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***Retrospective Study***

**Biliary tract intraductal papillary mucinous neoplasm: Report of 19 cases**

Wang X *et al.* Biliary tract intraductal papillary mucinous neoplasm

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**Abstract**

**AIM:** To gain a better understanding of biliary tract intraductal papillary mucinous neoplasm (BT-IPMN).

**METHODS:** From January 2000 to December 2013, 19 (5.5%) cases of BT-IPMN were retrospectively identified from a total of 343 biliary tract tumors resected in our single institution. Demographic characteristics, clinical data, pathology, surgical strategies, and long-term follow-up were analyzed.

**RESULTS:** The mean age of the 19 BT-IPMN cases was 53.8 years (range: 25–74 years). The most common symptom was abdominal pain (15/19 patients, 78.9%), followed by jaundice (7/19, 36.8%). Cholangitis was found associated with most BT-IPMN cases (16/19, 84.2%). Macroscopically visible mucin was detected in all 19 patients, based on original surgical reports. The most common abnormal preoperative imaging findings for BT-IPMN were bile duct dilation (all 19 cases) and intraluminal masses (10 cases, 52.6%). Thirteen (68.4%) cases involved the intrahepatic bile duct and hilum.We performed left hepatectomy in 11 (57.9%) patients, right hepatectomy in two (10.5%), bile duct resection in four (21.1%), and pancreatoduodenectomy in one (5.3%). One (5.3%) patient was biopsied and received a choledochojejunostomy because of multiple tumors involving the right extrahepatic and left intrahepatic bile ducts. Histology showed malignancy in 10 (52.6%) patients. The overall median survival was 68 mo. The benign cases showed a non-significant trend towards improved survival (median survival, 68 *vs* 48 mo, *P* = 0.347). The patient without tumor resection died of liver failure 22 mo after palliative surgery.

**CONCLUSION:** BT-IPMN is a rare biliary entity. Complete resection of the tumor is associated with good survival, even in patients with malignant disease.

**Key words:** Intraductal papillary mucinous neoplasm; Biliary tract; Papillary tumor; Mucinous tumor; Cystic tumor

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**Core tip:** Our study involved a large number of patients with biliary tract intraductal papillary mucinous neoplasm (BT-IPMN) from a large Chinese institution. We summarized the clinical features, radiological findings, pathology, surgical strategies, and long-term follow-up of BT-IPMN to achieve a better understanding of this rare disease. Our findings indicated that BT-IPMN is a rare biliary entity and complete resection of the tumor is associated with good survival, even in patients with malignant disease.

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**INTRODUCTION**

In the past decade, biliary tract intraductal papillary mucinous neoplasm (BT-IPMN) has been increasingly recognized as a unique type of biliary neoplasm, coinciding with widespread acceptance of the nomenclature of pancreatic intraductal papillary mucinous neoplasm (P-IPMN)[1-3]. As the name suggests, BT-IPMN is known to be a biliary counterpart of P-IPMN but with its own separate identity[4-9]. BT-IPMN is histologically defined as a mucinous and papillary neoplasm, with a clear origin from the biliary epithelium, with solitary or diffuse intraductal growth[1]. It is a rare neoplasm involving the intra- and extra-hepatic biliary tract and characterized by mucin-secreting papillary and/or cystic lesions. BT-IPMN is recognized as a precursor of invasive carcinoma (tubular adenocarcinoma or mucinous carcinoma) and 40%–80% of resected BT-IPMNs contain invasive components[10-12]. BT-IPMN has a more favorable prognosis compared with conventional cholangiocarcinoma[13,14]. The number of reports of BT-IPMN with strict histopathological criteria is limited. Moreover, most of the data regarding BT-IPMN are from retrospective studies with small samples. There is still controversy about several aspects of BT-IPMN, and the clinicopathological characteristics, surgical strategies and prognosis of BT-IPMN are largely unclear[1,2,7].

