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Mesopancreatic excision for pancreatic ductal adenocarcinoma improves local disease control and survival

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ABSTRACT

Background: Survival in ductal adenocarcinoma of the pancreatic head (hPDAC) is poor. After implementation of the circumferential resection margin (CRM) into standard histopathological evaluation, the margin negative resection rate has drastically dropped. However, the impact of surgical radicality on survival and the influence of malignant infiltration of the mesopancreatic fat remains unclear. At our institution, a standardized dissection of the mesopancreatic lamina and peri-pancreatic vessels are obligatory components of radical pancreatoduodenectomy. The aim of our study was to histopathologically analyze mesopancreatic tumor infiltration and the influence of CRM-evaluated resection margin on relapse-free and overall survival.

Method: Clinicopathological and survival parameters of 264 consecutive patients who underwent surgery for hPDAC were evaluated.

Results: The rate of R0 resection R0(CRM-) was 48.5%, after the implementation of CRM. Mesopancreatic fat infiltration was evident in 78.4% of all consecutively treated patients. Patients with mesopancreatic fat infiltration were prone to lymphatic metastases (N1 and N2) and had a higher rate of positive resection margin (R1/R0(CRM+)). In multivariate analysis, only R0 resection was shown to be an independent prognostic parameter. Local recurrence was diagnosed in only 21.1% and was significantly lower in patients with R0(CRM-) resected hPDACs (10.9%, $p < 0.001$).

Conclusion: Mesopancreatic excision is justified, since mesopancreatic fat invasion was evident in the majority of our patients. It is associated with a significantly improved local tumor control as well as longer relapse-free and overall survival.

Introduction

Kausch et al. first described a regional resection of the pancreatic head in 1909 [1]. This procedure was, however, popularized in 1935 by Allen Oldfather Whipple [2]. Because of a hospital mortality of approximately 25%, the operation was performed infrequently until 1980. Over the last decades, the advent of high-volume centers resulted in a significant decrease in morbidity and hospital mortality and thus allowed surgeons to gather extensive operative experiences. However, despite these advances, the survival outcome for hPDAC patients has not significantly changed over the last decade.

The hPDAC is estimated to become the second leading cause of cancer-related deaths by 2030 [3,4]. Surgical resection remains the only curative therapy. In contrast to most carcinomas, therapeutic advances to increase survival have been slow [5,6]. Poor survival outcome in pancreatic cancer patients is partially explained by late diagnoses and consequently advanced tumor stage. Thus only 20% of all patients are eligible for surgical therapy. Even after an initially curative surgical approach, tumor recurrence is frequently observed in pancreatic cancer patients [7].

Possibly, a more radical surgical approach could contribute to improved long term results in pancreatic cancer patients. Yet, the

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Abbreviations

CHA	common hepatic artery
CI	confidence interval
CRM	circumferential resection margin
FOLFIRINOX	folinic acid, fluororuracil, irinotecan, oxaliplatin
G	gemcitabine
GC	gemcitabine + capecitabine
GDA	gastroduodenal artery
hPDAC	ductal adenocarcinoma of the pancreatic head
HR	hazard ratio
L	lymphatic invasion
LEEPP	Leeds Pathology Protocol
MPE	mesopancreatic excision
OS	overall survival
PALN	para-aortic lymph nodes
PD	pancreatoduodenectomy
Pn	perineural invasion
PRS	Post-relapse survival
PV/SMV	portal/superior mesenteric vein
RFS	relapse free survival
SMA	superior mesenteric artery
UICC	Union for international cancer control
V	venous invasion

correlation between the degree of radical surgery and survival still remains contentious. Heterogeneous studies, lack of standardized pathological reporting systems, as well as frequently altered adjuvant treatment regimens over the past decades may have contributed to this effect [6,8–10]. Furthermore, the degree of radical surgery is difficult to standardize, as it depends on the surgeons' individual understanding.

In an era of standardization and quality management, the evaluation of the circumferential resection margin (CRM), a refined histopathological examination protocol, was implemented in 2004 according to the recommendations of the Royal College of Pathologists (LEEPP) [11,12]. Prior to this the examination of oral/aboral duodenal, bile duct and pancreatic neck resection margin represented the standard The modified pathological protocol also includes the ventral and dorsal pancreatic surfaces, as well as the medial pancreatic margin (i.e. the groove of the superior mesenteric vein and the surface facing the superior mesenteric artery). This technique allows a more detailed assessment of the resected specimen, as all upfront resection margins are taken into account [13,14].

Over the past decades, different surgical approaches in the resection for hPDAC with the goal to maximize safety and local control have been described [15,16]. Whereas some surgeons propagate a minimally invasive procedure, others prefer more radical strategies, such as the extended pancreatic resection [17–20].

In our point of view, the crucial component of the oncological resection of hPDAC is the complete dissection of the mesopancreatic lamina along the major retroperitoneal vessels (MPE: mesopancreatic excision), since this is presumably the most important site of primary tumor involvement and potential area for local recurrence [21].

However, the impact of a standardized extended resection and mesopancreatic fat infiltration on prognosis and margin negative resection rate has not yet been elucidated [15,16,19,22,23]. We herein systematically analyzed the tumor involvement of the mesopancreatic lamina, applying the implemented CRM according to the LEEPP.

