

Per oral cholangiopancreatography in pancreatic biliary diseases - Expert consensus statements

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Data sharing: No original data was used or reported in this paper. Only previously published data were reported in this consensus statement paper. No consent was obtained as no original data has been collected in preparation of this paper.

Conflict-of-interest: None of the authors have a conflict of interest as it pertains to this paper.

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Received: July 18, 2014

Peer-review started: July 18, 2014

First decision: October 14, 2014

Revised: November 19, 2014

Accepted: January 21, 2015

Article in press: January 21, 2015

Published online: April 21, 2015

Abstract

AIM: To provide consensus statements on the use of per-oral cholangiopancreatography (POCPS).

METHODS: A workgroup of experts in endoscopic retrograde cholangiopancreatography (ERCP), endosonography, and POCPS generated consensus statements summarizing the utility of POCPS in pancreaticobiliary disease. Recommendation grades used validated evidence ratings of publications from an extensive literature review.

RESULTS: Six consensus statements were generated: (1) POCPS is now an important additional tool during ERCP; (2) in patients with indeterminate biliary strictures, POCPS and POCPS-guided targeted biopsy are useful for establishing a definitive diagnosis; (3) POCPS and POCPS-guided lithotripsy are recommended for treatment of difficult common bile duct stones when standard techniques fail; (4) in patients with main duct intraductal papillary mucinous neoplasms (IPMN) POCPS may be used to assess extent of tumor to assist surgical

resection; (5) in difficult pancreatic ductal stones, POPS-guided lithotripsy may be useful in fragmentation and extraction of stones; and (6) additional indications for POCPS include selective guidewire placement, unexplained hemobilia, assessing intraductal biliary ablation therapy, and extracting migrated stents.

CONCLUSION: POCPS is important in association with ERCP, particularly for diagnosis of indeterminate biliary strictures and for intra-ductal lithotripsy when other techniques failed, and may be useful for pre-operative assessment of extent of main duct IPMN, for extraction of difficult pancreatic stones, and for unusual indications involving selective guidewire placement, assessing unexplained hemobilia or intraductal biliary ablation therapy, and extracting migrated stents.

Key words: Per oral cholangiopancreatography; Intraductal lithotripsy; Indeterminate biliary strictures; Cholangioscopy; Pancreatocopy

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Core tip: Per-oral cholangiopancreatography (POCPS) is now an important additional tool during endoscopic retrograde cholangiopancreatography. In patients with indeterminate biliary strictures, peroral cholangioscopy (POCS) and POCPS-guided targeted biopsy are useful for establishing a definitive diagnosis. POCS and POCPS-guided lithotripsy are recommended for treatment of difficult common bile duct stones when standard techniques fail. In patients with main duct intraductal papillary mucinous neoplasms POPS may be used to assess extent of tumor to assist surgical resection. In difficult pancreatic ductal stones, POPS-guided lithotripsy may be useful in fragmentation and extraction of stones. Additional indications for POCPS include selective guidewire placement, unexplained hemobilia, assessing intraductal biliary ablation therapy, and extracting migrated stents.

Ramchandani M, Reddy DN, Lakhtakia S, Tandan M, Maydeo A, Chandrashekhara TS, Kumar A, Sud R, Rerknimitr R, Makmun D, Khor C. Per oral cholangiopancreatography in pancreatic biliary diseases - Expert consensus statements. *World J Gastroenterol* 2015; 21(15): 4722-4734 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v21/i15/4722.htm> DOI: <http://dx.doi.org/10.3748/wjg.v21.i15.4722>

INTRODUCTION

Pancreatobiliary diseases are commonly encountered in day to day clinical practice. Endoscopic retrograde cholangiopancreatography (ERCP) and magnetic resonance cholangiopancreatography (MRCP) are performed to further delineate the pancreatobiliary anatomy and establish a diagnosis in these patients.

But these imaging modalities have limitation in that they are often only suggestive but not diagnostic of the disease. Per-oral cholangio-pancreatography (POCPS) was introduced in 1970. It provides direct visualization of the biliopancreatic system and thus offers the possibility for accurate diagnoses. POCPS may also effectively guide interventions. With new developments in cholangioscopic systems including high resolution video-cholangioscopes, incorporation of narrow band imaging and availability of a single operator cholangiopancreatocopy there is renewed interest among endoscopists to perform POCPS more routinely.

There are no established guidelines about the utility of POCPS including relatively new technologies. This review provides consensus statements by experts about indications for POCPS based on available literature.

MATERIALS AND METHODS

A modified Delphi process was performed to establish the consensus. The procedure was based on combination of the principles of evidence-based medicine through extensive review of literature, face to face meeting and voting. A planning group panel (DNR, MR, SL, MT) made a list of statements which was sent to all consensus members. The statements were divided into the topics of indications of POCPS including diagnostic and therapeutic uses of POCPS. These statements were proposed to the Consensus Group panel for discussion, revision, and voting. A password- secured Web site was populated with relevant literature assembled by the literature review team (DNR and MR). A comprehensive literature search was conducted in the Medline/PubMed and EMBASE databases.

RESULTS

Both databases were searched for 16 search terms: Direct endoscopic cholangioscopy, Duodenoscope assisted cholangioscopy, Peroral cholangioscopy, Cholangioscopy tissue sampling, Cholangioscopy endoscopic biopsy, Direct pancreatocopy, Pancreatocopy, Cholangioscopy biliary stone, Cholangioscopy lithotripsy, Spyglass, SpyScope, SpyBite, Direct visualization biliary, Direct visualization pancreatic, Digital cholangioscopy, and Digital pancreatocopy.

