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Original Article

Prognostication for recurrence patterns after curative resection for pancreatic ductal adenocarcinoma

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Backgrounds/Aims: This study aimed to investigate patterns and factors affecting recurrence after curative resection for pancreatic ductal adenocarcinoma (PDAC).

Methods: Consecutive patients who underwent curative resection for PDAC (2011-21) and consented to data and tissue collection (Barts Pancreas Tissue Bank) were followed up until May 2023. Clinico-pathological variables were analysed using Cox proportional hazards model.

Results: Of 91 people (42 males [46%]; median age, 71 years [range, 43–86 years]) with a median follow-up of 51 months (95% confidence intervals [CIs], 40–61 months), the recurrence rate was 72.5% (n = 66; 12 loco-regional alone, 11 liver alone, 5 lung alone, 3 peritoneal alone, 29 simultaneous loco-regional and distant metastases, and 6 multi-focal distant metastases at first recurrence diagnosis). The median time to recurrence was 8.5 months (95% CI, 6.6–10.5 months). Median survival after recurrence was 5.8 months (95% CI, 4.2–7.3 months). Stratification by recurrence location revealed significant differences in time to recurrence between loco-regional only recurrence (median, 13.6 months; 95% CI, 11.7–15.5 months) and simultaneous loco-regional with distant recurrence (median, 7.5 months; 95% CI, 4.6–10.4 months; $p = 0.02$, pairwise log-rank test). Significant predictors for recurrence were systemic inflammation index (SII) ≥ 500 (hazard ratio [HR], 4.5; 95% CI, 1.4–14.3), lymph node ratio ≥ 0.33 (HR, 2.8; 95% CI, 1.4–5.8), and adjuvant chemotherapy (HR, 0.4; 95% CI, 0.2–0.7).

Conclusions: Timing to loco-regional only recurrence was significantly longer than simultaneous loco-regional with distant recurrence. Significant predictors for recurrence were SII, lymph node ration, and adjuvant chemotherapy.

Key Words: Overall survival; Disease free survival; Multivariate analysis; Lymph node ratio; Systemic inflammation index

INTRODUCTION

Pancreatic cancer is the fourth most common cause of cancer related deaths in the UK [1]. Unlike other types of cancer, it has not seen an overall decline in deaths over the last two decades in the USA or Europe [1]. Pancreatic cancer has a poor mortality to incidence ratio of 98% and a poor 5-year overall survival (OS) rate of 6% [2,3]. Only surgery offers a potential cure. However, most cases are already metastatic at the time of diagnosis. Only 15%–20% of cases have a potentially resectable disease [4]. A proportion of these patients will then undergo curative resection and adjuvant therapy, which has been shown to increase 5-year OS rates to 28%–43% in the best outcome scenario [5,6]. Despite advances in modern medicine, a recent systematic review has shown that even after surgery, 47%–92% of patients will have pancreatic ductal adenocarcinoma (PDAC) recurrence [7].

Recurrence occurs mainly within the first two years after resection [5,8]. However, evidence suggests that recurrence at different sites behaves differently. Studies have reported that liver recurrence occurs earlier than recurrence at other sites while lung recurrence occurs later [9,10]. This also impacts survival after diagnosis of recurrence where lung recurrence has a better prognosis than recurrence at other sites [11]. De-

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spite multiple studies looking into PDAC recurrence, there has been no consensus on predictive factors of recurrence. To date, there are few studies reporting PDAC recurrence patterns and predictive factors in the UK. There are no national guidelines defining surveillance after resection for PDAC. Defining recurrence patterns and predictors could provide insight into how surveillance could be conducted. Thus, the aim of this study was to investigate patterns and factors affecting first site recurrence after curative resection of PDAC.

MATERIALS AND METHODS

Patient selection and characteristics

All consented patients from a prospectively maintained database Barts Pancreas Tissue Bank (Hampshire B Research Ethics Committee supported in January 2014, ref: 13/SC/0592; renewed 2019, ref: 18/SC/0630) were screened for eligibility (curative resection of PDAC) for this study. Patients with distant metastases diagnosed at the time of surgery were excluded. Patients with neoadjuvant chemotherapy were included. Only eight patients had venous resection. None had an arterial resection. The TNM 7th or 8th edition staging system was used. Resection margin status (R) was defined as R0 when the resection margin was ≥ 1 mm away from the tumour. It was defined as R1 when the resection margin was < 1 mm away from the tumour. Patients were excluded if they had an R2 margin status. The cut-off surgical resection date for inclusion into this study was November 1st, 2021. Follow-up was censored at May 1st, 2023. Of a total of 799 patients screened, 91 patients were included in this study (Fig. 1).

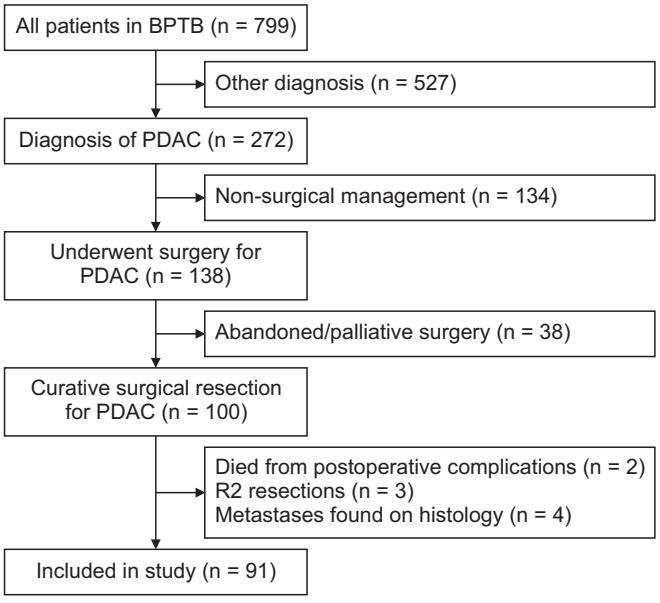

Fig. 1. Flow chart of patient enrolment in this study. BPTB, Barts Pancreas Tissue Bank; PDAC, pancreatic ductal adenocarcinoma.

