Sufficient Tissue Acquisition Rate of Peroral Cholangioscopy-guided Forceps Biopsy

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Abstract

Background: Peroral cholangioscopy (POCS)-guided forceps biopsy is a method for diagnosing indeterminate biliary strictures and for the preoperative identification of the exact perihilar and distal margins of biliary tract cancer (BTC). However, POCS-guided forceps biopsy may result in an insufficient amount of specimen at times. Aims: We evaluated the sufficient tissue acquisition rate and the factors affecting the sufficient tissue acquisition of POCS-guided forceps biopsy for the biliary tract. Methods: Patients who underwent POCS-guided forceps biopsy for biliary disease between September 2016 and October 2018 at our hospital were enrolled retrospectively. We evaluated the sufficient tissue acquisition rate of POCS-guided forceps biopsy for the biliary lesion and that for non-stenotic bile duct. In addition, the factors affecting the sufficient tissue acquisition rate of POCS-guided forceps biopsy were evaluated. Results and Conclusions : We enrolled 47 patients with the biliary disease and performed POCS-guided forceps biopsy for biliary lesion and POCS-guided forceps mapping biopsy for non-stenotic bile duct in 40 and 36 patients, respectively. The sufficient tissue acquisition rates of POCS-guided forceps biopsy for biliary lesions and that for non-stenotic bile duct were 86.4%, and 68.9%, respectively. In the multivariate logistic regression analyses, age and previous biliary stenting before POCS were factors affecting the sufficient tissue acquisition rate of POCS-guided forceps biopsy for the biliary lesion. For non-stenotic bile duct, the location of the biliary lesion, endoscopic sphincterotomy, and procedure time of POCS were factors affecting the sufficient tissue acquisition rate of POCS-guided forceps mapping biopsy.

Introduction

Biliary tract cancer (BTC), including intrahepatic cholangiocarcinoma (ICC), extrahepatic cholangiocarcinoma (ECC), gallbladder carcinoma (GC), and ampullary carcinoma (AC), is a disease with a poor prognosis. The 5-year survival rate and median survival time of BTC was 18.7% and 8.5 months, respectively [1]. Although the early diagnosis of BTC might improve the prognosis of that, BTC is often diagnosed at an advanced stage and is often unresectable because it is difficult to differentiate between BTC and benign biliary diseases, such as primary sclerosing cholangitis, immunoglobulin G subclass 4 (IgG4)-associated sclerosing cholangitis, xanthogranulomatous cholecystitis, and Mirizzi syndrome [2, 3]. It is important to distinguish BTC from benign biliary disease, as the treatment strategies and prognoses differ.

Endoscopic retrograde cholangiopancreatography (ERCP)-related tissue acquisition, such as bile aspiration cytology, biliary brush cytology, and forceps biopsy, is commonly used to diagnose indeterminate biliary lesions. Although the specificity of the pathological examination of ERCP-related tissue acquisition for indeterminate biliary strictures is almost 100%, the sensitivity of that is unsatisfactory, with a range of 6−72% [4, 5].

Recently, the utility of peroral cholangioscopy (POCS)-guided forceps biopsy to diagnose indeterminate biliary lesions has been reported [6, 7]. However, the sensitivity of POCS-guided forceps biopsy for indeterminate biliary stricture is unsatisfactory (60.1%) [8].

BTC has a clinical feature of superficial intraductal spread, in which epithelium extends continuously from the main lesion [9]. The frequency of superficial intraductal spread in cholangiocarcinoma is reported to be 14.6% [10]. The presence of superficial intraductal spread is related to non-curative resection for BTC so that it is essential to identify the exact perihilar and distal margins of the preoperative BTC. The usefulness of POCS-guided forceps mapping biopsy for preoperative identification of the longitudinal extension of BTC has been reported [11–13]. On the other hand, the diagnostic accuracy of the POCS visual findings for indeterminate biliary lesions was higher than that of the POCS-guided forceps biopsy findings [14].

Although POCS plays important roles for diagnosis of indeterminate biliary strictures and for preoperative identification of the longitudinal extension of BTC, the diagnostic performance of POCS-guided forceps biopsy is not enough. The working channel of the cholangioscope is narrow, so only a mini-forceps with a 1.0-mm diameter cup could be used for POCS-guided forceps biopsy. Therefore, only a small amount of specimen can be obtained by POCS-guided biopsy. This is a possible reason for the inability to determine a pathological diagnosis and to evaluate the longitudinal tumor extent by POCS-guided forceps biopsy. In this study, we examined the sufficient tissue acquisition rate of POCS-guided forceps biopsy for biliary lesions and that of POCS-guided forceps mapping biopsy for non-stenotic bile duct. We also evaluated the diagnostic performance of POCS-guided forceps biopsy for BTC and adverse events resulting from its use.

Methods

2.1. Study Population

Patients who underwent ERCP-related tissue acquisition with POCS for biliary disease between September 2016 and October 2018 at our hospital were retrospectively enrolled. Inclusion criteria were as follows: (1) Patients who underwent POCS-guided forceps biopsy for indeterminate biliary lesion; (2) Patients who underwent POCS-guided forceps mapping biopsy for BTC to identify longitudinal extension; (3) Patients aged 20 years or older when the endoscopic procedures were performed. Exclusion criteria were as follows: (1) Patients who did not provide consent; and (2) Patients who have been receiving chemotherapy for malignant diseases within one month prior to the acquisition of the pathological specimens.

