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Diagnostic Yield of a Novel 11-Fr Digital Cholangioscope for Indeterminate Biliary Disease Using Macroscopic-On-Site Evaluation: Prospective Comparative Study

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ABSTRACT

Background and Aim: A novel 11-Fr digital cholangioscope (eyeMAX) has recently become available. However, a prospective comparative study of the diagnostic yield of the eyeMAX and of a conventional cholangioscope (SpyGlass DS II) has not been reported. Therefore, the aim of this study was to prospectively compare the diagnostic yield of the eyeMAX and of the SpyGlass DS II for indeterminate biliary disease.

Patients and Method: Forceps biopsy was repeated until visible core tissue was obtained. The primary outcome of this study was the diagnostic accuracy of the biopsy specimens obtained by the eyeMAX. The secondary outcomes were comparisons of the diagnostic yield of visual findings, tissue size, number of forceps biopsies until MOSE positivity, and adverse events.

Results: Fifty patients were prospectively enrolled in the eyeMAX group. And 47 patients in the SpyGlass DS II group were enrolled as a historical control. The number of biopsies was significantly fewer in the eyeMAX group than in the SpyGlass DS II group ($p = 0.001$). Tissue size was larger in the eyeMAX group ($2.96 \pm 0.69\,mm^2$) than in the SpyGlass DS II group ($1.80 \pm 1.61\,mm^2$). The diagnostic accuracy was also higher in the eyeMAX group (96.0%, 48/50) than in the SpyGlass DS II group (80.9%, 38/47). The diagnostic accuracy for the final diagnosis was slightly higher in the eyeMAX group (93.5%, 47/50) than in the SpyGlass DS II group (89.3%, 42/47).

Conclusions: The eyeMAX has a favorable diagnostic yield in terms of visual findings and the forceps biopsy specimen.

Trial registration: 000049465

1 | Introduction

The initial methods in the diagnosis of biliary diseases involve the use of noninvasive or minimally invasive modalities, such as transabdominal ultrasound, computed tomography (CT), or endoscopic ultrasound (EUS). These methods, however, still require corroboration of the diagnosis by histopathological evaluation of biopsy specimens because, reportedly, approximately 14%–25% of cases that undergo surgical resection due to suspected malignancy are ultimately diagnosed as benign biliary disease [1–3]. In addition, because of recent improvements in chemotherapy, such as combination therapy with

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durvalumab or pembrolizumab [4, 5], accurate histological evidence needs to be obtained before systemic chemotherapy in inoperable malignant cases. For this, brush cytology or intraductal forceps biopsy under endoscopic retrograde cholangiopancreatography (ERCP) is traditionally performed [6]. However, the diagnostic yield of these techniques is not very high. Additionally, although direct visualization of biliary diseases can be performed by peroral cholangioscopy (POCS) under ERCP guidance, POCS using a conventional cholangioscope is limited by its poor maneuverability and limited strength. The SpyGlass Direct Visualization System (SpyGlass DS II Direct Visualization System; Boston Scientific, Natick, MA, USA) was developed to overcome these limitations. Although the clinical usefulness of SpyGlass DS II has already been reported [7–10], the diagnostic yield might still be insufficient because the dedicated forceps biopsy device is relatively small, which might lead to only a small sample size being obtained.

To overcome this limitation, a novel 11-Fr digital cholangioscope (eyeMAX, Micro-Tech, Nanjing, China) has recently become available. Due to the large working channel of this scope, it allows use of a large forceps biopsy device, leading to a larger size of the biopsy sample and hence a greater histological diagnostic yield. In addition, visibility of the biliary tract is improved by this new cholangioscope. However, the visual findings and results of histological evaluation with the use of the eyeMAX have still not been reported. In addition, a prospective comparative study of the diagnostic yield of the eyeMAX and of the SpyGlass DS II has not been reported. Therefore, the aim of this study was to prospectively compare the diagnostic yield of the eyeMAX and the SpyGlass DS II.

