Review

Endoscopic Ultrasound

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Intraductal papillary neoplasms of the bile ducts—what can be seen with ultrasound?

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ABSTRACT

Intraductal papillary neoplasm of the bile ducts is a rare tumor. Characteristic features include bile duct dilatation, cystic lesions with communication to the bile ducts, and intraluminal solid nodules arising from the bile duct wall. As in pancreatic intraductal papillary mucinous neoplasia, intestinal, pancreaticobiliary, gastric, and oncocytic types are described. Intraductal papillary neoplasm of the bile ducts has a high potential for malignancy, and patients should be surgically resected when possible. In this review, the complex imaging diagnosis is presented. The main focus is on contrast-enhanced ultrasound, an established method for many other indications whose potential on the biliary system should be better exploited. In the present article, typical contrast-enhanced ultrasound findings in intraductal papillary neoplasm of the bile ducts are demonstrated.

Keywords: Abdominal ultrasound; Bile duct nodules; Contrast-enhanced ultrasound; Guideline; Imaging; Intraductal papillary neoplasm of the bile duct

INTRODUCTION

The World Federation for Ultrasound in Medicine and Biology has published guidelines on the use of contrast-enhanced ultrasound (CEUS) for the evaluation of focal liver lesions[1–5] and the European Federation of Societies for Ultrasound in Medicine for the evaluation of nonhepatic indications.[6,7] Although applications of CEUS on the liver are well established, and other organs are also included in the broad spectrum of indications, with regard to the biliary system, the guidelines and a World Federation for Ultrasound in Medicine and Biology position paper on incidental biliary findings[8] limit the application of CEUS to the gallbladder and to interventions on the biliary system.

However, the bile ducts offer important targets for contrast-enhanced imaging. Contrast-enhanced ultrasound can be used to differentiate solid intraductal or intramural tumors from sludge, pus, and clots in the biliary system. Furthermore, it makes sense to consider the diagnostic potential and the meaningful use of CEUS in rare clinical entities. This article provides a comprehensive overview of intraductal papillary neoplasm of the bile ducts (IPNB), its appearance and diagnosis, and summarizes the ultrasound (US), CEUS, and EUS features of this rare disease.

Intraductal papillary neoplasm of the bile ducts

Intraductal papillary neoplasm of the bile duct is characterized by dilated intrahepatic or extrahepatic bile ducts lined with papillary or villous neoplastic glands with a delicate fibrovascular stalk. Intraductal papillary neoplasm of the bile duct was described by Chen et al.[9] as a new category of disease of grossly visible precancerous or early cancerous neoplastic lesions of the bile duct. Intraductal papillary neoplasm of the bile duct was first proposed as a distinct entity in the 2010 revision of the World Health Organization classification for liver and intrahepatic bile duct tumors.[10] Three intraepithelial preinvasive neoplasms of the bile ducts are distinguished: (i) biliary intraepithelial neoplasms (BilINs), (ii) IPNBs, and (iii) mucinous cystic neoplasms of the liver (MCNs-L), which is associated with an ovarian stroma and has no communication with the lumen of the bile ducts.[11] Biliary intraepithelial neoplasms and IPBNs are preinvasive neoplasms that precede cholangiocarcinoma. Because BilINs are purely intraepithelial neoplasms, they can be identified only microscopically. In contrast, IPNB is defined as an intraductal growing tumor that develops in the intrahepatic and extrahepatic bile ducts.[11,12] Intraductal papillary neoplasm of the bile ducts shows, in contrast to the BilINs grossly visible, exophytic growth in a dilated bile duct lumen, with histologically villous/papillary neoplastic epithelia with tubular components covering fine fibrovascular stalks.[11,13]

A variety of different terms have been used in the literature for the same disease entity of IPNB. This is confusing in parts. The World Health Organization (WHO) has proposed the term "intraductal papillary neoplasms of the bile duct in the Classification of Tumors of the Digestive System, fifth edition (2019).[11,14] A WHO "accepted" term is biliary papilloma and papillomatosis for the same

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entity. "Nonrecommended" terms of the WHO are "biliary adenoma," "intestinal adenoma," "papillary (villous) adenoma," tubulopapillary (tubulovillous) adenoma," "noninvasive papillary neoplasm (carcinoma)," "papillary carcinoma," and "mucin-secreting biliary tumor" [Table 1]. These terms can be found in literature reviews and case reports.[11] The term "biliary papillomatosis" has often been used to describe diffuse IPNB. In IPNB, all tumor development patterns ranging from low-grade intraepithelial neoplasia to invasive carcinoma can occur, including adenomas, carcinoma in situ, and invasive carcinoma.[15]

Intraductal papillary neoplasm of the bile duct is rare. Prevalence among bile duct tumors ranges from 4% to 15%. The disease usually manifests at age >50 years with s slight male predominance.[11] Incidence is higher in Asian countries than in others.[11] Risk factors for the development of IPNB are hepatolithiasis and liver fluke infection (*Clonorchis sinensis* [CS] or *Opisthorchis viverrine* [OV]),[16–18] cholecystolithiasis, and choledocholithiasis. In the study by Luvira et al.,[16] the male predominance was consistent with the high local incidence of OV infection, suggesting that OV is a likely etiological factor of the development of IPNB. In a meta-analysis, 27% of patients with IPNB from centers in China, Japan, and Korea had a parasitic infection with CS and hepatolithiasis.[19] Whether CS regularly leads to IPNB has not been documented. Diverse hepatobiliary morbidity has been documented for CS infection. Moderate CS infection was associated with an increased gallbladder stone prevalence, whereas moderate and heavy infections were associated with intrahepatic bile duct dilatation. *Clonorchis sinensis* is classified as definite carcinogen, causing fatal cholangiocarcinoma.[20] However, IPNB is rare, and CS infection is highly prevalent in Asia. Particularly, approximately 13 million cases of CS infection are estimated in China.[21] Among 696 villagers, 66.1% had CS infection. Ultrasound examination revealed, among others, bile duct dilatation in 20%, but this was not further verified. Adult worms of CS usually parasitize the intrahepatic bile ducts. This explains why intrahepatic dilatation rather than extrahepatic dilatation of the bile duct was observed. Further investigations to determine whether IPNB could explain the observed intrahepatic dilatation were not performed.[20,22] In a cross-sectional study conducted in the rural population in 10 villages along the Lalin River in northeast China, the prevalence of infection with CS was 29.3%.[23] Intrahepatic hepatolithiasis is considered a risk factor for IPNB. However, in the study by Han et al.,[24] intrahepatic hepatolithiasis was less common in the malignant IPNB group than in the benign IPNB group (11.3% *vs*. 40.7%). The simultaneous presence of viral hepatitis at the time of IPNB diagnosis is reported.[13,25] However, in the study by Han et al.,[24] viral hepatitis was more common in the benign IPNB group than in the malignant IPNB. In addition, there are case reports of co-occurrence with primary sclerosing cholangitis[26] and congenital biliary tract disease. Biliary malformations including choledochal cysts, Caroli disease, and familial adenomatous polyposis or Gardner syndrome are risk factors for IPNB.[11,27–29] An association with chlorinated organic solvents, including dichloromethane and 1,2-dichloropropane, has also been reported.[30]

