

Perioperative and Long-Term Outcome after Standard Pancreaticoduodenectomy, Additional Portal Vein and Multivisceral Resection for Pancreatic Head Cancer

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Abstract

Introduction The value of extended resection (portal vein, multivisceral) in patients with pancreatic adenocarcinoma (PDAC) is not well defined. We analyzed the outcome after standard resection (standard pancreaticoduodenectomy (SPR)), additional portal vein (PV) and multivisceral (MV) resection in PDAC patients.

Methods Clinicopathologic, perioperative, and survival data of patients undergoing pancreatic head resection (PHR) for PDAC 1994–2014 were reviewed from a prospective database.

Results Three hundred fifty nine patients had PHR for PDAC: 208 (58 %) underwent SPR, 131 (36 %) additional PV, and 20 (6 %) MV. The postoperative complication rate in MV (65 %) was slightly higher than in PV (56 %) or SPR (50 %; $p=0.32$). MV patients had higher in-hospital mortality (10 %) than SPR (3.8 %) and PV (1.5 %) patients ($p=0.12$). Nodal status was comparable, whereas more patients in PV and MV had final R0 resection ($p=0.02$). Five-year survival was 7 % after MV versus 17 % in patients without MV ($p=0.07$). Multivariate survival analysis identified resection margin, nodal disease, blood transfusions, and MV are set as independent risk factors for overall survival.

Conclusion Multivisceral pancreatic head resections for PDAC are associated with increased perioperative morbidity and mortality, without improving oncologic outcome. Portal vein resection can be performed safely to reach R0 resection and its survival benefits.

Keywords Pancreatic cancer · Prognosis · Multivisceral resection · Mesenterico-portal vein resection · Pancreaticoduodenectomy

Introduction

Pancreatic cancer (PC) is the fourth leading cause of cancer-related deaths in the US and Europe, and its mortality almost

equals incidence with a 5-year survival rate of less than 5%.¹ Complete resection of the tumor remains the only chance for cure. Despite all approaches of multimodal therapy, including neoadjuvant chemoradiation and adjuvant therapy, 5-year survival after resection is still limited to 15–25%.^{2,3} However, only a minority of the patients bear resectable disease at initial diagnosis and about one-third of those present with locally advanced stages. In some of these cases, extended pancreatic resection can be performed.⁴

In patients with resectable disease, perioperative mortality has decreased substantially during the last decades, especially at high volume centers.⁵ To date, portal vein resections are performed safely with acceptable oncologic outcomes, almost comparable with patients who received standard pancreaticoduodenectomy.^{6–9} There are only very limited published reports regarding multivisceral resection. The available data about multivisceral pancreatic resections, however, include entities other than pancreatic cancer^{10–13} or even mostly distal resections.¹⁰

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The aim of this study was to compare the perioperative and long-term outcome in patients undergoing standard pancreaticoduodenectomy, additional portal vein or multivisceral resection for cancer of the pancreatic head and to evaluate whether extended pancreatic resections are justified.

Patients and Methods

Data of all patients who underwent pancreaticoduodenectomy for primary non-metastasized adenocarcinoma of the pancreatic head between 1994 and 2014 ($n=359$) were identified from our prospective pancreatic database.

Surgical Technique and Perioperative Treatment

All patients underwent routine preoperative workup including a contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI). In general, if metastases were found on preoperative imaging, patients were not eligible for curative resection. Arterial infiltration ($>180^\circ$ circumference) or complete occlusion of the superior-mesenteric/portal vein was a further contraindication for (primary) resection. Involvement of/tumor contact to the portal vein alone did not contraindicate surgery. More than one-third of the patients in our series underwent portal vein resection. Further perioperative techniques have been published in detail before.^{15–18}

The standard pancreatic head resections for pancreatic head masses were either a Kausch-Whipple procedure (early study period) or a pylorus-preserving pancreaticoduodenectomy (PPPD; later study period) with reconstruction as pancreaticojejunostomy (PJ) or pancreaticogastrostomy (PG). Total pancreatectomy had to be performed in 7 % of the cases for complete resection.

Multivisceral pancreatic head resection was defined as a resection of further organs other than the pancreas or spleen. In Kausch-Whipple operations, the routine resection of the distal stomach was not classified as a multivisceral procedure.

