Comparison of prognosis according to preoperative biliary drainage (percutaneous transhepatic biliary drainage versus endoscopic retrograde biliary drainage) in patients with resected pancreatoduodenectomy

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ABSTRACT

Comparison of prognosis according to preoperative biliary drainage (percutaneous transhepatic biliary drainage versus endoscopic retrograde biliary drainage) in patients with resected pancreatoduodenectomy

Background: This study aims to determine the effect of the type of preoperative biliary drainage (BD) (percutaneous transhepatic biliary drainage, PTBD or endoscopic retrograde biliary drainage, ERBD) on the prognosis of patients who underwent pancreatoduodenectomy (PD) for periampullary tumor (PAT).

Methods: This retrospective, single-institution study included the patients who underwent PD for PAT from June 2006 to March 2021 in Severance Hospital. A total of 1265 patients were retrospectively analyzed, including those who preoperatively performed PTBD or ERBD.

Results: A total of 1265 patients were divided into two groups: those with preoperative BD (PBD, N=745) and those without preoperative BD (NPBD, N=520). The PBD group had more patients with preoperative jaundice and cholangitis ($p<0.001$, $p=0.003$). There was no statistical difference in postoperative complications between the two groups. NPBD group had longer operation time ($p<0.001$), and the PBD group had more intraoperative transfusion (0.003). A total of 745 patients with PBD were divided into four groups: PTBD (N=105), ERBD (N=613), PTBD &ERBD (N=18), and ERPD (N=9). There was no statistical difference in postoperative complications between PTBD and ERBD. There was no statistical difference in overall survival and disease-free survival between PTBD and ERBD ($p=0.063$, $p=0.584$). In a multivariate analysis of prognostic factors, preoperative BD did not significantly affect overall and disease-free survival ($p=0.357$, $p=0.876$).

Conclusions: PAT shows similar short-term perioperative outcomes and long-term survival regardless of the type of preoperative BD (PTBD versus ERBD) in patients with PD.

Key words : pancreatoduodenectomy, biliary drainage, periampullary tumor

1. Introduction

A periampullary tumor (PAT) arises from the head of the pancreas, including the ampulla of Vater (AoV), the distal common bile duct (CBD), and the second part of the duodenum [1]. Pancreatoduodenectomy (PD) is known as the standard surgical treatment for PAT. PAT is often accompanied by obstructive jaundice at the time of diagnosis due to stricture and obstruction of the distal common bile duct [2,3]. Patients with obstructive jaundice may progress to life-threatening conditions such as cholangitis, sepsis, and secondary cirrhosis [4-6].

In 2020, Shen et al. reported that patients who did not undergo preoperative biliary drainage (PBD) had a higher incidence of overall postoperative complications than those who underwent PBD (P=0.005) [7]. In 2022, Gao et al. also reported that patients who underwent PBD had a lower incidence of overall postoperative complications than those who did not undergo PBD (P=0.017) [8]. Therefore, PBD is recommended for patients with obstructive jaundice at the time of diagnosis while waiting for surgery [9,10]. NCCN guidelines recommend multidisciplinary discussion of drainage, especially in patients with potentially resectable disease [11]. However, there are no standard guidelines for which type of biliary drainage to perform in which patient [12].

The most commonly performed biliary drainage techniques for patients with obstructive jaundice are percutaneous transhepatic biliary drainage (PTBD) and endoscopic retrograde biliary drainage (ERBD) [13,14]. ERBD has the advantage of being less invasive and allowing for concurrent biopsy but has the disadvantage of being unable to perform in patients with gastroduodenal obstruction or those who cannot cooperate with endoscopic procedures, as well as the possibility of stent migration [14]. PTBD has the advantages of allowing visual confirmation of the drainage status, having little effect on the surgical scope, and being able to be maintained after surgery [13]. However, it has the disadvantages of not being performed on patients without biliary tract dilatation, and it is difficult to perform a biopsy [13].

From the surgeon's perspective, PTBD is maintainable after surgery and effective in decompressing the biliary tract. However, there are concerns about hepatic bleeding, adhesions around the drainage tube, and wound infection. ERBD allows for preoperative biopsy and is effective in decompressing the pancreas. However, depending on the type of stent, it is thought to affect inflammation and fibrosis of the tissue surrounding the bile duct and pancreas. In the case of metal stents, there is concern about difficulty in dissecting the tissue during surgery and increased bleeding.

Hu et al. compared the prognosis of hepatobiliary tumors according to the type of biliary drainage (PTBD or ERBD) before liver resection and reported that patients who underwent PTBD had a higher 30-day mortality rate than patients who underwent ERBD (P=0.004) [15]. However, there has been no study comparing the effects of PTBD and ERBD on the postoperative short- and long-term prognosis in patients who underwent PD for PAT.

This study aimed to compare and analyze the prognosis of patients who underwent PD for PAT according to the type of biliary drainage (PTBD or ERBD) to determine the effect of the type of biliary drainage on the postoperative prognosis.

2. MATERIALS AND METHODS

2.1. Data collection

The medical records of patients who underwent PD for PAT from June 2006 to March 2021 in Severance Hospital were retrospectively analyzed. A total of 1419 patients underwent PD for PAT during the study period. This study was performed on patients who had or did not have PBD. Therefore, 149 patients were excluded from this study due to incomplete data (lack of PBD data, follow-up failure, missing data, and other reasons). Five patients who had PBD more than 3 months before surgery were excluded. Our institution replaced PBDs within a maximum of 3 months for patients with long waiting times for surgery.

Case report forms were used to record the patients' demographic characteristics (age, sex, body mass index [BMI], comorbidities, American Society of Anesthesiologists Physical Status Classification System [16], pathologic diagnosis, neoadjuvant chemotherapy, adjuvant chemotherapy, operative method, operative time, intraoperative blood loss, intraoperative transfusion, postoperative hospital stay duration, postoperative complications, survival, and recurrence). The postoperative complications were graded according to the Clavien-Dindo classification system (minor complication: grades I-II; major complication: grades III-V) [17]. POPF was defined according to the updated International Study Group of Pancreatic Fistula (ISGPF) criteria established in 2016 [18]. This study was approved by the Institutional Review Board of Yonsei University College of Medicine (approval number: 4-2022-1038).

