Endoscopic Ultrasound-guided Radiofrequency Ablation for Pancreatic Adenocarcinoma

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Short Report

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Abstract

INTRODUCTION

Emerging data suggests neoadjuvant chemotherapy for resectable pancreatic ductal adenocarcinoma (PDAC) is associated with improved survival. However, less than 40% demonstrate a meaningful radiographic response to NAC. Endoscopic ultrasound-guided radiofrequency ablation (EUS-RFA) has emerged as a new modality to treat PDAC. We hypothesize that NAC plus EUS-RFA can be used in the management of resectable PDAC.

METHODS

Prospective review of PDAC patients meeting criteria of resectable tumor anatomy that underwent NAC chemotherapy plus EUS-RFA followed by pancreatic resection. Radiographic imaging, perioperative and short-term outcomes were recorded. Surgical pathology specimens were analyzed for treatment response.

RESULTS

Three eligible patients with resectable PDAC received 4 months of neoadjuvant chemotherapy plus EUS-RFA. One month after completion of neoadjuvant treatment, all 3 patients underwent standard pancreaticoduodenectomy without complications. After a 6 week recovery, all patients completed 2 months of post-op adjuvant chemotherapy.

CONCLUSIONS

In our institutional experience, this treatment protocol appears safe. Patients tolerated the combination of chemotherapy and endoscopic radiofrequency ablation. Patients underwent pancreatic resection with uneventful recovery. This novel neoadjuvant approach may provide a more effective alternative to chemotherapy alone.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the 3rd leading cause of cancer mortality in the US [1]. At present, less than 30% of patients are eligible for potentially curative treatment at the time of diagnosis [2]. Thus 70% or more of PDAC patients are only eligible for palliative chemotherapy with an estimated median survival of 12 months [3]. For those with cancers localized to the pancreas without vascular involvement, emerging data suggests neoadjuvant chemotherapy (NAC) is associated with improved outcomes [4]. Yet preoperative therapy has well-documented treatment challenges: (1) less than 40% demonstrate a meaningful radiographic response to NAC and (2) approximately 20% of resectable PDAC patients progress on systemic treatment [5]. Those who progress on NAC often are not surgical candidates. These disappointing statistics highlight the urgent need for better preoperative therapy.

Endoscopic ultrasound-guided radiofrequency ablation (EUS-RFA) has recently emerged as a new modality to treat pancreatic tumors [6, 7]. Initial published experience has been focused upon neuroendocrine tumors and mucinous cysts [8]. This therapy is virtually identical to EUS fine needle aspiration; however, the main difference is insertion of a RFA probe into the target lesion instead of biopsy needle [9]. Using this novel technique, focused RFA energy is applied to the pancreatic lesion resulting in thermal necrosis [6]. The result of EUS-RFA upon PDAC may include: (1) direct treatment or necrosis, (2) parenchymal disruption leading to improved penetration of chemotherapy and (3) systemic release of PDAC fragments which may induce a host immune response [10]. Any or all these mechanisms may potentiate the treatment effect of systemic NAC. We hypothesize that NAC plus EUS-RFA can be used in the management of resectable PDAC.

Methods

Institutional review of prospective EUS cohort study (HSC-MS-18-0192). All procedure performed in human subjects were in accordance with the ethical standards of the UTHealth Houston Committee for the Protection of Human Subjects and with the 1961 Helsinki Declaration. Inclusion criteria were: histologically proven PDAC, resectable status based upon radiology review, ECOG performance status, endobiliary stent placement. Using National Comprehensive Cancer Network Criteria resectable status was defined as: (1) no evidence of metastatic disease, (2) no involvement of superior mesenteric artery (SMA), superior mesenteric vein (SMV) or portal vein (PV), common hepatic artery (CHA), and (3) patent SMV/PV confluence. Eligible patients were treated with modified FOLFIRINOX: Oxaliplatin 85 mg/m2 IV over 2 hours, Leucovorin 400 mg/m2 IV over 2 hours, Irinotecan 150 mg/m2 IV over 90 minutes, Fluorouracil 2,400 mg/m2 IV continuous infusion (CI) over 46 hours beginning on Day 1 (repeat this cycle every 14 days) or Gemcitabine Nab-Paclitaxel +/- Cisplatin (GemAbraxane): Gemcitabine 500-1000mg/m2 over 30minutes, Nab-Paclitaxel 125mg/m2 over 30 minutes weekly, 3 weeks on and one week off (Day 1, 8, 15 every 28 days).

