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ORIGINAL ARTICLE

Factors Predicting Long-Term Survival Following Pancreatic Resection for Ductal Adenocarcinoma of the Pancreas: 40 Years of Experience

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Abstract
Background Long-term survival after resection for pancreas carcinoma has rarely been reported. Factors influencing long-term survival are still under debate. The aim of this study was to define predictors for long-term survival.
Methods Between 1972 and 2004, a total of 415 patients underwent resection. Data were collected in a prospective data base. Data of 360 patients were available for further analysis in 2011. All specimens of long-term survivors were histologically reviewed.
Results Long-term survivors ($n=69$) had a median survival of 91 months. Pathological re-evaluation of all specimens re-confirmed the diagnosis. Predictive factors for long-term survival in univariate analysis were no preoperative biliary stent, low CA 19-9 level, lack of blood transfusion, R0 resection, tumour diameter, and -grading, absence of lymph node or distant metastases, lymphangiosis, and perineural infiltration. Adjuvant chemotherapy showed a significant influence on overall survival but not on long-term survival. In multivariate analysis, lymph node ratio and volume of blood transfusion were predictors of long-term survival.
Conclusion Nearly 20 % of patients with pancreas carcinoma who undergo surgical resection have a chance of long-term survival. Survival beyond 5 years is predicted by clinical and tumour-specific factors. Adjuvant chemotherapy might prolong overall survival but is, according to these results, unable to contribute to long-term survival. There is still a risk of recurrence after a 5- or even a 12-year mark. Survival beyond 5 or even 12 years, therefore, does not assure cure.

Keywords Pancreas · Ductal adenocarcinoma · Long-term survival

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Introduction

In 2008, a total of 266,000 patients died from ductal pancreatic adenocarcinoma (DPAC) worldwide. [1] 2013 DPAC has an estimated annual incidence of 45,000 cases.[2] Mortality nearly equals incidence as only 5 % of all patients survive 5 years after diagnosis.[3] According to the literature, 15 % to 20 % of all patients with the diagnosis of DPAC have a resectable tumour.[4,5] Of all patients who undergo resection, 18 % to 27 % reach 5-year survival after the operation and are defined as "long-term survivors" (LTS).[6–10] Survival and long-term survival in this group of patients have been studied by many authors. Many studies are limited due to small number of LTS, inhomogenous histological diagnoses, and variable follow-up periods.[10–12] In addition, there is a lack of factors specifically identified as predictors of long-term survival in patients with DPAC. An identification of such factors is of a strong clinical relevance, since this group of patients might specially benefit from more intensive treatment

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modalities including a more liberal indication to an operative therapy.

This study reports on the largest consecutive series of LTS following resection of histologically confirmed DPAC. Various clinical factors were identified and their association with long-term survival were analysed. In addition, an overall survival analysis was performed.

Patients and Methods

Between October 1972 and September 2004, a total of 1,354 patients underwent pancreatic resection in the Department of Surgery of the University Medical Centre Mannheim. Between 1972 and 1997, all patients, except those who underwent distal pancreatectomy, and as of 1997, all patients who underwent any type of pancreatic resection were included and followed up in the prospective departmental pancreatic database.[10,13,14] Between 1972 and 1997, the patients with a distal pancreatectomy were not included in the prospective database. The results on distal pancreatectomy presented here involve only those performed from 1997 onwards (n =23). A histologically confirmed invasive ductal adenocarcinoma of the pancreas was present in 415 of these patients. Patients with other diagnosis were excluded from the analysis. The data of all patients examined comprised demographics, pathology report, TNM stage, preoperative presenting symptoms, preoperative procedures, lab work, the American Society of Anesthesiologists (ASA)-Score, details of the surgical therapy, the hospital course, and the postoperative survival. Follow-up was performed through personal contact with the patient or the patient's primary physician through ND and was terminated December 2011 or at the time of the patient's death. All deaths occurring within 30 days after surgery or throughout the hospital stay were classified as surgical mortality.

