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Clinicopathological difference between invasive pancreatic duct cancer and distal bile duct cancer of the pancreas head after pancreaticoduodenectomy

Masahide Ikeguchi, Kanenori Endo

ABSTRACT

Aims: The only curative treatment for patients with invasive pancreatic duct cancer (IPDC) and distal bile duct cancer (DBDC) of the pancreas head is pancreaticoduodenectomy (PD). However, the clinicopathological difference between IPDC and DBDC after PD has not been thoroughly discussed. In this study, we retrospectively analyzed the clinical and pathological difference between IPDC and DBDC in patients who underwent PD. **Methods:** Sixty-six patients who underwent curative PD were enrolled (IPDC, n = 35; DBDC, n = 31). Preoperative, intraoperative, and postoperative parameters and pathological factors (stages, lymph node metastasis, lymphatic invasion, vascular invasion, and perineural invasion) were compared. **Results:** Jaundice was frequently detected and preoperative biliary drainage was frequently performed in patients with DBDC (60.5% and 90.3%, respectively). Additionally, the preoperative serum total bilirubin concentration and C-reactive protein/albumin ratio were higher in patients with DBDC than IPDC. As a result, the occurrence of postoperative pancreatic fistula occurred more frequently in patients with DBDC. In contrast, lymph node metastasis, lymphatic invasion, and vascular invasion were detected more frequently in patients with IPDC. The overall 5-year survival rate of the 35 patients with IPDC (13.4%) was much worse than that of the 31 patients with DBDC (52.3%, $p < 0.001$). **Conclusion:** The oncological characteristics of IPDC are much different from those of DBDC. More effective treatment should be started in patients with IPDC as soon as possible.

Keywords: Distal bile duct cancer, Invasive pancreatic duct cancer, Pancreaticoduodenectomy, Prognosis

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INTRODUCTION

Patients with invasive pancreatic duct cancer (IPDC) of the pancreas head or distal bile duct cancer (DBDC) present similar clinical manifestations, such as jaundice and abdominal pain. In general, the diagnosis of IPDC and DBDC is based on histomorphological evaluation of endoscopic biopsy specimens using pretreatment endoscopic retrograde cholangiopancreatography (ERCP). The histological type of both pancreatic and biliary tract cancers is typically adenocarcinoma [1, 2]. Because of their anatomical and histopathological similarity, the distinction between IPDC and DBDC is sometimes difficult before treatment, even with the use of ERCP, computed tomography, or magnetic resonance imaging [3].

However, the treatment method is simple because surgical resection is the only established potentially curative treatment for patients with IPDC and DBDC.

However, the clinicopathological differences between IPDC and DBDC after pancreaticoduodenectomy (PD) have not been thoroughly discussed. In this study, we retrospectively analyzed the clinical and pathological differences between IPDC and DBDC in patients who underwent PD.

MATERIALS AND METHODS

Patients

From 2006 to 2018, 102 patients who were diagnosed with operable periampullary or pancreas head cancer underwent PD at Tottori Prefectural Central Hospital. The preoperative locations of tumors were diagnosed by computed tomography, magnetic resonance imaging, and retrograde cholangiopancreatography using ERCP. Of these patients, we enrolled 35 patients with IPDC and 31 patients with DBDC (histopathologically confirmed) in the present study. In the present study, we focused the clinicopathological differences between IPDC and DBDC, the remaining 36 patients diagnosed as duodenal cancer including cancer arising from papilla Vater excluded from this study. These 66 patients (35 patients with IPDC and 31 patients with DBDC) underwent curative PD (no residual tumors macroscopically). The patients were followed up at Tottori Prefectural Central Hospital until October 2019. No patients received chemotherapy or radiation therapy before the operation. Informed consent for medical treatment and use of clinical data from the medical records were obtained from all patients. This study was approved by the ethics review board of Tottori Prefectural Central Hospital (approval number: 2019-57).