Only articles published in English were included. One article was a methodologic publication^[1]. Excluded were articles representing interim reports, *in vitro* studies or animal studies, and editorials and letters. A total of 92 articles were retrieved per this search, out of which 18 were selected for review. Seventy-four (74) articles were excluded because they were not relevant to search objectives (36), articles reporting on less than 10 patients (34), or review articles without original data (4). A few exceptions of articles reporting on less than 10 patients were included in cases in

Table 1 Detailed evidence levels of respective references are provided for each consensus statement

Consensus statement	Evidence level distribution								Recommendation grade
	1++	1+	1-	2++	2+	2-	3	4	
1	0	0	0	1	8	1	7	16	B
2	0	0	0	4	15	1	7	9	B
3	0	1	0	1	13	1	5	10	A
4	0	0	0	0	3	2	3	11	C
5	0	0	0	0	2	1	1	7	C
6	0	0	0	0	4	0	3	8	C

which such articles represent the only original data on specific indications (5). The references of the 18 selected publications were then considered for the comprehensive literature review. Ultimately, 91 peer-reviewed journal articles were retained^[2-92].

Each article was given an evidence level rating using the GRADE scoring system^[1] ranging from 1++ to 4. In some cases the evidence level of an article was the same for all consensus statements it supports, but in many cases the evidence level was different for different consensus statements. Reference numbers and quality of evidence are provided for all consensus statements separately. Quality of evidence reflects the highest evidence level of applicable references. Detailed evidence levels of respective references are provided for each consensus statement in Table 1 below. The low number of evidence level 1 publications clearly results in a limitation of the current report.

Face-to-face meeting of the consensus group was held at Asian Institute of Gastroenterology, Hyderabad, India to review and discuss the evidence for all statements. All statements were edited and final approval was obtained from consensus panel. Consensus was considered to be achieved when 80% or above of members either voted "accept completely" or "accept with some reservation". A statement was dropped if when 80% or above of voting members indicated "reject completely" or "reject with some reservation". Every accepted statement was then graded to indicate the level of evidence available and the strength of recommendation. A "reference map" was created, listing all retained references and mapping them to the consensus statements for which they served as a reference. For each consensus statement separately, an overall grade of recommendation was attributed using the GRADE scoring system^[1] ranging from A to D. This recommendation grade relates to the strength of the evidence on which the recommendation is based and does not reflect clinical significance of the consensus statement.

The following consensus statements were identified by the workgroup: (1) POCPS is now an important additional tool during ERCP; (2) in patients with indeterminate biliary strictures, peroral cholangioscopy (POCS) and POCS-guided targeted biopsy is useful

Table 2 Consensus statement 1

POCPS is now an important additional tool during ERCP
 Recommendation Grade B
 Quality of evidence: 2++
 Direct visualization and the ability to sample and treat lesions aids in the care of patients by providing the correct diagnosis and allowing definitive treatment of lesions
 Cholangiopancreatography through an ERCP catheter is a simple, safe and effective procedure for diagnosing pancreatobiliary diseases
 Intraductal peroral cholangioscopy and pancreatoscopy-sampling techniques appear to offer an advantage over fluoscopy-guided ERCP sampling techniques for the diagnosis of pancreatobiliary lesions

POCPS: Peroral cholangiopancreatography; ERCP: Endoscopic retrograde cholangiopancreatography.

for establishing a definitive diagnosis; (3) POCS and POCS-guided lithotripsy is recommended for treatment of difficult common bile duct (CBD) stones when standard techniques fail; (4) in patients with main duct intraductal papillary mucinous neoplasms (IPMN) peroral pancreatoscopy (POPS) may be used to assess the extent of tumor to assist surgical resection; (5) in difficult pancreatic ductal stones, POPS-guided lithotripsy may be useful in fragmentation and extraction of stones; and (6) additional indications for POCPS include selective guidewire placement, unexplained hemobilia, assessing intraductal biliary ablation therapy, and extraction of migrated stents.

Consensus statement 1

Table 2 provides a capsule summary of the first consensus statement, namely that POCPS is now an important additional tool during ERCP.

When ERCP was introduced in 1970 followed by endoscopic sphincterotomy in 1974, there was a quantum advance in the diagnosis and treatment of pancreatobiliary disorders. However, in some instances direct endoscopic visualization of the biliary and pancreatic ducts may be needed to evaluate equivocal fluoroscopic findings during ERCP, for definitive pathologic diagnosis or to provide therapeutic interventions and cholangiopancreatography provides that direct visualization^[2-8]. A comprehensive technology status evaluation was reported by the American Society of Gastrointestinal Endoscopy in 2008^[4].