Forty-seven patients with biliary disease were enrolled in the study. Participants included 32 men and 15 women aged 26–88 years (median age, 73 years). Twenty-eight patients had BTC and 19 had benign biliary lesions (Table 1). We defined Cohort 1 as patients who received POCS-guided forceps biopsy for biliary lesions. Cohort 2 was defined as the group of patients who received POCS-guided forceps biopsy for non-stenotic bile duct. Stenotic bile duct and non-stenotic bile duct was defined by fluoroscopy finding of ERCP. The biliary lesion sites with caliber changes in the biliary tract diameter were defined as stenotic bile ducts, and other sites were defined as non-stenotic bile duct. This study was performed according to the guidelines described in the Helsinki Declaration for biomedical research involving human participants.

This study was performed according to the guidelines described in the World Medical Association Declaration of Helsinki statement of ethical principles for medical research involving human subjects. The study protocol was also approved by the institutional review board of Tottori University (No.18A178). In this retrospective study, informed consent was obtained from all participants using an opt-out approach.

2.2. Endoscopic Procedure

A side-viewing duodenoscope (JF260V/TJF240V; Olympus Corp., Tokyo, Japan) and a 0.025-inch hydrophilic guidewire (G−260−2545A; Olympus; MTA0025N48S; Medico's Hirata, Inc, Osaka, Japan; M00556700; Boston Scientific Corporation, Marlborough, MA USA) were used during ERCP. POCS was performed using a mini endoscope (M00546600 SpyGlass DS Access; Boston Scientific) direct visualization system. We inserted a cholangioscope into the bile duct over the guidewire, and POCS-guided forceps biopsy under direct vision was performed with M00546270 (SpyBite Biopsy Forceps; Boston Scientific) with a 1.0-mm diameter cup (Figure 1).

Almost all patients underwent endoscopic sphincterotomy (EST) by using a sphincterotome (Olympus CleverCut KD-V411M−0725; Olympus), if it was not previously performed. Eighteen patients in the study group had previously undergone EST. Endoscopic papillary balloon dilation (EPBD) was performed for 4 cases using a balloon dilatation catheter (ZR25−08−23, RN25−0630−18; KANEKA Medix Corporation, Osaka, Japan) because they received anti-thrombotic therapy. One patient underwent a precut papillotomy by using a needle knife (9913023121; MTW-Endoskopie W. Haag KG, Wesel, Germany).

2.3. Diagnostic Criteria and Definition of Sufficient tissue

The diagnosis of BTC was based on the pathological diagnosis of bile aspiration cytology, and transpapillary forceps biopsy, endoscopic ultrasonography-guided fine needle aspiration (EUS-FNA), or surgical specimen. Patients with benign disease had a final diagnosis based on clinical and radiological follow-up data. Biopsy specimens were stained with hematoxylin and eosin and, if necessary, immunostaining, including p53 and Ki−67, was also performed. Sufficient tissue was defined as a specimen that allowed the evaluation of the histological finding of the biliary epithelium. A specimen that contained only interstitial tissue was deemed insufficient (Figure 2). Malignancy or suspected malignancy was considered positive in histological findings.

We evaluated the sufficient tissue acquisition rate of POCS-guided forceps biopsy for biliary strictures in Cohort 1 and that of POCS-guided forceps mapping biopsy for non-stenotic bile duct in Cohort 2. The factors affecting sufficient tissue acquisition of POCS-guided forceps biopsy in each cohort were also evaluated. We evaluated the pathological diagnostic performance of the POCS-guided forceps biopsy for BTC. We also evaluated adverse events of POCS-guided forceps biopsy for biliary disease.

2.4. Statistical Analysis

Statistical analysis was performed using StatFlex ver. 6.0 for Windows (Artec Corp., Osaka, Japan). Categorical variables were compared using the chi-squared test, and continuous variables were compared using the Mann–Whitney U-test. All values are expressed as mean ± standard deviation or median with interquartile range. Subgroup analyses of age (<65 or ≥65 years), sex, malignant biliary disease, the location of the biliary lesion or stricture (distal or non-distal), length of biliary stricture (<15 or ≥15 mm), macroscopic types of BTC (flat type or non-flat type composed of nodular and papillary type), presence of acute cholangitis, level of serum T-Bil (<1.5 or ≥1.5 mg/dl), level of CEA (<5.0 or ≥5.0 ng/ml), level of CA19−9 (<35 or ≥35 U/ml), procedure time (≤75 minutes or >75 minutes), EST, and previous biliary stenting before POCS-guided forceps biopsy were assessed to determine the sufficient tissue acquisition rate of POCS-guided forceps biopsy. In Cohort 2, biopsy site (bifurcation of the bile duct or not, intrahepatic bile duct or extrahepatic bile duct, right side or left side) was also included in the subgroup analysis. We carried out univariate analyses to assess the sufficient tissue acquisition rate, and factors with P < 0.1 were included in the multivariate logistic regression analyses. The significance level was set at P < 0.05.

Results

3.1. Patient's Characteristics and Baseline Evaluation

Table 1 showed the characteristics of patients with biliary disease. In this study, the malignant group included 12 patients with perihilar cholangiocarcinoma, 14 patients with distal cholangiocarcinoma, one patient with intrahepatic cholangiocarcinoma and one patient with cystic ductal carcinoma. Macroscopic types of BTC included four papillary-type, 16 nodular-type, and eight flat-type. The benign group included nine patients with benign biliary strictures, three patients with IgG4-associated sclerosing cholangitis, three patients with primary sclerosing cholangitis, two patients with drug-induced cholangitis, one with intraductal papillary neoplasm of the bile duct (IPNB), and one with a peribiliary cyst. This study group included 24 patients with perihilar bile duct stricture, 19 patients with distal bile duct stricture, two patients with cystic duct stricture, and one patient with intrahepatic bile duct stricture. One patient did not have any biliary stricture, and he received POCS-guided forceps biopsy for distal bile duct near the ampulla of Vater in order to evaluate the hypertrophic extrahepatic bile duct. The median length of stricture in this study group was 16.6 mm (range, 0−46.0 mm). The median levels of serum total bilirubin (T-Bil), carcinoembryonic antigen (CEA), and carbohydrate antigen 19−9 (CA19−9) were 1.3 mg/dl (range, 0.3−14.8 mg/dl), 2.4 ng/ml (range, 0.8−10.1 ng/ml), and 34.6 U/ml (range, 0.8−4430.0 U/ml), respectively (Table 1). The median procedure time of POCS-guided forceps biopsy was 77 minutes (range, 26−170 minutes). The final clinical diagnosis was derived from surgical pathology in 15 patients. There were 18 patients with a final diagnosis based on clinical and radiological follow-up data (median follow up period, 7 months; range, 1−22 months). We performed both the POCS-guided forceps biopsy for biliary lesions and the POCS-guided forceps mapping biopsy for 29 patients with biliary disease. Eleven