Material and method

Patient selection and demographic data

All patients (n = 330) who underwent partial pancreatoduodenectomy for hPDAC with curative intent, irrespective of tumor stage and microscopic resection margin, at the University Hospital of Duesseldorf between 2003 and 2020 were screened for inclusion in this study from a prospectively maintained database. Inclusion criteria were surgically resected ductal adenocarcinomas of the pancreatic head (hPDAC) without neoadjuvant therapy, sufficient information on follow-up examinations and complete histopathology samples for re-evaluation. Patients who underwent surgery for periampullary lesions other than hPDAC or pancreatic tail resection or succumbed to 30-day in-hospital mortality were excluded from the study. Surgically resected UICC IV patients only entered histopathological correlation analysis and were excluded from survival analysis. See Fig. S1 for an overview of included patients. TNM staging, grading, perineural invasion as well as lymphatic and venous invasion were obtained from the original pathological reports. Histopathological slides were re-visited by an experienced pathologist for pancreatic cancer, with focus on mesopancreatic fat invasion and in order to re-evaluate the resection margins. Staging system was updated to the 8th Edition of the UICC TNM classification of malignant tumors [24]. Clinico-pathological data regarding overall survival, relapse free survival, post-relapse survival, age at the time of surgery, gender and results of follow-up examinations, including time of diagnosis of metastases and site of metastases were reviewed. The study was carried out in accordance to the guidelines of Good Clinical Practice and the Declaration of Helsinki. The study was approved by the Institutional Review Board (IRB) of the Medical Faculty, Heinrich Heine University Duesseldorf (IRB-no. 2019–473_2).

Operative procedure

After establishing a clear view of the duodenum and pancreas, a wide Kocher maneuver is performed to complete the mobilization of the pancreatic head displaying the left renal vein. A simultaneous transection of the mesopancreatic lamina followed by a para-aortic and interaortocaval lymphadenectomy to the right border of the superior mesenteric artery (SMA) and the portal vein/superior mesenteric vein (PV/SMV) is performed (Fig. 1A; green line and yellow outlined area). The dissection is then accomplished to the inferior border of the pancreatic neck. Following this, dissection of the hepatoduodenal ligament (left and right hepatic artery, common hepatic artery (CHA), gastroduodenal artery (GDA), common bile duct, and portal/superior mesenteric vein (PV/SMV)) completes surgical exploration. Lymphadenectomy and dissection of the common hepatic artery is performed up to its origin from the celiac trunk (CT). The jejunum, the ligament of Treitz and the duodenal bulb (or distal stomach) can then be transected. The jejunum is then mobilized to the patient's right side. After the pancreatic head is completely separated from the PV/SMV and the SMA, the pancreatic neck is divided. Next, lymphadenectomy and dissection of the portal vein and superior mesenteric vein is completed. If a possible tumor infiltration is present, venous resection and reconstruction is routinely performed. Sharp preparation along the SMA and the CT up to their aortic origins is carried