In a meta-analysis including 476 IPNB cases, upper abdominal pain (42%), jaundice (33%), and cholangitis (14%) were the most common clinical manifestations. Twelve percent were asymptomatic.[19] Usually, the liver enzymes are abnormal. Alkaline phosphatase was most frequently elevated. Among the tumor markers, carcinoembryonic antigen (CEA) and CA-19-9 may be elevated. CA-19-9 was elevated in up to 42%. However, highly varying values in the serum levels of the 2 tumor markers seem to indicate that they are unlikely to have a high sensitivity or specificity for diagnosing IPNB.[19] Han et al.[24] described that CEA and CA-19-9 were significantly higher in the malignant group than in the benign group of IPNB (CEA: 27.8% *vs*. 7.5% and CA-19-9: 52.5% *vs*. 21.7%). In the study by Zheng et al.,[18] 16.7% of IPNB patients had elevated CA-125 levels, and 13.3% of patients presented with elevated CA-19-9 levels. Pathologically confirmed mucinous cystic neoplasms with ovarian-type stroma were excluded. The tumor markers were not sensitive for early-stage IPNB.

Intraductal papillary neoplasm of the bile ducts is often compared with pancreatic intraductal papillary mucinous neoplasia (IPMN). Intraductal papillary neoplasm of the bile duct and pancreatic IPMN share the classification into 4 histological types, prominent intraductal papillary proliferation, ductal dilatation, duct-associated cyst formation, and possible mucin overproduction. Similar to pancreatic IPMN, IPNB can be histologically divided into 4 subtypes: intestinal IPNB, gastric IPNB, pancreatobiliary IPNB, and oncocytic IPNB. Intrahepatic IPNB had an equally high proportion of intestinal and pancreatobiliary types. The diffuse IPNB had a higher proportion of gastric type.[31] The gastric subtype is reported to be more frequently associated with low-grade dysplasia, whereas the pancreatobiliary IPNB subtype is commonly accompanied by high-grade dysplasia and aggressive behavior.[11,32–34] Pancreatobiliary IPNBs were associated with a significantly higher incidence of invasive disease compared with other tumor subtypes and higher expression of the well-recognized cancer antigen MUC1.[19] Similarities with pancreatic IPMN are found in the intestinal subtype, which belongs to type 1, and the oncocytic subtype. Intestinal IPNBs classified as type 1 were associated with *KRAS*, *GNAS*, and *RNF43* mutations. This is also reported for pancreatic IPMN.

Table 1

***Biliary tract tumors in the World Health Organization Classification of Tumors of the Digestive System 2019*[14]**

Bile duct tumors in chapter 8: tumors of the liver and intrahepatic bile ducts	Bile duct tumors in chapter 9: tumors of the gallbladder and extrahepatic bile ducts
Benign biliary tumors and precursors	Benign epithelial tumors and precursors
• Bile duct adenoma	• Pyloric gland adenoma of the gallbladder
• Biliary adenofibroma	• Biliary intraepithelial neoplasia
• Mucinous cystic neoplasm of the liver and biliary system	• Intracholecystic papillary neoplasm
• Biliary intraepithelial neoplasia	• Intraductal papillary neoplasm of the bile ducts
• Intraductal papillary neoplasm of the bile ducts	• Mucinous cystic neoplasm of the liver and biliary system
Malignant biliary tumors	Malignant epithelial tumors
• Intrahepatic cholangiocarcinoma	• Carcinoma of the extrahepatic bile ducts
	• Neuroendocrine neoplasms of the gallbladder and bile ducts

Thus, it is interpreted that type 1 intestinal IPNB is the counterpart of intestinal-type pancreatic IPMN. In nonintestinal IPNB and pancreatic IPMN, no or rare matching mutations have been reported, so these are not considered counterparts.[11,35–37] Again, oncocytic IPNB and oncocytic pancreatic IPMN have similar genetic and molecular characteristics, so they could be considered counterparts. In the study by Fukumura et al.,[36] both types 1 and 2 of IPNB compared with pancreatic IPMNs had different clinicopathological features. Intraductal papillary neoplasm of the bile duct shows less frequent mucin hypersecretion compared with pancreatic IPMN, more lateral spreading of the tumor, and more dilatation of the associated ducts.

Generally, IPNB differs from pancreatic IPMN by a higher histological grade, a more advanced stage, a higher incidence of associated invasive cancer, a worse prognosis, and some differences in genetic alterations.[11,32,33]

The IPNB is divided into 2 types [Table 2]. A classification of IPNB was proposed by Japanese and Korean pathologists. Type 1 IPNB is histologically similar to intraductal papillary mucinous neoplasms of the pancreas and typically develops in the intrahepatic bile ducts, whereas type 2 IPNB has a more complex histological architecture with irregular papillary branching or with foci of solid-tubular components and typically involves the extrahepatic bile ducts.[38]

Aoki et al.[39] differentiated the assignment to types 1 and 2: the type 1 IPNBs were associated with noninvasive phenotype, intestinal and oncocytic subtypes, development in the intrahepatic bile duct, overt mucin production, KRAS mutation, and relatively good prognosis. Type 2 IPNBs were associated with invasive phenotype, pancreatobiliary subtype, development in the extrahepatic bile duct, mutations in TP53 and SMAD4, aberrant expression of p53 and SMAD4, and poorer prognosis compared with type 1 IPNBs.[39]