2 | Patients and Method

Patients who required POCS using the eyeMAX at our hospital were eligible for enrollment in this prospective study (eyeMAX group). The inclusion criteria were as follows: (a) indeterminate biliary stricture, (b) age ≥ 18 years, (c) Eastern Cooperative Oncology Group performance status (ECOG PS) ≤ 3, (d) American Society of Anesthesiologists (ASA) class ≤ 3, and (e) estimated survival > 3 months. The exclusion criteria were as follows: (a) ASA class > 3; (b) ECOG PS 4; (c) estimated survival ≤ 3 months; (d) inaccessible papilla, such as due to surgically altered anatomy or malignant duodenal obstruction; and (f) refusal to participate in this study. As a historical control group that was enrolled retrospectively, consecutive patients who met the same inclusion and exclusion criteria and underwent POCS using the SpyGlass DS II were also evaluated (SpyGlass DS II group). The study was conducted according to the tenets of the Declaration of Helsinki for biomedical research involving human subjects, and all patients provided written informed consent for study participation. A priori approval for this study was given by the Human Research Committee of Osaka Medical and Pharmaceutical University (IRB No. 2022-110-1).

2.1 | Cholangioscopes, Biopsy Devices, and Procedural Protocol

The eyeMAX (11 Fr) digital cholangioscope was used in this study. The tip of this scope is extremely tapered (Figure 1a), which enables its easy insertion into the site of interest. In addition, the working channel is 2.0 mm in diameter (Figure 1b), and the dedicated biopsy forceps (Micro-Tech, Nanjing, China), with a cup length of 1.6 mm and opening width of 4.5 mm, allows large amounts of biopsy tissue to be obtained. In the control SpyGlass DS II group, an improved dedicated forceps biopsy device (SpyBite MAX, Boston Scientific), with a cup length of 1.0 mm and opening width of 4.2 mm, was used for obtaining biopsy specimens (Figure 1c).

Figure 2 shows the procedural protocols of each cholangioscope. All procedures were performed under deep sedation with capnography monitoring and antibiotic prophylaxis. The duodenoscope (TJF290, Olympus Medical, Tokyo, Japan) was inserted into the

