

Tissue acquisition for diagnosis of biliary strictures using peroral cholangioscopy or endoscopic ultrasound-guided fine-needle aspiration

Authors

Yun Nah Lee¹, Jong Ho Moon¹, Hyun Jong Choi¹, Hee Kyung Kim², Hyun Woo Lee¹, Tae Hoon Lee¹, Moon Han Choi¹, Sang-Woo Cha¹, Young Deok Cho¹, Sang-Heum Park¹

Institutions

- 1 Digestive Disease Center and Research Institute, Department of Internal Medicine, SoonChunHyang University School of Medicine, Bucheon and Seoul, Korea
- 2 Department of Pathology, SoonChunHyang University School of Medicine, Bucheon, Korea

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Bibliography

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Corresponding author

Jong Ho Moon, MD, PhD, Digestive Disease Center and Research Institute, SoonChunHyang University School of Medicine, Bucheon Hospital, 170 Jomaru-ro, Wonmi-gu, Bucheon 14584, Korea
 Fax: +82-32-6215018
jhmoon@schmc.ac.kr

ABSTRACT

Background Although endoscopic retrograde cholangiopancreatography (ERCP) is a first-line diagnostic modality for suspected malignant biliary stricture (MBS), the diagnostic yield of ERCP-based tissue sampling is insufficient. Peroral cholangioscopy-guided forceps biopsy (POC-FB) and endoscopic ultrasound-guided fine-needle aspiration biopsy (EUS-FNAB) are evolving as reliable diagnostic procedures for inconclusive MBS. This study aimed to evaluate

the usefulness of a diagnostic approach using POC-FB or EUS-FNAB according to the stricture location in patients with suspected MBS.

Methods Consecutive patients diagnosed with suspected MBS with obstructive jaundice and/or cholangitis were enrolled prospectively. ERCP with transpapillary forceps biopsy (TPB) was performed initially. When malignancy was not confirmed by TPB, POC-FB using a SpyGlass direct visualization system or direct POC using an ultraslim endoscope was performed for proximal strictures, and EUS-FNAB was performed for distal strictures as a follow-up biopsy.

Results Among a total of 181 patients, initial TPB showed malignancy in 122 patients, and the diagnostic accuracy of initial TPB was 71.8% (95% confidence interval [CI] 65.3%–78.4%). Of the 59 patients in whom TPB was negative for malignancy, 32 had proximal biliary strictures and underwent successful POC. The remaining 27 patients had distal strictures and underwent successful EUS-FNAB. The accuracy of malignancy detection using POC-FB for proximal biliary strictures and EUS-FNAB for distal biliary strictures was 93.6% (95%CI 84.9%–100%) and 96.3% (95%CI 89.2%–100%), respectively. The overall diagnostic accuracy for the combination of TPB with either POC-FB for proximal strictures and EUS-FNAB for distal strictures was 98.3% (95%CI 95.9%–100%) and 98.4% (95%CI 95.3%–100%), respectively.

Conclusions An approach using POC-FB or EUS-FNAB according to the stricture location may be useful in the diagnosis of suspected MBS.

University Hospital Medical Network Clinical Trials Registry UMIN000020193

TRIAL REGISTRATION: Single-center, prospective, observational study UMIN000020193 at <http://www.umin.ac.jp>

Introduction

In patients with biliary stricture and obstructive jaundice and/or cholangitis, endoscopic retrograde cholangiopancreatography (ERCP) is the first-line modality because this approach can be used to perform simultaneous tissue sampling and endoscopic

biliary drainage for biliary strictures. However, the diagnostic yield of ERCP-based tissue sampling is unsatisfactory, and several new diagnostic modalities have been introduced recently to improve the diagnostic accuracy of biliary strictures [1, 2].

Endoscopic ultrasound-guided fine-needle aspiration biopsy (EUS-FNAB) and peroral cholangioscopy (POC)-guided target biopsy are representative methods for tissue sampling from biliary strictures. In previous studies, EUS-FNAB was sensitive and highly specific for diagnosing malignancy in biliary strictures [3–6]. However, EUS-FNAB is unlikely to be used as a routine clinical procedure for proximal biliary strictures because its sensitivity was reported to be significantly lower than that for distal strictures, owing to the technical difficulty and risk of needle-tract seeding [7–9].

Newly developed POC systems, such as the SpyGlass direct visualization system (DVS; Boston Scientific Corp., Marlborough, Massachusetts, USA) and direct POC using an ultraslim endoscope, have led to great improvements in technical performance and diagnostic yields for biliary strictures [10,11]. However, the performance of POC-guided target biopsy for distal bile duct strictures is technically difficult, and this approach has a limited ability to diagnose biliary strictures caused by nonintraductal, extrinsic compressed malignancies, such as a pancreatic cancer [12–14].

Therefore, an approach that considers the characteristics of each diagnostic method is required in order to optimize the diagnosis of biliary stricture. In this study, we evaluated the usefulness of diagnostic approaches using peroral cholangioscopy-guided forceps biopsy (POC-FB) or EUS-FNAB according to the stricture location in patients with suspected malignant biliary stricture (MBS).

Methods

This was a prospective observational study comparing the diagnostic yields of POC-FB and EUS-FNAB by stricture location in patients with suspected MBS. Our institutional review board approved the study, and written informed consent was obtained from all patients. The study has been registered with the UMIN Clinical Trial Registry (UMIN 000020193).

Patients

Consecutive patients with suspected MBS that required tissue sampling were prospectively enrolled in the study. The inclusion criteria were: 1) stricture of the extrahepatic bile duct that was revealed by cross-sectional radiological imaging (computed tomography and/or magnetic resonance imaging); 2) clinical findings of obstructive jaundice and/or cholangitis; 3) age > 18 years; and 4) ability to provide informed consent.

