ORIGINAL ARTICLE

Recurrence patterns of pancreatic cancer after pancreatoduodenectomy: systematic review and a single-centre retrospective study

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Abstract

Background: Positive margins in pancreatoduodenectomy (PD) for pancreatic cancer, specifically the superior mesenteric artery (SMA) margin, are associated with worse outcomes. Local therapies targeting these margins could impact on recurrence. This study analysed recurrence-patterns to identify whether strategies to control local disease could have a meaningful impact.

Methods: (I) Systematic review to define recurrence patterns and resection margin status. (II) Additional retrospective study of PD performed at our centre.

Results: In the systematic review, 23/617 evaluated studies were included (n = 3815). Local recurrence was observed in 7–69%. SMA margin (6 studies) was positive in 15–35%. In the retrospective study (n = 204), local recurrence was more frequently observed with a positive SMA margin (66 vs.45%; p = 0.005). Furthermore, in a multivariate cox-proportional hazard model, only a positive SMA margin was associated with disease recurrence (HR 1.615; 95%CI 1.127–2.315; p = 0.009). Interestingly, median overall survival was 20 months and similar for patients who developed local only, metastases only or simultaneous recurrence (p = 0.124).

Conclusion: Local recurrence of pancreatic cancer is common and associated with similar mortality rates as those who present with simultaneous or metastatic recurrence. Involvement of the SMA margin is an independent predictor for disease progression and should be the target of future adjuvant local therapies.

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Introduction

In contrast to most other cancer types, the outcomes of pancreatic cancer remain poor.[1] The overall survival rates (OS) of patients with resectable pancreatic cancer who undergo surgery with curative intent have slowly improved over the last decade to more than 24 months, due to the widespread implementation of adjuvant chemotherapy.[2] Such results demonstrate the importance of adjuvant treatment, but these therapies are limited in efficacy and furthermore many patients do not receive any adjuvant chemotherapy (25–50%).[3,4]

The pancreas is intimately related to major vascular structures with no anatomical barrier between the two. Resection of the superior mesenteric vein (SMV) or portal vein (PV) have been implemented in most centres with satisfactory outcomes.[5,6] On the contrary, the plexus of the autonomic nerves around the superior mesenteric artery (SMA) lies between the uncinate process and the artery and is frequently invaded by cancer.[7] It is therefore more challenging to achieve a clear resection margin (R0) around the SMA in a pancreatoduodenectomy (PD). Consequently, positive (R1) SMA margin rates in PD surgical specimens of up to 45% have been reported even without

radiologic evidence of invasion.[8] Positive resection margins, and especially SMA margins, are associated with local recurrence and impaired survival.[9,10] Currently, adjuvant systemic therapy is the only available treatment to reduce the development of recurrent disease. Local adjuvant therapies, such as stereotactic body radiation therapy or irreversible electroporation have been shown to be safe and feasible strategies in patients with locally advanced pancreatic cancer and could potentially reduce the risk of recurrent disease.[11]

The aim of this study was to determine patterns and frequency of disease recurrence following PD for pancreatic cancer. Therefore, a systematic review of the current literature was performed, followed by a more in-depth analysis using a retrospective cohort study.

Methods

This study was divided into two sections: (i) a systematic review of the current literature defining recurrence patterns after PD for pancreatic cancer and (ii) a retrospective analysis of these recurrence patterns in patients undergoing PD at our centre. This study was registered and approved by the Internal Review Board of the Queen Elizabeth Hospital Birmingham (Registration number 14539).

