Intraductal ultrasonographic anatomy of biliary varices in patients with portal hypertension

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ABSTRACT

Background and Objectives: The term, portal biliopathy, denotes various biliary abnormalities, such as stenosis and/or dilatation of the bile duct, in patients with portal hypertension. These vascular abnormalities sometimes bring on an obstructive jaundice, but they are not clear which vessels participated in obstructive jaundice. The aim of present study was clear the bile ductal changes in patients with portal hypertension in hopes of establishing a therapeutic strategy for obstructive jaundice caused by biliary varices. **Materials and Methods:** Three hundred and thirty-seven patients who underwent intraductal ultrasound (IDUS) during endoscopic retrograde cholangiography for biliary abnormalities were enrolled. Portal biliopathy was analyzed using IDUS. **Results:** Biliary varices were identified in 11 (2.7%) patients. IDUS revealed biliary varices as multiple, hypoechoic features surrounding the bile duct: epicholedochal and paracholedochal. Epicholedochal varices were identified in all patients, but paracholedochal varices were observed only in patients with extrahepatic portal obstruction. **Conclusion:** IDUS was useful to characterize the anatomy of portal biliopathy in detail.

Key words: Biliary varices, intraductal ultrasound, portal biliopathy, portal hypertension

INTRODUCTION

Portal biliopathy denotes the present of various biliary abnormalities, such as stenosis and/or dilatation of the bile duct in patients with portal hypertension, especially in those with extrahepatic portal vein obstruction (EHPVO).^[1] This pathology results from compression of the bile ductal system because of portal cavernous formation,^[2-23] choledochal varices,^[24-26] or ischemic injury of the bile duct.^[1,4] Moreover, in patients with

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these abnormalities, obstructive jaundice is rarely observed.^[1-26]

Previously studies have reported that the frequency of portal biliopathy in patients with EHPVO is 81-100%^[6,10,11,15] and that the frequency of obstructive jaundice frequency is 5-14%.^[4,6,10,12] In patients with EHPVO, many kinds of varices are observed in the gastrointestinal tract as well as in other organs. This occurs due to the development of extensive collateral circulation involving paracholecystic, paracholedochal and pancreatoduodenal veins, all of which contribute to the development of portal biliopathy. These changes can also occur in other instances of portal hypertension (e.g., liver cirrhosis, primary biliary cirrhosis [PBC], Budd-Chiari syndrome, and left-sided portal hypertension because of pancreatic disease), although

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the frequency of portal biliopathy in such circumstances might be lower than that of EHPVO.

Various strategies have been used to manage portal biliopathy with obstructive jaundice, including placement of a biliary stent,^[1,16,19,22,26] porto-systemic shunting surgery,^[1,4,7,8,10,16,17] hepaticojejunostomy,^[1,7] operative biliary decompression, and splenectomy. Nevertheless, the anatomy of portal biliopathy has not been well investigated because EHPVO is rare disease such as 13% of portal hypertention,^[6] and because it is difficult to characterize the deep portion of the bile duct system. Thus, it is not clear which vessels are involved with the choledochal varices. Further, there is no established therapeutic strategy for management of choledochal varices leading to obstructive jaundice exists.

Endoscopic ultrasonography (EUS) can be useful for the diagnosis of various digestive diseases. In fact, EUS is very useful for the characterization of pancreatobiliary diseases because of the ability to place the EUS transducer in close proximity to the pancreatobiliary system.^[27,28] EUS allows high-resolution imaging of the entire gland, facilitating diagnosis of subtle abnormalities that are not otherwise detectable using other standard imaging modalities, such as computed tomography (CT), percutaneous ultrasound, and magnetic resonance imaging (MRI).^{[29-30])} Moreover, intraductal ultrasound (IDUS) using a high-frequency mini-probe (20 MHz) under endoscopic retrograde cholangiography (ERC) is especially useful for diagnosis of infiltration of bile duct cancer into the ductal wall and surrounding organs. IDUS is also superior to EUS in terms of characterizing the structure of the bile ducts.[31-33]

Although various pancreatobiliary disorders can cause portal hypertension, and although EUS is often performed to diagnose those disorders, a few series have also characterized portal biliopathy using EUS.^[3,12,34] For example, Palazzo *et al.*^[12] used EUS and reported that biliary varices as portal biliopathy could be classified into two different types: Vessels in the ductal wall and vessels surrounding the ductal wall. However, they did not clarify which vessels participated in obstructive jaundice, nor did they suggest any therapeutic strategy for management of portal biliopathy. By contrast, data obtained from IDUS might be helpful in formulating the therapeutic strategy for portal biliopathy by proving vital information regarding the anatomy of biliary varices.