Cholangioscopy was first used in clinical medicine and described in the literature in the mid-1970s using fiber optics and was later advanced into video imaging as described in several review articles^[2,8-11]. Clinical implementation of cholangiopancreatography for direct visualization and examination of the bile ducts, pancreatic ducts, tissue sampling and therapeutic intervention has been slow due to limitations in the available technology. Recent advancements in the technology hold promise as an advanced technique for cases that elude successful diagnosis or treatment by conventional ERCP or other imaging modalities^[8,12,13]. POCPS can be performed as a relatively safe and

Table 3 Consensus statement 2

<p>In patients with indeterminate biliary strictures, POCS and POCS-guided targeted biopsy is useful for establishing a definitive diagnosis</p> <p>Recommendation Grade B</p> <p>Quality of evidence: 2++</p> <p>Technical success: Technical success for POCS with or without POCS-guided biopsy is reported to be 66% to 95% when defined as ability to reach the targeted lesion and, if desired, obtain a biopsy adequate for histopathology</p> <p>Diagnostic accuracy: Diagnostic measures of POCS with or without POCS-guided biopsy for malignancy were explicitly reported for a total of 980 cases in 11 studies. Reported sensitivity ranged from 49% to 100% and specificity ranged from 77% to 100%. In three prospective trials reporting separately on POCS alone and on POCS-guided biopsy and representing 297 patients, the weighted average sensitivity and specificity were 83% and 96% for POCS alone and were lower at 56% and 81% for POCS-guided biopsy</p> <p>Intrinsic <i>vs</i> extrinsic strictures: POCS-guided biopsy is significantly higher for intrinsic than extrinsic tumors, and may be particularly useful in PSC patients prior to liver transplantation</p> <p>POCS findings in indeterminate strictures: Findings of POCS such as tortuous and irregularly dilated vessels, intraductal nodules or masses, infiltrative or ulcerated strictures, and papillary or villous mucosal projections are reported to be associated with malignancy. Generally POCS is reported to improve yield of associated ERCP-guided biopsy. POCS with NBI was reported to significantly improve diagnostic accuracy over white light POCS</p> <p>Altered patient management: Changed patient management following POCS is reported in as many as 2/3 of patients when measured. Impact of POCS on pre-operative diagnosis may impact a surgical decision. POCS combined with IDUS was reported useful in guiding patient management in portal biliopathy. POCS was also reported useful for assessment of anastomotic strictures after liver transplantation</p> <p>Complications: Reported overall complication rates range from 6.6% to 9%. The most common complication is cholangitis, reported in approximately 5% of cases. There is one report of fatal cholangitis</p>
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POCS: Peroral cholangioscopy; PSC: Primary sclerosing cholangitis; ERCP: Endoscopic retrograde cholangiopancreatography; NBI: Narrow band imaging; IDUS: Intraductal ultrasonography.

efficacious adjunct by those individuals with expertise in ERCP^[13] and has the advantages of direct visualization of the strictures or filling defects noted on fluoroscopy and inspection of the biliary epithelium for subtle abnormalities that might not be detected radiographically^[14]. Interpretation of stent-associated changes to the biliary epithelium may be difficult. The technology will not replace ERCP, but has been shown to improve the diagnostic accuracy of ERCP for biliary lesions and to improve bile duct clearance rates in cases of bile duct stones not amenable to conventional endoscopic therapy^[15-17]. POCPS and ERCP are complementary procedures and reports of the impact on the rate of complications for ERCP with POCPS compared to ERCP alone are inconsistent^[18-20]. POCPS has been assuming an increasingly important role in the diagnosis of various bile duct lesions, as well as the treatment of biliary stones^[9].

The single operator cholangioscopy system has proven to be a versatile diagnostic tool that can be applied in the various situations faced in an endoscopic practice^[7,21]. This technology has utility when imaging limitations of conventional ERCP are encountered^[22]. The primary indication for diagnostic intraductal endoscopy in the biliary tree is to evaluate strictures seen on abnormal imaging study or prior ERCP^[23]. POCPS allows direct visualization of any ductal abnormalities with the ability to sample by focused biopsies and treat with lithotripsy, which significantly aids in the care of patients^[23-25]. The significant technologic improvements in the design, optical resolution and maneuverability of the miniature endoscope, and cholangioscopy has assumed an increasingly important role in the diagnosis of various bile-duct lesions^[26]. The addition of direct endoscopic visualization of the bile duct to ERC/tissue sampling

may help to diagnose the cause of a bile-duct stricture and a filling defect and to increase sensitivity and accuracy^[26,27]. One POCPS system, the SpyGlass system, is reported^[28] to be the first in the area of ERCP that integrates visualization into a dedicated cannulation device instead of a device being entirely dedicated to a particular endoscope. There are however, some limitations in the current literature comparing POCPS to ERCP and a lack of randomized trials of tissue sampling techniques.

Pancreatocopy is of diagnostic value in addition to CT, transabdominal ultrasound and ERCP in the differential diagnosis of poorly defined pancreatic lesions^[29]. The technology is seen as especially useful in the differential diagnosis of cancer^[30].

Direct visualization of the bile duct lumen using endoscopic techniques is helpful in for the assessment of fine mucosal changes^[31]. A retrospective review of 30 patients with malignant extrahepatic cholangiocarcinoma, all of whom has no diagnosis established by conventional endoscopic modalities; SpyGlass-directed biopsies had the ability to make a tissue diagnosis in 77% of cases. The results suggest that single-operator SpyGlass (Boston Scientific) cholangioscopy with biopsies might be the appropriate strategy for patients in whom cholangiocarcinoma is suspected, but in whom the initial ERCP with brush cytology followed by endosonography (EUS)-FNA was nondiagnostic or negative^[32].