Systematic review of the literature about recurrence patterns

This systematic review was performed according to the Handbook for Systematic Reviews of Interventions of the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Guidelines.[12,13] A literature search of PubMed and MEDLINE (OvidSP) online libraries was performed from January 1990 until April 2018. The aim of this search was to identify studies that specifically evaluated the site of recurrence after PD for pancreatic cancer. An additional analysis of the involvement of resection margins and recurrence was a preference, but not a necessity to be included in the systematic review. Therefore, the following searches were performed on PubMed: (i) "Carcinoma, Pancreatic Ductal" [Mesh] AND "Neoplasm Recurrence, Local" [Mesh] AND "Pancreatoduodenectomy" [Mesh], (ii) "Neoplasm Metastasis" [Mesh] AND "Carcinoma, Pancreatic Ductal" [Mesh] AND "Pancreatoduodenectomy" [Mesh] AND "recurrence" [Mesh], and (iii) "Neoplasm Recurrence, Local" [MAJR] AND "Pancreatic Neoplasms/surgery" [MAJR]. Medline searches included: (i) "Pancreatic Cancer and Pancreatoduodenectomy and Recurrence" and (ii) "Pancreatic Cancer & Surgery & Recurrence". Duplicates were removed and MK and DB independently reviewed the abstracts and full papers. Case reports, letters to the editor, reviews, and manuscripts in non-English language were excluded. Additional exclusion criteria were manuscripts including cancers other than pancreatic cancer, other surgical procedures (i.e. distal or total pancreatectomy), analysis of the treatment of the actual recurrence and studies with overlapping populations. If abstracts seemed eligible for the study, the full manuscript was reviewed. The quality of the included studies was assessed according to the Newcastle-Ottawa Scale.[14] The outcomes investigated in this review are the occurrence of recurrence with specific site, overall survival (OS) from the moment of surgery and disease-free survival (DFS). The incidence of positive

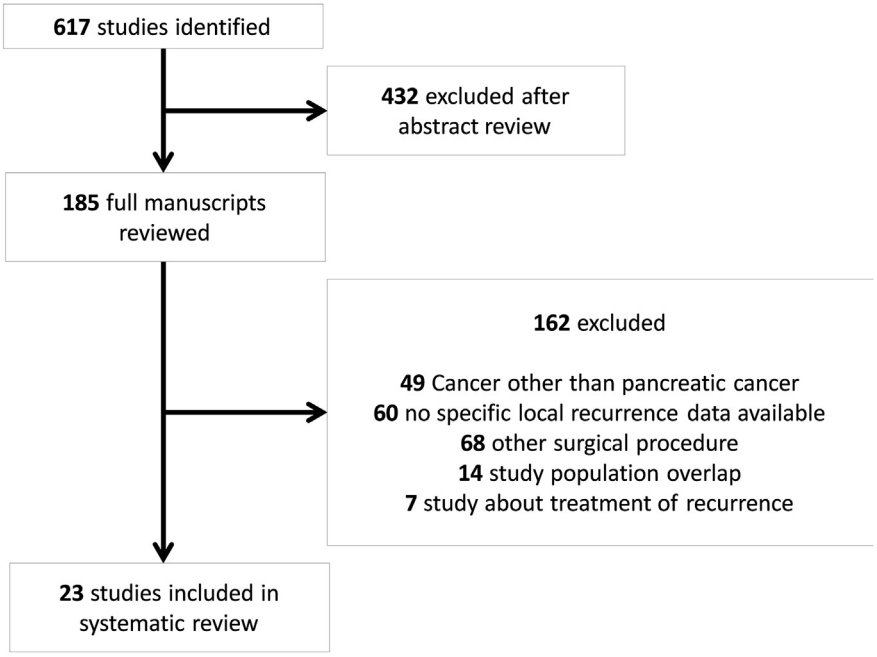

Figure 1 Flowchart of study selection for the systematic review

Table 1 Recurrence patterns and resection margins of all studies included in the systematic review