2.2. Definition

The data relating to PBD (Jaundice, Cholangitis, the serum value of preoperative carbohydrate antigen 19-9 (CA19-9) and pre-BD CA19-9, Duration of PBD, type of PBD, material of ERBD) was reviewed. The direct bilirubin level in the serum diagnosed the jaundice. The serum's direct bilirubin and white blood cell level diagnosed the cholangitis). The types of PBD were classified as PTBD, ERBD, PTBD & ERBD, and ERPD. Few cases with endoscopic nasobiliary drainage (ENBD) were excluded due to the lack of PBD data and the bias of the endoscopic approach. Pigtail

catheter sizes 6-18Fr was used for PTBD. Stents used in ERBD are classified mainly into plastic and metal. Plastic stents include standard, straight, single pigtail, double pigtail, and Amsterdam. Metal stents are uncovered and covered. The patients were classified into the PBD and non-PBD groups (NPBD). The PBD group was classified into the PTBD group and the ERBD group. The ERBD group was classified into the metal stent group and the plastic stent group.

2.3. Statistical analysis

Continuous variables are expressed as the mean ± standard deviation (SD) or median (interquartile range). Differences in continuous variables between the two groups were tested using the Student's t-test. Categorical variables are expressed as numbers (percentages). The associations among different categorical variables were determined using the Chi-squared, Fisher's exact, and Mann-Whitney tests. The Cox proportional hazards regression model was used for univariate and multivariate analyses. Statistical significance was defined as $P < 0.05$. Statistical analyses were performed using IBM®SPSS® software version 26 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. The characteristics and outcome of total patients according to the PBD (PBD versus NPBD)

1265 patients were divided into groups: those with PBD (PBD, N=745) and those without PBD (NPBD, N=520). The PBD group had more patients with preoperative jaundice and cholangitis ($p<0.001$, $p=0.003$). The NPBD group had more patients with tumors located in the pancreas than the PBD group (<0.0001). The PBD group had more patients with tumors located in CBD than the NPBD group (<0.0001). The NPBD group had more patients with IPMN, and the PBD group had more patients with CBD cancer (<0.0001). The PBD group had more patients with neoadjuvant and adjuvant chemotherapy ($p=0.049$, 0.002) (APPENDIES 1).

There was no statistical difference in postoperative complications between the two groups. NPBD group had longer operation time ($p<0.0001$), and the PBD group had more intraoperative blood loss and transfusion (<0.0001) (APPENDIES 1). NPBD group had better disease-free survival (DFS) outcomes than the PBD group ($p=0.019$) (APPENDIES 2).

3.2. Patients characteristics and oncological outcome according to the type of PBD (PTBD vs. ERBD)

A total of 745 patients with PBD were divided into four groups: PTBD (N=105), ERBD (N=613), PTBD &ERBD (N=18), and ERPD (N=9). ERBD group had more patients with high BMI and DM (p=0.030, p=0.029). PTBD group had more patients with ASA score 4 (p=0.019). ERBD group had more patients with tumors located in CBD (p=0.019). There was no significant difference in the serum's pre-BD CA19-9 and preoperative CA19-9 levels (p=0.969, p=0.164). Both groups showed significant reductions in CA19-9, but there was no significant difference in the degree of reduction (p=0.821). There was no significant difference in the change of CA19-9 level before and after BD between the two groups (p=0.821). The two groups had no significant difference in neoadjuvant chemotherapy, adjuvant chemotherapy, and operation methods (Table 1).

Table 1 Patients' baseline characteristics in preoperative biliary drainage (PTBD versus ERBD)

Variables	PTBD (n=105)	ERBD (n=613)	*P value*
Age, years	66.21 ± 9.73	64.5 ± 9.81	0.098
Gender (M: F)	67(63.8) : 38(36.2)	351(57.3) : 262(42.7)	0.239
BMI, kg/m^2	22.55 ± 2.88	23.22 ± 2.92	0.030
Comorbidity			
HTN	37 (35.2)	252 (41.1)	0.282
DM	41 (39.0)	174 (28.4)	0.029
ASA score			
1	10 (9.5)	62 (10.1)	0.865
2	56 (53.3)	315 (51.4)	0.752
3	35 (33.3)	232 (37.8)	0.385
4	4 (3.8)	4 (0.7)	0.019
Tumor location			
Pancreas	41 (39.0)	187 (30.5)	0.089
AoV	27 (25.7)	142 (23.2)	0.619
CBD	35 (33.3)	280 (45.7)	0.019
Duodenum	2 (1.9)	4 (0.7)	0.214

Pre BD CA19-9, U/ml	183.50 (52.85-544.00)	116 (41.6-357.00)	0.969
Preoperative CA19-9, U/ml	51.80 (22.85-174.00)	22.8 (10.6-63.00)	0.164
CA19-9 change, U/ml	66.90 (16.60-311.33)	67.6 (18.6-245.3)	0.821
Preoperative Jaundice	49 (46.7)	308 (50.2)	0.527
Preoperative Cholangitis	2 (1.9)	17 (2.8)	>0.999
Neoadjuvant chemotherapy	18 (17.1)	101 (16.5)	0.887
Adjuvant chemotherapy	56 (53.3)	337 (55.0)	0.832
Operation method			
Open	74 (70.5)	479 (78.1)	0.102
Laparoscopic	18 (17.1)	89 (14.5)	0.553
Robot-assisted	13 (12.4)	45 (7.3)	0.083

Continuous variables are expressed as the mean ± standard deviation. Categorical variables are expressed as numbers (percentages).

BMI: body mass index, HTN: hypertension, DM: diabetes mellitus, CBD: common bile duct, AoV: ampulla of Vater, BD: biliary drainage, CA19-9: carbohydrate antigen 19-9, PTBD: percutaneous transhepatic biliary drainage, ERBD: endoscopic retrograde biliary drainage

The ERBD group had more patients with CBD cancer (p=0.025) and more retrieved lymph nodes (LN) (p=0.034). There was no significant difference in cell differentiation, tumor size, positive LN, vascular resection, resection status (R), perineural invasion (LNI), and lymphovascular invasion (LVI) between the two groups (Table 2).

