

## A Difficult Diagnosis of Intraductal Papillary Neoplasia of the Bile Duct (IPNB): A Case Report and Review of Surveillance, Epidemiology, And End Results

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### Keywords:

Biliary tract neoplasms; Papilloma; Mucinous cystic neoplasm; Bile duct neoplasms

### Abbreviations:

CCA; Cholangiocarcinoma; IPNB: Intraductal Papillary Neoplasm of the Bile Duct

SEER: Surveillance Epidemiology and End Results; IPMN: Intraductal Mucinous Neoplasm of the Pancreas;

CT: Computed Tomography; MRCP: Magnetic Resonance Cholangiopancreatography; APC: Annual Percentage Change; MCN-L: Mucinous Cystic Neoplasm of the Liver; CEUS: Contrast Enhanced Ultrasound

## 1. Abstract

### 1.1. Background

Intraductal papillary neoplasm of the bile duct (IPNB) is a rare biliary tumor characterized by papillary growth in the bile duct, a high risk of malignant transformation, and an unknown prognosis. IPNB diagnosis has always been challenging, especially when the tumor is difficult to detect by imaging. Smaller IPNB tumors are difficult to diagnose preoperatively using only noninvasive imaging examination, and bile duct stones can impact the successful diagnosis of IPNB.

### 1.2. Case Report

A 61-year-old female patient with IPNB was admitted to our hospital with epigastric pain and obstructive jaundice. Imaging examination revealed only bile duct stones; no tumors were detected in the bile ducts. The patient underwent surgery at our institution, and a papillary mass with several stones and a large amount of mucus was found in the left hepatic duct. Postoperative pathology confirmed an intraductal papillary tumor with highly differentiated adenocarcinoma. The patient underwent genetic testing after surgery and is still receiving gene-targeted therapy.

### 1.3. Results

In the Surveillance, Epidemiology, and End Results (SEER) database, the incidence of IPNB is low and has decreased in recent years, but sex differences exist. Race, sex, tumor location and lymph node metastasis do not influence the prognosis of IPNB.

### 1.4. Conclusions

The incidence of IPNB is low, more men than women are diagnosed, and the prognosis is unknown. For suspicious patients, a variety of imaging examinations should be performed before surgery to confirm the diagnosis, which helps to make a comprehensive management plan before surgery.

## 2. Introduction

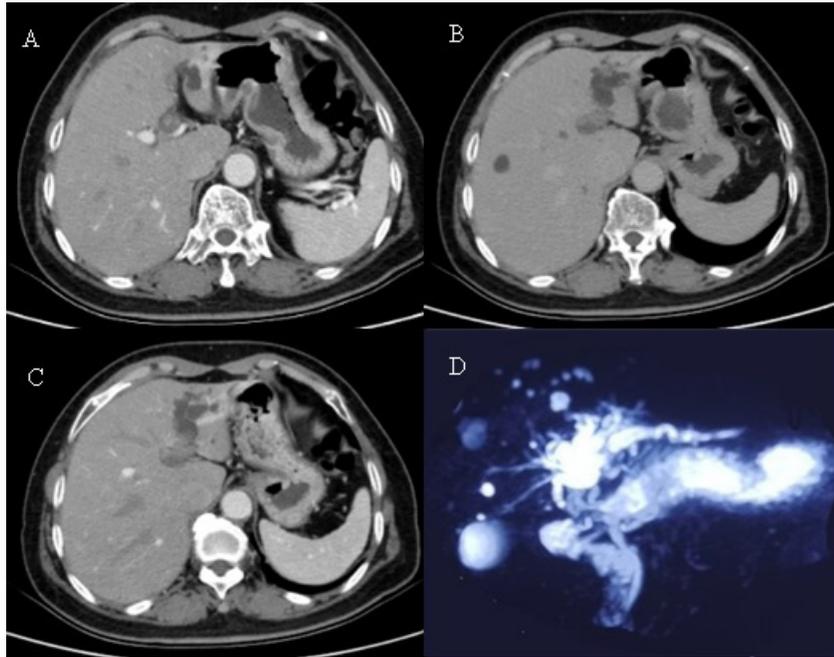
IPNB is a rare benign tumor of the biliary tract with malignant potential, accounting for 4%-38% of all biliary tract tumors. It is a precancerous lesion of cholangiocarcinoma (CCA), which mostly occurs in the hilar region and left hepatic duct [1]. Different from nonpapillary biliary tract tumors, IPNB is characterized by papillary growth in the bile duct with or without mucus secretion. IPNB can present as mild to highly heterogeneous hyperplasia or invasive carcinoma. The prognosis of IPNB is better than that of CCA,