Paper	Study design	N=	Total recurrence	Local	Local only	Simul-taneous	Metastases		Median survival (months)		Surgical resection margins		
							All	Distant only	OS	DFS	R1	R1 SMA margin	Posititve margin cut-off
Elmi, 2017[41]	Single centre retrospective	229	73%	33%	–	–	58%	–	–	17/30	23%	–	1 mm
Nitta, 2017[35]	Single centre retrospective	117	–	21%	–	–	–	–	14/20	7/10	74%	29%	1 mm
Balaj, 2016[17]	Single centre retrospective	48	–	69%	17%	52%	52%	–	24	–	42%	31%	1 mm
Asaoka, 2016[36]	Single centre retrospective	46	76%	22%	–	–	–	–	26	10	20%	–	Unknown
Kantor, 2015[18]	Single centre retrospective	144	50%	18%	14%	4%	32%	–	17/29	12/17	19%	–	Unknown
Sugimoto, 2014[45]	Single centre retrospective	170	–	45%	–	–	–	–	18	10	All R0 resections		
Dholakis, 2013[46]	Single centre retrospective	202	–	45%	–	–	50%	–	–	–	–	–	–
Papavasiliou, 2013[19]	Single centre retrospective	272	73%	16%	12%	4%	61%	57%	22/18	14/12	–	–	–
Jamieson, 2013[37]	Single centre retrospective	172	–	53%	–	–	47%	–	–	–	72%	–	1 mm
Delpero, 2013[15]	Multicentre prospective	150	47%	21%	11%	10%	36%	26%	20	17	61%	25%	1 mm
Assifi, 2013[38]	Single centre retrospective	221	–	21%	–	–	–	–	18	12	34%	–	Unknown
Mullinax, 2012[20]	Single centre retrospective	96	84%	40%	20%	20%	64%	44%	12	9–23	34%	–	Unknown
Zhang, 2012[21]	Single centre retrospective	79	–	49%	28%	22%	42%	–	21	9/7/8	58%	–	1 mm
Garcea, 2011[22]	Single centre retrospective	74	46%	16%	1%	15%	–	30%	35	27	54%	–	Unknown
Fatima, 2010[16]	Single centre retrospective	602	63%[a]	10%	9%	1%	49%	48%	18	13	25%	18%	Unknown
Kang, 2010[23]	Single centre retrospective	140	66%	39%	12%	24%	–	30%	12	8	All R0 resections		
Showalter, 2009[24]	Single centre retrospective	83	67%	17%	11%	6%	–	30%	20	–	36%	.	Unknown
Regine, 2008[47]	Multicentre RCT	388	–	22%	–	–	69%	–	19	–	>25% missing data		
Esposito, 2008[39]	Single centre retrospective	111	–	7%	–	–	–	–	–	–	76%	35%	1 mm
Raut, 2007[9]	Single centre retrospective	360	67%	8%	–	–	51%	.	25	–	17%	15%	0 mm
Doi, 2005[48]	Single centre retrospective	54	–	–	–	–	–	–	16	8	All R0 resections		
Iacono, 2002[49]	Single centre retrospective	25	92%	40%	24%	16%	52%	–	–	–	All R0 resections		
Bluemke, 1997[40]	Single centre retrospective	32	–	31%	–	–	59%	–	–	7	22%	–	–
Total		3815	47–92%	7–69%	1–28%	1–52%	32–69%	26–57%	12–35	7–30	17–76%	15–35%	

DFS, disease free survival; OS, overall survival; SMA, superior mesenteric artery.
[a] Data of type of recurrence available in 5% (n = 30) of the patients.

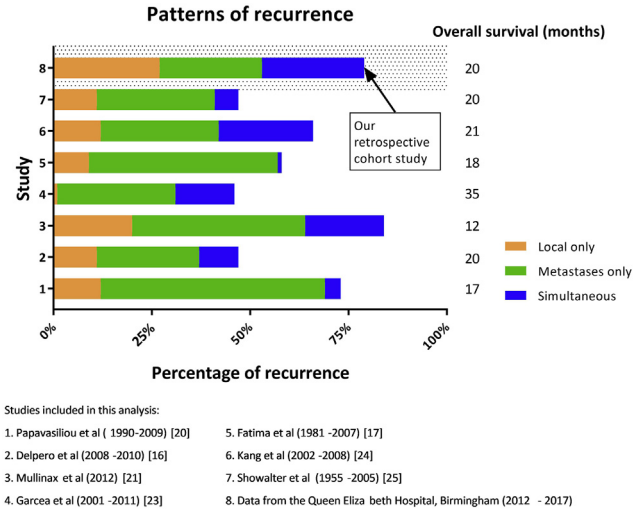

Figure 2 Full patterns of recurrence in seven studies of the systematic review

resection margins was also evaluated and if available, in relation to the site of recurrence and survival. The following data was extracted from the full texts: first author, title, year of publication, study design, population size, definition of (local) recurrence, incidence of recurrence and site, resection margin positivity (including specifically the SMA margin), DFS and OS. Studies were included in the final analysis if the site of recurrence was available.

