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BRIEF ARTICLE

Efficacy of SpyGlass™-directed biopsy compared to brush cytology in obtaining adequate tissue for diagnosis in patients with biliary strictures

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Abstract

AIM: To evaluate the diagnostic yield (inflammatory activity) and efficiency (size of the biopsy specimen) of SpyGlass™-guided biopsy *vs* standard brush cytology in patients with and without primary sclerosing cholangitis (PSC).

METHODS: At the University Medical Center Mainz, Germany, 35 consecutive patients with unclear biliary lesions (16 patients) or long-standing PSC (19 patients) were screened for the study. All patients underwent a physical examination, lab analyses, and abdominal ultrasound. Thirty-one patients with non-PSC strictures or with PSC were scheduled to undergo endoscopic retrograde cholangiography (ERC) and subsequent per-oral cholangioscopy (POC). Standard ERC was initially performed, and any lesions or strictures were localized. POC was performed later during the same session. The Boston Scientific SpyGlass System™ (Natick, MA, United States) was used for choledochoscopy. The biliary tree was visualized, and suspected lesions or strictures were biopsied, followed by brush cytology of the same area. The study endpoints (for both techniques) were the degree of inflammation, tissue specimen size, and the patient populations (PSC *vs* non-PSC). Inflammatory changes were divided into three categories: none, low activity, and high activity. The specimen quantity was rated as low, moderate, or sufficient.

RESULTS: SpyGlass™ imaging and brush cytology with material retrieval were performed in 29 of 31 (93.5%) patients (23 of the 29 patients were male). The median patient age was 45 years (min, 20 years; max, 76 years). Nineteen patients had known PSC, and 10 showed non-PSC strictures. No procedure-related complications were encountered. However, for both methods, tissues could only be retrieved from 29 patients. In cases of inflammation of the biliary tract, the diagnostic yield of the SpyGlass™-directed biopsies was greater than that using brush cytology. More tissue material was obtained for the biopsy method than for the brush cytology method (P = 0.021). The biopsies showed significantly more inflammatory characteristics and greater inflammatory activity compared to the cytological investigation (P = 0.014). The greater quantity of tissue samples proved useful for both PSC and non-PSC patients.

CONCLUSION: SpyGlass™ imaging can be recommended for proper inflammatory diagnosis in PSC patients. However, its value in diagnosing dysplasia was not addressed in this study and requires further investigation.

Key words: Cholangioscopy; Endoscopic retrograde cholangiopancreatography; Primary sclerosing cholangitis; Brush cytology; Biopsy

Core tip: Endoscopic retrograde cholangiography remains the gold standard method for diagnosing biliary tract diseases. However, choledochoscopy with the SpyGlass™ system enables direct visualization of the biliary tract. Furthermore, targeted biopsies can be performed. In our single-center study, the diagnostic yield of SpyGlass™-directed biopsy for inflammatory changes in primary sclerosing cholangitis (PSC) and non-PSC patients was significantly greater than that of brush cytology. The better diagnostic yield strongly correlated with significantly greater amounts of tissue for histological evaluation.

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INTRODUCTION

The precise diagnosis of biliary lesions and strictures is of crucial importance in patients with primary sclerosing cholangitis (PSC) or other biliary strictures because malignant tumors of the bile duct frequently have poor prognoses and high recurrence rates. Furthermore, the precise diagnosis of inflammatory activity influences medical and endoscopic treatments and might affect surveillance intervals.

The accurate assessment of bile duct stenosis (malignant *vs* inflammatory *vs* scar) is the ultimate goal of endoscopic retrograde cholangiopancreatography (ERCP) in patients with PSC. However, this differentiation remains challenging because endoscopic retrograde cholangiography (ERC) and other auxiliary fluoroscopy techniques do not permit the reliable diagnostic evaluation of biliary lesions[1,2]. Alternative diagnostic methods, such as endoscopic ultrasonography (EUS) with the use of miniprobes or probe-based endomicroscopy, are still of limited use[3].

Peroral cholangioscopy (POC) provides direct visualization of the biliary tree. This method also permits tissue sampling *via* targeted biopsies. The additional information provided by POC has been reported to change overall patient management and outcomes[4]. Furthermore, POC appears to be useful for clarifying filling defects during ERCP[5]. Recent data suggest that POC provides sufficient resolution and that in combination with biopsy, it can accurately diagnose biliary tract lesions[6]. POC is not a new process, as it has been used since the 1970s[7]. However, when first introduced, the procedure required two investigators, and the fiber-optic image quality was poor[8].

