Surgical Results of Pancreaticoduodenectomy for Pancreatic Ductal Adenocarcinoma: a Multi-institutional Retrospective Study of 174 patients

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Abstract. *Background: Postoperative pancreatic fistula (POPF) remains a major complication after pancreaticoduodenectomy (PD), and the prognosis of patients with pancreatic ductal adenocarcinoma (PDAC) after PD is poor. Patients and Methods: A multi-institutional retrospective study was performed in 174 patients who underwent PD for PDAC from 2007 to 2012. The details of clinical data were examined, and risk factors for POPF and poor prognostic factors after PD were identified. Results: POPF occured in 26 patients (15%), and 18 patients (10%) were diagnosed as Grade B/C POPF. The independent risk factors for Grade B/C POPF were body mass index (BMI) ≥25 (Odds Ratio [OR]=21.1, p=0.006) and absence of post-operative enteral nutrition (EN) (OR=10.2, p=0.04). The 1-, 3-, and 5-year overall survivals of patients with PDAC after PD were 76%, 35%, and 18%, respectively. R1/2 operation was identified as the only independent poor prognostic factor (Hazard Ratio=3.66; p=0.0002). Conclusion: Patients with BMI ≥25 should be closely monitored for POPF after PD. Post-operative EN might help prevent POPF. Performing R0 resection is an important goal for ensuring patient survival after PD for PDAC.*

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Key Words: Pancreaticoduodenectomy, pancreatic ductal adenocarcinoma, postoperative pancreatic fistula, overall survival, multi-institutional study.

In 1945, Whipple *et al*. reported that pancreaticoduodenectomy (PD) had a mortality rate over 30% (1). With advances in surgical management of PD, the recent mortality rate for PD has been reported to be less than 5% (2-4). Despite marked reductions in mortality rates, postoperative pancreatic fistula (POPF) remains the most common cause of morbidity, occurring in 5-40% of PD cases even in high-volume centers (4-6). Effective strategies to reduce POPF should, thus, be identified (7).

Risk factors for POPF have been extensively studied; those proposed include male gender (8), advanced age (9), high body mass index (BMI) (10), amylase level in drainage fluid (11), fatty pancreas (12, 13), main pancreatic duct

<3 mm (14), pancreasticojejunostomy (PJ) (15) and hospital patient volume (16). However, some of these factors can only be identified intra-operatively or post-operatively, and most of them remain controversial.

Survival rates of patients with pancreatic ductal adenocarcinoma (PDAC) after PD have been reported as poor with the 5-year survival rate ranging from 4 to 24% (17). Poor prognostic factors of patients with PDAC after PD have been extensively studied, and include tumor size ≥2 cm (18, 19), major vessel invasion (19), lymph node metastasis (17-19), R1/2 resection (18), hospital patient volume (20) and so on. It is possible that the poor prognostic factors could differ according to country, region, and even institution.

We herein report a multi-institutional retrospective study in 174 patients with PDAC who underwent PD in western Japan. We examined the details of surgical procedures, and surgical results of PD in patients with PDAC, and identified the risk factors for POPF and poor prognostic factors after PD.

Patients and Methods

Patients. From January 2007 to December 2012, 174 patients at 13 Institutions in western Japan underwent PD for PDAC, as confirmed by pathological examinations. All patients undergoing PD had an Eastern Cooperative Oncology Group Performance status 0-2. After the approval of each institutional review board, the medical records of patients in this series were examined and followed with a median follow-up period of 39 months.

Surgical technique. *En block* conventional PD, pylorus-preserving PD (PPPD), and substomach-preserving PD (SSPPD) with lymph node dissection were performed at the discretion of the surgeons (21-25). The selections of PJ or pancreaticogastrostomy (PG), duct-to-mucosa anastomosis or dunking, and external or internal drainage or no-stent drainage of the pancreatic duct also depended on surgeon's discretion. At least one closed drain was routinely inserted near the PJ or PG sites. Upon grading the pancreatic fistulas we referred to the established criteria of the International Study Group of Pancreatic Fistula (ISGPF) classification (26).

Statistical analysis. Continuous variables are expressed as means. To identify the independent risk factors for Grade B/C POPF, a stepwise logistic regression analysis was applied using 13 factors as follows: male gender, age ≥70, BMI ≥25, diabetic mellitus (DM) (+), hypertension (HT) (+), smoking (+), operations <5 cases/year, Institutes not certified by Japanese Society of Hepato-Biliary-Pancreatic Surgery (JHBPS), Stage II or more classified by the 6th edition, Japanese Pancreas Society (27), PJ anastomosis, duct-to-mucosa (–), R1/2 operation, and post-operative enteral nutrition (EN) (–).

