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OPINION REVIEW

Proposal of the term "gallstone cholangiopancreatitis" to specify gallstone pancreatitis that needs urgent endoscopic retrograde cholangiopancreatography

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Abstract

Opie's "pancreatic duct obstruction" and "common channel" theories are generally accepted as explanations of the mechanisms involved in gallstone acute pancreatitis (AP). Common channel elucidates the mechanism of necrotizing pancreatitis due to gallstones. For pancreatic duct obstruction, the clinical picture of most patients with ampullary stone impaction accompanied by biliopancreatic obstruction is dominated by life-threatening acute cholangitis rather than by AP, which clouds the understanding of the severity of gallstone AP. According to the revised Atlanta classification, it is difficult to consider these clinical features as indications of severe pancreatitis. Hence, the term "gallstone cholangiopancreatitis" is suggested to define severe disease complicated by acute cholangitis due to persistent ampullary stone impaction. It incorporates the terms "cholangitis" and "gallstone pancreatitis." "Cholangitis" refers to acute cholangitis due to cholangiovenous reflux through the foci of extensive hepatocyte necrosis reflexed by marked elevation in transaminase levels caused by persistent ampullary obstruction. "Gallstone pancreatitis" refers to elevated pancreatic enzyme levels consequent to pancreatic duct obstruction. This pancreatic lesion is characterized by minimal or mild inflammation. Gallstone cholangiopancreatitis may be valuable in clinical practice for specifying gallstone AP that needs urgent endoscopic retrograde cholangiopancreatography with endoscopic sphincterotomy.

Key Words: Gallstone pancreatitis; Gallstone hepatitis; Acute cholangitis; Necrotizing pancreatitis; Pathophysiology; Endoscopic retrograde cholangiopancreatography

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acute pancreatitis complicated by life-threatening acute cholangitis due to persistent ampullary stone impaction and needs urgent endoscopic retrograde cholangiopancreatography with endoscopic sphincterotomy. The term "gallstone cholangiopancreatitis" incorporates the terms "cholangitis" and "gallstone pancreatitis." "Cholangitis" refers to acute cholangitis due to cholangiovenous reflux through the foci of extensive hepatocyte necrosis reflexed by marked elevation in transaminase levels caused by persistent ampullary obstruction. "Gallstone pancreatitis" refers to elevated pancreatic enzyme levels consequent to pancreatic duct obstruction, the pancreatic lesion that is characterized by minimal or mild inflammation.

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INTRODUCTION

The presence of gallstones is an important etiologic factor for the development of acute pancreatitis (AP). Generally, obstruction of pancreatic outflow, which is frequently caused by transiently impacted stones at the ampulla of Vater, can cause gallstone AP [1]. Most patients with gallstone AP have a mild disease due to the eventual passage of stones, exhibiting rapid objective improvement. Nevertheless, the pathophysiology of severe disease in the remaining patients, refractory to conventional supportive therapy, remains controversial. In addition to the low incidence of gallstone AP in those with gallstones (3.4%[2], 7.7%[3]), the rapid disease course and the relative inaccessibility of pancreatic tissues for the examination of AP have hampered investigations of the mechanism of severe disease in gallstone AP[4]. Considering these issues, investigations in humans may rely on findings from either autopsies or emergency surgeries performed during the early disease course. Emergency surgeries were common until the 1980s; however, they are no longer a common practice. Based on autopsy findings, Eugene Opie proposed the "pancreatic duct obstruction" and "common channel" theories in 1901, which are generally accepted as explanations of the mechanisms involved in gallstone AP[4]. Opie's postulates can be summarized as follows: (1) Stones impacted at the terminal bile duct or the ampulla of Vater obstruct the bile and pancreatic ducts simultaneously. The obstructed pancreatic juice and bile may be forced backward into the pancreatic and hepatic parenchyma and penetrate their surrounding tissues, causing interstitial edematous pancreatitis and/or fat necrosis ("pancreatic duct obstruction" theory) and tissue stain with bile pigments and/or jaundice, respectively; and (2) Small stones about 3 mm in diameter that are large enough to lodge at the duodenal orifice mostly measured 2 mm to 2.5 mm but too small to obstruct the bile and pancreatic duct orifices, convert both ducts into a continuous closed channel. Contraction of the gallbladder overcomes any slight pressure difference between the bile and pancreatic ducts, which may lead to repeated bile reflux into the pancreatic duct, causing necrotizing pancreatitis (NP) ("common channel" theory).

Pancreatic duct obstruction theory stipulates that simultaneous obstruction of both ducts due to the large stone size and very short length of the common channel causes AP. However, severe disease caused by persistent ampullary stone impaction combined with biliopancreatic obstruction remains controversial. This is one of the main issues considered in this opinion review.

NP AND PASSED STONE

Common channel theory elucidates the cause of NP due to gallstones. Animal models have shown that protease activation is highly dependent on calcium release[5], with bile acids inducing calcium-releasing signals and contributing to pancreatic acinar cell damage[6]. However, questions on the evidence of bile reflux into the pancreatic duct

and the presence of impacted stones, which prevent wide acceptance of this postulate, have been raised. Recently, histological evidence of bile reflux into the pancreas as the cause of NP has been reported[7], and Opie's long-speculated "common channel" theory that NP represents the primary action of bile has been proven. In a case in the 1980s reported by Isogai *et al*[7], the operative cholangiogram did not demonstrate any bile duct stones. However, it revealed reflux of contrast material into the pancreatic duct, suggesting that an "anatomic" common channel was converted into a "functioning" common channel[8]. Kelly[9] noted that a functioning common channel is necessary for bile reflux and favors stone passage. Thus, regarding the presence of no impacted stones, virtually all small stones of a size that settle in the narrow duodenal orifice and allow bile reflux into the pancreatic duct may be evacuated and passed soon after triggering NP, thereby providing no evidence of their former impaction[7,10].

Long common channels[11], which allow for communication between the two ducts using impacted stones at the duodenal orifice, are not universally present in patients with gallstone AP. Hernández and Lerch[12] observed that the migration of gallstones through the biliary tract induces functional stenosis at the sphincter of Oddi, and a common channel between the pancreatic and bile ducts can arise. In 1909, Opie and Meakins[13] reported a case of NP with an anomalous duct of Santorini with a relatively wide orifice. They concluded that duodenal contents might have regurgitated into the pancreatic duct, causing NP; enterokinase, which is the most potent activator of pancreatic proteolytic enzymes, is present in these duodenal secretions. The passage of stones may cause a similar patulous sphincter, permitting duodenopancreatic reflux[14]. However, it may be difficult to prove histologically the reflux as the cause of NP since duodenal contents have no pigment to indicate their presence.

CONTROVERSIES RELATED TO BILIOPANCREATIC OBSTRUCTION

As Opie noted, pancreatic lesions caused by impacted ampullary stones may be interstitial edematous pancreatitis, of which clinical symptoms usually resolve within the first week[15]. It can also be fat necrosis, which is probably caused by lipase (one of the few pancreatic enzymes that require no activation), phagocytized by macrophages that may later be replaced with small foci of fibrotic tissues[16]. Acosta *et al*[17] noted that during the early stage of gallstone AP with persistent ampullary obstruction, a possible pancreatic complication is a pancreatic phlegmon, which includes a pancreatic inflammatory mass, peripancreatic fluid, and fat necrosis. Similarly, Oría *et al*[18] noted that biliopancreatic obstruction does not, by itself, contribute to persistent pancreatic inflammation or its worsening. Moreover, whether pancreatic duct obstruction without reflux causes NP in humans remains unknown[4]. Additionally, the clinical picture of most patients with ampullary stone impaction is often dominated by cholangitis and septicemia rather than by AP[14], which clouds the understanding of the severity of gallstone AP and leads to confusion and controversy regarding the management of patients with gallstone AP.

As noted previously, during the era of Opie, macroscopic findings of fat necrosis and/or interstitial edematous pancreatitis and those of jaundice and/or tissue stain with bile pigments were the indicators of persistent pancreatic duct and bile duct obstruction, respectively. The current availability of biochemical tests has shown that patients with gallstone AP have highly elevated liver and pancreatic enzyme levels during the early disease course. A histopathological study of liver biopsy specimens in gallstone AP patients with minimal or mild pancreatic inflammation (few patients with NP underwent liver biopsy) have shown that elevated serum transaminase levels reflect histopathological acute inflammatory hepatocyte necrosis (accumulation of neutrophils in and around the disappeared liver cell plate) and acute cholangitis (neutrophil infiltration in and around the bile duct lumen in the portal triad)[19]. Using electron microscopy, a disorganized liver cell plate, retained biliary material in the dilated canaliculi, and cytoplasm shedding into the Disse space have also been detected[19]. Thus, highly elevated liver enzyme levels during the early disease course in patients with gallstone AP reflect microscopic hepatocyte necrosis and cholangitis caused by the sudden blockage of the ampulla of Vater because of migrating bile duct stones[19]. Liver enzymes escape from degenerated and necrotic hepatocytes, causing marked hypertransaminemia. These hepatic histopathological simultaneous changes of cholestasis, acute cholangitis, and hepatocyte necrosis were consistent with those observed in patients with gallstone hepatitis[20], which will be discussed later. Based

on the hepatic histopathological changes in gallstone AP, Neoptolemos *et al*[21] concluded that there is a degree of obstruction in both bile and pancreatic ducts in gallstone AP. In contrast, the admission serum bilirubin reflects the degree of "persistent" bile duct obstruction due to the continued presence of bile duct stones. Thus, the elevation of serum transaminase is consistent with the concept of transient ampullary obstruction in gallstone AP and useful in establishing gallstone etiology. An elevated alanine transaminase (ALT) level is widely considered the most useful to identify the biliary etiology of AP, and a 1994 meta-analysis found that an ALT level of > 150 units/L has a positive predictive value for gallstone AP of 95%[22]. A prospective study conducted by Anderson *et al*[23] demonstrated that the higher the ALT, the more likely a biliary cause becomes; ALT levels of > 300 units/L and > 500 units/L have positive predictive values of 87% and 92%, respectively.

In 1991, Isogai *et al*[20] proposed the term "gallstone hepatitis" as a new clinical entity defined as a marked elevation in serum transaminase levels due to acute inflammatory liver cell degeneration and necrosis during the early stage of gallstone impaction in the bile duct. Marked elevation in transaminase levels alone may lead to a diagnosis of so-called hepatitis. However, the pathogenesis of gallstone hepatitis differs from ordinary hepatitis in that hepatocyte necrosis does occur as a consequence of cholestasis. Hepatocellular degeneration and necrosis have been histologically shown to be the acute inflammatory reactions to liver injury caused by acute bile duct obstruction, which is transient and reversible after its early resolution[20]. It is easily conceivable that if the bile duct is obstructed by impacted stones, it becomes a closed system filled with bile and that pathological changes in the bile duct such as bile stasis, increased pressure, or infection may affect the liver cells that bound the bile canaliculus and cause hepatocellular injury[20]. Mayer and McMahon[24] reported that transient ampullary obstruction causes a rapid rise in bile duct pressure and consequent liver cell damage. Animal models showed that a combination of bile stasis and inflammation causes a mechanical insufficiency of lymph circulation, leading to extensive liver cell necrosis[25]. In addition to a marked depression of the hepatic microcirculation, increased neutrophil infiltration in the liver represents a potential source of liver injury during acute biliary obstruction[26]. In about half of patients with gallstone hepatitis, the gross appearance of the gallbladder showed acute cholecystitis. However, acute cholecystitis was significantly more infrequent among patients with gallstone hepatitis than control patients, and acute inflammation of the gallbladder is thought to be secondary to bile duct obstruction[20]. Similarly, histological evidence of acute cholangitis is considered after bile duct obstruction and not the initial process responsible for transaminase elevation[20]. In 2016, Huh *et al*[27] proposed to exclude patients with acute cholangitis upon hospital admission from gallstone hepatitis. Marked elevation of serum transaminase levels is induced under conditions in which intrabile duct pressure dramatically surges[27].

These highly elevated liver test results (gallstone hepatitis) should heighten the clinician's awareness of coexisting acute biliary tract disease with gallstone AP. Hepatocytes with tight junctional complexes, which form a seal between the lumen of the bile canaliculus and the hepatic intercellular space, play a role in the creation of a canaliculi–sinusoidal barrier[28], and discontinuities in the junctional meshwork provide a direct pathway between the lumen of the bile canaliculus and the intercellular space[29]. Thus, elevated liver enzyme levels, a serological reflection of microscopic hepatocyte necrosis, indicate disruption to the barrier. It permits regurgitation of the bile into the circulating blood if the pressure in the bile canaliculus increases further due to persistent obstruction of the bile duct leading to acute ascending cholangitis.

Conventionally, clinicians have paid less attention to hepatobiliary diseases characterized by markedly elevated liver enzyme levels caused by impacted bile duct stones; this seems to be the Achilles heel in managing patients with gallstone AP. This may be unavoidable because the term "gallstone AP" refers to "pancreatitis" alone. The term "gallstone hepatopancreatitis" reflects elevated liver and pancreatic enzyme levels, which may better direct the clinician's attention to hepatobiliary pancreatic lesions occurring in both the liver and the pancreas caused by transiently impacted stones at the ampulla of Vater early in the gallstone AP course.

SUBDIVISION OF SEVERE DISEASE INTO TWO CATEGORIES

The revised Atlanta classification for AP defines moderately severe and severe AP as the presence of transient organ failure, local complications, or exacerbation of

comorbid diseases and as persistent organ failure, respectively[15]. Subsequently, a clinical dilemma arises: Are those patients with AP of gallstone etiology (*i.e.* gallstone AP) who have minimal or mild pancreatitis complicated with life-threatening acute cholangitis due to persistent ampullary stone impaction diagnosed with moderately severe or severe AP? It is difficult to consider these clinical features to be indicative of such severity of AP. To cope with the dilemma mentioned above, the author suggests the term "gallstone cholangiopancreatitis (CP)" to define severe disease with minimal or mild pancreatitis complicated with life-threatening acute cholangitis. The term "gallstone CP" incorporates the terms "cholangitis" and "gallstone pancreatitis." "Cholangitis" refers to acute ascending cholangitis due to cholangiovenous reflux through the foci of extensive hepatocyte necrosis reflexed by marked elevation in transaminase levels (gallstone hepatitis) caused by persistent ampullary obstruction. Conversely, "gallstone pancreatitis" refers to elevated pancreatic enzyme levels due to pancreatic duct obstruction, the pancreatic lesion that has minimal or mild inflammation (Figure 1A). It should be emphasized that in gallstone CP, the hepatobiliary pathology reflected by "cholangitis" outweighs the pancreatic lesion reflected by "gallstone pancreatitis." Currently, endoscopic retrograde cholangiopancreatography (ERCP) with endoscopic sphincterotomy (ES) is the widely accepted modality for gallstone AP with coexisting cholangitis and persistent biliary obstruction (*i.e.* gallstone CP)[10,30].

In contrast, NP resulting from the reflux of bile or duodenal contents into the pancreas uncomplicated with acute biliary tract disease due to the passage of stones is recommended to define "gallstone NP" (Figure 1B). This is because AP is generally an inflammation secondary to pancreatic tissue necrosis, irrespective of etiology, resulting from autodigestion by pancreatic enzymes[16]. Considering that stones responsible for NP generally pass into the duodenum early in the disease course or have already been evacuated and lost, ES may not be necessary for patients with gallstone NP. Additionally, a recent multicenter randomized controlled trial reported that compared with conservative treatment, urgent ERCP with ES (within 24 h after hospital presentation) did not reduce the composite endpoint of major complications or mortality in patients with predicted severe gallstone AP (Acute Physiology and Chronic Health Evaluation II score ≥ 8, Imrie score ≥ 3, or C-reactive protein level > 150 mg/L) and without cholangitis[31]. For future clinical trials on the role of urgent ERCP, American Gastroenterological Association has recommended that the timing of the ERCP interventions should be 24-48 h after diagnosis (24 h to allow spontaneous passage of the stone and 48 h to ensure that prolonged biliary obstruction does not occur)[10].

PERSPECTIVES ON GALLSTONE PANCREATITIS

In 2017, Campos *et al*[32] reported that pancreaticobiliary diseases are the most common cause of the marked increase in serum aminotransferase levels, considering the decrease in the prevalence of liver diseases (including viral infections) due to vaccination programs, social awareness campaigns, and an increased incidence of cholesterol calculi in developed countries, which was considered to be a new paradigm. The marked increase in serum aminotransferase levels in pancreaticobiliary diseases observed by Campos *et al*[32] was specifically in gallstone hepatitis or gallstone AP. Thus, gallstone AP is expected to be more often encountered. Gallstone AP is a disease diagnosed by the abnormal biochemical data of pancreatic and liver enzymes or may be missed if the blood tests are not performed. Once gallstone AP is diagnosed based on the acute onset of a severe epigastric pain accompanied by an elevation of pancreatic and liver enzyme levels and gallstones are demonstrated by image modalities, it should be properly managed based on the differences in clinical features and the mechanism by which gallstones initiate AP. The acute inflammatory hepatobiliary disease indicated by marked hypertransaminasemia (gallstone hepatitis) together with the pancreatic lesion reflected by a pancreatic enzyme elevation needs to be evaluated.

Within the first 72 h following its diagnosis, the key management strategy is to predict patients with gallstone CP who will benefit from ERCP with ES. It may be difficult to distinguish the inflammatory response caused by pancreatic injury from that due to biliary sepsis. Additionally, the diagnosis of coexisting acute cholangitis is not always straightforward, and the reliance on Charcot's triad criteria may be insufficient[18]. The sensitivity and specificity of endoscopic ultrasound in detecting common bile duct stones are superior to those of both transabdominal ultrasound and

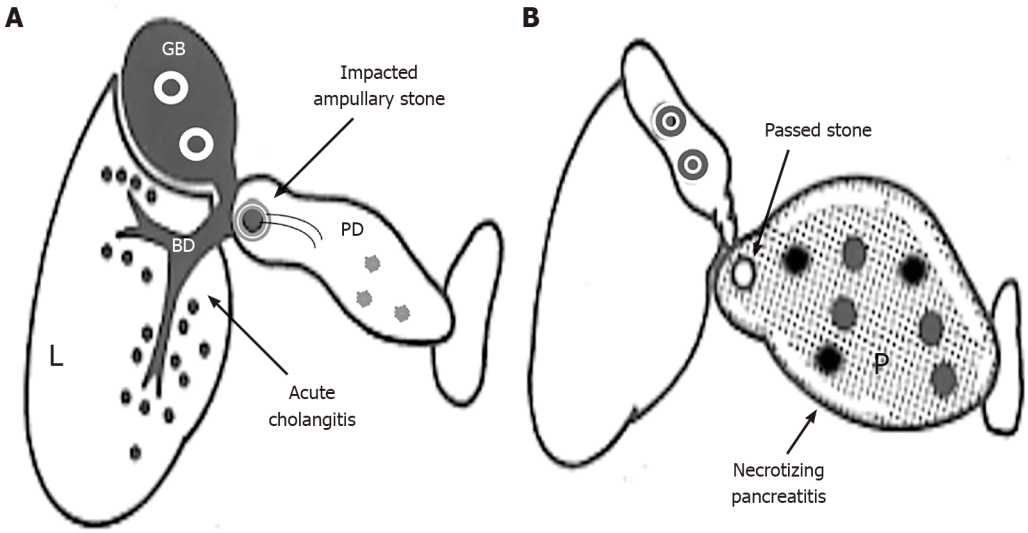

Figure 1 Subdivisions of gallstone pancreatitis with severe disease into gallstone cholangiopancreatitis and gallstone necrotizing pancreatitis. A: Gallstone cholangiopancreatitis with persistent ampullary stone impaction and ascending acute cholangitis complicated with minimal or mild pancreatic inflammation due to biliopancreatic obstruction; B: Gallstone necrotizing pancreatitis caused by the reflux of bile or duodenal contents into the pancreas (P), not complicated by acute biliary tract disease due to the passage of stones. L: Liver; BD: Bile duct; GB: Gallbladder; PD: Main pancreatic duct.

serum markers[33]. Hence, despite being invasive and not widely available, there is increasing use of endoscopic ultrasound to identify common bile duct stones in patients with gallstone AP. An endoscopic ultrasound-first strategy to establish the indication for ERCP with ES is expected[33].

If gallstone CP is ruled out and patients fail to improve after 5 to 7 d of initial treatment, contrast-enhanced computed tomography (CECT) is the most useful method for differentiating edematous pancreatitis from NP[34], and its findings are incorporated in the severity assessment of AP[35]. However, CECT should only be used when the value of the information obtained outweighs the disadvantages, such as impairment of renal function and allergic reaction[35]. Because an early CECT may underestimate the eventual extent of pancreatic and peripancreatic necrosis, a non-enhancing area of the pancreatic parenchyma identified using CECT should be considered as pancreatic parenchyma necrosis after the first week of the disease[15].

The algorithm for the diagnosis and initial treatment of gallstone AP is shown in Figure 2. The detailed management strategy for patients with gallstone NP has been suggested by a substantial evidence base[33], although this issue is beyond the scope of the present review.

CONCLUSION

Regarding gallstone AP, the disease severity caused by persistent ampullary stone impaction with biliopancreatic obstruction remains controversial. Based on the differences in clinical features and the mechanism by which gallstones initiate AP, the severe disease is subdivided into gallstone CP and gallstone NP. The term "gallstone CP" is suggested to define severe disease with minimal or mild pancreatitis complicated by life-threatening acute cholangitis due to persistent ampullary stone impaction. The term "gallstone CP" may be valuable in clinical practice for specifying gallstone AP that needs urgent ERCP with ES. Whereas severe disease with NP resulting from the reflux of bile or duodenal contents into the pancreas is defined as "gallstone NP," which is not complicated by acute biliary tract disease due to the passage of stones, and urgent ERCP may not be necessary.

Although elevation in serum transaminase levels in patients with gallstone CP reflects hepatic injury, which is inappropriate for use in multifactor prognostic systems of AP such as Ranson or Imrie score, the mechanism of transaminase elevation in patients with gallstone NP remains unclear without hepatic histopathological evidence, and further studies are needed.

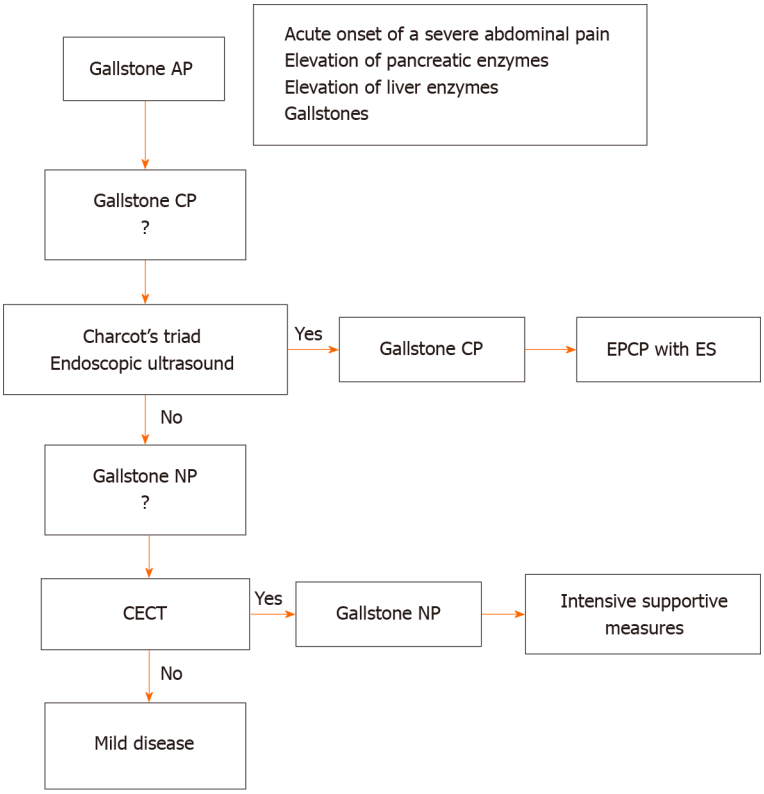

Figure 2 The algorithm for the diagnosis and initial treatment of gallstone pancreatitis. AP: Acute pancreatitis; CECT: Contrast-enhanced computed tomography; CP: Cholangiopancreatitis; ERCP: Endoscopic retrograde cholangiopancreatography; ES: Endoscopic sphincterotomy; NP: Necrotizing pancreatitis.

REFERENCES

1 **Acosta JM**, Ledesma CL. Gallstone migration as a cause of acute pancreatitis. *N Engl J Med* 1974; **290**: 484-487 [PMID: 4810815 DOI: 10.1056/NEJM197402282900904]
2 **Moreau JA**, Zinsmeister AR, Melton LJ 3rd, DiMagno EP. Gallstone pancreatitis and the effect of cholecystectomy: a population-based cohort study. *Mayo Clin Proc* 1988; **63**: 466-473 [PMID: 3361956 DOI: 10.1016/s0025-6196(12)65644-4]
3 **Armstrong CP**, Taylor TV, Jeacock J, Lucas S. The biliary tract in patients with acute gallstone pancreatitis. *Br J Surg* 1985; **72**: 551-555 [PMID: 4016539 DOI: 10.1002/bjs.1800720718]
4 **Pandol SJ**, Saluja AK, Imrie CW, Banks PA. Acute pancreatitis: bench to the bedside. *Gastroenterology* 2007; **132**: 1127-1151 [PMID: 17383433 DOI: 10.1053/j.gastro.2007.01.055]
5 **Krüger B**, Albrecht E, Lerch MM. The role of intracellular calcium signaling in premature protease activation and the onset of pancreatitis. *Am J Pathol* 2000; **157**: 43-50 [PMID: 10880374 DOI: 10.1016/S0002-9440(10)64515-4]
6 **Voronina S**, Longbottom R, Sutton R, Petersen OH, Tepikin A. Bile acids induce calcium signals in mouse pancreatic acinar cells: implications for bile-induced pancreatic pathology. *J Physiol* 2002; **540**: 49-55 [PMID: 11927668 DOI: 10.1113/jphysiol.2002.017525]
7 **Isogai M**, Kaneoka Y, Iwata Y. Histological evidence of bile reflux in necrotizing pancreatitis: a case report. *Med Case Rep Study Protoc* 2020; **1**: e0016 [DOI: 10.1097/MD9.0000000000000016]
8 **Kelly TR**. Gallstone pancreatitis. Local predisposing factors. *Ann Surg* 1984; **200**: 479-485 [PMID: 6207784 DOI: 10.1097/00000658-198410000-00009]
9 **Kelly TR**. Gallstone pancreatitis: pathophysiology. *Surgery* 1976; **80**: 488-492 [PMID: 968732]
10 **Vege SS**, DiMagno MJ, Forsmark CE, Martel M, Barkun AN. Initial Medical Treatment of Acute Pancreatitis: American Gastroenterological Association Institute Technical Review. *Gastroenterology* 2018; **154**: 1103-1139 [PMID: 29421596 DOI: 10.1053/j.gastro.2018.01.031]
11 **DiMagno EP**, Shorter RG, Taylor WF, Go VL. Relationships between pancreaticobiliary ductal anatomy and pancreatic ductal and parenchymal histology. *Cancer* 1982; **49**: 361-368 [PMID: 7032685 DOI: 10.1002/1097-0142(19820115)49:2<361::aid-cncr2820490225>3.0.co;2-o]
12 **Hernández CA**, Lerch MM. Sphincter stenosis and gallstone migration through the biliary tract. *Lancet* 1993; **341**: 1371-1373 [PMID: 8098791 DOI: 10.1016/0140-6736(93)90942-a]
13 **Opie EL**, Meakins JC. Data concerning the etiology and pathology of hemorrhagic necrosis of the pancreas (acute hemorrhagic pancreatitis). *J Exp Med* 1909; **11**: 561-578 [PMID: 19867267 DOI: 10.1084/jem.11.4.561]
14 Obstruction or reflux in gallstone-associated acute pancreatitis? *Lancet* 1988; **1**: 915-917 [PMID: 2895834 DOI: 10.1016/s0140-6736(88)91718-7]

15 **Banks PA**, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, Tsiotos GG, Vege SS; Acute Pancreatitis Classification Working Group. Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus. *Gut* 2013; **62**: 102-111 [PMID: 23100216 DOI: 10.1136/gutjnl-2012-302779]

16 **Klöppel G**, Maillet B. Histopathology of acute pancreatitis. In: Beger HG, Warshaw AL, Büchler MW, Carr-Locke DL, Neoptolemos JP, Russell C, Sarr MG. The Pancreas—volume 1. Hoboken: Blackwell Science, 1998: 404-409

17 **Acosta JM**, Katkhouda N, Debian KA, Groshen SG, Tsao-Wei DD, Berne TV. Early ductal decompression *vs* conservative management for gallstone pancreatitis with ampullary obstruction: a prospective randomized clinical trial. *Ann Surg* 2006; **243**: 33-40 [PMID: 16371734 DOI: 10.1097/01.sla.0000194086.22580.92]

