

The role of intraductal ultrasound in endoscopic biliary brushing for sampling in patients with malignant biliary strictures: a bicentric retrospective study

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Abstract

Background Endoscopic biliary brushing is the first line modality for sampling in patients with indeterminate biliary stricture (BS); however, its sensitivity is limited. Endoscopic intraductal ultrasound (IDUS) is also a useful approach for the diagnosis of biliary malignancies. However, whether IDUS can guide the sampling by biliary brushing has not been reported.

Methods We retrospectively analyzed patients who underwent endoscopic retrograde cholangiopancreatography for BS in 2 tertiary care hospitals and assessed the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of IDUS and brush cytology.

Results The study involved 530 patients with BS, including 333 in the IDUS group and 197 in the non-IDUS group. Both groups exhibited similar baseline characteristics. The diagnostic ability of IDUS imaging was as follows: sensitivity 70.7%, specificity 82.4%, PPV 81.5%, NPV 72.0%, and accuracy 76.3%. Brush cytology alone demonstrated an overall sensitivity of 45.2%, with specificity 98.2%, PPV 97.2%, NPV 56.0%, and accuracy 67.2%. The sensitivity was similar in patients with or without IDUS, whereas it was significantly higher in patients with biliary mucosal invasion indicated by IDUS (55.1% vs. 30.3%, $P=0.003$).

Conclusion Although IDUS cannot improve the detection rate of biliary brushing for malignancy, it helps identify patients with malignant BS to be sampled more easily by brushing.

Keywords Endoscopic retrograde cholangiopancreatography, biliary stricture, intraductal ultrasound, brush cytology

Ann Gastroenterol 2025; 37 (XX): 1-6

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Conflict of Interest: None

Funding: This research was funded by a key subject of clinical research projects at Shanghai General Hospital (CCTR-2022ZD03 for Xiaobo Cai).

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Received 23 September 2024; accepted 16 December 2024; published online 25 February 2025

DOI: <https://doi.org/10.20524/aog.2025.0942>

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Introduction

Biliary stricture (BS) arises from a range of entities from benign to malignant conditions [1,2]. Malignant biliary stricture (MBS) is commonly caused by cholangiocarcinoma, pancreatic carcinoma, gallbladder carcinoma, and other types of malignancies [2]. The diagnosis of MBS is difficult, and almost 20% of cases cannot be definitively diagnosed by routine imaging, or even endoscopic retrograde cholangiopancreatography (ERCP). Of these “indeterminate” BS, 70% are found to be malignant [3]. Therefore, early MBS diagnosis is critical for a better prognosis. Pathological or cytological evidence is the gold standard for malignancy diagnosis, and ERCP-based sampling approaches play an important role. Among these, ERCP-based biliary brushing is the first-line approach for sampling, although its sensitivity is relatively low at only around 40% [4]. Biliary intraductal ultrasound

(IDUS) is frequently employed in the diagnosis of BS, as it offers the advantages of simplicity, easy performance and low cost. The probe can be inserted directly into the bile duct to scan lesions or the surrounding structures, providing information for evaluating the tumor itself, or the spread along the duct [5]. Multiple studies have shown that the sensitivity of IDUS is 80-90%, with specificity 83%, while it is also able to improve the diagnostic accuracy of ERCP from 58-83% for MBS [6-8]. Theoretically, IDUS can indicate the invasion of the malignancy through the wall of the bile duct, while the mucosal invasion facilitates the sampling of biliary brushing. However, it has not been reported whether the sampling success rate and diagnostic sensitivity of brush cytology for MBS could be improved under the guidance of IDUS. For this purpose, we analyzed patients who underwent brush cytology for BS to investigate the diagnostic ability of brush cytology with the assistance of IDUS.