Variants of IPNB are bile duct dilatation with microscopic IPNB (superficial spreading IPNB) and IPNB from the peribiliary glands.[11] In microscopic IPNB, the papillary tumor is macroscopic and on imaging is not visible. In IPNB from the peribiliary glands, the tumor does not originate from the biliary tract epithelium but arises in the peribiliary glands. Pedica et al.[40] reported that 4.6% of peribiliary cysts in alcoholic cirrhosis had low-grade IPNB confined to the cysts, suggesting that these lesions may be incidental and incipient IPNBs arising in the cyst-dilated peribiliary glands. These IPNBs differ from the majority of IPNBs, which may arise from the epithelia lining the biliary tract.[40] Approximately 36% of IPNBs showed invasion through the bile duct wall into adjacent organs.[39] In a meta-analysis of 476 IPNB patients, at least 43% had invasive carcinoma, whereas 20% demonstrated carcinoma in situ, and only 38% had benign disease.[19] The majority of tumors (63%) were restricted to the bile duct wall and less frequently with transmural (28%) or lymphatic dissemination (9%).[19] In several other studies, lymph node metastases were present in 6% to 8.2% of IPNBs at the time of surgical resection.[16,31,41] More than one-third of IPNBs are associated with increased mucin production. The high viscosity of the mucin is one factor causing bile duct dilatation and obstruction.[31,42–44] Mucin hypersecretion is more commonly associated with intrahepatic IPNBs than with extrahepatic IPNBs.[11,31,35,39]

Intraductal papillary neoplasms of the bile duct can present in the large intrahepatic and extrahepatic bile ducts, but typically not in the intrahepatic small bile ducts.[13,16,19,39,41] In intrahepatic IPNBs, tumors were more frequently located in the left lobe of the liver (74.4%). A high proportion (41%) of patients had multiple tumors.[19] Intraductal papillary neoplasms of the bile duct can also occur separately multilocular.[16,31]

Gordon-Weeks et al.[19] described that the pooled prevalence of intrahepatic tumors in Asian studies was 58.2% compared with only 24.2% in studies from the United States and Europe. Tumors from Western study centers had higher rates of invasive disease (55.9% *vs*. 37.4%), were less frequently associated with mucin production (40.3% *vs*. 47.9%), and were more frequently of the pancreaticobiliary subtype (50.1%). In Asian study centers, the intestinal subtype was the most common (43.2%).[19] The appearance of IPNB was described by Kim et al.[31,45] as polypoid (35%), cast-like (23%), superficial spreading (28%), and cyst-forming (15%). There are several morphological and anatomical classifications.

The classification according to the definition of the Japan Biliary Association is based on the dilatation of the bile duct and the presence of cysts.[34] A classification of Kim et al.[13] was based on the bile duct dilatation and the presence of intraductal masses or stricture; these 2 classifications were combined into a "modified anatomical classification" by Kim et al.[31] [Table 3, Figure 1]. Extrahepatic, intrahepatic, and diffuse types are distinguished. The intrahepatic type is further subdivided into the cystic form and the duct-ectatic form. In the study by Kim et al., 68.5% of the 387 patients were intrahepatic, 26.6% were extrahepatic, and 4.1% belonged to the diffuse type.

Luvira et al[16] proposed a new classification based on radiopathological appearance. The IPNBs were categorized into 5 classes[46] [Table 4 and Figure 2]. Most of their IPNB patients were class I (46.6%). The proportion of malignant IPNBs in all patients was 84.5%. All classes II and V tumors were malignant IPNBs. The overall incidence of lymph node involvement in patients who received regional lymph

Table 2

***Characteristics of type I and type II IPNB*[11,32,36,38,39]**

IPNB	Type I	Type II
Comparison to pancreatic IPMN	Similar to prototypes of IPMN, depending on subtype	Is different from IPMN, depending on subtype
Localization	More frequently intrahepatic	More frequently extrahepatic
Mucin hypersecretion	More frequently (50%)	Less often (15%)
Stromal invasion	Less than 50%	More than 80%
Grade of neoplasm intraepithelial	Low-grade dysplasia (approximately 10% of all IPNB), high-grade dysplasia with regular structures (approximately 30%)[11]	High-grade dysplasia with irregular structures (approximately 60%)[11]
Subtypes	Intestinal and oncocytic[11,39]	Pancreatobiliary and intestinal,[11] pancreatobiliary[39]
Prognosis	Relatively good	Poorer

IPMN: intraductal papillary mucinous neoplasia; IPNB: intraductal papillary neoplasm of the bile ducts.

Table 3

***Modified anatomical classification of IPNB according to Kim et al.*[31]**

Type	Subtypes	Characteristics
Extrahepatic		The main lesions are limited to the common bile duct and common hepatic duct
Intrahepatic	• Cystic form • Duct-ectatic form	The main lesions are located at the periphery beyond the first confluence of the intrahepatic bile ducts
Diffuse		The main lesions are located over a wide range of the intrahepatic and extrahepatic bile ducts

IPNB: intraductal papillary neoplasm of the bile ducts.

node dissection was 17.1%. There was no lymph node involvement in class III tumors[46].

Imaging

The diagnostic algorithm for the workup of biliary tract disease includes US, computed tomography (CT), magnetic resonance imaging (MRI), magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography (ERCP), cholangioscopy, EUS, and, in Asiatic publications, intraductal miniprobe ultrasound (IDUS), whereas not all of the methods are required each time. Although ultrasound is the basic investigation, publications on IPNB usually demonstrate image documentation on CT and MRI. Contrast-enhanced ultrasound is an important method for hepatic and extrahepatic indications, but its application is still underrepresented in investigations of the biliary system in everyday practice. The most important morphologic changes of IPNB are evident on all of these imaging modalities. These features are diffuse or segmental bile duct dilatation with or without cystic changes, intraductal lesions, and ductal and periductal invasion including macroinvasion into the liver. Prolonged biliary dilatation leads to atrophy of the affected liver segments. The size of IPNBs, including cystic lesions, has been described as 0.5 to 17 cm (median, 2.2–6.0 cm).[31,42,47,48]

Conventional B-mode ultrasound has described localized or generalized biliary dilatation and intraductal echogenic lesions.[49] Intraluminal mucin does not always present anechoically but often reveals echogenic "streaks." Cystic parts may show wall thickening. Nodules are delineated with variable echogenicity but are usually described as hyperechoic. Small vessels, also within nodules, can be delineated in Color Duplex or Power Doppler ultrasound. The visualization of infiltrative changes in the adjacent liver tissue or neighboring organs depends on the extent of invasion. In this case, a discontinuity of the biliary tract wall with hypoechoic, irregular boundaries to the surrounding area is to be expected.