The exclusion criteria were: 1) known bile duct stricture without clinical and radiological image findings suggestive of malignancy (e.g. primary biliary cirrhosis or postoperative biliary stricture); 2) the presence of contraindications for ERCP; 3) altered gastrointestinal anatomy or duodenal obstruction; and 4) coagulopathy (international normalized ratio > 1.5 or platelet count < 80 000/mm³).

Diagnostic approach for suspected MBS

All procedures were achieved using standardized protocols by three experienced investigators. Initially, ERCP was performed on enrolled patients for biliary drainage for obstructive jaundice and/or cholangitis, and transpapillary forceps biopsy (TPB) was used for biliary stricture tissue sampling. ERCP was performed using a standard duodenoscope (JF or TJF-260V; Olympus Medical Systems, Co., Ltd., Tokyo, Japan) on patients under conscious sedation. To identify the location and length of the biliary stricture, cholangiography was achieved by injecting contrast medium (Omnipaque; GE Healthcare, Seoul, Korea), and intraductal ultrasonography (IDUS) was performed immediately. The IDUS probe (UM-G20-29R; Olympus Optical, Co., Ltd., Tokyo, Japan) was 2.0 mm in diameter and had a radial scanning catheter with a scanning frequency of 20 MHz.

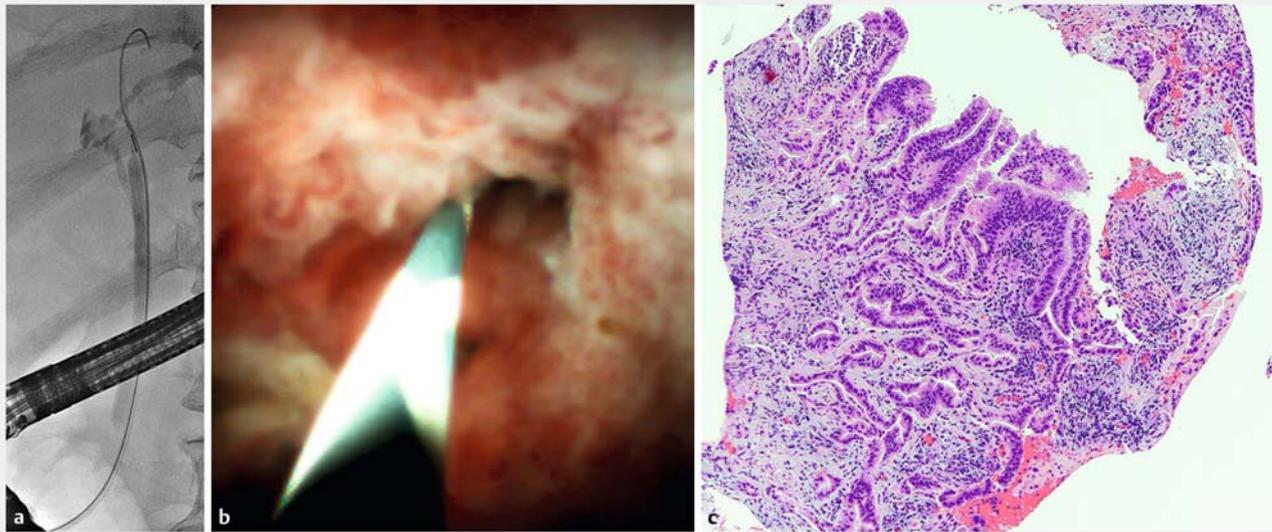
Strictures were classified as proximal or distal, according to their location. Based on prior radiological imaging and IDUS, biliary strictures located in suprapancreatic portions were defined as proximal and those in intrapancreatic portions were defined as distal. A fluoroscopy-guided TPB of each biliary stricture was performed during ERCP after endoscopic sphincterotomy. A 5 Fr conventional forceps with a cup diameter of 1.8 mm (FB-39Q; Olympus Medical Systems) was used for TPB, and four to six specimens were obtained from each stricture.

When malignancy was not detected on the initial TPB for suspected MBS, the stricture was defined as an indeterminate biliary stricture. The diagnostic modality for follow-up biopsy was decided according to the location of the indeterminate biliary stricture. In patients with proximal strictures, POC-FB was performed; EUS-FNAB was applied for patients with distal strictures.

POC-guided biopsy for proximal biliary strictures

Prophylactic antibiotics were administered to all patients, and carbon dioxide (Colosense CO-3000; Mirae Medics, Co., Seoul, Korea) was used for insufflation during ERCP and POC. POC-guided biopsy was performed using one of two types of single-operator cholangioscope according to the diameter of the distal common bile duct (CBD). When the diameter of the distal CBD was < 10 mm, the indeterminate biliary stricture was evaluated using a first-generation or digital system (DS) of the SpyGlass (Boston Scientific Corp.). Tissue sampling was achieved using SpyBite biopsy forceps (Boston Scientific Corp.) with a cup diameter of 1.0 mm. The SpyGlass was advanced through the accessory channel of a duodenoscope. Cannulation into the biliary tree was performed with an over-the-guidewire or a free-hand technique (► Fig. 1, ► Video 1).

In patients with distal CBD > 10 mm in diameter, direct POC using an ultraslim endoscope (GIF-XP260NS and GIF-XP290N; Olympus Medical Systems) was performed, and 5 Fr conventional biopsy forceps (FB-39Q; Olympus Medical Systems) with a cup diameter of 1.8 mm was used for tissue sampling of indeterminate biliary strictures. Direct POC using an ultraslim endoscope was performed by three experienced investigators using a standardized protocol (► Fig. 2, ► Video 2) [15].