and some studies have shown that the pathway of carcinogenesis is different from that of CCA [2-4]. IPNB has been described as an intrabiliary tumor similar to intraductal mucinous neoplasm of the pancreas (IPMN). IPNB shares the same histological subtypes as IPMN: pancreaticobiliary, gastric, intestinal, and eosinophilic [5], but IPNB is more aggressive than IPMN. The similarity between IPNB and IPMN is also reflected in the fact that they express the same immunophenotype, i.e., the MUC protein. However, the types of MUC expressed by each subtype of IPNB are significantly different from those expressed by IPMN [6], and it is still unclear whether the expression of MUC proteins is as predictive of prognosis for IPNB as it is for IPMN. The previous nomenclature for IPNB includes bile duct papilloma, papillomatosis, and papillary adenocarcinoma. In 2010, the WHO uniformly named IPNB, defining it as a new biliary tract tumor and classifying it into four types: IPNB with low, medium, and high intraepithelial heterogeneous hyperplasia and IPNB with invasive carcinoma [7]. Scholars now generally believe that IPNB is a precancerous lesion of CCA. The recognition of IPNB is still insufficient, its pathogenesis and epidemiology are not clear, and no uniform diagnostic principles or treatment guidelines have been established thus far. The present case of an IPNB patient is the first we have encountered. In this case report, we describe the patient's clinical data, review the relevant literature, and analyze the incidence and prognosis of IPNB by searching the case data of IPNB patients in SEER.

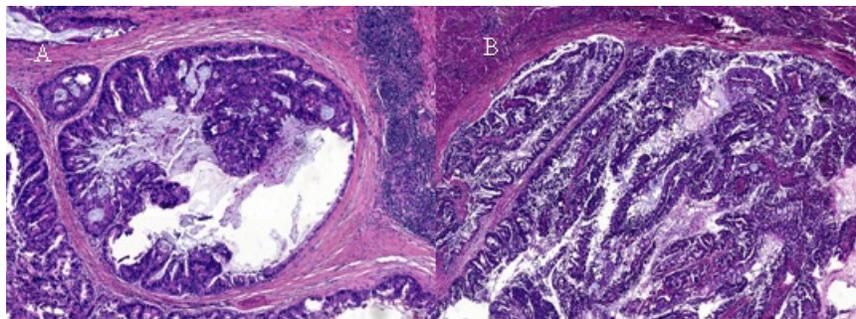
### 3. Case Report

A 61-year-old female was admitted to our hospital on July 28, 2021, with the chief complaint of "intermittent epigastric pain for more than 8 months and jaundice for 1 month". The patient developed intermittent epigastric pain with no obvious cause more than 8 months prior, and jaundice appeared 1 month prior with no fever or chills and no nausea or vomiting. Ultrasonography revealed a slightly hyperechoic mass in the proximal left hepatic duct bile duct with multiple dilated distal bile ducts. The patient had a history of cerebral infarction, diabetes mellitus type 2, and hypertension. For further evaluation of the lesion with 64-slice contrast-enhanced computed tomography (CT) and magnetic resonance