After 1 month of chemotherapy, patients underwent EUS RFA (Fig. 1). Using EUS guidance, we performed transduodenal/transgastric electrode needle probe (TaeWoong Medical) placement into the PDAC. Color Doppler scanning was performed to avoid adjacent blood vessels. RFA was performed up to measured electrical resistance of 200 Ohm or rapid change in Ohms. Treatment was confirmed by noting liquefaction with real-time EUS. A total of 2 or 3 EUS-RFA sessions were performed at month 2, 3 and 4 of the neoadjuvant regimens decided upon by completeness of RFA as deemed by interventional gastroenterologist. Four weeks after NAC completion, patients underwent standard pancreaticoduodenectomy (PD). Per prespecified protocol, patients were also administered 2 months of adjuvant chemotherapy to be started within 8 weeks of PD resection. Standard demographics and perioperative variables were recorded. Pre- and post RFA axial imaging was compared using standard RECIST criteria [11].

The Abcam Trichrome Stain (ab150686) kit was used for connective tissue staining. Bouin's Fluid was preheated to 60^{o} C and section was incubated for 60 minutes. Section was then stained with Weigert's

Iron Hematoxylin, Biebrich Scarlet, Phosphomolybdic Acid, Aniline Blue Solution, and Acetic Acid Solution. For the Hematoxylin and Eosin stain, the section was incubated with Modified Harris Hematoxylin Stain (Cardinal Health S7439-33), Richard-Allen Scientific Signature Series Clarifier (Thermo Scientific 22-050-117), Scott's Bluing Reagent (Polysciences 24605-1), and Eosin-Y stain (Cardinal Health S7439-24). Sections were mounted with Cytoseal XYL (Epredia 8312-4). The Aperio LV1 (Leica) scanner was used for composite images.

Results

A total of 3 patients successfully completed preoperative chemotherapy and EUS-RFA sessions (Table 1). Clinical demographics of the 3 patients are listed in table #1. All patients were deemed to have resectable PDAC (clinical stage II) as tumor size noted to be > 2.0 cm on axial imaging. All started on NAC initially with modified FOLFIRINOX for 2 months followed by Gemcitabine/Abraxane for the remainder of systemic treatment. One month after NAC initiation, patients underwent EUS-RFA of the pancreatic head cancer. In each case, real time EUS was performed to observe liquefaction (Fig. 2a) and thermal necrosis (Fig. 2b).

Table 1
Patient Demographics

	Patient #1	Patient #2	Patient #3
Age	62	69	67
Gender	M	M	F
Race	Caucasian	Caucasian	African-American
BMI	28.0	30.5	28.0
Comorbidity			
Diabetes	Yes	No	No
HTN	No	Yes	Yes
BPH	No	Yes	No
Hyperlipidemia	No	Yes	No
Hypothyroid	Yes	No	No
Chronic Pancreatitis	Yes	No	No
Pre-Treat Tumor Size (cm)	3.0	3.2	2.7
CA19-9	21	< 3	1987
Chemotherapy Doses	MFOLFIRINOX (6)	MFOLFIRINOX (7)	MFOLFIRINOX (4)
	Gem/nab-P (5)	Gem/nab-P (3)	Gem/nab-P (11)
Post-Treatment Tumor Size (cm)	2.7	2.7	2.4
Pathology			
Residual tumor (cm)	0.40	< 1.0	< 1.0
	Minimal response (3)	Near complete response (1)	Near complete response
Perineural invasion	No	No	Yes
LVI	No	No	No
Lymph nodes resected	29	20	32
Lymph nodes involved	0	0	0

Patient #1 experienced a grade III adverse event secondary to unplanned hospital admission for fever, sepsis and abdominal pain between week 1 and 2 of the second Gemcitabine/Abraxane cycle. This hospital admission was prior to the first EUS-RFA treatment and responded to intravenous fluids, bowel

rest and antibiotics. Patient #1 went on to complete all planned preoperative treatment without additional adverse events. Patient #2 and #3 tolerated all therapy without any adverse events or complications.

