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Clinicopathological findings and imaging features of intraductal papillary neoplasm of the bile duct: comparison between contrast-enhanced ultrasound and contrast-enhanced computed tomography

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Abstract

Purpose Intraductal papillary neoplasms of the bile duct (IPNBs) are a group of rare lesions with uncertain clinical findings and imaging features. We aim to investigate the clinicopathological features and imaging findings of IPNBs on contrast-enhanced ultrasound (CEUS) and contrast-enhanced computed tomography (CECT).

Methods From February 2005 to March 2018, 30 patients with pathologically confirmed IPNBs were retrospectively identified in our hospital. Demographic, clinical, and pathological data, CEUS and CECT features and surgical strategies were analyzed.

Results The most common clinical manifestations were abdominal pain (53.3%), jaundice (23.3%), and acute cholangitis (10.0%). Among all lesions, 5/30 (16.7%) lesions presented as dilated bile ducts only, while 13/30 (43.3%) lesions presented as dilated bile ducts with intraductal papillary masses, and 12/30 (40.0%) presented as solid masses with dilated bile ducts. For the 20 patients who underwent both CEUS and CECT, 18 lesions were hyperenhanced on CEUS, and 17 lesions were hyperenhanced on CECT in the arterial phase. In total, 16 and 18 lesions showed washout in the portal and late phases on CEUS, while the corresponding number of lesions that showed washout in the portal and late phases on CECT were 11 and 13. Twelve lesions (40.0%) showed atypical hyperplasia, while 16/30 (53.3%) lesions underwent malignant transformations.

Conclusions There are 3 major forms of IPNBs on grayscale ultrasound, including diffusely dilated bile ducts without visible mass; focal dilated bile duct with intraductal papillary masses; and solid mass surrounded by dilated bile ducts. The enhancement patterns of IPNBs on CEUS and on CECT were consistent. IPNB has a high malignant potential, and patients should be treated with surgical resection after the diagnosis is established.

Keywords Intraductal papillary neoplasms of the bile duct · Clinicopathological features · Contrast-enhanced ultrasound · Contrast-enhanced computed tomography

Abbreviations

IPNB	Intraductal papillary neoplasms of the bile duct
CEUS	Contrast-enhanced ultrasound
CECT	Contrast-enhanced computed tomography
ICC	Intrahepatic cholangiocarcinoma
CPS	Contrast pulse sequencing
CHI	Contrast harmonic imaging
CA125	Carbohydrate antigen 125
CA19-9	Carbohydrate antigen 19-9

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Introduction

Intraductal papillary neoplasms of the bile duct (IPNBs) are a group of rare intraductal papillary lesions characterized by localized, multifocal or diffuse papillary neoplasia in the biliary tree (intrahepatic/extrahepatic bile duct and gall bladder) [1, 2]. According to previous reports, approximately 50.0–90.3% of IPNBs were found to be located in the intrahepatic bile duct [3, 4], especially in the left lobe bile duct system [4], while other reports showed that the most common location was the hepatic hilum (59%) [5]. Imaging features that predict IPNBs include dilated bile ducts and intraductal masses. In addition to these findings, the enhancement patterns of IPNBs are indistinguishable from those of most malignant focal liver lesions on contrast-enhanced computed tomography (CECT) and show hyperenhancement in the arterial phase and washout in the portal and late phases [6]. Moreover, IPNBs are often found with different degrees of dysplasia [7] and have a high malignant potential as a premalignant disease [8]. Malignant IPNBs account for 2.9% to 8.9% of intrahepatic cholangiocarcinoma (ICC) and are known as the intraductal growth type of ICC [9]. Therefore, the preferred treatment is hepatectomy because the papillary tumors and associated mucin may also cause recurrent obstructive jaundice and cholangitis [10].

