

Clinical Practice Guidelines for Peroral Cholangioscopy

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ABSTRACT

Background/Purpose: Peroral cholangioscopy (POCS) has emerged as a valuable endoscopic modality for the diagnosis and treatment of biliary tract diseases. Despite its growing clinical application, no standardized clinical practice guidelines have previously been established in Japan. In response, here we describe how the Japan Biliary Association (JBA) developed evidence-based guidelines to support the safe and effective implementation of POCS.

Methods: Following the Minds 2020 methodology, a multidisciplinary committee formulated 31 key clinical, background, and future research questions across six domains: definitions, indications and roles, procedures, special cases, adverse events, and diagnostic/therapeutic outcomes. Recommendations were based on a systematic review of literature, supplemented by expert consensus where evidence was limited.

Results: Key topics include appropriate indications, management of antithrombotic therapy, necessity of papillary intervention, antibiotic prophylaxis, procedural risks, and the role of POCS-guided biopsy and lithotripsy. Notably, the guidelines highlight the utility of POCS in evaluating indeterminate biliary strictures, papillary cholangiocarcinoma, and difficult bile duct stones, while addressing adverse events such as cholangitis and perforation.

Conclusions: These guidelines are intended to serve as a practical reference for clinicians and endoscopists involved in biliary endoscopy, with the flexibility of their adaptation based on institutional practices and patient characteristics.

1 | Introduction

In recent years, peroral cholangioscopy (POCS) has become increasingly widespread. To ensure that POCS can be

performed safely and effectively, a fundamental set of guidelines is necessary. However, no clinical practice guidelines for POCS have previously been established in Japan. In response, the Japan Biliary Association (JBA) developed new

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TABLE 1 | Members of peroral cholangioscopy (POCS) clinical practice guideline committee.

Members of the POCS Clinical Practice Guideline Committee	
Chairperson	Takao Itoi (Department of Gastroenterology and Hepatology, Tokyo Medical University)
Chairperson in charge of the guideline development	Takao Itoi (Department of Gastroenterology and Hepatology, Tokyo Medical University)
Development members	Akio Katanuma (Department of Gastroenterology and Hepatology, Sapporo Medical University School of Medicine)
	Shomei Ryozaawa (Department of Gastroenterology, Saitama Medical University International Medical Center)
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	Hironari Kato (Department of Gastroenterology and Hepatology, Okayama University Graduate School of Medicine and Dentistry)
	Nobuhiko Hayashi (Third Department of Internal Medicine, University of Toyama)
Chairperson of the Evaluation Committee	Yoshinori Igarashi (Division of Gastroenterology and Hepatology, Toho University Omori Medical Center)
Evaluation Committee members	Atsushi Irisawa (Department of Gastroenterology, Dokkyo Medical University School of Medicine)
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clinical guidelines for POCS, aiming to provide a basic scientific methodology-based framework. The writing is in line with that of the “Clinical Practice Guidelines for Endoscopic Papillectomy (EP) [1].”

Given the limited high-quality evidence available in this field, expert consensus is often required during the development process. It is our hope that these guidelines will serve as a valuable reference in the clinical practice of POCS.

2 | Methods

2.1 | Committee Members of POCS Clinical Practice Guideline Development

Nine pancreatobiliary endoscopists were included as members of the guideline development committee by the JBA. Additionally, four JBA-certified senior instructors served as reviewers to evaluate the guidelines (Table 1). The selection of the members of the guideline development group by the JBA adhered to specific criteria, to ensure credibility and balanced representation. The criteria were: expertise in POCS, academic contributions to the field, extensive clinical experience in pancreatobiliary endoscopy, and active involvement in relevant professional societies.

2.2 | Target Population

The target population for these guidelines includes patients undergoing diagnostic and therapeutic procedures with POCS. Intended users are clinicians performing POCS and their supervising physicians. This guideline provides standard recommendations; however, flexible adaptation is necessary based on individual patient preferences, age, comorbidities, social circumstances, and institutional factors.

2.3 | Development of the Guideline

The guideline development process followed the internationally recognized standards of evidence-based medicine (EBM), specifically adhering to the “Minds Clinical Practice Guideline Development Manual 2020.”

2.3.1 | Creation of Clinical Questions (CQs) and Literature Review

The guideline development committee established six key sections: definitions, indications and roles, procedures, management of special cases, adverse events, and diagnostic and therapeutic outcomes. Each section consists of critical CQs aimed at providing recommendations for clinical practice. For each CQ, relevant components (PICO: P, patients; I, interventions; C, comparisons/controls/comparators; O, outcomes) were thoroughly examined. Based on the defined PICO criteria, comprehensive literature searches were conducted, and the gathered evidence was meticulously reviewed.

