

Predicting post-recurrence survival for patients with pancreatic cancer recurrence after primary resection: A Bi-institutional validated risk classification

A. Floortje van Oosten^{a, c, 1}, Lois A. Daamen^{a, b, 1}, Vincent P. Groot^a, Nanske C. Biesma^a, Joseph R. Habib^c, Iris W.J.M. van Goor^a, Benedict Kinny-Köster^{c, d}, Richard A. Burkhart^c, Christopher L. Wolfgang^d, Hjalmar C. van Santvoort^a, Jin He^c, I. Quintus Molenaar^{a, *}

^a Department of Surgery, Regional Academic Cancer Center Utrecht, UMC Utrecht Cancer Center & St. Antonius Hospital Nieuwegein, the Netherlands

^b Division of Imaging and Oncology, University Medical Center Utrecht Cancer Center, Utrecht University, Utrecht, the Netherlands

^c Department of Surgery, The Johns Hopkins University School of Medicine, Baltimore, MD, USA

^d Department of Surgery, New York University Langone Medical Center, New York City, NY, USA

ARTICLE INFO

Article history:

Received 12 September 2022

Received in revised form

7 March 2023

Accepted 19 April 2023

Available online 29 April 2023

Keywords:

Pancreatic ductal adenocarcinoma

Recurrence

Post-recurrence survival

Survival after recurrence

Risk score

ABSTRACT

Background: Over 80% of patients will develop disease recurrence after radical resection of pancreatic ductal adenocarcinoma (PDAC). This study aims to develop and validate a clinical risk score predicting post-recurrence survival (PRS) at time of recurrence.

Methods: All patients who had recurrence after undergoing pancreatectomy for PDAC at the Johns Hopkins Hospital or at the Regional Academic Cancer Center Utrecht during the study period were included. Cox proportional hazard model was used to develop the risk model. Performance of the final model was assessed in a test set after internal validation.

Results: Of 718 resected PDAC patients, 72% had recurrence after a median follow-up of 32 months. The median overall survival was 21 months and the median PRS was 9 months. Prognostic factors associated with shorter PRS were age (hazard ratio [HR] 1.02; 95% confidence interval [95%CI] 1.00–1.04), multiple-site recurrence (HR 1.57; 95%CI 1.08–2.28), and symptoms at time of recurrence (HR 2.33; 95%CI 1.59–3.41). Recurrence-free survival longer than 12 months (HR 0.55; 95%CI 0.36–0.83), FOLFIRINOX and gemcitabine-based adjuvant chemotherapy (HR 0.45; 95%CI 0.25–0.81; HR 0.58; 95%CI 0.26–0.93, respectively) were associated with a longer PRS. The resulting risk score had a good predictive accuracy (C-index: 0.73).

Conclusion: This study developed a clinical risk score based on an international cohort that predicts PRS in patients who underwent surgical resection for PDAC. This risk score will become available on www.evidencio.com and can help clinicians with patient counseling on prognosis.

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1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) is an aggressive malignancy, which is expected to be the second leading cause of cancer-related death in the Western world by 2030 [1,2]. Radical resection of localized PDAC combined with either neoadjuvant or

adjuvant chemotherapy provides the best chance of long-term survival. Patients who have undergone surgical resection in combination with chemotherapy for PDAC have a 5-year survival ranging between 19 and 22% [3,4]. These dismal survival rates are largely related to the propensity of PDAC to recur locally and/or systemically. Up to 80% of patients will develop disease recurrence within 5 years, and up to 60% of patients will develop recurrence within 2 years [5–8].

Prognostic factors for predicting survival after pancreatectomy have been studied extensively. Preoperative carbohydrate antigen 19–9 (CA19–9) levels, a positive resection margin status, lymph node metastasis, severe postoperative complications, and not

* Corresponding author. Dept. of Surgery, UMC Utrecht Cancer Center and St. Antonius Hospital Nieuwegein, Regional Academic Cancer Center Utrecht, PO Box 85500, 3508, GA, Utrecht, the Netherlands.

E-mail address: i.q.molenaar@umcutrecht.nl (I.Q. Molenaar).

¹ A.F. van Oosten and L.A. Daamen have contributed equally to this paper.

administering adjuvant therapy are known factors associated with survival [9–12]. Little is known, however, about factors that predict survival at time of recurrence. Several recent studies have shown that PDAC recurrence behaves heterogeneously and that post-recurrence survival (PRS) is dependent on the location and timing of recurrence, however it remains unclear to what degree other features can predict survival at the time of recurrence [13,14]. Given that most patients develop disease recurrence at some point following pancreatectomy, a better understanding of patient and recurrence factors associated with favorable outcomes can help clinicians with patient counseling on prognosis. As a result, a clinical tool that predicts PRS at time of recurrence may provide a basis for a more individualized approach to the treatment of recurrence.

The aim of this study is, therefore, to develop and validate a clinical risk score that predicts PRS after pancreatectomy for PDAC at the time of recurrence diagnosis. We used an international cohort of patients from two academic pancreatic centers.