Final preoperative imaging in these patients demonstrated radiographic evidence of tumor reduction. Following EUS-RFA treatment, the radiographic characteristics of the PDAC demonstrated a more homogeneous appearance with evidence of necrosis and early cyst cavity formation (Fig. 3). The borders of the pancreatic head masses appeared more distinct following the RFA treatment. Using standard RECIST criteria, a partial radiographic response of at least 30% decrease in tumor size was not observed.

After 4 months NAC, patients had 4-week treatment break followed by surgery. All patients underwent standard pancreaticoduodenectomy without complications and discharged to home. The average length of stay was 6 days and there were no unplanned readmissions or ER visits. Pathology demonstrated margin negative (R0) resection in all cases. In each case, there was no pathologic involvement of lymph nodes. At a median postoperative follow-up of 13 months, all patients remain free of recurrent disease.

On the surgical pathology, the primary tumor specimens demonstrated significant treatment effect. On sectioning the lesions were largely fibrotic and necrotic. Hematoxylin and Eosin composite low magnification image of post resection ablation site demonstrated small residual foci of tumor cells and normal pancreas (Fig. 4). The ablation site lacked any discernable tumor cells as evidenced by a lack of staining for pankeratin (Fig. 4i) or S100P (Fig. 4ii) expressing cells in the region. In contrast, in the area with tumor cells, expression of both pankeratin and S100P was present (Fig. 4i, Fig. 4ii). Masson's trichrome staining was used to evaluate stromal composition in the resected specimen (Fig. 5). The ablation site consisted of dense collagen 1 staining (blue) with limited evidence of myofibroblasts and no evidence of epithelial cells (Fig. 5iii). Extensive blood cells and vascularization was evident adjacent to the ablation site. In contrast, stroma in the foci of tumor region (Fig. 5iv) contained elongated red smooth muscle staining intercalated in collagen indicating myofibroblast differentiation in this area.

Conclusion

Herein we describe a novel treatment protocol for resectable PDAC with the use of NAC + EUS-RFA. To the best of our knowledge, this is the first literature report of pancreaticoduodenectomy following NAC plus EUS-RFA for patients with resectable PDAC. The primary goal of this initial experience was to determine the safety and feasibility of this treatment protocol. Although EUS-RFA in the treatment of PDAC is not currently standard of care, this RFA therapeutic modality is FDA-approved for solid tumors. All patients were enrolled in a prospective cohort study and understood the experimental design. We also sought to determine if this therapy would impact the complex nature of pancreatic resection, specifically pancreaticoduodenectomy. According to current published reports, resection rate following NAC is 70–90% as some PDAC patients are found to be unresectable at the time of surgery [12]. In these three cases, there was no appreciable scarring or fibrosis from the RFA that prevented, negatively influenced or potential prevented the standard pancreaticoduodenectomy (Whipple operation).

Chemotherapy in combination with surgery for PDAC is tolerated; however, both modified FOLFIRNOX and Gem/nab-P have noted toxicities and adverse events [13]. In this report, patients tolerated 4 months of NAC plus EUS-RFA. Following the RFA treatment, there were no adverse events specific to the ablation observed. The protocol was designed to provide at least 1 month of NAC before the first EUS-RFA. This was done to ensure some component of systemic treatment in the event there was a complication following RFA. After the 1st, 2nd and 3rd months of NAC, patients underwent RFA treatments. This was followed by a final month of chemotherapy and then a 4-week break before surgery. All 3 patients underwent successful pancreaticoduodenectomy without evidence of anastomotic leak or delayed gastric emptying complications that are frequent with this procedure. Thus, in this limited initial experience, NAC + EUS-RFA is both feasible and well-tolerated. It is unclear if EUS-RFA is superior or equivalent to radiotherapy in the treatment of PDAC. The role of neoadjuvant radiation has not been well established as available data does not demonstrate improving resection rates or overall survival [14]. The recent PREOPANC trial compared neoadjuvant chemoradiation to upfront surgery for resectable and borderline resectable PDAC [15]. This trial showed benefit to neoadjuvant chemoradiation; however, the treatment effect was only 1.4 months improved overall survival. The current European PREOPANC2 trial comparing neoadjuvant chemoradiation (gem/nab-P) to total neoadjuvant chemotherapy (mFOLFIRINOX) is open and accruing patients [16].

