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ORIGINAL ARTICLE

Preoperative predictors for early and very early disease recurrence in patients undergoing resection of pancreatic ductal adenocarcinoma

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Abstract

Background: This study aimed to identify predictors for early and very early disease recurrence in patients undergoing resection of pancreatic ductal adenocarcinoma (PDAC) resection with and without neoadjuvant therapy.

Methods: Included were patients who underwent PDAC resection (2014–2016). Multivariable multinomial regression was performed to identify preoperative predictors for manifestation of recurrence within 3, 6 and 12 months after PDAC resection.

Results: 836 patients with a median follow-up of 37 (interquartile range [IQR] 30–48) months and overall survival of 18 (IQR 10-32) months were analyzed. 670 patients (80%) developed recurrence: 82 patients (10%) <3 months, 96 patients (11%) within 3–6 months and 226 patients (27%) within 6–12 months. LogCA 19–9 (OR 1.25 [95% CI 1.10–1.41]; $P < 0.001$) and neoadjuvant treatment (OR 0.09 [95% CI 0.01–0.68]; $P = 0.02$) were associated with recurrence <3 months. LogCA 19–9 (OR 1.23 [95% CI 1.10–1.38]; $P < 0.001$) and 0–90° venous involvement on CT imaging (OR 2.93 [95% CI 1.60–5.37]; $P < 0.001$) were associated with recurrence within 3–6 months. A Charlson Age Comorbidity Index ≥4 (OR 1.53 [95% CI 1.09–2.16]; $P = 0.02$) and logCA 19–9 (OR 1.24 [95% CI 1.14–1.35]; $P < 0.001$) were related to recurrence within 6–12 months.

Conclusion: This study demonstrates preoperative predictors that are associated with the manifestation of early and very early recurrence after PDAC resection. Knowledge of these predictors can be used to guide individualized surveillance and treatment strategies.

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the most lethal digestive cancer with a 5-year survival of 12–17% after resection.[1–3] Despite recent advancements in PDAC detection, systemic therapy and surgical techniques, survival rates have only slightly improved over the last decade.[1,4,5] For patients with non-metastasized, borderline resectable or resectable PDAC, radical resection combined with chemotherapy offers the best chance for long-term survival. Nevertheless, local or distant tumor recurrence occurs in almost all patients, mostly within two years after resection.[6–8] With limited effective treatments available, patients with PDAC recurrence face a poor survival of only 3–9 months after diagnosis.[6,9]

The time interval between PDAC resection and disease recurrence affects survival substantially. A shorter disease-free survival (DFS) is thought to reflect unfavorable tumor biology with a more rapid progression to death.[10] Tumor relapse within 12 months after resection, also referred to as early PDAC recurrence, is associated with a very poor prognosis.[6,10] Pancreatic resection is still a major operation with a considerable risk of serious short- and long-term complications and a significant recovery period of at least a few months.[11–13] For patients who develop PDAC recurrence shortly after pancreatic resection, the risk-benefit ratio of such major surgery is doubtful. Moreover, approximately half of patients will not start or fail to complete adjuvant chemotherapy after PDAC resection due to post-operative complications, delayed recovery, and reduced performance status.[14,15] Failure to complete systemic therapy is associated with a significantly worse DFS and overall survival (OS).[16] Consequently, adequate patient selection for PDAC resection is increasingly emphasized and the role of neoadjuvant therapy is emerging, especially in the era of more potent chemotherapeutic options. Knowledge on preoperative predictors for early and very early disease recurrence after PDAC resection could support shared-decision making regarding upfront resection or neoadjuvant treatment strategies.

The objective of this study was to identify predictors for manifestation of early and very early disease recurrence within 3, 6 and 12 months in patients undergoing PDAC resection with and without neoadjuvant therapy.

Methods

This study has been reported in line with the strengthening the reporting of cohort studies in surgery (STROCSS) criteria.[17] The study protocol was submitted to the international clinical trial registry (clinicaltrials.gov – registration number NCT04605237).

Study design

A nationwide, observational cohort study was performed in 16 centers participating in the Dutch Pancreatic Cancer Group (DPCG). The study was approved by the institutional review board of each participating center. All patients registered in the mandatory, prospective Dutch Pancreatic Cancer Audit who underwent resection of PDAC between 2014 and 2016 were included.[18] Diagnosis of PDAC was confirmed by pathological examination of the resected specimen. Exclusion criteria were macroscopically positive resection as judged during surgery (R2 resection), as this was considered residual disease and a disease-free interval could not be assessed, and death within 90 days after surgery not related to very early PDAC recurrence.

Data collection

Baseline and perioperative data were extracted from the prospective clinical audit database, including age, sex, BMI, weight loss, and information on vascular involvement and tumor size assessed on preoperative CT imaging. Venous involvement included the superior mesenteric vein and/or portal vein; arterial involvement comprised the superior mesenteric artery, coeliac trunk and/or common hepatic artery. According to the DPCG criteria, patients were deemed to have locally advanced PDAC in case of arterial involvement >90° or venous involvement >270° or occlusion.[19] Borderline resectable PDAC was defined as arterial involvement ≤90°, or 90°–270° venous contact without occlusion.[19] Infor-

mation regarding the patients' history, Eastern Cooperative Oncology Group (ECOG) performance score, preoperative serum CA 19–9, tumor location, pathology outcomes, and administration of neoadjuvant and adjuvant therapy was collected from the patients' records. Preoperative Charlson Age-Comorbidity Index (CACI) was calculated using the MDCalc CACI calculator.[20] Data on follow-up, recurrence diagnosis and survival were collected retrospectively from the patients' records within each participating hospital.