Table 2 Oncological outcomes in preoperative biliary drainage (PTBD versus ERBD)

Variables	PTBD (n=105)	ERBD (n=613)	*P value*
Diagnosis			0.740
PDAC	40 (38.1)	177 (28.9)	0.066
IPMN	0	8 (1.3)	0.611

NET	1 (1.0)	4 (0.7)	0.547
AOV cancer	27 (25.7)	141 (23.0)	0.618
CBD cancer	35 (33.3)	279 (45.5)	0.025
Duodenal cancer	2 (1.9)	4 (0.7)	0.214
Cell differentiation			0.507
Well	16 (15.2)	98 (16.0)	0.887
Moderate	71 (67.6)	369 (60.2)	0.160
Poorly	13 (12.4)	99 (16.2)	0.384
Undifferentiation	3 (2.9)	18 (2.9)	>0.999
Unknown	2 (1.9)	29 (4.7)	0.295
Tumor size, cm	2.63 ± 1.04	2.45 ± 1.14	0.131
Positive LN	1.4 ± 2.06	1.47 ± 2.81	0.817
Retrieved LN	16.54 ± 10.23	18.97 ± 10.93	0.034
Vascular resection	16 (15.2)	71 (11.6)	0.289
R status			
R0	85 (81.0)	503 (82.1)	0.891
R1	19 (18.1)	104 (17.0)	0.780
R2	1 (1.0)	6 (1.0)	>0.999
Perineural invasion	77 (73.3)	394 (64.3)	0.076
Lymphovascular invasion	44 (41.9)	213 (34.7)	0.186

Continuous variables are expressed as the mean ± standard deviation. Categorical variables are expressed as numbers (percentages).

PDAC: pancreatic ductal adenocarcinoma, IPMN: intraductal papillary mucinous neoplasm, NET: neuroendocrine tumor, AoV: ampulla of Vater, CBD: common bile duct, LN: lymph node, R: residual tumor, PTBD: percutaneous transhepatic biliary drainage, ERBD: endoscopic retrograde biliary drainage

3.3. Postoperative Complications according to the type of PBD (PTBD vs. ERBD)

Table 3 shows the postoperative complications between the PTBD and ERBD groups. There was no statistically significant difference in postoperative pancreatic fistula (POPF), biliary leak, chyle leak, delayed gastric emptying, postoperative bleeding, intra-abdominal abscess, wound problem, and Major complication. The ERBD group had more patients with intraoperative transfusion (p=0.048). There was no significant difference in operation time, the amount of intraoperative blood loss, and the day of hospital stay.

Table 3 Postoperative complications in preoperative biliary drainage (PTBD versus ERBD)

Variables	PTBD (n=105)	ERBD (n=613)	*P value*
POPF			
No POPF	73 (69.5)	419 (68.4)	0.822
Biochemical leak	19 (18.1)	115 (18.8)	0.894
Grade B	12 (11.4)	69 (11.3)	>0.999
Grade C	1 (1.0)	10 (1.6)	>0.999
Biliary leak	5 (4.8)	15 (2.4)	0.195
Chyle leak	6 (5.7)	41 (6.7)	0.833
DGE	14 (13.3)	123 (20.1)	0.109
Postoperative Bleeding	5 (4.8)	24 (3.9)	0.599
Intraabdominal Abscess	0 (0.0)	10 (1.6)	0.372
Wound problem	5 (4.8)	45 (7.3)	0.412
Major complication	12 (11.4)	84 (13.7)	0.543
(≥C-D grade III)			
Operation time, min	487.76 ± 311.29	484.20 ± 207.12	0.910
Intraoperative blood loss, ml	621.05 ± 698.68	517.21 ± 486.00	0.146
Intraoperative transfusion	21 (20.0)	78 (12.7)	0.048

Hospital stay, days	18.96 ± 9.14	20.07 ± 10.67	0.315

Continuous variables are expressed as the mean ± standard deviation. Categorical variables are expressed as numbers (percentages).

POPF: postoperative pancreatic fistula, DGE: delayed gastric emptying, C-D grade: Clavien-Dindo classification system, PTBD: percutaneous transhepatic biliary drainage, ERBD: endoscopic retrograde biliary drainage

3.4. Long-term survival outcomes

Figure 1 shows the Kaplan-Meier curve of OS and DFS between PTBD and ERBD. There was no statistically significant difference in OS and DFS between them (p=0.063, p=0.584).

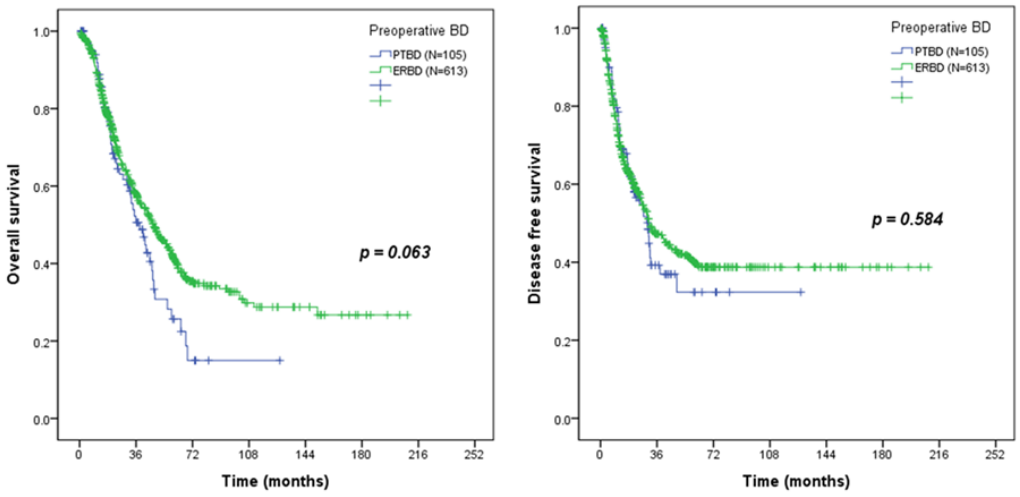

Figure 1 Kaplan-Meier survival curve of overall survival and disease-free survival according to the type of preoperative biliary drainage. The type of preoperative biliary drainage is divided into the percutaneous transhepatic biliary drainage group (PTBD) and the endoscopic retrograde biliary drainage group (ERBD). There was no statistically significant difference in overall survival and disease-free survival between PTBD and ERBD.

Figure 2 shows the Kaplan-Meier curve of OS and DFS according to the type of tumor. There was no significant difference in the survival curves between the two groups when classified by tumor type [pancreatic ductal adenocarcinoma (PDAC): p=0.177, p=0.969, AoV cancer: p=0.454, p=0.349, CBD cancer: p=0.587, p=0.972].