In the study by Zheng et al.[18] on CEUS and contrast-enhanced CT, 43.3% of IPNBs presented as focal or cystic-like dilated bile ducts (group II) with intraductal papillary masses and 40.0% as solid mass and a few distal dilated bile ducts around the mass (group III). In the minority of 16.7%, only the bile ducts were dilated without detectable solid nodules (group I).[18] However, the size in both groups of IPNBs with nodular changes and also their enhancement in the CEUS did not differ statistically significantly. In type I without nodular changes, no malignant masses were histologically detected in the surgical specimen. Malignancies were detected in both groups with nodular changes. There were no significant differences between the 2 groups with nodular lesions. The nodules in group II were all hyperechoic to the liver parenchyma. In group III, half of the nodules were hyperechoic or isoechoic to the liver parenchyma. One nodule was hypoechoic to the adjacent steatosis hepatis.[18]

Typical ultrasonographic features of IPNB in the study by Siripongsakun et al.[50] were hyperechoic nodules (37.5%), focal bile duct dilatation (37.5%), and diffuse bile duct dilatation with intraductal nodules originating from the bile duct wall (25%). However, smaller, rather unspecific changes were also seen, such as a cluster of septated cysts without demonstrable solid components in the right liver lobe. Attention was also paid to irregularities on the bile duct surface. On MRI, the corresponding lesion appeared as a tortuous cystic dilatation of the peripheral bile duct segment. However, bile duct dilatations und hyperechoic nodules did also occur with BilIN, and ultrasound could not differentiate between BilIN and IPNB, although in BilIN, bile duct dilatation was common (76.9%), and hyperechoic nodules were rarer (23.1%) but also possible.[50]

Ma et al.[42] described a giant cystic lesion in the liver with inhomogeneous hypoechoic center and inhomogeneous hyperechoic periphery. Multiple nodules were located on the inner wall. These showed stippled or striated blood flow signals on Color Doppler US. On complex imaging, the nodules show papillary or coral reef–like patterns that extend from the inner wall into the cyst lumen.

Contrast-enhanced ultrasound

Contrast-enhanced ultrasound of the biliary system can distinguish between enhanced and nonenhanced lesions and thus distinguish

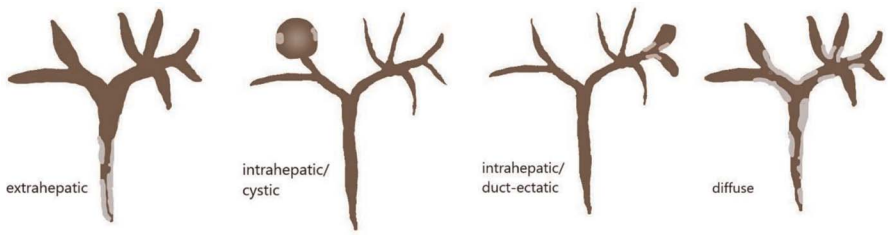

Figure 1. Modified anatomical classification of IPNB according to Kim et al.[31] IPNB: intraductal papillary neoplasm of the bile ducts.

Table 4

***Morphological classification of intraductal papillary neoplasm according to Luvira et al.*[46]**

Class		Appearance
I	Classic intrahepatic IPNB	Presence of an intraductal tumor with unilateral intrahepatic duct dilatation
II	Extrahepatic IPNB	Presence of an intraductal tumor with bilateral intrahepatic duct dilatation
III	Cystic variant	Cystic tumor with a papillary tumor inside and the presence of bile duct communication
IV	Micropapillary lesion	Disproportional bile duct dilatation in the absence of any discernible tumor
V	Macroinvasion of the liver	Presence of a mass-forming tumor incorporates with intraductal tumor

IPNB: intraductal papillary neoplasm of the bile ducts.

solid tumors from sludge, soft bile stones, or blood clots[51–53] [Figures 3–6]. Contrast-enhanced ultrasound is performed on transabdominal US as well as on EUS using a low mechanical index (CELMI-EUS) and SonoVue (sulfur hexafluoride) or, in the Asian region and some other countries, Sonazoid (perfluorobutane) as US contrast agents.

In the study by Liu et al.[54] on CEUS, solid components of lesions appeared hyperenhanced (12/13) or isoenhanced (1/13) in the arterial phase, whereas all showed hypoenhancement in the portal and late phases. It was not possible to distinguish between malignant and nonmalignant lesions. However, malignant solid lesions were larger. Intraductal mass length >3.0 cm was more commonly found in malignant IPNBs.[54] Tominaga et al.[55] reported CEUS in a cystic solid IPNB. Its postoperative histology revealed a well-differentiated adenocarcinoma. The cystic portion was 25 mm. The intracystic solid portion was echogenic, papillary nodular in configuration. Contrast-enhanced ultrasound was performed with perflubutane. The flow behavior in the arterial phase was analyzed in the time-intensity curve. Contrast-enhanced ultrasound showed a significant enhancement of the nodular area compared with the surrounding cystic lesion and liver parenchyma in the time-intensity curve. When considering the illustrated time-intensity curve, the nodule in the arterial phase shows an earlier and stronger enhancement than the wall of the IPNB and later the surrounding liver. The portal venous and late phases are not represented. Whether the time sequence of the enhancement allows conclusions to be drawn about benignity or malignancy should be investigated further. It is crucial to differentiate a solid nodule in the cystic lesion from sludge and to substantiate the indication for surgery.[55]

Zheng et al.[18] studied patients with IPNB on CEUS and CT. Forty percent had atypical hyperplasia, and 53.3% underwent malignant transformation. Typical behavior for all IPNB on CEUS was hyperenhancement in the arterial phase (23/25) and hypoenhancement in the portal venous and late phase (16/20). Isoenhancement was seen in 2 of 25 in the arterial phase, and 4 of 25 and 2 of 25 in the portal venous and late phases, respectively. The enhancement in the arterial phase was in the majority homogeneous (22/25), and only a few lesions showed heterogeneous enhancement (3/25). The enhancement corresponded to that in the CT. Generally, there were no significant differences between CEUS and CECT in the arterial, portal, or late phases. Contrast-enhanced ultrasound revealed 2 of 27 nodular lesions that could not be delineated on CECT.[18]

EUS and intraductal ultrasound

EUS and IDUS can estimate the depth of tumor invasion in the common bile duct because of their proximity and high resolution[56]; CELMI-EUS,[57–59] like CEUS, can distinguish between solid tumors, sludge, and clots. Because of the higher spatial resolution of EUS, smaller lesions that escape other imaging modalities can be detected by CELMI-EUS. This can help confirm the diagnosis of IPNB. EUS can evaluate regional lymph nodes and assess their potential for malignancy based on sonomorphology and with the aid of elastography. Solid lesions can be targeted by EUS–fine-needle biopsy. Similar experience exists for the main duct IPMNs of the pancreas. Contrast-enhancing nodules are a worrisome criterion and represent an indication for surgery.[60,61] Cui et al.[51] demonstrated an IPNB on CELMI-EUS, with several intrabiliary papillary masses up to 10 mm adhering to the dilated extrahepatic and intrahepatic bile duct and in the gallbladder. Except in the prepapillary region, a clear demarcation between the mass and the bile duct wall was seen. In the prepapillary region, invasion of the wall and infiltration of the surrounding tissue were suspected and demonstrated by endosonographic strain-elastography. EUS-elastography showed a homogeneous hard (blue) elastographic pattern of a multilocular, wall-adherent mass lesion with wall penetration and infiltration of surrounding tissue.[51] The performance of modular cholangioscopy seems to have advantages over IDUS. However, some studies include IDUS in the diagnosis of IPNB.[11] The accuracy of IDUS for preoperative determination of tumor extent was 100% in 9 patients with IPNB.[62]