Intraoperative frozen section analysis was routinely obtained from the parenchymal resection margin and common bile duct throughout the study period. In recent years, the retroperitoneal margin was also examined intraoperatively. Other margins underwent frozen section analysis if intraoperatively indicated.

Multimodal Therapy

Since 2003, 30 patients underwent neoadjuvant therapy for locally advanced disease. Postoperative adjuvant treatment of all patients was heterogeneous. In the early study period, patients did not routinely undergo adjuvant treatment after curative resection. After publication of randomized trials,

most patients underwent adjuvant chemotherapy after margin negative resection.¹⁹ Patients with positive resection margins were preferentially treated with postoperative chemoradiation or additive chemotherapy, some of them in prospective multicenter studies.

Parameters

For this study, the following parameters (among many others) were specifically evaluated: type of resection, portal vein resection, other resected organs, intraoperative blood transfusion, as well as operative time and postoperative complications. The histopathological evaluation followed a standardized protocol of a high-volume academic center; however, it did not meet the recently introduced Leeds protocol.²⁰ Perineural invasion and invasion of veins or lymphatic vessels were excluded from this analysis since they were not documented in most early cases.

Follow-up and Statistical Analysis

Long-term survival status was assessed by contacting the general practitioners and/or oncologists of the patients (until 2001) or by the cancer registry of the comprehensive cancer center at our institution (after 2001). SPSS software (IBM SPSS Statistics 19.0) for Windows was used for data management and analysis. All deaths, including perioperative death, were included in our survival analysis. Overall survival was analyzed by the Kaplan–Meier method, with a log-rank test for the comparison of subgroups. Multivariate survival analysis was performed by the Cox proportional hazard model (forward selection strategy using a likelihood ratio statistic; inclusion p value=0.1) including the report of relative risks and their 95 % confidence interval.

Results

Since 1994, 359 patients underwent pancreaticoduodenectomy (PD) or total pancreatectomy for non-metastasized pancreatic adenocarcinoma. Median age was 66 (range 31–89) years, 52 % were female. All demographic data and perioperative outcome results are depicted in Table 1.

Two-hundred-eight patients (58 %) underwent resection in standard technique (SPR) of pancreaticoduodenectomy, 131 patients (36 %) had additional portal vein resection (PV), and 20 (6 %) received PD including additional resection of other visceral organs (MV). Those additionally resected organs were mainly adjacent organs such as the colon or stomach (Table 2). The liver resections were performed for direct contact/infiltration of the primary tumor but not for liver metastases. Twelve of the 20 multivisceral resections were

Table 1 Demographic, surgical, pathological, and postoperative data of 359 patients undergoing pancreaticoduodenectomy ($n=208$), additional portal venous ($n=131$), and multivisceral ($n=20$) resection

	All $n=359$	Standard pancreaticoduodenectomy $n=208$	Pancreaticoduodenectomy+portal vein resection $n=131$	Pancreaticoduodenectomy+multivisceral resection $n=20$	<i>P</i> value
Age, years (median; range)	67 [31–89]	66 [31–84]	67 [36–85]	62 [40–89]	0.07
Male sex (<i>n</i> ; %)	175 [49 %]	101 [49 %]	65 [50 %]	9 [45 %]	0.93
Operation technique					
Whipple	41 [11.4 %]	23 [11.1 %]	16 [12.2 %]	2 [10 %]	0.001
PPPD	293 [81.6 %]	176 [84.6 %]	106 [80.9 %]	11 [55 %]	
Total pancreatectomy	25 [7.0 %]	9 [4.3 %]	9 [6.9 %]	7 [35 %]	
Operation time min (median; range)	441 [184–785]	427; [184–720]	463; [260–785]	477; [346–760]	0.001
PRC in ml (median; range)	0; [0–5,400]	0; [0–4,800]	0; [0–5,400]	0; [0–1,800]	0.88
Tumor size mm (median; range)	29 [1–130]	28.5; [1–130]	30; [3–80]	25; [18–60]	0.48
Resection margin ($n=356$)					
R0	259 [72.8 %]	157 [76.2 %]	84 [64.6 %]	18 [90 %]	0.02
R1	97 [27.2 %]	49 [23.8 %]	46 [35.4 %]	2 [10 %]	
Nodal status ($n=358$)					
N0	105 [29.3 %]	67 [32.4 %]	32 [24.4 %]	6 [30 %]	0.3
N1	253 [70.7 %]	140 [67.6 %]	99 [75.6 %]	14 [70 %]	
Complications					
Overall complications	190 [52.9 %]	104 [50 %]	73 [55.7 %]	13 [65.0 %]	0.32
Operation-associated complications	128 [35.7 %]	75 [36.1 %]	44 [33.6 %]	9 [45 %]	0.6
Operative revision	35 [9.7 %]	19 [9.1 %]	13 [9.9 %]	3 [15 %]	0.7
Mortality					
In-hospital mortality	12 [3.3 %]	8 [3.8 %]	2 (1.5 %)	2 [10 %]	0.12
30-day mortality	9 [2.5 %]	6 [2.9 %]	2 [1.5 %]	1 [5 %]	0.56
90-day mortality	16 [4.7 %]	10 [5.1 %]	4 [3.3 %]	2 [10 %]	0.4
Median survival (months)	19.7	19.7	21.6	12	