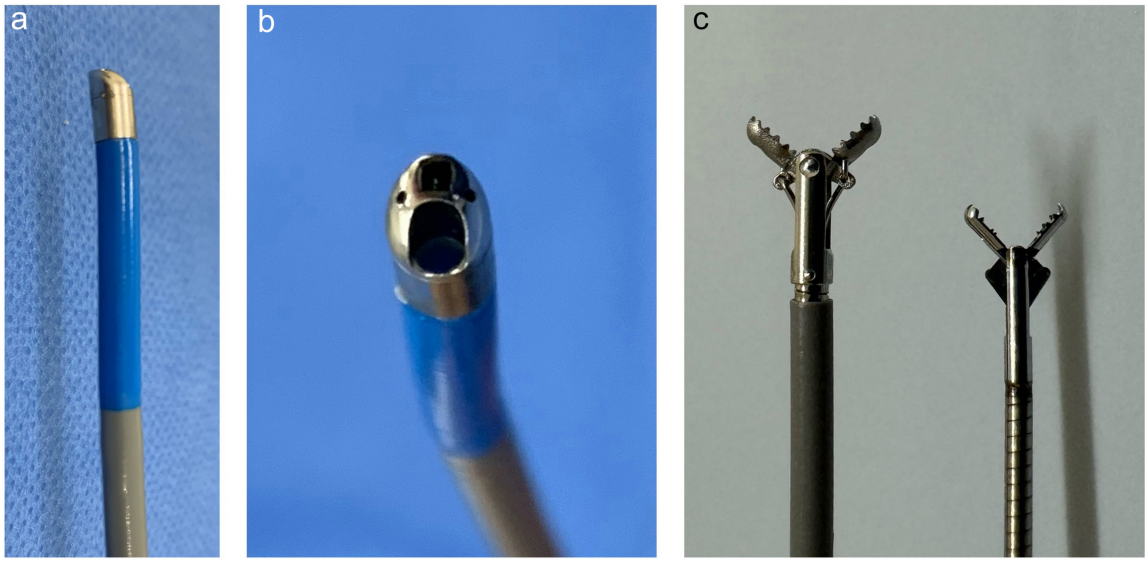

FIGURE 1 | (a) The tip of the eyeMAX (11 Fr) digital cholangioscope is extremely tapered. (b) The working channel is 2.0 mm in diameter. (c) The dedicated biopsy forceps (Micro-Tech, Nanjing, China) with a cup length of 1.6 mm and opening width of 4.5 mm (left side). The dedicated forceps biopsy device (SpyBite MAX, Boston Scientific) with a cup length of 1.0 mm and opening width of 4.2 mm (right side).

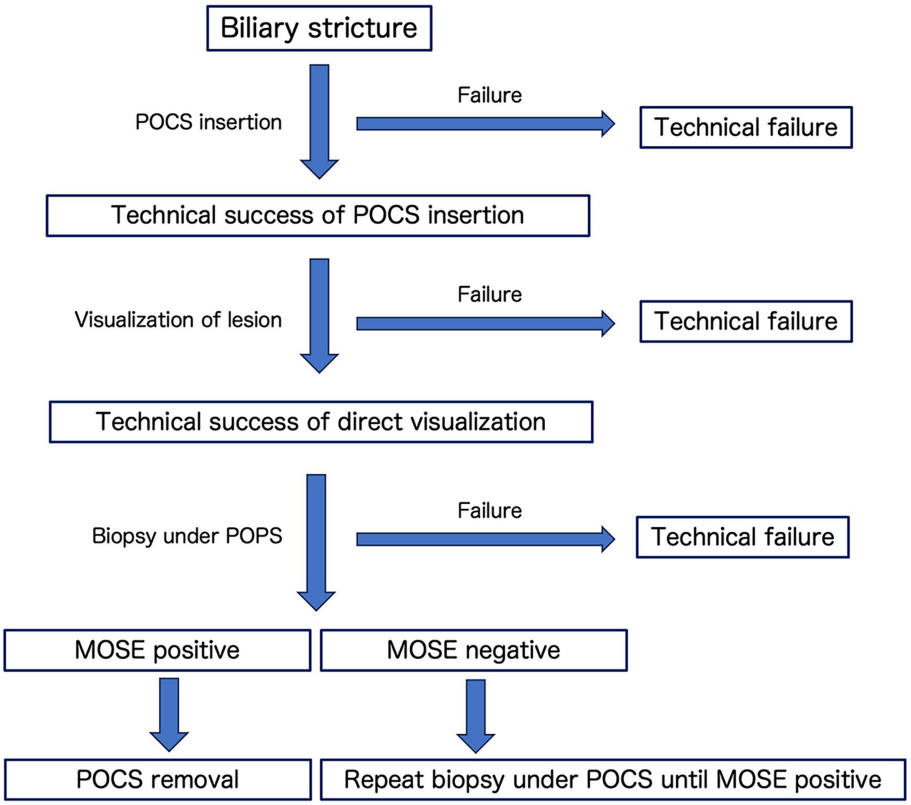

FIGURE 2 | The procedural protocols of both cholangioscopes.

