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Survival Determinants after Pancreatectomy With Vascular Resection for Pancreatic Cancer

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To investigate the morbidity, mortality, and survival of patients with pancreatic cancer after pancreatectomy with vascular resection and to clarify the favorable prognostic survival factors. Pancreatic cancer is a malignant tumor. Many revisions have been made to surgical procedures to improve the prognosis of resectable pancreatic cancer. Several studies have compared no-vein and vein resection with pancreaticoduodenectomy, recording their feasibility and equal rates of operative mortality, incidence, and survival. Factors identified as potentially relevant to survival outcomes include population, perioperative treatment, and clinical pathologic factors, but these are still controversial. From January 1, 2003, to December 31, 2010, 63 patients with advanced pancreatic cancer underwent pancreatectomy with vascular resection. They were divided into 2 groups: one group had a survival time of <2 years (group 1) and the other a survival time of >2 years (group 2). Their clinical data, surgical techniques, perioperative parameters, and histopathologic data from a prospective database were analyzed. Major venous resection with reconstruction was performed in 61 patients (96.83%); major venous and artery resection with reconstruction in 1 patient (1.58%); and arterial resection with reconstruction in another patient (1.58%). The median survival time and the actuarial 1-, 2-, and 3-year survival rates for all patients are 19.94 months and 45.0%, 27.4%, and 17.6%, respectively. Group 1 contained 42 patients and group 2 contained 21 patients. A multivariate analysis identified tumor size, tumor differentiation, lymph-node status, nerve invasion, and metastasis (TNM) staging of the pancreatic cancer, tumor grade,

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operating time, and chemotherapy after surgery as independent predictors of long-term survival. TNM staging, tumor grade, operating time, and chemotherapy are independent predictors of survival after pancreatectomy.

Key words: Pancreatic cancer – Vascular resection – Survival determinants

Because it is highly malignant, pancreatic cancer is still one of the most challenging tumors. Despite recent progress in diagnostic techniques, the early detection of pancreatic cancer is still quite difficult, so most patients undergo surgery at the time of diagnosis. Radical resection is believed to offer the only chance of cure to patients with pancreatic cancer. However, unfavorable results can appear shortly after surgery in most patients with tumor recurrence. The 5-year survival rate after curative resection is reported to be around 10% to 17%.[1–5]

To improve the prognosis of patients with resectable pancreatic cancer, many revisions to the surgical procedure and adjuvant therapy have been tested. Expanded retroperitoneal lymph-node dissection did not improve the survival rate in randomized controlled trials.[6–8] To improve the resection rate of pancreatic cancer, regional pancreatectomy was advocated in which the whole tumor is resected, together with any portal vein/superior mesenteric vein (PV/SMV) involved in the tumor; arteries [celiac artery, aorta, and superior mesenteric artery (SMA)]; and the surrounding lymph pipeline, followed by venous and arterial reconstruction.[9] However, extending the venous or arterial resection, with the subsequent complex vascular reconstruction, is reportedly associated with a significant mortality rate,[9,10] and the long-term survival rate is not satisfactory. As the surgical techniques used and the perioperative care of the patient undergoing pancreatic cancer resection have improved, surgery has become more radical, and the operative mortality and disability rates have decreased.[11–17] Over the past 10 years, lower surgical mortality rates after pancreaticoduodenectomy have been reported in many clinical medical centers.[18–21] Regional tumor resection when a main vein is involved in the tumor, with no occlusion of the portal vein, is no longer considered inadvisable if the surgeon considers that vein resection and reconstruction could be completed to a negative margin resection (R0).[22–24] At present, vein resection during radical surgery for pancreatic cancer accounts for about 20% of pancreaticoduodenectomies at large pancreatic surgery centers.[25–27] Several studies have compared no-vein and vein resection in pancreaticoduodenectomy, recording their equal feasibility and equal rates of operative mortality, incidence, and survival.[28–30] Factors identified as potentially relevant to the survival outcomes include population, perioperative treatment, and clinical pathologic factors, but these are still controversial.

