

ORIGINAL ARTICLE

Added value of intra-operative ultrasound to determine the resectability of locally advanced pancreatic cancer following FOLFIRINOX chemotherapy (IMAGE): a prospective multicenter study

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Abstract

Background: Determining the resectability of locally advanced pancreatic cancer (LAPC) after FOLFIRINOX chemotherapy is challenging because CT-scans cannot reliably assess vascular involvement. This study evaluates the added value of intra-operative ultrasound (IOUS) in LAPC following FOLFIRINOX induction chemotherapy.

Methods: Prospective multicenter study in patients with LAPC who underwent explorative laparotomy with IOUS after FOLFIRINOX chemotherapy. Resectability was defined according to the National Comprehensive Cancer Network guidelines. IOUS findings were compared with preoperative CT-scans and pathology results.

Results: CT-staging in 38 patients with LAPC after FOLFIRINOX chemotherapy defined 22 patients LAPC, 15 borderline resectable and one resectable. IOUS defined 19 patients LAPC, 13 borderline resectable and six resectable. In 12/38 patients, IOUS changed the resectability status including five patients from borderline resectable to resectable and five patients from LAPC to borderline resectable. Two patients were upstaged from borderline resectable to LAPC. Tumor diameters were significantly smaller upon IOUS (31.7 ± 9.5 mm versus 37.1 ± 10.0 mm, $p = 0.001$) and resectability varied significantly ($p = 0.043$). Ultimately, 20 patients underwent resection of whom 14 were evaluated as (borderline) resectable on CT-scan, and 17 on IOUS.

Discussion: This prospective study demonstrates that IOUS may change the resectability status up to a third of patients with LAPC following FOLFIRINOX chemotherapy.

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Introduction

Pancreatic cancer is notorious for its limited treatment options and poor survival.¹ Surgical resection combined with (neo-) adjuvant chemotherapy offers the best chance of long-term survival.² This combination is, however, only feasible in approximately 10% of patients, as 60% of patients present with metastatic disease, 30% with locally advanced, unresectable pancreatic cancer (LAPC) and half of patients do not receive adjuvant chemotherapy after resection.^{3,4}

In LAPC, an upfront radical (R0) resection is not possible due to extensive perivascular tumor infiltration.² Recent studies demonstrate that in 25–30% of patients with LAPC treated with FOLFIRINOX chemotherapy (a combination of 5-fluorouracil, oxaliplatin, leucovorin and irinotecan), the tumor can be downstaged to (borderline) resectable disease.⁵ Response evaluation following FOLFIRINOX is, however, difficult as computed tomography (CT) imaging cannot reliably differentiate viable tumor infiltration from post-chemotherapeutic desmoplastic reaction.^{6,7} This is currently one of the major challenges in the treatment of LAPC. As a result of this low diagnostic accuracy, some experts now advocate routine surgical exploration in all patients with LAPC with radiological non-progressive disease following FOLFIRINOX.^{7,8}

During surgical exploration, however, it is often still difficult to determine resectability. Multiple biopsies are typically sent for frozen section to support this process, but this is very time consuming as it requires extensive dissection and may increase morbidity. Therefore there is a need for diagnostic tools that can accurately determine the extent of vascular tumor infiltration during explorative surgery.

Due to its high spatial resolution, intra-operative ultrasound (IOUS) might be of additional value when defining vascular involvement and has previously been used for other tumors to determine resectability during surgical exploration with promising results.⁹ The aim of this study was to compare the outcomes of IOUS, with preoperative CT scan and surgical exploration in patients with LAPC who were treated with induction FOLFIRINOX chemotherapy.

Methods

This study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.¹⁰

The IMAGE study included patients in whom upfront radical resection was considered not feasible and who had received FOLFIRINOX induction chemotherapy, followed by exploratory laparotomy in five centers of the Dutch Pancreatic Cancer Group (DPCG) between April 2016 and January 2018. At the start of surgical exploration, prior to any dissection, IOUS was performed by an experienced interventional radiologist.