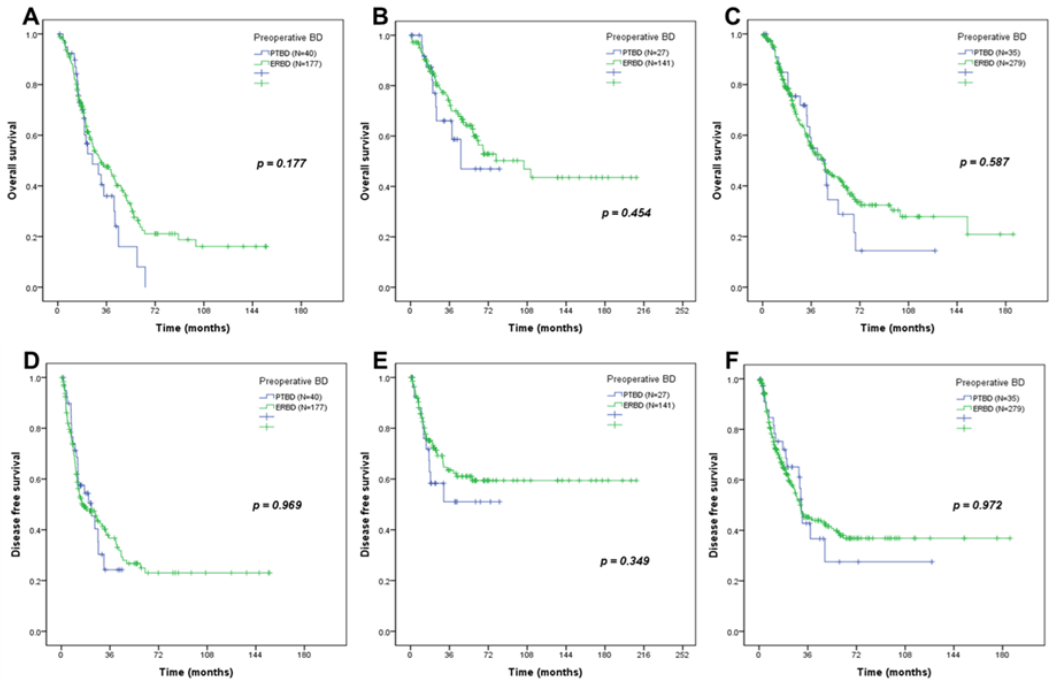

Figure 2 Kaplan-Meier survival curve of overall survival and disease-free survival comparing preoperative biliary drainage according to the tumor type. Tumor types included pancreatic ductal adenocarcinoma, intraductal papillary mucinous neoplasm (IPMN), neuroendocrine tumor (NET), ampulla of Vater cancer (AoV), common bile duct (CBD) cancer, and duodenal cancer. Due to the small data size, IPMN, NET, and duodenal cancer were not analyzed. In PDAC (A, D), AoV cancer (B, E), and CBD cancer (C, F), there were no statistically significant differences in overall survival and disease-free survival between the percutaneous transhepatic biliary drainage group (PTBD) and endoscopic retrograde biliary drainage group (ERBD).

3.5. Prognostic factor of survival outcome

Table 4 shows the Univariate and Multivariate analysis of OS and DFS.

In overall survival, ASA score, tumor location, preoperative CA19-9, major complication, operation time, intraoperative blood loss, intraoperative transfusion, hospital stay, diagnosis, tumor size, positive LN, retrieved LN, vascular resection, R status, PNI, LVI, neoadjuvant chemotherapy, adjuvant chemotherapy, operation method significantly affected the prognosis of patients in the univariate analysis* (HR 0.890,1.000, 1.529, 1.000, 2.020, 1.000, 1.000, 1.404, 0.997, 1.000, 1.047, 1.094, 0.995, 1.000, 1.037, 1.502, 1.995, 1.878, 1.121, 0.577, respectively). However, in the multivariate analysis**, tumor location, preoperative CA19-9, intraoperative transfusion, LVI, neoadjuvant chemotherapy, and operation method significantly affected the prognosis of patients

(HR 1.000, 1.000, 2.718, 2.704, 1.837, 0.564, respectively). Preoperative BD did not significantly affect the prognosis of patients (p*=0.495, p**=0.357).

In disease-free survival, Age, ASA score, tumor location, preoperative CA19-9 (>35), operation time, intraoperative blood loss, intraoperative transfusion, diagnosis, tumor size, positive LN, retrieved LN, PNI, LVI, adjuvant chemotherapy, operation method significantly affected the prognosis of patients in the univariate analysis*(HR 0.995, 0.815, 1.000, 1.399, 1.000, 1.000, 1.285, 1.000, 1.035, 1.091, 0.993, 1.425, 1.647, 1.540, 0.659, respectively). However, in the multivariate analysis**, ASA score, tumor location, operation time, intraoperative transfusion, positive LN, PNI, LVI, adjuvant chemotherapy, and operation method significantly affected the prognosis of patients (HR 0.756, 1.000, 1.000, 1.522, 1.070, 1.374, 1.632, 1.561, 0.685, respectively). Preoperative BD did not significantly affect the prognosis of patients (p*=0.697, p**=0.876).

Table 4 Univariate and Multivariate analysis of overall survival and disease-free survival

Variables	Overall survival				Disease free survival			
	HR	**95% CI**	***P****	***P****	**HR**	**95% CI**	***P****	***P****
Age	1.021	1.007-1.036	0.345	NS	0.995	0.982-1.008	0.023	0.471
Gender (M vs. F)	0.854	0.679-1.075	0.772	NS	0.842	0.667-1.064	0.616	NS
Preoperative BMI	0.985	0.947-1.026	0.689	NS	0.971	0.933-1.011	0.716	NS
HTN	0.941	0.733-1.209	0.596	NS	1.007	0.781-1.299	0.167	NS
DM	1.017	0.796-1.300	0.073	NS	0.882	0.681-1.143	0.780	NS
ASA (1, 2 vs. 3, 4)	0.890	0.578-1.370	0.007	0.700	0.815	0.623-1.065	0.003	0.019
Tumor location			<0.0001	0.107			<0.0001	0.004
Pancreas	1		0.001	0.016	1		<0.0001	0.002
AoV	0.294	0.144-0.600	<0.0001	0.355	3.535	0.287-43.514	<0.0001	0.043
CBD	0.547	0.321-0.934	0.685	0.968	4.769	0.374-61.536	0.938	NS
Duodenum	0.0001	0.0001-0.0001	0.686	NS	0.146	0.020-1.094	0.220	NS