In CT, the enhancement pattern of IPNB is isodense or hyperdense during the late arterial phase and nonhyperdense during the portal- venous and delayed phases. Computed tomography may also show infiltration of the neoplasm along the ductal wall, and intense marginal enhancement at the base of the lesion has also been described.[50] The typical CT findings are intraductal lesions, infiltration

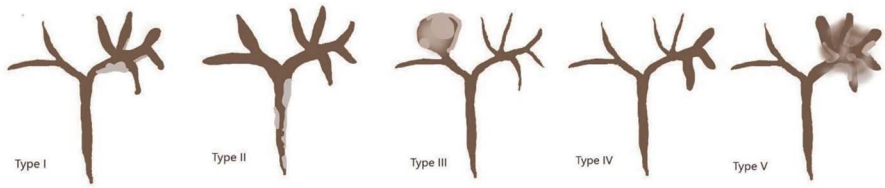

Figure 2. Morphological classification of intraductal papillary neoplasm according to Luvira et al.[46]

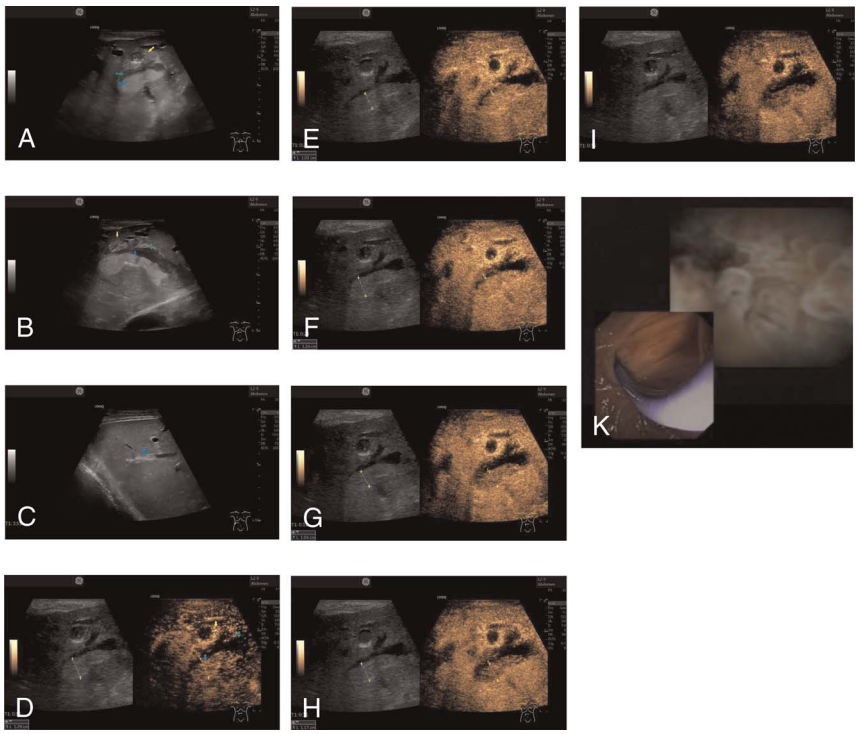

Figure 3. Intraductal papillary neoplasm of the bile duct, macroscopically confirmed by cholangioscopy and histologically confirmed by forceps biopsy. Patient was a 79-year-old man. B-mode ultrasound shows a dilated bile duct branch centrally in the liver with hypoechoic band-like changes in the wall (green arrow). In the lumen, however, there are extensive hyperechoic lesions (blue arrow). Ventrally of this branch, another bile duct branch is visualized with a thickened hyperechoic wall in a transverse scan (yellow arrow). The lumen contains hypoechoic contents and hyperechoic reflexes (A). The same changes continue in the left lobe of the liver (B). At the periphery of the right lobe of the liver, there is a dilated bile duct branch whose lumen is filled with hyperechoic material (blue arrow) (C). On contrast-enhanced ultrasound in the arterial phase at 16 seconds, the hyperechoic intraluminal changes (blue arrow) and the hyperechoic wall thickening of the transverse bile duct branch section (yellow arrow) both show hyperenhancement. The band-shaped hypoechoic wall changes show no enhancement (green arrow) (D). This continues through the arterial phase at 21 (E) and 23 seconds (F). At the end of the arterial phase at 31 seconds, hypoenhancement of the intraluminal hyperechoic lesions begins, whereas hyperenhancement of the thickened hyperechoic wall of the transverse bile duct branch section is still maintained (G). At the beginning of the portal venous phase at 33 seconds (H) and 35 seconds (I), washout of the intraluminal structures continues, whereas hyperenhancement of the hyperechoic wall thickening is preserved. Retrograde modular cholangioscopy shows the papillary structures in the bile duct (K). Cholangioscopy image courtesy of Steffen Hornoff, Sana-Hospital Berlin-Lichtenberg.

along the bile duct wall, and intense enhancement at the base of the lesions.[19] On CECT, mural nodule >12 mm was identified as a predictor of malignancy in intrahepatic IPNB, and enhancement of every mural nodule was a predictor of malignancy in extrahepatic IPNB.[24]

On T1-weighted MRI scans, IPNB appears isointense or hypointense, and on T2-weighted MRI scans, IPNB is generally hyperintense. Intraductal papillary neoplasm of the bile duct typically demonstrates isointensity or hyperintensity during the late arterial phase but does not remain hyperintense during the portal venous and delayed phases.[63] On MRI, focal bile duct dilatation and nonfunctioning bile excretion of hepatocyte-specific agent are the most sensitive findings with sensitivities in the range of 84.6% to 100%.[50] Yoon et al.[64] reported that the additional diffusion-weighted imaging (MRI) is better to assess the invasiveness of tumors but not tumor extent.[19,64]

On magnetic resonance cholangiopancreatography, biliary dilatation presents with irregular filling defects.[50]

Recently, fluorodeoxyglucose positron emission tomography has been evaluated as a prognostic tool in studies from Korea. In 101 patients with IPNB who underwent liver resection, a maximum standard unit value cutoff of 3.0 appeared to effectively discern high-grade and carcinoma from low-grade neoplasia.[65]

In ERCP, the expansion of the IPNB represents filling defects, communication between cystic portions and bile ducts, and mucin overproduction. A brush cytology or forceps biopsy may be taken.[24,66] Similar to the "fish mouth" appearance of the pancreatic main duct IPMN, mucin, in this case bilious tinged mucin, can empty from the major papilla.