Retrospective analysis of recurrence patterns

Medical records of all consecutive patients undergoing PD from 2007 to 2015 for pancreatic cancer (pancreatic ductal adenocarcinoma) were retrospectively assessed. All other indications for a PD (i.e. ampullary carcinoma, cholangiocarcinoma and benign lesions) were not included in this study. Patients who died within 90 days after the procedure and those with incomplete follow-up data were also excluded. The pathology reports of the resected specimen were evaluated, with specific interest for the extent of tumour invasion and margin clearance. A resection margin was considered clear (R0) if the malignant tissue was at least 1 mm away from the transected tissue. In our centre, all patients are considered for adjuvant chemotherapy if their clinical status allows it. Before and after adjuvant chemotherapy, all patients undergo a CT-scan. Additional follow up includes regular 3-month visits in the first year and yearly follow up until five years after surgery. Patients do not undergo regular follow up cross-sectional imaging, but CT-scans are performed in case of suspected local or metastatic recurrence. Follow up included timing of specific patterns of local and metastatic recurrence. The type of recurrence was considered at the first moment of recurrence (local only, metastatic only, or simultaneous local and metastatic recurrence). Metastatic recurrence was divided into four groups: distant lymph nodes, peritoneal, liver, and other (lungs, bone, etc). DFS and OS were recorded and evaluated according to the involvement of specific margins and the type of recurrence.

Statistical analysis

Estimated median survival of DFS and OS were constructed using Kaplan–Meier curves according to the involvement of specific margins and the type of recurrence. Comparison between groups was performed using log-rank tests. Continuous variables were expressed as median and interquartile range, where appropriate. Continuous variables were compared using the Mann–Whitney U test. *P*-values <0.05 were considered statistically significant. To compare categorical variables, the Chi-square test or the Fisher's exact test were used. Categorical variables were expressed in quantities and percentages. A Cox Proportional Hazard modelling was used to identify factors associated with DFS. The multivariate model was constructed using a stepwise backward likelihood estimation. Data were analysed with IBM SPSS Statistics version 24 (IBM Corporation, Armonk, New York, USA). Graphical images were constructed using Prism version 7.04 (GraphPad Software, La Jolla, CA, USA).

Results

Systematic review of the literature about recurrence patterns

The literature search identified 617 potential studies with 432 excluded based on abstract review. The remaining 185 full manuscripts were reviewed and a further 162 excluded due to five criteria (Fig. 1) with 23 studies included in the final systematic review. The majority (21; 91%) of the studies were retrospective cohort studies, the remaining two studies were a national multicentre prospective study and a randomized controlled trial. An overview of the included studies and a quality assessment according to the Newcastle–Ottawa Scale is shown in Supplementary Table 1. The 23 studies included a total of 3815 patients and the study population size ranged from 25 to 602 patients.

Regarding pathologic assessment of the resected margins, four studies only included R0-resections and in one study more than 25% of the margin status data was missing. In total, 16 studies (n = 2564) reported margin status and the R1-rates ranged from 17 to 76% (Table 1). Seven studies used 1 mm as the cut-off for a positive margin, one study 0 mm and the margin cut-off was unknown in eight studies. Specific positivity of the SMA margin was described in six studies (n = 1388). The SMA margin was positive in 15%–35% of the patients in these studies. Of these six studies, three investigated the relation between a positive SMA margin and recurrence/survival rates. Delpero *et al.* reported impaired survival rates in patients with a positive SMA margin (19.5 vs. 9.6 months; $p = 0.017$).[15] Furthermore, a hazard ratio of 1.27 (95%CI 1.00–1.63; p = 0.05) for a combined endpoint of

recurrence and death by Fatima and colleagues.[16] In contrast, Raut *et al.* did not find a significant relation between a positive SMA margin specifically and OS rates (HR 1.28; 95%CI 0.92–1.78; $p = 0.140$).[9]

Patterns of disease recurrence are demonstrated in Table 1. As the main outcome inclusion criterion, all studies reported the incidence of local recurrence, ranging from 7% to 69%. However, there was a large variety in how studies reported the recurrence patterns. The overall recurrence rate (47–92%) was reported in 11 studies and metastatic recurrence (32–69%) in 14 studies. Not all studies reported recurrence as local only, metastases only or simultaneous recurrence. Of the studies who did report with this method (7 studies; $n = 1417$), local only recurrence was observed in 3–22%, metastatic recurrence only in 26–60% and simultaneous recurrence in 1–30% (Fig. 2). Median DFS was reported in 15 studies ($n = 2426$), but not all described DFS of the entire study population, but only for the specific investigated groups of that study. Median DFS ranged from 7 to 30 months. OS was reported in 18 studies ($n = 3216$) and ranged from 12 to 35 months.