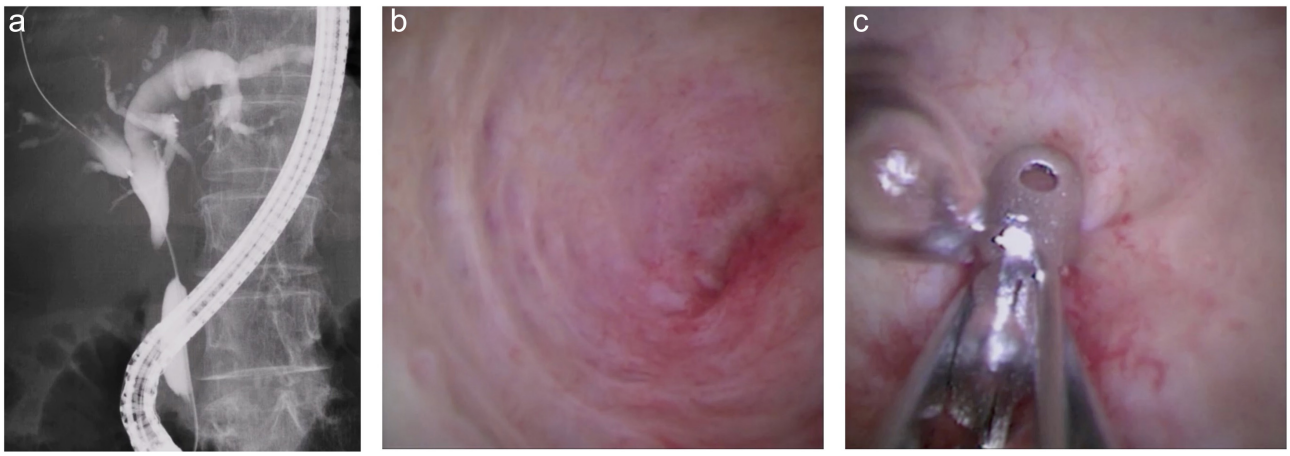

FIGURE 3 | (a) Biliary stricture is observed in the distal common bile duct. (b) Tumor with tortuous and dilated vessels, and irregular nodulations is observed. (c) Forceps biopsy is performed.

duodenum, and biliary cannulation was performed using a standard ERCP catheter with a 0.025-inch guidewire. Contrast medium was injected to evaluate the site of the biliary stricture, and the guidewire was passed into the biliary tract through the stricture site (Figure 3a). Then, endoscopic sphincterotomy was performed. POCS insertion into the biliary tract was subsequently attempted. After successful identification of the lesion (Figure 3b), forceps biopsy was performed under direct visualization (Figure 3c). If the procedures failed at any step, the procedure was considered as a technical failure, and forceps biopsy under fluoroscopic guidance was alternatively attempted.

2.2 | Definitions of Diagnostic Yield of Visual Evaluation and Forceps Biopsy

The visual findings were evaluated independently by three endoscopists (T.O., S.U., and A.O.) using the Mendoza Classification [11]. Briefly, if tortuous and dilated vessels, irregular nodulations, raised intraductal lesions, irregular surface with or without ulcerations, and friability were observed, the lesions were considered malignant. If, on the other hand, the characteristics of the lesion included a villous pattern (micronodule or without vascularity), polypoid pattern (adenoma or granuloma

pattern without vascularity), or inflammatory pattern (regular or irregular fibrous and congestive pattern with regular vascularity), the lesion was considered benign according to the Carlos Robles-Medranda classification [12]. For forceps biopsy, macroscopic on-site evaluation (MOSE) was performed in the eyeMAX and SpyGlass DS II groups by the three endoscopists who performed the visual evaluations (T.O., S.U., and A.O.), as previously described [9]. In case of disagreement in interpretation, a decision was made after discussion. If visible core tissue was not obtained, forceps biopsy was repeated until visible core tissue was obtained (Figure 4a). For histological evaluation, adequate core tissue was defined as an architecturally intact piece of tissue measuring more than 5 mm. In MOSE negative cases, repeated biopsy was performed until MOSE positivity was obtained. In this study, the histological assessment of "malignancy or suspicious of malignancy" was considered malignancy. Also, atypical and benign findings were considered benign cases. In both malignant and benign cases, tissue size was considered adequate when the tissue included cells and could be histologically evaluated. Three endoscopists (S.U., A.O., and N.N.), who were trained in the method by pathologists, measured tissue size as follows. Initially, the slide containing the largest amount of tissue from among the obtained tissue specimens was selected for each case. The area of the tissue sample was calculated digitally using the NIS-Elements imaging software program (Figure 4b). To prevent measurement errors, the measurement was performed four times and the average value was used in the analysis. The final diagnosis was based on the results of pathological evaluation of specimens obtained at surgical resection. In non-resected cases, the final diagnosis was based on the patient's clinical course. At the end of follow up, if absence of disease regression or lack of evidence of disease progression was observed, the patient's final diagnosis was considered as "no malignancy." Primary sclerosing cholangitis (PSC) and IgG-4-related cholangitis were finally diagnosed based on the magnetic resonance cholangiopancreatography (MRCP) findings and serum IgG-4 levels, as well as the results of pathological examination.

