Hepatobiliary & Pancreatic Diseases International 18 (2019) 569–575

Contents lists available at ScienceDirect

Hepatobiliary & Pancreatic Diseases International

journal homepage: www.elsevier.com/locate/hbpd

Original Article/Pancreas

Prediction of survival after left-sided pancreatic resection for adenocarcinoma: Introduction of a new prognostic score

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ARTICLE INFO

Article history:
Received 2 February 2019
Accepted 17 June 2019
Available online 26 June 2019

Keywords:
Pancreatic cancer
Mortality
Risk factors

ABSTRACT

Background: Due to the clinically unapparent course the entity of left-sided pancreatic adenocarcinoma is often diagnosed at advanced stages, resulting in small numbers of patients qualifying for pancreatectomy. This study strives to develop a prognostic model for survival after left-sided pancreatic resection.

Methods: A total of 54 patients were analyzed. Pre- and intra-operative predictive factors for 18-month mortality were identified with multivariable binary logistic regression analysis and compiled into a prognostic model. The applicability was evaluated by assessment of the area under the receiver operating characteristic curve (AUROC). The model was internally validated applying a randomized backwards bootstrapping analysis.

Results: The 18-month mortality rate was 74.1% ($n = 40$). Mean survival was 19.1 months. A prognostic model for 18-month mortality after left sided-pancreatectomy showed an AUROC >0.800:

18-month mortality risk in% = Exp(Y) / (1 + Exp(Y)) *with*

y= -0.927 + (1.724, if CA 19-9 elevated, otherwise 0) + (1.212 × number of intra-operative transfused packed red blood cells) + (2.771, if prior abdominal surgery, otherwise 0) − (3.612, if gastric resection, otherwise 0)

This model was internally validated in 40 randomized backwards bootstrapping steps with AUROCs ranging from 0.757 to 0.971.

Conclusions: The 18-month mortality risk for patients after left-sided pancreatectomy for adenocarcinoma of the pancreatic body can be assessed with the number of intra-operatively transfused packed red blood cells, elevated CA 19-9 levels, additional gastric resection and prior abdominal surgeries in the patient's history.

Introduction

The incidence of the devastating diagnosis of pancreatic ductal adenocarcinoma (PDAC) has been increasing [1,2]. Population and age increase are assumed causes for this observation [2]. The 5-year survival rate is reported to be less than 5% [3]. Especially body and tail PDAC are hard to diagnose due to its initial unapparent course [4]. While curative R0 pancreatectomy is the therapy of choice, about 80% of the patients suffering from PDAC of the body or tail are found to have already progressed beyond resectability at time of diagnosis [5]. Furthermore, survival rates are still poor after potentially curative surgery plus aggressive adjuvant chemotherapy [6].

Several risk factors associated with poor outcome after pancreatectomy for left-sided PDAC have been identified. Tumor size and differentiation, lymph node metastases, high expression of carbohydrate antigen 19-9 (CA 19-9), incomplete resection, and vascular or perineural invasion are known risk factors for poor prognosis [7–10]. Recently, Hwang and colleagues identified the lymph node ratio, as well as intra-operatively received blood transfusions to be independent risk factors for tumor recurrence [11]. Moreover, extended resections including the portal vein or the coeliac axis are controversially debated [12]. Previous studies have combined patients suffering from PDAC of the pancreatic head with those of the pancreatic body and tail in their analyses, which might bias results because of the different surgical approach, different anatomical locations and courses of disease [13–15].

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https://doi.org/10.1016/j.hbpd.2019.06.007

Even though PDAC of the body and tail is a rare entity with a known generally poor outcome, a prognostic model at time of surgery is needed to predict survival for those patients, who still have a chance of potentially curative left-sided pancreatectomy at time of diagnosis.

This study strives to propose a prognostic model for patient survival after left-sided pancreatectomy for PDAC of the body and tail.

Methods

Study population

This is a retrospective study including 80 adult patients with PDAC of the pancreatic body and/or tail undergoing left-sided pancreatic resection consecutively between January 1, 1995 and March 1, 2014 at Hannover Medical School, Germany, a tertiary reference center for hepatobiliary surgery. Of these patients, 26 were excluded due to missing data >5%. Further analyses were subsequently conducted with the remaining 54 patients.

