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Late benign biliary complications after pancreatoduodenectomy

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ABSTRACT

Background: Pancreatoduodenectomy sometimes causes late benign biliary complications, such as biliary stricture and/or hepaticolithiasis, which require intervention. The risk factors and timing of late biliary complications remain unclear. The purpose of this study was to clarify the incidence, timing of occurrence, and risk factors for late biliary complications after pancreatoduodenectomy.
Methods: A total of 732 patients who underwent pancreatoduodenectomy between 2002 and 2016 were included in this retrospective study. Postoperative late biliary complications were defined as symptomatic benign biliary stricture and hepaticolithiasis, requiring radiologic or endoscopic intervention. Perioperative variables were collected to analyze the risk factors for late biliary complications. The treatment of late biliary complications was then evaluated.
Results: A total of 28 patients (3.8%) developed late biliary complications with a median interval of 23.4 (0.7–98.9) months. Late biliary complications consisted of hepaticolithiasis ($n = 11$) and stricture ($n = 27$) (including overlap). The 5-year cumulative incidence of late biliary complications was 7.3%. A multivariate analysis showed that a common hepatic duct diameter of < 4 mm was an independent risk factor for late biliary complications. The 5-year cumulative incidence of late biliary complications in patients with a common hepatic duct diameter of < 4 mm was significantly higher than that of patients with a common hepatic duct diameter of ≥ 4 mm (27.6% vs 1.3%, $P < .001$). For initial treatment, endoscopic intervention (balloon dilation, lithotomy, and stenting) was successfully performed in 21 patients (75.0%), and percutaneous transhepatic intervention was performed in 7 (25.0%). No patients underwent surgery.
Conclusion: The occurrence of late biliary complications was associated with a common hepatic duct diameter of < 4 mm. At the end of follow-up, high-risk patients should be adequately informed about late biliary complications and their symptoms.

Pancreatoduodenectomy (PD) is widely conducted for the treatment of periampullary tumors and other diseases. Recent improvements in surgical techniques and perioperative management have reduced the rates of surgical morbidity and mortality after PD to 41%–48% and 0.7%–3.3%,[1–4] Most reports about complications after PD have focused on early postoperative complications, such as pancreatic fistula, surgical site infection and delayed gastric emptying.[1–8] In contrast, few reports have described late complications, including biliary stricture after PD.[9–13] Patients who undergo PD sometimes develop late benign biliary complications, even after years of follow-up. These late biliary complications (LBCs), including biliary stricture of hepaticojejunostomy (H-J) and hepaticolithiasis, require endoscopic, percutaneous transhepatic or surgical intervention. However, the preoperative condition, surgical procedure for H-J, and incidence of bile leakage vary among individuals. Thus, the risk factors and the timing of LBCs remain unclear.

The purpose of this study was to clarify the incidence, timing of occurrence, and risk factors for late biliary complications after PD.

Patients and methods

A total of 1,009 patients underwent PD at the Shizuoka Cancer Center Hospital, Japan, between September 2002 and December 2016. Among these, 84 patients were excluded because they underwent hepatopancreatoduodenectomy for broadly spreading cholangiocarcinoma and 24 patients were excluded because they under-

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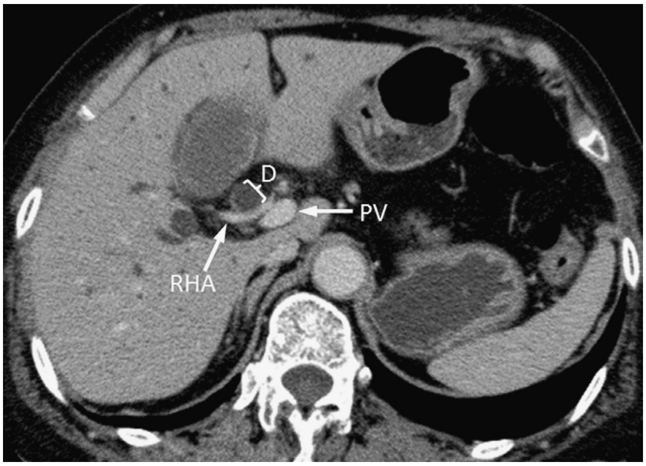

Fig 1. The common hepatic duct (CHD) diameter on multidetector-row computed tomography. *D*, diameter of the CHD; *RHA*, right hepatic artery; *PV*, portal vein.

went total pancreatectomy. A total of 2 patients with a history of previous H-J were excluded, because primary H-J was not performed as reconstruction at the time of PD. Another 167 patients had no available enhanced multidetector-row computed tomography (MDCT) images before preoperative biliary drainage and were excluded because the bile duct diameter cannot be correctly measured on imaging. The remaining 732 patients were included in the present study. This retrospective study protocol was approved by the institutional review board of Shizuoka Cancer Center, Japan.

