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Applications of Cholangiopancreatography in Pancreaticobiliary Diseases

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Abstract

Recent advances in imaging technology provide improved direct visualization of the common bile duct (CBD) and pancreatic duct (PD) using small caliber endoscopes and thus allow a wide array of therapeutic interventions. This chapter will review the technique of cholangiopancreatography (CP), indications, effectiveness, and complications as well as the current commercially available options. We will discuss various methods of diagnostic and therapeutic cholangioscopy such as intraductal tissue sampling and biopsy in patients with indeterminate biliary strictures along with its role in the management of difficult bile duct stones. Finally, we will also analyze the role of pancreatoscopy in the evaluation of suspected neoplasms of the pancreas, assessment of pancreatic duct (PD) strictures, and in the treatment of pancreatic duct stones.

Keywords: cholangioscopy, pancreatoscopy, endoscopic retrograde cholangiopancreatography (ERCP), biliary diseases, pancreatic diseases

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1. Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) has been largely used as a technique to evaluate and treat diseases of both the biliary tract and the pancreatic duct.

The use of contrast during ERCP only allows for indirect visualization of these structures without direct assessment of disease arising within the ducts and the potential use of a wide array of therapeutic techniques that are now available for gastroenterologists and advanced endoscopists.

Ever since it was described in the early 1940s [1], cholangioscopy has permitted direct visualization of the bile duct and subsequent treatment of bile duct stones when palpation and probing of the bile duct were not efficacious in achieving adequate clearance of common bile duct stones. The use of both small endoscopes and probes used to directly visualize and treat diseases of the biliary tract and the pancreatic duct, eliminating the need for contrast media has been collectively named as cholangiopancreatography (CP).

2. Description of equipment and techniques

Cholangiopancreatography can be performed by either an endoscope-based system or a probe- or catheter-based system.

The endoscope-based systems use the scope itself as the main working tool whereas the catheter-based techniques require the use of the working/accessory channel of an endoscope in order to reach the common bile duct or the pancreatic duct. Cholangioscopy was initially performed by surgeons using a direct surgical approach to the bile duct. The peroral technique of cholangioscopy, using the endoscope-based technique or catheter-based technique was first reported in the 1970s [2].

Finally, there are three other techniques by which CP can be performed, and these include: direct peroral cholangioscopy (DPOC), surgical, and percutaneous cholangioscopy. These are not so widespread since they are technically challenging and are performed by endoscopists, surgeons, and interventional radiologists, respectively.

2.1. Endoscope-based systems

Endoscope-based systems utilize a “mother” duodenoscope and a “daughter or baby” cholangiopancreatography. This system requires two separate endoscopic operators to perform the procedure. One of the operators holds the position of the duodenoscope while the other operator performs the diagnostic and therapeutic cholangiopancreatography [3–5].

The currently available instruments for endoscope-based cholangiopancreatography in the United States are the following [6]:

- Olympus Corporation fiberoptic peroral cholangioscope (CHF-BP30) with a distal diameter of 3.1 mm, a working channel of 1.2 mm, and a working length of 187 cm. This endoscope can be passed through a duodenoscope with a minimum 4.2 mm accessory channel and has an angle of view of 90° [7].
- Pentax Corporation fiberoptic peroral cholangioscope (FCP- 9P) with a distal diameter of 3.1 mm, a working channel of 1.2 mm, a field of view of 90°, and a working length of 190 cm. This scope can be used with both the PENTAX Medical ED-3490TK Therapeutic Duodenoscope and the ED-3690TK Large-Channel Therapeutic Duodenoscope [8].

Endoscope-based systems have the following technical difficulties: limited steerability, poor irrigation capabilities, high repair costs, fragility with repeated use, and the need to have two

operators in a large number of cases [6, 9–11]. These limitations along with improved new systems have gradually eliminated the need for endoscope-based systems.

2.2. Probe- or catheter-based systems

Probe- or catheter-based systems do not require the assistance of a separate endoscopist to perform the CP but are rather inserted through the working channel of a therapeutic endoscope or duodenoscope.

The only available catheter-based single-operator system in the United States (US) is the SpyGlass™ Direct Visualization System (Boston Scientific Corporation), which is a disposable probe inserted through the accessory channel of a therapeutic duodenoscope. The SpyGlass™ Direct Visualization System (Boston Scientific Corporation) was designed to overcome the limitations of traditional cholangioscopes, to provide optically-guided therapeutics for targeted bile and pancreatic duct stone therapy, and also to help in the evaluation of pancreaticobiliary ductal strictures [12]. In our experience, the SpyGlass™ Direct Visualization System offers improved ergonomics by being lighter and easy to operate, something that is especially important during longer procedures where hand fatigue could be an issue. This system became first available in 2007 and is now available in two different generations.

