Review

A Review of Type 1 and Type 2 Intraductal Papillary Neoplasms of the Bile Duct

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[Abstract] Intraductal papillary neoplasm of the bile duct (IPNB) is a heterogeneous disease similar to intraductal papillary mucinous neoplasm of the pancreas. These lesions have been recognized as one of the three major precancerous lesions in the biliary tract since 2010. In 2018, Japanese and Korean pathologists reached a consensus, classifying IPNBs into type l and type 2 IPNBs. IPNBs are more prevalent in male patients in East Asia and are closely related to diseases such as cholelithiasis and schistosomiasis. From a molecular genetic perspective, IPNBs exhibit early genetic variations, and different molecular pathways may be involved in the tumorigenesis of type 1 and type 2 IPNBs. The histological subtypes of IPNBs include gastric, intestinal, pancreaticobiliary, or oncocytic subtypes, but type 1 IPNBs typically exhibit more regular and well-organized histological features than type 2 IPNBs and are more commonly found in the intrahepatic bile ducts with abundant mucin. Due to the rarity of these lesions and the absence of specific clinical and laboratory features, imaging is crucial for the preoperative diagnosis of IPNB, with local bile duct dilation and growth along the bile ducts being the main imaging features. Surgical resection remains the optimal treatment for IPNBs, but negative bile duct margins and the removal of lymph nodes in the hepatic hilum significantly improve the postoperative survival rates for patients with IPNBs.

Keywords: intraductal papillary neoplasm of the bile duct; subclassification; neoplasms; precancerous tissue; prognosis

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Since the 1960s, tumors characterized by intraductal papillary growth in the biliary system have been identified[1, 2]. However, due to a lack of clinical understanding of this kind of biliary disease, various names (fig. 1) have been used in international reports to describe its various macroscopic characteristics, such as mucin-hypersecreting bile duct tumors, papillomatosis of the bile duct, biliary papillary tumors, intraductal papillary neoplasia of the liver, intraductal growth type of peripheral cholangiocarcinoma, and intraductal papillary mucinous neoplasm of the biliary tract (IPMN-BT)[2–7]. Subsequently, Barton and Zen *et al*[8, 9] demonstrated a striking similarity between IPMN-BT and intraductal papillary mucinous neoplasm of the pancreas (IPMN-P), suggesting that these papillary tumors may represent distinct neoplasms. It was not until 2010 that the World Health Organization (WHO) accepted the proposal by Zen and Nakanuma *et al*[9, 10] to include this unique entity in the Classification of Digestive System Tumors as a precursor lesion of cholangiocarcinoma, named intraductal papillary neoplasm of the bile duct (IPNB), which can progress to IPNB with associated invasive carcinoma[11].

To facilitate clinician understanding and practice, a statement was jointly published by pathology experts from Japan and Korea in 2018[12] detailing their consensus on the concepts, pathological features, subclassification, and other aspects of IPNBs. Notably, this consensus subclassified IPNBs into two types, “type 1 IPNB” (classical IPNB) and “type 2 IPNB” (so-called papillary carcinoma or cholangiocarcinoma), which were included in the WHO Classification of Tumors of the Digestive System in 2019[13].

This article reviews the research progress in epidemiology and etiology, pathological classification and diagnosis, imaging features and classification, treatment, and prognosis since the subclassification of IPNBs was proposed. The similarities and differences between conventional IPNBs and novel subclassifications of IPNBs, as well as the controversies and challenges, are also emphasized.