Therefore, the goal of this study was to use IDUS to characterize bile ductal changes in patients with portal hypertension in hopes of establishing a therapeutic strategy for obstructive jaundice caused by biliary varices.

MATERIALS AND METHODS

Patients

The present study enrolled 377 patients with biliary abnormalities who underwent IDUS during ERC at Fukushima Medical University Hospital from January 2001 to December 2011. Patients included 226 males and 151 females, aged 65.7 \pm 12.5 (mean \pm standard deviation [SD]) years. Indications for ERC/IDUS were suspicion of bile duct tumor in 149 patients, bile duct stone in 102 patients, primary sclerosing cholangitis (PSC) in 10 patients, pancreatic mass in 41 patients, chronic pancreatitis in 13 patients, autoimmune pancreatitis in six patients, tumor of ampulla in 18 patients, other bile-duct abnormalities in 34 patients, and obstructive jaundice attributable to EHPVO in four patients [Table 1]. Sixty-eight patients had underlying disease causing portal hypertension (including left-sided portal hypertension, including EHPVO in four patients, PSC in 10 patients, and pancreatic disorders in 54 patients).

Informed consent was obtained from each patient. The study protocol conformed to ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Institutional Review Board.

Endoscopic retrograde cholangiography and intraductal ultrasound

Endoscopic retrograde cholangiography was performed using a side-viewing scope (JF230, JF240, TJF240, JF260V; Olympus Medical Systems Co., Ltd., Tokyo,

Underlying disease	Number of patients (n = 377) %		Age (mean ± SD)	Gender (male:female)
Bile duct cancer	149	39.5	69.9±9.4	102:47
Stone of bile duct	102	27.1	63.7±13.4	54:47
PSC	10	2.6	54.5±14.3	5:5
Pancreatic cancer	41	10.9	66.0±11.2	21:20
Chronic pancreatitis	13	3.4	58.3±13.7	10:3
AIP	6	1.6	55.5±14.9	5:1
Ampulla tumor	18	4.8	72.8±7.3	9:9
PBM	6	1.6	45.2±10.0	1:5
SOD	5	1.3	67.4±13.0	1:4
EHPVO	4	1.1	49.5±11.4	2:2
Other	23	6.1	61.3±15.5	16:7

PSC: Primary sclerosing cholangitis, AIP: Autoimmune pancreatitis, PBM: Pancreticobiliary malfunction, SOD: Sphincter oddi dysfunction, EHPVO: Extra hepatic portal venous obstruction, SD: Standard deviation, IDUS: Intraductal ultrasound Japan) with patients under mild conscious sedation via administration of 5-10 mg of diazepam. For contrast medium, sodium and meglumine diatrizoate (Urografin; Nippon Schering KK, Japan) was used.

Intraductal ultrasound examination was performed to evaluate biliary abnormalities that were revealed by ERC imaging. After injection of contrast medium into the bile duct through the ampulla, a 0.035- or 0.025-inch guidewire (Jag-wire, Boston Scientific Japan Co., Tokyo; and/or Tracer Metro, Cook Japan Co., Tokyo; and/or Visiglide, Olympus Medical Systems Co., Ltd., Tokyo, Japan) was inserted into the bile duct. A 20 MHz mini-probe (UM-G20-29R; Olympus Medical Systems Co., Ltd., Tokyo, Japan) was passed through the biopsy channel of the scope and was inserted transampullarily into the bile duct following a guidewire. IDUS images were monitored on the ultrasound system (EU-M20/ MH-241; Olympus Medical Systems Co., Ltd., Tokyo, Japan). The IUDS probe was moved from the hiatus to the ampulla, and each sectional view of the bile duct was recorded. These recorded images were assessed with complete agreement by six experienced endosonographers who each had more than 5 years' experience.