patients received only the POCS-guided forceps biopsy for indeterminate biliary lesions, and Seven patients received only the POCS-guided forceps mapping biopsy for non-stenotic bile duct to determine the longitudinal extension of BTC. Therefore, Cohort 1 and Cohort 2 included 40 and 36 patients, respectively (Figure 3).

3.2. Diagnostic Performance and Tissue Acquisition Rate of POCS-guided Forceps Biopsy for Biliary Tract Cancer.

The total and the median number of biopsies for indeterminate biliary lesions were 140 and 3 (range, 2–8) in Cohort 1, respectively. The total number of POCS-guided forceps mapping biopsies was 196 in Cohort 2. By the location in the bile duct, 93 specimens were obtained from the perihilar bile ducts of 25 patients (41 specimens from the confluence of the hepatic ducts of 23 patients), 31 specimens from the distal bile ducts of 15 patients, 22 specimens from the junction of the cystic ducts of 11 patients, 27 specimens from the first order branch of the intrahepatic ducts of 12 patients, and 23 specimens from the second order branch of the intrahepatic ducts of 12 patients. Eleven patients received biliary stenting before POCS-guided forceps biopsy. In Cohort 1, 21 patients were with BTC, and 19 patients were with benign. Cohort 1 included 22 patients with perihilar bile duct stricture, 15 patients with distal bile duct stricture, 2 patients with cystic duct stricture, and 1 patient with extrahepatic bile duct hypertrophy. Table 2 summarizes the diagnostic performance of POCS-guided forceps biopsy to differentiate BTC from benign biliary disease. The values for sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and the accuracy of POCS-guided forceps biopsy were 76.2%, 94.7%, 94.1%, 78.3%, and 85.0%, respectively (Table 2). The sufficient tissue acquisition rate of POCS-guided forceps biopsy for biliary lesions was 86.4% (121/140).

3.3. Factors Affecting the Sufficient Tissue Acquisition of POCS-guided Forceps Biopsy for Biliary Lesion.

Table 3 summarizes the result of analyses for the sufficient tissue acquisition in POCS-guided forceps biopsy for biliary lesions. In the univariate analyses, age, sex, the location of the biliary lesion, and previous biliary stenting before POCS were factors with $P < 0.1$ and were included in the multivariate logistic regression analyses. Age <65 years old (odds ratio 0.170, 95% confidence interval [CI] 0.044–0.649, $P = 0.004$) and previous biliary stenting before POCS (odds ratio 0.199, 95% CI 0.053–0.756, $P = 0.017$) were the significant factors affecting the sufficient tissue acquisition rate in the multivariate analysis.

3.4. Tissue Acquisition Rate of POCS-guided Forceps Biopsy for Non-Stenotic Bile Duct.

Cohort 2 included 17 patients with perihilar bile duct stricture, 16 patients with distal bile duct stricture, two patients with cystic duct stricture, and one patient with intrahepatic bile duct lesion. The sufficient tissue acquisition rate of POCS-guided forceps mapping biopsy for non-stenotic bile duct was 68.9% (135/196), which was significantly lower than that of POCS-guided forceps biopsy for biliary lesion (P < 0.001). The sufficient tissue acquisition rates of POCS-guided forceps mapping biopsy were calculated by the location in the bile duct: the distal bile duct (58.1%), the junction of the cystic duct (86.4%), the perihilar bile duct (77.4%; including the confluence of the hepatic duct 82.9%), the first order branch of the intrahepatic bile duct (37.0%), and the second order branch of the intrahepatic bile duct (69.6%) (Table 4).

3.5. Factors Affecting the Sufficient Tissue Acquisition of POCS-guided Forceps Biopsy for Non-Stenotic Bile Duct.

Table 5 summarizes the results of the analyses for the sufficient tissue acquisition in POCS-guided forceps mapping biopsy for a non-stenotic bile duct. In the univariate analyses, age, malignant lesion, the location of the biliary lesion, the length of stricture, the biopsy site in the intrahepatic bile duct, procedure time, and EST were factors with P < 0.1, and were included in the multivariate logistic regression analyses. The biliary lesion in the distal bile duct (odds ratio 0.322, 95% CI 0.139−0.744, P = 0.008), procedure time of 75 min or less (odds ratio 3.012, 95% CI 1.092−8.312, P = 0.033), and EST (odds ratio 7.041, 95% CI 2.117−23.421, P = 0.002) were the significant factors affecting the sufficient tissue acquisition rate in the multivariate analyses.

3.6. Adverse Events

Adverse events following POCS-guided forceps biopsy occurred in eight patients (17.0%), with four patients (8.5%) developing acute pancreatitis, including one case of severe pancreatitis; and three patients (6.4%) developing cholangitis. Severe hemorrhage related to the precut papillotomy occurred in one patient (2.1%). No perforations were observed, all cases were resolved with conservative treatment, and there was no procedure-related mortality (Table 6).