The overall survival (OS) curves were generated by the Kaplan-Meier method and compared by the log-rank test. To identify the independent poor prognostic factors of patients with PDAC after PD, we performed multivariate analysis with the Cox proportional hazard model using 14 clinical, surgical, and tumor-related variables: gender (male *vs*. female), age (≥ *vs*. <70 years) BMI (≥ *vs*. <25), DM (presence *vs*. absence), HT (presence *vs*. absence), smoking (presence *vs*. absence), operations/year (≥ *vs*. <5 cases year), certificated institute by JHBPS (yes *vs*. no), stage (≥ *vs*. <II), anastomosis (PJ *vs*. PG), duct-to-mucosa (presence *vs*. absence), curability (R0 *vs*. R1/2), post-operative EN (presence *vs*. absence), and adjuvant chemotherapy (presence *vs*. absence).

All statistical analyses were performed with JMP® Pro 11 (SAS Institute Inc., Cary, NC, USA). *p*-Values less than 0.05 were considered significant.

Results

Summary of clinical data of all 174 patients with PD for PDAC. Clinical data of all 174 patients with PD for PDAC are summarized in Table I. The distributions of PD/PPPD/SSPPD were 76/42/56, PJ/PG anastomosis 129/45, duct-to-mucosa anastomosis/dunking 123/51, and external/internal/no stent drainage of pancreatic duct 136/34/4. The distribution of tumor stages of I/II/III/IVa/IVb was 11/13/78/45/27, and the curability of PD evaluated by R0/1/2 was 136/34/4. The R0 resection rate in our series was 78.2%. POPF happened in 26 patients (14.9%), and the distribution of Grades A/B/C was 8/14/4. The rate of Grade B/C POPF in our series was 10.3%. Adjuvant chemotherapy was performed in 102 patients (58.6%).

Independent risk factors for Grade B/C POPF. The results of stepwise logistic regression analysis are summarized in Table II. The independent risk factors for Grade B/C POPF were BMI≥25 (Odds Ratio [OR]=21.1, p=0.006) and absence of post-operative EN (OR=10.2, p=0.04). The methods of anastomosis such as PJ (p=0.86) or duct to mucosa (–) anastomosis (p=0.99) were not independent risk factors for Grade B/C POPF.

Survival of patients with PDAC after PD. The OS curve of all 174 patients is shown in Figure 1A. The 1-, 3-, and 5-year survival rates were 76%, 35%, and 18%, respectively. The OS curves differed significantly according to tumor stage (Figure 1B), with the survival of patients with advanced tumor stage being significantly worse.

The results of multivariate analysis with the Cox proportional hazard model are summarized in Table III. The only independent poor prognostic factor for patients experiencing PDAC after PD was R1/2 operation (Hazard Ratio [HR]=3.66, p=0.0002). Advanced tumor stage (II or more) (p=0.16) and absence of adjuvant chemotherapy (p=0.44) were not independent poor prognostic factors in our series.

Discussion

POPF is the most challenging complication after PD. Because it is associated with substantial mortality and morbidity, some authors have defined it as the "Achilles heel" of PD (28). In our series, the incidence of POPF after

Table I. *Summary of clinical data of all 174 patients with PD for PDAC.*

Variables	Value
Patient background	
Age (years)	68.7
Male/Female	92/82
BMI	21.6
DM (+) (%)	54 (31%)
Preoperative chemotherapy (+) (%)	10 (6%)
Preoperative biliary drainage (+) (%)	70 (40%)
Surgical factors	
Operation time (min)	459
Blood loss (g)	1204
Transfusion (+) (%)	79 (45%)
PD/PPPD/SSPPD	76/42/56
PJ/PG anastomosis	129/45
Duct to mucosa +/–	123/51
External/internal/no stent	99/69/6
R0/1/2	136/34/4
Postoperative enteral nutrition	47 (27%)
Tumor-related factors	
Stage I/II/III/IVa/IVb	11/13/78/45/27
CEA (ng/ml)	7.9
CA19-9 (IU/l)	1518
Short-term surgical results	
POPF Grade A/B/C	8/14/4
Removal of drain (median; days)	15
Hospital stay (days)	24
Adjuvant chemotherapy	102 (59%)

PD; Pancreaticoduodenectomy, PDAC; pancreatic ductal adenocarcinoma, BMI; body mass index, DM; diabetes Mellitus, PPPD; pylorus-preserving PD, SSPPD; substomach-preserving PD, PJ; pancreaticojejunostomy, PG; pancreaticogasterectomy, CEA; carcinoembryonic antigen, CA19-9; carbohydrate antigen 19-9, POPF; postoperative pancreatic fistula.