18 **Oría A**, Cimmino D, Ocampo C, Silva W, Kohan G, Zandalazini H, Szelagowski C, Chiappetta L. Early endoscopic intervention *vs* early conservative management in patients with acute gallstone pancreatitis and biliopancreatic obstruction: a randomized clinical trial. *Ann Surg* 2007; **245**: 10-17 [PMID: 17197959 DOI: 10.1097/01.sla.0000232539.88254.80]

19 **Isogai M**, Yamaguchi A, Hori A, Nakano S. Hepatic histopathological changes in biliary pancreatitis. *Am J Gastroenterol* 1995; **90**: 449-454 [PMID: 7872285]

20 **Isogai M**, Hachisuka K, Yamaguchi A, Nakano S. Etiology and pathogenesis of marked elevation of serum transaminase in patients with acute gallstone disease. *HPB Surg* 1991; **4**: 95-105; discussion 106 [PMID: 1931784 DOI: 10.1155/1991/95059]

21 **Neoptolemos JP**, Ogunbiyi O, Wilson PG, Carr-Locke DL. Etiology, pathogenesis, natural history, and treatment of biliary acute pancreatitis. In Beger HG, Warshaw AL, Büchler MW, Carr-Locke DL, Neoptolemos JP, Russell C, Sarr MG. The Pancreas. Volume 1. Hoboken: Blackwell Science; 1998. 521-547

22 **Tenner S**, Dubner H, Steinberg W. Predicting gallstone pancreatitis with laboratory parameters: a meta-analysis. *Am J Gastroenterol* 1994; **89**: 1863-1866 [PMID: 7942684]

23 **Anderson K**, Brown LA, Daniel P, Connor SJ. Alanine transaminase rather than abdominal ultrasound alone is an important investigation to justify cholecystectomy in patients presenting with acute pancreatitis. *HPB (Oxford)* 2010; **12**: 342-347 [PMID: 20590910 DOI: 10.1111/j.1477-2574.2010.00173.x]

24 **Mayer AD**, McMahon MJ. Biochemical identification of patients with gallstones associated with acute pancreatitis on the day of admission to hospital. *Ann Surg* 1985; **201**: 68-75 [PMID: 2578276]

25 **Ruszyák I**, Földi M, Szabó G. Lymphatics and lymph circulation: physiology and pathologY. In: Youlten L. London: Pergamon press, 1967: 727-735

26 **Koeppel TA**, Trauner M, Baas JC, Thies JC, Schlosser SF, Post S, Gebhard MM, Herfarth C, Boyer JL, Otto G. Extrahepatic biliary obstruction impairs microvascular perfusion and increases leukocyte adhesion in rat liver. *Hepatology* 1997; **26**: 1085-1091 [PMID: 9362346 DOI: 10.1002/hep.510260501]

27 **Huh CW**, Jang SI, Lim BJ, Kim HW, Kim JK, Park JS, Lee SJ, Lee DK. Clinicopathological features of choledocholithiasis patients with high aminotransferase levels without cholangitis: Prospective comparative study. *Medicine (Baltimore)* 2016; **95**: e5176 [PMID: 27759652 DOI: 10.1097/MD.0000000000005176]

28 **Boyer JL**. Tight junctions in normal and cholestatic liver: does the paracellular pathway have functional significance? *Hepatology* 1983; **3**: 614-617 [PMID: 6345333 DOI: 10.1002/hep.1840030423]

29 **Robenek H**, Herwig J, Themann H. The morphologic characteristics of intercellular junctions between normal human liver cells and cells from patients with extrahepatic cholestasis. *Am J Pathol* 1980; **100**: 93-114 [PMID: 7395970]

30 **Fogel EL**, Sherman S. ERCP for gallstone pancreatitis. *N Engl J Med* 2014; **370**: 150-157 [PMID: 24401052 DOI: 10.1056/NEJMct1208450]

31 **Schepers NJ**, Hallensleben NDL, Besselink MG, Anten MGF, Bollen TL, da Costa DW, van Delft F, van Dijk SM, van Dullemen HM, Dijkgraaf MGW, van Eijck CHJ, Erkelens GW, Erler NS, Fockens P, van Geenen EJM, van Grinsven J, Hollemans RA, van Hooft JE, van der Hulst RWM, Jansen JM, Kubben FJGM, Kuiken SD, Laheij RJF, Quispel R, de Ridder RJJ, Rijk MCM, Römkens TEH, Ruigrok CHM, Schoon EJ, Schwartz MP, Smeets XJNM, Spanier BWM, Tan ACITL, Thijs WJ, Timmer R, Venneman NG, Verdonk RC, Vleggaar FP, van de Vrie W, Witteman BJ, van Santvoort HC, Bakker OJ, Bruno MJ; Dutch Pancreatitis Study Group. Urgent endoscopic retrograde cholangiopancreatography with sphincterotomy *vs* conservative treatment in predicted severe acute gallstone pancreatitis (APEC): a multicentre randomised controlled trial. *Lancet* 2020; **396**: 167-176 [PMID: 32682482 DOI: 10.1016/S0140-6736(20)30539-0]

32 **Campos S**, Silva N, Carvalho A. A New Paradigm in Gallstones Diseases and Marked Elevation of Transaminases: An Observational Study. *Ann Hepatol* 2017; **16**: 285-290 [PMID: 28233751 DOI: 10.5604/16652681.1231588]

33 **van Dijk SM**, Hallensleben NDL, van Santvoort HC, Fockens P, van Goor H, Bruno MJ, Besselink MG; Dutch Pancreatitis Study Group. Acute pancreatitis: recent advances through randomised trials. *Gut* 2017; **66**: 2024-2032 [PMID: 28838972 DOI: 10.1136/gutjnl-2016-313595]

34 **Larvin M**, Chalmers AG, McMahon MJ. Dynamic contrast enhanced computed tomography: a precise technique for identifying and localising pancreatic necrosis. *BMJ* 1990; **300**: 1425-1428 [PMID: 2379000 DOI: 10.1136/bmj.300.6737.1425]

35 **Hirota M**, Takada T, Kawarada Y, Hirata K, Mayumi T, Yoshida M, Sekimoto M, Kimura Y, Takeda K, Isaji S, Koizumi M, Otsuki M, Matsuno S; JPN. JPN Guidelines for the management of acute pancreatitis: severity assessment of acute pancreatitis. *J Hepatobiliary Pancreat Surg* 2006; **13**: 33-41 [PMID: 16463209 DOI: 10.1007/s00534-005-1049-1]

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MINIREVIEWS

Endoscopic ultrasonography-guided celiac plexus neurolysis in patients with unresectable pancreatic cancer: An update

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Abstract

Pancreatic cancer produces disabling abdominal pain, and the pain medical management for pancreatic cancer is often challenging because it mainly relies on the use of narcotics (major opioids). However, opioids often provide suboptimal pain relief, and the use of opioids can lead to patient tolerance and several side effects that considerably reduce the quality of life of pancreatic cancer patients. Endosonography-guided celiac plexus neurolysis (EUS-CPN) is an alternative for pain control in patients with nonsurgical pancreatic cancer; EUS-CPN consists of the injection of alcohol and a local anesthetic into the area of the celiac plexus to achieve chemical ablation of the nerve tissue. EUS-CPN *via* the transgastric approach is a safer and more accessible technique than the percutaneous approach. We have reviewed most of the studies that evaluate the efficacy of EUS-CPN and that have compared the different approaches that have been performed by endosonographers. The efficacy of EUS-CPN varies from 50% to 94% in the different studies, and EUS-CPN has a pain relief duration of 4–8 wk. Several factors are involved in its efficacy, such as the onset of pain, previous use of chemotherapy, presence of metastatic disease, EUS-CPN technique, type of needle or neurolytic agent used, *etc.* According to this review, injection into the ganglia may be the best technique, and a good visualization of the ganglia is the best predictor for a good EUS-CPN response, although more studies are needed. However, any of the 4 different techniques could be used to perform EUS-CPN effectively with no differences in terms of complications between the techniques,

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but more studies are needed. The effect of EUS-CPN on pain improvement, patient survival and patient quality of life should be evaluated in well-designed randomized clinical trials. Further research also needs to be performed to clarify the best time frame in performing a EUS-CPN.

Key Words: Pancreatic cancer; Endosonography; Celiac plexus neurolysis; Opioids; Echoendoscopy

Core Tip: In this review, we analyzed the efficacy of the celiac plexus neurolysis through echoendoscopy (EUS-CPN) technique in patients with unresectable pancreatic cancer. The use of opioids for pain control are associated with numerous side effects that reduce the quality of life of pancreatic cancer patients, and the use of EUS-CPN is a safe and effective approach to pain management and allows for the reduction in the opioid doses used. There are different techniques to perform a EUS-CPN, all of which are described in this article. However, there are concerns about the efficacy of EUS-CPN (since it produces a reduction in pain for a short time), the ideal time to perform this technique is unknown, and it is also unknown whether this technique has any influence on patient survival and quality of life.

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INTRODUCTION

Pancreatic cancer is one of the solid tumors with the worst prognosis. Unfortunately, it is often diagnosed at an advanced stage of the disease, and only 12%–20% of cases are resectable at the time of diagnosis. Over 50% of patients with pancreatic cancer will not survive within the first year after diagnosis, and this disease has an overall five-year survival rate under 10%[1,2].

Chronic abdominal pain is a frequent symptom in patients with advanced pancreatic cancer due to the perineural invasion of tumor cells, and pain is present in 70%–90% of the patients at diagnosis and has very complex medical management[3,4].

Pain management in patients with pancreatic cancer usually begins with the administration of nonopioid analgesics followed by opioids in refractory cases. Opioids have many adverse effects, such as nausea, constipation, urinary retention, drowsiness, and patient tolerance or dependence.

Currently, many other therapeutic alternatives have been evaluated as complementary treatments, such as celiac plexus neurolysis (CPN) with various agents, which can be administered either percutaneously or transgastrically[5,6].

Pain originating in the intra-abdominal viscera, such as the pancreas, is transmitted by the afferent nerve fibers through the celiac plexus and finally reaching the central nervous system through the posterior root of the spinal cord at the level of T12-L2. The celiac plexus is a group of nerve fibers that converge into the celiac ganglia located in the retroperitoneum and is immediately adjacent to the anterolateral wall of the aorta at the origin of the celiac trunk. Traditionally, access to the celiac plexus has been percutaneous, and it is necessary to avoid the different structures located between the skin and the celiac plexus while performing a percutaneous access to the celiac plexus [5]. However, endosonography (EUS) allows the endosonographer to perform CPN close enough to the celiac plexus through the gastric wall, which could allow a safer and more effective access. EUS-CPN was first described by Wiersema *et al*[6] in 1996.

EUS-CPN is performed by the injection of a neurolytic agent directly into the celiac plexus, which causes an irreversible ablation. Pure ethanol is often used as the neurolytic agent in association with a local anesthetic agent, such as bupivacaine, and nociceptive afferent nerve fibers are blocked with these agents to achieve pain

reduction. EUS-CPN is performed to ameliorate pain and reduce the dose of analgesics in these patients, because the use of analgesics often causes a reduction in patient survival or quality of life.

In this review, we focused on patients with unresectable pancreatic cancer because pancreatic cancer is common and still affects a large number of cases. The options for pain management in these patients must be understood by all gastroenterologists and endoscopists. However, other pathologies, such as biliary tract tumors and patients with chronic pancreatitis, may require a CPN or celiac plexus block, respectively. Due to the large amount of evidence for the use of EUS-CPN in unresectable pancreatic cancer patients, we wanted to focus on this pathology to avoid performing such an extensive review and to focus on the management of chronic abdominal pain with this technique. We also wanted to further understand whether our interventions in this specific pathology have any impact on the survival and quality of life of patients.

INDICATIONS

EUS-CPN is performed in patients with chronic or uncontrolled abdominal pain associated with nonresectable pancreatic cancer; however, to ensure that EUS-CPN is effective, we must carefully select the patients who receive this technique. Current evidence does not precisely indicate when the best time is to perform an EUS-CPN[7].

EUS-CPN is useful in patients with uncontrolled pain or when the adverse effects of opioids reduce the patient's quality of life. Furthermore, other causes of pain must be investigated and ruled out prior to treatment, such as carcinomatosis, liver or bone metastases and peptic ulcers, because these conditions could lead to a partial or non-response to EUS-CPN.

CONTRAINDICATIONS

EUS-CPN should not be performed in patients with resectable pancreatic tumors because this technique may be difficult to perform, and it is mandatory to discuss borderline patients within a multidisciplinary team before performing a EUS-CPN. There are no absolute contraindications, but there are certain situations where a EUS-CPN should not be performed. The contraindications of EUS-CPN are shown in Table 1.

TECHNIQUE

Over the years, CPN has been performed *via* different techniques. It was initially described in 1914 as an intraoperative procedure[8], and since then, assistance with fluoroscopy, computed tomography or abdominal ultrasonography has been utilized [5]. In 1996, Wiersema described for the first time an endosonography-guided celiac plexus neurolysis (EUS-CPN) by a transgastric approach[6]. EUS-CPN allows for a more accurate and safer technique due to the use of color Doppler to avoid vessels that could be close to the needle path. It can be performed in an outpatient setting depending on the clinical status of the patient.

STEPS

Patient medical records must be reviewed to rule out previous surgeries or anatomical abnormalities and to evaluate the radiological images to study the location of the lesion, to evaluate for any possible infiltration of the celiac trunk and to determine if there is another pathology present.

The left decubitus position is the preferred position to perform a EUS-CPN. Deep sedation is also recommended for patients undergoing a EUS-CPN along with appropriately monitored anesthesia. The breathing rate, pulse oximetry, blood pressure and heart rate of the patients must be thoroughly monitored throughout the procedure.

The administration of at least 500 mL intravenous saline solution is needed before and after the procedure to minimize the risk of hypotension, as hypotension is one of the most common adverse effects after the procedure, only second to the hyperactivity

Table 1 Contraindications of endosonography-guided celiac plexus neurolysis

Absolute	Relative
Resectable pancreatic cancer	Esophagueal or gastric varices[21,26]
Coagulopathy (INR > 1.5)	Previous gastric surgery[2,14]
Low platelet count (< 50000 units)	Anomalies of celiac trunk[12]

of the parasympathetic nervous system[3,9-15].

The evidence is not clear regarding the administration of prophylactic antibiotics for EUS-CPN. Infectious complications due to EUS-CPN are rare, so most of the previous studies did not use prophylactic antibiotics[11-14].

An examination with radial echoendoscopy may be initially performed to explore the celiac trunk area. Then, a linear echoendoscope is introduced until reaching the origin of the celiac trunk, which is the first large vessel of the abdominal aorta just beneath the diaphragm. The diaphragm is a structure indirectly located by the visualization of the left diaphragmatic crus, 40–45 cm distal to the superior dental arch. Immediately under the celiac trunk is the origin of the superior mesenteric artery and the myenteric plexus (Figure 1).

The celiac plexus is located in the anterior wall of the aorta and is on both sides of the origin of the celiac trunk, and it is sometimes 1 mm above it or can sometimes be several millimeters below it (Figure 2). To locate this area, the echoendoscope should be rotated both clockwise and counterclockwise. The puncture area must be carefully selected, and before introducing the needle, it is recommended to use color Doppler in the target area of the puncture to make sure there are no vascular structures in the path of the needle.

TYPE OF NEEDLE

Any EUS needle may be used, as previous demonstrated in several studies, and these needles can range from small caliber needles, such as 25-gauge needles, to larger caliber needles, such as 19-gauge needles. Certainly, the use of a larger caliber needle will allow for an easier injection of substances.

One specific needle was designed for this technique: it is a 20-gauge needle with a dumpling pattern and conical tip [EchoTip® Ultra Celiac Plexus Neurolysis Needle, Cook Medical, Limerick (Ireland)], which allows the injection to be sprayed in a radial and uniform way and allows for adequate diffusion of the substance into the celiac plexus (Figure 3).

When the puncture area is selected, the needle must be primed with local anesthetic (usually bupivacaine or lidocaine) to avoid the injection of air into the puncture area.

Once the needle has been introduced, aspiration to confirm negative pressure must be performed to make sure that the needle was not placed into a vessel prior to injecting the substance, because the injection of these substances in a blood vessel wall or into the systemic circulation can be critical and life threatening.

NEUROLYTIC AGENT

Usually, the average injected volume of 0.25% bupivacaine is 10 to 20 mL, followed by 10 to 20 mL of 98% alcohol, although these quantities may vary slightly depending on the study. Optionally, some contrast agents can be used, even though the use of these is not clear. Ishiwatari *et al*[16] compared the use of phenol as compared to ethanol as a neurolytic agent and found no differences in pain control or complications.

TYPE OF APPROACHES

The different approaches for EUS-CPN are showed in Figure 4.

Bilateral approach/technique[6,17], once the celiac trunk has been located, the objective of this approach is to inject substances on both sides of it. It is recommended to make slow and rotatory clockwise movements without losing the longitudinal axis

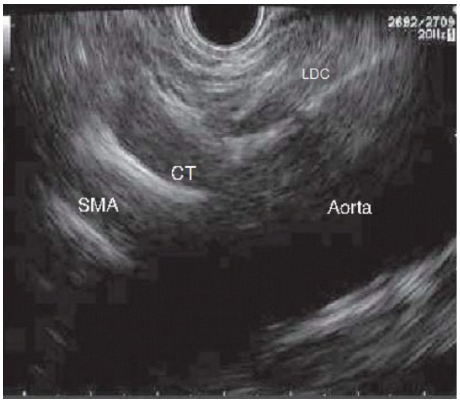

Figure 1 Sagittal plane of the aorta where we can see left diaphragmatic crus, celiac trunk and superior mesenteric artery emerging from Aorta. SMA: Superior mesenteric artery; LDC: Left diaphragmatic crus; CT: Celiac trunk.

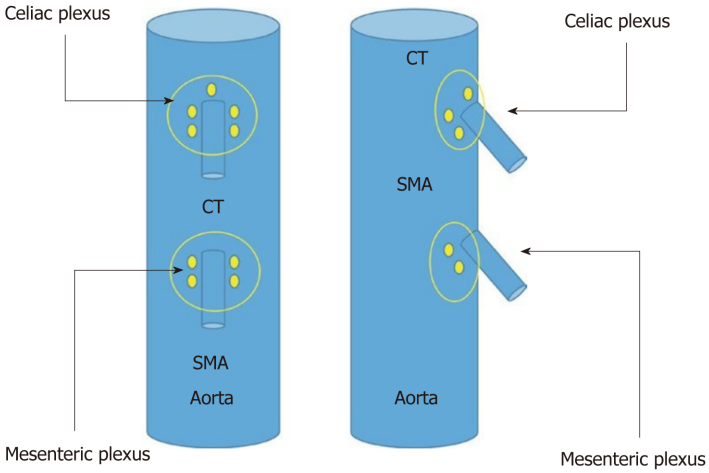

Figure 2 Schematic vision (frontal and lateral) of the situation of celiac and mesenteric plexus. SMA: Superior mesenteric artery; CT: Celiac trunk.

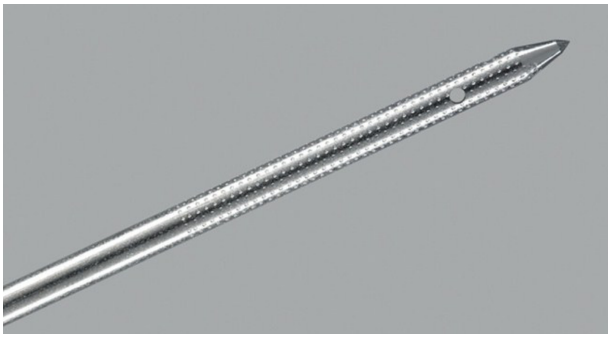

Figure 3 Specific needle designed for endosonography-guided celiac plexus neurolysis (Cook Medical, Limerick, Ireland).

of the aorta. With these movements, we are able to see the "injection windows", as shown in Figure 5.

Central approach/technique[9,10] is begun from the starting position at the origin of the celiac trunk and without losing the longitudinal axis of the aorta, the injection is performed in a cranial plane from the starting position, as shown in Figure 6.

Broad approach/technique was first described in 2010 by Sakamoto *et al*[18], and this approach is based on the injection of the substances above and on both sides of the origin of the superior mesenteric artery, without losing the longitudinal axis of the aorta, and by aiming for a broader diffusion of the neurolytic agent (Figure 5). In this technique, the needle reaches a greater depth; therefore, it is recommended to use a 25-

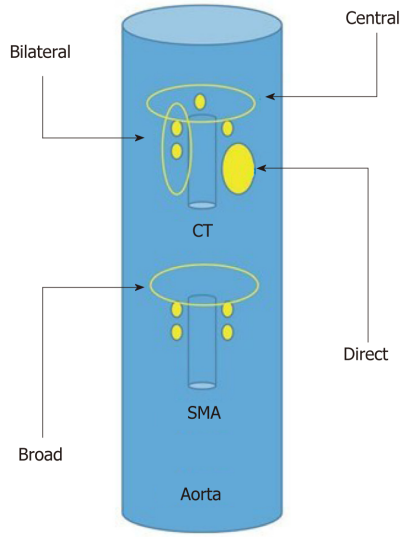

Figure 4 Schematic representation of the different endosonography-guided celiac plexus neurolysis approaches. SMA: Superior mesenteric artery; CT: Celiac trunk.

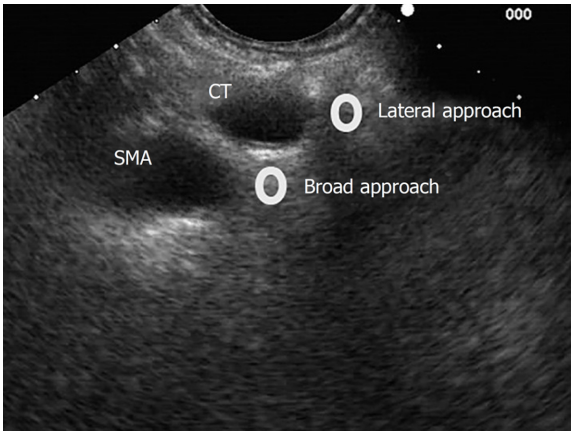

Figure 5 Lateral and broad approaches for endosonography-guided celiac plexus neurolysis. SMA: Superior mesenteric artery; CT: Celiac trunk.

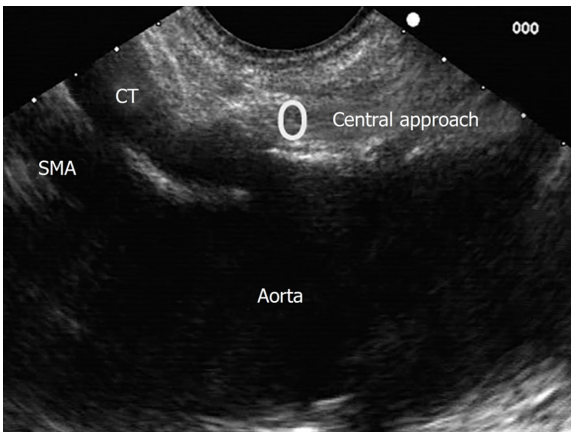

Figure 6 Central approach for endosonography-guided celiac plexus neurolysis. SMA: Superior mesenteric artery; CT: Celiac trunk.

gauge needle.

Direct approach/technique[11] is based on the direct injection of each celiac ganglia to distribute the alcohol and anesthetic doses. Celiac ganglia are sometimes visible as hypoechoic structures, which are almond shaped, are between 2 to 20 mm and are

usually located around the aorta at the origin of the celiac trunk. The right celiac ganglion is usually located 6 mm inferior to the origin of the celiac trunk, while the left celiac ganglion is located 9 mm below the origin of the celiac trunk. During the injection in the center of the ganglia, "ballonization" and an increase in volume will be seen. If this is not seen, the needle is probably misplaced.

AFTER THE PROCEDURE

Before extracting the needle, 3 mL of saline solution is injected to prevent the injection of ethanol into the path of the needle. If this injection of saline is not performed, it could result in the exacerbation of pain after the procedure. Patients should be monitored for at least two hours after the intervention, and the patient's blood pressure should be monitored.

RESULTS

The efficacy, study design, dose and type of neurolytic agent, follow-up and complications of EUS-CPN are summarized in Table 2[18-24].

EFFICACY OF CPN

Several studies have been performed to evaluate the efficacy of EUS-CPN. Globally, there has been a great variability shown in the efficacy of this technique for pain control associated with pancreatic cancer. The range of efficacy varies from 50% to 94% in the previous studies[6,7,9-11,13-19,23,24].

However, the available current literature has limitations due to the different quality of the studies (some of them are retrospective), and they differ in the injection technique, type and volume of neurolytic agent, number of patients and follow-up. In addition, the definitions for categorizing pain control vary in the different studies: improvement or resolution of pain, reduction of the Visual Analogue Scale (VAS) or Likert scale, reduction of the dose of opioids, *etc*.[6,7,9-11,13-19,23,24].

EUS-CPN was first performed by Wiersema *et al*[6] with an efficacy of 88% in 30 patients over 10 wk. In the first clinical trial, Wyse *et al*[7] randomized 96 patients with unresectable pancreatic cancer to either early treatment with EUS-CPN or a conventional medical treatment with analgesics and opioids. Clinical significance was observed with a reduction of 28% and 60% in the Likert scale at 4 and 10 wk of follow-up, respectively. A reduction in the dose of analgesics was also observed.

Momentary efficacy was observed in four systematic reviews and three meta-analyses. The studies demonstrated a reduction in pain in more than 50% of the patients during the 4–8 wk follow-up[15,25-27]. In addition, one of the systematic reviews concluded that pain control allowed for a reduction in the opioid dose with significantly fewer adverse effects in the treated group ($P < 0.0001$), but this was during the short term.

Based on this evidence, we can conclude that EUS-CPN significantly reduces the pain associated with pancreatic cancer (but does not make the pain disappear completely) and can reduce the dose of opioids[7,23,25,26]. The combination of an EUS-CPN plus analgesic opioids could be superior to opioid therapy alone[7]. However, this should be demonstrated in randomized clinical trials (RCTs) to further validate these findings[26,28].

IMPACT OF CPN ON QUALITY OF LIFE AND SURVIVAL

Current evidence supports the efficacy of CPN. However, the effect on the patient's quality of life is controversial, and there is no effect on survival. Changes in the quality of life were measured with different QOL scores Digestive Disease Questionnaire-15 [7].

On the one hand, Wyse *et al*[7] observed that the addition of EUS-CPN to the treatment regimen had no outcomes effect on the quality of life in patients. Lu *et al*[25] found in a their systematic review that EUS-CPN significantly reduced significantly the dose of opioids with a diminution of their adverse effects, but there wiwasth no

Table 2 Endosonography-guided celiac plexus neurolysis efficacy in current literature

Ref.	Design	*n*	Technique	Neurolytic agent	Pain control (follow up)	Complications
Wiersema *et al*[6]	Retrospective	30	Bilateral	3 mL bupivacaine (0.25%) + 10 mL ethanol (98%)	88% (10 wk)	Diarrhea 13.3%, Pain 3.3%
Gunaratnam *et al* [17]	Prospective	58	Bilateral	3-6 mL bupivacaine (0.25%) + 10 mL ethanol (98%)	78% (24 wk)	Pain 8.6%
Levy *et al*[11]	Retrospective	17	Direct	8 mL bupivacaine (0.25%) + 12 mL ethanol (99%)	94% (2-4 wk)	Hypotension 35%, pain 41% and diarrhea 16%
Sahai *et al*[9]	Prospective	160	Central *vs* Bilateral	10 mL bupivacaine (0.5%) + 20 mL ethanol	45.9% *vs* 70.5% (7 d). $P < 0.05$	Bleeding 0.7%
Sakamoto *et al* [18]	Retrospective	67	Broad *vs* bilateral	3 mL lidocaine (1%) + 9 mL ethanol (98%)	Mean VAS scores 3.9 *vs* 2.5 (7 d) and 4.8 *vs* a 3.4 (30 d) $P < 0.05$	None
Wyse *et al*[7]	RCT	48	Bilateral *vs* analgesia	10 mL bupivacaine (0.50%) + 20 mL ethanol	Likert scale reduction 28% (4 wk) + 60% (12 wk) $P < 0.05$	None
LeBlanc *et al*[10]	RCT	50	Central *vs* bilateral	20 mL lidocaine (0.75%) + 10 mL ethanol (98%)	69% *vs* 81% (61.9%)(14wk)	Hypotension 2% pain 36%
Iwata *et al*[19]	Retrospective	47	Central, direct or bilateral	2-3 mL bupivacaine + 20 mL ethanol	68% (7 wk)	Hypotension 17%, diarrhea 23% and inebriation 8%
Ascunce *et al*[20]	Retrospective	64	Bilateral	10 mL lidocaine (1%) + 20 mL ethanol (98%)	50% (1 wk). OR 15.61 of response if celiac ganglia was detected	Hypotension 2%, pain 2% and diarrhea 23%
Wiechowska-Kozłowska *et al* [12]	Retrospective	29	Central *vs* bilateral	2 mL lidocaine (2%) + 20 mL ethanol (98%)	86% (1-2 wk)	Hypotonia 3.4%, pain 6.9% and diarrhea 10.3%
Téllez-Ávila *et al* [21]	Retrospective	53	Central *vs* bilateral	10 mL lidocaine (1%) + 10-20 mL ethanol (98%)	48% *vs* 56% (4 wk)	Transitory pain 0% *vs* 3%
Seicean *et al*[22]	Retrospective	32	Central	10 mL lidocaine (1%) + 10-15 mL ethanol	75% (2 wk)	None
Doi *et al*[13]	RCT	68	Direct *vs* central	1-2 mL bupivacaine (0.25%-0.5%) + 10-20 mL ethanol	73.5% *vs* 45.5% (7 d) $P < 0.05$	Hypotension 2.9% *vs* 6%, pain 29.4% *vs* 21.2% and diarrhea 5.9% *vs* 9.1%. No diferences
Ishiwatari *et al* [16]	Retrospective	22	Direct or bilateral	1-2 mL bupivacaine (0.5%) + 40-60 mL ethanol or 20-25 mL fenol	83% (fenol) *vs* 69% (ethanol) (7 d)	Diarrhea 9%, hypotension 4.5%, pain 4.5% and inebriation 4.5%
Hao *et al*[23]	Retrospective	41	Central or direct	10 mL bupivacaine (2%) + 20 mL ethanol	Pain < 3 mo improve 84% (3 d), 96% (7 d) and 68% (90 d). Pain > 3 mo improve 75% (3 d), 81% (7 d) and 50% (90 d)	Hypotension 4.9%
Minaga *et al*[14]	Retrospective observational	112	Broad ± direct	3 mL lidocaine (1%) + 9 mL ethanol (98%)	Pain improvement 77. 7% (1 wk)+ 67.9% (4 wk)	Inebriation 8%, hypotension 4.5%, pain 3.6% and diarrhea 3.6%
Levy *et al*[24]	RCT	110	Direct *vs* bilateral	4 mL bupivacaine (0.25%) + 20 mL ethanol (99%)	Pain improvement 46.2% *vs* 40.4%. No changes on quality of life	Hypotension 11.7% *vs* 20%, diarrhea 10% *vs* 12.2%. Pain 8.3% *vs* 44.9% ($P < 0.05$)

VAS: Visual analogue scale. RCT: Randomized clinical trial.

differences in terms of quality of life.

