Predictive Factors of Biliary Tract Cancer in Anomalous Union of the Pancreaticobiliary Duct

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Abstract: The assessment of malignancies associated with anomalous union of the pancreaticobiliary duct (AUPBD) is essential for the design of appropriate treatment strategies. The aim of the present study is to measure the incidence of AUPBD-related pancreaticobiliary malignancy and to identify predictive factors. This retrospective cohort study included cases of 229 patients with AUPBD between January 1999 and December 2013. The impact of bile duct dilatation on the incidence of AUPBD-related pancreaticobiliary disease was measured, and predictive factors were evaluated.

Among 229 patients with AUPBD, 152 had common bile duct dilatation (≥10 mm) (dilated group) and 77 did not (<10 mm) (nondilated group). Intrahepatic cholangiocarcinoma occurred more frequently in the nondilated group than in the dilated group (3.9% vs 0%, P = 0.05). By univariate analysis, age, type of AUPBD, and the level of lipase were significant predictors of malignancy and to identify predictive factors. This retrospective cohort study included cases of 229 patients with AUPBD between January 1999 and December 2013. The impact of bile duct dilatation on the incidence of AUPBD-related pancreaticobiliary disease was measured, and predictive factors were evaluated.

Intrahepatic cholangiocarcinoma may occur more frequently in AUPBD patients without bile duct dilatation. Age ≥45 years, P-C type, and biliary lipase level ≥45,000 IU/L are significantly associated with AUPBD-related biliary tract cancer.

INTRODUCTION

Anomalous union of the pancreaticobiliary duct (AUPBD) is a rare congenital anomaly in which the pancreatic and biliary ducts join anatomically outside of the duodenal wall, usually forming a markedly long common channel. The most clinically important feature of AUPBD is its association with carcinoma of the biliary tract, that is, bile duct and gallbladder cancer. In the literature, the incidence of bile duct and gallbladder cancer is 3.6% to 4.9% and 6.8% to 14.8% in AUPBD patients, respectively. In general, the stasis and regurgitation of pancreatic juice into the bile duct and gallbladder is believed to be the main mechanism of carcinogenesis in AUPBD. Since the action of the sphincter muscle does not functionally affect the junction in AUPBD, persistent reflux of pancreatic juice into the biliary tract occurs. This results in recurrent inflammation of the bile duct and gallbladder epithelium, and leads to hyperplasia and metaplasia, which might induce malignant transformation of the biliary epithelium. To support this hypothesis, studies were conducted to clarify the correlation between refluxed pancreatic juice enzymes and occurrence of biliary tract cancer by measuring pancreatic enzyme levels in bile; however, these studies failed to identify a clear association between amylase levels and the development of biliary tract cancers.

Although controversy remains regarding the mechanism of carcinogenesis, many studies demonstrated that biliary tract cancers develop preferentially at sites where there is stasis of activated pancreatic enzymes, such as in the dilated bile duct or gallbladder. In this regard, prophylactic flow-diversion surgery consisting of extraperitoneal bile duct resection along with cholecystectomy is widely accepted as the treatment of choice for AUPBD patients with bile duct dilatation to prevent development of both bile duct and gallbladder cancer. For AUPBD without bile duct dilatation, prophylactic cholecystectomy alone is generally performed and advocated in many institutions owing to the concept that the stasis of pancreatic enzymes occurs mainly in the gallbladder; however, some experts suggest excision of the extrahepatic biliary tract and cholecystectomy in AUPBD patients without biliary dilatation because reflux of pancreatic enzyme would still occur after...
cholecystectomy, thereby predisposing the patient to other biliary tract cancers. Therefore, the optimal surgical approach to AUPBD without bile duct dilatation remains debatable, and the occurrence of biliary tract cancer in AUPBD without bile duct dilatation needs to be clarified.

In this context, we assessed the incidence of biliary tract cancer in AUPBD patients with and without bile duct dilatation. In addition, factors predictive of biliary tract cancer in patients with AUPBD were evaluated.

METHODS

Patients

We conducted this study in patients with AUPBD diagnosed by endoscopic retrograde cholangiopancreatography (ERCP) from January 1999 to December 2013 at the Asan Medical Center. The patients enrolled were divided into 2 groups based on bile duct dilatation. The medical records of the patients were reviewed retrospectively, and the following information was extracted: clinical characteristics, clinical course, occurrence of biliary tract cancer, ERCP findings, and level of refluxed pancreatic enzymes in the common bile duct. This study was approved by the institutional review board at Asan Medical Center.

