

Negative Impact of Preoperative Endoscopic Biliary Drainage on Prognosis of Pancreatic Ductal Adenocarcinoma After Pancreaticoduodenectomy

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Abstract. *Background/Aim:* Patients with obstructive jaundice due to cancer of the pancreatic head often undergo preoperative endoscopic biliary drainage (EBD). The aim of the study was to evaluate the long-term impact of preoperative EBD following pancreaticoduodenectomy (PD) for pancreatic ductal adenocarcinoma. *Patients and Methods:* We studied 106 patients who underwent PD for pancreatic ductal adenocarcinoma between May 2000 and November 2013 at the Jikei University Hospital. We retrospectively examined perioperative findings as predictors of prognosis and the relationship between preoperative EBD and recurrence rate as well as overall survival. *Results:* In univariate analysis, significant factors associated with poor disease-free survival consisted of the presence of EBD ($p=0.0213$), poor tumor differentiation ($p=0.0023$) and tumor-node-metastasis (TNM) classification IV ($p=0.0027$), while significant factors associated with poor overall survival consisted of the presence of EBD ($p=0.0047$), poor tumor differentiation ($p<0.0001$), TNM classification IV ($p=0.0031$) and microscopic or macroscopic residual tumor ($p=0.0184$). In multivariate analysis, poor tumor differentiation ($p=0.0033$) and TNM classification IV ($p=0.0020$) were independent factors for poor disease-free survival, while the presence of EBD ($p=0.0435$), poor tumor differentiation ($p=0.0009$), TNM classification IV ($p=0.0447$) and microscopic or macroscopic residual tumor ($p=0.0184$) were independent factors for poor overall survival. *Conclusion:* Preoperative EBD may have a negative impact on prognosis after PD for pancreatic ductal adenocarcinoma.

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Obstructive jaundice is the most common symptom in patients with periampullary cancer, including ductal adenocarcinoma of the pancreatic head. In the absence of radiological signs of locoregional unresectable or metastatic disease, surgical resection is the only potentially curative treatment for pancreatic ductal adenocarcinoma (1). Because surgery for jaundiced patients is thought to increase the risk of perioperative complications, preoperative biliary drainage is often performed (2). In several experimental studies and retrospective case series, preoperative biliary drainage reduced morbidity and mortality after surgery (3, 4). However, a multicenter and randomized trial showed that the complication rate in patients undergoing preoperative biliary drainage was higher than that in patients who proceeded directly to surgery (5). Therefore, the value of preoperative biliary drainage as a routine procedure for alleviating obstructive jaundice remains controversial. The most common method of achieving preoperative biliary drainage is by endoscopic retrograde cholangiopancreatography and stent placement (6). For malignant colonic obstruction, self-expanding metallic stent insertion has been suggested as a promising alternative to emergency surgery (7). Recently, Sabbagh *et al.* reported that overall survival of patients with left-sided malignant colonic obstruction with self-expanding metallic stent insertion is worse as compared with immediate surgery (8). The worse prognosis associated with stent insertion may be related to compression of the tumor.

The aim of this study was to evaluate the long-term impact of preoperative endoscopic biliary drainage (EBD) following pancreaticoduodenectomy (PD) for pancreatic ductal adenocarcinoma.

Patients and Methods

Between May 2000 and November 2013, 107 consecutive patients underwent PD for pancreatic ductal adenocarcinoma in the Department of surgery, Jikei University Hospital, Tokyo, Japan. Of these, one patient was excluded due to lack of data, leaving the remaining 106 patients for the study. Preoperatively, patients with

Table I. Patient's characteristics.

Factor	Median or number	Range or %
Age (years)	68	37-83
Gender		
Male	61	58%
Female	45	42%
Concomitant diabetes mellitus		
Present	37	35%
Absent	69	65%
Preoperative biliary drainage		
Endoscopic biliary drainage	46	43%
Percutaneous biliary drainage	15	14%
Absent	45	42%
Preoperative serum T-bil (mg/dl)	1.2	0.4-11.8
Duration of operation (min)	545	330-992
Intraoperative blood loss (mL)	963	200-37,010
Portal vein reconstruction		
Present	24	23%
Absent	82	77%
Postoperative hospital stay (days)	25	12-386
Surgical site infection		
Present	13	12%
Absent	93	88%
Pulmonary complications		
Present	14	13%
Absent	92	87%
Postoperative pancreatic fistula		
B or C	11	10%
A or absent	95	90%
Tumor differentiation		
Well or moderately	95	90%
Poorly	11	10%
TNM classification		
0 or I	4	4%
II	14	13%
III	58	55%
IV	30	28%
Curability		
R0	72	68%
R1 or 2	34	32%
Adjuvant chemotherapy		
Present	79	75%
Absent	27	25%