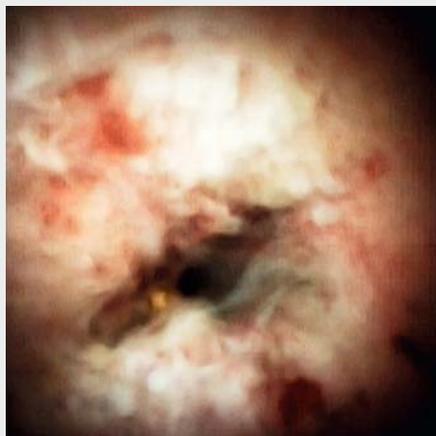


► **Fig. 1** Peroral cholangioscopy (POC)-guided biopsy was used with the SpyGlass digital system (DS; Boston Scientific Corp., Marlborough, Massachusetts, USA) to diagnose indeterminate proximal biliary stricture. **a** Cholangiogram showing a stricture of the proximal common bile duct, which was not malignant on initial transpapillary forceps biopsy. **b** A cholangioscopic image taken with the SpyGlass DS, shows a stricture with irregular tortuous vessels at the site of the proximal biliary stricture. POC-guided target biopsy using SpyBite forceps was achieved. **c** Adenocarcinoma was diagnosed by histology (hematoxylin and eosin stain, $\times 100$).

EUS-FNAB for distal biliary strictures

In patients with distal biliary strictures, when malignancy was not detected on the initial TPB, EUS-FNAB was performed as follow-up biopsy. EUS-FNAB was performed according to a standardized protocol by three experienced investigators using a linear-array echoendoscope (GF-UCT240; Olympus Medical Systems) in patients under conscious sedation.

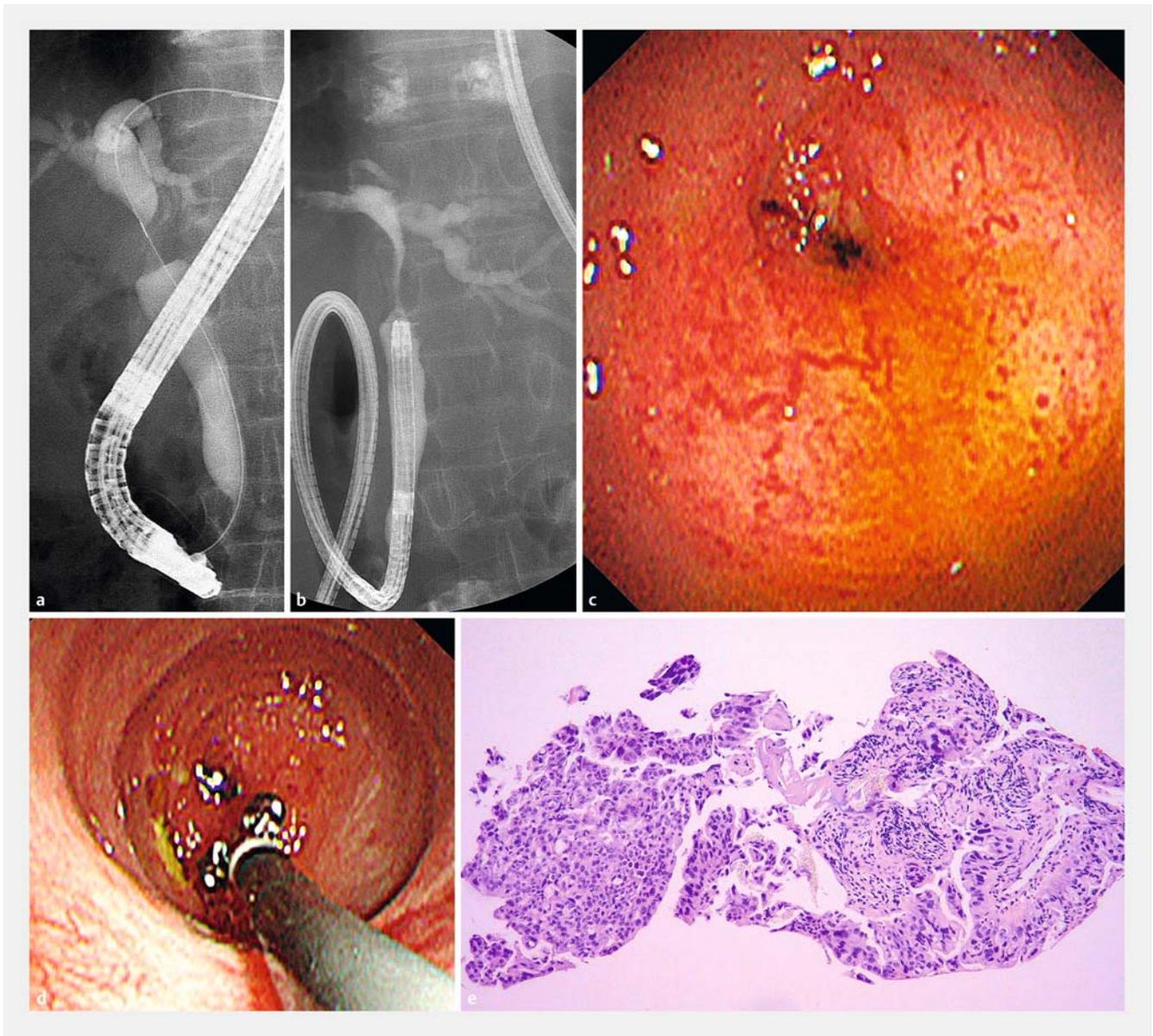
FNAB was performed from the stomach using a standard 22-gauge, or from the duodenum with a 25-gauge, FNAB device (Echotip ProCore; Wilson-Cook Medical, Winston-Salem, North Carolina, USA). After puncturing the stricture, the stylet was removed, and suction was applied using a 5–10-mL syringe. A triple approach comprising simultaneous cytopathological and histological evaluations with on-site examination was used for specimen preparation and analysis (► **Fig. 3**) [16].