In this experience, all patients appeared to have a meaningful pathologic response as residual tumor was less than 1 cm. This may be a significant benefit of this treatment as standard NAC response rates are quoted to be less than 35% seen in the PRODIGE and SWOG-1505 trials [12]. In two of the three patients the final preoperative CT scan demonstrated a more organized, homogenous mass consistent with necrosis. Standard hematoxylin and eosin staining demonstrated areas of fibrosis in the pathology specimens. In addition, there appeared to be a concentrated areas of endothelial proliferation at the periphery of the ablation zone. These areas of vascular proliferation may enhance chemotherapy penetration into the PDAC. In addition, thermal necrosis and tumor disruption may release PDAC immunogenic material. Thus, treatment of the primary tumor may impact other distant sites of metastasis, the so-called “abscopal effect.” This phenomenon may provide an additional systemic immunotherapy against the PDAC. Future studies are needed to confirm these hypotheses.

At this point, it is too early to determine if this novel protocol may be associated with any significant harm or benefit. The initial peri-operative recovery was normal in this small group. There was no evidence of vascular thrombosis or injury of the superior mesenteric/portal vein confluence, superior mesenteric artery or common hepatic artery from the RFA. A recent report of a phase-II randomized trial of EUS-RFA for PDAC demonstrated a similar safety profile [17]. This trial included both borderline resectable or locally-advanced PDAC and was eventually closed as the RFA probe was no longer produced. Unfortunately, subject accrual was slow and did not meet prespecified criteria. The patients that did receive chemotherapy + EUS-RFA demonstrated a higher response rate; however, there was no difference in the outcomes measure. In our institutional experience, outcome data is not mature and it is unknown if this treatment will improve upon long-term survival. The median survival following standard NAC in the recent SWOG 1505 demonstrated at only 24 months [12]. This quoted statistic for resectable PDAC as

well as known survival rates for the past several decades highlight the need for better systemic treatments. The encouraging radiographic and pathologic responses suggest this protocol requires further study.

This initial experience of neoadjuvant chemotherapy plus EUS-RFA appears promising. These results have led to the design of the PANcreatic CAncer RaDiofrequency AbLation-1 trial (PANCARDINAL-1) clinicaltrials.gov (NCT04990609). This is a single-arm phase II trial designed to further test the safety and feasibility of this protocol and is currently recruiting and enrolling patients. This new EUS-RFA therapy may provide another modality of PDAC treatment. At this time, EUS-RFA is not standard of care and use should be limited to the context of a clinical trial. Currently there are many unknowns for pancreatic radiofrequency ablation. It will take several years to determine if this is truly an effective therapy. The optimal timing and number of ablation sessions needed to maximize treatment effect. This report provides initial details of this EUS-RFA protocol and future studies will determine this role.

Declarations

Disclosures:

Dr. Nirav Thosani has received a grant from Emcision, royalties from UpToDate, consulting fees from Boston Scientific and Pentax America, and honorarium from Abbvie.

Dr. Putao Cen has received honorarium from Eisai, Pfizer and Taohi, she also is on the advisory board for Seagen.

Drs. Rowe, Faraoni, Bailey-Lundberg, and Wray have no conflicts of interest or financial ties to disclose.