Since the clinical findings, as well as imaging features, of IPNBs are still uncertain due to the rarity of the disease, the preoperative diagnosis of IPNBs mainly relies on biopsy, which is an invasive method and may lead to false-negative diagnoses when the tumor is small [9]. Contrast-enhanced ultrasound (CEUS), a noninvasive and convenient imaging modality, has been indicated to be a powerful alternative method to detect and characterize focal liver lesions in clinical practice [11]. This study summarizes our experiences in order to gain a better understanding of the clinicopathological features and to investigate and compare the imaging findings of IPNBs on CEUS with CECT.

Materials and methods

Patients

The institutional review board approval of this study was obtained from the ethics committee of our hospital. Informed consent from the patients was waived by the ethical committee of our hospital in this study. We retrospectively reviewed the demographic, clinical, and pathological data as well as the CEUS and CECT examinations and surgical strategies of 30 patients with pathologically confirmed IPNB in our hospital from February 2005 to March 2018. Pathologically confirmed mucinous cystic neoplasms with ovarian-type stroma and lesions without microscopic or macroscopic mucin secretion were excluded.

CEUS

The CEUS examinations were performed using an Acuson Sequoia 512 scanner (Siemens Medical Solutions, Mountain View, CA, USA) equipped with a 4V1 vector transducer (frequency range 1.0–4.0 MHz) using contrast pulse sequencing (CPS, Mechanic Index from 0.15 to 0.21) or an Aplio 500 or Aplio XV (Toshiba Medical Systems, Tokyo, Japan) scanner equipped with a 375BT convex transducer (frequency range 1.9–6.0 MHz) using contrast harmonic imaging (CHI, Mechanic Index from 0.05 to 0.10).

After scanning the entire liver with grayscale imaging, the location, size, border, and shape of each lesion was evaluated and recorded. After initiating CPS or CHI being, we used an SF6-filled microbubble agent (SonoVue; Bracco, Milan, Italy) as the ultrasound contrast agent. Each patient was injected with 2.4 ml of dispersion into the antecubital vein in a bolus fashion and then received a flush of 5 ml 0.9% saline solution after each injection. After the injection, the target lesion and the surrounding liver parenchyma were observed for 6 min, and the arterial (from 10–20 s after the injection to 30–45 s), portal (from 30–45 s to 120 s after the injection) and late (121–360 s after the injection) phases [11] were stored on a hard disk. All the grayscale US and CEUS examinations were performed by radiologists in our hospital with more than 3 years of experience in liver CEUS.

CECT

In addition, 27/30 patients also underwent CECT examinations 1 week before or after the CEUS examination. The CECT examinations were performed with a computed tomography system (Aquilion 64, Toshiba, Tokyo, Japan). The examination for each patient was performed with the following procedure: First, the patient received an unenhanced helical sequence scan through the epigastrium. Then, different volumes of contrast agent (Ultravist 300, Schering, Berlin, Germany) (1.5 ml/kg) were injected into the antecubital vein (3–4 ml/s). The following CT acquisition parameters were used: 120 kV; 200–250 mAs; collimation 64 mm × 0.5 mm; slice thickness 0.5 mm; slice increments 0.5 mm; and pitch 0.9. Additionally, the arterial (0–45 s after the injection), portal (46–120 s after the injection) and late (121–360 s after the injection) phases were recorded.

Image analysis

Two experienced radiologists (M.X. and L.D.C), who had at least 5 years of experience in liver CEUS and were unaware of any information of the patients involved, randomly reviewed the CEUS and CECT records and evaluated the enhancement patterns, levels and various other features, such as the location, border of the lesions, etc. The enhancement pattern was subdivided as homogeneous or heterogeneous, and the level of enhancement was subdivided into hyperenhanced, isoenhanced and hypoenhanced [12].

Statistical analysis

In our study, continuous data were presented as the mean ± standard deviation (SD) or median and interquartile range. Comparisons between the groups were made with the Student's *t* test when the data were normally distributed. Qualitative data were analyzed by χ^2 test or Fisher's exact probability test, and paired qualitative data were analyzed with the McNemar test. The statistical analyses were performed using SPSS version 20.0 (SPSS Inc., Chicago, IL, United states). A p value < 0.05 was considered statistically significant.