Post-FOLFIRINOX resectability was defined according to the National Comprehensive Cancer Network (NCCN) guidelines.¹¹ Resectable disease was defined as the absence of arterial tumor contact (of the celiac trunk, superior mesenteric artery or hepatic artery) and tumor contact with the superior mesenteric vein or portal vein $\leq 180^\circ$ without contour irregularity. Borderline resectable disease was defined as a maximum of 180° of arterial contact and/or unreconstructable venous involvement (of the porto-mesenteric vein).¹¹ LAPC was defined as $>180^\circ$ arterial contact and/or unreconstructable venous involvement. Patients with (borderline) resectable disease after chemotherapy or with LAPC undergoing local ablative treatment requiring laparotomy were considered eligible for surgical exploration with IOUS. Metal stents were not considered a contra-indication for IOUS. Patients with progressive disease after induction chemotherapy, according to the Response Evaluation Criteria In Solid Tumors (RECIST),¹² were excluded from surgical exploration, independently of their resectability status on CT-scan. In case of metastases during surgical exploration, patients were excluded from this study and no further exploration was performed.

All post-FOLFIRINOX CT-scans consisted of a chest and abdominal CT-scan according to a biphasic protocol with a late arterial phase (35–40 s after intravenous contrast injection) and a late portal phase (60–70 s after intravenous contrast injection). CT-scans are performed on a Siemens Sensation 64-slice CT-scanner after injection of 1.5–2.0 ml/kg (with a maximum of 120 ml) Ultravist (Bayer) contrast medium with an injection rate of 3.5 ml/s. Only axial images and coronal and sagittal reconstructions were used for the evaluation of the CT-scans. Tumor characteristics including diameters in three directions, visceral extent, vascular tumor involvement and consequently resectability were scored with predefined scoring forms (Appendix 1), by a centralized expert panel consisting of three experienced abdominal radiologists (with at least 4 years of experience) and an experienced pancreatic surgeon. The radiologists who scored the restaging CT-scans did not perform IOUS in the present study.

In all cases, IOUS was performed with a high frequency 12 MHz linear probe (Esaote, Genua, Italy or Philips Epiq 5, Eindhoven, the Netherlands), directly placed on the surface of the pancreas after laparotomy, or on the stomach if a transgastric approach was preferred by the radiologist. The IOUS procedures of the pancreas were performed by dedicated abdominal radiologists trained for IOUS by a proctor or by the proctor himself. Prior to the present study, the proctor had already performed >40 IOUS procedures of patients with LAPC following induction chemotherapy. Tumor characteristics were assessed using a standardized IOUS protocol with the same scoring form as was used for CT-evaluation to

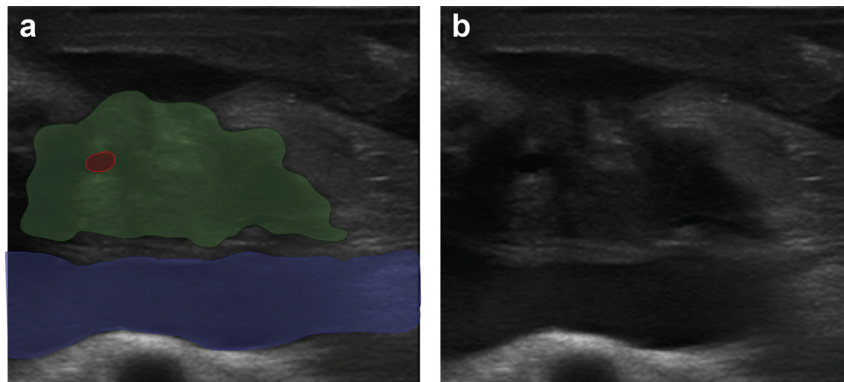


Figure 1 Intra-operative ultrasound in a patient with pancreatic cancer and $>270^\circ$ portal vein involvement on CT scan. IIOUS images to illustrate differentiation between hypo-echoic tumor tissue (green) and hyper-echoic tissue between the portal vein (blue) and tumor (green). Hepatic artery is shown in red. The IIOUS demonstrates that the portal vein has no tumor infiltration

reduce the chance of interpretation bias by the radiologists (Appendix 1).