Statistical Analyses

The primary endpoint of the study was long-term survival (survival>60 months) after the operation. Patients who survived ≥60 months following the operation were compared to those who died within the first 60 months after the operation. Chi-square test, Fisher's exact test, Cochrane–Armitage Trend test, 2 sample t test, or Mann–Whitney's U test was performed as appropriate. As a multivariate model, logistic regression was used in order to evaluate several factors associated with and predicting long-term survival simultaneously. Log rank test was used to identify factors with a positive influence on survival time in general. Cox regression model was used as a multiple analysis to identify independent factors associated with overall survival. Statistical significance was accepted at the probability level of 0.05. Values are described as percentage, as mean±standard deviation or as median with range as appropriate. All statistical calculations were performed using the SAS software (release 9.2; SAS Institute Inc., Cary, NC, USA).

Results

A total of 415 patients with a histologically confirmed diagnosis of DPAC were included in this study. Thirty-five patients (8 %) were lost to follow-up and were excluded from the further analysis. Some of these patients came from abroad for the operation and returned to their homeland thereafter. In other cases, the patients or the treating physician could not be reached under the contact information. From the remaining 380 patients, 20 (5 %) died perioperatively and were excluded from the further survival analysis. A total of 360 patients with an average age of 62.0±9.8 years were included and analysed in this study. The most common symptoms at presentation were weight loss (56.8 %), abdominal pain (47.6 %), and jaundice (73.6 %), with 39.4 % of the patients receiving a biliary stent prior to the operation. Of the 360 resections, 55.3 % was Kausch–Whipple resections, 35.6 % PPPDs, 6.3 % distal pancreatectomies, and 2.8 % total pancreatectomies. Synchronous procedures were performed on 30 patients (8 %). Adjuvant chemotherapy was routinely given to patients from 1998 onwards resulting in a total of 104 (28.9 %) patients having undergone chemotherapy. None of the patients in Mannheim received neoadjuvant chemotherapy during the study period.

The follow-up range was between 2 and 312 months. The median survival rate was 17 months. Sixty-nine patients (19.2 %) had a survival rate≥60 months after the operation (so-called "LTS"), 291 (80.8 %) died within the first 5 years. Of the 69 LTS, 33 (48 %) died throughout the study period. The predominant cause of death among LTS was recurrent disease (n =28). In the three cases, the cause of death was unknown. Two patients died due to other causes. A histopathological re-evaluation of the specimen of the LTS was performed by a specialized pancreatic pathologist (PS). The review was performed on stained sections from fixed surgical specimens. The re-evaluation did not lead to a change in the diagnosis in any of the cases. The clinical factors were examined regarding their influence on long-term and overall survival.

Long-Term Survival

Preoperative Factors

The absence of a preoperative biliary stent was a statistically significant factor: as opposed to 43.3 % of the patients who died within the first 60 months following the operation only 22.3 % of the LTS received a preoperative stent (p =.0016;

Table 1 Univariate analysis, long-term survival: preoperative factors

	Total (%) $n = 360$	Survival ≥ 5 years (%) $n = 69$	Survival < 5 years (%) $n = 291$	P
Hypertension	42.1	33.3	45.7	0.1318
Diabetes mellitus	26.2	17.4	28.4	0.0624
Cardiac disease	31.3	37.3	28.9	0.2769
Pulmonary disease	18.4	21.6	17.2	0.4951
Chronic Pancreatitis	14.9	15.1	14.8	0.9657
ASA Score I/II	59.9	71.0	57.1	**0.0089***
vs. III/IV	40.1	29.0	42.9	
Alcohol use	5.5	0.0	6.7	0.1073
Jaundice	73.6	65.2	75.6	0.0787
Preoperative Stent	39.4	22.3	43.3	***0.0016****
Abdominal pain	47.6	49.3	47.2	0.7570
Back pain	12.7	11.9	12.8	0.8448
Gastric/duodenal obstruction	6.9	7.4	6.8	0.7942
Albumin g/l mean (range)	38.9 (14.9–56.0)	40.0 (26.7–54.5)	38.2 (14.9–56.0)	0.0573
Bilirubin mg/dl mean(range)	3.3 (0.15–31.0)	2.2 (0.2–22.3)	3.7 (0.15–31.0)	0.0734
CEA μg/l mean (range)	2.5 (0–952)	1.9 (0.9–50.5)	2.7 (0.0–952.0)	0.2413
CA 19-9 kU/l mean (range)	146.0 (0–80245)	72.0 (0–12023.0)	156.0 (1.2–80245.0)	***0.0491****