The first single-operator choledochoscopy system was introduced in 2005 by Boston Scientific and is known as the SpyGlass™ direct visualization system. The system enables a single investigator to perform cholangioscopy and targeted biopsies of bile duct abnormalities[9]. After the SpyGlass™ direct visualization system was introduced, its clinical application was reported in several publications. The main aspects addressed in these studies were the accessibility, direct view, and characterization of abnormal biliary lesions[10,11]. A recent study showed that the sensitivity of SpyGlass™ for gross assessment was significantly superior to that of ERC (81% *vs* 53%)[12].

However, ERC remains the gold standard for diagnosing biliary lesions in PSC[13]. Although brush cytology is the preferred investigation method for strictures and PSC-associated lesions, the poor sensitivity has been reported to be a major problem. Cytology achieves fairly good specificity, but its sensitivity is poor (approximately 50%)[14-19]. Cholangioscopy-guided biopsy appears to have the potential to overcome the problems associated with inadequate tissue sampling.

Thus, the aim of the present study was to evaluate the diagnostic yield (inflammatory activity) and efficiency (the biopsy specimen size for histological evaluation) of SpyGlass™-guided biopsy versus standard brush cytology.

MATERIALS AND METHODS

Patient recruitment

From January 2009 to February 2011 at the University Medical Center of Mainz, Germany, 35 consecutive patients with unclear biliary lesions (16 patients) or longstanding PSC (19 patients) were screened for the study. Thirty-one patients were finally included in the study after providing informed consent. All patients underwent a physical examination, lab analyses (Table 1), and abdominal ultrasound prior to ERCP and POC.

Endoscopic system and technique

The Boston Scientific SpyGlass™ and the Boston Scientific SpyScope™ were used for choledoscopy. The choledochoscope was advanced through a standard therapeutic duodenoscope (Pentax ED-3480T, Pentax, Hamburg). The choledochoscope (Boston Scientific™) was passed through the working channel of the "mother" scope (Pentax ED-3480T duodenoscope). All procedures were

Table 1 Patient characteristics

	All patients	PSC	Non-PSC	*P* value
Patients (*n*)	29	19	10	-
Age	(48.9 ± 16.7)	(42.1 ± 13.9)	(61.9 ± 13.9)	0.00172
ALT	(100.2 ± 129.1)	(69.5 ± 41.1)	(155.4 ± 203.9)	0.21921
AST	(74.5 ± 69.0)	(63.7 ± 104.7)	(93.9 ± 107.7)	0.39791
Gamma GT	(411.4 ± 470.7)	(314.7 ± 288.4)	(585.2 ± 674.8)	0.25288
AP	(310.4 ± 212.6)	(285.0 ± 177.3)	(356.0 ± 269.6)	0.46748
Bilirubin	(3.0 ± 4.9)	(2.9 ± 5.0)	(3.3 ± 5.1)	0.83431
CRP	(20.8 ± 32.0)	(15.4 ± 25.9)	(30.3 ± 40.5)	0.31297
Leukocytes	(8.1 ± 3.1)	(8.2 ± 3.3)	(7.7 ± 2.6)	0.66937

PSC: Primary sclerosing cholangitis; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; CRP: C-reactive protein.