Pre BD CA19-9 (≤35 vs. >35)	0.696	0.481-1.007	0.214	NS	0.793	0.553-1.136	0.168	NS
Preoperative CA19-9 (≤35 vs. >35)	1.529	1.086-2.155	<0.0001	0.040	1.399	1.005-1.947	0.002	0.122
CA199 change	1.000	1.000-1.000	0.036	0.324	1.000	1.000-1.000	0.304	NS
A major complication, ≥C-D grade III (No vs. Yes)	2.020	1.425-2.861	0.005	0.128	1.771	1.216-2.578	0.364	NS
Operation time	1.000	1.000-1.001	<0.0001	0.687	1.000	1.000-1.001	0.001	0.042
Intraoperative blood loss	1.000	1.000-1.000	<0.0001	0.255	1.000	1.000-1.000	<0.0001	0.295
Intraoperative transfusion (No vs. Yes)	1.404	1.014-1.946	<0.0001	<0.0001	1.285	0.904-1.826	0.006	0.005
Hospital stay	0.997	0.986-1.008	<0.0001	0.282	0.999	0.986-1.011	0.169	NS
Diagnosis			<0.0001	0.864			<0.0001	0.324
PDAC	1		<0.0001	0.589	1		<0.0001	0.387
IPMN	0.157	0.021-1.164	0.069	NS	0.422	0.100-1.776	0.290	NS
NET	0.0001	0.0001-0.0001	>0.9999	NS	0.397	0.082-1.928	0.198	NS
AOV cancer	0.0001	0.0001-0.0001	<0.0001	0.974	0.155	0.012-1.968	<0.0001	0.097
CBD cancer	0.0001	0.0001-0.0001	0.742	NS	0.141	0.011-1.821	>0.9999	NS
Duodenal cancer	0.0001	0.0001-0.0001	0.686	NS	0.0001	0.0001-0.0001	0.220	NS
Cell differentiation	1.447	1.108-1.888	0.980	NS	1.347	1.027-1.767	0.907	NS

(Well/Moderate vs. Poorly/Unknown)								
Tumor size	1.047	0.953-1.151	0.015	0.493	1.035	0.939-1.141	0.016	0.665
Positive LN	1.094	1.052-1.138	<0.0001	0.227	1.091	1.049-1.134	<0.0001	<0.0001
Retrieved LN	0.995	0.985-1.006	0.005	0.631	0.993	0.982-1.004	0.003	0.248
Vascular resection	1.000	0.712-1.405	<0.0001	0.552	0.914	0.637-1.312	0.053	NS
R status (R0 vs. R1,R2)	1.037	0.784-1.371	0.036	0.357	0.964	0.719-1.291	0.351	NS
PNI (No vs. Yes)	1.502	1.114-2.026	<0.0001	0.345	1.425	1.057-1.920	<0.0001	0.022
LVI (No vs. Yes)	1.995	1.566-2.543	<0.0001	<0.0001	1.647	1.293-2.099	<0.0001	<0.0001
Preoperative BD (PTBD vs. ERBD)	0.946	0.689-1.300	0.495	0.357	1.020	0.740-1.405	0.697	0.876
Neoadjuvant Chemotherapy (No vs. Yes)	1.878	1.324-2.663	0.038	0.015	1.269	0.887-1.816	0.216	NS
Adjuvant Chemotherapy (No vs. Yes)	1.121	0.871-1.442	<0.0001	0.155	1.540	1.193-1.989	<0.0001	<0.0001
Operation method (Open vs. MIS)	0.577	0.405-0.823	<0.0001	0.027	0.659	0.479-0.906	<0.0001	0.014

*Univariate analysis **Multivariate analysis

NS: not significant, HR: hazard ratio, M: male, F: female, BMI: body mass index, HTN: hypertension, DM: diabetes mellitus, ASA: American Society of Anesthesiologists Physical Status Classification System, AoV: ampulla of Vater, CBD: common bile duct, BD: biliary drainage, CA19-9: carbohydrate antigen 19-9, C-D grade: Clavien-Dindo classification system, PDAC: pancreatic ductal adenocarcinoma, IPMN: intraductal papillary mucinous neoplasm, NET: neuroendocrine tumor, LN: lymph node, R: residual tumor, PNI: perineural invasion, LVI: lymphovascular invasion, PTBD: percutaneous transhepatic biliary drainage, ERBD: endoscopic retrograde biliary drainage, MIS: minimal invasive surgery

4. Discussion

This study aimed to determine whether the type of PBD affected the short- and long-term prognosis of patients who underwent PD with PAT. PTBD and ERBD showed no significant difference in the occurrence of complications after PD. PTBD and ERBD showed no significant difference in OS and DFS. ERBD and PTBD showed no significant difference in survival according to the type of tumor (PDAC, AoV cancer, CBD cancer). Also, the material of ERBD did not significantly affect the postoperative complications and survival outcome.

In patients diagnosed with PAT and with obstructive jaundice, PBD is performed while awaiting surgery. In 1999, Povoski et al. reported the association of PBD with postoperative outcomes following pancreaticoduodenectomy [10]. This study strongly discourages routine PBD because it increases postoperative morbidity and mortality rates but recommends that it be performed only when necessary [10]. In cases of resectable tumors with obstructive jaundice, preoperative drainage is recommended for cases with acute cholangitis or refractory symptomatic jaundice for which neoadjuvant treatment is planned [10]. In cases of unresectable tumors, it is recommended to consider it to alleviate obstructive jaundice [10]. In 2020, Gong et al. reported the effect of preoperative biliary stents on outcomes after pancreaticoduodenectomy [19]. In this meta-analysis study, PBD is related to postoperative complications such as wound problems and DGE [19]. However, the overall mortality, severe complications, abdominal hemorrhage, bile leakage, IAA, and pancreatic fistula rates were not significantly different between patients with and without PBD [19]. There are still concerns about the need for PBD and the complications it can cause.