For qualitative parameters, relative frequencies in % are given. Quantitative variables are presented by mean values and range

Table 1). In comparison to the patients with jaundice without a stent, those with jaundice with a stent revealed a significantly higher rate of wound infection (4.88 % vs. 13.14 %, $p = 0.02$). Regarding the preoperative lab results the only factor with a statistically significant association with long-term survival was a low CA 19-9 level ($p = 0.049$; Table 1).

Intraoperative Factors

There were two parameters which were associated with long-term survival with a strong statistical significance: (a) lack of blood transfusion ($p = 0.004$) and (b) a lower volume of transfusion ($p = 0.002$; Table 2).

Histopathological Factors and Adjuvant Chemotherapy

The influence of histopathological findings on long-term survival was of a strong statistical significance. Tumour size ($p = 0.03$), pT1/2 status ($p < 0.0001$), lack of distant metastases ($p = 0.05$), R0 status ($p = 0.001$), well-differentiated tumour (G1, G2; $p = 0.003$), and absence of lymph node metastases ($p < 0.0001$) were significantly associated with long-term

Table 2 Univariate analysis, long-term survival: perioperative and postoperative factors (relative frequencies or mean and range, respectively)

	Total (%)	Survival ≥ 5 years (%) $n = 69$	Survival < 5 years (%) $n = 291$	P
Blood transfusion	67.7	53.0	71.3	***0.0044****
Blood transfusion (ml)	600 (0–9,000)	300 (0–3,000)	600 (0–9,000)	***0.0023****
Blood loss (ml)	900 (0–7,000)	800 (300–4,000)	1,000 (0–7,000)	0.4541
Operation duration (min)	365 (135–900)	350 (204–630)	365 (135–900)	0.1626
Postoperative pancreatitis	4.2	2.9	4.5	0.7452
Relaparotomies	8.9	5.8	9.6	0.3155
Pancreatic fistula	6.1	7.3	5.8	0.5870
Delayed gastric emptying	11.4	10.1	11.7	0.7220
Intraabdominal abscess	4.4	5.8	4.1	0.5209
Postoperative sepsis	1.0	0.0	1.7	0.5879
Surgical site infection	8.1	4.3	8.9	0.2081
Cardiac complications	0.8	1.4	0.7	0.4729
Respiratory complications	4.2	4.3	4.1	1.0000
Adj. chemotherapy	29	33.8	28.6	**0.3990**

Table 3 Univariate analysis, long-term survival: histopathological findings (relative frequencies or mean and range, respectively)

	Total (%)	Survival ≥ 5 years (%) $n = 69$	Survival < 5 years (%) $n = 291$	*P*
Tumour diameter (mm)	30.0 (18.0–88.0)	24.0 (18.0–34.0)	63.0 (32.0–88.0)	***0.0317****
pT1/pT2	19.8	39.1	15.2	***<0.0001****
pT3/pT4	80.2	60.9	84.8	
pN+	64.4	40.6	70.1	***<0.0001****
LNR	0.10 (0.00–0.81)	0.02 (0.00–0.33)	0.11 (0.00–0.81)	***0.0012****
pR1/2	23.5	8.7	27.4	***0.0011****
M+	5.0	0.0	6.1	***0.0497****
pG1+pG2	66.6	78.3	63.8	***0.0032****
pG3	33.4	21.7	36.2	
Perineural invasion	20.0	5.9	23.5	***0.0011****
Vascular invasion	24.6	14.6	28.5	0.0583
Lymphatic invasion	50.7	41.2	53.0	0.0792

survivor. A lower lymph node ratio (LNR: number of positive lymph nodes per total number of lymph nodes identified) was a significant predictor of long-term survival: median 0.02 in LTS versus median 0.11 in short-term survivors ($p = 0.0012$; Table 3). LTS (33.8 %) and 28.6 % of the short-term survivors received adjuvant chemotherapy. This difference did not reach statistical significance ($p = 0.3990$).