cholangiopancreatography (MRCP) was subsequently carried out. CT showed a round high-density shadow in the left hepatic duct, there was no enhancement in each phase of enhancement, and intrabiliary calculi were considered. The upstream bile duct was dilated and irregular, and inside the duct, uneven density shadows were observed. CT also revealed multiple intrahepatic hemangiomas and hepatic cysts, as well as gallbladder neck stones. In MRCP, only stones in the left hepatic duct were observed, and the bile duct in the left lobe of the liver was dilated (Figure 1). Laboratory tests revealed the following: total bilirubin, 42.2  $\mu\text{mol/L}$  (reference range: 1.6-20.6  $\mu\text{mol/L}$ ); direct bilirubin, 10.0  $\mu\text{mol/L}$  (reference range: 0.0-6.6  $\mu\text{mol/L}$ ); AST, 182 U/L (reference range: 0-40 U/L); ALT, 120 U/L (reference range: 0-40 U/L); CEA, 2.05 ng/ml (reference range: 0-5 ng/ml); AFP, 5.03 ng/ml (reference range: 0.89-8.78 ng/ml); and CA19-9, 10.93 UI/mL (reference range: 0-35 UI/mL). Serology for hepatitis B and C infection was negative. The patient's initial diagnosis was bile duct stones, obstructive jaundice, hepatic hemangioma, and hepatic cyst. Laparoscopic cholecystectomy + choledochotomy and lithotripsy were planned. Laparoscopic exploration revealed mild atrophic sclerosis of the left lobe of the liver. After the gallbladder was removed, the left hepatic duct was incised, and the cholangioscope was inserted. The left hepatic duct was filled with milky white jelly-like tissue mixed with several stones. An exophytic papillary mass, approximately 1 cm in diameter, was observed on the wall of the left hepatic duct, which was inseparable from the left hepatic duct. During the operation, tumors in the bile duct of the hilar were not excluded, and left hepatectomy + caudate lobectomy + extrahepatic cholangiotomy + Roux-Y anastomosis of the right hepatic duct and jejunum was performed. Postoperative pathology showed that the left intrahepatic duct papillary tumor was accompanied by severe epithelial dysplasia, the focal point was accompanied by infiltrating well-differentiated adenocarcinoma, and the embolus in the bile duct showed well-differentiated adenocarcinoma (Figure 2). After surgery, the patient underwent genetic testing, which showed mutations in the APC, KEAP1, KRAS, SGK1, SMARCA4, and STK11 gene loci. The patient is currently receiving targeted therapy and is in good health without signs of recurrence.



**Figure 1.** Characteristic findings of imaging examinations. (A) Axial contrast enhanced CT (arterial phase) showed a round high-density shadow in the left hepatic duct without enhancement. (B.C) Plain scan CT demonstrated irregular shape and inhomogeneous density shadow in the bile duct of left hepatic lobe without enhancement. (D) Magnetic Resonance-Cholangio-Pancreatography (MRCP) revealed extensively dilated bile ducts.

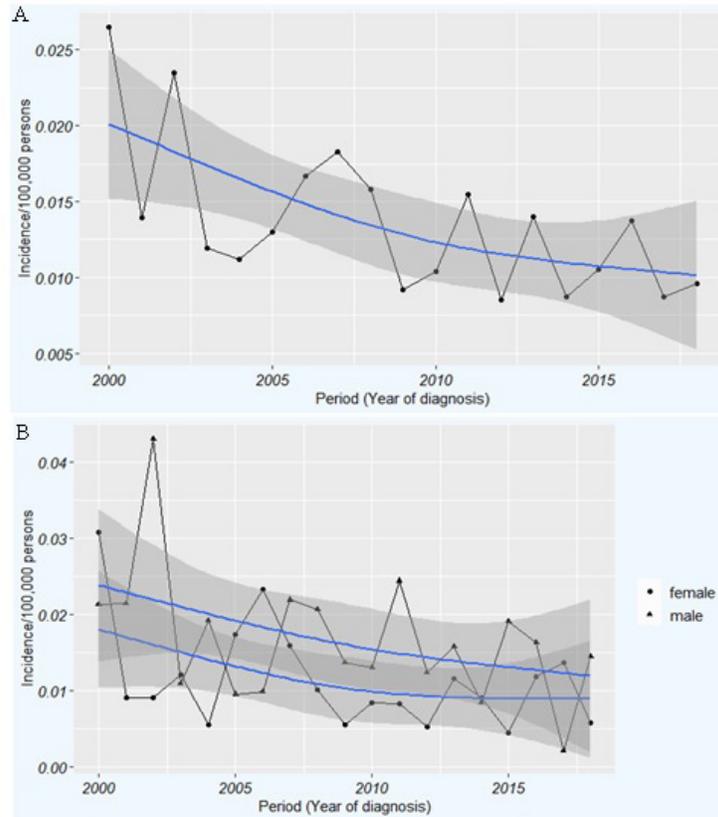


**Figure 2.** (A) Highly heterogeneous biliary epithelium; tumor papillary growth in the bile duct, partially breaking through the bile duct to become an invasive carcinoma; tumor secretes mucus to fill the bile duct.; (B) Pancreaticobiliary duct-type papillary tumor with a vascular core filling the entire bile duct.