Single-operator cholangiopancreatocopy through an ERCP catheter is a simple, safe and effective procedure for diagnosing pancreatobiliary diseases^[33]. Intraductal peroral cholangioscopy and pancreatocopy-sampling techniques appear to offer an advantage over fluoroscopy-guided ERCP sampling techniques for the diagnosis of pancreatobiliary lesions^[34]. As technology progresses,

Table 4 Summary of diagnostic accuracy parameters reported in relevant references

Ref.	Grading	Article type	Sensitivity	Specificity	Positive predictive value	Negative predictive value
[34]	4	Review	92%	93%	89%	95%
[12]	2+	Prospective	78%	82%	49%	98%
[13]	2+	Prospective	95%	79%	82%	82%
[21]	2++	Prospective	100%	77%	71%	100%
[35]	2+	Prospective	NR	NR	88%	94%
[14]	2+	Prospective	NR	NR	89%	96%
[15]	4	Retrospective	66%	98%	NR	NR
[26]	2+	Retrospective	98%	90%	NR	NR
[32]	2+	Retrospective	57%	100%	NR	NR
[36]	2+	Retrospective	77%	NR	NR	NR
[37]	2++	Prospective	99%	96%	99%	95.8%
[38]	2+	Prospective	NR	NR	100% visual 38% biopsy	92% visual 100% biopsy

NR: Not reported.

it is likely that the utilization of cholangioscopy will increase^[27].

Recommendation Grade: B. Quality of evidence: 2++.

Consensus statement 2

Table 3 provides a capsule summary of the second consensus statement, namely that POCS and POCS-guided targeted biopsy is useful for establishing a definitive diagnosis.

Technical success: Technical success is typically defined as ability to reach and visualize the targeted area and additionally, in cases of POCS-guided biopsy, ability to obtain biopsies adequate for histology. Explicitly reported technical success levels for POCS of indeterminate strictures or filling defects without biopsy^[21,24,26,31] were 83%, 85%, 93%, and 100%, and with biopsy^[21] was 87%. Overall procedural success in this indication in the largest prospective series^[21] was 89% (202/226) with 140 cases with and 86 cases without POCS-guided biopsy.

Recommendation Grade: B. Quality of evidence: 2++.

Diagnostic accuracy: A well-conducted review^[34] summarizes several studies on POCPS and reports mean POCS-guided tissue sampling to have 92% sensitivity, 93% specificity, 89% positive predictive value, and 95% negative predictive value for the diagnosis of malignancy. This is in line with diagnostic accuracy measures reported from four prospective studies^[12,13,21,35] all using the SpyGlass system, and reporting on respectively 226, 36, 35 and 52 cases in which POCS was used to assess indeterminate strictures with POCS-guided biopsy with one year of follow-up. Sensitivity and specificity of visual POCS impression only were 78% and 82%, 95% and 79%, and 100% and 77% respectively^[12,13,21]. Sensitivity and specificity of POCS-guided biopsy were 49% and 98%, 82% and 82%, 71% and 100% and 88% and

94%, respectively^[12,13,21,35]. In a prospective series of 62 cases^[14] using Olympus or Pentax cholangioscopes, sensitivity and specificity of POCS with or without biopsy were 89% and 96%. Several retrospective series^[15,26,32,36] on POCS in indeterminate strictures or filling defects respectively 130, 97, 89, and 30 cases were studied. Associated sensitivity and specificity of POCS with or without biopsies for diagnosis of malignancy were respectively 66% and 98%, 98% and 90%, 57% and 100%, and 77% and no reported specificity. A prospective study of 144 patients with peroral video cholangioscopy (PVCS)^[37] reported 99% sensitivity, 96% specificity, 99% positive predictive value, and 95.8% negative predictive value for the diagnosis of malignancy. Another prospective study of 33 patients^[38] reported the sensitivity and specificity, were 100% and 92%, for the PVCS visual findings and 38% and 100%, for the cholangioscopy-guided forceps biopsy findings. A prospective multicenter study of 87 patients in Japan^[39] with biliary tract diseases who underwent PVCS reported the accuracy rate of PVCS to evaluate the presence or absence of mucosal cancerous extension by endoscopic retrograde cholangiography (ERC) alone, ERC with PVCS, and ERC with PVCS+biopsy were 74%, 84%, and 93%, respectively. Table 4 provides a summary of diagnostic accuracy parameters reported in relevant references.

Recommendation Grade: B. Quality of evidence: 2++.

Intrinsic vs extrinsic strictures: The sensitivity of POCS alone and of POCS-guided biopsy in 45 patients with confirmed malignancy^[21] was respectively 84% and 66% for intrinsic lesions (32) and was respectively 62% and 8% for extrinsic lesions. A comprehensive review^[6] of POCPS also reported that intraductal tissue sampling in the hands of experienced endoscopists, increases diagnostic yield particularly in cholangiocarcinoma. A large retrospective series^[36] identified the need for a special handling protocol for small intraductal biopsies of intrinsic lesions. POCS was reported^[40-43] to be useful for assessing