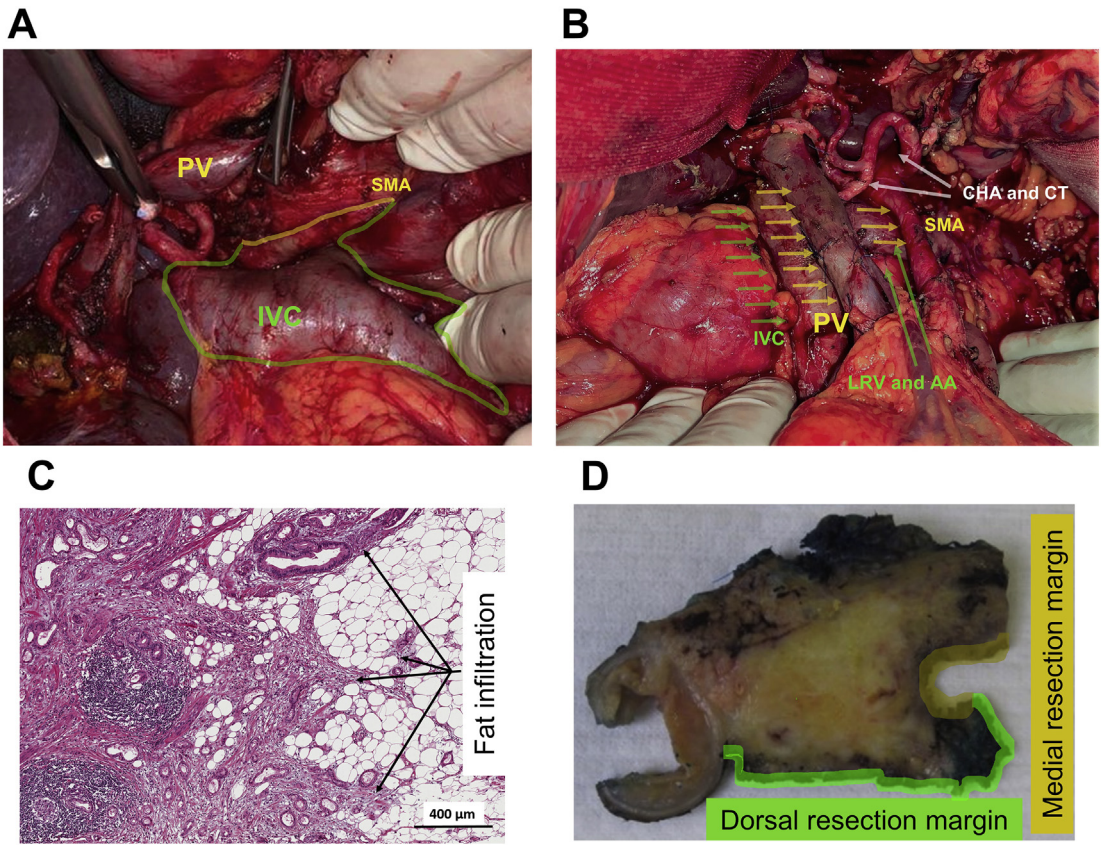


Fig. 1. A. Intraoperative picture demonstrating MPE from patients' right side, note the yellow and green lining during posterior and medial approach for local control of posterior and medial resection margin respectively. **B.** Intraoperative picture demonstrating the surgical site after structured radical partial pancreatoduodenectomy for hPDAC. Complete skeletonization of the SMA is only carried out for 180° of the right circumference. Only in selected cases in which tumor encasement is intraoperatively suspicious, an extended dissection >180° of the SMA is carried out. AA: abdominal aorta; CHA: common hepatic artery; IVC: inferior vena cava; LRV: left renal vein; PV: portal vein; SMA: superior mesenteric artery. Green arrows indicating mesopancreatic excision in the posterior resection margin (AA, IVC and LRV). Yellow arrows indicating mesopancreatic excision in the medial resection margin (PV and SMA) **C.** H&E staining of hPDAC with microscopic infiltration of mesopancreatic fatty tissue (50x). **D.** Pathological specimen of the pancreatic head with infiltration of the peripancreatic fatty tissue. The specimen was inked using a pre-defined color code (posterior surface: black, anterior surface: blue, medial surface: green). Grossing was done according to the axial slicing technique (pT3 pN2 (5/47) L1 V0 Pn1).

out. To avoid persistent diarrhea only 180°–270° of the right circumference of the SMA are dissected. If cancerous involvement is intraoperatively suspected, dissection of the SMA is extended to the left circumference (Fig. 1A and B).

In summary, the aim of the procedure is a complete dissection of perineural and lymphatic tissue and structures surrounding the pancreatic head/uncinate process (CHA, GDA, CT, SMA, PV, SMV), in an "en bloc" resection (Fig. 1B). We designated this surgical process mesopancreatic excision.

All resections were performed by trained hepatobiliary surgeons of our department. A pylorus sparing partial pancreatoduodenectomy was favored, and nearly all reconstructions were performed with two retrocolic jejunal limbs (an end-to-side pancreaticojejunostomy, an end-to-side hepaticojejunostomy), as well as one antecolic jejunal limb (end-to-end duodenojejunostomy or end-to-side gastrojejunostomy). Two side-to-side Roux-en-Y anastomoses were fashioned for the three jejunal limbs.

Pathological analysis

The CRM evaluation was implemented at the University Hospital of Duesseldorf in September 2015. The oral/aboral duodenal, bile duct and pancreatic neck resection margin, as well as the dorsal resection margin and, if applicable, portal vein specimen were examined according to the LEEPPs pathological protocol. Additionally the mesopancreatic adipose tissue was histopathologically evaluated for cancerous infiltration (Fig. 1C). Histopathological slides originating before 2015 were re-visited by a pathologist experienced in the hepatopancreaticobiliary system, and if sufficient slides were available, a CRM status with evaluation of the mesopancreatic fat was evaluated. This included the evaluation not only of the dorsal, but also ventral and medial CRM. In addition, the "1-mm rule" was implemented: A minimum margin clearance of 1 mm defined R0(CRM negative), whereas margin clearances between 0 and 1 mm were judged as R0(CRM positive) (Fig. 1C and D) [25].

Postoperative tumor board and follow-up

All patients were pre- and postoperatively evaluated and discussed in an interdisciplinary tumor board regarding adjuvant therapy and further procedure. If the follow-up examinations were performed at our institution, irrespective of the adjuvant treatment constellation, computed tomography of the thorax and abdomen was performed every 3 months for the first 2 years, followed by every 6 months thereafter. Patients with suspicious metachronous masses were discussed in the tumor board for further therapy. If follow-up procedures were performed at other institutions, survival records of patients were gathered from the legal registration office.

Statistics

The Wilcoxon test was used to analyze the differences in clinicopathological data. The Mann-Whitney *U* test was used to examine numerical data and to correlate between clinico-pathological variables. For categorical data, the chi-square test or fisher exact test was applied. Overall survival (OS), relapse free survival (RFS), local recurrence free survival and post-relapse survival (PRS) were included for outcome measures. OS was determined as the period from the date of surgery until the date of death or last follow-up. RFS described the period from the date of surgery until the date of diagnosed metachronous metastases or local recurrence. Local recurrence free survival determined the period between the date of surgery until the diagnosis of local recurrence. PRS included the period between relapse diagnosis and death or last follow-up. Kaplan-Meier curves were generated and analyzed using the log-rank (Mantel Cox) test, and hazard ratios (HR) with 95% confidence intervals (CI) were estimated. To perform a multivariate survival analysis, significant variables from the univariate analysis were included into a forward logistic regression analysis. Analyses were performed using SPSS statistics for Windows (version 26.0; SPSS, Inc., Chicago, IL, USA). Statistical significance was defined as $p < 0.05$.