Retrospective analysis of recurrence patterns

During the study period, 263 patients underwent PD for pancreatic cancer in our centre. Twenty patients died in the first 90 days and 39 were lost to follow up or had incomplete data and were excluded. This led to an inclusion of 204 patients in this study. Baseline patient and surgical characteristics are shown in Table 2. The median age of the patients was 68 years and 55% were male. Most were T3 tumours (98%) and positive lymph nodes were observed in 84% (30% N1 and 54% N2) of the resection specimens. The majority of the tumours invaded surrounding tissues, including perineural tissue (86%).

Table 2 Baseline, resectional, postoperative and pathological characteristics of patients undergoing pancreatoduodenectomy

Patient characteristics			**Pathology**		
Age (years)	68	(60–73)	**Tumour invasion**		
Male gender	144	(55%)	Perineural	175	(86%)
Body mass index (kg/m^2)	24.5	(22.0–27.7)	Perivascular (SMA/SMV)	109	(53%)
Preoperative			Duodenum	116	(57%)
INR	1.1	(1.0–1.2)	Bile duct / ampulla	192	(94%)
Serum bilirubin (μmol/L)	29	(13–93)	Peripancreatic fatty tissue	33	(16%)
CA 19-9 ($n = 166$) (U/ml)	153	(50–697)	**TNM grading (8th Edition)**		
Previous medical history			*Tumour*		
Hypertensionrowhead	71	(35%)	T1	40	(20%)
Diabetes mellitus	45	(22%)	T2	146	(71%)
Cardiovascular disease	22	(11%)	T3	17	(8%)
Preoperative biliary drainage	151	(74%)	T4	1	(1%)
Locally advanced disease[a]	7	(3%)	*Nodes*		
Resection			N0	33	(16%)
PPPD	191	(94%)	N1	61	(30%)
Classic Whipple	13	(6%)	N2	110	(54%)
Venous reconstruction	53	(26%)	Lymph node ratio	0.21	(0.07-0.35)
Postoperative pancreatic fistula			**Resection margin**		
Grade A	8	(4%)	R0	101	(50%)
Grade B	7	(3%)	R1	103	(50%)
Grade C	1	(1%)	**Site of involved margin**		
Postoperative chemotherapy	156	(76%)	SMA/posterior	74	(36%)
Gemcitabine	145	(70%)	SMV	24	(12%)
Gemcitabine + other	7	(3%)	Pancreas (anterior)	8	(4%)
FOLFIRINOX	4	(2%)	Transection	31	(15%)
			Bile duct / ampulla	6	(3%)
			Duodenum	7	(3%)

INR, international normalized ratio; PPPD, pylorus-preserving pancreatoduodenectomy; SMA, superior mesenteric artery; SMV, superior mesenteric vein. Continuous variables are displayed as median (interquartile range).
[a] Pancreatic cancer requiring neoadjuvant chemotherapy prior to resection.

Table 3 Patterns of pathologic margin involvement and recurrence of pancreatic cancer after pancreatoduodenectomy

Recurrence	Overall (n = 204)	R0 (clear margins n = 101)	R1 any margin (n = 103)	p-value (R0 vs. R1 overall)	R1 including SMA margin (n = 74)	p-value (R0 vs. R1 incl SMA)	R1 other margins[a] (n = 29)	p-value (R0 vs. R1 other)
Overall	163 (79%)	72 (71%)	91 (88%)	*0.002*	68 (92%)	*0.001*	23 (79%)	*0.391*
Local	109 (53%)	45 (45%)	64 (62%)	*0.012*	49 (66%)	*0.005*	15 (52%)	*0.495*
Metastatic disease	106 (52%)	50 (50%)	56 (54%)	*0.487*	41 (55%)	*0.44*	15 (52%)	*0.833*
Lymph nodes	25 (12%)	11 (11%)	14 (14%)	–	10 (14%)	–	4 (14%)	–
Peritoneal	23 (11%)	*8 (8%)*	*15 (15%)*	–	12 (16%)	–	3 (10%)	–
Liver	58 (28%)	27 (27%)	31 (30%)	–	23 (31%)	–	8 (28%)	–
Distant metastases	34 (17%)	23 (23%)	11 (11%)	–	10 (14%)	–	1 (3%)	–
Recurrence pattern				*0.013*		*0.004*		*0.734*
No Recurrence	41 (20%)	29 (29%)	12 (12%)	–	6 (8%)	–	6 (21%)	–
Only local	56 (28%)	22 (22%)	34 (33%)	–	27 (37%)	–	7 (24%)	–
Only metastases	53 (26%)	27 (27%)	26 (25%)	–	19 (26%)	–	7 (24%)	–
Simultaneous	54 (26%)	23 (23%)	31 (30%)	–	22 (30%)	–	9 (31%)	–
Timing of recurrence				*0.009*		*0.003*		*0.691*
≤18 months	123 (60%)	53 (53%)	69 (67%)	–	52 (70%)	–	17 (59%)	–
>18 months	40 (20%)	19 (19%)	22 (21%)	–	16 (22%)	–	6 (21%)	–