Intraductal ultrasound images of biliary varices and its evaluation

A normal bile duct was viewed as having three layers: Internal hypoechoic, middle hyperechoic, and external hypoechoic. No echo features of vessels were visible in these layers [Figure 1]. Biliary varices on an IDUS image [Figure 2] were defined as follows:

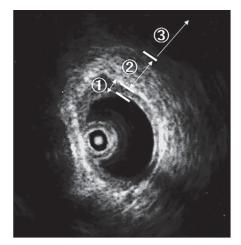


Figure 1. Intraductal ultrasound (IDUS) image of the bile duct in a normal patient. A normal bile duct is shown as three layers: Internal hypoechoic, middle hyperechoic, and external hypoechoic. No echo feature of the vessel occurs in these layers. On IDUS, each bile ductal layer is reflected from mucosa to the adventitia (1), serosa (2), and external serosa (3), respectively

- 1. Multiple hypoechoic lumens, which were similar to esophageal varices, were visible inside or outside the bile duct, especially in the part of stricture;
- 2. Fine particles were moving close together, as turbulent blood flow in the lumens; and
- 3. The above two criteria were visible, without the following: Bile tumor, pancreatic tumor, swollen lymph nodes, stone, or inflammatory wall thickness.

The maximum diameter of vessels was measured at three points (upper, middle, lower bile duct).

Statistical analysis

Data processing was performed by using the software Statcel 3 (OMS Edition, Saitama, Japan). Data were expressed as mean \pm SD.

RESULTS

Summary of characteristics and imaging findings in patients diagnosed with biliary varices

The frequency of biliary varices was 2.9% (11/377) in patients who had undergone ERC/IDUS to diagnose biliary abnormalities [Table 1]. Of the patients included in this series, 18.0% (68/377) had portal hypertension, EHPVO in four patients, PSC in 10 patients, and pancreatic disorders in 54 patients. The frequencies of biliary varices in each diseases are summarized in Table 2 and included EHPVO in four patients (100%: 4/4), PSC in two patients (20.0%: 2/10), chronic pancreatitis in one patient (7.7%: 1/13), pancreatic cancer in three patients (0.7%: 1/149).

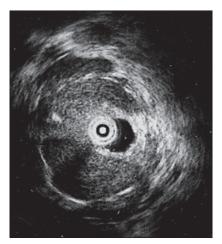


Figure 2. Intraductal ultrasound (IDUS) image of the bile duct in patient with portal hypertention. Biliary varices on IDUS imaging. Biliary varices are visible; these varices cause the formation of a biliary stricture

The background and details of the 11 patients who had biliary varices are given in Table 3. In patients with EHPVO, bile stenosis on ERC caused by biliary varices was visible over a wide area of the bile duct. On the other hand, in patients with pancreatic disorders, biliary varices were seen at the lower bile duct. In patients with PSC, the location of biliary varices followed a uniform pattern. In all patients with EHPVO, varices were present in other gastrointestinal organs. One patient with EHPVO had jaundice because of biliary varices. No patient showed hemorrhage from biliary varices.

Detection of biliary varices on each imaging modality Regarding the detection capability of biliary varices, IDUS was superior to other modalities (e.g., percutaneous ultrasound, CT scan and MRI) [Table 4].

Table 2. Frequency of biliary varice

Underlying disease	Frequency					
	Number (biliary varices)	Number (all)	%			
EHPVO	4	4	100			
PSC	2	10	20			
Chronic pancreatitis	1	13	7.7			
Pancreatic cancer	3	41	7.3			
Bile duct cancer	1	149	0.7			
Stone of bile duct	0	102	0			
AIP	0	6	0			
Ampulla tumor	0	18	0			
PBM	0	6	0			
SOD	0	5	0			
other	0	23	0			
Total	11	377	2.9			

PSC: Primary sclerosing cholangitis, AIP: Autoimmune pancreatitis, PBM: Pancreticobiliary malfunction, SOD: Sphincter oddi dysfunction, EHPVO: Extra hepatic portal venous obstruction

Table 3. Detail of 11 patients with detected biliary varices

Anatomic analysis of biliary varices using intraductal ultrasound

Intraductal ultrasound revealed biliary varices as multiple, hypoechoic features surrounding the bile duct wall. These varices could be classified into one of two groups according to their location in the sectional image of bile duct: Epicholedochal and paracholedochal [Figures 3-6]. The epicholedochal varices were vessels in the serosa or subserous area (second layers of bile duct on IDUS image: [Figures 3 and 4]). In contrast, paracholedochal varices were located in vessels adjacent to and distal from the serous membranes (third layer of bile duct on IDUS: [Figures 5 and 6]). In one patient with obstructive jaundice, severe epicholedochal varices were present.