2. Methods

We performed a post hoc analysis of a prospective databases from two academic pancreatic centers: the Johns Hopkins Hospital (JHH; Baltimore, United States of America) and the Regional Academic Cancer Center Utrecht (RACU; Utrecht, the Netherlands). The study was approved by the institutional review boards of both centers. Patients who underwent pancreatectomy for PDAC at the JHH between 2016 and 2018, and at the RACU between 2014 and 2019 who had disease recurrence during their follow-up period were included. Excluded were patients with metastatic disease at first PDAC diagnosis.

2.1. Demographic, clinicopathological, and treatment characteristics

Data were extracted from the prospectively maintained institutional databases. Standard demographic details were captured. Clinicopathological variables included preoperative chemotherapy, last preoperative CA19-9, type of procedure (i.e. pancreateoduodenectomy, distal or total pancreatectomy), tumor size, nodal status, tumor grade, lymphovascular and perineural invasion, and margin status. The resection margin was defined as R0 when there were no identifiable tumor cells within 1 mm of the resection margin, and as R1 when carcinoma cells were present within 1 mm of the resection margin [15]. Preoperative Charlson Comorbidity Index (CCI) was calculated using the MDCalc CCI calculator [16]. Postoperative data included complications, adjuvant chemotherapy regimens, symptoms and CA19-9 at time of recurrence. Data were supplemented from the patients' records in case of missing values.

2.2. Follow-up and recurrence definitions

Standardized follow-up differed between the two institutions. The patient follow-up at JHH was performed by either a surgical, medical, or radiation oncologist at the outpatient clinic of JHH or one of the affiliated hospitals [6]. In general, an enhanced computed tomography (CT) of the chest, abdomen and pelvis was performed every 3 months within the first 2 years postoperatively. An enhanced CT-scan was performed every year thereafter for another 5 years. At the RACU, patients underwent symptomatic follow-up every 3 months within the first 2 years postoperatively, without standardized blood work or CT-imaging surveillance [17]. Patients were instructed to contact their surgical or medical oncologist when they developed symptoms suggestive of recurrence, after which further diagnostic testing was performed.

The date of recurrence and first location of disease recurrence

were documented based on radiological or histological evidence. Confirmation of recurrence with a biopsy was not routinely obtained. Recurrence locations were stratified into five mutually exclusive categories: 'local-only', 'liver-only', 'lung-only', 'multiple-site', and 'other'. Multiple-site recurrence included local and distant recurrence, and recurrence at multiple distant sites (i.e. lung and liver, and/or carcinomatosis).

Post-recurrence survival (PRS) was calculated from the date of recurrence to the date of death or last follow-up. Overall survival (OS) was defined as the time from the date of surgery to either date of death or last follow-up. Recurrence-free survival (RFS) was defined as the time between the date of surgery and the date of recurrence. OS and RFS were calculated from the date of surgery rather than start of neoadjuvant therapy, as we adjusted for neoadjuvant chemotherapy in our prediction model.

2.3. Statistical analysis

Descriptive statistics were used to describe baseline characteristics. Missing data were considered to be missing at random and handled using multiple imputations with the iterative Markov chain Monte Carlo method (5 imputations; 10 iterations) [18,19]. To prevent multicollinearity, highly correlated predictors were excluded from imputation. Kaplan-Meier curves were performed to assess PRS; results were reported as median with 95% confidence intervals (95% CI). In case of missing data on vital status, patients were censored from the date of their last follow-up appointments.

The entire cohort was divided at random into a training set (70%, $n = 362$) and test set (30%, $n = 152$). Multivariable Cox proportional hazard analysis was performed in the training set to identify factors independently associated with PRS. Results were presented as hazard ratio's (HR) with corresponding 95% CI and P -values. Akaike's information criterion (AIC) was used to select the best predictive model for PRS. The final model was internally validated in 1000 bootstrap and performance of the final model was assessed using discrimination and calibration indices. The discriminative ability was evaluated using the concordance statistic (C-statistic). Calibration was assessed by calculating a calibration slope, with perfect calibration characterized by a calibration slope of 1 and intercept of 0.

The final model was used to compile a risk score, which was designed as a graphical representation of the model. The reference line at the top of the risk score assigns points to each predictor between 0 and 100. The predictive variables are displayed below with bars that scale their effect size, demonstrating the relative weight of each variable and allowing for points to be assigned to each clinical characteristic. The summation of points and corresponding score that predicts the probability of a relatively better or worse PRS can be read from the bottom line. For each patient, a risk score was calculated. Based on the Youden's Index, patients in both training and test sets were divided into having either a relatively good or poor prognosis. Risk stratification was subsequently validated in the separate test set by plotting Kaplan-Meier curves for the good and poor prognostic groups. The established risk score will become available as an easy-to-use online calculator on www.evidencio.nl after publication.

A two-sided P -value < 0.05 was considered statistically significant. Statistical analyses were carried out using R language environment (version 1335, Mice, pROC, rms, MASS packages; <http://R-project.org>).

3. Results

3.1. Characteristics

During the study period, a total of 718 patients underwent a

pancreatectomy for PDAC. In total, 514 (72%) patients had documented recurrence at last follow-up and were included in the study. Median follow-up of the entire cohort was 31.8 months (IQR 24.7–44.5); for the JHH cohort the median follow-up was 33.1 months (IQR 25.3–47.7) and for the RACU cohort the median follow-up was 27.6 months (IQR 20.2–33.3).