In addition to the CQs, the committee formulated background questions (BQs) and future research questions (FRQs). BQs covered topics necessary for understanding the clinical contexts and that are essential for comprehending the CQs. FRQs identified areas lacking high-quality research, outlining issues that should be addressed in future studies.

Following evaluation and recommendations by the review committee, the questions (CQs, BQs, and FRQs) underwent revisions, culminating in a total of 31 questions.

The literature search process involved an extraction of relevant keywords from each CQ. Academic papers were retrieved from PubMed and the Cochrane Library (for English literature), and NPO Japan Medical Abstracts Society. The primary search term was “peroral cholangioscopy,” with searches extending until August 2023. Relevant studies outside the search period or in unlisted databases were manually added.

2.3.2 | Systematic Review Process

To formulate the recommendations for each CQ, both beneficial and harmful outcomes were identified and their respective importance assigned. The selected studies were evaluated for bias risk and non-directness (i.e., how closely the study's conditions matched real clinical practice). Evidence from randomized controlled trials (RCTs) and observational studies was synthesized into a “body of evidence” and rated according to the GRADE approach, with the evidence quality rated on a four-point scale (A, B, C, and D) (Table 2).

2.3.3 | Determination of the Strength of the Recommendations

The strength of the recommendations was determined based on the findings of systematic reviews, considering the overall certainty of evidence and the balance between benefits and harms across outcomes. The guideline committee held meetings specifically to finalize the recommendations for each CQ through voting, which required at least two-thirds of the committee and working committee members' participation. Members with conflicts of interest abstained. Recommendations achieving over 80% consensus were adopted. If consensus was not achieved initially, results were disclosed, followed by discussions and repeat voting. In cases where consensus remained unattainable, no recommendation was adopted.

3 | Results

Additional comments and references for the BQs and FRQs other than that of Q3.1-1 are provided in Appendix S1. The bases for the recommendations in these guidelines include the clinical background, medical insurance system, and framework in Japan. To be applicable to different medical systems in other countries, decisions should be made in accordance with the context of each country.

TABLE 2 | Recommended grades and evidence levels.

Recommended grade
1. Strongly recommended
2. Recommended (proposed, recommended with conditions)
None: Not explicitly recommended
Evidence levels: based on
A: Strong evidence
B: Moderate evidence
C: Weak evidence
D: Very weak evidence

3.1 | Definition

3.1.1 | (Q) What is POCS? (BQ)

- POCS refers to an endoscopic technique used for the direct visualization of the biliary tract. It consists of two primary methods: (1) the “mother-baby” system, where a small-diameter endoscope (baby scope) is inserted through the working channel of a duodenoscope (mother scope) to access the bile duct, and (2) peroral direct cholangioscopy (PDCS), in which a small-caliber endoscope is directly inserted into the bile duct via the papilla without the use of a mother scope.

Comment: POCS involves two techniques: mother-baby cholangioscopy (POCS) is performed by using a small scope inserted through a duodenoscope's channel, and PDCS, by directly inserting an ultrathin endoscope into the bile duct. Mother-baby POCS was first reported by Takekoshi et al in 1975 [2]. Subsequently, digital enhancement and integration of narrow-band imaging (NBI) were introduced in 2003 [3, 4] and disposable digital systems (SpyGlass™, SpyScopeDS™ DS), became available from 2007. PDCS, first described by Urakami et al. [5], offers high-resolution imaging with larger accessory channels but has challenging bile duct insertion. The choice of cholangioscopy depends on clinical objectives and institutional preferences.

Table 3 summarizes the currently available POCS in Japan. Among the mother-baby type digital cholangioscopes, the CHF-B290 (Olympus Corporation) features an 80° field of view and bidirectional tip deflection, and supports image-enhancement technologies such as narrow-band imaging (NBI). Since it employs a digital imaging approach, it provides high-resolution endoscopic views; however, it is also more prone to tip damage during procedures. Regarding the disposable cholangioscopes, the SpyScope DS II (Boston Scientific Corporation) was upgraded in 2018 with enhanced brightness control and image resolution. In 2023, two slim-type disposable scopes—eyeMAX (Micro-Tech) and DRES Slim Scope (Japan Lifeline)—were introduced, expanding the options for narrow-caliber biliary access. Currently, the choice between

digital reusable and disposable cholangioscopes depends on procedural objectives, institutional resources, and operator preferences.

3.2 | Indications and Roles

3.2.1 | (Q) What Are the Indications for POCS? (BQ)

- POCS is indicated for the endoscopic diagnosis of various biliary diseases and treatment of difficult bile duct stones.

3.2.2 | (Q) What Are the Contraindications for POCS? (BQ)

- Contraindications for POCS include severe jaundice, acute cholangitis, and acute pancreatitis.