Definitions

Anomalous union of the pancreaticobiliary duct was defined as a common channel greater than 15 mm in length on a cholangiogram. Bile duct dilatation was defined as an extrahepatic duct with a maximum diameter of ≥10 mm on a cholangiogram; however, if bile duct dilatation was deemed to be due to obstruction by a tumor and/or stone, it was not regarded as bile duct dilatation. AUPBD-related biliary tract cancer consists of gallbladder cancer, extrahepatic cholangiocarcinoma (ECC), and intrahepatic cholangiocarcinoma (ICC). ECC was defined as cancer arising from the hepatic duct bifurcation to the distal common bile duct. Intrahepatic biliary tract cancer was defined as cancer occurring in the bile ducts within the liver. Cases of AUPBD were classified into 2 categories: P-C type, in which the pancreatic duct joins the bile duct; or C-P type, in which the bile duct joins the pancreatic duct (Figure 1). Bile sampling was performed during ERCP at the common bile duct. The levels of amylase and lipase were measured, and the correlation between these levels and biliary tract cancers was investigated.

Statistical Analysis

Statistical analysis was performed using SPSS (SPSS for windows, version 21.0, SPSS Inc., Chicago, IL). The baseline characteristics were assessed using the independent t test for continuous variables, whereas the chi-square test was used for categorical variables. Multivariate logistic regression was used to determine whether the factors affected the incidence of biliary cancer. The odd ratios (ORs) and 95% confidence intervals (95% CIs) were determined. Receiver-operating characteristic (ROC) curve analysis was used to determine cut-off values, based on highest sensitivity and specificity, for classification of patients. Due to the wide range of enzyme levels, values obtained by applying the common logarithm to amylase levels were used to calculate the OR. The appropriate lipase level cut-off value was defined by the ROC curve. The cut-off value was used to determine the relative risk associated with age and the biliary lipase level. The chi-square test was used to compare the incidence of biliary tract cancer between the groups generated by classification based on cut-off values.

RESULTS

Patient Characteristics

From January 1999 to December 2013, 229 patients (0.5%) were diagnosed as having AUPBD out of 46,049 ERCP referrals. The mean age of the subjects was 48.79 ± 14.08 years, and the male-to-female ratio was 2.47:1 (163:66 cases). The mean extrahepatic bile duct diameter was 17.77 ± 13.03 mm. One
hundred sixty-eight (73.4%) patients had P-C type, and 61 (26.6%) had C-P type. The mean level of amylase and lipase was 89805.1 ± 187930.5 IU/L and 248231.7 ± 686426.8 IU/L, respectively. In 229 AUPBD patients, 76 patients were diagnosed with gallbladder cancer, 10,065 patients with ECC, and 3 with ICC. During the study period, a total of 1111 patients were newly diagnosed gallbladder cancer, 10,065 patients with ECC, and 3659 patients with ICC in our center. The incidence of AUPBD in gallbladder cancer, ECC, and ICC were 6.84%, 0.08%, and 0.07%, respectively.

**Clinical Baseline**

Of the 229 patients, bile duct dilatation was present in 152 patients (dilated group) and absent in the remaining 77 patients (nondilated group). The mean diameter of the bile duct was 23.9 ± 14.4 mm in the dilated group and 8.1 ± 1.9 mm in the nondilated group (P < 0.001). No significant statistical difference in baseline clinical characteristics, including age and sex, was observed between the 2 groups. The P-C type was more common in the nondilated group than in the dilated group (P = 0.009). No significant differences in levels of refluxed pancreatic enzymes were observed between the 2 groups. ICC and pancreatitis were more frequent in the nondilated group. In particular, ICC was seen only in the nondilated group (P = 0.014). For other pancreaticobiliary diseases, including gallbladder cancer (P = 0.184), ECC (P = 0.271), and pancreatic cancer (P = 0.688), the incidence did not differ statistically between the 2 groups (Table 1).