Table II. *Independent risk factors for Grade B/C POPF.*

Variables	Odds Ratio	95% C.I.	*p*-Value
BMI ≥25	21.1	2.40-185	0.006
Postoperative enteral nutrition (–)	10.2	1.08-100	0.04
Stage II or more	1.39	0.16-11.9	0.76
R1/2 operation	1.98	0.41-9.59	0.40
Operations <5 cases/year	3.97	0.64-24.4	0.14
Institutes not certified by JSHPBS	1.22	0.27-5.59	0.80
Age ≥70	1.28	0.35-4.76	0.71
PJ anastomosis	1.27	0.03-16.7	0.86
Duct-to-mucosa (–)	1.02	0.35-8.80	0.99
Male	1.25	0.63-5.60	0.74
Smoking (+)	1.14	0.10-4.33	0.28
DM (+)	1.30	0.29-5.85	0.73
HT (+)	3.53	0.74-16.7	0.11

POPF; Postoperative pancreatic fistula, C.I.; Confidence Interval, JSHBPS; Japanese Society of Hepato-Biliary-Pancreatic Surgery, PG; pancreaticogastrostomy, DM; diabetes Mellitus, HT; hypertension.

Table III. *Independent poor prognostic factors of patients with PDAC after PD.*

Variables	Hazard Ratio	95% C.I.	*p*-Value
R1/2 operation	3.66	1.84-7.30	0.0002
Stage II or more	4.26	0.55-33.3	0.16
Operation ≥5 cases/year	1.47	0.69-3.16	0.31
Certified institutes by JSHPBS	1.48	0.63-3.45	0.37
BMI ≥25	1.37	0.41-4.62	0.61
Age ≥70	1.34	0.68-2.63	0.39
PJ anastomosis	1.81	0.80-4.07	0.15
POPF (+)	1.28	0.58-2.86	0.54
Male	1.19	0.60-2.35	0.61
Smoking (+)	1.39	0.66-2.95	0.39
Postoperative enteral nutrition (+)	1.29	0.59-2.82	0.52
DM (+)	1.01	0.50-2.07	0.97
Postoperative septic complication (+)	2.88	0.32-25.8	0.35
Adjuvant chemotherapy (–)	1.29	0.67-2.46	0.44

PDAC; Pancreatic ductal adenocarcinoma, PD; pancreaticoduodenectomy, C.I.; Confidence Interval, JSHBPS; Japanese Society of Hepato-Biliary-Pancreatic Surgery, BMI; Body mass index, PJ; pancreaticojejunostomy, POPF; postoperative pancreatic fistula, DM; diabetes mellitus.

PD was approximately 10%, which appears to be comparable to the POPF rate of 10-30% reported from studies at other high-volume Centers (8-16).

Although the risk factors of POPF have been studied extensively, a soft pancreatic parenchyma called a "soft pancreas" is the only risk factor that has been validated (29, 30). The softness of the pancreatic parenchyma derives from pathological infiltration of fat (12, 13). However, the discrimination of "soft pancreas" is subjective, and the extent of pancreatic fat can only be pathologically analyzed post-operatively, circumstances that limit these factors' utility as risk factors of POPF. Fatty pancreas is more frequently observed in obese patients (31); therefore, it seemed logical that high BMI such as ≥25 in our series was found to be an independent risk factor for POPF after PD. In a recent report, Percorelli *et al*. demonstrated that a large amount of visceral fat is an independent predictor for POPF after PD (32).

Okabayashi *et al*. investigated 100 patients who underwent PD and identified as an independent predictor for POPF "not having early EN through the jejunostomy catheter" (p=0.007) (33). However, in several reports, no difference in POPF rates has been reported in trials comparing EN with other nutritional routes, and the meta-analysis of Shen showed no significant difference between EN and other nutritional routes concerning POPF (34). The clinical effects of peri-operative EN would depend on many parameters such as patients' pre-operative nutritional condition, timing of EN, duration of EN, composition of EN, and so on.