Peroral modular cholangioscopy can be performed as an adjunct. This shows the intraductal changes of the bile duct epithelium with intraductal tumor growth. The extension and borders of IPNB in the bile ducts can be delineated. Cholangioscopic forceps biopsies can be targeted to areas suggestive of malignancy. A prerequisite for accessibility is clearing the bile ducts of mucin to ensure adequate intraductal cholangioscopic visibility. Accurate delineation of tumor margins is important for planning the extent of surgical resection. Any flat intraepithelial changes are difficult or impossible to delineate on radiologic imaging. Transhepatic access for cholangiography is reserved for patients with surgically altered anatomy in whom the major papilla cannot be accessed endoscopically. For percutaneous

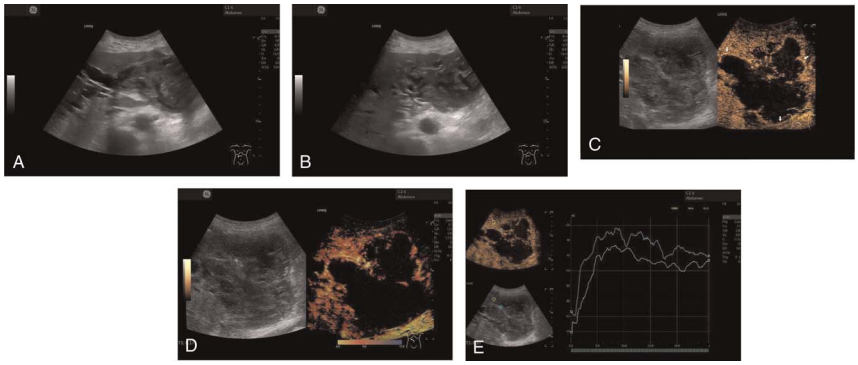

Figure 4. Cholangioscopically confirmed cystic IPNB variant with concomitant biliary dilatation in a 78-year-old female patient. B-mode ultrasound shows a hypoechoic inhomogeneous lesion of approximately 100 × 70 mm in the left liver lobe. The adjacent bile ducts are dilated (A). The lesion is very inhomogeneous; no anechoic parts are visible (B). Contrast-enhanced ultrasound with SonoVue demonstrates hyperenhancement in some areas of the wall (arrow). The entire hypoechoic changes of the lesion are nonenhanced and thus do not correspond to any vital tissue (C). In parametric imaging, it can be seen that the hyperenhanced wall portions in the contrast-enhanced ultrasound appear above all others (D). The time-intensity curve shows the flow in the arterial phase. The wall changes enhance faster and more intensely than the surrounding parenchyma (E). IPNB: intraductal papillary neoplasm of the bile ducts.

cholangioscopy, however, several interventions are initially required to create a sufficiently wide transhepatic fistula.[66–68]

Intraductal papillary neoplasm of the bile ducts usually affects the biliary epithelium multifocally, and the actual extent of the tumors often exceeds the predictions of preoperative imaging. Therefore, it is recommended to perform cholangioscopy, either intraoperatively or perorally, together with an intraoperative frozen-section examination to determine the extent of the disease and to establish the optimal surgical plan.[16] Intraductal papillary neoplasm of the bile duct has a high potential for malignancy. All patients should therefore be operated on if possible. To plan the correct surgical strategy and extent of resection, it is crucial to confirm the diagnosis and correctly predict the extent of IPNB. It would be interesting to use contrast-enhanced imaging to develop criteria to determine whether nodular changes are still benign or already malignant. In individual cases, this should not be decisive for the further procedure, as every operable patient should be submitted to surgical resection.

Preoperative biopsy

Biopsy sampling can be performed by percutaneous ultrasonographically guided needle biopsy if solid lesions can be delineated. In ERCP, forceps biopsy can be performed if filling defects can be reached with forceps under radiographic vision. Alternatively, brush cytology may be obtained from stenosed areas. In retrograde or transhepatic cholangioscopy, the intraductal tumors can be targeted and biopsied with the cholangioscopic mini forceps. The prerequisite is that the bile ducts are cleared of mucin to have visibility. Under cholangioscopic vision, malignant-appearing tumor areas can be targeted for biopsy. However, the specimens obtained by cholangioscopic forceps are very small. Fine-needle biopsy can also be performed by EUS-FNB. The characteristic cytomorphological features are complex papillary clusters of columnar cells with vacuolated cytoplasm, enlarged nuclei, and fine granular chromatin in relatively cellular specimen.[69] Han et al.[24] investigated the pathologic discrepancies of preoperative biopsy versus postoperative histology. In extrahepatic IPNB, the biopsy was performed during ERCP under radiographic guidance. In intrahepatic IPNB, the biopsy was performed by percutaneous transhepatic cholangioscopy under endoscopic view. Biopsies obtained from intrahepatic IPNB had a sensitivity of 76.9%, specificity of 100%, positive predictive value of 100%, and negative predictive value of 71.4%. Biopsies from extrahepatic IPNB had a sensitivity of 69.5%, specificity of 83.3%, positive predictive value of 94.1%, and negative predictive value of 41.6%. For extrahepatic IPNB, the negative predictive value was 41.6%. This means that approximately 60% of patients were misdiagnosed as nonmalignant. This is attributed to biopsy collection under ERCP in this study. Ultimately, it means that any IPNB is potentially malignant and should be resected.[24] A case of cutaneous needle tract seeding of an IPNB has been reported 23 months after the percutaneous biopsy.[70]