Author Contributions

All authors contributed to the study conception and design. The first draft of the manuscript was written by Curtis Wray and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

CW- manuscript draft and revision

PC- study design and manuscript revision

EF- H&E stain and immunohistochemistry, manuscript revision and interpretation

BB- H&E stain and immunohistochemistry

JR- manuscript draft and revision

JB – data analysis and interpretation

NT- study design and manuscript revision

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Figures

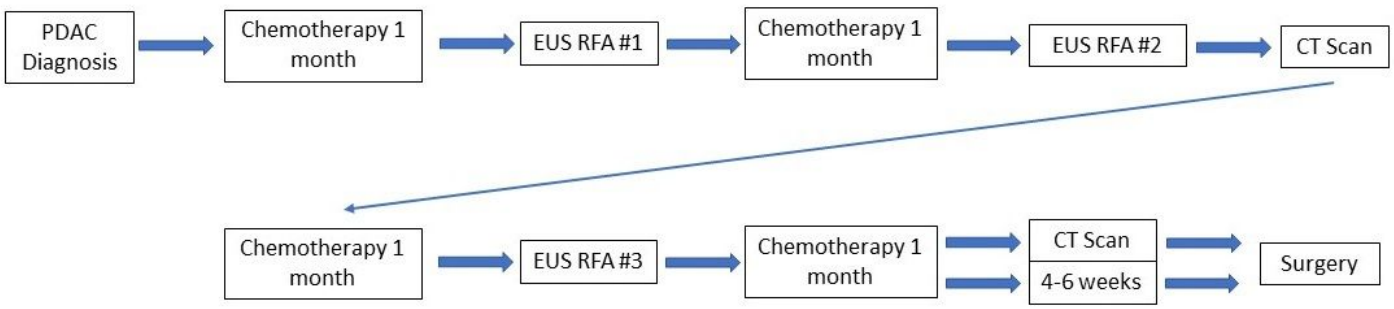

Figure 1

Schematic of treatment protocol

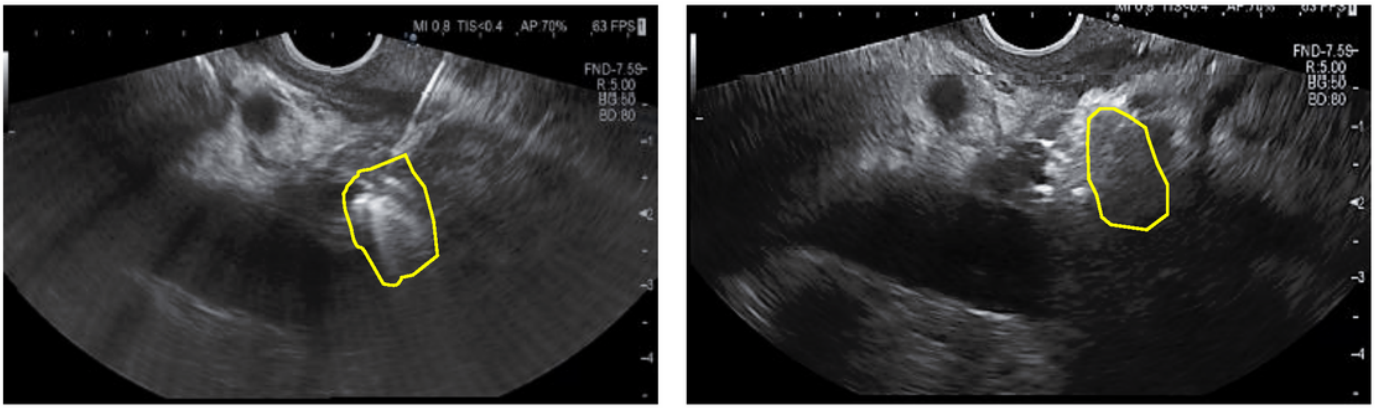

Figure 2

Ultrasound images of pancreatic lesion during and after endoscopic ablation

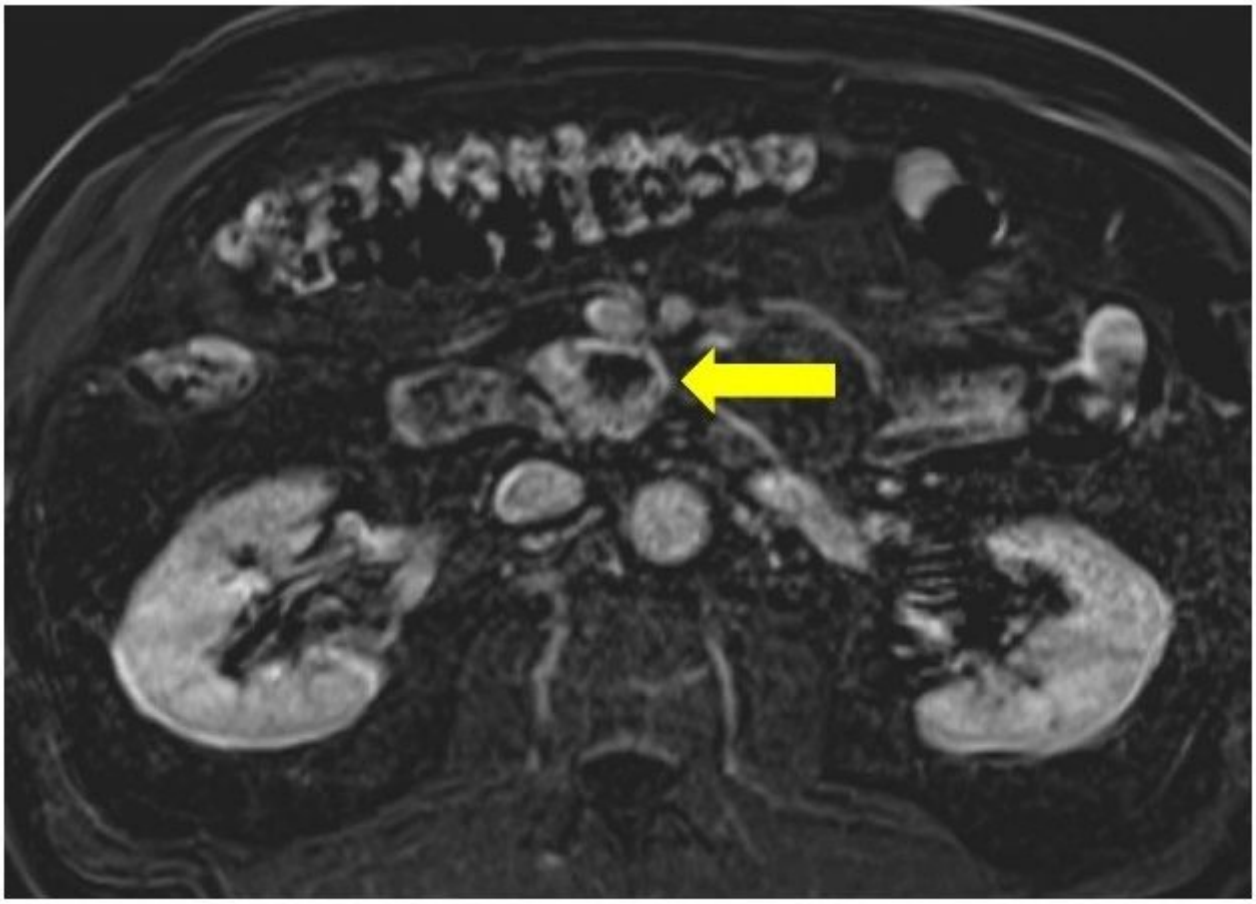

Figure 3

Axial magnetic resonance image of pancreatic ductal adenocarcinoma following endoscopic radiofrequency ablation