1 EPIDEMIOLOGY AND ETIOLOGY

Due to the rarity of IPNBs, the exact incidence rate in the population remains unknown[14]. It is currently believed that IPNBs account for 4%–15% of bile duct tumors; type 1 tumors are more common than type 2 tumors and occur more frequently in male patients aged between 40 and 70 years[15–17]. The prevalence of this disease is higher in East Asian populations such as those in China, Japan, Korea, and Thailand, than that in European and American populations. However, there are no significant geographical differences in terms of sex ratio or age range[14, 18]. These observations suggest that IPNBs are highly correlated with diseases prevalent in East Asia, such as hepatolithiasis, clonorchiasis infection, and adenomas[5, 19]. In addition, certain chlorinated

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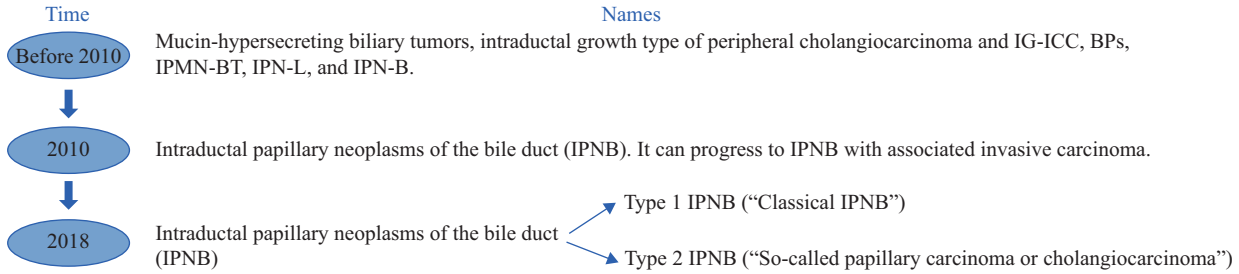

Fig. 1 Historical naming of IPNBs

chemicals have also been identified as contributing factors to IPNBs, as evidenced by a case in a Japanese printing factory in the early 21st century[20, 21]. The epidemiological characteristics of IPNBs are highly similar to those of conventional cholangiocarcinoma.

IPNBs demonstrate significant early genetic changes and different molecular pathways may be involved in the tumorigenesis of type 1 and type 2 IPNBs. For example, mutations in *KRAS* and *GNF43* are enriched in type 1 IPNBs, while mutations in *TP53*, *SMAD4*, *KMT2C*, and *ERBB2* are apparently more common in type 2 IPNBs[22–24]. In addition, a comprehensive analysis by Goeppert *et al*[25] revealed mutations in *CTNNB1* and *CDKN2A* in the early stages of IPNB, which are lost when the disease progresses to invasive cancer. Notably, no *GNAS* mutations have been identified. Additionally, Tomita *et al*[26] reported that fibroblast growth factor 10 (FGF10)-induced papillary changes and progression are inhibited by activators of the FGF10-FGFR2-RAS-ERK signaling pathway, suggesting this pathway as a potential therapeutic target for IPNBs. Furthermore, changes in the transcription factor EVI1 and in the PD-1/PD-L1 axis play critical roles in triggering tumorigenesis and provide important directions for precise treatment of IPNBs[27, 28].

2 PATHOLOGY

2.1 Histological Features

IPNBs are characterized by intraductal papillary or villous biliary neoplasms covering delicate fibrovascular stalks. Macroscopically, the affected ducts in the liver typically exhibit cystic dilation with abundant mucin, while in the extrahepatic ducts, cylindrical or fusiform dilation of the affected bile ducts is often observed[12].

2.2 Histological Grade

As a precursor lesion of cholangiocarcinoma, IPNB is described by the term "intraepithelial neoplasia" in the WHO Classification of Tumors of the Digestive System, 5th edition (2019). IPNB is classified into a two-tiered grading system, low-grade dysplasia (LGD) and high-grade dysplasia (HGD); the original three-tiered grading system and the ambiguous term "carcinoma *in situ*" have not been recommended[13]. When IPNB progresses to invasive cancer, it is called an intraductal papillary neoplasm of the bile duct with associated invasive carcinoma[11]. The frequency of LGD in type 1 IPNB is greater than that in type 2 IPNB, but HGD and associated invasive carcinoma are not uncommon[29].