Preoperative data

We recorded the patients' preoperative parameters, including the occurrence of jaundice and a history of smoking or alcohol intake. Blood samples were routinely taken from each patient before the operation. The fasting blood sugar level, serum amylase level, serum total bilirubin level (the preoperative bilirubin was after drainage), serum albumin level, C-reactive protein level, total lymphocyte count, and tumor marker levels (carcinoembryonic antigen and carbohydrate antigen 19-9) were recorded. The C-reactive protein/albumin ratio (CAR), neutrophil/lymphocyte ratio (NLR), and prognostic nutritional index (PNI) were calculated preoperatively. The PNI was calculated using the following formula: 10 × serum albumin concentration (g/dL) + 0.005 × lymphocyte count (cells/mm^3) in the peripheral blood [4]. The CAR has been used in combination with other parameters to not only diagnose chronic inflammation but also assess the nutritional status of patients with cancer. Additionally, the pretreatment CAR has been shown to be a significant prognostic indicator in various carcinomas [5–7]. Also, the NLR and PNI are markers of chronic systemic inflammation and the patients' immune status and nutritional condition [8–10]. We analyzed and compared these CAR, NLR, and PNI (prognostic markers of cancer patients) in different type of carcinomas.

Surgical procedures and intraoperative parameters

All patients underwent open laparotomy. Reconstruction after PD with or without partial resection of the portal vein was performed by Child's method. Pancreaticojejunostomy was performed and an internal short stent was placed across the pancreaticojejunostomy, but no stent was placed following choledochojejunostomy. The operation time and intraoperative blood loss were compared between the two groups.

Pathological parameters

Clinical and pathological staging of IPDC and DBDC was performed using the American Joint Committee on Cancer TNM staging system, 6th edition [11]. The positive cases of lymphatic invasion, vascular invasion, and perineural invasion of tumor cells were compared between the two groups.

Postoperative parameters

Postoperative complications were analyzed by reviewing the patients' clinical data. The severity of postoperative complications was graded according to the Clavien–Dindo classification [12]. Clavien–Dindo grade ≥III complications were considered major complications. Postoperative pancreatic fistula (POPF) was defined and classified by the international study group of pancreatic fistula (ISGPF) [13]. Grade B (symptomatic, clinically apparent, and requires diagnostic evaluation and specific medical treatment or prolonged drainage for longer than three weeks) and grade C (requires a major change in clinical management or deviation from the normal clinical pathway) were considered as POPF in this study. The occurrence of POPF, the hospital stay, operation-related death, and overall survival (OS) were compared between the groups.

Statistical analysis

Differences between two normally distributed parameters were compared using the χ^2 test and Fisher's exact probability test. The Mann–Whitney *U* test was used to compare differences between two parameters with non-normal distributions. Long-term OS was calculated using the Kaplan–Meier method, and the prognostic difference between the two groups was compared using the log-rank test. All data were analyzed by StatView software (Abacus Concepts, Inc., Berkeley, CA, USA). A p value of <0.05 was considered statistically significant.

RESULTS

The patients' preoperative details are shown in Tables 1 and 2. Jaundice was frequently detected and preoperative biliary drainage was frequently performed in patients with DBDC (60.5% and 90.3%, respectively). Thus, the preoperative serum total bilirubin concentration and CAR were higher in patients with DBDC than IPDC. Glucose tolerance abnormalities were more frequently detected in patients with IPDC than DBDC. In contrast, the mean preoperative serum carbohydrate antigen 19-9 level was significantly higher in patients with DBDC than IPDC. In both groups, accurate preoperative diagnoses were obtained in >85% of patients (Table 1).

Pathologically, lymph node metastasis, lymphatic invasion, and vascular invasion were detected more frequently in patients with IPDC than DBDC. However, the rate of perineural invasion was similar in both groups. Thus, the pathological stages were more advanced in patients with IPDC than DBDC (Table 3).

No difference was found in the operation time or intraoperative blood loss between the two groups, but combined partial resection of the portal vein was performed more frequently in patients with IPDC than DBDC. Major postoperative complications occurred in 34/66 (51.5%) patients (IPDC, 14/35 [40.0%] and DBDC, 20/31 [64.5%]). Among the complications, POPF occurred more frequently in patients with DBDC than IPDC. Four patients (IPDC, n = 2; DBDC, n = 2) died of postoperative peritonitis secondary to leakage at the pancreaticojejunostomy site at one month (n = 2), two months (n = 1), and eight months (n = 1) postoperatively. Thus, the operative mortality rate in our series was 6.1% (Table 4). The OS rates, including the deaths from operative complications, were quite different between the two groups (Figure 1). The overall 5-year survival rate of the 31 patients with DBDC (52.3%) was much better than that of the 35 patients with IPDC (13.4%, $p < 0.001$).