Results

Clinical presentation

Among the patients, there were eighteen men and twelve women who had a mean age of 59.4 ± 12.2 years (range 38–74 years). All patients were Asian. The clinical manifestations consisted of right upper quadrant pain ($n = 16$), which was the most common presenting symptom, jaundice ($n = 7$), and acute cholangitis ($n = 3$); the disease was detected in asymptomatic patients ($n = 5$) during routine examinations. One patient complained of abdominal pain with jaundice. Five patients were detected to have elevated carbohydrate antigen 125 (CA125) levels during serological testing (up to 548.79 kU/l), and four patients had elevated carbohydrate antigen 19-9 (CA19-9) levels (up to 138.16 kU/l). Only one patient was found to have both elevated CA125 and CA19-9 levels at the same time. Coexisting diseases such as hepatolithiasis ($n = 10$) and clonorchiasis ($n = 3$) were present in some patients.

US and contrast-enhanced features

By consensus review on the grayscale images, each case was finally classified as one of the following types (Table 1):

Type I: No visible mass was detected, but there were diffusely dilated intrahepatic and extrahepatic bile ducts (Fig. 1a). Five cases were classified as this type (5/30, 16.7%), and two patients had cholangitis.

Type II: Intraductal papillary masses were detected, and there was notable presentation of focally dilated bile ducts (Fig. 2a). The cystic part of the lesion was connected with the bile duct. Thirteen cases were classified as this type and eleven of all the papillary masses were hyperechoic and distinguishable from the normal liver parenchyma.

Type III: Solid mass type, with surrounding dilated bile ducts and/or distal bile duct dilatation (Fig. 3a). Six masses were hyperechoic while five were isoechoic. Only one mass was hypoechoic in this type due to the patient's fatty liver, which made her normal liver parenchyma show higher echo than normal.

On CEUS, masses of type II and III showed different levels of enhancement (Table 1). In the arterial phase (Figs. 2, 3), 22/25 lesions showed hyperenhancement and 3/25 showed isoenhancement compared with the surrounding liver parenchyma. In total, 22/25 lesions showed homogenous enhancement and 3/25 showed heterogenous enhancement. In the portal phase (Figs. 2, 3), 4/25 lesions were isoenhanced, while 21/25 lesions were hypoenhanced. In the late phase (Figs. 2, 3), 2/25 lesions were isoenhanced, and 23/25 lesions were hypoenhanced. As shown in Table 1, there were no significant differences between the features of type II and III masses on both US and CEUS.

Comparison between CEUS and CECT

All of the selected patients underwent CEUS examinations, and 27 of the patients also underwent CECT examinations. There were 7 patients who had no detectable masses through CECT. Among them, 5 patients were categorized with grayscale US as type I, and 2 patients were categorized on grayscale US as type II.

For the remaining 20 patients, the lesion locations were the same as those indicated by the results from grayscale US. Through the noncontrast CT scan, 19/20 cases were hypodense. As with the outcome of ultrasound, the same patient who showed hypoechoic regions in her tumor on account of her fatty liver also showed hyperdense regions with noncontrast CT scan, which was a different result from that of the other patients. The enhancements of CECT are shown in Table 2. No significant differences were found between type II and III masses on CECT.

As for the 20 IPNB patients whose tumors could be detected through both CEUS and CECT, we compared the contrast manifestations on CEUS with those on CECT (Figs. 1, 2, 3). There were 18 hyperenhanced lesions on CEUS in the arterial phase, while 17 lesions showed hyperenhancement on CECT ($p = 1.000$) in the arterial phase. In total, 16 and 18 lesions showed washout in the portal and late phases on CEUS, while the corresponding

Table 1 Characteristics of the US and CEUS (n = 30)

