease [14].

Electrochemotherapy (ECT) is a non-thermal, ablative local treatment which uses reversible electroporation to increase the transition of hydrophilic molecules into the cell [1,15]. Thus, ECT potentiates local chemotherapeutic effects without or with minimal risk for systemic side effects as the doses of intravenously applied chemotherapeutic drugs, such as bleomycin, are reduced [15,16]. ECT has been used for both skin and deep-seated tumours, and the feasibility, safety and efficacy of ECT in treating colorectal liver metastases and primary liver tumours has been demonstrated [17–20]. However, there are only a few published studies investigating ECT in the treatment of pancreatic adenocarcinoma. Available data suggest that ECT with bleomycin or other biochemical molecules could have a role in the treatment of malignant pancreatic tumours [21–23].

With the intent to improve survival in pancreatic head carcinoma by lowering the chance of local disease recurrence, we designed a prospective pilot study (PanECT study) investigating a novel, hybrid treatment consisting of surgical resection and intraoperative ECT of the posterior resection surface. This report presents the study protocol with a detailed description of the hybrid treatment, as well as preliminary results and a broad discussion.

## 2. Patients and methods

### 2.1. Study design

The prospective pilot study was designed in collaboration with the University Medical Centre (UMC) Ljubljana and the Institute of Oncology Ljubljana. The study was registered at [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT04281290) and ethical approval was obtained from National Medical Ethics Committee of the Republic of Slovenia (0120-174/2019/8; 16 July 2019). The pilot study ultimately aims to include 20 patients, and at the time of writing, patient recruitment remains in progress, and only preliminary results are presented in this report. The main aim of the study is to assess the feasibility and safety of a hybrid approach with surgical resection and additional intraoperative ECT of the posterior resection surface in pancreatic head carcinoma. The secondary goal involved assessing the efficacy by examining disease-free survival (DFS) and overall survival (OS) outcomes after surgical resection and ECT treatment. The main intention of performing intraoperative ECT was to prevent local disease recurrence. This report describes the procedure and discusses the safety, feasibility, and efficacy in the first 7 patients included in the study.

### 2.2. Patients

The study was performed at the Department of Abdominal Surgery, University Medical Centre Ljubljana, Slovenia. The patients presented in this report were recruited between July 2020 and July 2022. During the above period, there were still several COVID-19 outbreaks in our hospital, so the study was interrupted several times.

Enrolment was offered to all patients with resectable pancreatic ductal adenocarcinoma (PDAC) of the pancreatic head in accordance with the inclusion and exclusion criteria (Table 1). The patients were eligible if the tumour lesion was resectable and there were no signs of metastatic disease. After extensive discussion with the patients describing the purpose and the study protocol, eligible patients were included in the study following their completion of the informed consent process.

**Table 1**

Inclusion and exclusion criteria for performing ECT of the posterior resection surface in pancreatic cancer.

Inclusion criteria
1. Resectable cancer of the pancreatic head.
2. Age > 18 years.
3. Life expectancy more than three months.
4. Patients with Karnofsky performance status of $\geq 70$ or World Health Organization (WHO) < 2
5. Signed informed consent with a clear understanding of the information given.
6. The patient was presented to and discussed by the MDT for pancreatic tumours before the enrolment in the study
Exclusion criteria
1. Resection of the vessels if the borderline resectable tumour was found.
2. Patients with a history of malignant tumours, except for surgically treated noninvasive cervical cancer or surgically treated or irradiated basal cell carcinoma, were excluded.
3. Confirmed visceral, bone, or widespread metastases.
4. Life-threatening infection, heart failure, liver failure, renal failure (creatinine >150 $\mu\text{mol/L}$ ), or other critical systemic pathologies.
5. Severe reduction in respiratory function.
6. Age < 18 years.
7. Neoadjuvant radio-chemotherapy.
8. Allergic reaction to bleomycin.
9. Epilepsy, arrhythmias, heart failure with or without pacemaker.
10. Pregnant women.
11. Participants who were incapable of understanding the purpose of the study.