Multivariate Analysis for Long-Term Survival

In multivariate analysis using the Cox regression model the only factors which independently predicted long-term survival were (a) a lower lymph node ratio ($p = 0.0024$, odds ratio 1, 732) and (b) the lack of perioperative blood transfusion ($p = 0.0061$, odds ratio 1,188; Table 4).

Overall Survival

Preoperative biliary stenting had a statistically significant negative influence on overall survival ($p = 0.0034$) as well as a body-mass index (BMI)>25 ($p = 0.047$) and daily alcohol consumption (>250 ml of wine or 500 ml beer; $p = 0.009$). Normal preoperative CA 19-9 level was the only preoperative lab result which was significantly associated with better overall survival ($p = 0.0007$). Sepsis as a postoperative complication and re-laparotomy had a statistically significant negative influence on overall survival ($p = 0.0088$ and $p = 0.016$, respectively). Lack of perioperative blood transfusion was also associated with a higher survival rate in general ($p = 0.0013$).

Table 4 Multivariate analysis, long-term survival

	P	Odds ratio
Blood transfusion	***0.0061****	1.188
LNR	***0.0024****	*1.732*

T1 or T2 status ($p = 0.0002$), absence of distant metastasis ($p = 0.0002$), free margins ($p = <0.0001$), well-differentiated tumours ($p = 0.0157$), N0 status ($p < 0.0001$), low LNR ($p = 0.0009$), and adjuvant chemotherapy ($p = 0.0363$) had a statistically significant influence on the overall survival.

Multivariate Analysis for Overall Survival

The multivariate analysis revealed M0 status ($p < 0.0001$), lack of venous infiltration ($p = 0.0045$), and lower LNR ($p = 0.0002$) to be factors which were independently associated with a longer overall survival.

Long-Term Survivors with a More Than 10-Years Survival Rate

A total of 22 patients were alive 10 years after the operation. Four of these patients died due to recurrent disease. Fifteen patients were still alive after 12 years. Six of them died, all due to recurrent disease. Comparing all patients with a survival rate >120 months with the rest of the patients revealed lack of bleeding ($p = 0.05$), lack of lymph node metastases ($p = 0.005$), R0 status ($p = 0.032$), and a pT1/pT2 status ($p = 0.0003$) as a significant predictive factor for survival length >120 months.

Discussion

Survival analyses on patients with DPAC have often been performed.[11,15] According to these analyses and the present study the chance of surviving 5 years following resection of DPAC is around 20 %. A total of 20 patients (5 %) died within the first 30 days after the operation (perioperative mortality). Including these patients in the long-term survival calculation would have revealed a long-term survival rate of 18.2 % (69/

380). Since the analysis was mainly aimed at tumour related long-term survival, those patients who died within the first 30 days following the operation were excluded from the further analysis. To the authors' best knowledge, this is the first large series with a follow-up period of more than three decades which compares LTS with patients who die early after resection for DPAC.

It has been reported in the literature that histopathology review of LTS can lead to a change in diagnosis in up to 6 % of the cases.[16] The histopathological specimens of all of the patients with a long-term survival were re-evaluated by a pathologist specialized on pancreatic diseases (PS), who verified the diagnosis in all of these 69 patients.

In the multivariate analysis, LNR and blood transfusion were shown to be independent factors predicting long-term survival. In addition, lack of venous infiltration and metastasis, as well as a low LNR, were the independent factors predicting overall survival. The outcome of the multivariate analysis of overall survival is different than the multivariate analysis of long-term vs. short-term survival because different statistical tests and methods (multiple Cox analysis vs. logistic regression analysis) are used with different statistical variables. In addition, multiple test models are very sensitive. Therefore, changing one variable can lead to a completely different outcome within the same population. In the following, the statistically significant factors for the long-term and the overall survival will be discussed.