	Type I ($n=5$)	Type II ($n=13$)	Type III ($n=12$)	p value
Bile duct				
Dilated	5	13	12	
Mean size, cm (range)	NA	5.7 ± 1.9 (2.6–9.0)	4.4 ± 1.2 (1.1–7.3)	0.067
Location				0.067
Left lobe intrahepatic bile duct	NA	9	3	
Right lobe intrahepatic bile duct	NA	2	2	
Extrahepatic	NA	2	7	
Border				0.688
Clear	NA	7	8	
Unclear	NA	6	4	
2-D US				0.155
Hyperechoic	NA	11	6	
Isoechoic	NA	2	5	
Hypoechoic	NA	0	1	
Arterial phase of CEUS				0.220
Hyperenhanced	NA	10	12	
Isoenhanced	NA	3	0	
Enhancement pattern of CEUS				1.000
Homogeneous	NA	11	11	
Heterogeneous	NA	2	1	
Portal phase of CEUS				0.593
Isoenhanced	NA	3	1	
Hypoenhanced	NA	10	11	
Late phase of CEUS				0.480
Isoenhanced	NA	2	0	
Hypoenhanced	NA	11	12	

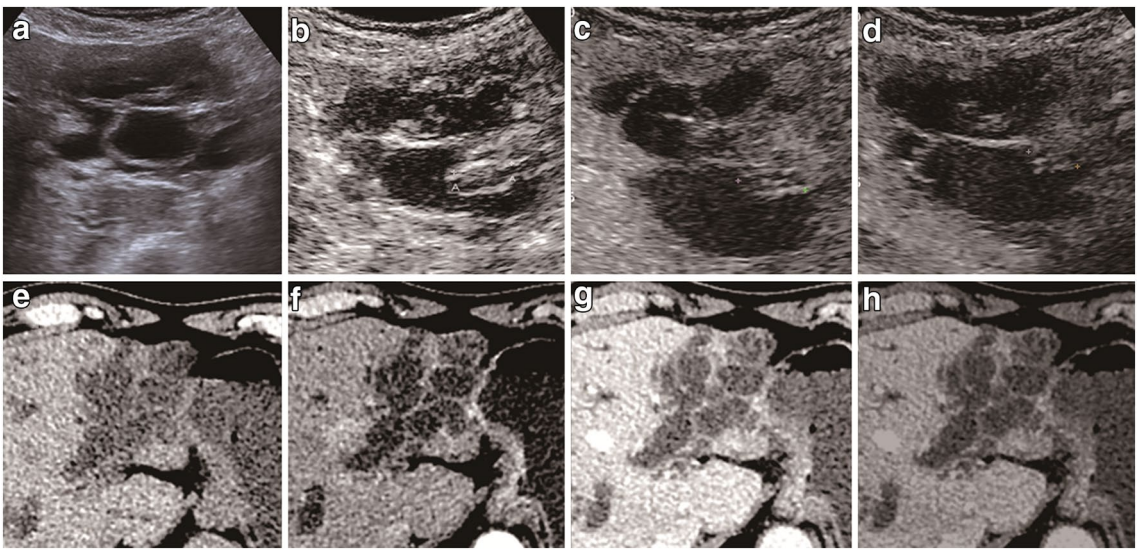

Fig. 1 Representative images of type I IPNB on US and CT of a 47-year-old woman. **a** Diffusely bile duct dilatation were shown on BUS. **b** Enhancement of bile duct wall on CEUS (arterial phase) with no mass. **c** Isoenhancement of bile duct wall in portal phase on CEUS. **d** Isoenhancement of bile duct wall in late phase on CEUS. **e** Diffusely bile duct dilatation was shown on CT. **f** Enhancement of bile duct wall on CECT (arterial phase) with no mass. **g** Isoenhancement of bile duct wall in portal phase on CECT. **h** Isoenhancement of bile duct wall in late phase on CECT