Differential diagnosis

The differential diagnosis includes all other cystic lesions of the liver or biliary tract and diseases associated with dilatation of the bile ducts. The communication of the cystic ectasia to the bile ducts is not visible in up to half of the patients. This means that other cystic liver lesions must also be considered.[48,71] An important differential diagnosis of the cystic variant of IPNB is MCN-L.[35,72–78] This again is also rare and is reported to be less than 5% of cystic lesions of the liver. Hepatic mucinous cystic neoplasm has previously been known as biliary cystadenoma or cystadenocarcinoma. Mucinous cystic neoplasm of the liver is differentiated from IPNB by the presence of subepithelial ovarian like–stroma and absence of communication with the bile duct lumen. They are unilocular or multilocular cystic lesions of mucin-positive neoplastic columnar epithelium with fibrous walls and septa between the cysts. Predominantly (85%–100%) women are affected while in IPNB, it is older men. Most commonly, MCNs-L are located in the left lobe of the liver, often in segment IV. On imaging, MCN-L often presents as a multilocular cyst with septation. Preoperative differentiation between cystic variant of IPNB and MCN-L is difficult. Simultaneously dilated bile ducts and intraluminal lesions are typical of IPNB.[34,76,77,79–82] In turn, both MCN-L and the cystic variant of IPNB must be distinguished from hydatid cysts.[83–87] Because IPNB manifests with focal dilatation of the bile ducts, diseases that cause focal biliary dilatation may mimic IPNB and must be distinguished. With focal biliary dilatation, it is important to exclude an intrahepatic stone or mass, such as cholangiocarcinoma, causing biliary obstruction. Diseases leading to distal obstruction of the common bile duct must be differentiated from extrahepatic IPNB. These are pancreatic head processes, obstruction of the papilla

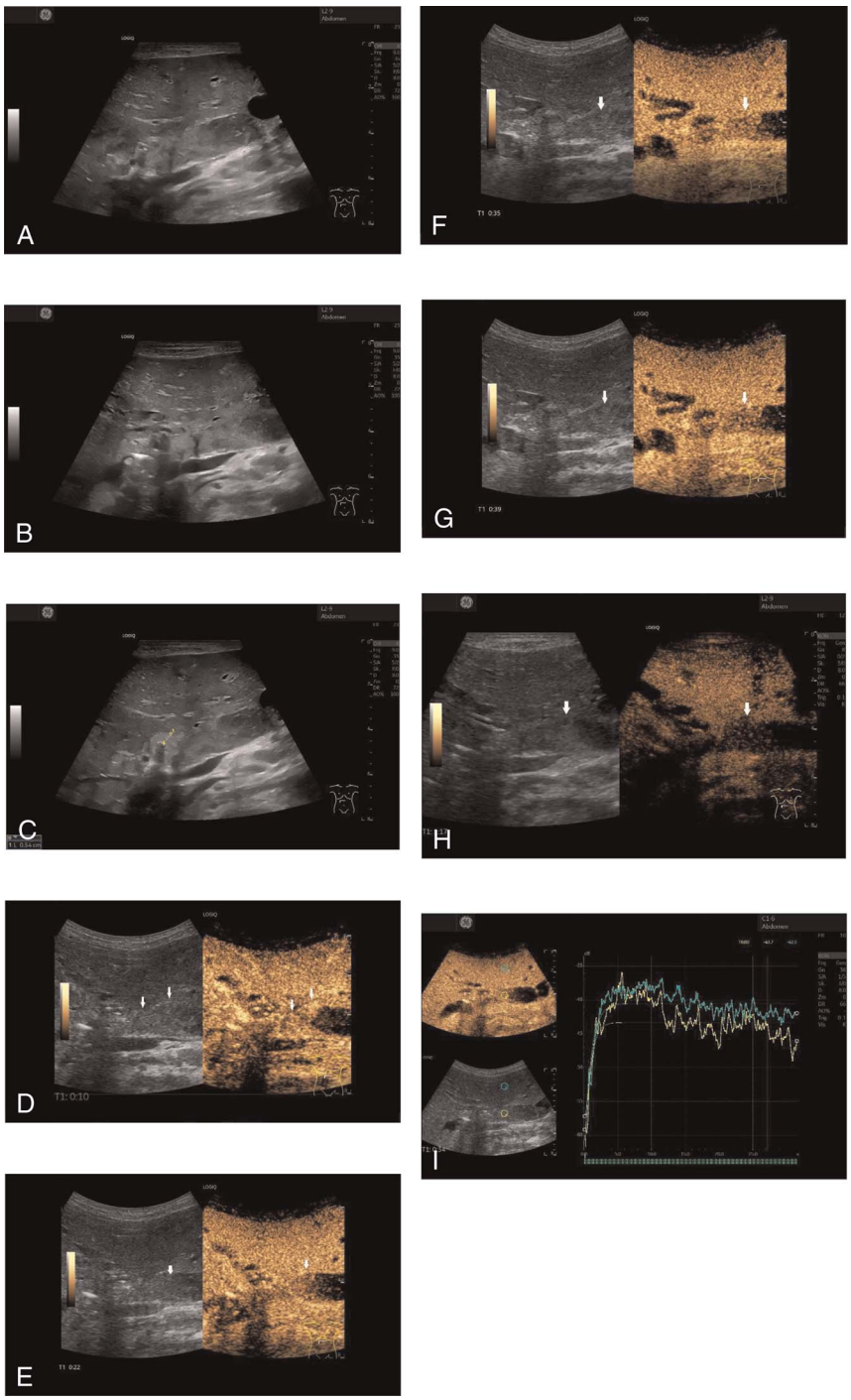

Figure 5. Intraductal papillary neoplasm of the bile ducts in a 56-year-old female patient with familial polyposis coli, after colectomy with pouch formation and duodenopancreatectomy for papillary adenoma. B-mode ultrasound shows the biliodigestive anastomosis with dilated bile duct branch. Near the anastomosis there are hyperechoic internal structures, which are arranged in a band-like wall arrangement (A). The dilated bile duct branches are filled with hyperechoic internal structures (B). In addition, a duct branch is visible with a thickened hyperechoic wall (C). On CEUS, the hyperechogenic changes are hyperenhanced in the arterial phase at 10 seconds (D). After 22 (E) and 35 seconds (F) at the beginning of the portal venous phase, the internal structures are still enhanced, but slightly less compared with the surrounding liver parenchyma. At 39 seconds in the early portal venous phase, there is a slight hypoenhancement (G) with slowly progressing washout (H), linear transducer, 1.17 minutes after injection of 2.0 mL SonoVue. The flow dynamics in the TIC represent the flow in the arterial phase (I). CEUS: contrast-enhanced ultrasound; TIC: time-intensity curve.