Typically, tissue with a hypoechoic aspect on IIOUS was scored as tumor tissue, whereas vessel walls and surrounding fat tissue are often hyperechoic due to the reflection of ultrasound waves (Fig. 1). Vascular structures were scored not involved with viable tumor if no interruption of the hyper-echoic vascular wall was observed upon IIOUS. All surgical procedures were performed in high-volume centers (i.e. performing >20 pancreatoduodenectomies annually). Both CT, IIOUS and surgical exploration findings were taken into consideration before deciding to perform a resection. Resected specimens were pathologically assessed for radicality including vascular resection margins. A radical resection margin (R0) was defined as a tumor-free resection margin of at least 1 mm in all directions, according to the Royal College of Pathologists definition.¹³

Statistical analysis

Continuous data are presented as means and standard deviations (SD) in case of a normal distribution, or as medians and interquartile ranges (IQR) in case of a non-normal distribution. Categorical data (binary, ordinal and nominal) are presented as frequencies and percentages. Paired samples T-test was used to compare means. Resectability status was compared between the two modalities using a two-sided McNemar–Bowker test of symmetry. Diagnostic accuracy for resectability could not accurately be determined as the IIOUS findings were used in the decision making process to proceed with a resection. Moreover, a golden reference standard (i.e. pathological proof) was not always available for patients who did not undergo resection. A p -value <0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics for Windows version 24.0 (IBM Corp., Orchard Road Armonk, New York, US).

Results

A total of 38 patients with LAPC were included with a mean age of 63 ± 8 years. This included 27 tumors of the pancreatic head/uncinate process, nine of the pancreatic body and two of the pancreatic tail. Twenty-three patients were female. Median CA19-9 at diagnosis was 140 U/mL (IQR 40–396). Patients received a median of four cycles (IQR 4-4) of FOLFIRINOX prior to surgical exploration. Because of toxicity, one patient switched to a combination of gemcitabine with nab-paclitaxel after two courses of FOLFIRINOX prior to restaging.

At restaging, 6/38 patients were classified as having a RECIST partial response and 32/38 as having RECIST stable disease. Median CA19-9 decreased to 78 U/mL (IQR 17–135) in 28 patients of whom CA19-9 levels were available pre-and post-chemotherapy. Of these, 18/28 had a decrease in CA19-9 of at least 30%.¹⁴ Based on the pre-operative CT-scan, 22 patients were defined as LAPC, 15 as borderline resectable and one patient as resectable. Median time between CT-restaging (i.e. within 1–2 weeks after the last cycle of chemotherapy) and surgery was four weeks (IQR 3–5).

During explorative laparotomy, IIOUS typically demonstrated smaller tumor diameters (31.7 ± 9.5 mm versus 37.1 ± 10.0 mm, $p = 0.001$) and in most cases also less extensive vascular infiltration compared with the last preoperative CT-scan (Table 1). Upon IIOUS, 19 patients were defined as LAPC, 13 as borderline resectable and six patients as resectable. Consequently, IIOUS changed the resectability status in 12/38 patients. Five patients with borderline resectable disease on CT-scan were deemed primary resectable on IIOUS. Of these patients, two showed less involvement of the superior mesenteric artery (SMA) as well as the porto-mesenteric vein (PMV) when using IIOUS. Two patients demonstrated less involvement of the common hepatic artery (CHA) and the PMV compared to CT-

Table 1 Tumor characteristics upon pre-operative CT and intra-operative ultrasound imaging in 38 patients with locally advanced pancreatic cancer

	CT (n = 38)	IOUS (n = 38)
Size in mm, mean (sd)	37 (10)	32 (9)
Arterial involvement, no.		
Celiac Trunk		
No contact	32	32
1–180°	1	2
>180°	5	4
Hepatic Artery		
No contact	21	29
1–180°	11	4
>180°	6	5
Superior Mesenteric Artery ^a		
No contact	11	21
1–180°	15	8
>180°	11	8
Venous involvement, no.		
Porto-Mesenteric Vein		
No contact	2	8
1–180°	26	20
>180°	10	10

sd: standard deviation; mm: millimetre; IOUS: intra-operative ultrasound; CT: computed-tomography imaging.