Outcomes

OS was defined as the time from the date of pancreatic resection to the date of death or last follow-up. DFS was calculated from the date of resection to the date of diagnosis of PDAC recurrence or last follow-up, if tumor relapse did not occur. In the Netherlands, the majority of patients receive a periodic, symptomatic follow-up approach without standardized blood tests or imaging surveillance.[21] Patients are instructed to contact their pancreatic surgeon or oncologist as soon as they develop symptoms suggestive of PDAC recurrence, following which further diagnostic testing will be performed. Therefore, in most patients, clinical symptoms were the first sign of disease recurrence.[22] However, the diagnosis of PDAC recurrence was either pathologically confirmed or radiologically determined through cross-sectional imaging leading to clinical consequences if pathology was not obtained. Based on DFS, patients were subdivided into four groups: manifestation of PDAC recurrence <3 months, 3–6 months or 6–12 months after resection and no/late recurrence (≥12 months).

Statistical analysis

Descriptive statistics were used to describe baseline characteristics. Missing data were handled using multiple imputation (5 imputations; 10 iterations).[23,24] Univariate and multivariable multinomial regression analysis were performed to identify preoperative factors associated with PDAC recurrence <3 months, 3–6 months and 6–12 months after resection as compared with no/late disease recurrence (≥12 months). Initial selection of potential predictors was performed based on existing literature, and categories were defined from published cut-off points. Variables included were sex, CACI, BMI, weight loss, ECOG performance score, serum CA 19–9, and tumor size, tumor location, and venous and arterial involvement on CT imaging. For the CACI score, patients were dichotomized to a threshold of 4 points.[10] Preoperative weight loss was defined as > 5% in the past four weeks or >10% in the past six months.[25] ECOG performance score was dichotomized to 0–1 and 2–4. Serum CA 19–9 was transformed on a logarithmic scale. Tumor size was categorized based on the 8th AJCC definition for T stage.[26] Both venous and arterial involvement were categorized as no, 0–90° and >270° involvement.[19] As venous resection in borderline resectable tumors has been shown to achieve survival rates comparable to primary resectable tumors, sensitivity analysis was performed in a subset of patients who underwent venous resection.[27] Results were presented as odds ratio's (OR) with corresponding 95% confidence intervals (CI) and *P*-values. Receiver operating characteristic (ROC) analysis using the point closest to the upper left corner method was performed to calculate the optimal threshold values for preoperative serum CA 19–9 (U/ml) to predict disease recurrence within 3 months, 3–6 months or 6–12 months, or a DFS ≥12 months (with or without recurrence) in patients within the original dataset with a preoperative CA 19–9 value > 5 mmol/L. Cut-off values were presented with sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy and area under the curve (AUC). Statistical analyses were carried out using R language environment ("mice", "nnet" and "pROC" packages; http://www.R-project.org). A two-sided *P*-value < 0.05 was considered statistically significant.

Results

Patient cohort

After exclusion of seven patients with an R2 resection (1%) and 49 patients with a 90-day postoperative mortality not related to very early PDAC recurrence (6%), a total of 836 patients with a median follow-up of 37 months (IQR 30–48 months) and median OS of 18 months (IQR 10–32 months) were included (Appendix I). Neoadjuvant treatment was administered to 73 patients in trial setting (9%),[28,29] whilst 763 patients (91%) underwent upfront resection. Adjuvant chemotherapy was given to 530/805 patients (66%): 334/450 patients (72%) with a CACI <4 received adjuvant chemotherapy, as compared with 196/355 patients (53%) with a CACI ≥4 ($P < 0.001$). Information on CA 19-9 measurements and imaging surveillance was available in 714 patients (85%) and 748 patients (89%), respectively. Serum CA 19–9 was measured every 3- or 6-months in 87 patients (12%). Imaging was performed with a 3- or 6-monthly interval in 109 patients (15%), of whom 88 patients (81%) participated in clinical studies with a study-specific follow-up. In 589 patients (79%), imaging was performed by discretion of the clinician (i.e. based on clinical symptoms) supervising the patient's follow-up.