3.2.3 | (Q) What Is the Role of POCS in Patients With Bile Duct Stones? (BQ)

- It is used for lithotripsy and stone removal in cases where conventional endoscopic stone extraction is difficult, such as in large, stacked, or impacted stones, including those associated with Mirizzi syndrome.

3.2.4 | (Q) What Is the Role of POCS in Primary Sclerosing Cholangitis (PSC)? (BQ)

- POCS should be considered for the differential diagnosis of cholangiocarcinoma.

3.2.5 | (Q) What Is the Role of POCS in IgG4-Related Sclerosing Cholangitis (IgG4-SC)? (BQ)

- POCS is used for the differential diagnosis of malignant diseases and for evaluating endoscopic findings before and after steroid therapy.

3.2.6 | (Q) Is Image-Enhanced Endoscopy (IEE), Such as NBI or Texture and Color Enhancement Imaging (TXI), Useful? (FRQ)

- NBI is useful for differentiating benign from malignant biliary lesions and for assessing lateral tumor spread. Newer image-enhancement technologies such as TXI and red dichromatic imaging (RDI) also have potential utility.

3.3 | Procedures

3.3.1 | (Q) What Information Should be Provided When Obtaining Informed Consent for POCS? (BQ)

- In addition to the standard informed consent for endoscopic retrograde cholangiopancreatography (ERCP), patients should be informed of the indications for cholangioscopy, procedural details, potential benefits, alternative treatment options, possible adverse events, and their management.

3.3.2 | (Q) What Are the Requirements for Endoscopists Performing POCS? (BQ)

- It is recommended that endoscopists should have acquired sufficient proficiency in basic pancreatobiliary

TABLE 3 | Specifications of the currently available peroral cholangioscopes.

Product name	EVIS LUCERA ELITE	SpyScopeDS II	eyeMAX	DRES slim scope
Manufacturer	Olympus	Boston Scientific	Micro-Tech	Japan Lifeline
Product number	CHF-B290	M00546610	CDS11006/CDS22006	DRES-FS26
Reusability	Reusable	Disposable	Disposable	Disposable
Field of view	80°	120°	120°	96°
IEE mode	Available (NBI, TXI, RDI)	Unavailable	Unavailable	Unavailable
Outer diameter (mm)	3.3	3.6	3.9/3.2	2.6
Bending capability	2 directions	4 directions	4 directions	None
Up/Down angulation	70°/70°	90°/90°	90°/90°	—
Right/Left angulation	—	90°/90°	90°/90°	—
Length (mm)	1920	2140	2190	1950
Working channel diameter (mm)	1.3	1.2	1.8/1.1	None (0.68 GW channel)
Water jet (independent)	No	Yes	Yes	Yes

Abbreviations: IEE, image-enhanced endoscopy; NBI, narrow band imaging; RDI, red dichromatic imaging; TXI, texture and color enhancement imaging.

endoscopic procedures under the supervision of an experienced mentor.

3.3.3 | (Q) What Imaging Studies Are Necessary Before Performing POCS? (BQ)

- It is recommended to perform imaging studies such as computed tomography (CT), magnetic resonance cholangiopancreatography (MRCP), and ERCP to assess the overall anatomy of the biliary tract.

3.3.4 | (Q) Is Papillary Procedures Necessary for Performing POCS? (CQ)

- Papillary procedure is recommended when performing POCS. (Weak recommendation, evidence quality: C).

Comment: Papillary procedures are essential for therapeutic POCS aimed at bile duct stone removal. In contrast, it is not mandatory for diagnostic POCS, although it is commonly performed to facilitate cholangioscope insertion and prevent adverse events, such as pancreatitis or cholangitis due to papillary edema. Consequently, most reports assume papillary intervention when performing POCS, and no studies have compared outcomes with or without the procedure [6–25]. Arnelo et al. reported that out of 45 cases of POCS, endoscopic sphincterotomy (EST) was performed in 40 (89%), with post-procedural pancreatitis occurring in 4 (8.9%), three of which had no papillary procedure [17]. Papillary procedures include EST, endoscopic papillary balloon dilation (EPBD), and endoscopic papillary large balloon dilation (EPLBD). Nishikawa et al. noted that additional EPBD is required in 18% (6/33) of diagnostic POCS cases despite prior EST [13]. Minami et al. reported that among 90 therapeutic POCS cases, 65.6% (59/90) are treated with EST alone, while 34.4% (31/90) required EST plus EPLBD [24]. While EST is the standard, EPBD or EPLBD may be selected depending on patient factors or procedural needs. Recently, small-caliber cholangioscopes, including the slim scope with an outer diameter of 2.6 mm, have been developed. Thus, the necessity of papillary procedures should be tailored to the diameter of the cholangioscope.