Detailed demographic, clinicopathologic and treatment characteristics are summarized in Table 1. The median age was 68 years (IQR 60–73), and 52% of patients were men. The median preoperative CA19-9 was 86 (IQR 28.8–250). In the entire cohort, 50% of patients ($n = 255$) received neoadjuvant chemotherapy, and 30% received neoadjuvant chemoradiotherapy ($n = 155$). The majority of these patients were derived from the JHH cohort, where 66% ($n = 243$) received neoadjuvant chemotherapy and 43% ($n = 155$) received neoadjuvant chemoradiotherapy. In the RACU cohort, 8% received neoadjuvant chemotherapy in trial setting ($n = 13$) and 0% ($n = 0$) received neoadjuvant chemoradiotherapy. Most patients ($n = 398$; 77%) underwent a pancreaticoduodenectomy. A margin-negative resection was achieved in 336 patients (65%); 289 patients (79%) in the JHH cohort and 47 patients (31%) in the RACU cohort underwent a margin-negative resection. Adjuvant chemotherapy was given to 340 patients (66%).

3.2. Recurrence and survival outcomes

Recurrence data and survival outcomes are presented in Table 2. Patients most often experienced multiple site recurrence ($n = 229$, 44%), followed by isolated local ($n = 151$, 29%), liver only ($n = 76$, 15%), and lung only ($n = 50$, 10%) recurrence. The most common recurrence location at JHH was multiple site recurrence ($n = 130$, 36%), closely followed by local recurrence ($n = 129$, 35%). Liver only recurrence occurred in 15% ($n = 56$) of JHH patients, lung only in 12% ($n = 43$) and other site recurrences in 2% ($n = 7$). In the RACU cohort, multiple site recurrence was also the most predominant location ($n = 98$, 66%), with single locations occurring less frequently: local only ($n = 22$, 15%), liver only ($n = 20$, 13%), and lung only ($n = 7$, 5%). At time of recurrence, 42% of patients ($n = 215$) experienced symptoms and the median CA19-9 was 170 (IQR 30–1188). In total, 59% of patients ($n = 304$) received treatment for recurrence.

At last follow-up, 400 patients (78%) had died. Survival status of 5 patients were missing and were, therefore, not included in the survival analysis. The OS for all patients with recurrence was 21.2 months (95% CI 20.1–23.6); for the JHH cohort the median OS was 23.8 months (95% CI 21.1–26.9) and for the RACU cohort 16.4 months (95% CI 14.8–20.6). Median RFS was 10.5 months (95% CI 9.6–11.3) for the entire cohort: 10.3 months (95% CI 9.1–11.3) for

Table 1
Baseline characteristics of patients with pancreatic cancer recurrence after primary resection.

Variable	All Patients ($n = 514$)	JHH Patients ($n = 365$)	RACU Patients ($n = 149$)
Age, median years (IQR)	68 (60–73)	68 (60–73)	69 (61–76)
Female, n (%)	249 (48%)	179 (49%)	70 (47%)
Charlson Comorbidity Index, n (%)			
< 4 points	447 (87%)	322 (88%)	125 (84%)
≥ 4 points	67 (13%)	43 (12%)	24 (16%)
Preoperative CA19-9 (U/mL), median (IQR)	86.0 (28.8–250.0)	70.9 (26.0–202.1)	170 (38.1–540.0)
Neoadjuvant therapy, n (%)			
None	259 (50%)	122 (33%)	137 (92%)
Neoadjuvant chemotherapy	255 (50%)	243 (67%)	12 (8%)
Neoadjuvant chemoradiotherapy	155 (30%)	155 (43%)	0 (0%)
Surgery type			
Pancreaticoduodenectomy	398 (77%)	279 (76%)	119 (80%)
Distal pancreatectomy	90 (18%)	77 (21%)	13 (9%)
Total pancreatectomy	26 (5%)	9 (3%)	17 (11%)
Complications, n (%)			
Clavien-Dindo grade \leq II	285 (55%)	190 (52%)	95 (64%)
Clavien-Dindo grade \geq III	229 (45%)	175 (48%)	54 (36%)
Resection margin status, n (%)			
R0 (> 1.0 mm)	336 (65%)	289 (79%)	47 (31%)
R1 (≤ 1.0 mm)	178 (35%)	76 (21%)	102 (69%)
Differentiation grade, n (%)			
Good	24 (5%)	14 (4%)	10 (7%)
Moderate	290 (56%)	220 (60%)	70 (47%)
Poor	201 (39%)	131 (36%)	68 (46%)
Tumor size, cm, median (IQR)	3.5 (2.4–23.0)	2.8 (2.0–3.6)	3.5 (2.7–4.5)
T-stage, n (%)			
1–2	380 (74%)	288 (79%)	91 (61%)
3–4	133 (26%)	76 (21%)	57 (39%)
Lymph node status, n (%)			
N0	165 (32%)	148 (41%)	17 (11%)
N1	173 (34%)	127 (35%)	46 (31%)
N2	176 (34%)	90 (25%)	86 (58%)
Micr. Perineural invasion, n (%)	426 (83%)	284 (78%)	142 (96%)
Micr. Lymphovascular invasion, n (%)	281 (55%)	172 (47%)	109 (73%)
Adjuvant chemotherapy, n (%)			
No adjuvant	174 (33%)	108 (30%)	66 (44%)
FOLFIRINOX	97 (19%)	80 (16%)	17 (11%)
Gemcitabine	233 (45%)	167 (33%)	66 (44%)
Other	10 (1%)	10 (3%)	0 (0%)
Adjuvant chemoradiotherapy, n (%)	33 (6%)	33 (9%)	0 (0%)