Patients and methods

Study population and design

This study retrospectively included patients who underwent ERCP for BS in Shanghai General Hospital and Shanghai Sixth People's Hospital between January 2020 and January 2024. The criteria for inclusion were as follows: 1) age 18-90 years; 2) indication of BS by magnetic resonance imaging or cholangiography; and 3) accepting ERCP and endoscopic biliary brush. Exclusion criteria were: 1) no endoscopic biliary brushing; and 2) unclear diagnosis by the end of the follow up. The study was approved by the appropriate institutional review boards.

Procedures

All patients were hospitalized for ERCP, performed by experienced endoscopists (more than 300 ERCP procedures per year). Antibiotics were given intravenously before the procedure, and intravenous sedation or general anesthesia was used during the process. After cannulation, routine cholangiography determined the location and length of the stricture, after which a thin, high-frequency probe was sent through a wire to explore the bile duct. The brush catheter was then inserted along the guidewire and brushed back and forth over the stricture [9]. IDUS images were saved during the procedure. At the end of the study, after all patients with

BS of various causes had completed follow up and received definitive diagnoses, the IDUS images were uniformly collected and interpreted by an experienced endoscopist (CX), blinded to the clinical and pathological results. Characteristics of malignancy included irregular wall thickening, hypoechoic lesions within the bile duct wall, loss or compression of the bile duct wall's layered structure, and mucosal or vascular invasion. Fig. 1 shows representations of IDUS imaging. Complications, including bleeding, post-ERCP pancreatitis (PEP), cholangitis, cholecystitis, and perforation, were assessed 24 h after the procedure.

Definitions

Pathologists classify brush cytological results as "non-malignant", "atypical", "suspicious" or "malignant". The cytological results were considered malignant when the report indicated "suspicious" or "malignant". MBS was diagnosed by cytology or histology on tissue samples obtained during the initial or subsequent ERCP procedure, endoscopic ultrasound-guided fine-needle aspiration/biopsy (EUS-FNA/B), or surgical specimens. Clinical events, such as tumor invasion, metastasis, dyscrasia or death from malignancy-related complications during follow-up for 6 months, were also considered as evidence of malignancy. Complications included bleeding, PEP, cholangitis, cholecystitis and perforation. Bleeding included hematemesis and/or melena, and a decrease in hemoglobin levels of more than 2 g/dL after the ERCP procedure [10]. PEP was identified as follows: high serum amylase level >3 times the upper limit of normal after 24 h following ERCP, and new or worsening abdominal pain that necessitated at least 2 days of hospitalization [11]. Cholangitis was diagnosed by a body temperature $\geq 38^{\circ}\text{C}$ lasting more than 24 h and clinical manifestations of cholangitis, with leukocytosis (white blood cell count $\geq 10 \times 10^9/\text{L}$) after ERCP [10]. Cholecystitis was defined as right upper abdominal and/or systemic inflammation, and symptoms with imaging features that were not present before the procedure [12]. Perforation indicated gas or luminal contents outside the gastrointestinal tract, as detected by imaging [10].

Statistical analysis

Continuous variables were presented as mean \pm standard deviation, and differences between groups were assessed using an independent sample t-test. Categorical variables were represented as frequencies and percentages and compared using Fisher's exact test or Pearson's χ^2 test. We documented the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of IDUS imaging and brush cytology. The data were processed and examined using statistical software (SPSS software version 26.0; SPSS Inc., Chicago, USA). Two-tailed P-values <0.05 were deemed statistically significant.

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Results

Patient demographics and clinical characteristics

From January 2020 to January 2024, 1160 patients with BS were reviewed, and 630 patients were excluded. Eventually, 530 patients were included (Fig. 2). Among these, 333 patients (62.8%) underwent IDUS, while 197 patients (37.2%) did not have IDUS for reasons unrelated to biliary disease, such as patients having serious underlying medical conditions that required a time-limited procedure, financial limitations or equipment malfunction. A total of 310 patients with BS were confirmed as malignant: 44 cases determined by cytology or histology from ERCP, 91 cases identified with EUS-FNA/B, and 131 cases confirmed through surgical