2.3 Subclassification of IPNBs and Their Pathological Features

2.3.1 Type 1 IPNBs (Classical IPNBs) Type 1 IPNBs are commonly found in the intrahepatic bile ducts and contain mucin in the lumen. The pathological features of type 1 IPNBs are highly similar to those of IPMN-P. Type 1 IPNBs are composed of a lining tumor epithelium and a thin fibrovascular stalk, and their growth pattern is relatively uniform (fig. 2A)[22]. Furthermore, the papillary matrix is usually thin and may coexist with well-formed tubular components[12, 29].

2.3.2 Type 2 IPNBs (So-called Papillary Carcinomas or Cholangiocarcinomas) Type 2 IPNBs are typically found in extrahepatic bile ducts and rarely contain mucin. The lesions are mainly structurally complex papillary tumors, with slender fibrovascular stalks (height >5 mm above the adjacent biliary mucosa) and occasional thickening, mostly accompanied by irregular branches (fig. 2B). Notably, edematous wide-based lesions, tubular and sieve-like components, and some solid components can also be observed, but these generally account for less than 50% of the ductal contents (table 1 for comparison)[12, 29].

However, it is important to acknowledge that some lesions may have some pathological features of both type 1 and type 2 IPNBs, making their classification challenging[30]. In addition, it is unclear whether type 2 IPNB is an extreme papillary variant of conventional cholangiocarcinoma[12].

2.4 Histological Subtypes and Immunohistochemistry

IPNBs can be histologically subtyped as gastric, intestinal, pancreatobiliary, or oncocytic (gIPNB, iIPNB, pbIPNB, and oIPNB, respectively). These tumors do not solely appear in the tissue and show geographical

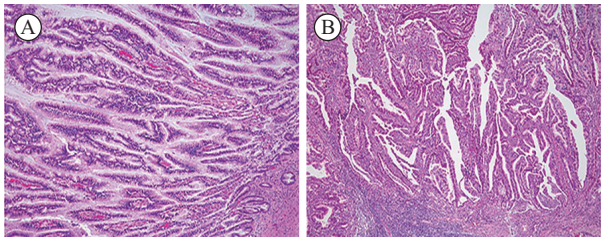

Fig. 2 Hematoxylin and eosin staining of IPNBs (×4)
A: Type 1 IPNB: lining tumor epithelium and a thin fibrovascular stalk coexist with well-formed tubular components; B: Type 2 IPNB: thickened fibrovascular stalks, mostly accompanied by irregular branches Adapted from: Aoki Y, *et al*[22].

differences, with pbIPNBs being the most common in the United States, while iIPNBs are more common in some Asian countries[24, 31]. At present, pbIPNBs are known to be common among type 2 IPNBs, and the pbIPNB subtype most commonly shows matrix invasion among the 4 subtypes, followed by the intestinal subtype. However, no significant differences in the gastric or oncocytic subtypes have been observed between type 1 and 2 IPNBs[29, 32].

In terms of immunohistochemical staining of IPNBs (table 2), Xian *et al*[24] reported that mucin (MUC)1 is prominently expressed in pbIPNBs but is not expressed in iIPNBs. Additionally, negative MUC2 expression and a high frequency of S100P expression are important for diagnosing pbIPNB[15]. gIPNBs and oIPNBs are positive for MUC5A and HepPar1 but negative for MUC1. Cytokeratin (CK)19 is frequently expressed in both precancerous lesions and infiltrative tumors. Nakanuma *et al*[29] suggested that CK20 is typically expressed in iIPNBs. However, a minority of gIPNBs exhibit CK20 expression, which is absent in pbIPNBs and oIPNBs.

Although the correlation between the 2 sub-classifications of IPNB and the 4 subtypes based on histology and immunohistochemical data is not particularly prominent, future breakthroughs in understanding the tumor microenvironment, histology, and immunology will improve not only the accuracy and convenience of IPNB diagnosis but also the efficacy of IPNB treatment through precisely targeted therapy[32, 33].