### 2.3. Surgical procedure with ECT

Exploratory laparotomy was performed in every patient to exclude macroscopic signs of disease progression, including peritoneal carcinosis or liver metastases. Precise inspection of the tumour and the assessment of its resectability followed. If the tumour was resectable, a standard surgical procedure for the resection of PDAC was performed: either a Whipple procedure or a pancreaticoduodenectomy with preserved pylorus (PPPD) [24]. Fresh frozen samples from the ductal resection margins (pancreatic and main hepatic duct) were analysed to confirm disease-free margins. Patients were operated on by three experienced hepato-pancreato-biliary (HPB) surgeons, all performing ECT in line with the study protocol. After surgical resection and before commencing the reconstruction, the posterior resection margin was treated with ECT to lower the risk of local disease recurrence.

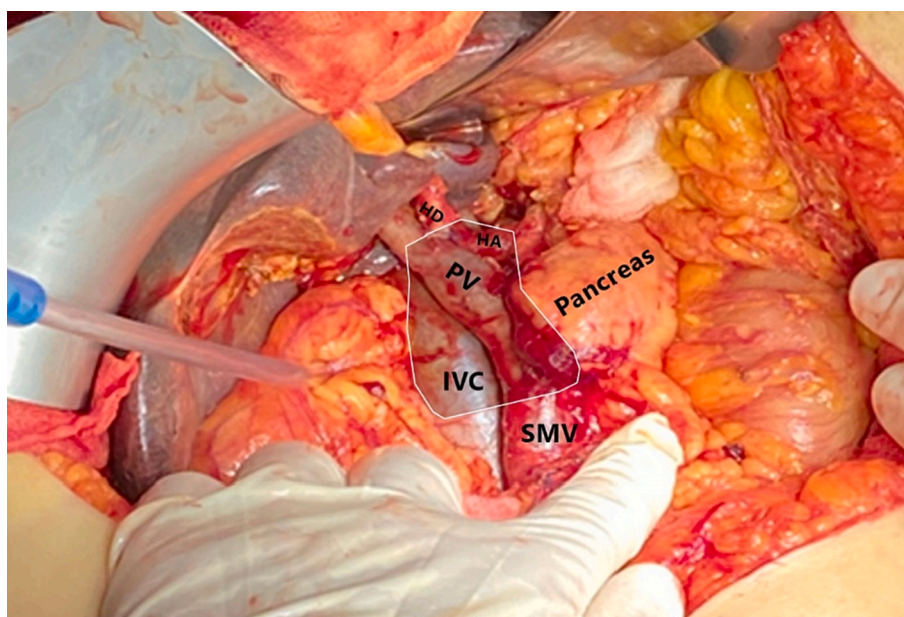
The intraoperative ECT procedure was performed according to the Standard Operating Procedures for treating cutaneous tumours with modification to treat the posterior resection surface according to the published recommendations [25]. ECT was performed 8 min after intravenous bolus administration of bleomycin (Bleomycin PHC 15 e. (United States Pharmacopeia)). The received dose was calculated according to the body surface area and was 15 mg/m<sup>2</sup> for each patient. Electric pulses were delivered by a Cliniporator Vitae® electric pulse generator (IGEA SpA, Carpy, Italy). To prevent the delivery of pulses during the vulnerable period of the heart, the synchronization of electric pulse triggering was achieved using the AccuSync ECG triggering device. As the size of the resection area varied from patient to patient, the number of electric pulse applications to treat the entire area also varied. Each application consisted of 8 electric pulses, duration 100  $\mu\text{s}$ , repetition 5 kHz, amplitude 960 V, delivered by plate electrodes with 8 mm distance in-between.

As we treated the surface containing major blood vessels, plate electrodes were used. After the removal of the tumor, the vessels were exposed and there was no supporting tissue around them. Our concern was that physical damage caused by puncturing those vessels could lead to significant bleeding. The plates of electrodes were 30 mm long and the distance between plates was 8 mm (Fig. 1). No conductive gel was used, as is usual in the treatment of skin tumours.

Electrodes were set at different locations to cover the whole posterior resection area between the following landmarks (Fig. 2):



**Fig. 1.** Fixed plate electrodes (P-30-8B; IGEA SpA, Carpy, Italy) were used for the ECT treatment. The length of the plates is 30 mm, and the spacing between the plates measures 8 mm.