**Factors Predictive of AUPBD-related Biliary Tract Cancer**

Univariate analysis showed significant differences in age, biliary amylase level, biliary lipase level, and type of AUPBD between patients with biliary tract cancer and those without (Table 2). By multivariate analysis, age (odds ratio [OR] 1.042, 95% confidence interval [CI] 1.011–1.073, P < 0.05), biliary lipase level (OR 4.132, 95% CI 1.420–12.021, P < 0.05), and type of AUPBD (OR 3.327, 95% CI 1.031–10.740, P < 0.05) showed a correlation with the incidence of AUPBD-related biliary tract cancer (Table 3).

**Age and AUPBD-related Biliary Tract Cancer**

The mean age of AUPBD patients with biliary tract cancer (53.8 ± 11.2 yrs) was significantly higher than that of those without biliary tract cancer (45.5 ± 15.3 yrs) (P < 0.05). The youngest patient with biliary tract cancer was a 29-year-old woman with gallbladder cancer. By logistic regression, the odds of biliary tract cancer increased by 1.042 with each year of age (95% CI 1.011–1.073, P < 0.05). The age cut-off for biliary tract cancer was calculated using the ROC curve. When the best cut-off point was set at 45 years, the area under the ROC curve (AUC) was 0.662. The sensitivity and specificity were 80.2% and 49.7%, respectively. The occurrence of biliary tract cancer in patients aged ≥45 years was significantly higher than that in patients aged <45 years (OR 3.640, 95% CI 2.001–6.621, P < 0.05) (Figure 2).

**AUPBD Type and AUPBD-related Biliary Tract Cancer**

Univariate analysis showed that biliary tract cancers were significantly associated with certain AUPBD types: the P-C type was more frequently detected in patients with biliary tract cancer (P < 0.05). Multivariate analysis showed that the odds of biliary tract cancer was 3.327 higher in the P-C type than in the C-P type (95% CI 1.031–10.740, P < 0.05). Ninety-one of 229 patients underwent surgical bile duct resection, in which 35 and

| TABLE 1. Comparison Between AUPBD Patients With and Without Bile Duct Dilation |
|----------------------------------------|-----------------|-----------------|-----------------|
|                                       | Dilated Group (n = 152) | Nondilated Group (n = 77) | P-value |
| Age, y                                 | 48.3 ± 14.7        | 49.6 ± 12.67     | 0.523     |
| Sex                                    |                  |                  |           |
| Male/female                            | 106/46           | 57/20            | 0.612     |
| Type of AUPBD                          |                  |                  |           |
| P-C/C-P                                | 103/49           | 65/12            | <0.001    |
| CBD diameter, mm                       | 23.9 ± 14.4       | 8.1 ± 1.9        | <0.001    |
| Level of pancreatic enzyme             |                  |                  |           |
| Amylase, IU/L                          | 75,073 ± 179,109 | 118,985 ± 202,926| 0.170     |
| Lipase, IU/L                           | 262,627 ± 794,593| 219,729 ± 398,942| 0.720     |
| Disease of the gallbladder, n (%)      |                  |                  |           |
| Cancer                                 | 46 (30.3)         | 30 (39.0)        | 0.184     |
| Cholelithiasis                         | 3 (1.9)           | 3 (3.9)          | 0.401     |
| Adenomyomatosis                        | 5 (3.3)           | 3 (3.9)          | 1.000     |
| Cholecystitis                          | 54 (35.5)         | 17 (22.1)        | 0.133     |
| Disease of the bile duct, n (%)        |                  |                  |           |
| Extrahepatic cholangiocarcinoma        | 6 (3.9)           | 1 (1.3)          | 0.271     |
| Intrahepatic cholangiocarcinoma        | 0                 | 3 (3.9)          | 0.014     |
| Cholecystolithiasis                    | 14 (9.2)          | 3 (3.9)          | 0.189     |
| Cholangitis                            | 15 (9.9)          | 2 (2.6)          | 0.062     |
| Disease of the pancreas, n (%)         |                  |                  |           |
| Pancreatic cancer                      | 4 (2.6)           | 3 (3.9)          | 0.688     |
| Pancreatitis                            | 1 (0.7)           | 0                | 1.000     |
| Pancreatitis                           | 2 (1.3)           | 8 (10.4)         | 0.003     |

AUPBD = anomalous union of the pancreaticobiliary duct.
56 patients were C-P type and P-C type, respectively. The pathologic results of resected bile ducts were compared to evaluate the difference of histological features of the bile duct dependent on AUPBD types, and there were no significant differences between C-P type and P-C type (Table 4).