^a From one patient the degrees of SMA contact could not be evaluated.

scan and one patient showed limited involvement of the SMA and CHA. Five patients with LAPC on CT-scan were deemed borderline resectable on IOUS due to less involvement of the CHA and PMV in two cases, the SMA and CHA in one case, less involvement of the PMV in one case and less extensive

Table 2 NCCN resectability status according to the pre-operative CT-scan and intra-operative ultrasound

CT-staging		IOUS-staging			Total
		Resectable	Borderline	LAPC	
CT-staging	Resectable	1	0	0	1
	Borderline	5	8	2	15
	LAPC	0	5	17	22
Total		6	13	19	38

IOUS: intra-operative ultrasound; CT: computed-tomography imaging; LAPC: locally advanced pancreatic cancer. The bold numbers indicate the patients in which a difference was seen between CT and ultrasound. Resectability status varied significantly between the two modalities ($p = 0.043$).

involvement of arterial jejunal branches of the SMA in the last case. Two patients with borderline resectable disease on CT-scan had LAPC according to IOUS (Table 2). The patients who were evaluated as LAPC upon IOUS (and borderline resectable on CT-scan) demonstrated more extensive involvement of a collateral connecting the superior mesenteric artery with the hepatic artery in one case and more extensive involvement of the common hepatic artery in the second case. The first patient did not undergo resection after frozen sections demonstrated vital tumor tissue surrounding the collateral feeding the hepatic artery. The second patient did undergo resection (total pancreatectomy), after frozen sections demonstrated no vital tumor tissue surrounding the common hepatic artery. Upon statistical analysis, resectability status was scored significantly different between the two modalities ($p = 0.043$). An example of the discrepancy between CT-scan and IOUS is shown in Fig. 2.

Twenty patients finally underwent resection and 18 patients had unresectable disease during exploration. An R0-resection was achieved in 8/20 patients. Of the 20 resections, 14 were judged as (borderline) resectable on CT-scan, and 17 as (borderline) resectable on IOUS. Two patients underwent resection despite being diagnosed as NCCN LAPC upon CT-scan and IOUS. Both patients had tumor infiltration of the first jejunal branches of the superior mesenteric vein. However, it was considered borderline resectable by the surgeon, and a resection was performed. For the remaining patient that was upstaged from borderline resectable on CT-scan to unresectable on IOUS, a resection was proceeded after frozen section investigation showed no evidence for vital adenocarcinoma around the hepatic artery (i.e. desmoplastic reaction). Of the eight patients with an R0 resection, five were evaluated as (borderline) resectable on CT-scan and seven as (borderline) resectable on IOUS (Table 3).

Discussion

It is well known that CT-scans cannot accurately determine the extent of vascular involvement of pancreatic cancer after FOLFIRINOX treatment. This first prospective multicenter study shows that IOUS may be helpful during surgical exploration of LAPC after FOLFIRINOX chemotherapy as it changed the resectability status based on CT-scan in approximately one-third of the patients.