Therefore, PBD should be performed only in patients who need it, but there are questions about what type of PBD to insert. PBD is divided mainly into internal drainage and external drainage. External drainage includes PTBD and ENBD. Internal drainage can be done by placing an internal drainage stent through endoscopic retrograde cholangiopancreatography or percutaneous transhepatic cholangiography [13,14]. PTBD has been reported to have a significant effect on prognosis compared to ERBD in patients undergoing hepatic resection for hepatobiliary tumors [20,21]. Since PTBD is performed percutaneously, there is a risk of wound infection or intra-abdominal abscess formation. In 2020, Hu et al. reported that PTBD was significantly associated with 30-day death or serious morbidity ($p=0.004$), overall surgical site infection ($p=0.019$), and superficial surgical site infection ($p=0.010$) [15]. ERBD was reported to have a significant effect on prognosis compared to PTBD in patients undergoing PD [22]. In 2014, Kitahata et al. reported that internal drainage is more likely to clog than external drainage and cause cholangitis, increasing the incidence of postoperative complications such as DGE [22]. Also, there is concern about tumor spreading when ERBD is directly placed on the tumor in AoV cancer. In 2017, Ahn et al. reported ERCP is an independent risk factor for postoperative recurrence in patients with AoV cancer [23].

In addition, by placing a stent in the surgical area, it is believed that inflammation and fibrosis of the surrounding tissue are induced, making it difficult to detach during surgery and prone to bleeding, especially in the case of metal stents [14,24]. Research on those issues is still lacking, and a consensus has not been reached.

In this study, these problems were reviewed and examined from various aspects. There was no significant difference in postoperative complication between PBD and NPBD except for chyle leak, operation time, intraoperative blood loss, and transfusion. It is thought that PBD has more CBD cancer patients and more retrieved LNs, which may be related to chyle leaks. It is believed that NPBD patients underwent surgery without decompressing the cholangitis, so the operation time was longer. The high incidence of cancer patients and vascular resection cases in PBD patients may be related to increased intraoperative bleeding and transfusion. This also showed a significantly higher recurrence rate in the disease-free survival curve. However, there was no difference in the overall survival curve. Therefore, even considering the unevenness of the data, it was difficult to see in our data that implementing PBD significantly increased postoperative complications known as wound problems, DGE, and mortality rates.

PTBD and ERBD also did not significantly differ in the occurrence of postoperative complications. However, although there was no statistically significant difference in the amount of bleeding between PTBD and ERBD patients, PTBD patients tended to receive slightly more intraoperative blood transfusions. It seems necessary to confirm the correlation with the fact that PTBD patients had more diabetes patients and high morbidity patients with ASA scores of 4 or higher. Due to the nature of retrospective studies, there is insufficient evidence as there was no control (collaboration with the anesthesia department) over the transfusion criteria and situations. As a result of analyzing whether the type of PBD affects long-term survival, our data showed no significant difference in survival. Whether there was a difference depending on the type of tumor, but there was no difference again. The type of PBD did not affect the independent risk factors affecting the survival rate.

In the case of PTBD, there are not many types of pigtail catheters, but in the case of ERBD, there are various types and materials of stents [24]. Therefore, we compared and analyzed them according to the ERBD material. It was divided mainly into metal stent and plastic stent, and there was no significant effect on the occurrence of postoperative complications. There was no significant effect on bleeding and operation time during surgery. In addition, the material of ERBD did not show a significant difference in survival. Based on the results of this study, the impact of PBD on the prognosis of PD patients does not overwhelm the oncologic characteristics of the tumor. In addition, regardless of the type of PBD, if there is no technical event associated with PBD during surgery, it does not significantly affect the occurrence of postoperative complications.

There are still many small institutions where ERBD and PTBD are performed in a limited manner. PBD is recommended to be performed appropriately to treat obstructive jaundice while PD patients wait for surgery. At this time, there is no restriction on the type of PBD to be performed, and the institution can consider any PBD that can be performed efficiently. Also, in the case of

ERBD, considering the semi-permanence of the stent, whether it is a plastic or metal stent, a metal stent is appropriately considered in cases where there is a long-term waiting period for surgery and palliative stenosis and maintenance of a plastic stent is difficult [25]. For any PBD, treating obstructive jaundice before surgery and treating inflammation before surgery can help the patients waiting for surgery.

This study has limitations due to its retrospective nature and has uneven data sizes depending on the type of PBD. First, ERBD was performed more often than PTBD in patients who underwent PD for PAT. There may be a bias in the data, but we confirmed no significant difference in the data characteristics between the two groups. In the future, when much PTBD data is secured, PSM analysis will be helpful for accurate analysis. Second, PAT patients include both benign and malignant tumor patients. Considering the limited PD data and the lack of data for each disease group, they were all included and analyzed. However, it would be helpful to conduct a comparative analysis by limiting tumors when a large amount of data is secured for a more accurate analysis. Third, this study does not include patients who underwent PBD, lost follow-up while waiting, or did not receive surgery. Therefore, it is limited in determining whether performing PBD has a better prognosis than not performing it. Fourth, this study only performed a comparative analysis of the most commonly used ERBD and PTBD. Although the data on ENBD and ERPD were insufficient to conduct the analysis, it would be helpful to analyze various types of PBD in the future. Fifth, this study did not limit the preoperative period of PBD. PBD is often performed not in the surgical department but in other hospitals or transferred to surgery after treatment in the internal medicine department. Therefore, it is not easy to completely control the situation of preoperative drainage treatment and collect data.

5. Conclusion

In conclusion, PAT shows similar short-term perioperative outcomes and long-term survival regardless of the type of PBD (PTBD versus ERBD) in patients with PD.

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Appendices 1

<Table 1> Total patients' baseline characteristics according to PBD

Variables	NPBD (n=520)	PBD (n=745)	*P value*
Age, years	63.18 ± 9.53	64.8 ± 9.73	0.005
Gender (M: F)	301 (57.9): 219 (42.1)	436 (58.5): 309 (41.5)	0.862
BMI, kg/m^2	23.51 ± 3.01	23.14 ± 2.93	0.031
Comorbidity			
HTN	217 (41.7)	299 (40.1)	0.601
DM	174 (33.5)	226 (30.3)	0.244
ASA score			0.567
1	39 (7.5)	72 (9.7)	0.190
2	280 (53.8)	387 (51.9)	0.529
3	196 (37.7)	277 (37.2)	0.860
4	5 (1.0)	9 (1.2)	0.789
Tumor location			<0.0001
Pancreas	302 (58.1)	242 (32.5)	<0.0001
AoV	82 (15.8)	175 (23.5)	0.001
CBD	101 (19.4)	322 (43.2)	<0.0001
Duodenum	35 (6.7)	6 (0.8)	<0.0001
Preoperative CA19-9, U/ml	102.43 ± 358.80	298.96 ± 1322.23	<0.0001
Preoperative Jaundice	85 (16.3)	361 (48.5)	<0.0001
Preoperative Cholangitis	2 (0.4)	19 (2.6)	0.003
Neoadjuvant chemotherapy	68 (13.1)	129 (17.3)	0.049
Adjuvant chemotherapy	235 (45.2)	404 (54.2)	0.002

Operation method			0.784
Open	392 (75.4)	571 (76.6)	0.639
Laparoscopic	88 (16.9)	115 (15.4)	0.484
Robot-assisted	40 (7.7)	59 (7.9)	0.916

Continuous variables are expressed as the mean ± standard deviation. Categorical variables are expressed as numbers (percentages).