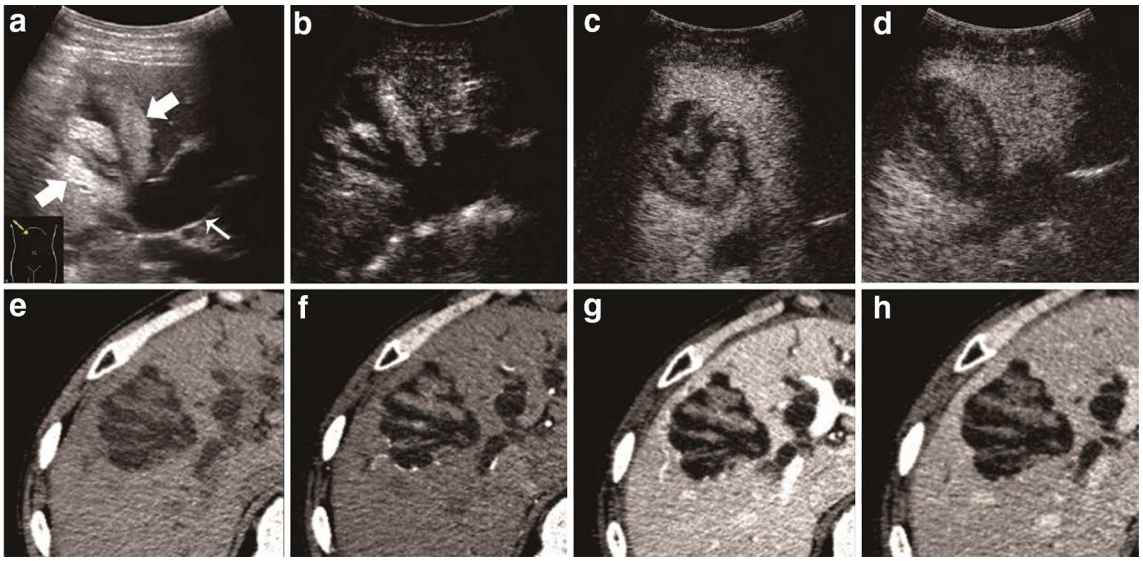

Fig. 2 Representative images of type II IPNB on US and CT of a 62-year-old man. **a** Focal dilated bile duct with hyperechoic intraductal papillary masses on US. **b** Hyperenhanced mass in arterial phase on CEUS. **c** Isoenhanced mass in portal phase on CEUS. **d** Hypoenhanced mass in late phase on CEUS. **e** Focal dilated bile duct with hypodensity intraductal papillary masses on CT. **f** Hyperenhanced mass in arterial phase on CECT. **g** Hypoenhanced mass in portal phase on CECT. **h** Hypoenhanced mass in late phase on CECT