Data collection and follow-up

Data missing from Barts Pancreas Tissue Bank database were gathered from Electronic Health Records of Barts Health NHS Trust. Preoperative blood test results were collected within two months prior to surgery—at the time of referral, preoperative assessment or on the day of surgery, whichever was the latest. Postoperative CA19-9 levels were taken within three months of the date of recurrence. Symptom information was collected preoperatively. If a patient underwent a PET scan within two months prior to surgery, SUVmax data were obtained. Posterior resection margin was defined as posterior surface (retroperitoneum). Anterior margin was defined as anterior surface of the pancreas. Loco-regional recurrence was defined as involvement of the pancreatic bed, remnant pancreas, superior mesenteric vessels, regional lymph nodes, and anastomotic site.

Standard follow-up regimen after curative surgical resection for PDAC was a computed tomography (CT) scan, CA19-9 blood test, and a clinic appointment at 6-monthly intervals for a duration of five years. Patients who were referred to oncology postoperatively had regular follow-up appointments and CT scans as directed by the oncologist, occasionally from the hospital that referred them. CT scans were the main modality of choice for detecting recurrence. Ratification occurred at multi-disciplinary team (MDT) meeting without histological confirmation of recurrence. Only the first site(s) of recurrence were recorded and categorised into loco-regional alone, liver alone, lung alone, peritoneal alone, simultaneous loco-regional with distant metastases, and multiple distant metastases. These patients were censored on the last known date of follow-up during data analysis. There was one patient with PDAC within intraductal papillary mucinous neoplasm who developed a second primary pancreatic cancer in the tail of the pancreas five years following a pylorus-preserving pancreaticoduodenectomy. This patient was censored at the date of diagnosis of the second primary during data analysis.

Statistical analysis

Survival and recurrence analysis were undertaken by first converting continuous variables into categorical variables. This was achieved using the X-tile software (Rimm Lab, Yale School of Medicine) to identify optimal cut-off values after Monte Carlo correction [12]. Cut-off values were then rounded off to the nearest round number if applicable. All other statistical analyses were undertaken using SPSS version 28 (IBM Corp.). Univariate analysis was undertaken using the Cox proportional hazards regression model. Kaplan–Meier curves were generated for each variable. A cut-off p-value of 0.05 was used to determine statistically significant covariates. Covariates with significant numbers of missing values (> 10%) were not included in multivariate analysis. Age was also excluded from multivariate analysis as it was not a biological factor of PDAC. Remaining covariates were then subject to a test for multi-collinearity and excluded if predictor variables were highly correlated with a

Table 1. Patient characteristics, variables, survival analysis, and recurrence analysis

Variable	n	Overall survival				Disease-free survival			
		Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
		p-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)
Age (yr, at surgery)		0.004*				0.112			
< 78	75		1				1		
≥ 78	16		2.5 (1.3–4.6)				1.6 (0.9–3.0)		
Sex		0.532				0.957			
Male	42		1				1		
Female	49		0.9 (0.5–1.4)				1 (0.6–1.6)		
Ethnicity		0.972				0.741			
Caucasian	75		1				1		
Afro-Caribbean	7		1.1 (0.4–3.1)				1.4 (0.6–3.5)		
Asian	6		1 (0.4–2.5)				1.2 (0.5–3.0)		
BMI (kg/m^2)		0.409				0.162			
< 22	18		1				1		
≥ 22	72		0.8 (0.4–1.4)				0.7 (0.4–1.2)		
Operation		0.121				0.22			
PD	19		1				1		
PPPD	45		0.6 (0.3–1.1)				0.7 (0.4–1.3)		
DP	22		0.4 (0.2–0.9)				0.5 (0.3–1.1)		
Others	5		0.4 (0.1–1.3)				0.3 (0.1–1.3)		
Vessel resection		0.453				0.573			
No	75		1				1		
Yes	8		1.4 (0.6–3.6)				1.3 (0.5–3.0)		
T stage		0.4				0.056			
0	3		1				1		
1	10		0.8 (0.2–4.4)				0.4 (0.1–2.7)		
2	40		1.6 (0.4–6.9)				2.1 (0.5–8.9)		
3	38		1.8 (0.4–7.6)				2 (0.5–8.3)		
N stage		< 0.001*		0.002*		< 0.001*		0.08	
0	26		1		1		1		1
1	46		3.6 (1.8–7.3)		0.5 (0.2–1.5)		3.3 (1.7–6.4)		3.1 (1.1–8.6)
2	19		7.7 (3.3–17.9)		2.1 (0.6–7.5)		4.9 (2.2–10.6)		2.3 (0.7–7.1)
Tumour differentiation[a)]		0.119				0.371			
Well/moderate	46		1				1		
Poor	41		1.5 (0.9–2.5)				1.3 (0.8–2.0)		
Tumour resection status		0.009*		0.868		0.004*		0.308	
R0	35		1		1		1		1
R1	54		2.1 (1.2–3.6)		1 (0.5–1.8)		2.2 (1.3–3.7)		1.4 (0.7–2.9)
Number of R1 margins		0.02*				0.004*			
0 (R0)	35		1				1		
1	16		1.6 (0.8–3.6)				1.5 (0.7–3.2)		
2	23		2.3 (1.2–4.4)				2.6 (1.4–4.9)		
≥ 3	13		2.7 (1.3–5.7)				3.2 (1.5–6.7)		
R1 location[b)]									
Anterior	16	0.125	1.7 (0.9–3.2)			0.06	1.8 (1.0–3.4)		
Posterior	23	0.955	1 (0.5–1.9)			0.484	0.8 (0.4–1.5)		
SMV	25	0.326	1.4 (0.7–2.5)			0.139	1.6 (0.9–2.9)		
SMA	6	0.473	1.4 (0.6–3.6)			0.092	2.3 (0.9–6.1)		
Uncinate	28	0.041*	2 (1.0–3.9)			0.015*	2.3 (1.2–4.3)		

