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REVIEW

Endoscopic management of benign biliary strictures

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Abstract

Endoscopic management of biliary obstruction has evolved tremendously since the introduction of flexible fiberoptic endoscopes over 50 years ago. For the last several decades, endoscopic retrograde cholangiopancreatography (ERCP) has become established as the mainstay for definitively diagnosing and relieving biliary obstruction. In addition, and more recently, endoscopic ultrasonography (EUS) has gained increasing favor as an auxiliary diagnostic and therapeutic modality in facilitating decompression of the biliary tree. Here, we provide a review of the current and continually evolving role of gastrointestinal endoscopy, including both ERCP and EUS, in the management of biliary obstruction with a focus on benign biliary strictures.

Key words: Gastrointestinal endoscopy; Endoscopic cholangiopancreatography; Bile ducts; Biliary tract; Stricture; Stents

Core tip: Benign biliary strictures (BBSs) are commonly encountered by advanced endoscopists. As our understanding of longstanding techniques involving biliary dilation and plastic stent placement evolves, newer therapeutic options such as self-expandable metal stents and endoscopic ultrasound have become available. Here we review the literature pertaining to the most common etiologies of BBSs with current considerations for their respective endoscopic management.

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INTRODUCTION

Benign biliary strictures (BBSs) originate from a variety of etiologies (Table 1), most commonly post-operative

Table 1 Etiologies of benign biliary strictures

Postsurgical
Cholecystectomy (open or laparoscopic)
Liver transplantation (*i.e.*, anastomotic biliary stricture)
Bilio-enteric anastomosis
Sphincterotomy
Inflammatory
Chronic pancreatitis
Primary sclerosing cholangitis
Immunoglobulin G4-related cholangiopathy
Acquired immune deficiency syndrome cholangiopathy
Vasculitis
Other
Ischemia (*e.g.*, post-liver transplantation)
Trauma
Portal biliopathy
Infection (*e.g.*, Clonorchiasis)
Radiation injury
Idiopathic

injury (*e.g.*, post-cholecystectomy), chronic pancreatitis, and chronic cholangiopathies (*e.g.*, primary sclerosing cholangitis). The clinical presentation of BBSs depends greatly on the context, including the onset, degree, and sterility of obstruction, and ranges from subclinical (*i.e.*, incidentally detected biochemical abnormalities) to severe and life-threatening[1,2]. The diagnostic evaluation to determine the etiology of a BBS and exclude the possibility of underlying malignancy generally entails cholangiography *via* magnetic resonance (MRCP) and/or endoscopic retrograde cholangiopancreatography (ERCP) (with biliary brushings for cytology and/or intraductal biopsies for histology) in addition to serologic testing with serum liver tests and tumor marker carbohydrate antigen 19-9 (CA 19-9). Therapeutic interventions are aimed at providing durable biliary decompression, with options including ERCP, percutaneous, and surgical techniques.

Given its efficacy, safety, and less disruptive nature, ERCP has become the first-line therapeutic option for management of most cases of biliary obstruction, including but not limited to BBSs[3]. Since the introduction of ERCP in the 1970s, this technique has progressively evolved and enhanced the management of a variety of disorders of the biliary tract[4]. Currently, a wide array of catheters, guidewires, papillotomes, stents, and other accessories are available to facilitate diagnostic and therapeutic maneuvers in the management of BBSs.

In this review, we discuss the current role of, evidence for, and approach to endoscopic management in patients with BBSs.

PRINCIPLES OF BBS MANAGEMENT

Pre-procedure preparation

Owing to advancements in non-invasive imaging, ERCP has largely been supplanted by cross-sectional imaging for purposes of initial diagnosis. MRCP, facilitated by the high T2-signal intensity of bile as well as improvements

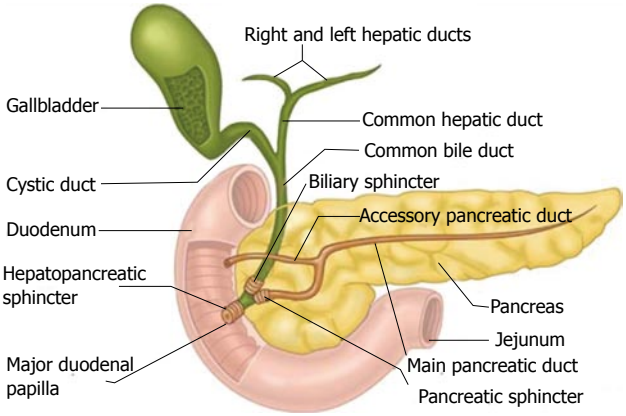

Figure 1 Normal biliopancreatic anatomy.

in MR imaging methods and post-processing tools, has essentially become the preferred modality for diagnostic cholangiography, with relatively few indications remaining for diagnostic ERCP[5]. Not all patients require cross-sectional imaging with MRCP or computed tomography prior to ERCP; however, having such data available can provide a useful roadmap and clarify the pre-procedural plan by shedding light on the patient's pancreatobiliary anatomy, which often does not follow the conventional teaching (Figure 1), and underlying disease. Patients who proceed to ERCP should, as with other endoscopic procedures, be fasting for a sufficient amount of time to allow gastric emptying (*e.g.*, 4-6 h), and careful review and management of antithrombotic medications (if applicable) should be undertaken[6]. Pre-procedural antibiotics should be administered in selected patients in whom adequate drainage is not anticipated such as those with complex hilar strictures and PSC.

Deep biliary access

Once bile duct cannulation has been achieved, attempts at guidewire passage beyond the BBS may prove challenging depending on the severity and anatomic location of obstruction. BBSs can be more difficult to traverse than neoplastic strictures due to greater asymmetry, angulation, and density of fibrous tissue[7]; nevertheless, forceful maneuvers should be avoided, as these may result in the creation of a false tract or perforation. If necessary, guidewire passage can be facilitated by: (1) positioning an inflated stone extraction balloon just below the stricture and withdrawing it, which allows for traction and better alignment between the guidewire and stricture axes; or by (2) selection of an alternative guidewire tailored to the particular stricture anatomy.

Multiple types of guidewires are commercially available and vary in their properties, including diameter, construction material (nitinol, stainless steel), type of coating (hydrophilic *vs* nonhydrophilic), and tip morphology (straight, angled) (Table 2). Comparative studies between guidewires are lacking, but standard 0.035-inch hydrophilic guidewires can be used for most BBSs, whereas tighter strictures may require

Table 2 Commonly used guidewires in endoscopic retrograde cholangiopancreatography

	Diameter (inch)	Length (cm)	Core material	Sheath material	Tip material/ properties	Tip shape	Comments	Cost ($)
Monofilament								
Amplatz (Boston Scientific)	0.038	260	Stainless steel	Uncoated	Platinum	Straight	Extremely stiff	149[1]
Coiled								
Standard (Cook Medical)	0.035	480	Stainless steel	Uncoated	Stainless steel coil	Straight	Must remove prior to sphincterotomy	90
Coated								
Tracer metro direct (Cook Medical)	0.021, 0.025, 0.035	260, 480	Nitinol	Teflon	Platinum; hydrophilic (5 cm)	Straight, angled	Kink resistant, graduated endoscopic markings	196
Delta (Cook Medical)	0.025, 0.035	260	Nitinol	Polyurethane	Hydrophilic (fully)	Straight	Kink resistant, fully hydrophilic, must remove prior to sphincterotomy	151
Roadrunner (Cook Medical)	0.018	260, 480	Nitinol	Teflon	Platinum	Straight, angled	Kink resistant, must remove prior to sphincterotomy	184
Jagwire (Boston Scientific)	0.025, 0.035 0.038 (260)	260, 480	Nitinol	Endo-Glide™	Tungsten, hydrophilic (5 cm)	Straight, angled; trim, round	Kink resistant, guidewire extension (0.035, 200) available	357/box of 2
Hydra Jagwire (Boston Scientific)	0.035	260, 450	Nitinol	Endo-Glide™	Tungsten, two hydrophilic tips (5 cm, 10 cm)	Straight, angled; round	Kink resistant; two tips of varying stiffness on a single guidewire	536/box of 2
NaviPro (Boston Scientific)	0.018, 0.025, 0.035	260	Nitinol	Endo-Glide™	Hydrophilic (fully)	Straight, angled	Fully hydrophilic; 0.035-in also available in stiff	1124/box of 5
Visiglide (Olympus)	0.025, 0.035	270, 450	Superelastic alloy	Fluorine	Hydrophilic (7 cm)	Straight; angled	0.025-in has same stiffness as 0.035-in guidewire	255
XWire (ConMed)	0.025, 0.035	260, 450	Regiliant™ Nitinol	PTFE	Nitinol and Tungsten and PTFE, hydrophilic (5 cm)	Straight; angled	5cm radiopaque tip; 0.035-in also available in stiff	460/box of 3 (260 cm) 583/box of 3 (450 cm)

Other less commonly used guidewires include Dreamwire (Boston Scientific), Savary-Gilliard (Cook Medical), Tracer Metro (Cook Medical), Fusion (Cook Medical), FXWire (ConMed), and Flex-Ez (Hobbs Medical). [1]Cost data obtained from ASGE "Guidewires for use in GI endoscopy," Table 1[97]. PTFE: Polytetrafluoroethylene.

guidewires with a smaller diameter and/or angled tip. Once a stricture has been traversed, the guidewire can be exchanged, if needed, for a stiffer or nonhydrophilic guidewire to facilitate dilation and stenting. Biliary sphincterotomy (*i.e.*, papillotomy) is also frequently necessary if large (cumulative) caliber stenting is anticipated.

Stricture dilation

Stricture dilation (*i.e.*, stricturoplasty) is primarily performed using a dilating balloon or bougie-like tapered catheter. Typical dilating balloon sizes range from 4 to 12 mm, and selection can generally be guided by upsizing 1-2 mm from the diameter of the distal bile duct. In the case of post-liver transplantation (LT) anastomotic biliary strictures (ABSs), dilating to the size of the adjacent donor or recipient duct, whichever is smaller, can be used as a guide[8]. Particular caution should be taken, however, when dilating ABSs during the early post-operative period (< 30 d after surgery) or while a patient is still on high dose immunosuppression, as both of these scenarios may be associated with a higher risk for anastomotic injury or disruption[8-12]. In such instances, less aggressive dilation using a smaller balloon or alternatively a tapered dilating catheter is advisable. With respect to duration of dilation intraprocedurally, most endoscopists adhere to 30 to 60 s of dilation, or until the stricture waist is fractured, before balloon deflation.

Stenting

Balloon dilation alone, although immediately effective, is associated with a high rate of stricture recurrence (up to 47%) depending on the underlying nature of the BBS[13]. Therefore, insertion of biliary stents is frequently required to maintain stricture patency while permitting ductal remodeling. Moreover, placement of several, large-bore plastic stents side-by-side (*i.e.*, multiple or "maximal" endoscopic stenting[8,14]) for up to 1 year has been shown to be superior than inserting only a single stent; this is therefore the currently recommended approach for the majority of BBSs[8,14-18].

The main limitation of endoscopic stenting in this setting is the need to undergo multiple ERCPs for stent exchange. This stems from the relatively short patency time of plastic biliary stents, although there is evidence to support that occlusion rates are similar between stents with dwell times shorter and longer than 6 mo[19]. In addition, and as alluded to above, placement of maximal stents may lessen the need

Table 3 Commonly used partially-covered and fully-covered self-expandable metal stents

Stent name (manufacturer)	Covering	Core material	Diameter (mm)	Length (cm)	Delivery system (Fr)	Features
Wallflex RX	Partial	Platinol	8, 10	4, 6, 8	8.5	Closed cell construction; retrieval loop; looped and flared ends; restrainable
(Boston Scientific)	Full	Platinol	8, 10	4, 6, 8	8.5	
Wallstent (Boston Scientific)	Partial	Elgiloy	8, 10, 12	2, 4, 4.2, 6, 6.8, 8, 9, 9.4	6, 7, 9	Closed cell construction; restrainable
Niti-S ComVi (Taewoong Medical)	Partial	Nitinol	6, 8, 10	4, 5, 6, 7, 8, 9, 10, 12	8	Open cell; triple layered construction: mesh, membrane, and mesh to reduce migration
	Full	Nitinol	6, 8, 10	4, 5, 6, 7, 8, 9, 10, 12	8	
Niti-S Kaffes (Taewoong Medical)	Full	Nitinol	6, 8, 10	4, 5, 6, 7, 8	9	Long retrieval string
Niti-S (Taewoong Medical)	Partial	Nitinol	6, 8, 10	4, 5, 6, 7, 8, 9, 10, 12	8	Retrieval string at proximal end
	Full	Nitinol	6, 8, 10	4, 5, 6, 7, 8, 9, 10, 12	8.5	
Niti-S Bumpy (Taewoong Medical)	Full	Nitinol	6, 8, 10	4, 5, 6, 7, 8, 9, 10, 12	8.5	Irregular cell sizes; retrieval string at proximal end; flared ends
Nitinella Plus (ELLA-CS)	Partial	Nitinol	8, 10	4, 6, 8, 10	9	Reconstrainable; kink-resistant
	Full	Nitinol	8, 10	4, 6, 8, 10	9	
Hanarostent (M.I. Tech)	Full	Nitinol	8, 10	4, 6, 8, 10	8	Larger flared ends
Micro-Tech (Micro-Tech)	Partial	Nitinol	10	4, 6, 8, 10	9	
	Full	Nitinol	10	4, 6, 8	9	
Gore Viabil (CONMED)	Full (with sideholes)	Nitinol	8, 10	6, 8, 10	8.5	Sideholes allow branch drainage; anchoring fins
	Full (without sideholes)	Nitinol	8, 10	6, 8, 10	8.5	
Allium BIS (Allium Medical)	Full	Nitinol	8, 10	6, 8, 10, 12	10	Anchoring segment; non-shortening

for frequent stent exchange, as biliary drainage can continue to occur even after stent occlusion *via* the inter-stent spaces (*i.e.*, "wick effect")[8]. Avoiding multiple ERCPs can also be facilitated by placement of one or more (covered) self-expandable metal stents (SEMSs) instead of plastic stents. SEMSs offer an attractive alternative because of innate properties that allow them to self-expand to diameters 3 times that of 10-Fr plastic stents, thus resulting in longer duration of patency. SEMSs can also be delivered using smaller deployment systems (*i.e.*, 8-8.5-Fr) that do not require as aggressive dilation at the time of stent placement or biliary sphincterotomy. SEMSs of various configurations and properties are currently available[1]; to date, however, none are approved by the United States Food and Drug Administration for the treatment of BBSs. The three major categories of stents, uncovered, partially-covered, and fully-covered, are briefly reviewed below.