Disease-free and overall survival

A total of 670 patients (80%) developed PDAC recurrence after a median DFS of 10 months (IQR 5–16 months) (Appendix I). Median OS in all patients with recurrence was 15 months (IQR 10–27 months). Recurrence manifested within 3 months in 82 patients (10%), within 3–6 months in 96 patients (11%), within 6–12 months in 226 patients (27%), and 432 patients (52%) had a DFS ≥12 months (with or without PDAC recurrence). Patients most often experienced multiple site recurrence (n = 353, 53%), followed by local-only (n = 139, 21%), liver-only (n = 111, 16%), lung-only (n = 34, 5%) and other isolated distant recurrence (n = 33, 5%). Median OS in patients who developed recurrence within 3, 3–6 and 6–12 months was 5 months (IQR 3–12

Table 1 Baseline characteristics of 836 patients who underwent PDAC resection with manifestation of disease recurrence within 3 months, after 3–6 months, after 6–12 months, or no/late disease recurrence (≥12 months)

	DFS <3 months (n = 82)	DFS 3–6 months (n = 96)	DFS 6–12 months (n = 226)	No/late recurrence (≥12 months) (n = 432)
Age in years, mean ± SD	68 ± 9	68 ± 10	67 ± 9	66 ± 9
Male sex, n (%)	41 (50)	53 (55)	124 (55)	240 (56)
BMI in kg/m^2, mean ± SD	24 ± 4	25 ± 4	25 ± 4	25 ± 4
CACI, n (%)				
<4	47 (57)	49 (51)	109 (48)	258 (60)
≥4	35 (43)	47 (49)	117 (52)	174 (40)
ECOG performance score, n (%)				
0	32 (39)	35 (37)	95 (42)	191 (44)
1	35 (43)	50 (52)	95 (42)	190 (44)
2	13 (16)	7 (7)	25 (11)	37 (9)
3	1 (1)	4 (4)	11 (5)	13 (3)
4	1 (1)	0 (0)	0 (0)	0 (0)
Weight loss, n (%) [a]	27 (33)	36 (38)	84 (37)	125 (29)
Serum CA 19–9 (U/ml), median (IQR)	250 (57–1158)	243 (52–773)	210 (57–732)	77 (23–263)
Serum CA 19–9 < 5 U/ml, n (%)[b]	6 (7)	6 (6)	12 (5)	40 (9)
Location tumour, n (%)				
Head	69 (84)	88 (92)	192 (85)	363 (84)
Body/tail	13 (16)	8 (8)	34 (15)	69 (16)
Vascular involvement on CT imaging, n (%)				
Venous involvement[c]				
No	51 (62)	47 (49)	142 (63)	299 (69)
0–90°	9 (11)	25 (26)	30 (13)	48 (11)
90–270°	21 (26)	24 (25)	54 (24)	85 (20)
>270°	1 (1)	0 (0)	0 (0)	0 (0)
Arterial involvement[d]				
No	70 (85)	81 (85)	207 (92)	388 (90)
0–90°	4 (5)	6 (6)	4 (2)	17 (4)
>90°	8 (10)	9 (9)	14 (6)	27 (6)
Tumour size on CT imaging in cm, mean ± SD	2.9 ± 1.0	2.9 ± 1.1	2.8 ± 1.0	2.9 ± 1.2
Neoadjuvant therapy, n (%)				
None	81 (99)	87 (91)	210 (92)	385 (89)
FOLFIRINOX chemotherapy	0 (0)	5 (5)	8 (4)	18 (4)
Gemcitabine chemo(radio)therapy	1 (1)	4 (4)	8 (4)	29 (7)
Type of surgery, n (%)				
Open	63 (77)	83 (87)	182 (80)	355 (82)
Laparoscopic	13 (16)	8 (8)	29 (13)	66 (15)
Robot-assisted	6 (7)	5 (5)	15 (7)	11 (3)
Operation procedure, n (%)				
Pancreatoduodenectomy	79 (96)	90 (94)	207 (91)	382 (88)

Table 1 (*continued*)

