Long-term survival after resections for pancreatic ductal adenocarcinoma. Single centre study

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Aim. To analyse the 5-year survival rate of patients undergoing radical surgery for pancreatic ductal adenocarcinoma (PDAC) and to identify prognostic factors.

Methods. A prospectively maintained database of 90 consecutive patients who underwent radical resection for PDAC was analysed. Survival was evaluated using the Kaplan-Meier method. Log-rank test and Cox regression analysis were used for the evaluation of prognostic factors. P values less than 0.05 were considered significant.

Results. Mean age ($\pm$ standard deviation) was 63.2 ± 8.6 years (female 28.9% and male 71.1%). Tumour localisation was in the head in 76 (84.5%), multifocal in 3 (3.3%) and in the body/tail in 11 (12.2%). Pancreatic head resection was performed in 75 (83.3%), total pancreatectomy in 4 (4.4%) and distal pancreatectomy with splenectomy in 11 (12.2%), with standard lymphadenectomy. Venous resection was in 4 (4.4%). Thirty-day and in-hospital mortality occurred in 1 (1.1%), 90-day mortality was 3.3%. On univariate analysis absence of perineural and vascular invasion, stage, absence of lymph node infiltration and no need for transfusion were associated with improved overall survival. On multivariate analysis vascular invasion HR=3.137 (95%CI: 1.692-5.816; $P = 0.0003$) and postoperative complications HR=2.004 (95%CI: 1.198-3.354; $P = 0.008$) were identified as significant independent predictors of survival. The five-year survival rate was 18.9%, with five-year recurrence-free survival of 16.7%.

Conclusion. Vascular invasion and postoperative complications were independent prognostic factors after curative resections of pancreatic cancer in studied cohort.

Key words: pancreatic ductal adenocarcinoma, long term survival, complications, surgical therapy

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INTRODUCTION

The incidence of pancreatic cancer in the Czech Republic is rising. In Europe (2012), the highest world age-standardised incidence rates for pancreatic cancer are in the Czech Republic for both men (11.9/100000) and women (7.9/100000) (ref.¹⁻³). The European Health Report (2012) named pancreatic cancer as the leading cause of cancer-related deaths in Europe. The prognosis for patients with pancreatic cancer is extremely poor, with the overall 5-year survival rate of only about 6% (ref.^{1,4}). The diagnosis of pancreatic carcinoma at an early stage is uncommon. Radical resection is the only curative treatment modality that is possible in only 15-20% of cases. The National Cancer Database reported that nearly 38% of radical resection candidates will not undergo surgery⁵. A quarter of patients have a locally advanced disease with approximately 53% of patients presenting with distant metastases. Several studies have analysed the prognostic factors of long-term survival and evaluated the 5-year survival in resected patients⁶⁻¹⁵ (Tables 1 and 2).

The aim of this study was to evaluate factors affecting the long-term survival (5-year survival) in a single tertiary centre; on a group of radically resected patients who had pancreatic cancer. A secondary aim was to identify the factors affecting their survival.

METHODS

Selection of patients

A database was prospectively maintained by the authors from January 2006. Patients who underwent surgery between January 2006 and December 2010 were evaluated in the present report. The main inclusion criteria included patients with pancreatic ductal adenocarcinoma (PDAC) on histopathological examination, and potentially curative resection (patients with R2 resections were not excluded). 7th edition UICC TNM classification (2011) was used to stage the tumours. All 90 consecutive patients underwent a standard pancreatic resection with a standard lymphadenectomy. Informed consent was waived as the study con-

Table 1. Long term survival studies.