Table 1. Continued 1

Variable	n	Overall survival				Disease-free survival			
		Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
		p-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)
Invasion[c]		< 0.001*		0.361		< 0.001*		0.188	
None	2								
Lymphovascular	6		1		1		1		1
Perineural	13								
Both	66		3.4 (1.6–7.1)		1.5 (0.6–3.7)		3.3 (1.6–6.6)		2 (0.7–5.3)
Max tumour size (mm)		0.033*		0.798		0.006*		0.223	
< 22	15		1		1		1		1
≥ 22	71		2.3 (1.1–4.8)		1.1 (0.4–3.2)		3 (1.4–6.7)		2 (0.7–5.6)
Tumour location		0.092				0.064			
Head, uncinate	63		1				1		
Tail	16		0.8 (0.4–1.4)				0.9 (0.5–1.7)		
Body, neck	10		0.3 (0.1–1.0)				0.3 (0.1–0.9)		
Lymph node ratio		< 0.001*		0.026*					
< 0.12	34		1		1				
≥ 0.12	55		5.4 (2.9–10.2)		3.7 (1.2–11.4)				
Lymph node ratio						< 0.001*		0.005*	
< 0.33	62						1		1
≥ 0.33	27						4.7 (2.6–8.3)		2.8 (1.4–5.8)
ASA score		0.751				0.764			
1, 2	44		1				1		
3, 4	38		0.9 (0.6–1.5)				0.9 (0.6–1.5)		
Smoking status		0.101				0.042*		0.291	
Never	46		1				1		1
Ex-smoker	27		1.8 (1.0–3.2)				1.9 (1.1–3.3)		1.7 (0.9–3.3)
Current smoker	18		1.1 (0.5–2.2)				1 (0.5–2.0)		1.4 (0.6–3.0)
Diabetes		0.284				0.165			
None	57		1				1		
Yes	34		0.8 (0.5–1.3)				0.7 (0.4–1.2)		
Neo-adjuvant chemotherapy		0.619				0.173			
None	82		1				1		
Yes	9		0.8 (0.3–1.9)				0.5 (0.2–1.3)		
Adjuvant chemotherapy		0.002*		0.01*		0.004*		0.002*	
None	34		1		1		1		1
Yes	56		0.5 (0.3–0.8)		0.4 (0.2–0.8)		0.5 (0.3–0.8)		0.4 (0.2–0.7)
Adjuvant radiotherapy		0.185				0.44			
None	87		1				1		
Yes	4		0.4 (0.1–1.6)				0.6 (0.2–2.0)		
Recurrence		< 0.001*		< 0.001*					
None	25		1		1				
Yes	66		11.7 (4.1–33.3)		36.8 (6.0–224.6)				
Type of recurrence[d]									
Loco-regional	41	0.948	1 (0.6–1.7)						
Liver	32	0.043*	1.7 (1.0–3.0)						
Lung	20	0.349	1.3 (0.8–2.3)						
Peritoneal	14	0.171	1.5 (0.8–2.8)						

Table 1. Continued 2

Variable	n	Overall survival				Disease-free survival			
		Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
		p-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)
Simultaneous loco-regional + distant metastases	29	0.02*	1.9 (1.1–3.1)						
Multiple distant metastases	14	0.004*	2.5 (1.3–4.8)						
Blood tests									
Preoperative CA19-9 (U/mL)		0.003*							
< 500	52		1						
≥ 500	21		2.5 (1.4–4.6)						
Preoperative CA19-9 (U/mL)						0.001*			
< 250	43						1		
≥ 250	30						2.5 (1.4–4.4)		
Pre-recurrence CA19-9 (U/mL)		< 0.001*							
< 1,500	48		1						
≥ 1,500	14		3.8 (1.8–7.7)						
Pre-recurrence CA19-9 (U/mL)						0.017*			
< 100	24						1		
≥ 100	38						2.1 (1.1–3.7)		
CRP (mg/L)		0.44				0.587			
< 3	7		1				1		
≥ 3	33		1.5 (0.6–3.8)				1.3 (0.5–3.4)		
Albumin (g/L)		0.328				0.702			
< 35	7		1				1		
≥ 35	81		0.7 (0.3–1.5)				0.8 (0.3–2.1)		
Platelets ($\times 10^9$/L)		0.723				0.135			
< 300	51		1				1		
≥ 300	37		1.1 (0.7–1.8)				1.5 (0.9–2.4)		
Neutrophil ($\times 10^9$/L)		0.003*		0.333	1.4 (0.7–2.7)	0.013*		0.804	
< 5	46		1				1		1
≥ 5	42		2.3 (1.3–3.8)				1.9 (1.1–3.1)		1.1 (0.6–2.0)
Lymphocyte ($\times 10^9$/L)		0.112				0.288			
< 1	7		1				1		
≥ 1	81		0.5 (0.2–1.2)				0.6 (0.2–1.5)		
Monocyte ($\times 10^9$/L)		0.217				0.219			
< 0.7	53		1				1		
≥ 0.7	35		1.4 (0.8–2.3)				1.4 (0.8–2.2)		
Preoperative bilirubin (μmol/L)		0.08							
≤ 12	37		1						
> 12	48		1.6 (1.0–2.7)						
Preoperative bilirubin (μmol/L)						0.013*		0.642	
< 10	34						1		1
≥ 10	51						2 (1.1–3.4)		0.8 (0.4–1.8)
Blood test-based scoring systems									
Glasgow prognostic score		0.904				0.92			
0	27		1				1		
≥ 1	13		1 (0.5–2.3)				1 (0.5–2.4)		

