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Severe Postoperative Complications Adversely Affect Long-Term Survival After R1 Resection for Pancreatic Head Adenocarcinoma

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Abstract
Background Survival after pancreatic head adenocarcinoma surgery is determined by tumor characteristics, resection margins, and adjuvant chemotherapy. Few studies have analyzed the long-term impact of postoperative morbidity. The aim of the present study was to assess the impact of postoperative complications on long-term survival after pancreaticoduodenectomy for cancer.
Methods Of 294 consecutive pancreatectomies performed between January 2000 and July 2011, a total of 101 pancreatic head resections for pancreatic ductal adenocarcinoma were retrospectively analyzed. Postoperative complications were classified on a five-grade validated scale and were correlated with long-term survival. Grade IIIb to IVb complications were defined as severe.
Results Postoperative mortality and morbidity were 5 and 57 %, respectively. Severe postoperative complications occurred in 16 patients (16 %). Median overall survival was 1.4 years. Significant prognostic factors of survival were the N-stage of the tumor (median survival 3.4 years for N0 vs. 1.3 years for N1, $p = 0.018$) and R status of the resection (median survival 1.6 years for R0 vs. 1.2 years for R1, $p = 0.038$). Median survival after severe postoperative complications was decreased from 1.9 to 1.2 years ($p = 0.06$). Median survival for N0 or N1 tumor or after R0 resection was not influenced by the occurrence and severity of complications, but patients with a R1 resection and severe complications showed a worsened median survival of 0.6 vs. 2.0 years without severe complications ($p = 0.0005$).
Conclusions Postoperative severe morbidity per se had no impact on long-term survival except in patients with R1 tumor resection. These results suggest that severe complications after R1 resection predict poor outcome.

Introduction

Modern treatment of pancreatic cancer has become multidisciplinary, but surgery still plays a pivotal role. Its overall impact on long-term survival remains important. The ultimate goal of surgery has not changed, and radical local resection must be attempted to achieve a high R0 resection rate [1]. Until recently, a high postoperative morbidity rate had been considered acceptable [2–4]. It must be taken into account that operative indications have been expanded to include, for example, routine portal vein resection. Also, an increasing number of elderly patients with severe co-morbidities are nowadays considered surgical candidates. To offset these negative factors, advances in perioperative medicine and centralization of pancreas surgery have had a positive effect on mortality rates, which are currently <5 % [5–7].

In the current literature, postoperative morbidity rates range widely, from 20 % up to 70 % [2, 3, 7]. Notwithstanding that postoperative complication rates are still high, the large range indicates significant shortcomings in regard to assessing and reporting complications. Indeed, until recently, there were no standardized classifications of pancreatic fistula, postoperative bleeding complications,

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and delayed gastric emptying after pancreas resection [8–10]. The current widely accepted Dindo-Clavien complication classification now allows grading complications according to their severity [11]. The clinical focus of postoperative complications has been traditionally their consequences on the short-term course. There is also good evidence that increased morbidity negatively affects the patient's quality of life. Morbidity also has an impact on health care resources (i.e., prolonged hospital stay, higher costs) [12–15].

When assessing long-term outcome after pancreatic cancer resection, technical aspects of surgery and tumor characteristics have commonly been taken into account as risk factors influencing survival. Favorable prognostic factors are R0 resection, negative nodes, small tumor size, and well-differentiated tumors without perineural or perivascular invasion [16–18]. Moreover, postoperative adjuvant chemotherapy has been shown to increase survival [19, 20]. The role of postoperative complications on long-term survival has been largely neglected until now. This is especially true for pancreatic cancer surgery, with only a few studies that have assessed this particular aspect.

Therefore, the aim of the current study was to assess the impact of postoperative complications, stratified by their severity, on long-term survival of patients after pancreatic head resection for ductal adenocarcinoma.

Materials and Methods

Patients and Data Collection

A database including more than 150 items for each patient who underwent pancreas resection at the Department of Visceral Surgery, University Hospital of Lausanne (CHUV) has been established. Patients who were operated on from 2000 to 2008 were retrospectively entered, while patients operated since 2009 were prospectively entered.