	DFS <3 months (n = 82)	DFS 3–6 months (n = 96)	DFS 6–12 months (n = 226)	No/late recurrence (≥12 months) (n = 432)
Distal pancreatectomy	3 (4)	6 (6)	15 (7)	48 (11)
Total pancreatectomy	0 (0)	0 (0)	4 (2)	2 (1)
Vascular resection, n (%)				
No	61 (74)	59 (61)	158 (70)	336 (78)
Venous	20 (25)	35 (36)	64 (28)	93 (21)
Arterial	0 (0)	2 (2)	2 (1)	3 (1)
Both	1 (1)	0 (0)	2 (1)	0 (0)
Pathologic tumour size in cm, mean ± SD	3.3 ± 1.2	3.7 ± 1.2	3.4 ± 1.3	3.0 ± 1.2
Tumour differentiation, n (%)				
Well/moderate	48 (59)	55 (57)	137 (61)	334 (77)
Poor	34 (41)	41 (43)	89 (39)	98 (23)
Lymphovascular invasion, n (%)	62 (76)	76 (79)	154 (68)	254 (59)
Perineural invasion, n (%)	76 (93)	91 (95)	207 (92)	357 (82)
Total lymph nodes, median (IQR)	13 (9–19)	14 (11–21)	15 (10–21)	16 (10–20)
Positive lymph nodes, median (IQR)	3 (1–6)	3 (1–5)	3 (1–5)	1 (0–3)
Resection margin status, n (%)				
R0 > 1.0 mm	28 (34)	38 (40)	96 (42)	233 (54)
R1 ≤ 1.0 mm	54 (66)	58 (60)	129 (57)	199 (46)
Major postoperative complications, n (%) [e]	24 (29)	23 (24)	57 (25)	97 (22)
Hospital stay in days, median (IQR)	13 (10–18)	11 (9–18)	12 (8–18)	10 (8–15)
Adjuvant chemotherapy, n (%)	29 (35)	41 (43)	144 (64)	331 (77)
CACI <4	16 (55)	27 (66)	82 (57)	217 (66)
CACI ≥4	13 (45)	14 (34)	62 (43)	114 (34)
Use of CA 19-9 during follow-up,n (%)				
No	30 (36)	41 (43)	57 (25)	126 (29)
Yes, not routinely	49 (60)	47 (49)	142 (63)	247 (57)
Yes, routinely	3 (4)	8 (8)	26 (12)	59 (14)
Use of imaging procedures during follow-up, n (%)				
No	8 (9)	2 (2)	8 (4)	40 (9)
Yes, not routinely	71 (87)	87 (91)	184 (81)	316 (73)
Yes, routinely	3 (4)	7 (7)	33 (15)	76 (18)
Survival status, n (%)				
Dead	79 (96)	94 (98)	220 (97)	224 (52)
Alive	3 (4)	2 (2)	6 (3)	208 (48)
DFS in months, median (IQR)	1 (0–2)	4 (3–5)	8 (7–10)	24 (16–36)
OS in months, median (IQR)	5 (3–12)	7 (5–12)	12 (10–16)	31 (22–40)
Location recurrence, n (%)				
Local-only	11 (13)	12 (13)	41 (18)	111 (26)
Liver-only	39 (48)	21 (22)	30 (13)	26 (6)
Lung-only	2 (2)	3 (3)	6 (3)	47 (11)

(*continued on next page*)

Table 1 (*continued*)

	DFS <3 months (n = 82)	DFS 3–6 months (n = 96)	DFS 6–12 months (n = 226)	No/late recurrence (≥12 months) (n = 432)
Multiple site	26 (32)	51 (53)	144 (64)	220 (51)
Other isolated distant site	4 (5)	9 (9)	5 (2)	28 (6)

PDAC, pancreatic ductal adenocarcinoma; SD, standard deviation; BMI, body mass index; CACI, Charlson Age-Comborbidity Index; ECOG, Eastern Cooperative Oncology Group; CA 19–9, carbohydrate antigen 19–9; IQR, interquartile range; CT, computed tomography; FOLFIRINOX, fluorouracil, leucovorin, irinotecan, and oxaliplatin; DFS, disease-free survival, measured from the date of resection until the date of recurrence diagnosis; OS, overall survival, measured from the date of resection until the date of death or last follow-up.
[a] Preoperative weight loss was defined as > 5% in the past four weeks or >10% in the past six months.
[b] In case of a preoperative serum CA 19–9 < 5 U/ml, patients were considered Lewis antigen negative.
[c] Venous involvement comprised involvement of the superior mesenteric vein and/or portal vein.
[d] Arterial involvement comprised involvement of the superior mesenteric artery, hepatic artery or celiac trunk.
[e] Major postoperative complications were defined as complications requiring a surgical or radiological intervention, intensive care unit (ICU) admittance, single- or multi-organ failure, or patient demise; - no imputations were performed for these variables.

Table 2 univariable multinomial regression analysis to identify preoperative risk factors for manifestation of disease recurrence within 3 months, 3–6 months or 6–12 months, as compared with no recurrence or late recurrence (≥12 months), in 836 patients who underwent PDAC resection

Preoperative risk factors	DFS <3 months (n = 82)			DFS 3–6 months (n = 96)			DFS 6–12 months (n = 226)		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Sex (male vs. female)	0.80	0.50–1.29	0.37	0.99	0.63–1.54	0.96	0.97	0.70–1.34	0.87
CACI (≥4 vs. < 4)	1.10	0.68–1.77	0.70	1.41	0.90–2.19	0.13	**1.58**	**1.14–2.19**	**< 0.01**
BMI (continuous)	0.94	0.88–1.00	0.05	1.01	0.96–1.07	0.65	1.01	0.97–1.05	0.78
Weight loss (yes vs. no)[a]	1.24	0.75–2.05	0.41	1.44	0.91–2.30	0.12	**1.46**	**1.04–2.05**	**0.03**
ECOG performance score (2–4 vs. 0–1)	1.45	0.76–2.74	0.26	0.96	0.49–1.89	0.92	1.23	0.77–1.95	0.39
Serum CA 19–9 (log)	**1.28**	**1.14–1.45**	**< 0.001**	**1.26**	**1.13–1.40**	**< 0.001**	**1.26**	**1.16–1.37**	**< 0.001**
Tumour size in cm on CT imaging									
≤2 cm	*ref*			*ref*			*ref*		
>2 cm - ≤ 4 cm	1.36	0.78–2.39	0.28	1.40	0.83–2.35	0.21	1.34	0.92–1.95	0.13
>4 cm	1.25	0.55–2.85	0.60	1.13	0.51–2.50	0.77	1.23	0.70–2.14	0.48
Location tumour on CT imaging (body/tail vs. head)	0.97	0.51–1.86	0.93	0.47	0.22–1.02	0.06	0.93	0.60–1.45	0.75
Vascular involvement on CT imaging									
Venous involvement[b]									
No	*ref*			*ref*			*ref*		
0–90°	1.15	0.54–2.45	0.72	**3.35**	**1.89–5.93**	**< 0.001**	1.29	0.78–2.12	0.33
>90°	1.53	0.88–2.67	0.13	**1.82**	**1.05–3.15**	**< 0.05**	1.33	0.90–1.98	0.15
Arterial involvement[c]									
No	*ref*			*ref*			*ref*		
0–90°	1.36	0.45–4.06	0.59	1.79	0.70–4.57	0.23	0.43	0.14–1.31	0.14
>90°	1.65	0.72–3.77	0.24	1.64	0.75–3.59	0.22	0.98	0.51–1.91	0.96
Neoadjuvant therapy	**0.10**	**0.01–0.74**	**0.02**	0.84	0.40–1.79	0.66	0.63	0.35–1.13	0.12