**Fig. 2.** The exposed posterior resection surface after pancreatoduodenectomy with anatomical structures marked. The area between landmarks where ECT was performed is shaded and demarked with a white line. Legend: HD – hepatic duct, HA – hepatic artery, IVC – inferior vena cava, SMV – superior mesenteric vein, PV – portal vein.

- the lateral border of the inferior vena cava on the right,
- resection margin of the common hepatic duct at the upper right,
- truncus coeliacus at the top,
- resection surface of the pancreas on the left,
- level of the left renal vein at the bottom.

#### 2.4. Hospital follow-up

All patients enrolled in the study were closely monitored after the hybrid treatment. Supervision was carried out in the ICU on the first few postoperative days. The objective was to identify both immediate and delayed post-operative complications and assess their association with ECT treatment. In the ICU, vital functions were monitored, including ECG, to exclude postoperative cardiac arrhythmia. Laboratory tests were performed regularly, including hemogram, electrolytes, inflammatory

markers, and liver panel. We determined amylase/lipase from the abdominal drain on the 3rd and 7th days to exclude or confirm pancreatic fistula. As the ECT of the posterior resection surface included treatment of the major vessels in the vicinity of the liver, abdominal US with Doppler was performed twice 7 days after the operation to assess blood flow through the hepatic artery and portal vein. When patients were stable and the laboratory results normalized, they were transferred to a general ward before being discharged home.

After receiving the histopathology report of the resected specimen, patients were presented to the HPB multidisciplinary team to determine if they were suitable for adjuvant systemic chemotherapy.

#### 2.5. Outpatient follow-up

The outpatient follow-up protocol is presented in [Table 2](#). According

**Table 2**

Outpatient follow-up protocol. The performed examination at each time interval is marked in the table.

Time after treatment	History	Clinical examination	Tu markers (Ca19-9, CEA)	Abdominal US	Abdominal CT or MRI
1 month	x	x	x	x	
3 months	x	x	x		x
6 months	x	x	x		x
1 year	x	x	x		x
1,5 years	x	x	x	x	
2 years	x	x	x		x

to the literature, approximately 90% of disease recurrence or progression occurs in the first two years [5], so we planned three abdominal CT scans and regular check-ups of tumour markers in the first year to detect any late complications or potential early disease recurrence. After 2 years, the patient will be followed every 6 months.

DFS was defined as the length of time during which a patient survived without experiencing a recurrence of the disease following treatment. Recurrence was defined by an increase in tumour markers Ca19-9 and CEA beyond the normal range and/or the detection of one or more lesions on US/CT imaging.

Hospital complications and complications after hospital discharge are reported along with Clavien-Dindo classification. Briefly, the Clavien-Dindo classification was introduced in 2004 and is now well established in reporting surgical complications [26]. It consists of 7 grades (I, II, IIIa, IIIb, IVa, IVb and V), where grade I-II are mild complications, grade III complications require surgical, endoscopic or radiological intervention without (IIIa) or with (IIIb) general anaesthesia. Grade IV are severe, life-threatening complications and grade V means death of the patient.

**2.6. Statistical analysis**

All analyses are descriptive as we present preliminary results, and the study sample is small. Therefore, based on the nature and extent of distribution, the data are presented using appropriate measures such as medians, means, standard deviations, percentages, and frequencies.

**3. Results**

During the study period, a total of seven patients who met the inclusion criteria agreed to take part in our pilot study. Patients, operation type, ECT treatment properties, and tumour characteristics are

presented in Table 3. Additional data are described and summarised in the feasibility, safety, and efficiency sections.

**3.1. Feasibility**

ECT of the posterior resection surface was feasible in all 7 patients. The study included three male and four female patients, with a median age of 72 (range: 67–84). Due to individual anatomical characteristics, the size of the posterior resection surface area differed among patients. To cover the whole determined area, the number of electric pulse applications varied, ranging from 22 to 64 (median 27) applications.