3.3.5 | (Q) Is Withdrawal of Antithrombotic Agents Necessary Prior to POCS? (CQ)

- We propose that, in accordance with the [guidelines for gastroenterological endoscopy in patients undergoing antithrombotic treatment](#), diagnostic POCS, including observation and biopsy, be categorized as having a low-risk of bleeding, and that therapeutic interventions such as electronic hydraulic lithotripsy (EHL) or laser lithotripsy (LL) be categorized as having a high-risk of bleeding. (Weak recommendation, evidence quality: C).

Comment: The Japan Gastroenterological Endoscopy Society (JGES) guidelines for patients undergoing antithrombotic

treatment [26] did not mention a bleeding risk classification for POCS. However, the European Society of Gastrointestinal Endoscopy (ESGE) guidelines [27, 28] classify POCS as a low-risk procedure, stating that aspirin or other antithrombotic agents need not be discontinued, warfarin may be continued if PT-INR is within the therapeutic range, but direct oral anticoagulants (DOACs) should be withheld on the morning of the procedure. Although POCS-guided biopsy is not directly addressed, previous prospective studies report overall adverse event rates of 1.7%–13.9% [8, 13, 14, 19, 20, 29–33], with cholangitis and pancreatitis being the most common, and bleeding being infrequent (0%–2.5%). In a study involving antithrombotic withdrawal [32], biopsy, performed in 72.4% of 290 patients, had a 1.7% rate of adverse events, which included three cases of cholangitis, one of pancreatitis, and one of bleeding. In another study without withdrawal [30], biopsy was performed in 80.8% of 52 patients with a 3.8% adverse event rate. No increased bleeding risk was observed regardless of antithrombotic withdrawal.

The cup diameter of the biopsy forceps used during POCS was smaller than that of standard forceps used in conventional endoscopy. Therefore, similar to conventional endoscopic observation, POCS-guided biopsy is considered a low-risk procedure for bleeding.

In contrast, therapeutic procedures such as EHL or LL are classified as high-risk due to potential bleeding-related difficulty or serious adverse events like perforation [33, 34]. It should be noted that EST, which is frequently performed to facilitate POCS, is classified as a high-risk procedure for bleeding in the JGES guidelines [26]. Therefore, antithrombotic management should adhere to the relevant recommendations in these guidelines (Table 3).

3.3.6 | (Q) Is Antibiotic Administration Necessary Before and/or After POCS? (CQ)

- Administration of prophylactic antibiotics is suggested for patients undergoing POCS. (Weak recommendation, evidence quality: D)

Comment: Cholangitis occurs more frequently after POCS than conventional ERCP, with reported rates ranging from 0% to 15.8% (Table 4) [20, 24, 35–40]. The primary cause is believed to be increased biliary pressure due to saline irrigation during the procedure¹. Although no studies directly examine antibiotics and cholangitis as outcomes, one study found significantly lower rates in those who received prophylactic antibiotics (1.0% vs. 12.8%, $p < 0.001$) [38]. Bacteremia occurred in 8.8% of patients without antibiotics³, with higher rates following biopsy (28.5% vs. 4.6%, $p = 0.014$) [36]. In liver transplant recipients, cholangitis occurred in 3.8% despite antibiotic use, but 69.6% had positive bile cultures [37]. A study comparing pre-/post-procedure antibiotics with post-only use showed lower cholangitis rates in the former (4.6% vs. 11.5%, $p = 0.09$) [24]. According to ESGE, the use of antibiotics prophylaxis against gram-negative bacteria is recommended as prophylaxis before ERCP when incomplete biliary drainage is anticipated, in severely immunocompromised patients, and when performing cholangioscopy [27]. While

high-quality evidence is lacking, pre-procedural antibiotic use appears beneficial.

3.3.7 | (Q) What Are the Methods for Securing the Visual Field During Biliary Assessment in POCS? (BQ)

- Although both saline irrigation and CO₂ insufflation are available methods, saline irrigation is generally the standard approach used in clinical practice.

3.3.8 | (Q) What Precautions Should be Taken During the POCS Procedure? (BQ)

- Endoscopists should take precautions against adverse events such as perforation and increased intraductal pressure.

3.3.9 | (Q) What Are the POCS Findings Suggestive of Malignancy? (BQ)

- POCS findings suggestive of malignancy include papillary or nodular elevations, mucosal friability, and irregularly dilated or tortuous vessels.

3.3.10 | (Q) What Are the Characteristics of POCS-Guided Biopsy? (In Comparison With Fluoroscopy-Guided Biopsy) (BQ)

- POCS-guided biopsy is characterized by the ability to perform targeted sampling under direct visualization, although the specimen volume is smaller compared to that of fluoroscopy-guided biopsy.