Uncovered SEMSs are plagued by the ingrowth of reactive tissue (*i.e.*, epithelial hyperplasia), which can lead to stent occlusion as well as irretrievable embedding of a stent in the ductal wall[20]. As a result, uncovered SEMSs should not be used in the treatment of BBSs[17]. Partially-covered stents, which leave proximal and distal ends bare, are consequently less prone to becoming embedded in issue and thus have improved ease of retrieval. In the largest study of partially-covered SEMSs used to treat BBSs of various etiologies (n = 79), Kahaleh *et al*[21] reported a stricture resolution rate of 90% following a 4-mo stenting period and 12-mo follow-up time. Although all attempted stent retrievals were successful in this study, the potential for tissue hyperplasia involving the bare ends, as reported in other studies, still exists[22,23]. In an effort to further reduce the risk of stent ingrowth and improve removability, fully-covered SEMSs (lined with silicone, polyether polyurethane, polyurethane, expanded polytetrafluoroethylene, or other materials) have been developed and investigated in the treatment of BBSs (Table 3). Most studies of fully-covered SEMSs, barring those with a predominance of patients with particularly refractory strictures (*e.g.*, chronic pancreatitis), have reported favorable clinical success rates, ranging 80% to 90%, as well as low recurrence rates ($\leqslant$ 10%)[24-33]. A tradeoff of this stent design, however, is their predilection for migration, with several studies reporting fully-covered SEMS migration rates between 20% to 40%[24,25,28,31-33]. Of particular concern is the potential for a migrated SEMS to complicate stent removal (proximal migration) or cause bowel obstruction (distal migration). Recent studies investigating anti-migratory modifications to fully-covered SEMSs (*e.g.*, anchoring fins) have reported reduced albeit not clinically insignificant rates of migration[27,29,30]. The role of fully-covered and partially-covered SEMSs is described further in forthcoming sections.

CONSIDERATIONS FOR SPECIFIC BBS ETIOLOGIES

Post-operative strictures

Post-cholecystectomy: Cholecystectomy remains a common etiology of BBSs, with an incidence of 0.2% to 0.7% among patients undergoing laparoscopic cholecystectomy[34]. Post-cholecystectomy BBSs develop as a consequence of bile duct injury that may occur intraoperatively (dissection, electrocautery, clip

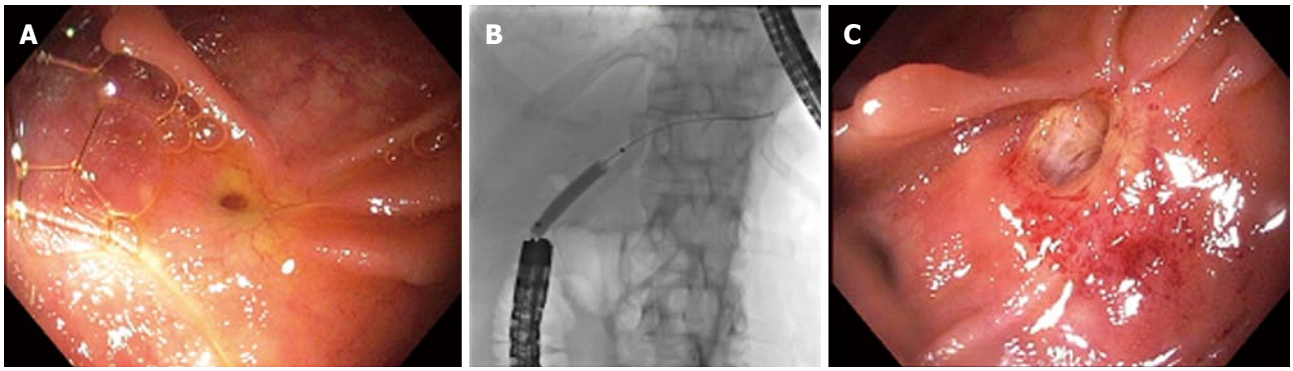

Figure 2 Anastomotic biliary stricture at the site of hepaticojejunostomy in a liver transplantation patient. A: Endoscopic view of hepaticojejunal anastomotic biliary stricture; B: Radiographic image taken during balloon dilation demonstrating the stricture waist; C: Endoscopic view immediately post-dilation of the anastomotic biliary stricture.

or suture placement, ligation) and/or post-operatively (adhesion formation)[35]. Long-term data of post-operative BBSs treated with multiple plastic stents and intermittent stent exchange (approximately every 3 mo) over the course of a year have demonstrated promising success rates ranging from 80% to 100%[15,18,36,37]. This approach has thus become the current standard of care when treating post-operative BBSs[38]. It should be noted, however, that post-operative strictures located at the hepatic ductal confluence may be less responsive to endoscopic stenting than strictures located more distally (25% *vs* 80% resolution rate)[15].

There are limited data regarding the use of fully-covered and partially-covered SEMSs in the treatment of post-cholecystectomy strictures. These data are derived from a small subset of patients with post-cholecystectomy strictures included in SEMSs studies. For example, in a large, multicenter study of fully-covered SEMS (n = 187), 18 patients with post-cholecystectomy strictures (14 of which were previously treated with plastic biliary stents) underwent SEMS placement. After 10-12 mo of stenting, 13 patients (72%) experienced stricture resolution without need for immediate re-stenting. Two-thirds, however, experienced stent migration by 12 mo, and 6 patients (33%) experienced cholangitis, fever or pancreatitis[39]. Based on these findings, SEMSs cannot be routinely recommended for treatment of post-cholecystectomy strictures.

Post-LT: Among patients who have undergone LT, BBSs are among the most common post-operative complications, with their incidence ranging from 5% to 15% and 28% to 32% following deceased donor and living donor LT, respectively, and even higher rates in cardiac death donor LT[12,40,41]. Post-LT BBSs can manifest early (< 30-90 d) or late (> 90 d) in the post-LT course and may occur at the anastomosis (*i.e.*, ABS) or elsewhere in the biliary tree (*i.e.*, non-anastomotic biliary stricture, NABS). Endoscopic therapy is the first line management approach for ABSs and for select NABSs, with percutaneous intervention and surgical revision or redo-LT being reserved for endoscopic treatment failures. ABSs and NABSs are further discussed below.

ABSs are a consequence of local trauma at the surgical juncture between the recipient's and donor's extrahepatic ducts (most commonly CBD-CBD choledocho-choledochostomy) and account for 80% of post-LT biliary strictures[42]. They appear as a short, single stricture localized to the anastomosis. Earlier presentations (< 30-90 d) generally respond well to endoscopic dilation (Figure 2) and a relatively brief period of plastic stenting (approximately 3 to 6 mo), whereas later presentations may require up to 1-2 years of stenting to avoid stricture recurrence based on the few available published series[42-44]. Unfortunately, most studies regarding management of ABSs are retrospective and heterogeneous (*e.g.*, in stricture etiology, severity, and other variables), yet several have shown consistent long-term success rates of approaching 90% to 100% with balloon dilation and multiple or maximal plastic stent therapy[8,45-49]. ABSs may also be treated with SEMSs, but this has been less studied and seldom practiced for a variety of reasons[23-26]. For example, a multicenter trial of partially-covered SEMSs was associated with a modest long-term success rate of 53%, and removal of the stent was technically demanding in 6 out of 21 (29%) patients due to embedding of the bare ends[23]. Conversely, studies using fully-covered SEMSs have reported more promising success rates (ostensibly due to longer dwell times), ranging 92% to 100%, but with higher stent migration rates (as high as 24%)[24-26].

NABSs account for 10%-25% of post-LT biliary strictures[50,51] and are typically a sequela of donor-recipient ABO incompatibility, prolonged graft ischemic time peri-LT, or post-LT hepatic artery thrombosis[52]. NABSs are often referred to as ischemic strictures, although it should be noted that not all NABSs have a clearly ischemic etiology. In contrast to ABSs, NABSs may be either unifocal or distributed diffusely throughout the extra- and/or intrahepatic biliary tree (Figure 3), are more technically challenging to access and treat, and have lower long-term endoscopic treatment success rates (50% to 75%)[45,53]. Nevertheless, maximal

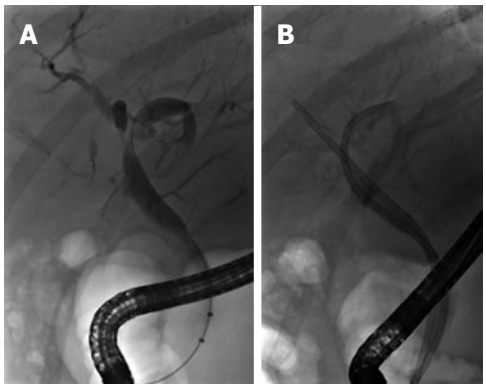

Figure 3 Anastomotic and nonanastomotic biliary strictures in a liver transplantation patient. A: Anastomotic biliary stricture and hilar nonanastomotic biliary strictures are present; B: Radiographic image taken immediately following placement of a 10-Fr 15 cm Cotton-Leung (Cook Medical) and a 10-Fr 22 cm (cut down to 16 cm) Johlin (Cook Medical) plastic biliary stent.

stenting, as with ABS, may result in graft preservation and overall favorable outcomes in a considerable proportion of patients with NABSs[14,45,53-55], although some will ultimately require re-transplantation[10,45,56].

Chronic pancreatitis

BBSs develop in approximately 25% of patients with chronic pancreatitis and represent a major clinical challenge[1]. These strictures occur in the distal CBD, and their refractory nature is largely attributable to robust periductal fibrosis secondary to the underlying chronic inflammatory process[57]. It is important to rule out underlying malignancy in this context, as it can have an initial presentation similar to BBSs and pancreatic cancer can occur in the setting of established chronic pancreatitis. With respect to treatment of chronic pancreatitis-associated BBS, biliary decompression is indicated in patients who are symptomatic (*e.g.*, cholangitic, deeply jaundiced), and as with post-operative BBSs, insertion of multiple plastic stents with 3-4 exchanges over a year appears to offer the highest likelihood of long-term benefit. Studies range in overall success of endoscopic therapy from 44% to 92%, with lower rates among those with dystrophic calcification of the pancreatic head[15,58-60]. Surgical intervention (*e.g.*, Puestow pancreaticojejunostomy, Traverso-Longmire pancreaticoduodenectomy[61]) is indicated in patients who fail endoscopic management and are fit for surgery[57,60].

A number of studies have investigated the role of fully as well as partially-covered SEMSs in chronic pancreatitis. Fully-covered SEMSs have demonstrated success rates ranging from 43% to 77% in patients with chronic pancreatitis-associated BBSs, but stent migration have historically been a common problem, as is the case with post-operative BBSs[21,27,62,63]. A recent, multicenter study of 118 patients with chronic pancreatitis-associated BBSs, however, found that fully-covered SEMS placement was associated with an 80% stricture resolution rate (median stent dwell time 11 mo) and a more acceptable stent migration rate (19% at 12 mo)[39]. Studies using fully-covered SEMSs with antimigratory modifications, or partially-covered SEMSs, have also reported encouraging stricture resolution rates (approximately 90%), and with even lower rates of stent migration[29,63,64].

Primary sclerosing cholangitis

Primary sclerosing cholangitis (PSC) is an idiopathic disorder characterized by periductal inflammation and fibrosis involving the intrahepatic and/or extrahepatic biliary tree. Up to 50% of patients with PSC will develop "dominant" strictures, which are loosely defined as a CBD stenosis of $\leqslant$ 1.5 mm in diameter or hepatic duct stenosis $\leqslant$ 1 mm in diameter, during their disease course[65,66]. A major challenge in the setting of a PSC-associated dominant stricture is excluding underlying malignancy (*i.e.*, cholangiocarcinoma), which develops in up to 20% of patients with PSC[67-70]. At a minimum, brush cytology and/or intraductal biopsies, are required. If available, advanced cytologic and imaging methods should also be considered.

The overarching goal of endoscopic therapy in PSC-associated dominant BBSs is to improve signs, symptoms and sequelae of biliary obstruction; when performed appropriately (including both patient selection and procedural technique), endoscopic therapy can improve Mayo PSC risk score, which has been shown to translate into improved survival[68,71-74]. Biliary (balloon) dilation alone is the preferred therapeutic approach, as stenting has been shown to result in slightly higher rates of complications (*i.e.*, stent occlusion and cholangitis) in some series[75,76]. Repeated dilation (*i.e.*, multiple ERCP sessions) may be necessary in some patients to achieve maximal clinical benefit[77]. If dilation is unsuccessful (*i.e.*, persistent stricture waist), short-term stentings with plastic biliary stents has been shown to be safe and effective with durable benefit[78]. Prophylactic antibiotics should also be administered periprocedurally to reduce the risk of ERCP-related cholangitis unless full biliary drainage is highly anticipated[79,80].

Altered anatomy after hepatobiliary surgery

Biliary-enteric strictures can occur following pancreaticoduodenectomy (Whipple procedure), partial liver resection, and liver transplantation with Roux-en-Y hepaticojejunostomy in 12%-28% of patients[81,82]. Endoscopic therapy of these strictures was once felt to be impossible due to surgical alterations in intestinal anatomy that precluded access *via* conventional endoscopic methods. However, the use of colonoscopes and more recently, device-assisted enteroscopes (single, double, and short double balloon), combined with more widespread training of advanced endoscopists have brought these strictures within reach[83]. In patients post-standard Whipple, the hepaticojejunostomy is almost always reachable, whereas pylorus preserving Whipple, and choledocho- and hepaticojejunostomy

Roux-en-Y render more challenging, but often still conquerable anatomy in the hands of an experienced endoscopist with balloon-enteroscopes. A recent meta-analysis included 15 studies and 461 patients with surgically altered pancreaticobiliary anatomy (Roux-en-Y bypass, Roux-en-Y reconstruction, and standard and pylorus preserving Whipple) undergoing single-balloon enteroscopy-assisted ERCP. The pooled enteroscopy, diagnostic, and procedural success rates were 81%, 69%, and 62%, though a high degree of heterogeneity was reported[84]. Limiting analysis to patients with Roux-en-Y reconstruction or Whipple yielded higher diagnostic and procedural success rates at 79% and 63% with much lower heterogeneity[85]. In a retrospective study of patients with biliary-enteric strictures following surgical repair of iatrogenic cholecystostomy injuries (n = 32), Lee *et al*[86] reported balloon dilation alone to be successful in 66% of patients with only 1 (5%) recurrence over a mean 13.1 years of follow-up.

An endoscopic approach can be limited by time, availability, and endoscopist expertise. When unsuccessful, percutaneous transhepatic access (with or without rendezvous techniques)[86], percutaneous drains, and surgical revision remain alternative therapeutic options.

ENDOSCOPIC ULTRASOUND IN BBS MANAGEMENT

Even in expert hands, attempts at therapeutic ERCP for BBSs may fail in 2% to 10% of cases due to inability to cannulate the bile duct (*e.g.*, surgically altered anatomy, tumor infiltration) or traverse a tight bile duct stricture. In select cases, endoscopic ultrasound (EUS) may serve as ancillary therapeutic techniques prior to proceeding with options such as percutaneous or surgical intervention. EUS can be employed in a rendezvous technique that establishes transpapillary guidewire access, thereby allowing conventional ERCP with balloon dilation of a BBS followed by stent placement (if indicated).