Surgical treatment

All patients were operated with concomitant splenectomy. Distant metastases were present in 12 patients (22.2%). Portal vein resection was performed in 8 patients (14.8%), gastrectomy in 7 patients (13.0%), liver resection in 6 patients (11.1%), left adrenal gland resection in 6 patients (11.1%), whereas partial colon resection was performed in 5 patients (9.3%) and the resection of the coeliac axis was performed in 3 patients (5.6%) (Table 1).

Histopathology

Histopathological parameters were tumor diameter (T), number of infiltrated lymph nodes (N), distant metastases (M) and tumor differentiation (G). Tumor free resection margins were described as R0 and were achieved in 33 patients (61.1%). Microscopic infiltration was categorized as R1 ($n=17$; 31.5%) and macroscopic infiltration of resection margin as R2 ($n=4$; 7.4%). Tumor stages were classified according to the International Union Against Cancer (UICC, 7th edition).

Study endpoints

The primary study endpoint was 18-month mortality after left-sided pancreatic resection. This endpoint was chosen based on the visual appearance of initial Kaplan-Meier curve analysis (Fig. 1). As it can be seen, the curve decreases up to the point of 18 months after the procedure, coming to a steady state of nearly 20% cumulative survival. The curve is very slowly decreasing from the point of 18 months to its basic level of 10% cumulative survival. Therefore, this turning point in the Kaplan-Meier curve was defined as cut-off for the binary analysis of survival and prognostic modelling.

Definition of variables

Prior abdominal surgeries were defined as abdominal surgeries that were not associated with the diagnosis of PDAC. The upper cut-off for serum levels of CA 19-9 was set at 37 IU/mL [16]. The upper cut-off for serum levels of CEA was defined as 5 ng/mL.

Accordance to TRIPOD

Transparent reporting of multivariable prediction modelling for individual prognosis or diagnosis (TRIPOD) was used according to the TRIPOD-statement, because this work introduces a newly developed prognostic model [17].

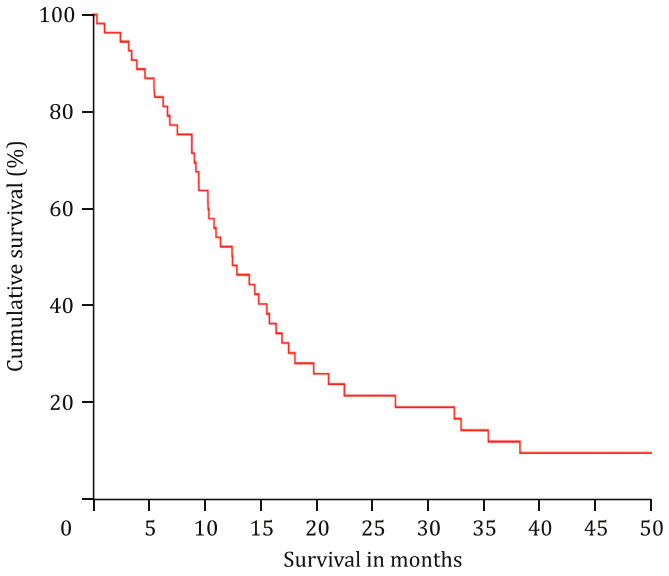

Fig. 1. The Kaplan-Meier curve shows survival in month after left-sided pancreatectomy for adenocarcinoma.

Statistical analysis

Distribution of continuous data was assessed with the Kolmogorov-Smirnov test. Normally distributed data were presented as mean and standard deviation (SD), whereas not normally distributed data were given as median and range. For continuous data the Student's *t*-test was applied when comparing normally distributed variables and the Mann-Whitney *U* test when comparing not-normally distributed variables. Categorical variables were compared with Pearson's Chi-square test. Kaplan–Meier analysis with log-rank test was applied where appropriate.