2.3 | Outcomes and Statistical Analysis

The primary outcome of this study was the diagnostic accuracy of the biopsy specimens obtained by the eyeMAX compared with the final diagnosis. The secondary outcomes were comparison of the diagnostic yield of visual findings, tissue size, number of forceps biopsies until MOSE positivity, and adverse events in the eyeMAX group compared with the SpyGlass DS II group. Stricture diameter was measured using ERCP. Indeterminate biliary stricture was defined in cases that met the following criteria, as previously described [13]: (1) biliary stricture that was indeterminate according to laboratory data and the findings of the noninvasive diagnostic modality, such as CT, with or without ERCP; and (2) negative results of bile juice cytology, including brush cytology or transpapillary forceps biopsy, with a persistent clinical suspicion of malignant disease.

Descriptive statistics are presented as the mean ± standard deviation (SD) or the median and range for continuous variables and as the frequency for categorical variables. The two groups were compared using analysis of variance for continuous factors, Kruskal–Wallis tests for number of events, and Fisher's exact test for categorical factors. Differences with $p < 0.05$ were considered significant. All data were statistically analyzed using SPSS version 13.0 statistical software (SPSS, Chicago, IL, USA).

3 | Results

In this prospective study, 50 patients (mean age 75 years, 28 males) who underwent POCS using the eyeMAX were enrolled between July 2023 and March 2024. As a historical control, 47 patients (mean age 75 years, 28 males) who underwent POCS using the SpyGlass DS II between April 2022 and June 2023 were enrolled. Table 1 shows the patients' characteristics. In the eyeMAX group, a final diagnosis of malignant disease was made in 23 patients (cholangiocarcinoma, $n = 15$; pancreatic cancer, $n = 4$; gallbladder cancer, $n = 2$; others, $n = 2$) and benign disease was seen in the remaining 27 patients (PSC, $n = 3$; IgG4-related cholangitis, $n = 4$; inflammatory biliary stricture, $n = 13$; others, $n = 7$). On the other hand, in the SpyGlass DS II group, malignant disease was the final diagnosis in 27 patients (cholangiocarcinoma, $n = 24$; others, $n = 3$), and benign disease was seen in 20 patients (PSC, $n = 4$; inflammatory biliary stricture, $n = 8$; others, $n = 8$). There were no significant differences in the final diagnosis between the two groups ($p = 0.06$). However, the elevated type of cholangiocarcinoma

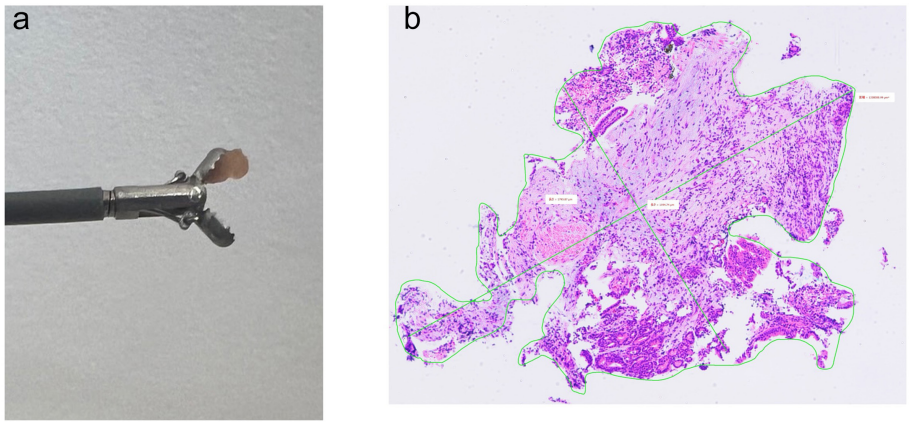

FIGURE 4 | (a) Forceps biopsy is repeated until visible core tissue was obtained. (b) The area of the tissue sample is calculated digitally using the NIS-Elements imaging software program.