IQR, interquartile range; CA, carbohydrate antigen; PD, pancreaticoduodenectomy (classic or pylorus-preserving); micr., microscopic.

Table 2
Recurrence data and survival outcomes.

Variable	All Patients (n = 514)	JHH Patients (n = 365)	RACU Patients (n = 149)
Recurrence site, n (%)			
Local only	151 (29%)	129 (35%)	22 (15%)
Liver only	76 (15%)	56 (15%)	20 (13%)
Lung only	50 (10%)	43 (12%)	7 (5%)
Multiple site	229 (44%)	130 (36%)	98 (66%)
Other distant	9 (2%)	7 (2%)	2 (1%)
Symptoms at time recurrence, n (%)	215 (42%)	95 (26%)	120 (81%)
CA19-9 at time of recurrence (U/mL), median (IQR)	170 (30–1188)	98 (22–1517)	803 (110–12617)
Treatment Recurrence			
None	210 (41%)	112 (31%)	98 (66%)
Yes	304 (59%)	253 (69%)	51 (34%)
Survival status at last follow-up, n (%)			
Dead	400 (78%)	276 (76%)	124 (83%)
Alive	113 (22%)	89 (24%)	24 (16%)
Survival (median months, 95% CI)			
Overall survival	21.2 (20.1–23.6)	23.8 (21.1–26.9)	16.4 (14.8–20.6)
Recurrence-free survival	10.5 (9.6–11.3)	10.3 (9.1–11.3)	10.6 (9.1–13.1)
Post-recurrence survival	8.9 (7.9–10.2)	11.1 (9.5–12.0)	4.0 (3.1–5.0)

CA, carbohydrate antigen; 95% CI, 95% Confidence interval.

the JHH cohort and 10.6 months (95% CI 9.1–13.1) for the RACU cohort. Median PRS was 8.9 months (95% CI 7.9–10.2; Fig. 1) for the entire cohort: 11.1 months (95% CI 9.5–12.0) for the JHH cohort, and 4.0 months (95% CI 3.1–5.0) for the RACU cohort. Patients with multiple site recurrence had the shortest median PRS of 4.8 months (95% CI 4.3–5.7; Fig. 2). Patients with liver only recurrence had a PRS of 9.0 months (95% CI 7.1–13.6) and patients with local only recurrence had a median PRS of 13.1 months (95% CI 11.1–17.8). Patients with lung only recurrence had the longest median PRS of 16.8 months (95% CI 13.4–23.0).

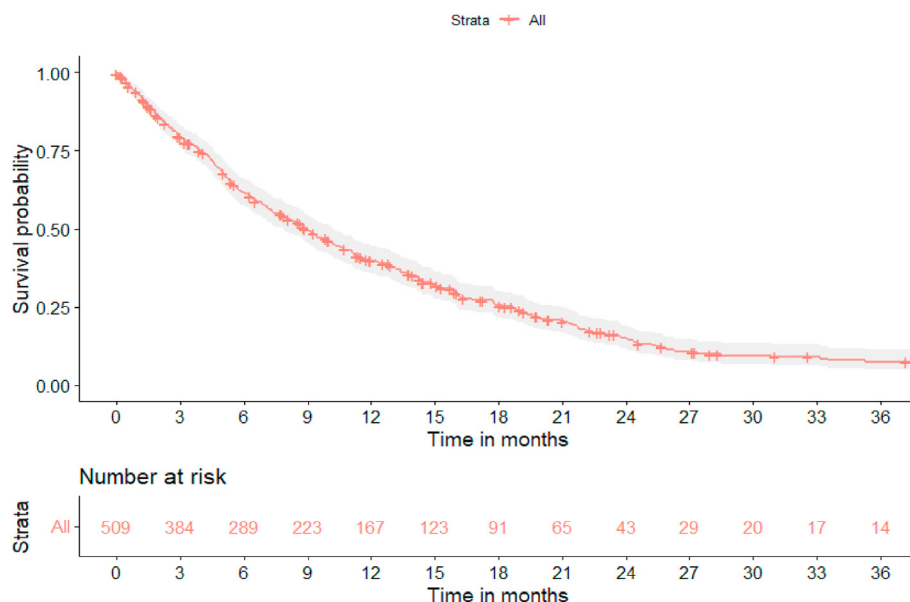
3.3. Predictors of post-recurrence survival