Previous studies have suggested that IOUS can accurately determine the vascular involvement in chemo-naïve patients with pancreatic cancer, with a sensitivity and specificity of 92% and 93% respectively.¹⁵ Until now, no studies investigated the diagnostic accuracy of IOUS in patients after neoadjuvant chemotherapy. This may especially be relevant in patients treated with FOLFIRINOX, since previous studies have shown that CT-scan is not accurate enough in this setting.^{7,16} A major downside of IOUS is that it requires

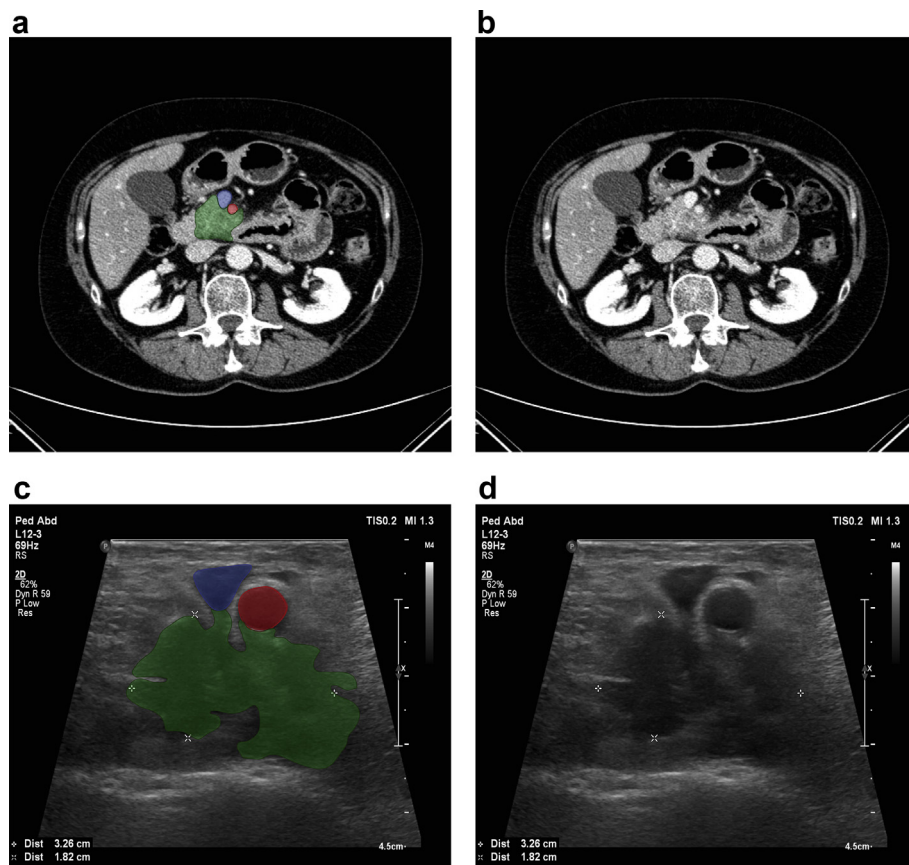


Figure 2 Pre-operative CT-scan and IOUS in a patient with pancreatic cancer after 4 cycles of FOLFIRINOX. (a, b) Upon CT-scan, 90–180° tumor infiltration (green) was seen around the superior mesenteric vein (blue) and 180–270° contact with the superior mesenteric artery (red), rendering this patient unresectable. (c, d) Upon IOUS less tumor infiltration was seen: <90° (green) around the superior mesenteric vein (blue) and 90–180° with the superior mesenteric artery (red), rendering this patient borderline resectable

exploratory laparotomy and hence does not contribute to the selection procedure in advance of the surgical exploration, it may provide valuable information to facilitate the decision to proceed with a resection intra-operatively. During surgical exploration, surgeons highly valued the additional real-time information on vascular tumor involvement as more focus could be applied to the most endangered resection margins. This facilitates both the targeted sampling of tissue for frozen section, and the decision to proceed with exploration and can therefore avoid unnecessary dissection and associated morbidity.