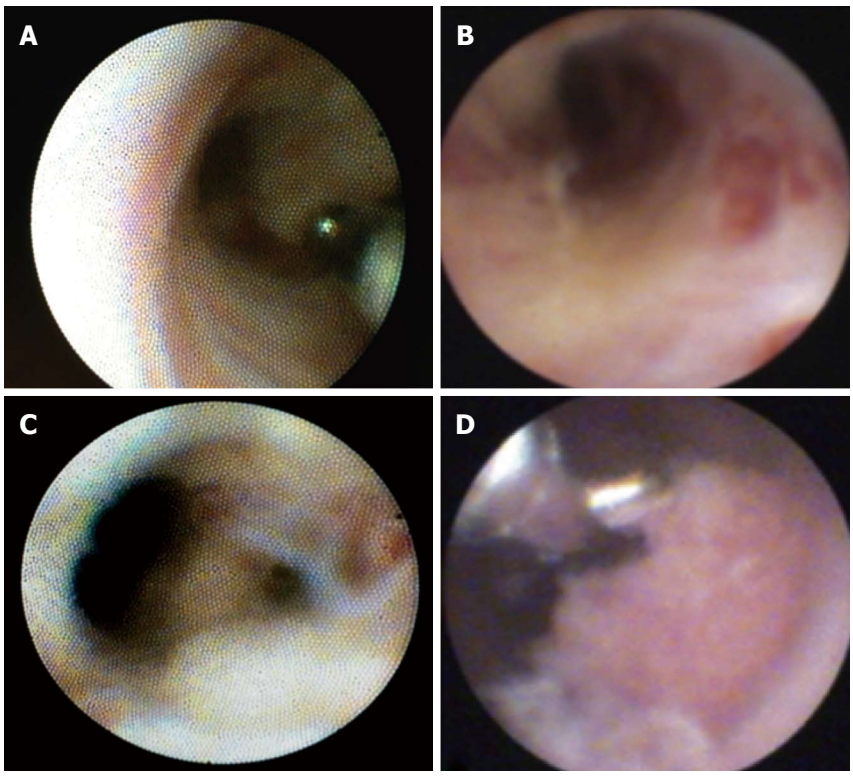

Figure 1 SpyGlass™ visualization of the bile duct. A: A normal bile duct; B: Chronic inflammation, with scars; C: Active inflammation, with mucus fibrin; D: Targeted biopsy of a lesion.

performed using Propofol (1% Disoprivan, AstraZeneca, Switzerland) as sedation.

Before POC, a standard retrograde cholangiogram with biliary sphincterotomy was performed to localize the strictures and to facilitate ductal access and therapy. The choledochoscope was introduced into the bile duct through the guidewire *via* the working channel. For patients in whom the wire could not be advanced beyond a lesion or stenosis, the guidewire was advanced to the stricture under direct visualization of the bile duct whenever possible.

ERCP, POC, and tissue sampling techniques

Standard ERC was initially performed, and any lesions or strictures were localized. Subsequently, POC was performed during the same session. The biliary tree was inspected, and suspicious lesions or strictures were biopsied; at least two or three biopsies per lesion or stricture were taken for histological examination (Figure 1). In addition, brush cytology of the same area was performed with a Cook medical Double Lumen Biliary Brush™ (Cytology). A single pathologist who specialized in biliary pathology graded the biopsy specimens and the brush cytology (T.H.) in a standardized manner. The inflammatory changes were divided into 4 categories (none, low, moderate, high) according to the number of leukocytes. For the biopsies, 5 high-power fields (HPFs, 0.309 mm^2) were observed, and the leukocytes were semiquantitatively analyzed as follows: no activity, < 10 leukocytes/HPF; low activity < 100 leukocytes/HPF; moderate activity > 100 leukocytes/HPF; and high activity > 150 leukocytes/HPF. In the case of the cytological specimens,

Table 2 Quantity of material

		Brush			Total
		Small	Moderate	Sufficient	
Biopsy	Small	3	4	0	7
	Moderate	6	4	2	12
	Sufficient	9	1	0	10
Total		18	9	2	29

Quantity of material by method. Bowker's test for symmetry of contingency tables yielded a *P*-value of 0.021.

Table 3 Inflammatory activity

		Brush				Total
		None	Low	Moderate	High	
Biopsy	None	0	1	0	0	1
	Low	0	11	0	0	11
	Moderate	0	8	0	0	8
	High	1	6	0	2	9
Total		1	26	0	2	29

Signs of inflammation by method. Bowker's test for symmetry of contingency tables yielded a *P*-value of 0.014.

semiquantitative evaluation revealed the following activity levels: none, < 5 leukocytes/HPF; low, < 50 leukocytes/HPF; and high, > 50 leukocytes/HPF. The quantity of specimens was rated as low, moderate, or sufficient, according to the cell number in an HPF (0.306 mm^2); in the case of cytology, the quantities were as follows: low, < 10 cells/HPF; moderate, < 20 cells/HPF; and sufficient, > 50 cells/HPF). In biopsy specimens, either the number of specimens (low, one tissue fragment; moderate, at least two tissue fragments; sufficient, at least three tissue fragments) or the number of mucosal folds/villi was encountered (low, one villus; moderate, at least two villi; sufficient, at least three villi).

