ORIGINAL

Short- and long-term outcomes of pancreatectomy in patients with hemodialysis

Hiroki Teraoku, Yuji Morine, Tetsuya Ikemoto, Yu Saito, Shinichiro Yamada, Shohei Okikawa, Katsuki Miyazaki, and Mitsuo Shimada

Department of Surgery, Tokushima University, Tokushima, Japan

Abstract : Background : Several reports have shown the high mortality rate of pancreatic resection in patients with hemodialysis (HD), however, its long-term outcome remains unclear. In this study, we examined cases of pancreatic resection in patients with HD and conducted a literature review. Methods : Four patients with HD who underwent pancreatic resection from 2004 to 2019 were enrolled. To compare the clinicopathological variables of HD and non-HD patients, 161 non-HD patients who had undergone surgical resection for pancreatic cancer were enrolled. Results : Among four cases of pancreatic resection with HD, three cases were malignant diseases. All patients with HD had some co-morbidities (100% in HD group, 45.3% in the non-HD group) and postoperative complications (100% in the HD group, vs 46.6% in the non-HD group). Although one patient had severe postoperative complications and length of postoperative hospital stay was longer, the 30- and 90-day mortality rates were both 0% in patients with HD. However, three cases in the HD group (75%) died approximately 6 months after surgery, including one cancer-related death. Conclusions : Pancreatic surgery in patients with HD should be carefully indicated, especially pancreaticoduodenectomy or total pancreatectomy, because of the poor prognosis induced by non-cancer-related causes of death. J. Med. Invest. 70 : 105-109, February, 2023

Keywords **:** *Hemodialysis, Pancreas, Surgery, Pancreatic resection, Pancreaticoduodenectomy*

INTRODUCTION

Hemodialysis (HD) is a popular treatment for end-stage kidney disease. The number of HD patients is increasing worldwide and is expected to rise further in the future (1). Dialysis increases the risk of developing diseases such as cardiovascular, cerebrovascular, and infectious diseases. In Japan, the standardized mortality ratio for all-cause mortality in patients with HD was reported as 4.6-fold greater than that in the general population (2). Regarding the malignancies, it was reported as 2-fold greater (2). Regarding the association between dialysis patients and pancreatic disease, there is a retrospective report of high prevalence of pancreatic cysts and intraductal papillary mucinous neoplasm (IPMN) in dialysis patients (odds ratio : pancreatic cysts 6.38, IPMN 9.39) (3). It is generally known that kidney cancer increases in dialysis patients, however, there is no report that the incidence of pancreatic cancer increases in HD patients.

HD is well known as one of the greatest risk factors for patients undergoing surgery. In abdominal surgery, it has been reported that dialysis increases postoperative complications and mortality in colorectal (4, 5), gastric (6), liver (7), and pancreatic surgery (8-11). In pancreatic surgery with HD, the rate of postoperative complications was reported as 30.6%–100%, and severe complications such as reintubation, cardiac arrest, bleeding, and septic shock were significantly higher compared with non-HD patients. Shinkawa *et al*. reported that pancreaticoduodenectomy in patients with HD increased postoperative complications, with a 30-day mortality rate of 5.2% and a 90-day mortality rate of 17.3%, which is 10.9 times that of non-dialysis patients (8).

Pancreatic cancer is one of the leading causes of cancer mortality in developed countries and one of the most lethal malignant neoplasms (12, 13). According to GLOBOCAN 2012 estimates, pancreatic cancer causes more than 331,000 deaths per year (accounting for 4.0% of all deaths), ranking it as the seventh leading cause of cancer death. The incidence and mortality of pancreatic cancer worldwide is expected to increase due to aging societies.

Although it has been reported that pancreatic resection in dialysis patients has poor short-term results, the long-term outcomes are unclear. In addition to the increasing incidence of pancreatic cancer, it is expected that the number of dialysis patients will increase in the future. As a result, the need for pancreatic resection in dialysis patients is expected to increase in the future. Therefore, it is necessary to clarify the outcomes of pancreatic resection in patients with HD. Thus, in this study, we summarized the outcomes of four cases of pancreatic resection in patients with HD including long-term prognosis with an accompanying literature review.