Our study involved a large number of patients with BT-IPMN from a large Chinese institution. The purpose of this study was to summarize the demographic and clinical features, radiological findings, pathology, surgical strategies, and long-term follow-up of BT-IPMN for a better understanding of this rare disease.

**MATERIALS AND METHODS**

From January 2000 to December 2013, 19 patients with BT-IPMN were retrospectively identified in our institution. All diagnosis was established using strict histopathological criteria for BT-IPMN: a mucinous and papillary neoplasm demonstrating clear origin from the biliary epithelium, with solitary or diffuse intraductal growth[1]. We excluded mucinous cystic neoplasms of the liver (with ovarian or mesenchymal stroma)[15], lesions originating from the periampullary region of the duodenum[16], and lesions without microscopic or macroscopic mucin secretion. All 19 BT-IPMNs were histologically classified into benign (low- or middle-grade dysplasia) and malignant (high-grade dysplasia or invasive carcinoma)[17]. Clinical data were obtained from the electronic medical records or external medical reports. Demographic characteristics, clinical presentation, preoperative evaluation, pathology, surgical therapy, postoperative course, and long-term outcomes were included. Postoperative complications were recorded in real time into our prospective complication database. All events recorded within 30 d after surgery were considered to be postoperative complications. Survival was measured from the date of operation to date of death or date of last follow-up. We conducted telephone interviews and/or outpatient interview to follow up these patients. This study was approved by the Ethics Committee of Sichuan University.

***Statistical analysis***

Survival probability was estimated using the Kaplan–Meier method. Statistical analysis was performed using SPSS for Windows version 16.0 (IBM, Armonk, NY, United States). *P*< 0.05 was considered statistically significant.

**RESULTS**

***Demographic characteristics***

Nineteen (5.5%) cases of BT-IPMN were identified from a total of 343 biliary tract tumors resected from 2000 to 2013 using strict histopathological criteria for BT-IPMN[1]. As shown in Table 1, the mean age was 53.8 years (range: 25–74 years), and male patients (11/19, 57.9%) were more commonly affected. Most patients with BT-IPMN (12/19, 63.2%) were aged > 50 years when diagnosed, and six (31 .6%) were in their 50s.

***Clinical presentation***

The most common symptom was abdominal pain (15/19, 78.9%), followed by jaundice (7/19, 36.8%) and weight loss (3/19, 15.8%). Only one (5.3%) of 19 cases was asymptomatic. Sixteen (84.2%)patients presented with acute or chronic cholangitis, of whom six (31.6%) had repeated episodes of cholangitis. Four (21.1%)patients also had an association with schistosomiasis. Thirteen (68.4%) cases involved the intrahepatic bile duct and hilum, while only five (26.3%) involved solely the extrahepatic bile duct, and one (5.3%) presented with tumor in multiple locations. The serum carbohydrate antigen (CA) 19-9 level was > 22 U/mL in eight(42.1%)patients. Elevated serum carcinoembryonic antigen (CEA) level (> 3.4 ng/dL) was detected in five (26.3%)patients. Clinical presentation is shown in Table 2.

***Imaging characteristics***

As shown in Table 3, all cases underwent imaging examinations, such as abdominal ultrasonography (US), computed tomography (CT) and magnetic resonance imaging (MRI). The most common abnormal preoperative imaging findings for BT-IPMN were bile duct dilation (all 19 cases) and intraluminal masses (10 cases, 52.6%) (Figure 1), and 10 (52.6%)patients showed cyst-like bile duct dilatation. Stones were detected in 12 (63.2%)patients; most of which(10 cases, 83.3%) were located in the proximal biliary duct of the tumors. There was no cholecystolithiasis. Liver atrophy was observed in seven (36.8%)patients.