Only patients who underwent pancreatic head resection for pancreatic ductal adenocarcinoma from January 2000 to July 2011 were included. Among the 294 patients registered, 101 pancreaticoduodenectomies (PDs) for pancreatic ductal adenocarcinomas were identified and selected for further analysis. Not included were all cases of ampullary adenocarcinoma, common bile duct adenocarcinoma, duodenal cancer, and resections for benign disease. Also excluded were patients who underwent total pancreatectomy and pancreatic left resection. Patients who died during hospitalization for PD were excluded because this study focused solely on the outcome of patients surviving the index operation.

Survival data were obtained by reviewing hospital records and/or the local tumor registry or by direct contacting the individual patient. Informed consent was obtained from all patients. The local ethics committee approved the study.

Assessment of Postoperative Morbidity and Mortality

Postoperative mortality was defined as patient death during the first 30 days postoperatively or during hospitalization following pancreatic head resection. Postoperative morbidity was assessed with the focus on postoperative surgery-related complications that were identified according to most recent international definitions [8–10]. Postoperative nonsurgical morbidity was also recorded taking into account every event that deviated from the normal operative course. Postoperative complications were defined as all medical and surgical complications that occurred during the hospitalization for PD.

Specific definitions for surgical complications were used: pancreatic fistula—any measurable volume of fluid from a drain on or after postoperative day (POD) 3 with an amylase level more than three times the serum amylase activity [8]; delayed gastric emptying—inability to return to a standard diet by the end of the first postoperative week or prolonged ($\geq$4 days) nasogastric intubation [10]; hemorrhage—blood loss from a drain or nasogastric tube, transfusion $\geq$3 units packed red blood cells, or the need for invasive treatment [9]. Other postoperative complications recorded were intraabdominal infection (fluid or abscess), wound infection, bile leak, gastric leak, small bowel obstruction, portal vein thrombosis, and cholangitis.

Complications were graded according to their severity on a validated five-point scale (grades I, II, IIIa–b, IVa–b, V) [11]. Complications requiring treatment under general anesthesia or intensive care unit treatment—graded IIIb to IVb—were defined as severe complications.

Pathologic staging was performed according to the American Joint Committee on Cancer guidelines on TNM staging (www.cancerstaging.org). Surgical margins were assessed and considered R1 if microscopic tumor invasion was present at the resection margin.

Definitions of Risk Factors

Alcohol intake was estimated and classified according to national guidelines (www.sfa-ispa.ch, Swiss Federal Commission for Alcohol Problems): Regular daily alcohol consumption should be limited for men and women to $\leq$25 g of pure alcohol. Smoking was defined as active smoking at the time the pancreatic cancer was diagnosed or a positive smoking history. Jaundice was defined as the clinical signs of yellow colorization of the skin and eyes as well as bilirubin levels >2 mg/l (34 μmol/L). Any unwanted weight loss that occurred simultaneously or

within 3 months prior to the diagnosis of pancreatic cancer was assessed as a risk factor ("weight loss").

Data Analysis

The impact of complications and their severity on long-term outcome was assessed. If a patient had several complications, the one with the highest grade was chosen for further analysis. The patients were then stratified according to resection margin status (R0 vs. R1/2). Student's t test, the χ^2 test, and Fisher's exact test were used for the univariate analysis to detect the patient's operative or pathologic factors that could predict the occurrence of postoperative complications.

The median survival and overall survival rates were determined using Kaplan-Meier survival curves. Overall survival was defined as the time span from the index operation to the date of death for any reason. The log-rank test was used for comparison of different variables. Significant parameters on univariate analysis were taken into account for subsequent multivariate analysis using Cox's proportional hazard regression. Differences were considered significant at $p < 0.05$. The mean follow-up time was 1.7 ± 1.4 years.

Results

Complications

There were 101 PDs performed in 57 men and 44 women with a mean age of 68 years (range 39–85 years) for pancreatic ductal adenocarcinoma. The early mortality rate related to the index operation (grade V complications, in-hospital mortality) was 5 % ($n = 5$). These five patients were excluded from further analysis of long-term outcome (Table 1).