Lymphnode Ratio (LNR)

Low LNR was identified as the only independent prognostic factor for both overall survival and long-term survival. Of the patients with a negative nodal status 32.2 % achieved long-term survival. In comparison, only 12.2 % of the lymph node positive patients were alive ≥60 months following the operation ($p<0.0001$). In the literature, in uni- and multivariate analyses, lymph node metastasis is one of the most significant factors predicting survival.[10,15,17] In the present study, negative nodal status was not only a significant factor for overall survival, but also a significant predictor of long-term survival.

A number of lymph nodes resected and examined have proven to be a separate prognostic factor in many solid tumours such as gastric, esophagus, and colorectal tumours.[18–20] Several groups have recently assessed the influence of LNR on prognosis of patients with PDAC.[21–24] In their studies on a series of 905 patients from the Johns Hopkins University, the authors identified the LNR as the most potent predictor for survival after panreaticoduodenectomy for pancreatic cancer.[24] In all these studies, the cut-off level for LNR leading to a poor prognosis was in a range between 0.15 and 0.2. In the present study in the multivariate analysis, the lymph node ratio was proven to be an independent factor associated with long-term survival and with overall survival. This study is the first series to describe a positive prognostic effect of LNR, not only on overall survival, but also on long-term survival after pancreatectomy for DPAC.

Blood Transfusion

The multivariate analysis showed that perioperative blood transfusion was one of two factors which independently had an influence on long-term survival. In a number of solid tumours, perioperative blood transfusion has been reported as a negative prognostic factor.[7,25–27] In a meta-analysis, it could be shown that transfusion of less than 2 units was associated with longer survival in DPAC.[15] A possible explanation for these findings could be that allogenic blood transfusion could induce immunosuppression in the host.[15] This in turn could lead to a higher recurrence rate in a patient after tumour resection.[15] The requirement for blood transfusion may also be just a surrogate maker for the locally more advanced tumours or the more difficult ones to resect. In one large series, univariate analysis could not identify intraoperative blood loss as a significant factor influencing long-term survival in PDAC.[9] Contrary to their results, the present study identified perioperative blood transfusion as an independent prognostic factor for long-term survival.

Microvascular Invasion

In the multivariate analysis, venous infiltration was identified as an independent prognostic factor for the overall survival. Microvascular invasion is a generally rare finding. In accordance with the literature, the present results demonstrate that the impact of microvascular invasion on survival is more profound compared to perineural infiltration. Microvascular invasion could lead to earlier metastases and have a greater effect on the survival.[15]

Lack of Distant Metastasis (M0)

In accordance with previous findings, lack of distant metastasis was one of the three independent prognostic factors for overall survival in the multivariate analysis ($p=0.0005$). Throughout the study period, 5 % of the patients revealed an M+ status. It has to be stated that a preoperatively diagnosed M+ status has always been a contraindication for operation in this centre. In the above-mentioned cases, the M+ status was an intraoperative surprising finding in form of a small superficial lesion on the liver, which was not diagnosed preoperatively. In the cases of young patients in excellent general condition these small superficial lesions were then removed and the operation was continued as usual. In the histology, they turned out to be small hepatic metastatic lesions of the DPAC. If intraoperatively the surgeon discovered lesions which were macroscopically obviously metastatic lesions

and the patient was not in a good condition, the operation was terminated without resection. Such patients were not included in this study.

In addition to the results of the multivariate analysis, adjuvant chemotherapy and perioperative biliary stenting were two statistically significant factors in the univariate analysis which are worthwhile mentioning.

Adjuvant Chemotherapy

The CONKO-001 trial and the ESPAC-1 trial demonstrated the benefit of adjuvant chemotherapy.[28–30] The present results are in accordance with this regarding overall survival but could not show an impact on long-term survival. This has to interpreted with caution as chemotherapy was routinely given to patients only from 1998 onwards resulting in a limited number of patients having undergone chemotherapy ($n = 104$). In addition, another drawback is that in earlier years there were no standard protocols for the chemotherapy.