Preoperative evaluation

The preoperative assessment was performed by ultrasonography (US) and enhanced MDCT. The preoperative diagnosis and stage were basically evaluated on US and enhanced MDCT. Other imaging examinations, such as magnetic resonance imaging, positron emission tomography, or endoscopic ultrasound were performed as necessary. The internal diameter of the common hepatic duct (CHD) was measured before biliary drainage at the level between hepatic duct confluence and right hepatic artery (RHA) on an axial slice of an MDCT scan by independent diagnostic radiologists (T.A., M.E.; Fig 1). The mean diameter of the two independent measurements was then calculated and defined as the CHD diameter in this study. Most jaundiced patients underwent preoperative biliary drainage (PBD). Endoscopic drainage (endoscopic biliary stenting, endoscopic naso biliary drainage) was the first choice; the second choice was percutaneous transhepatic biliary drainage (PTBD). The other patients did not undergo PBD before surgery based on the decision of the surgeon.

Pancreatoduodenectomy

The standard procedure for PD at our institution is subtotal stomach-preserving PD. The dividing level of the hepatic duct varies among patients. In principle, reconstruction was carried out using a modified Child method via end-to-side pancreatojejunostomy, end-to-side H-J, and end-to-side gastrojejunostomy. Management of the H-J consisted of approximation of the CHD stump and jejunal wall and end-to-side single-layer anastomosis. Patients with multiple biliary orifices at the stump basically underwent single H-J after side-to-side-connection of hepatic ducts, while others underwent multiple anastomoses. The suture thread used for the H-J was 5–0 monofilament absorbable suture, polydioxanone (PDS-II; Ethicon, Inc., Somerville, NJ, USA). The suture technique (interrupted or continuous sutures) and intraoperative biliary stenting were performed according to the surgeon's preference. Prophylactic drains were routinely placed near the H-J and pancreatojejunostomy.

Postoperative follow-up

The patients were followed up with imaging examinations and the measurement of tumor markers every three to six months after surgery. LBCs were defined as biliary stricture and hepaticolithiasis requiring endoscopic or radiological treatment. The basic approach for treating LBCs was an endoscopic procedure. Temporary reflex cholangitis, which occurred in some patients, was not included as an LBC because it could be treated with short-term medication on an outpatient basis. The survival time without LBCs was defined as the interval between the date of surgery and the date of the last follow-up examination without LBCs. Patients with biliary stenosis associated with tumor recurrence were censored at the time. The median length of follow-up was 23.5 months.

Statistical analyses

Some of the continuous variables were expressed as medians with ranges and compared using the Mann-Whitney *U* test. Categorical variables were compared using the χ^2 test or Fisher exact test, as appropriate. The cut-off CHD diameter for LBCs was calculated based on a receiver operating characteristic (ROC) curve. The cumulative probability of LBCs was estimated using the Kaplan-Meier method and compared using a log-rank test. The independent risk factors for LBCs were determined using the Cox proportional hazards model. Variables with a P value of < 0.05 in the univariate analysis were included in the multivariate analysis. P values of < 0.05 were considered to indicate statistical significance. Statistical analyses were performed using the Statistical Package for the Social Sciences software program (v 21.0 J; IBM Japan Inc, Tokyo, Japan).

Results

The median CHD diameter of all 732 patients was 9.7 mm (2.1–26.4). A total of 28 of the 732 patients (3.8%) developed LBCs. The LBCs consisted of stricture alone ($n = 17$), hepaticolithiasis alone ($n = 1$) and both ($n = 10$). The background characteristics of the patients with and without LBCs are summarized in Table 1. The patients with LBCs had a thinner CHD duct ($P < .001$), lower total bilirubin level ($P < .001$), lower rate of preoperative biliary drainage ($P < .001$), lower incidence of preoperative cholangitis ($P = .025$), and higher rate of impaired hepatic arterial flow ($P = .012$) in comparison with patients who had no LBCs. Postoperative infectious complications, including anastomotic leakage ($P = .305$), postoperative pancreatic fistula ($P = .140$) and intraabdominal abscess ($P = .465$), were not associated with LBCs. Patients with pancreatic neuroendocrine tumors (P-NETs) and duodenal tumors had a significantly higher incidence of LBCs than those without these lesions (13.6% vs 3.5%, $P = .015$ and 13.5% vs 3.0%, $P < .001$). In contrast, LBCs only developed in 1.7% of patients with pancreatic cancer ($P = .005$). There was no difference in the incidence of LBCs in patients with other diseases. An ROC curve demonstrated that a CHD diameter of 4.05 mm was the optimum cut-off point for the prediction of LBCs; the area under the curve (AUC) was 0.902 (Fig 2). In this study, we used a cut-off value of 4.0 mm for descriptive purposes (sensitivity 83.1%, specificity 85.7%). A total of 126 patients had a preoperative CHD diameter of < 4 mm; 23 (18.3%) of these patients developed LBCs. In contrast, only 5 of the 606 patients (0.8%) with a CHD diameter of ≥ 4 mm developed LBCs ($P < .001$).

The cumulative probability curve of LBCs for all patients is shown in Fig 3, *A*. The 5-year cumulative probability of LBCs was