specimens. The remaining cases were diagnosed according to clinical evidence for malignancy after follow-up for more than 6 months. A total of 159 patients with benign biliary stricture (BBS) and 174 patients with MBS were included in the IDUS group, while 61 patients with BBS and 136 patients with MBS comprised the non-IDUS group. The proportion of MBS was 174/333 (52.3%) and 136/197 (69.0%) in the IDUS and non-IDUS groups, respectively. The causes of MBS included 95 cases of cholangiocarcinoma, 110 cases of pancreatic carcinoma, 28 cases of ampullary carcinoma, 16 cases of liver cancer, 15 cases of gallbladder carcinoma, and 46 cases of metastatic cancer, while the causes of BBS included 28 cases of postoperative strictures, 8 cases of autoimmune cholangiopathy, 1 case of primary sclerosing cholangitis (PSC), 157 cases of inflammatory strictures, and 26 cases attributed to other causes. The baseline characteristics exhibited no

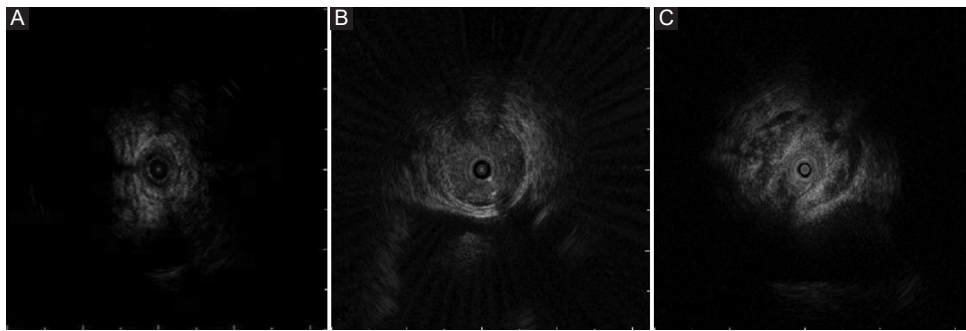


Figure 1 Representations of IDUS imaging. (A) Benign biliary strictures. (B) With mucosal invasion. (C) Without mucosal invasion
IDUS, intraductal ultrasonography

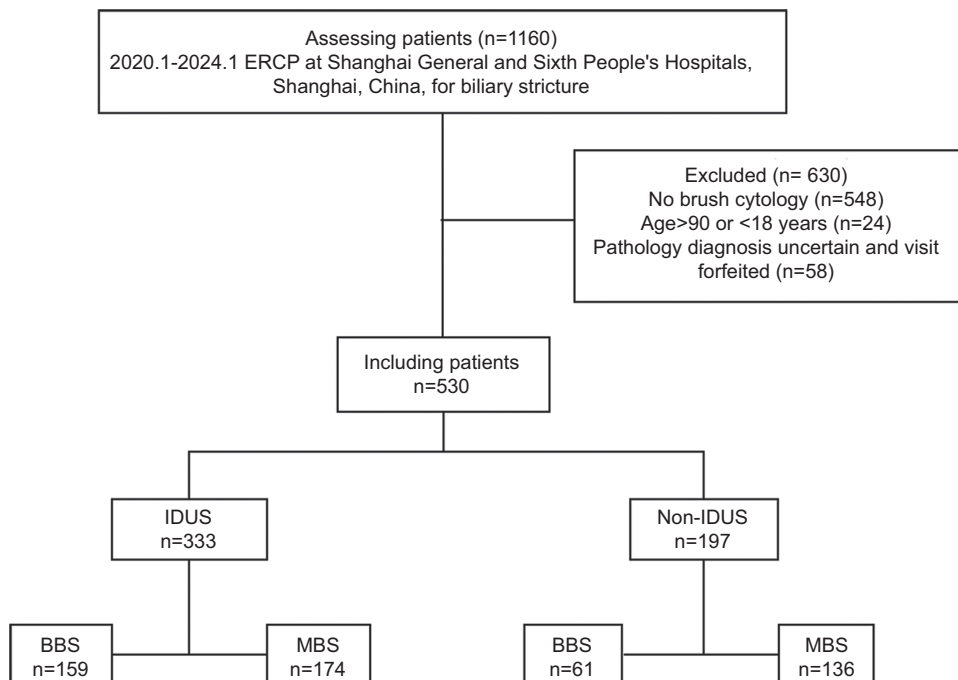


Figure 2 Patient flow diagram

ERCP, endoscopic retrograde cholangiopancreatography; IDUS, intraductal ultrasonography; MBS, malignant biliary stricture; BBS, benign biliary stricture