**3.2. Safety**

No adverse reactions associated with ECT were observed, and there were no reported intraoperative or postoperative complications within the initial 24-hour period following treatment. There were no allergic reactions to bleomycin. All patients had abdominal US Doppler performed twice in the postoperative period to assess liver vessels. We observed segmental stenosis of the portal vein in only one patient (No. 4), with no evidence of portal thrombosis. The other 6 patients had normal US Doppler features of liver vessels (hepatic artery, portal vein, inferior vena cava).

During the hospital stay, we noticed the following complications: surgical site infection, postoperative paralytic ileus, deep vein thrombosis, paroxysmal atrial fibrillation, and postoperative pancreatic fistula (grade B). Only one complication was classified as Clavien-Dindo grade 3a, and all others were Clavien-Dindo grade 2 or less. The Clavien-Dindo grade for each complication is stated in Table 4. Despite the mentioned complications, the hospital mortality was 0%.

In contrast, during follow-up after hospital discharge, we observed complete or partial portal vein thrombosis in 3 out of 7 patients (43%).

**Table 3**

Patients, type of operation, properties of ECT treatment and tumour characteristics.

Patients				ECT of posterior resection surface				Tumour characteristics				
No.	Age	Sex	ASA score	Date of treatment	Type of procedure	Bleomycin dose (mg)	Number of applications	Histology type	Size (mm)	Type of differentiation	TNM	R status
1	72	M	3	13. 07. 2020	PPPD	26,5	25	PDAC	20	G2	T3b N2	0
2	81	F	2	31. 07. 2020	Whipple	24,2	38	PDAC	23	G2-G3	T2 N1	1
3	67	F	3	14. 08. 2020	Whipple	28,7	64	PDAC	20	G3	T2 N2	0
4	84	F	3	13. 05. 2022	PPPD	26,7	30	PDAC	35	G2	T2 N0	0 (only 1 mm posterior margin)
5	67	M	3	27.06.2022	Whipple	30,0	27	PDAC	25	G2	T2 N2	0 (only 1 mm posterior margin)
6	80	F	3	05. 07. 2022	PPPD	24,3	22	PDAC and ECHC	15	G3	T2 N0	0 (3 mm posterior margin)
7	69	M	2	12. 07. 2022	Whipple	29,7	25	PDAC	45	G1	T3 N0	0 (1.5 mm posterior margin)

No. – number; ECT – electrochemotherapy; ASA - American Society of Anaesthesiologists; M/F – male/female; PPPD –pancreaticoduodenectomy with preserved pylorus; PDAC – pancreatic ductal adenocarcinoma; ECHC – extrahepatic cholangiocarcinoma.

**Table 4**

Noted complications after hybrid treatment for each patient. The Clavien-Dindo grade of hospital complications is stated in the brackets.

No.	Age	Sex	ASA score	Hospital stay (days)	30-days morbidity	90-days morbidity
1	72	M	3	10	Surgical site infection (1) Postoperative gastroparesis (2)	Portal vein thrombosis
2	81	F	2	13	Deep vein thrombosis of the great saphenous vein (2)	/
3	67	F	3	12	/	Urinary tract infection with urosepsis Suspected cholangitis Portal vein thrombosis
4	84	F	3	10	PAF – 2nd postoperative day (2) Segmental stenosis of the portal vein with no signs of thrombosis or portal hypertension (1)	Partial portal vein thrombosis
5	67	M	3	7	/	/
6	80	F	3	9	/	/
7	69	M	2	86	Postoperative pancreatic fistula (grade B) (3a)	

No. – number; ASA – American Society of Anaesthesiologists; M/F – male/female; PAF – paroxysmal atrial fibrillation.

Only one patient had signs and symptoms of portal hypertension due to portal vein thrombosis. All patients with portal vein thrombosis had disease progression confirmed. All observed complications during the hospital stay and subsequent follow-up are presented in Table 4.

### 3.3. Efficacy

The duration of the follow-up period is insufficient for evaluating the efficacy of the treatment. Nevertheless, each patient was followed up for at least 6 months. At the time of writing, three patients included in the study had confirmed disease progression (patients 1, 3 and 4), two patients had liver metastases (patients 1 and 4), and only one patient had both liver metastases and local recurrence suspected on CT (patient 3). Two patients with disease progression died (patients 1 and 3). Only one patient was suitable for adjuvant systemic chemotherapy (patient 6). It is noteworthy that at the time of writing, the 81-year-old patient, who was treated in July 2020 with R1 resection and has been followed for 28 months, feels well and has no signs of disease recurrence. Follow-up of 5 patients is still ongoing.