- First-generation SpyGlass™ Direct Visualization System became available in 2007. The components of this single-operator cholangioscopy (SOC) system include a SpyScope™ access and delivery 10F catheter which contains a 1.2 mm diameter working channel and two dedicated irrigation channels. This catheter is introduced through a duodenoscope or therapeutic endoscope with a minimum working channel diameter of 4.2 mm. The catheter is capable of tip deflection up to 30° in four directions. Finally, this SOC system contains a reusable SpyGlass™ Fiber Optic Probe which can provide 6000-pixel images [9, 12, 13]. The first prospective clinical study validating the use of single-operator cholangioscopy with the use of the first-generation SpyGlass™ was published by Chen et al. [9] in 2011 with an overall procedure (for both adequate biopsy specimen for histological examination or stone visualization and initiation of fragmentation) success rate of 89%. The first prospective evaluation of SpyGlass™ Direct Visualization System involved 75 patients and was reported by Draganov et al. [14] in 2011. They reported complete stone clearance in 92% of patients with bile duct stones, and in 91% of those patients, this was achieved in the first session. In non-stone-related procedures, this was successful in 98% of patients and, in 20% of patients, new findings—not appreciated in cholangiography—were revealed during the SpyGlass™ Direct Visualization System session.
- Second-generation SpyGlass™ Direct Visualization System was made available in 2015 and has the ability to have an improved setup, ease of use, and image quality [15]. Compared to the first-generation system, this newest system is based on a 10.5 F catheter and delivers enhanced visualization and improved image quality through a digital sensor with 4× more resolution, a 60% wider field of view, automatic light control, and light-emitting diode (LED) illumination. There are dedicated irrigation and aspiration connections to clear the field of view, a redesigned 1.2 mm working channel, and a fixer imager for consistent steering [16, 17].

The following accessories are available or compatible with the SpyGlass™ Direct Visualization Systems:

- SpyScope™ DS Access & Delivery Catheter (**Figures 1–3**), single-use only. This catheter provides dual controls which allow for a 4-way deflection and a locking mechanism that ensures stabilization of direct visualization.
- SpyGlass™ Direct Visualization System's fiberoptic probe is designed to optimize light delivery to the anatomy and to acquire and transmit endoscopic images back to the camera. The probe connector on the proximal end attaches to the light guide and ocular [18]. The SpyGlass™ is inserted through the catheter allowing direct visualization of the pancreaticobiliary anatomy. The fiberoptic probe is reusable up to 10–20 times, although there are reports of its optical resolution deteriorating after 10 uses [19], whereas the rest of the cholangioscope is single use [6].
- Camera, camera head, and ocular. The camera utilizes a $\frac{1}{4}$ CCD color-image sensor that provides three types of video outputs (RGBs, S-video, or composite). A multi-pin cable connector helps to facilitate the camera connection to the unit, and the ocular makes possible focus and transmission of the image obtained through the SpyGlass Probe™ [18].
- Light source and cable (**Figure 4**). A flexible fiber-optic bundle facilitates the transmission of light provided from a 300 W Xenon source into the SpyGlass Probe™ [18].
- Irrigation footswitch (100–240 V, 50/60 Hz, 25 VA) which provides 0–375 ml/min $\pm 20\%$ using SpyGlass™ Irrigation tube set which allows clearance of debris from the ducts and a better visualization of the anatomic structures.
- SpyGlass Probe™ Trays. This allows storage and protection when the probe is not in use and when it is being disinfected.
- Sony High Resolution 1280 $\times$ 1024 video monitor (17.5"W $\times$ 15.8"H $\times$ 4.75"D).

Figure 1. SpyGlass™ Direct Visualization System Access and Delivery Box (Courtesy of Gulshan Parasher, MD).

Figure 2. SpyGlass™ Direct Visualization System Access and Delivery Catheter mounted on a therapeutic duodenoscope. The capped white end is the suction port and the uncapped port is the accessory channel (Courtesy of Gulshan Parasher, MD).

Figure 3. SpyGlass™ Direct Visualization System Access and Delivery Catheter mounted on a therapeutic duodenoscope. The capped white end is the suction port and the uncapped port is the accessory channel (Courtesy of Gulshan Parasher, MD).

Figure 4. SpyGlass™ Direct Visualization System Light Source and Cable (Courtesy of Gulshan Parasher, MD).

- Cart (3-Joint Arm and Isolation Transformer). It provides a space for ease of transfers between endoscopy rooms and also for storage of the whole unit. The flexible 3-joint arm allows the endoscopist to place the camera in an optimal position for visualization and comfort. This cart can also include an isolation transformer.
- Power Cable Pack. This pack helps to simplify electrical connections during transfers between rooms.
- SpyBite™ Biopsy Forceps, single-use forceps. This allows direct tissue sampling under direct visualization and is advanced through the therapeutic channel of the SpyScope™ catheter. The specification of the biopsy forceps are as follows: 1 mm outer diameter, 4.1 mm biopsy cup opening at 55°, and a central spike in the specimen cup that aids in securing samples in challenging lesions.