EUS-guided biliary access and drainage can also be performed by needle puncture of the gastric wall and advancement into the left hepatic duct tributaries (*i.e.*, hepaticogastrostomy)[87-90] or through the duodenal wall into the CBD (*i.e.*, choledochoduodenostomy)[91,92]. Thereafter, drainage can be internalized through the papilla without requiring a rendezvous approach (although combination approaches can be useful as well)[93,94]. As alluded to before, this technique is particularly useful when biliary cannulation or access to the papilla cannot be achieved due to duodenal obstruction or other causes[95,96].

Adverse events

Adverse events related to endoscopic management of biliary strictures may occur secondary to stricture access or dilation, and stent placement or dwell time (early or late). Sphincterotomy can be associated with pancreatitis, luminal perforation, or bleeding, as seen in patients undergoing ERCP for other indications. Stricture dilation (particularly in the setting of a fresh surgical anastomosis) and stent deployment also run the risk of perforation. Stent-related adverse events include early or late migration, impaction or embedment (metal stents), or occlusion with the potential for cholangitis. Plastic stents therefore necessitate removal or exchange in 3 mo with concurrent removal of all stones and sludge.

CONCLUSION

Endoscopic therapy provides a minimally invasive, safe, and reliable first-line management option for most BBSs. An approach involving multiple plastic stent placement and intermittent stent exchanges works well in post-cholecystectomy strictures and ABSs, whereas other stricture types, such as NABSs and chronic pancreatitis-associated strictures, tend to be more challenging, with some patients ultimately requiring surgical intervention. The recent and rapid evolution of SEMSs may provide an alternative means to treat some BBSs while reducing the need for frequent ERCPs, but additional studies that better define their application, complications, and cost-effectiveness remain needed. Lastly, applications of therapeutic EUS for biliary disease are becoming increasingly recognized and implemented, and continued advancements in both ERCP and EUS are anticipated.

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REVIEW

Cell-block procedure in endoscopic ultrasound-guided-fine-needle-aspiration of gastrointestinal solid neoplastic lesions

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Abstract

In the present review we have analyzed the clinical applications of endoscopic ultrasound-guided-fine-needle-aspiration (EUS-FNA) and the methodological aspects obtained by cell-block procedure (CBP) in the diagnostic approach to the gastrointestinal neoplastic pathology. CBP showed numerous advantages in comparison to the cytologic routine smears; in particular, better preservation of cell architecture, achievement of routine haematoxylin-eosin staining equivalent to histological slides and possibility to perform immunohistochemistry or molecular analyses represented the most evident reasons to choose this method. Moreover, by this approach, the differential diagnosis of solid gastrointestinal neoplasias may be more easily achieved and the background of contaminant non-neoplastic gastrointestinal avoided. Finally, biological samples collected by EUS-FNA CBP-assisted should be investigated in order to identify and quantify further potential molecular markers.

Key words: Endoscopic ultrasound-guided-fine-needle-aspiration; Cell-block procedure; Gastrointestinal tract; Immunohistochemistry; Diagnosis

Core tip: Cell-block procedure (CBP) represents the most suitable complement in diagnostic cytopathology of many gastrointestinal lesions. Hence this method allows high quality morphological evaluation and immunocytochemical analyses. On this way, the differential diagnosis of solid gastrointestinal neoplasms may be more easily achieved and the background of contaminant non-neoplastic gastrointestinal avoided, with an evident gain compared to the traditional cytological techniques. In the present review, the application of CBP in gastrointestinal solid lesions approached by endoscopic ultrasound-guided-fine-needle-aspiration, the methodological aspects and the accuracy of this diagnostic process are analyzed and discussed.

Ieni A, Barresi V, Todaro P, Caruso RA, Tuccari G. Cell-block procedure in endoscopic ultrasound-guided-fine-needle-aspiration of gastrointestinal solid neoplastic lesions. *World J Gastrointest Endosc* 2015; 7(11): 1014-1022 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i11/1014.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i11.1014

INTRODUCTION

Endoscopic ultrasound-guided-fine-needle-aspiration (EUS-FNA) represents a useful diagnostic procedure in the field of gastrointestinal pathology[1-3]. It is performed by using a curved linear array video-echo-endoscope equipped with various needles which provide cytological samples; in this way, the ability to obtain cytologic material is greatly increased due to direct visualization, with a consequent better opportunity to perform an accurate diagnosis. Since its introduction, EUS-FNA emerged as a minimally-invasive, safe and accurate technique for the diagnosis of various luminal, submucosal and extra luminal gastrointestinal neoplasms[4].

The European Society of Gastrointestinal Endoscopy published the guidelines for EUS-guided sampling, with comments on the technical prerequisites for maximizing the diagnostic yield of this procedure[5]. However, the acquisition of diagnostic samples should be approached in different ways depending on the type of the lesion. Moreover, the actual efficacy of EUS-FNA partly depends on the site, size and characteristics of the target tissue as well as on the expertise, training and interaction between endosonographer and cytopathologist[6,7].

Cell-block procedure (CBP) is a diagnostic tool which has been carried out by using different procedural steps and protocols over the years[7-11]. This technique presents several advantages compared to the cytologic routine smear: preservation of cell architecture, achievement of routine haematoxylin-eosin staining equivalent to that of surgical samples and, finally, the possibility to perform ancillary methods, such as immunohistochemistry or molecular analyses[7,8,12,13]. In particular, CBP allows the availability of an adequate number of serial sections, with increased possibility to detect malignant cells and contaminating or reactive non-neoplastic elements[6,7,13].

Aims of the present review are to discuss the application of CBP in gastrointestinal solid lesions approached by EUS-FNA and to analyze the methodological aspects and accuracy of this diagnostic process.

Methodological aspects of EUS-FNA

One of the most debated issues on EUS-FNA relates to the number of needle passes required to provide adequate diagnostic material. The presence of a well trained cytopathologist, able to evaluate the quality of samples, is probably crucial in order to decrease the number of unsatisfactory results and to reduce the need for additional passes. Indeed, the prompt cytopathology response may be useful for the endosonographer to know whether the needle aspirate is diagnostic or not[2,4,14-19]. Although it has been repeatedly reported that on-site cytological evaluation improves the diagnostic yield and accuracy of EUS-FNA, other factors, such as the localization, nature, presentation, size and sonography characteristics of the lesion, may influence the number of needle passes[2-4,20]. In detail, the percentage of adequate specimens and sensitivity of EUS-FNA are lower in intra-parietal lesions of the gastrointestinal tract (GI) compared to those of lesions in other sites[1,21,22]. In addition, the diagnostic yield and accuracy for EUS-FNA also depend on the size of the lesion and they are significantly lower in lesions less than 10 mm in size[1,23,24]. On the whole, two to five needle passes are considered to be sufficient to obtain enough diagnostic material for a correct diagnosis by EUS-FNA[2,3,20,22,25,26]. The needle size is another relevant factor. 19-G needle seems to be the most adequate to provide higher amount of diagnostic material, especially when the cytopathologist is not present in the endoscopy room. Nonetheless the 22-G or 25-G are the most commonly used needles for the cytological sampling of gastrointestinal lesions because of their easier penetration without any further complications[2,16,27,28].

Finally, a special technical training in EUS-FNA should be mandatory, as recommended by the American Society of Gastrointestinal Endoscopy which codifies the minimum number of cases that should be analyzed depending on the site of lesion[29-31].

Needle-based confocal laser endomicroscopy (CLE) is a novel endoscopic method, in which imaging is based on tissue illumination and detection of tissue-reflected fluorescence; interestingly this technique gives high-quality images which are similar to those obtained by traditional histology[32-34]. The development of tissue specific contrast agents might further extend the application of CLE to pancreatic masses, either solid or cystic, intra-parietal or submucosal gastric and esophageal tumours, biliary tract and ampullary lesions[2,33,35].

Methodological aspects and advantages of CBP

CBP has been extensively used in cytology as a helpful tool to achieve a definitive diagnosis[8-10,36,37]. CBP may be carried out by using different protocols based on various fixatives and embedding techniques[8,10,38-40].

In the manual traditional method, following the rapid on-site evaluation of specimen adequacy and preliminary cytological diagnosis by quick stains, the needles and syringes used in the procedure are rinsed with 10 mL of 50% ethanol into a special container in order to recover further material. All content is centrifuged in a 10 mL disposable centrifuge tube at 4000 rpm for 6 min to create 1 or 2 pellets; the

supernatant fluid is decanted and the pelleted material obtained by sedimentation is immediately fixed in a freshly prepared solution of 4% neutral buffered formalin for 45 min. Then, the cell pellets are placed in a cassette and stored at 80% ethanol until they are ready for processing in an automatic tissue processor[36].

CBP may be based on thrombin or albumin methods. In the former, six drops of discarded human plasma and six drops of thromboplastin-DS are added to the cell sediment in order to form a clot, while in the latter 3-4 drops of 22% bovine albumin and 95% ethanol are added to the cell sediment to form a precipitate[9,41]. Whatever is the method, clots or/and precipitates are embedded in paraffin at 56 ℃ to realize cell blocks which are cut into 3 μm thick sections routinely stained with H and E or mounted on poly-lysine-coated glasses for immunocytochemical and molecular procedures.

A novel automated method for cell block production is the Cellient™ Automated Cell Block System. Compared to the traditional manual method, the automated one allows to achieve higher cellularity and better cellular presentation in terms of architecture and details; in addition it is faster and more reliable due to lack of operator dependency[9,39,42]. Gorman and coll. showed that Cellient cell blocks gives an adequate cellularity in all the analyzed cases, while formalin and thrombin cell blocks show a progressively decreasing adequacy[37]. The main drawback of Cellient system is methanol-based fixation, which may have negative impact on the following immunohistochemical analysis[8,9]. Indeed weaker staining intensity for ER, PR, MIB-1 and HER2 was shown by using this procedure[8,37,43,44]. However this issue may be overcome by formalin pre-fixation prior to Cellient[9]. Thirty minutes pre-fixation seems to be preferable to longer fixation to ensure good morphological quality[9].

On the whole, CBP allows the collection of higher quantity of diagnostic material. Hence it may be relevant in reducing the false negative diagnoses in EUS-FNA, which may depend, not only on erroneous interpretation of the cytological samples, but also on the availability of low cytological material. In addition it was shown that CBP greatly increases the diagnostic accuracy of EUS-FNA[7,22]. CBP also represents the most appropriate method to obtain cytological preparations for subsequent immunocytochemistry. Indeed immuno-stains on CBP sections show minimal background and appear similar to those observed in surgical pathology material. In addition, numerous serial sections may be obtained from a single cell block, allowing the evaluation of a large spectrum of antigens, also in archival samples. The number of antibodies that can be applied in routinely CBP has been expanding over the years[2,3,7-9,13,37]. The possibility to test serial sections with different antibodies may allow to identify and discriminate gastrointestinal hyperplastic or reactive contaminating cells from well differentiated tumour cells[7,13,45].

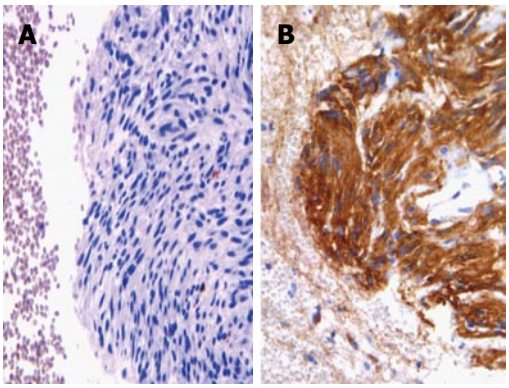

Figure 1 Cell block from gastrointestinal stromal tumour exhibiting aggregates of spindle cells with elongated nuclei (haematoxylin-eosin, × 200) (A), with an evident immunoreactivity for CD117 (immunoperoxidase, × 200, Mayer's Haemalum nuclear counterstain) (B).

CLINICAL APPLICATION OF EUS-FNA CBP-ASSISTED IN GI TRACT

Subepithelial/intramural neoplasms of the gastrointestinal wall

Although conventional endoscopy, CT scan and MRI may identify subepithelial/intramural lesions in the gastrointestinal wall, they can not reveal the nature and origin of those lesions. A wide range of subepithelial tumours, such as leiomyomas, neurinomas, granular cells tumours, gastrointestinal stromal tumours (GISTs), neuroendocrine tumours, leiomyosarcomas and lymphomas, may involve the GI tract[1,6,46] and many of those neoplastic entities exhibited over-lapping cytological features[6,46], being composed by monomorphic, uniform spindle shaped cells with eosinophilic cytoplasm, vesicular elongated nuclei characterized by finely granular chromatin, sometimes dispersed and inconspicuous nucleoli (Figure 1A). For this reason, the use of immunocytochemistry, which is easily applicable to CBP, may be helpful for the differential diagnosis. In detail, the coexistence of smooth muscle actin and desmin stains strongly supports the muscle origin of the lesion, while positivity for CD-34, CD-117 (Figure 1B) or S-100 suggests other diagnostic hypotheses, such as inflammatory fibroid polyp, GIST or schwannoma[6,46,47]. The assessment of the growth fraction by using Ki-67 labeling index (Figure 2A) may further discriminate the benign or malignant nature of intra-parietal neoplasias, and may allow distinction among leiomyoma, leiomyosarcoma, spindle cells amelanotic melanoma or undifferentiated sarcomatoid carcinoma[6,46,48].

The great efficacy of EUS-FNA associated with the higher accuracy obtained by CBP are helpful to achieve the correct preoperative diagnosis of a sub-epithelial mass which is relevant to establish the operative planning and type of surgery, and to avoid unnecessary procedures for extensive malignant lesions[6,46,49]. In addition, periodic follow-up with EUS is considered to be more acceptable to evaluate eventual changes in

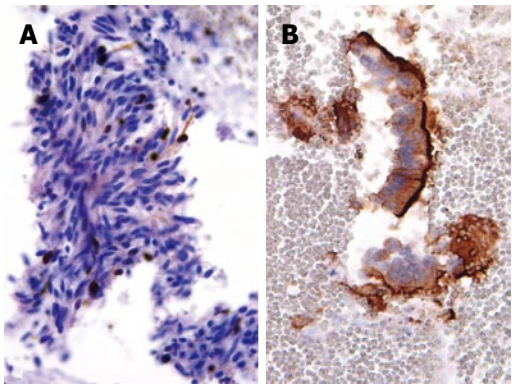

Figure 2 Spindle cells of gastric gastrointestinal stromal tumour documented only a sporadic nuclear Ki67 immunopositivity (immunoperoxidase, × 400, Mayer's Haemalum nuclear counterstain) (A) in benign contaminant gastrointestinal cells, the apical cytoplasm showed a peculiar CD10 immunoreactivity (immunoperoxidase, × 400, Mayer's Haemalum nuclear counterstain) (B).