► **Video 1** Peroral cholangioscopy-guided biopsy using the SpyGlass digital system (Boston Scientific Corp., Marlborough, Massachusetts, USA) on indeterminate proximal biliary stricture. Online content viewable at: <https://doi.org/10.1055/a-0645-1395>



► **Video 2** Direct peroral cholangioscopy-guided biopsy using an ultraslim endoscope on indeterminate proximal biliary stricture. Online content viewable at: <https://doi.org/10.1055/a-0645-1395>



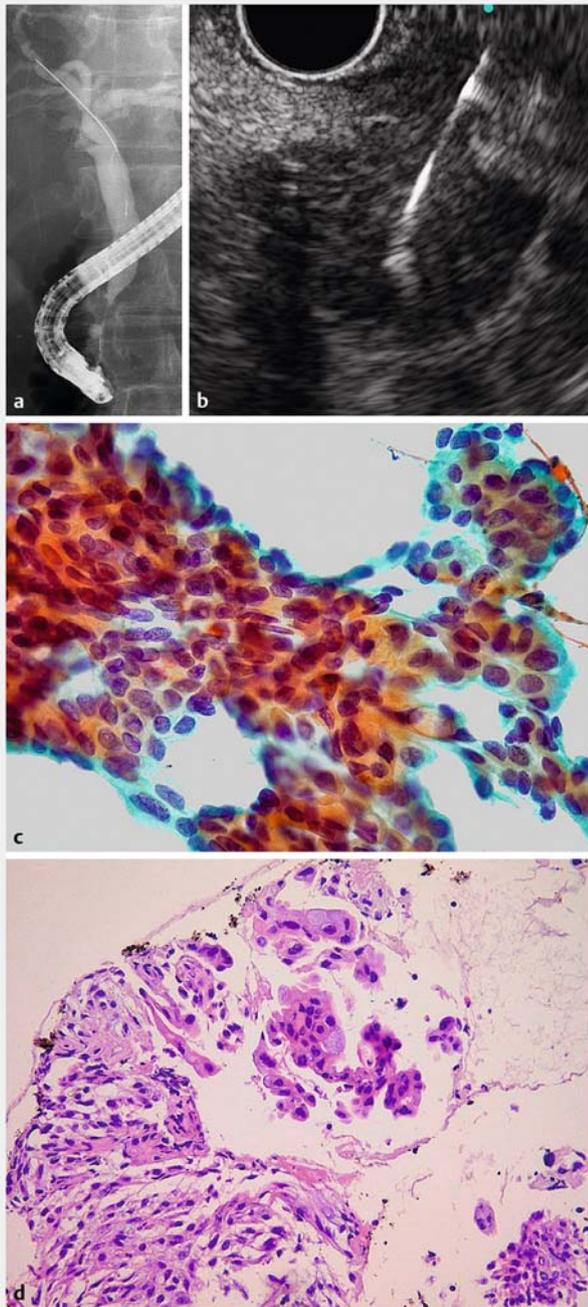
► **Fig. 2** Direct peroral cholangioscopy (POC)-guided biopsy for diagnosis of indeterminate proximal biliary stricture. **a, b** Cholangiograms. **a** An indeterminate stricture located at the proximal common bile duct. **b** An ultraslim endoscope advancing toward the stricture for direct POC. **c, d** Cholangioscopic images. **c** An infiltrative stricture with irregularly dilated and tortuous vessels. **d** Target biopsy of the stricture using forceps under direct visualization. **e** Adenocarcinoma (hematoxylin and eosin stain, $\times 100$) was diagnosed by direct POC-guided target biopsy.

Histological diagnosis

One expert unblinded pathologist examined the pathological results of TPB, POC-FB, and EUS-FNAB. The acquired tissue samples were classified using the following categories: 1) malignant, 2) atypical, 3) benign, or 4) nondiagnostic (insufficient tissue sampling for pathological diagnosis). Samples classified as malignant were categorized as malignant, whereas samples classified as atypical, benign, and nondiagnostic were categorized as nonmalignant. The diagnosis of malignancy on EUS-FNAB was established when at least one specimen preparation method (on-site cytology, definite cytology, or histology) yielded positive findings for malignancy.

Standard references for final diagnosis

Final diagnosis was confirmed using one of the following criteria: 1) definite result of malignancy in a surgical specimen or biopsy of a metastatic lesion; 2) malignant diagnosis by TPB or EUS-FNAB or POC-FB, and clinical/imaging follow-up compatible with malignant disease; and 3) malignancy not found on TPB and EUS-FNAB or POC-FB, and clinical/imaging follow-up compatible with benign disease for at least 12 months.



► **Fig. 3** Endoscopic ultrasound (EUS)-guided fine-needle aspiration biopsy (EUS-FNAB) for a diagnosis of indeterminate distal biliary stricture. **a** Cholangiogram showing narrowing of the distal common bile duct with dilation of the proximal bile duct. **b** As malignancy was not confirmed by transpapillary forceps biopsy, EUS-FNAB was conducted for the diagnosis of distal biliary strictures, and malignancy was confirmed by cytology and histology. **c** Cytology (Papanicolaou stain, $\times 200$). **d** Histology (hematoxylin and eosin stain, $\times 200$)

Outcome measurements

The primary outcome was the diagnostic accuracy of the approach using POC-FB and EUS-FNAB according to the location of the indeterminate biliary stricture.

The secondary outcomes were as follows: the diagnostic accuracy of initial TPB and diagnostic yield of initial TPB combined with POC-FB or EUS-FNAB for suspected MBS; technical success of POC-FB and EUS-FNAB; and number of adverse events associated with POC-FB and EUS-FNAB.