Table 1. Continued 3

Variable	n	Overall survival				Disease-free survival			
		Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
		p-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)
Systemic inflammation index		0.01*		0.007*					
< 350	11		1		1				
≥ 350	77		3.4 (1.3–8.6)		11.4 (2.0–66.1)				
Systemic inflammation index						0.011*		0.01*	
< 500	21						1		1
≥ 500	67						2.3 (1.2–4.3)		4.5 (1.4–14.3)
Neutrophil-lymphocyte ratio		0.004*		0.189		0.014*			
< 2	20		1		1		1		
≥ 2	68		2.7 (1.4–5.2)		0.4 (0.1–1.6)		2.3 (1.2–4.4)		
Platelet-lymphocyte ratio		0.084				0.038*		0.778	
< 150	41		1				1		1
≥ 150	47		1.6 (0.9–2.6)				1.7 (1.0–2.8)		0.9 (0.4–2.1)
Prognostic nutrition index		0.091							
< 50	31		1						
≥ 50	57		0.6 (0.4–1.1)						
Prognostic nutrition index						0.284			
< 55	63						1		
≥ 55	25						0.7 (0.4–1.3)		
Lymphocyte-monocyte ratio		0.01*		0.086					
< 2	19		1		1				
≥ 2	69		0.4 (0.2–0.8)		0.5 (0.2–1.1)				
Lymphocyte-monocyte ratio						0.026*		0.638	
< 4.5	76						1		1
≥ 4.5	12						0.4 (0.1–0.9)		1.4 (0.4–4.8)
PET SUVMax		0.846							
< 7	12		1						
≥ 7	8		1.1 (0.3–3.8)						
PET SUVMax						0.176			
< 6	8						1		
≥ 6	12						2.3 (0.7–7.5)		
Symptoms									
Pain		0.012*		< 0.001*		0.099			
No	53		1		1		1		
Yes	38		1.9 (1.1–3.1)		3.6 (1.8–7.2)		1.5 (0.9–2.4)		
Jaundice		0.005*		0.667		0.011*		0.107	
No	44		1		1		1		1
Yes	47		2.1 (1.2–3.5)		0.9 (0.4–1.7)		1.9 (1.2–3.1)		0.5 (0.2–1.2)
Weight loss		0.917				0.42			
No	53		1				1		
Yes	38		1 (0.6–1.6)				0.8 (0.5–1.3)		
Nausea		0.744				0.533			
No	71		1				1		
Yes	20		1.1 (0.6–2.0)				1.2 (0.7–2.1)		
Vomiting		0.572				0.929			
No	79		1				1		
Yes	12		0.8 (0.4–1.8)				1 (0.5–2.1)		

Table 1. Continued 4

Variable	n	Overall survival				Disease-free survival			
		Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
		p-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)
Diarrhoea		0.784				0.516			
No	70		1				1		
Yes	21		0.9 (0.5–1.7)				0.8 (0.5–1.5)		
Constipation		0.171				0.124			
No	78		1				1		
Yes	13		1.6 (0.8–3.0)				1.7 (0.9–3.2)		
Other symptoms		0.95				0.526			
No	68		1				1		
Yes	23		1 (0.5–1.8)				0.8 (0.5–1.5)		
Post recurrence therapy		0.403							
No	59		1						
Yes	32		1.2 (0.7–2.1)						

BMI, body mass index; PD, pancreaticoduodenectomy; PPPD, pylorus-preserving pancreaticoduodenectomy; DP, distal pancreatectomy; SMV, superior mesentric vein; SMA, superior mesentric artery; ASA, American Society of Anesthesiologists; CRP, C-reactive protein; HR, hazard ratio; CI, confidence interval.
[a]There were only 2 patients with well-differentiated tumour gradings. These patients were combined with patients with moderately differentiated tumour gradings for data analysis. [b]Analysis did not include R0 patients as all margins were significant on inclusion of R0 patients. Each variable was analysed against all other margins. [c]Lymphovascular and perineural invasion were combined for statistical analysis due to small numbers. [d]Each site of recurrence was compared against any other site of recurrence.
*$p < 0.05$.

variance inflation factor ≥ 5 and/or a tolerance value < 0.2 [13]. Multivariate survival analysis was then performed for remaining covariates with a cut-off *p*-value of 0.05 for significance.

RESULTS

Patient demographic

A total of 91 patients were identified in the Barts Pancreas Tissue Bank database who underwent curative surgical resection for PDAC between March 2011 and November 2021 (Fig. 1). The study population consisted of 42 males (46%) with a median age of 71 years (range, 43–86 years) at the time of surgery. The median follow-up time was 51 months (95% confidence interval [CI], 40–61 months). There were 61 patients (67%) with PDAC in the head of the pancreas, 16 (18%) with PDAC in the tail, 4 (4%) with PDAC in the body, 3 (3%) with PDAC in the uncinated process, and 7 (8%) with multifocal PDAC. Nine patients (10%) received neo-adjuvant chemotherapy, of which only one had gemcitabine + capecitabine while the rest had folfirinox. Fifty-six patients (62%) received adjuvant chemotherapy, of which 17 (19%) had folfirinox and 38 (42%) had gemcitabine +/– capecitabine while 1 (1%) had insufficient data.