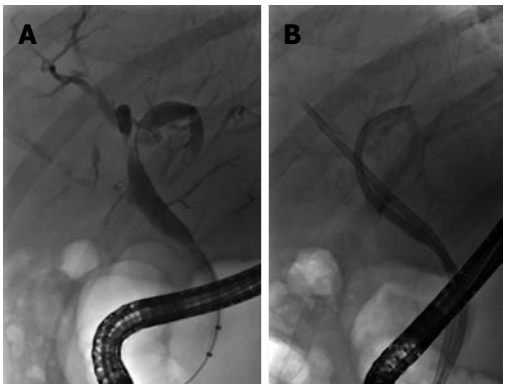

Figure 3 Well differentiated pancreatic carcinoma with a pseudoglandular pattern (haematoxylin-eosin, × 400) (A), a nuclear strong p53 immunostaining was encountered in neoplastic elements (immunoperoxidase, × 400, Mayer's Haemalum nuclear counterstain) (B).

tumour size in those patients who refused surgery[49-51].

Solid pancreatic masses

The pre-operative correct diagnosis of ductal pancreatic adenocarcinoma is crucial for patients management and prognosis, and to reduce costs due to unwarranted procedures[1,13,52,53]. The cytological detection of pancreatic ductal adenocarcinoma is usually not difficult for the experienced cytopathologist; indeed this neoplasia is characterized by distinctive cytological features, such as the presence of groups of atypical cells with irregular roundish hyperchromatic dense nuclei, evident nucleoli, mitotic figures and absence of the honeycomb benign pattern[13]. Frequently, pancreatic smears exhibited a hemorrhagic background with clusters or small aggregates of epithelial cells, occasionally arranged in glandular or pseudo-papillary structures. Nevertheless, in a subset of carcinomas the cytological diagnosis may be hard to achieve, due to the presence of extensive necrosis, associated inflammation, contaminating intestinal epithelial cells or limited sampling[7,13,54]. In those cases, again CBP appears as a significant tool for the pathologist, either the microscopic evaluation and application of immunostainings in serial sections. In fact, it has been shown that carcinoembryonic antigen was expressed in neoplastic pancreatic elements of great majority of ductal adenocarcinomas[13]. However, carbohydrate antigen (CA 19-9) represented the most widely used biomarker for pancreatic cancer, even if it showed limitations in differential diagnosis between pancreatic neoplasms, being positive also in solid pseudopapillary tumour and not only in cancer[55-61]. An intriguing challenge, even for the expert cytopathologist, is represented by the distinction between well differentiated pancreatic neoplastic cells and gastrointestinal epithelial contaminating elements, sampled by EUS-FNA through the stomach or the duodenum[7,13,55-58]. Several efforts were made to solve this crucial diagnostic point[7,13,20,55-58]. Firstly, it was reported that a mucin panel comprising four antibodies (MUC1, MUC2, MUC5AC, MUC6) may be helpful in differentiating normal/reactive gastroduodenal cells from neoplastic pancreatic elements[55]. Successively, the utility of immunocytochemistry against CD10 was highlighted (Figure 2B); indeed this antigen is expressed at the apical membrane of the benign contaminant gastrointestinal cells, but not in the neoplastic elements of well differentiated pancreatic adenocarcinoma[7,13,59,60]. The absence of CD10 stain in pancreatic adenocarcinomas has been also documented in surgical histological samples[59,60]. However, CD10 expression has been evidenced in 100% of solid pseudo-papillary pancreatic neoplasms[61-63] and in 30% of pancreatic endocrine tumours with focal staining[7,63,64]. As a consequence, CD10 immunostaining alone cannot be used for the differential diagnosis of pancreatic lesions[7]. An immunohistochemical panel against CK7, CDX2, chromogranin A and synaptophysin is useful for the differential diagnosis among invasive ductal carcinomas, endocrine tumours and acinar cell tumours of the pancreas[12,20,65]. Finally, a further analysis of p53 immunoreactivity may be of diagnostic help in pancreatic pathology (Figure 3); indeed immunocytochemical positivity for mutant p53 protein with long half-life has been recorded in 50%-70% of pancreatic carcinomas, but not in chronic pancreatitis[66-68].

Solid hepatic lesions

A variety of hepatocellular nodules (hyperplastic, benign, dysplastic and malignant) and secondary tumors can be detected in the liver and subjected to EUS-FNA, especially when they were confined to left hepatic lobe[3,69,70]. In particular, while a significant rate of lesions smaller than 1 cm in diameter is missed by CT and MRI, EUS shows excellent diagnostic accuracy in the identification of hepatic lesions less than 0.5 cm in size[69-72]. It is noteworthy that most of < 1 cm hepatic lesions are non-malignant, whereas the large majority of lesions exceeding 2 cm are represented

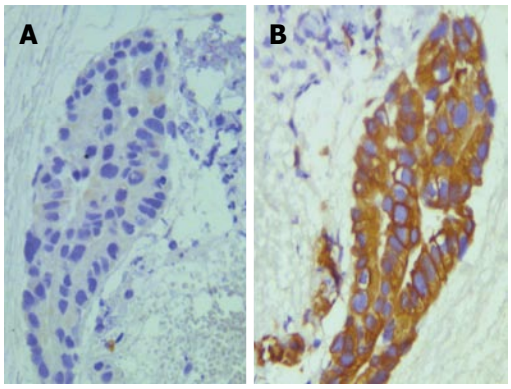

Figure 4 Peripheral cholangiocarcinoma with a papillary pattern (haematoxylin-eosin, × 400) (A), in a serial section obtained from CBP neoplastic elements exhibited an evident cytokeratin 7 immunoreaction (B) (immunoperoxidase, × 400, Mayer's Haemalum nuclear counterstain).

by hepatocellular carcinomas (HCCs); hence in the group of lesions greater than 2 cm a diagnosis of non-malignancy should induce the suspicion of a diagnostic error[73]. Although nodular precursors such as liver regenerative (LRN) or low-grade dysplastic (LGDN) and high grade dysplastic (HGDN) nodules are related to hepatocarcinogenesis, they should be discriminated from adenomas and differentiated HCCs. LGDN category also includes the so-called LRN and it shows mild increase in cell density with a monotonous pattern and bland cytological atypia[73]. On the other hand, HGDN always exhibit more marked cytological atypia and irregular trabecular pattern[73]. Discrimination of well differentiated and hypovascular HCCs from dysplastic nodules may be particularly challenging; in those cases, CBP associated with EUS-FNA or EUS-guided biopsy are warranted, as recently acknowledged[74]. Several immunomarkers were proposed for the distinction between well differentiated HCC and non-malignant lesions[75]. Specifically, Glypican 3 appeared as a good tissue marker with 77% sensitivity and 96% specificity for HCC[74]. In addition, Heat Shock Protein 70 was reported as the most abundantly up-regulated gene in early HCC, and the protein for which it encodes can be detected by immunocytochemistry in up to 78% of the cases with 95% specificity[74]. Finally, Glutamine Synthetase is overexpressed in malignant hepatocytes with diffuse and strong pattern in 50% of HCCs[74,76]. The combined use of the aforementioned was proposed in order to increase the diagnostic accuracy in cases with dubious morphology[76], and so the availability of serial consecutive sections obtained from CBP applied to EUS-FNA could represent the gold standard. With regards to cytokeratins (CK) profile, CK8 and 18 are expressed in both normal and neoplastic hepatocytes, while about 70% of HCC are negative for CK7, CK19, and CK20[73,77]. Furthermore, the combined use of CK7 and CK20 may help to identify the origin of adenocarcinomas occurring in GI tract; in particular, CK7 and CK20 expression in cholangiocarcinomas (CC) varies along the biliary tract, with higher sensitivity of $CK7^+/CK20^-$ profile in peripheral CC compared to non-peripheral ones (Figure 3)[73,77]. On the other hand, $CK7^+/CK20^+$ profile supports the diagnosis of pancreatic adenocarcinoma, while $CK7^-/CK20^+$ is the typical pattern of colonic cancer[73,77].

Gallbladder and biliary tract lesions

Approach by EUS-FNA of the lesions of biliary tract, and mainly of the hilar ones, may avoid the risk of unnecessary extensive surgery[78,79]. Indeed the sensitivity and specificity of obtaining diagnostic samples in biliary neoplasms is variable by endoscopic-retrograde cholangiography[3]. Moreover, the endoscopic retrograde cholangiopancreaticography (ERCP), used at times for hilar cholangiocarcinomas, has frequently inconclusive diagnosis[80]. Consequently, a morphological diagnosis on cytological samples provided by EUS-FNA and submitted to CBP may allow to recognize the nature of malignant biliary lesions (Figure 4) and to change the preplanned surgical approach. Generally, tumour cells appear in loosely structured groups or disorder flat sheets exhibiting as cytologic atypia that varies depending upon tumour grade; occasionally, tumour cells may exhibit cytoplasmic vacuolization and focal mucin secretion. What's more, regional lymph nodes may be evaluated for metastasis by EUS-FNA in patients with unresectable hilar carcinomas[81,82].

A sensitivity and accuracy of 95% have been recorded for EUS-FNA in distal biliary malignancies[7,83] and similar values have been reported in patients with obstructive jaundice due to nodular lesion such as epithelial and non-epithelial tumours, lymphomas and metastases[84-86].

In gallbladder masses, the CBP-assisted EUS-FNA procedure has been used either for diagnostic and staging purposes, with rates of sensitivity and specificity ranging between 80% and 100%, especially in lesions of the gallbladder wall[87-91].

In ampullary tumours, EUS-FNA has higher diagnostic accuracy in the distinction between benign and malignant tumours compared to other operative procedures such as biopsy or brushing cytology during ERCP[92,93]. In addition, it is of help in the identification of patients with low or high grade dysplasia or affected by adenocarcinomas[93].

In this anatomical district, some very severe complications such as bile peritonitis and cholangitis have been described[1]; they probably represent a consequence of inadvertent needle penetration inside intrahepatic or common bile ducts as well as gallbladder. By contrast, bleeding is mild and self-limited, even when patients were taken aspirin or anti-inflammatory drugs, in absence of portal hypertension[1].

CONCLUSION

The clinical applications of EUS-FNA and the methodological advantages obtained by CBP in the diagnosis of solid neoplasms of the GI tract were reviewed.

Although on-site cytological evaluation during the ultra-sonographic needle aspirative procedure may increase the diagnostic yield of EUS-FNA, in our opinion CBP represents its most appropriate diagnostic complement. Indeed this method allows high quality morphological microscopic evaluation and multiple immunocytochemical analyses. By this approach, the differential diagnosis of neoplasms may be more easily achieved, and the background of contaminant non-neoplastic gastrointestinal avoided, which represent evident advantages compared to the traditional cytological techniques. Finally, the identification and quantification of potential molecular markers may represent a promising field to be further investigated on the same biological samples collected by EUS-FNA CBP-assisted.

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REVIEW

Endoscopic retrograde pancreatography: When should we do it?

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Abstract

Endoscopic retrograde pancreatography (ERP) is an accurate imaging modality in the diagnosis of pancreatobiliary diseases. However, its use has been substantially reduced due to the invasiveness of procedure, the risk of complications and the widespread availability of non-invasive cross-section imaging techniques (computed tomography, magnetic resonance imaging, and endoscopic ultrasound). Since the introduction of endoscopic sphincterotomy, ERP has transformed from diagnostic method to an almost exclusively therapeutic procedure. Pancreatic duct injection substantially increased the risk of post-ERP pancreatitis (1.6%-15.7%); therefore, according to international guidelines ERP is recommended only in cases where biliary intervention is required. However, the role of ERP in the management of pancreatic diseases is currently not clearly defined, but in some cases the filling of pancreatic duct may provide essential information complementing the results of non-invasive imaging techniques. The aim of this publication is to systematically summarize the literature dealing with the diagnostic yield of ERP. We would like to define the precise indications of ERP and overview a diagnostic protocol of pancreatic diseases depending on international guidelines and the opinion of Hungarian experts, because it may improve the diagnostic accuracy, minimize of burden of patients and reduce the risk of procedure related complications.

Key words: Endoscopic retrograde cholangiopancreatography; Endoscopic pancreatography; Autoimmune pancreatitis; Pancreas divisum; Chronic pancreatitis

Core tip: Since the development and widespread availability of non-invasive imaging techniques the importance of diagnostic endoscopic pancreatography (ERP) has substantially reduced. However, in some complicated cases or during pancreatic interventional endoscopic procedures such as minor papilla sphincterotomy, pancreatic sphincterotomy, pancreatic stent implantation, ERP may provide essential information. This article seeks to summarize the results of previous studies and recommendations of international guidelines

to define the diagnostic yield and correct indications of ERP.

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INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is an invasive procedure that provides radiological visualization of the detailed structure and the pathological changes of the biliary tree and pancreatic ducts by injection of contrast agent into the common bile duct (CBD) and the main pancreatic duct (MPD). Since its development in 1968, it has become a widely used and accurate imaging modality in the diagnosis of pancreatobiliary diseases[1]. Since the introduction of endoscopic sphincterotomy in 1974[2], ERCP has become the most important minimal invasive treatment method for various biliary and pancreatic diseases including bile duct or pancreatic duct stones (choledocholithiasis or wirsungolithiasis), benign and malignant biliary and pancreatic duct obstructions. Recently ERCP has transformed from a diagnostic method to an almost exclusively therapeutic procedure due to the widespread availability of noninvasive cross-section imaging techniques such as abdominal ultrasound (AUS), computed tomography (CT), magnetic resonance cholangiopancreatography (MRCP) and endoscopic ultrasound (EUS)[3]. Numerous studies emphasize the disadvantages of ERCP such as post-ERCP complications and the burden to patients. In a meta-analysis of 21 prospective trials the incidence of mild-to-moderate complications reached 5.17%, and that of severe events up to 1.67%[4] (Table 1). Post-ERCP pancreatitis (PEP) is the most frequent complication with approximately 3.5% but its incidence ranges widely (1.6%-15.7%) depending on the patient selection and the definition of pancreatitis[5-7]. Pancreatic duct injection substantially increased the risk of PEP, therefore the role of diagnostic endoscopic pancreatography (ERP) gradually decreased. International guidelines recommend ERCP only in cases where biliary intervention is required[3-8], but the indication of ERP is not clearly defined. According to the current guidelines routine rectal administration of 100 mg diclofenac or indomethacin immediately before or after ERCP is strongly recommended to prevent PEP. In patients with MPD filling and increased patient or procedure related risk factors for PEP temporary application of prophylactic small caliber pancreatic stents is also recommended to reduce the risk of severe PEP[9].

The aim of this article is to systematically review the literature dealing with the diagnostic yield of ERP in various pancreatic diseases, and to define the principles and indications of ERP depending on the recommendations of international guidelines and the opinion of Hungarian experts (Tables 2 and 3) .