These two types of categorized varices were evaluated in detail according to each underlying disorder (e.g.,

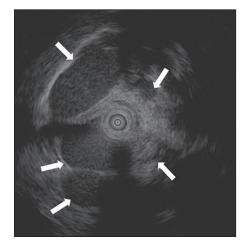


Figure 3. Intraductal ultrasound image of severe epicholedochal varices. Epicholedochal varices (arrow) are apparent in the second layer (serosa). Obstructive jaundice occurs due to development of severe epicholedochal varices

Case	Case Underlying disease		Gender	Loc	Location		Bleeding	Other varices	Therapy for
				On ERC	On IDUS				biliary varices
1	EHPVO	37	Male	U~L	U~L	+	_	Eso., Sto., Rec., GB	Plastic stent
2	EHPVO	63	Female	U~L	U~L	_	_	Eso.	Follow-up
3	EHPVO	40	Female	U~M	U~M	_	_	Eso.	Follow-up
4	EHPVO	58	Male	U~L	U~L		_	Eso., Sto.	Follow-up
5	Pancreatic cancer (secondary EHPVO)	74	Female	Μ	M~L	+	_	_	Plastic stent
6	Pancreatic cancer	73	Female	L	L	+	_	_	Follow-up
7	Pancreatic cancer	77	Female	L	L	_	_	_	Follow-up
8	Chronic pancreatitis	76	Female	L	L	_	_	Sto.	Follow-up
9	PSC	51	Female	U	U~L	_	_	Eso.	Follow-up
10	PSC	59	Male	U	U	_	_	_	Follow-up
11	Bile duct cancer	78	Male	_	U	+	_	_	Follow-up

PSC: Primary sclerosing cholangitis, EHPVO: Extra hepatic portal venous obstruction, U: Upper bile duct, M: Middle bile duct, L: Lower bile duct, Eso.: Esophagus, Sto.: Stomach, Rec.: Rectum, GB: Gall bladder, ERC: Endoscopic retrograde cholangiography, IDUS: Intraductal ultrasound

EHPVO, pancreatic disease, PSC and bile duct cancer), as shown in Table 5. Epicholedochal varices were identified in all patients, but paracholedochal varices were observed only in patients with EHPVO. Biliary

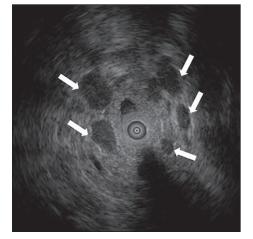


Figure 4. Intraductal ultrasound image of mild epicholedochal varices (arrow). No obstructive jaundice is seen in a patient with mild epicholedochal varices

Table 4. Detection capability for the diagnosis of biliary varices using imaging devices

Imaging devices	Frequency				
	Number (biliary varices)	Number (all examination)	%		
US	3	5	60		
СТ	7	11	63.6		
MRI	3	7	42.9		
IDUS	11	11	100		

US: Ultrasound, CT: Computed tomography, MRI: Magnetic resonance imaging, IDUS: Intraductal ultrasound

Table 5. Degree of biliary varices on IDUS images

varices were identified over a wide area of the bile duct in patients with EHPVO. The varices developed at the lower bile duct in patients with pancreatic disorders and mainly at the upper bile duct in patients with PSC or bile duct cancer.

Treatment for biliary varices

In one patient with obstructive jaundice, drainage treatment was performed via placement of an indwelling stent. In another patient, beta-blocker was administered prophylactically for portal hypertension, although jaundice was not present.