Table 5 Consensus statement 3

<p>POCS and POCS-guided lithotripsy is recommended for treatment of difficult CBD stones when standard techniques fail Recommendation Grade A Quality of evidence: 1+ Technical success: Technical success for POCS and POCS-guided lithotripsy for the treatment of difficult CBD stones when standard techniques fail range from 71%-100% Direct visualization advantage: One of the key therapeutic benefits of POCS is the capacity to directly visualize and treat large intraductal stones. Studies show that nearly all bile duct stones which failed conventional endoscopic removal (5%-10% of patients) could be removed non-surgically using POCS and POCS-guided lithotripsy Residual stone detection: The diagnosis of small bile duct stones can be difficult with an ERCP. In those cases, POCS is able to detect residual stones missed on routine ERCP. Complications: The most common complication reported is cholangitis (4.0%). Reported overall complications rates range from 3.8% to 13.3% The results support the non-surgical management of difficult bile duct stones, particularly in patients at high risk for surgery</p>
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POCS: Peroral cholangioscopy; CBD: Common bile duct; ERCP: Endoscopic retrograde cholangiopancreatography.

inflammation and for excluding cancer in patients with primary sclerosing cholangitis (PSC) prior to liver transplantation. However, a recent study of 30 patients^[42] reported that despite an increase in the biopsy rate, an improvement in dysplasia detection in patients with PSC could not be demonstrated.

Recommendation Grade: B. Quality of evidence: 2++.

POCS findings in indeterminate strictures:

Several publications report on correlations between various POCS findings and relative risk for malignancy. Reported findings include tumor vessels stated to be irregularly dilated and tortuous^[8,13,34]. They also include intraductal nodules or masses, infiltrative or ulcerated strictures, and papillary or villous mucosal projections^[13,34]. On the other hand, smooth mucosa without neovascularization or homogenous granular mucosa without a mass seemed associated with benign conditions^[13]. Direct correlation between such findings and a firm diagnosis is not perfect, and is hampered by imperfect inter-observer agreement^[44].

One study specifically reported^[31] on POSC to assess the presence and extent of intraepithelial tumor spread prior to surgical resection. Correlations were discussed between nodular-type carcinoma, papillary-type carcinoma and POCS findings of irregular fine granular patterns and fish-egg-like patterns with small red nodules, while non-cancerous mucosa appeared as white flat normal mucosa and hyperplastic mucosa had a scale-like appearance. POCS-guided biopsy was attempted. Conclusions were that diagnostic accuracy of POCS-guided biopsy was higher than ERCP findings, but that the cholangioscope could not be passed through the tumor sites in approximately 15% of cases. One publication^[45] reported that the ability of POCS using narrow band imaging (NBI) to document surface structure was significantly better using conventional white light imaging. The study specifically reported improved visualization of vessels and improved ability to pre-operatively identify proximal and distal extent of cancerous lesions.

Recommendation Grade: C. Quality of evidence:

2+.

Altered patient management: A large prospective trial^[21] reported that diagnostic POCS was deemed by attending investigators to have altered patient management in 63% (143/226) of cases. In a retrospective review of POCS cases from four centers in Texas, authors reported^[23] that SpyGlass POCS modified a preoperative diagnosis of a malignant biliary stricture in 69% (20/29) cases, prevented unnecessary surgery in 7% (2/29) cases, and changed diagnosis from malignant to benign in 45% of patients with strictures. A case series of five patients^[46] with symptomatic portal biliopathy suggested utility of POCS for determining patient management. POCS also has potential utility in determining treatment of post liver transplantation anastomotic strictures^[47-53].

Recommendation Grade: B. Quality of evidence: 2++.

Complications: Overall complications were explicitly reported in three prospective studies^[12,13,21] at levels of 7.6% (17/226), 5.7% (2/35), and 8.4% (3/36), and in four retrospective series^[15,26,32,33] at 2.0% (2/97), 8.9% (16/179), 6.7% (2/30), and 13.3% (2/15). Thus the weighted mean overall complication rate was 7.1% (44/618).

The most common complication was cholangitis, explicitly reported^[12,13,15,26,32,33] in 5.7% (2/35), 5.6% (2/36), 5.0% (9/179), 2.0% (2/97), 0% (0/30), and 6.7% (1/15) of cases respectively, amounting to a mean incidence of cholangitis of 4.1% (16/392). One review^[54] reported that cholangitis, pancreatitis and perforation rates were higher in POCS than in ERCP alone.

Recommendation Grade: B. Quality of evidence: 2++.

Consensus statement 3

Table 5 provides a capsule summary of the third consensus statement, namely that POCS and POCS-guided lithotripsy is recommended for treatment of difficult CBD stones when standard techniques fail.

Table 6 Consensus statement 4

In patients with main duct IPMN POPS may be used to assess the extent of tumor to assist surgical resection
 Recommendation Grade C
 Quality of evidence: 2+

Technical success: Technical success for POPS in patients with IPMN is reported between 73% and 92% when defined as ability to reach and examine the targeted lesion

Diagnostic accuracy: Diagnostic measures of POPS with or without POPS-guided biopsy for malignancy in IPMN are rarely reported in detail, and range from 50% to 68% sensitivity and from 87% to 100% specificity. Diagnostic accuracy seems better in main duct IPMN than in side branch IPMN

POPS findings in IPMN: The most commonly reported POPS findings associated with malignancy in IPMN are villous patterns and vascular images

Granular mucosa and fish-like patterns without vascularity were not associated with malignancy

POPS and IDUS: Some studies document enhanced diagnostic accuracy when POPS is combined with endosonographic measures, particularly IDUS

Pre-operative and intra-operative POPS: The role of POPS to pre-operatively provide diagnostic information on malignancy and to pre-operatively and/or intra-operatively document the location and extent of dysplastic IPMN is generally reported

IPMN: Intraductal papillary mucinous neoplasms; POPS: Peroral pancreatoscopy; IDUS: Intraductal ultrasonography.