On the other hand, Seicean *et al*[22] found little improvement in some factors associated with quality of life, such as the functional status or sleep quality, and there was no change in the acceptance of the disease and enjoyment of life.

Current evidence has not shown any clinical significance in terms of survival to recommend an EUS-CPN[7,26]. Although it has not been demonstrated that EUS-CPN significantly improves the quality of life of patients, the reduction of adverse effects associated with opioids could have some impact on the quality of life of these patients, which can be important[22,26].

PREDICTORS OF RESPONSE

CPN is usually performed as a palliative treatment in patients refractory to common analgesics. However, since Wiersema *et al*[6] performed the first EUS-CPN, they found that patients who had not received previous chemotherapy had significantly greater pain relief than patients who received chemotherapy.

It is known that chemotherapy improves the patient's pain and quality of life[7,24]. Patients who received chemotherapy before EUS-CPN could be impacted by the effect of the technique. In fact, as concluded by Wyse *et al*[7], pain improvement was seen earlier in patients who had not received previous chemotherapy than in patients who did receive chemotherapy.

In a different study, Hao *et al*[23] observed a significant improvement in the pain scales of the patients who had an onset of pain earlier than 3 mo, and an improvement of pain was then observed in both the short and long terms.

The best time to perform an EUS-CPN remains unclear[7]. It could be possible that a delay in performing an EUS-CPN or its application in patients who have received other treatments for pain control could decrease the efficacy of the EUS-CPN; however, there is not enough evidence to support this theory[7,17,21].

Few studies have also compared the different techniques of EUS-CPN[9,12,14,15,23,26]. Iwata *et al*[19] observed that the direct invasion of the celiac plexus and the distribution of ethanol on only the left side of the artery negatively influenced pain control [13].

A retrospective study by Ascunce *et al*[20] evaluated the efficacy of the bilateral technique. They concluded that the direct visualization of the celiac ganglia while performing a EUS-CPN (which needed to be referenced in the endoscopic report) was a good predictor of the response (OR 15.61).

BILATERAL *VS* CENTRAL TECHNIQUE

As mentioned above, there are several techniques for performing a EUS-CPN. We reviewed those studies that compared the different techniques to analyze which technique may be the most effective and that had fewer adverse effects[9,13,14,18,21,24].

On the one hand, bilateral and central techniques have shown comparative outcomes in a few studies[10,25,26], and the only exception was in a study performed by Sahai *et al*[9] in 2009. The bilateral approach improved the pain control compared to the central technique (70.5% *vs* 45.9%; $P < 0.05$), but the effect lasted only one week.

On the other hand, in a meta-analysis published in 2009, a subgroup analysis was performed that evaluated the different approaches that were performed. The bilateral approach was more effective than the central technique in terms of pain control (84.5% *vs* 45.9%; $P < 0.05$)[15].

Finally, one more recent meta-analysis of 437 patients concluded that comparable pain control was obtained with both approaches; however, the bilateral approach significantly reduced the dose of opioids compared to the central technique[25].

GANGLIA INJECTION

Direct injection of neurolytic agents into the ganglia has been demonstrated to be effective for pain relief associated with pancreatic cancer. The rate of effectiveness has varied from 65% to 94% in different studies,[11,13,14] and one of these studies was a clinical trial. Doi *et al*[13] demonstrated significant pain relief with the injection directly into the ganglia compared to the central approach, but the injections were only beneficial for one week (73.5% *vs* 45.5%).

Despite having good results in several studies, other studies have been published that have shown some concerns regarding this technique.

Levy *et al*[24] published a randomized double blind clinical trial comparing direct ganglia injection to central CPN, and no differences were found in pain control or in improving the quality of life with either technique. However, the median survival was significantly higher in patients treated with direct ganglia injection (10.5 mo *vs* 5.6 mo), particularly for patients with nonmetastatic disease.

Recently, Koulouris *et al*[28] performed a systematic review and meta-analysis on the efficacy of three EUS-CPN techniques on pain control: central, bilateral and ganglia injection. Pain control was achieved in 68% of the patients at week 2 and 53% of the

patients at 4 wk of follow-up. There was no difference between the techniques in terms of age, sex, tumor localization, stage or baseline pain before the intervention. Major bias could have been present in this review, because low-quality studies were included (not randomized studies), the measurement of treatment response was different, and the influence of other treatments (opioids or chemotherapy) was not evaluated in this study. However, no differences in the complications between the techniques were found.

CPN OVER THE MESENTERIC ARTERY (BROAD TECHNIQUE)

Few studies have evaluated the broad technique or have compared it to the other techniques. Sakamoto *et al*[18] compared the broad CPN technique against the bilateral technique, and this study showed that there was better pain control with the broad approach at 7 and 30 d of follow-up. There were no differences in the adverse events. Another study comparing the broad CPN technique against the broad CPN plus direct ganglia injection technique showed significantly better pain control with the combination of both techniques (OR 3.69 in the 1st week and OR 6.37 in the 1st month) [14]. Adequate pain management has been obtained by this approach of using both techniques, but more studies are needed to confirm these findings.

COMPLICATIONS

EUS-CPN is described as a safe procedure[6,7,9-11,13-19,23,24]. A total of 44% of complications have been reported, but most of them have been minor and transient. Diarrhea and interim hypotension are frequently observed due to the parasympathomimetic response. Pain exacerbation is another common adverse effect (8%) associated with ethanol injection. Transient inebriation was observed in three Japanese studies [13,14,16].

Major complications have been reported in less than 1% of patients; however, these patients frequently have fatal outcomes. Infection, bleeding, retroperitoneal abscesses, paraplegia and ischemia have been previously reported in the literature[29-34]. Usually, these complications are associated with an incorrect injection site of the neurolytic agent. EUS-CPN must be performed by expert endoscopists and at hospitals with a high volume of procedures.

NEW TECHNIQUES OF EUS-CPN

Recently, other techniques of EUS-CPN have been described with encouraging results. In 2012, Wang *et al*[35] achieved a EUS-CPN by the insertion of a radioactive seed, I^{125}, directly into the celiac ganglia. Twenty-three patients were included in this study, and there was a significant reduction in pain control and the dose of opioids.

In 2015, Facciorusso *et al*[36] suggested in a case report that the use of an EUS-CPN associated with the injection of ethanol directly into the tumor could enhance the effects of neurolysis; however, more studies of this approach are needed to confirm the results. Recently in 2019, Bang *et al*[37] published that an EUS-CPN could be performed with a radiofrequency ablation of the celiac ganglia. Twelve patients were included in this study, and they compared this technique against the traditional EUS-CPN. Radiofrequency ablation obtained better results not only regarding the pain associated with pancreatic cancer, but there was also an improvement in the quality of life scales. However, more studies are needed to validate these approaches.

CONCLUSION

EUS-CPN is a safe and effective therapeutic alternative for short-term pain control in unresectable pancreatic cancer patients. It can allow for a dose reduction of opioids, which are responsible for serious adverse effects that reduce the quality of life of these patients. However, an improvement in patient survival or quality of life after using an EUS-CPN has not been demonstrated in the current literature.

The strengths of our review are the large number of studies collected (many of them are clinical trials) with an acceptable number of patients, and many studies have demonstrated favorable results in the use of EUS-CPN in these patients, even though this technique has been performed by expert endoscopists in centers with a high volume of patients. We also present a scheme for performing this technique that shows a good applicability, and most of the complications of this technique are minor and preventable. There are several techniques for performing an EUS-CPN, all of which are valid, and the most commonly used technique is the central technique, which is known by all expert endoscopists in this field and is the technique we currently perform in our centers.

Therefore, we can conclude that the best predictor for a good response could be the celiac ganglia visualization during the EUS-CPN technique. However, any of the 4 different techniques could be offered to effectively perform an EUS-CPN with no differences in complications between the techniques based on this review.

According to this review, a universal pain reduction scale should be used to design further research and to prevent heterogeneity of the results among the studies. EUS-CPN must be performed by expert endosonographers to achieve the best approach and to have a good outcome from this technique as well as to avoid serious adverse events.

Further research is needed to clarify when to perform an EUS-CPN and whether it should be included as a first-line therapy in addition to traditional medical treatment, whether it should be performed as a prevention prior to chemotherapy or if it should be reserved for patients with uncontrolled pain that is refractory to major opioids. Well-designed RCTs are required to evaluate the improvement of pain, survival and quality of life in these patients.

REFERENCES

1 **Bilimoria KY**, Bentrem DJ, Ko CY, Ritchey J, Stewart AK, Winchester DP, Talamonti MS. Validation of the 6th edition AJCC Pancreatic Cancer Staging System: report from the National Cancer Database. *Cancer* 2007; **110**: 738-744 [PMID: 17580363 DOI: 10.1002/cncr.22852]

2 **Sirri E**, Castro FA, Kieschke J, Jansen L, Emrich K, Gondos A, Holleczek B, Katalinic A, Urbschat I, Vohmann C, Brenner H. Recent Trends in Survival of Patients With Pancreatic Cancer in Germany and the United States. *Pancreas* 2016; **45**: 908-914 [PMID: 26745860 DOI: 10.1097/MPA.0000000000000588]

3 **Mekaroonkamol P**, Willingham FF, Chawla S. Endoscopic management of pain in pancreatic cancer. *JOP* 2015; **16**: 33-40 [PMID: 25640780 DOI: 10.6092/1590-8577/2890]

4 **Caraceni A**, Portenoy RK. Pain management in patients with pancreatic carcinoma. *Cancer* 1996; **78**: 639-653 [PMID: 8681303 DOI: 10.1002/(SICI)1097-0142(19960801)78:3<639::AID-CNCR45>3.0.CO;2-X]

5 **Noble M**, Gress FG. Techniques and results of neurolysis for chronic pancreatitis and pancreatic cancer pain. *Curr Gastroenterol Rep* 2006; **8**: 99-103 [PMID: 16533471 DOI: 10.1007/s11894-006-0004-x]

6 **Wiersema MJ**, Wiersema LM. Endosonography-guided celiac plexus neurolysis. *Gastrointest Endosc* 1996; **44**: 656-662 [PMID: 8979053 DOI: 10.1016/s0016-5107(96)70047-0]

7 **Wyse JM**, Carone M, Paquin SC, Usatii M, Sahai AV. Randomized, double-blind, controlled trial of early endoscopic ultrasound-guided celiac plexus neurolysis to prevent pain progression in patients with newly diagnosed, painful, inoperable pancreatic cancer. *J Clin Oncol* 2011; **29**: 3541-3546 [PMID: 21844506 DOI: 10.1200/JCO.2010.32.2750]

8 Kappis M. Erfahrungen mit Lokalansthesie bei Bauchoperationen. Verh Dsch Ges Cire 1914; 43: 87

9 **Sahai AV**, Lemelin V, Lam E, Paquin SC. Central vs. bilateral endoscopic ultrasound-guided celiac plexus block or neurolysis: a comparative study of short-term effectiveness. *Am J Gastroenterol* 2009; **104**: 326-329 [PMID: 19174816 DOI: 10.1038/ajg.2008.64]

10 **LeBlanc JK**, Al-Haddad M, McHenry L, Sherman S, Juan M, McGreevy K, Johnson C, Howard TJ, Lillemoe KD, DeWitt J. A prospective, randomized study of EUS-guided celiac plexus neurolysis for pancreatic cancer: one injection or two? *Gastrointest Endosc* 2011; **74**: 1300-1307 [PMID: 22000795 DOI: 10.1016/j.gie.2011.07.073]

11 **Levy MJ**, Topazian MD, Wiersema MJ, Clain JE, Rajan E, Wang KK, de la Mora JG, Gleeson FC, Pearson RK, Pelaez MC, Petersen BT, Vege SS, Chari ST. Initial evaluation of the efficacy and safety of endoscopic ultrasound-guided direct Ganglia neurolysis and block. *Am J Gastroenterol* 2008; **103**: 98-103 [PMID: 17970834 DOI: 10.1111/j.1572-0241.2007.01607.x]

12 **Wiechowska-Kozłowska A**, Boer K, Wójcicki M, Milkiewicz P. The efficacy and safety of endoscopic ultrasound-guided celiac plexus neurolysis for treatment of pain in patients with pancreatic cancer. *Gastroenterol Res Pract* 2012; **2012**: 503098 [PMID: 22474439 DOI: 10.1155/2012/503098]

13 **Doi S**, Yasuda I, Kawakami H, Hayashi T, Hisai H, Irisawa A, Mukai T, Katanuma A, Kubota K,

Ohnishi T, Ryozawa S, Hara K, Itoi T, Hanada K, Yamao K. Endoscopic ultrasound-guided celiac ganglia neurolysis vs. celiac plexus neurolysis: a randomized multicenter trial. *Endoscopy* 2013; **45**: 362-369 [PMID: 23616126 DOI: 10.1055/s-0032-1326225]

14 **Minaga K**, Kitano M, Sakamoto H, Miyata T, Imai H, Yamao K, Kamata K, Omoto S, Kadosaka K, Sakurai T, Nishida N, Chiba Y, Kudo M. Predictors of pain response in patients undergoing endoscopic ultrasound-guided neurolysis for abdominal pain caused by pancreatic cancer. *Therap Adv Gastroenterol* 2016; **9**: 483-494 [PMID: 27366217 DOI: 10.1177/1756283X16644248]

15 **Puli SR**, Reddy JB, Bechtold ML, Antillon MR, Brugge WR. EUS-guided celiac plexus neurolysis for pain due to chronic pancreatitis or pancreatic cancer pain: a meta-analysis and systematic review. *Dig Dis Sci* 2009; **54**: 2330-2337 [PMID: 19137428 DOI: 10.1007/s10620-008-0651-x]

16 **Ishiwatari H**, Hayashi T, Yoshida M, Ono M, Masuko H, Sato T, Miyanishi K, Sato Y, Takimoto R, Kobune M, Miyamoto A, Sonoda T, Kato J. Phenol-based endoscopic ultrasound-guided celiac plexus neurolysis for East Asian alcohol-intolerant upper gastrointestinal cancer patients: a pilot study. *World J Gastroenterol* 2014; **20**: 10512-10517 [PMID: 25132769 DOI: 10.3748/wjg.v20.i30.10512]

17 **Gunaratnam NT**, Sarma AV, Norton ID, Wiersema MJ. A prospective study of EUS-guided celiac plexus neurolysis for pancreatic cancer pain. *Gastrointest Endosc* 2001; **54**: 316-324 [PMID: 11522971 DOI: 10.1067/mge.2001.117515]

18 **Sakamoto H**, Kitano M, Kamata K, Komaki T, Imai H, Chikugo T, Takeyama Y, Kudo M. EUS-guided broad plexus neurolysis over the superior mesenteric artery using a 25-gauge needle. *Am J Gastroenterol* 2010; **105**: 2599-2606 [PMID: 20823834 DOI: 10.1038/ajg.2010.339]

19 **Iwata K**, Yasuda I, Enya M, Mukai T, Nakashima M, Doi S, Iwashita T, Tomita E, Moriwaki H. Predictive factors for pain relief after endoscopic ultrasound-guided celiac plexus neurolysis. *Dig Endosc* 2011; **23**: 140-145 [PMID: 21429019 DOI: 10.1111/j.1443-1661.2010.01046.x]

20 **Ascunce G**, Ribeiro A, Reis I, Rocha-Lima C, Sleeman D, Merchan J, Levi J. EUS visualization and direct celiac ganglia neurolysis predicts better pain relief in patients with pancreatic malignancy (with video). *Gastrointest Endosc* 2011; **73**: 267-274 [PMID: 21295640 DOI: 10.1016/j.gie.2010.10.029]

21 **Téllez-Ávila FI**, Romano-Munive AF, Herrera-Esquivel Jde J, Ramírez-Luna MA. Central is as effective as bilateral endoscopic ultrasound-guided celiac plexus neurolysis in patients with unresectable pancreatic cancer. *Endosc Ultrasound* 2013; **2**: 153-156 [PMID: 24949384 DOI: 10.7178/eus.06.007]

22 **Seicean A**, Cainap C, Gulei I, Tantau M, Seicean R. Pain palliation by endoscopic ultrasound-guided celiac plexus neurolysis in patients with unresectable pancreatic cancer. *J Gastrointestin Liver Dis* 2013; **22**: 59-64 [PMID: 23539392]

23 **Hao SJ**, Xu WJ, Di Y, Yao L, Yang F, Jiang YJ, Li J, Jin C, Zhong L, Fu DL. How to improve the efficacy of endoscopic ultrasound-guided celiac plexus neurolysis in pain management in patients with pancreatic cancer: analysis in a single center. *Surg Laparosc Endosc Percutan Tech* 2014; **24**: 31-35 [PMID: 24487155 DOI: 10.1097/SLE.0000000000000032]

24 **Levy MJ**, Gleeson FC, Topazian MD, Fujii-Lau LL, Enders FT, Larson JJ, Mara K, Abu Dayyeh BK, Alberts SR, Hallemeier CL, Iyer PG, Kendrick ML, Mauck WD, Pearson RK, Petersen BT, Rajan E, Takahashi N, Vege SS, Wang KK, Chari ST. Combined Celiac Ganglia and Plexus Neurolysis Shortens Survival, Without Benefit, *vs* Plexus Neurolysis Alone. *Clin Gastroenterol Hepatol* 2019; **17**: 728-738.e9 [PMID: 30217513 DOI: 10.1016/j.cgh.2018.08.040]

25 **Lu F**, Dong J, Tang Y, Huang H, Liu H, Song L, Zhang K. Bilateral vs. unilateral endoscopic ultrasound-guided celiac plexus neurolysis for abdominal pain management in patients with pancreatic malignancy: a systematic review and meta-analysis. *Support Care Cancer* 2018; **26**: 353-359 [PMID: 28956176 DOI: 10.1007/s00520-017-3888-0]

26 **Arcidiacono PG**, Calori G, Carrara S, McNicol ED, Testoni PA. Celiac plexus block for pancreatic cancer pain in adults. *Cochrane Database Syst Rev* 2011; CD007519 [PMID: 21412903 DOI: 10.1002/14651858.CD007519.pub2]

27 **Kaufman M**, Singh G, Das S, Concha-Parra R, Erber J, Micames C, Gress F. Efficacy of endoscopic ultrasound-guided celiac plexus block and celiac plexus neurolysis for managing abdominal pain associated with chronic pancreatitis and pancreatic cancer. *J Clin Gastroenterol* 2010; **44**: 127-134 [PMID: 19826273 DOI: 10.1097/MCG.0b013e3181bb854d]

28 **Koulouris AI**, Alexandre L, Hart AR, Clark A. Endoscopic ultrasound-guided celiac plexus neurolysis (EUS-CPN) technique and analgesic efficacy in patients with pancreatic cancer: A systematic review and meta-analysis. *Pancreatology* 2021; **21**: 434-442 [PMID: 33461931 DOI: 10.1016/j.pan.2020.12.016]

29 **Mittal MK**, Rabinstein AA, Wijdicks EF. Pearls & oy-sters: Acute spinal cord infarction following endoscopic ultrasound-guided celiac plexus neurolysis. *Neurology* 2012; **78**: e57-e59 [PMID: 22371417 DOI: 10.1212/WNL.0b013e318248df51]

30 **Fujii L**, Clain JE, Morris JM, Levy MJ. Anterior spinal cord infarction with permanent paralysis following endoscopic ultrasound celiac plexus neurolysis. *Endoscopy* 2012; **44** Suppl 2 UCTN: E265-E266 [PMID: 22814912 DOI: 10.1055/s-0032-1309708]

31 **Minaga K**, Kitano M, Imai H, Miyata T, Kudo M. Acute spinal cord infarction after EUS-guided celiac plexus neurolysis. *Gastrointest Endosc* 2016; **83**: 1039-40; discussion 1040 [PMID: 26551729 DOI: 10.1016/j.gie.2015.10.044]

32 **Ahmed HM**, Friedman SE, Henriques HF, Berk BS. End-organ ischemia as an unforeseen complication of endoscopic-ultrasound-guided celiac plexus neurolysis. *Endoscopy* 2009; **41** Suppl 2: E218-E219 [PMID: 19757362 DOI: 10.1055/s-0029-1214941]

33 **Gimeno-García AZ**, Elwassief A, Paquin SC, Sahai AV. Fatal complication after endoscopic ultrasound-guided celiac plexus neurolysis. *Endoscopy* 2012; **44** Suppl 2 UCTN: E267 [PMID: 22814913 DOI: 10.1055/s-0032-1309709]

34 **Jang HY**, Cha SW, Lee BH, Jung HE, Choo JW, Cho YJ, Ju HY, Cho YD. Hepatic and splenic infarction and bowel ischemia following endoscopic ultrasound-guided celiac plexus neurolysis. *Clin Endosc* 2013; **46**: 306-309 [PMID: 23767046 DOI: 10.5946/ce.2013.46.3.306]

35 **Wang KX**, Jin ZD, Du YQ, Zhan XB, Zou DW, Liu Y, Wang D, Chen J, Xu C, Li ZS. EUS-guided celiac ganglion irradiation with iodine-125 seeds for pain control in pancreatic carcinoma: a prospective pilot study. *Gastrointest Endosc* 2012; **76**: 945-952 [PMID: 22841501 DOI: 10.1016/j.gie.2012.05.032]

36 **Facciorusso A**, Maso MD, Barone M, Muscatiello N. Echoendoscopic ethanol ablation of tumor combined to celiac plexus neurolysis improved pain control in a patient with pancreatic adenocarcinoma. *Endosc Ultrasound* 2015; **4**: 342-344 [PMID: 26643704 DOI: 10.4103/2303-9027.170428]

37 **Bang JY**, Sutton B, Hawes RH, Varadarajulu S. EUS-guided celiac ganglion radiofrequency ablation *vs* celiac plexus neurolysis for palliation of pain in pancreatic cancer: a randomized controlled trial (with videos). *Gastrointest Endosc* 2019; **89**: 58-66.e3 [PMID: 30120957 DOI: 10.1016/j.gie.2018.08.005]

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MINIREVIEWS

Tips and tricks for the diagnosis and management of biliary stenosis-state of the art review

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Abstract

Biliary stenosis may represent a diagnostic and therapeutic challenge resulting in a delay in diagnosis and initiation of therapy due to the frequent difficulty in distinguishing a benign from a malignant stricture. In such cases, the diagnostic flowchart includes the sequential execution of imaging techniques, such as magnetic resonance, magnetic resonance cholangiopancreatography, and endoscopic ultrasound, while endoscopic retrograde cholangiopancreatography is performed to collect tissue for histopathological/cytological diagnosis or to treat the stenosis by insertion of stent. The execution of percutaneous transhepatic drainage with subsequent biopsy has been shown to increase the possibility of tissue diagnosis after failure of the above techniques. Although the diagnostic yield of histopathology and imaging has increased with improvements in endoscopic ultrasound and peroral cholangioscopy, differential diagnosis between malignant and benign stenosis may not be easy in some patients, and strictures are classified as indeterminate. In these cases, a multidisciplinary workup including biochemical marker assays and advanced technologies available may speed up a diagnosis of malignancy or avoid unnecessary surgery in the event of a benign stricture. Here, we review recent advancements in the diagnosis and management of biliary strictures and describe tips and tricks to increase diagnostic yields in clinical routine.

Key Words: Biliary stenosis; Cholangioscopy; Metal stent; Endoscopic ultrasound; Endoscopic ultrasound-guided fine needle aspiration; Biliary stenosis treatment

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Core Tip: Biliary stenosis remains a diagnostic and therapeutic challenge due to the difficulty in obtaining a tissue diagnosis to differentiate a malignant from a benign stricture. The diagnostic and therapeutic workup of patients with a suspected malignant biliary stricture should be discussed at a multidisciplinary team meeting in a tertiary center. The use of all available diagnostic tools such as magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography, endoscopic ultrasound-fine needle aspiration, and cholangioscopy should be evaluated to avoid unnecessary surgery or a delay in diagnosis. Here, we focus on the most recently published findings regarding the diagnosis and therapy of biliary stricture.

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INTRODUCTION

A biliary stricture (BS) is a narrowing of the biliary tree caused by benign or malignant conditions. Differential diagnosis between the different forms of BS can be challenging, as the etiology may remain indeterminate even after carrying out complete laboratory, imaging, and tissue-based diagnostic investigations[1]. Despite improvements in endoscopic techniques and a greater knowledge of the underlying causes of the condition acquired over the last decade, about 15%-20% of patients with indeterminate BS undergoing surgery are found to have a benign disease, with high postoperative mortality (10%) reported in many Western referral centers[1-4]. Patients with indeterminate BS or a diagnosis of indeterminate dysplasia at histopathological evaluation require a multidisciplinary approach involving gastroenterologists, surgeons, radiologists, and oncologists for diagnosis and appropriate treatment.

ETIOLOGY

Most cases of BS are malignant BS (MBS) due to pancreatic adenocarcinoma, cholangiocarcinoma (CC), liver metastases, hepatocellular carcinoma, ampullary carcinoma, or gallbladder carcinoma. Rare causes of MBS are lymphoma and metastases to regional lymph node (RLN)s. Benign BS (BBS) accounts for up to 30% of all BS and may have a different etiology, although most are iatrogenic caused by biliary damage during surgery (*e.g.*, post-laparoscopic cholecystectomy) or after liver transplantation (stenosis of biliary anastomosis). Chronic pancreatitis and autoimmune pancreatic/biliary disease can also induce BBS[4] (Table 1).

DIAGNOSTIC WORKUP

The choice of the most appropriate diagnostic and therapeutic pathway is based on the localization of the stricture in the biliary tract. The commonly used Bismuth-Corlette classification[5] distinguishes five types of BS: type I – limited to the common hepatic duct, below the level of the confluence of the right and left hepatic ducts; type II – involving the confluence of the right and left hepatic ducts; type III – (1) Extending to the bifurcation of the right hepatic duct; or (2) Extending to the bifurcation of the left hepatic duct; type IV – extending to the bifurcations of both right and left hepatic ducts or with multifocal involvement; type V – a stricture at the junction of the common bile duct and cystic duct.

Table 1 Etiology of benign biliary stenosis

Iatrogenic	Post-cholecystectomy
	Post-liver transplantation (anastomotic, non-anastomotic)
	Hepaticojejunostomy anastomotic strictures
Autoimmune disease	Primary or secondary sclerosing cholangitis
	Autoimmune cholangitis (IgG4-related)
	Autoimmune pancreatitis
Chronic disease	Pancreatitis
	Choledocholithiasis
	Sarcoidosis
Infectious disease	Recurrent cholangitis, HIV cholangiopathy, tuberculosis
Ischemic disease	
Abdominal trauma	

HIV: Human immunodeficiency virus; IgG: Immunoglobulin G.

First step: Clinical presentation and biochemical parameters

Patients with BS are rarely asymptomatic; the most common clinical presentation is jaundice. Weight loss, fever, nausea, vomiting, pruritus, dark urine, discolored stool, and anorexia can also be present. Clinical history and symptoms are only in part useful for differential diagnosis as they may be similar in both benign and malignant forms of BS.