PPPD pylorus-preserving pancreaticoduodenectomy, PRC packed red blood cells

Table 2 Type of surgical resection and involved organs in 359 patients undergoing pancreatic head resection for pancreatic cancer

Extent of resection	n (%)
Standard pancreaticoduodenectomy	208 (58.6 %)
Pancreaticoduodenectomy+portal vein resection	131 (37 %)
Pancreaticoduodenectomy+multivisceral resection	20 (3 %)
+Small bowel	1
+Colon	7
+Liver	5
+Stomach	6
+Adrenal gland	1
+Portal vein	12

performed with simultaneous portal vein resection (Table 2). Most patients underwent PPPD, but total pancreatectomy was more frequent in the MV group (33 %; Table 1). Time of surgery was significantly longer in PV and MV ($p<0.001$; Table 1).

The median tumor diameter in the three groups SPR, PV, und MV was comparable (28 mm, 29 mm and 25 mm, respectively). Over 70 % of the patients had positive nodes (no difference between the groups). The rate of negative resection margins was relatively high in the MV group (90 %; $p=0.02$ compared to SPR and PV).

Morbidity and Mortality

The overall complication rate in the entire study group was 53 % (Table 1). Surgery-related complications occurred in 36 %, and 9.7 % of the patients required re-laparotomy for complications. Postoperative outcomes in the SPR and PV groups were comparable, whereas patients after MV had non-significantly higher complication and reoperation rates (Table 1).

Postoperative in-hospital mortality was higher after MV (10 % vs. 3.8 % in SPR and 1.5 % in PV; $p=0.12$). Ninety-day mortality (4.7 %) was fairly comparable to in-hospital mortality, but 30-day mortality (2.5 % in the entire group) showed fewer differences between the groups (Table 1).

Oncologic Outcome (Table 3)

The overall 3- and 5-year survival was 26 % and 16 %, respectively (median survival 19.7 months; Table 1). The best overall outcome was seen in patients who underwent complete resection with negative resection margins and without lymph node involvement (44 % 3-year and 32 % 5-year survival, $n=83$; Table 3). In univariate survival analysis nodal disease, the

resection margin, intraoperative blood transfusions and (with borderline significance) grading, and the extent of resection influenced survival (Table 3 and Fig. 1). Patients undergoing additional portal vein or multivisceral resection had an outcome inferior to that of patients undergoing standard resection. In a subgroup analysis (after exclusion of patients with multivisceral resection), however, survival after PD with portal vein resection was not significantly inferior to that after standard resection (Fig. 1). Age, gender, the presence of postoperative complications and tumor size did not correlate with long-term outcome.

In final multivariate survival analysis, positive resection margins, positive nodes, intraoperative blood transfusions, and multivisceral resections were independently correlated with poor survival (Table 4).

Discussion

Complete resection is the only chance for cure in patients with pancreatic cancer. Although incidence almost equals mortality, long-term survivors (more than 10 years) have been described,²¹ and about 1 of 4 patients is still living 3 years after resection.¹⁵ Node-negative patients who can undergo margin-free resection even have a 5-year survival of $>30\%$.