Multivariable principal component analysis was used to understand the underlying data structure better and to identify correlated variables for prognostic score design to avoid multicollinearity in regression. Variables with a factor correlation $\geq|0.500|$ were subjected to a clinically informed decision on the exclusion of one of the highly correlated variables from multivariable regression. The initial multivariable binary logistic regression model was developed using purposeful selection of pre-operative, intra-operative and tumor specific variables with *P* values in univariate binary logistic regression ≤ 0.300 to avoid over fitting as proposed by Hosmer et al. [18]. The final multivariable binary logistic regression model was assessed for model-fit with the Hosmer–Lemeshow test. Sensitivity, specificity and overall correctness of the proposed model were determined using receiver operating characteristic (ROC) curve analysis. Areas under the ROC curve (AUROCs) larger than 0.700 indicate a potentially useful prognostic factor or model [19]. Cut-off values of potential prognostic models were determined with the best Youden index (Youden index = sensitivity + specificity − 1) [20]. The developed final prognostic model was internally validated using randomized backwards bootstrapping in 40 random samples of the original study population using ROC curve analyses of the logits. For all statistical tests a *P* value < 0.05 was defined as significant. Statistical analysis was performed using the software package JMP Pro 11.2 (SAS Institute, Cary, NC, USA).

Table 1
The descriptive statistics of patients undergoing left-sided pancreatectomy for adenocarcinoma with less versus more than 18 months survival.

Variables	Survival ≤ 18 months ($n=40$)	Survival > 18 months ($n=14$)	P value
Pre-operative data			
Age (yr)	65.2 ± 10.6	65.4 ± 9.1	0.906
Sex male	20 (50.0%)	6 (42.9%)	0.645
Epigastic pain	28 (70.0%)	9 (64.3%)	0.694
Loss of weight	16 (40.0%)	6 (42.9%)	0.852
Back pain	9 (22.5%)	2 (14.3%)	0.499
CEA elevated	11 (27.5%)	4 (28.6%)	0.939
CA 19–9 elevated	27 (67.5%)	6 (42.9%)	0.107
Insulin-dependent diabetes[a]	9 (23.1%)	3 (21.4%)	0.899
Thrombocyte count (thousand/μL)[b]	222 ± 76	252 ± 52	0.155
Prior abdominal surgeries	16 (40.0%)	1 (7.1%)	**0.013**
Pre-operative hospital stay	3.5 ± 4.1	2.7 ± 2.2	0.925
Intra-operative data			
Extended lymphadenectomy	11 (27.5%)	3 (21.4%)	0.651
Portal vein resection	7 (17.5%)	1 (7.1%)	0.317
Liver resection	6 (15.0%)	0	0.050
Resection at coeliac axis	2 (5.0%)	1 (7.1%)	0.769
Gastric resection	4 (10.0%)	3 (21.4%)	0.295
Colon resection	4 (10.0%)	1 (7.1%)	0.745
Left adrenal resection	4 (10.0%)	2 (14.3%)	0.668
Number of pRBCs	1.4 ± 1.7	0.5 ± 1.0	0.086
Transfusion of fresh frozen plasma	9 (22.5%)	2 (14.3%)	0.499
Carcinoma of pancreatic body	18 (45.0%)	6 (42.9%)	0.890
Carcinoma of pancreatic tail	14 (35.0%)	6 (42.9%)	0.603
Crossover growth of carcinoma	8 (20.0%)	2 (14.3%)	0.628
Postoperative data			
Diameter of tumor (cm)[c]	5.1 ± 2.1	4.6 ± 3.8	0.067
Peripancreatic invasion[a]	34 (85.0%)	10 (76.9%)	0.512
UICC 7 stages			
Ia	0	0	n.a.
Ib	4 (10.0%)	4 (28.6%)	0.111
IIa	12 (30.0%)	6 (42.9%)	0.386
IIb	14 (35.0%)	2 (14.3%)	0.125
III	1 (2.5%)	0	0.436
IV	9 (22.5%)	2 (14.3%)	0.499
Number of positive lymph nodes[c]	1.5 ± 2.4	0.7 ± 1.1	0.326
Lymph nodes examined < 10[c]	25 (64.1%)	9 (69.2%)	0.658
Lymph node ratio[c]	0.15 ± 0.21	0.10 ± 0.15	0.444
N0[c]	21 (52.5%)	8 (66.7%)	0.382
N1[c]	19 (47.5%)	4 (33.3%)	0.382
M0	30 (75.0%)	12 (85.7%)	0.390
M1	10 (25.0%)	2 (14.3%)	0.390
Tumor grading			
G1	0	1 (7.1%)	0.097
G2	23 (57.5%)	8 (57.1%)	0.984
G3	17 (42.5%)	5 (35.7%)	0.655
Surgical complications[a]	15 (38.5%)	2 (14.3%)	0.081
Postoperative stay (d)	18.6 ± 9.2	14.9 ± 5.2	0.191
Postoperative chemotherapy[a]	12 (30.0%)	4 (30.8%)	0.958
Pancreatic fistula	5 (12.5%)	0	0.075
Bleeding	1 (2.5%)	1 (7.1%)	0.458
Intra-abdominal abscess	3 (7.5%)	0	0.172
Thrombosis of coeliac trunc or portal vein	2 (5.0%)	0	0.268
Surgical site infection	2 (5.0%)	0	0.268
Resection status			
R0	23 (57.5%)	10 (71.4%)	0.351
R1	15 (37.5%)	2 (14.3%)	0.091
R2	2 (5.0%)	2 (14.3%)	0.283