***Operative strategies and outcomes***

As shown in Table 4, the most commonly performed procedure was a left hepatectomy in 11 (57.9%)patients, compared with a right hepatectomy in two (10.5%) patients, and four (21.1%)patients underwent bile duct excision alone. One (5.3%) patient required pancreaticoduodenectomy for tumor clearance and another received biopsy and choledochojejunostomy for multiple tumors of the extrahepatic, right and left intrahepatic bile ducts. No death occurred within 30 d after surgery.

Four (21.1%)patients had postoperative complications, including one each with stress ulcer, intra-abdominal abscess, pneumonia associated with bile leakage, and wound infection. Bile leakage occurred in a 68-year-old patient who underwent local bile duct excision with postoperative pneumonia. The bile leakage and pneumonia led to prolonged hospitalization (65 d) and readmission, and was cured through percutaneous drainage and antibiotics. In addition, three patients had postoperative complications that were cured by conservative therapy. Lymphadenectomy was routinely performed, however, no lymph node metastasis was detected in our series.

***Gross appearance***

The gross appearance of BT-IPMN varies with the size of the tumor. The mean tumor size was 3.54 cm (range: 0.5–12 cm) (Table 1). This tumor may present as an intraluminal mass (Figure 2) and/or cyst-like bile duct dilation. Typically, the smaller tumors may be less likely to show cystic-like bile duct dilation and often appear as intraluminal masses. Intraluminally growing intraductal papillary neoplasm (10/19 cases, 52.6%) (Table 3) and visible mucin (19 cases, 100%) (Table 4) on the surface of the tumor were typical characteristics of BT-IPMN.

***Histopathology***

Microscopically, BT-IPMN was mucinous and composed of papillary proliferation of biliary epithelial cells with intraductal growth. Mucin was noted microscopically in all 19 patients (Figure 3), based on postoperative histopathological examination (Table 4). Malignant components (high-grade cytological atypia or invasive carcinoma) were found in 10 (52.6%)of 19 cases, with three (15.8%) invasive carcinomas (Table 4). Furthermore, BT-IPMN is known to be classified into four histopathological subtypes (*i.e.*, gastric, intestinal, pancreatobiliary, and oncocytic) based on morphological appearance and mucin staining properties[15], which are identical to those of P-IPMN.

***Follow-up and survival***

All patients underwent US or CT every 6–12 mo after surgery. Follow-up data were collected by telephone or outpatient interview. Margin-negative resection was achieved in 18 (94.7%) patients, and palliative surgery was performed in one (5.3%). The median follow-up period was 73 mo. Eight patients with BT-IPMN died, including five malignant cases and three benign. All five malignant cases died of tumors or tumor-related causes, including one patient who died of liver failure caused by tumor at 22 mo after palliative surgery. One benign BT-IPMN case (33.3%) died of subsequentsmall cell lung cancer with 26 mo survival. Overall median survival was 68 mo for the entire cohort (Table 4). Compared with 48 mo in the malignant group, the benign cases were likely to be associated with improved median survival of 68 mo (*P* = 0.347). The survival curve for patients with benign BT-IPMN (*n* = 9) and those with malignant BT-IPMN (*n* = 10) is shown in Figure 4.

**DISCUSSION**

Although wide consensus has not yet been reached, BT-IPMN has been increasingly recognized as a unique type of biliary neoplasm and a biliary counterpart of P-IPMN[1,7]. The World Health Organization recognized intraductal papillary neoplasm of the bile duct (IPNB) as a distinct pathological entity in 2010[10]. Ohtsuka *et al*[16] suggested that IPNB with or without macroscopically visible mucin secretion differed in terms of pathological features. In our study, BT-IPMN was defined as mucinous papillary neoplasm, demonstrating clear origin from the biliary epithelium[1], and excluded lesions (such as IPNB) without microscopic or macroscopic mucin secretion. To some extent, BT-IPMN is a presumed subtype of IPNB, which has more similarity to P-IPMN than IPNB itself[16].