Table 1 Frequency of procedure related complications of endoscopic retrograde pancreatography (6.85%) depending of the results of endoscopic retrograde pancreatography[4]

	Mild to moderate	Severe	Death
Pancreatitis	3.07%	0.40%	0.11%
Bleeding	0.95%	0.39%	0.05%
Perforation		0.60%	0.06%
Infection	1.15%	0.28%	0.11%
Total	5.17%	1.67%	0.33%

PANCREAS DIVISUM

Pancreas divisum (PD) is the most common congenital anomaly of the pancreas in which the dorsal and ventral pancreatic duct drain separately into the duodenum. Recently ERP has been the gold standard imaging modality for the diagnosis of PD due to its high diagnostic accuracy[10,11], but the rate of complete pancreatography and the success of minor papilla cannulation significantly influence the sensitivity of ERP[12] (Figure 1). The high rate of complications is the greatest disadvantage of ERP, therefore noninvasive procedures, such as MRCP and EUS are increasingly spreading worldwide in this indication as well. Sensitivity and specificity of MRCP in the detection of PD is 52%-73.3% and 96.8%-97%, and the diagnostic accuracy can further be improved with the use of secretin stimulation (73.3%-86% and 97%)[13,14] (Figure 2). A comparison study carried out by Lai *et al*[15]. has shown that adequate evaluation of the pancreatic duct by EUS is possible in 78% of cases, and the sensitivity, specificity, and positive and negative predictive values for EUS are 95%, 97%, 86%, and 99%

ERP has an important therapeutic role in the endoscopic treatment (including minor papillotomy with or without pancreatic duct stenting) of patients with symptomatic PD. There is no prospective randomized controlled trial comparing endoscopic and surgical therapy, but previous retrospective studies could not detect any differences between the pooled overall response rates of the two treatment groups (endoscopic *vs* surgical treatment 54.3-79.2 *vs* 51.4-83.3 depending on the indication)[16].

ACUTE PANCREATITIS

The importance of ERCP in the identification of the etiology of acute pancreatitis (AP) has rapidly decreased in the recent decades due to the widespread availability of noninvasive imaging modalities[17]. The diagnosis of uncomplicated AP is mainly based on the clinical symptoms, elevated serum levels of pancreatic enzymes

Table 2 Indication of endoscopic retrograde pancreatography based on the opinion of Hungarian experts

	Indicated	Slightly indicated	Not indicated	Description
Pancreas divisum	83.6%	16.7%	0%	During therapeutic intervention
Acute pancreatitis	16.7%	50%	33.3%	Recurrent "idiopathic" acute pancreatitis
Chronic pancreatitis	83.3%	16.7%	0%	Complicated chronic pancreatitis (MPD stricture, pancreatic duct stones, chronic abdominal pain, obstructive jaundice)
Autoimmune pancreatitis	66.7%	33.3%	0%	Suspicion of autoimmune pancreatitis which has not identified by noninvasive imaging techniques
Pancreatic neoplasia	0%	50%	50%	Suspicion of pancreatic neoplasia with obstructive jaundice
Pancreatic cystic neoplasia	0%	16.7%	83.3%	In case of IPMN ERP associated with high risk of complications Pancreatic cysts and pseudocysts generally do not communicate with the pancreatic duct therefore the ERP cannot identify them
Pancreatic injury	100%	0%	0%	Suspicion of pancreatic ductal injury in stable patients
Postoperative pancreatic fistula	100%	0%	0%	Suspicion of pancreatic fistula Suspicion of fistula formation

ERP: Endoscopic pancreatography; MDP: Main pancreatic duct; IPMN: Intraductal papillary mucinous neoplasms.

Table 3 Indication of endoscopic retrograde pancreatography in the case of suprapapillary bile duct stenosis based on the opinion of Hungarian experts

Indicated	Not indicated	Description
50%	50%	ERP may help differentiate between cholangiocarcinoma and pancreatic illnesses

ERP: Endoscopic pancreatography.

(amylase, lipase) and the morphological changes in the pancreas on the AUS, CT or MRI images[18]. Therapeutic ERCP with biliary sphincterotomy and removal of CBD stones can effectively improve the outcome, and according to the recent international guidelines it is indicated in acute biliary pancreatitis within 24-71 h, if noninvasive examinations prove the presence of acute cholangitis or raise the suspicion of CBD obstruction in association with acute pancreatitis[19,20]. On the contrary, failed biliary cannulation and repeated MPD filling in patients with acute biliary pancreatitis may worsen the overall outcome and therefore some data suggest that small caliber prophylactic pancreatic stents may be applied as a bridging procedure to prevent complications in this group of patients[21].

In 10%-15% of patients with recurrent acute pancreatitis if the complete noninvasive diagnostic evaluation could not reveal the exact cause and etiology, and as a consequence the diagnosis of "idiopathic" acute pancreatitis may arise. Therefore in patients with idiopathic acute pancreatitis, after the cessation of an acute inflammatory attack an ERCP with biliary and/or pancreatic sphincter of Oddi manometry, an endoscopic ultrasound, and secretin enhanced MRCP may leads to a diagnosis of biliary microlithiasis, sphincter of Oddi dysfunction, PD, cystic fibrosis, a choledochocele, annular pancreas, an anomalous pancreatobiliary junction, small pancreatobiliary tumors, or early stage of chronic pancreatitis[22,23].

CHRONIC PANCREATITIS

Chronic pancreatitis (CP) is a progressive fibroinflammatory disorder with irreversible destruction of the pancreatic parenchyma and ducts. Frequently the complications, such as bile duct stenosis, obstructive jaundice, diabetes mellitus or malabsorption call the attention for the presence of the disease[24]. In advanced stages the recognition of parenchymal fibrosis and moreover calcification is relatively easy with AUS, CT, MRI and EUS, and typical ductal alterations with ERCP or MRCP[25]. The early recognition of CP and its differentiation from pancreatic cancer (PC) sometimes represents a real diagnostic challenge[26]. Currently ERCP has been replaced by EUS (especially with elastography), MRI, CT, and MRCP in the early diagnosis of CP. However, ERCP plays an essential role in the more precise identification of complications such as obstructive jaundice, pancreatic stones, MPD strictures, chronic abdominal pain, and also gives the opportunity for the minimally invasive treatment (pancreatic sphincterotomy or balloon dilatation, pancreatic duct stenting, *etc.*)[27] (Figure 3). The European Society of Gastroenterology recommends the endoscopic treatment as the first-line therapy for painful uncomplicated CP, and highlights its effectivity in the management of obstructive jaundice and pancreatic stones associated with CP[3] (Figures 4 and 5). In cases of complicated CP the long-term efficacy of surgical intervention is superior to endoscopy in most patients[28,29]. Despite the fact, that repeated pancreatography is usually necessary during the endoscopic intervention of the pancreatic duct, the risk of PEP is significantly reduced in CP as compared to the general population. However, the role of ERP as first examination in the diagnosis of suspected complicated CP is questionable[6]. Therefore, in our clinical practice, we perform ERCP in CP patients only in case of chronic pancreatic pain and suspected MPD obstruction (stricture with prestenotic dilatation) based on MRCP or EUS. In these patients, pancreatic sphincterotomy, pancreatic

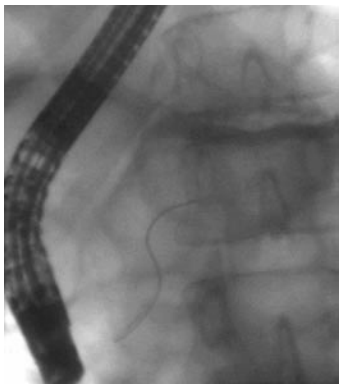

Figure 1 Endoscopic retrograde pancreatography image: Pancreas divisum with minor papilla cannulation.

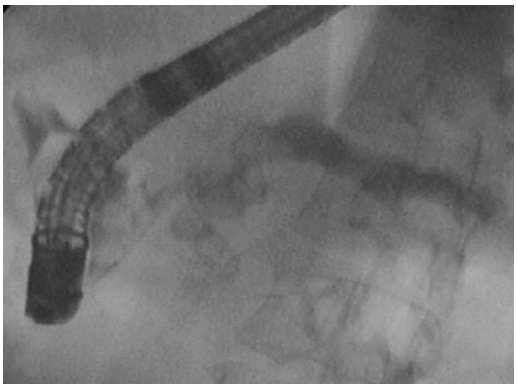

Figure 3 Endoscopic pancreatography image: Chronic pancreatitis with Wirsungolithiasis.

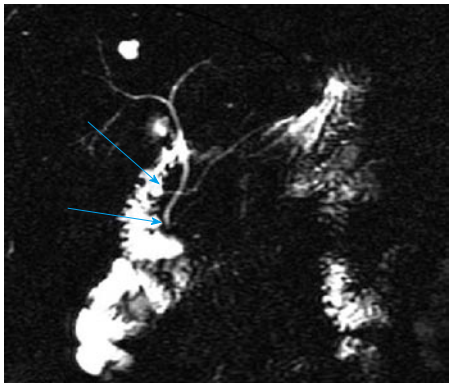

Figure 2 Secretin enhanced magnetic resonance cholangiopancreatography image: Pancreatic divisum and juxtapapillary diverticulum.

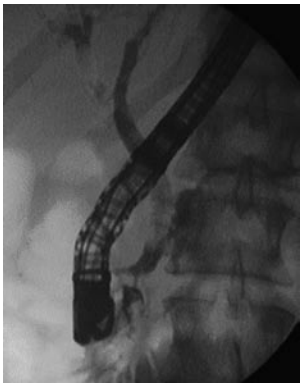

Figure 4 Endoscopic pancreatography image: Pancreatic duct stenosis with prestenotic dilatation after preventive pancreatic stent implantation.

stricture dilatation and multiple plastic or self-expanding metal stenting during ERP proved to be useful to achieve long term symptomatic improvement.

AUTOIMMUNE PANCREATITIS

Autoimmune pancreatitis (AIP) is an uncommon inflammatory disorder of the pancreas with a presumed autoimmune etiology[30]. It may present with a wide variety of clinical and morphological features including painless obstructive jaundice, asymptomatic focal mass or diffuse enlargement of the pancreas which mimic PC[31]. The diagnosis of AIP requires a multidisciplinary approach including imaging studies, histology, serology, assessment of other organ involvement and the therapeutic response to steroid treatment[32,33]. There were differences in the diagnostic approach and the techniques used between different countries. For instance, ERP is usually ignored in Western counties to avoid PEP in contrast to Japan where this examination is usually performed[34]. The correct diagnosis requires detailed information equally about the pancreatic parenchyma and ducts. In typical cases of AIP a diffusely enlarged or "sausage shaped" pancreas with featureless borders and/or loss of lobular architecture can be detected with AUS, CT and MRI[35]. In 30%-40% of the cases focal mass is found, which can lead to false diagnosis of pancreatic malignancy[36,37]. Ductal imaging, ERP and MRCP may show a long, narrow ductal stricture (greater than one-third the length of the MPD) or multiple, non-continuous strictures without marked upstream dilation, and side branches arising from the stricture[38-40]. However, given that ERCP is an invasive method which debit the patient and can cause adverse effects (pancreatitis, bleeding), the noninvasive MRCP is becoming the first choice examination for pancreatobiliary diseases. Previous comparison studies have shown that MRCP is less sensitive in the differentiation of focal form of AIP and PC, therefore cannot completely replace ERCP for the diagnostic evaluation of AIP[41,42]. The multicenter study carried out by Suguma *et al*[43]. has highlighted the ability of ERP to diagnose AIP based on ERP feature alone is limited, but taken together with clinical symptoms, serology and/or histology it can be useful.

PANCREATIC NEOPLASIA

Previously ERCP was the gold standard in the diagnosis of PC. Localized MPD stenosis with focal ductal branch dilation and with distal dilation of MPD ("double duct" sign) were the most frequently detectable morphological

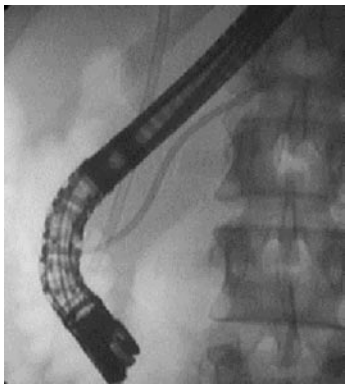

Figure 5 Endoscopic pancreatography image: Bile duct and pancreatic duct stent implantation in chronic pancreatitis.

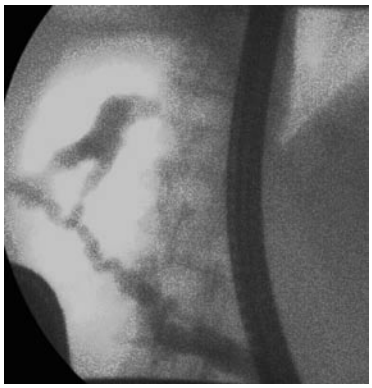

Figure 6 Endoscopic retrograde pancreatography image: Postoperative pancreaticopleural fistula.

changes[44,45]. The current role of ERCP is therapeutic rather than diagnostic. In cases of inoperable locally advanced and metastatic pancreatic malignancy the development of obstructive jaundice constitutes an absolute indication of ERCP[46]. Malignant biliary stenosis may be treated with plastic, but preferably with self-expandable metallic stent implantation[3]. Pancreatography, ERCP-guided brush cytological sampling and/or biopsy of the pancreatic duct may be useful to prove malignancy, but EUS-guided fine needle aspiration (EUS-FNA) is the first-choice sampling procedure in suspected unresectable pancreatic solid and cystic lesions due to minimal invasiveness, lower complication rate and higher sensitivity compared to ERCP sampling[47]. A meta-analysis performed by Li *et al*[48]. showed that ERCP combined with EUS was associated with a high diagnostic yield compared to ERCP or EUS alone, but the complete length of procedures substantially increased, however, it can be reduced if the two examination are performed under the same sedation, but the rate of complication is not elevated[49].

CYSTIC PANCREATIC LESIONS

Cystic pancreatic lesions represent a great diagnostic problem because of the morphological similarities between benign and malignant cysts and because of the possibility of malignant transformation[50] and the increasing number of the detected lesions due to the improvement of the abdominal imaging modalities and their availabilities. The differentiation between the four types of pancreatic cystic neoplasms (PCN) substantially may influence the therapeutic approach. Serous cystadenomas (SCA) and solid pseudopapillary neoplasms (SPN) are associated with lower malignant potential compared to intraductal papillary mucinous neoplasms (IPMN) and mucinous cystic neoplasms (MCN). Previously ERP was the gold standard diagnostic procedure in the identification and classification of IPMN. Diffuse or segmental dilation of the MPD or its side branches connected to the cyst can be recognized on the ERP images, with no other cause of the dilatation. The pathognomonic characteristic of IPMN is the gaping orifice of Vater papilla with thick mucus oozing (fish mouth papilla)[51]. The international consensus guidelines do not recommend the routine ERP for the morphological and cytological diagnosis of IPMN (fluid sampling or brushing of MPD) due to the invasiveness of the procedure and the high risk of complications. Currently MRCP, EUS and EUS-guided sampling are most preferred[52,53]. The other malignant cyst type and the pancreatic pseudocysts generally do not communicate with the pancreatic duct, therefore the ERP cannot identify them.