The current set up time for the system is under 5 min (compared to 23 min with the first-generation system) and the equipment is designed to fit on a standard endoscopy cart. The newest version of the system provides an integrated digital sensor along with an automatic white balance and focus feature. Digital single-operator cholangiopancreatography (DSOCP) systems like the SpyGlass™ Direct Visualization Systems have been shown to provide enhanced image quality with shorter procedure times thus limiting radiation exposure when compared to the fiberoptic single-operator cholangiopancreatography (FSOCP) systems [20].

The SpyGlass™ Direct Visualization Systems are compatible with some electrohydraulic lithotripsy (EHL) systems (from Northgate Technologies, Inc.) and with holmium laser probes (from Lumenis) and can be used in conjunction to manage large and impacted biliary and pancreatic ductal stones. The financial feasibility of incorporating cholangiopancreatography into an endoscopy is complex. This can be a profitable venture with large diagnostic and therapeutic CP caseload. Important variables include case volume, purchase cost, and procedure length. The single-use cholangioscope can decrease the potential for contamination, but the initial start-up cost for the system averages at least 50,000.00 USD (United States Dollars) and this has significantly limited the widespread use of this technology in non-tertiary centers.

The two main limitations of the SpyGlass™ Direct Visualization Systems are image quality that is impeded by the use of fiberoptic technology and a relatively small accessory channel providing passage only for dedicated accessories [21, 22].

2.3. Direct peroral cholangioscopy (DPOC)

Direct peroral cholangioscopy (DPOC) is a technically challenging procedure which involves passage of an ultraslim gastroscope capable of providing high-resolution images of the bile duct as well as providing therapeutic interventions [23–26]. Although the use of ultraslim gastroscopes is not approved by the Food and Drug Administration (FDA) for CP, its use has been reviewed by the American Society for Gastrointestinal Endoscopy (ASGE) [27].

The advantages of DPOC are summarized in **Table 1** [28–33]. The use of carbon dioxide (CO₂) and water is highly recommended during DPOC since it decreases the risks of air embolism [6, 34].

Table 2 summarizes the currently available ultraslim endoscopes for use in DPOC in the United States [6, 35–41].

The average price for an ultraslim endoscope is roughly around 30,000.00 USD (United States Dollars).

Two different techniques for DPOC have been described:

- Direct peroral cholangioscopy over a stiff guidewire with or without an overtube: this technique involves the use of a standard ERCP to access the bile duct and the subsequent insertion of a stiff guidewire which will eventually be exchanged by an ultraslim endoscope, which serves as a cholangioscope [6, 42–45]. The use of an overtube helps in overcoming the gastric loop that can be formed with ultraslim gastroscopes [44, 46].
- Direct peroral cholangioscopy using a free-hand technique: this involves the use of ERCP with sphincterotomy and subsequent passage of an ultraslim endoscope without the use of a stiff guidewire. The papilla is difficult to be cannulated directly with an ultraslim endoscope. Therefore, the ultraslim endoscope is advanced to the third portion of the duodenum, and subsequently, a “J maneuver” is used to cannulate the papilla and insertion into the common bile duct [47, 48].
- Direct peroral cholangioscopy using the balloon anchoring method: this method involves the use of a guidewire and a biliary stone extraction balloon in order to help anchor the ultraslim gastroscope. After a standard ERCP, a biliary sphincterotomy is performed, and a guidewire is introduced into the common bile duct along with a balloon that is subsequently inflated and displaced upstream to help straighten the common bile duct and to allow a better navigation with the cholangioscope [6, 49, 50].

2.4. Percutaneous and surgical cholangioscopy

Percutaneous cholangioscopy can be performed by both endoscopists and interventional radiologists. This technique involves the insertion of a cholangioscope through a mature (3–5 weeks) percutaneous fistulous tract [6, 51] from the abdominal wall into the biliary tree. This technique can allow the insertion of the SpyGlass™ Direct Visualization System [52]. A number of diagnostic and therapeutic techniques can be performed, such as percutaneous cholangiography, electrohydraulic and laser lithotripsy, removal of difficult stones, tissue sampling, intraluminal brachytherapy, and stenting of the hepatic and biliary ducts [53, 54].

Advantages of direct peroral cholangioscopy (DPOC)

- Single operator
- Usage of chromoendoscopy
- Utilization of argon plasma coagulation (APC)
- Use of photodynamic therapy
- Use of confocal laser endomicroscopy
- Employment of narrow-band imaging (NBI) to detect fine mucosal structures and tumor vessels
- Decreases the costs associated with SpyGlass™ Direct Visualization Systems or other platforms

Table 1. Advantages of direct peroral cholangioscopy (DPOC).

Available ultraslim endoscopes in the United States (U.S.)					
Company	Working length	Outer diameter	Angle of view	Accessory channel size	Other capabilities
Olympus Corporation					
GIF-XP 190 N/Gastroscope	1100 mm	5.4 mm	140°	2.2 mm	Narrow-band imaging (NBI)
GIF-XP 180 N/Gastroscope	1100 mm	5.5 mm	120°	2.0 mm	Narrow-band imaging (NBI)
GIF-N180/Gastroscope	1100 mm	4.9 mm	120°	2.0 mm	Narrow-band imaging (NBI)
Transnasal Endoscope (PEF-V)	650 mm	5.3 mm	120°	2.0 mm	Used in combination with the VISERA video system to provide high-resolution images
Pentax Corporation					
EG-1690 K	1100 mm	5.4 mm	120°	2.0 mm	i-SCAN digital image processing
Fujinon Corporation					
EG-530 N	1100 mm	5.9 mm	120°	2.0 mm	N/A
Transnasal Endoscope (EG-530 NP Transnasal)	1100 mm	4.9 mm	120°	2.0 mm	Not compatible with high-frequency applications

Table 2. Available ultraslim endoscopes in the United States (U.S.).