The diagnostic accuracy was defined as the ratio of the sum of true-positive and true-negative values divided by the number of lesions, where “true-positive” referred to the presence of malignant cells. The technical success of POC was defined as successful advancement of the ultraslim endoscope or SpyScope into the obstructed segment of the biliary tree. Technical success of POC-guided tissue sampling was established when tissue sampling using biopsy forceps was achieved under direct visualization of the target stricture and macroscopically visible tissue was confirmed. Technical success of EUS-FNAB was defined as proper puncture of the target stricture with the acquisition of some visible samples or fragments of tissue. Adverse events were defined as any postprocedure events that could be attributed to POC-FB or EUS-FNAB.

All patients underwent follow-up investigations with laboratory and radiological tests for at least 1 day after POC-FB or EUS-FNAB. Excessive bleeding at the site of biopsy, perforation, cholangitis, and pancreatitis were recorded as per normal practice.

Statistical analysis

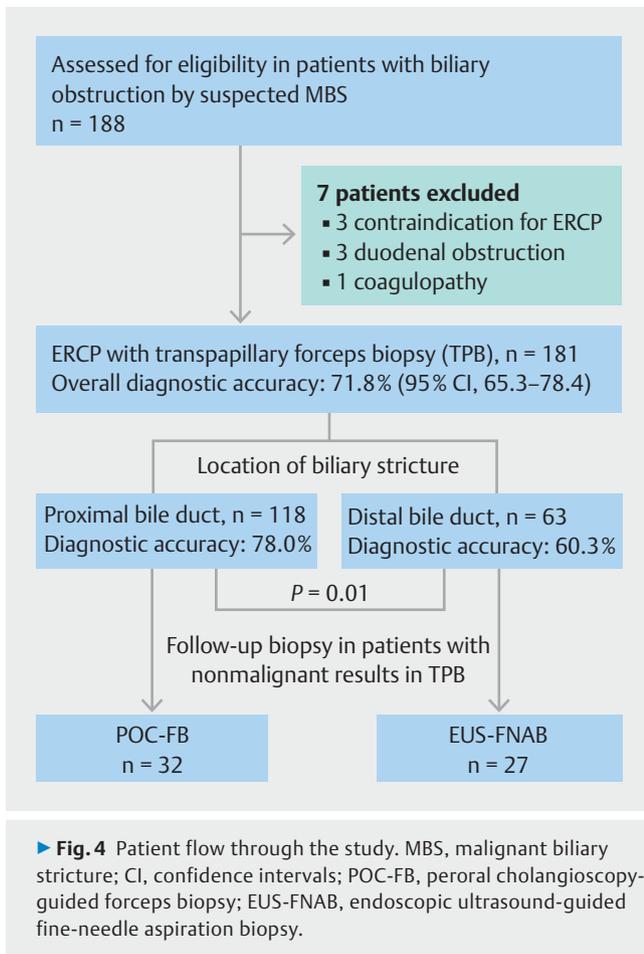
Categorical parameters including sex, location of stricture, final diagnosis, technical success, needle gauge, and adverse events were expressed as frequencies and percentages. Continuous variables including age, length of stricture, follow-up duration, number of samplings during POC, and number of needle passes during EUS-FNAB were summarized and expressed as medians with interquartile ranges (IQRs). Sensitivity, specificity, and accuracy analyses were performed, and the data were reported with exact 95% confidence intervals (CIs) and compared using the chi-squared test used to compute *P* values.

All statistical analyses were performed using the SPSS for Windows software package (version 19.0; IBM Corp., Armonk, New York, USA). *P* values of <0.05 were taken to indicate statistical significance.

Results

In total, 188 patients were screened between January 2014 and November 2016. Among them, seven were excluded for the following reasons: contraindication for ERCP ($n=3$), inability to perform ERCP because of duodenal obstruction ($n=3$), and coagulopathy ($n=1$). The remaining 181 patients underwent ERCP with TPB for suspected MBS.

Finally, a total of 181 patients (103 males, 78 females; median age 73.0 years [IQR 61.5–79.0 years]) with biliary obstruction by suspected MBS were analyzed. Findings of initial TPB



performed during ERCP were positive for malignancy in 122 patients with suspected MBS, and the sensitivity of the initial TPB was 70.5% (95%CI 63.3%–76.8%). The overall diagnostic accuracy of initial TPB was 71.8% (95%CI 65.3%–78.4%), and was

significantly greater in patients with proximal biliary strictures than in those with distal biliary strictures (78.0% vs. 60.3%; $P=0.01$) (► **Fig. 4**).

Among the 59 patients with indeterminate biliary strictures, tissue sampling was respectively obtained by POC-FB in 32 patients with proximal biliary strictures and by EUS-FNAB in 27 patients with distal biliary strictures. Of the 59 patients with indeterminate biliary strictures, previously obtained cross-sectional radiological imaging showed that the strictures were not caused by visible masses in five patients with proximal biliary stricture and in seven patients with distal biliary stricture. The final diagnoses of suspected MBS in patients with proximal biliary strictures were cholangiocarcinoma (n = 23), hepatocellular carcinoma (n = 2), gallbladder cancer (n = 1), and benign stricture (n = 6). The final diagnoses in patients with distal biliary strictures were pancreatic cancer (n = 21), cholangiocarcinoma (n = 2), gallbladder cancer (n = 2), and benign stricture (n = 2) (► **Table 1**).

The median follow-up duration of 181 patients was 108 days (IQR 65–192 days). Malignancy was observed in 173 of 181 patients (95.6%) with final diagnoses. The diagnosis of malignancy was based on surgical pathology in 47 patients and other tissue diagnosis in 38 patients. In 88 patients, malignancy was confirmed by TPB or POC-FB or EUS-FNAB results and clinical/imaging follow-up. Among the eight patients (4.4%) diagnosed with benign disease, the diagnosis was based on surgical pathology in one patient, and negative TPB and POC-FB or EUS-FNAB results and clinical/imaging follow-up in seven patients. The median follow-up duration of eight patients with benign disease was 481 days (IQR 407–568.5 days).