Discussion

In recent years, POCS has become a widely-used method for the diagnosis of indeterminate biliary stricture. POCS allows optical viewing of the biliary system, as well as targeted forceps biopsies under direct vision. Some studies reported that the use of POCS can improve the diagnostic accuracy of indeterminate biliary lesions [6, 12]. On the other hands, the sensitivities of POCS-guided forceps biopsy for malignant biliary stricture (60.1%) and cholangiocarcinoma (66.2%) were still insufficient [8] and were similar for fluoroscopic tissue acquisition [7, 15]. Moreover, the sensitivity and accuracy of POCS-guided forceps biopsy for indeterminate biliary lesions were lower than those of visual findings for POCS in past study [13]. Because of the narrow working channel of the cholangioscope, only a mini-forceps with a 1.0-

mm diameter cup was used for the diagnosis in POCS-guided forceps biopsy so that the specimen obtained by POCS is relatively small. A small amount of tissue sampling by POCS-guided forceps biopsy may be related to the insufficient pathological diagnostic ability of that for indeterminate biliary lesions. In the tissue amount, less tissue was obtained from POCS-guided forceps biopsy than fluoroscopy-guided biopsy [16]. Indeed, POCS-guided tissue acquisition may only result in an insufficient amount of tissue. In our study, the sufficient tissue acquisition rate of POCS-guided forceps biopsy for biliary lesions was acceptable (86.4%), and there were only 3 patients with biliary lesions in which a sufficient amount of tissue could not be obtained. Meanwhile, the sensitivity of POCS-guided forceps biopsy for BTC was not acceptable (76.2%), and it was unsatisfactory compared to the sufficient tissue acquisition rate. A working channel with a larger diameter for larger capacity forceps might improve the diagnostic utility for the indeterminate biliary lesion [17]. In the multivariate logistic regression analyses, we found that the previous biliary stenting before POCS was a factor affecting low tissue acquisition rate. In any case with POCS-guided forceps biopsy for biliary lesion, it may be better to avoid previous biliary stenting as much as possible except for patients with acute obstructive suppurative cholangitis. If it was impossible, multiple biopsies or combination of other tissue acquisition methods, such as biliary brush cytology, and forceps biopsy in fluoroscopy, might be needed.

Superficial intraductal spread, which is a feature of BTC, is present in 14.6% of patients with BTC in previous studies [3, 10]. The presence of superficial intraductal spread is related to positive resection margins, local recurrence, and poor prognosis after surgery. Therefore, it is essential to identify the exact perihilar and distal margins of the preoperative BTC. Hijioka et al. reported the usefulness of fluoroscopic mapping biopsy procedures to distinguish between benign and malignant foci [18]. However, that method did not allow targeted forceps biopsies under direct vision of the biliary system, and it was uncertain whether the biopsy site was true or not. On the other hand, POCS-guided forceps mapping biopsy allowed targeted forceps biopsy under direct and fluoroscopic vision of the biliary system. Although recent studies reported the usefulness of POCS-guided forceps biopsy in the preoperative assessment of the longitudinal extension of BTC, the sensitivity of that was not necessarily sufficient [12, 13, 19]. In our study, the sufficient tissue acquisition rate of POCS-guided forceps biopsy for non-stenotic bile duct was also insufficient (68.9%). Reasons for this may be not only the small amount of specimen obtained by POCS-guided forceps biopsy but also the technical difficulty of the limited flexion of the cholangioscope tip, especially in lesions above the biliary stricture as it may be inadequate to target the desired biopsy site [20]. Furthermore, the desired biopsy site above the curvature of the biliary tract might be a negative factor in the sufficient tissue acquisition. Therefore, we think it is important to evaluate the factors affecting the sufficient tissue acquisition of POCS-guided forceps biopsy.

In previous studies, there were a few reports about the factors affecting the accuracy or sensitivity of ERCP-related tissue acquisition for BTC or malignant biliary stricture [21–23]. However, no study reported on the factors affecting the sufficient tissue acquisition of ERCP-related tissue acquisition, including POCS-guided forceps biopsy, for BTC or malignant biliary stricture. Therefore, we selected some candidate factors related to the sufficient tissue acquisition from the factors affecting the accuracy or sensitivity of ERCP-related tissue acquisition for BTC or malignant biliary stricture.

In multivariate logistic regression analyses, we found that the presence of the lesion in the distal bile duct and the POCS-guided forceps mapping biopsy without EST were factors affecting a low tissue acquisition rate. The reason for those might be the limited flexion of the cholangioscope tip making it difficult to target the desired biopsy site. Multiple biopsies might be needed to improve the sufficient tissue acquisition of POCS-guided forceps mapping biopsy for patients with distal bile duct lesions. It is uncertain why the procedure time of 75 minutes or less was a factor affecting a high tissue acquisition rate of POCS-guided forceps mapping biopsy. Speculation includes that the biliary epithelium may be detached from the biliary tract as the procedure time of POCS increases and that the specimen which can be evaluated for a histological finding of the biliary epithelium may be lost. In any case, it is difficult to shorten the procedure time of POCS-guided forceps biopsy and increase the sampling. A more flexible cholangioscope with a wide working channel and a larger capacity forceps might help to improve the sufficient tissue acquisition rate.

This study has some limitations. First, this was a retrospective analysis of a small number of cases in single-center. Second, patients who were diagnosed through clinical follow-up were also included in this study. Therefore, it was unclear whether the cases with negative pathological findings were truly benign biliary disease or not. Third, the accuracy of POCS-guided forceps mapping biopsy to diagnose tumor longitudinal extension was not uncertain because few patients underwent surgery and high rate of positive resection margins in patients underwent surgery in the study. A prospective long-term study including a larger number of patients is required to strengthen the investigation.