MATERIALS AND METHODS

Patients

Four patients who underwent surgical resection for pancreatic tumors at Tokushima University Hospital from 2004 to 2019 were retrospectively enrolled. The average period from the start of dialysis to surgery was 7.1 years (2.5–20 years). Two patients were diagnosed with pancreatic cancer, one patient was diagnosed with intraductal papillary mucinous carcinoma (IPMC),

LIST OF ABBREVIATIONS :
HD : hemodialysis, IPMN : intraductal papillary mucinous neoplasm, IPMC : intraductal papillary mucinous carcinoma, NET : neuroendocrine tumor, PD : pancreaticoduodenectomy, DP : distal pancreatectomy, TP : total pancreatectomy, ICU : intensive care unit, BMI : body mass index, DIC : disseminated intravascular coagulation

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Address correspondence and reprint requests to Hiroki Teraoku, Department of Digestive and Pediatric Surgery, Institute of Biomedical Sciences, Tokushima University Graduate School, 3-18-15 Kuramoto-cho, Tokushima 770-8503, Japan and Fax : +81-88-631-9698. E-mail : teraoku.hiroki@tokushima-u.ac.jp

and one patient was diagnosed with pancreatic neuroendocrine tumor (NET). Pancreaticoduodenectomy (PD) was performed in two cases, total pancreatectomy (TP) in one case, and distal pancreatectomy (DP) in one case. Frailty was assessed by the clinical frailty score (14). HD was restarted on postoperative day 1 in all cases.

To compare the clinicopathological variables between HD and non-HD patients, 161 non-HD patients who underwent surgical resection for pancreatic cancer at Tokushima University Hospital from 2004 to 2019 were enrolled.

This study was approved by the research ethics committee of Tokushima University Hospital. Written informed consent was obtained from all patients. Pathological diagnosis was evaluated by hematoxylin and eosin staining at the Pathology Department of Tokushima University Hospital.

Surgical procedures

Pancreaticoduodenectomy was performed by subtotal stomach-preserving pancreaticoduodenectomy (SSPPD). For reconstruction by SSPPD, the jejunum was brought through the transverse mesocolon by the retro-colic route. Pancreaticojejunostomy was performed with an internal stent, and hepaticojejunostomy was performed without a stent. Gastrojejunostomy was performed by end-to-side two-layer anastomosis with Braun's anastomosis. In one case of TP, the procedure from PD to TP was intraoperatively changed due to a positive surgical margin. D1 lymph node dissection was performed for NET, and D2 for malignant cases. No cases underwent additional portal vein resection or combined resection of other organs.

Statistical analysis

All statistical analyses were performed using JMP 14 (SAS Institute, Cary, NC, USA). Survival curves were generated by the Kaplan–Meier method.

RESULTS

Patients' background and clinical outcomes in HD patients

Four cases of pancreatic resection with HD are summarized in Table 1. Three cases were malignant diseases, and performance statuses were maintained in all cases, which was the background for the presence of many comorbidities. The average period from the start of dialysis to surgery was 7.1 years (2.5–20

Table 1. Four cases of pancreatic resection in patients with hemodialysis

	Case1	Case2	Case3	Case4
Age (years)	69	74	62	49
Gender	male	male	male	female
BMI	19.1	21.7	18.0	33.4
Hemoglobin (g/dl)	11.0	15.5	9.9	9.8
Platelet ($\times 10^4$/ul)	16.6	15.5	9.0	28.6
Albumin (g/dl)	3.1	3.8	3.3	3.5
Creatinine (mg/dl)	9.36	13.04	5.93	5.15
Diagnosis	PDAC	PDAC	IPMC	NET
Period of HD (years)	3	3	20	2.5
Renal disease	Nephrosclerosis	Glomerular nephritis	DM	DM
ASA-PS	2	2	2	2
Frailty	-	-	-	-
Co-morbidities	HT	HT, Cerebral infarction Post-pneumectomy	HT, DM Post-nephrectomy	HT, DM, HL, OMI Total hysterectomy
Preoperative biliary drainage	-	-	ENBD	-
Operative procedure	PD	PD	TP	DP
Lymph node dissection	D2	D2	D2	D1
Operative time (minutes)	622	589	577	332
Blood loss (ml)	600	420	490	140
Transfusion	-	-	-	-
Post-op. complications	SSI	Pneumonia, ARDS PF, Abscess	Refractory ascites	PF, Abscess
Clavian-Dindo classification	II	IVb	IIIa	IIIa
pStage	IIb	IIb	IIb	-
ICU stay (days)	6	53	3	3
Post-op. stay (days)	89	103	80	51
Outcome	Transfer	Transfer	Transfer	Discharge
Long-term prognosis	Dead on 134 POD	Dead on 179 POD	Dead on 143 POD	Alive for 4.5 years
Cause of death	GI hemorrhage	Respiratory failure	Cancer death	-