Technical success: Technical success for POCS and POCS-guided lithotripsy for the treatment of difficult CBD stones is defined as stone fragmentation and removal. POCS and POCS-guided lithotripsy for the treatment of difficult CBD stones when standard techniques fail, including ERCP stone extraction and mechanical lithotripsy, ranges from 71%-100%^[4,7,22,55-58]. Explicitly reported technical success levels for POCS and POCS-guided lithotripsy were 83.3%, 100%, 71.2%, 83.3%, 96.4%, 92.3%, 100%, 79.2%, 81%, 100%, 95%, 100%, 88.9%, 97% in prospective studies and case series^[7,12,21,59-69] and 90.2%, 90%, 73% in retrospective studies^[15,23,70]. Intra-hepatic stones appear to be managed mostly transhepatically and are not discussed in this paper.

Recommendation Grade: A. Quality of evidence: 1+.

Direct visualization advantage: One of the key therapeutic benefits of POCS is the capacity to directly visualize and treat large intraductal stones not removed at ERCP^[6,21]. Studies have shown that nearly all bile duct stones which failed conventional endoscopic removal (5%-10% of patients) could be removed non-surgically using POCS and POCS-guided lithotripsy^[21,27].

POCS has proven to be valuable in complicated choledocholithiasis, especially in guiding the positioning of an electrohydraulic lithotripsy (EHL) probe or laser fiber on the surface of stone^[2,12,21,65]. The direct visualization helped prevent injury during ERCP from an EHL probe positioning under fluoroscopy.

Recommendation Grade: B. Quality of evidence: 2++.

Residual stone detection: An additional advantage of POCS is successful identification of stones missed on ERCP^[58]. Stones can be clearly differentiated from filling defects because of soft-tissue masses and more readily discerned than during ERCP when associated with other biliary abnormalities such as strictures^[21]. In a prospective study, of 66 patients who underwent POCS-directed EHL or laser lithotripsy, 11% had 1 or more stones identified only by POCS but not by

ERCP^[21]. Other prospective studies identified additional stones *via* cholangioscopy not seen at ERCP in 18% (9/49), 28% (9/32) patients^[62,64]. Retrospective reviews of patients with altered GI anatomy^[71,72] reported 21% (4/19) patients in whom bile duct stones appeared to be completely removed by cholangiography and PCOS detected residual stones.

Recommendation Grade: B. Quality of evidence: 2++.

Complications: Overall complications have a low incidence^[73] and were explicitly reported in 7 prospective studies^[7,12,21,60,61,64,69] at levels of 13.3% (8/60), 5.7% (2/35), 6.1% (4/66), 8.4% (3/36), 5.3% (4/75), 3.8% (2/53), 4.3% (3/69). In a retrospective study^[33], the complication rate was reported at 9% (16/179). Several studies and a comprehensive review reported no complications in patients that underwent POCS and POCS-guided lithotripsy for the treatment of difficult CBD stones^[27,59,62]. Thus the weighted mean overall complication rate was 7.7% (39/504). The most common complication is cholangitis, explicitly reported^[7,12,13,21,64] in 5.0% (3/60), 5.7% (2/35), 3.0% (2/66), 5.6% (2/36), 1.9% (1/53) of cases or procedures respectively, amounting to a mean incidence of cholangitis of 4.0% (10/250). Cholangitis was often mild and could be treated with oral antibiotics^[64] but severe and fatal cases were reported^[15].

Recommendation Grade: A. Quality of evidence: 1+.

Consensus statement 4

Table 6 provides a capsule summary of the fourth consensus statement, namely that in patients with main duct IPMN POPS may be used to assess the extent of tumor to assist surgical resection.

Technical success: Technical success is typically defined as the ability to reach the IPMN lesions and examine them under POPS, which requires clearing the view of mucus. It is explicitly reported in three publications^[74-76] as 73% in 41 patients, 82% in 11

Table 7 Consensus statement 5

<p>In difficult pancreatic ductal stones, POPS-guided lithotripsy may be useful in fragmentation and extraction of stones Recommendation Grade C Quality of evidence: 2+ POPS-guided EHL or laser lithotripsy: EHL was reported for 17 cases, with stone clearance reported in 71% (12/17). Laser lithotripsy was reported for 9 cases, with stone clearance reported in 100% (9/9). Stone clearance was reported in 70% (32/46) with EHL or laser lithotripsy in 39 of those cases POPS-guided EHL vs ESWL: POPS-guided EHL compared to ESWL for treatment of pancreatic duct stones is reported as difficult and as being only rarely indicated</p>

POPS: Peroral pancreatoscopy; EHL: Electrohydraulic lithotripsy; ESWL: Extracorporeal shock-wave lithotripsy.

patients and 92% in 13 patients.

Recommendation Grade: C. Quality of evidence: 2-.

Diagnostic accuracy: Study reports^[77-79] and one comprehensive review^[6] of POPS for assessment of presence or absence of malignancy in IPMN ranges in sensitivity from 50% to 68%, and in specificity from 75% to 100%. In the three study reports, 60 patients in one study underwent POPS without biopsy and a combined 23 patients underwent POPS with POPS-guided biopsy. Diagnostic accuracy of POPS for malignancy in patients with main duct IPMN seems^[6,77] better than for patients with side branch IPMN.