In conclusions, previous biliary stenting was a factor affecting a low tissue acquisition rate of POCS-guided forceps biopsy for the biliary lesion. In the POCS-guided forceps mapping biopsy for non-stenotic bile duct, the presence of the lesion in the distal bile duct, the POCS-guided forceps mapping biopsy without EST, and the long procedure time of POCS were factors affecting low tissue acquisition rates.

Declarations

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Tables

Table 1. Baseline characteristics of study patients.

	Biliary disease ($n = 47$)
Age (range), years	73 (42–88)
Sex, male/female	32/15
Location of stricture	
Perihilar	24
Distal	19
Cystic duct	2
Intrahepatic bile duct	1
None	1
Length of stricture, mm	16.6 (0–46.0)
Acute cholangitis (presence/absence)	12/35
Total bilirubin, mg/dL	1.3 (0.3–14.8)
Tumor marker	
CEA, ng/mL	
Malignant	2.6 (0.8–8.3)
Benign	2.2(0.9–10.1)
CA19-9, U/mL	
Malignant	73.3 (9.4–4430.0) *
Benign	9.3 (0.8–309.5)
Malignant	28
Biliary tract cancer	28
Benign	19
Benign biliary stricture	9
IgG4-associated sclerosing cholangitis	3
Primary sclerosing cholangitis	3
Drug-induced cholangitis	2
Intraductal papillary neoplasm of bile duct	1
Peribiliary cyst	1

Values are presented as number or median (range). Abbreviations: CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; IgG4, immunoglobulin G subclass 4. * $p < 0.001$ compared with the benign biliary disease using the Mann–Whitney U-test.

Table 2. Diagnostic ability of peroral cholangioscopy-guided forceps biopsy for differentiating biliary tract cancer from benign biliary disease.

	Sensitivity, %	Specificity, %	PPV, %	NPV, %	Accuracy, %
POCS-guided forceps	76.2 (16/21)	94.7 (18/19)	94.1 (16/17)	78.3 (18/23)	85.0 (34/40)

Abbreviation: POCS, peroral cholangioscopy; PPV, positive predictive value; NPV, negative predictive value

Table 3. Factors affecting the sufficient tissue acquisition of peroral cholangioscopy-guided forceps biopsy for biliary lesions.

Univariate analyses			
Subgroup	Odds ratio	95% CI	*p* Value
Age, <65 years or ≥65 years	0.289	0.103–0.805	<u>0.018</u>
Sex, male or female	2.612	0.972–7.023	<u>0.057</u>
Malignancy or Benign	1.290	0.489–3.398	0.607
Location of biliary lesion, distal or not-distal	3.630	1.004–13.126	<u>0.049</u>
Length of stricture of biliary lesion, <15mm or ≥15mm	1.036	0.389–2.759	0.943
Macroscopic type, flat type or not-flat type	1.023	0.233–4.496	0.976
Cholangitis, presence or absence	4.926	0.628–38.647	0.129
T-Bil, <1.5 mg/dl or ≥1.5 mg/dl	2.020	0.758–5.385	0.160
CEA, < 5.0 ng/ml or ≥5.0 ng/ml	0.673	0.143–3.167	0.616
CA19-9, U/ml <35 U/ml or ≥35 U/ml	0.873	0.328–2.322	0.785
Procedure time, ≤75 min or >75 min	1.249	0.460–3.394	0.663
EST or non-EST	1.703	0.433–6.700	0.446
Previous biliary stenting, presence or absence	0.379	0.127–1.125	<u>0.081</u>
Multivariate analyses			
Subgroup	Odds ratio	95% CI	*p* Value
Age, <65 years or ≥65 years	0.170	0.044–0.649	0.004
Sex, male or female	2.629	0.843–8.200	0.096
Location of biliary lesion, distal or not-distal	1.881	0.442–8.009	0.393
Previous biliary stenting, presence or absence	0.199	0.053–0.756	0.017

Abbreviations: CI, confidence interval; T-Bil, total bilirubin; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen; EST, endoscopic sphincterotomy. *p* Value: Logistic regression model.

Table 4. The sufficient tissue acquisition rate of peroral cholangioscopy-guided forceps biopsy for biliary lesions and non-stenotic bile duct.

Biopsy site	Sufficient tissue acquisition rate, %
Biliary lesions	86.4 (121/140)
Non-stenotic bile duct	68.9 (135/196)
Distal bile duct	58.1 (18/31)
Junction of the cystic duct	86.4 (19/22)
Perihilar bile duct	77.4 (72/93)
Confluence of the hepatic duct	82.9 (34/41)
Right hepatic duct	75.0 (12/16)
Left hepatic duct	70.4 (19/27)
Branch of intrahepatic bile duct	52.0 (26/50)
First order branch of intrahepatic bile duct	37.0 (10/27)
Right first order branch of intrahepatic bile duct	29.4 (5/17)
Left first order branch of intrahepatic bile duct	50.0 (5/10)
Second order branch of intrahepatic bile duct	69.6 (16/23)
Right second order branch of intrahepatic bile duct	66.7 (4/6)
Left second order branch of intrahepatic bile duct	70.6 (12/17)

Abbreviation: POCS, peroral cholangioscopy.

Table 5. Factors affecting the sufficient tissue acquisition of peroral cholangioscopy-guided forceps biopsy for non-stenotic bile duct.