PDAC, pancreatic ductal adenocarcinoma; OR, odds ratio; CI, confidence interval; CACI, Charlson Age-Comorbidity Index; BMI, Body Mass Index; ECOG, Eastern Cooperative Oncology Group; CA 19–9, carbohydrate antigen 19–9; CT, computed tomography; FOLFIRINOX, fluorouracil, leucovorin, irinotecan, and oxaliplatin.
[a] Preoperative weight loss was defined as > 5% in the past four weeks or >10% in the past six months.
[b] Venous involvement comprised involvement of the superior mesenteric vein and/or portal vein.
[c] Arterial involvement comprised involvement of the superior mesenteric artery, hepatic artery or celiac trunk.

Table 3 Multivariable multinomial regression analysis to identify preoperative risk factors for manifestation of disease recurrence within 3 months, 3–6 months or 6–12 months, as compared with no recurrence or late recurrence (≥12 months), in 836 patients who underwent PDAC resection

Preoperative risk factors	DFS <3 months (n = 82)			DFS 3–6 months (n = 96)			DFS 6–12 months(n = 226)		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Sex (male vs. female)	0.86	0.52–1.40	0.54	0.90	0.57–1.43	0.66	0.94	0.67–1.31	0.70
CACI (≥4 vs. < 4)	1.08	0.65–1.79	0.76	1.39	0.87–2.23	0.17	**1.53**	**1.09–2.16**	**0.02**
BMI (continuous)	0.95	0.89–1.02	0.13	1.02	0.96–1.08	0.55	1.01	0.97–1.06	0.60
Weight loss (yes vs. no)[a]	1.02	0.59–1.75	0.95	1.10	0.67–1.81	0.71	1.23	0.85–1.78	0.27
ECOG performance score (2–4 vs. 0–1)	1.20	0.61–2.34	0.60	0.83	0.41–1.68	0.60	1.03	0.63–1.69	0.90
Serum CA 19–9 (log)	**1.25**	**1.10–1.41**	**< 0.001**	**1.23**	**1.10–1.38**	**< 0.001**	**1.24**	**1.14–1.35**	**< 0.001**
Tumour size in cm on CT imaging									
≤2 cm	*ref*			*ref*			*ref*		
>2 cm - ≤ 4 cm	1.32	0.74–2.35	0.34	1.23	0.72–2.11	0.46	1.27	0.86–1.89	0.22
>4 cm	1.08	0.45–2.61	0.87	1.13	0.48–2.62	0.79	1.15	0.63–2.09	0.65
Location tumour on CT imaging (body/tail vs. head)	1.30	0.65–2.62	0.46	0.64	0.29–1.44	0.28	1.16	0.71–1.87	0.56
Vascular involvement on CT imaging									
Venous involvement[c]									
No	*ref*			*ref*			*ref*		
0–90°	1.11	0.50–2.47	0.80	**2.93**	**1.60–5.37**	**<0.001**	1.25	0.73–2.11	0.42
With venous resection[b]	*0.22*	*0.02–1.94*	*0.17*	***5.86***	***1.57–21.90***	***<0.01***	*2.76*	*0.96–7.94*	*0.06*
>90°	1.61	0.88–2.94	0.12	1.63	0.90–2.93	0.10	1.40	0.91–2.16	0.13
With venous resection[b]	*0.56*	*0.18–1.76*	*0.32*	*1.99*	*0.67–5.91*	*0.22*	*1.15*	*0.53–2.53*	*0.72*
Arterial involvement[d]									
No	*ref*								
0–90°	1.23	0.39–3.89	0.73	1.17	0.44–3.16	0.75	0.36	0.11–1.11	0.08
>90°	2.16	0.89–5.26	0.09	1.43	0.61–3.39	0.41	1.01	0.49–2.06	0.98
Neoadjuvant therapy	**0.09**	**0.01–0.68**	**0.02**	0.75	0.33–1.73	0.50	0.73	0.38–1.38	0.33