Table 1 Baseline characteristics

Characteristics	Non-IDUS (n=197)	IDUS (n=333)	P-value
Age	67.7±1.4	68.9±1.2	0.638
Sex			0.146
Male (no., %)	102 (51.8%)	194 (58.3%)	
Female (no., %)	95 (48.2%)	139 (41.7%)	
Baseline laboratory tests			
WBC (×10 ⁹ /L) (mean±SD)	6.1±0.3	6.5±0.2	0.527
TBIL (μmol/L) (mean±SD)	170.3±12.8	150.0±12.4	0.171
GGT (U/L) (mean±SD)	466.9±42.2	489.9±38.7	0.692
AKP (U/L) (mean±SD)	370.0±28.9	372.5±24.8	0.097
ALT (U/L) (mean±SD)	141.2±14.5	140.8±11.7	0.258
AST (U/L) (mean±SD)	128.6±12.1	124.4±9.8	0.052
CA 19-9 (U/mL) (mean±SD)	518.2±77.7	524.3±74.1	0.859
CEA (ng/mL) (mean±SD)	12.2±3.0	12.2±2.8	0.778
D-D (mg/L) (mean±SD)	1.6±0.3	1.5±0.2	0.761
Stricture location			0.283
Proximal (no., %)	55 (27.9%)	73 (21.9%)	
Middle (no., %)	16 (8.1%)	32 (9.6%)	
Distal (no., %)	126 (64.0%)	228 (68.5%)	
Stricture length (cm) (mean±SD)	2.4±0.1	2.3±0.1	0.338

IDUS, intraductal ultrasonography; WBC, white blood cells; TBIL, serum total bilirubin; GGT, γ -glutamyl transpeptidase; AKP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; CA 19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; D-D, D-Dimer

significant differences between the groups with and without IDUS (Table 1).

Diagnostic values of IDUS imaging and brush cytology

Brush cytology showed a sensitivity of 45.2%, with specificity 98.2%, PPV 97.2%, NPV 56.0%, and accuracy 67.2% for MBS in the 530 patients with biliary brushing. IDUS imaging had a sensitivity of 70.7%, with specificity 82.4%, PPV 81.5%, NPV 72.0% and accuracy 76.3% for MBS in the 333 patients undergoing IDUS (Table 2). The diagnostic sensitivities of brush cytology for cholangiocarcinoma, pancreatic cancer, ampullary carcinoma, liver cancer, gallbladder cancer, and metastatic cancer were 57.9%, 48.2%, 28.6%, 12.5%, 60.0%, and 28.3%, respectively, while the corresponding values for IDUS imaging were 75.0%, 69.8%, 66.7%, 85.7%, 77.8%, and 62.1%, respectively (Supplementary Table 1).

Diagnostic values of brush cytology with the assistance of IDUS

The total sensitivity of brush cytology was similar in the IDUS and non-IDUS groups (47.1% vs. 42.6%, $P=0.490$). For different types of malignancy, the sensitivity of brush cytology in the IDUS or non-IDUS group was 62.5% or 53.2% for cholangiocarcinoma ($P=0.409$), 47.6% or 48.9% for pancreatic cancer ($P>0.99$), 38.9% or 10.0% for ampullary carcinoma ($P=0.194$), 14.3% or 11.1% for liver cancer ($P>0.99$), 77.8% or 33.3% for gallbladder carcinoma ($P=0.136$), and 24.1% or 35.3% for metastatic cancer