Results

Demographic data

During the study period, 330 patients were treated curatively for hPDAC. In 50 patients, histopathological slides or MP adipose tissue were not available for re-evaluation. Sixteen patients deceased during the first 30 postoperative days and were excluded from the study (Clavien-Dindo V; 30-day mortality rate: 4.8%). The remaining 264 patients were included for further analysis (Table 1, Fig. S1). Median hospital stay was 22 days (range: 17–295 days). Perioperative morbidity was observed in 28.4% of the patients (Clavien-Dindo II: 16 patients, Clavien-Dindo III: 49 patients, Clavien-Dindo IV: 10). The median age of all patients at the time of surgery was 69 years (range 41–90 years). Of the included cohort, 211 (79.9%) patients had no distant metastases (M0), while 53 (20.1%) patients were classified as M1 postoperatively. In 28 patients, positive para-aortic lymph nodes were evident postoperatively, while in 25 patients resectable synchronous hepatic metastases were evident and resected intraoperatively.

One-hundred and eighty-eight (71.2%) patients died during the follow-up period. In total, 156 patients received gemcitabine mono therapy, while 41 patients received a combination therapy with gemcitabine. Nineteen patients were treated with FOLFIRINOX (5-fluorouracil, leucovorine, irinotecan, and oxaliplatin). Thus, 81.8% of all patients received an adjuvant therapy.

Histopathological results

Resection status

Histopathological analyses and resection status are summarized in Table i (supplemental). Two hundred twenty-eight patients were examined before 2015 and needed sophisticated histopathological re-evaluation, whereas in 85 patients, CRM evaluation in the context of a standardized pancreatic protocol was primarily applied (Table i supplemental). Of the 228 patients without primary CRM implementation, histopathological slides were available for 179 patients (Table i supplemental). Between 2003 and 2015, the rate of margin negative resections (R0) was 76.3% (Table i supplemental). When applying the 1 mm rule, true negative resection margins were still present after re-evaluation in 76 patients (42.5%) ($p = 0.016$). The remaining 56 patients (31.3%) had tumor residues within the 1 mm margin R0(CRM+), which had been missed in the previous histopathological analysis (Table i supplemental). Following the 1 mm-rule in all patients (n = 264) with CRM assessment (2003–2020), 128 patients (48.5%) were staged as R0(CRM-), whereas 78 patients (29.6%) had tumor infiltration into the 1 mm resection margin R0(CRM+). Fifty-eight patients (21.9%) were staged as R1 following re-evaluation (Table i supplemental).

Patients who received surgery after 2015 showed a significantly higher rate of venous invasion (V1) and margin negative resections (R0(CRM-)), all other clinicopathological variables were homogenously distributed (Table ii supplemental). All studied clinicopathological data were homogenously distributed between R0(CRM-) and R1/R0(CRM+) resected patients (Table iii supplemental).

Mesopancreatic evaluation

In all 264 patients with CRM assessment (Tables i–iii supplemental), paraffin embedded histopathologic specimens were available for retrospective re-evaluation of the mesopancreatic fat tissue of the peripancreatic dorsal resection margin. Tumor infiltration of adipose tissue was evident in 207 patients (78.4%). In only 57 patients, mesopancreatic adipose tissue had no tumor infiltration (21.6%) (Table 2). Statistical analysis (chi-squared test and fisher exact test) revealed a significantly higher rate of lymphatic metastases (N1 and N2) and positive resection rate (R1/R0(CRM+)) in patients with MP infiltration (Table 2). All other studied clinicopathological variables were homogenously distributed (Table 2). Surprisingly, mesopancreatic fat invasion was equally distributed between the strictly size based T-stage categories and the rate of mesopancreatic fat invasion was not significantly increased in M1 resected patients when compared to M0 patients (Table 2). Histopathological correlation analysis was re-evaluated excluding UICC IV patients and a similar distribution of the studied clinicopathological variables was confirmed in this subgroup (Table iv supplemental).

Overall survival analysis

Follow up data of all 264 patients was obtained using official records from the registration office. Survival analysis was only performed in M0 resected patients (n = 211). The median OS of the 211 M0 resected patients was 40.77 months (95%CI: 32.38–49.16 months).

In univariate analysis (n = 211), the following clinicopathological parameters were associated with prognostic impact: N-status, grading, multidrug chemotherapeutic regime and positive resection margin (Table 3). The median OS was stratified according to the resection status. In the “true” margin negative patients (R0(CRM-); n = 106) the median OS (58.51 months, 95%CI: 43.99–73.03 months) was significantly longer, compared to the margin positive patients (R1 and R0(CRM+); n = 105) (median: 22.81 months, 95% CI: 18.33–27.29 months) ($p < 0.001$) (Table 3, Fig. 2A). In patients with adjuvant therapy (n = 156 patients), we observed a significant prolonged OS when multidrug based regimes (Gemcitabine based or FOLFIRINOX) were applied. The median OS in those patients was 44.72 months vs. 20.91 months in the gemcitabine mono group ($p = 0.038$) (Table 3). In multivariate analysis, only negative resection margin (R0(CRM-)) remained as an independent prognostic factor (Table 3).

Pathological mesopancreatic fat assessment and overall survival (OS) analysis

Survival analysis was performed in the 211 M0 resected patients (Table 2 and Table iv supplemental). The median OS in patients with

Table 1
Demographic table of all 264 studied patients. Staging is revised to the 8th edition of the UICC TNM classification of malignant tumors. Statistical significance was calculated by Mann-Whitney *U* test and chi squared test. ** indicates a *p-value* ≤ *0.01*; * indicates a *p-value* ≤ *0.05*.