3.4 | Management Approach in Special Cases

3.4.1 | (Q) Is POCS Feasible in Patients With Surgically Altered Gastrointestinal Anatomy? (FRQ)

- POCS is feasible in patients with surgically altered anatomy, and the choice of scope should be adapted according to the type of reconstruction.

3.4.2 | (Q) Is POCS Feasible via the Endosonographically/EUS-Guided Created Route (ESCR)? (FRQ)

- POCS can be performed via ESCR, and in institutions with sufficient expertise, it may serve as an alternative in cases where ERCP is difficult or not feasible.

3.4.3 | (Q) Is Cholangioscopy Feasible via the Percutaneous Route? (BQ)

- Cholangioscopy via the percutaneous route is feasible; however, there are currently no commercially available devices specifically designed for this approach.

3.5 | Adverse Events

3.5.1 | (Q) What Are the Adverse Events Associated With POCS? (BQ)

- The reported incidence of early adverse events ranges from 0% to 25.4%, including bleeding, perforation, pancreatitis, cholangitis, and air embolism.

3.5.2 | (Q) Is the Incidence of Adverse Events Higher With POCS Compared to ERCP? (CQ)

- Although there is no significant difference in the incidence of adverse events between POCS and ERCP, adverse events specific to POCS should be taken into consideration. (No recommendation, evidence quality: D)

Comment: POCS is generally performed after papillary procedures such as ERCP, EPBD, or EST, and is indicated for difficult bile duct stones and indeterminate strictures. Therefore, it is difficult to accurately compare the incidence of adverse events between POCS alone and ERCP while excluding the influence of the preceding papillary interventions. Furthermore, due to heterogeneity in study designs, evaluation criteria, and definitions of adverse events, a clear recommendation could not be provided.

As reported, the overall early adverse event rate of POCS ranges from 0% to 25%, with a pooled estimate of 7% (95% CI: 6%–9%) [41]. The most common events include cholangitis (4%) [8], pancreatitis (2%) [8], and perforation (1%) [42], which differ in nature from those typically seen with ERCP [43–46]. The low rate of severe pancreatitis in POCS may be attributed to the preceding papillary procedures.

Five RCTs comparing POCS and ERCP have shown no significant differences in adverse event rates between the two techniques, although two cases of perforation were reported in the POCS groups [20, 47–50]. A meta-analysis of 19 RCTs, including three of the above five, focused on lithotripsy procedures, demonstrating that POCS does not increase the risk of adverse events compared to EPBD, EST, EPLBD, or mechanical lithotripsy [51].

While overall safety appears comparable, several adverse events specific to POCS have been reported. These include bile leakage during EHL, bile duct perforation with LL, and increased risks of bacteremia or liver abscess when POCS is performed in cases of biliary strictures [10, 33, 36, 52–56]. One prospective study

TABLE 4 | Summary of studies on antibiotic administration and cholangitis incidence in POCs.

Author (ref.)	Year	Study design	No. of cases (procedures)	Purpose (n)	Antibiotic use (timing)	Cholangitis rate
Sethi et al. [35]	2011	Retrospective	402	Diagnostic: 318 Therapeutic: 84	Yes (before procedure)	1.0% (4/402)
Othman et al. [36]	2016	Prospective	57	Diagnostic: 25 Therapeutic: 32	No	7.0% (4/57)
Hüsing-Kabar et al. [37]	2017	Prospective	26	Therapeutic: 26 (liver transplant)	Yes (before to 3 days after)	3.8% (1/26)
Turowski et al. [38]	2018	Retrospective	206 (250 ^a)	Diagnostic: 78 (94 ^a) Therapeutic: 128 (156 ^a)	Yes: n = 102 (before) No: n = 148	Yes: 1.0% (1/102) No: 12.8% (19/148) ($p < 0.001$)
Ang & Kwek [39]	2019	Retrospective	47	Diagnostic: 18 Therapeutic: 29	Yes (during to 3 days after)	10.6% (5/47)
Gerges et al. [20]	2020	Prospective	31	Diagnostic: 31	Yes (before procedure)	0%
Minami et al. [24]	2021	Retrospective	183	Diagnostic: 93 Therapeutic: 90	Yes: Before & after: n = 87 After only: n = 96	Overall: 8.2% (15/183) Before & after: 4.6% (4/87) After only: 11.5% (11/96) ($p = 0.09$)
Yu et al. [27]	2022	Retrospective	19	Diagnostic: 19 (liver transplant)	Yes (before to 3 days after)	15.8% (3/19)

Abbreviation: POCs, peroral cholangioscopes.