NPBD: non-preoperative biliary drainage, PBD: preoperative biliary drainage, M: male, F: female, BMI: body mass index, HTN: hypertension, DM: diabetes mellitus, ASA: American Society of Anesthesiologists Physical Status Classification System, AoV: ampulla of Vater, CBD: common bile duct, CA19-9: carbohydrate antigen 19-9

<Table 2> Oncological outcomes according to PBD

Variables	NPBD (n=520)	PBD (n=745)	*P value*
Diagnosis			
PDAC	158 (30.4)	229 (30.7)	0.901
IPMN	106 (20.4)	10 (1.3)	<0.0001
NET	47 (9.0)	5 (0.7)	<0.0001
AOV cancer	79 (15.2)	174 (23.4)	<0.0001
CBD cancer	99 (19.0)	321 (43.1)	<0.0001
Duodenal cancer	31 (6.0)	6 (0.8)	<0.0001
Cell differentiation			
Well	56 (10.8)	117 (15.7)	0.013
Moderate	228 (43.8)	457 (61.3)	<0.0001
Poorly	56 (10.8)	116 (15.6)	0.016
Undifferentiation	1 (0.2)	22 (3.0)	<0.0001
Unknown	179 (34.4)	33 (4.4)	<0.0001

Tumor size, cm	2.57 ± 1.32	2.47 ± 1.14	0.182
Positive LN	1.09 ± 2.42	1.43 ± 2.68	0.017
Retrieved LN	16.16 ± 10.71	18.57 ± 10.85	<0.0001
Vascular resection	28 (5.4)	92 (12.3)	<0.0001
R status			0.379
R0	416 (80.0)	611 (82.0)	0.381
R1	101 (19.4)	123 (16.9)	0.264
R2	3 (0.6)	8 (1.1)	0.540
Perineural invasion	238 (45.8)	486 (65.2)	<0.0001
Lymphovascular invasion	148 (28.5)	269 (36.1)	0.005

Continuous variables are expressed as the mean ± standard deviation. Categorical variables are expressed as numbers (percentages).

NPBD: non-preoperative biliary drainage, PBD: preoperative biliary drainage, PDAC: pancreatic ductal adenocarcinoma, IPMN: intraductal papillary mucinous neoplasm, NET: neuroendocrine tumor, LN: lymph node, R: residual tumor

<Table 3> Postoperative complications according to PBD

Variables	NPBD (n=520)	PBD (n=745)	*P value*
POPF			0.957
No POPF	361(69.4)	511 (68.6)	0.758
Biochemical leak	94 (18.1)	137 (18.4)	**0.941**
Grade B	56 (10.8)	86 (11.5)	0.718
Grade C	9 (1.7)	11 (1.5)	0.820
Biliary leak	20 (3.8)	20 (2.7)	0.257
Chyle leak	19 (3.7)	50 (6.7)	0.023
DGE	82 (15.8)	140 (18.8)	0.177

Postoperative Bleeding	14 (2.7)	29 (3.9)	0.273
Intraabdominal Abscess	7 (1.3)	11 (1.5)	>0.999
Wound problem	35 (6.7)	55 (7.4)	0.739
Major complication (≥C-D grade III)	71 (13.7)	97 (13.0)	0.801
Operation time, min	528.02 ± 158.78	484.82 ± 223.75	<0.0001
Intraoperative blood loss, ml	405.72 ± 584.46	533.21 ± 526.73	<0.0001
Intraoperative transfusion	36 (6.9)	106 (14.2)	<0.0001
Hospital stay, days	19.0 ± 11.58	19.88 ± 10.47	0.160

Continuous variables are expressed as the mean ± standard deviation. Categorical variables are expressed as numbers (percentages).

NPBD: non-preoperative biliary drainage, PBD: preoperative biliary drainage, POPF: postoperative pancreatic fistula, DGE: delayed gastric emptying, C-D grade: Clavien-Dindo classification system

<Table 4> Postoperative complication according to the materials of ERBD (Metal vs. Plastic)

Variables	Metal (n=30)	Plastic (n=565)	*P value*
POPF			0.248
No POPF	26 (86.7)	382 (67.6)	0.028
Biochemical leak	3 (10.0)	108 (19.1)	0.212
Grade B	1 (3.3)	66 (11.7)	0.236
Grade C	0	9 (1.6)	>0.9999
Biliary leak	0	13 (2.3)	>0.9999
Chyle leak	2 (6.7)	36 (6.4)	>0.9999
DGE	3 (10.0)	115 (20.4)	0.166
Postoperative Bleeding	1 (3.3)	22 (3.9)	>0.9999

Intraabdominal Abscess	1 (3.3)	9 (1.6)	>0.406
Wound problem	1 (3.3)	40 (7.1)	0.713
Major complication (≥C-D grade III)	7 (23.3)	72 (12.7)	0.101
Operation time, min	401 (303.75-573.75)	500 (390.5-614.5)	0.047
Intraoperative blood loss, ml	400 (200-607.5)	350 (200-600)	0.993
Intraoperative transfusion	5 (16.7)	66 (11.7)	0.387
Hospital stay, days	19 (14-28.25)	17 (13-23)	0.215

Continuous variables are expressed as the mean ± standard deviation (SD). Categorical variables are expressed as numbers (percentages).