Table 2. Recurrence statistics

Recurrence location	Location specific only	Total recurrence at these sites
Loco-regional	12 (18)	41
Liver	11 (17)	32
Lung	5 (8)	20
Peritoneal	3 (5)	14
Simultaneous loco-regional + distant metastasis	29 (44)	29
Multiple distant metastases	6 (9)	14

Values are presented as number (%) or number only.

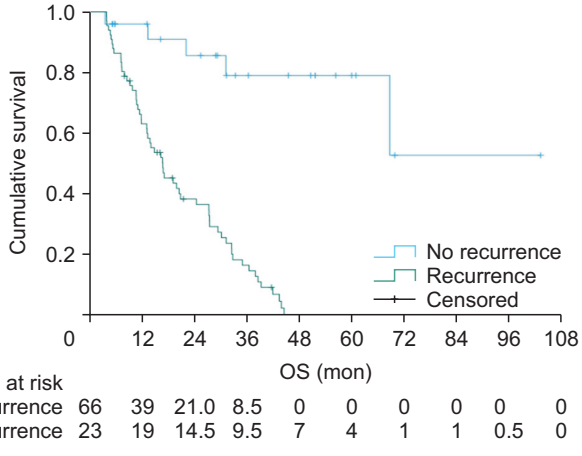

Fig. 2. Kaplan–Meier OS curve for recurrence vs. no recurrence. OS, overall survival.

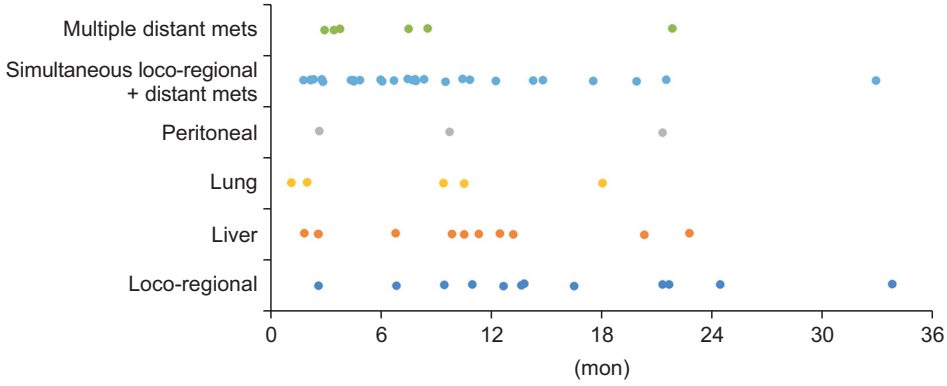

Fig. 3. Scatter plot of disease-free survival stratified by location specific recurrence.

Recurrence pattern analysis

The recurrence rate in this study was 72.5% (n = 66; loco-regional alone [n = 12], liver alone [n = 11], lung alone [n = 5], peritoneal alone [n = 3], simultaneous loco-regional and distant metastasis [n = 29], and multiple distant metastatic recurrence [n = 6]) (Table 1, 2). No patient had solitary distant metastasis. One-year and 2-year OS rates were 63% and 38%, respectively, in the recurrence group and 96% and 85%, respectively, in the non-recurrence group (Fig. 2). The 5-year OS rate for the non-recurrence group was 47% (deaths due to other causes). The median time to recurrence was 8.5 months (95% CI, 6.6–10.5 months) and median survival after recurrence was 5.3 months (95% CI, 4.0–6.5 months). Stratification by recurrence location revealed significant differences in disease-free survival between loco-regional only recurrence (median, 13.6 months; 95% CI, 11.7–15.5 months) and simultaneous loco-regional with distant recurrence (median, 7.5 months; 95% CI, 4.6–10.4 months; p = 0.02, pairwise log-rank test) (Fig. 3, 4, Table 3).

Univariate analysis revealed that N stage, positive tumour resection status, number of R1 margins, uncinate positive margin, simultaneous lymphovascular and perineural invasion, maximum tumour size ≥ 22 mm, lymph node ratio (LNR) ≥ 0.33, smoking status, adjuvant chemotherapy, preoperative CA19-9 level ≥ 250 U/mL, postoperative CA19-9 level ≥ 100 U/mL,

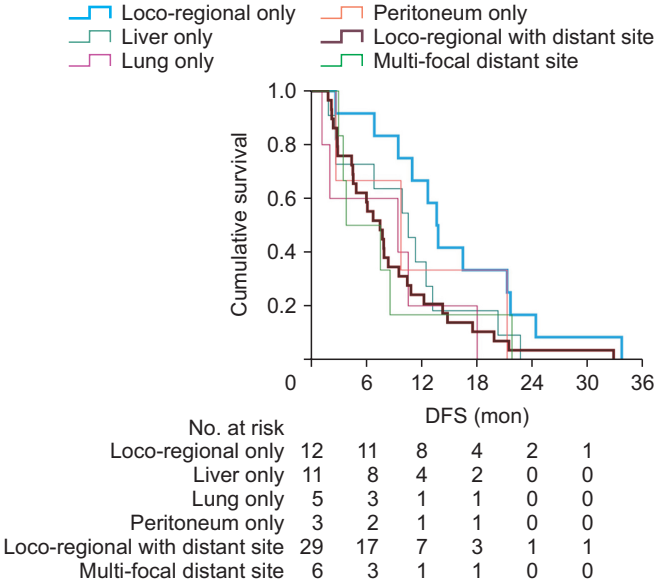

Fig. 4. Kaplan–Meier survival curve for DFS stratified by recurrence location. DFS, disease-free survival.