Statistical significance is reached with p-value < 0.05.
[a] Other: superior mesenteric vein 12%, pancreas transection 15%, bile duct 3%, duodenum 3%.

Recurrence of pancreatic cancer was observed in 79% of the patients. Table 3 summarises patterns of margin involvement and recurrent disease among the retrospective cohort with the aim of defining the relationship between margin involvement and patterns of recurrence and significance of involvement at the SMA. Some 50% of patients had positive margins and the SMA margin was involved in 36%. There was an equal distribution in the anatomical location of recurrence: 27% presented first with only local recurrence, 26% had only metastatic recurrence and 26% had simultaneous local and metastatic recurrence. The liver was the most common site for metastatic disease (28% of all patients). Overall, patients with R1 margins in surgery developed recurrence more often (88% vs. 71%; p = 0.002). More specifically, local recurrence was observed in 62% after R1 resections, compared to 45% in R0 resection (p = 0.012), while no difference was observed for metastatic recurrence (R1 54% vs. R0 50%; p = 0.487). A detailed analysis of the SMA and other margins showed that local recurrence was more frequently observed in patients with an involved SMA margin (66% vs. 45%; p = 0.005), whilst there was no difference in occurrence of local recurrence in patients with R0 and R1 margins if the SMA margin was NOT the involved margin (R1 52% vs. R0 45%; p = 0.495). Furthermore, the patterns of recurrence analysis also revealed a trend towards more local only or simultaneous recurrence, instead of metastatic recurrence, in patients with positive SMA margins (p = 0.013).

The majority of the patients (60%) developed recurrence within 18 months after surgery, while 19% had first signs of recurrence after 18 months. The median DFS for patients with recurrence was 12 months and no difference was observed between the three types of recurrence (p = 0.781) (Fig. 3a). The median OS of patients was 20 months and comparable for the three recurrence groups as well (p = 0.124) (Fig. 3b). Patients with R1 resections had an inferior DFS, compared to those who had a R0 resection (12 vs. 16 months; p < 0.001) (Fig. 3c). More specifically, in an analysis of those with clear margins versus a positive SMA margin, the difference was 11 vs. 16 months; p < 0.001) (Fig. 3d). Univariate and multivariate cox proportional hazard models including factors associated with DFS are displayed in Table 4. An involved SMA margin was an independent factor associated with disease recurrence in the multivariate model (HR 1.115; 95% CI 1.127–2.315; p = 0.009), while other positive margins were not (HR 1.317; 95%CI 0.812–2.137; p = 0.265). Other independent clinical factors in this model were preoperative biliary stenting, adjuvant chemotherapy, tumour size and N status.

Discussion

This study defines recurrence patterns following PD for pancreatic cancer and the impact that microscopic cancer at surgical resection margins has upon this. The systematic review of 23 studies showed a wide variety in reported local, metastatic and simultaneous recurrence. Local recurrence was reported by all studies, but just 11 reported isolated local recurrence.[15–24] The incidence of isolated local recurrence varied between 1