Refluxed Pancreatic Enzymes and AUPBD-related Biliary Tract Cancer

The refluxed pancreatic enzymes were measured in 149 patients. Multiple logistic regression analysis revealed that AUPBD patients with biliary tract cancer tended to have higher lipase levels than those without biliary tract cancer (OR 4.132, 95% CI 1.420–12.021, \( P < 0.05 \)). ROC curve analysis determined the biliary lipase level cut-off value for AUPBD-related biliary tract cancer occurrence as 40,000 IU/mL (AUC 0.627) at the highest sensitivity (59.2%) and specificity (59%) (Figure 3A). Biliary tract cancer occurred more frequently in AUPBD patients with \( \geq 40,000 \) IU/mL than in those with \( <40,000 \) IU/mL (OR 2.235, 95% CI 1.085–4.604, \( P < 0.05 \)) (Figure 3B). The amylase level did not show any significant correlation with biliary tract cancer.

Occurrence of Bile Duct Cancers in AUPBD Patients With Predictive Factors

In this study, 41 patients had all 3 predictive factors, and among these, a bile duct cancer occurred in 23 patients. Hence, the positive predictive value for bile duct cancers in patients with all 3 predictive factors was 56.1%. In contrast, of the 146 patients who did not experience bile duct cancer, only 8 had all 3 predictable factors. However, the analysis of occurrence of each biliary tract cancer depending on predictive factors could not reach statistical significance because of the small number of each bile duct cancer (ECC, \( n = 7 \); ICC, \( n = 3 \)) except for gallbladder cancer (Table 5).

DISCUSSION

The present study focused on the incidence of biliary tract cancer in patients with AUPBD with and without bile duct

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**TABLE 2. Univariate Analysis of Factors Predictive of AUPBD-related Bile Duct Cancer**

| With Biliary Tract Cancer | Without Biliary Tract Cancer | \( P \) |
|---------------------------|-----------------------------|-------|
| Age, yrs                  | 53.77 ± 11.20               | 45.54 ± 15.26 | <0.001 |
| Bile duct dilatation (\( \leq 10 \text{mm} > 10 \text{mm} \)) | 51/35                      | 101/42          | 0.079 |
| Amylase, IU/L             | 152,066 ± 299,823           | 60,156 ± 101,379 | 0.004 |
| Lipase, IU/L              | 470,484 ± 1091,911          | 139,327 ± 299,823 | 0.033 |
| Type of AUPBD (P-C/C-P)   | 71/15                       | 97/46           | 0.02  |

AUPBD = anomalous union of the pancreaticobiliary duct.

**TABLE 3. Multivariate Analysis of Factors Predictive of AUPBD-related Bile Duct Cancer**

|                      | Odds Ratio | 95% CI | \( P \) |
|----------------------|------------|--------|--------|
| Age                  | 1.042      | 1.011–1.073 | 0.007  |
| Bile duct dilatation (\( \leq 10 \text{mm} > 10 \text{mm} \)) | 0.589    | 0.268–1.295 | 0.188  |
| Amylase              | 1.291      | 0.979–1.701 | 0.07   |
| Lipase               | 4.132      | 1.420–12.021 | 0.009  |
| Type of AUPBD (P-C/C-P) | 3.327 | 1.031–10.740 | 0.044  |

AUPBD = anomalous union of the pancreaticobiliary duct, CI = confidence interval.
TABLE 4. The Pathologic Findings of Bile Duct in Accordance With Types of AUPBD

| Type of AUPBD       | C-P Type (n = 35) | P-C Type (n = 56) | P  
|---------------------|------------------|------------------|---
| Chronic inflammation| 7                | 15               | 0.462  
| Dysplasia           |                  |                  | 0.571  
| Low grade           | 0                | 2                |        
| High grade          | 1                | 1                |        
| Intraductal papillary necplasm | 2               | 2                | 0.942  
| BilIN               | 0                | 1                | 0.427  
| Adenocarcinoma      | 1                | 1                | 0.853  
| Total               | 12               | 25               | 0.328  

AUPBD = anomalous union of the pancreaticobiliary duct.

dilatation, and evaluated potential predictive factors for AUPBD-related biliary tract cancer. The results showed that the risk of ICC was higher in AUPBD patients with a nondilated bile duct. This finding is of great interest and, to the best of our knowledge, is documented here for the first time. Our results also provide factors that can be used to predict AUPBD-related biliary tract cancer, including age ≥45 years, P-C type, and biliary lipase level ≥40,000 IU/L.