Preoperative Biliary Stenting

The DROP trial could demonstrate that routine preoperative biliary drainage in patients undergoing surgery for DPAC increases the rate of serious complications.[31,32] In our series, patients with a preoperative stent had significantly higher rate of wound infections in comparison to those with jaundice without a stent and to all other patients without a stent. The absence of a preoperative biliary stent was shown to be a statistically significant factor contributing to long-term survival in the univariate analysis. Although this could not be proven in the multivariate analysis preoperative stent is an important factor predicting long-term survival in this group of patients. Preoperative stent is an indicator for an overall reduced general condition prior to the operation. Most patients who receive a stent prior to operation have a cholangitis with impaired liver function and impaired coagulation leading to a more complicated course of the disease. As a result, preoperative stent can be regarded as a surrogate marker for an overall worse outcome and a reduced survival rate.

Long-Term Survival and Recurrence Following DPAC

Sixty-nine patients (19.2 %) were alive after 5 years. Twenty-two patients were still alive after 10 years, 15 patients achieved a 12-year mark. From the 69 LTS 33 (48 %) died throughout the study period. Twenty-eight of these 33 patients (85 %) died due to recurrent disease. Only in one case the recurrence was diagnosed prior to the 5-year mark. Almost all of the patients who died due to recurrence (26/28) had a local recurrence. One patient with a survival rate of 74 months had a pulmonary metastasis. Another patient with a survival rate of 116 months was diagnosed with cerebral metastasis and died in the same year of the diagnosis. If the patients with recurrence were in generally good condition they all received a palliative therapy. None of the patients—except for the above-mentioned patient with a pulmonary lesion—received an operative therapy due to recurrent disease.

Out of a total of 22 patients who survived a 10-year mark following resection due to DPAC, 4 died due to recurrent disease. From 15 patients who reached the 15-year mark, 6 died, all due to recurrent disease.

These numbers underline the fact that DPAC is a lethal disease with extremely marginal chances of permanent cure. Along with certain intrinsic factors of the tumour, surgery with minimal blood loss, removal of lymph nodes (low LNR) and complete removal of the tumour maximizes the chances of long-term survival for the patients. Although according to the findings of this study the risk of recurrence falls with the increasing number of survival years following resection, there is still a risk of recurrence after a 5-year mark or even after a 12-year mark. In the past PDAC has been declared an "incurable disease".[33] Long-term follow-up of the patients shows that a more than 10-year survival or event a 20-year survival is possible,[11] especially after resection with a low LNR and no residual tumour tissue. Despite of this fact the risk of recurrence is still present and long-term survival does not assure cure.

There are certain drawbacks in our study. First of all, this is a retrospective analysis from a prospective database, and 8 % of patients was lost to follow-up. Furthermore, adjuvant chemotherapy was only begun in 1998, preventing unbiased interpretation of the survival data of patients having received adjuvant chemotherapy versus those who did not.

Conclusion

This study represents one of the largest series of long-term survivors with the longest follow-up period reported up to date. Long-term survival after resection due to ductal pancreatic adenocarcinoma is possible. The results of this analysis demonstrate that preoperative intrinsic tumour-related factors (lack of metastasis, small tumour size, low tumour marker) are predictors of long-term survival and could be the basis for selecting appropriate candidates for individualized tumour therapy and surgery. In order to maximize the chance of long-term survival, surgery as primary therapy (as opposed to preoperative stenting) should be the goal. Removal of lymph nodes (low LNR), curative surgical resection with optimized local control, and minimal blood loss are essential prerequisites in surgery for long-term survival. Survival beyond 5 or even 12 years, however, does not assure cure. There is still a risk of recurrence after a 5- or a 12-year mark. The most common type of recurrence is local. It is, therefore,

absolutely essential to clinically follow-up the patients with ductal pancreatic adenocarcinoma even years after resection.

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