Table 2 Diagnostic values of brush cytology and IDUS imaging

Diagnostic values	Brush cytology	IDUS imaging
Sensitivity (%)	45.2	70.7
Specificity (%)	98.2	82.4
PPV (%)	97.2	81.5
NPV (%)	56.0	72.0
Accuracy (%)	67.2	76.3

IDUS, intraductal ultrasonography; PPV, positive predictive value; NPV, negative predictive value

($P=0.505$) (Supplementary Table 2). However, in patients with MBS and IDUS examination, the sensitivity of brush cytology was 55.1% when mucosal invasion was indicated and 30.4% when it was not, a statistically significant difference ($P=0.003$). For the different types of malignancies, the sensitivity of brush cytology was 67.7% or 50.0% for cholangiocarcinoma with or without mucosal invasion ($P=0.330$), 54.8% or 33.3% for pancreatic cancer ($P=0.180$), 50.0% or 16.7% for ampullary carcinoma ($P=0.316$), 16.7% or 0.0% for liver cancer ($P>0.99$), 85.7% or 50.0% for gallbladder carcinoma ($P=0.417$), and 35.3% or 8.3% for metastatic cancer ($P=0.187$) (Table 3).

Complications

Procedure-related complications occurred in 104 of the 530 patients (19.6%). Pancreatitis and cholangitis were the most common complications, with an incidence of 9.7% and 6.6%, respectively. However, the incidence of bleeding, pancreatitis,

Table 3 Sensitivity of brush cytology guided by intraductal ultrasonography for different types of malignancies with and without mucosal invasion

Types of malignancies	With mucosal invasion		Without mucosal invasion		P-value
	n	Sensitivity (%)	n	Sensitivity (%)	
Cholangiocarcinoma	34	67.6	14	50.0	0.330
Pancreatic carcinoma	42	54.8	21	33.3	0.180
Ampullary carcinoma	12	50.0	6	16.7	0.316
Liver cancer	6	16.7	1	0.0	>0.99
Gallbladder carcinoma	7	85.7	2	50.0	0.417
Metastatic cancer	17	35.3	12	8.3	0.187
Total	118	55.1	56	30.4	0.003

Table 4 Complications in the IDUS and non-IDUS groups

Complications	IDUS (N=333)	Non-IDUS (N=197)	P-value
Bleeding	12 (3.6)	3 (1.5)	0.187
Pancreatitis	38 (11.4)	13 (6.6)	0.093
Cholangitis	23 (6.9)	12 (6.1)	0.857
Cholecystitis	1 (0.3)	1 (0.5)	>0.99
Perforation	1 (0.3)	0 (0.0)	>0.99

IDUS, intraductal ultrasonography

cholangitis, cholecystitis, or perforation did not differ between the IDUS and non-IDUS groups (Table 4).

Discussion

IDUS has become a common diagnostic tool for biliary diseases in recent years [8,13]. In this study, IDUS imaging had a sensitivity of 70.7%, specificity 82.4%, PPV 81.5%, NPV 72.0% and accuracy 76.3% for diagnosing MBS. Although several approaches were applied in biliary sampling, such as no-biliary forceps biopsy under X-ray guidance, peroral cholangioscopy (POCS), and EUS-FNA/B, ERCP-based brush cytology is the most widely used sampling approach for MBS [14-16]. However, the sensitivity of brush cytology is reported to range from only 40-60%, with a specificity of 95-100% [17-19]. Our study found that brush cytology had an overall sensitivity of 45.2% with a specificity of 98.2%, which was similar to previous reports.