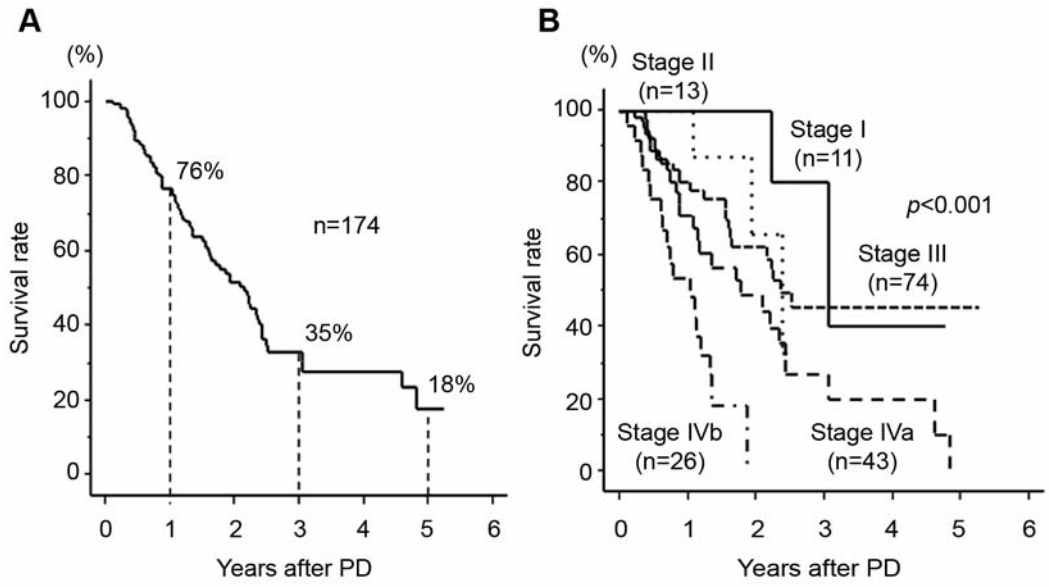

Figure 1. *The OS curve of all 174 patients is shown (A). The 1-, 3-, and 5-year survival rates were 76%, 35%, and 18%, respectively. The OS curves differed significantly, according to tumor stage (p<0.001) (B), with the survival of patients with advanced tumor stage being significantly worse.*

According to our own results, one possible preventative method for POPF after PD would be applying EN for patients with BMI ≥25. We previously reported meticulous surgical techniques such as using surgical loupes at 5.0× magnification and the VIO soft-coagulation system for PJ anastomosis (25). We still have not accomplished "zero POPF" after PD, however, severe and evident POPF has rarely happened with various novel techniques. McMillan *et al*. denied the preventative effects of octreotide for POPF after PD (35), however, another pharmacological agents that may impacts for POPF after PD should be identified.

As shown in Figure 1A, we found that the 1-, 3-, and 5-year survival rates of patients with PDAC after PD were approximately 76%, 35%, and 18%, respectively. These rates appear to be comparable to the 5-year survival rate of 4-24% in previous reports (17-20). There is little doubt that incomplete resection led to poor outcomes, and many reports have demonstrated the significance of a negative resection margin for patients' good survival (18, 36). We also identified "R1/2 operation" as an independently poor prognostic factor in patients with PDAC after PD. Our rate of R0 resection was relatively high 78.2%, compared to the rate of 55-85% in previous reports (17-20, 37); however given our results, we should strive to achieve R0 operation for more patients with PDAC to improve patient survival.

John *et al*. found that the lymph node metastasis was more important than R1 resection in predicting patients' survival after PD (37). In our analysis, shown in Figure 1B, the survival curve of patients with advanced tumor stage was significantly worse than that of others (p<0.001). However, advanced tumor stage defined as "stage II or more" was not an independent poor prognostic factor of patients with PDAC after PD in our series (HR=4.26, p=0.16). Patients with tumor size ≥2.0 cm and/or lymph node metastasis are diagnosed as stage II or more in the 6th Japanese Pancreas Society grading system. When we used the factor "the presence of lymph node metastasis" in our Cox proportional hazard model rather than "stage II or more", lymph node metastasis was still not an independent poor prognostic factor of patients with PDAC after PD (HR=2.35, p=0.38).

In conclusion, patients with BMI ≥25 should be closely monitored for POPF after PD. Post-operative EN might have preventative effects against POPF after PD. Achieving R0 resection is an important goal for improving patient survival after PD for PDAC.

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