Biochemical parameters are not unequivocally indicative of the nature of BS, although increased levels of bilirubin, alkaline phosphatase, and alanine transaminase are considered strong predictors of malignancy[3,6]. Normal bilirubin associated with increased transaminases may also be suggestive of malignant disease, while normal bilirubin levels and normal liver function tests are unlikely to be indicative of primary biliopancreatic neoplasia[7]. Elevated levels of alkaline phosphatase, gamma glutamyl transpeptidase, carbohydrate antigen 19-9 (CA19-9), and carcinoembryonic antigen were associated with MBS in a multivariate analysis[8].

Among serum biomarkers, CA19-9 is the most common and validated tumor marker, showing high sensitivity and specificity for the diagnostic assessment of pancreatic cancer and seems to be useful in the early detection of this disease[9-11]. Diagnostic accuracy of CA19-9 in the diagnosis of pancreatic neoplasia is increased when associated with the assessment of CA242, which displays a high sensitivity (89%, 95% confidence interval (CI): 80%-95%) without impairing specificity (75%, 95%CI: 67%-82%)[10]. In CC, the sensitivity and specificity of CA19-9 are 72% and 84%, respectively[12]. CA19-9 showed variable diagnostic power among European, Asian, and American populations, possibly related to different genetic factors, cut-off value range, and assay method in the different studies[12]. However, it should be remembered that Lewis negative blood type patients (5%-10% of the Caucasian population), who cannot synthesize CA19-9, may have false-negative results[11]. False-positive cases may be due to other medical conditions, both benign and malignant, responsible for increased CA19-9 levels, such as acute diabetes, cholangitis, pancreatitis, obstructive jaundice, liver cirrhosis, and hepatocellular, ovarian, bronchial, colon, and gastric cancers[11].

New biomarkers, including glypican-1, microRNA, macrophage inhibitory cytokine 1, and osteopontin, have been studied for their diagnostic, predictive, and prognostic potential, but none have as yet been sufficiently validated for use in routine clinical settings[1,11,13].

Tips: Liquid biopsy

As a non-invasive molecular diagnostic tool, liquid biopsy has been attracting increasing attention for its promising application in cancer patients. This technique is based on the analysis of circulating free DNA, circulating tumor cells, circulating cell-free RNA, and circulating tumor DNA (ctDNA) and is expected to have a major impact on cancer diagnosis and management. Although available data regarding

circulating tumor DNA analysis in biliary tract tumors are limited, the evaluation of circulating tumor DNA may prove to have considerable application in diagnosis, monitoring of response to chemotherapy, and possible target therapy[14]. Liquid biopsy of bile is emerging as a promising option for the molecular diagnosis of MBS, as several bile biomarkers including proteins, metabolites, and microRNAs have been described. Selected reaction monitoring is a flexible high-throughput analytical approach based on targeted mass spectrometry used to quantify cancer biomarkers in human bile. The selected reaction monitoring assay was able to simultaneously quantify 31 peptides in human bile, indicating that the evaluation of cancer-related bile protein allows differentiation between MBS and BBS. The use of bile biomarkers in combination with serum CA19-9 was found to be highly accurate for the diagnosis of MBS and was proposed as an adjunctive technique in clinical practice[15].

Second step: Imaging and histopathological assessment

Cross-sectional imaging: Transabdominal ultrasound is a highly sensitive (> 90%) first-level technique able to detect indirect signs of BS, such as dilation of the distal tract and the intrahepatic branches. Transabdominal ultrasound is very useful as a screening test in the case of suspected biliary obstruction but has very low sensitivity in detecting strictures or masses[3,4,16].

Other non-invasive imaging techniques available to define the extension of and differentiate between BBS and MBS are multidetector computed tomography (MDCT), magnetic resonance imaging (MRI), magnetic resonance cholangiopancreatography (MRCP), and positron emission tomography (PET). The diagnostic flowchart currently used in the differential diagnosis of BS includes MDCT and/or MRI plus MRCP, and occasionally PET as the standard imaging methods for preoperative assessment of suspected MBS. The choice of specific imaging techniques for evaluating and staging MBS depends on tumor localization (distal or intrahepatic biliary tract) and origin (primitive biliary or pancreatic). Since there is no single ideal imaging modality, a multimodality approach is frequently adopted in potential candidates for surgery[17-19] (Figure 1).

MDCT is a routine imaging investigation for the preoperative assessment of intrahepatic and extrahepatic stenosis. MDCT provides a comprehensive evaluation of the primary tumor and adjacent structures, such as hepatic artery or portal and superior mesenteric vein as well as of the whole abdomen, to exclude potential metastasis. Diagnostic accuracy in characterizing stricture extent is low, ranging from 75% to 90%. Recently, intraprocedural cone-beam computed tomography (CT) has proven to be effective in the three-dimensional characterization of BS. The pre-contrast phase is useful for detecting possible intraductal stones as cause of obstruction and in differentiating stones from tumors[16,18]. The arterial and venous post-contrast phase is able to identify the inflammatory/benign process of the suspected lesion and allows for an evaluation of the location and aspect of enhancement. In addition, delayed phases (usually 3-5 min after contrast medium injection) are helpful for the differential diagnosis of intrahepatic CC, which shows delayed phase enhancement due to its abundant fibrous stroma[18]. In a recent meta-analysis, MDCT demonstrated a pooled sensitivity of 89% and specificity of 92% for the detection of portal vein and hepatic artery involvement in perihilar CC[19]. The diagnostic accuracy of MDCT is 75%-92% for the longitudinal tumor extent of perihilar CC and 60%-88% for resectability due to underestimation of the proximal extent of the tumor. CT cholangiography imaging obtained with multiplanar reconstruction and minimum intensity projections was recently proposed as an alternative to MRCP for BS assessment, especially in patients with contraindication to MRI[20].

Due to the lack of associated ionizing radiation and the possibility of obtaining high-quality imaging of the biliary tract, MRI and MRCP are the techniques of choice in the diagnosis of BS, with high sensitivity in detecting the precise site and length of the stenosis but low sensitivity in differentiating malignant from benign strictures. The use of hepatocyte-specific MRI agents and diffusion-weighted imaging proved useful in tumor characterization[19]. MRI with MRCP is the method of choice in the case of suspected perihilar CC. MRCP has a high sensitivity in detecting BS (up to 98%), with a reported sensitivity and specificity in differentiating between malignant and benign forms ranging from 38% to 90% and from 70% to 85%, respectively. In addition, MRCP has high accuracy (88%-96%) in predicting the extent of bile duct involvement in MBS [4,16-19]. MRI can include two-dimensional and three-dimensional MRCP. Two-dimensional MRCP is performed in a single section of 4-8 cm thickness during breath holds and is less affected by motion artifacts, as it allows rapid acquisition. However, it may not reveal intraductal lesions due to the partial volume averaging artifact. In contrast, three- dimensional MRCP provides an excellent overall visualization of the

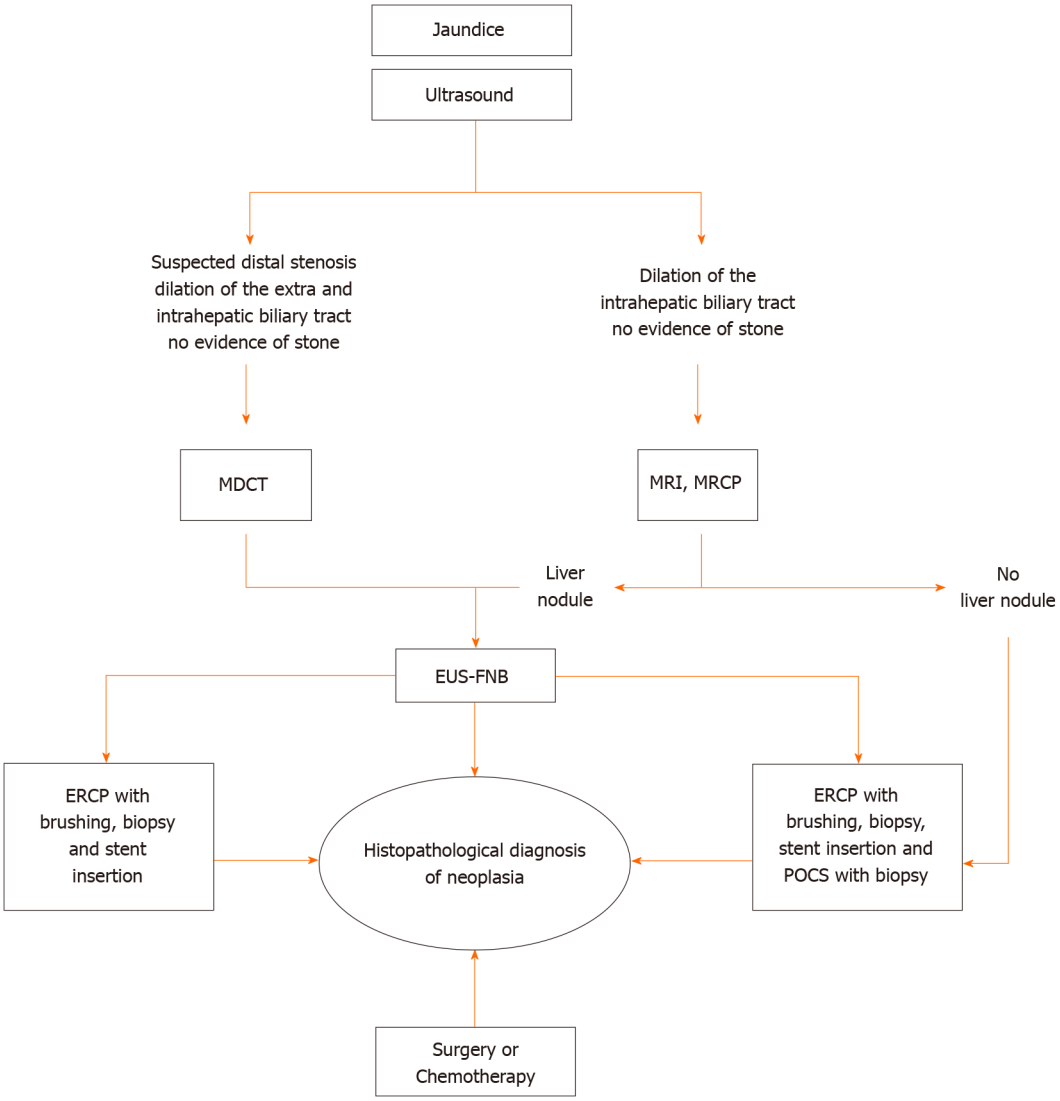

Figure 1 Algorithm of imaging investigations in biliary stenosis. MDCT: Multidetector computed tomography; MRI: Magnetic resonance imaging; MRCP: Magnetic resonance cholangiopancreatography; EUS-FNA: Endoscopic ultrasound-fine needle aspiration; ERCP: Endoscopic retrograde cholangiopancreatography; POCS: Peroral cholangioscopy.

biliary tree and an enhanced delineation of fine anatomical structures and small pathological features. Acquisition time is long, however, making it more susceptible to motion artifacts[19].

PET/CT is useful in the case of suspected distant metastasis or nodal metastases. In patients with resectable MBS, PET may help in the selection of candidates for surgery [19-21]. Dual-time-point fluorine-18 fludeoxyglucose integrated with PET/CT scan (18F- FDG PET/CT) was found to be effective in differentiating between BBS and MBS [20], although inflammation of the biliary tract or the presence of mucinous CC may cause false-positive and false-negative results[19]. The diagnostic power of 18F-FDG PET/CT for the diagnosis of primary tumor, lymph node invasion, and distant metastases was evaluated in a systematic review and meta-analysis of 2125 patients [22]. The study confirmed 18F-FDG PET/CT as a useful diagnostic tool in selected cases, as it provides valuable information in patients with indeterminate BS. 18F-FDG PET/CT changed the treatment plan in almost 20% of previously defined resectable MBS, avoiding unnecessary non-curative resection[22]. However, the routine use of 18F-FDG PET/CT as an imaging tool in tumor diagnosis remains controversial due to its low specificity (51%).

Tips: PET/MRI

Whole-body 18F-FDG-PET/MRI seems to hold great promise because of its ability to diagnose and stage potentially resectable MBS, providing in a single examination both MRI and PET information[19].

Tricks: Differential diagnosis using contrast-enhanced CT or MRI

The length of the involved biliary tract and contrast-enhanced morphological features are useful to differentiate BBS from MBS. Segmental involvement > 12 mm and thickening > 1.5 mm associated with luminal irregularity, asymmetry, and incremental enhancement may indicate the presence of MBS[18].

ENDOSCOPIC/RADIOLOGICAL IMAGING

Endoscopic retrograde cholangiopancreatography (ERCP) is the standard technique used to evaluate BS, as it combines the radiological imaging of cholangiography and the possibility of obtaining a histopathological diagnosis by multimodal sampling (guided brushing, biopsy, or bile aspiration). ERCP generates high-resolution fluoroscopic images that provide information regarding stricture site, length, and presence of irregularity of the biliary wall. Although fluoroscopic imaging has an accuracy of 80% in distinguishing a benign from a malignant stricture, tissue sampling by biliary brushing or endoluminal biopsy is required to histologically confirm the differential diagnosis.

Brush cytology is a simple tool with minimal adverse events but with very low sensitivity. Endoluminal forceps biopsy (Figure 2) requires sphincterotomy, which may be challenging to perform especially in the case of strictures above the bifurcation of the common bile duct. Standard ERCP with brushing has a 26%-73% sensitivity in the detection of malignancy[23]. The overall diagnostic yield of histopathological diagnosis ranges from 6% to 70%[24,25]. In a systematic review and meta-analysis, the pooled sensitivity reported for brush cytology and forceps biopsy was 45.0% and 48.1%, respectively; combining the two methods increased sensitivity up to 59.4%[23]. To improve the diagnostic accuracy of histological/cytological sampling during ERCP, Lee *et al*[24] evaluated aspiration cytology plus brush cytology or brush cytology plus biopsy or aspiration cytology plus biopsy. In terms of cancer type (CC *vs* non-CC), diagnostic sensitivity was higher for CC in the brush cytology plus biopsy or aspiration cytology plus biopsy group than in the aspiration cytology plus brush cytology group (100% *vs* 69.4%, respectively; $P < 0.001$) but not for non-CC (57.1% *vs* 57.1%, respectively)[24].

False-negative samples may be attributable to histopathological interpretation, tumor characteristics, and procedural factors. The combination of transpapillary tissue sampling followed by brushing and bile aspiration by nasobiliary drainage seems to increase sensitivity up to 72% in the diagnosis of MBS[26].

Pneumatic dilatation of the stenotic tract before tissue sampling with large biopsy forceps was found in a retrospective study to improve sensitivity from 40% to 71% and diagnostic accuracy from 55% to 87% compared to biopsy sampling without dilatation, with no difference in complication rate between the two procedures[27]. Fluorescence in situ hybridization (FISH) is used to analyze brush cytology specimens for chromosomal abnormalities in malignant cells. Although FISH is able to detect chromosomal changes in 80% of malignant biliary neoplasia, the combination of cytology and FISH revealed a sensitivity for malignancy of only 50%-60% in BS. A triple modality approach combining brush cytology, forceps biopsy, and FISH resulted in a marked increase in sensitivity for the diagnosis of CC compared with single modality testing and should be considered in the evaluation of indeterminate BS[26].

Tricks

Tube-assisted biopsy: Following biliary cannulation, a 10 Fr Soehendra biliary dilatation catheter is advanced over a guidewire in the stenosis in the left biliary tree. The tube is then placed as close as possible to the stricture area and the guidewire removed. Conventional endobiliary biopsy forceps are inserted through the tube into the area of the stricture for tissue collection[28].

Endoscopic transpapillary biopsy using the "tunnel" technique: This technique consists of the use of an 11.5 Fr biliary dilatation catheter as a tunnel for biopsy forceps after cutting the tapered tip. Following biliary cannulation, the catheter is advanced over a 0.035-inch guidewire and a 6 Fr catheter in the left biliary duct, where the previously identified stenosis is located. Next, the guidewire and 6 Fr catheter are removed, and 7 Fr biopsy forceps inserted in the 11.5 Fr catheter to collect tissue[29].

Endoscopic transpapillary biopsy using the "zipline" technique: A looped nylon thread is added to one cup of a pair of forceps with 2 mm-wide cups; the loop is then

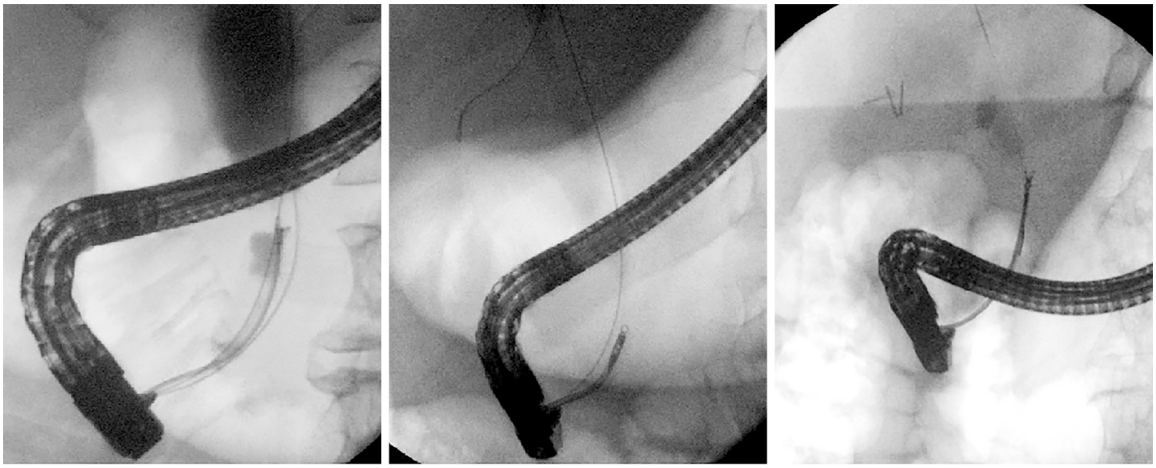

Figure 2 Three cases of patients with distal stenosis in which the diagnosis of cholangiocarcinoma was made by forceps biopsy during endoscopic retrograde cholangiopancreatography.

inserted over a guidewire and the forceps are advanced into the right bile duct[30].

Tips: How to improve ERCP histological results

Perform at least 10 brush passes under continuous fluoroscopy after meticulously preparing everything required for fixing the tissue sample in order to avoid contamination or air-drying artifacts. Combine different sampling methods and, if confident, perform brush and biopsy before and after stricture dilatation. Take at least four biopsy samples and work closely with the pathologist[31].

CHOLANGIOSCOPY

Direct visualization of the biliary tract by SpyGlass peroral cholangioscopy (POCS) system (Boston Scientific, Marlborough, Massachusetts) introduced in 2007[32] enhances

the diagnostic power of ERCP in patients with indeterminate BS by providing intraductal imaging of the stenotic duct or of the lesion suggestive of malignancy. Over the past two decades, three types of cholangioscopy platforms have become available. The most recently introduced is a digital single-operator cholangioscopy (D-SOC) ultra-slim endoscope inserted into the bile duct through the working channel of a duodenoscope and advanced into the papilla, providing excellent image quality achieved by image- enhanced endoscopy. Several studies demonstrated its high performance in the diagnosis of BS, with a > 70% sensitivity but < 50% specificity[33-35]. In a recent systematic review of published studies evaluating the diagnostic performance of any type of POCS, the sensitivity, specificity, and diagnostic accuracy of POCS for diagnosing MBS ranged from 38%-100%, 49%-100%, and 50%-100%, respectively, with a technical success rate of 82%-100%[34].

Although D-SOC allows viewing of the biliary tract from the inside, its use is limited by the high cost of the equipment and the lack of standardization in the interpretation of visual features of the biliary ducts. Endoscopic features defined as suggestive of MBS at cholangioscopy are nodular or papillary masses with irregular surface, fragile mucosa, and dilated and tortuous vessels (Figure 3). Kim *et al*[35] reported an association between the detection of tortuous vessels and malignancy with a sensitivity of 61% and specificity of 100%[35]. A recent meta-analysis on D-SOC in the visual interpretation of indeterminate BS reported a 94% sensitivity and 95% specificity, a diagnostic accuracy of 94%, a positive predictive value of 93%, and a negative predictive value of 98% in the diagnosis of MBS[36].

In a prospective study on 289 patients with indeterminate BS enrolled in 20 centers in Asia, the Middle East, and Africa, the use of two POCS systems (SpyGlass Legacy and SpyGlass DS digital system) was able to detect stricture/filling or bile duct defect in 98.6% of patients, providing a visual diagnostic impression in 87.2% and adequate biopsies in 92.9% of cases, with low rate of complication (1.7%)[37]. A limitation of this study was that it did not investigate patients with primary biliary disease. In two other

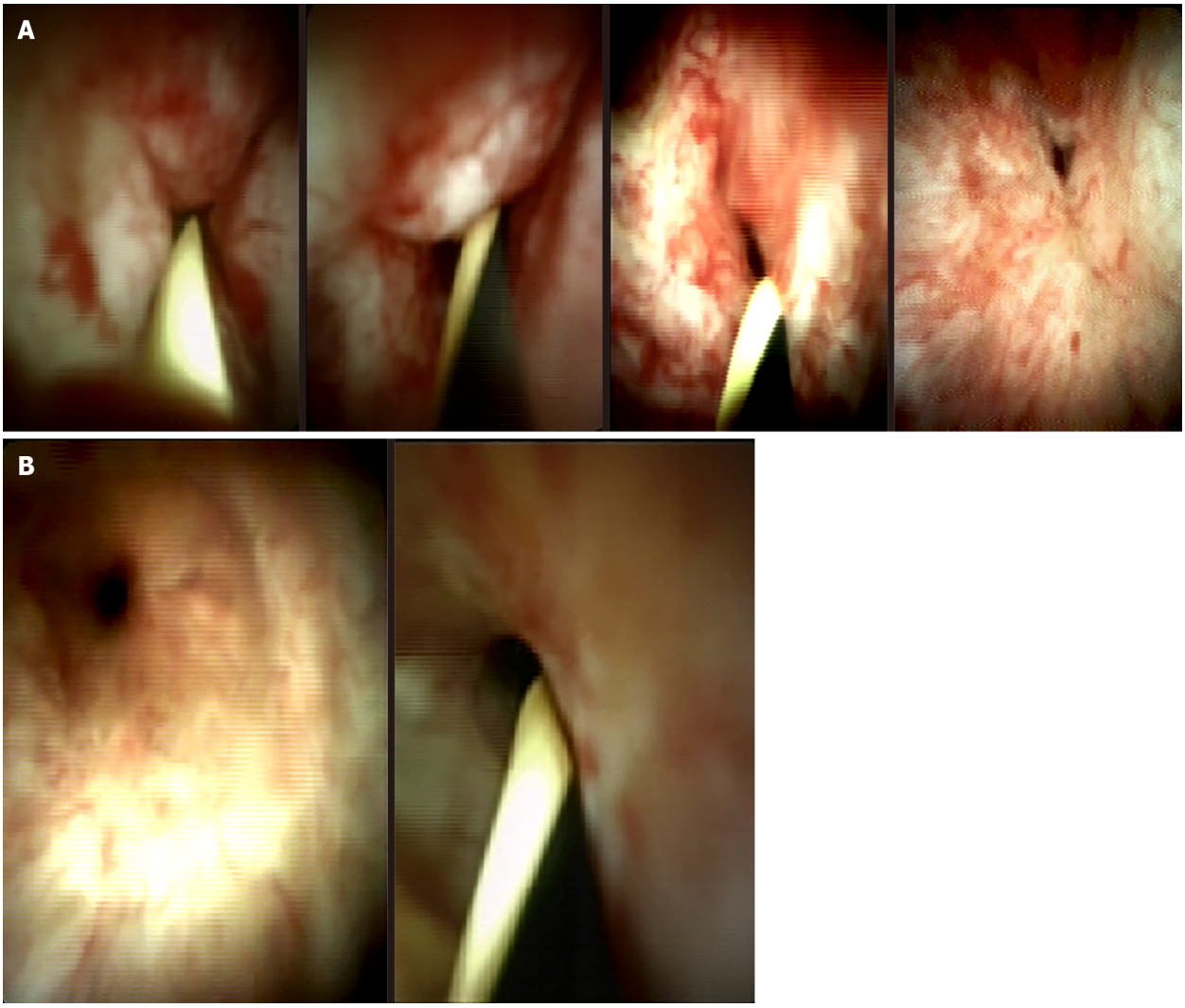

Figure 3 Digital (SpyGlass) cholangioscopy images. A: Cholangiocarcinoma; B: Benign stenosis.

recent studies from the United States and the Netherlands, which included patients with primary sclerosing cholangitis in their populations, POCS did not increase diagnostic sensitivity for CC over that of ERCP with brush cytology[38,39]. The lack of a standardized classification of image findings detected during cholangioscopy still causes problems of interpretation and may be responsible for unsatisfactory diagnostic accuracy[38,39].

To overcome this limit, Robles-Medranda *et al*[40] proposed in 2018 a classification system based on neoplastic and non-neoplastic findings including villous, polypoid, inflammatory, ulcerated, flat, or honeycomb patterns, which revealed an outstanding 96% sensitivity, 92% specificity, 96% negative predictive value, and an interobserver agreement up to 90%[40]. Similar results were found by Gerges *et al*[41], who reported a sensitivity of visualization of 95.5%[41]. In 2020, the Monaco classification was proposed for indeterminate BS based on eight visual criteria: presence of stricture, lesion (mass, nodule, or polypoid appearance), mucosal features, papillary projections, ulceration, abnormal vessels, scarring, and pronounced pit pattern. Final diagnostic accuracy based only on visual impression was 70%, with a high interobserver agreement for presumptive diagnosis (k = 0.31)[42].

The diagnostic accuracy of D-SOC is further improved by D-SOC-guided biopsy, which allows precise tissue sampling of the detected lesions. In a meta-analysis by Wen *et al*[43], SpyBite (Boston Scientific) biopsy showed a pooled sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio of 0.74 (95%CI: 0.67-0.80), 0.98 (95%CI: 0.95-1.00), 10.52 (95%CI: 5.45-20.32), 0.31 (95%CI: 0.23-0.41), and 65.18 (95%CI: 26.79-158.61), with a lower complication rate mainly ERCP-related. Acute cholangitis was the most common complication with a rate of 1.8%[43].

A point of great debate is the number of biopsies needed to obtain adequate tissue for a diagnostic histopathological assessment. Based on currently available studies, the number of biopsies is not defined with any certainty, but more than two biopsies are required to reach a sensitivity > 70%[23,43]. In a randomized multicenter investigation, an average of six biopsy specimens were taken during POCS, achieving a sensitivity of 68.2%, which increased up to 95.5% if visual impression at cholangioscopy was added to biopsy forceps performance[41].

The possible increase in diagnostic power using rapid on-site evaluation of D-SOC microbiopsy was recently assessed in a single-center prospective randomized trial among patients with indeterminate BS[44]. The authors concluded that there were no significant differences between the off-site and on-site groups in terms of diagnostic accuracy (90% *vs* 87.5%), sensitivity (76.9% *vs* 75%), and specificity (100% *vs* 100%). However, a greater number of biopsies was necessary to obtain a diagnosis in the off-site cohort (n = 3-4) than in the on-site cohort (n = 1)[44].

A precise evaluation of the extension of the neoplasia along the biliary wall in surgical candidate patients is of key importance in ensuring curative resection. D-SOC visualization of the biliary ducts allows the evaluation of intraductal cancer extension, not evident with diagnostic methods previously used and may guide the choice of surgical treatment, avoiding unnecessary surgery in the case of locally advanced neoplasia. In a retrospective study investigating the use of D-SOC for preoperative evaluation of extrahepatic biliary tumor, the visual impression accuracy of SpyGlass and SpyBite was 95.0% and 80.5%, respectively. D-SOC modified a previous classification of perihilar CC in 42% of patients and changed surgical management in 21% of cases[45]. Despite its high diagnostic accuracy, cholangioscopy is an expensive and difficult-to- handle technique that requires extensive experience in the performance of ERCP and adequate training in the interpretation of digital images and technique of execution. Several complications may occur during cholangioscopy, and the rate of serious adverse events ranges from 1% to 7%, with estimated rates of pancreatitis, cholangitis, and perforation of 2%, 4%, and 1%, respectively[46]. Cholangitis was reported in 8% of patients undergoing D-SOC; the administration of antibiotics during or immediately after the procedure seems to reduce the risk of this complication[47].

A cost-benefit analysis of D-SOC compared to conventional ERCP in the diagnosis of BS, based on data from two of the largest Belgian hospitals performing cholangioscopy, revealed that the adoption of D-SOC led to a 31% reduction in the number of procedures needed to obtain a diagnosis and saved about 5% of the allocated budget [48].

ENDOSCOPIC ULTRASOUND

Endoscopic ultrasound (EUS) is a diagnostic tool based on double endoscopic and ultrasonographic vision thanks to a high-frequency transducer placed on the tip of the endoscope. Due to the ease in identifying the biliary tract from the stomach and the duodenum, EUS may be considered a first-level procedure in identifying the cause of obstructive jaundice or in the diagnostic assessment of distal BS or unresectable intrahepatic CC (Figure 4).