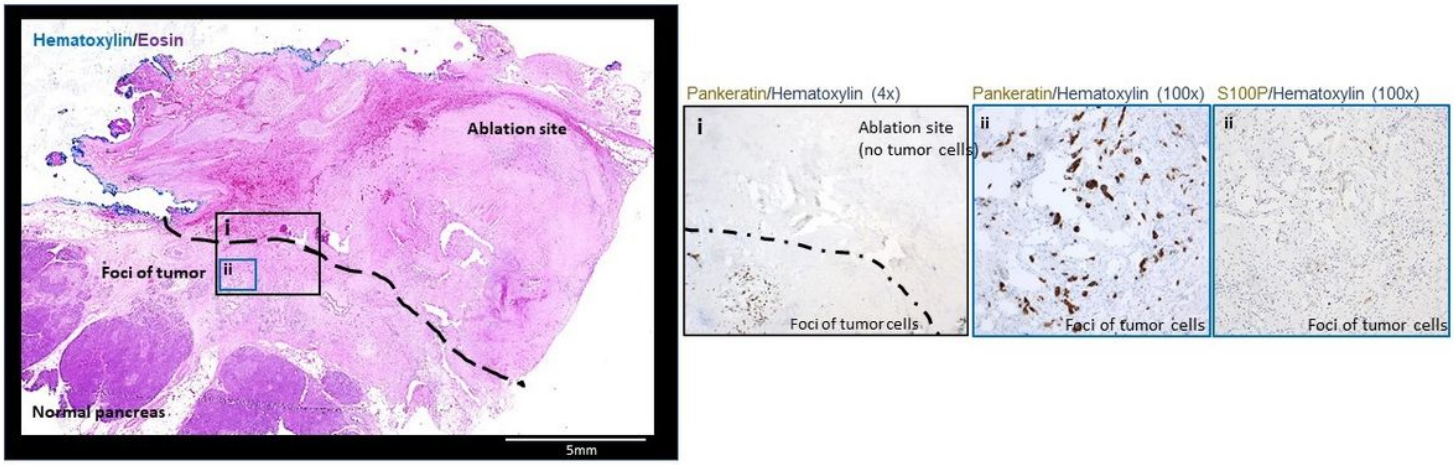

Figure 4

Surgical pathology section of pancreatic adenocarcinoma. Hematoxylin and eosin, pankeratin and S100P stain and immunohistochemistry.

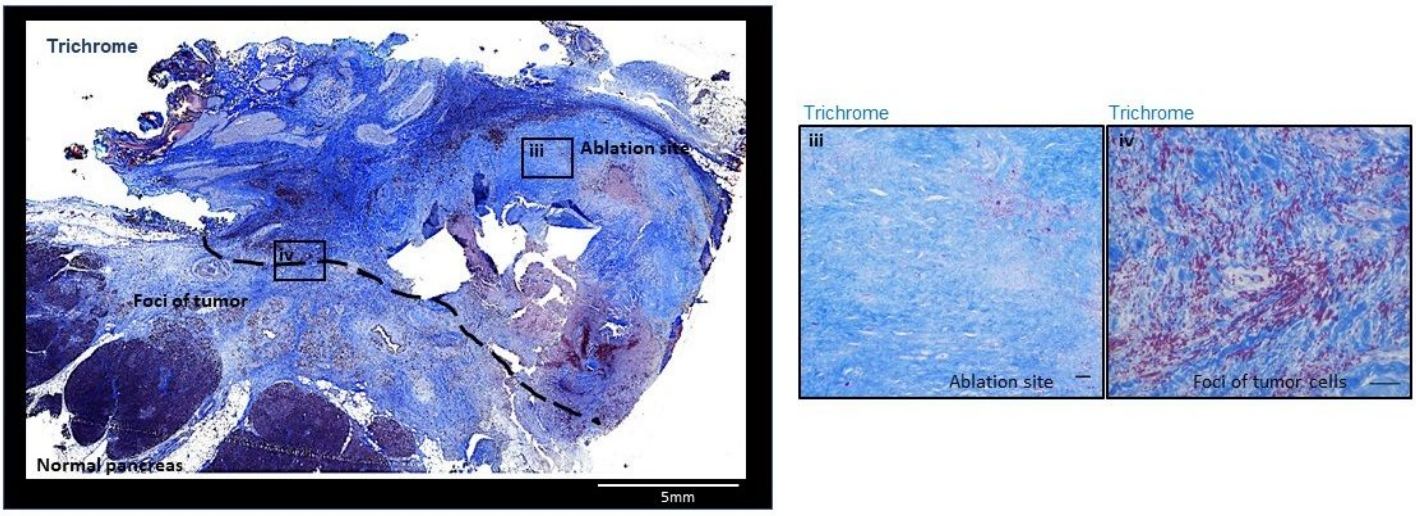

Figure 5

Surgical pathology section of pancreatic adenocarcinoma. Masson's trichrome stain.