Study	Period	No.	PD (%)	R0 (%)	R1/2 (%)	N+ (%)	VR (%)	Median survival (months)	5-yr survival, n (%)
Our study	2006-2010	90	83	nr	nr	51.6	4	17	17 (18.9)
Cleary (ref. ⁶)	1988-1996	123	91	nr	15	43	10	14	18 (15)
Han (ref. ⁷)	1985-1999	123	81	76	24	54	14	15	11 (9)
Howard (ref. ⁸)	1990-2002	226	90	70	28/2	56	6	13	9 (4)
Cameron (ref. ⁹)	1969-2003	405	100	nr	nr	nr	nr	nr	73 (18)
Ferrone (ref. ¹¹)	1983-2001	618	85	73	27/0	nr	0	nr	75 (12)
Schnelldorfer (ref. ¹²)	1981-2001	357	100	77	18/5	49	13	17	62 (17)
Katz (ref. ¹³)	1990-2002	329	92	84	16/0	48	33	24	88 (27)
Wentz (ref. ¹⁴)	1984-2009	169	nr	nr	nr	nr	nr	15	46 (27)
Robinson (ref. ²⁴)	2002-2009	134	100	32	68/0	89.5	nr	nr	25 (18.6)
Kimura (ref. ¹⁵)	1988-2008	147	61	nr	nr	nr	nr	nr	18 (12)
Yamamoto (ref. ⁴)	2000-2008	96	nr	nr	nr	nr	nr	27	20 (34)

PD - pancreatoduodenectomy, N+ - nodal positive status, VR - vascular resection, nr - not reported

Table 2. Factors affecting survival.

Study	Size	Jaundice	N0	LNR	N+	G	Stage	R0	Comp	CHT	ca	19-9	ALB	VI	PNI	PVI	NPAR	BT
Our study			u				u		m					u,m	u			u
Cleary (ref. ⁶)	u	u	u			u,m	u,m											
Han (ref. ⁷)	u		u				u,m	u										
Howard (ref. ⁸)	m					m		m	m									
Ferrone (ref. ¹¹)			m				m					u,m						
Schnelldorfer (ref. ¹²)	u		u,m										u					
Katz (ref. ¹³)			u,m	u				u									u,m	
Hartwig (ref. ²²)	u		u	u				u				u						
Wentz (ref. ¹⁴)			u	u,m		u		u		u	m							
Robinson (ref. ²⁴)			u	u,m											m			
Kimura (ref. ¹⁵)					u,m			u,m			u				u,m			
Yamamoto (ref. ⁴)	u,m		u				u	u,m			u					u		
Strobel (ref. ²³)			u	u	u													

N0 - nodal negative status, LNR - lymph node ratio, N+ - nodal positive status, G - grade, R0 - radical resection, CHT - adjuvant chemotherapy, ALB - albumine, VI - vascular invasion, PNI - perineural invasion, PVI - portal vein infiltration, Comp - complications, NPAR - no previous attempt of resection, BT - blood transfusion, u - univariate analysis, m - multivariate analysis

ducted was a historic cohort. Factors analysed, included the age and gender of the patient, histopathological grading of the disease, histopathological evaluation including perineural invasion, vascular invasion and lymphatic invasion, lymph node infiltration, stage, postoperative complications with severity assessed according to Clavien-Dindo (CD) (ref.¹⁶), need for transfusion, redo-surgery and the administration of postoperative chemotherapy. Specific complications of pancreatic surgery were defined according to the ISGPS (International Study Group for Pancreatic Surgery) (ref.¹⁷⁻¹⁹). Adjuvant oncological therapy was indicated in accordance with the criteria and the recommendations of the Czech Oncological Society.

Follow-up

All patients were followed up by either the operating surgeon, oncologist or their GP. Data on all 90 patients were collected by direct contact with the patient or by telephone contact, with either their GP or a family member.

Patients surviving over 5 years were followed up personally by the operating surgeon.

Statistical analysis

Prospectively collected data was analysed with the statistical program, IBM SPSS Statistics version 22 (USA). The survival was evaluated using Kaplan-Meier method. The statistical significance of prognostic factors was assessed using the log-rank test and Cox regression analysis. P values less than 0.05 were considered significant.

RESULTS

During the studied period, resections with curative intent were performed in 90 patients, 64 males (71.1%) and 26 females (28.9%). Mean age ($\pm$ standard deviation) was 63.2 ± 8.6 years. The median age of all patients was 63 years (range 40-81 years). Tumour localisation was within

Table 3. Complications and reinterventions.