The biliary examination usually starts from the stomach by identifying the biliary duct from the liver hilum and continues from the duodenal bulb to the second portion of the duodenum, studying the entire extrahepatic duct until the intrapancreatic portion. An endoscopic and ultrasonographic assessment of the ampulla and the gallbladder may also be performed to complete the investigation.

EUS has a diagnostic accuracy > 95% in identifying biliary thickening suggestive of malignancy compared to MRCP[48] (Figure 5). Given its high diagnostic accuracy in excluding a pathological thickening of the biliary wall, if performed at the beginning of the diagnostic process, EUS can avoid having to carry out an invasive procedure such as ERCP and any related complications[49].

The possibility of obtaining tissue from a clear mass by guided-EUS fine needle aspiration (EUS-FNA) increases the diagnostic power of EUS (Figures 6 and 7). EUS-FNA has a pooled sensitivity and specificity of 80% and 97%, respectively, in the diagnosis of malignancy in the biliary tract[50]. The advantage of performing EUS-FNA and ERCP in a single session should not be understated, as it reduces the duration of diagnostic workup in patients with BS and allows the selection of patients requiring therapeutic ERCP, thus avoiding an invasive procedure in absence of clear pathological thickening of the biliary tract (Figure 8). Zaheer *et al*[51] reported that EUS changed the diagnosis in 36% of patients from malignant to benign[51].

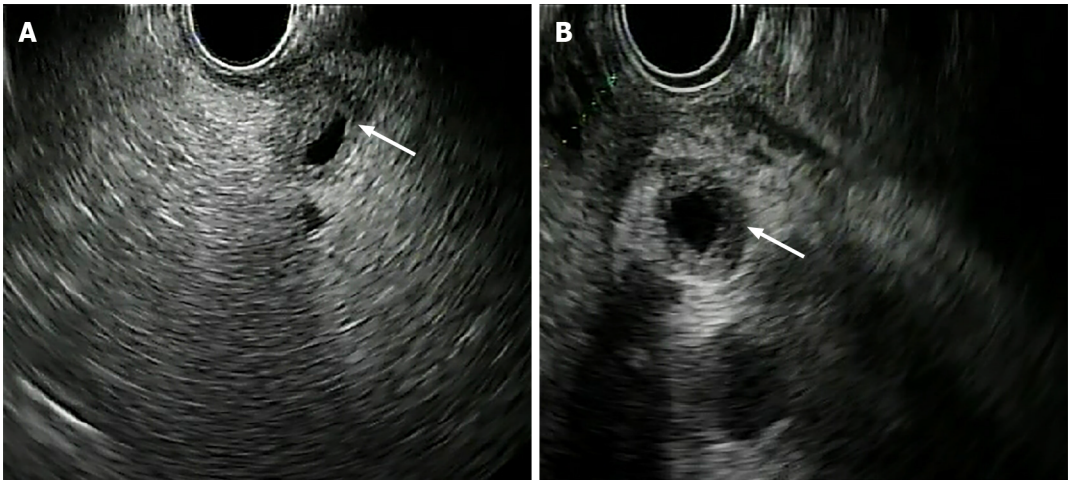

Figure 4 Two cases of cholangiocarcinoma evaluated with endoscopic ultrasound. A: Distal stenosis of the main biliary tract; B: Stenosis of the proximal-middle tract of the main biliary duct. Arrows indicate the stenotic tract.

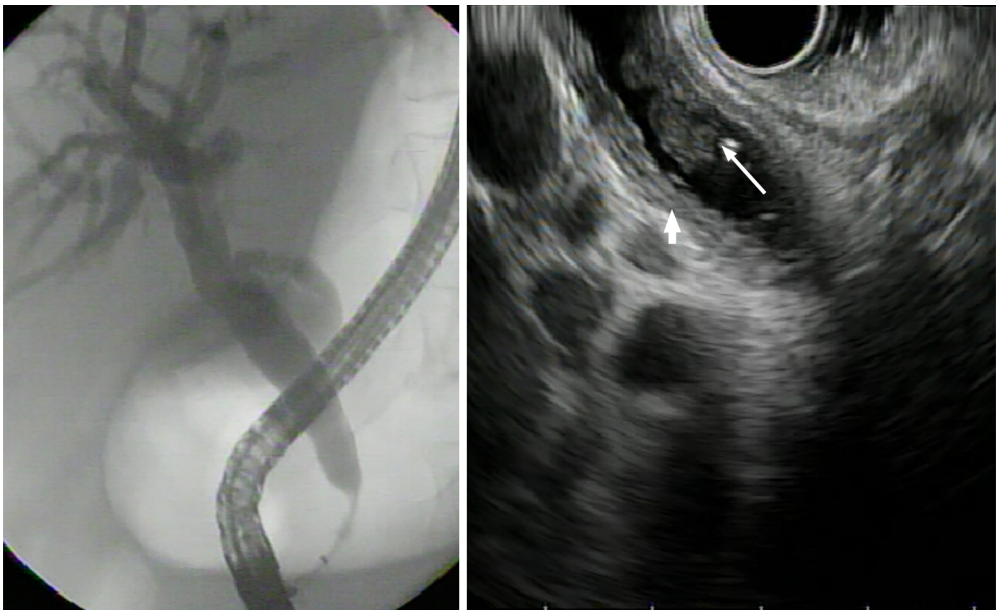

Figure 5 Endoscopic retrograde cholangiopancreatography and endoscopic ultrasound image of a stenotic tract of the distal biliary duct. In the endoscopic ultrasound image, the nodule inside the main biliary tract (large arrow) and thickening of the bile duct wall (small arrow) are visible.

The combination of EUS-FNA and ERCP-based tissue sampling in the same session has a diagnostic yield of up to 85%, whereas the overall accuracy of EUS-FNA tissue sampling is significantly higher than that of ERCP in the differential diagnosis of MBS (76% *vs* 58%)[52]. An additional advantage offered by EUS-FNA is the possibility of obtaining histological samples from an extraductal lesion not reachable by ERCP. In a retrospective multicenter study on 263 patients with suspected MBS, EUS, and ERCP were carried out in the same session and the diagnostic power of samples collected from BS by EUS-FNA and intraductal biopsy, cytology *via* nasobiliary drainage, or brushing by ERCP was compared[53]. This study found an overall sensitivity and diagnostic accuracy of 73.6% and 76.1% for EUS-FNA, 56.5% and 60.5% for ERCP-based tissue sampling, and 85.8% and 87.1% for the combination of both tissue-sampling methods[53].

As the therapeutic options for CC are surgical resection or liver transplantation, a precise definition of the tumor extension is crucial in guiding the treatment choice. RLN metastasis and margin status are the most important predictors of post-surgical outcome[54]. In this context, EUS-FNA proved to be the preferred technique in the identification and sampling of lymph nodes. In a retrospective study of consecutive patients with CC undergoing EUS staging with EUS-FNA of RLN, EUS identified

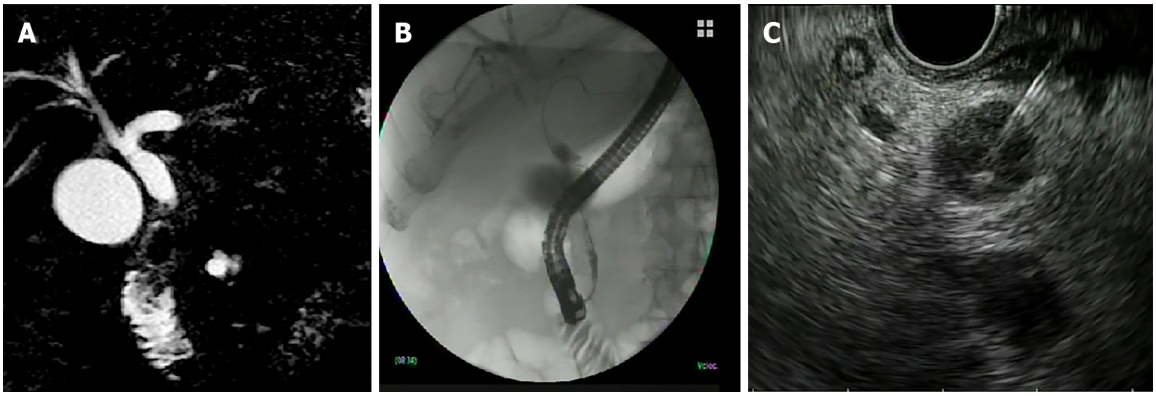

Figure 6 Adenocarcinoma of the main biliary tract. A: Magnetic resonance image of suspected neoplastic stenosis; B: Endoscopic retrograde cholangiopancreatography image confirming the stenosis; C: Endoscopic ultrasound-guided fine needle aspiration of the stenotic tract for tissue diagnosis.

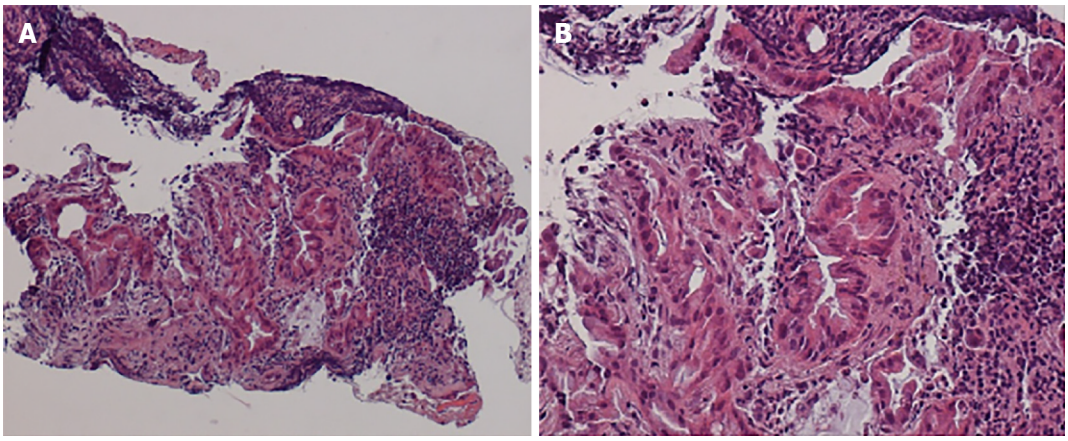

Figure 7 Histology of specimen collected by endoscopic ultrasound-fine needle aspiration from cholangiocarcinoma in a hepatic nodule. A: Hematoxylin and eosin staining, magnification × 40; B: Hematoxylin and eosin staining, magnification × 100.

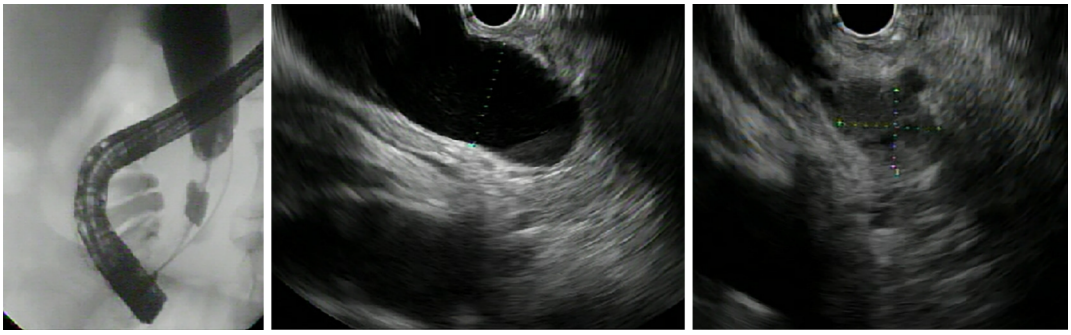

Figure 8 Diagnosis of cholangiocarcinoma of the distal tract of the main biliary duct, obtained in a single session by biopsy during endoscopic retrograde cholangiopancreatography and endoscopic ultrasound-guided fine needle aspiration. Endoscopic ultrasound images show dilation of the common bile duct and stenosis of the distal tract due to a neoplastic nodule.

positive RLN in 86% of patients and detected a higher percentage of positive RLN than cross-sectional imaging (83% *vs* 50%); EUS-FNA revealed metastatic RLN in 17% of patients[55]. According to the authors, preoperative staging with EUS and EUS-FNA of RLN should be considered in patients with any type of CC[56].

Tips

The choice of endoscopic technique to obtain a tissue-based differential diagnosis of BS should be tailored according to the stricture location. In patients where ERCP transpapillary forceps biopsy resulted non-diagnostic, POCS-guided forceps biopsy

should be preferred in proximal BS, whereas EUS-FNA biopsy may be more appropriate for distal BS[55].

INTRADUCTAL ULTRASOUND

Intraductal ultrasound (IDUS) involves a 2-mm high-frequency radial probe (12-20 MHz) introduced through the working channel of a duodenoscope. On IDUS visualization, the normal wall of the bile duct appears as three layers: an inner hyperechoic layer corresponding to mucosa, a middle hypoechoic layer corresponding to smooth muscle fibers, and an outer hyperechoic layer corresponding to connective tissue[57]. IDUS could be particularly effective in the assessment of CC, especially where no mass is detected, and may be used to distinguish BBS from MBS. Sonographic features associated with MBS are hypoechoic or heterogeneous echo-poor infiltrating tissue with irregular borders breaking the normal sonographic pattern of the bile duct wall, eccentric and irregular wall thickening, sessile mass, invasion of surrounding tissues, and presence of enlarged lymph nodes[58].

In a retrospective study by Chen *et al*[59], IDUS showed a sensitivity, specificity, positive predictive value, negative predictive value, and accuracy rate of 96.9%, 79.0%, 82.0%, 96.2%, and 88.0%, respectively, in distinguishing MBS from BBS. Combining IDUS and ERCP-guided tissue sampling improved the accuracy rate from 88.0% to 96.8% and specificity from 79.0% to 96.8%. A length > 20 mm and a wall thickness > 7 mm has a positive predictive value > 90% for malignancy[59]. A recent prospective study confirmed an > 80% accuracy of IDUS in detecting malignancy in patients with negative ERCP cytology and histology and corroborated its usefulness in targeting biopsy sampling with improvement in diagnostic accuracy[60]. However, this technique is not routinely performed, and its use is progressively decreasing in favor of D-SOC.

Third step: Endoscopic treatment of biliary stenosis

Endoscopic treatment of BS, both benign and malignant, is well documented and widely accepted. The European Society of Gastrointestinal Endoscopy guidelines defined the correct choice of stent according to the location and etiology of the stenosis [61]. In BS related to liver transplantation, chronic pancreatitis, or post-cholecystectomy strictures, the treatment of choice is temporary insertion of multiple plastic stents or a fully covered self-expandible metal stent (FC-SEMS) depending on the etiology and location of the stricture, diameter of the common bile duct, and operator expertise. With FC-SEMS insertion, the possibility of stent migration (9% of cases reported) with consequential failure of stricture resolution should be kept in mind[62]. A recent review by Larghi *et al*[63] described different strategies used to treat anastomotic BS after liver transplantation, comparing the advantages and disadvantages of plastic multi-stenting treatment *vs* placement of a metal stent reported in the literature, including four randomized controlled trials (Figure 9). The authors concluded that insufficient data are currently available to define which type of treatment is better than another, suggesting the need for a multicenter international randomized trial to draw definitive conclusions. Even less conclusive results are available for the treatment of refractory strictures, especially for hilar anastomotic strictures after liver transplants and hepaticojejunostomies. A recent single-center study aimed at evaluating the use of FC-SEMS for hilar BBS recently reported that temporary placement of an FC-SEMS is feasible and effective for refractory BBS, with a technical success rate of 100%, stricture resolution rate of 96.6%, and complication rate of 12.0%[64].

For MBS, the European Society of Gastrointestinal Endoscopy recommendations advise against routine preoperative biliary drainage in patients with surgical indication in absence of cholangitis, severe symptomatic jaundice, delayed surgery, or in the case of neoadjuvant therapy. A 10 mm-diameter SEMS is recommended for extrahepatic MBS before surgery. Palliative biliary drainage should be performed by ERCP with FC-SEMS or partially covered SEMS insertion. Surgical biliodigestive anastomosis and percutaneous biliary drainage should be indicated in selected cases where ERCP cannot be performed due to its high rate of complications and impact on the patient's quality of life[65,66].

Described for the first time in 2001, endoscopic ultrasound biliary drainage (EUS-BD) is an emerging technique useful in patients in whom ERCP biliary drainage failed or is not technically feasible due to duodenal stenosis or unreachable papilla[67,68]. A meta-analysis comparing EUS-BD *vs* percutaneous transhepatic biliary drainage in 312

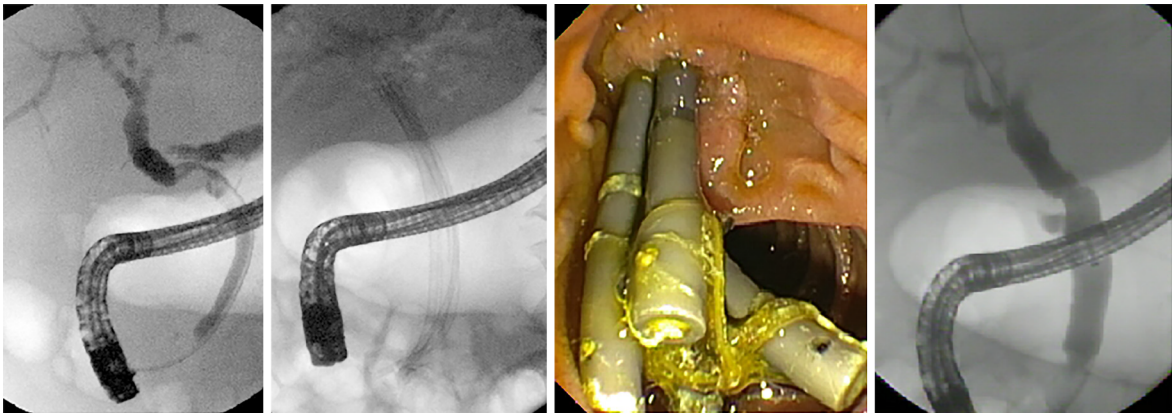

Figure 9 Multi-stenting treatment of anastomotic stenosis after liver transplantation. The image on the far right shows complete resolution of the stenosis.

patients demonstrated that clinical success was similar for both techniques, but complications were less frequent with EUS-BD[69]. Despite the apparently high cost of the device, reintervention rates and costs were found to be lower with EUS-BD in a retrospective expertise-based study[70]. In a systematic review and meta-analysis, Dhindsa *et al*[71] evaluated the technical success, clinical outcome, and rate of adverse events of EUS-BD reported in 23 studies published in peer-reviewed journals. The pooled rate of clinical success was 87.0%, technical success 91.5%, reintervention 6.5%, and adverse events 17.9%. The most common adverse events were biliary leaks and infection or stent migration, although a precise evaluation of the incidence of complication was hampered by the variability of adverse event rates, the heterogeneity of EUS-BD, performed *via* hepatogastrostomy, cholecystostomy, or choledochoduodenostomy, and the different techniques of drainage, such as plastic stents, metal stents, lumen-apposing metal stents (LAMS), nasobiliary drainage tubes, or a combination of these, used in the different studies[71].

The use of devices designed for EUS-guided drainage, such as LAMS (Boston Scientific, Marlborough, Massachusetts, United States), was first reported in 2011 and significantly contributed to improving the technical success and safety of EUS-BD. Nevertheless, this type of procedure requires an operator expert in interventional EUS and should be performed in a tertiary care referral center after a multidisciplinary discussion of the clinical case[72].

In a recent study by Anderloni *et al*[73] involving 46 consecutive patients with malignant distal biliary duct obstruction over a 3-year period, choledochoduodenostomy using LAMS showed a technical success rate of 93.5% and a clinical success rate of 97.7%, with an incidence of complication of 11.6%. The most serious complication was fatal bleeding, occurring in one case after 17 d from stent placement, while the remaining were food impaction in the stent and one migration of the stent [73]. In line with these results, a French multicenter study reported a technical and clinical success rate of 98.5% and 97.1%, respectively, with a short-term adverse event rate of 1.6% and a 6-mo stent patency rate of 91.4%[74]. Of note, in this French study the procedures were performed by 12 operators in 10 different centers. Each operator had experience of routine diagnostic EUS, including FNA and ERCP in the previous 5 years, and only four operators had previously performed > 20 EUS-BD. No difference in terms of technical success between operators was reported[74]. Despite these findings, data regarding the efficacy of EUS-BD by LAMS and the precise timing of intervention need to be confirmed in a randomized controlled trial.

Future treatment for BS

Radiofrequency ablation was recently proposed for the treatment of endobiliary malignancy, ablation of intraductal extension of ampullary adenomas, and recanalization of occluded metal stents[75]. The use of radiofrequency ablation in hilar BS was evaluated by Inoue *et al*[76] in a retrospective study of patients with unresectable malignant hilar biliary obstruction treated with radiofrequency ablation followed by biliary drainage with SEMS. The recurrence rate of biliary obstruction was 38.5% within a median time of 230 d. The findings of this study open up new therapeutic perspectives in patients with unresectable hilar BS, but further investigations are necessary to optimize the technique and determine its indication.

CONCLUSION

The management of BS can be complicated due to the difficulty in obtaining a correct differential tissue diagnosis between benign and malignant stenosis, especially in cases of hilar stenosis and when the tumor grows along the wall of the biliary tract. A shared multidisciplinary management approach to patients with BS is therefore necessary in order to exploit all the diagnostic techniques currently available and to select the most suitable therapy based on recent findings in the scientific literature.

REFERENCES

1 **Bowlus CL**, Olson KA, Gershwin ME. Evaluation of indeterminate biliary strictures. *Nat Rev Gastroenterol Hepatol* 2016; **13**: 28-37 [PMID: 26526122 DOI: 10.1038/nrgastro.2015.182]
2 **Singh A**, Gelrud A, Agarwal B. Biliary strictures: diagnostic considerations and approach. *Gastroenterol Rep (Oxf)* 2015; **3**: 22-31 [PMID: 25355800 DOI: 10.1093/gastro/gou072]
3 **Fernandez Y Viesca M**, Arvanitakis M. Early Diagnosis And Management Of Malignant Distal Biliary Obstruction: A Review On Current Recommendations And Guidelines. *Clin Exp Gastroenterol* 2019; **12**: 415-432 [PMID: 31807048 DOI: 10.2147/CEG.S195714]
4 **Tummala P**, Munigala S, Eloubeidi MA, Agarwal B. Patients with obstructive jaundice and biliary stricture ± mass lesion on imaging: prevalence of malignancy and potential role of EUS-FNA. *J Clin Gastroenterol* 2013; **47**: 532-537 [PMID: 23340062 DOI: 10.1097/MCG.0b013e3182745d9f]
5 **Bismuth H**, Corlette MB. Intrahepatic cholangioenteric anastomosis in carcinoma of the hilus of the liver. *Surg Gynecol Obstet* 1975; **140**: 170-178 [PMID: 1079096]
6 **Garcea G**, Ngu W, Neal CP, Dennison AR, Berry DP. Bilirubin levels predict malignancy in patients with obstructive jaundice. *HPB (Oxford)* 2011; **13**: 426-430 [PMID: 21609376 DOI: 10.1111/j.1477-2574.2011.00312.x]
7 **Thomasset SC**, Saunders D, Holland A, Dennison AR, Garcea G. Malignant biliary strictures in patients with a normal bilirubin and/or normal liver enzymes. *HPB (Oxford)* 2015; **17**: 969-974 [PMID: 26256123 DOI: 10.1111/hpb.12468]
8 **Park JY**, Jeon TJ. Factors Associated with Malignant Biliary Strictures in Patients with Atypical or Suspicious Cells on Brush Cytology. *Clin Endosc* 2019; **52**: 168-174 [PMID: 30625267 DOI: 10.5946/ce.2018.105]
9 **Xing H**, Wang J, Wang Y, Tong M, Hu H, Huang C, Li D. Diagnostic Value of CA 19-9 and Carcinoembryonic Antigen for Pancreatic Cancer: A Meta-Analysis. *Gastroenterol Res Pract* 2018; **2018**: 8704751 [PMID: 30584422 DOI: 10.1155/2018/8704751]
10 **Zhang Y**, Yang J, Li H, Wu Y, Zhang H, Chen W. Tumor markers CA19-9, CA242 and CEA in the diagnosis of pancreatic cancer: a meta-analysis. *Int J Clin Exp Med* 2015; **8**: 11683-11691 [PMID: 26380005]
11 **Hasan S**, Jacob R, Manne U, Paluri R. Advances in pancreatic cancer biomarkers. *Oncol Rev* 2019; **13**: 410 [PMID: 31044028 DOI: 10.4081/oncol.2019.410]
12 **Liang B**, Zhong L, He Q, Wang S, Pan Z, Wang T, Zhao Y. Diagnostic Accuracy of Serum CA19-9 in Patients with Cholangiocarcinoma: A Systematic Review and Meta-Analysis. *Med Sci Monit* 2015; **21**: 3555-3563 [PMID: 26576628 DOI: 10.12659/msm.895040]
13 **Lourdusamy V**, Tharian B, Navaneethan U. Biomarkers in bile-complementing advanced endoscopic imaging in the diagnosis of indeterminate biliary strictures. *World J Gastrointest Endosc* 2015; **7**: 308-317 [PMID: 25901209 DOI: 10.4253/wjge.v7.i4.308]
14 **Rizzo A**, Ricci AD, Tavolari S, Brandi G. Circulating Tumor DNA in Biliary Tract Cancer: Current Evidence and Future Perspectives. *Cancer Genomics Proteomics* 2020; **17**: 441-452 [PMID: 32859625 DOI: 10.21873/cgp.20203]
15 **Adrait A**, Dumonceau JM, Delhaye M, Annessi-Ramseyer I, Frossard JL, Couté Y, Farina A. Liquid Biopsy of Bile based on Targeted Mass Spectrometry for the Diagnosis of Malignant Biliary Strictures. *Clin Transl Sci* 2021; **14**: 148-152 [PMID: 33048472 DOI: 10.1111/cts.12890]
16 **Kapoor BS**, Mauri G, Lorenz JM. Management of Biliary Strictures: State-of-the-Art Review. *Radiology* 2018; **289**: 590-603 [PMID: 30351249 DOI: 10.1148/radiol.2018172424]
17 **NCCN**. NCCN clinical practice guidelines in oncology. Hepatobiliary cancers. Version 5.2020. [cited 20 March 2021]. Available from: https://www.nccn.org/
18 **Joo I**, Lee JM, Yoon JH. Imaging Diagnosis of Intrahepatic and Perihilar Cholangiocarcinoma: Recent Advances and Challenges. *Radiology* 2018; **288**: 7-13 [PMID: 29869969 DOI: 10.1148/radiol.2018171187]
19 **Ruys AT**, van Beem BE, Engelbrecht MR, Bipat S, Stoker J, Van Gulik TM. Radiological staging in patients with hilar cholangiocarcinoma: a systematic review and meta-analysis. *Br J Radiol* 2012; **85**: 1255-1262 [PMID: 22919007 DOI: 10.1259/bjr/88405305]
20 **Rizzo S**, De Piano F, Buscarino V, Pagan E, Bagnardi V, Zanagnolo V, Colombo N, Maggioni A, Del Grande M, Del Grande F, Bellomi M, Aletti G. Pre-operative evaluation of epithelial ovarian cancer patients: Role of whole body diffusion weighted imaging MR and CT scans in the selection of patients suitable for primary debulking surgery. A single-centre study. *Eur J Radiol* 2020; **123**: 108786 [PMID: 31862634 DOI: 10.1016/j.ejrad.2019.108786]

21 **Choi EK**, Yoo IeR, Kim SH, O JH, Choi WH, Na SJ, Park SY. The clinical value of dual-time point 18F-FDG PET/CT for differentiating extrahepatic cholangiocarcinoma from benign disease. *Clin Nucl Med* 2013; **38**: e106-e111 [PMID: 23354026 DOI: 10.1097/RLU.0b013e318266f402]

22 **Lamarca A**, Barriuso J, Chander A, McNamara MG, Hubner RA, ÓReilly D, Manoharan P, Valle JW. ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}FDG-PET) for patients with biliary tract cancer: Systematic review and meta-analysis. *J Hepatol* 2019; **71**: 115-129 [PMID: 30797051 DOI: 10.1016/j.jhep.2019.01.038]

23 **Navaneethan U**, Njei B, Lourdusamy V, Konjeti R, Vargo JJ, Parsi MA. Comparative effectiveness of biliary brush cytology and intraductal biopsy for detection of malignant biliary strictures: a systematic review and meta-analysis. *Gastrointest Endosc* 2015; **81**: 168-176 [PMID: 25440678 DOI: 10.1016/j.gie.2014.09.017]

24 **Lee SJ**, Lee YS, Lee MG, Lee SH, Shin E, Hwang JH. Triple-tissue sampling during endoscopic retrograde cholangiopancreatography increases the overall diagnostic sensitivity for cholangiocarcinoma. *Gut Liver* 2014; **8**: 669-673 [PMID: 25368755 DOI: 10.5009/gnl13292]

25 **Tanaka H**, Matsusaki S, Baba Y, Isono Y, Sase T, Okano H, Saito T, Mukai K, Murata T, Taoka H. Usefulness of Endoscopic Transpapillary Tissue Sampling for Malignant Biliary Strictures and Predictive Factors of Diagnostic Accuracy. *Clin Endosc* 2018; **51**: 174-180 [PMID: 28854772 DOI: 10.5946/ce.2017.082]