Age in years		
Median (range)	69 (41–90)	
Gender	N	%
Male	142	53.8
Female	122	46.2
T-stage		
T1	16	6.1
T2	141	53.4
T3	99	37.5
T4	8	3.0
N-stage		
N0	40	15.2
N1	119	45.1
N2	105	39.8
M-stage		
M0	211	79.9
M1hep	25	9.5
M1PALN	28	10.6
Grading		
G1/G2	147	55.7
G3	117	44.3
Pn		
Pn0	51	19.3
Pn1	191	72.3
missing	22	8.3
L		
L0	125	47.3
L1	118	44.7
missing	21	8.0
V		
V0	180	68.2
V1	62	23.5
missing	22	8.3
CTx		
No CTx	48	18.2
Gemcitabine mono	156	59.1
MD CTx	60	22.7

CTx: chemotherapy; Hep: hepatic; L: lymphatic invasion; MD: multidrug; PALN: para-aortic lymph nodes; Pn: perineural invasion; V: venous invasion.

Table 2
Correlation analysis of patients stratified according to positive and negative mesopancreatic infiltration at the dorsal resection margin, n = 264. In over 78.4% of all patients, mesopancreatic fat was infiltrated by the tumor. Patients with mesopancreatic fat infiltration were prone to lymphatic metastases and showed a higher rate of positive resection margins (R1/R0(CRM+)). Statistical significance was calculated by chi squared test. ** indicates a *p-value* ≤ *0.01*; * indicates a *p-value* ≤ *0.05*.

	No mesopancreatic fat infiltration n = 57		Mesopancreatic fat infiltration n = 207		*p-value*
Age in years					
Median (range)	67.5 (47–90)		69.0 (41–88)		
Gender	**n**	**%**	**n**	**%**	*0.456*
Male	28	49.1	114	55.1	
Female	29	50.9	93	44.9	
T-stage					*0.706*
T1	5	8.8	11	5.3	
T2	31	54.4	110	53.1	
T3	20	35.1	79	38.2	
T4	1	1.8	7	3.4	
N-stage					***0.007***
N0	15	26.3	25	12.1	
N1	17	29.8	102	49.3	
N2	25	43.9	80	38.6	
M-stage					*0.709*
M0	45	78.9	166	80.2	
M1hep	5	8.8	20	9.7	
M1PALN	7	12.3	21	10.1	
Grading					*0.053*
G1/G2	38	66.7	109	52.7	
G3	19	33.3	98	47.3	
Pn					*0.258*
Pn0	15	26.3	36	17.4	
Pn1	40	70.2	151	72.9	
Missing	2	3.5	20	9.7	
L					*1.000*
L0	28	49.1	97	46.9	
L1	27	47.4	91	43.9	
Missing	2	3.5	19	9.2	
V					*0.379*
V0	38	66.7	142	68.6	
V1	17	29.8	45	21.7	
Missing	2	3.5	20	9.7	
R-status					***0.001***
R0(CRM-)	39	68.4	89	48.0	
R1/R0(CRM+)	18	31.6	118	57.0	
CTx					*0.178*
No CTx	16	28.1	32	15.5	
26	45.6	130	62.8		
MD CTx	15	26.3	45	21.7	

CRM: circumferential resection margin; CTx: chemotherapy; hep: hepatic; L: lymphatic invasion; MD: multidrug; PALN: para-aortic lymph nodes; Pn: perineural invasion; V: venous invasion.

positive mesopancreatic fat infiltration (n = 166) was 38.87 months (95%CI: 29.97–47.76 months), which was not significantly different from the median OS of 46.67 months (95%CI: 32.86–60.49 months) in patients with negative mesopancreatic infiltration (n = 45) (*p = 0.054*).

Analyzing those 166 patients with mesopancreatic fat infiltration, patients who received true margin negative resection R0(CRM-) showed a significantly higher median OS when compared to margin positive patients R1/R0(CRM+) (R0(CRM-): n = 76; 60.23 months vs. R1/R0(CRM+): n = 90; 21.90 months) (*p < 0.001*) (Fig. 2B). In the 106 margin negative patients R0(CRM-), the median overall survival was similar in patients with (n = 76, 60.24 months) and without mesopancreatic infiltration (n = 30, 47.20 months) (*p = 0.965*) (Fig. 2C).

Relapse free survival analysis (RFS), site of relapse and post-relapse survival (PRS)

Follow-up data of relapse free survival was available in 133 M0 resected patients, the median RFS was 24.35 months (95%CI: 17.43–31.28 months).

At univariate analysis, higher T-stage, positive venous invasion (V1) and positive margin resection (R1) were associated with worse RFS (Table 4). The median RFS (39.62, 95CI: 27.35–51.89 months) in the 73 patients after true R0 resections R0(CRM-) was significantly higher when compared to the 60 margin positive resected patients (R1 and R0(CRM+); median RFS: 11.82, 95%CI: 9.39–14.24 months) (*p < 0.001*) (Fig. 3A). In multivariate analysis venous invasion (V1) and margin positive resected patients (R1 and R0(CRM+)) were independent prognostic factors for RFS (Table 4).

Out of the 133 patients, 83 patients were diagnosed with metachronous relapse (Table 5). Follow up analysis revealed that systematic relapse was not prevented by degree of surgical radicality (*p = 0.796*). Most patients succumbed to metachronous disease independent of the resection margin status (R0(CRM-) vs. R1/R0(CRM+)) (fisher exact test: *p = 0.091*). However, in 73 R0(CRM-) resected patients, only 8 patients (10.9%) were diagnosed with local recurrence, compared to 20 (33.3%) out of 60 patients with an insufficient surgical tumor clearance (R1/R0(CRM+)) (*p = 0.004*) (Table 5). Thus, patients following R0(CRM-) resection had a significantly longer local recurrence free survival (*p = 0.041*)

Table 3
Univariate and multivariate survival analyses for overall survival of M0 resected patients; n = 211. Analyses were performed by log-Rank test and cox logistic forward regression. *p-value* ≤ *0.05* is considered statistically significant.