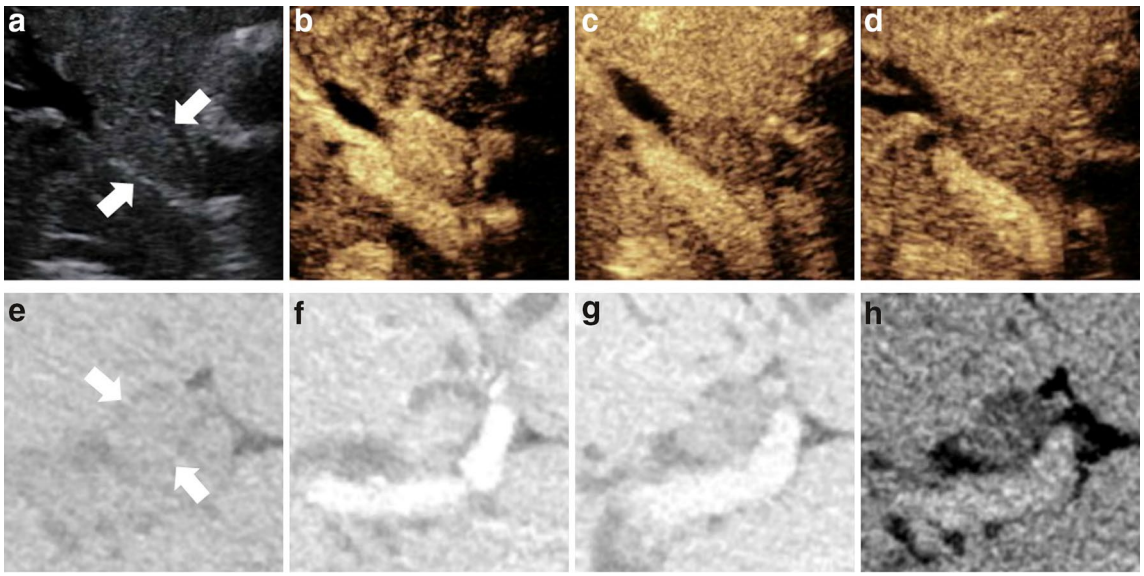

Fig. 3 Representative images of type III IPNB on US and CT of a 49-year-old man. **a** Hyperechoic solid mass with dilated bile ducts around and distal bile duct dilatation on BUS. **b** Hyperenhanced mass in arterial phase on CEUS. **c** Hypoenhanced mass in portal phase on CEUS. **d** Hypoenhanced mass in late phase on CEUS. **e** Hypodensity solid mass with dilated bile ducts around and distal bile duct dilatation on CT. **f** Hyperenhanced mass in arterial phase on CECT. **g** Hypoenhanced mass in portal phase on CECT. **h** Hypoenhanced mass in late phase on CECT

number of lesions that showed washout on CECT were 11 and 13 ($p = 0.178$, $p = 0.127$, respectively). Generally, there were no significant differences between CEUS and CECT in the arterial, portal or late phases according to the McNemar test.

Operative strategies and pathology findings

Operative strategies

In this study, 29/30 patients underwent operations, except for one patient who had a biopsy only. Nineteen patients

Table 2 Characteristics of the CT and CECT ($n=27$)

	Type I	Type II	Type III	p value
Noncontrast CT scan				1.000
Hypodense	0	10	9	
Hyperdense	0	0	1	
No mass	5	2	0	
Arterial phase of CECT				1.000
Hyperenhanced	NA	9	8	
Hypoenhanced	NA	1	2	
Enhancement pattern of CECT				0.303
Homogeneous	NA	6	9	
Heterogeneous	NA	4	1	
Portal phase of CECT				0.319
Hyperenhanced	NA	2	2	
Isoenhanced	NA	2	0	
Hypoenhanced	NA	6	8	
Late phase of CECT				0.513
Hyperenhanced	NA	1	2	
Isoenhanced	NA	1	0	
Hypoenhanced	NA	8	8	

received a left lobectomy, and 5 of them also received an extrahepatic bile duct excision. Three patients underwent a right lobectomy (including one patient who received an extrahepatic bile duct excision), and one patient only had a segmentectomy. The other six patients received an extrahepatic bile duct excision only. Among all these patients, 12 patients also received a choledochojejunostomy. In addition, a lymphadenectomy was routinely performed.

The five patients who were classified as type I also received surgery without any distinguishable masses. One of the patients was misdiagnosed as having Caroli's disease before the operation, one patient had a thickened bile duct wall, one patient had a focal hypermetabolic focus located in the left lobe intrahepatic bile duct on (18) F-FDG PET/CT, and the other two patients were found to have cholangitis.

Gross pathology

The bile ducts involved were variably dilated. The lesions located in left lobe of liver (17/29), right lobe of liver (4/29), hepatic hilum (11/29), gall bladder (1/29). Majority of the lesions (25/29) showed multiple or diffuse papillary and fragile tumors presenting on the inner surface of the biliary tree. Two patients had multifocal tumors, one involving intrahepatic bile duct of the left lobe, common bile duct and gall bladder, and the other involving intrahepatic bile duct of the left lobe and common bile duct.

Microscopic pathology

Four lesions showed mild-moderate atypical hyperplasia in the epithelial cells, and 8/30 lesions showed moderate-severe atypical hyperplasia. Sixteen lesions had already progressed to be malignant and showed features such as mitotic figs, hyperchromasia, loss of polarity, etc. This result proves that IPNBs have high premalignant potential. Only 2/30 lesions showed neither atypical hyperplasia nor malignancy. Nine of the sixteen malignant lesions were highly differentiated, while 5 lesions were moderately differentiated. The other 2 lesions were partially highly differentiated and partially moderately differentiated. Since a lymphadenectomy was routinely performed on all the patients who underwent operations, the pathological result revealed that only 1 lymph node in 1 patient was found to be malignant and that the lymph node was located in the lesser omentum.