The RECIST-criteria are often used to describe tumor response following induction chemotherapy and are used together with the vascular involvement to select patients for surgical exploration.¹² However, a partial response according to RECIST in pancreatic cancer after FOLFIRINOX is difficult to objectify with CT. This may lead to missed opportunities to resect. Previous prospective series showed only a 40% sensitivity of a CT-based RECIST partial response for

Table 3 Resectability on IOUS and CT-scan versus surgical radicality

		Resectability on CT-scan		Total
		Non-resectable	(borderline) Resectable	
Underwent resection?	No	16	2	18
	Yes, R0	3	5	8
	Yes, R1	3	9	12
Total		22	16	38
		Resectability on IOUS		Total
		Non-resectable	(borderline) Resectable	
Underwent resection?	No	16	2	18
	Yes, R0	1	7	8
	Yes, R1	2	10	12
Total		19	19	38

IOUS: intra-operative ultrasound; CT: computed-tomography imaging; R0: radical resection; R1: irradical resection.

resectability in patients with LAPC following induction chemotherapy¹⁴ and no correlation with tumor size decrease with R0 resection.⁶ In addition, vascular involvement and thus resectability is not accurately measured by CT-scan after FOLFIRINOX therapy.⁷ As was also demonstrated in the present study, only six patients showed a partial response on CT, with 1/6 patients being classified as resectable and 2/6 as borderline resectable. Nevertheless, 20 patients ultimately underwent a resection, demonstrating the low sensitivity of CT-scans for resectability of LAPC after FOLFIRINOX. As neoadjuvant treatment is increasingly administered to patients with LAPC, future studies should focus on improving the selection of patients with initial LAPC treated with FOLFIRINOX for surgical exploration. A factor that may be of added value in this setting is regression of tumor-vessel contact as described by Cassinotto et al.⁶ This prospective study found a decrease in tumor-vessel contact to be a reliable predictor of resectability after chemo-radiotherapy in patients with LAPC irrespective of the tumor diameter or the degree of residual vascular involvement. These results seem promising and ought to be validated in a cohort of patients with LAPC treated with FOLFIRINOX chemotherapy.

Another procedure that may contribute to the more accurate selection of patients for surgical exploration is endoscopic ultrasound (EUS). Previous studies have suggested that EUS can more accurately determine vascular involvement of pancreatic cancer than CT-imaging in chemo-naïve patients.^{17,18} In addition, EUS may allow for targeted tissue sampling through fine-needle aspiration to distinguish between vital tumor and fibrosis. Future studies should assess the diagnostic accuracy of EUS for resectability in patients with LAPC treated with (FOLFIRINOX) induction chemotherapy, in order to reduce the rate of futile surgical explorations in these patients. Besides anatomical factors (i.e. tumor response, vascular involvement), biological criteria may be of great importance in the selection of patients for surgery.¹⁹ Biomarkers such as CA19-9 and plasma microRNAs have been previously described to be useful in selecting patients for surgery after induction chemotherapy and should be used in addition to current imaging modalities.^{14,20,21}

The results of this study should be interpreted in light of several limitations. First, this was a non-blinded study, since the performing radiologist was aware of the outcomes of the restaging CT-scans. This is, however, similar to clinical practice and this study was therefore deliberately not designed as a head-to-head comparison of IOUS with CT. Second, although pathological results from resected patients were available, intra-operative pathological confirmation of the exact IOUS findings (i.e. the differences between IOUS and CT assessment) was not routinely performed when resection was not performed. Therefore diagnostic accuracy tests (e.g.