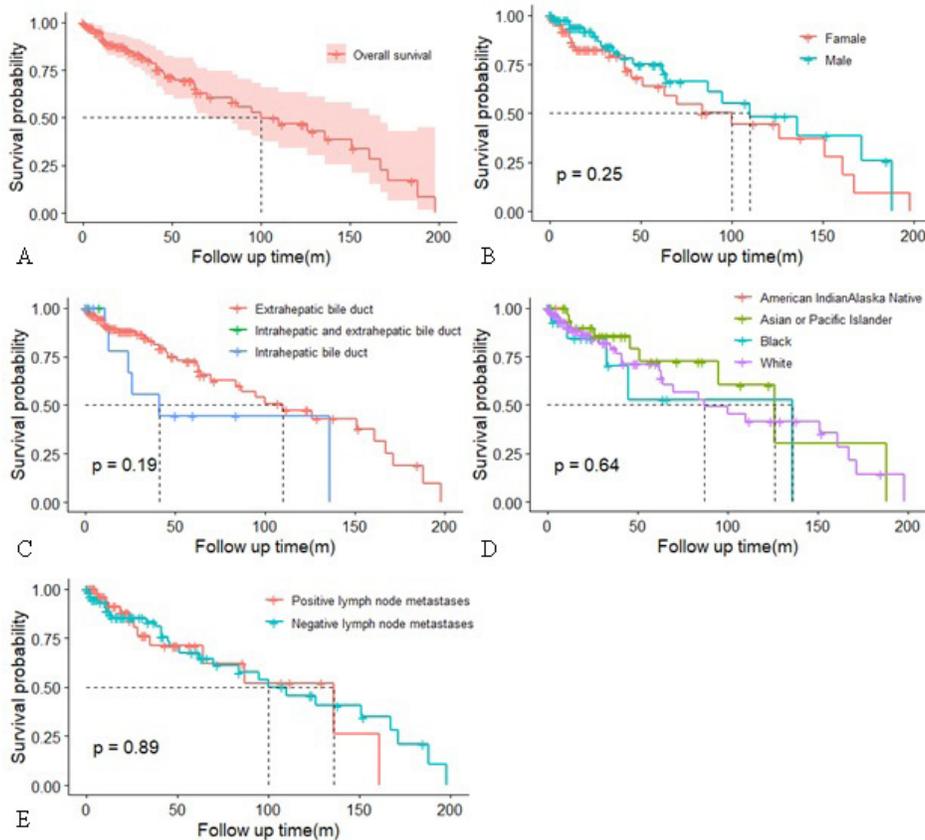
#### 4. Analysis of Incidence and Survival Rate of Seer Database

We searched the US SEER incidence database for the years 2000 to 2018 and retrieved records of 161 patients with IPNB. Of these cases, 88 (55%) were male, and 73 (45%) were female; 15 (9%) were in the intrahepatic biliary tract, and 144 (89%) were located in the extrahepatic biliary tract; 2 cases showed invasion of both the intrahepatic and extrahepatic biliary tracts; and lymph node metastasis was found in 81 (50%) patients. From 2000 to 2018, the

overall incidence trended downward, with an annual percentage change (APC) of -4.1% ( $p < 0.05$ ). The incidence in men was higher than that in women ( $p = 0.04$ ) (Figure 3). The overall prognosis of the patients was good, with a median survival of more than 8 years. Sex, race, tumor location and lymph node metastases had no significant effect on prognosis (Figure 4). The statistical software used R i386 4.0.5, and the difference was considered meaningful when  $p < 0.05$ .



**Figure 3.** (A) The incidence of IPNB in the SEER database from 2000 to 2018. The overall incidence trended downward. (B) The incidence is higher in men than in women ( $p=0.04$ ).