In addition, percutaneous cholangioscopy, used in conjunction with DPOC, has been successful in the treatment of intrahepatic and bile duct stones in patients with surgically altered anatomy such as Roux-en-Y hepaticojejunostomy [55–58].

Finally, gastrointestinal surgeons can also perform direct surgical cholangioscopy, which involves the use of a cholangioscope during open abdominal wall surgery or laparoscopic surgery to evaluate and treat biliary pathology when the endoscopic approach fails [59–63].

3. Indications for cholangioscopy

3.1. Intraductal lithotripsy of common bile duct (CBD) or hepatic duct (HD) stones

Perhaps, the most studied and used indication for cholangioscopy is the evaluation and management of difficult biliary stones that failed with the standard methods of stone extraction such as mechanical lithotripsy and balloon extraction during endoscopic retrograde cholangiopancreatography.

Intraductal lithotripsy during cholangioscopy can be performed using electrohydraulic lithotripsy (EHL) and laser lithotripsy (LL).

Electrohydraulic lithotripsy was first used in the Soviet Union for the fragmentation of minerals, but it was not until the 1970s that this technology was introduced for the management of biliary stones [64, 65]. This method has been traditionally used for the management of difficult biliary stones with some reports of up to 95% of success extraction of gallstones refractory to conventional endoscopic basket extraction [66] although the general stones fragmentation rates are approximately 80% [67–72].

EHL utilizes a bipolar probe which discharges sparks in an aqueous medium with the aid of a generator. The sparks generate high-frequency hydraulic pressure waves that impact the stone resulting in subsequent fragmentation. The EHL equipment is portable, compact, and inexpensive [73, 74].

EHL can be performed under the guidance of fluoroscopy or through a cholangioscope. Fluoroscopy offers only a two-dimensional view of the stone, whereas direct cholangioscopy offers a direct view of the stone and also aids in positioning the probe, minimizing bile duct trauma [73]. During EHL, saline irrigation of the duct is performed as saline provides an aqueous medium for the shock waves to travel as well as it helps in clearance of stone debris [64, 75].

Electrohydraulic lithotripsy is associated with an overall complication rate that has been reported around 7–9% by some authors [73, 76] and its most common reported complications or side effects include hemobilia, cholangitis, common bile duct injury (less than 1%), and delayed common bile duct strictures [64, 73] (**Table 3**).

Laser lithotripsy involves the use of laser probes inserted through the therapeutic or accessory channel of an endoscope that subsequently transmit thermal energy or shock waves in order to fragment and dissolve stones in the common bile duct. The use of LL in humans was first described by Lux et al. in 1986 [77]. There are two main forms in which LL can help fragment stones, one is by using a laser in a continuous fashion with the subsequent generation of heat directed toward a stone [67], whereas the other is by using a laser delivered in a pulsed fashion acting through the shockwave effect in order to fragment and dissolve stones [67, 78–80]. The use of continuous laser has been associated with coagulation and subsequent perforation of the wall of the common bile duct [67, 79]. LL can be used through the cholangioscopic, fluoroscopic, or transhepatic approach [73]. The laser of a wavelength of 504 nm (nm) is absorbed by the pigment consistent of stones [67] and in some studies, pigmented stones have been fragmented using less energy than cholesterol stones [80].

The efficacy of LL in achieving ductal clearance has been reported to be 64–97% [73, 81, 82]. Reports of rare adverse events include pancreatitis, transient hemobilia, cholangitis, and bile duct injury [81] (**Table 3**). As per some authors, laser lithotripsy is not only used as an alternative to electrohydraulic lithotripsy for gallstones that failed clearance by standard techniques such as endoscopic sphincterotomy with balloon/basket extraction and to mechanical lithotripsy (ML), but also is sometimes preferred over EHL since it provides targeted and directed therapy with less potential for injury to the common bile duct [64, 83].

The financial cost of LL, approximately \$100,000.00 USD for the initial setup, has limited its use [64]. There are different types of lasers available for LL and they differ in their type of energy, power, wavelength, and pulse width [83]. Nevertheless, short wavelength laser has been the most used in the current therapy of gallstones. Coumarin (504 nm), rhodamine-6G (595 nm), neodymium (Nd):yttrium-aluminum-garnet (YAG) (1064 nm), and alexandrite:YAG (750 nm) are very effective in stone fragmentation with a 80–95% success rate [64] with holmium (Ho):YAG laser (wavelength of 1949 nm) being the most used nowadays. Holmium (Ho):YAG laser has been deemed very safe for lithotripsy since its wavelength is near the optical coefficient of water and its depth of tissue penetration is much shallower than Nd:YAG (0.5, 5 mm, respectively) resulting in minimal injury to the duct wall [64, 83] (**Figure 5**).