DISCUSSION

IPDC and DBDC are major malignant tumors arising from the pancreas head, and the histological type of both cancers is adenocarcinoma. Although the two tumors have many similarities, their oncological behaviors are quite different. Yokoyama et al. [14] reported that the incidence rates of overall morbidity, infectious complications, and pancreatic fistula were significantly higher in patients with DBDC than IPDC. They concluded that the main reasons for this difference were a significantly smaller main pancreatic duct diameter and higher incidence of a soft pancreas (95% vs. 29%) in patients with DBDC than IPDC. Indeed, in our study, POPF more frequently occurred in patients with DBDC (64.5%) than IPDC (31.4%), and the difference was significant ($p < 0.007$). However, we could not prove the correlation between the occurrence of POPF and the pancreatic duct diameter or incidence of a soft pancreas individually because we did not check these parameters at the time of the operations. However, we found that obstructive jaundice and preoperative biliary drainage were more frequent and that the preoperative serum total bilirubin concentration and CAR were significantly higher in patients with DBDC than IPDC. These facts indicate that high inflammation and a poor nutritional condition may continue until immediately before the operations in these patients.

In cases with tumors of pancreas head, distal bile duct, and papilla Vater, we usually did endoscopic biopsy using ERCP, and at that time, when we decided obstruction of bile duct, we basically performed the stent insertion to bile duct to reduce serum bilirubin level and control inflammation of the bile duct in our department. However, in this study, we found high percentage of POPF in patients with DBDC. It is difficult to decide biliary drainage may cause the POPF or not. Further studies should be needed to improve the correlation between biliary drainage and the occurrence of POPF after PD, and we may change our strategy for biliary drainage in patients with obstructive jaundice. A recent

Table 1: Preoperative clinical differences between the two groups

	IPDC (n = 35)	DBDC (n = 31)	p
Gender (male/female)	22/13	22/9	0.485
Mean age (years, SD)	72.5 (8.1)	75.4 (8.2)	0.113
Mean BMI (SD)	22.3 (3.4)	22.3 (2.9)	0.512
Both consumption of tobacco and alcohol (yes, %)	10 (28.6%)	11 (35.5%)	0.547
Occurrence of jaundice (yes, %)	15 (39.5%)	23 (60.5%)	0.01
Preoperative biliary drainage (yes, %)	18 (51.4%)	28 (90.3%)	0.001
Accurate preoperative diagnosis (yes, %)	30 (85.7%)	29 (93.5%)	0.536

BMI: body mass index, DBDC: distal bile duct cancer, IPDC: invasive pancreatic duct cancer, SD: standard deviation.

Table 2: Preoperative laboratory data between the two groups

	IPDC (n = 35)	DBDC (n = 31)	p
Mean total bilirubin (mg/dL, SD)	1.7 (1.8)	2.2 (2.5)	0.165
Mean fasting blood sugar (mg/dL, SD)	158.3 (70.9)	115.6 (22.7)	0.001
Mean serum amylase (U/L, SD)	108.1 (83.9)	106.6 (59.8)	0.375
Mean CEA levels (ng/mL, SD)	6.6 (8.3)	4.5 (2.6)	0.492
Mean CA 19-9 levels (U/mL, SD)	481.7 (646.4)	744.6 (3677.9)	0.003
Mean CAR levels (SD)	0.13 (0.23)	0.53 (1.06)	0.042
Mean NLR levels (SD)	2.3 (0.8)	2.7 (2)	0.883
Mean PNI levels (SD)	44.7 (6.9)	43.8 (7.9)	0.521

CA 19-9: carbohydrate antigen 19-9, CAR: C-reactive protein/albumin ratio, CEA: carcinoembryonic antigen, DBDC: distal bile duct cancer, IPDC: invasive pancreatic duct cancer, NLR: neutrophil/lymphocyte ratio, PNI: prognostic nutritional index, SD: standard deviation.