[a] Missing value 1 patient (1.9%).
[b] Missing value 3 patients (5.5%).
[c] Missing value 2 patients (3.7%).
CEA: carcinoembryonic antigen; CA19-9: carbohydrate antigen 19–9; pRBCs: packed red blood cells; SD: standard deviation; UICC: the International Union Against Cancer.

Results

Clinical characteristics and descriptive statistics

The descriptive statistics of the study population are shown in Table 1. The study population consisted of 28 females and 26 males with a median age of 65 years (range: 41–85 years). Observed median survival in the current study cohort was 19.1 months (range 0.5–156.5 months) which equals the median follow-up. The 18-month mortality rate was 74.1% ($n=40$).

Twenty-four patients (44.4%) suffered from adenocarcinoma of the pancreatic body, whereas the tumor was localized in the

Table 2
The results of univariable binary logistic regression analysis with the dependent variable 18-month survival.

Variables	Univariable binary logistics regression		Multivariable binary logistics regression	
	P value	OR (95% CI)	*P* value	OR (95% CI)
Age	0.947			
Sex male	0.645			
Epigastic pain	0.694			
Loss of weight	0.852			
Back pain	0.499			
CEA elevated	0.939			
CA 19–9 elevated	0.107		**0.032**	5.606 (1.051–29.904)
Insulin-dependent diabetes	0.899			
Thrombocyte count (thousand/μL)	0.194		0.968	
Prior abdominal surgeries	**0.013**	8.667 (1.030–72.932)	**0.004**	15.981 (1.497–170.585)
Pre-operative hospital stay	0.463			
Diameter of tumor	0.533			
Tumor diameter > 4 cm	0.111		0.514	
UICC 7 stages	0.075		0.968	
Number of positive lymph nodes	0.179		0.246	
Lymph node ratio	0.397			
N-status	0.382			
Lymph nodes examined <10	0.658			
M-status	0.390			
Tumor grading	0.390			
Resection status	0.811			
Extended lymphadenectomy	0.651			
Portal vein resection	0.317			
Liver resection	0.999			
Resection at coeliac axis	0.769			
Gastric resection	0.295		**0.013**	0.027 (0.001–0.920)
Colon resection	0.745			
Left adrenal resection	0.668			
Intra-operative number of pRBCs	0.061		**0.001**	3.361 (1.177–9.599)
Intra-operative transfusion of fresh frozen plasma	0.499			
Distant metastasis	0.390			
Carcinoma of pancreatic body	0.890			
Carcinoma of pancreatic tail	0.603			
Crossover growth of carcinoma	0.628			

All variables with *P* values <0.300 in univariable binary logistic regression were included in the final multivariable binary logistic regression model. CEA: carcinoembryonic antigen; CA19-9: carbohydrate antigen 19–9; pRBCs: packed red blood cells; OR: odds ratio; 95% CI: 95% confidence interval: UICC: the International Union Against Cancer.

pancreatic tail in 20 patients (37.0%). Ten patients (18.5%) showed crossover carcinoma from the pancreatic body to the tail. Distant metastases were found in 12 patients (22.2%).