Over the last decade, pancreatic surgery has become safer, especially in high-volume centers. Perioperative in-hospital mortality in the US decreased from 7.8 % in 1998 to 4.6 % in 2003.²² Not only safer surgery but also limited oncologic alternatives have driven the surgeons across the world to extend the operative procedures to remove pancreatic cancers. These advanced operations include total pancreatectomy, pancreaticoduodenectomy with portal vein resection, arterial resection, other multivisceral resections, or even the resection of liver metastases in designated patients.^{11,12} We compared the outcome of 208 limited resections (SPR), 131 portal vein (PV), and 20 multivisceral resections (MV) in our series of 359 patients undergoing pancreatic head resection for pancreatic cancer. The overall outcome and in-hospital mortality were worse in patients undergoing MV, while perioperative and long-term outcomes of PV and SPR were comparable.

Unlike the other published studies regarding multivisceral pancreatic resections^{11–14}, we only included pancreatic head resections (including total pancreatectomy) in patients with (non-metastasized) pancreatic cancer. We explicitly excluded distal resections to create a more comparable and homogenous patient group. Total pancreatectomy *per se* and portal vein resection were not considered as multivisceral resections.

Pancreaticoduodenectomy with additional portal vein resection can be performed safely at experienced centers.^{6,8,9} Postoperative mortality after PD with portal vein resection was low in our series, morbidity was not higher than after

Table 3 Overall survival after pancreatic head resection for pancreatic cancer^a

Parameter	Number	3-year-survival (%)	5-year-survival (%)	<i>P</i> value
All	358 ^b	26	16	
Gender				0.68
Female	183	24	17	
Male	175	30	16	
Age				0.72
≤65	154	27	13	
>65	204	26	20	
Any complication				0.66
Yes	189	27	17	
No	169	26	16	
Surgical complication				0.96
Yes	127	29	16	
No	231	26	16	
Nodal status ^c				0.01
Negative	105	36	24	
Positive	252	22	13	
Resection margin ^c				0.001
Negative	258	32	19	
Positive	97	12	10	
Intraoperative blood transfusion				0.01
Yes	145	19	13	
No	212	32	18	
Tumor size ^c				0.38
≤30 mm	210	28	17	
>30 mm	132	23	15	
Grading ^c				0.09
1+2	215	27	18	
3+4	134	22	11	
Multivisceral resection				0.07
No	339	27	17	
Yes	19	21	7	
Extend of pancreatic head resection				0.08
Standard	208	31	22	
+Portal vein	131	19	9	
Multivisceral	19	21	7	
Portal vein resection				0.08
No	215	31	22	
Yes	143	19	8	
R0 N0 resection				<0.001
Yes	83	44	32	
No	275	21	12	
Standard resection	208	31	22	0.08
Extended resection	150	20	9	

^a Univariate analysis of 3- and 5-year survival

^b Survival information about one patient was not available

^c Some parameters were not available in selected cases (see numbers)

Factors that were included in multivariate analysis are indicated by italics

standard PD. In addition, long-term survival was not significantly inferior to that in patients without extended resection. A systematic review by Chua et al. also reported comparable perioperative and oncologic outcomes in 9 of 10 studies on vascular resection.²³

In contrast to standard PD, postoperative morbidity and the rate of relaparotomy were slightly (but not significantly) increased after multivisceral resection. Increased morbidity was also reported in three published studies on multivisceral resections.^{11–13} In our series, postoperative in-hospital