## 4. Discussion

A prospective study was carried out to assess the feasibility and safety of intraoperative ECT of the posterior resection surface after pancreaticoduodenectomy as a hybrid treatment approach in adenocarcinoma of the pancreatic head (PanECT study). The study protocol and preliminary results are presented.

Our preliminary results confirmed the feasibility and safety of the hybrid approach treatment. Although we noticed some hospital complications, only postoperative pancreatic fistula (grade B) was classified as Clavien-Dindo 3a, demanding prolonged antibiotic treatment, several

percutaneous drain insertions by an interventional radiologist and a longer length of hospital stay. All other hospital complications were classified as Clavien-Dindo 2 or less. Meanwhile, it is noteworthy that pancreatic surgery (Whipple procedure or PPPD) bears relatively high morbidity (up to 40%) and mortality (3–5%) [27]. The most common and severe complication is a postoperative pancreatic fistula, which occurs in approximately 20% of patients [27]. The study sample is too small to statistically estimate the correlation between ECT treatment and potentially higher complication rates. Nonetheless, our findings suggest that ECT does not increase the likelihood of postoperative complications or influence mortality following pancreatic surgery. However, a randomised controlled trial would be needed to properly validate this assumption.

We found no serious vascular side effects in the first 30 postoperative days. Unexpectedly, however, we observed portal vein thrombosis in 3/7 patients (43%) in the subsequent follow-up. Typically, portal vein thrombosis occurs in individuals with cirrhosis or underlying prothrombotic conditions [28]. There are several acquired and inherited risk factors, but liver cirrhosis, solid malignant tumours, abdominal surgery, abdominal inflammation, hormonal therapy and myelodysplastic syndrome are the most common causes [29,30]. It is important to emphasise that pancreatic cancer bears a high prothrombotic tendency, with thrombotic complications observed in up to 36% of cases [31]. Thus, all 3 patients with portal vein thrombosis had more risk factors for developing thrombosis, and the exact role of ECT treatment in thrombosis is unclear. Abdominal ultrasounds were performed on all patients in the days after treatment, and all showed normal portal vein and hepatic artery blood flow with no evidence of thrombosis. Only one patient exhibited segmental portal vein stenosis without any evidence of thrombosis.

In the available literature, a solitary instance of late-onset portal vein thrombosis is documented. This particular case occurred 90 days after the treatment of a locally advanced pancreatic cancer, specifically following irreversible electroporation using needle electrodes (Nanoknife system - Angiodynamics, Lanthan) [32]. To date, there are no published articles regarding thrombosis occurrence in reversible electroporation with ECT treatment.

Interestingly, studies performed in the HPB region indicate that ECT is safe and feasible without significant side effects [1,17–19,21,33,34]. Several studies have demonstrated the feasibility, safety, and efficacy of ECT for treating primary liver tumours and colorectal liver metastasis, with no adverse effects associated with ECT treatment [17,18,35–37]. Additionally, a prospective study on six porcine models demonstrated that ECT did not result in hemodynamically significant thrombosis or any clinically significant damage to the major blood vessels or bile ducts within the liver [19]. According to a recent study conducted on a porcine model, ECT treatment of the pancreas was demonstrated to be safe, with no observed complications such as pancreatic fistula, pancreatitis, or a vascular injury [38].

Several clinical studies have also performed ECT of pancreatic carcinoma in humans as a palliative treatment. In a study involving 11 patients with locally advanced pancreatic cancer, ECT was administered, and no significant complications were observed. Furthermore, patients reported a reduction in pain levels [21]. In a similar study of 13 patients, 3 experienced splenic infarction without splenic vascular thrombosis and no additional sequelae [34]. In a recent observational study, five patients diagnosed with locally advanced pancreatic cancer received chemotherapy, but neither disease progression nor downstaging was observed. Thus, intraoperative ECT was performed with palliative intent. Based on their findings, the authors reached the conclusion that ECT is feasible and secure treatment option for pancreatic cancer [39]. In addition to ECT, treatments with irreversible electroporation have been used to treat locally advanced pancreatic cancer within clinical studies. The exact role of irreversible electroporation is yet unknown, but a recent review of the literature showed a range of 12–42% of severe complications (Clavien-Dindo grade 3 or

higher) [40]. This finding highlights the importance of performing local treatment modalities in that anatomical region with caution.