The statistical comparison of patients within 18-month mortality and those survived longer showed that patients within 18-month mortality had significantly more prior abdominal surgeries in their medical history (40.0% vs 7.1%, $P=0.013$).

Identification of risk factors for 18-month mortality

Table 2 summarizes pre-operative, intra-operative and tumor specific variables and their influences on 18-month mortality after left-sided pancreatic resection. In univariate binary regression analyses only prior abdominal surgeries had a significant impact on 18-month survival [odds ratio (OR)= 8.667; 95% confidence interval (95% CI): 1.030–72.932; $P=0.013$].

In the final multivariable binary logistic regression model elevated CA19-9 (OR= 5.606; 95% CI: 1.051–29.904; $P=0.032$), prior abdominal surgeries (OR= 15.981; 95% CI: 1.497–170.585; $P=0.004$), gastric resection (OR= 0.027; 95% CI: 0.001–0.920; $P=0.013$) and the number of intra-operatively transfused packed red blood cells (pRBCs) (OR= 3.361; 95% CI: 1.177–9.599; $P=0.001$) were identified as significant independent factors for 18-month survival.

Mortality risk prediction model

The prognostic model for the prediction of 18-month mortality as determined with multivariable binary logistic regression reads as follows:

$$18-\text{month mortality risk}(\%) = \text{Exp}(Y)/(1+\text{Exp}(Y)) \; with$$
$$y = -0.927 + (1.724,\ if\ CA\ 19-9\ elevated,\ otherwise\ 0) +$$
$$(1.212 \times number\ of\ intra-operative\ transfused\ packed\ red\ blood\ cells) +$$
$$(2.771,\ if\ prior\ abdominal\ surgery,\ otherwise\ 0) -$$
$$(3.612,\ if\ gastric\ resection,\ otherwise\ 0)$$

This model demonstrated a good model-fit (Hosmer–Lemeshow, $P=0.950$). The prognostic model for the prediction of 18-month mortality displayed an AUROC of 0.858 (Fig. 2).

The determined cut-off value of the logit for the proposed prognosti0063 model was 0.864 using the best Youden-index [20].

The sensitivity of prediction of the proposed prognostic model was assessed at 65.0%, whereas specificity was 92.9% resulting in an overall correctness of 79.0%. Kaplan–Meier analysis shows significantly decreased survival for patients with logits of the proposed prognostic model above versus below the determined cut-off value of the logit of the proposed prognostic model at 0.864 (log-rank test, $P=0.013$; Fig. 3).

Internal validation of the developed prognostic model

The prognostic model was internally validated with systematically randomized backwards bootstrapping and displayed AUROCs > 0.700 (mean: 0.874; standard deviation 0.052; range: 0.757–0.971). The developed model was able to reliably predict

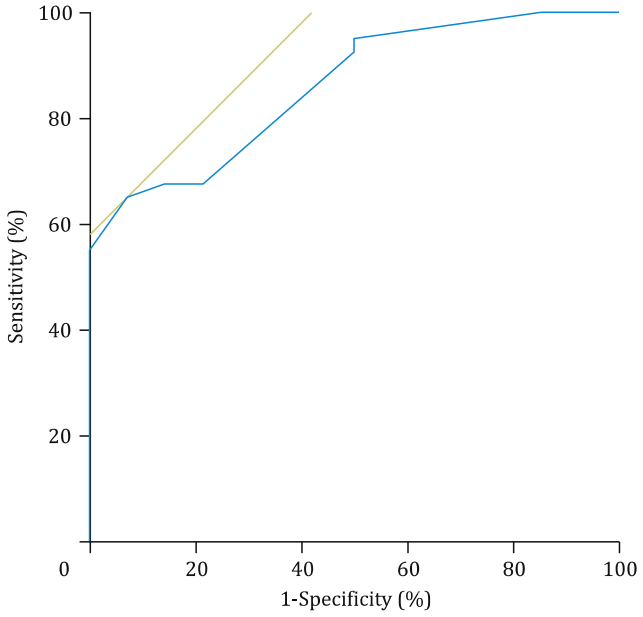

Fig. 2. The receiver operating characteristic curve shows the proposed prognostic model with an area under the receiver operating characteristic curve (AUROC) of 0.858.