BT-IPMN shares some radiological and clinicopathological features with P-IPMN, but important differences between them may still exist. The frequency of malignancy was significantly higher in patients with BT-IPMN (64%–89%) than in those with P-IPMN (23%–30%)[1,2,7,18]. Consistent with previous studies, the rate of malignant BT-IPMN in our series was > 50%. The reason for the higher rate of malignancy in patients with BT-IPMN may include the following. First, as several recent reports have suggested, the majority of BT-IPMNs are of intestinal or pancreatobiliary subtype, resembling those of main-duct-type P-IPMN, which is more aggressive than branch duct P-IPMN[3,7,19]. Second, the biliary tract and the main pancreatic duct have identical embryological development from the hepatic diverticulum in the foregut mesoderm[2,7].

In the present study, BT-IPMN mostly presented in patients aged 50–70 years, which is consistent with several other studies[1,3,7,10,20]. Although more male BT-IPMNs patients were found in our study, no difference was found in sex distribution based on previous reports[1,7,10]. The most common presenting symptom was abdominal pain (79%), probably due to biliary stone, cholangitis, or high pressure of biliary tract causing mucin hypersecretion, which are associated with BT-IPMN[10,21]. Intraluminal hypersecretion of mucin from the bile duct may intermittently impede bile flow, leading to repeated episodes of cholangitis. Repeated cholangitis was found in approximately 32% of patients with BT-IPMN in our study, as a typical clinical presentation of BT-IPMN. Nearly 63% of BT-IPMNs were associated with biliary stones; most of which (83.3%) were proximal biliary stones. These findings indicated that the process of inflammatory stimulation may play a role in development of BT-IPMN. BT-IPMNs were predominantly located in the intrahepatic bile duct and hilum (68%). Despite these variable locations, the primary site of tumor origin does not affect the progress or prognosis of the disease[10,20,21]. Dilated bile ducts, intraluminal lesions and/or gross cystic dilatation originating from the biliary tract are the most common abnormal preoperative imaging findings in BT-IPMN. Simultaneous proximal and distal bile duct dilation was found in approximately 68% of patients with BT-IPMN in our study. It has diagnostic significance, just like diffused pancreatic duct dilation for P-IPMN. The large amount of mucin discharged into the duct system leads to diffuse duct dilation.

Surgery is the first choice of treatment for patients with BT-IPMN without distant metastasis[22]. Determination of the optimal surgical strategy depends on the site and extent of the lesions. Intraoperative choledochoscopy and surgical margin frozen section are performed to assess tumor location and extension, including superficial spreading along the biliary epithelium[23].Hepatectomy should be performed for tumor located in intrahepatic bile duct. Pancreatoduodenectomy and bile duct resection are performed to treat tumor located in the extrahepatic bile duct. Furthermore, Jarnagin *et al*[24] have suggested that regional lymphadenectomy is recommended for tumors localized in the hilum or distal bile duct. Lymph node metastasis is rare in benign BT-IPMN. It is less common even in patients with invasive carcinoma arising from BT-IPMN, compared with conventional cholangiocarcinoma[8]. No patient in our series suffered from lymph node metastases. Portal vein resection is an option for tumors with blood vessel involvement[8]. Theoretically, resection of the entire biliary tract by liver transplantation could be a better option for curative treatment of diffuse BT-IPMN. Palliative surgery was performed in one patient (5%) with diffuse BT-IPMN in our study.

Only one patient died 22 mo after palliative surgery, with poorer survival than the overall median survival of 68 mo. Rocha *et al*[10] found that R0 resection was associated with better median survival than R1 resection. Additionally, although the median survival for the benign group was better than for malignant cases (68 *vs* 48 mo), it was not significantly different (*P* = 0.347). The relatively short follow-up period and small sample size may attribute to statistical difference. One patient with benign BT-IPMN died of subsequent small cell lung cancer, which may also play a role in statistical difference. However, the difference may reflect an intrinsic difference in tumor biology. Complete tumor resection is associated with good survival, even in patients with malignant BT-IPMN.