neutrophil level ≥ 5×10^9/L, preoperative bilirubin > 10 μmol/L, systemic inflammation index (SII) ≥ 500, neutrophil-lymphocyte ratio (NLR) ≥ 2, platelet-lymphocyte ratio ≥ 150, lympho-

Table 3. Kaplan–Meier analysis of disease-free survival stratified by recurrence location

Recurrence location and p-value	Loco-regional only	Liver only	Lung only	Peritoneal only	Simultaneous loco-regional + distant metastasis	Multiple distant metastases
Loco-regional only						
Liver only	0.09					
Lung only	0.06	0.38				
Peritoneal only	0.4	0.94	0.43			
Simultaneous loco-regional + distant metastasis	0.02*	0.48	0.88	0.64		
Multiple distant metastases	0.1	0.5	0.99	0.8	0.97	

*p < 0.05.

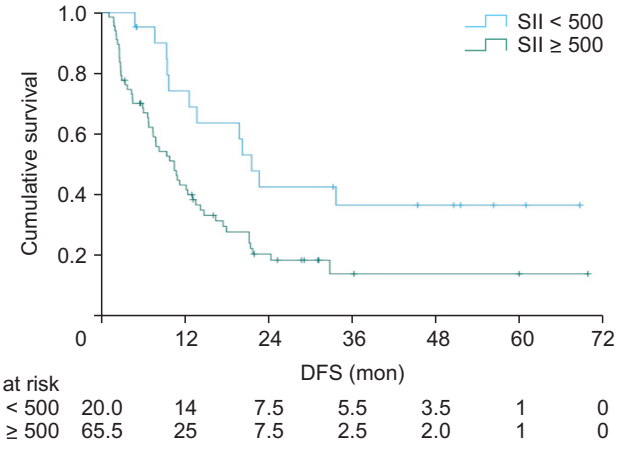

Fig. 5. Kaplan–Meier DFS curve for SII < 500 vs. ≥ 500. SII, systemic inflammation index; DFS, disease-free survival.

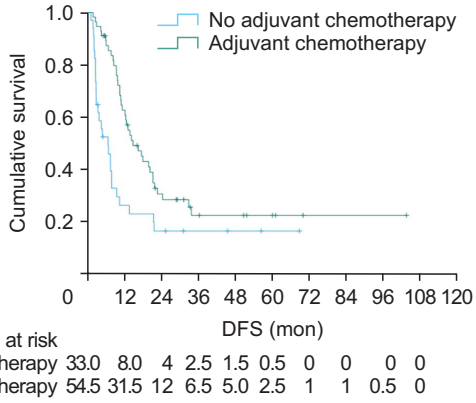

Fig. 7. Kaplan–Meier DFS curve for adjuvant chemotherapy vs. no adjuvant chemotherapy. DFS, disease-free survival.

cyte-monocyte ratio (LMR) ≥ 4.5, and jaundice were significant predictors for recurrence.

In multivariate analysis, preoperative CA19-9 level ≥ 250 U/mL and postoperative CA19-9 level ≥ 100 U/mL were excluded due to missing data. Number of R1 margins and uncinate positive margins were also excluded as information was not available for the total study population. NLR ≥ 2 was excluded due to multi-collinearity. A total of 82 cases were included in the multivariate analysis. Significant predictors for recurrence were SII ≥ 500, LNR ≥ 0.33, and adjuvant chemotherapy. Kaplan–Meier survival curves were generated for each significant predictor (Fig. 5–7).

Resection margin analysis

Resection margin status was analysed further. It was found be to significantly predictive of loco-regional recurrence (p = 0.034; hazard ratio [HR], 2.1; 95% CI, 1.1–4.1), but not predictive of other types of recurrence (liver, p = 0.255, HR: 1.5, 95% CI: 0.7–3.2; lung, p = 0.064, HR: 2.7, 95% CI: 1.0–7.5; peritoneal, p = 0.245, HR: 2, 95% CI: 0.6–6.7; simultaneous loco-regional and distant sites, p = 0.173, HR: 1.7, 95% CI: 0.8–3.7; multiple distant sites, p = 0.305, HR: 1.9, 95% CI: 0.6–6.1). However, 57% of patients (n = 20) with R0 resections still developed recurrence.

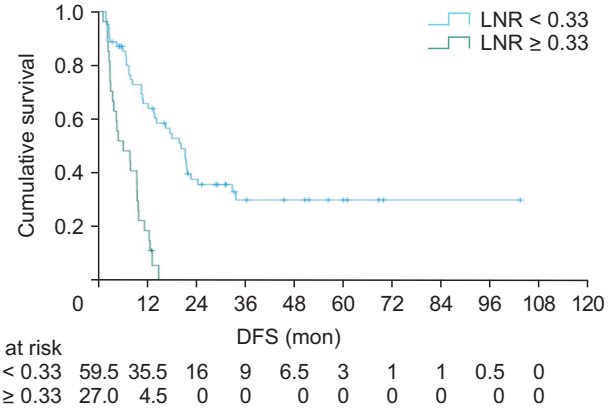

Fig. 6. Kaplan–Meier DFS curve for LNR < 0.33 vs. ≥ 0.33. LNR, lymph node ratio; DFS, disease-free survival.

Survival analysis

At the time of this study, 63 patients (69%) had died. The median OS was 22 months (95% CI, 13.6–30.4 months). One-year and 2-year OS rates were 71% and 50%, respectively.