	POPF	PPH	Wound	Abscess	DJAleak	RedoSurg	Total
IIIa	2			3			5
IIIb	3	3	1		1	8	8
IV	1					1	1
V	1					1	1
n 90	7.8%	3.3%	1.1%	3.3%	1.1%	11.1%	16.7%

POPF - pancreatic fistula, PPH - postpancreatectomy haemorrhage, DJA - duodenojejunalanastomosis

the head of pancreas in 76 (84.5%) cases, body/tail in 11 (12.2%) and multifocal in 3 (3.3%) cases. Surgical procedures performed included pancreatic head resection in 75 (83.4%) patients, total pancreatectomy in 4 (4.4%), and distal pancreatectomy with splenectomy in 11 (12.2%) patients. All these procedures were performed with a standard lymphadenectomy. A vascular (venous) resection was performed in 4 cases (4.4%). Thirty-day mortality and in-hospital mortality occurred in 1 case (1.1%), the 90-day mortality was 3.3%. Median survival was 16.9 months (95%CI: 12.1 – 21.7). Median survival in the N0 group is 22.0 months (95%CI: 10.3 – 33.7), median survival in the Npositive group is 13.3 months (95%CI: 10.4 – 16.2). Forty-seven patients (52.2%) did not experience any postoperative complications (CD 0), non-severe complications (CD I+II) were observed in twenty-seven (30%), five patients (5.6%) needed postoperative interventions without general anesthesia (CD IIIa) while ten (11.1%) required a redo-surgery (CD IIIb-V), and one patient died (1.1%, CD V).

Table 3 summarises types of postoperative complications encountered at different severity levels according to Clavien-Dindo classification, which required management. Clinically relevant postoperative pancreatic fistulas (POPF B,C) were the most common complications and all 7 patients (7.8%) required re-intervention. A drainage procedure was needed in 3 patients and a salvage pancreatectomy was required in 4 patients with sepsis due POPF type C. Other interventions undertaken for the remaining complications included three (3.3%) redo-surgeries for life-threatening postpancreatectomy haemorrhage (PPH, all early, type B), re-suturing of insufficient duodenojejunal anastomosis (1.1%), laparotomy re-suturing due its insufficiency in one patient (1.1%) and CT drainage of peripancreatic abscesses in three (3.3%). Patients with locally advanced tumours (pT3), with moderately and poorly differentiated tumours (G2-3), with or without lymph node involvement, perineural invasion, lymphatic invasion and vascular invasion were indicated for postoperative oncological therapy. Patients were in good general health (performance status 0-1 according to WHO), without significant weight loss. The provided treatment was either a modified DeGramont regimen of Leucovorin and 5-Fluorouracil, or Gemcitabine monotherapy. Treatment was initiated 4-7 weeks after the surgical procedure and lasted 6 months on average. Four to eight cycles of chemotherapy were administered. Relative contraindications for postoperative adjuvant therapy were comorbidity, poor

nutritional status, age and patient's non-compliance. Information about oncological treatment were obtained in 80% patients. Adjuvant therapy following resection were administered in 75% of them (69.8% gemcitabine, 9.4% fluoropyrimidine based, in 20.8% was not known).

Table 4. Univariate analysis of prognostic variables.

Prognostic factors	number of patients	P
Age	89	0.518
≤ 63	45	
> 63	44	
Gender	89	0.303
female	26	
male	63	
Grade	83	0.172
Well	11	
Moderate	34	
Poor	38	
Perineural invasion	84	0.022
PN+	56	
PN-	28	
Vascular invasion	83	0.0003
VI+	18	
VI-	65	
Lymphatic invasion	83	0.293
LI+	23	
LI-	60	
Lymph node infiltration	89	0.001
N0	43	
N+	46	
Stage	89	0.013
Early stage	42	0.003
Advanced stage	47	
Complications Clavien-Dindo	90	0.087
0	47	
I-IV	43	
Blood transfusion	82	0.034
Yes	54	
No	28	
Redo surgery	89	0.995
No	79	
Yes	10	
Chemotherapy	71	0.538
yes	53	
no	18

Fig. 1. Kaplan-Meier analysis – Perineural invasion (PNI).

Fig. 2. Kaplan-Meier analysis – Vascular invasion (VI).

Fig. 3. Kaplan-Meier analysis – Lymph node infiltration (LNI).

Fig. 4. Kaplan-Meier analysis – Stage (TNM UICC).