PANCREATIC INJURY

Blunt pancreatic trauma can frequently lead to acute pancreatitis with or without MPD disruption. Pancreatic injuries caused by blunt abdominal trauma are relatively rare with an overall incidence of 0.2%-12%[54]. Pancreatic injury occurs as a result of the traumatic compression of the pancreas between the vertebral column and the anterior abdominal wall. Pancreatic injury is more common in children and young adults because of decreased protective intra-abdominal fat. CT is the primary imaging modality of choice in patients with blunt abdominal trauma, with the sensitivity for pancreatic parenchymal injury between 67%-85%[55]. Although pancreatic ductal injury can frequently be detected with non-invasive MRCP, ERCP is the most accurate diagnostic tool for the assessment of ductal injury[56]. Besides, it can also provide endoscopic treatment. Delays in ERCP have led to significantly higher complication rates[57]. Although ERCP is the most useful procedure for the diagnosis of pancreatic ductal injury in stable patients, surgery should be considered without hesitation if the patient's condition is unstable. Recently, some case series proved that pancreatic duct plastic stent placement with and without pancreatic sphincterotomy can be an effective endoscopic therapy in resolving pancreatic duct disruption and preventing chronic fistula formation[58]. Although stent implantation can improve the clinical condition and resolve fistula and pseudocyst, stent induced ductal stricture is a major

long-term complication.

POSTOPERATIVE PANCREATIC FISTULA

Postoperative pancreatic fistula (POPF) formation is a frequent and severe complication of pancreatic surgery[59,60]. Its incidence ranges from 2% to 51% depending on the definition used. POPF was defined by International Study Group on Pancreatic Fistula as a measurable drain output on or after postoperative day 3 with an amylase content greater than 3 times the serum amylase activity[61]. In the early postoperative phase the upper abdominal discomfort associated with fever, tachycardia slower recovery and persistently high drain output raises the suspicion of postoperative complication, such as pancreatic fistula (Figure 6). The amylase level of drain fluid is extremely elevated in a typical case[62]. ERCP and MRCP are the two most widely used imaging modality in the confirmation of POPF with high diagnostic accuracy. In case of pancreaticopleural fistula their sensitivity may reach to 78% and 80%[63]. Recently ERCP was the most preferred investigation for confirming the diagnosis of POPF, but its use is reduced due to invasive nature and elevated risk of infective complications arising from fistula filling. However, it has the advantage of direct visualization of MPD and precise location of fistula, and the ability to simultaneously perform endoscopic therapeutic maneuvers[64].

PANCREATOBILIARY MALJUNCTION

Pancreatobiliary maljunction (PBM) is a rare congenital malformation in which the CBD and the pancreatic duct are united outside the duodenal wall with or without dilation of CBD[65]. The sphincter of oddi is located in the distal part of the common channel, therefore it cannot properly regulate the outflow of biliopancreatic juice, resulting regurgitation of bile into the MPD and pancreatic juice into the CBD. The elevated intraductal pressure often causes dilatation of CBD, and the chronic biliopancreatic reflux increases the risk of development of malignancy. The diagnosis of PBM is based on the identification of the anomalous union between the pancreatic and bile ducts by ERCP, MRCP, EUS or intraductal ultrasound. ERCP is the most accurate imaging method, and it provides an opportunity for the biliary intervention (biliary stone extraction, stent implantation) and bile sampling as well. High biliary levels of pancreatic enzymes are suggestive of regurgitation of pancreatic juice into the common bile duct[66]. In atypical PBM cases with relatively short common channel, the diagnostic accuracy of MRCP and EUS is lower, but they are very effective in the detection of PBM associated pancreatobiliary cancers at an early stage[67].

CONCLUSION

ERP is still one of the most accurate diagnostic procedures in patients with suspected pancreatic ductal disorders, including idiopathic acute recurrent pancreatitis, chronic pancreatitis, pancreatic ductal injuries and fistula formation, pancreatic cystic neoplasms and early pancreatic cancer. However, before performing ERP, endoscopists should carefully evaluate the extent of the clinically necessary pancreatogram, if there any, to establish the diagnosis. Increasingly widespread application of noninvasive methods for the diagnosis of pancreatobiliary diseases (such as MRCP and EUS), and less frequent use of diagnostic ERP could dramatically decrease post-ERCP complications. In contrast, pancreatic interventional endoscopic procedures, such as pancreatic sphincterotomy, dilatations and pancreatic stent implantation are necessitates for complete pancreatic ductal contrast filling and analysis of digitally enhanced pancreatogram with fluoroscopy to completely understand the anatomy and intraductal pathology before the initiation of endoscopic therapy.

In case of distal biliary obstruction, when the non-invasive imaging modalities are available we do not recommend the filling of pancreatic duct, selective biliary drainage is proposed. ERP should be considered in case of suspected pancreatic ductal differences, such as pancreatic injury, fistula or congenital malformation, and when pancreatic ductal intervention is necessary.

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REVIEW

Current status of endoscopic biliary drainage for unresectable malignant hilar biliary strictures

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Abstract

The management of jaundice and cholangitis is important for improving the prognosis and quality of life of patients with unresectable malignant hilar biliary strictures (UMHBS). In addition, effective chemotherapy, such as a combination of gemcitabine and cisplatin, requires the successful control of jaundice and cholangitis. However, endoscopic drainage for UMHBS is technical demanding, and continuing controversies exist in the selection of the most appropriate devices and techniques for stent deployment. Although metallic stents (MS) are superior to the usual plastic stents in terms of patency, an extensive comparison between MS and "inside stents", which are deployed above the sphincter of Oddi, is necessary. Which techniques are preferred remains as yet unresolved: for instance, whether to use a unilateral or bilateral drainage, or a stent-in-stent or side-by-side method for the deployment of bilateral MS, although a new cell design and thin delivery system for MS allowed us to accomplish successful deployments of bilateral MS. The development of techniques and devices for re-intervention after stent occlusion is also imperative. Further critical investigations of more effective devices and techniques, and increased randomized controlled trials are warranted to resolve these important issues.

Key words: Malignant hilar biliary obstruction; Biliary drainage; Metallic stents; Stent-in-stent; Side-by-side

Core tip: The development of useful surgical devices, such as plastic or metallic stents, catheters and guidewires, has allowed us to achieve successful endoscopic drainage for unresectable malignant hilar biliary strictures (UMHBS), a technically demanding procedure. However, the most appropriate method of endoscopic drainage for UMHBS remains a contentious issue: for instance, whether to use a unilateral or bilateral drainage, or a stent-in-stent or side-by-side method for the deployment of bilateral metallic stents (MS) to accomplish successful deployments of bilateral MS.

Further critical investigations of more effective devices and techniques, and increased randomized controlled trials are warranted to resolve these important issues.

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INTRODUCTION

The management of jaundice and cholangitis is important for improving the prognoses of patients with unresectable malignant hilar biliary strictures (UMHBS). In addition, effective chemotherapy, such as combination therapy with gemcitabine and cisplatin, for the treatment of cholangiocarcinoma requires the coincident effective management of both jaundice and cholangitis. Several methods exist for biliary drainage including: surgical drainage, percutaneous transhepatic drainage using ultrasound, and endoscopic transpapillary drainage. Of these, endoscopic transpapillary drainage has become the favoured method because of its minimal invasiveness while preserving the patient's quality of life. The development of useful surgical devices, such as plastic or metallic stents, catheters and guidewires, has allowed us to achieve successful endoscopic drainage for UMHBS, a technically demanding procedure. However, the most appropriate method of endoscopic drainage for UMHBS remains a contentious issue. In the present study, we review the current literature concerning endoscopic biliary drainage for patients with UMHBS.

PLASTIC *VS* METALLIC STENTS, AND NEWLY DESIGNED PLASTIC STENTS

Several studies have highlighted the advantages of metallic stents (MS) compared with plastic stents (PS) (Table 1)[1-4]. According to these studies, the median patencies of MS for UMHBS were of longer duration than those of PS (3.4-12.0 mo *vs* 1.2-6.7 mo); in spite of this, the technical success rate for the deployment of MS was similar to that of PS (83.3%-100% *vs* 85.2%-100%). In a randomized controlled trial comparing PS and MS as reported by Mukai *et al*[4], the 6-mo patency was significantly higher for the MS patient group than the PS group (81% *vs* 20%); the 50% patency period was 359 d for the MS group and 112 d for the PS group. In addition, the MS group had the advantage in terms of the number of re-interventions and the total cost of treatment compared with the PS group.

Reports concerning newly designed plastic stents are also increasing. PS occlusion occurs as a result of biofilm formation and bacterial adherence to the wall of the stent following the reflux of duodenal juice into the PS and bile duct. To avoid this phenomenon, Pedersen *et al*[5] reported a method of deploying PS above the sphincter of Oddi; such stents were named "inside stents". Recently, several reports have emerged on the deployment of "inside stents" with attached nylon thread that is easily removed from the distal end of the stent for UMHBS (Figure 1). Ishiwatari *et al*[6] reported on 26 patients with UMHBS and successfully deployed "inside stents" showing a median patency period of 136 d. Kaneko *et al*[7] reported that the patency of "inside stents" was 190 d. Inatomi *et al*[8] compared the patency period of conventional PS, MS and "inside stents" and found the patency period of "inside stents" to be significantly longer than that of conventional PS (142 d *vs* 32 d, $P = 0.04$), but was not significantly different to that of MS (142 d *vs* 150 d, $P = 0.83$). Further investigation is necessary to determine whether the patency period of "inside stents" is comparable to that of MS. However, the absolute advantage of PS, including "inside stents", are enable to be removed easily compared to MS. We intend to deploy PS more frequently as a temporal drainage procedure if UMHBS are completely cured *via* chemotherapy or other effective treatments.

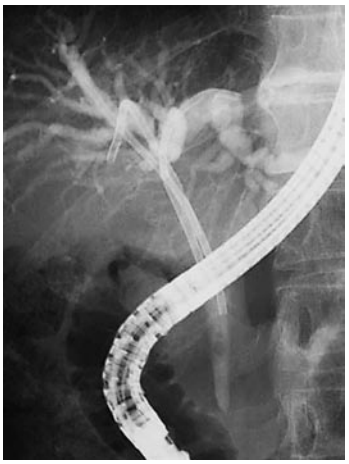

Figure 1 Multiple "inside stents" deployed above the sphincter of Oddi.

UNILATERAL *VS* BILATERAL DRAINAGE

One of controversies regarding unilateral and bilateral drainage is the perceived technical difficulty of these procedures, with bilateral stent deployment generally thought to be more difficult than unilateral stent deployment. There have only been two randomized controlled trials (RCTs) on this issue to date. In one undertaken by De Palma *et al*[9] comparing the unilateral and bilateral deployment of PS, the technical and clinical successes of the bilateral deployment group were significantly lower than those of the unilateral deployment group (Table 2). On the other hand, in a

Table 1 The results of comparison between metallic and plastic stents

Ref.	No. of patients		Successful deployment % (*n*)		*P* value	Patency (mo)		*P* value
	MS	PS	MS	PS		MS	PS	
Sangchan *et al*[1]	54	54	83 (45/54)	85 (46/54)	0.792	3.4	1.2	> 0.001
Perdue *et al*[2]	35	33	97 (34/35)	85 (28/33)		NA	NA	
Liberato *et al*[3]	249	231	99 (246/249)	88 (204/231)	> 0.001	6.3	4.7	> 0.0001
Mukai *et al*[4]	30	30	100 (30/30)	100 (30/30)		12	3.7	0.0002

PS: Plastic stents; MS: Metallic stents; NA: Not available.

Table 2 The results of comparison between unilateral and bilateral stent deployment

Ref.	No. of patients		Successful deployment [% (*n*)]		*P* value	Successful drainage [% (*n*)]		*P* value	Stent patency (mo)		*P* value	Survival period (mo)		*P* value
	Unilateral	Bilateral	Unilateral	Bilateral		Unilateral	Bilateral		Unilateral	Bilateral		Unilateral	Bilateral	
De Palma *et al*[9]	PS 79	PS 78	89 (70/79)	77 (60/78)	0.041	81 (64/79)	73 (57/78)	0.0482	NA	NA		4.7	4.7	0.482
Mukai *et al*[4]	PS 15	PS 15	100 (15/15)	100 (15/15)		100 (15/15)	100 (15/15)		3.4	3.7	0.746	NA	NA	
	MS 14	MS 16	100 (14/14)	100 (16/16)		100 (14/14)	100 (16/16)		12.1	9.8	0.3467	NA	NA	
Liberato *et al*[3]	PS 27	PS 40	NA	95 (38/40)		NA	95 (38/40)		4.0	4.2	0.0004	NA	NA	
	MS 33	MS 45	NA	93 (42/45)		NA	93 (42/45)		NA	6.8	> 0.0001	NA	NA	
Chang *et al*[10]	PS or MS 69	PS or MS 29	NA	NA		NA	NA		5.6	NA		2.7	7.5	> 0.01
Naitoh *et al*[11]	MS 17	MS 29	100 (17/17)	90 (26/29)		94 (16/17)	90 (25/26)		7.0	16.3	0.009	5.5	6.8	0.559
Iwano *et al*[12]	MS 63	MS 19	95 (60/63)	90 (17/19)		NA	NA		4.4	4.2	0.3220	5.7	6.1	0.4908

PS: Plastic stents; MS: Metallic stents; NA: Not available.

RCT by Mukai *et al*[4] comparing PS and MS, successful deployment was achieved in all patients undergoing the deployment of PS or MS, regardless of what type of deployment was employed. In other retrospective studies comparing the unilateral and bilateral deployment of MS, the technical success rate was similar for these two groups[3,10-12]. However, evidences of no obvious differences on the difficulty between unilateral and bilateral deployment are not still enough. Further RCTs at high-volume centers are warranted.

Another matter in question is whether bilateral drainage is superior to unilateral drainage in the management of jaundice and cholangitis, which relates to stent patency and survival periods. There are several studies showing no difference between unilateral and bilateral drainage on stent patency and survival periods, but several studies highlight an opposite stance[3,4,9-12]. Bilateral drainage, as the initial drainage, may not always be necessary for patients with UMHBS for the management of jaundice cholangitis. However, the function of the drained segment of the liver will diminish as the tumor gradually occupies the drain segment, which impacts on patient mortality. Vienne *et al*[13] analyzed the outcomes of drainage effectiveness during endoscopic stenting for malignant hilar biliary strictures. The main significant factor associated with drainage effectiveness was a liver volume drainage of > 50% (odds ratio 4.5, $P = 0.001$), which was associated with longer survival (119 d *vs* 59 d, $P = 0.005$). In addition, Mukai *et al*[4] reported that around 50% of patients required bilateral drainage to reduce jaundice and cholangitis, but instead recommended unilateral drainage. Miura *et al*[14] reported the results of preoperative biliary drainage for malignant hilar biliary stricture. Thirty-one of 122 patients (25.4%) initially underwent multiple biliary drainage; however 69 of 122 (56.6%) required multiple biliary drainage by the time of the operation. They concluded that patients with Bismuth-II, Bismuth-IIIa, and Bismuth-IV were at high risk for multiple biliary drainage. These results suggest that effective drainage of a malignant hilar biliary stricture frequently requires bilateral or multiple drainage.