A total of 58 patients were found to have complications. Hence the overall complication rate was 57 % (58/101 patients with complications grades I–IV). Among the 101 patients, 16 (16 %) developed severe postoperative complications (grades IIIb, IVa, IVb). The distribution of the grades and types of complications is shown in Table 1.

Length of Hospital Stay and Complication-Related Delay of Adjuvant Treatment

Length of hospital stay (LOS) after the index operation was strongly correlated with the occurrence and severity of postoperative complications. The overall median LOS was 18 days (mean 22 ± 12 days, range 8–72 days), which was similar to those without severe complications (median 17 days, mean 18 ± 8 days, range 8–45 days). In the case of severe postoperative complications (grades III, IV), the mean hospital stay was significantly prolonged, up to 39 ± 17 days ($p < 0.0001$). The mean LOSs stratified by the severity of complications were 18, 23, and 25 days for complications of grades I, II, and IIIa, respectively, compared to 38, 37, and 42 days for grades IIIb, Iva, and IVb. These data clearly show increased LOS for patients with severe postoperative complications.

Of the 96 patients who survived the index operation, 45 (47 %) benefited from postoperative adjuvant treatment. The proportions of patients who did or did not receive adjuvant treatment after encountering severe postoperative complications was equal: In all, 8 (50 %) patients with severe postoperative complications had adjuvant chemotherapy, as did 36 (45 %) patients without severe postoperative complications ($p = 0.8$). However, the patients with severe complications experienced a significantly prolonged interval between PD and the beginning of adjuvant chemotherapy (mean 82 days, median 76 days) compared to patients with no or minor complications (mean 55 days, median 49 days) ($p = 0.0051$).

Risk Factors

As shown in Table 2, there were no specific preoperative or intraoperative risk factors that were related with the possible occurrence of severe postoperative complications. Patients with preoperative co-morbidities (smoking, alcohol abuse, cardiac or pulmonary disease, diabetes mellitus) were not at increased risk for postoperative severe complications. In addition, neither the type of reconstruction of the pancreaticoenteric drainage nor the need of a vascular resection was associated with an increased risk for severe complications.

Analysis of Long-Term Survival

The median survival of the overall patient group was 1.4 years (range 0.3–8.9 years), and the 1-, 3-, and 5-year survival rates were 66, 30, and 15%, respectively. Among the various factors that have been analyzed, N status and R status were statistically significant risk factors with a negative impact on long-term survival. Long-term survival of patients with severe complications was 1.2 years compared to 1.9 years for patients without severe complications—of note, the difference was not statistically significant (Table 3). A multivariate analysis showed that only R0 resection was a significant predictor of survival [hazard ratio (HR) 0.59; 95 % confidence interval (CI) 0.35–1.00; $p = 0.05$). In a subgroup analysis assessing long-term survival of patients with R0 versus R1 resection and the occurrence of severe complications, patients with R1 resections and severe complications had significant

Table 1 Morbidity after pancreaticoduodenectomy for ductal adenocarcinoma ($n = 101$)

Morbidity	No.	%
Total no.	58	57.0
Complication grade		
I	10	9.9
II	21	20.8
IIIa	11	10.9
IIIb	9	8.9
IVa	3	3.0
IVb	4	4.0
Severe complications (≥IIIb)		
No	80	79.0
Yes	16	16.0
Type of complication		
Delayed gastric emptying	21	20.8
Wound infection	19	18.8
Extraabdominal infection	19	18.8
Pancreatic fistula	9	8.9
Hemorrhage	9	8.9
Intraabdominal infection	8	7.9
Portal vein thrombosis	3	3.0
Cholangitis	4	4.0
Respiratory failure	6	5.9
Small bowel obstruction	3	3.0
Cardiac	3	3.0
Pulmonary embolism	3	3.0
Gastric leak	2	2.0
Bile leak	2	2.0
Others	2	2.0

worse outcome (2.0 years vs. 0.6 years, $p = 0.0005$) (Table 4; Fig. 1). Corresponding trends were identified for N0 and N1 stages, although they did not reach statistical significance.