Univariate analyses			
Subgroup	Odds ratio	95% CI	*p* Value
Age, <65 years or ≥65 years	3.431	0.990–11.892	0.052
Sex, male or female	1.483	0.784–2.805	0.226
Malignancy or Benign	0.473	0.205–1.092	0.079
Location of biliary lesion, distal or not-distal	0.461	0.238–0.890	0.021
Length of stricture of biliary lesion, <15 mm or ≥ 15mm	2.442	1.160–5.142	0.019
Macroscopic type, flat type or not-flat type	0.889	0.400–1.975	0.772
Cholangitis, presence or absence	1.242	0.578–2.670	0.578
T-Bil, <1.5 mg/dl or ≥1.5 mg/dl	0.783	0.415–1.479	0.451
CEA, < 5.0 ng/ml or ≥5.0 ng/ml	0.429	0.121–1.520	0.190
CA19-9, U/ml <35 U/ml or ≥35 U/ml	1.128	0.596–2.134	0.711
Biopsy site the bifurcation of the bile duct or not	1.235	0.652–2.338	0.517
intrahepatic bile duct or extrahepatic bile duct	0.540	0.270–1.080	0.081
right side or left side	0.503	0.208–1.215	0.127
Procedure time, ≤75 min or >75 min	2.837	1.239–6.496	0.014
EST or non-EST	5.476	1.879–15.956	0.002
Multivariate analyses			
Subgroup	Odds ratio	95% CI	*p* Value
Age, <65 years or ≥65 years	2.917	0.563–15.122	0.202
Malignancy or Benign	2.198	0.627–7.701	0.218
Location of biliary lesion, distal or not-distal	0.322	0.139–0.744	0.008
Length of stricture of biliary lesion, <15 mm or ≥15 mm	1.368	0.541–3.460	0.508
Biopsy site, intrahepatic bile duct or extrahepatic bile duct	0.467	0.216–1.008	0.052
Procedure time, ≤75 min or >75 min	3.012	1.092–8.312	0.033
EST or non-EST	7.041	2.117–23.421	0.002
Age, <65 years or ≥65 years	2.917	0.563–15.122	0.202

Abbreviations: CI, confidence interval; T-Bil, total bilirubin; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen; EST, endoscopic sphincterotomy. *p* Value: Logistic regression model.

Table 6. The adverse event of peroral cholangioscopy-guided forceps biopsy.

Adverse event	POCS-guided forceps biopsy (n = 47)
Pancreatitis	8.5 % (4/47)
Bleeding	2.1 % (1/47)
Infection	6.4 % (3/47)
Perforation	0
Cardiac	0
Pulmonary	0
Medication reaction	0
Other	0
Overall	17.0 % (8/47)