3 CLINICAL CHARACTERISTICS AND LABORATORY TEST RESULTS

According to a multicenter cohort study of 397 patients in Korea and a meta-analysis by Gorden-weeks in 2016[34, 35], the most common clinical manifestation in IPNB patients was abdominal pain, followed by jaundice and cholangitis. It should be noted that the possibility of these manifestations occurring in type 2 IPNB is higher than that in type 1 IPNB. Nevertheless, there are also many asymptomatic individuals, which may be related to the absence of bile duct stones or obstruction caused by massive mucin secretion.

In 2020, a collaborative study involving 694 patients with IPNB from Japan and Korea revealed that laboratory test results for aspartate aminotransferase (AST), alanine aminotransferase, alkaline phos-phatase, γ-glutamyl transferase, total bilirubin, carcinoembryonic antigen, and carcinoembryonic antigen 19-9, among others, were significantly higher in type 2 IPNB patients than in type 1 IPNB patients. However, laboratory results for lactate dehydrogenase, triglycerides, total cholesterol, white blood cell count, red blood cell count, hemoglobin, C-reactive protein levels and hepatitis B screening results showed no significant differences. Moreover, the differences in laboratory test results typically correspond to the patients' clinical presentations[36].

4 IMAGING FEATURES

IPNB patients typically suffer from bile duct stones and cholangitis, as well as varying degrees of bile duct dilatation and distortion, which makes this type of disease susceptible to misdiagnosis via noninvasive imaging techniques[37]. Therefore, IPNBs are often diagnosed and differentially diagnosed via a variety of imaging techniques (table 3). However, compared to conventional IPNBs, distinguishing IPNB subclassifications based on specific imaging features remains challenging.

4.1 Ultrasonography

Zheng *et al*[38] classified IPNBs into 3 types based on features observed through grayscale ultrasound. Type 1 IPNB is characterized by diffuse dilation of the bile duct with no visible mass, which must be distinguished from biliary dilatation caused by conditions such as congenital cholangiectasis. Type 2 IPNB is defined as localized bile duct dilation accompanied by papillary masses, which

Table 1 Comparison of pathological features between type 1 IPNB and type 2 IPNB

Features	Type 1 IPNB	Type 2 IPNB
Histological features	Lining tumor epithelium and a thin fibrovascular stalk, coexisting with well-formed tubular com-ponents	Thickened fibrovascular stalks, mostly accompanied by irregular branches, tubular or sieve-like com-ponents, and some solid components can also be observed.
Organization structure	Uniform, with a thin papillary matrix	Complex, with edematous wide-based lesions
Histologic grade	Most are LGD, HGD with regular growth patterns.	Most HGD, invasive cancer
Massive mucin production	Frequently	Uncommonly
Relation to IPMN	Similar	Unlike IPMN prototypes
Common locations	Intrahepatic bile duct	Extrahepatic bile ducts (containing the porta hepatis)

HGD: high-grade dysplasia; IPMN: intraductal papillary mucinous neoplasm; LGD: low-grade dysplasia

Table 2 Histologic subtypes classified by MUC and cytokeratin

Histological subtype	Profile of MUCs				Cytokeratin		
	MUC1	MUC2	MUC5AC	MUC6	CK7	CK19	CK20
iIPNB	–	+	+	–	+	+	+
gIPNB	+	–	+	+	+	+	+
pbIPNB	+	–	+	–	+	+	–
oIPNB	–	–	+	+	+	+	–

gIPNB, iIPNB, pbIPNB, oIPNB): gastric, intestinal, pancreatobiliary, and oncocytic types of IPNB, respectively; MUCs: mucin core proteins