Univariate analysis			
			p-value
Median age (<vs. > median)			*0.077*
T-stage (T1/T2 vs. T3/T4)			*0.896*
N-stage (N0/N1 vs. N2)			***0.003***
Grading (G1/G2 vs. G3)			***0.028***
Pn (Pn0 vs. Pn1)			*0.145*
L (L0 vs. L1)			*0.984*
V (V0 vs. V1)			*0.064*
R-status (R0(CRM-) vs. R1/R0(CRM)+)			***<0.001***
Gemcitabine mono vs Multidrug CTx			***0.038***
Multivariate analysis			
	p-value	HR	95%CI
R-status (R0(CRM-) vs. R1/R0(CRM)+)	*0.002*	*1.859*	*1.257–2.750*

CTx: chemotherapy; CI: confidence interval; HR: hazard ratio; multidrug: gemcitabine based or FOLFIRINOX; L: lymphatic invasion; Pn: perineural invasion; V: venous invasion.

(Fig. 3B). The median RFS in the 28 patients before diagnosed isolated local recurrence was similar when compared to the median RFS in the 55 patients before diagnosed systemic relapse ($p = 0.853$) (Table 5). The median PRS of patients suffering from isolated local recurrence vs. systemic relapse (median PRS 7.57 months, 8.10 months respectively) was again not significantly different ($p = 0.704$) (Table 5, Fig. 3C).

Discussion

Prognosis of hPDAC has not improved significantly over the past decades and several attempts to improve oncological results by more radical surgical approaches remained inconclusive. Remarkably, refined histopathological assessment, implementing CRM, revealed that about 80% of pancreatic resections displayed microscopic tumor residues at the surgical margins [12], suggesting that a more thorough surgical approach might lead to a better therapeutic outcome.

In this context, consequent mesopancreatic excision (MPE) may contribute to increase the rate of true R0 resections (R0(CRM-)) [27–30]. Peparini et al. suggested that removal of the tissue around the SMA and CT might reduce the number of R1 resections, though he attributed some of the microscopic findings to epithelial-mesenchymal transition with uncertain dignity [30]. To date, it is not understood how frequently the mesopancreatic fat is infiltrated by hPDAC and if these findings are of oncologic relevance [15,16,31].

The aim of the herein presented study was to quantify the rate of mesopancreatic fat infiltration when applying the refined histopathological standard [32]. We further assessed the impact of MPE on the surgical margin status, as well as the impact on long-term survival. Mesopancreatic excision was defined as an excision of the entire mesentery that envelops the pancreas. This is the dorsal mesogastrium caudate to the stomach and proximal to the jejunum. Vascular limits of these planes are the inferior border of the CT and its major branches and the superior border of the SMA down to the first jejunal arteries as seen in Fig. 1A. The anatomic hallmarks of dissection around the SMA are well described by Inoue et al. and correspond to their level III [19].

Not surprisingly, follow up analysis revealed that these R0(CRM-) resected patients had a significant prognostic benefit with respect to OS and RFS (58.51 and 39.62 months respectively). These encouraging results are in contrast to the remaining patients, whose median OS and RFS were calculated with only 22.81 and 11.82 months. The refined analysis of the mesopancreatic fat revealed tumor involvement in 78.4% of the cases, which might explain the high rate of margin positive resections frequently observed. Consequent MPE in our cohort resulted in a true R0 resection rate of 48.5%, which is superior to most results in the literature [11,12,32–34]. Also, OS and RFS in this study are superior to recently published results in R0(CRM-) patients without MPE [32,33], indicating that MPE may deliver a significant survival benefit for the patient with PDAC.

When stratifying relapse free survival according to the site of relapse, it was found that true margin negative patients had a significantly longer local RFS, whereas no impact on systemic relapse was distinguishable. Compared with previous studies reporting local recurrence rates of up to 75% [7,33,35–41] in our cohort of R0(CRM-) resected patients, we found only 10.9%