The intention of this study was to identify the prognostic factors for a survival time of >2 years after radical surgery, by analyzing the clinical features of patients who have survived for >2 years after surgery. The clinicopathologic factors affecting survival time (more or less than 2 years) were assessed in detail, and the key factors affecting survival time were investigated.

Materials and Methods

In the period between January 1, 2003, and December 31, 2010, 533 patients with carcinoma of the pancreas were admitted to the General Surgical Department of the Ruijin Hospital School of Medicine at Shanghai Jiaotong University. In this patient population, 63 individuals underwent pancreatectomy with vascular resection (VR) with curative intent. None of them were lost to follow-up. A retrospective analysis of the clinical data and the records of the 63 patients were the basis of this study. The patients were divided into 2 groups: 1 group had a survival time of <2 years after surgery (group 1) and the other a survival time of >2 years (group 2). In this study, we excluded all patients with neuroendocrine cancer, adenocarcinoma of the ampulla of Vater, distal bile duct cancer, or cystic pancreatic neoplasms. The ethics committee of the Union of Physicians in Shanghai approved this prospective study. Preoperative assessments included a physical examination; blood examination; analysis of tumor markers [carcinoembryonic antigen (CA 19-9)]; chest radiography; abdominal ultrasonography; magnetic resonance imaging or contrast-enhanced computed tomography; and estimation of the American Society of Anesthesiologists (ASA) score. The patient demographics, clinical manifestations, and outcomes were evaluated to

Table 1 Univariate Analysis of Prognostic Factors of Early Death

Variable	Death, n (%)	Total	*P* Value	OR	95% CI
Sex					
Male	28 (77.8)	36	0.031	3.250	1.093–9.663
Female	14 (51.9)	27			
Tumor size					
$\leq$10 cm^2	22 (55.0)	40	0.007	0.183	0.047–0.717
>10 cm^2	20 (87.0)	23			
Tumor histopathology type					
Adenocarcinoma	37 (74.0)	50	0.001	—	—
Neuroendocrine carcinoma	1 (11.0)	9			
Anaplastic carcinoma	2 (10.0)	2			
Pseudopapillary tumor of pancreas	2 (10.0)	2			
Tumor grade					
I	0 (0)	9	0.000	—	—
II	31 (73.8)	42			
III	11 (91.7)	12			
Nodal metastasis					
Yes	23 (85.2)	27	0.005	5.145	1.478–17.907
No	19 (52.8)	36			
Nerve metastasis					
Yes	25 (83.3)	30	0.007	4.706	1.449–15.286
No	17 (51.5)	33			
Tumor stage					
IB	0 (0.)	6	0.002		
IIA	17 (65.4)	26			
IIB	18 (81.8)	22			
III	1 (50.0)	2			
IV	6 (85.7)	7			
Operation time					
1	3 (17.6)	17	0.000	0.038	0.009–0.170
2	39 (84.8)	46			
Postoperative chemotherapy					
Yes	6 (28.6)	21	0.000	0.067	0.019–0.240
No					
Radiotherapy					
Yes	0 (0)	3	0.009	3.333	2.265–4.906
No	42 (70.0)	60			
Patient state					
Live	0 (0)	13	0.000		
Death in tumor	41 (83.7)	49			
Death in others	1 (100)	1			

OR, odds ratio; CI, confidence interval.

identify the prognostic factors for survival after tumor resection. The variables studied included: age; sex; blood transfusion; VR; type of pancreatic resection; postoperative complications (infection, bleeding, and pancreatic fistula); and tumor size, tumor differentiation, lymph-node status, nerve invasion, and metastasis (TNM) staging [according to the 2017 National Comprehensive Cancer Network (NCCN) Guidelines]. All the patients were followed-up by telephone. In a univariate analysis, the presence of nodal metastasis and nerve metastasis, the duration of postoperative chemotherapy and radiotherapy, sex, tumor histopathology type, tumor grade, tumor stage, tumor size, and operation time were statistically significantly associated with a higher risk of early death after pancreatic carcinoma surgery (Table 1). These indicators were analyzed with logistic regression. The probability of early cancer–related death after surgical resection according to the presence or absence of different statistically significant risk factors is shown in Table 2.