The prognostic risk factors identified in the training set with the multivariable analysis are presented in Table 3. Treatment of recurrence was treated as a time-varying covariate in this multivariable analysis. Three variables proved to be independently associated with a worse PRS, including age (HR 1.02; 95% CI

1.00–1.04; $P = 0.02$), multiple-site recurrence (HR 1.57; 95% CI 1.08–2.28; $P = 0.02$), and symptoms at time of recurrence (HR 2.33; 95% CI 1.59–3.41; $P < 0.001$). Receipt of gemcitabine-based (HR 0.58; 95% CI 0.36–0.93; $P = 0.02$) or FOLFIRINOX adjuvant chemotherapy (HR 0.45; 95% CI 0.25–0.81; $P = 0.01$), and an RFS longer than 12 months (HR 0.55; 95% CI 0.37–0.83; $P = 0.004$) were independently associated with a better PRS. CA19-9 at time of recurrence was not associated with PRS (HR 1.03; 95% CI 0.98–1.09; $P = 0.25$), nor were any of the histopathological factors of the surgical specimen (all $P > 0.05$).

3.4. A risk score for post-recurrence survival

The best predictive model included all statistically significant risk factors (Fig. 3) and had an area under the curve of 0.71 (Supplemental Fig. 1) to predict continuous PRS. The C-index after internal validation in 1000 bootstrap samples was 0.725. The calibration slope was 0.939. The cut-off chosen using Youden's Index

**Fig. 1.** Kaplan-meier curve of post-recurrence survival for entire cohort.

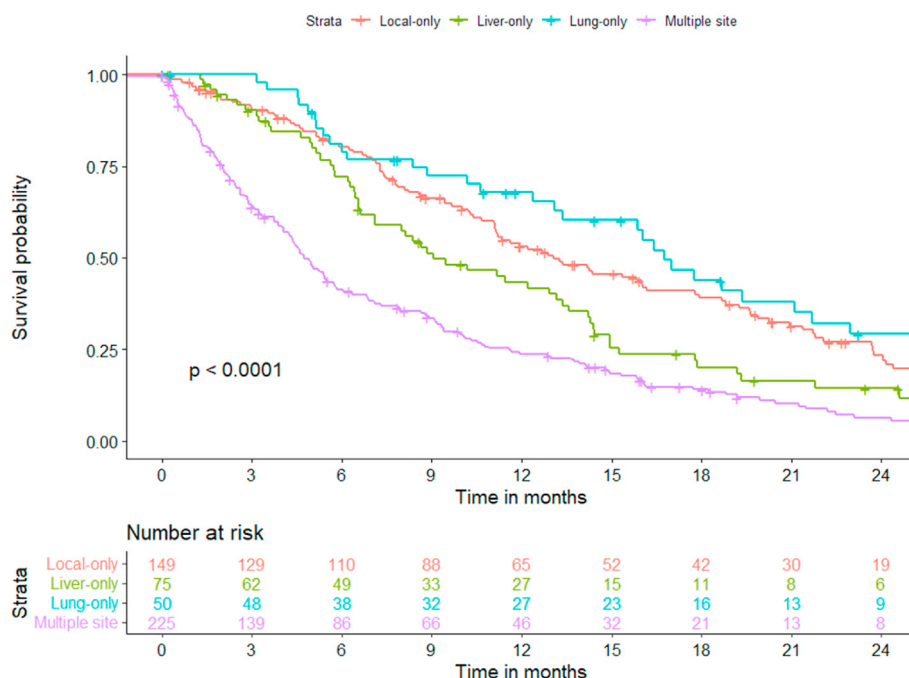


Fig. 2. Post-recurrence survival curves for different recurrence patters. For clarity, the curve for “other” recurrence has been omitted.

Table 3

Multivariable cox regression analysis in training set.

Clinical Characteristics	Hazard Ratio (HR)	95% Confidence Interval (95% CI)	P-value
Age*	1.019	1.003–1.037	0.02
Gender			
Female vs. male	1.007	0.751–1.352	0.96
Charlson-Comorbidity Index*	1.030	0.911–1.163	0.64
Log CA19-9 at time of recurrence diagnosis	1.033	0.978–1.091	0.25
Neoadjuvant therapy			
Neoadjuvant chemotherapy versus none	1.179	0.771–1.805	0.45
Neoadjuvant chemoradiotherapy versus none	1.042	0.651–1.669	0.86
Surgery type			
Distal pancreatectomy versus PD	1.160	0.766–1.756	0.48
Total pancreatectomy versus PD	0.803	0.455–1.418	0.45
Differentiation grade			
Moderate versus good	1.628	0.794–3.336	0.18
Poor versus good	1.554	0.743–3.251	0.24
Tumor size, cm*	0.996	0.984–1.009	0.56
Margin status			
R1 vs. R0	0.876	0.675–1.411	0.90
Neural invasion			
Yes vs. no	0.960	0.589–1.564	0.87
Number of positive lymph nodes*	1.021	0.974–1.070	0.39
Major complications			
Yes vs. no	0.875	0.642–1.193	0.40
Adjuvant chemotherapy			
Gemcitabine-based versus none	0.576	0.357–0.928	0.02
FOLFIRINOX versus none	0.451	0.251–0.811	0.01
Other versus none	0.467	0.158–1.381	0.17
Disease-Free Survival			
6–12 months versus <6 months	0.771	0.524–1.134	0.19
>12 months versus <6 months	0.550	0.366–0.826	0.004
Recurrence locations			
Liver-only versus local-only	1.121	0.695–1.808	0.64
Lung-only versus local-only	0.568	0.291–1.110	0.10
Multiple-site versus local-only	1.570	1.083–2.276	0.02
Other distant versus local-only	0.904	0.184–4.449	0.90
Symptoms at time of recurrence			
Yes vs. no	2.334	1.594–3.417	<0.001

Significant values on multivariable analysis are shown in bold ($P \leq 0.05$).