Discussion

Successful treatment of pancreatic ductal adenocarcinoma is nowadays not based solely on surgery but also on oncologic treatment using chemotherapy alone or combined chemoradiation. Nevertheless, complete tumor resection with attenuated morbidity must be attempted in all patients with resectable disease. The current trial has been performed to assess the impact of postoperative complications stratified according to their severity on long-term survival after pancreatic head resection for cancer. It demonstrated that morbidity after PD is high (57 %), and that severe postoperative complications (grade IIIb to IVb) occurred in 16 % of patients. Long-term survival was predominantly

Table 2 Potential parameters influencing occurrence of severe postoperative complications

Variable	No severe complications ($n = 80$)	Severe complications ($n = 16$)	p
Age (years)	67	67	0.89
Age			1.0
>70 years	34	7	
<70 years	46	9	
Sex			0.78
Male	44	10	
Female	36	6	
Smoking			0.77
No	54	10	
Yes	26	6	
Alcohol abuse			0.24
No	70	12	
Yes	10	4	
Cardiac co-morbidity			0.51
No	61	14	
Yes	19	2	
Pulmonary co-morbidity			0.36
No	73	13	
Yes	7	3	
Diabetes mellitus			0.52
No	62	11	
Yes	18	5	
BMI (kg/m^2)	25	25	0.74
Weight loss			0.42
No	46	7	
Yes	34	9	
Jaundice			0.76
No	21	5	
Yes	59	11	
Biliary stent			0.26
No	35	6	
Yes	45	10	
ASA			0.35
I	4	2	
II	56	11	
III	18	3	
IV	1	0	
Operating time (min)	361	382	0.39
Vascular reconstruction			0.37
No	59	10	
Yes	21	6	
Pancreatic anastomosis			0.58
PJ	46	11	
PG	33	5	
T stage			0.36

Table 2 continued

Variable	No severe complications ($n = 80$)	Severe complications ($n = 16$)	p
T1	2	1	
T2	15	1	
T3	54	10	
T4	7	3	
N stage			0.45
N0	14	1	
N1	66	15	
R status			0.27
R0	52	8	
R1	28	8	
Tumor differentiation			
Well	11	2	
Moderate	46	8	
Poor	17	4	0.90

BMI body mass index; *PJ* pancreaticojejunal; *PG* pancreatogastric

determined by tumor-related factors, such as N-stage and R status. Postoperative complications per se had no impact on survival, but they contributed to a worse prognosis when they were in patients at risk for early tumor recurrence (i.e., in case of incomplete tumor resection, R1/2).

The traditional approach to looking at complications is based on a *short-term perspective* and therefore is focused on the hospital LOS, costs, and consumption of health care resources [13–15]. Also, complications are often used as a surrogate parameter to estimate the quality of surgery. More recently, the *long-term consequences* of complications with their possible impact on quality of life, use of adjuvant treatment, and most importantly survival time has gained more attention as hitherto underestimated issues. In most series, the impact of complications has been assessed as an additional endpoint, among others, and some recently published trials were focused on that particular aspect as the primary point of interest [1, 6, 11, 21–26]. The results have been somewhat controversial.

DeOliveira et al. validated the Dindo-Clavien classification of complications in a large series of pancreatic resections at Johns Hopkins Hospital. Despite the fact that no statistically significant correlation between the type and severity of complications with long-term survival could be detected, patients with a grade IV pancreatic fistula had a worse outcome than patients with grade II and III pancreatic fistulas [11]. Another randomized controlled trial from the same institution evaluated the role of extended retroperitoneal lymphadenectomy for periampullary adenocarcinoma. It found that although increased morbidity was observed in patients with an extended resection the long-term survival remained unchanged [21]. It can be speculated whether a possible oncologic benefit of a more radical resection may be reversed by more complications. Patients who were included in the ESPAC-1 trial were separately