Recommendation Grade: C. Quality of evidence: 2+.

POPS findings in IPMN: Studies^[6,22,29,33,76,77,79-83] focused on identifying POPS findings that seem associated with malignancy in IPMN generally point to villous or papillary tumors and proliferation of blood vessels to be correlated with malignancy. Conversely^[33,77,80], granular mucosa with fish-egg-like patterns without vascular images seem associated with benign IPMN lesions.

Recommendation Grade: C. Quality of evidence: 2+.

POPS and IDUS: One careful study^[77] in 60 patients undergoing pre-operative POPS, 40 of 60 patients also underwent intraductal ultrasonography (IDUS). For POPS sensitivity and specificity were 65% and 88% respectively. Using IDUS findings of protrusions of 1 mm or more, sensitivity and specificity were 68% and 89% respectively. For POPS and IDUS combined in 40 patients, sensitivity and specificity were 91% and 82% respectively. Authors concluded POPS and IDUS combined provides improved differential diagnosis between malignant and benign IPMN. Another series^[84] also point to the value of POPS in combination with ERCP and EUS and IDUS for examination of pancreatic duct IPMN.

Recommendation Grade: D. Quality of evidence: 3.

Pre-operative and intra-operative POPS: Location of the IPMN lesion and extent of dysplasia can help guide surgery in pre-operative settings^[4,27,81,85] or even intra-operatively^[86] to better determine the resection

line in the pancreas.

Recommendation Grade: D. Quality of evidence: 3.

Consensus statement 5

Table 7 provides a capsule summary of the fifth consensus statement, namely that in difficult pancreatic ductal stones, POPS-guided lithotripsy may be useful in fragmentation and extraction of stones.

POPS-guided EHL and LL: EHL guided by POPS was quantitatively reported in two^[23,33] publications with successful pancreatic stone clearance in 50% (3/6) and 100% (1/1) of cases. Stones were mostly in the head of the pancreas. There were no serious adverse events. Laser lithotripsy (LL) by POPS was reported in two^[7,87] publications with successful pancreatic stone clearance in 100% (9/9) of cases. There were no complications in the patients with pancreatic duct stones. All four reports used the SpyGlass system. Stones were described as difficult to remove as stones were impacted, cast-like, or located above a distal PD stricture. A new prospective study^[88] reported stone clearance was reported in 70% (32/46) with EHL or laser lithotripsy in 39 of those cases; mechanical lithotripsy was used in the remaining 7 cases. Per oral pancreatoscopy related complications were found in 10%. Dilation of the stricture and biliary and pancreatic sphincterotomy are common in POPS-guided EHL. Several qualitative reports^[4,22,61,89] support that POPS may be helpful for identification of pancreatic duct stones missed in prior imaging studies, and also that intended POPS-guided EHL can sometimes be avoided after careful assessment of the pancreatic duct stones under POPS.

Recommendation Grade: C. Quality of evidence: 2+.

POPS-guided EHL vs extracorporeal shock-wave lithotripsy: A comprehensive review^[6] of various techniques used to perform POCPS specifically comments on the use of extracorporeal shock-wave lithotripsy (ESWL) and POPS-guided EHL in combination. A small series of 6 patients reached 50% stone clearance and symptom improvement. A single case report^[90] identified the value of intraductal EHL for non-calcified pancreatic stones. Where possible, ESWL alone is reported as easier than POPS-guided

Table 8 Consensus statement 6

Additional indications for POCPs include selective guidewire placement, unexplained hemobilia, assessing intraductal biliary ablation therapy, and extraction of migrated stents
 Recommendation Grade C
 Quality of evidence: 2+
 The primary indications of peroral cholangiopancreatography are indeterminate stricture, indeterminate filling defect and stones, but the application of the technology is vast and is forever expanding. While not many cases are performed and documented, the indications extend to selective guidewire placement, unexplained hemobilia, assessment of intraductal biliary ablation therapy as well as the extraction of migrated stents
 These additional indications have been reported in clinical studies as well as comprehensive reviews of POCPs

POCPs: Peroral cholangiopancreatography.

EHL, but an ERCP is typically still needed to clear distal pancreatic duct stones or stone fragments.

Recommendation Grade: D. Quality of evidence: 4.

Consensus statement 6

Table 8 provides a capsule summary of the sixth consensus statement, indicating that additional indications for POCPs include selective guidewire placement, unexplained hemobilia, assessing.

Selective guidewire placement: Peroral cholangioscopy has successfully been used in a number of studies^[14,61] for selective guidewire placement, including access to disease segments in complicated bile duct strictures or openings of cystic ducts that are difficult to access by conventional ERCP. SpyGlass was successfully used to enter the cystic duct for guidewire placement and gallbladder stenting in a patient with pre-transplant cirrhosis and symptomatic cholelithiasis who had previously failed multiple attempts to cannulate the cystic duct for gallbladder stenting at ERCP^[12].

An overview^[16] of the SpyGlass system for cholangiopancreatography in 2009 focused on indications, clinical applications and studies to date and attempted to clarify the role of this important technology which allows for direct visualization of the bile and pancreatic ducts, tissue acquisition and access for therapeutic interventions, including stone removal. A notable therapeutic indication is the facilitation of selective guidewire access to the gallbladder or intrahepatic ducts.