Uchida *et al*[15] reported on the relationship between the number of deployed MS, the effectiveness of chemotherapy, the patency period of MS, and the survival period. Patients were divided into two groups, one in which four or three MS were deployed (4- or 3-branched group), or a group in which two or one MS was deployed (2- or 1-branched group). Although neither patency period nor survival time exhibited significant differences between the two groups, among the patients achieving complete response, partial response, or stable disease defined by World Health

Table 3 The results of comparison between stent-in stent and side-by-side method for deployment of bilateral metallic stents

Ref.	Method for deployment	No. of patients	Successful deployment % (*n*)	Successful drainage % (*n*)	Occlusion % (*n*)	Stent patency (mo)
Kawamoto *et al*[16]	SIS	9	100 (9/9)	100 (9/9)	33 (3/9)	NA
Lee *et al*[17]	SIS	10	80 (8/10)	100 (8/8)	25 (2/8)	7.2
Park *et al*[18]	SIS	35	94 (33/35)	100 (33/33)	6 (2/33)	5
Kim *et al*[19]	SIS	34	85 (29/34)	100 (29/29)	31 (9/29)	6.2
Chahal *et al*[20]	SIS	21	100 (21/21)	NA	38 (8/21)	6.3
Kogure *et al*[21]	SIS	12	100 (12/12)	92 (11/12)	50 (6/12)	6.7
Hwang *et al*[22]	SIS	30	87 (26/30)	100 (26/26)	39 (10/26)	4.7
Lee *et al*[23]	SIS	84	95 (80/84)	93 (78/84)	31 (24/78)	7.9
Dumas *et al*[24]	SBS	45	73 (33/45)	100 (33/33)	3 (1/33)	NA
Cheng *et al*[25]	SBS	36	97 (35/36)	NA	31 (11/35)	5.6
Chennat *et al*[26]	SBS	16	100 (16/16)	75 (11/16)	25 (4/16)	4.3
Lee *et al*[27]	SBS	44	91 (40/44)	98 (39/40)	45 (18/40)	5.2

SIS: Stent-in-stent; SBS: Side-by-side; NA: Not available.

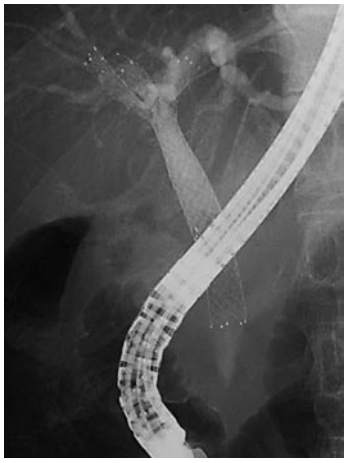

Figure 2 Multiple metallic stents deployed by the stent-in-stent method.

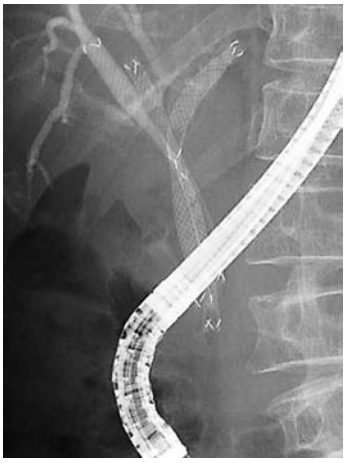

Figure 3 Multiple metallic stents deployed by the side-by-side method.

Organization during chemotherapy, the patency period and survival time of the 4- or 3-branched group were significantly longer than those of the 2- or 1-branched group. They concluded that the deployment of multiple MS prevented biliary infection and deterioration of liver function, which resulted in a long duration of stent patency and the continuation of stable chemotherapy in the disease control group. Consecutive and effective chemotherapy requires the preservation of the functional volume of the liver, and unilateral drainage is less effective than bilateral drainage for this perspective.

STENT-IN-STENT *VS* SIDE-BY-SIDE METHODS

Two methods exist for the endoscopic deployment of bilateral MS for UMHBS: stent-in-stent (SIS; Figure 2) and side-by-side (SBS; Figure 3) methods. Although several reports have been published on each method, no obvious difference was noted (Table 3). The technical success rate is 80%-100% for SIS[16-23] and 73.3%-100% for SBS[24-27], with the patency periods being 140-238 d and 130-169 d, respectively. There are only two retrospective reports on a comparison between SIS and SBS. The rate of successful deployment did not differ between SIS and SBS in both reports but several uncertainties existed surrounding complications and the patency period of these techniques. Naitoh *et al*[28] noted the incidence of complications was significantly higher (44% *vs* 13%, $P = 0.016$), and the cumulative stent patency was significantly longer, ($P = 0.047$) in the SBS, compared to the SIS, group. The median patency period was 469 in the SBS group and 181 d in the SIS group. On the other hand, no differences in complications rates and the patency period between SIS and SBS were reported by Kim *et al*[29]. A prospective randomized control trial, using the same type and diameter of MS, is needed for the evaluation of differences between SIS and SBS methods for the deployment of bilateral MS.

PROGRESS IN METALLIC STENTS FOR BILATERAL DEPLOYMENT

For the reliable and successful deployment of bilateral MS, several new MS designs have been described. The most difficult part for the successful deployment of a bilateral MS by SIS is the deployment of the second MS.

Table 4 The results of re-intervention after stent occlusion in the patients undergoing deployment of bilateral metallic stents

Ref.	Method for deployment	No. of patients	Occlusion % (*n*)	Endoscopic re-intervention % (*n*)	Bilateral or multiple drainage at endoscopic re-intervention % (*n*)
Naitoh *et al*[28]	SIS	24	42 (10/24)	90 (9/10)	NA
	SBS	25	20 (5/25)	100 (5/5)	NA
Lee *et al*[27]	SBS	40	45 (18/40)	92 (12/13)[1]	50 (6/12)
Fujii *et al*[33]	SIS	55	55 (30/55)	100 (30/30)	67 (20/30)
Lee *et al*[23]	SIS	78	31 (24/78)	96 (23/24)	83 (20/24)
Law *et al*[31]	SBS	17	53 (9/17)	75 (6/8)	75 (6/8)
	SIS	7	43 (3/7)	100 (3/3)	100 (3/3)

[1]Five patients with comorbidity underwent initial percutaneous intervention. SIS: Stent-in-stent; SBS: Side-by-side; NA: Not available.

This is because, in addition to the stricture, we have to negotiate the mesh of the first metallic stent when placing the second stent. Therefore, the clever cell design of a MS is crucial for the successful deployment of a bilateral MS by SIS. A newly designed MS with a large, open-celled wire mesh for the deployment of a bilateral MS has been reported in several studies[17,19,21], making the deployment of a bilateral MS for UMHBS a more feasible procedure. Lee *et al*[23] reported on the feasibility and efficacy of a newly designed, closed-cell and cross-wired MS: the technical success rate of endoscopic bilateral SIS deployment was 95.2%, and the median patency period was 238 d.

The difficulty of deployment of a bilateral MS by SBS is also related to the insertion of the second MS along the first MS. This is because we have to advance the second MS against the resistance of the first, already expanded MS. Therefore, although a delivery stuck in the mesh of the initially deployed MS sometimes results in an unsuccessful deployment, a thin delivery overcomes this issue. Kawakubo *et al*[30] reported that 6-Fr delivery systems could facilitate a single-step, simultaneous, SBS placement through the accessory channel of the duodenoscope. The rate of successful deployment was 84.6%, and the median procedure time was 25 min. Law *et al*[31] reported that a 6-Fr delivery MS were used for the deployment of a bilateral MS in 17 patients by SBS and seven patients by SIS. The rate of successful deployment was 100% for both groups, although SBS was attempted prior to SIS in four of seven patients in the SIS group. The 6-Fr delivery can pass through the mesh of the MS more easily, which may facilitate the deployment of a bilateral MS by not only the SBS, but also the SIS method.

RE-INTERVENTION AFTER STENT OCCLUSION IN PATIENTS UNDERGOING BILATERAL DEPLOYMENT OF METALLIC STENTS

Biliary tract cancer is the cause of most UMHBS, and effective chemotherapeutic agents, such as a gemcitabine plus cisplatin combination, have been described in several reports on the treatment of unresectable biliary tract cancer. Valle *et al*[32] reported that the median overall survival was 11.7 mo among 204 patients receiving a gemcitabine plus cisplatin combination, which is longer than the stent patency period already reported. Therefore, stent occlusion that causes jaundice and cholangitis will often happen in the course of chemotherapy, and re-intervention after stent occlusion plays an important role in continuing effective chemotherapy, especially in patients with the deployment of a bilateral MS whose re-intervention is thought to be difficult.

The results of re-intervention after stent occlusion in patients with a bilateral MS deployment are shown in Table 4. Few reports have analyzed the results of re-intervention in any great detail. Fujii *et al*[33] deployed multiple MS using a SIS method in 55 patients with UMHBS. Of these patients, 30 developed a MS occlusion. In twenty of the 30 patients, multiple PS deployments were attempted, with successful PS deployment and clinical success achieved in all 20 patients. Lee *et al*[23] reported on the success rate of bilateral stent deployment as a re-intervention procedure for patients undergoing the deployment of bilateral MS using a SIS method. Of 24 patients with a MS occlusion in which bilateral stent deployment was attempted, twenty patients achieved a successful deployment of bilateral stents. The clinical success of the deployment of bilateral MS was 79.2% (19/24). Law *et al*[31] reported on re-intervention after stent occlusion for 11 patients undergoing the deployment of bilateral MS using an SIS or SBS method. Successful re-intervention was defined as the ability to access and perform interventions in both the right and left hepatic ducts, and this was accomplished in 9 out of 11 patients (3/3 SIS, 6/8 SBS). Re-intervention after stent occlusion will be an important issue to resolve in coming years, with continued improvements seen in the prognosis of patients with UMHBS due to effective chemotherapy.

CONCLUSION

In the present review, we have described the current status of endoscopic biliary drainage in patients with UMHBS. Endoscopic biliary drainage for UMHBS is still technically demanding, with many unresolved issues,

including the choice of PS or MS, the choice of unilateral or bilateral drainage, and the use of either SIS or SBS deployment of bilateral MS. The development of new devices and techniques for stent deployment, and further randomized controlled trials are warranted to resolve these matters in question. The development of new methods of re-intervention after stent occlusion is also important to manage patient jaundice and cholangitis over a longer time period as continued advances in chemotherapy prolong the survival of patients with UMHBS.

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Update on novel endoscopic therapies to treat gastroesophageal reflux disease: A review

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Abstract

Endoscopic treatments for gastroesophageal reflux disease (GERD) have become increasingly popular in recent years. While surgical intervention with the Laparoscopic Nissen Fundoplication remains the gold standard, two endoscopic interventions, specifically, are gaining traction in clinical use (EsophyX and Stretta). The EsophyX (EndoGastric Solutions, Inc., Redmond, WA, United States) was developed as a method of restoring the valve at the GE junction through an endoluminal fundoplication (ELF) technique. Long-term data suggests that transoral incisional fundoplication (TIF) with EsophyX may be effective for symptom control and proton pump inhibitor reduction or cessation for up to 2-6 years. There is no evidence that EsophyX is more effective than surgical intervention. TIF may be most effective for patients with HH < 2 cm and Hill Grade I/II valves. Stretta (Mederi Therapeutics, Greenwich, CT, United States) was approved by the Food and Drug Administration in 2000. It delivers radiofrequency energy to the lower esophageal sphincter and gastric cardia. Published reviews of the literature are conflicted in their recommendations of Stretta in the management of GERD. The literature suggests that the Stretta procedure has an acceptable safety profile and may be effective in reducing symptom burden and quality of life scores up to 8 years post-intervention. However, there does not appear to be any sustained improvement in objective outcomes and there is no evidence that Stretta results in improved outcomes as compared to surgical intervention. Treatment modalities for GERD, as a field, suffer from a lack of standardization in primary and secondary outcomes. Although many studies have looked at health related quality of life, the tools used to do so are markedly heterogeneous. Future directions for the endoscopic treatment of GERD include novel techniques like endoscopic submucosal dissection.

Key words: Endoscopy; Reflux; Gastroesophageal reflux disease management; EsophyX; Stretta

Core tip: While surgical intervention with the Laparoscopic Nissen Fundoplication remains the gold standard for reflux, endoscopic treatments for gastroesophageal reflux disease have become increasingly popular in recent years. This review of endoscopic methods focuses on two procedures: the Esophyx, a procedure involving endoluminal fundoplication of the gastroesophageal junction, and Stretta, a procedure involving radiofrequency ablation of the gastro-esophageal junction. While these techniques have an acceptable safety profile and lead to subjective improvement in reflux, their objective efficacy remains unclear. The review highlights the lack of standardisation of outcome measures and heterogeneity of assessment tools.

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INTRODUCTION

The most widely accepted definition of gastroesophageal reflux disease (GERD), developed by the International consensus group, is "a condition that develops when stomach contents cause troublesome symptoms and/or complications"[1]. In North America, it has a prevalence of 18.1%-27.8%[2] and is estimated to be the most common reason for an outpatient gastrointestinal clinic visit[3]. This translates into significant economic burden through health-care associated costs, as well as reduced quality of life (QOL) for affected persons.

GERD is a multifactorial disease process. Factors affecting the development of GERD include mechanical impairment of the gastroesophageal (GE) junction, hiatal hernias (HH), and esophageal acid exposure (EAE). Pathological reflux can result in GERD type symptoms (heartburn, regurgitation, heartburn) and mucosal disease (esophagitis, strictures, metaplasia and cancer)[4].

The treatment of GERD changed dramatically after the advent of proton pump inhibitors (PPIs)[5]. In conjunction with lifestyle modifications, they are the current first line therapy for GERD[6]. While PPIs are often effective, there are patients who will be non-responders, require chronic PPI use or be subject to side effects of PPI therapy[7]. These side effects include enteric infections (*Clostridium difficile*), increased susceptibility to pneumonia, hypergastrinemia, osteoporosis and drug-drug interactions[8,9]. Furthermore, PPIs have a high drug expense and patient compliance with chronic daily use may be limited[10,11].

More invasive treatment options include surgical and endoscopic interventions. Laparoscopic Nissen Fundoplication (LNF) is considered the gold standard of treatment[12]. LNF differs from medical treatment in that it is directed at the underlying cause of GERD. The literature has demonstrated that LNF is able to provide improved relief of GERD symptoms and reduced PPI use with good long-term cost efficacy[13,14]. Furthermore, LNF may be more effective for those patients with abnormal symptoms[7,15].