T-bil: Total bilirubin, TMN: tumor-nodes-metastasis, R0: microscopic curative resection, R1: microscopic residual tumor, R2: macroscopic residual tumor.

jaundice or suspicion of obstruction of the common bile duct underwent endoscopic retrograde cholangiopancreatography. If biliary obstruction was detected, a biliary plastic stent or an endoscopic nasobiliary tube was placed (EBD). Otherwise, the patient underwent percutaneous transhepatic external biliary drainage. Tumor-Nodes-Metastasis (TNM) staging was based on the sixth Japanese edition of the General Rules for the Study of Pancreatic Cancer of 2009 (9). Postoperatively, the patients received adjuvant chemotherapy using gemcitabine or S-1, excluding the patients diagnosed with stage 0 disease or those who refused

Table II. Univariate analysis of disease-free and overall survival after pancreaticoduodenectomy for pancreatic ductal adenocarcinoma.

Factor	N	Disease-free survival		Overall survival	
		Median (years)	p-value	Median (years)	p-value
Age (years)					
<65	40	0.62	0.1156	1.45	0.7770
≥65	66	0.82		1.28	
Gender					
Male	61	0.74	0.4204	1.31	0.1745
Female	45	0.74		1.39	
Concomitant diabetes mellitus					
Present	37	0.64	0.6858	1.15	0.3195
Absent	69	0.75		1.42	
Preoperative biliary drainage					
Present	61	0.62	0.0674	1.18	0.0612
Absent	45	1.10		1.81	
Endoscopic biliary drainage					
Present	46	0.60	0.0213	1.12	0.0047
Absent	60	1.10		1.70	
Portal vein reconstruction					
Present	24	0.55	0.2093	1.19	0.1091
Absent	82	0.78		1.43	
Surgical site infection					
Present	13	0.64	0.2041	1.22	0.6487
Absent	93	0.79		1.39	
Pulmonary complications					
Present	14	0.50	0.8741	1.15	0.1772
Absent	92	0.75		1.43	
Postoperative pancreatic fistula					
B or C	11	0.75	0.8519	1.15	0.8978
A or absent	95	0.74		1.42	
Tumor differentiation					
Well or moderately	95	0.79	0.0023	1.44	<0.0001
Poorly	11	0.47		0.77	
TNM classification					
IV	30	0.74	0.0027	1.36	0.0031
Others	76	0.82		1.52	
Curability					
R0	72	0.87	0.0809	1.61	0.0184
R1 or 2	34	0.58		1.14	
Adjuvant chemotherapy					
Present	79	0.79	0.8579	1.44	0.8010
Absent	27	0.52		1.08	

TMN: Tumor-nodes-metastasis, R0: microscopic curative resection, R1: microscopic residual tumor, R2: macroscopic residual tumor.

treatment. After June 2011, almost all patients received adjuvant chemotherapy using gemcitabine and intra-arterial transfusion of nafamostat mesilate, which is now an ongoing phase II clinical trial for patients with pancreatic ductal adenocarcinoma after pancreatic resection at our hospitals (10).

Firstly, we retrospectively investigated the relationship between clinical variables and disease-free or overall survival after PD in patients with pancreatic cancer by univariate and multivariate