So far, ICC has not received significant attention in the treatment of AUPBD, because the stasis of reﬂuxed pancreatic juice in the intrahepatic bile duct is considered to have a relatively lower risk of stasis than that in the extrahepatic bile duct or gallbladder. Although AUPBD is believed to increase the risk of ICC, limited data exist in the literature concerning the association between ICC and AUPBD. Only a few case reports have documented the occurrence of ICC in AUPBD patients.14

In this study, ICC occurred in 3 AUPBD patients, and all cases of ICC occurred in patients without bile duct dilatation (P = 0.014). This result suggests that a nondilated bile duct in AUPBD is associated with a high risk of ICC. This finding can be explained by the continuity equation, which states that the speed of a liquid is directly inversely proportional to the cross-sectional area of the vessel. Thus, because the cross-sectional area is smaller in a nondilated bile duct than in dilated bile duct, faster flow would be generated in a nondilated bile duct, resulting in reﬂuxed pancreatic juice reaching the liver, where it may cause ICC. Therefore, we recommend that clinicians pay renewed attention to the development of ICC in AUPBD patients, particularly in those who have a nondilated bile duct.

Prophylactic bile duct resection along with cholecystectomy is the standard treatment for AUPBD with bile duct dilatation. A dilated common bile duct is considered a favorable anatomical location for the development of biliary tract cancer since stagnation of reﬂuxed pancreatic juice is predicted to occur more frequently in a dilated duct than in a nondilated duct.15

The results of the present study conﬁrm this conjecture because 6 of 7 patients with extrahepatic biliary tract cancer were in the dilated duct group. By contrast, there has been controversy over the optimal treatment for AUPBD without extrahepatic bile duct dilatation. The reason for this controversy is that the risk of developing biliary tract cancer is lower than that of developing gallbladder cancer; however, in our study, the incidence of extrahepatic biliary tract cancer did not differ significantly between the 2 groups (P = 0.271), and ICC was signiﬁcantly more common in patients without extrahepatic bile duct dilatation (P = 0.014). As a result, cholecystectomy alone may not sufﬁce, and further surgical management including bile duct excision may be necessary. Some investigators recommended removal of the extrahepatic bile duct along with the gallbladder to prevent cancer development in the remnant nondilated bile duct.3,16 According to a study by Kim et al,10 of 55 patients with AUPBD, conducted to evaluate the occurrence of biliary tract cancer, ECC occurred more frequently in patients without bile duct dilatation than in those with bile duct dilatation (30.0% vs 4.0%; P = 0.015). They recommended extrahepatic bile duct excision, biloenteric anastomosis, and cholecystectomy as a treatment of choice for AUPBD without bile duct dilatation; however, routine excision of the extrahepatic bile duct in AUPBD patients presents the risk of postoperative adverse events in 9.7% to 20% of the cases.17,18 In the literature, extrahepatic bile duct excision is associated with increased risk of biliary anastomotic leak, biliary strictures, intrahepatic bile duct calculi, and attendant cholangitis, which is recognized as important factors affecting postoperative quality of life.17,19,20 Thus, factors predictive of malignancy are required to identify patients with the greatest risk of cancer in whom the risk of postoperative adverse events is outweighed by the drastic reduction in cancer risk offered by surgery.