POPF: postoperative pancreatic fistula, DGE: delayed gastric emptying, C-D grade: Clavien-Dindo classification system, ERBD: endoscopic retrograde biliary drainage

Appendices 2

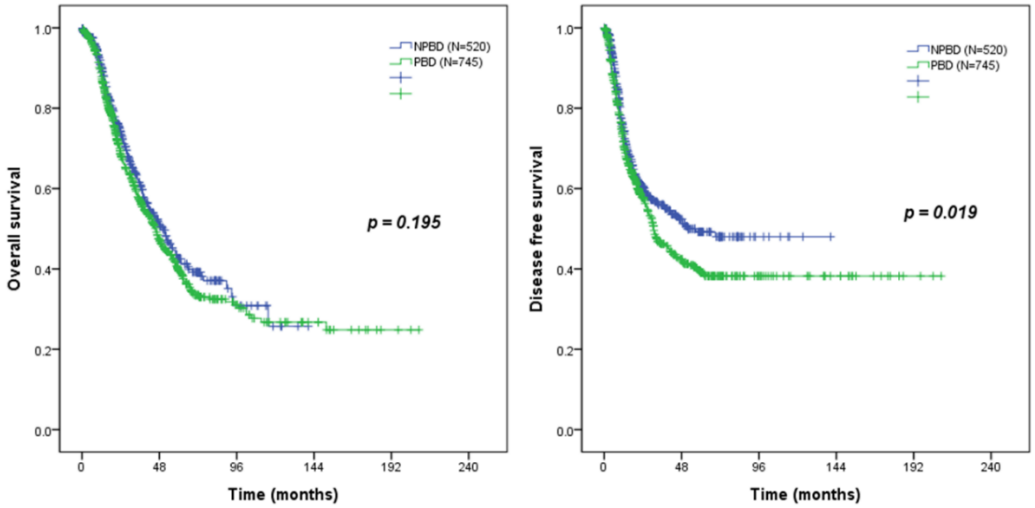

Figure 1 Kaplan-Meier survival curve of overall survival and disease-free survival according to preoperative biliary drainage. There was no statistically significant difference in overall survival and disease-free survival between the preoperative biliary drainage group (PBD) and non-preoperative biliary drainage group (NPBD).

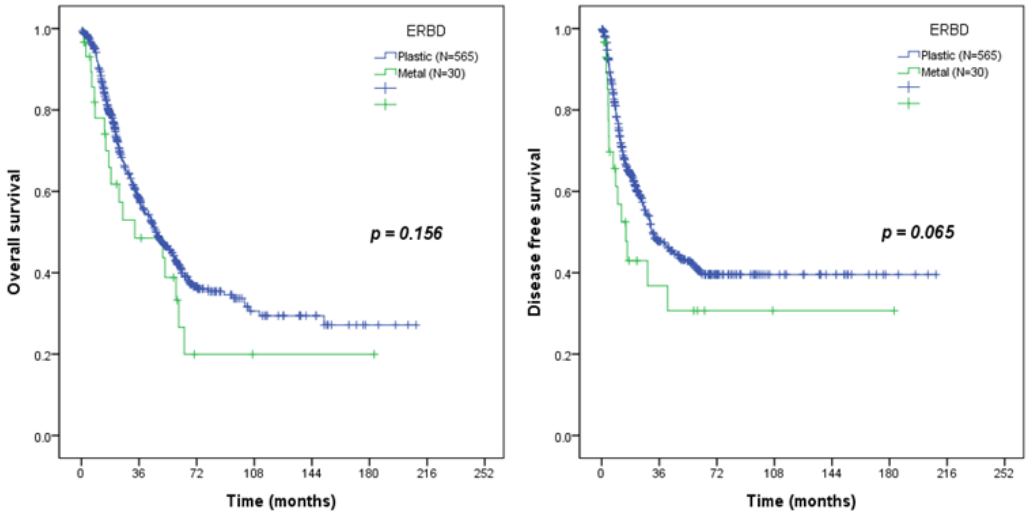

Figure 2 Kaplan-Meier survival curve of overall survival and disease-free survival according to the material of endoscopic retrograde biliary drainage (ERBD). The material of ERBD is divided into plastic and metal stents. There was no statistically significant difference in overall survival and disease-free survival between the plastic stent group and the metal stent group.

Abstract in Korean

팽대부주위종양으로 췌십이지장절제술 환자의 수술 전 담즙 배액술 (경피경간 담즙배액술, 내시경적 역행성 담즙배액술) 에 따른 예후 비교

연구 배경 및 목적: 본 논문의 목적은 수술 전 담즙 배액술(BD)의 종류(경피적 경간 담즙 배액술, PTBD 또는 내시경적 역행성 담즙 배액술, ERBD)가 팽대부주위종양(PAT)으로 췌장십이지장절제술(PD)을 받은 환자의 예후에 미치는 영향을 확인하는 것입니다.

연구 재료 및 방법: 본 후향적 단일 기관 연구는 2006년 6월부터 2021년 3월까지 세브란스병원에서 PAT로 PD을 받은 환자들을 대상으로 했습니다. 수술 전 PTBD또는 ERBD을 시행한 환자를 포함하여 총 1,265명의 환자를 후향적으로 분석했습니다.

연구 결과: 총 1,265명의 환자를 수술 전 BD를 시행한 환자군(PBD, N=745)과 수술 전 BD를 시행하지 않은 환자군(NPBD, N=520)으로 나누었습니다. PBD군은 수술 전 황달과 담관염이 더 많았습니다($p<0.001$, $p=0.003$). 두 군 간에 수술 후 합병증 발생률은 통계적으로 유의미한 차이가 없었습니다. NPBD군은 수술 시간이 더 길었고 ($p<0.001$), PBD군은 수술 중 수혈이 더 많았습니다(0.003). 총 745명의 PBD 환자를 PTBD(N=105), ERBD(N=613), PTBD & ERBD(N=18), ERPD(N=9)의 네 그룹으로 나누었습니다. PTBD와 ERBD 간에 수술 후 합병증 발생률에 통계적으로 유의한 차이는 없었습니다. PTBD와 ERBD 간에 전체 생존율과 무병 생존율에 통계적으로 유의한 차이는 없었습니다($p=0.063$, $p=0.584$). 예후 인자에 대한 다변량 분석에서 수술 전 BD는 전체 생존율과 무병 생존율에 유의미한 영향을 주지 않았습니다 ($p=0.357$, $p=0.876$).

결론: PAT는 PD 환자의 수술 전 BD 종류(PTBD 대 ERBD)에 관계없이 유사한 단기간 수술 결과와 장기간 생존 결과를 보여줍니다.

핵심되는 말 : 팽대부주위종양, 췌십이지장절제술, 담즙배액술