3.2. Intraductal assessment of strictures and suspected biliary malignancies

Direct visualization of strictures and suspected biliary malignancies with cholangioscopy has allowed a more careful assessment of them along with the possibility of obtaining targeted biopsies of the suspected tissues. This is certainly a step forward since traditional ERCP offers only a fluoroscopic indirect visualization of the suspected abnormality and brushings do not offer direct tissue sampling.

As described, earlier, the SpyBite™ Biopsy Forceps (Boston Scientific Corporation) allows guided tissue sampling under direct visualization through the therapeutic channel of the SpyScope™ catheter.

A tertiary center prospective study by Draganov et al. [84] in 2011 evaluated the accuracy of cholangioscopy-guided mini-forceps (SpyBite™ Biopsy Forceps) sampling and compared it with standard cytology brushings and forceps biopsies for the tissue diagnosis of indeterminate biliary lesions. This study demonstrated that when comparing the three methods of sampling, mini-forceps biopsy by SpyBite™ provided significantly better sensitivity and overall accuracy compared with standard cytology brushing ($P < 0.0001$) and standard forceps biopsy ($P = 0.0215$). For standard cytology brushings, the sensitivity, accuracy, and negative

Complications of electrohydraulic lithotripsy (EHL) and of laser lithotripsy (LL)
Hemobilia
Cholangitis
Common bile duct (CBD) injury (less than 1%)
Delayed common bile duct strictures
Pancreatitis

Table 3. Complications of electrohydraulic lithotripsy (EHL) and of laser lithotripsy (LL).

Figure 5. A 36-year-old female presenting with choledocholithiasis. (A) Magnetic resonance cholangiopancreatography (MRCP) showing a stone (arrow) in the common bile duct with (B) subsequent ERCP showing a filling defect in the CBD. This patient underwent (C) ERCP with SpyGlass™ Direct Visualization System showing a CBD stone. (D) Holmium laser lithotripsy (LL) of the CBD stone achieved (E) fragmentation and (F) subsequent successful basket extraction of the stone with (G) fluoroscopy showing adequate clearance of it (Courtesy of Gulshan Parasher, MD and Thomas C. Queen, MD).

predictive value (NPV) reported by them were 5.9, 38.5, and 36%, respectively. For standard forceps, they reported a sensitivity of 29.4%, accuracy of 53.8%, and NPV of 42.8%. Finally, mini-forceps (SpyBite™ Biopsy Forceps) biopsies had the highest sensitivity, accuracy, and NPV when compared to standard cytology brushings and standard biopsies. The values reported by the authors were 76.5, 84.6, and 69.2%, respectively. We as authors believe that indeterminate biliary lesions should always be sampled with the SpyBite™ Biopsy Forceps since they significantly increase the yield for histologic diagnosis.

One systematic review by Navaneethan et al. [85] reported that biopsies with SpyBite™ had a sensitivity of 76.5% compared with brushings (5.8%) and biopsies (29.4%) in the assessment of indeterminate biliary strictures.

The sensitivity and specificity for studies, who have only used direct cholangioscopic visualization for the evaluation of malignancy, have ranged from 88 to 100% and 77 to 92%, respectively [86–94]. Cholangiopancreatography using chromoendoscopy, autofluorescence imaging (AFI), and narrow-band imaging (NBI) has been associated with a higher ability to detect malignancy [95].

In contrast, the overall sensitivity, specificity, and accuracy of cholangioscopy for tissue diagnosis of indeterminate biliary duct strictures using targeted biopsies have been reported to be between 48 and 100%, 55 and 100%, and 70%, respectively [6, 13, 85, 87–92, 94, 96–103]. Although the optimal number of biopsies warrants further study, one study series suggested that a minimum of six biopsies should be taken to prevent inadequate material for histopathological analysis [104]. The use of concomitant endoscopic ultrasound (EUS) with cholangioscopy has been associated with increases in sensitivity and specificity in the detection of pancreaticobiliary neoplasia [105].

4. Indications for pancreatoscopy

Many of the same devices (i.e., SpyGlass™ Direct Visualization Systems) used for cholangioscopy can be used for the visual assessment and lithotripsy of pancreatic duct stones, sampling of PD strictures, and to evaluate suspected pancreatic malignancies. Currently, SpyGlass™ Direct Visualization Systems is the only system approved by the FDA for its use in pancreatoscopy [6].

4.1. Intraductal lithotripsy for pancreatic duct (PD) stones

Although the number of studies evaluating the use of pancreatoscopy for clearance of pancreatic duct stones is limited, the use of EHL sometimes along in combination with extracorporeal shockwave lithotripsy (ECSWL) has been reported to be effective in complete clearance of PD stones in approximately in 59–100% of cases [6, 106–110]. As per Komanduri et al., this data for complete clearance is hard to interpret since electrohydraulic lithotripsy was combined with decompressive surgery or ECSWL [6, 111].