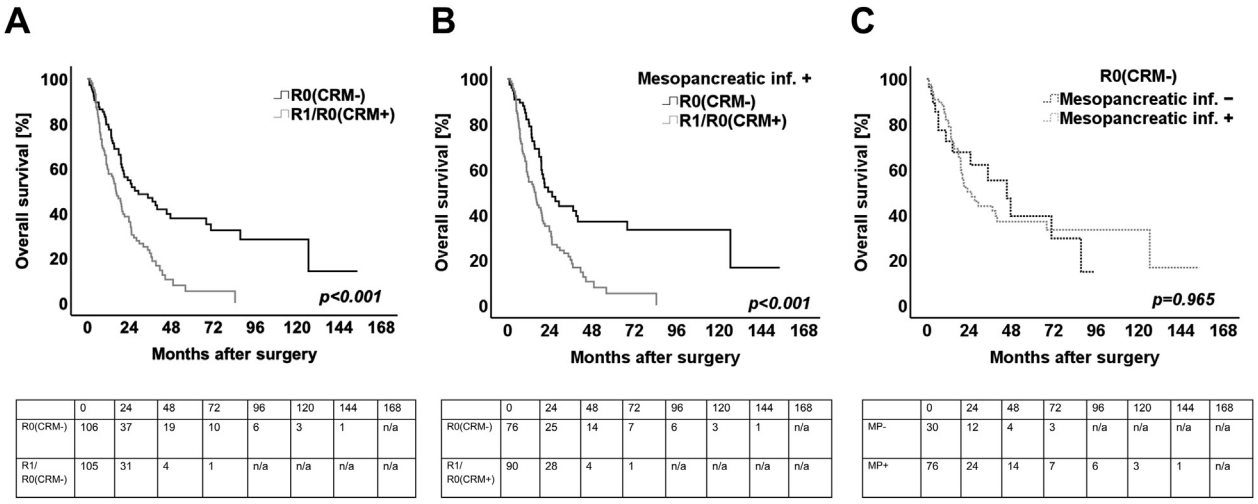


Fig. 2. Kaplan-Meier curves for **A.** overall survival in correlation with positive and negative resection status in CRM evaluated patients. **B.** overall survival of the 166 patients with positive mesopancreatic fat infiltration at the dorsal resection margin. Margin negative resections provided survival benefit in patients with mesopancreatic fat infiltration. *Inf.: infiltration* **C.** overall survival of 106 margin-negative resected patients with mesopancreatic fat infiltration (n = 76) and without mesopancreatic fat infiltration (n = 30) at the dorsal resection margin. Patients with margin negative resections and peri-pancreatic fat infiltration showed a similar survival outcome when compared to patients with margin positive resections without peri-pancreatic fat infiltration. *Inf.: infiltration; MP = mesopancreatic.* Log rank test was used to test for significance. *p-value* ≤ *0.05* is regarded as significant.

Table 4
Univariate and multivariate analysis for relapse free survival of total cohort, n = 133. Resection status and venous invasion were indicators for poor relapse free survival. Analyses were performed by log-Rank test and cox logistic forward regression. *p-value ≤ 0.05* is considered statistically significant.

Univariate analysis			
			p-value
Median age (<vs. > median)			*0.134*
T-stage (T1/T2 vs. T3/T4)			***0.005***
N-stage (N0/N1 vs. N2)			*0.051*
Grading (G1/G2 vs. G3)			*0.218*
Pn (Pn0 vs. Pn1)			*0.519*
L (L0 vs. L1)			*0.375*
V (V0 vs. V1)			***0.003***
R-status (R0(CRM-) vs. R1/R0(CRM)+)			***<0.001***
Gemcitabine mono vs Multidrug CTx			*0.774*
Multivariate analysis			
	p-value	HR	95%CI
V (V0 vs. V1)	***0.029***	*1.81*	(1.061–3.096)
R-status (R0(CRM-) vs. R1/R0(CRM)+)	***0.011***	*1.88*	(1.155–3.044)

CTx: chemotherapy; CI: confidence interval; G: gemcitabine; GC: gemcitabine combination; HR: hazard ratio; multidrug: gemcitabine or FOLFIRINOX; L: lymphatic invasion; Pn: perineural invasion; V: venous invasion.

locoregional recurrences, which might be attributed to our radical clearance of the mesopancreatic lamina. Regarding patients with MPE and R0(CRM-) status, those who remained free of distant metastases (n = 27) showed an impressive median OS of 127.4 months.

On the other hand, the comparably low rate of local recurrence might also be expected in a collective with a large proportion of early tumor stages. However, implementing the redefined 8th UICC edition, the majority of the patients in our collective presented with rather advanced tumor stages (40.5% ≥pT3, 39.8% N2 and 44.3% G3-differentiation). These are generally considered oncologic high risk patients with low OS and RFS. Thus, it seems prudent to conclude that the observed low rate of local recurrence in our cohort might be attributed to MPE and local surgical radicality. Considering the high rate of mesopancreatic fat infiltration (78.4% of the patients), it seems conceivable that the omission of MPE might have resulted in far higher rates of margin positive resections and thus early local recurrence.

Interestingly, cancerous infiltration of the mesopancreatic tissue did not correlate with the strictly size-based T-stage and survival outcome was similar in R0(CRM-) resected patients with or without mesopancreatic infiltration. This indicates that mesopancreatic fat infiltration might be a sign of unfavorable tumor topography, instead of a sign for adverse tumor biology [42]. This is further underlined by the similar rate of mesopancreatic infiltration in patients with synchronously metastasized hPDACs.

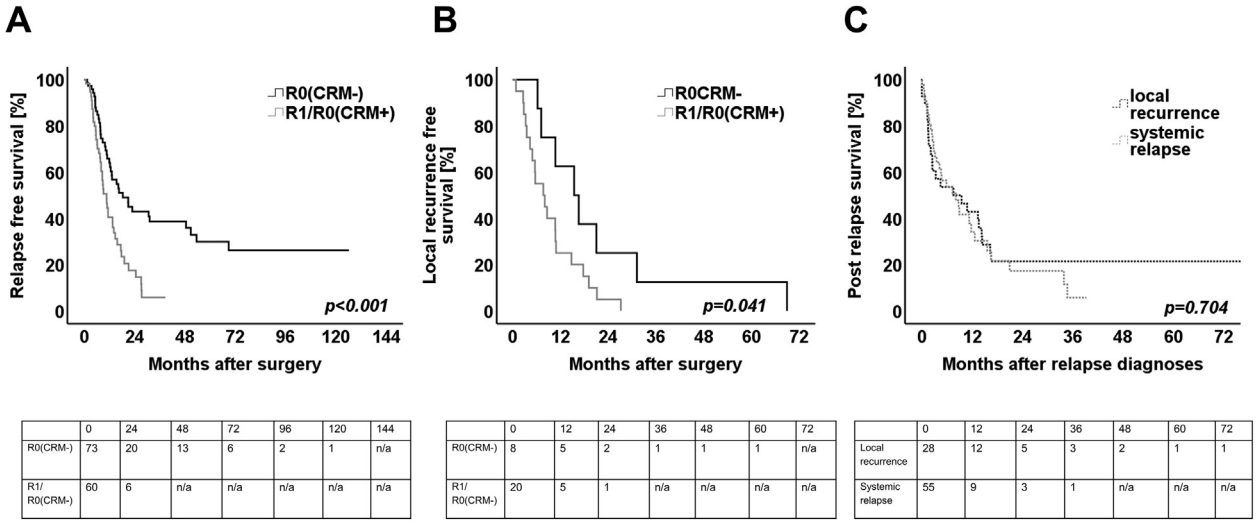
A limitation of this study is the long-time span with some changes in adjuvant therapy in our cohort of patients. The distribution of different adjuvant protocols between patients with or without CRM infiltration and between patients with or without mesopancreatic infiltration was homogenous. Surgery and perioperative management was performed by the same team during the entire study period.