Table 3 The utility of different imaging techniques in patients with IPNB

Imaging techniques	Utility
US, CEUS, IDUS	Excluding conditions such as biliary sludge, nonshadowing stones, and blood clots; IDUS: assessing the depth of invasion and lymph node involvement, no superior diagnostic value for type 1 IPNB
CT, CECT, PET	Differentiation from conventional cholangiocarcinoma, evaluating the extensive infiltration, determination of surgical approach
MRI, CEMR, MRCP	Detecting subtle lesions, better identification of cholelithiasis and conventional cholangiocarcinoma
PTC and ERC	Determination of tumor location, mucin detection and drainage

CEUS: contrast-enhanced ultrasonography; CECT: contrast-enhanced computed tomography; CEMR: contrast-enhanced magnetic resonance image; CT: computed tomography; ERC: endoscopic retrograde cholangiography; IDUS: intraductal ultrasonography; MRCP: magnetic resonance cholangiopancreatography; MRI: magnetic resonance image; PET: positron emission tomography; PTC: percutaneous transhepatic cholangiography; US: ultrasonography

can be easily confused with mucinous cystic tumors. The key point of identification is the presence or absence of a connection with the bile duct. Type 3 IPNB is characterized by a solid mass surrounded by bile duct dilation and distal bile duct dilation and must be differentiated from conventional cholangiocarcinoma[39]. In addition, Liu and Chatterjee *et al*[40, 41] reported that IPNB masses showed high enhancement during the arterial phase and low enhancement during the portal venous or late phases on contrast-enhanced ultrasonography (CEUS). The bile duct proximal to the mass did not show enhancement, which helps to obtain a reliable diagnosis. CEUS is helpful for excluding biliary sludge, non-shadowing stones, and blood clots but has no superior diagnostic value for type 1 IPNB. Intraductal ultrasonography (IDUS) not only overcomes the limitations of conventional ultrasound due to obesity and intestinal gas retention but also helps evaluate the depth of tumor invasion of the bile duct wall and whether lymph nodes are involved. This approach is crucial for clinicians to determine the resectability of tumors and patient prognosis.

4.2 Computed Tomography

IPNBs appear as localized bile duct dilatations and patchy masses with bile duct stenosis on both computed tomography (CT) and contrast-enhanced CT (fig. 3A)[42–44]. Tumor growth along the medial aspect of the bile duct wall, enhancement of the basal margin of the tumor, and relative density or hyperdensity in the arterial phase compared to the liver parenchyma can also be observed on contrast-enhanced CT. The above features have a positive predictive value of more than 90% for differentiating conventional cholangiocarcinoma. Additionally, Ikeno, Takanami, and Youn *et al*[45–47] noted that IPNB masses (especially in patients with HGD or invasive cancers) exhibit hypermetabolic fluorodeoxyglucose (FDG) uptake on PET imaging, suggesting that FDG-PET is a favorable option.

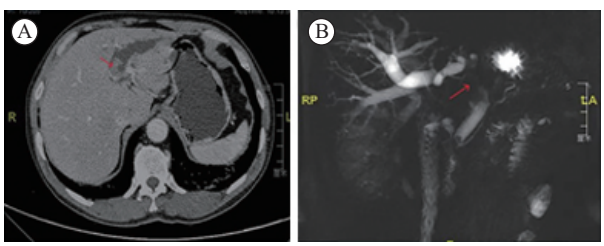

Fig. 3 A: Contrast-enhanced CT image of type 1 IPNB; B: MRCP 3image of type 2 IPNB
The red arrows represent the tumor.