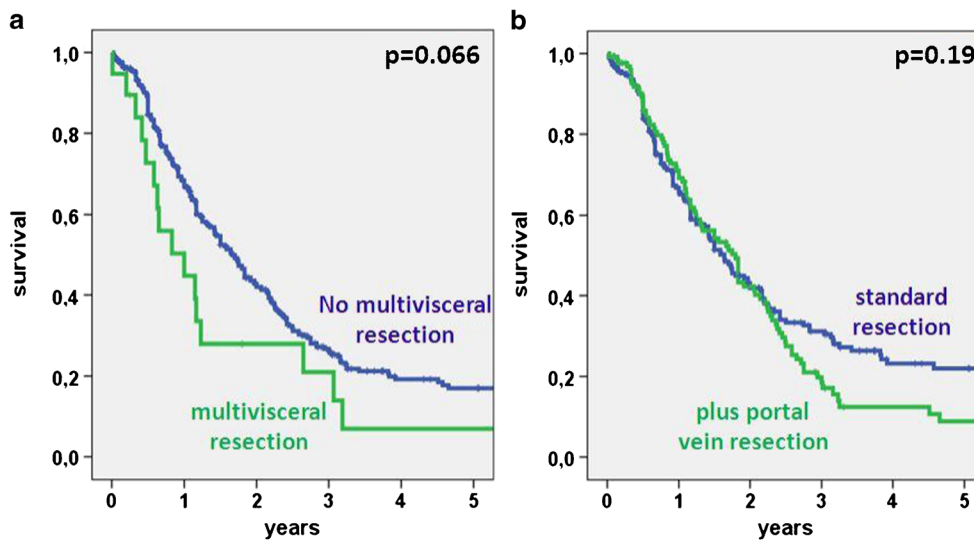


Fig. 1 Survival analysis of 358 patients after pancreatic head resection for pancreatic cancer: **a** Patients with multivisceral resection ($n=19$) vs. patients without multivisceral resection ($n=339$). **b** Patients with portal

vein resection ($n=131$) vs. patients after standard resection ($n=208$). Patients with multivisceral resections were excluded in this subgroup analysis

mortality was 10 % after PD with MV. Although not statistically significant (also because of the small number of events), this was higher than after standard resection or PD with vein resection. Mortality was not significantly increased in three other studies^{10,11,14} whereas postoperative mortality was three times higher after MV in a recent large analysis of the National Surgical Quality Improvement Project database.¹³

We could identify multivisceral resection as an independent risk factor for poor long-term survival in our analysis. It is of note that oncologic outcome in this subgroup was worse despite a rather high rate of free resection margins (90 %). In contrast to our findings, Hartwig et al. reported similar oncologic outcomes in the groups with or without multivisceral resections in a matched-pair analysis.¹¹ However, these authors had included various cancer entities, and most procedures were distal pancreatic resections. In the series by Burdelski et al.¹², survival was worse after multivisceral resection (compared to standard resection) only in univariate but not in multivariate analysis. About one-third of the patients in their MV group, however, had distant metastasis. This fact may explain a worse outcome in this subgroup and allows only limited comparison with our results.

Table 4 Multivariate survival-analysis of 358 patients who underwent pancreaticoduodenectomy for pancreatic cancer: independent risk factors for poor survival. Multivisceral resection included small bowel ($n=1$), colon ($n=7$), liver ($n=5$), stomach ($n=6$), and adrenal gland ($n=1$)

	<i>P</i> value	RR	95 % CI
Positive resection margin	0.006	1.5	1.1–2.0
Intraoperative blood transfusion	0.019	1.4	1.1–1.7
Multivisceral resection	0.018	1.9	1.1–3.3
Lymph node involvement	0.039	1.4	1.0–1.8

Intraoperative blood transfusion was an independent risk factor for overall survival in our study. The negative impact of blood transfusions on survival after pancreaticoduodenectomy was already demonstrated by Cameron et al. in 1991²⁴ and confirmed again in 2007 by Yeh et al.²⁵ The underlying mechanisms, however, still remain unclear; speculations include immunosuppressive effects of transfused blood .

Our study has several limitations: its partial retrospective cohort design, the small number of patients with multivisceral resections, and the limited available data about adjuvant therapy. Until recently, surgical margin evaluation was not assessed according to published extended workup protocols for pancreatoduodenectomy specimen.²⁰ However, a more intensified pathological examination is now performed at our institution, including inking of the critical retroperitoneal area.

The poor prognosis in patients after multivisceral resection together with increased perioperative morbidity and mortality must be considered by surgeons when performing such extensive procedures. Further studies are necessary to examine whether multimodal treatment with modern chemotherapeutic regimen (e.g., FOLFIRINOX²⁶) and/or neoadjuvant chemoradiation^{27,28} may improve the outcome after surgery in locally advanced pancreatic cancer.

Conclusions

PD with additional portal vein resections can be performed safely with acceptable morbidity rates to achieve a complete resection and its survival benefits. Multivisceral resections for pancreatic head cancer, however, are associated with an increased perioperative risk and a worse oncologic outcome.

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