Surgical Techniques

The patients' ages ranged from 31 to 74 years, with a median of 57.81 years. There was a slight predominance of male patients (Table 3). The general eligibility criteria for pancreatectomy with VR were

Table 2 Significant predictors of survival time with <2 years in 63 patients resected with a vascular resection for pancreatic cancer

Predictor	B	SE	Wald	Sig	Exp(B)	95% CI for Exp(B)
Operation time	–3.322	1.279	6.750	0.009	0.036	0.003–0.442
Tumor grade	–2.809	1.307	4.618	0.032	0.060	0.005–0.781
Tumor stage	–1.624	0.738	4.844	0.028	0.197	0.046–0.837
Postoperative chemotherapy	–3.320	1.313	6.394	0.011	0.036	0.003–0.474

B, regression coefficient; SE, standard error; Wald, chi-square value; Sig, significance; Exp(B), odd ratio

as follows: (1) after an exploratory laparotomy, patients without peritoneal scattering or distant metastases; (2) tumor invasion near-end to the branch near the PV, SMA, or SMV; (3) cancer infiltrating the celiac trunk; (4) no hypercoagulopathy syndrome. Pylorus-preserving pancreaticoduodenectomy or classic pancreaticoduodenectomy were the standard management techniques for a neoplasm located to the right of the portal-mesenteric axis, whereas for those on the left of the SMV, distal splenopancreatectomy was the operation of choice. Pancreatic body and tail neoplasms are frequently treated with either subtotal pancreatectomy or total pancreaticoduodenectomy. The incisal margins for the transection of the pancreas and bile duct are routinely tested with frozen pathology sections. Standard lymphadenectomy was performed as described elsewhere.[31,32]

The vascellum was released from the tissue and organs around it, distally and proximally, to ensure enough vascellum control when the neoplasm infiltrated the portal-mesenteric axis. When the infiltrating neoplasm wrapped around the middle or distal PV, the splenic vein was continuously

Table 3 Patient demographics, preoperative, and operative data of 63 patients with vascular resection

Project name	G1	G2	Total	%
Sex, male/female	28/14	8/13	36/27	57.1/42.9
Age, y, median (range)	57.02	59.38	57.81	31–74 (SD: 8.758)
Symptoms, jaundice/abdominal pain/others	2/26/14	3/15/3	5/41/17	7.93/65.07/26.98
Concomitant symptoms				
Diabetes mellitus	8	4	12	19.0
High blood pressure	5	7	12	19.0
Chronic pancreatitis	0	0	0	0
Hepatitis	3	0	3	4.8
Cardiac insufficiency	7	4	11	17.5
Pulmonary insufficiency	6	1	7	11.1
High blood lipids	0	1	1	1.6
Preoperative acute pancreatitis	0	0	0	0
Operation				
Pancreaticoduodenectomy with vascular resection	37	21	58	92.06
Subtotal pancreatectomy with vascular resection	5	0	5	7.93
Vascular reconstruction technique				
Vein end-to-end anastomosis	38	19	57	90.47
Vein end-to-end anastomosis with splenic vein	1	0	1	1.58
Vein end-to-end anastomosis with polytetrafluoroethylene	2	0	2	3.17
Vein lateral venorrhaphy	0	1	1	1.58
Vein end-to-end anastomosis with artery anastomosis	1	0	1	1.58
Pure artery reconstruction	1	0	1	1.58
Operation time, min, median (range)	439.76	449.33	442.95	280–780 (SD: 108.688)
Blood transfusion in surgery, mL	1678.57	2404.76	1920.63	0–8300 (SD: 1671.865)
Blood transfusion post-surgery, mL	1545.24	1195.24	1428.57	0–10900 (SD: 1899.782)
Postoperative hospital stay, d, median (range)	27.55	25.57	26.89	12–66 (SD: 13.367)
Medical complications	22	4	26	41.30
Chemotherapy				
Intraoperative chemotherapy	23	14	37	58.70
Postoperative chemotherapy	17	17	34	53.96
Radiotherapy	0	3	3	4.80
Death in tumor, n	41	8	49	77.80
Survival time, mo, median (range)	10.07	39.67	19.94	1–57 (SD: 16.421)