Radical approach to MPE non-surprisingly does not influence the rate of distant metastases. Consecutively, a systemic approach will continue to be necessary to enable long term survival in patients with ductal adenocarcinoma of the pancreatic head [6,10]. We suggest that complete local control through radical MPE is a prerequisite for a curative oncologic approach. It results in very low rates of local recurrence.

It has been established that the negative impact of local recurrence and distant metastases on OS is comparable [39]. Local tumor control achieved by MPE might be an encouraging step towards a significant improvement of oncologic results in patients with PDACs.

Conclusion

The results of this study histopathologically justify a standardized radical surgical approach including complete mesopancreatic excision. It is the first study demonstrating the rate of mesopancreatic fat invasion and that mesopancreatic excision during pancreatoduodenectomy for hPDACs results in an increased R0(CRM-) resection rate, OS and RFS compared to published data.



	0	24	48	72	96	120	144
R0(CRM-)	73	20	13	6	2	1	n/a
R1/ R0(CRM-)	60	6	n/a	n/a	n/a	n/a	n/a

	0	12	24	36	48	60	72
R0(CRM-)	8	5	2	1	1	1	n/a
R1/ R0(CRM-)	20	5	1	n/a	n/a	n/a	n/a

	0	12	24	36	48	60	72
Local recurrence	28	12	5	3	2	1	1
Systemic relapse	55	9	3	1	n/a	n/a	n/a

Fig. 3. Kaplan-Meier curves for **A.** relapse free survival of the 133 patients with detailed follow-up. Tumor relapse was significantly influenced by resection status. **B.** survival until local recurrence diagnosis. Local recurrence free survival was significantly longer in the 8 R0(CRM-) resected patients compared to the 20 R1/R0(CRM+) resected patients. **C.** Post-relapse survival dependent on relapse location. Survival in the 28 patients after diagnosed isolated local recurrence was similar when compared to the 55 patients after diagnosed systemic relapse. Log rank test was used to test for significance. *p-value ≤ 0.05* is regarded as significant.

Table 5
Relapse free survival, post-relapse survival and metachronous disease, n = 133. Follow-up analyses for metachronous disease in 83 patients. Systematic relapse was homogenously distributed between resection status. Patients after margin negative resections were diagnosed with a significantly lower rate of local recurrence. Relapse free survival and post-relapse survival between patients with isolated local recurrence and systemic relapse were of no significant difference. Statistical significance was calculated by chi squared test and log-Rank test. ** indicates a *p-value* $\leq$ *0.01*; * indicates a *p-value* $\leq$ *0.05*.

	No metastases			Systemic relapse			Local recurrence		
	n	%	*Fisher exact test (p-value)*	n	%	*Fisher exact test (p-value)*	n	%	*Fisher exact test (p-value)*
R0(CRM-) n=73	35	47.9		30	41.1		8	10.9	
R1/ R0(CRM+) n=60	15	25.0	***<0.001***	25	41.7	*0.796*	20	33.3	***0.004***
Relapse-free survival				Median (95%CI) months			Median (95%CI) months		
				12.9 (9.9-15.9)			13.1 (8.2-18.1)		
Log rank test (p-value)				*0.853*					
Post-relapse survival				Median (95%CI) months			Median (95%CI) months		
				8.10 (2.6-13.6)			7.57 (0.0-17.2)		
Log rank test (p-value)				*0.704*					

Ethics approval and consent to participate

This study was approved by the local institutional review board (Heinrich Heine University, Duesseldorf, Germany; study-no.: 2019–473_2). All procedures performed in this study were in accordance with the ethical standards in the 1964 Declaration of Helsinki and its later amendments. Informed consent was waived because no data regarding the cases were disclosed.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Author contributions

Study conception (S-A.S), design (A.R, WT.K) and overall analysis (S-A.S) and interpretation of data and drafting of the manuscript (S-A.S, G.F, L.H, A.R.), revising the manuscript (L.H, A.R, G.F, N.L, A.K, I.E, V.K, T.L, WT.K.), data acquisition (S-A.S; L.H), analysis (S-A.S) and interpretation (S-A.S; G.F, A.R, V.K, T.L., I.E, WT.K), manuscript preparation (S-A.S; N.L, A.R, WT.K), conceptual contributions and manuscript revision (A.K, N.L, I.E, V.K, T.L, WT.K.).

Declaration of competing interest

No potential conflicts of interest were disclosed.

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Not applicable.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pan.2021.02.024.

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