5-year survivors

Seventeen patients (18.9%) survived more than 5 years. The range of survival is 62-117 months with median of 74 months. The five-year survival rate in the N0 subgroup was 32.6% (95%CI: 18.6% - 46.6%), range is 62-117 months, median 68 months, while the five-year survival rate for the N+ subgroup was only 6.5% (95%CI: 0-13.7%), the range is 81-106 months, median 82 months. Of the group of 5-year survivors, 70.6% patients showed no evidence of recurrence. 29.4% experienced recurrent disease. The paraaortal lymph node metastases were diagnosed in two of these in the second year after surgery. Radio/chemotherapy in second line was successful in both. The total five-year relapse-free survival (RFS) rate is 15.6% (range is 14-117 months), with a mean of 66.0 ± 28.8 months and median of 67 months. Table 4 shows the analysis of the prognostic significance of studied factors. The univariate analysis confirmed that the absence of perineural invasion ($P = 0.022$) (Fig. 1) and vascular invasion ($P =$

0.0003) (Fig. 2) in the histopathological examination of resected specimens, absence of lymph node infiltration ($P = 0.001$) (Fig. 3), stage ($P = 0.013$) (Fig. 4), early stage (I,IIa vs. IIb,III,IV) ($P = 0.003$), and no blood transfusion ($P = 0.034$) were associated with longer overall survival. The operation time (median was 294 min) ($P = 0.057$) and complications free postoperative course (CD0) ($P = 0.087$) were associated with longer overall survival, but were not statistically significant. On multivariate analysis vascular invasion HR = 3.137 (95%CI: 1.692-5.816; $P = 0.0003$) and postoperative complications (I-IV) HR = 2.004 (95%CI: 1.198-3.354; $P = 0.008$) were identified as significant independent predictors of survival.

DISCUSSION

PDAC has a dismal prognosis, even in those patients who are able to undergo radical resection. In the last 10

years, there have been several studies evaluating 5-year survival and prognostic factors in pancreatic cancer patients after resection (Tables 1 and 2). The most frequently identified prognostic factors in these studies were N0 status and clear resection margins. The evaluation of resection margins has been modified according to the Leeds pathology protocol (LEEPP) (ref.^{20,21}). The N-positive group can be stratified more accurately according to the number of positive nodes. The largest prospective study investigating these factors was conducted by the Heidelberg group. The Hartwig study 2011 (1071 pts/8 years), which evaluated prognostic factors and survival in patients undergoing resection for PDAC, identified tumour size, nodal status and distant metastases as independent predictors of patient survival. Additional prognostic parameters included age over 70, preoperative presence of IDDM, CA 19-9 over 400 U/mL, negative resection margins according to the Leeds protocol, G1 grade and lymph node ratio (LNR) larger than 0.2. In the group of patients without the above-mentioned risk factors, 5-year survival was reached by more than 54%; however, the overall 5-year survival rate (OS) was not reported²². Another prospective study (811 pts/12 years) by Strobel (2015), evaluated lymph nodes and the stratification of different prognoses according to the number of positive lymph nodes (PLN). The study demonstrated the importance of obtaining a high number of examined lymph nodes (ELN) (median 24, range 18-32), and the superiority of PLN compared to LNR in predicting survival. In the N-positive group, median survival of patients with 1 PLN was comparable to the survival of N0 patients²³. In this present analysis, demographic factors, tumour characteristics, stage, operative characteristics and postoperative therapy and their impact on long survival were studied. Age, gender, lymphatic invasion (LI), mild vs. severe complications, redo-surgeries and postoperative chemotherapy were factors not affecting long term survival in this analysis. Operation time, absence of complications (CD = 0) and hospital stay affected long term survival, but were not statistically significant. On univariate analysis no vascular invasion (VI), no perineural invasion (PNI), no lymph node infiltration, stage, early stage I and IIa and no blood transfusion were associated with better long-term survival. On multivariate analysis, the independent favourable predictors of long survival were absence of vascular invasion and absence of postoperative complications. The vascular invasion in tumours was not studied in the cited cohorts presenting OS except in the Robinson's study; however, the authors were unable to prove that this factor had a statistically significant effect on the 5-year survival²⁴. Other studies proved, in accordance with our study, that PNI and VI were associated with poor survival following pancreaticoduodenectomy²⁵⁻²⁷. Surprisingly, one study presented VI along with PNI to be an independent favourable prognostic factor in patients with locally advanced and metastatic pancreatic cancer²⁸. In that large cohort the PNI, VI and LI was only detected in 7.2%, 6.1% and 3.3% respectively, contrarily to our study, where it was seen in 66.7%, 21.7% and 27.7%. In our study only N-positive/negative status