Technical characteristics of POC-FB and EUS-FNAB

POC was performed successfully in all 32 patients with proximal biliary strictures. POC was performed using a direct POC with an ultraslim endoscope in 12 patients (37.5%) and with Spy-

► **Table 1** Baseline characteristics and final diagnoses for patients with indeterminate biliary strictures.

	Location of biliary stricture		P
	Proximal (n = 32)	Distal (n = 27)	
Age, median (IQR), years	71.5 (56.5–76.5)	66.0 (59.0–77.0)	0.40
Sex (male/female), n	20/12	16/11	0.51
Length of stricture, median (IQR), mm	21.5 (15.5–38.8)	25.0 (19.0–32.0)	0.50
Final diagnosis, n (%)			0.19
▪ Malignant	26 (81.3)	25 (92.6)	
– Cholangiocarcinoma	23	2	
– Pancreatic cancer	0	21	
– Gallbladder cancer	1	2	
– Hepatocellular carcinoma	2	0	
▪ Benign	6 (18.8)	2 (7.4)	

IQR, interquartile range.

► **Table 2** Technical characteristics and outcomes of peroral cholangioscopy-guided forceps biopsy and endoscopic ultrasound-guided fine-needle aspiration biopsy in patients with indeterminate biliary strictures.

POC-FB in proximal biliary strictures (n = 32)	
Technical success of POC, n (%)	32 (100)
Direct POC using an ultraslim endoscope, n (%)	12 (37.5)
▪ SpyGlass DVS	20 (62.5)
– First generation	14
– Digital system	6
Technical success of POC-guided biopsy, n (%)	31 (96.9)
Number of tissue samples, median (IQR)	4.0 (3.0–4.0)
Tissue specimen adequate for histological examination, n (%)	31 (100)
Adverse events, n (%)	2 (6.3)
EUS-FNAB in distal biliary strictures (n = 27)	
Technical success of EUS-FNAB, n (%)	27 (100)
Number of needle passes, median (IQR)	3.0 (2.0–3.0)
Tissue specimen adequate for histological examination, n (%)	27 (100)
Needle gauge, n (%)	
▪ 25 gauge	22 (81.5)
▪ 22 gauge	5 (18.5)
Adverse events, n (%)	1 (3.7)
POC-FB, peroral cholangioscopy-guided forceps biopsy; EUS-FNAB, endoscopic ultrasound-guided fine-needle aspiration biopsy; DVS, direct visualization system; IQR, interquartile range.	

Glass DVS in 20 patients (62.5%). Direct POC-FB was successful in all 12 patients. In one patient, insertion of the SpyBite forceps up to the stricture segment failed. POC-FB was a technical success in 31 patients (96.9%), and tissue specimens that were adequate for histological examination were obtained from all 31 patients. Cholangitis was observed in two patients (6.3%) after POC.

No technical failure of EUS-FNAB occurred, and tissue specimens that were adequate for histological examination were obtained from 27 patients with distal biliary strictures. One episode of minor bleeding occurred during EUS-FNAB and was managed conservatively (► **Table 2**).

Diagnostic yields of POC-FB and EUS-FNAB

In 32 patients with proximal biliary strictures that were negative for malignancy on initial TPB, POC-FB was performed as follow-up biopsy for suspected MBS in 31 patients. Of these, 24 patients (77.4%) were found to be positive for malignancy by POC-FB. EUS-FNAB was performed as follow-up biopsy for 27 patients with distal biliary strictures that were negative for malignancy on initial TPB. Among them, malignancy was observed in 24 patients (88.9%) by EUS-FNAB. The sensitivity for malig-

► **Table 3** Pathological results and diagnostic yield of peroral cholangioscopy-guided forceps biopsy and endoscopic ultrasound-guided fine-needle aspiration biopsy according to location of the indeterminate biliary stricture.

	Biopsy method by stricture location	
	POC-FB in proximal strictures (n = 31)	EUS-FNAB in distal strictures (n = 27)
Pathological result, n		
▪ Malignant	24	24
▪ Atypical	6	1
▪ Benign	1	2
▪ Nondiagnostic	0	0
Diagnostic yield, % (95%CI)		
▪ Sensitivity	92.3 (74.9–99.1)	96.0 (79.7–99.9)
▪ Specificity	100 (47.8–100)	100 (15.8–100)
▪ Accuracy	93.6 (84.9–100)	96.3 (89.2–100)
POC-FB, peroral cholangioscopy-guided forceps biopsy; EUS-FNAB, endoscopic ultrasound-guided fine needle aspiration biopsy; CI, confidence interval.		

nancy of POC-FB in patients with proximal biliary strictures and EUS-FNAB in patients with distal biliary strictures was 92.3% (95%CI 74.9%–99.1%) and 96.0% (95%CI 79.7%–99.9%), respectively. The diagnostic accuracy was 93.6% (95%CI 84.9%–100%) in patients with proximal biliary strictures and 96.3% (95%CI 89.2%–100%) in patients with distal biliary strictures (► **Table 3**).

Overall diagnostic yield of initial TPB combined with follow-up biopsy

Among patients with proximal biliary strictures, the combination of initial TPB and follow-up POC-FB for patients with initial TPB findings that were negative for malignancy showed a sensitivity of 98.2% (95%CI 93.7%–99.8%) for the diagnosis of malignancy. Among patients with distal biliary strictures, the combination of initial TPB and follow-up EUS-FNAB showed a sensitivity of 98.4% (95%CI 91.2%–99.9%). The overall diagnostic accuracies of initial TPB combined with follow-up biopsy using POC-FB in patients with proximal biliary strictures and EUS-FNAB in patients with distal biliary strictures were 98.3% (95%CI 95.9%–100%) and 98.4% (95%CI 95.3%–100%), respectively (► **Table 4**). In two patients with false-negative results for malignancy in initial TPB and POC-FB, malignancy was confirmed by percutaneous liver biopsy and follow-up TPB, respectively. One patient with false-negative results for malignancy in initial TPB and EUS-FNAB was diagnosed as having malignancy by surgical resection.