4.3 Magnetic Resonance Imaging

Currently, magnetic resonance imaging (MRI) combined with magnetic resonance cholangiopancreatography (MRCP) is widely used in clinical biliary disease imaging due to its high contrast resolution, which can assist in the detection of subtle lesions. As demonstrated by routine MRI studies by Lee and Joo[48, 49], MRCP has great advantages in detecting and evaluating the tumor heterogeneity of IPNBs and intraductal tumors (fig. 3B). Most IPNBs exhibit low signal intensity on T1-weighted images and high signal intensity on T2-weighted images. Disproportionate upstream and downstream dilation of the bile ducts is primarily depicted as linear and curvilinear low signal stripes on MRCP, which is a special finding in recent years called the "thread sign", mainly observed in extrahepatic bile ducts[50]. In addition, the features of invasive cancer associated with IPNBs mainly include liver capsule retraction, liver parenchymal atrophy, soft tissue enhancement in the duct with no enhancement around the bile duct, thickening of the bile duct wall, and a tumor diameter greater than 2.5 cm[48, 51]. Recently, through apparent diffusion coefficient (ADC) histogram analysis, Jin *et al*[52] found that wall nodule size and skewness are factors that predict the invasiveness of IPNB through ADC histogram analysis. Notably, Jeon *et al*[53] performed a multivariate analysis to distinguish between type 1 and type 2 IPNBs using important MRI manifestations, including extrahepatic location and absence of bile duct tumor segment dilatation.

4.4 Percutaneous Transhepatic Cholangiography and Endoscopic Retrograde Cholangiopancreatography

Yoon *et al*[54] discovered through percutaneous transhepatic cholangiogrpahy (PTC) that the most common imaging feature of IPNBs is an abnormal filling defect inside the bile duct. Moreover, multiple round or oval filling defects and irregularly blurred bile duct walls are common imaging characteristics observed under PTC or endoscopic retrograde cholangiopancreatography (ERC). However, Yeh and Chung *et al*[55, 56] suggested that in some patients, IPNBs secrete a large amount of mucus, which reduces the fluidity of bile and prevents contrast agents from fully displaying all lesions in the bile duct, leading to missed diagnoses. Furthermore, PTC and ERC were also unable to accurately assess the extent of superficial spread or to determine the location of the surgical margin. Therefore, bile duct state evaluation by either PTC or ERC

may not be the optimal choice[57].

4.5 Percutaneous Transhepatic Cholangioscopy and Peroral Cholangioscopy

The visualization of IPNBs via cholangioscopy provides more intuitive insight than simple imaging procedures. Bile duct obstruction due to IPNBs is usually partial and associated with mucus, and the tumor inside the duct appears as a rod shape, occasionally showing a coral reef-like mucosal projection. In addition, the surface of papillary tumors visible under the scope may have small, irregular velvety or serrated contours. With the introduction of the SpyGlass SOC system and ultraslim upper endoscope, the operation of peroral cholonagioscopy (POCS) has been simplified. However, diagnosing type 1 IPNB complicated by a large number of biliary stones is difficult. Itoi *et al*[58–60] reported that POCS performed with narrow-band imaging (NBI) is more beneficial for observing the fine mucosal structure and tumor vessels than conventional POCS, as POCS with NBI allows direct observation from the initial ERC. In addition, compared with POCS, percutaneous transhepatic cholangioscopy (PTCS) is simpler and more convenient and has a shorter examination pathway. However, time to form a sinus tract is needed when using PTCS, and there is a risk of sinus implantation metastasis, tumor seeding, bile fistula, and bleeding complications[61]. Nevertheless, in patients with intrahepatic type 1 IPNBs in the presence of large amounts of mucus secretion or stones, PTCS has the advantage over POCS of allowing easy determination of the extent of the lesion and thus guiding clinicians in selecting appropriate surgical strategies. Although the pathological results obtained via cholangioscopy still do not accurately reflect the extent of tumor infiltration, PTCS may allow for the placement of a stent or tube for the reduction of jaundice in preparation for surgical resection while determining the borders of the mass; thus, Lim *et al*[62] reported that both POCS and PTCS are necessary tools for preoperative diagnosis.