was analysed. In the N0 subgroup, the 5-year survival rate was markedly higher than in the N-positive group and more than three quarters of the 5-year survivors had a status of N0. Clinically relevant postoperative complications requiring re-interventions (CD IIIa-V) occurred in 16.7%. Some studies considered severe complications CD IIIb-V. In this study, the rate of severe complications requiring redo-surgeries was 11.1%. The most frequently encountered postoperative complications were clinically relevant POPF (46.7%) and PPH (20%). Redo-surgery rate was not evaluated in cited studies, in this study it did not affect survival. Compared with other studies, 5-year OS was 18.9%, and a low 30-day and in-hospital mortality rate (1.1%) was observed. The median survival, however, was 16.9 months. Almost 65% of patients in our study died within 2 years of having surgery and this is comparable with a large study conducted in Johns Hopkins Hospital (2008). The latter showed a 40% survival rate in patients who had undergone adjuvant CHT as opposed to a 31% survival rate in those who were just observed within the 2 years after surgery²⁹. Several RCT demonstrated improved survival with gemcitabine as adjuvant chemotherapy after radical surgery in PDAC patients^{30,31}. Adjuvant chemotherapy was proven to be an independent prognostic factor of survival in the analysis of our previous smaller cohort³⁰. In this extended cohort where data on postoperative chemotherapy was available (80%), postoperative chemotherapy was administered to 75% of them. More than two thirds (69.8%) were treated with gemcitabine, 9.4% with fluoropyrimidine-based chemotherapy and in 20.8% the type of chemotherapy was not known. Chemotherapy in the presented cohort was not proven to be a significant factor affecting survival, probably due to the high rate of chemotherapy administration, but postoperative complications, in accordance with other studies, were associated with adjuvant therapy omission or delays^{29,32}. Based on this analysis, several measures were taken. Resection margins (R0/R1) were not evaluated in this study, due to the absence of standard evaluation criteria during the studied period. The use of the Leeds Pathology Protocol (LEEPP), according to The Royal College of Pathologists, had not been implemented at the time of study and therefore was not used^{20,21}. The Leeds protocol has now been implemented as a standard.

After analysing of postoperative complications, the technique used for pancreaticojejunal anastomosis has now been changed to a standardised duct-to-mucosa pancreaticojejunal anastomosis (PJA) in order to achieve a reduction in these PJA-related complications. Only a very small number of portal vein resections was performed (4.4%) in this group and only one patient underwent neoadjuvant therapy. According to ISGPS and their criteria for borderline resectability, mesenterico-portal vein resections have been introduced into the surgical standard³³. Neoadjuvant therapy is only administered in selected patients after multidisciplinary discussion; the protocol has not been yet standardised in our institution.

CONCLUSION

Radical resection still represents the only potentially curative procedure in patients with PDAC. Surgical resection, when performed without complications and followed by adjuvant chemotherapy can lead to long-term survival. In the present cohort of patients with a potentially curative resection, 18.9% survived more than 5 years, and the 5-year relapse-free survival rate was 15.6%. The rate of adjuvant oncological therapy was in 75% and most of them with gemcitabine (69.8%). The absence of vascular invasion on the histopathological examination of the resected specimens and complication free postoperative course were identified as independent favourable prognostic factors.

ABBREVIATIONS

CD, Clavien Dindo system; CHT, Chemotherapy; CI, Confidence interval; CT, Computed tomography; ELN, Evaluated lymph node; GP, General practitioner; HR, Hazard ratio; IDDM, Insulin dependent diabetes mellitus; ISGPS, International study group for pancreatic surgery; LEEPP, Leeds pathology protocol; LI, Lymphatic invasion; LNR, Lymph node ratio; OS, Overall survival; PDAC, Pancreatic ductal adenocarcinoma; PJA, Pancreaticojejunal anastomosis; PLN, Positive lymph node; PNI, Perineural invasion; POPF, Postoperative pancreatic fistula; PPH, Postpancreatectomy haemorrhage; RFS, Relaps free survival; RCT, Randomized controlled trial; TNM, Tumor node metastasis classification; UICC, Union for international cancer control; VI, Vascular invasion.

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