^aNumbers in parentheses indicate the number of procedures.

found a significantly higher rate of post-procedural bacteremia when biopsies were performed during POCS in stricture cases (28.5% vs. 4.6%, $p = 0.014$) [36].

Several cases of air embolism have been reported in studies where thin upper gastrointestinal endoscopes—originally designed for transnasal use—were inserted into the bile duct, using balloon catheter as anchoring techniques [57–59]. With ERCP, perforation may occur at less common sites, such as the extrahepatic bile duct or gallbladder. These adverse events have been reported in association with LL or elevated perfusion pressure [27, 60–61]. During the procedure, fluoroscopic imaging should be performed as needed, to monitor for the presence of free air [34].

In summary, although the overall adverse event rates of POCS and ERCP appear to be comparable, unique adverse events specific to POCS do exist. Therefore, caution is warranted in high-risk situations, such as when managing biliary strictures or performing lithotripsy using energy-based devices.

3.5.3 | (Q) Is Biliary Drainage Necessary After POCS to Prevent Cholangitis? (CQ)

- Biliary drainage after cholangioscopy is suggested in cases of impaired bile outflow, such as residual bile duct stones or biliary strictures. (Weak recommendation, evidence quality: D)

Comment: POCS can increase intraluminal pressure of the biliary tract due to irrigation, potentially leading to higher post-procedural cholangitis rates compared to ERCP [35, 62]. Although prophylactic antibiotics are recommended [38], evidence supporting routine biliary drainage after POCS remains limited [20, 33, 38, 41, 63]. Drainage may not be necessary in all cases but is advisable when biliary obstruction is present, such as with residual stones, strictures, or papillary edema [41, 48, 49, 64].

3.5.4 | (Q) How Should Post-POCS Cholangitis be Diagnosed and Managed? (CQ)

- Post-POCS cholangitis should be diagnosed and graded in accordance with the American Society for Gastrointestinal Endoscopy (ASGE) lexicon (2010) and Tokyo Guidelines 2018. In cases of post-POCS cholangitis, appropriate treatment, including biliary drainage, is suggested. (Weak recommendation, evidence quality: C)

Comment: Post-POCS cholangitis is commonly diagnosed and graded using the criteria for post-ERCP cholangitis [38, 49, 50, 65]. The ASGE lexicon (2010) [46] defines cholangitis as a new-onset fever $> 38^{\circ}\text{C}$ lasting > 24 h with cholestasis. Severity is assessed per Tokyo Guidelines 2018 [45]. POCS may increase biliary pressure due to irrigation, contributing to cholangitis through bacterial overgrowth, pressure elevation, and cholangiovenous reflux [45]. Prevention includes antibiotic prophylaxis, avoiding excessive irrigation, and ensuring adequate drainage when biliary obstruction is suspected [33, 48, 66].

3.5.5 | (Q) How Should Suspected Perforation be Diagnosed and Managed? (CQ)

- When perforation is suspected, it must be confirmed by imaging studies, such as CT. If perforation is diagnosed, coordination with surgical teams is essential, and biliary drainage or surgical intervention should be considered. (Strong recommendation, evidence quality: D)

Comment: POCS is associated with various adverse events, among which, perforation—including both biliary and duodenal perforations—requires particular attention due to the risk of life-threatening adverse events, such as bile leakage and peritonitis. The reported incidence is generally $< 5\%$ [24, 33, 67–72]. Perforation may result from elevated biliary pressure (e.g., gallbladder perforation) [34, 67, 73], stone removal under cholangioscopic guidance [33, 67], or endoscopic instrumentation causing injury to the bile duct or duodenum [24, 69, 71]. Some cases are only identified post-procedurally on imaging. Fluoroscopic monitoring during POCS is important, and if perforation is suspected, immediate CT should be performed. Minor perforations near the papilla or within the bile duct can often be managed conservatively with biliary drainage and nasogastric decompression [33, 69–70]. In contrast, duodenal or gallbladder perforations, or large defects, may require surgical intervention [34, 67, 69]. Early diagnosis and close collaboration with surgical teams are essential.

3.6 | Diagnostic and Therapeutic Outcomes

3.6.1 | (Q) Is POCS Useful for Differentiating Between Benign and Malignant Biliary Strictures? (CQ)

- POCS and POCS-guided biopsy are useful diagnostic tools for evaluating biliary strictures of indeterminate malignant potential. (Weak recommendation, evidence quality: B)

Comment: Although various imaging modalities such as ultrasound, CT, MRCP, EUS, and ERCP are used to evaluate biliary lesions, differentiating benign from malignant strictures can be difficult. POCS allows direct visualization of the biliary mucosa and is positioned as a third-step diagnostic tool for cholangiocarcinoma [74]. Reported diagnostic sensitivity ranges from 67% to 100% for POCS alone and 38%–100% when combined with POCS-guided biopsy [75, 76]. Japanese studies have shown high diagnostic accuracy [6, 14, 77]. Therefore, POCS and POCS-guided biopsy are considered useful for diagnosing indeterminate biliary strictures.