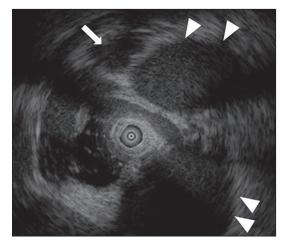


Figure 5. Intraductal ultrasound image of severe paracholedochal varices. Paracholedochal varices (arrowhead) are visible adjacent to and distal from the second layer (serosa). These varices do not promote formation of bile duct stenosis. Rather, the epicholedochal varices (arrow) cause the bile duct stenosis

Underlying disease	Location	Epi-chole	dochal varices	Paracholedochal varices		
		Presence rate (%)	Mean diameter (mm)	Presence rate (%)	Mean diameter (mm)	
EHPVO (n=4)	U	4/4 (100)	3.0±0.8	3/4 (75)	4.0±3.4	
	Μ	4/4 (100)	3.3±0.5	3/4 (75)	5.5±4.3	
	L	4/4 (100)	4.5±1.3	0	_	
Secondary EHPVO	U	0	_	0	_	
(pancraetic cancer) (<i>n</i> =1)	Μ	1/1 (100)	5	1/1 (100)	9	
	L	1/1 (100)	3	0	_	
Pancreatic disorder (<i>n</i> =3)	U	0	_	0	_	
	Μ	0	-	0	_	
	L	3/3 (100)	2.5±0.7	0	_	
PSC (<i>n</i> =2)	U	2/2 (100)	3.5±2.1	0	_	
	Μ	1/2 (50)	1.0±1.4	0	_	
	L	1/2 (50)	1.0±1.4	0	_	
Bile duct cancer (<i>n</i> =1)	U	1/1 (100)	_	0	_	
	Μ	0	_	0	_	
	L	0	_	0	_	

PSC: Primary sclerosing cholangitis, EHPVO: Extra hepatic portal venous obstruction, U: Upper bile duct, M: Middle bile duct, L: Lower bile duct, IDUS: Intraductal ultrasound



Figure 6. Intraductal ultrasound image of mild paracholedocal varices (arrow head). These varices also do not promote formation of bile duct stenosis

DISCUSSION

Portal biliopathy is a biliary abnormality caused by portal cavernous formation, choledochal varices, and fibrosis in patients with portal hypertension (e.g., liver cirrhosis, PBC, Budd-Chiari syndrome, and left-sided portal hypertension due to pancreatic disorders). Portal biliopathy is often seen in patients with EHPVO. On the other hand, frequencies of portal biliopathy in other disease are not clear in the previous literature. Moreover, there is no established therapeutic strategy for portal biliopathy that leads to obstructive jaundice. The present study used IDUS to analyze the mechanism of portal biliopathy that causes obstructive jaundice. Later in this discussion, based on data gained from this modality, we propose a therapeutic strategy for the management of portal biliopathy, especially when biliary varices are present.

Intraductal ultrasound with high-frequency images under ERC is useful for diagnosis of bile ductal abnormalities, as IDUS can directly access the lesion that causes biliary abnormalities. In contrast, biliary varices cannot always be detected by US, CT, and MRI.^[3,8,15,16,18-23,26] Indeed, the present study demonstrated that IDUS was superior to other imaging modalities for detection of biliary varices. EUS is also useful for diagnosis of various pancreatobiliary disorders, mainly because of the ability to place the transducer in close proximity to the pancreatobiliary system via the digestive tract, thereby generating high resolution images.^[27-30] Consequently, EUS can represent biliary varices in a greater degree than other conventional modalities. However, in contrast to EUS, IDUS can detect the detailed bile ductal wall and outside of bile duct. This was the first study to use IDUS to characterize biliary varices.

Intraductal ultrasound can be used to categorize biliary varices into one of two groups:

- 1. Vessels in the bile ductal wall (serosa and sub-serosa) and
- 2. Vessels surrounding the bile duct (separate from and/ or adjacent to external serosa).

We defined the former as epicholedochal varices, and the latter as paracholedochal varices. Previously, investigators characterized two venous systems along the biliary tract, according to surgical anatomy in a human and in an experimental portal hypertension model: Epicholedochal plexus by Saint,^[35] which forms a fine reticular network over the bile ductal wall; and paracholedochal veins by Petren,^[36] running parallel to the bile duct. In addition, Palazzo et al.[12] reported that biliary varices were identified in two different locations by EUS: Inside the bile ductal wall and the surrounding bile duct wall. Therefore, the two categories of biliary varices characterized in the present study are consistent with observations from previous studies. Specifically, epicholedochal varices and paracholedochal varices on IDUS reflect the above-mentioned dilated epicholedochal plexus of Saint,^[35] and the paracholedochal veins of Petren,^[36] respectively.