TABLE 1 | Patients' characteristics.

	eyeMAX	SpyGlass DS II	*p*
Total patients (*n*)	50	47	—
Median age (years, range)	75 (38–89)	75 (31–98)	0.6022
Sex (male/female)	28/22	28/19	0.7217
Final diagnosis, *n*			0.0588
Malignant			
Cholangiocarcinoma	15	24	
Pancreatic cancer	4	0	
Gallbladder carcinoma	2	0	
Others	2	3	
Benign			
Primary sclerosing cholangitis	3	4	
IgG4-related cholangitis	4	0	
Inflammatory biliary stricture	13	8	
Others	7	8	
Biopsy site, *n*			0.1943
Intrahepatic bile duct	13	18	
Extrahepatic bile duct	37	29	
Mean diameter of the stricture, mm (±SD)	13.53 ± 7.51	14.91 ± 9.72	0.4318
Technical success of cholangioscope insertion, % (*n*)	100 (50/50)	100 (47/47)	—
Technical success of direct visualization of lesion, % (*n*)	100 (50/50)	100 (47/47)	—
Technical success of forceps biopsy for lesion, % (*n*)	100 (50/50)	100 (47/47)	—
Number of biopsies until obtaining MOSE positivity, % (*n*)			0.001
1	92 (46)	61.7 (29)	
2	8.0 (4)	27.7 (13)	
3	0 (0.0)	10.6 (5)	
Mean tissue size, mm^2 (±SD)	2.96 ± 8.76	1.80 ± 1.61	0.3718
Adverse events, *n*			0.5545
Bleeding	1	0	
Acute pancreatitis	1	1	
Cholangitis	2	3	

was more frequent in the SpyGlass DS II group than in the eyeMAX group (18 patients vs. 4 patients, $p = 0.007$). Regarding biopsy sites, there was no significant difference between the eyeMAX group (intrahepatic bile duct, $n = 13$; extrahepatic bile duct, $n = 37$) and the SpyGlass DS II group (proximal, $n = 18$; distal, $n = 29$) ($p = 0.194$). Additionally, the mean stricture length was not significantly different (13.53 ± 7.51 mm vs 14.91 ± 9.72 mm in the eyeMAX and SpyGlass DS II groups, respectively) ($p = 0.432$). After successful biliary access, successful POCS insertion was obtained in all patients. Direct visualization and forceps biopsy were also successfully performed in all patients. Therefore, evaluation of diagnostic yield was conducted in all patients (eyeMAX group, $n = 50$; SpyGlass DS II, $n = 47$). As procedural results, the number of biopsies performed until obtaining MOSE positivity was significantly lower in the eyeMAX group than in the SpyGlass DS II group ($p = 0.001$). Although tissue size was larger in the eyeMAX group (2.96 ± 0.69 mm^2) than in the SpyGlass DS II group (1.80 ± 1.61 mm^2), the difference was not statistically significant ($p = 0.3718$). Adverse events were observed in four patients each in the eyeMAX group (bleeding, $n = 1$; acute pancreatitis, $n = 1$; cholangitis, $n = 2$) and SpyGlass DS II group (acute pancreatitis, $n = 1$; cholangitis, $n = 3$). All adverse events were successfully treated conservatively.

Tables 2 and 3 show a comparison of the diagnostic yield in terms of visual findings and following forceps biopsy between the eyeMAX and SpyGlass DS II groups. The sensitivity of visual findings for malignancy was higher in the eyeMAX group (91.3%, 21/23) than in the SpyGlass DS II group (66.7%, 18/27). In addition, the diagnostic accuracy was also higher in the eyeMAX group (96.0%, 48/50) than in the SpyGlass DS II group (80.9%, 38/47). The sensitivity of histopathological evaluation of the forceps biopsy specimen for malignancy was slightly higher in the eyeMAX group (91.3%, 21/23) than in the SpyGlass DS II group (85.2%, 23/27). Also, the diagnostic accuracy for the final diagnosis was slightly higher in the eyeMAX group (93.5%, 47/50) than in the SpyGlass DS II group (89.3%, 42/47).