Endoscopic treatments for GERD have become increasingly prevalent in recent years. There has been increased interest in these interventions by both patients and practitioners as an alternative to surgical intervention[12]. Endoscopic intervention is less invasive, typically involves a day procedure and avoids side effects of LNF such as bloating and dysphagia[9,16]. They are less permanent interventions; yet do not preclude the patient from being a future candidate for LNF[17-19]. Historically, endoscopic treatments have been divided into three separate categories: radiofrequency (RF) treatment of the GE junction, plication of the lower esophageal sphincter (LES) and injection of biopolymers[6,9]. Currently, there are two endoscopic interventions being used clinically - transoral incisional fundoplication (TIF) with the Esophyx device and RF treatment with the Stretta device.

The intent of this review is to provide an update on more recently published data regarding the two endoscopic interventions for GERD that are currently in clinical use (Stretta and EsophyX). Prior reviews have summarized short-term effects and suggest that long-term efficacy be studied and the appropriate patient populations be identified[16,20]. In the majority of published studies to date, the most common primary endpoint is subjective reduction in daily symptoms ($\geqslant$ 50%) or improvement in health related quality of life (HRQL) scores. Objective end point outcomes (pH studies, resolution of esophagitis and reduction of HH) have not been routinely studied in all patients up to this point in time.

DISCUSSION

Esophyx

The EsophyX (EndoGastric Solutions, Inc., Redmond, WA, United States) was developed as a method of restoring the valve at the GE junction through an endoluminal fundoplication (ELF) technique. The device is inserted transorally under direct vision with an endoscope. It allows for creation of 2-3 cm and 210°-300° fundoplication at the level of the GE junction. Twelve or more polypropylene, full thickness fasteners are used to create the omega-shaped valve. In a revision of the device (TIF 2), the fasteners are deployed 3-5 cm above the GE junction to create a flap valve similar to that of a LNF[12,16,21].

Randomized controlled trials

The first published randomized controlled trial (RCT) in 2011 by Svoboda *et al*[22] compared TIF against the gold standard Nissen fundoplication. The authors concluded no significance difference between the two therapies,

with a significant reduction in length of stay in favor of TIF (2.9 d *vs* 6.4 d).

The RESPECT trial was published in 2015[18]. It included 129 randomized patients. Results included a significant elimination of troublesome regurgitation in 67% (58 of 87) of TIF patients as compared to 45% (19 of 42) of PPI/sham patients. TIF patients also had significant decrease in EAE. At 18-mo follow, 71% (30 of 42) of the PPI/sham had crossed over to TIF and 28% (24 of 87) of the TIF group had resumed PPI.

The TEMPO trial was an open-label, randomized study of 60 patients who were followed up to 6 mo, with a primary end point of elimination of daily bothersome symptoms[23]. Troublesome regurgitation was eliminated in 97% (29/30) of patients undergoing TIF and off PPI, *vs* 50% (9 of 18) in the PPI group. At 6 mo, 90% (35 of 39) patients undergoing TIF had complete cessation of PPI use. EAE was normalized in 54% (21 of 39) of the TIF group *vs* 52% (11 of 21) in the PPI group. At 6 mo, 90% (18 of 20) of the TIF group had reduction of complete healing of esophagitis *vs* 38% (5 of 13) in the PPI group. Overall, the authors demonstrated that TIF had a more significant effect on controlling GERD symptoms compared to PPI.

A RCT was performed by Witteman *et al*[24], comparing TIF *vs* PPI treatment for GERD in 60 patients. They were followed up to 12 mo, with crossover of the PPI group to TIF at 6 mo. At 6 mo follow-up, HRQL scores were increased by ⩾ 50% in 55% of the TIF group *vs* 5% of the PPI group. Change in EAE, normalization of pH and healing of esophagitis was non-significant between the groups. While TIF2 had a significant increase in LES pressure, the total number of reflux episodes did not improve. In the TIF group, PPI was discontinued in 74%. Hill grade Ⅰ valves were created in 90% at the time of TIF, with only 35% remaining at 12 mo.

Long-term follow-up trials

Trials with long-term follow-up are limited in the literature. Bell *et al*[25] looked at prospectively collected data on TIF performed on 127 patients. Two year follow-up was completed on 100 patients with a primary endpoint of ⩾ 50% improvement in their regurgitation score. Of the 88 patients presenting with daily symptoms, 70% (60) reached the primary endpoint. Of the 98 patients starting with daily PPI use, 69 (70%) had complete cessation of PPI. HRQL scores remained stable to the 24 mo follow-up point. In regards to objective endpoints, 31 patients underwent endoscopic screening with healing of esophagitis seen in 75% (12 of 16). Furthermore, pH testing was performed in 50 patients preoperatively and 14 patients at 2 years. Eight of 14 (57%) patients had normalization of esophageal acid exposure.

Testoni *et al*[26], followed 50 patients who underwent TIF 2.0 with EsophyX. Mean follow-up was 52.7 mo, with 14 patients reaching 6-year follow-up. HRQL scores were significantly reduced compared to pre-intervention. In regards to PPI use, ⩾ 50% reduction or cessation was seen in 87.8% (36 of 41) at 24 mo, 84.4% (27 of 32) at 3 years, and 85.7% (12 of 14) at 6 years. There was no significant change in LES pressure at any time point. Overall, long-term response was best predicted by initial response in the first 6-12 mo, with best candidates for TIF being patients with Hill grade Ⅰ/Ⅱ valves and a hiatal hernia < 2 cm.

Literature reviews

In 2013, Wendling *et al*[19], published a systematic review of 15 observational studies of TIF. There was significant improvement in HRQL score compared to baseline score on PPI. Overall, the patient satisfaction rate with TIF was 72% at a mean of 8.5 mo. PPI cessation rates varied widely, with an overall rate of 67% at a mean follow-up time of 8.3 mo. There was weak correlation between discontinuation and follow-up length. None of the included studies were able to demonstrate reduced post-procedure EAE time. In total, there were 18 complications, with the most common being hemorrhage (1.1%) and an overall failure rate of 8.1%.

Overall, the limited long-term data reviewed here suggests that TIF with EsophyX may be effective for symptom control and PPI reduction or cessation for up to 2-6 years. There is no evidence that EsophyX is more effective than LNF. TIF may be most effective for patients with HH < 2 cm and Hill Grade Ⅰ/Ⅱ valves[23,26,27]. The ideal patient population has yet to be fully elucidated. The safety profile is acceptable, with low complication rates and no associated mortality.

STRETTA

Stretta (Mederi Therapeutics, Greenwich, CT, United States) was approved by the FDA in 2000. It delivers radiofrequency energy to the LES and gastric cardia. A gastroscope is first inserted to measure the distance to the Z-line. The gastroscope is then withdrawn and a catheter with a four channel RF generator is placed 1 cm proximal to the Z-line. Radiofrequency energy is then delivered to the muscularis propria for approximately 60 s to a target temperature of 65-85 degrees Fahrenheit. Tissue temperatures are constantly monitored using a thermocouple incorporated into the active electrodes[28]. Additional treatments are delivered by rotating the catheter circumferentially, as well as advancing it distally for a span of 2 cm towards the gastric cardia[12,16]. The mechanism of action of radiofrequency treatment for GERD has yet to be fully elucidated, but is thought to work *via* neurolysis or tissue necrosis causing local inflammation, collagen deposition and muscular thickening of the LES, resulting in fewer transient relaxations in LES pressure[28-30]. Clinical use was previously limited by safety concerns for esophageal perforation. In recent studies, the most commonly seen side effect was chest pain, which was self-limited and did not require intervention[31].

Gastroparesis has also been identified[32].

As it has been on the market for approximately 15 years, Stretta has been the topic of multiple studies and reviews, including four RCTs[29,32-34]. More recently published studies have focused on long-term efficacy of the procedure.

RCTs

In 2003, Corley *et al*[34], published the first randomized, sham-controlled trial for RFA in GERD patients, with follow-up at 0, 6, and 12 mo. At 6 and 12 mo, patients treated with RFA had significantly improved heartburn symptoms as well as improved QOL scores. No improvement was seen in the sham group. Prior to a medication withdrawal protocol there was no difference in daily PPI use between groups. Following this protocol the RF group reduced PPI usage by 46% compared to 29% in the sham group. There was no difference in EAE between RF and sham groups at 6 mo. A sub-group analysis of responders (> 50% reduction in QOL score) was shown to have significant decreases in 24-h acid exposure. Additionally, there was no difference in LES pressure or esophagitis between groups.

In 2008, Coron *et al*[29] published a prospective, randomized trial comparing PPI use *vs* RF energy in patients with PPI-dependent GERD. Results for their primary outcome demonstrated reduction or discontinuation of PPI in 18/23 (78%) of patients treated with RFA *vs* 8/20 (40%) in their control group at 6 mo follow-up. At 12 mo, this decreased to 12/23 (56%) and 7/20 (35%), respectively. Their secondary outcomes showed no difference in heartburn scores, no difference in QOL surveys, no difference in mean daily dose of PPI at 6 or 12 mo (P = 0.05) and no change in 24 h pH monitoring or endoscopic grade of esophagitis.

In another prospective, randomized, double-blinded, sham-controlled trial by Aziz *et al*[32] in 2010, patients were treated with either a single dose Stretta, a double dose of Stretta or with a sham procedure. At 12 mo there was a significant improvement in GERD-related symptoms in both active treatments, but not the sham group. In the double-dose group 50% were completely off their PPI, while only 16.6% in the single-dose group and none in the sham group were completely off of PPI therapy. LES pressure and esophageal acid exposure time was improved in both the single and double-dose treatment groups, with non-significant changes seen in the sham group.

In the latest RCT in 2012, Arts *et al*[33] reported outcomes of a double blind, sham-controlled study looking at the effect of the Stretta procedure on GERD symptoms, esophageal acid exposure and GE junction distensibility. They hypothesized that the procedure may decrease GE junction distensibility, thereby reducing the volume of refluxate and subsequently symptomatology. Symptom score was significantly reduced after the Stretta procedure, but not following a sham procedure. No change between the Stretta and sham groups was demonstrated in 3 or 6 mo follow-up endoscopy or 24-h pH monitoring. Medication use was not affected by initial Stretta procedure of sham. Finally, resting LES pressure did not change at 0, 3 or 6 mo following Stretta or sham procedure.

Long-term follow-up trials

Triadafilopoulos, in 2002, looked at Stretta durability at 6 and 12-mo follow-up[31]. They demonstrated significant improvement in heartburn scores, HRQL scores and patient satisfaction scores at both time periods. Eighty-eight percent of patients required daily PPI use at baseline, which decreased to 30% at 12 mo. Distal esophageal acid exposure time also decreased from 10.2% to 6.4%.

A prospective observational study of long term outcomes by Liang *et al*[35] in 2014, reported follow-up results on 138 of 152 initial patients. Overall symptom score was reduced at 6 mo and was sustained to the 5-year follow-up mark. At 6 mo, 38 (27.5%) of patients were completely off of PPI, which increased to 59 (42.8%) at 5 years.

Dughera *et al*[36] published long-term follow-up results of their single center study. Eight-year follow-up was achieved in 26 of 86 patients. In total, 7 patients restarted daily use of a PPI, of which 5 went on to have LNF. Overall, there was a significant decrease in heartburn score and increase in HRQL score that was still present at 8 year follow-up. Furthermore, 20/26 remained completely off a PPI. While none of the 26 patients developed endoscopic evidence of esophagitis, median LES pressure did not demonstrate any improvement at 8 years.

In the longest reported follow-up data, Noar *et al*[37] performed a 10-year, open label, prospective trial of patients with refractory GERD treated with Stretta. In total, 149 of 217 patients reached the 10-year follow-up, of which 72% had normalization of HRQL. Furthermore, 64% had $\geqslant$ 50% reduction in baseline PPI use with discontinuation in 41% at the 10 year mark. Fifty-one of 149 patients had no endoscopic evidence of erosive esophagitis at 10 years.

Literature reviews

Published reviews of the literature are conflicted in their recommendations of Stretta in the management of GERD. The most recent systematic review in 2014 by Lipka *et al*[38] concluded that was no evidence for the efficacy of radiofrequency ablation for the treatment of GERD. Their review included 4 randomized trials, all of which were determined to be of poor methodological quality. Overall outcomes showed no significant benefit of Stretta over sham therapy for mean time pH was less than 4, mean change in LES pressure, increase in discontinuation of PPI or improvement in HRQL scores[38]. This was in direct contrast to an earlier Review by Perry *et al*[3] and a subsequent recommendation review by the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES)[3,20,39]. Perry *et al*[3] found, in their 2012 review of 18 studies, that radiofrequency

produced significant improvement in reflux symptoms, with improved heartburn scores, esophageal acid exposure and QOL scores. The methodologically validity of both reviews continues to be debated[38,39].

Overall, the data suggests that the Stretta procedure has an acceptable safety profile and may be effective in reducing symptom burden and QOL scores up to 8 years post-intervention. There does not appear to be any sustained improvement in objective outcomes and there is no evidence that Stretta results in improved outcomes as compared to surgical intervention.

Limitations

Treatment modalities for GERD, as a field, suffer from a lack of standardization in primary and secondary outcomes. Although many studies have looked at HRQL, the tools used to do so are markedly heterogeneous. Furthermore, whether more subjective measures such as QOL and symptom control are equivalent to objective measurements has not yet been elucidated[17]. Subjective symptom improvement is clinically relevant, but there is no established correlation to severity of reflux[12]. PPI use is quantified in studies and is an objective outcome, but is not a specific marker for GERD and may be used for dyspepsia. Manometry and pH studies are more objective markers but may have less clinical relevance, particularly for the patient if symptom control is not improved.

Future direction

In a preliminary, prospective, single-arm trial, Ota *et al*[40], looked at a novel endoscopic fundoplication technique using endoscopic submucosal dissection (ESD) in 13 patients. Scarring post-ESD results in narrowing of the GE junction and reduced reflux. The demonstrated improved symptoms in 92% (12 of 13), cessation of PPI use in 23% (3 of 13) and reduced PPI use in 23% (3 of 13). There was no change demonstrated in pH studies.

Future directions may be aimed more towards novel surgical interventions, such as the LINX reflux management system, a ring of linked magnetic beads laparoscopically placed around the LES that improves pressure without any anatomical change[7,10]. The EndoStim is another device placed laparoscopically that delivers electrical energy to the LES in order to increase resting pressure[7,10].

CONCLUSION

In theory, endoscopic management of GERD is promising field with obvious advantages of a less invasive procedure, however the majority of procedures and devices released are no longer available for lack of reported efficacy. The published data for the two procedures with the most evidence, EsophyX and Stretta, generally show improvement over baseline (PPI therapy alone) or sham procedure but currently are second-line procedures to surgical intervention[20].

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