Most recent studies have included the use of laser lithotripsy combined with electrohydraulic lithotripsy with an overall success rate of 74–79% in the management of main pancreatic duct stones [112, 113].

Furthermore, the use of intraductal lithotripsy for PD stones might help not only to decrease the pain and opioid/narcotic dependence in patients with chronic calcific pancreatitis but can

also decrease the risk associated with the more invasive surgical approaches like the lateral pancreaticojejunostomy (LPJ) [112–114].

4.2. Intraductal assessment of pancreatic duct (PD) strictures and suspected pancreatic malignancies

Evaluation and direct visualization with narrow-band imaging (NBI) of intraductal papillary mucinous neoplasms (IPMNs) and pancreatic duct strictures have been one of the most well-studied indications for peroral pancreatoscopy (POPS) with one study reporting the ability of POPS to visualize and diagnose up to 63% of pancreatic cancers, 80% of benign strictures, and 95% of IPMNs [115]. In this study, neoplasia assessment was based on the presence of coarse-friable mucosa, papillary projections, and tumor. As per the authors, tumor vessels and papillary projections/tumor were observed when pancreatic cancer was less than 2 cm, but not when the tumor was larger than 2 cm. Other studies like the one from Arnelo et al. [116] have reported the correct identification of main duct (MD-IPMN) and branch duct (BD-IPMN) in up to 76 and 78% of cases, respectively.

Table 4 summarizes the endoscopic findings that have been correlated with malignant pancreatic lesions with a sensitivity and specificity of 68 and 87%, with some authors reporting a lower sensitivity for BD-IPMN compared to MD-IPMN [6, 117, 118] (**Figures 6–9**).

Pancreatotomy findings suspicious for intraductal papillary mucinous neoplasms (IPMNs)
Coarse-friable mucosa
Tumor vessels
Papillary projections
Fish egg-like, villous, and prominent mucosal protrusions
Tumor

Table 4. Pancreatotomy findings suspicious for Intraductal papillary mucinous neoplasms (IPMNs).

Figure 6. SpyGlass™ Direct Visualization System showing tumor vessels characteristic of an IPMN. (Courtesy of Gulshan Parasher, MD).

Peroral pancreatoscopy can be used along with intraductal ultrasonography (IDUS) to differentiate between benign and malignant intraductal papillary-mucinous tumors (IPMTs) [117], and also it has been described as a tool to obtain pancreatic juice cytology and aid in the diagnosis of IPMNs [119]. Narrow-band imaging offers a better detection of vascular patterns and protrusions and should be used whenever possible during POPS [120].

Figure 7. SpyGlass™ Direct Visualization System showing papillary projections characteristic of an IPMN (Courtesy of Gulshan Parasher, MD).

Figure 8. SpyGlass™ Direct Visualization System showing “egg-like protrusions” characteristic of an IPMN (Courtesy of Gulshan Parasher, MD).

Figure 9. SpyGlass™ Direct Visualization System showing “egg-like protrusions” characteristic of an IPMN (Courtesy of Gulshan Parasher, MD).

Intraoperative pancreatoscopy of the main PD combined with intraductal biopsies plays a significant role in the surgical management of patients with IPMNs and should be considered in all patients presenting with a sufficiently dilated main PD since it can alter the initial operative planning up to approximately 20% of cases [6, 121]. Post-endoscopic ERCP pancreatitis is a well-known side effect of POPS and has been reported to happen in up to 17% of cases [116].

5. Unusual indications of cholangiopancreatography (CP)

Some uncommon indications for the use of cholangiopancreatography include selective guide-wire placement, assessing unexplained hemobilia or intraductal biliary ablation therapy such as radiofrequency ablation of tumor ingrowth, photodynamic therapy for cholangiocarcinoma, and retrieval of migrated pancreatic and biliary stents [122].

Finally, successful endoscopic transpapillary gallbladder drainage and stenting using the SpyGlass™ Direct Visualization System has also been reported [123].

6. Efficacy and safety of cholangiopancreatography (CP)

Although there are numerous studies evaluating the safety and efficacy of cholangiopancreatography in the assessment and treatment of biliary and pancreatic stones, indeterminate biliary strictures, and suspected pancreatic malignancies, the authors have selected the ones with the highest and most relevant impact on our practice as gastroenterologists and endoscopists, and these are presented as follows.

Arya et al. [76] evaluated the safety and success of patients who underwent peroral endoscopic fragmentation of bile duct stones with electrohydraulic lithotripsy under direct cholangioscopic control using a “mother-baby” endoscopic systems and showed that of the 94 patients, successful fragmentation (61 complete, 28 partial) was achieved in 89 of 93 patients (96%) (one patient was excluded from analysis due to a broken endoscope) in difficult choledocholithiasis and intrahepatic stones. In those with successful EHL, fragmentation balloon or basket extraction was used to remove the remaining fragments. One EHL session was needed in 76% of patients, whereas two or more sessions were needed in 24% of patients. The complications reported by the authors included: cholangitis and/or jaundice (13 patients); mild hemobilia (1 patient); mild post-ERCP pancreatitis (1 patient); biliary leak (1 patient); and bradycardia (1 patient). There were no deaths related to EHL.