In univariate analysis, age ≥ 78, N stage, positive tumour resection status, number of R1 margins, uncinate positive margin, simultaneous lymphovascular and perineural invasion, maximum tumour size ≥ 22 mm, LNR ≥ 0.12, adjuvant chemotherapy, PDAC recurrence status, any liver recurrence, simultaneous locoregional + distant metastases recurrence, multiple distant metastases recurrence, preoperative CA19-9 level ≥ 500 U/mL, postoperative CA19-9 level ≥ 1,500 U/mL, neutrophil level ≥ 5×10^9/L, SII ≥ 350, NLR ≥ 2, LMR ≥ 2, pain, and jaundice were significant prognostic factors for OS.

In multivariate analysis, preoperative CA19-9 level ≥ 500 U/mL and postoperative CA19-9 level ≥ 1,500 U/mL were excluded due to missing data. Uncinate positive margin, any liver recurrence, simultaneous loco-regional with distant recurrence, and multiple distant site recurrence covariates were also excluded as these covariates were not present in the total study population. The number of R1 margins as a covariate was then excluded due to multi-collinearity. A total of 82 cases were included in the multivariate analysis. Significant predictors for prognosis in multivariate analysis were N stage, LNR ≥ 0.12, adjuvant chemotherapy, recurrence, SII, and pain.

Recurrence location and overall survival

OS stratified by recurrence location revealed significant differences between loco-regional only recurrence and simulta-

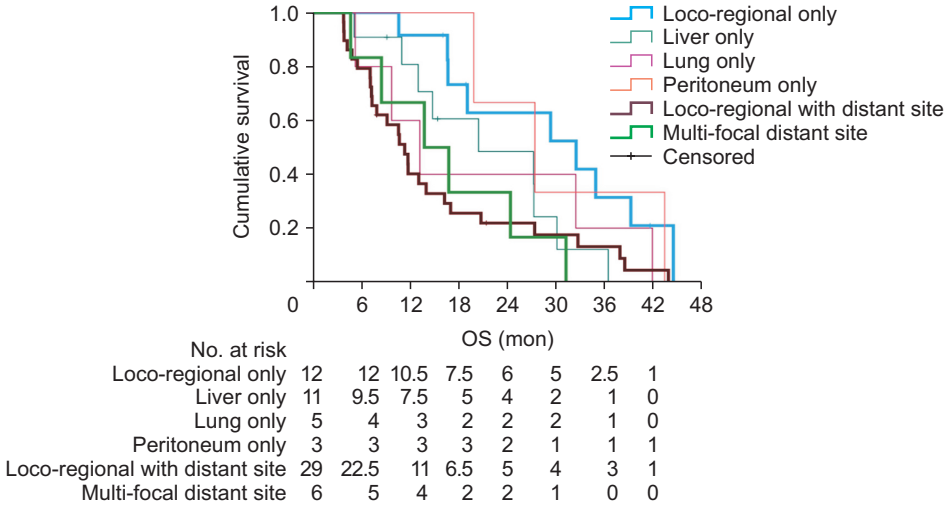

Fig. 8. Kaplan–Meier survival curve for OS stratified by recurrence location. OS, overall survival.

neous loco-regional with distant recurrence (p = 0.01, pairwise log-rank test) as well as locoregional only recurrence and multiple distant site recurrence (p = 0.02, pairwise log-rank test) (Fig. 8, Table 4). The OS was 32.5 months (95% CI, 12.8–52.2 months) for loco-regional alone, 20.4 months (95% CI, 3.8–37 months) for liver alone, 13.2 months (95% CI, 5.7–20.6 months) for lung alone, 27.4 months (95% CI, 15.3–39.5 months) for peritoneal alone, 11.3 months (95% CI, 8.0–14.5 months) for simultaneous loco-regional and distant metastatic recurrence, and 13.7 months (95% CI, 3.7–23.7 months) for multiple distant metastases.

Analysis comparing any liver recurrence against any other recurrence location demonstrated a significantly worse OS (p = 0.041; HR, 1.7; 95% CI, 1.0–2.9). Similarly, simultaneous loco-regional recurrence had worse OS (p = 0.02; HR, 1.9; 95% CI, 1.1–3.1) as well as multiple distant site recurrence (p = 0.004; HR, 2.5; 95% CI, 1.3–4.8). No significantly worse OS was found for loco-regional (p = 0.948; HR, 1; 95% CI, 0.6–1.7), lung (p = 0.349; HR, 1.3; 95% CI, 0.8–2.3), or peritoneal (p = 0.171; HR, 1.5; 95% CI, 0.8–2.8) recurrence.

DISCUSSION

Patterns of recurrence

Despite a complex major surgery for resection of PDAC with an intention to cure, recurrence is common. This study found a significant difference between first site loco-regional only recurrence and simultaneous loco-regional and distant recurrence. Other studies have reported a relatively shorter disease-free interval for liver recurrence than lung recurrence [5,14,15]. A Japanese study analysing 524 patients who underwent PDAC resections found that the median time to recurrence was five months for liver as compared to 18 months for lung [9]. Histological differences such as venous invasion were noticed between liver and lung recurrence [9,16]. Kubo et al. [16] also found that even in patients receiving neo-adjuvant therapy, the presence of microscopic invasion could increase the risk of recurrence, particularly hepatic relapse. It has been postulated that the close proximity of PDAC to the portal venous system might lead to earlier recurrence in the liver [17]. Molecular alterations in PDAC such as SMAD4 gene mutation as well as those affecting DNA repair mechanisms could potentially lead

Table 4. Kaplan–Meier analysis of overall survival stratified by recurrence location

Recurrence location and p-value	Loco-regional only	Liver only	Lung only	Peritoneal only	Simultaneous loco-regional + distant metastasis	Multiple distant metastases
Loco-regional only						
Liver only	0.07					
Lung only	0.23	0.68				
Peritoneal only	0.9	0.25	0.34			
Simultaneous loco-regional + distant metastasis	0.01*	0.38	0.56	0.2		
Multiple distant metastases	0.02*	0.41	0.41	0.17	0.95	

*p < 0.05.

to different sites of recurrence [18,19]. These variables could not be assessed in this study. They could explain the difference in recurrence patterns from other studies.