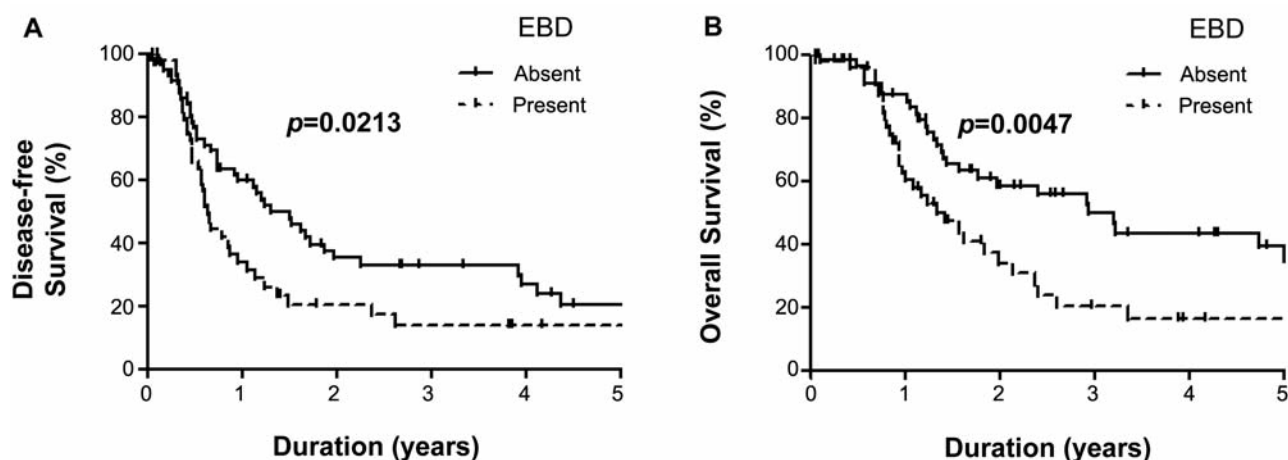


Figure 1. Kaplan-Meier curves of disease-free (A) and overall (B) survival in relation to endoscopic biliary drainage (EBD) in patients after pancreaticoduodenectomy for pancreatic ductal adenocarcinoma.

analyses. The analysis included the following 13 factors: age, gender, diabetes mellitus, preoperative biliary drainage, EBD, portal vein reconstruction, surgical site infection, postoperative pulmonary complications, postoperative pancreatic fistula, tumor differentiation, TNM classification based on tumor pathology, curability and adjuvant chemotherapy.

We then analyzed patient characteristics in relation to EBD, using the following 15 factors: age, gender, diabetes mellitus, preoperative serum total bilirubin, duration of operation, intraoperative blood loss, portal vein reconstruction, postoperative hospital stay, surgical site infection, postoperative pulmonary complications, postoperative pancreatic fistula, tumor differentiation, TNM classification based on tumor pathology, curability and adjuvant chemotherapy.

Recurrence of pancreatic cancer was defined as newly detected hypovascular abdominal or extra-abdominal tumors by computed tomography (CT), magnetic resonance imaging (MRI), with or without an increase in tumor markers. For recurrence of pancreatic cancer, chemotherapies or conversion to other chemotherapy were given based on performance status.

Postoperative pancreatic fistula was defined by the guideline of the International Study Group on Pancreatic Fistula (ISGPF) (11). Postoperative pancreatic fistula is classified into three categories by the ISGPF as follows: transient pancreatic fistula (no clinical impact; grade A); fistula requiring a change in management or adjustment in the clinical pathway (grade B); fistula requiring a major change in clinical management or deviation from the normal clinical pathway (grade C). Grade B and C were defined as postoperative pancreatic fistula in this study.

This study was approved by the Ethics Committee of the Jikei University School of Medicine (21-121).

Statistical analysis. The data are expressed as the mean±standard deviation (SD). Univariate analysis was performed using the log-rank test, non-paired *t*-test and Chi-square test. Multivariate analyses were performed using the Cox proportional regression model. All *p*-values were considered statistically significant when the associated probability was less than 0.05.

Table III. Multivariate analysis of disease-free survival after pancreaticoduodenectomy.

Factor	Odds ratio (95% CI)	<i>p</i> -Value
Endoscopic biliary drainage (Present)	1.445 (0.898-2.324)	0.1292
Pathologic grade (Poorly)	3.111 (1.459-6.631)	0.0033
TNM classification (IV)	2.185 (1.331-3.587)	0.0020

CI: Confidence interval, TMN: tumor-nodes-metastasis.

Table IV. Multivariate analysis of overall survival after pancreaticoduodenectomy.

Factor	Odds ratio (95% CI)	<i>p</i> -Value
Endoscopic biliary drainage (Present)	1.716 (1.016-2.900)	0.0435
Pathologic grade (Poorly)	3.540 (1.679-7.466)	0.0009
TNM classification (IV)	2.067 (1.210-3.530)	0.0078
Curability (R1 or 2)	1.723 (1.013-2.930)	0.0447

CI: Confidence interval, TMN: tumor-nodes-metastasis, R1: microscopic residual tumor, R2: macroscopic residual tumor.

Results

Patient's characteristics. Characteristics of the patients, and preoperative, intraoperative and postoperative variables and course are listed in Table I. A total of 61 patients (58%) underwent preoperative biliary drainage. Out of these, 46 received EBD (biliary plastic stent in 40 and nasobiliary tube in six) and 15 received percutaneous transhepatic biliary

Table V. Univariate analysis of patients characteristics in relation to preoperative endoscopic biliary drainage.