Table 3: Pathological differences between the two groups

	IPDC (n = 35)	DBDC (n = 31)	p
Tumor stage			
IA	3	4	0.012
IB	0	6	
IIA	5	5	
IIB	23	9	
III	4	7	
Positive of lymph node metastasis (%)	26 (74.3)	10 (32.3)	0.001
Positive of lymphatic invasion (%)	30 (85.7)	18 (58.1)	0.012
Positive of vascular invasion (%)	33 (94.3)	17 (54.8)	<0.001
Positive of perineural invasion (%)	29 (82.9)	24 (77.4)	0.579

DBDC: distal bile duct cancer, IPDC: invasive pancreatic duct cancer.

Table 4: Intraoperative and postoperative differences between the two groups

	IPDC (n = 35)	DBDC (n = 31)	p
Mean operation time (minutes, SD)	376 (101.5)	387.8 (116.9)	0.7
Partial resection of portal vain (number, %)	6 (17.1)	1 (3.2)	0.067
Mean intraoperative blood loss (mL, SD)	946.7 (497)	1146.1 (1049.9)	0.829
Blood transfusion (yes, %)	11 (31.4)	11 (35.5)	0.656
Occurrence of POPF (%)	11 (31.4)	20 (64.5)	0.007
Mean postoperative hospital stay (days, SD)	37.7 (37.6)	45.1 (39.4)	0.385
Operation-related death (%)	2 (5.7)	2 (6.5)	0.9
Overall 5-year survival rate (%)	13.4%	52.3%	<0.001

DBDC: distal bile duct cancer, IPDC: invasive pancreatic duct cancer, POPF: postoperative pancreatic fistula, SD: standard deviation.

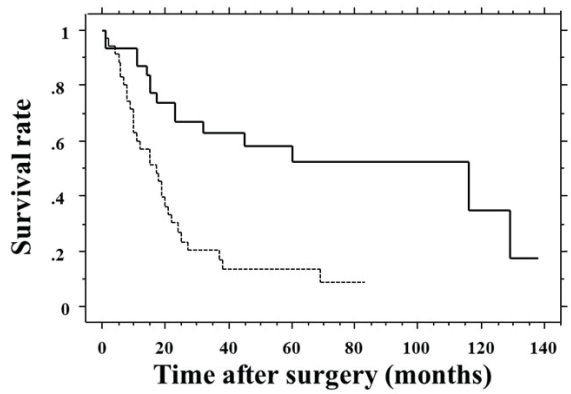

Figure 1: The 5-year overall survival rate of the 31 patients with DBDC (solid line) was much better than that of the 35 patients with IPDC (dotted line, p < 0.001).

report indicated that early surgery following preoperative biliary drainage reduced the occurrence of POPF. Shin et al. [15] recommended the performance of PD within two weeks after biliary drainage in patients with obstructive jaundice.

Notably, however, the prognosis of patients with IPDC is significantly worse than that of patients with DBDC. Kim et al. [16] reported that the 5-year OS rate of patients with DBDC was 50.3% and that of patients with IPDC was 13.0%, respectively (p < 0.001). Additionally, Pomianowska et al. [17] reported that the 5-year OS rate was 6% for IPDC and 26% for DBDC. The authors also reported that lymph node involvement was more frequently detected in IPDC (75%) than in DBDC (57%). In the present study, lymphatic invasion and vascular invasion were detected more frequently in patients

with IPDC than DBDC. This difference in the invasive ability of cancer cells may underlie the prognostic difference between IPDC and DBDC. Gonzalez et al. [18] concluded that smaller tumor size, lower rate of margin positivity, earlier onset of symptoms, increased ease of total resection due to tumor location, and the relatively younger mean age of DBDC patients compared to IPDC patients may be the main reason of better prognosis of patients with DBDC. Few papers have described the biological differences between pancreatic cancer cells and cholangiocarcinoma cells. Takenami et al. [19] concluded that five proteins and two biomarker panels are promising for distinguishing pancreas head cancer from distal bile duct cancer. These biomarkers may help to distinguish IPDC from DBDC.

CONCLUSION

Even no significant difference in treatment strategy for patients with IPDC and DBDC, biological characteristics of IPDC much differ from DBDC. Thus, more effective treatment should be considered in patients with IPDC.

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Author Contributions

Masahide Ikeguchi – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Kanenori Endo – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Written informed consent was obtained from the patient for publication of this article.

Conflict of Interest
Authors declare no conflict of interest.

Data Availability
All relevant data are within the paper and its Supporting Information files.