Ethical considerations

The ethics committee of Rheinland-Pfalz, Germany, approved this study (No. 837.432.07 (5967)).

Statistical analysis

Practical limitations allowed us to collect material from 31 patients; 2 samples did not meet our quality criteria. The material collection proved to be sufficient to detect the differences between the two groups. Statistical analysis was performed using the R statistical language. Bowker's test was used to reject the null hypothesis of symmetry in contingency tables (Tables 2 and 3):

$$\sum_{i<j} \frac{(n_{ij} - n_{ji})^2}{n_{ij} + n_{ji}}$$

, where B is χ^2 distributed with $[n(n-1)]/2$ degrees of freedom.

All reported *P* values are the result of a data exploration process.

RESULTS

All 31 patients underwent brush cytology and biopsy. No procedure-related complications were encountered. However, for both methods, tissues could be retrieved from only 29 patients. In one patient, SpyGlass™ failed to obtain any tissue material; in another patient, no cytological specimens could be obtained using brush cytology.

The patient and laboratory characteristics are summarized in Table 1. Twenty-three of the 29 patients were male, and the median patient age was 45 years (range, 20-76 years). Nineteen patients had known PSC, and 10 showed non-PSC strictures. The patient characteristics did not significantly differ between the two groups. Four patients had a suspicion of malignant strictures during endoscopy that was not confirmed by histologic results.

The biopsy method revealed significantly more tissue material ($P = 0.021$) than the brush method (Table 2, Figure 2). In 10 patients, the number of biopsy specimens was sufficient; by contrast, only 2 patients demonstrated sufficient numbers of specimens by brush cytology. In 27 patients, no or little inflammatory activity was detected using the brush method, compared to 12 patients using the biopsy method. Using SpyGlass™-directed biopsy, a greater degree of inflammatory activity (classified as moderate or high) was observed in 17 of 29 (58.62%) patients ($P = 0.014$) (Table 3). Brush cytology failed to reveal any significant signs of inflammation because of the paucity of material. A common characteristic of the two techniques was that a greater quantity of test material predicted stronger signs of inflammation. The subgroup analysis between the PSC and non-PSC patients did not reveal any significant differences in the assessment of inflammatory activity with regard to the biopsy or brush method, respectively (Tables 4, 5). Neither brush cytology nor biopsy detected any malignant strictures or dysplasia in the patients.

The brush method demonstrated a positive correlation between the amount of test material and the characteristics of inflammation. This method typically produced little study material and revealed only a few features of inflammation. SpyGlass™-directed biopsy showed moderate or high levels of inflammation in 17 of 29 cases.

A significantly greater quantity of material was obtained with the biopsy-directed procedure. Brush cytology showed adequate signs of inflammation in two cases (Table 2). We observed no differences in the outcomes of the patients with or without PSC. Furthermore, no significant difference was noted in the patients with elevated laboratory parameters of inflammation with regard to the histopathological signs of inflammation.

DISCUSSION

SpyGlass™ is a single-operator system that allows direct visualization of the biliary and pancreatic tracts[9,20]. SpyGlass™ provides significantly greater sensitivity to clarify biliary strictures compared to ERCP[12,21,22]. The largest study in the literature (comprising nearly 300 patients)