**Figure 4.** Disease-specific survival (DSS) analysis of IPNB in SEER. (A) Overall DSS of IPNB. (B) DSS according to sex. DSS is not significantly different between the male and female groups. (C) DSS according to the tumor site. DSS shows no significant differences among the three groups. (D) DSS according to race. DSS shows no significant differences among the four groups. (E) DSS according to metastasis of lymph node. DSS shows no significant differences between the positive lymph node metastasis and negative lymph node metastasis groups.

## 5. Discussion

As a rare disease, IPNB is characterized by its papillary growth in the bile duct, sometimes with mucus, and can progress to invasive carcinoma. Data from 2000 to 2018 in the SEER database revealed that the incidence of IPNB in the United States was relatively low during this period, showing a decreasing trend in recent years, and the incidence in males was higher than that in females. IPNB has been reported in the literature mostly in Eastern countries, with a trend of dissemination in Western countries. Since eastern cases are mostly associated with hepatolithiasis or *Clonorchis sinensis* infection, it has been suggested that both of these factors may be related to the etiology of IPNB [3,4,6]. However, this conclusion is not supported in cases from Western countries due to differences in the incidence of hepatolithiasis and *Clonorchis sinensis* between Eastern and Western countries. IPNB is mostly found in the left lobe of the liver, and the most common pathological subtype is the pancreaticobiliary type, followed by the intestinal, gastric, and oncocytic subtypes, with the invasive component mostly found in the pancreaticobiliary and gastric types [6,8]. More than one-third of IPNBs have mucus secretion, which occupies the lumen of the bile duct, covers the surface of the papillary lesion, and can cause dilatation of the upstream bile duct [9,10]. Mucus secretion was more common in intrahepatic biliary IPNB than in extrahepatic biliary IPNB and in intestinal and gastric subtypes than in oncocytic and pancreaticobiliary subtypes. Moreover, IPNBs with mucus secretion are mostly carcinomas in situ and are much less invasive than IPNB without mucus secretion [2,9,11,12]. The case we reported herein was a patient with pancreaticobiliary IPNB. The tumor originated in the left hepatic duct with massive mucus secretion and developed into an invasive carcinoma. Several bile duct stones were also found in the left hepatic duct. It is relatively difficult to diagnose IPNB, mainly because the clinical symptoms of IPNB are not specific. It is also difficult to distinguish IPNB from other tumors of the biliary tract, such as CCA and mucinous cystic neoplasm of the liver (MCN-L), by radiology alone. Cases of IPNB mostly appear on ultrasound, CT, MRI, and other imaging examinations as papillary-like masses in the bile duct with upstream bile duct dilatation or focal plaque-like masses with biliary stenosis, but some may simply exhibit bile duct dilatation with no occupancy on radiology [8,13]. This may be due to multiple small stones and mucus in the bile duct. In our patient, no tumor was found growing in the inner wall of the left hepatic duct on preoperative CT and MRCP examinations, which has not been reported in the literature. ERCP can obtain more direct images, which can reveal the tumor growth characteristics and extent and help determine the distal extent of resection [2]. However, the presence of mucus can make it difficult for the contrast medium to pass retrogradely through the bile duct. Currently, the only way to confirm the diagnosis is to perform cholangioscopy and biopsy in suspected cases [14,14]. For patients with a low tumor location, cholangioscopy