Other comprehensive reviews^[4,6,49,58] of peroral cholangioscopy authors have noted that cholangioscopy also facilitates selective guidewire placement into complicated bile duct strictures, intrahepatic ducts and the gallbladder or opening of a cystic duct that is difficult to access by conventional ERCP.

Recommendation Grade: C. Quality of evidence: 2+.

Unexplained hemobilia: POCS for the assessment of unexplained hemobilia is a rare but useful method. In a comprehensive review^[27] of intraductal biliary and pancreatic endoscopy, authors note that a diagnostic indication of cholangioscopy is the evaluation of hemobilia of unknown etiology. Other comprehensive

reviews^[2,6] of applications of POCS, indicated the procedure can be used for both the localization and treatment of hemobilia. In a retrospective review of 61 patients, hemobilia was indicated in 4 cases and the site of bleeding was identified in all cases^[52].

Recommendation Grade: C. Quality of evidence: 2+.

Assessment of intraductal biliary ablation therapy: Cholangiopancreatography has been further developed for further applications such as tumor ablation, according to a comprehensive review conducted in 2009^[6] and a review of SpyGlass^[22] specifically.

Recommendation Grade: D. Quality of evidence: 4.

Extraction of migrated stents: Proximal (upstream) migration of pancreatic duct stents is a recognized complication that occurs in up to 5.2% of patients^[91]. A case review^[91] of a single patient demonstrates that with POCS, they were able to visualize the distal end of a migrated stent; the 4-way deflection of the cholangioscope allowed for maneuverability to successfully cannulate the stent with a guidewire and then remove it.

In a prospective observational clinical feasibility study of 35 patients^[12] the indication for POCS was gallbladder stent placement in 1 patient (3%). In another study of 22 patients^[92], 25 cholangioscopy attempts were made and 22 were successful (88%; 19 patients). A biopsy forceps under cholangioscopic visualization was used to release a dislodged fully covered self-expanding metal stent in the CBD. Authors felt that cholangioscopy is useful in improving diagnostic validity and offering new therapeutic interventions. The stent was then removed using a duodenoscope.

In a prospective study of 12 patients^[24] at University of Chicago, 18 cholangioscopies with the mother-baby endoscope were performed and a fragmented stent was the indication in one patient. Authors concluded that direct visualization of the biliary tree with the ability to sample or treat lesions significantly aided in the care of all patients in whom the baby endoscope was successfully passed by providing the correct diagnosis

and, when appropriate, by allowing definitive treatment of lesions.

A comprehensive review^[58] of peroral cholangioscopy indicated that there are both diagnostic and therapeutic applications. Authors note that a primary therapeutic indication is endoscopic extraction, including stone removal but that another indication is removal of proximally migrating stents that cannot be removed by conventional ERCP.

Recommendation Grade: C. Quality of evidence: 2+.

DISCUSSION

A workgroup of experts in the field of POCPS established six consensus statements regarding the utility of POCPS, with associated recommendation grades A (1), B (2), or C (3). Overall, the consensus points to POCPS being an important tool in association with ERCP, particularly for diagnosis of indeterminate biliary strictures and for intra-ductal lithotripsy when other lithotripsy techniques have failed. It also states that POCPS may be useful for pre-operative assessment of the extent of main duct tumors in IPMN, for fragmentation and extraction of difficult pancreatic stones, and for unusual indications including selective guidewire placement, unexplained hemobilia, assessing intraductal biliary ablation therapy, and extraction of migrated stents.

The six consensus statements are as follows: (1) POCPS is now an important additional tool during ERCP. Recommendation grade B; (2) In patients with indeterminate biliary strictures, POCPS and POCPS-guided targeted biopsy are useful for establishing a definitive diagnosis. Recommendation grade B; (3) POCPS and POCPS-guided lithotripsy are recommended for treatment of difficult CBD stones when standard techniques fail. Recommendation grade A; (4) In patients with main duct IPMN POCPS may be used to assess extent of tumor to assist surgical resection. Recommendation grade C; (5) In difficult pancreatic ductal stones, POCPS-guided lithotripsy may be useful in fragmentation and extraction of stones. Recommendation grade C; and (6) Additional indications for POCPS include selective guidewire placement, unexplained hemobilia, assessing intraductal biliary ablation therapy, and extracting migrated stents. Recommendation grade C.

COMMENTS

Background

Per-oral cholangiopancreatography (POCPS) is not a new imaging modality to assist the gastroenterological endoscopist in diagnosis and treatment of pancreaticobiliary diseases. However, recent technological advances have made this modality more broadly used. Given the relatively high incidence of pancreaticobiliary ductal disorders in Asia, consensus statements from users in the region seem relevant.

Research frontiers

Constant technological improvements are ongoing and are anticipated to make POCPS an increasingly adopted modality in the management of patients with pancreaticobiliary disease.

Innovations and breakthroughs

Recent advancements include the addition of narrow band imaging, single operator cholangiopancreatoscopes, and ultra-thin gastroscopes.

Applications

This paper provides a concise review of available evidence of the clinical utility of POCPS in a wide range of indications.

Terminology

In this paper cholangiopancreatography was abbreviated to "POCPS" which is not necessarily universally adopted terminology.

Peer-review

The paper includes a commendable and extensive review of the literature. It is well-written but do have some suggestions to hopefully enhance its strength.

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P- Reviewer: Lin CH, Sakai Y, Shah RJ S- Editor: Ma YJ
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ISSN 1007-9327



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