* Continuous.

PD: pancreaticoduodenectomy, classic or pylorus-preserving.

was 174.5. This score was used as a cut-off to stratify patients into one of two groups: the relatively better prognosis (i.e. a risk score of < 174.5 and the relatively worse prognosis group (i.e. a risk score of > 174.5).

Patients in the test set were stratified to one of the two risk groups. Patients in the poor prognosis group had a PRS of 5.3 months (95% CI 4.4–7.3). The better prognosis group had a median PRS of 14.3 months (95% CI 11.1–19.6, $P < 0.001$; Fig. 4A). The model was tested separately in the two institutional cohorts, demonstrating the discriminative predictive ability and generalizability of the model. The poor prognosis group in the JHH cohort had a median PRS of 6.0 months (95% CI 5.0–8.6; Fig. 4B). Patients with the better prognostic score had a median PRS of 14.9 months (95% CI 13.3–16.8; $P < 0.0001$). In the RACU cohort, patients in the poor prognosis group had a median PRS of 3.8 months (95% CI 2.9–4.9; Fig. 4C) versus 6.5 months (95% CI 6.0 – NA; $P < 0.0001$) in the better prognosis group. To demonstrate the discriminatory potential of the predictive model, an example of stratification in three groups (poor, intermediate and better prognosis) is provided in the supplemental materials (Supplemental Fig. 2).

4. Discussion

PDAC recurrence after oncologic resection has a significant impact on patients' prognosis. This study is the first to establish and validate a risk score for PRS in an international cohort of patients with PDAC recurrence after resection. The final model incorporated known factors, such as timing and location of recurrence, as well as other prognostic factors. Specifically, age, multiple-site recurrence and symptoms at time of recurrence were associated with a limited PRS, while RFS longer than 12 months and receipt of FOLFIRINOX and Gemcitabine-based adjuvant chemotherapy were associated with a better PRS. The discriminative ability of the risk score to stratify patients into a poor and better prognosis group, based on their individual risk score, was good in both institutional cohorts. This clinical tool can help clinicians with counseling of prognosis and establishing a more individualized approach to recurrence treatment.

Timing and location of recurrence were predictive of the duration of PRS. Multiple studies have demonstrated that early recurrence, defined as recurrence within 12 months, has a dismal prognosis [20–22]. In a previous study, patients with early recurrence had 1- and 2-year PRS rates of 20 and 6%, whereas patients with late recurrence had a 1- and 2-year PRS rates of 45 and 22%

[20]. In our study, we also found that an RFS longer than 12 months was significantly associated with a longer PRS. Furthermore, initial recurrence patterns have been shown to be predictive of survival. Multiple-site recurrence and liver-only recurrence are associated with a significantly worse PRS compared to lung- or local-only recurrence sites [13,23,24]. This study reiterates the importance of location for predicting PRS, as multiple-site recurrence was independently predictive of a worse PRS with a median PRS of 4.8 months. The other recurrence locations were not independently associated, but had a clinically relevant difference in median PRS.

We expand on these findings by accounting for additional predictive factors, such as age, adjuvant treatment and symptoms at time of recurrence. Only a handful of other variables have been studied in this context. A recent study found that besides timing and location, poor performance status and tumor invasiveness were correlated with a worse PRS [25]. In another study, total pancreatectomy, poor tumor differentiation and treatment of recurrence were independent predictors of PRS [22]. Given that the aim of this study was to establish a risk score at the time of recurrence, we decided to include treatment of recurrence as a time-varying covariate. In doing so, this study is the first to create a comprehensive model that can be clinically relevant at the time of recurrence diagnosis for physician and patient alike.

Histopathological factors that have prognostic significance postoperatively, did not have prognostic value at time of recurrence. A margin-positive resection, positive lymph nodes, and tumor differentiation were not associated with a worse PRS. Their effect on PRS could, however, be mitigated through their effect on the timing of recurrence. A previous study demonstrated that pathologic findings of poor tumor differentiation, microscopic lymphovascular invasion and a positive lymph node ratio >0.2 were independently associated with early recurrence [20]. Another explanation could be that the tumor biology of the primary tumor differs from that of the metastases. Future studies will have to elucidate the unique biological characteristics of different recurrence patterns by studying methylation, genetic, or proteomic signatures.