Table 3 Potential parameters influencing long-term survival after pancreaticoduodenectomy ($n = 96$)

Parameter	Median survival (years)	p
Sex		0.40
Male	1.8	
Female	1.3	
Age		0.29
<70 years	1.3	
>70 years	1.8	
Smoking		0.12
No	1.9	
Yes	1.1	
Alcohol abuse		0.90
No	1.3	
Yes	2.0	
ASA		0.52
I	3.0	
II	1.7	
III	1.1	
IV	–	
T stage		0.076
T1	–	
T2	1.8	
T3	1.3	
T4	0.9	
N stage		0.018
N0	3.4	
N1	1.3	
Tumor differentiation		0.52
Well	2.5	
Moderate	1.4	
Poor	1.1	
R status		0.0376
R0	1.6	
R1	1.2	
Tumor size (mm)		0.44
<30	1.8	
≥30	1.2	
Adjuvant chemotherapy		0.82
No	1.6	
Yes	1.4	
Severe complications		0.06
No	1.9	
Yes	1.2	

ASA: American Society of Anesthesiologists

Table 4 Effect of complications on significant parameter of survival after pancreaticoduodenectomy

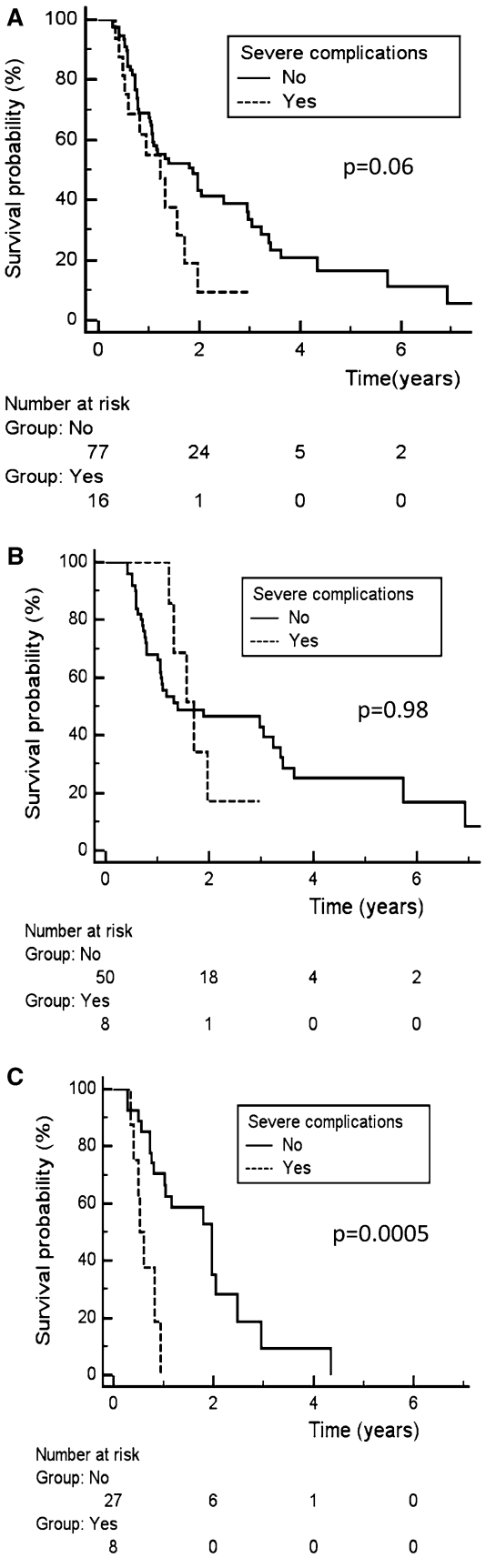
Parameter	Median survival (years)		*p*
	No severe complications	Severe complications	
R status			
R0	1.4	1.7	0.98
R1	2.0	0.6	0.0005
N status			
N0	6.9	1.2	0.33
N1	1.3	1.3	0.17

assessed regarding whether the type of surgery and the occurrence of complications had a negative impact on survival and the beneficial effects of adjuvant radiochemotherapy. However, no such negative impact could be detected [22].