HD, hemodialysis ; BMI, body mass index ; ASA-PS, American Society of Anesthesiologists physical status ; ICU, intensive care unit ; POD, post-operative days ; PDAC, pancreatic ductal adenocarcinoma ; IPMC, intraductal papillary mucinous carcinoma ; NET, neuroendocrine tumor ; HT, hypertension ; DM, diabetes mellitus ; HL, hyperlipidemia ; OMI, old myocardial infarction; ENBD, endoscopic nasobiliary drainage ; SSI, surgical site infection ; ARDS, acute respiratory distress syndrome ; PF, pancreatic fistula ; GI, gastrointestinal ; PD, pancreaticoduodenectomy ; DP, distal pancreatectomy ; TP, total pancreatectomy

years).

Regarding postoperative results, postoperative complications occurred in all cases, and three of four cases had complications of Clavian–Dindo IIIa or higher. One patient (case 2) stayed in the intensive care unit (ICU) for a long time because of acute respiratory discomfort syndrome (ARDS) and respiratory failure accompanied by tracheostomy. Although the 30- and 90-day mortality rates were 0%, it was not possible for the 3 patients who were received PD or TP to leave the hospital, with the exception of the DP case. Regarding the long-term prognosis, one case died due to cancer recurrence and two cases died suddenly due to gastrointestinal bleeding and respiratory failure. These patients (75%) died approximately 6 months after surgery, resulting in an extremely poor prognosis. Only the DP case (case 4) was discharged from hospital and remains alive 4.5 years later without recurrence.

Clinical outcomes of pancreatic resection in HD and non-HD patients

In this study, statistical comparisons were not performed due to the small number of cases. The clinical variables of pancreatic resection in HD and 161 non-HD patients who underwent surgical resection for pancreatic cancer around the same period were shown in Table 2.

Regarding the patients' backgrounds, there were no much differences between the two groups in terms of age, sex, body mass index (BMI), or frailty. Although the proportion of patients with at least one co-morbidity was higher in the dialysis group (100% in HD group, 45.3% in the non-HD group), surgical outcomes including surgical time, blood loss, and blood transfusion in HD patients was seemed to be acceptable. Postoperative complications occurred in all cases in the HD group and were more frequent than those in the non-HD group (100% in the HD group, 46.6% in the non-HD group). The proportion of pancreatic fistula was 50% in the HD group. Length of postoperative hospital stay was longer in HD patients (84.5 days in the HD group, 29 days in the non-HD group). In the HD group, the 30- and 90-day mortality rates were 0%, although the postoperative complication rate was high and the postoperative hospital stay was long.

The survival curves are shown in Figure 1. Although a simple comparison could not be made due to the small number of patients and the differing patient backgrounds, the survival curve of dialysis patients seemed to be worse than that of pancreatic cancer patients.

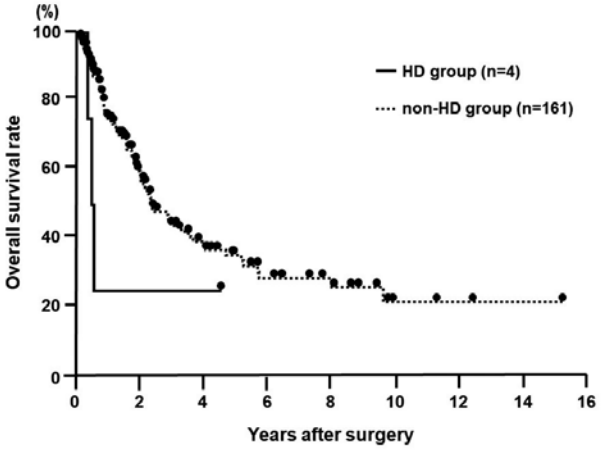

Figure 1. Kaplan–Meier curves of overall survival in the HD group and non-HD group.