Correlation between grayscale ultrasound classification and pathology

Type I patients had no malignant masses, while type II and type III patients had 10 and 6 masses, respectively, that already progressed to be malignant. The malignancy rate between type I and type II were significantly different ($p=0.007$). There were no significant differences between the malignancy rates of type I and type III ($p=0.102$) or type II and type III ($p=0.226$).

Discussion

IPNB is a rare kind of tumor that was first reported as biliary papillomatosis by Chappet in 1894 [13] and is often misdiagnosed or unrecognized before surgery. In the 2010 World Health Organization classification [14], IPNB was identified as a distinct clinical and pathological entity, which included various previous diagnosis such as biliary papillomatosis, mucin-hypersecreting bile duct tumor, mucin-producing cholangiocarcinoma and biliary tract intraductal papillary mucinous neoplasm. IPNBs are classified into several groups (IPN with low-or intermediate-grade intraepithelial neoplasia, IPN with high-grade intraepithelial neoplasia and IPN with an associated invasive carcinoma) according to its degree of malignancy. Furthermore, IPNBs have 4 histological subtypes (pancreaticobiliary, intestinal, gastric, and oncocytic) that are classified by its mucin core proteins and cytokeratins [4]. The chaotic classifications led to the uncertainty in radiology features of this rare entity.

A previous study reported that IPNBs commonly occur in middle-age patients or patients older than 60 years old [15, 16], and the reported male-to-female ratio is 2:1 [17]. In our study, the male-to-female ratio was 3:2, and the

average age was 59.2 years old. Mostly, patients presented with right upper quadrant pain. Jaundice and acute cholangitis were also common symptoms, but some patients had no symptoms [18]. As tumor markers, CA19-9 and CA125 are often found to be elevated in biliary malignancies [19, 20]. In this study, 5/30 (16.7%) patients had elevated CA125 levels (up to 548.79 kU/l), and 4/30 (13.3%) patients had elevated CA19-9 levels (up to 138.16 kU/l). Five of these eight patients' tumors underwent malignant transformations, while the other three were diagnosed as moderate-severe atypical hyperplasia. Therefore, these markers were not sensitive for early stage IPNB.

CT and MRI are frequently used in diagnosing IPNBs, and the most common findings were a combination of biliary duct dilatation and intraductal masses [10]. However, there is limited evidence for the sensitivity and specificity of ultrasound in diagnosing IPNBs. In our study, we classified IPNBs according to grayscale US. For cases classified as type I, we found out that no tumor could be detected on 2-D US or CEUS (5/30, 16.7%), and only diffusely dilated intrahepatic and extrahepatic bile ducts with/without hepatolithiasis could be seen. These type I lesions might be in an early stage of disease development and were readily misdiagnosed as congenital cholangiectasis or common duct stones with bile duct dilation. For the visible masses, type II cases showed focal or cystic-like dilated bile ducts with intraductal masses that resemble cystadenoma. When comparing between cystadenoma and cystadenocarcinoma, the communication between the "cystic" component and the surrounding bile duct is of great importance [21]. Another essential piece of information that our study reveals that the "solid" component is mostly hyperechoic, and the "nodules" on the "cystic wall" were always larger with a papillary shape. Type III cases were defined as those with a solid mass and a few distal dilated bile ducts around the mass. This mass formation type should be carefully differentiated from hepatocellular carcinoma and intra/extrahepatic cholangiocarcinoma. Liu et al. [22] also classified INPBs according to grayscale US into the following three types: bile duct dilation with intraductal mass type, bile duct dilation without intraductal mass type and cystic-solid mixed type. The main differences of our classification method are that we emphasized the shape and the location of the mass and that we considered the cystic part to be some kind of dilated bile duct. In addition to the hyperechoic appearance of the masses on CEUS, the enhanced clear boundary surrounded by liver parenchyma or bile ducts also support the diagnosis of IPNB. Given the proximal bile duct dilation of this type of mass, a more confident diagnosis could be made.