separated to attain freedom. Whether segmental operative resection was executed, as a sleeve or tangential resection of the transverse PV/SMV, depended on the location of the tumor. A tangential operation, performed when the neoplasm adhered to the right side of the PV/SMV, was frequently reconstructed with a simple venous suture. An autogenous venous patch (splenic or saphenous vein) was infrequently used to avoid venous narrowing, when more than one-third of the side wall required resection. Segmental resection was consistently performed when the vasculature infiltrated more than 50% of the tumor circumference. The preferred reconstructive surgery was primary end-to-end anastomosis after segmental resection. Venous reconstruction was achieved by bridging the autologous venous vessels (saphenous, polytetrafluoroethylene, or splenic vein) only when tension-free anastomosis was not technically feasible. Because any venous vascular convergence must be removed, it is necessary to discuss whether or not the splenic vein stump should be reinserted, and the choice will depend on the presence or absence of enough lateralization at the hilum of the spleen through the short gastric vein. In 2 of 21 patients who underwent segmental sleeve arterial resection, a united VR involving both the portal-mesenteric axis and the mesenteric, celiac trunk, or hepatic artery was performed. Such an extended resection was strictly limited to patients with a good preoperative status (ASA I–II). Conventional prophylactic heparinization was performed with low-molecular-weight heparin in all patients.

Morbidity and Mortality

Postoperative mortality was defined as death within 30 days of surgery. Major postoperative complications were defined as hemorrhage, pneumonia, reoperation, pancreatic fistula, intra-abdominal abscess, and delayed gastric emptying. Pancreatic fistula, intra-abdominal hemorrhage, and delayed gastric emptying were defined according to the standard definitions of the International Study Group of Pancreatic Surgery.[33,34]

Statistical Analysis

The distributions of continuous variables are reported as medians and interquartile ranges (25th, 50th, and 75th percentiles). Categorical variables are presented as numbers and percentages. Survival was defined as the time from resection to death. Survival probability was estimated according to the Kaplan–Meier method. A multivariate analysis was used to estimate the statistically significant predictors of pancreatectomy with VR for pancreatic cancer, and was executed with a binary logistic regression model. All continuous data fields were made dichotomous based on significant cutoff points, determined in the analysis or taken as the median value. A value of $P < 0.05$ was considered statistically significant in all statistical analyses. All statistical analyses were performed with statistical software (SPSS for Windows, version 11.0; SPSS, Inc., Chicago, Illinois).

Results

Details of patients and hospital courses

Demographic, operative, and clinical data, including preoperative jaundice, sex, age, abdominal pain, concomitant symptoms, operative time, blood transfusion during surgery, blood transfusion after surgery, chemotherapy, radiotherapy, medical complications, survival time, and the different types of reconstruction after resection of the pancreatic neoplasm in 63 patients are given in Table 3. Tangential resection of the SMV was performed in 1 patient. In this case, primary lateral venorrhaphy restored sufficient portal vein blood flow. A total of 61 patients were treated with complete venous resection. The venous axis was subsequently reconstructed with various kinds of anastomoses. When reconstruction was complete, the blood flow was clinically tested during the operation. The patency of the reconstructed veins was assessed with Doppler ultrasound in the postoperative period.