Abbreviations: POCS, peroral cholangioscopy.
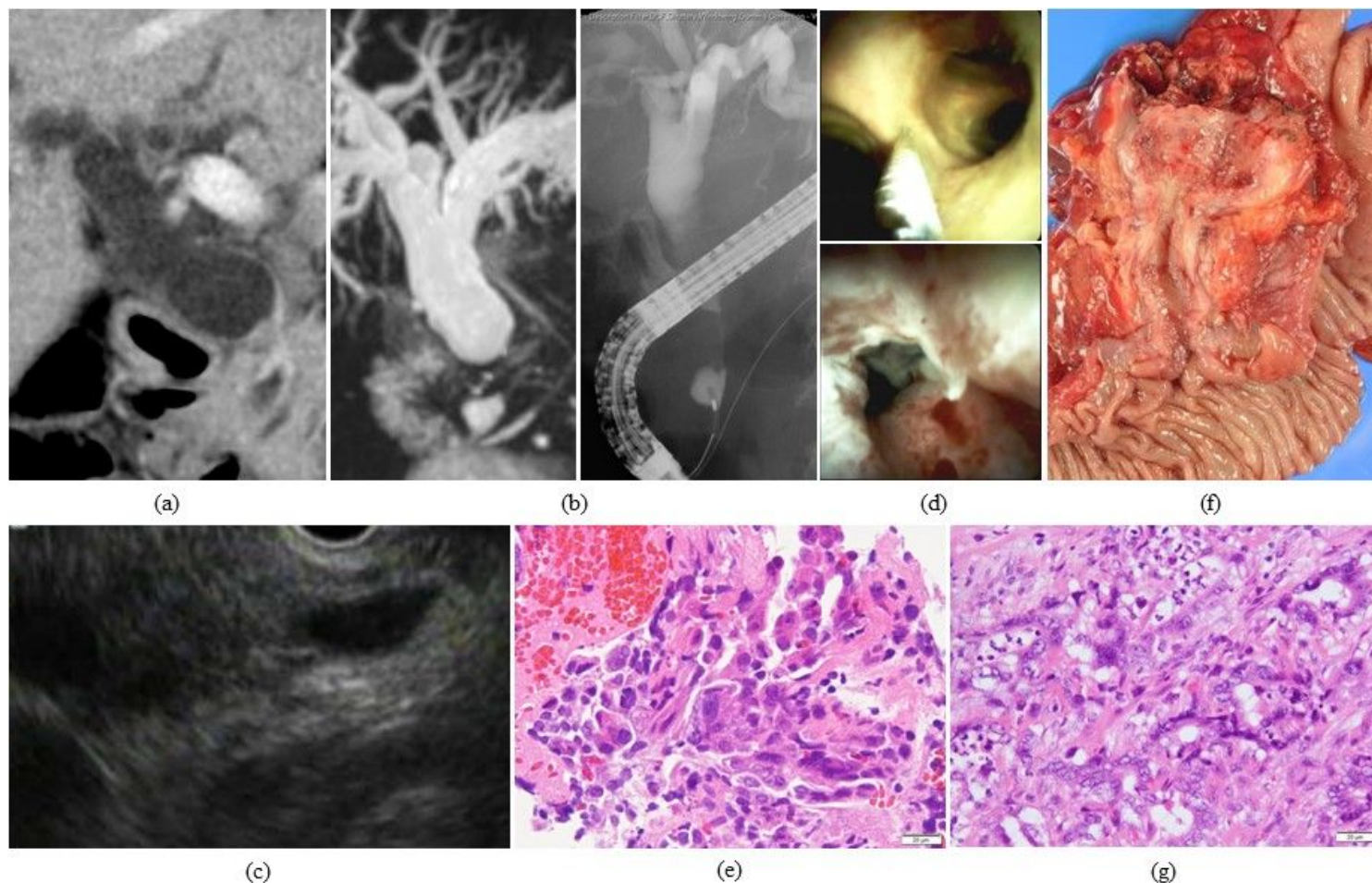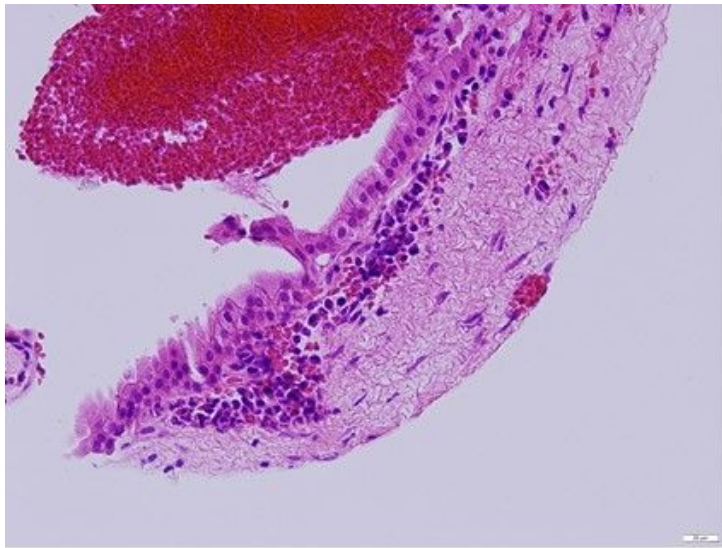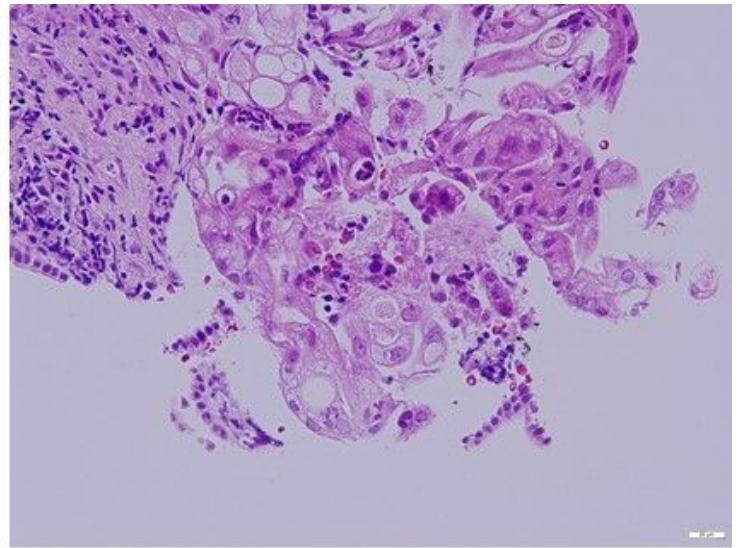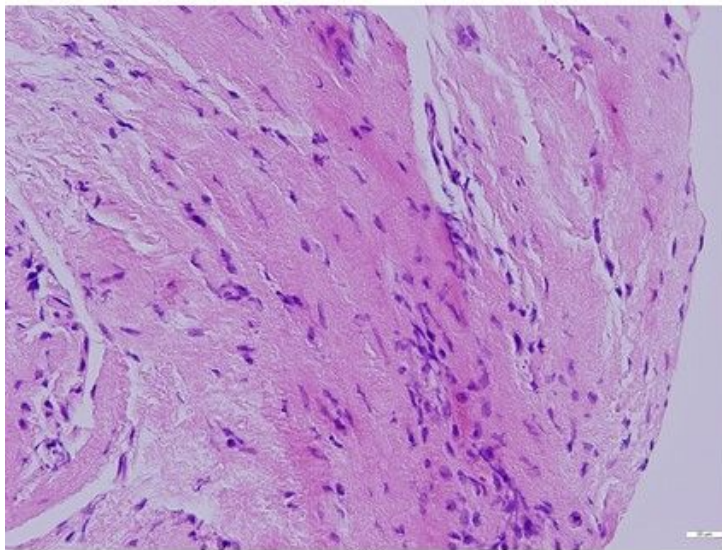
Figures