26 **Nanda A**, Brown JM, Berger SH, Lewis MM, Barr Fritcher EG, Gores GJ, Keilin SA, Woods KE, Cai Q, Willingham FF. Triple modality testing by endoscopic retrograde cholangiopancreatography for the diagnosis of cholangiocarcinoma. *Therap Adv Gastroenterol* 2015; **8**: 56-65 [PMID: 25729431 DOI: 10.1177/1756283X14564674]

27 **Pörner D**, Kaczmarek DJ, Heling D, Hausen A, Mohr R, Hüneburg R, Matthaei H, Glowka TR, Manekeller S, Fischer HP, Toma M, Nattermann J, Strassburg CP, Gonzalez-Carmona MA, Weismüller TJ. Transpapillary tissue sampling of biliary strictures: balloon dilatation prior to forceps biopsy improves sensitivity and accuracy. *Sci Rep* 2020; **10**: 17423 [PMID: 33060723 DOI: 10.1038/s41598-020-74451-9]

28 **Ko SW**, Lee SS, So H, Hwang JS, Song TJ, Lee SK, Kim MH. A novel method of biopsy for indeterminate pancreaticobiliary strictures: tube-assisted biopsy. *Endoscopy* 2020; **52**: 589-594 [PMID: 32219796 DOI: 10.1055/a-1127-3265]

29 **Perri V**, Orlandini B, Tringali A, Boškoski I, Costamagna G. Endoscopic transpapillary biopsy using a self-assembled device: the tunnel technique. *Endoscopy* 2020; **52**: 616-617 [PMID: 31995827 DOI: 10.1055/a-1089-7315]

30 **Hamada T**, Takahara N, Nakai Y, Kanai S, Saito T, Koike K. The "zipline" technique for endoscopic transpapillary biliary biopsy. *Endoscopy* 2020; **52**: 236-237 [PMID: 31593988 DOI: 10.1055/a-1015-6609]

31 **Dumonceau JM**, Delhaye M, Charette N, Farina A. Challenging biliary strictures: pathophysiological features, differential diagnosis, diagnostic algorithms, and new clinically relevant biomarkers - part 1. *Therap Adv Gastroenterol* 2020; **13**: 1756284820927292 [PMID: 32595761 DOI: 10.1177/1756284820927292]

32 **Chen YK**. Preclinical characterization of the Spyglass peroral cholangiopancreatoscopy system for direct access, visualization, and biopsy. *Gastrointest Endosc* 2007; **65**: 303-311 [PMID: 17258991 DOI: 10.1016/j.gie.2006.07.048]

33 **Navaneethan U**, Hasan MK, Kommaraju K, Zhu X, Hebert-Magee S, Hawes RH, Vargo JJ, Varadarajulu S, Parsi MA. Digital, single-operator cholangiopancreatoscopy in the diagnosis and management of pancreatobiliary disorders: a multicenter clinical experience (with video). *Gastrointest Endosc* 2016; **84**: 649-655 [PMID: 26995690 DOI: 10.1016/j.gie.2016.03.789]

34 **Kulpatcharapong S**, Pittayanon R, J Kerr S, Rerknimitr R. Diagnostic performance of different cholangioscopes in patients with biliary strictures: a systematic review. *Endoscopy* 2020; **52**: 174-185 [PMID: 31923922 DOI: 10.1055/a-1083-6105]

35 **Kim HJ**, Kim MH, Lee SK, Yoo KS, Seo DW, Min YI. Tumor vessel: a valuable cholangioscopic clue of malignant biliary stricture. *Gastrointest Endosc* 2000; **52**: 635-638 [PMID: 11060188 DOI: 10.1067/mge.2000.108969]

36 **de Oliveira PVAG**, de Moura DTH, Ribeiro IB, Bazarbashi AN, Franzini TAP, Dos Santos MEL, Bernardo WM, de Moura EGH. Efficacy of digital single-operator cholangioscopy in the visual interpretation of indeterminate biliary strictures: a systematic review and meta-analysis. *Surg Endosc* 2020; **34**: 3321-3329 [PMID: 32342216 DOI: 10.1007/s00464-020-07583-8]

37 **Almadi MA**, Itoi T, Moon JH, Goenka MK, Seo DW, Rerknimitr R, Lau JY, Maydeo AP, Lee JK, Nguyen NQ, Niaz SK, Sud R, Ang TL, Aljebreen A, Devereaux BM, Kochhar R, Reichenberger J, Yasuda I, Kaffes AJ, Kitano M, Peetermans J, Goswamy PG, Rousseau MJ, Reddy DN, Lakhtakia S, Lee YN, Rai VK, Kamada K, Tanaka R, Tonozuka R, Tsuchida A, Song TJ, Ramchandani MK; SpyGlass AMEA Registry Group. Using single-operator cholangioscopy for endoscopic evaluation of indeterminate biliary strictures: results from a large multinational registry. *Endoscopy* 2020; **52**: 574-582 [PMID: 32289852 DOI: 10.1055/a-1135-8980]

38 **Kaura K**, Sawas T, Bazerbachi F, Storm AC, Martin JA, Gores GJ, Abu Dayyeh BK, Topazian MD, Levy MJ, Petersen BT, Chandrasekhara V. Cholangioscopy Biopsies Improve Detection of Cholangiocarcinoma When Combined with Cytology and FISH, but Not in Patients with PSC. *Dig Dis Sci* 2020; **65**: 1471-1478 [PMID: 31571103 DOI: 10.1007/s10620-019-05866-2]

39 **de Vries AB**, van der Heide F, Ter Steege RWF, Koornstra JJ, Buddingh KT, Gouw ASH, Weersma

RK. Limited diagnostic accuracy and clinical impact of single-operator peroral cholangioscopy for indeterminate biliary strictures. *Endoscopy* 2020; **52**: 107-114 [PMID: 31858509 DOI: 10.1055/a-1061-7067]

40 **Robles-Medranda C**, Valero M, Soria-Alcivar M, Puga-Tejada M, Oleas R, Ospina-Arboleda J, Alvarado-Escobar H, Baquerizo-Burgos J, Robles-Jara C, Pitanga-Lukashok H. Reliability and accuracy of a novel classification system using peroral cholangioscopy for the diagnosis of bile duct lesions. *Endoscopy* 2018; **50**: 1059-1070 [PMID: 29954008 DOI: 10.1055/a-0607-2534]

41 **Gerges C**, Beyna T, Tang RSY, Bahin F, Lau JYW, van Geenen E, Neuhaus H, Nageshwar Reddy D, Ramchandani M. Digital single-operator peroral cholangioscopy-guided biopsy sampling *vs* ERCP-guided brushing for indeterminate biliary strictures: a prospective, randomized, multicenter trial (with video). *Gastrointest Endosc* 2020; **91**: 1105-1113 [PMID: 31778656 DOI: 10.1016/j.gie.2019.11.025]

42 **Sethi A**, Tyberg A, Slivka A, Adler DG, Desai AP, Sejpal DV, Pleskow DK, Bertani H, Gan SI, Shah R, Arnelo U, Tarnasky PR, Banerjee S, Itoi T, Moon JH, Kim DC, Gaidhane M, Raijman I, Peterson BT, Gress FG, Kahaleh M. Digital Single-operator Cholangioscopy (DSOC) Improves Interobserver Agreement (IOA) and Accuracy for Evaluation of Indeterminate Biliary Strictures: The Monaco Classification. *J Clin Gastroenterol* 2020 [PMID: 32040050 DOI: 10.1097/MCG.0000000000001321]

43 **Wen LJ**, Chen JH, Xu HJ, Yu Q, Liu K. Efficacy and Safety of Digital Single-Operator Cholangioscopy in the Diagnosis of Indeterminate Biliary Strictures by Targeted Biopsies: A Systematic Review and Meta-Analysis. *Diagnostics (Basel)* 2020; **10** [PMID: 32887436 DOI: 10.3390/diagnostics10090666]

44 **Bang JY**, Navaneethan U, Hasan M, Sutton B, Hawes R, Varadarajulu S. Optimizing Outcomes of Single-Operator Cholangioscopy-Guided Biopsies Based on a Randomized Trial. *Clin Gastroenterol Hepatol* 2020; **18**: 441-448.e1 [PMID: 31351135 DOI: 10.1016/j.cgh.2019.07.035]

45 **Pereira P**, Santos S, Morais R, Gaspar R, Rodrigues-Pinto E, Vilas-Boas F, Macedo G. Role of Peroral Cholangioscopy for Diagnosis and Staging of Biliary Tumors. *Dig Dis* 2020; **38**: 431-440 [PMID: 31940612 DOI: 10.1159/000504910]

46 **ASGE Technology Committee**. Komanduri S, Thosani N, Abu Dayyeh BK, Aslanian HR, Enestvedt BK, Manfredi M, Maple JT, Navaneethan U, Pannala R, Parsi MA, Smith ZL, Sullivan SA, Banerjee S. Cholangiopancreatoscopy. *Gastrointest Endosc* 2016; **84**: 209-221 [PMID: 27236413 DOI: 10.1016/j.gie.2016.03.013]

47 **Turowski F**, Hügle U, Dormann A, Bechtler M, Jakobs R, Gottschalk U, Nötzel E, Hartmann D, Lorenz A, Kolligs F, Veltzke-Schlieker W, Adler A, Becker O, Wiedenmann B, Bürgel N, Tröger H, Schumann M, Daum S, Siegmund B, Bojarski C. Diagnostic and therapeutic single-operator cholangiopancreatoscopy with SpyGlassDS™: results of a multicenter retrospective cohort study. *Surg Endosc* 2018; **32**: 3981-3988 [PMID: 29532224 DOI: 10.1007/s00464-018-6141-0]

48 **Deprez PH**, Garces Duran R, Moreels T, Furneri G, Demma F, Verbeke L, Van der Merwe SW, Laleman W. The economic impact of using single-operator cholangioscopy for the treatment of difficult bile duct stones and diagnosis of indeterminate bile duct strictures. *Endoscopy* 2018; **50**: 109-118 [PMID: 29172216 DOI: 10.1055/s-0043-121268]

49 **Scheiman JM**, Carlos RC, Barnett JL, Elta GH, Nostrant TT, Chey WD, Francis IR, Nandi PS. Can endoscopic ultrasound or magnetic resonance cholangiopancreatography replace ERCP in patients with suspected biliary disease? *Am J Gastroenterol* 2001; **96**: 2900-2904 [PMID: 11693324 DOI: 10.1111/j.1572-0241.2001.04245.x]

50 **Sadeghi A**, Mohamadnejad M, Islami F, Keshtkar A, Biglari M, Malekzadeh R, Eloubeidi MA. Diagnostic yield of EUS-guided FNA for malignant biliary stricture: a systematic review and meta-analysis. *Gastrointest Endosc* 2016; **83**: 290-8.e1 [PMID: 26422979 DOI: 10.1016/j.gie.2015.09.024]

51 **Zaheer A**, Anwar MM, Donohoe C, O'Keeffe S, Mushtaq H, Kelleher B, Clarke E, Kirca M, McKiernan S, Mahmud N, Keeling N, MacMathuna P, O'Toole D. The diagnostic accuracy of endoscopic ultrasound in suspected biliary obstruction and its impact on endoscopic retrograde cholangiopancreatography burden in real clinical practice: a consecutive analysis. *Eur J Gastroenterol Hepatol* 2013; **25**: 850-857 [PMID: 23411866 DOI: 10.1097/MEG.0b013e32835ee5d0]

52 **de Moura DTH**, Ryou M, de Moura EGH, Ribeiro IB, Bernardo WM, Thompson CC. Endoscopic Ultrasound-Guided Fine Needle Aspiration and Endoscopic Retrograde Cholangiopancreatography-Based Tissue Sampling in Suspected Malignant Biliary Strictures: A Meta-Analysis of Same-Session Procedures. *Clin Endosc* 2020; **53**: 417-428 [PMID: 31684700 DOI: 10.5946/ce.2019.053]

53 **Jo JH**, Cho CM, Jun JH, Chung MJ, Kim TH, Seo DW, Kim J, Park DH; Research Group for Endoscopic Ultrasonography in KSGE. Same-session endoscopic ultrasound-guided fine needle aspiration and endoscopic retrograde cholangiopancreatography-based tissue sampling in suspected malignant biliary obstruction: A multicenter experience. *J Gastroenterol Hepatol* 2019; **34**: 799-805 [PMID: 30378169 DOI: 10.1111/jgh.14528]

54 **Nakagawa T**, Kamiyama T, Kurauchi N, Matsushita M, Nakanishi K, Kamachi H, Kudo T, Todo S. Number of lymph node metastases is a significant prognostic factor in intrahepatic cholangiocarcinoma. *World J Surg* 2005; **29**: 728-733 [PMID: 15880276 DOI: 10.1007/s00268-005-7761-9]

55 **Lee YN**, Moon JH, Choi HJ, Kim HK, Lee HW, Lee TH, Choi MH, Cha SW, Cho YD, Park SH. Tissue acquisition for diagnosis of biliary strictures using peroral cholangioscopy or endoscopic ultrasound-guided fine-needle aspiration. *Endoscopy* 2019; **51**: 50-59 [PMID: 30184609 DOI: 10.1055/a-0645-1395]

56 **Malikowski T**, Levy MJ, Gleeson FC, Storm AC, Vargas EJ, Topazian MD, Abu Dayyeh BK, Iyer PG, Rajan E, Gores GJ, Roberts LR, Chandrasekhara V. Endoscopic Ultrasound/Fine Needle Aspiration Is Effective for Lymph Node Staging in Patients With Cholangiocarcinoma. *Hepatology* 2020; **72**: 940-948 [PMID: 31860935 DOI: 10.1002/hep.31077]

57 **Tabibian JH**, Visrodia KH, Levy MJ, Gostout CJ. Advanced endoscopic imaging of indeterminate biliary strictures. *World J Gastrointest Endosc* 2015; **7**: 1268-1278 [PMID: 26675379 DOI: 10.4253/wjge.v7.i18.1268]

58 **Sun B**, Hu B. The role of intraductal ultrasonography in pancreatobiliary diseases. *Endosc Ultrasound* 2016; **5**: 291-299 [PMID: 27803901 DOI: 10.4103/2303-9027.191607]

59 **Chen L**, Lu Y, Wu JC, Bie L, Xia L, Gong B. Diagnostic Utility of Endoscopic Retrograde Cholangiography/Intraductal Ultrasound (ERC/IDUS) in Distinguishing Malignant from Benign Bile Duct Obstruction. *Dig Dis Sci* 2016; **61**: 610-617 [PMID: 26423079 DOI: 10.1007/s10620-015-3896-1]

60 **Kim HS**, Moon JH, Lee YN, Choi HJ, Lee HW, Kim HK, Lee TH, Choi MH, Cha SW, Cho YD, Park SH. Prospective Comparison of Intraductal Ultrasonography-Guided Transpapillary Biopsy and Conventional Biopsy on Fluoroscopy in Suspected Malignant Biliary Strictures. *Gut Liver* 2018; **12**: 463-470 [PMID: 29409305 DOI: 10.5009/gnl17205]

61 **Dumonceau JM**, Tringali A, Papanikolaou IS, Blero D, Mangiavillano B, Schmidt A, Vanbiervliet G, Costamagna G, Devière J, García-Cano J, Gyökeres T, Hassan C, Prat F, Siersema PD, van Hooft JE. Endoscopic biliary stenting: indications, choice of stents, and results: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline - Updated October 2017. *Endoscopy* 2018; **50**: 910-930 [PMID: 30086596 DOI: 10.1055/a-0659-9864]

62 **Zheng X**, Wu J, Sun B, Wu YC, Bo ZY, Wan W, Gao DJ, Hu B. Clinical outcome of endoscopic covered metal stenting for resolution of benign biliary stricture: Systematic review and meta-analysis. *Dig Endosc* 2017; **29**: 198-210 [PMID: 27681297 DOI: 10.1111/den.12742]

63 **Larghi A**, Tringali A, Rimbaş M, Barbaro F, Perri V, Rizzatti G, Gasbarrini A, Costamagna G. Endoscopic Management of Benign Biliary Strictures After Liver Transplantation. *Liver Transpl* 2019; **25**: 323-335 [PMID: 30329213 DOI: 10.1002/lt.25358]

64 **Sato T**, Kogure H, Nakai Y, Ishigaki K, Hakuta R, Saito K, Saito T, Takahara N, Hamada T, Mizuno S, Tada M, Isayama H, Koike K. A prospective study of fully covered metal stents for different types of refractory benign biliary strictures. *Endoscopy* 2020; **52**: 368-376 [PMID: 32092770 DOI: 10.1055/a-1111-8666]

65 **Stark A**, Hines OJ. Endoscopic and operative palliation strategies for pancreatic ductal adenocarcinoma. *Semin Oncol* 2015; **42**: 163-176 [PMID: 25726060 DOI: 10.1053/j.seminoncol.2014.12.014]

66 **Nennstiel S**, Weber A, Frick G, Haller B, Meining A, Schmid RM, Neu B. Drainage-related Complications in Percutaneous Transhepatic Biliary Drainage: An Analysis Over 10 Years. *J Clin Gastroenterol* 2015; **49**: 764-770 [PMID: 25518004 DOI: 10.1097/MCG.0000000000000275]

67 **Giovannini M**, Moutardier V, Pesenti C, Bories E, Lelong B, Delpero JR. Endoscopic ultrasound-guided bilioduodenal anastomosis: a new technique for biliary drainage. *Endoscopy* 2001; **33**: 898-900 [PMID: 11571690 DOI: 10.1055/s-2001-17324]

68 **Kunda R**, Pérez-Miranda M, Will U, Ullrich S, Brenke D, Dollhopf M, Meier M, Larghi A. EUS-guided choledochoduodenostomy for malignant distal biliary obstruction using a lumen-apposing fully covered metal stent after failed ERCP. *Surg Endosc* 2016; **30**: 5002-5008 [PMID: 26969661 DOI: 10.1007/s00464-016-4845-6]

69 **Baniya R**, Upadhaya S, Madala S, Subedi SC, Shaik Mohammed T, Bachuwa G. Endoscopic ultrasound-guided biliary drainage *vs* percutaneous transhepatic biliary drainage after failed endoscopic retrograde cholangiopancreatography: a meta-analysis. *Clin Exp Gastroenterol* 2017; **10**: 67-74 [PMID: 28408850 DOI: 10.2147/CEG.S132004]

70 **Sportes A**, Camus M, Greget M, Leblanc S, Coriat R, Hochberger J, Chaussade S, Grabar S, Prat F. Endoscopic ultrasound-guided hepaticogastrostomy *versus* percutaneous transhepatic drainage for malignant biliary obstruction after failed endoscopic retrograde cholangiopancreatography: a retrospective expertise-based study from two centers. *Therap Adv Gastroenterol* 2017; **10**: 483-493 [PMID: 28567118 DOI: 10.1177/1756283X17702096]

71 **Dhindsa BS**, Mashiana HS, Dhaliwal A, Mohan BP, Jayaraj M, Sayles H, Singh S, Ohning G, Bhat I, Adler DG. EUS-guided biliary drainage: A systematic review and meta-analysis. *Endosc Ultrasound* 2020; **9**: 101-109 [PMID: 32295967 DOI: 10.4103/eus.eus_80_19]

72 **Binmoeller KF**, Shah J. A novel lumen-apposing stent for transluminal drainage of nonadherent extraintestinal fluid collections. *Endoscopy* 2011; **43**: 337-342 [PMID: 21264800 DOI: 10.1055/s-0030-1256127]

73 **Anderloni A**, Fugazza A, Troncone E, Auriemma F, Carrara S, Semeraro R, Maselli R, Di Leo M, D'Amico F, Sethi A, Repici A. Single-stage EUS-guided choledochoduodenostomy using a lumen-apposing metal stent for malignant distal biliary obstruction. *Gastrointest Endosc* 2019; **89**: 69-76 [PMID: 30189198 DOI: 10.1016/j.gie.2018.08.047]

74 **Jacques J**, Privat J, Pinard F, Fumex F, Chaput U, Valats JC, Cholet F, Jezequel J, Grandval P, Legros R, Lepetit H, Albouys J, Napoleon B. EUS-guided choledochoduodenostomy by use of electrocautery-enhanced lumen-apposing metal stents: a French multicenter study after implementation of the technique (with video). *Gastrointest Endosc* 2020; **92**: 134-141 [PMID: 32084411 DOI: 10.1016/j.gie.2020.01.055]

75 **Larghi A**, Rimbaș M, Tringali A, Boškoski I, Rizzatti G, Costamagna G. Endoscopic radiofrequency biliary ablation treatment: A comprehensive review. *Dig Endosc* 2019; **31**: 245-255 [PMID: 30444547 DOI: 10.1111/den.13298]

76 **Inoue T**, Ibusuki M, Kitano R, Kobayashi Y, Ohashi T, Nakade Y, Sumida Y, Ito K, Yoneda M. Endobiliary radiofrequency ablation combined with bilateral metal stent placement for malignant hilar biliary obstruction. *Endoscopy* 2020; **52**: 595-599 [PMID: 32208498 DOI: 10.1055/a-1133-4448]

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ORIGINAL ARTICLE

Retrospective Cohort Study

Clinical impact of gastrointestinal endoscopy on the early detection of pharyngeal squamous cell carcinoma: A retrospective cohort study

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Abstract

BACKGROUND

In recent years, with the growing availability of image-enhanced gastrointestinal endoscopy, gastroenterologists have contributed to the early detection of pharyngeal squamous cell carcinomas (SCC).

AIM

To clarify the clinical characteristics of pharyngeal SCCs detected by gastrointestinal endoscopy.

METHODS

This is a retrospective cohort study conducted in a single-center, a university hospital in Japan. We retrospectively assessed the clinical records of 522 consecutive patients with oropharyngeal or hypopharyngeal SCC who were

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examined in our hospital between 2011 and 2018. The lesions were classified into two groups: Group GE (detected by gastrointestinal endoscopy) and Group non-GE (detected by means other than gastrointestinal endoscopy). The clinical characteristics were compared between the two groups. Continuous data were compared using the Mann–Whitney *U* test. Pearson's χ^2 test or Fisher's exact test was used to analyze the categorical data and compare proportions. The Kaplan–Meier method was used to estimate the cumulative patient survival rates.

RESULTS

In our study group, the median age was 65 years and 474 patients (90.8%) were male. One hundred and ninety-six cases (37.5%) involved the oropharynx and 326 cases (62.5%) involved the hypopharynx. Three hundred and ninety-five cases (75.7%) had some symptoms at the time of diagnosis. One hundred and forty-five (27.8%) cases had concurrent ESCC or a history of ESCC. One hundred and sixty-four (31.4%) cases were detected by gastrointestinal endoscopy and classified as Group GE. The proportions of asymptomatic cases, cTis-1 cases and cases with no lymph node metastasis were significantly higher in Group GE than Group non-GE (61.6% *vs* 7.3%, $P < 0.001$, 32.9% *vs* 12.0%, $P < 0.001$ and 69.5% *vs* 19.0%, $P < 0.001$). Endoscopic laryngo-pharyngeal surgery or endoscopic submucosal dissection were performed in only 0.6% of the lesions in Group non-GE but in 21.3% of the lesions in Group GE ($P < 0.001$). Overall survival was significantly longer in Group GE than in Group non-GE ($P = 0.018$). The 2-year and 4-year survival rates were 82.5% and 70.7% in Group GE, and 71.5% and 59.0% in Group non-GE, respectively.

CONCLUSION

Gastrointestinal endoscopy plays an important role in the early detection and improving the prognosis of pharyngeal SCCs.

Key Words: Gastrointestinal imaging; Head and neck imaging; Gastrointestinal endoscope; Hypopharyngeal neoplasm; Oropharyngeal neoplasm; Endoscopic surgery

Core Tip: This is the first study to explore the detection modality of oropharyngeal and hypopharyngeal squamous cell carcinomas (SCC). In this study, 31.4% of pharyngeal SCCs (15.4% of oropharyngeal SCCs and 42.3% of hypopharyngeal SCCs) were detected by gastrointestinal endoscopy. The clinical characteristics of the lesions detected by gastrointestinal endoscopy include a higher proportion of asymptomatic cases, cTis-1 cases, cases with no lymph node metastasis and cases treated by endoscopic laryngo-pharyngeal surgery/endoscopic submucosal dissection, leading to a better prognosis. This study highlights the important role of gastrointestinal endoscopy in the early detection and treatment of SCC in the otolaryngology field.

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INTRODUCTION

The pharynx is the most common site of head and neck cancer and, because pharyngeal cancers are often diagnosed at an advanced stage, the prognosis is poor[1-3]. Standard surgical resection or chemoradiotherapy (CRT) for advanced pharyngeal cancer lesions may severely reduce the patient's quality of life, with disorders of swallowing and speech function. Similar to other gastrointestinal tumors, superficial

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pharyngeal cancer can be treated by minimally invasive endoscopic resection that preserves organ function[4-6]. Therefore, strategies for the detection of pharyngeal cancer at an early stage and treatment with endoscopy, including endoscopic submucosal dissection (ESD) and endoscopic laryngo-pharyngeal surgery (ELPS), are crucial for preserving the quality of life and improving prognosis.

In recent years, image-enhanced endoscopy (IEE) systems, including narrow-band imaging (NBI) and blue laser imaging, have been reported to be useful for the early detection of cancer in the pharynx and esophagus[7,8]. Patients with head-and-neck squamous cell cancer (HNSCC) or esophageal squamous cell carcinoma (SCC) (ESCC) have a high risk of synchronous and metachronous SCCs, which has been recognized as the field cancerization phenomenon[9,10]. Therefore, patients with present or previous HNSCC or ESCC require careful endoscopic observation of the pharynx with IEE[11,12]. In general, pharyngeal cancers have been most often detected by otolaryngologists using rhino-laryngoscopy. Recently, many superficial pharyngeal cancers have been discovered by gastroenterologists, with the growing availability of IEE in gastrointestinal endoscopy. However, few studies have shown how much gastroenterologists contribute to the detection and treatment of pharyngeal cancer.

Previously, we investigated the modalities of detection of superficial hypopharyngeal cancerous lesions (Tis, T1 and T2), treated in our institution, and reported that gastroenterologists detected more hypopharyngeal cancer than otolaryngologists (75.2% to 24.8%)[13]. The aim of this study was to clarify the clinical characteristics of pharyngeal SCCs detected with gastrointestinal endoscopy, including superficial to advanced lesions.

MATERIALS AND METHODS

Patients

In this retrospective study, we assessed the clinical records of consecutive patients with oropharyngeal or hypopharyngeal SCC who underwent a detailed examination, including definitive diagnosis by pathologists and staging based on the TNM classification, in our hospital between January 2011 and December 2018. The first lesion detected during the study period was included in the analysis. If multiple lesions were detected at the same time, the largest lesion was included. We excluded patients who had undergone prior treatment of pharyngeal cancer at another hospital and/or had unspecified details of detection modality. The following data were reviewed retrospectively: The physician who detected the primary lesion (gastroenterologist, otolaryngologist, dentist, general physician), indication for examination of the pharynx, clinical manifestation, age at incidence, sex, tumor location, primary treatment, TNM classification[14], past history of ESCC, patient vital status (alive, deceased, lost to follow-up) and follow-up time.

We defined those with lesions detected by gastrointestinal endoscopy as Group GE and those with lesions detected by means other than gastrointestinal endoscopy (rhino-laryngoscopy or direct visualization by otolaryngologists, dentists and general physicians) as Group non-GE.

The oropharynx was divided into the following four subsites: (1) Anterior wall: Base of tongue; (2) Superior wall: Inferior surface of soft palate and uvula; (3) Lateral wall: Tonsil, tonsillar fossa, and pillars; and (4) Posterior wall. The hypopharynx was divided into the following three subsites: (1) Pyriform sinus; (2) Posterior wall; and (3) Post-cricoid region. We defined the symptomatic group as patients with any one of the following conditions: Sore throat, painful swallowing, pharyngeal discomfort, bleeding, swelling of cervical lymph nodes or hoarseness.

We evaluated the proportion of Group GE among all pharyngeal cancer, the clinical differences between Group GE and Group non-GE, and the trends in proportion of Group GE.

This study was approved by the ethical committee of our hospital and performed in accordance with the ethical principles associated with the Declaration of Helsinki.

Patient and public involvement

Patients and the public were not involved in the design, conduct, reporting, or dissemination of plans of the research.

Statistical analysis

Continuous data were compared using the Mann–Whitney U test. Pearson's χ^2 test or Fisher's exact test were used to analyze the categorical data and compare proportions.

The survival rates of patients were plotted using Kaplan–Meier curves, and the difference was evaluated using the log rank test. Cox regression analysis was used to estimate the hazard ratio and to calculate the 95% confidence interval. SPSS version 21.0 (IBM Corporation, Armonk, NY, United States) was used for all statistical analyses. P values < 0.05 (two-sided) denoted statistically significant differences. The statistical methods of this study were reviewed by our expert biostatistician, Jun Morinaga, MD.