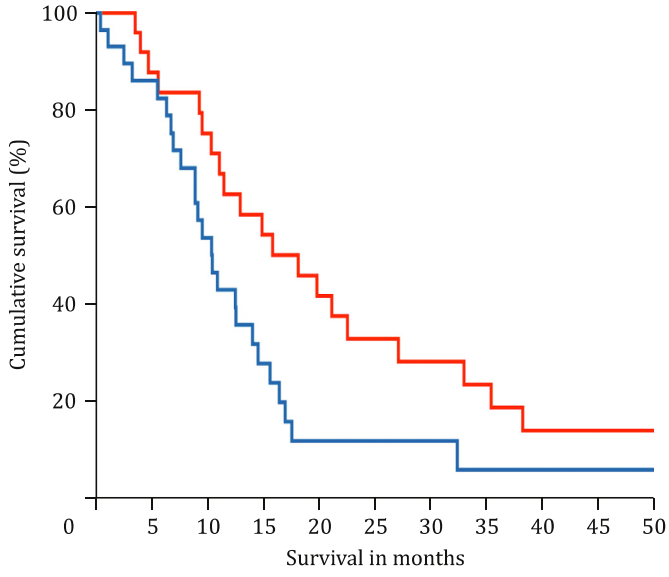

Fig. 3. The Kaplan Meier curve shows depicting survival below (red line) and above (blue line) the cut-off value of 0.864 of the prognostic score ($P=0.013$; log-rank test).

18-month mortality in each randomly chosen subgroup of the original study population. The subgroups consisted of random samples of 60% of the study population. The chosen subgroups for random sampling and bootstrapping analysis were 60% of the total study population to allow the highest possible sample size with on the other hand a sufficient lack of overlay between the subgroups.

Discussion

This study proposes for the first time an internally validated prognostic model with pre- and intra-operative predictive factors for 18-month survival after left-sided pancreatectomy for the rare entity of adenocarcinoma of the pancreatic body and tail.

A striking observation of the current study is the significant influence of abdominal surgeries in the patient's medical history on survival after left-sided pancreatectomy. Per definition, these surgeries occurred independently from the diagnosis of PDAC. Especially exploratory laparoscopies or laparotomies are not included in this variable. Clinically one might explain this context by adhesions that may cause higher rates of surgical complications or surgical site infections. However, in multivariable principal component analysis there were no strong factor correlations of $|R|>0.500$ for prior abdominal surgeries and surgical complications, surgical site infections or distant metastases. Unfortunately, due to the closed dataset of the investigated institutional database the exact surgical procedure in the patient's previous history is not always known. It might well be that patients who received a previous colon resection have a more severe comorbidity than patients, who received a previous laparoscopic appendectomy of cholecystectomy.

In the current data, the number of pRBCs was identified as a significant independent risk factor for patient survival in multivariable binary logistic regression. This aspect has already been identified as an independent risk factor for tumor recurrence after pancreatectomy in recent study [11]. Transfusion of blood products is a concern of major interest in many types of cancers including hepatocellular carcinoma and colorectal cancer, and is frequently found to be associated with tumor recurrence [21,22]. It is known that blood transfusion leads to immunomodulatory effects suppressing the immune system of the patient [23]. The underlying mechanism of the immunomodulatory effects remains unclear at this point. Several possibilities are the focus of current research, ranging from natural killer cell suppression to increased T-cell activity [24,25]. Lo and colleagues suggested recently based on studies in a mouse model that the acellular plasma fraction of each pRBC supports pancreatic cancer progression [26].

Beyond the immunomodulatory effect of pRBCs, it might well be that the necessity for intra-operative blood transfusion expresses the patient's pre-operatively comprised health as a result of progressed tumors or other comorbidity. Interestingly, there was no factor correlation $\geq|0.500|$ between the number of pRBCs and the extent of surgery, the UICC 7 stage or postoperative surgical complications. Unfortunately, comorbidities were not available for analysis while they are likely to play an important role in postoperative survival.

Several studies show the prognostic relevance of pre-operative CA 19–9 levels in PDAC [27]. In this context it is interesting to note that this tumor marker was elevated in 61.1% ($n=33$) of the current cohort and there was no significant difference in the distribution of those patients within 18-month mortality as opposed to the longer survivors, possibly indicating a limited stand-alone predictive value on comparatively short-term survival.