Whether IDUS can improve the sampling ability of biliary brushing for MBS has not been reported. Our results demonstrated that the sensitivity of brush cytology was not significantly improved by the assistance of IDUS (47.1% vs. 42.6%, $P=0.490$). It is easy to understand that IDUS can indicate the location of the stricture, which is similar to the cholangiogram and leads to similar brushing actions. However, from the perspective of successful sampling, it is easier to acquire malignant cells by brushing when the mucosa of

the bile duct is invaded, which may be indicated by IDUS. Intriguingly, our results showed that the sensitivity of brush cytology in patients with mucosal invasion indicated by IDUS was 55.1%, compared to only 30.4% in patients without mucosal invasion ($P=0.003$), which supports the value of IDUS for successful sampling by brushing. Therefore, IDUS plays a crucial role in guiding further interventions. When IDUS suggests that malignancy sampling by brushing would be difficult, additional diagnostic approaches, such as biopsy via cholangiogram or POCS, or EUS plus fine-needle biopsy, should be applied.

To our knowledge, this is the first report on the use of IDUS guidance for brush sampling to diagnose MBS. For malignancies that do not originate from biliary epithelium, like pancreatic, liver or metastatic cancer, the variation was more obvious, explaining the reason for the relatively low detection rate in such types of malignancies compared to cholangiocarcinoma. However, significance was not achieved because of the limited sample size. Therefore, IDUS offers the ability to identify patients with MBS who can be easier to sample. For patients without biliary mucosal invasion indicated by IDUS, other types of biliary sampling approaches, apart from brushing, should be applied to promote the success rate.

Our study also had some limitations. First, this was a retrospective study that included patients from 2 centers. Second, although we reviewed 1160 patients with BS and eventually included 530 patients in this study, the sample size was still not large. Third, the visual impression of IDUS was subjective, and judgment may vary among different endoscopists. Furthermore, the patients with BS were not randomly allocated into different groups according to the performance of IDUS, despite the basic parameters being similar. Although IDUS is routinely applied in patients with BS who undergo ERCP in our 2 centers, 197 patients did not have IDUS in this study, because of device inaccessibility, mechanical problems, or other circumstances that did not involve selection bias from the endoscopists.

In conclusion, our findings indicate that IDUS helps identify patients with MBS who may be more easily sampled by biliary brushing. However, our findings need to be confirmed by large-scale prospective randomized studies.

Acknowledgment

This research was funded by a key subject of clinical research projects at Shanghai General Hospital (CCTR-2022ZD03 for Xiaobo Cai).

Summary Box

What is already known:

- Diagnosing malignant biliary stricture (MBS) is challenging because of the limitations of current sampling methods
- Brush cytology based on endoscopic retrograde cholangiopancreatography is the first-line sampling method, but its sensitivity remains low
- Intraductal ultrasound (IDUS) provides real-time imaging to evaluate the characteristics of biliary stricture

What the new findings are:

- The sensitivity of brush cytology would be higher in patients with biliary mucosal invasion detected by IDUS
- IDUS helps identify patients with MBS who may be more easily sampled by biliary brushing

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Supplementary material

Supplementary Table 1 Sensitivities of brush cytology and IDUS imaging for different types of malignancies

Types of malignancies	n	Brush cytology	IDUS imaging
		Sensitivity (%)	Sensitivity (%)
Cholangiocarcinoma	95	57.9	75.0
Pancreatic carcinoma	110	48.2	69.8
Ampullary carcinoma	28	28.6	66.7
Liver cancer	16	12.5	85.7
Gallbladder carcinoma	15	60.0	77.8
Metastatic cancer	46	28.3	62.1

IDUS, intraductal ultrasonography

Supplementary Table 2 Sensitivities of brush cytology with and without IDUS for different types of malignancies

Types of malignancies	IDUS		Non-IDUS		P-value
	n	Sensitivity (%)	n	Sensitivity (%)	
Cholangiocarcinoma	48	62.5	47	53.2	0.409
Pancreatic carcinoma	63	47.6	47	48.9	>0.99
Ampullary carcinoma	18	38.9	10	10.0	0.194
Liver cancer	7	14.3	9	11.1	>0.99
Gallbladder carcinoma	9	77.8	6	33.3	0.136
Metastatic cancer	29	24.1	17	35.3	0.505
Total	174	47.1	136	42.6	0.490

IDUS, intraductal ultrasonography