The small number of patients in the present study prevented us from making strong conclusions. Moreover, a major limitation was the retrospective nature of the study. Diagnostic modalities for BT-IPMN including imaging and pathology have varied at different times. Nevertheless, due to the scarcity of patients, we are still justified in speculating on the trends that can be observed in this limited set of data. More multicenter prospective studies are necessary to identify the clinical and pathological characteristics of BT-IPMN.

In conclusion, BT-IPMN is a rare biliary entity. Complete resection of the tumor is associated with good survival, even in patients with malignant BT-IPMN.

**COMMENT**

***Background***

In the past decade, biliary tract intraductal papillary mucinous neoplasm (BT-IPMN) has been increasingly recognized as a unique type of biliary neoplasm, coinciding with widespread acceptance of the nomenclature of pancreatic intraductal papillary mucinous neoplasm. BT-IPMN is a rare neoplasm involving the intra- and extrahepatic biliary tracts and is characterized by mucin-secreting papillary and/or cystic lesions. However, there is still controversy over several aspects of BT-IPMN.

***Research frontiers***

BT-IPMN is a rare biliary entity. The number of reports of BT-IPMN with strict histopathological criteria is limited. Most of the data regarding BT-IPMN are from retrospective studies with small samples. There is still controversy surrounding several aspects of BT-IPMN, and clinicopathological characteristics, surgical strategies and prognosis are largely unclear.

***Innovations and breakthroughs***

This study involved a large number of patients with BT-IPMN from a large Chinese institution. The authors summarized the clinical features, radiological findings, pathology, surgical strategies, and long-term follow-up of BT-IPMN, and achieved a better understanding of this rare disease. The findings indicate that BT-IPMN is indeed a rare biliary entity and complete resection of the tumor is associated with good survival, even in patients with malignant disease.

***Applications***

BT-IPMN is a rare biliary entity. Complete resection of the tumor is associated with good survival, even in patients with malignant disease.

***Terminology***

BT-IPMN is histologically defined as a mucinous and papillary neoplasm demonstrating a clear origin from the biliary epithelium, with solitary or diffuse intraductal growth.

***Peer review***

It’s a very interesting paper. The data are clearly presented and extensively discussed on the basis of the recent relevant international literature.

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**Table 1 Demographic characteristics of patients *n* (%)**

|  |  |
| --- | --- |
| **Feature** | **Value** |
| Patients | 19 |
| Age, yr |  |
|  ≤ 40  | 3 (15.8) |
|  40–50  | 4 (21.1) |
|  50–60  | 6 (31.6) |
|  ≥ 60  | 6 (31.6) |
| Mean age, yr (range) | 53.8 (25-74) |
| Sex |  |
| Male | 11 (57.9) |
| Female | 8 (42.1) |

**Table 2 Clinical features of biliary tract intraductal papillary mucinous neoplasm *n* (%)**

|  |  |
| --- | --- |
| **Feature** | **Value** |
| Patients | 19 |
| Presenting symptoms |  |
|  Abdominal pain | 15 (78.9) |
|  Jaundice | 7 (36.8) |
|  Weight loss | 3 (15.8) |
| Without any symptoms | 1 (5.3) |
| Schistosomiasis1 | 4 (21.1) |
| Presence of cholangitis | 16 (84.2) |
| Repeated episodes cholangitis | 6 (31.6) |
| Location |  |
|  Intrahepatic and hilum | 13 (68.4) |
| Extrahepatic | 5 (26.3) |
|  Multifocal | 1 (5.3)  |
| Average maximum tumor diameter, cm (range)  | 3.54 (0.5-12) |
| Serum chemistry |  |
| Elevated carcinoembryonic antigen value (> 3.4 ng/dL)  | 5 (26.3) |
| Elevated CA 19-9 value (> 22 U/mL) | 8 (42.1) |

1Schistosomiasis of the liver was detected by postoperative histological examination.