PDAC, pancreatic ductal adenocarcinoma; OR, odds ratio; CI, confidence interval; CACI, Charlson Age-Comorbidity Index; BMI, Body Mass Index; ECOG, Eastern Cooperative Oncology Group; CA 19–9, carbohydrate antigen 19–9; CT, computed tomography; FOLFIRINOX, fluorouracil, leucovorin, irinotecan, and oxaliplatin.
[a] Preoperative weight loss was defined as > 5% in the past four weeks or >10% in the past six months.
[b] Sensitivity analysis was performed in a subset of patients who underwent venous resection to assess the potential benefit on the impact of venous tumor involvement.
[c] Venous involvement comprised involvement of the superior mesenteric vein and/or portal vein.
[d] Arterial involvement comprised involvement of the superior mesenteric artery, hepatic artery or celiac trunk.

months), 7 months (IQR 5–12 months) and 12 months (IQR 10–16 months), respectively. Median OS in patients with no or late recurrence was 31 months (IQR 22–40 months) (Table 1).

Preoperative predictors for early and very early PDAC recurrence

Results of the univariable multinomial analysis are presented in Table 2. Multivariable multinomial regression identified serum logCA 19–9 (OR 1.25 [95% CI 1.10–1.41]; $P < 0.001$) and neoadjuvant treatment (OR 0.09 [95% CI 0.01–0.68]; $P = 0.02$) to be associated with recurrence <3 months. Serum logCA 19–9 (OR 1.23 [95% CI 1.10–1.38]; $P < 0.001$) and venous tumor involvement of 0–90° on CT imaging (OR 2.93 [95% CI 1.60–5.37]; $P < 0.001$) were found to be associated with manifestation of recurrence after 3–6 months. A CACI score of ≥4 (OR 1.53 [95% CI 1.09–2.16]; $P = 0.02$) and serum logCA 19–9 (OR 1.24 [95% CI 1.14–1.35]; $P < 0.001$) were related to manifestation of recurrence within 6–12 months (Table 3).

After stratification for venous resection, sensitivity analysis showed that venous tumor involvement 0–90° on CT imaging remained associated with manifestation of recurrence after 3–6 months (OR 5.86 [95% CI 1.57–21.90]; $P < 0.01$) (Table 3).

Preoperative serum CA 19–9 threshold values

In our cohort, preoperative serum CA 19–9 of 261.0 U/ml was considered the optimal threshold for the prediction of PDAC recurrence <3 months after resection, with an accuracy of 64% (Table 4). The optimal cut-off values for manifestation of disease

Table 4 Optimal threshold values for preoperative serum CA 19–9 (U/ml) to predict disease recurrence within 3 months, 3–6 months or 6–12 months, or a DFS ≥12 months (with or without recurrence) as calculated in patients with a preoperative CA 19–9 value > 5 mmol/L within the original dataset (n = 469)

Disease-free survival	Threshold CA 19–9 (U/ml)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	AUC (%)
<3 months (n = 30)	261.0	67	64	11	97	64	66
3–6 months (n = 59)	200.5	59	58	17	91	58	59
6–12 months (n = 141)	182.5	62	60	40	78	60	63
≥12 months (with or without recurrence) (n = 239)	155.5	65	66	67	64	65	69

CA, carbohydrate antigen; DFS, disease-free survival; PPV, positive predictive value; NPV, negative predictive value; AUC, area under the curve.

recurrence within 3–6 months and 6–12 months were 200.5 U/ml (accuracy 58%) and 182.5 (accuracy 60%), respectively. A preoperative serum CA 19–9 value of <155.5 U/ml (accuracy 65%) was associated with a DFS ≥12 months (with or without recurrence).

Discussion

This study shows preoperative predictors for the manifestation of early and very early disease recurrence after PDAC resection using data from a nationwide, unselected cohort of patients. Preoperative serum CA 19–9 was found to be the most important predictor for both early and very early PDAC recurrence. Omission of neoadjuvant therapy, 0–90° venous tumor involvement on preoperative CT imaging, and a CACI score ≥4 were associated with the manifestation of disease recurrence within 3 months, 3–6 months and 6–12 months, respectively. Preoperative knowledge of these predictors might be useful in daily clinical practice, as it could help to inform patients on their prognosis and guide shared treatment decision making. With modest accuracy, a preoperative serum CA 19–9 of >200 U/ml was found to be associated with manifestation of PDAC recurrence <6 months.

The development of FOLFIRINOX chemotherapy has led to significant survival benefits for PDAC patients, and the importance of optimal delivery of systemic treatment is increasingly emphasized.[4] However, it was shown previously that a substantial part of patients does not receive systemic therapy in the adjuvant setting.[14,15] In addition, promising results of neoadjuvant therapy have been published.[30,31] Two recent randomized trials demonstrated benefit of neoadjuvant therapy, especially in patients with borderline resectable disease.[28,32] Neoadjuvant therapy was suggested to lead to higher margin-negative resection (R0) rates, down staging, optimal delivery of systemic therapy, early treatment of micro-metastasis, and better selection for pancreatic resection by identifying patients with highly aggressive tumours.[28,32] For selected patients with resectable PDAC with high serum CA 19–9 values, a high CACI score, or with certain tumor characteristics such as vascular involvement on preoperative CT imaging, neoadjuvant therapy might be the preferred treatment strategy. However, ongoing randomized trials are addressing the potential benefits of neoadjuvant treatment over upfront surgery in patients with primary resectable tumors and have to be awaited.