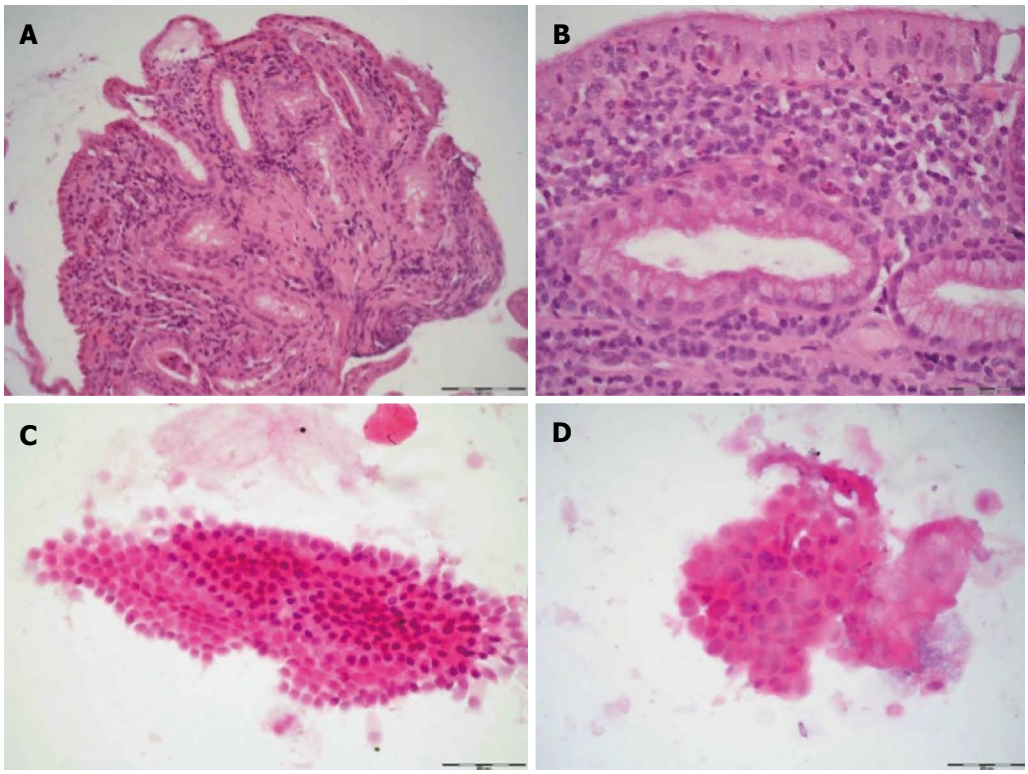

Figure 2 Comparison of biopsy and brush cytology. Histological examination of the biopsy (A, B) shows parts of the bile duct wall with regularly shaped epithelium (original magnification, × 100 A, × 400 B). A detailed view in B confirms marked inflammation with numerous lymphocytes and neutrophilic granulocytes infiltrating the bile duct mucosa. Cytological analysis of the same patient was in the upper figures (original magnification C, D), demonstrating regular epithelial cells and few leukocytes.

showed that SpyGlass™ could visualize 96% of all strictures and that 88% of the identified strictures or lesions could be successful biopsied[23]. Other studies reported a higher diagnostic value of SpyGlass™-guided biopsy compared to brush cytology[24-26]. However, to date, the diagnostic yield for PSC has not been clarified. Thus, we investigated the diagnostic value of SpyGlass™-directed biopsy versus brush cytology in patients with or without PSC. Furthermore, we evaluated whether the biopsy or brush cytology characteristics differed between PSC and non-PSC patients. We clearly demonstrated that SpyGlass™-guided biopsy obtained greater quantities of tissue specimens and provided a more accurate diagnosis of inflammatory changes. This result is important because the degree of inflammation might alter the medical treatment or refine the surveillance of PSC patients.

Our study focused on the amount of tissue obtained and the presence of inflammatory changes. Although malignant changes were suspected in four of our patients during endoscopy, the specimens could not confirm dysplasia or carcinoma. However, malignancies have been identified using SpyGlass™, with a reported accuracy of 77% in patients with suspected cholangiocarcinoma[4,25-28]. Our study could not clarify whether SpyGlass™ is beneficial in identifying PSC-associated dysplasia.

In our study, biopsy specimens were obtained using SpyGlass™ in 28 of 29 cases (96.5%). This percentage is greater than that previously reported[11], which might be because we performed at least 2-3 passes of the biopsy forceps (Spybite™) at the area of interest.

Brush cytology often failed to reveal signs of inflammation because of the paucity of material. The most important result of our study was that tissue acquired by directed biopsy was associated with greater signs of inflammation that allowed a more precise diagnosis because SpyGlass™-directed biopsy acquired a greater amount of sample, at quantities adequate for analysis. Pathological examination improved the diagnosis of inflammation by the amount of specimens. This result occurred significantly more often in the biopsied specimens. These data are relevant with regard to patients with unknown biliary strictures and concur with another study in which the initial working diagnosis was modified after a SpyGlass™ investigation in 68.9% of patients with biliary strictures[29]. Specific risk populations (*e.g.*, patients with PSC or prolonged chronic inflammation of the bile duct) are subject to an increased risk of cancer[30,31]. As POC provides direct information about the bile duct, it may serve as an important and informative extension of ERC[22].