can observe the characteristics of tumor growth along the epithelium directly and clarify whether accompanying mucus secretion is present the tumor tissue, which can aid in pathological examination to clarify the diagnosis. However, similar to ERCP, for intrahepatic bile duct tumors, it is difficult to directly observe the tumor with choledochoscopy, and the diagnostic performance may not be better than CT and MRI. Percutaneous biliary biopsy appears to be a relatively straightforward diagnostic tool, but there is no literature showing that a percutaneous biopsy for IPNB in the intrahepatic bile ducts would be more beneficial for patients. For intrahepatic IPNB, only conventional examinations such as enhanced CT and enhanced MRI are available for diagnosis. For suspicious cases, the use of higher-resolution machines is recommended so that small lesions can be found. The combined use of multiple examination methods can help to improve the diagnostic accuracy. Contrast-enhanced ultrasound (CEUS) is not different from enhanced CT in examining IPNB and can be used as a routine examination [16]. There is a literature report that the imaging features of magnetic resonance cholangiography help to differentiate IPNB with invasive carcinoma from IPNB with intraepithelial neoplasia [17]. The imaging of IPNB with invasive carcinoma mostly shows an intraductal visible mass, tumor size  $\geq 2.5$  cm, multiplicity of the tumor, bile duct wall thickening, and adjacent organ invasion. Patients with IPNB mostly present with abdominal pain, obstructive jaundice, and acute cholangitis, but these symptoms are not specific for the diagnosis of IPNB. The specificity and sensitivity of alkaline phosphatase and CEA for the diagnosis of IPNB are also suboptimal. A significant increase in CA19-9 levels in patients with advanced IPNB has been reported in the literature [18]. The IPNB patients we reported had developed invasive carcinoma, but their CA19-9 levels were still in the normal range, indicating that not all cases of advanced IPNB are accompanied by elevated CA19-9. Surgical resection is the first choice of treatment for IPNB, and every effort should be made to achieve R0 resection, especially for patients suspected of having an invasive component. Lymph node metastases were found intraoperatively in 6%-8.2% of patients with IPNB [9]. Optional procedures involve partial hepatectomy combined with partial extrahepatic biliary resection and pancreaticoduodenectomy for tumors in the terminal bile duct or hepatopancreatic duct. Patients with IPNB who have extensive biliary metastasis may also be considered for liver transplantation, but the indications are very limited [9,19]. Early surgery has better results and can prevent the tumor from further progressing into invasive cancer. Internationally accepted guidelines for the treatment of IPMN stipulate that secondary surgery must be performed for high-grade atypical hyperplasia or invasive carcinoma in the resected stump of the pancreas, while additional resection is not necessary for patients with low-grade atypical hyperplasia in the stump [20]. There are no guidelines as to whether a positive IPNB resection stump requires a second procedure. Unlike the pancreas,

complete resection of the bile duct cannot be performed unless pancreaticoduodenectomy is performed. Therefore, to improve the patient's prognosis, the bile duct should be removed as far away from the tumor as possible to ensure R0 resection [2]. When the tumor cannot be completely removed, percutaneous transhepatic biliary drainage and chemotherapy can be used as palliative treatment, and it has also been reported that palliative chemotherapy can be applied after partial hepatectomy [6]. Our patient had intrahepatic IPNB with negative lymph node metastasis and achieved R0 resection. The patient underwent genetic testing after surgery and is still undergoing targeted therapy with no recurrence. The postoperative median survival of IPNB patients is significantly better than that of CCA patients [2,3]. Among the 161 patients we retrieved, the median survival time was 8 years. Sex, race, tumor location, and lymph node metastasis were not prognostic factors. Many studies have collectively shown that lymph node metastasis and the presence or absence of negative bile duct margins are independent risk factors affecting the prognosis of patients with IPNB [2,9,21,22]. However, there are still controversies. Luvira et al. [23] found that there was no significant difference in the prognosis of 98 IPNB patients with positive lymph node metastasis and 26 patients with negative lymph nodes. Due to the low incidence of IPNB, the current research on the risk factors affecting the prognosis of IPNB mostly consists of small-sample single-center studies. In the future, multicenter studies with a larger sample size are needed to explore the prognostic influencing factors of IPNB.

## 6. Conclusion

We report the case of a patient who had an intraductal biliary mass with massive mucus secretion that was not diagnosed clearly before the operation. The pathology confirmed IPNB with invasive cancer. The patient underwent partial hepatic and biliary resection and is still receiving gene-targeted therapy. IPNB is a benign tumor of biliary epithelial origin with malignant potential. The overall incidence of IPNB is low, but it is higher in men than women, and it varies greatly between the East and the West. Diagnosing IPNB is difficult, so a variety of tests should be used to confirm the diagnosis before surgery. A clear diagnosis of IPNB should be made as early as possible to avoid tumor progression. Intraoperatively, R0 resection should be achieved to the greatest extent possible, and avoiding positive margins can help to improve patient prognosis. Research on the prognostic factors for IPNB is necessary to meet the challenges associated with precancerous lesions and early cholangiocarcinoma treatment.

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