RESULTS

From January 2011 to December 2018, 563 lesions (oropharyngeal and hypopharyngeal SCCs) in 535 patients were examined in our hospital. Of those, 41 lesions and 13 patients were excluded (28 lesions in 26 patients were excluded due to multiple primary lesions; seven lesions in seven patients had been treated at another hospital; and the details of the detection process were not specified for six lesions in six patients). Hence, a total of 522 lesions in 522 patients were enrolled in this study. The median duration of follow-up was 25.8 mo.

The characteristics of the study population are listed in Table 1. The median age was 65 years and 474 patients (90.8%) were male. One hundred and ninety-six cases (37.5%) were in the oropharynx and 326 cases (62.5%) were in the hypopharynx. Three hundred and ninety-five cases (75.7%) had symptoms of some kind at the time of diagnosis. The most common reason for the examination was the investigation of symptoms (71.1%). One hundred and sixty-four (31.4%) cases were detected by gastrointestinal endoscopy (Group GE). Among 358 cases detected other than by gastrointestinal endoscopy (Group non-GE), almost all lesions were detected by otolaryngologists (341 lesions) and the remainder were detected by dentists (14 lesions) and general physicians (three lesions). One hundred and forty-five (27.8%) cases had concurrent ESCC or a history of ESCC.

A comparison between Group GE and Group non-GE is shown in Table 2. There were no significant differences in sex or age. The proportion of symptomatic cases was significantly lower in Group GE (38.4% *vs* 92.7%, P < 0.001). The common reasons for the examination were follow-up or diagnostic work-up for ESCC (39.0%), incidental esophago-gastro-duodenoscopy (EGD) (28.7%) and investigation of symptoms (28.0%) in Group GE and investigation of symptoms (90.8%) in Group non-GE. Incidental EGD included screening for gastric cancer (46.8%), surveillance of gastric cancer (10.6%), investigation of abdominal symptom (10.6%), and others (31.9%). As for the primary site, the proportion of oropharynx lesions was significantly lower in Group GE than Group non-GE (15.9% *vs* 47.5%, P < 0.001). The proportion of lesions with concurrent or a history of ESCC was significantly higher in Group GE than Group non-GE (51.2% *vs* 17.0%, P < 0.001). The proportions of cTis-1 cases and cases with no lymph node metastasis were significantly higher in Group GE than Group non-GE (32.9% *vs* 12.0%, P < 0.001 and 69.5% *vs* 19.0%, P < 0.001). Meanwhile, there were no significant differences in the proportion of cases with distant metastases. As for the modality of treatment, ELSP/ESD was performed in only 0.6% of cases in Group non-GE, while 21.3% of cases in Group GE were treated with ELPS/ESD (P < 0.001). We showed a case of T1 hypopharyngeal cancer located in the left pyriform sinus and detected by gastrointestinal endoscopy with NBI (Figure 1). Under general anesthesia, *en bloc* resection by ESD was successfully completed.

Figure 2 shows the subsite of primary lesions and the proportion of Group GE by subsite. The proportions of Group GE in the oropharynx and hypopharynx were 15.4% and 42.3%, respectively. In the oropharynx, the proportions of Group GE in the anterior (8.0%) and lateral wall (8.5%) were significantly lower than the posterior wall (50.0%). On the other hand, in the hypopharynx, there was no significant difference in the proportion of Group GE by subsite.

Figure 3A shows a comparison of the proportion of Group GE between the first and second half periods (2011–2014 and 2015–2018). The proportion of Group GE was significantly larger in the second half period (24.0% *vs* 36.2%, P = 0.004). Consistent with this tendency, the proportion of cTis-1 lesions was significantly higher in the second half period (13.2% *vs* 22.0%, P = 0.015) (Figure 3B).

Kaplan–Meier curves of survival are shown in Figure 4. Overall survival was significantly longer in Group GE than in Group non-GE (HR: 0.63; 95%CI: 0.43-0.93; P = 0.018). The 2-year and 4-year survival rates were 82.5% and 70.7% in Group GE, and 71.5% and 59.0% in Group non-GE, respectively.

Table 1 Characteristics of the study population

	***n* = 522**
Sex, male/female	474 (90.8%)/48
Age, median, yr	65 (37-92)
Location	
Oropharynx	196 (37.5%)
Hypopharynx	326 (62.5%)
Symptomatic/Asymptomatic	395 (75.7%)/127
Indication for examination	
Investigation of symptoms	371 (71.1%)
Incidental EGD	47 (9.0%)
f/u or diagnostic work-up of ESCC	66 (12.6%)
f/u or diagnostic work-up of HN	17 (3.3%)
Incidental dental check	7 (1.3%)
Other	14 (2.7%)
Detected by GE/non-GE	164 (31.4%)/358
cTis-1/2/3/4	97 (18.6%)/177/102/146
cN -/+	182 (34.9%)/340
cM -/+	504 (96.6%)/18
Concurrent or history of ESCC y/n	145 (27.8%)/377

Summary of continuous variables, indicated as median and interquartile ranges. Categorical variables are indicated as the number of subjects and percentages. EGD: Esophagogastroduodenoscopy; f/u: Follow-up; ESCC: Esophageal squamous cell carcinoma; HN: Head and neck cancer; GE: Gastrointestinal endoscopy.

DISCUSSION

This study investigated the impact of gastrointestinal endoscopy on the detection of pharyngeal SCC. Of total 522 lesions, 164 (31.4%) in Group GE had a higher proportion of asymptomatic cases, cTis-1 cases, cases with no lymph node metastasis and cases treated by ELPS/ESD than Group non-GE, leading to a better prognosis. To the best of our knowledge, this is the first study to explore the detection modality of oropharyngeal and hypopharyngeal SCC in a large number of cases.

Until the advent of NBI, gastrointestinal endoscopists were unable to observe the pharynx in detail, thereby posing a challenge to the detection of pharyngeal cancer using gastrointestinal endoscopy. In 2010, the usefulness of NBI for the early detection of cancer in the pharynx was reported. Muto *et al*[7] conducted a multicenter, prospective, randomized controlled trial; 320 patients with ESCC were randomly assigned to primary white light imaging (WLI) followed by NBI or primary NBI followed by WLI in a back-to-back fashion. They reported that the sensitivity and accuracy were significantly higher in the NBI-first group than the WLI-first group in both the head and neck region and the esophagus (100% *vs* 7.7%; $P < 0.001$ for sensitivity, 85.7% *vs* 62.9%; $P = 0.02$ for accuracy, respectively). In a study of 424 consecutive patients subjected to surveillance endoscopy who had previously undergone CRT and/or surgery for esophageal SCC, Nonaka *et al*[15] reported that the detection rate for pharyngeal cancer was significantly higher when using NBI endoscopy with magnification (10.9%) compared with conventional endoscopy (1.2%) ($P < 0.0001$). Following these reports, careful endoscopic observation of the pharynx with IEE for patients with ESCCs became gradually popular among Japanese gastroenterologists[11,12,16,17]. These observations revealed the usefulness of gastrointestinal endoscopy for the detection of pharyngeal cancer among patients with esophageal SCC. However, the proportion and clinical characteristics of the lesions detected by gastrointestinal endoscopy among patients with pharyngeal cancer remained unclear. The advantage of the present study is to elucidate the clinical characteristics of

Table 2 Comparison between Group gastrointestinal endoscopy and Group non- gastrointestinal endoscopy

	Group GE *n* = 164	Group non-GE *n* = 358	*P* value
Sex, male	153 (93.3%)	321 (89.7%)	0.197
Age, median, yr	68 (42–90)	67 (37–92)	0.278
Asymptomatic/Symptomatic	101 (61.6%)/63 (38.4%)	26 (7.3%)/332 (92.7%)	< 0.001
Indication for examination			< 0.001
Investigation of symptoms	46 (28.0%)	325 (90.8%)	
Incidental EGD	47 (28.7%)	0	
f/u or diagnostic work-up of ESCC	64 (39.0%)	2 (0.6%)	
f/u or diagnostic work-up of HN	7 (4.3%)	10 (2.8%)	
Incidental dental check	0	7 (2.0%)	
Other	0	14 (3.9%)	
Location oropharynx/hypopharynx	26 (15.9 %)/138 (84.1%)	170 (47.5%)/188 (52.5%)	< 0.001
History or concurrent of ESCC, y/n	84 (51.2%)/80	61 (17.0%)/297	< 0.001
cTis-1/cT2-4	54 (32.9%)/110	43 (12.0%)/315	< 0.001
cN -/+	114 (69.5%)/50	68 (19.0%)/290	< 0.001
cM -/+	161 (98.2%)/3	343 (95.8%)/15	0.205
Treatment			
ELPS/ESD	35 (21.3%)	2 (0.6%)	< 0.001
Non-ELPS/ESD	129 (78.7%)	356 (99.4%)	
Surgery	23 (14.0%)	79 (22.1%)	
RT/CRT	84 (51.2%)	212 (59.2%)	
Chemotherapy	5 (3.0%)	13 (3.6%)	
BSC	9 (5.5%)	40 (11.2%)	
Unknown	8 (4.9%)	12 (3.4%)	

Continuous variables, indicated as the median and interquartile range. Categorical variables are indicated as the number of subjects and percentage. EGD: Esophagogastroduodenoscopy; f/u: Follow up; ESCC: Esophageal squamous cell carcinoma; HN: Head and neck cancer; ESD: Endoscopic submucosal dissection; ELPS: Endoscopic laryngo-pharyngeal surgery; GE: Gastrointestinal endoscopy; RT: Radiotherapy; CRT: Chemoradiotherapy; BSC: Best supportive care.

pharyngeal SCCs detected by gastrointestinal endoscopy.

A recent systematic review and meta-analysis revealed that the prevalence of head and neck second primary tumors in patients with ESCC was 6.7%, and 60% of all head and neck second primary tumors were located in the hypopharynx, with 18% in the oropharynx[18]. In our study, the percentage of concurrent ESCC or with a history of ESCC was 27.8%. Considering these data, the careful endoscopic observation of the pharynx of patients with present or previous ESCC is efficient, but it is insufficient because 70.7% of pharyngeal SCCs were not relevant to ESCCs. In Group non-GE, 92.7% of cases were symptomatic and only 0.6% of cases were treated by ELPS/ESD. The problem appears to be that patients do not visit hospital and receive an otolaryngology examination unless the cancer has progressed to a symptomatic stage. On the other hand, in Group GE, only 38.4% of cases were symptomatic and the proportion of cases treated by ELPS/ESD was significantly higher (21.3%) than Group non-GE. It is important to detect pharyngeal SCCs with gastrointestinal endoscopy while patients remain asymptomatic for further improvement in prognosis and preservation of function. On this basis, we should not pass through the pharynx without due caution in patients with risk factors (*e.g.*, smoking, alcohol consumption), even if they have no history of ESCC and no symptoms. In the present study, pharyngeal cancer was detected in hospitals, as well as clinics and health examination centers. Moreover, the numbers of lesions detected by gastrointestinal endoscopy have been increasing (Figure 3). Furthermore, due to advances in endoscopic treatment, we have been able

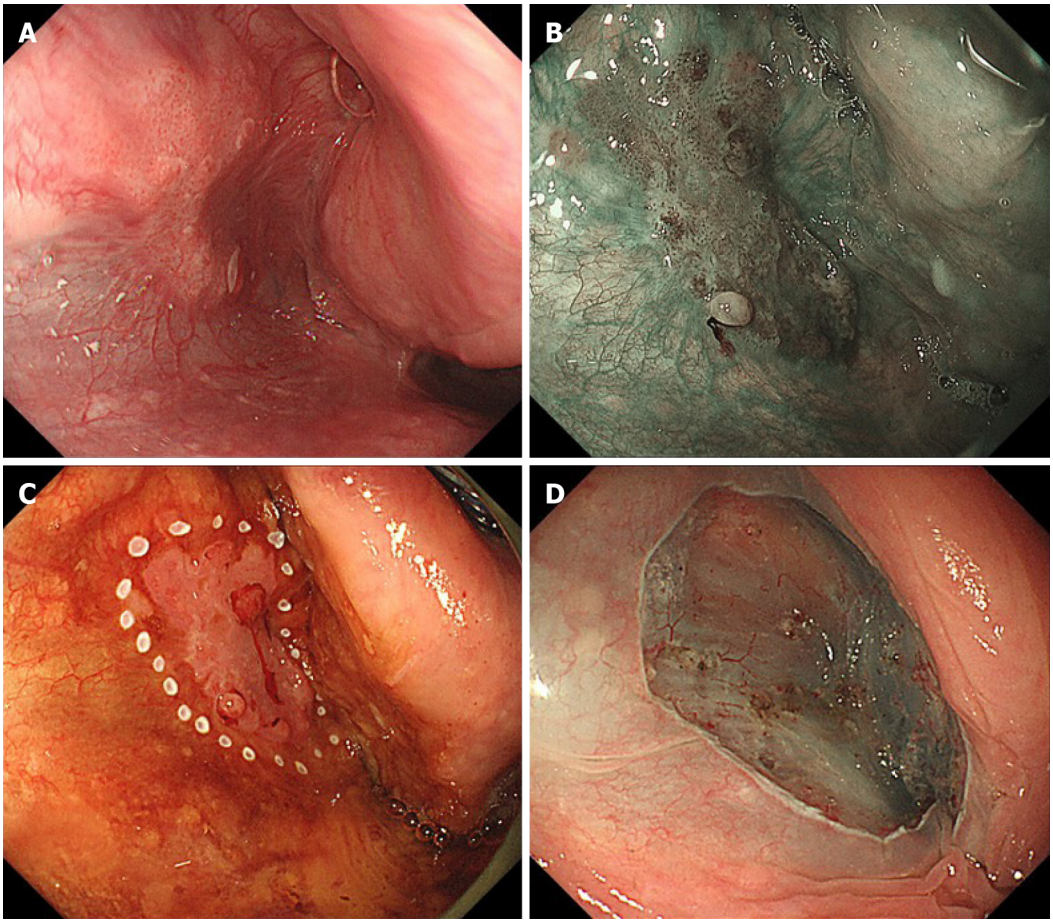

Figure 1 A case of T1 hypopharyngeal cancer located in the left pyriform sinus, detected by gastrointestinal endoscopy. A: The lesion was recognized as a slightly reddish area under white light image endoscopy; B: The lesion was clearly visualized using narrow-band imaging; C, D: Under general anesthesia, *en bloc* endoscopic submucosal dissection was successfully completed.

to remove superficial pharyngeal lesions by ELPS/ESD, without impairment of pharyngeal function[19,20]. We emphasize that gastrointestinal endoscopists can improve the prognosis of patients with pharyngeal cancer by careful observation of the pharynx in routine clinical practice, and should take a more active role both in the detection and treatment of this type of cancer.

In our study, the proportions of lesions in the anterior and lateral wall of oropharynx were extremely low in Group GE (7.8% and 8.5%, respectively). One of the reasons is that the lateral and anterior walls of the oropharynx are anatomically difficult to observe using transoral endoscopy, so even advanced cancer may be easily missed if the endoscope is passed too quickly through the oropharynx[21]. The other cause is possibly related to human papillomavirus (HPV). HPV infection has been identified as a risk factor for oropharyngeal SCCs, especially involving the tonsils and base of the tongue[22]. Because HPV infects the basal layer of the tonsillar crypt, cancer arises from the deeper areas and is not always exposed at the luminal surface at an early stage. Thus, endoscopic diagnosis tends to be difficult compared to HPV-unrelated pharyngeal SCCs[23]. In this study, we were not able to show the percentage of HPV-related cancer due to insufficient data. Although early pharyngeal cancers were detected mostly by gastroenterologists, considering that some lesions are difficult to detect with gastrointestinal endoscopy, pharyngeal examination conducted by otolaryngologists and gastroenterologists in cooperation will be required for further improvement of cancer detection.

There were some limitations in the present study. Firstly, it is a retrospective review of hospital records from a single center. Therefore, the history of gastrointestinal endoscopic examination was uncertain in Group non-GE and we could not determine how often gastroenterologists had missed the pharyngeal lesions. Furthermore, we could not survey the experiences of individual physicians or the accessibility to gastrointestinal endoscopy and otolaryngology services in individual residential areas. In the future, a prospective study should be designed to address this subject. Secondly, there was referral filter bias because almost all ELPS/ESD cases were treated in our

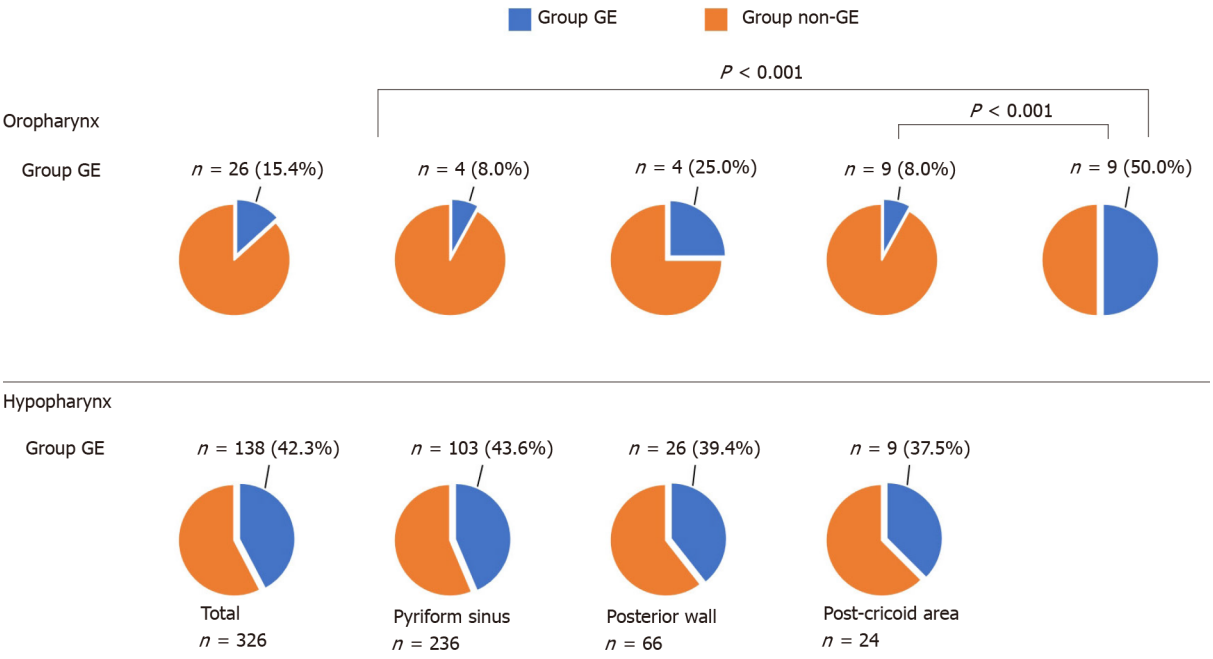

Figure 2 The subsites of primary lesions and the proportion of Group gastrointestinal endoscopy by subsite. The proportions of Group gastrointestinal endoscopy (GE) in the oropharynx and hypopharynx were 15.4% and 42.3%, respectively. Among the lesions in the oropharynx, the proportions of Group GE in the anterior and lateral wall were lower than the posterior wall. There was no significant difference in the proportion of Group GE by subsite in the hypopharynx.

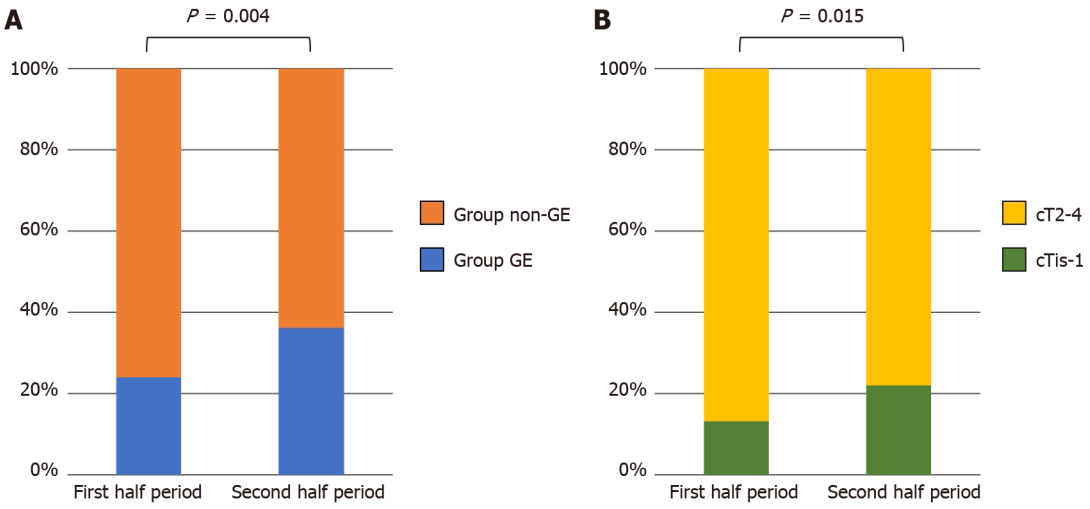

Figure 3 Trends in the detection modality and clinical stage of pharyngeal cancer. A: A comparison of the proportion of Group gastrointestinal endoscopy between the first and second half periods (2011–2014 and 2015–2018); B: A comparison of the proportion of cTis-1 lesions between first and second half periods (2011–2014 and 2015–2018). Group GE: Group gastrointestinal endoscopy.

hospital in Kumamoto prefecture. This would increase the proportion of Group GE. However, as our hospital is the only university hospital in Kumamoto prefecture, most advanced cases which required surgery or CRT were referred here, as well as ELPS/ESD cases, and we consider our data represent the current situation in Kumamoto prefecture.

CONCLUSION

Gastrointestinal endoscopy is playing an increasingly important role in the detection of pharyngeal SCCs, considering that 31.4% of all cases and almost all asymptomatic cases were detected by gastrointestinal endoscopy. For preserving the quality of life

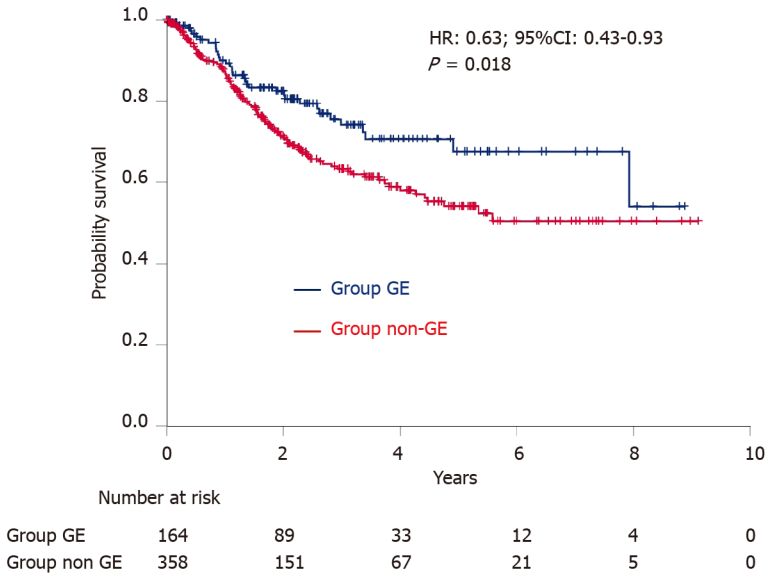

Figure 4 Kaplan–Meier estimates of overall survival. HR: Hazard ratio; CI: Confidence interval; GE: Gastrointestinal endoscopy.

and improving the prognosis of pharyngeal SCCs, it is important to detect the lesions using gastrointestinal endoscopy, while they are asymptomatic.

ARTICLE HIGHLIGHTS

Research background

Recently, many pharyngeal cancers have been discovered by gastroenterologists, with the growing availability of image enhanced endoscopy in gastrointestinal endoscopy. However, few studies have shown how much gastroenterologists contribute to the detection and treatment of pharyngeal cancer. In particular, the details of the lesions detected by the gastrointestinal endoscopy are unknown.

Research motivation

To highlight that gastrointestinal endoscopists should take a more active role both in the detection and treatment of pharyngeal cancer.

Research objectives

To clarify the importance of gastrointestinal endoscopy in detection and treatment of pharyngeal cancer.

Research methods

In this retrospective cohort study, the authors assessed the clinical records of consecutive 522 patients with oropharyngeal or hypopharyngeal cancer in our hospital between January 2011 and December 2018. The lesions were classified into two groups: Group GE (detected by gastrointestinal endoscopy) and Group non-GE (detected by means other than gastrointestinal endoscopy), and the clinical characteristics were compared between the two groups.

Research results

Of total 522 lesions, 164 (31.4%) in Group GE had a higher proportion of asymptomatic cases (61.6% *vs* 7.3%, $P < 0.001$), cTis-1 cases (32.9% *vs* 12.0%, $P < 0.001$), cases with no lymph node metastasis (69.5% *vs* 19.0%, $P < 0.001$) and cases treated by endoscopic laryngo-pharyngeal surgery/endoscopic submucosal dissection (21.3% *vs* 0.6%, $P < 0.001$) than Group non-GE, leading to a better prognosis.

Research conclusions

To the best of our knowledge, this is the first study to explore the detection modality of oropharyngeal and hypopharyngeal squamous cell carcinomas (SCC) in a large number of cases. Gastrointestinal endoscopy plays an important role in the early

detection and improving the prognosis of pharyngeal SCCs.

Research perspectives

In the future, a multicenter prospective study should be designed in a set up where equal accessibility to gastrointestinal endoscopy and otolaryngology services is available.