Figure 1

A case of bile duct stricture diagnosed as distal cholangiocarcinoma with peroral cholangioscopy (POCS)-guided forceps biopsy. (a) Computed tomography scan revealed an irregular nodule in the distal bile duct; (b) magnetic resonance cholangiopancreatography and endoscopic retrograde cholangiography showed stenosis in the distal bile duct; (c) endoscopic ultrasonography showed an irregular nodule in the distal bile duct; (d) POCS revealed the irregular granular mucosa that existed distal bile duct. POCS-guided forceps biopsy was performed for the biliary stricture in the distal bile duct and for the non-stenotic extrahepatic and intrahepatic bile ducts to identify the longitudinal extension margin of the cholangiocarcinoma; (e) hematoxylin and eosin staining revealed adenocarcinoma in specimens obtained from the biliary stricture; (f) this patient underwent pancreatoduodenectomy; and (g) this patients was diagnosed with distal cholangiocarcinoma histologically.
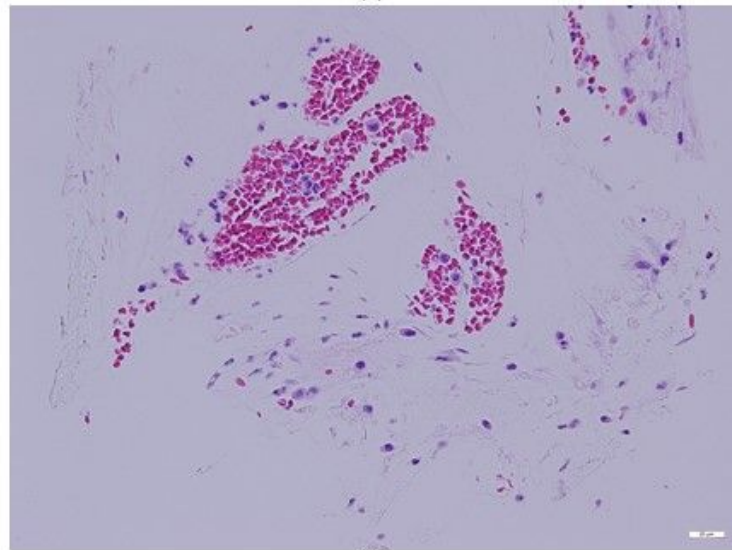
Figure 2

Histopathological findings of specimens obtained by peroral cholangioscopy-guided forceps biopsy. (a) A sufficient specimen containing biliary epithelium without atypia is shown (normal). (b) A sufficient specimen with biliary epithelial cells with severe atypia is revealed (adenocarcinoma). (c) An insufficient specimen containing interstitial tissue is shown. (d) An insufficient specimen containing only hematocytes is revealed.
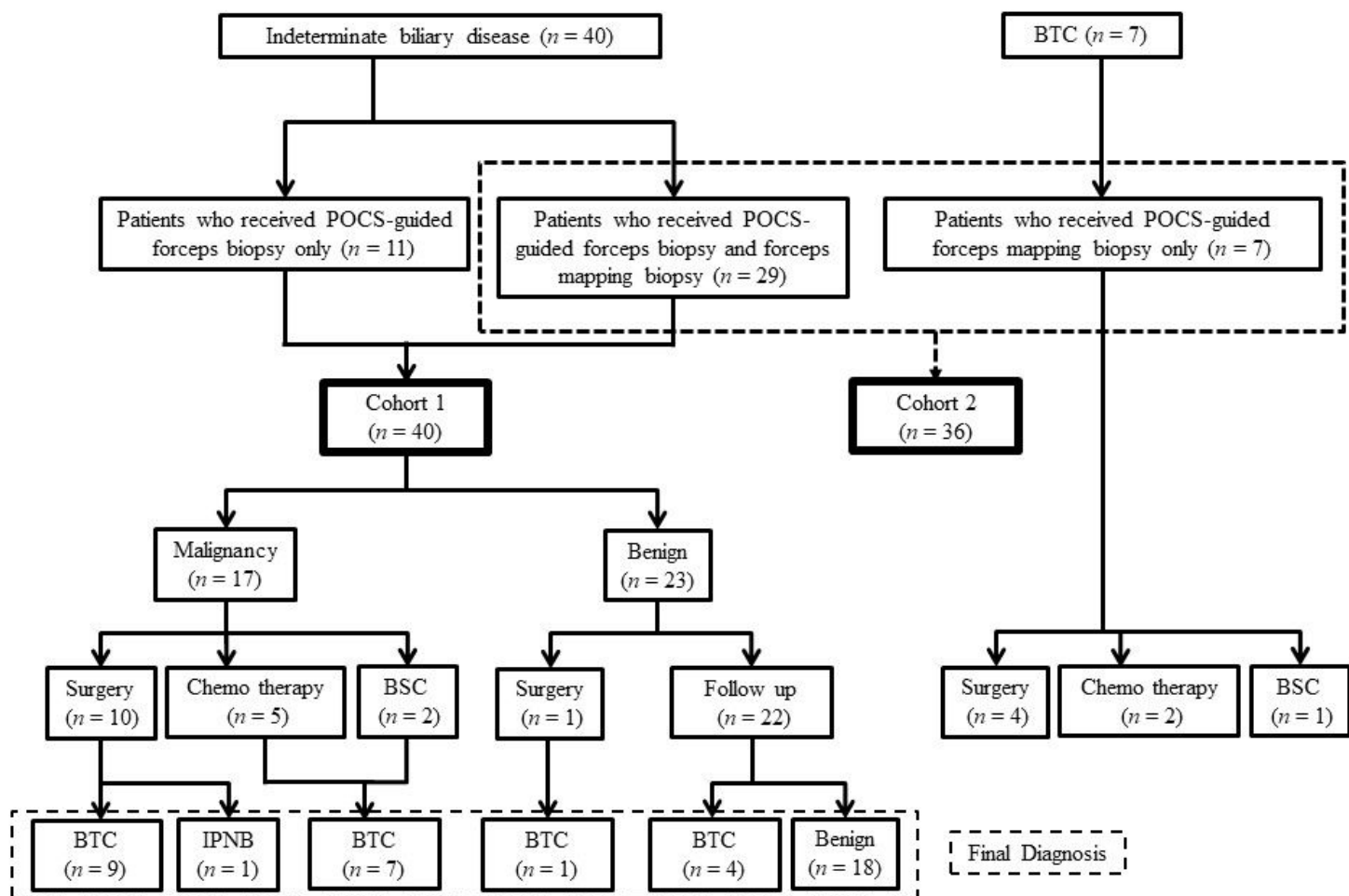
Figure 3

Diagnostic flowchart of patients included in the study. Abbreviations: BTC, biliary tract cancer; POCS, peroral cholangioscopy; BSC, best supportive care; IPNB, intraductal papillary neoplasm of the bile duct.