3.6.2 | (Q) Is POCS Effective for Assessing the Extent of Biliary Tumors? (CQ)

- POCS is effective in evaluating the extent of papillary and nodular-expanding types of cholangiocarcinoma, including intraductal papillary neoplasms of the bile duct. (Weak recommendation, evidence quality: B)

Comment: POCS is positioned as a third-step modality in cholangiocarcinoma diagnosis [74] and is particularly effective in assessing horizontal tumor spread, especially in papillary and

nodular-expanding types, including intraductal papillary neoplasms [78, 79]. Such spread often exceeds 2 cm and is difficult to evaluate by CT, magnetic resonance cholangiopancreatography (MRCP), or EUS/intraductal ultrasound (IDUS). POCS enables direct visualization and targeted biopsy of the biliary epithelium [1]. The diagnostic accuracy for lateral tumor extension improves from 69.8% to 88% with POCS alone to 86.7%–100% when combined with POCS-guided biopsy [13, 14, 80–83].

3.6.3 | (Q) Is POCS-Guided Lithotripsy Effective for the Treatment of Difficult Common Bile Duct (CBD) Stones? (CQ)

- POCS-guided lithotripsy is considered effective for the management of difficult CBD stones. (Weak recommendation, evidence quality: B)

Comment: POCS-guided lithotripsy has shown efficacy for difficult CBD stones resistant to conventional extraction methods [62, 63]. Two meta-analyses reported stone clearance rates of 91%–94%, adverse event rates of 6.1%–8.9%, and an average of 1.3 sessions [62, 63]. A new meta-analysis of four RCTs (Table 5) [46–50] showed higher stone clearance with POCS (odds ratio [OR] 4.4, 95% CI: 1.16–16.84) and no significant increase in adverse events (OR 0.68, 95% CI: 0.25–1.83) (Figure 1). POCS is recommended particularly for stones with a diameter greater than that of the distal bile duct [50]. However, risks such as perforation must be considered, especially in patients with narrow ducts.

3.6.4 | (Q) Is POCS-Guided Lithotripsy Effective for Intrahepatic Stones? (CQ)

- POCS-guided lithotripsy may be considered as a treatment option for intrahepatic stones. (Weak recommendation, evidence quality: C)

Comment: With the widespread use of ERCP, per-oral endoscopic treatment has become standard for intrahepatic stones, replacing percutaneous transhepatic cholangioscopy (PTCS). Recent advances in POCS have made POCS-guided lithotripsy a potential option [84–87]. Four single-arm studies reported stone clearance rates of 57%–64% with conventional scopes and 94% with the newer four-way POCS (SpyGlass DS) [85]. No significant difference in adverse events was observed compared to traditional methods. POCS may be especially effective in impacted stones or stones upstream of strictures. However, long-term follow-up is essential due to the risks of recurrence, hepatic atrophy, or cholangiocarcinoma [84, 86–87].

3.6.5 | (Q) Is There a Difference in Clinical Outcomes Between EHL and LL in POCS-Guided Stone Fragmentation? (CQ)

- In POCS-guided lithotripsy for difficult bile duct stones, no significant difference in stone clearance rates has been reported between EHL and LL. (No recommendation, evidence quality: D)

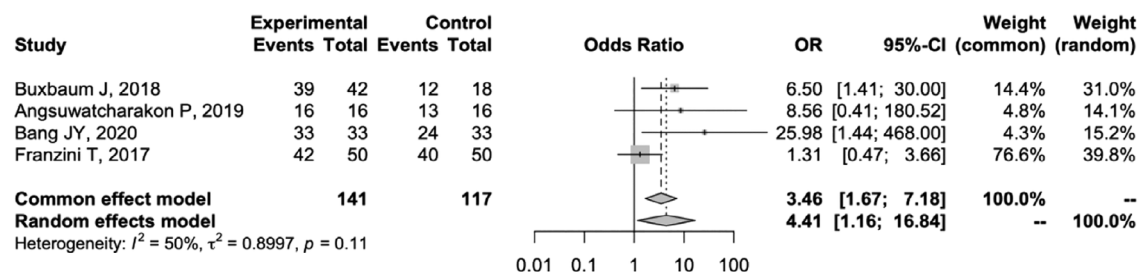
TABLE 5 | Summary of RCTs comparing POCS-guided lithotripsy with conventional stone extraction methods for difficult CBD stones.