**Table 3 Imaging features of biliary tract intraductal papillary mucinous neoplasm *n* (%)**

|  |  |
| --- | --- |
| **Feature** | **Value** |
| Patients | 19 |
| Imaging appearance |  |
|  Biliary stones | 12 (63.2) |
|  Proximal | 10 (83.3) |
|  Proximal and distal | 2 (16.7) |
|  Cholecystolithiasis | 0 |
| Dilated bile duct | 19 (100) |
|  Proximal | 6 (31.6) |
|  Proximal and distal | 13 (68.4) |
| Cyst | 10 (52.6) |
| Lesion | 10 (52.6) |
| Liver atrophy | 7 (36.8) |
| Imaging examination |  |
| Ultrasonography | 19 (100) |
| Computed tomography | 15 (78.9) |
| Magnetic resonance imaging | 12 (63.2) |
| Intraoperative choledochoscopy | 8 (42.1) |
|  Endoscopic retrograde cholangiography | 4 (21.1) |

**Table 4 Operative strategies and outcomes for biliary tract intraductal papillary mucinous neoplasm *n* (%)**

|  |  |
| --- | --- |
| **Feature** | **Value** |
| Patients | 19 |
| Operation |  |
| Left hepatectomy | 11 (57.9)  |
|  lobectomy | 6 (54.5) |
| Segmentectomy | 5 (45.5) |
| Right hepatectomy | 2 (10.5)  |
| Segmentectomy | 2 (100) |
| Pancreaticoduodenectomy | 1 (5.3)  |
| Bile duct excision | 4 (21.1) |
| Biopsy and choledochojejunostomy | 1 (5.3)  |
| Complications |  |
|  Stress ulcer  | 1 (5.3) |
|  Intra-abdominal abscess  | 1 (5.3) |
|  Pneumonia and bile leakage | 1 (5.3) |
|  Wound infection | 1 (5.3) |
|  Total | 4 (21.1) |
| Death within 30 d after surgery | 0 |
| Pathology |  |
| Benign | 9 (47.4) |
| Malignant | 10 (52.6) |
| Invasive component | 3 (15.8) |
| Presence of mucin |  |
|  Macroscopic visible mucin | 19 (100) |
|  Microscopic mucin | 19 (100) |
| Lymph node metastasis | 0 |
| Median follow-up period (mo) | 73 |
| Death | 8 (42.1) |
|  Benign | 3 (37.5) |
|  Malignant | 5 (62.5) |
| Overall median survival (mo) | 68 |



A B

**Figure 1 Imaging presentation of biliary tract intraductal papillary mucinous neoplasm.** A: Magnetic resonance cholangiography shows dilation of proximal biliary tract and a filling defect in the extrahepatic biliary tract (arrow); B: MRI shows an intra-luminal polypoid lesion originating from the extrahepatic biliary tract (arrow). MRI: Magnetic resonance imaging.



**Figure 2 Gross appearance of resected specimen reveals a nodular lesion in the distal common bile duct with massive mucin deposition throughout the bile duct.**



A B

**Figure 3 Histopathology presentation of biliary tract intraductal papillary mucinous neoplasm.** A: HE staining of common bile duct BT-IPMN, composed of papillary proliferation of atypical biliary epithelial cells (magnification, 40 ×); B: HE staining showing high-grade cytological atypia and mucin in the numerous goblet cells. (magnification, 100 ×). HE: hematoxylin and eosin.



**Figure 4 Kaplan–Meier curve depicts the survival time after surgery for patients with benign biliary tract intraductal papillary mucinous neoplasm (*n* = 9) and those with malignant biliary tract intraductal papillary mucinous neoplasm (*n* = 10).** A patient with malignant multifocal biliary tract intraductal papillary mucinous neoplasm underwent palliative surgery (choledochojejunostomy and biopsy).