The first study evaluating the success rate of single-operator cholangioscopy was published by Chen et al. in 2011 [9]. This was a multicenter prospective clinical cohort study involving 15 endoscopy referral centers in the United States and Europe, and 297 patients requiring an evaluation of bile duct disease or biliary stone therapy. Procedural success was defined as either visualization of lesions and collection of biopsy specimens if indicated, or visualization of stones and its subsequent fragmentation. The overall procedure success rate for the aforementioned procedures was 89% (95% CI, 84–92%). Eighty-eight percent of patients who underwent biopsies had adequate tissue for diagnosis with biopsies associated with a sensitivity of 49% for diagnosing malignancy, whereas visual impression from SOC had a sensitivity of 78% for the same purpose. Sensitivity was higher for intrinsic bile duct malignancies. Procedure success for SOC-directed stone therapy, defined as visualization of biliary stones and initiation of stone fragmentation and removal, was achieved in 92% of 66 patients with stones and complete stone clearance during the study SOC session was achieved in 71% of cases. The incidence of serious procedure-related adverse events was 7.5% for diagnostic SOC (17 patients; early cholangitis in 7, bacteremia in 2, transient hypotension in 2, abdominal pain/distention in 2, pancreatitis in 1, elevation on amylase/lipase with no clinical pancreatitis in 1, ERCP-related nausea with emesis, abdominal pain, gas, and cramping, and radiculopathy in 1) and 6.1% for SOC-directed stone therapy (five events in 4 patients; cholangitis in 2 patients, 1 patient with ERCP-related duodenal perforation and SOC-related desaturation secondary to aspiration, and bile duct perforation in one patient).

A retrospective, single tertiary center, study by Aljebreen et al. [124] evaluated the efficacy and safety of Spyglass™-guided electrohydraulic lithotripsy for difficult common bile duct stones not amenable to conventional endoscopic therapy. In this cohort, all patients who underwent Spyglass™-guided EHL were compared with a historical cohort who had extracorporeal shockwave lithotripsy. Of a total number of 13 patients who underwent Spyglass™-guided EHL, bile duct clearance was achieved in all of the cases with 76% of patients requiring one ERCP session to clear the CBD and 23.1% requiring two or more sessions for the same purpose. Eleven percent of patients experienced cholangitis and 4.4% had pancreatitis as adverse effects. Although the study enrolled a small number of patients (13 in total), it showed that cholangioscopic-guided EHL was an effective therapy for difficult bile duct stones and a higher a CBD clearance rate compared to ESWL (100 versus 64.4%).

The largest, multi-center prospective, clinical study evaluating the technical success and safety of single-operator cholangioscopy-Ho:YAG laser-guided lithotripsy for the management

of difficult bile duct stones was published by Patel et al. [83]. This study was performed in patients with refractory bile duct stones who failed endoscopic retrograde cholangiopancreatography. Cholangioscopic-guided Holmium laser lithotripsy resulted in complete removal of bile duct stones in 97% of patients. In 74% of patients, biliary clearance was accomplished in one endoscopic session. The average stone size in patients with a single stone was 20.2 mm (range, 10–36 mm). Successful extraction of stones in this group of patients occurred in 46 of 47 patients (98%) and was similar to that of the other patients (21/22, 95%). To facilitate the removal of fragmented stones, endoscopic papillary balloon dilation (12–18 mm) and mechanical lithotripsy were performed in conjunction with laser lithotripsy in 7 and 17%, respectively. Laser lithotripsy failed in two patients who ultimately required biliary surgery. One patient had multiple large cystic duct stones, and the other failure occurred in a patient in which the stone (21 mm) was embedded in the common bile duct. The study reported an overall adverse event rate of 4.1%, with 2 patients experiencing minor bleeding of bile duct wall and 1 patient with mild post-ERCP pancreatitis.

A systematic review by Navaneethan et al. [85] published in 2015 evaluated the utility of SpyGlass™ Direct Visualization System peroral cholangioscopy and targeted biopsies for malignant strictures and cholangiocarcinoma (CCA) involving 456 patients showed that for cholangioscopy-guided biopsies, the sensitivity was 60.1% and the specificity was 98.0% in regards to malignant biliary strictures. The same author has reported in a previous meta-analysis that fluorescence in situ hybridization (FISH) increases the specificity for the diagnosis of CCA in patients with primary sclerosing cholangitis (PSC) [125].