Table 2. Clinicopathological variables between HD and non-HD patients

Factors		HD (n = 4)	Non-HD (n = 161)
Age (years)	Median	65.5 (49-74)	70.0 (42-89)
Gender	Male / Female	3 / 1	81 / 80
BMI	Median	20.4 (18.0-33.4)	22.1 (14.9-35.3)
Hemoglobin (g/dl)	Median	10.5 (9.8-15.5)	13.0 (7.9-17.4)
Platelet ($\times 10^4$/ul)	Median	14.1 (9.0-28.6)	21.2 (3.5-60.9)
Albumin (g/dl)	Median	3.4 (3.1-3.8)	3.9 (1.8-4.9)
Creatinine (mg/dl)	Median	7.65 (5.15-13.04)	0.68 (0.46-2.60)
Frailty	Negative / Positive / N.A.	4 / 0	109/ 33/ 19
Any co-morbidities	Negative / Positive	0 / 4 (100%)	88 / 73 (45.3%)
Operative procedure	PD / DP / TP	2 / 1 / 1	102 / 54 / 5
Combined resection of PV	Negative / Positive	4 / 0	137 / 24
R	R0 / R1,2	4 / 0	123 / 38
Op. time (minutes)	Median	573 (332-622)	437 (143-771)
Blood loss (ml)	Median	455 (140-600)	241 (10-3481)
Transfusion	Negative / Positive	4 / 0	150 / 11
Post-op. complications	Negative / Positive	0 / 4 (100%)	86 / 75 (46.6%)
PF	Negative / Positive	2 / 2 (50%)	117 / 44 (27.3%)
C-D grade IIIb ≦	Negative / Positive	3 / 1 (25%)	155 / 6 (3.7%)
ICU stay (days)	Median	4.5 (3-53)	3 (1-12)
Post-op. stay (days)	Median	84.5 (51-103)	29 (12-206)
30-day mortality	Alive / Dead	4 / 0 (0%)	161/ 0 (0%)
90-day mortality	Alive / Dead	4 / 0 (0%)	157 / 4 (2.5%)

HD, hemodialysis ; BMI, body mass index ; N.A., not available ; PV, portal vein ; PD, pancreaticoduodenectomy ; DP, distal pancreatectomy ; TP, total pancreatectomy ; PF, pancreatic fistula

DISCUSSION

In this study, we investigated four cases of pancreatic resection with HD. In these cases, 30- and 90-day mortality were both 0% ; therefore, the short-term outcome of pancreatic resection with HD appeared to be acceptable. However, three of four cases died approximately 6 months after surgery. One case died due to early recurrence of pancreatic cancer, and the other two cases died from other diseases. Case 1 died suddenly on postoperative day 134 because of gastrointestinal hemorrhage at the transferred hospital. The most suspected cause of death was an anastomotic ulcer. Case 2 died due to respiratory failure on postoperative day 179 at the transferred hospital. This patient required long-term ICU admission due to postoperative respiratory failure and ARDS, and the cause of death was likely to be pneumonia. From this result, the short-term outcomes of pancreatic resection in dialysis might be acceptable, but middle- and long-term outcomes might be poor. Therefore, we searched previous reports of pancreatic resection in HD patients, and summarized their prognoses as well as our result as a literature review in Table 3.

Shinkawa *et al*. retrospectively investigated pancreaticoduodenectomy in 307 patients with HD using a Japanese national inpatients database (8). In this report, increased postoperative complications (bleeding, acute coronary event, peritonitis, sepsis, and disseminated intravascular coagulation), with a 30-day mortality rate of 5.2% and a 90-day mortality rate of 17.3% (10.9 times that of non-dialysis patients), were reported. Norman *et al*. (10) and Feyko *et al*. (11) also showed increased postoperative complications, with 30-day mortality rates of 21.4% and 5.1%, respectively. However, middle- to long-term outcomes were not investigated in these reports. Only Uchida *et al*. described the long-term prognosis, and one patient died of another disease 21 months after pancreatic surgery among three patients of PD with HD (9). Therefore, the long-term outcomes of pancreatic surgery in patients with HD are still unclear, however, it might be poor due to death from other diseases after pancreatic surgery.