In the present study, we found that the incidence of biliary tract cancer increases with age in patients with AUPBD. In
AUPBD patients
dence of gallbladder cancer tended to show a marked increase in
woman. A previous nationwide survey reported that the inci-
deration that can be used to make treatment decisions, which
and bile duct resection before the age of 40 because
youngest patient with gallbladder cancer was a 41-year-old
A previous nationwide survey reported that the inci-
cancer was 21% in patients between 19 and 44 years of age,
and 48% in patients ≥45 years of age. A few reports on age and
of AUPBD-related biliary tract cancer recommended
cancer tended to increase as the levels of pancreatic
biliary reflux in benign and malignant gallbladder diseases,
and the bile duct was joined to the pancreatic duct.
Therefore, reflux of pancreatic juice would occur to a lesser
juice may be constantly under high pressure, resulting in a
continuous reciprocal reflux of pancreatic juice. By contrast, the
juice forms a shaft in the P-C type, the pancreatic
bile duct, and the bile duct is joined to the pancreatic duct.
Therefore, reflux of pancreatic juice would occur to a lesser
extent than in the P-C type.
The presence of extremely high levels of pancreatic
enzymes is predictive of a risk of developing biliary tract cancer
remains questionable. According to a nationwide survey in
Japan, high biliary amylase levels in AUPBD patients are
not associated with biliary cancer. By contrast, Beltran
et al, 23 who conducted a study of 108 patients with normal
pancreatobiliary junction to investigate occult pancreatobiliary
reflux in benign and malignant gallbladder diseases,
reported significantly higher biliary lipase levels in gallbladder
cancer patients than in patients with a benign gallbladder
pathology. Our results showed that the occurrence of biliary
cancer tended to increase as the levels of pancreatic
enzymes increased, and that the biliary lipase level was sig-
ificantly associated with the occurrence of biliary tract cancer
(OR 4.132, 95% CI 1.420–12.021, P < 0.05). AUPBD-related biliary tract cancer was detected more frequently in patients
whose lipase levels in the common bile duct were >40,000 IU/L
than in other patients; however, amylase levels did not show any
statistical significance by multivariate analysis (OR 1.291, 95% CI
0.979–1.701, P = 0.07). On the basis of our results, we
suggest that AUPBD patients with high levels of biliary lipase
need close follow-up so as not to miss the occurrence of
AUPBD-related biliary cancer.
The present study has several limitations. Firstly, it is
inherently limited by its retrospective nature. Secondly, the
study was conducted at a single medical center, and, thus, our
results may not be generalizable. Thirdly, AUPBD was diag-
nosed only by ERCP, and patients who may have been diag-
nosed by other imaging modalities, such as magnetic resonance
cholangiopancreatography, endoscopic ultrasonography, or by
anatomical examination after surgery, were not included. This
factor could have introduced selection bias in our results.
In conclusion, our study demonstrates that the incidence of
ICC is higher in AUPBD patients without bile duct dilatation.
Age, type of AUPBD, and biliary lipase level are significantly
associated with AUPBD-related biliary tract cancers. Hence,
clinicians should exercise caution concerning the possibility
of biliary tract cancer in AUPBD patients, particularly in patients
≥45 years of age, with the P-C type and a biliary lipase level
≥40,000 IU/L. In addition, cholecystectomy and extrahepatic
bile duct excision might be considered as a primary treatment
for AUPBD patients with those predictive factors, even when
they do not have bile duct dilatation.

### Table 5. The Association Between Predictable Factors and Each Biliary Tract Cancer

| Predictor                          | OR     | 95% CI          | P      |
|-----------------------------------|--------|----------------|--------|
| Gallbladder cancer                 |        |                |        |
| Predictable factors               |        |                |        |
| Age (≥45/<45 yrs)                  | 4.045  | 2.118–7.125    | <0.001 |
| Type of PBM (P-C/C-P)              | 2.709  | 1.341–5.470    | 0.004  |
| Lipase (>40,000/<40,000 IU/mL)     | 2.478  | 1.211–5.070    | 0.012  |
| Extrahepatic cholangiocarcinoma    |        |                |        |
| Age                               | 1.581  | 0.300–8.330    | 0.710  |
| Type of PBM (P-C/C-P)              | 0.472  | 0.100–2.170    | 0.387  |
| Lipase                            | 0.543  | 0.480–6.119    | 1.000  |
| Intrahepatic cholangiocarcinoma    |        |                |        |
| Age                               | 1.252  | 0.112–14.012   | 1.000  |
| Type of PBM (P-C/C-P)              | 0.723  | 0.064–8.118    | 1.000  |
| Lipase                            | 0.974  | 0.940–1.010    | 1.000  |

CI = confidence interval, OR = odd ratio.
REFERENCES

1. Kamisawa T, Ando H, Hamada Y, et al. Diagnostic criteria for pancreaticobiliary maljunction 2013. J Hepatobiliary Pancreat Sci. 2014;21:159–161.

2. Hasumi A, Matsui H, Sugioka A, et al. Precancerous conditions of biliary tract cancer in patients with pancreaticobiliary maljunction: reappraisal of nationwide survey in Japan. J Hepatobiliary Pancreat Surg. 2000;7:551–555.