Note that there were no complications related to the SpyGlass™ examination. In addition to the expected result of improved detection of inflammation in SpyGlass™-directed biopsy, we also demonstrated that the method was easy and safe, as previously reported[32].

The present study had some limitations. First, we had to perform brush cytology after biopsy, and the influence of the quantity of the brush cytology specimens remains unknown. Second, this study was performed at a single

Table 4 Inflammatory activity in primary sclerosing cholangitis patients

		Brush				Total
		None	Low	Moderate	High	
Biopsy	None	0	0	0	0	0
	Low	0	6	0	0	6
	Moderate	0	4	0	0	4
	High	1	6	0	2	9
Total		1	16	0	2	19

Signs of inflammation (by method) for the patients diagnosed with PSC. Bowker's test for symmetry of contingency tables yielded a *P*-value of 0.088.

Table 5 Inflammatory activity in non-primary sclerosing cholangitis patients

		Brush				Total
		None	Low	Moderate	High	
Biopsy	None	0	1	0	0	1
	Low	0	5	0	0	5
	Moderate	0	4	0	0	4
	High	0	0	0	0	0
Total		0	10	0	0	10

Signs of inflammation (by method) for the patients who were not diagnosed with PSC. Bowker's test for symmetry of contingency tables yielded a *P*-value of 0.544.

center with a limited number of patients. Third, a single pathologist performed all the histopathological examinations.

In conclusion, the diagnostic yield of SpyGlass™-directed biopsy for inflammatory changes in PSC and non-PSC patients was significantly greater than that of brush cytology. The better diagnostic yield strongly correlated with the greater amount of tissue specimens obtained from the SpyGlass™-directed biopsy. A total of 2-3 biopsies must be obtained from suspicious areas in the biliary tract. Further studies are needed to fully clarify the benefit of the better inflammatory diagnosis in PSC and to investigate the potential of SpyGlass™ in diagnosing PSC-associated dysplasia.

COMMENTS

Background

Patients with primary sclerosing cholangitis (PSC) suffer from chronic and relapsing inflammation of the biliary tract. Endoscopic retrograde cholangiopancreatography is recommended procedure to stage the disease and to clarify inflammatory strictures. Spyglass™ as a single operator cholangioscopy system provides direct visualization of the biliary tract with the possibility of direct biopsies.

Research frontiers

Cholangioscopy is basically not a new process. It has been introduced since the 1970´s as a so-called mother-baby endoscopy technique, in which a thin choledochoscope (baby-scope) was pushed through the instrumentation channel of the duodenoscope (mother-scope) during the endoscopic retrograde cholangiography (ERC). The procedure required two investigators and the quality of the fiber-optic images was poor. The first single-operator choledochoscopy system was introduced in 2005 by Boston Scientific, and is known as the SpyGlass™ direct visualization system.

Innovations and breakthroughs

Precise diagnosis of biliary lesions and strictures is still difficult but of crucial importance for the patients. However, neither ERC nor other auxiliary fluoroscopy-techniques permit reliable diagnostic evaluation of biliary lesions. The gold standard for the diagnosis of biliary lesions, especially in PSC, is still ERC. A recent study showed that the sensitivity of SpyGlass™ for gross assessment was significantly superior to that of ERC (81% *vs* 53%) and biliary strictures could be significant better characterized. Furthermore the SpyGlass™ system allows optical guided biopsy sampling with definite histologic diagnosis and high accuracy.

Applications

This study indicates that the diagnostic yield of SpyGlass™-directed biopsies for inflammatory changes in PSC and non-PSC patients is significantly higher than that of brush cytology. The better diagnostic yield is strongly correlated with the larger amount of tissue specimens, which can be obtained with SpyGlass™ directed biopsies.

Terminology

The SpyGlass System was developed to overcome the limitations of the so called traditional cholangioscopy. Integrated irrigation channels and a 1.2 mm diameter therapeutic channel make for the first time optical guided biopsies and therapeutic stone management possible. Thus, this system enables for a single investigator during ongoing ERC to perform targeted biopsy of bile duct lesions and to perform laser therapy of complicated bile duct stones.

Peer review

This study is well conducted even if only a few patients were included. In this study the advantages of direct cholangioscopy with the possibility of using a single operator cholangioscopy and with the possibility of direct biopsies are well described. The results showing significant advantages of biopsy versus brush cytology in grading inflammation and non-inflammatory changes in the bile duct.

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