Histopathology

The histopathologic data are summarized in Table 4, including the tumor location, tumor histopathology type, tumor size, tumor grade, regional lymph nodes, nerve metastasis, vascular invasion, and tumor stage. Tumor size (maximal area) was recorded when the pancreaticoduodenectomy specimen was evaluated pathologically. In 30 (47.60%) patients, extrapancreatic perineural invasion was present in the nerve plexus surrounding the splenic, celiac, common hepatic, and/or superior mesenteric arteries. Invasion was detected in various parts of the vasculature. According to the 2007 NCCN Practice Guidelines in Oncology (TNM classification

Table 4 Pathologic data of 63 patients undergoing PPPD with vascular resection

Project name	Total	%
Tumor location		
Head of pancreas	45	71.42
Pancreatic neck	13	20.63
Pancreatic body and tail	5	7.93
Tumor size (range) cm^2	10.01	0.75–30.0 (SD: 6.05)
Tumor histopathology type		
Adenocarcinoma	58	92.10
Neuroendocrine carcinoma	1	1.60
Anaplastic carcinoma	2	3.20
Pseudopapillary tumor of pancreas	2	3.20
Tumor grade		
I	6	9.50
II	45	71.40
III	12	19.00
Regional lymph nodes		
Lymph nodes metastasis	24	38.10
No metastasis	39	61.90
Nerve metastasis, yes/no	30/33	47.60/52.40
Vascular invasion		
Coeliac artery, yes/no	3/60	4.8/95.2
Common hepatic artery, yes/no	1/62	1.6/98.4
Splenic artery, yes/no	0/63	0/100
Splenic vein, yes/no	5/58	7.9/92.1
Portal vein, yes/no	22/41	34.9/65.1
Superior mesenteric vein, yes/no	50/13	79.4/20.6
Superior mesenteric artery, yes/no	3/60	4.8/95.2
Tumor stage		
Tis	0	0
IA/IB	0/1	0/1.6
IIA/IIB	31/22	49.2/34.9
III	2	3.2
IV	7	11.1

PPPD, pancreaticoduodenectomy.

system), 1 patient had stage IB disease, 31 had stage IIA disease, 22 had stage IIB disease, 2 had stage III disease, and 7 had stage IV disease.

Analysis of Prognostic Factors for Early Death

In a univariate analysis, the presence of several factors was statistically significantly associated with a higher risk of early death after surgery for pancreatic carcinoma (Table 1). These factors were used in a logistic regression analysis. The results are given in Table 2 and show that tumor grade, tumor stage, postoperative chemotherapy, and operation time were significant predictors of a survival time of less than 2 years in 63 patients treated with VR for pancreatic cancer.

Discussion

The most common malignancy of the pancreas, pancreatic adenocarcinoma, remains a major cause of death from cancer in Asia and the Western world. Approximately 60% of pancreatic cancers occur in the head of the pancreas. There have been many efforts to increase the safety and acceptability of pancreaticoduodenectomy since the introduction of this operative procedure.[35] Today, we routinely perform pancreaticoduodenectomy for periampullary cancer, and sometimes even for benign disease, with acceptably low operative morbidity and mortality.[36–38] Many surgeons undertake more radical resections to extend the indications for pancreaticoduodenectomy because radical resection remains the only potentially curative treatment for pancreatic cancer. Vascular adhesion or invasion is usually 1 of the limiting factors for radical surgical resection, and surgeons have performed pancreaticoduodenectomy with infiltrated VR to address this problem. Moore[39] reported the first VR in 1951, and Fortner[40] further refined the concept of *en bloc* pancreatectomy in 1973. Fortner reasoned that the neoplastic invasion of the adjacent blood vessels could be limited by the *en bloc* resection of the arteries (type 2 resection) and veins (type 1 resection) involved. Our experience in radically resectable surgery with VR has increased in recent years. It has been reported that the perioperative mortality in more acceptable than that accompanying pancreaticoduodenectomy without VR in many clinical centers, but pancreaticoduodenectomy with VR remains controversial because there is as yet no evidence of improved survival.[41] Several previous studies have identified tumor-associated biologic characteristics that are important in the prognoses of pancreatic adenocarcinoma patients after resection. For example, the status of the resection, tumor size, and lymph-node status have all been identified as significant determinants of survival.[42,43] Recently, a single-center study reported that the lymph-node ratio is a prognostic factor for pancreatic adenocarcinoma.[44] Most clinical researchers are eager to identify the patients who will live for a long time after pancreatectomy with VR for pancreatic cancer. It has been reported that several prognostic factors affect long-term survival after pancreatectomy, including tumor size, cellular differentiation, tumor involvement at the resection margin, and lymph-node metastasis.[45–47] However, we cannot yet say which factors are prognostic after pancreatectomy with VR for pancreatic carcinoma because the