Author	Year	RCT type	Patients (n)	POCS group (n)	Control group (n)	Stone extraction method in control group	Stone clearance rate (%)	Adverse event rate (%)	Significant difference in clearance	Significant difference in adverse events
Franzini et al. [47]	2017	Multicenter	100	50	50	Basket + Balloon	82% vs. 80%	4% vs. 12%	No	No
Buxbaum et al. [48]	2018	Single center	60	42	18	Basket + Balloon	93% vs. 67%	10% vs. 11%	Yes ^a	No
Angsuwatcharakon et al. [49]	2019	Multicenter	32	16	16	Mechanical lithotripter + Basket	100% vs. 81%	13% vs. 6%	No ^a	No
Bang et al. [50]	2020	Single center	66	33	33	Basket + Balloon	100% vs. 73%	9% vs. 3%	Yes	No

Abbreviations: CBD, common bile duct; POCS, peroral cholangioscopy; RCT, randomized controlled trial.

^aYes indicates statistical significance at $p < 0.05$.

a) Stone clearance rate



b) Adverse event rate

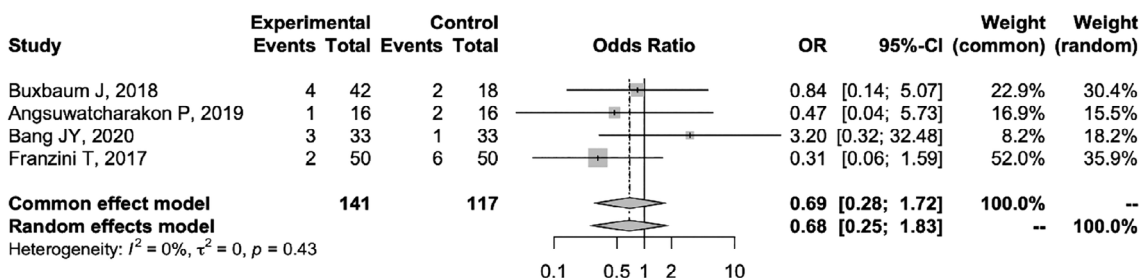


FIGURE 1 | Meta-analysis of four RCTs evaluating the efficacy of POCS-guided lithotripsy. (a) stone clearance rate, (b) adverse event rate.

Comment: In POCS-guided treatment of bile duct stones, reported stone clearance rates range from 76% to 100% for EHL and 82%–100% for LL, with adverse event rates of 3%–22% and 2%–18%, respectively [33, 38, 42, 48, 50, 53, 54, 65, 88–98]. A multicenter retrospective study found no significant difference in clearance rates but showed longer procedure times with EHL [33]. A recent systematic review reported better efficacy and safety for LL [99], though based on single-arm studies. Ho-YAG lasers, now preferred over Nd-YAG, are safer due to shallow tissue penetration but may still cause perforation [33, 50]. EHL delivers shock waves via water-mediated discharge, effective for fragmentation but associated with bile leakage [33, 54].

However, as most studies are retrospective or single-arm in nature, and no large-scale RCTs have been conducted to directly compare EHL with LL, the current evidence is insufficient to support a clear recommendation.

3.6.6 | (Q) What Is the Recurrence Rate and Management of Bile Duct Stones After POCS-Guided Lithotripsy? (BQ)

- The reported recurrence rate ranges from 0% to 25%. Treatment options for recurrent stones include transpapillary endoscopic therapy, extracorporeal shock wave lithotripsy (ESWL), and PTCS-guided intervention.

Author Contributions

Kazumasa Nagai and **Takao Itoi**: conception and design. **Kazumasa Nagai**, **Akio Katanuma**, **Shomei Ryozaawa**, **Yoshinobu Okabe**, **Naoki Okano**, **Hiroki Kawashima**, **Hironari Kato**, and **Nobuhiko Hayashi**: analysis and interpretation of the data. **Kazumasa Nagai**, **Akio Katanuma**, **Shomei Ryozaawa**, **Yoshinobu Okabe**, **Naoki Okano**, **Hiroki**

Kawashima, **Hiroshi Kawakami**, **Hironari Kato**, and **Nobuhiko Hayashi**: drafting of the article. **Takao Itoi**, **Atsushi Irisawa**, **Etsuro Hatano**, **Ichiro Yasuda**, **Yoshinori Igarashi**: critical revision of the article for important intellectual content. All authors have read and approved the submitted version of the paper.

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Ethics Statement

The authors have nothing to report.

Conflicts of Interest

Takao Itoi has received lecture fees from Olympus and Boston Scientific. Akio Katanuma has received lecture fees from Olympus.

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Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1:** jhbp70036-sup-0001-Supinfo.docx.