5 MORPHOLOGICAL CLASSIFICATION

There are additional criteria for the morphological classification of IPNBs, such as bile duct dilatation, cyst formation, tumor protrusion or superficial spread, invasive growth, and site of disease. A total of 5 levels of classification and a more detailed 7-level morphological classification currently exist internationally[63–66]. Most notably, Kim *et al*[67] recently simplified the morphological classification of IPNBs into 3 categories in a "modified anatomical classification" (fig. 4): intrahepatic, extrahepatic (including the left and right hepatic ducts), and diffuse, with the intrahepatic type being further categorized into cystic and ductal dilatation (which are more common in patients with type 1 IPNBs). The "modified anatomical classification" did not show significant differences in survival analysis compared with other classifications and is more favorable for clinical practice.

6 DIFFERENTIAL DIAGNOSIS

Due to the low prevalence of IPNBs and their ambiguous imaging features, extensive clinical experience is required for the differential diagnosis of these neoplasms. IPNBs need to be distinguished not only from other precancerous lesions of the bile ducts, such as mucinous cystic neoplasms (MCNs) and biliary intraepithelial neoplasms (BillNs)[68], but also from other malignant diseases, such as cholangiocarcinoma and colorectal cancer metastases[18, 49, 69]. The key points for differential diagnosis are shown in table 4.

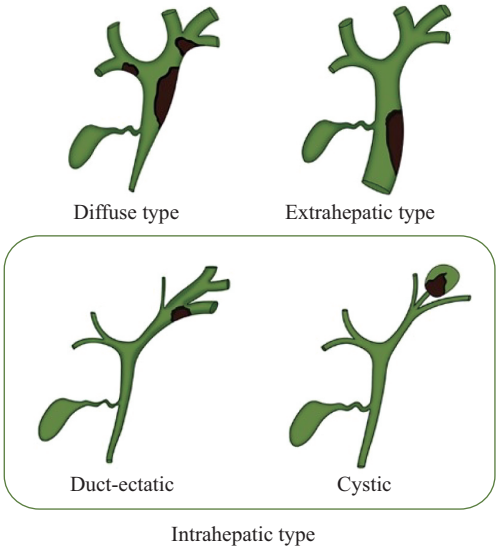

Fig. 4 Chematic diagram of "modified analytical classification"

Table 4 Differentiation, diagnosis, and identification points of IPNB

Differential diagnosis		Identification points
Benign biliary diseases	Cholelithiasis	Frequent Charcot's triad and no significant neoplasia of the bile duct wall
	Hepatic cysts	There is no mural nodule and the downstream bile duct is often not dilated.
	Congenital cholangiectasis	Many have childhood onset and may present with an abnormal pancreaticobiliary junction without mural nodules or septa.
Precancerous lesions	MCN	Patients are mostly female and show a "cyst in the middle of the cyst", mostly non communicating with the biliary tree, and an ovarian like stroma beneath the epithelium.
	BillN	It is often only identified microscopically and the fibrovascular pedicle is less than 3 mm.
Malignant tumors	ICC	Solid peritubular lesions, which may present with capsular constriction, peripheral bile duct dilatation, and satellite nodules
	Colorectal liver metastasis	The patient had a history of colorectal cancer and was positive for CK20 and MUC2 to aid in the diagnosis.

BillN: biliary intraepithelial neoplasm; ICC: intrahepatic cholangiocarcinoma; MCN: mucinous cystic neoplasm

7 TREATMENT

Surgical excision of IPNBs according to the location of the lesion is recognized as the best treatment option for intrahepatic IPNBs. Lobectomy is typically used to resect IPNBs located within the liver. For IPNBs involving the hepatic hilum, hemihepatic resection of the affected bile ducts and hepato-intestinal anastomosis can be performed. For tumors in the lower portion of the common bile duct, pancreaticoduodenectomy is the optimal strategy. In addition, liver transplantation or combined radical pancreaticoduodenectomy may be considered a therapeutic option for multicenter recurrent intrahepatic IPNBs and for diffuse IPNBs[70, 71]. The new subclassification of IPNBs is more helpful to physicians in choosing surgical strategies than the conventional single umbrella term. This is because type 2 IPNBs are more likely to occur in the extrahepatic bile ducts and are often infiltrative than type 1 IPNB[12], and these differences clearly result in different primary surgical approaches. In any case, ensuring pathologically negative bile duct (R0) margins and removing regional lymph nodes remain essential procedures[72, 73].