► Table 4 Overall diagnostic yield of first transpapillary forceps biopsy combined with follow-up biopsy methods according to location of the suspected malignant biliary stricture.

	Total (n=180)	Proximal stricture TPB+ POC-FB (n=117)	Distal stricture TPB+ EUS-FNAB (n=63)
Diagnostic yield, % (95%CI)			
▪ Sensitivity	98.3 (95.0–99.6)	98.2 (93.7–99.8)	98.4 (91.2–99.9)
▪ Specificity	100 (59.0–100)	100 (47.8–100)	100 (15.8–100)
▪ Accuracy	98.3 (96.5–100)	98.3 (95.9–100)	98.4 (95.3–100)
TPB, transpapillary forceps biopsy; CI, confidence interval; POC-FB, peroral cholangioscopy-guided forceps biopsy; EUS-FNAB, endoscopic ultrasound-guided fine-needle aspiration biopsy.			

Discussion

The diagnostic capabilities of ERCP-based tissue sampling techniques, such as brush cytology and/or TPB, are not very good. However, ERCP is still a first-line diagnostic modality for MBS, especially in patients with jaundice and/or cholangitis. This prioritization is because tissue sampling of the biliary stricture and decompression of the bile duct can be performed simultaneously during ERCP, and the exact location and extent of the stricture can be determined. Several diagnostic modalities for suspected MBS have been developed and studied to complement TPB. IDUS has been used to differentiate malignant from benign strictures, and to confirm local tumor T- and-N staging, with high sensitivity and specificity [17, 18]. IDUS provides additional clinically important information, such as the extent of potentially cancerous infiltration and the origin of the stricture (intrinsic or extrinsic) [19, 20]. However, pathological analysis of tissues acquired from strictures or metastatic lesions is still required for management decisions. Among new diagnostic modalities, POC and EUS-FNAB are representative methods that can be used for tissue sampling and imaging in patients with suspected MBS.

Direct visualization of the bile duct by POC in a mother–baby system was possible several decades ago, but the clinical application of the mother–baby system is restricted because of its inconvenience and limitations in the performance of the endoscope [21]. The recent development of new types of POC, such as the SpyGlass DVS and direct POC using an ultraslim endoscope, has led to expansion of the use of POC in multiple diagnostic and therapeutic areas for pancreaticobiliary diseases. The SpyGlass DVS is a dedicated single-operator cholangioscopic system. It is advanced over a guidewire into the bile duct through the working channel of a therapeutic duodenoscope. In a meta-analysis, a first-generation SpyGlass DVS showed a pooled sensitivity of 74.7% (95%CI 63.3%–84.0%) for the diagnosis of suspected MBS with negativity for malignancy in samples obtained through brushing and/or TPB [22]. The first-generation SpyGlass DVS had several limitations, including inferior image quality compared with that of conventional endoscopes, poor image stability, and difficulty in catheter manipulation [10, 21, 23]. A new digital version of the SpyGlass DVS with enhanced functionality was introduced. Al-

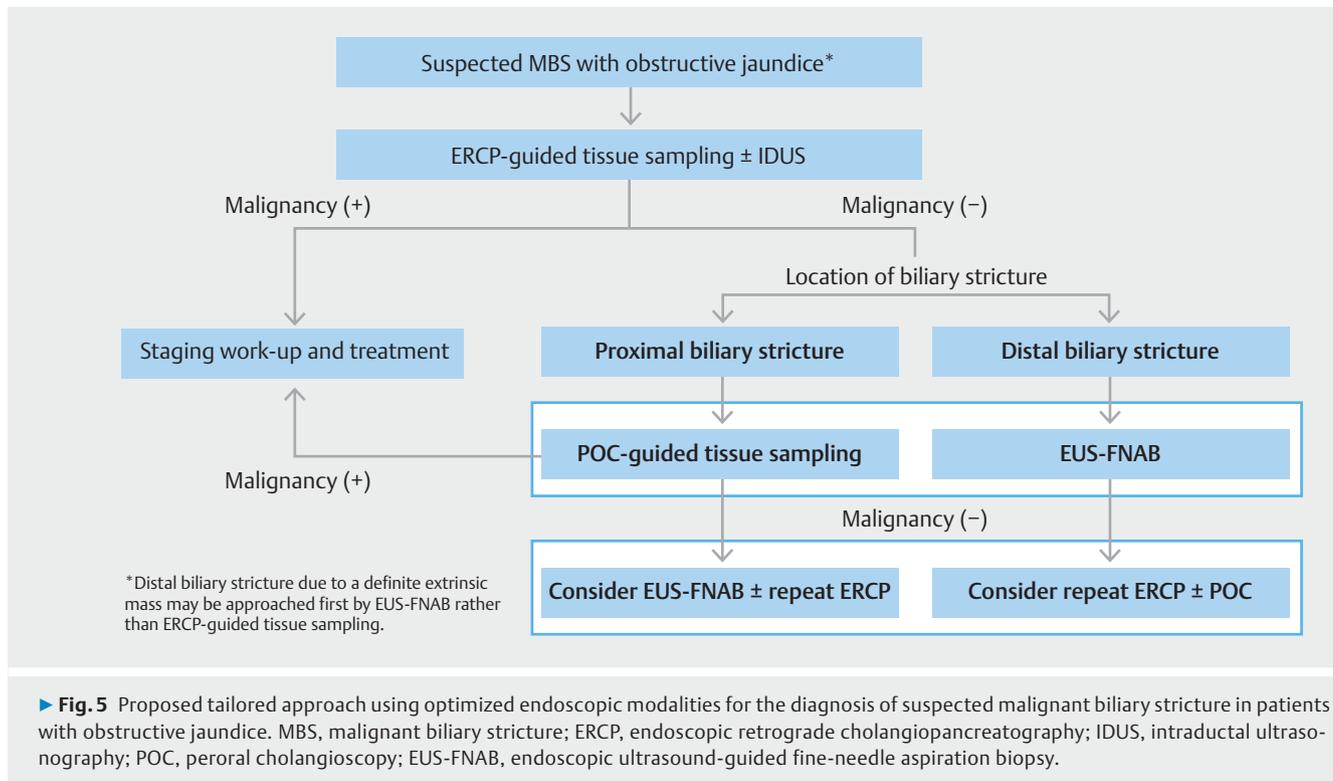
though few studies have been performed, forceps biopsy guided by this new SpyGlass DVS showed a high sensitivity of 80%–85% for the diagnosis of suspected MBS [10, 24].