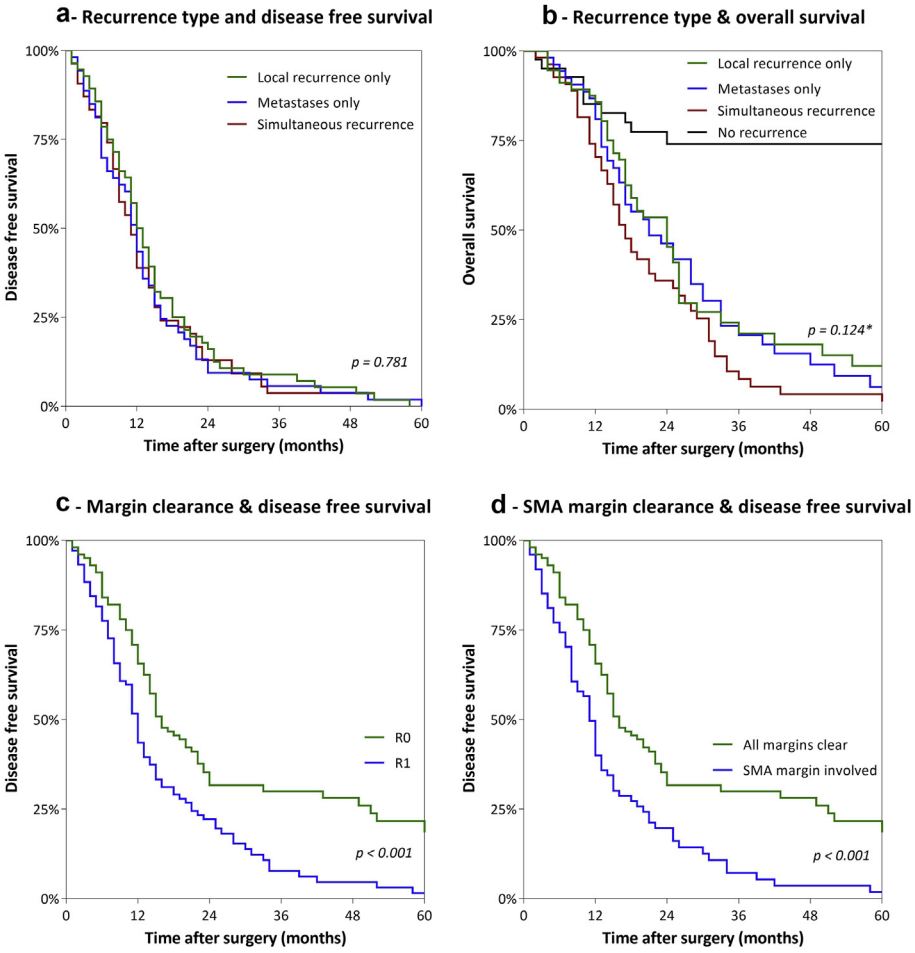

Figure 3 Survival analyses after pancreatoduodenectomy for pancreatic cancer. a: Type of recurrence and disease free survival. b: Type of recurrence and overall survival. * p-value represents the comparison of patients with local only, metastases only and simultaneous recurrence. c: Clearance of resection margins and disease free survival. d: Clearance of the superior mesenteric artery (SMA) margin and disease free survival

and 28%. This wide range in recurrence rate is likely the result of differences in duration in follow up and variations in clinical practice, including resection of borderline tumours and the use of the novel neoadjuvant therapies. Only 7 studies in the review correlated sites of margin positivity with recurrence patterns.[15,16,19,20,22–24] A more in-depth analysis of a single centre series was performed to study the relationship between the site of margin involvement and patterns of recurrence as this data was lacking from the systematic review. These results showed that isolated local recurrence affects nearly one third of all patients. Perhaps unsurprisingly this relates to margin positivity at the time of surgery, especially the SMA margin. Furthermore, those patients with a positive SMA margin had significantly impaired DFS rates, compared to those with negative resection site margins. Patients with local recurrence had similar overall survival rates with those who had initial metastatic or simultaneous recurrence, highlighting the impact of margin involvement on the course of the disease after surgical resection.

Systemic chemotherapy should not be the sole solution to preventing disease recurrence. Survival among patients undergoing PD for pancreatic cancer have gradually improved over recent years due to improvement of adjuvant chemotherapy regimens.[2,25–27] Most recently, the PRODIGE-24 phase III trial showed that patients receiving a novel regimen of adjuvant FOLFIRINOX had a median OS of 54 months.[28] However, these systemic therapies come with a risk of toxicity and due to the large variety in genetics of pancreatic malignancies, they do not target all tumours.[29] As a result, the majority of the patients still develop recurrent disease.[30] Furthermore many patients receive no chemotherapy, let alone more effective therapies.[3,4] Current treatment pathways do not include specific strategies to target cancer at the surgical margin. There is thus a potential opportunity for targeted therapeutic intervention to the surgical margin. Small chemotherapy-loaded carriers that can be left behind after the surgical resection to deliver high concentrations of chemotherapy on a selective area, are such a potential

Table 4 Univariate and multivariate cox proportional hazard models of factors associated with time to disease recurrence (disease free survival) after pancreatoduodenectomy