A recent 10-year single center experience by Attwell et al. [112] evaluated the safety and efficacy of endoscopic retrograde cholangiopancreatography with peroral pancreatoscopy (POP) with electrohydraulic lithotripsy/laser lithotripsy for 46 patients with chronic calcific pancreatitis using a 10F cholangioscope (POP-Endo, 31 patients) and catheter-based system (POP-Cath, 15 patients) in which EHL/LL was performed. Stone extraction without EHL or LL was performed in 7 (15%) of 46 patients. Technical success for POP-Endo versus POP-Cath was 27 (87%) of 31 versus 15 (100%) of 15 patients ($P = 0.29$). Complete clearance of pancreatic duct stones was achieved in 21 (68%) of 31 versus 11 (73%) of 15 patients, respectively ($P = 0.519$). The authors reported peroral pancreatoscopy-related complications in 9 patients (10%). Six patients developed mild post-ERCP pancreatitis (3 in POP-Endo and 3 in POP-Cath). Two patients developed exacerbations of abdominal pain requiring overnight observation or emergency department evaluation after post-procedure discharge, and one patient developed perforation during combined EUS-guided pancreatography and POP. This was managed conservatively.

Peroral pancreatoscopy has been used sporadically for diagnosis of a number of pancreatic neoplasms, especially intraductal papillary mucinous neoplasm of the main pancreatic duct, besides ductal adenocarcinoma. The role of peroral pancreatoscopy in the evaluation of 79 patients with indeterminate pancreatic duct strictures, dilations, or with suspected or known main duct IPMN was published by El Hajj et al. [126] in 2014. The technical success of POP was achieved in 97% of cases. In the PD neoplasia group (33 patients), the final diagnosis was based on index confirmatory POP-guided tissue sampling in 29 patients (88%). The authors showed that tissue sampling has a higher sensitivity (91 versus 87%), specificity (95 versus 86%), positive predictive value (PPV) (94 versus 83%), negative predictive value (NPV) (93

versus 91%), and accuracy (94 versus 87%) when compared to visual impression only. Among 102 POPs, the adverse event rate was of 12% (seen in 12 patients) with 7 patients (7%) experiencing a flare-up of baseline abdominal pain that required admission for more than 24 h, and with 5 patients (5%) having serious adverse events (4 patients with post-procedure acute pancreatitis and 1 patient with moderate post-sphincterotomy bleeding requiring hospitalization, endotherapy, and blood transfusion).

Peroral pancreatoscopy with ductal visualization for the diagnosis of main duct IPMN lesions has a sensitivity of 67–100% compared with computed tomography (CT) (16–32%), intraductal ultrasound (56–100%), and endoscopic ultrasound (55–92%) [6, 117, 127].

Finally, a multicenter retrospective study by Adler et al. [128] evaluating the frequency and severity of adverse events with single-operator cholangiopancreatography in 222 patients undergoing single cholangioscopy and pancreatoscopy included post-ERCP pancreatitis (N. = 11, 3.9%, all mild), post-ERCP cholangitis (N. = 4, 1.4%), bleeding (N. = 3, 1%), and perforation (N. = 2, 0.7%). In addition, his study showed that vigorous irrigation of the bile ducts was not associated with increased rates of post-procedure cholangitis although some authors recommend that antibiotic prophylaxis for all patients undergoing cholangioscopy should be considered [129], given some studies reporting increased rates of cholangitis when ERCP is performed with cholangiopancreatography [130].

Overall cholangiopancreatography appears to be a safe and effective technique with acceptable morbidity. The applications of cholangiopancreatography are similar through the world as they are in the United States.

7. Future directions of cholangiopancreatography (CP)

Cholangiopancreatography continues to be an effective and evolving technique. The current cholangioscopes have improved significantly as far as digital imaging is concerned and availability of disposable devices continues to have a great impact on future development in this field.

The future cholangioscope would see continued improvement in digital imaging resulting in higher resolution high definition (HD) scopes along with narrow-band imaging capabilities. This may help to address some of the limitations in visibility that occur at times with the existing digital systems.

Minimizing the electronics and increasing the size of the accessory channel may improve therapeutic capabilities as well as the yield of tissue sampling. The use of near infra-red (NIR) fluorescence cholangiopancreatography in the detecting of pancreaticobiliary malignancies is also a promising field which will warrant more study in the near future [131].

8. Summary

Substantial advances in cholangiopancreatography have resulted in the widespread adoption of this procedure into advanced endoscopy practice in many centers worldwide.

Recent advancement in the field of cholangiopancreatography have provided gastroenterologists and endoscopists with invaluable tools that not only significantly aided in the evaluation and treatment of suspected biliary and pancreatic diseases (difficult biliary stones, indeterminate biliary strictures, pancreatic duct stones, pancreatic duct strictures, and suspected pancreatic neoplasms) but most importantly also have reduced the morbidity and mortality associated with the more aggressive and invasive surgical procedures used to evaluate and treat these type of disorders in the past.

Newer cholangioscopes are continuously developed by different manufacturers utilizing improved optics and technology to further increase the efficacy and safety of the technique of cholangiopancreatography.

Finally, it is very important to note that the best outcomes from these procedures occur when they are performed by well-trained and experienced endoscopists in tertiary centers. Whenever possible, these patients, especially patients with previously failed procedures and the elderly, should be referred to these centers for further evaluation and treatment.

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