Direct POC using an ultraslim upper endoscope is another single-operator cholangioscopic system that incorporates optical enhancement techniques and takes high resolution images. In particular, an ultraslim endoscope with a large working channel diameter of 2.0mm enables the performance of interventional procedures, such as tissue sampling. Furthermore, a previous study showed that it had a high technical success rate when used with direct POC-guided biopsy sampling [21].

Although newly developed POC-guided biopsy techniques have shown high diagnostic yields for suspected MBS, the acquisition of adequate tissue samples from biliary strictures in the distal CBD remains difficult. The maintenance of a stable POC position is difficult in patients with distal CBD strictures because POCs can be withdrawn easily from the distal CBD. In addition, many distal CBD strictures develop through extrinsic malignancies, such as pancreatic cancer, and even POC-guided biopsy has a significantly lower sensitivity for the diagnosis of extrinsic malignant lesions (8%) compared with intrinsic malignant lesions (66%) of biliary strictures [12].

Compared with POC-guided biopsy, EUS-FNAB is technically easier to perform in patients with distal CBD strictures than in those with proximal CBD strictures. This difference exists because the distal CBD is located close to the duodenal wall and is visualized on EUS without difficulty, whereas the proximal perihilar bile ducts are closer to the liver and farther away from the duodenal wall [6]. The sensitivity of EUS-FNAB was reported to be significantly higher for distal biliary strictures than for proximal biliary strictures in previous studies [6, 7]; however, the impact of biliary stricture location on the diagnostic accuracy of EUS-FNAB has not been established because few relevant studies have been performed [3].

In the present study, our approach to the diagnosis of suspected MBS was based on stricture location, and the advantages and disadvantages of POC-FB and EUS-FNAB. Our results showed that POC-FB for proximal biliary strictures and EUS-FNAB for distal biliary strictures had high sensitivities of 92.3% (95%CI 74.9%–99.1%) and 96.0% (95%CI 79.7%–99.9%), respectively. The improved technical success rates in this study suggest that POC-FB will be used more readily for the diagnosis



of inconclusive biliary stricture in clinical practice. Finally, the initial TPB combined with follow-up biopsy using POC-FB in patients with proximal biliary strictures and EUS-FNAB in patients with distal biliary strictures showed high overall diagnostic accuracies of 98.3% (95%CI 95.9%–100%) and 98.4% (95%CI 95.3%–100%), respectively. Based on our results, we propose the tailored diagnostic approach based on the use of POC-FB or EUS-FNAB according to the location of the stricture when malignancy is not diagnosed on ERCP-based tissue sampling in patients with suspected MBS and obstructive jaundice (► Fig. 5).

However, there are several limitations to evaluating suspected malignant biliary stricture using POC systems, including high costs and the possibility of adverse event (cholangitis, pancreatitis). Also, the standardization of endoscopic techniques and prevention of air or carbon dioxide embolization are still required for direct POC using an ultraslim endoscope [11, 21, 25, 26]. In addition, clear criteria guiding the choice of POC systems for individual patients are lacking. In the current study, direct POC using an ultraslim endoscope was used for the patients with distal CBD >10 mm in diameter considering the cost, image quality, and diameter of the working channel. In addition, POC-FB during direct POC was performed using a conventional biopsy forceps with larger cup diameter than that of SpyBite biopsy forceps. Although no randomized, prospective, comparative study on the diagnostic yields of biopsies performed using the SpyBite forceps and a conventional biopsy forceps has appeared, the diagnostic yields of POC-FB could be affected by the type of POC system employed. A biopsy forceps with a large cup may obtain more biliary stricture tissue, improving the diagnostic yield of POC-FB [27].

This study has several limitations. First, it lacked a control group. POC-FB and EUS-FNAB were not compared because this study was descriptive and our goal was to determine the diagnostic yields of approaches involving these modalities according to stricture location in patients with suspected MBS. Second, no crossover analysis of EUS-FNAB and TPB in patients with negative findings for malignancy was performed. Third, two types of POC system were used in the study; direct POC was preferred because it involved the use of larger forceps, which increased the accuracy of histopathological diagnosis. Therefore, the diagnostic yields of our study may be different from results obtained when using only one type of POC system. Fourth, although biliary decompression in distal CBD stricture was needed for the management of cholangitis and/or jaundice, a small cholangiocarcinoma or small pancreatic head mass may not be easily visible on EUS when the biliary system is decompressed after initial ERCP. Finally, three highly experienced endoscopists at a single center conducted all procedures; thus, the results may not reflect practices or technologies used at other institutions.

Despite the development of new technologies, accurate pathological diagnosis of biliary stricture remains problematic because biliary strictures develop into various morphological types and have various causes. Therefore, a tailored approach using optimized endoscopic modalities that are specific to the characteristics of a given biliary stricture is needed to achieve a high diagnostic yield for suspected MBS. In conclusion, an approach using POC-FB or EUS-FNAB according to the stricture location may be useful for the diagnosis of suspected MBS.

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Competing interests

None

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