The recurrence rate within the first year after surgery was 48% (n = 44), decreasing to 21% (n = 19) in the second year and 3% (n = 3) in the third year, consistent with other studies demonstrating a high rate of recurrence within the first year (40%–61%) [9,20,21] possibly due to undiagnosed micro-metastases at the time of surgery [22]. These sub-clinical micro-metastases could then be classified as postoperative recurrence within a short postoperative timeframe [8,23]. In order to diagnose micro-metastases, circulating tumour cells or circulating tumour DNA may help [24,25]. Adjuvant and/or neo-adjuvant chemotherapy may reduce recurrence rates and alter recurrence patterns [6,26]. However, the natural history of PDAC without systemic therapy points to an aggressive disease [27,28].

Predictors of recurrence

This study investigated more than 40 covariates, significantly more than most other studies. Only LNR, adjuvant chemotherapy, and SII were found to be significant predictors of recurrence in multivariate analysis. While most studies looked at LNR and its association with prognosis, several studies looked at its association with recurrence and found significant results [10,29,30]. A large study with 692 patients found that LNR was associated with recurrence and only distant recurrence on further analysis [10]. However, this was disputed by another recent study which found that LNR was significantly associated with overall recurrence, but not with local or distant recurrence specifically [29]. In the present study, LNR was significantly predictive of recurrence in all locations apart from peritoneal recurrence possibly due to the low number. Implications of LNR as a predictor of recurrence could help guide prognosis selection for adjuvant treatment. Further mechanistic studies to determine how LNR predicts recurrence could guide therapy or increase surveillance. This study used the optimum cut-off value to stratify the covariate into a categorical variable, which was opposed to other studies where either the median value was used as the cut-off value or how the value was obtained was not mentioned. More work is needed in this area to determine a specific cut-off value for further clinical application.

Adjuvant chemotherapy is known to reduce recurrence after surgical resection for PDAC as evidenced by several recent randomised controlled trials (RCTs) [5,6]. However, even in a secondary analysis of ESPAC4, one of the largest RCTs for adjuvant treatment, there was no statistically significant difference in recurrence or survival statistics between recurrence sites [5]. However, not all patients would be fit enough to undergo adjuvant chemotherapy after a major resection for PDAC. Neo-adjuvant therapy has been reported to reduce the risk of early local recurrence and recommended to be used together with adjuvant therapy [31]. A systematic review has confirmed that local recurrence, but not distant metastasis, is reduced when neo-adjuvant therapy is used [32]. In the present study, neo-adjuvant therapy was not significantly associated with overall, local, or distant recurrence, although numbers were small.

SII can be easily obtained preoperatively. It has been reported to be predictive of OS and disease-free survival in different types of cancer [33,34]. There is at least one study in advanced pancreatic cancer, but several others with resection of other cancers [35-37]. A large prospective study with 321 patients has reported that SII is predictive of OS, but not recurrence [38]. However, another study with 590 patients has found that SII is an independent predictor of recurrence [39]. The present study corroborates findings of the latter study. However, there are limitations to its use. Neo-adjuvant therapy was not accounted for when studying SII. Furthermore, it has also been reported that its accuracy is reduced when bilirubin levels are high as it can cause immunomodulatory effects [39].

Resection margin status (R1 vs. R0) in pancreatic cancer has been studied extensively. Several studies have reported that R1 margin is correlated with recurrence [7,10,40,41]. However, others have found no significant difference in recurrence with R1 margins vs. R0 margins [42,43]. Some studies have analysed this further and found that the resection margin status is only significantly associated with local recurrence [7,10,44], consistent with findings of the present study, which found that R1 status was significantly associated with loco-regional recurrence. However, heterogeneity exists when reporting resection margin status. A large South Korean study with 558 patients has reported that R1 margin can predict early recurrence [41]. However, it only studied patients with distal pancreatectomies. Although a large trial with 912 patients reported no difference in DFS, all patients had adjuvant therapy in that trial [43]. A systematic review also noted issues with studies reporting total recurrence as opposed to isolated recurrence [7], while another study noted existing differences in definitions of R1 status [45]. In the present study, 57% of patients with R0 resection still developed recurrence. In several studies, resection margin status was reported to be not significantly associated with OS [43,45]. Standardised resection margin reporting will help reduce reporting variations of R1 margin after PDAC resection.

Limitations

This study was limited by its small population size which reduced the power of the study. There was also heterogeneity in surveillance for patients in this study as some were followed up in the tertiary HPB center while some were followed up by their oncologists. Follow-up regimens varied significantly across oncologist groups. Furthermore, some patients also diagnosed with recurrence after developing symptoms. Some factors made it difficult to determine the exact time point when recurrence occurred. Lastly, in some instances, postoperative CT scans were difficult to interpret as postoperative inflammation appeared similar to recurrence. Thus, MDT decision was used as consensus reporting.

In conclusion, timing to loco-regional only recurrence was significantly longer than simultaneous loco-regional with distant recurrence. Significant predictors for recurrence were LNR, adjuvant chemotherapy, and SII. More research with large national cohorts is needed to investigate patterns and predictive factors affecting recurrence after curative resection for PDAC.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Conceptualization: AA, HMK. Data curation: AA, AM, HMK. Methodology: All authors. Visualization: AA, DU, HMK. Writing - original draft: AA, HMK. Writing - review & editing: All authors.

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