Serum CA 19–9 is the most widely assessed biomarker for PDAC, with elevated levels being associated with decreased survival.[33] Less is known about the correlation between CA 19–9 and (early) recurrence. In our study, an increase in preoperative CA 19–9 was the most important prognostic factor and was highly associated with early and very early PDAC recurrence in multivariable analysis. It was shown that preoperative serum CA 19–9 values of >200 U/ml were associated with a DFS <6 months. It is, however, important to be aware of potential false-negative serum CA 19-9 measurements in patients with a Lewis blood group-negative phenotype (Leα-β-), including approximately 5–10% of general population.

In multivariable analysis, 0–90° venous tumor involvement was found to be associated with the manifestation of PDAC recurrence within 3–6 months. This study therefore suggests that the risk of early recurrence is increased not only for anatomic borderline resectable tumors (either per DPCG or NCCN), but for tumors with any vascular contact op preoperative CT imaging. This is in line with previous studies, which showed that vascular involvement on preoperative CT imaging was associated with more unfavorable tumor characteristics and development of PDAC recurrence.[34,35] However, survival outcomes after venous resection in borderline resectable tumors have been shown to be comparable to primary resectable tumors.[27] This might signify the need for more vascular resections or initial systemic treatment in patients with any venous or arterial tumor involvement.

In line with our findings, previous studies have shown an association between a CACI ≥4 and early recurrence or death within 12 months after pancreatic resection.[10,36] Patients with a higher CACI score have a decreased likelihood of receiving adjuvant therapy, contributing to a poor prognosis.[37] This was supported by our data, according to which significantly less patients with a CACI ≥4 received adjuvant therapy, as compared with patients with a CACI score of <4.

Several limitations of this study need to be addressed. First, although a prospective database was used for baseline and

perioperative data, data on follow-up and recurrence diagnosis were collected retrospectively. As a consequence, information on recurrence state was missing in 13% of patients, which could have led to information bias. Nevertheless, we performed multiple imputation to handle missing data, which is proven to be sufficient if data are missing at random, even for a large number of missing values.[24] Second, no standardized follow-up imaging was performed in general, as this is not recommended in current national and European guidelines.[38] However, based on shared-decision making or following participation in a clinical study, a small part of patients (14%) did receive follow-up imaging. It might be possible that patients who received follow-up imaging had a better *a priori* prognosis which could have led to confounding by indication. In addition, if standardized follow-up imaging was performed in all patients, this might have altered the duration of DFS and subsequent classification for some patients in this study. However, even with standardized surveillance, a substantial part of patients are known to present with symptoms as a first sign of recurrence within the follow-up intervals.[22] As this study reports on risk factors associated with the *manifestation* of disease recurrence within a certain time-interval, the results of this study are highly applicable and generalizable. Third, interpretation of the results should account for the study context, including only patients who underwent PDAC resection, and excluding patients having disease progression during neoadjuvant treatment or unresectable disease at laparotomy.

In conclusion, this nationwide, observational cohort study demonstrates preoperative predictors that are associated with the manifestation of early and very early recurrence after PDAC resection. Knowledge of these predictors can be used to inform patients on their prognosis and guide individualized surveillance and treatment strategies, in particular when neoadjuvant treatment is considered.

Conflict of interest

None to declare.

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Appendix I. Missing data table including the original cohort of 836 patients who underwent PDAC resection and dataset after multiple imputation

	Original cohort (n = 836)	Missing values, n (%)	After imputation (n = 836)
Age in years, mean ± SD	67 ± 9	0 (0)	67 ± 9
Male sex, n (%)	459 (55)	0 (0)	459 (55)
BMI in kg/m^2, mean ± SD	25 ± 4	3 (0)	25 ± 4
CACI, n (%)		0 (0)	
<4	463 (55)		463 (55)
≥4	373 (45)		373 (45)
ECOG performance score, n (%)		308 (37)	
0	229 (43)		354 (42)

(*continued*)