	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age (years)	0.995	0.979–1.012	*0.587*	–	–	–
BMI (kg/m^2)	0.991	0.958–1.025	*0.598*		–	–
Female gender	1.073	0.789–1.460	*0.654*	–	–	–
Preoperative biliary stent	1.428	0.995–2.049	*0.053*	1.458	1.005–2.116	*0.047*
Neoadjuvant chemotherapy	0.956	0.391–2.334	*0.92*	–	–	–
Adjuvant chemotherapy	0.634	0.439–0.916	*0.015*	0.454	0.308–0.670	*<0.001*
Tumour size (mm)	*1.019*	*1.001–1.035*	*0.012*	1.023	1.006–1.040	*0.007*
Positive N status	3.347	2.011–5.570	*<0.001*	3.197	1.867–5.474	*<0.001*
Venous reconstruction	1.109	0.762–1.613	*0.588*	–	–	–
Resection margin						
R0	1.000			1.000		
R1 other margins	1.485	0.925–2.384	*0.102*	1.317	0.812–2.137	*0.265*
R1 SMA margin	1.961	1.401–2.745	*<0.001*	1.615	1.127–2.315	*0.009*

BMI, body mass index; CI, confidence interval; HR, hazard ratio; SMA, superior mesenteric artery. Statistical significance is reached with p-value < 0.05.

strategy and could be effective in reducing the risk for local recurrence.[31]

The burden of local recurrence can be explained by the phenomenon of tumour budding, which is an infiltrative growth pattern consisting of isolated tumour cells or small cell clusters located at the invasive front of some types of carcinomas and a known risk factor for poor prognosis in pancreatic cancer.[32] Furthermore, high-grade tumour budding is associated with development of distant metastasis and an in-depth analysis of the SMA margin by Liu *et al.* showed that high-grade tumour budding is common in the tissue surrounding the SMA, suggesting a positive SMA margin may not only be responsible for local recurrence, but also a pathway for distant metastasis.[33] To quantify which patients might suffer as a consequence of disease at the margin we therefore hypothesise the cohort are those with local recurrence only or a positive SMA margin, thus including one fourth to one third of the patients undergoing pancreatic head resection. From another point of view, there is increasing attention for the wide variation in molecular subtypes amongst patients with pancreatic cancer.[34] According to this fundamental tumour biology, some patients are more likely to develop metastases on different sites with different prognoses. The mechanism of disease progression in these cases is not fully understood, but these recurrence patterns are less likely to be dependent on the status of the resection margin and subsequent local recurrence.

This study highlights the systematic failure of PD surgery to provide an oncologically sound treatment for pancreatic cancer. This is in concordance with the results of 16 studies in the systematic review, where 17%–76% of patients had a R1 resection.[9,15–18,20–22,24,35–41] The SMA margin was positive in 36% in our cohort, compared to 15–35% in the six studies that specifically assessed this margin.[9,15–17,35,39] Positive resection margins are a known risk factor for recurrence and mortality and we observed a significant impaired DFS for patients with positive margins at our centre.[42] Patients with disease at the SMA margin had a 5 month median reduction in survival in our single centre series. Only three studies in the systematic review studied the correlation between status of this margin and outcome and two of them found a significant relation with recurrence or mortality.[9,15,16] There is thus a sound basis to develop strategies to augment the surgical margin at PD surgery. This is not without precedent; similar strategies are used in the treatment of threatened margins in rectal cancer.[43,44]

This study has limitations. The duration of DFS are likely overestimated as scans are typically performed when a patient develops symptoms. However, data between studies is largely concordant supporting the reported observations. Some 185 full manuscripts were reviewed as part of the systematic review, but only 23 were included in the final analysis. This was the result of many studies not reporting local recurrence specifically, studies also including distal or total pancreatic resections and cancers other than pancreatic ductal adenocarcinoma. Although all studies in the systematic review reported the incidence of local recurrence, there was a wide variation in the described patterns of recurrence and missing data on isolated local or metastatic recurrence was common. Only a small part of the studies reported the three different forms of recurrence of our cohort

study. Therefore, it was not possible to perform a formal meta-analysis.

In conclusion, local recurrence of pancreatic cancer is common after PD and is related to a systematic failure of pancreatoduodenectomy to clear surgical margins. Developing novel strategies to augment the surgical margin could improve outcomes.

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Conflict of interest

None declared.

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Appendix A. Supplementary data

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