In contrast, at least six studies reported a worse survival caused by the occurrence of postoperative complications, even if definitions of the severity of complications in three studies were lacking [1, 24, 25]. One recent study assessed complications with the Dindo-Clavien classification and found that severe postoperative complications (grades III and IV) predicted worse long-term survival, whereas overall postoperative complications had no significant influence [23]. Two other studies did not evaluate the impact of complications directly, but the absence of postoperative bile leaks and low systemic inflammatory response predicted a better outcome after resection of pancreatic adenocarcinoma [6, 26].

Long-term survival after surgery for pancreatic ductal adenocarcinoma is influenced by many factors. For example, tumor-related aspects play a pivotal role (i.e., tumor size and invasion, lymph node affection, tumor differentiation, perineural or vascular invasion, resection margins) [16, 18, 20, 27]. Of note, the presence of tumor cells within 1 mm of the resection margin is considered a R1 resection [28, 29]. Adjuvant chemotherapy is nowadays accepted as a valuable treatment option to prolong survival (ESPAC, German multicenter study) [22, 30, 31]. In our series, N-stage and R status were statistically significant predictive factors that had a major impact on outcome, whereas tumor differentiation, adjuvant chemotherapy and severe complications did not change long-term survival in the overall patient group. However, patients with incomplete tumor resection (R1 or R2) who are at increased risk for early tumor recurrence had a shortened long-term survival if severe complications were piggybacked.

The question then arises: How can these clinical observations can be explained? First, severe complications delay the



◀**Fig. 1** Effect of severe complications on survival and function of R status. **a** Entire cohort. **b** R0 resections. **c** R1 resections

timely beginning of adjuvant chemotherapy. In our series, a median delay of 27 days was observed in patients with severe complications: The median time to adjuvant chemotherapy was 86 days with severe complications and 49 days without severe complications. The time between surgery and the beginning of adjuvant chemotherapy was only 46 days in the ESPAC-1 trial, and chemotherapy was found to prolong survival [22]. Effective management of postoperative complications necessitates resources of experienced, high-volume centers. Indeed, the effects of hospital and surgeon case volumes on mortality after pancreatic resection is well documented [7, 32–35]. Second, mortality related to complications can occur with a delay of several weeks. For example, major visceral arterial bleeding caused by a ruptured pseudoaneurysm has been described up to 30 weeks after the index operation and hence represents a late sequela of pancreatic fistula [36, 37]. Third, impaired caloric intake and maldigestion due to exocrine pancreatic insufficiency may induce significant malnutrition. Such patients remain particularly susceptible to infections. Fourth, persisting postoperative weakness impairs regularly ambulation, and patients remain in bed even when they discharged home. Thrombosis formation and an increased risk of pulmonary embolism are important consequences. Fifth, a significant number of patients are not able to stop smoking. Active smoking promotes tumor recurrence and infectious complications [38]. All these aforementioned risks may be responsible for general immunosuppression, causing more infections and, even worse, reducing tumor suppression capacity with earlier tumor recurrence or metastasis formation.

Underestimated features are the pathophysiologic effects of postoperative complications. Postoperative systemic inflammatory response syndrome (SIRS) depends on the duration and magnitude of surgical interventions [39]. Severe postoperative complications can set off a SIRS with high levels of markers of inflammation or infection, such as C-reactive protein (CRP), procalcitonin, and interleukins. Jamieson et al. demonstrated that systemic inflammatory responses with increased CRP levels predicted the outcome after pancreas head resection for ductal adenocarcinoma [26]. Postoperative inflammatory response certainly affects the host-versus-tumor response and possibly tumor biology, which could be deleterious particularly after incomplete resection [40].

Conclusions

Postoperative morbidity, in particular severe complications, has a deleterious effect on long-term survival after pancreatic head resection for cancer. Its role may have been underestimated so far, and more attention must be given to its prevention and effective treatment.

Conflict of interest The authors declare no potential or real conflicts of interest.

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