Factor	Endoscopic biliary drainage		p-Value
	Present (n=46)	Absent (n=60)	
Age (years)	66.3±9.5	66.5±10.4	0.9343
Gender (Male:Female)	27:19	34:26	0.8341
Concomitant diabetes mellitus (Present:Absent)	15:31	22:38	0.6640
Preoperative serum T-bil (mg/dl)	2.3±2.0	1.8±2.1	0.2334
Duration of operation (min)	576.3±104.9	538.6±133.5	0.1174
Intraoperative blood loss (mL)	1,484.8±1,525.5	2,041.7±4,975.9	0.4656
Portal vein reconstruction (Present:Absent)	12:34	12:48	0.4580
Postoperative hospital stay (days)	25.1±12.0	37.4±49.6	0.1027
Surgical site infection (Present:Absent)	7:39	6:54	0.4170
Pulmonary complications (Present:Absent)	5:41	9:51	0.5336
Postoperative pancreatic fistula (B or C:A or Absent)	6:40	5:55	0.4306
Tumor differentiation (Well or moderately:Poorly)	41:5	54:6	0.8843
TNM classification (IV:others)	15:31	15:45	0.3887
Curability (R0:R1 or 2)	31:15	41:19	0.9180
Adjuvant chemotherapy (Present:Absent)	34:12	45:15	0.8987
In-hospital mortality (Present:Absent)	1:45	2:58	0.7213

^aMean±SD, T-bil: Total bilirubin, TMN: tumor-nodes-metastasis, R0: microscopic curative resection, R1: microscopic residual tumor, R2: macroscopic residual tumor.

drainage. By TNM classification, the patients were staged with disease as follows: 0 (n=1), I (n=3), II (n=14), III (n=58) and IV (n=30). In this period, in-hospital mortality was 2.8% (3 patients).

Univariate and multivariate analysis of disease-free survival and overall survival. Table II lists the relationship between the clinical variables and disease-free as well as overall survival after PD in patients with pancreatic ductal adenocarcinoma. In univariate analysis, the presence of EBD ($p=0.0213$, Figure 1A), poorly differentiated tumor ($p=0.0023$) and TNM classification IV ($p=0.0027$) were associated with significantly poor disease-free survival. The presence of EBD ($p=0.0047$, Figure 1B), poorly differentiated tumor ($p<0.0001$), TNM classification IV ($p=0.0031$) and microscopic or macroscopic residual tumor ($p=0.0184$) were associated with significantly poor overall survival. In multivariate analysis, poor tumor differentiation ($p=0.0033$) and TNM classification IV ($p=0.0020$) were independent factors associated with poor disease-free survival (Table III). For survival, the presence of EBD ($p=0.0435$), poorly differentiated tumor ($p=0.0009$), TNM classification IV ($p=0.0447$) and microscopic or macroscopic residual tumor ($p=0.0184$) were independent factors of poor overall survival (Table IV).

Association between patient characteristics and EBD. Table V lists the association between patient characteristics and EBD. Univariate analysis demonstrated that all factors in regard to EBD were comparable.

Discussion

To our knowledge, this is the first report to suggest that preoperative EBD may have a negative impact on prognosis after PD for pancreatic cancer. A Cochrane review of randomized trials comparing preoperative biliary drainage versus early surgery without preoperative biliary drainage in patients with obstructive jaundice has been reported (12). Four trials used percutaneous transhepatic biliary drainage and two used EBD. There was no significant difference in the overall mortality between the two groups. However, the majority of trials were carried out prior to 1994 and many of the surgeries were bypass or palliative resections. Furthermore, various forms of percutaneous and endoscopic drainage procedures were used in these trials. Therefore, the mechanism of the negative impact on prognosis is still unclear. Maruthachalam *et al.* have reported that insertion of a self-expanding metallic stent increase the level of circulating neoplastic cells in patients with obstructive colorectal cancer (13). Tumor compression by EBD may therefore lead to the dissemination of cancer cells, resulting in poor prognosis.

Although the oncological significance of routine preoperative biliary drainage remains controversial, selective groups of patients who benefit from this include those with cholangitis, symptomatic jaundice such as pruritus, and those with primary unresectable or borderline-resectable disease undergoing neoadjuvant therapy. A prospective randomized controlled trial which compared endoscopic and

percutaneous drainage reported that the endoscopic group had higher success rates and lower complication rates (17). The majority of the complications in the percutaneous group were bile leak, abscess, cholangitis and fistula. Further assessment of tumor recurrence and patient survival by EBD and percutaneous biliary drainage may improve outcome after pancreatic resection for pancreatic ductal adenocarcinoma with obstructive jaundice.

The major limitation of the current study is its retrospective and single-institutional design. Considering the only study, it is difficult to recommend percutaneous transhepatic biliary drainage as the first-line method of drainage.

In conclusion, preoperative EBD may have a negative impact on prognosis after PD for pancreatic ductal adenocarcinoma.

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