	Original cohort (n = 836)	Missing values, n (%)	After imputation (n = 836)
1	239 (45)		370 (44)
2	46 (9)		82 (10)
3	13 (3)		28 (4)
4	1 (0)		2 (0)
Weight loss, n (%)[a]	141 (32)	391 (47)	271 (32)
Serum CA 19–9 (U/ml), median (IQR)	128 (32–486)	270 (32)	126 (31–485)
Serum CA 19–9 < 5 U/ml, n (%)[b]	42 (7)		63 (8)
Location tumour, n (%)		0 (0)	
Head	712 (85)		712 (85)
Body/tail	124 (15)		124 (15)
Vascular involvement on CT imaging, n (%)			
Venous involvement[c]		81 (10)	
No	488 (65)		538 (64)
0–90°	101 (13)		113 (14)
90–270°	165 (22)		184 (22)
>270°	1 (0)		1 (0)
Arterial involvement [d]		69 (8)	
No	691 (90)		746 (89)
0–90°	29 (4)		32 (4)
>90°	47 (6)		58 (7)
Tumour size on CT imaging in cm, mean ± SD	2.9 ± 1.1	257 (31)	2.9 ± 1.1
Neoadjuvant therapy, n (%)		0 (0)	
None	763 (91)		763 (91)
FOLFIRINOX chemotherapy	31 (4)		31 (4)
Gemcitabine chemo(radio)therapy	42 (5)		42 (5)
Type of surgery, n (%)		2 (0)	
Open	756 (90)		758 (90)
Laparoscopic	72 (9)		72 (9)
Robot-assisted	6 (1)		6 (1)
Operation procedure, n (%)		0 (0)	
Pancreatoduodenectomy	683 (82)		683 (82)
Distal pancreatectomy	116 (14)		116 (14)
Total pancreatectomy	37 (4)		37 (4)
Vascular resection, n (%)		2 (0)	
No	613 (74)		615 (74)
Venous	211 (25)		211 (25)
Arterial	7 (1)		7 (1)
Both	3 (0)		3 (0)
Pathologic tumour size in cm, mean ± SD	3.2 ± 1.2	18 (2)	3.2 ± 1.2
Tumour differentiation, n (%)		92 (11)	
Well/moderate	510 (69)		574 (69)
Poor	234 (31)		262 (31)
Lymphovascular invasion, n (%)	414 (67)	220 (26)	546 (65)
Perineural invasion, n (%)	644 (88)	108 (13)	731 (87)
Total lymph nodes, median (IQR)	15 (10–21)	14 (2)	15 (10–21)

(*continued on next page*)

(*continued*)

	Original cohort (n = 836)	Missing values, n (%)	After imputation (n = 836)
Positive lymph nodes, median (IQR)	2 (0–4)	4 (0)	2 (0–4)
Resection margin status, n (%)		8 (1)	
R0 > 1.0 mm	391 (47)		396 (47)
R1 ≤ 1.0 mm	437 (53)		440 (53)
Major postoperative complications, n (%) [e]	201 (24)	0 (0)	201 (24)
Hospital stay in days, median (IQR)	11 (8–16)	0 (0)	11 (8–16)
Adjuvant chemotherapy, n (%)	530 (66)	31 (4)	545 (65)
CACI <4	334 (63)		342 (63)
CACI ≥4	196 (37)		203 (37)
Use of CA 19-9 during follow-up, n (%)		122 (15)	
No	219 (31)		–
Yes, not routinely	408 (57)		–
Yes, routinely	87 (12)		–
Use of imaging procedures during follow-up, n (%)		88 (11)	
No	50 (7)		–
Yes, not routinely	589 (79)		–
Yes, routinely	109 (14)		–
Survival status, n (%)		0 (0)	
Dead	617 (74)		617 (74)
Alive	219 (26)		219 (26)
Overall survival in months, median (IQR)	18 (10–32)		18 (10–32)
Disease recurrence, n (%)	587 (81)	107 (13)	670 (80)
DFS in months, median (IQR)	10 (6–17)		10 (5–16)
OS in months, median (IQR)	15 (10–28)		15 (10–27)
Disease recurrence <3 months, n (%)	43 (6)		82 (10)
OS in months, median (IQR)	4 (3–8)		5 (3–12)
Disease recurrence 3–6 months, n (%)	88 (12)		96 (11)
OS in months, median (IQR)	7 (5–11)		7 (4–12)
Disease recurrence 6–12 months, n (%)	204 (28)		226 (27)
OS in months, median (IQR)	12 (10–15)		11 (7–14)
No/recurrence ≥12 months, n (%)	394 (54)		432 (52)
OS in months, median (IQR)	31 (22–40)		31 (22–40)
Location recurrence, n (%)		19 (3)	
Local-only	116 (21)		139 (21)
Liver-only	81 (14)		111 (16)
Lung-only	30 (5)		34 (5)
Multiple site	312 (55)		353 (53)
Other isolated distant site	29 (5)		33 (5)

PDAC, pancreatic ductal adenocarcinoma; SD, standard deviation; BMI, body mass index; CACI, Charlson Age-Comborbidity Index; ECOG, Eastern Cooperative Oncology Group; CA 19–9, carbohydrate antigen 19–9; IQR, interquartile range; CT, computed tomography; FOLFIRINOX, fluorouracil, leucovorin, irinotecan, and oxaliplatin; DFS, disease-free survival, measured from the date of resection until the date of recurrence diagnosis; OS, overall survival, measured from the date of resection until the date of death or last follow-up.
[a] Preoperative weight loss was defined as > 5% in the past four weeks or >10% in the past six months.
[b] In case of a preoperative serum CA 19–9 < 5 U/ml, patients were considered Lewis antigen negative.
[c] Venous involvement comprised involvement of the superior mesenteric vein and/or portal vein.
[d] Arterial involvement comprised involvement of the superior mesenteric artery, hepatic artery or celiac trunk.
[e] Major postoperative complications were defined as complications requiring a surgical or radiological intervention, intensive care unit (ICU) admittance, single- or multi-organ failure, or patient demise; - no imputations were performed for these variables.