Targeted drugs (such as MEK inhibitors and radiolabeled targeted molecules)[26, 32], immunotherapy drugs (anti-PD-1 monoclonal antibodies)[28], and chemotherapy drugs (mainly fluorouracil and gemcitabine)[69] can be used to provide preoperative treatment and symptom relief. In addition, endoscopic techniques such as endoluminal radiofrequency ablation, argon plasma coagulation and photodynamic therapy followed by stent placement can achieve the expected effect of removing visible tumors and restoring bile duct patency[74–78]. These treatment modalities provide alternative strategies for IPNB patients with postoperative tumor recurrence, those unable to undergo surgery, or those with advanced cancer[79].

8 PROGNOSIS AND FOLLOW-UP

The 5-year survival rate of patients with IPNBs after surgical resection is 68%–80%. Kubota *et al*[36] reported that type 1 IPNB patients had a 5-year cumulative survival rate of 75.2%, whereas type 2 IPNB patients had a 50.9% survival rate. In addition, there was a significant difference in terms of disease-free survival, but there was no difference in terms of the incidence of invasion of the hepatic arteries, hepatic veins, or portal veins, which are better than those in conventional cholangiocarcinoma[34, 36, 64]. You *et al*[73] reported that nearly half of patients relapse within the first year after surgery, with an average survival time of 16 months after recurrence. Numerous studies[22, 73, 80–82] have confirmed that R1 margins and lymph node metastasis are significant risk factors for reduced survival in patients with IPNBs. Moreover, the abundant expression of MUC6 has a marginal protective effect on patients treated with IPNB, possibly due to its ability to suppress invasion progression[83, 84].

After analysis of the postoperative pathological and immunohistochemical results, follow-up examinations are recommended every 3 or 6 months for at least 2 years after surgery[37, 73].

9 DISCUSSION

Since IPNB was classified as a unique entity similar to IPMN-P with higher survival rates, nearly a decade has passed until the WHO adopted the IPNB subclassification statement proposed by Japanese and Korean experts in 2019. However, the WHO did not specify the specific diagnostic and classification criteria for this subclassification. Onoe *et al*[30] attempted to use a scoring system and found that there were still abundant gray-zone lesions between type 1 and type 2 IPNBs, leading to disagreement among researchers regarding the proposed classification method. Even in the 2015 Armed Forces Institute of Pathology (AFIP) atlas, the term IPNB was not used[85]. How to distinguish type 1 and type 2 IPNB conveniently and accurately has become one of the important challenges that researchers urgently need to solve.

The risk factors and clinical manifestations of IPNB patients are similar to those of patients with conventional cholangiocarcinoma, which may indirectly confirm that IPNBs follow the path of adenoma-carcinoma progression. However, at the microscopic level, such as within the microenvironment, according to molecular genetics and histology, there are significant differences between type 1 and type 2 IPNBs. The identification of these differences is an important breakthrough for future differential diagnosis and precise treatment of type 1 and type 2 IPNBs. Early diagnosis and correct subclassification of IPNB facilitates the selection of appropriate treatment strategies and improves prognoses. Therefore, we believe that this new classification will be more clinically useful and rational than the traditional generic term in the future.

The classification of IPNBs into type 1 and type 2 IPNBs and their inclusion in digestive system tumor guidelines are profound and multidisciplinary achievements for researchers worldwide. This subclassification largely corresponds to the differences that exist between the two types of IPNB in terms of molecular and microenvironment information, imaging features and morphological classification, treatment modality, and prognosis. The IPNB classification has excellent clinical value, but the accompanying confusion, debates, and significant challenges need to be addressed.

Conflict of Interest Statement

We declare no conflicts of interest for this article. The corresponding author is responsible for reviewing this policy with all the authors.

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