Laparoscopic surgery is a minimally invasive surgery and is equal to open abdominal surgery even regarding cancer survival. Recently, the safety and feasibility of laparoscopic surgery were reported for colorectal surgery in patients with dialysis. Higashino *et al*. reported that there were no significant differences in short-term outcomes and overall or disease-free survival rates in 14 dialysis patients (17). Obara *et al*. also showed that there were no significant differences in the short-term results, disease-free survival rate, or cancer-specific survival rate in propensity score matching analysis, although the overall survival rate was significantly lower in HD patients (18). There are no reports summarizing laparoscopic pancreatic surgery in dialysis patients, and further investigation is necessary in the future.

When considering the health of older individuals, the concept of frailty is important. In recent years, the Clinical Frailty Score (CFS) was proposed (14). We previously reported the significance of frailty in prognosis after pancreatic surgery (19), whereby frailty could be an independent prognostic factor in overall survival. In the current study, the four patients maintained the activity of daily living and had no frailty before surgery ; however, their long-term prognosis was miserable due to non-cancer-related death. From this finding, HD patients had a high risk of postoperative complications, even among non-frail patients, and the indication of pancreatic resection in patients with HD should be decided carefully.

Recently, the usefulness of preoperative rehabilitation, "pre-rehabilitation", was described. Its effect has already been shown in several randomized clinical trials and a systematic review (20-22). In cases of pancreatic cancer, long-term pre-rehabilitation is not realistic because pancreatic cancer progresses quickly and has high malignant potential. However, preoperative intervention, even for a short period (1 or 2 weeks), could maintain and continuously improve physical function after surgery in patients with pancreatic cancer.

Limitations of this study include its small number of patients and single-center retrospective nature. Due to the small number of cases, the precise and reliable statistical analysis could not be performed in this study. Therefore, we excluded the statistical analysis. Also, we showed the long-term prognosis of pancreatic surgery in HD patients, however, its long-term prognosis remains unclear. Therefore, it is necessary to investigate its

Table 3. Literature review of pancreatic resection in patients with hemodialysis

Authors	Articles	Ref.	Cases	Procedures	Postop. complications (details)	30-day mortality	Long-term outcome
Ishii Y, *et al*.	J Med. 1996	(15)	1	DP	0%	0%	N.A.
Uchida H *et al*.	Surg Today. 2008	(9)	3	PD	100% (Cholangitis, PF)	0%	1 patient died of other disease 21m from surgery
Otani T, *et al*.	Hepatogastroenterology. 2008	(16)	1	PD	100% (Large amount of ascites)	0%	N.A.
Norman KS, *et al*.	HPB surg. 2014	(10)	28	PD, DP	N.A. (Reintubation ($p<0.05$), Cardiac arrest ($p<0.05$), Bleeding ($p<0.05$), Septic shock ($p<0.05$))	21.4%	N.A.
Feyko J, *et al*.	Am Surg. 2016	(11)	59	PD	N.A.(Wean ventilation ($p<0.05$), Reintubation($p<0.05$), Myocardial infarction ($p<0.05$), Sepsis ($p<0.05$))	5.1%	N.A.
Shinkawa H, *et al*.	Surgery. 2019	(8)	307	PD	30.4% (Bleeding ($p<0.05$), Acute coronary event ($p<0.05$), Peritonitis ($p<0.05$), Sepsis ($p<0.05$), DIC ($p<0.05$))	5.2%	N.A.
Our report			4	PD, DP, TP	100% (C-D IIIa<: 75%)	0%	1 patient died of cancer 2 patients died of other diseases

DP ; distal pancreatectomy, PD ; pancreaticoduodenectomy, TP ; total pancreatectomy, PF ; pancreatic fistula, DIC ; disseminated intravascular coagulation, C-D ; Clavian–Dindo classification, N.A. ; not assessed

outcomes, including long-term outcomes, in a large-scale study.

CONCLUSIONS

In conclusion, pancreatic surgery in patients with HD should be carefully indicated, especially regarding pancreaticoduodenectomy or total pancreatectomy. It should be kept in mind that dialysis patients have a high risk of other critical diseases, even after good postoperative results.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest to disclose.

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