Strikingly, additional gastric resection had a protective impact on 18-month survival (Table 2). This may indicate a relevant prognostic role in a radical surgical approach to resection to achieve R0 status. This hypothesis is further supported by the fact, that none of the other extended resections (e.g. liver resection, colon resection or portal vein resection) could be identified as independent risk factors of survival.

Most strikingly, none of the parameters analyzed in the current study cohort apart from prior abdominal surgery was distributed unequally between the patients within 18-month mortality as opposed to the longer survivors. In this context also postoperative complications were analyzed. Those complications were not overabundant in the study population with survival less than 18 months (Table 1). Surprisingly, also UICC 7 tumor stages were not distributed unequally between those patients. UICC 7 stage Ia was not found in the current study population, which is not surprising, since as mentioned above, PDAC of the body and tail is mostly diagnosed in advanced stages. However, UICC 7 stage IV was diagnosed in both groups despite of the difference in survival rates.

The fact that only one variable prior abdominal surgeries in the patient's history as well as additional liver resection were distributed significantly different between both sub-cohorts according to survival might underline the dreadfulness of this fatal diagnosis that is frequently described in literature. Survival rates are poor in the entire cohort independent of the pre-operative tumor stages.

The TNM-status was fully considered in the regression analyses (Table 2). These analyses were performed in close alignment with the methodology as described by Hosmer and Lemeshow [18]. On the basis of this methodology, the *P* value of univariate analysis of tumor size > 4 cm and number of lymph node metastases were included in multivariate modelling. However, in the multivariate regression analysis both variables were shown to be not statistically significant. This result points out that TNM-status is of course of relevance for the outcome after surgery, although the variables are not independent from each other and/or other included variables. According to Hosmer and Lemeshow, only independent variables were integrated into the prognostic model.

Our study has no external validation which may cause a center bias. However, external validation of this prognostic model is a real challenge, because the rare entity of the disease large series are scarce. A prospective validation study preferably in a multicenter design would be desirable to confirm our findings. The impact of further treatment, such as postoperative chemotherapy, is not included in the calculation of the presented prognostic scores. This is mainly due to the intention to develop a statistical model, which allows the prediction of outcome with pre- and intra-operatively available information. Also comorbidities of the patients, which may influence the recovery from surgery, are not included in the prognostic score. Due to the small incidence of PDAC and its bad prognosis, our center applies a radical operative approach for these patients with the hope to give these patients a notable chance for prolonged survival. Therefore, metastasectomies might be overrepresented in the investigated study population. This aspect needs to be kept in mind for further studies.

The clinical implications of the current study are threefold. Firstly, the developed prognostic model is a reliable tool for the physician to estimate the survival after the PDAC operation. This allows identification of patients at high risk for futile postoperative outcome by raising awareness, enabling implementation of a more rigorous aftercare scheme to identify complications earlier, possibly resulting in better outcome. Secondly, the study's results show that a special focus has to be put on limiting transfusion of pBRCs to improve outcome. Good preparation for these challenging procedures is even more of the essence to reduce pRBC requirements. Thirdly, the innovative finding of prior abdominal surgeries in the patient's medical history as a significant, independent risk factor, further rises awareness even in the pre-operative course to advise the patient and carefully plan treatment options.

In conclusion, transfusion of pBRCs, prior abdominal surgeries, and CA 19–9 are risk factors of survival of patients with PDAC. The current study adds a considerable tool to everyday clinical practice in the care for patients suffering from left-sided pancreatic carcinoma, which is warranted to be externally assessed in the nearest future.

Contributors

GJ, SH, GG, and KA performed the research and wrote the first draft. QZ, OF, and WM collected and analyzed the data. SH and KJ proposed the study. All authors contributed to the design and interpretation of the study and to further drafts. GG and KA share the last authorship. KA is the guarantor.

Funding

None.

Ethical approval

All patients provided informed consent that their data may be used for scientific purpose at the time of hospital admission, which is the general policy of our institution. Patient data were anonymized and de-identified prior to analysis.

Competing interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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