A strength of this study is that it combined data from two international high-volume centers that have different follow-up strategies after PDAC resection. The rate of symptomatic recurrence was significantly higher in the RACU cohort, due to its follow-up strategy. This difference may have influenced the results. Noticeable, for instance, is the difference in recurrence patterns. The Dutch RACU cohort experienced relatively more multiple-site

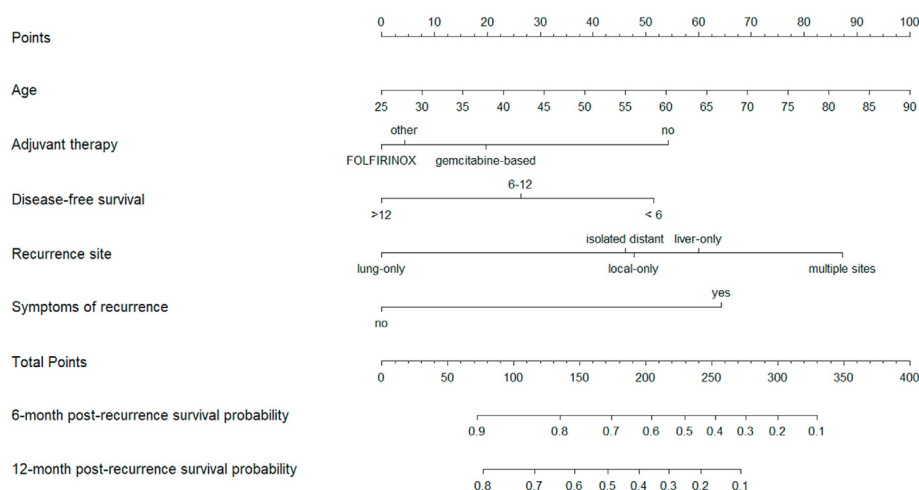


Fig. 3. Graphical representation of risk model.

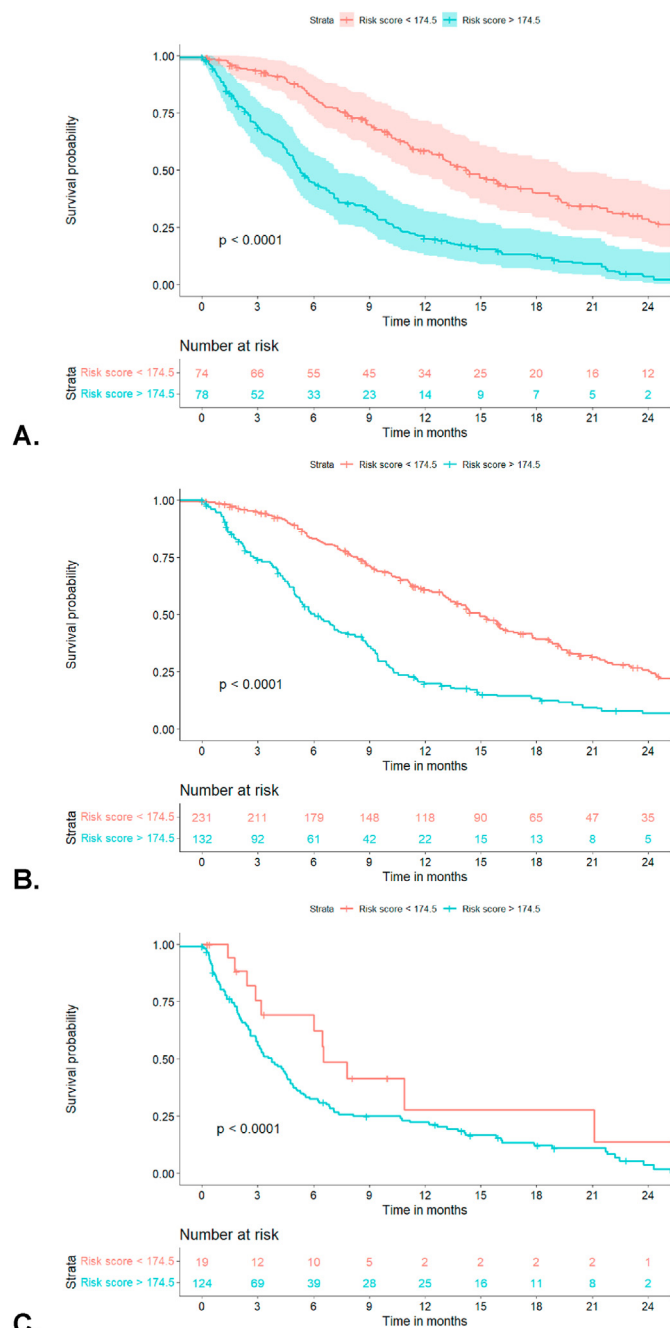


Fig. 4. Post-recurrence survival curve stratified by risk score for (A) Test Set, (B) JHH Cohort, and (C) RACU Cohort.