Sakamoto et al. [23] macroscopically classified mucin-producing cholangiocarcinoma into the following three types: duct-ectatic type (characterized by papillary masses located in diffusely dilated intrahepatic bile ducts, mostly the main duct), cystic type (characterized by a large cystic lesion which is connected to the intrahepatic bile ducts, mostly the branch duct), and intermediate type (a mix of the above two types). This kind of classification can be applied to the three different forms of IPNB US features that we summarized above. In the early stage, benign IPNB tumors themselves might not be found as masses through US or CEUS, and only bile duct dilatation can be observed. As the disease progresses, the papillary tumors transform to be malignant and eventually appear as dilated bile ducts with intraductal papillary masses (cystic type) or solid masses surrounded by dilated bile ducts (duct-ectatic type). These findings also proved that various US/CEUS findings can be considered as image manifestations of different malignant transformation stages of the disease.

Liu et al. [24] reported that identifiable CT features could be used to characterize IPNBs by local bile duct dilatation as the nodule grew along the interior surface of the dilated bile duct. In this study, the features above were also present on CECT. In addition, according to the McNemar test, there were no significant differences between CEUS and CECT in the arterial, portal or late phase.

The pathological characteristics of IPNB included dilated bile ducts and grossly visible prominent papillary tumors, which are the same as those in the previous report [8]. IPNB was considered to be a disease with low probability of malignancy in the past. However, according to a review of the English literature in 2003 [25], an invasive component was identified in 43% of 476 IPNB cases, and the histological analysis suggested that IPNB was a borderline or low grade malignant neoplasm with a high malignant potential [13] that was associated with mutations in various key genes [26]. In our study, the lesions also showed different degrees of dysplasia (12/30, 40.0%) and had a high rate of malignancy (16/30, 53.3%). Therefore, IPNBs should no longer be considered as a benign disease, and patients should be treated with surgical resection after the diagnosis is established.

According to our data, type II and type III masses might be correlated with malignancy, and type I cases tended to have a lower malignancy tendency. Lim et al. [27] focused on patients who presented symptomatically with biliary duct dilatation but no mass. The findings specific to underlying IPNB included hepatic parenchymal atrophy of the affected segment, the presence of high-volume mucin and the presence of a spreading, superficial tumor that was frequently noninvasive. In another study of IPNBs with CT [6], 97% of patients had radiologically identified masses, and all these tumors were carcinoma. This result might suggest that in IPNB patients who do not have visible masses, the underlying histology may be more likely to indicate benign tumors. However, we need more research to determine whether type I cases had lower invasion or if they were just in the early stage of IPNB.

Conclusion

In conclusion, as a rare biliary disease, IPNB has a rather high malignant potential, and patients should undergo resection much earlier than what is widely believed. Our study demonstrated that IPNBs have three typical imaging forms (diffusely dilated bile ducts without any visible mass; focal dilated bile duct with intraductal papillary masses; solid mass surrounded by dilated bile ducts and distal bile duct dilatation) and that the enhancement patterns of IPNBs on CEUS and CECT were consistent. Considering its convenience and noninvasive nature, CEUS can be added as a routine examination for IPNB to help accurately identify the disease and predict its level of malignancy.

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Author contributions Wei Wang and Bing Liao designed the research. Quan-Yuan Shan collected data; Ming Xu and Li-Da Chen evaluated the images and videos of US and CT. Hang-Tong Hu analyzed the data; Yang Huang edited tables and Figures; Qiao Zheng and Si-Min Ruan wrote the paper; Xiao-Yan Xie and Ming-De Lu edited the paper and polished the language.

Compliance with ethical standards

Conflict of interest The author declare that they have no competing interest.

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