characteristics of the long-term survivors are not yet clear.

In our study, diverse clinicopathologic characteristics were identified when we compared the actual long-term survivors after pancreatectomy with or without VR. Only 4 factors independently affected survival: postoperative chemotherapy, operating time (280–780 minutes), tumor grade, and tumor stage. The mean operating time was similar to those reported elsewhere, and other studies have reported operating times of 500–660 minutes.[48] Our study showed good outcomes with appropriate postoperative chemotherapy, low tumor grade, and low tumor stage, with little mortality. Moreover, long operating times seemed to be associated with shorter survival, suggesting that operative trauma promotes early cancer recurrence arising from immunosuppression. The mechanisms of immunosuppression have been studied by many investigators, and it can be caused by surgical stress. Monocyte is human histocompatibility leukocyte antigen-D related, and monocyte expression is suppressed after surgery, resulting in impaired antigen presentation.[49] Surgical stress also causes the reduced secretion of interferon-c, interleukin 2 (IL-2), and tumor necrosis factor α by T lymphocytes and IL-12 by monocytes.[50,51] Therefore, the main feature of postoperative immunosuppression seems to be the depression of cell-mediated immunity. Several adjuvant trials for pancreatic cancer have been guided partly by the results of ongoing trials and, where available, how survival relates to involvement margin, and the outcome of studies of new agents and drugs for advanced pancreatic cancer. The phase III trial conducted by Germany-based Eli Lilly examined disease-free survival as the primary endpoint, observing the effects of treatment with the adjuvant gemcitabine in 368 pancreatic cancer patients. The results of the preliminary study showed the advantage of gemcitabine treatment, but the results did not demonstrate its superiority to folinic acid and fluorouracil, which was tested in the European Study Group for Pancreatic Cancer 1 trial, achieving a 5-year survival rate of 29% and an overall median survival of 21.6 months.[52,53] In this study, we found that gemcitabine-based adjuvant chemotherapy was effective in both groups of patients and improved the prognosis of pancreatic cancer.

According to our study, tumor grade and tumor stage are important factors affecting long-term survival. These 2 factors are essentially linked because tumor grade is the basis of tumor staging. However, previous studies have identified other prognostic factors that increase long-term survival after pancreatectomy, including cellular differentiation, tumor size, and the resection margin of the tumor.[45–47]

In summary, our results show that VR during pancreaticoduodenectomy for pancreatic cancer results in acceptable perioperative morbidity and mortality rates, and can therefore be safely performed. Vascular resection for pancreatic cancer is very important for the control of local macroscopic cancer if complete tumor clearance is to be achieved. The TNM staging of a pancreatic cancer, tumor grade, operating time, and chemotherapy after surgery are independent predictors of long-term survival. Preserving the patient's general condition with palliative chemotherapy after the operation should be an important principle in the surgical treatment of pancreatic cancer to improve the long-term survival of patients. The subgroup of patients who will most benefit from pancreaticoduodenectomy with VR must be identified in future studies. With systemic control and improvements in adjuvant therapies, more radical surgical treatment of local advanced cancer might yet be justified.

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