4 | Discussion

The present study found that the diagnostic yield in the eyeMAX group was favorable compared with that in the SpyGlass DS II group, both on visual evaluation and on histological evaluation of the forceps biopsy specimen. In addition, the number of biopsies required to achieve MOSE positivity was significantly lower in the eyeMAX group. To the best of our knowledge, this is the first trial of the eyeMAX assessing both visual findings and histological evaluation.

In cases of indeterminate biliary strictures, the differential diagnosis between malignant and benign biliary diseases using noninvasive diagnostic modalities, such as CT or MRCP, might be challenging. To prevent misdiagnosis, POCS might be clinically useful for diagnosing indeterminate biliary strictures because it allows direct visualization and direct biopsy. As one of the POCS techniques, direct POCS (D-POCS) using a dedicated, ultraslim, upper endoscope has been reported. This technique has the advantage of enabling narrow-band imaging (NBI). Shin et al. performed a comparative study of conventional white-light imaging (WLI) and NBI for indeterminate biliary strictures [14]. In their study, in the 71 patients, D-POCS was successfully performed in 67 patients (technical success rate, 94.4%). Although the sensitivity, specificity, and accuracy of visual findings under WLI were 75.0%, 82.9%, and 82.8%, respectively, the diagnostic yields improved to 87.5%, 91.4%, and 91.3%, respectively, when NBI was used. Therefore, they concluded that D-POCS using NBI provides a higher diagnostic accuracy than POCS under conventional WLI. However, this technique might be relatively complex, requiring expert hands. Indeed, despite several studies at high volume centers, technical success of D-POCS was not always achieved in all patients [14–16]. The procedure time might also be prolonged with D-POCS because it requires changing the duodenoscope to a dedicated ultraslim upper endoscope. In addition, if biliary drainage is required, changing back to the duodenoscope is needed to deploy the drainage tube. On the other hand, POCS using a disposable digital single-operator cholangioscope (DSOC), such as the SpyGlass DS II, is a technically simple procedure. According to a recent meta-analysis including D-POCS and DSOC [7], the overall pooled sensitivity and specificity were 88% (95% CI 83–91) and 95% (95% CI 89–98), respectively. As subgroup analysis, diagnostic yield was compared between D-POCS and DSOC, indicating no significant difference in sensitivity and specificity between them ($p = 0.37$). Therefore, although a randomized controlled trial between D-POCS and DSOC is still needed, similar efficacy with respect to diagnostic yield on visual evaluation might be obtainable regardless of which POCS method is used. However, DSOC has an important disadvantage in terms of obtaining tissue because the cup diameter of the dedicated biopsy device is smaller than that of the forceps biopsy device of D-POCS, which can also accept fluoroscopic guidance biopsy forceps. Sekine et al. conducted a comparative study of DSOC and fluoroscopic guidance for suspected bile duct cancer [17]. In their study, the sensitivity, specificity, and accuracy of DSOC and fluoroscopic guidance were 54%, 100%, and 61%, and 64%, 100%, and 69.5%, respectively. This result might be due to the size of the sample obtained. Indeed, tissue size was significantly larger under fluoroscopic guidance ($1.77 \pm 2.00\,mm^2$) than with DSOC ($0.90 \pm 2.00\,mm^2$). To obtain a larger amount of tissue, dedicated biopsy forceps, such as SpyBite MAX (Boston Scientific), is now available. In the present study, the mean tissue sample size was $1.80 \pm 1.61\,mm^2$. This result was almost identical to our previous prospective evaluation ($1.80 \pm 1.6\,mm^2$) [9], indicating that the present study might be reliable. However, this tissue size might not be sufficient for improving the diagnostic yield. Indeed, according to a meta-analysis, biopsy obtained from D-POC had significantly higher sensitivity than that of DSOC (92% vs. 79%; $p = 0.004$) [7].