sensitivity, specificity for resection) could not be performed. Currently the prospective multicenter ULTRAPANC study is pending in the Netherlands, which will assess the diagnostic accuracy of IOUS using standardized scoring methods and pathology as reference standard in patients undergoing explorative laparotomy for pancreatic cancer. Third, five out of 11 patients with a different resectability status after IOUS already had (borderline) resectable disease on CT-scan. The clinical relevance of IOUS in this category of patients can be discussed since these patients may also have undergone a resection without IOUS. Fourth, although IOUS predicted resectability more often than CT-scan, the actual R0 rate was only 40% in the present cohort, demonstrating that radical resections remain challenging in patients with LAPC. Compared with previously published series, this proportion may be low.²² An explanation could be that the patients in the present study only received four cycles of FOLFIRINOX prior to surgery. Although the evidence to support this hypothesis is limited, it might be that eight cycles of FOLFIRINOX and/or adding radiotherapy to the induction scheme further improves the R0-rate in these patients.^{23,24} However, patients undergoing resection after induction chemotherapy may still benefit from an R1 resection.²⁵ Although the R0 rate was only 57% in the cohort study by Vogel et al., median overall survival of the resected patients was still 34 months (versus 15 months for non-resected patients).²⁵ Finally, the delay of several weeks between CT-restaging and exploration may have allowed for tumor progression. However, this bias cannot explain the fact that IOUS mainly down-staged patients to (borderline) resectable disease. Strengths of this study include the prospective study design, the multicenter approach in consecutive patients with initial unresectable disease and the standardized reporting of both CT and IOUS outcomes scored by dedicated abdominal radiologists.

Taking these considerations in account, the current results imply that IOUS is a promising tool to determine resectability and support the process of surgical exploration of LAPC following FOLFIRINOX chemotherapy. Although the exact diagnostic value of IOUS should be established in future, larger studies, the present study shows that IOUS is capable of providing valuable information to the surgeon, changing the resectability status in a third of patients.

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Conflicts of interest

MG Besselink, OR Busch and HW van Laarhoven received a grant (no. 2013-5842) from the Dutch Cancer Society (KWF Kankerbestrijding) for studies on pancreatic cancer. For the remaining authors none were declared.

Appendix 1 CT-imaging and intra-operative ultrasound evaluation form

Tumor visible ?	No Yes	
Tumor localization		1 Head of pancreas/uncinate process 2 Body of pancreas 3 Tail of pancreas
Largest tumor diameter mm	
Peri-pancreatic ingrowth	No Yes:	1 Peripancreatic fat: a Towards superior mesenteric artery b Transverse mesocolon c Mesenteric root d Towards caval vein/aorta e Cranially towards celiac trunk f Dorsally of pancreatic body/tail g Other: 2 Duodenum 3 Stomach 4 Hepatoduodenal ligament (i.e. common hepatic duct, hepatic artery, portal vein) 5 Jejunum 6 Colon 7 Left adrenal gland 8 Spleen 9 Other:
Contact with superior mesenteric artery	No Yes, please answer 1-5	1 $\leq 90^\circ$ $90^\circ - \leq 180^\circ$ $180^\circ - \leq 270^\circ$ $>270^\circ$ 2 Deformation: Yes No 3 Lumen reduction: No $\leq 50\%$ $> 50\%$ Occlusion 4 Tumor thrombus: Yes No 5 Length contact: mm
Contact with celiac trunk	No Yes, please answer 1-5	1 $\leq 90^\circ$ $90^\circ - \leq 180^\circ$ $180^\circ - \leq 270^\circ$ $>270^\circ$ 2 Deformation: Yes No 3 Lumen reduction: No $\leq 50\%$ $> 50\%$ Occlusion 4 Tumor thrombus: Yes No 5 Length contact: mm
Contact with hepatic artery	No Yes, please answer 1-5	1 $\leq 90^\circ$ $90^\circ - \leq 180^\circ$ $180^\circ - \leq 270^\circ$ $>270^\circ$ 2 Deformation: Yes No 3 Lumen reduction: No $\leq 50\%$ $> 50\%$ Occlusion 4 Tumor thrombus: Yes No 5 Length contact: mm
Contact with portal/superior mesenteric vein	No Yes, please answer 1-5	1 $\leq 90^\circ$ $90^\circ - \leq 180^\circ$ $180^\circ - \leq 270^\circ$ $>270^\circ$ 2 Deformation: Yes No 3 Lumen reduction: No $\leq 50\%$ $> 50\%$ Occlusion 4 Tumor thrombus: Yes No 5 Length contact: mm
R0/R1 resection possible?	No Yes Doubtful	If no or doubtful, please explain:
Other remarks?	No Yes:	

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