Although the causal relationship between hybrid treatment and thrombosis is unlikely due to the long-time interval between hybrid treatment and thrombosis, we recommend that future studies explore the precise role of ECT as a potential risk factor in the development of the portal vein thrombosis or visceral vessel thrombosis in general.

Considering the unfavourable prognosis associated with pancreatic cancer due to the relatively high incidence of local recurrence or distant metastasis following surgical treatment, additional treatment of the posterior resection surface is reasonable. However, the anatomical position of the pancreatic head among important blood vessels demands local treatment modalities that preserve the vessel wall and do not cause damage to the intima leading to thrombosis. Accordingly, we used plate electrodes because major blood vessels (portal vein and inferior vena cava) represent most of the posterior resection surface area. Puncturing these blood vessels with needle electrodes could have led to serious complications such as bleeding or vasospasm. In addition, we used bleomycin as a chemotherapeutic drug because its effectiveness has been confirmed in clinical and preclinical studies [1,41]. We recognise several limitations in our study. First, although the feasibility and safety of the treatment have been demonstrated, the sample size of 7 patients is insufficient to draw firm conclusions on efficacy. To ascertain the efficacy of hybrid treatment, a longer duration of follow-up and a larger patient population are required. Furthermore, although there are several landmarks for standardising the treated posterior resection area, the size of the area varies and therefore requires different pulse applications. The number of applied pulses was also affected by the anatomical vessel variation in the patients.

## 5. Conclusion

Current evidence suggests that ECT of pancreatic cancer is foremost a palliative option offering mostly pain relief. A pilot prospective study was conducted to assess the feasibility, safety, and efficacy of intraoperative ECT of the posterior resection surface after pancreaticoduodenectomy as a hybrid treatment strategy in PDAC of the pancreatic head. ECT was performed with bleomycin and plate electrodes were used to deliver electric pulses. Our preliminary results demonstrate the safety and feasibility of this approach. However, additional patients and a longer follow-ups period are necessary to validate efficacy. To our knowledge, hybrid treatment with additional intraoperative ECT following surgical resection was used for the first time.

Disease progression was evident in 3 out of 7 (43%) patients, who further showed features of portal vein thrombosis after hospital discharge. However, a causal relationship between hybrid treatment and thrombosis is doubtful due to the considerable time interval between the treatment and the development of thrombosis. Future studies may nonetheless investigate the exact role of ECT as a risk factor for thrombosis.

Pancreatic cancer continues to be among the most lethal forms of cancer, and further research is needed to improve early detection and radical treatment. At present, surgical resection remains the only curative treatment option, but the associated high percentage of disease recurrence adversely impacts survival outcomes. Therefore, a hybrid approach combining surgery with intraoperative electrochemotherapy is safe and feasible and might improve the oncological outcomes of this challenging disease.

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## 7. Institutional Review Board Statement

The ethical approval was obtained the National Medical Ethics Committee of the Republic of Slovenia (0120-174/2019/8; 16 July 2019).

## 8. Informed Consent Statement

All subjects participating in the study provided informed consent prior to their involvement.

## CRedit authorship contribution statement

**Žan Čebren:** Conceptualization, Methodology, Investigation, Formal analysis, Writing – original draft. **Mihajlo Djokić:** Conceptualization, Investigation, Writing – original draft. **Miha Petrič:** Investigation, Writing – original draft. **Maja Čemažar:** Methodology, Conceptualization, Writing – review & editing. **Maša Bošnjak:** Investigation, Writing – original draft. **Gregor Serša:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Blaž Trovšek:** Conceptualization, Methodology, Investigation, Writing – review & editing.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Data availability

Data will be made available on request.

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