Vateri, choledocholithiasis, and stenoses of various origins of the distal common bile duct. Biliary obstruction may in turn be associated with biliary liver abscesses. Endoscopic interventions on the bile ducts in IPNB can also lead to superinfection. In the cystic variant, these parts can undergo abscess formation. Signet ring cell carcinoma, mixed adenoneuroendocrine carcinoma, anaplastic carcinoma, and other rare tumors occasionally show a grossly visible polypoid lesion within the dilated bile duct lumen.[35]

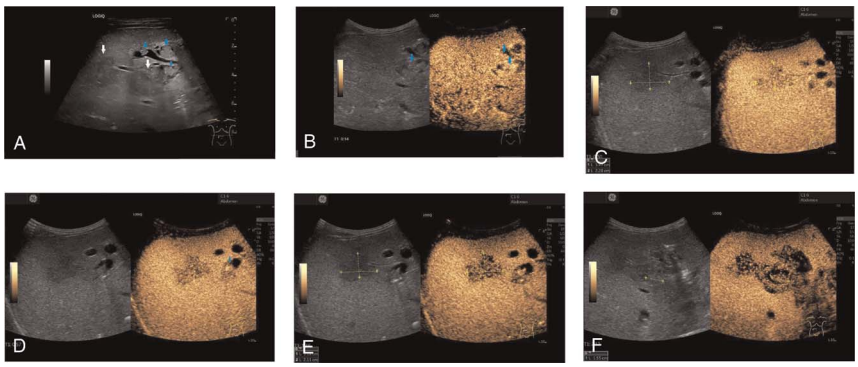

Figure 6. Intraductal papillary neoplasm of the bile ducts, histologically confirmed by cholangioscopy and forceps biopsy in a 57-year-old female patient. Dilated bile ducts in the right lobe of the liver with isoechoic nodular internal structures (blue arrows) in several locations. Multiple hypoechoic lesions (white arrows) in the right lobe of the liver adjacent to the course of the biliary tree (A). On contrast-enhanced ultrasound in the arterial phase at 14 seconds, the internal intraductal structures are hyperenhanced (blue arrows) compared with the homogeneously enhancing liver parenchyma (B). At the end of the arterial phase at 30 seconds, there is an incipient washout in the liver in the region of the hypoechoic liver lesions (C). The intraductal lesion (blue arrow) in the bile duct remains hyperenhanced in the portal venous phase and does not show any washout. The adjacent liver parenchyma shows progressive hypoenhancement without any associated structural change in the B-Mode scan. This dynamic is suggestive of an invasive process with liver infiltration (D). In the late portal venous phase after 1.46 minutes, the progressive washout continues in the liver and adjacent to the bile duct branch with the still hyperenhanced intraductal lesion (E). In the late phase at 2.12 minutes, broad hypoenhanced changes are shown. These can correspond to the course of the bile ducts. However, only a few hypoechoic changes are visible in the B-mode. Above all, no anechoic inner lumina are recognizable. In connection with the parabiliary changes shown in D and E, the finding suggests an invasive process (F).

Treatment

The present data show that IPNB is a slow-growing tumor that has significant potential to develop into invasive disease if malignancy is not already present at the time of diagnosis. For this reason, early surgical resection should be performed in all patients in whom IPNB is suspected on clinical findings and imaging. The type of surgical resection for IPNB depends on the location of the disease in the bile duct system. These might require hemihepatectomy, segmentectomy, or duodenopancreatectomy with biliodigestive anastomosis.[16,88,89] The median survival of 148 IPNB patients after curative-intent hepatic resection was 1326 days with 1-, 3-, and 5-year overall survival of 83.6%, 64.4%, and 47%, respectively. For malignant IPNB, univariate analysis showed that serum CA-19-9 level, lymph node metastasis, and completeness of resection were significant prognostic factors. Intraductal papillary neoplasm of the bile duct had a substantial more favorable prognosis than conventional cholangiocarcinoma.[16] Intraductal papillary neoplasm of the bile duct type 1 is associated with a better prognosis, whereas type 2 is associated with a poor prognosis.[39,41]

In the study by Kubota et al.[41] evaluating 594 IPNB patients, there were significant differences in 5-year cumulative survival rates between types 1 and 2 IPNB: 75.2% versus 50.9%, and 5-year cumulative disease-free survival rates: 64.1% versus 35.3%, between the 2 groups. The average disease-specific survival rate was 90.9% in type 1 patients and 58.7% in type 2 patients.[39] In the case of extensive findings, the indication for liver transplantation should be considered.[90,91] Choi et al.[90] present a case of a male patient with biliary papillomatosis with malignancy who underwent living donor liver transplantation and was still alive for 10 years despite lung metastasis 5 years after transplantation. For tumor mass reduction before a planned operation or in the in the palliative situation, when patients cannot be operated on or tumors are very extensive, tumor mass reduction and restoration of passage can be carried out by argon plasma coagulation therapy[92–94] or photodynamic therapy.[90,95,96]

Endoscopic stenting in ERCP is difficult when multilocular tumors are present. Individual tumors can be bridged by stents. The marked mucin production often leads to occlusion of the biliary stents.

CONCLUSION

Intraductal papillary neoplasm of the bile duct is a rare biliary tract disease that more commonly affects middle-aged to elderly adults with a slight male predominance. The disease is characterized by biliary dilatation and bile duct–associated cystic lesions with intraductal contrast-enhancing nodules and has a high potential for malignancy. Malignancy risk and poorer prognosis are more common in extrahepatic IPNB and type 2 IPNB, respectively. Even though IPNB has similar 4 histological types as pancreatic IPMN, the prognosis is worse. Ultrasound is used to describe biliary dilatations, cystic lesions, and internal structures. Contrast-enhanced ultrasound can be used in particular to differentiate the internal structures as (enhancing) vital tissue from (nonenhancing) mucin and other nonvital echogenic structures. In our experience, the intraductal papillomatous mucosal changes present as hyperechogenic band-like thickenings with hyperenhancement on CEUS. The intraluminal vital nodes are hyperenhanced in the arterial phase and then show a washout.

Timely diagnosis is important because, due to the risk of malignancy, every patient should be operated on if not prevented by the spread of the significant or significant comorbidities.

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Conflicts of Interest

Siyu Sun and Christoph F. Dietrich are Editors-in-Chief of the journal, and Christian Jenssen is an Editorial Board Member. This article was subject to the journal's standard procedures, with peer review handled independently of the editors and their research

groups. The authors declare that they have no financial conflict of interest with regard to the content of this report.

Author Contributions

Ideation and planning of the work was done by Kathleen Möller and Christoph F. Dietrich. Data collection and analysis were performed an the first draft of the manuscript was written by Kathleen Möller. Christoph F. Dietrich accompanied the work with valuable advice, literature references and with his incredible experience. Christian Jenssen and Barbara Braden wrote valuable additions. All authors commented on and corrected earlier versions of the manuscript and provided valuable comments. All authors read and approved the final manuscript. Special thanks are due to Christoph F. Dietrich and Siegbert Faiss for their constant reliable support.

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