recurrences and fewer local site recurrences compared to the American JHH cohort. From the above it could be argued that the standardized follow-up is able to capture recurrence at an earlier, local stage, prior to any systemic spread. However, the inclusion of both follow-up strategies more accurately represents real-world clinical practice. Currently, no consensus exists about standardized follow-up after surgery. While, theoretically, it is very plausible that standardized follow-up improves early recurrence detection, timely initiation of recurrence-oriented treatment and with that overall survival [17]; no level-1 evidence on the subject is available. Therefore, we are looking forward to the results of the currently ongoing nationwide randomized RADAR-PANC trial (NCT04875325) which is assessing the added benefit of standardized surveillance for recurrence after pancreatic resection. The risk

model that was established using these data held true in both the standardized and symptomatic follow-up settings, making these results more generalizable. Moreover, the inclusion of the symptomatic follow-up strategy ensured that sufficient patients with symptomatic recurrence were included to assess the association between symptoms and post-recurrence survival. Another difference between the two institutions is the number of margin-negative resections. Reported margin-negative resection rates vary substantially in the literature, ranging between 15 and 83%, which can be attributed to differences in surgical and pathologic techniques [26]. The use of neoadjuvant chemoradiotherapy could also explain this difference, which has been shown to sterilize resection margins. Currently, a consensus on a definition of margin clearance within a neoadjuvant setting is lacking [27].

Recurrence of PDAC following resection imposes a difficult choice when considering the pursuit of additional treatment for recurrence. The risk score presented in this study can further assist patients and physicians when discussing challenging clinical choices at time of recurrence, balancing quality of life with further treatment options. In a recent study, patients with isolated local recurrence and an RFS longer than 9 months were shown to benefit from stereotactic body radiation therapy [28,29]. In select cases, resection of solitary local, liver or pulmonary lesions was proven to improve survival for patients with an RFS of more than 15 months (40.6 vs. 8.2 months). Patients with isolated pulmonary recurrence have also been shown to have a significantly better PRS when they received any treatment (PRS 26 months) compared to when they received best-supportive care (PRS 8 months) [30].

Serum CA19-9 is the most widely assessed biomarker for PDAC and it is the only clinically approved biomarker by the FDA. Elevated pre- and postoperative CA19-9 levels have been correlated with both RFS and OS [31–33]. However, only few studies have focused on the use of CA19-9 during follow-up and the correlation with PRS. In this study, an elevated CA19-9 level at time of recurrence was not associated with a shorter PRS. CA19-9 may serve as an early and reliable predictor for PDAC recurrence, as it is elevated in approximately 60% of patients prior to recurrence detection, but it likely does not accurately reflect the variety of tumor dynamics and biology [34]. These findings indicate that future research should focus on identifying other tumor biomarkers, such as circulating tumor cells, circulating tumor DNA, and exosomes, that more accurately represent tumor dynamics and biology [35–37].

The current study provides a clinical risk score that can aid physicians in counseling of patients with recurrence of PDAC after resection. However, this risk score should be considered in light of its limitations. First, although this study analyzed data from two prospectively maintained databases from two academic centers, the study was of retrospective nature with all the inherent and associated bias risks. Second, our data merely captured the location of tumor recurrence, without commenting on the extent of recurrent disease. Future studies should further investigate how to classify the extent of tumor recurrence, either based on volume and/or number of lesions. Lastly, many patients choose to receive further therapy at local institutions, limiting the accuracy of data on type and frequency of therapy for recurrence that would have potentially exposed correlations not currently established.

In conclusion, this international cohort study found that age, multiple-site recurrence, and symptoms at time of recurrence diagnosis are associated with worse PRS. Furthermore, RFS longer than 12 months and FOLFIRINOX or gemcitabine-based adjuvant chemotherapy proved to be associated with a better PRS. The risk score that was established was validated in both cohorts and provided good stratification for a poor versus relatively better prognosis after recurrence diagnosis in both symptom-based and standardized follow-up cohorts.

Disclosure of funding

This study was supported in the form of grants for a research fellowship by AFvO by the Prins Bernhard Cultuurfonds (the Netherlands), VSB Fonds (the Netherlands), Prof. Michaël-van Vloten Fonds (the Netherlands), the Living with Hope Foundation (the Netherlands).

Conflicts of interest

None to declare.

CRediT authorship contribution statement

A. Floortje van Oosten: Conceptualization, Methodology, data acquisition, Writing – original draft. **Lois A. Daamen:** Conceptualization, Methodology, Formal analysis, data acquisition, Writing – review & editing. **Vincent P. Groot:** Conceptualization, Methodology, data acquisition, Writing – review & editing. **Nanske C. Biesma:** Methodology, data acquisition, Writing – review & editing. **Joseph Habib:** Methodology, data acquisition, Writing – review & editing. **Iris W.J.M. van Goor:** Methodology, data acquisition, Writing – review & editing. **Benedict Kinny-Köster:** Methodology, data acquisition, Writing – review & editing. **Richard A. Burkhart:** Methodology, data acquisition, Resources, Writing – review & editing. **Christopher L. Wolfgang:** Methodology, data acquisition, Resources, Writing – review & editing, Supervision. **Hjalmar C. van Santvoort:** Methodology, data acquisition, Resources, Writing – review & editing, Supervision. **Jin He:** Methodology, data acquisition, Resources, Writing – review & editing, Supervision. **I. Quintus Molenaar:** Methodology, data acquisition, Resources, Writing – review & editing, Supervision.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejso.2023.04.009>.

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