On the other hand, eyeMAX has several advantages. First, it might allow better visibility than the SpyGlass DS II. The present study showed higher sensitivity and accuracy with the eyeMAX than with the SpyGlass DS II, even though the eyeMAX group included more various diseases than the SpyGlass DS II group. However, despite the improved visibility, the differential diagnosis between malignant biliary diseases and PSC or IgG4-related cholangitis might still be challenging [18]. Therefore, to improve the diagnostic yield of visual findings, various modalities, such as artificial intelligence or a magnifying function, might be needed [19]. However, no matter how much the visual findings improve, a sufficient quantity of tissue is still required

TABLE 2 | Diagnostic yield of visual findings.

	eyeMAX	SpyGlass DS II
Sensitivity, % (*n*)	91.3 (21/23)	66.7 (18/27)
Specificity, % (*n*)	100 (27/27)	100 (20/20)
Positive predictive value, % (*n*)	100 (21/21)	100 (18/18)
Negative predictive value, % (*n*)	93.1(27/29)	69.0 (20/29)
Accuracy, % (*n*)	96.0 (48/50)	80.9 (38/47)

TABLE 3 | Diagnostic yield of forceps biopsy.

	eyeMAX	SpyGlass DS II
Sensitivity, % (*n*)	91.3 (21/23)	85.2 (23/27)
Specificity, % (*n*)	96.3 (26/27)	95.0 (19/20)
Positive predictive value, % (*n*)	95.5 (21/22)	95.8 (23/24)
Negative predictive value, % (*n*)	92.9 (26/28)	82.6 (19/23)
Accuracy, % (*n*)	93.5 (47/50)	89.3 (42/47)

to make an accurate histopathological diagnosis, since recent improvements in systemic chemotherapy, such as immune check point inhibitors, have widened the scope of chemotherapy to a larger variety of malignancies [4, 5]. Second, the cup size of the eyeMAX biopsy device is large because of the larger diameter of the cholangioscope. The mean tissue size of the eyeMAX was 1.16 mm^2 larger than that of the SpyGlass DS II. However, no significant difference was observed. In the eyeMAX group, various kinds of malignant diseases were observed. In pancreatic cancer, the forceps biopsy site was on the distal side of the common bile duct, and therefore, biopsy itself might not be easy. Further, in case of gallbladder cancer or metastatic disease, because the biopsy site was on the lateral side, a sufficient biopsy may not be able to performed. These facts might affect tissue size obtained. However, we believe that the difference of obtaining sample size would be clinically useful for histopathologists. Indeed, the diagnostic yield of forceps biopsy was favorable in the eyeMAX compared with the SpyGlass DS II in the present study.

The present study has several limitations. First, although this study was prospective, it was a nonrandomized trial in a single center. Second, the final diagnosis in the eyeMAX group might not have been the same as in the SpyGlass DS II group, although a significant difference was not observed. In addition, the sensitivity of the SpyGlass DS II group was lower than in previous studies. This fact might have been influenced by the elevated type, in which the surface of the mucosa was only slightly elevated without surface abnormality, which was more common in the SpyGlass DS II group than in the eyeMAX group. Also, to obtain a preoperative diagnosis, a large number of forceps biopsies are not very necessary. However, because of improvement of systemic chemotherapy for targeting genes, a large amount of tissue is required. Based on this fact, forceps biopsy should be repeatedly performed. Therefore, the present study might not reflect clinical practice, although its results may be helpful when selecting the kind of cholangioscope to use.

Moreover, our investigation could be a landmark study for future research, as it provides a prospective evaluation of diagnostic yield, including evaluation of the obtained tissue size.

In conclusion, the eyeMAX has a favorable diagnostic yield in terms of visual findings and the forceps biopsy specimen compared with the SpyGlass DS II. Because MOSE can be sufficiently obtained with the eyeMAX cholangioscope, the number of biopsies required to achieve MOSE positivity might be lower with the eyeMAX than with the SpyGlass DS II. Further randomized, controlled trials are needed to verify our results.

Conflicts of Interest

The authors declare no conflicts of interest.

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