Intraductal ultrasound analysis of biliary varices in the present study yielded information regarding the respective mechanisms of the development of biliary varices in each disease and therefore, provided useful information to guide the therapeutic strategy. Epicholedochal varices developed in all patients that showed biliary varices (i.e., those patients with EHPVO, pancreatic disease, and PSC). On the other hand, paracholedochal varices were visualized only in patients with EHPVO. These findings reflect the specific hemodynamics of portal hypertension for each respective disease.

Epicholedochal varices were considered to be formed by increasing blood flow in the epicholedochal plexus of Saint. The blood flow of epicholedochal plexus was originally hepatopetal, that is stagnated as portal hypertention was developed.

Consequently, the epicholedochal plexus became congested, and epicholedochal varices developed. From this point of view, epicholedochal varices will develop in the state of portal hypertension regardless of the underlying disease. In addition, epicholedochal varices will directly influence the occurrence of obstructive jaundice according to their specific location.

Increased blood flow in paracholedochal veins of Petren (which exist as a hepatofugal route from the gastric and pancreaticoduodenal veins to the portal vein) caused by portal obstruction may promote formation of paracholedochal varices. This is especially likely in the context of EHPVO, because paracholedochal veins are used as hepatopetal collaterals (portal cavernous formation), and these veins might form the varices. Moreover, the epicholedochal plexus is reportedly connected to the paracholedochal veins.^[35] For that reason, increasing the blood flow in the paracholedochal veins could promote the development of pericholedochal varices. These altered hemodynamics may mediate the high frequency of biliary varices and obstructive jaundice in patients with EHPVO. In contrast, few hepatofugal collaterals develop in PSC patients, which might explain why paracholedochal varices are uncommon. Further, hemodynamics tends to be variable among patients with pancreatic disorders; therefore, variceal hemodynamics cannot be discussed indiscriminately. However, because there is no reason for development of paracholedochal veins in patients with pancreatic disorders, development of epicholedochal varices might not be severe and might not cause icterus.

We previously used EUS to characterize the existence and role of two different collaterals around the esophageal wall:^[37] Peri-esophageal collateral veins, which are directly involved in the development of esophageal varices, and para-esophageal collateral veins, which serve as a drainage route of portal hypertension. An interesting result of the present study is that the hemodynamics of biliary varices resemble those of esophageal collaterals. For esophageal varices, paraesophageal collateral veins serve as a drainage route participating in the development of varices via connecting veins between the periesophageal and paraesophageal collateral veins. Furthermore, paracholedochal varices are feeders into epicholedochal varices via connecting veins, especially in patients with EHPVO. In patients with portal hypertension, veins that originally serve as drainage routes sometimes serve as feeders and support the development of varices through destruction of valves connecting veins of drainage.[38,39]

In the present study, we placed a plastic biliary stent via endoscopy for treatment of biliary varices. The utility of surgery for biliary obstruction secondary to varices in patients with EHPVO has been described in previous reports.^[1,4,7,8,16,17,40] However, it is not clear which is the better treatment: Endoscopic stent placement or surgery (direct decompressive procedure and formation of a porto-systemic shunt). Sezgin et al.^[5] reported that endoscopic treatment is a safe first-line treatment for patients with biliary obstruction caused by EHPVO. In the present study, severe epicholedochal varices and paracholedochal varices developed widely in patients with EHPVO, suggesting that the risk of massive intraoperative hemorrhage is high. Direct surgery entails a risk of massive hemorrhage. Therefore, we believe that endoscopic placement of a plastic stent is treatment of choice for patients with obstructive jaundice due to biliary varices. In addition, administration of betablockers might be necessary for decompression of portal hypertension, because the plastic stent will not address portal hypertension. On the other hand, in the case of bleeding, devascularization via direct surgical procedure is necessary for control of bleeding. The risk of variceal hemorrhage is low for biliary varices in patients without EHPVO, because paracholedochal varices associated with epicholedochal varices do not develop. For that reason, a plastic stent is sufficient to control obstructive jaundice. We believe that assessment of biliary varices using IDUS will be useful to guide the therapeutic strategy for patients with obstructive jaundice due to biliary varices.

CONCLUSIONS

This study used IDUS to clarify the anatomy of biliary varices and two types of collaterals (i.e., epicholedochal and paracholedochal varices). This information will help guide formulation of the therapeutic strategies for biliary varices.

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