3. Funahiki T, Matsubara T, Miyakawa S, et al. Pancreaticobiliary maljunction and carcinogenesis to biliary and pancreatic malignancy. Langenbecks Arch Surg. 2009;394:159–169.

4. Yamao K, Mizutani S, Nakazawa S, et al. Prospective study of the detection of anomalous connections of pancreatobiliary ducts during routine medical examinations. Hepatogastroenterology. 1996;43:1238–1245.

5. Tashiro S, Imaizumi T, Ohkawa H, et al. Pancreaticobiliary maljunction: retrospective and nationwide survey in Japan. J Hepatobiliary Pancreat Surg. 2003;10:345–351.

6. Sharma SS. Pancreaticobiliary ductal union in cholangiocarcinoma. Gastrointest Endosc. 1994;40:171–173.

7. Takuma K, Kamisawa T, Tabata T, et al. Importance of early diagnosis of pancreaticobiliary maljunction without biliary dilatation. World J Gastroenterol. 2012;18:3409–3414.

8. Jeong IH, Jung YS, Kim H, et al. Amylase level in extrahepatic bile duct in adult patients with choledochal cyst plus anomalous pancreatobiliary ductal union. World J Gastroenterol. 2005;11:1965–1970.

9. Sugiyama Y, Kobori H, Hakamada K, et al. Altered bile composition in the gallbladder and common bile duct of patients with anomalous pancreaticobiliary ductal junction. World J Gastroenterol. 2000;24:17–20 [discussion 21].

10. Kim Y, Hyun JJ, Lee JM, et al. Anomalous union of the pancreaticobiliary duct without choledochal cyst: is cholecystectomy alone sufficient? Langenbecks Arch Surg. 2014;399:1071–1076.

11. Ohuchida J, Chijiwa K, Hiyoshi M, et al. Long-term results of treatment for pancreaticobiliary maljunction without bile duct dilatation. Arch Surg. 2006;141:1066–1070.

12. Kamisawa T, Takuma K, Anjiki H, et al. Pancreaticobiliary maljunction. Clin Gastroenterol Hepatol. 2009;7:884–888.

13. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol. 2010;17:1471–1474.

14. Shimamura K, Kurokasi I, Sato D, et al. Intrahepatic cholangiocarcinoma arising 34 years after excision of a type IV-A congenital choledochal cyst: report of a case. Surg Today. 2009;39:247–251.

15. Sugiyama M, Atomi Y. Anomalous pancreaticobiliary junction without congenital choledochal cyst. Br J Surg. 1998;85:911–916.

16. Singh J, Yoshida EM, Scudamore CH. Choledochal cysts: part 1 of 3: classification and pathogenesis. Can J Surg. 2009;52:434–440.

17. Takeshita N, Ota T, Yamamoto M. Forty-year experience with flow-diversion surgery for patients with congenital choledochal cysts with pancreaticobiliary maljunction at a single institution. Ann Surg. 2011;254:1050–1053.

18. Sakaguchi T, Suzuki S, Suzuki A, et al. Late postoperative complications in patients with pancreaticobiliary maljunction. Hepatogastroenterology. 2007;54:585–589.

19. Ward J, Sheridan MB, Guthrie JA, et al. Bile duct strictures after hepatobiliary surgery: assessment with MR cholangiography. Radiology. 2004;231:101–108.

20. vanSonnenberg E, D’Agostino HB, Easter DW, et al. Complications of laparoscopic cholecystectomy: coordinated radiologic and surgical management in 21 patients. Radiology. 1993;188:399–404.

21. Kobayashi S, Ohnuma N, Yoshida H, et al. Preferable operative age of choledochal dilation types to prevent patients with pancreaticobiliary maljunction from developing biliary tract carcinogenesis. Surgery. 2006;139:33–38.

22. Deng YL, Cheng NS, Lin YX, et al. Relationship between pancreaticobiliary maljunction and gallbladder carcinoma: meta-analysis. Hepatobiliary Pancreat Dis Int. 2011;10:570–580.

23. Kamisawa T, Ando H, Suyama M, et al. Japanese clinical practice guidelines for pancreaticobiliary maljunction. J Gastroenterol. 2012;47:731–759.

24. Beltran MA, Vracko J, Cumsille MA, et al. Occult pancreaticobiliary reflux in gallbladder cancer and benign gallbladder diseases. J Surg Oncol. 2007;96:26–31.