REFERENCES

1 **Wahlberg PC**, Andersson KE, Biörklund AT, Möller TR. Carcinoma of the hypopharynx: analysis of incidence and survival in Sweden over a 30-year period. *Head Neck* 1998; **20**: 714-719 [PMID: 9790293 DOI: 10.1002/(sici)1097-0347(199812)20:8<714::aid-hed9>3.0.co;2-2]

2 **Eckel HE**, Staar S, Volling P, Sittel C, Damm M, Jungehuelsing M. Surgical treatment for hypopharynx carcinoma: feasibility, mortality, and results. *Otolaryngol Head Neck Surg* 2001; **124**: 561-569 [PMID: 11337663 DOI: 10.1067/mhn.2001.115060]

3 **Rikitake R**, Ando M, Saito Y, Yoshimoto S, Yamasoba T, Higashi T. Current status of superficial pharyngeal squamous cell carcinoma in Japan. *Int J Clin Oncol* 2017; **22**: 826-833 [PMID: 28501947 DOI: 10.1007/s10147-017-1135-9]

4 **Hanaoka N**, Ishihara R, Takeuchi Y, Suzuki M, Uemura H, Fujii T, Yoshino K, Uedo N, Higashino K, Ohta T, Kanzaki H, Hanafusa M, Nagai K, Matsui F, Iishi H, Tatsuta M, Tomita Y. Clinical outcomes of endoscopic mucosal resection and endoscopic submucosal dissection as a transoral treatment for superficial pharyngeal cancer. *Head Neck* 2013; **35**: 1248-1254 [PMID: 22941930 DOI: 10.1002/hed.23106]

5 **Hanaoka N**, Ishihara R, Takeuchi Y, Suzuki M, Otozai S, Kida K, Yoshii T, Fujii T, Yoshino K, Sugawa T, Kitamura K, Kanemura R, Koike R, Uedo N, Higashino K, Akasaka T, Yamashina T, Kanesaka T, Matsuura N, Aoi K, Yamasaki Y, Hamada K, Iishi H, Tomita Y. Endoscopic submucosal dissection as minimally invasive treatment for superficial pharyngeal cancer: a phase II study (with video). *Gastrointest Endosc* 2015; **82**: 1002-1008 [PMID: 26234696 DOI: 10.1016/j.gie.2015.06.021]

6 **Koritala T**, Zolotarevsky E, Bartley AN, Ellis CD, Krolikowski JA, Burton J, Gunaratnam NT. Efficacy and safety of the band and slough technique for endoscopic therapy of nonampullary duodenal adenomas: a case series. *Gastrointest Endosc* 2015; **81**: 985-988 [PMID: 25440288 DOI: 10.1016/j.gie.2014.09.043]

7 **Muto M**, Minashi K, Yano T, Saito Y, Oda I, Nonaka S, Omori T, Sugiura H, Goda K, Kaise M, Inoue H, Ishikawa H, Ochiai A, Shimoda T, Watanabe H, Tajiri H, Saito D. Early detection of superficial squamous cell carcinoma in the head and neck region and esophagus by narrow band imaging: a multicenter randomized controlled trial. *J Clin Oncol* 2010; **28**: 1566-1572 [PMID: 20177025 DOI: 10.1200/JCO.2009.25.4680]

8 **Tomie A**, Dohi O, Yagi N, Kitae H, Majima A, Horii Y, Kitaichi T, Onozawa Y, Suzuki K, Kimura-Tsuchiya R, Okayama T, Yoshida N, Kamada K, Katada K, Uchiyama K, Ishikawa T, Takagi T, Handa O, Konishi H, Naito Y, Itoh Y. Blue Laser Imaging-Bright Improves Endoscopic Recognition of Superficial Esophageal Squamous Cell Carcinoma. *Gastroenterol Res Pract* 2016; **2016**: 6140854 [PMID: 27738428 DOI: 10.1155/2016/6140854]

9 **Slaughter DP**, Southwick HW, Smejkal W. Field cancerization in oral stratified squamous epithelium; clinical implications of multicentric origin. *Cancer* 1953; **6**: 963-968 [PMID: 13094644 DOI: 10.1002/1097-0142(195309)6:5<963::AID-CNCR2820060515>3.0.CO;2-Q]

10 **Katada C**, Yokoyama T, Yano T, Kaneko K, Oda I, Shimizu Y, Doyama H, Koike T, Takizawa K, Hirao M, Okada H, Yoshii T, Konishi K, Yamanouchi T, Tsuda T, Omori T, Kobayashi N, Shimoda T, Ochiai A, Amanuma Y, Ohashi S, Matsuda T, Ishikawa H, Yokoyama A, Muto M. Alcohol Consumption and Multiple Dysplastic Lesions Increase Risk of Squamous Cell Carcinoma in the Esophagus, Head, and Neck. *Gastroenterology* 2016; **151**: 860-869.e7 [PMID: 27492616 DOI: 10.1053/j.gastro.2016.07.040]

11 **Morimoto H**, Yano T, Yoda Y, Oono Y, Ikematsu H, Hayashi R, Ohtsu A, Kaneko K. Clinical impact of surveillance for head and neck cancer in patients with esophageal squamous cell carcinoma. *World J Gastroenterol* 2017; **23**: 1051-1058 [PMID: 28246479 DOI: 10.3748/wjg.v23.i6.1051]

12 **Kato M**, Ishihara R, Hamada K, Tonai Y, Yamasaki Y, Matsuura N, Kanesaka T, Yamamoto S, Akasaka T, Hanaoka N, Takeuchi Y, Higashino K, Uedo N, Iishi H. Endoscopic surveillance of head and neck cancer in patients with esophageal squamous cell carcinoma. *Endosc Int Open* 2016; **4**: E752-E755 [PMID: 27556090 DOI: 10.1055/s-0042-106720]

13 **Kumai Y**, Shono T, Waki K, Murakami D, Miyamaru S, Sasaki Y, Orita Y. Detection of hypopharyngeal cancer (Tis, T1 and T2) by ENT physicians *vs* gastrointestinal endoscopists. *Auris Nasus Larynx* 2020; **47**: 135-140 [PMID: 31153665 DOI: 10.1016/j.anl.2019.05.007]

14 **Amin MB**, Edge S. AJCC Cancer Staging Manual, 8th ed. Springer International Publishing, 2017: XVII, 1032

15 **Nonaka S**, Saito Y, Oda I, Kozu T, Saito D. Narrow-band imaging endoscopy with magnification is useful for detecting metachronous superficial pharyngeal cancer in patients with esophageal squamous cell carcinoma. *J Gastroenterol Hepatol* 2010; **25**: 264-269 [PMID: 19874445 DOI: 10.1111/j.1440-1746.2009.05993.x]

16 **Katada C**, Tanabe S, Koizumi W, Higuchi K, Sasaki T, Azuma M, Katada N, Masaki T, Nakayama M, Okamoto M, Muto M. Narrow band imaging for detecting superficial squamous cell carcinoma of the head and neck in patients with esophageal squamous cell carcinoma. *Endoscopy* 2010; **42**: 185-190 [PMID: 20195988 DOI: 10.1055/s-0029-1243963]

17 **Katada C**, Muto M, Tanabe S, Higuchi K, Sasaki T, Azuma M, Ishido K, Masaki T, Nakayama M, Okamoto M, Koizumi W. Surveillance after endoscopic mucosal resection or endoscopic submucosal dissection for esophageal squamous cell carcinoma. *Dig Endosc* 2013; **25** Suppl 1: 39-43 [PMID: 23480401 DOI: 10.1111/j.1443-1661.2012.01407.x]

18 **van de Ven S**, Bugter O, Hardillo JA, Bruno MJ, Baatenburg de Jong RJ, Koch AD. Screening for head and neck second primary tumors in patients with esophageal squamous cell cancer: A systematic review and meta-analysis. *United European Gastroenterol J* 2019; **7**: 1304-1311 [PMID: 31839955 DOI: 10.1177/2050640619856459]

19 **Iizuka T**, Kikuchi D, Hoteya S, Nakamura M, Yamashita S, Mitani T, Takeda H, Yahagi N. Clinical advantage of endoscopic submucosal dissection over endoscopic mucosal resection for early mesopharyngeal and hypopharyngeal cancers. *Endoscopy* 2011; **43**: 839-843 [PMID: 21833903 DOI: 10.1055/s-0031-1271112]

20 **Tateya I**, Muto M, Morita S, Miyamoto S, Hayashi T, Funakoshi M, Aoyama I, Higuchi H, Hirano S, Kitamura M, Ishikawa S, Kishimoto Y, Morita M, Ito J. Endoscopic laryngo-pharyngeal surgery for superficial laryngo-pharyngeal cancer. *Surg Endosc* 2016; **30**: 323-329 [PMID: 25917165 DOI: 10.1007/s00464-015-4213-y]

21 **Hamada K**, Ishihara R, Yamasaki Y, Akasaka T, Arao M, Iwatsubo T, Shichijo S, Matsuura N, Nakahira H, Kanesaka T, Yamamoto S, Takeuchi Y, Higashino K, Uedo N, Kawahara Y, Okada H. Transoral endoscopic examination of head and neck region. *Dig Endosc* 2018; **30**: 516-521 [PMID: 29637617 DOI: 10.1111/den.13071]

22 **Ramqvist T**, Grün N, Dalianis T. Human papillomavirus and tonsillar and base of tongue cancer. *Viruses* 2015; **7**: 1332-1343 [PMID: 25803099 DOI: 10.3390/v7031332]

23 **Okami K**. Clinical features and treatment strategy for HPV-related oropharyngeal cancer. *Int J Clin Oncol* 2016; **21**: 827-835 [PMID: 27380170 DOI: 10.1007/s10147-016-1009-6]

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ORIGINAL ARTICLE

Retrospective Study

Follow-up outcomes in patients with negative initial colon capsule endoscopy findings

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Author contributions: Nakaji K analyzed the data and wrote the manuscript; Nakaji K, Kumamoto M, Yodozawa M, and Okahara K performed the colon capsule endoscopy and collected the data; Suzumura S supervised the statistical analysis and Nakae Y supervised the study.

Institutional review board statement: The Ethical Review Committee at Aishinkai Nakae Hospital approved this retrospective study on February 12, 2021 (approval No. 015).

Informed consent statement: Informed consent was obtained in the form of an opt-out procedure.

Conflict-of-interest statement: The authors declare no conflicts of interest for this article.

Data sharing statement: No additional data are available.

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Abstract

BACKGROUND

Colon capsule endoscopy (CCE), which became clinically applicable in 2006, is a simple and noninvasive procedure to evaluate colonic diseases; the accuracy of second-generation CCE, introduced in 2009, has dramatically improved. Currently, CCE is used as an alternative method for colorectal cancer screening, as well as for evaluating the mucosal lesions of inflammatory bowel disease, in cases where performing colonoscopy (CS) is difficult. However, the outcomes of CCE are uncertain.

AIM

To investigate the outcomes of Japanese patients with negative findings (no polyps or colorectal cancer) on initial CCE.

METHODS

This retrospective, single-center study was conducted at the Endoscopic Center at Aishinkai Nakae Hospital. This study included patients who underwent continuous CCE between November 2013 and August 2019, that exhibited no evidence of polyps or colorectal cancer at the initial CCE, and could be followed up using either the fecal immunochemical test (FIT), CS, or CCE. The observational period, follow-up method, presence or absence of polyps and colorectal cancer, pathological diagnosis, and number of colorectal cancer deaths were evaluated.

RESULTS

Thirty-one patients (mean age, 60.4 ± 15.6 years; range, 28–84 years; 14 men and 17 women) were enrolled in this study. The reasons for performing the first CCE

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were screening in 12, a positive FIT in six, lower abdominal pain in nine, diarrhea in two, and anemia in two patients. The mean total water volume at the time of examination was 3460 ± 602 mL (2250–4800 mL), and a total CS was performed in 28 patients (90%). The degree of cleanliness was excellent in 15 patients and good in 16, and no poor cases were observed. No adverse events, such as retention or capsule aspiration, were observed in any of the patients. The mean follow-up period was 3.1 ± 1.5 years (range, 0.3–5.5 years). Follow-up included FIT in nine, CS in 20, and CCE in four patients (including duplicate patients). The FIT was positive in two patients, while CS revealed five polyp lesions (three in the ascending colon, one in the transverse colon, and one in the descending colon), with sizes ranging between 2 mm and 8 mm. Histopathological findings revealed a hyperplastic polyp in one patient, and adenoma with low grade dysplasia in four patients; colorectal cancers were not recognized. In the follow-up example by CCE, polyps and colorectal cancer could not be recognized. During the follow-up period, there were no deaths due to colorectal cancer in any of the patients.

CONCLUSION
We determined the outcomes in patients with negative initial CCE findings.

Key Words: Colon capsule endoscopy; Negative findings; Observation; Colorectal polyps; Colorectal cancer; Colorectal cancer death

Core Tip: Colon capsule endoscopy is becoming popular as a screening test for colorectal cancer in patients where colonoscopy is difficult. Its accuracy is comparable to that of colonoscopy; however, the outcomes are unknown. This study evaluated the follow-up methods, presence or absence of polyps and colorectal cancer, and cancer deaths after follow-up in Japanese patients with negative capsule endoscopy findings.

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INTRODUCTION

The number of patients with colorectal cancer has been increasing in Japan[1], compared with the United States. It is the primary cause of cancer death in women, and third most common cause in men[1]. In Japan, fecal occult blood testing using the two-day method is performed for colorectal cancer screening in patients aged 40 years or older, while colonoscopy (CS) is performed in patients with at least one positive fecal immunochemical test (FIT)[1]. Still, although CS is the gold standard for colorectal cancer screening, the frequency of CS following a positive FIT is approximately 60%[1]. This may be due to fear of perforation and hemorrhage caused by the invasive nature of CS. Colon capsule endoscopy (CCE) is noninvasive and convenient; additionally, during the coronavirus disease 2019 (COVID-19) pandemic, CCE has drawn attention as a home-based test that does not pose a risk of severe acute respiratory syndrome coronavirus 2 infection[2]. Second-generation CCE has dramatically improved accuracy by incorporating a wide field of view and adaptive frame rate (adjusting 4–35 images/s to accommodate the capsule movement)[3], and is now regarded a noninvasive method for colorectal cancer screening in patients where CS is difficult[4]. Since 2020 in Japan, the indications have been expanded to include patients with the physical burdens associated with CS, such as hypertension, diabetes, and chronic obstructive pulmonary disease; the number of examinations is therefore expected to increase in the future.

Conversely, there are concerns regarding CCE overlooking colorectal polyps and cancers during long-term follow-up that CS would otherwise have been detected in patients who present negative initial CCE results; intermediate cancers and cancer deaths may have been caused as a result. To the best of our knowledge, there are no reports regarding the long-term follow-up of patients screened for colorectal cancer with initial negative initial CCE results; therefore, we evaluated the efficacy of initial CCE results through the follow-up of patients without polyps or colorectal cancer.

MATERIALS AND METHODS

Patient selection

This retrospective, single-center study included consecutive patients who underwent CCE at the outpatient unit of Aishikai Nakae Hospital for colorectal cancer screening between November 2013 and August 2019 due to difficulty performing CS (either the colonoscope could not be inserted into the cecum, or CS was expected to be challenging to perform due to postoperative adhesions). Of these patients, those without findings on initial CCE (defined as those without polyps of any size and/or cancerous lesions) were followed up. Inclusion criteria for the study were patients who underwent follow-up with either FIT, CS, or CCE; patients were excluded if they had inflammatory bowel disease or were previously found to have a polyp or colorectal cancer. Exclusion criteria for performing CCE included dysphagia, pacemaker placement, and possible pregnancy. This study was conducted under the Declaration of Helsinki and was approved by the ethics committee of Aishinkai Nakae Hospital on February 12, 2021 (No. 015). Informed consent was obtained in the form of opt-out on the bulletin board in the hospital. Those who were withdrew were excluded from the study.

Definition of follow-up from initial CCE

Follow-up from initial CCE was defined as patients reexamined over 3-month intervals after the first CCE, either by the FIT, CS, or CCE. The FIT was performed on two separate days; one positive test was considered positive, and two negative tests were considered negative.

The CCE procedure

PillCamCOLON2 (Medtronic, Minneapolis, United States) was used for all patients. Pretreatment began the day before the examination. The patients ingested a low-residue diet test meal at home for breakfast, lunch, and dinner, and at 19:00, they drank a hypertonic solution by dissolving 50 g of magnesium citrate (Magcolol P; Horii Pharmaceutical Co., Ltd., Osaka) in 180 mL of water. Before bedtime, they had 10 mg of 0.75% sodium picosulfate with 100 mL of water. On the day of the examination, the patients fasted during the morning, after which they drank 1000 mL of ascorbic acid-containing hypertonic polyethylene glycol solution (Asc-PEG; Mobiprep; EA Pharma, Tokyo) and 500 mL of water. The patients' stool frequency and properties were checked, and stool was required for a clear liquid state. Thereafter, the sensor array was fitted, and the capsule was swallowed after taking 20 mg of mosapride with 100 mL of water. Metoclopramide (10 mg) was injected intramuscularly when the small intestine did not reach 60 min after capsule swallowing. An additional 10 mg of metoclopramide was administered if the capsule did not reach the small intestine after 120 min). Once in the small intestine, 30 mL of aromatic castor oil and 100 mL of Asc-PEG were added. After reaching the large intestine, patients ingested 400 mL of Asc-PEG and 250 mL of water over 30 min. Subsequently, 500 mL of Asc-PEG and 250 mL of water were taken (over 30 min) to expel the capsule. After the capsules reached the small intestine, exercises-such as walking and stair ascending and descending exercises-were encouraged. If capsules were not expelled by 5 p.m. of the same day, the following options were considered: (1) An intramuscular injection of 10 mg metoclopramide; (2) Oral administration of 30 mg castor oil and 100 mg water; (3) Oral administration of 50 g of magnesium citrate dissolved in 180 mg of water, or (4) Administration of 60 mg of glycerin enema if there was no discharge of the colon capsule (Figure 1).

CCE reading

After completing the study, the data recorder was downloaded to a workstation equipped with dedicated interpretation software (RAPID software v8.0 or v8.3). The

Day procedure	
-1	Low residual diet
	A hypertonic solution prepared by dissolving 50 mg of magnesium citrate in 180 mg of water
	10 mg of 0.75% sodium picosulfate and 80 mg of water at bedtime
0	500-1000 mg of ascorbic acid-containg polyethylene glycol solution and 250-500 mg of water until the stool became clear
	Capsule ingestion with 20 mg of mosapride
	Booster 1: 30 mg of castor oil and 100 mg of acid-containg polyethylene glycol solution
	Booster 2: 400 mg of ascorbic acid-containg polyethylene glycol solution and 250 mg of water
	Booster 3: 500 mg of ascorbic acid-containg polyethylene glycol solution and 250 mg of water
	Other options (If the capsule did not discharge): Intramuscular administration of 10 mg of metoclopramide or oral administration of 30 mg of castor oil and 100 mg of water or oral administration of 50 mg of magnesium citrate dissolved in 180 mg of water
	60 mg of glycerin enema

Figure 1 Colon capsule endoscopy procedure.

following parameters were examined: laxative dose, intestinal transit time (time from the capsule reaching the duodenum to the end of the ileum), colonic transit time (time from capsule reaching the cecum to exit the anus), total colic observation rate (when the capsule emptying through the anus or dentate line can be confirmed), and intestinal lavage rate. Intestinal cleanliness was graded on a 4-point Leighton-Rex scale [5] by five segments of the large intestine, defined as "excellent" (only a tiny amount of stool), "good" (small amounts of stool or cloudy fluid, but not sufficient to interfere with interpretation), "fair" (cloudy fluid if it completely precluded reliable examination), and "poor" (a large amount of stool). The cleanliness of the entire colon was evaluated as appropriate by adopting the lowest rating for each segment. The findings were read by a Japanese Society for Capsule Endoscopy certified support technician and one or more experienced physicians.

Adverse events were defined as the retention of capsules (stay in the intestine with the inability to confirm anal emptying of the capsule for at least 14 d) and consequent intestinal obstruction, Mallory-Weiss syndrome, intestinal perforation, vomiting due to oral laxatives, and aspiration pneumonia. In this study, we investigated the following data in patients: (1) Observation period; (2) Follow-up method; (3) Presence or absence of polyps and colorectal cancer; (4) Final pathologic diagnosis; (5) Presence or absence of adverse events, and (6) Cancer-related deaths.

Statistical analysis

All continuous variables are presented as means and standard deviations. Statistical analysis was performed using IBM SPSS Statistics for Windows (SPSS Inc., Chicago, IL, United States).

RESULTS

During the study, 208 patients underwent CCE for colorectal cancer screening; 82 patients were found to be negative for polyps and/or cancerous lesions after the first CS capsule. Of these, 31 patients were followed up *via* either FIT, CS, or CCE; the remaining 51 patients were not followed-up *via* either FIT, CS, or CCE since their initial CCE. The characteristics of patients with negative CCE results are shown in Table 1. The mean age of the cohort was 60.4 years, and 45.2% (n = 14) were male. The most common reason for performing CCE was screening results (n = 12; patients aged over 40 years, with no symptoms). No adverse events, such as retention or capsule aspiration, were observed.

Table 1 Characteristics of patients with negative colon capsule endoscopy results, n (%)

Total number of patients		*n* = 31
Gender (*n*)		
	Female	17
	Male	14
Age (yr, range)		60.4 ± 15.6 (28 - 84)
Reasons (*n*)		
	Screening	12
	Fecal immunochemical test positive (*n*)	6
	Lower abdominal pain (*n*)	9
	Diarrhea (*n*)	2
	Anemia (*n*)	2
Indication (*n*)		
	Incomplete colonoscopy (*n*)	0
	Anticipated difficulty of total colonoscopy (*n*)	31
CCE completion		28 (90)
Cleanliness (*n*)	Excellent, good, fair, poor	15, 16, 0, 0
Total water content		3460 ± 602 mL (2250-4800 mL)
Adverse events (*n*)		0

CCE: Colon capsule endoscopy.

The characteristics of colonic polyps found during the follow-up period of patients with negative CCE results are shown in Table 2; the mean follow-up period was 3.1 years. CS was the most common method of follow-up after initial CCE (*n* = 20). Five colonic polyps (three in the ascending colon, one in the transverse colon, and one in the descending colon) were identified through follow-up CS; based on the Narrow-band imaging International Colorectal Endoscopic classification[6], these were classified as type 1 and 2 polyps. Histopathological findings included a hyperplastic polyp in one patient, and adenoma with low grade dysplasia in four patients, while in cases followed-up by CCE, colonic polyps and colorectal cancer could not be identified. Excluding symptomatic patients, screening was followed by CS in seven, FIT in three, and CCE in two patients for an average of 2.8 years; no polyps or colorectal cancers were found through either method. During the follow-up period, no deaths due to colorectal cancer occurred in any of the patients. Representative images of follow-up on CS are presented in comparison with the initial CCE findings (Figure 2).

DISCUSSION

To the best of our knowledge, this is the first follow-up study of negative initial CCE findings in Japanese patients. Colorectal cancer was not observed in any of the cases, while only small polyps were detected during the follow-up period. The widespread use of screening tests for colorectal cancer screening with FIT is expected to increase the frequency of CSs in the future; however, the number of skilled physicians performing CS is limited. Additionally, as the COVID-19 pandemic continues in the future, conventional endoscopic education becomes difficult[7]; the number of skillful physicians performing CS may not be expected to increase accordingly[7]. To compensate for this situation, noninvasive and straightforward CCE screening for colorectal cancer has been and should continue to be examined. However, the diagnostic reading of CCE is challenging. It usually requires a reading of 50000–60000 frames, may have only one or a few frames of essential findings, and is always at risk of overlooking an interpreter's findings[8]; thus, initial reviews by other clinical staff

Table 2 Characteristics of polyp lesions identified *via* colonoscopy during the follow-up period from colon capsule endoscopy negative results

	Number	Size (mm)	Shape	Histology	Intervals (years)
Cecum	0	-	-	-	-
Ascending colon	3	4, 4, 2	Semipedunculated type	Tubular adenoma with low grade dysplasia	5, 5, 1.8
Transverse colon	1	8	Semipedunculated type	Tubular adenoma with low grade dysplasia	2.4
Descending colon	1	3	Semipedunculated type	Hyperplastic polyp	1.8
Sigmoid colon	0	-	-	-	-
Rectum	0	-	-	-	-

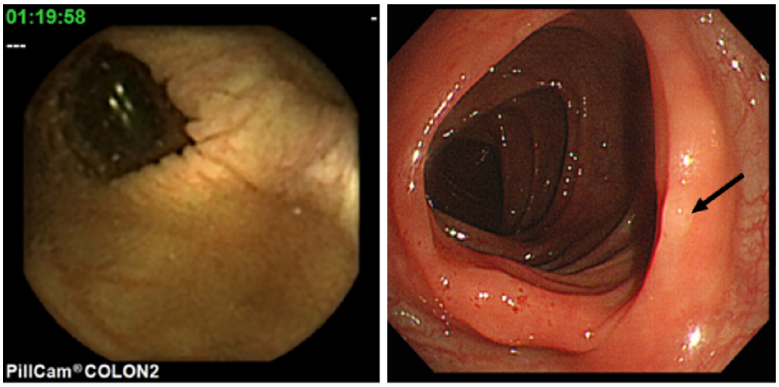

Figure 2 Representative images. Follow-up on colonoscopy (Right) is presented with the initial negative colon capsule endoscopy findings (Left): An arrow indicates an adenoma with low grade dysplasia in the transverse colon. CCE: Colon capsule endoscopy; CS: Colonoscopy.

(for example, endoscopic nurses) are required[9]. Additionally, while interpretive assistance using artificial intelligence has been studied[10], it is not yet a widely established method in routine clinical practice at the research stage. Follow-up of CCE is therefore necessary-including examination of interval cancers-without overlooking significant polyp findings observed during the initial CCE that would have been detected by CS.

In the guidelines for colorectal cancer screening[11], sigmoidoscopy, multitargeted stool DNA testing (FIT-DNA), computed tomography colonography (CTC), and CCE are recommended for patients aged 50–75 years when FIT or CS is not desirable. At these intervals for follow-up, FIT is recommended annually, CS every 10 years, FIT-DNA every 3 years, sigmoidoscopy every 5 years, CTC every 5 years, and CCE every 5 years. In our review of CCE, no advanced neoplasia was found at approximately 5-year intervals; colorectal screening with CCE every 5 years was therefore considered appropriate for Japanese patients in this study.

In a review of other modalities with negative imaging, Heisser *et al*[12] reported in a meta-analysis of CS studies that when stratified according to negative CS results from 1–5 years, 5–10 years, or more than 10 years, the detection of polyps was 20.7%, 23.0%, and 21.9%, respectively; advanced neoplasia, including cancer, was observed in 2.8%, 3.2%, and 7.0% of cases, respectively. In a retrospective study of negative CTC results from a single institution, Pickhardt *et al*[13] reported that 12.1% of the patients had polyps 6 mm or larger in diameter, while 0.1% had advanced neoplasia-including cancer-in 10 years of follow-up. Although direct comparison is difficult due to differences regarding the number of patients, the definition of negative findings, and the duration of observation compared with this study, the 5-year follow-up results of their study demonstrated that 12.9% of all polyp lesions, 3.2% of polyps 6 mm or more, 0% of advanced neoplasia including cancer, and the other negative results were better than the other modalities.

In this study, CS was the most common method used for follow-up after the first CCE, followed by FIT and CCE. The widespread use of CS in Japan and the high cost of CCE may have contributed to this observation. At present, there is a report regarding improvement of the capsule discharge rate using castor oil as a booster[14].

Our study demonstrated that polyp lesions found after the first CCE were more frequent in the ascending colon. Evaluation of negative CS and CTC results indicated that many cases of polyps were found in the right-sided colon during the follow-up period. Although the cause is unknown, it is believed that in our case, the lesions were often overlooked as the capsule had passed quickly in the ascending colon.

This study has several limitations. First, this was a single-center retrospective study with a small number of cases; however, as a single-center study, follow-up of the same patient was possible. Second, the observational period was considerably short; additional long-term follow-up is necessary in the future. Third, the follow-up method was not standardized; this is a limitation of retrospective studies, and it is of particular concern that all patients who underwent the FIT were negative at follow-up in the present study. Still, there have been reports of colorectal cancer in FIT-negative patients[15]; thus, the possibility of colorectal cancer inclusion in these cases cannot be ruled out. It is necessary to follow up in CS in these cases. Fourth, there is a possibility that lesions could be overlooked during interpretation of the first CCE; however, in this study, we thoroughly reviewed the entire image. Further progress regarding the interpretation of CCE by artificial intelligence will help to provide more accurate interpretations. Finally, because CCE moves back and forth, the possibility of overcounting polyp lesions and flat polyp lesions has not been investigated in this study and should be considered in the future.

CONCLUSION

In the present study, follow-up of patients with negative initial CCE results revealed no colorectal cancer; only small polyps were found.

ARTICLE HIGHLIGHTS

Research background

Colon capsule endoscopy (CCE) is a noninvasive and easy procedure for detecting colorectal lesions when difficult to perform colonoscopy (CS). The incidence of CCE has been increasing due to its noninvasive nature and low risk of infection during the Covid-19 pandemic; however, its follow-up on efficacy remains unknown.

Research motivation

Currently, guidelines recommend that patients with no significant findings on initial CCE should repeat CCE every five years, or follow up with another screening test. However, there is limited evidence in clinical practice.

Research objectives

The study's main objective was to investigate the follow-up outcomes in Japanese patients without polyp and colonic cancer at the initial CCE.

Research methods

Thirty-one consecutive Japanese patients negative for polyp and cancer lesions on initial CCE were analyzed.

Research results

We propose that researchers conduct a multicenter, prospective, long-term follow-up of initial CCE screening results.

Research conclusions

Our study determined the outcomes of Japanese patients with negative CCE results.

Research perspectives

The mean follow-up period was 3.1 years; CS was determined to be the most common method of follow-up after the initial CCE (n = 20). Five colonic polyps (three in the ascending colon, one in the transverse colon, and one in the descending colon) were identified through follow-up CS; based on the Narrow-band imaging International Colorectal Endoscopic classification, these were classified as type 1 and 2 polyps. Histopathological findings included a hyperplastic polyp in one patient, and adenoma

with low grade dysplasia in four patients; no deaths due to colorectal cancer, or severe adverse events, were observed in any patient during follow-up.

REFERENCES

1 **Hotta K**, Matsuda T, Kakugawa Y, Ikematsu H, Kobayashi N, Kushima R, Hozawa A, Nakajima T, Sakamoto T, Mori M, Fujii T, Saito Y. Regional colorectal cancer screening program using colonoscopy on an island: a prospective Nii-jima study. *Jpn J Clin Oncol* 2017; **47**: 118-122 [PMID: 28172923 DOI: 10.1093/jjco/hyw155]

2 **MacLeod C**, Wilson P, Watson AJM. Colon capsule endoscopy: an innovative method for detecting colorectal pathology during the COVID-19 pandemic? *Colorectal Dis* 2020; **22**: 621-624 [PMID: 32403190 DOI: 10.1111/codi.15134]

3 **Hosoe N**, Limpias Kamiya KJL, Hayashi Y, Sujino T, Ogata H, Kanai T. Current status of colon capsule endoscopy. *Dig Endosc* 2021; **33**: 529-537 [PMID: 32542702 DOI: 10.1111/den.13769]

4 **Hosoe N**, Hayashi Y, Ogata H. Colon Capsule Endoscopy for Inflammatory Bowel Disease. *Clin Endosc* 2020; **53**: 550-554 [PMID: 31914721 DOI: 10.5946/ce.2019.156]

5 **Leighton JA**, Rex DK. A grading scale to evaluate colon cleansing for the PillCam COLON capsule: a reliability study. *Endoscopy* 2011; **43**: 123-127 [PMID: 21038293 DOI: 10.1055/s-0030-1255916]

6 **Puig I**, Kaltenbach T. Optical Diagnosis for Colorectal Polyps: A Useful Technique Now or in the Future? Gut Liver 2018; 12: 385-392 [PMID: 29278867 DOI: 10.5009/gnl17137]

7 **Segal JP**, Smith PJ, Verma AM. The impact of COVID-19 on endoscopy training needs to be considered in the context of a global pandemic. *Gastrointest Endosc* 2020; **92**: 1146-1147 [PMID: 33160504 DOI: 10.1016/j.gie.2020.06.036]

8 **Yang YJ**. The Future of Capsule Endoscopy: The Role of Artificial Intelligence and Other Technical Advancements. *Clin Endosc* 2020; **53**: 387-394 [PMID: 32668529 DOI: 10.5946/ce.2020.133]

9 **Shiotani A**, Honda K, Kawakami M, Murao T, Matsumoto H, Tarumi K, Kusunoki H, Hata J, Haruma K. Evaluation of RAPID(®) 5 Access software for examination of capsule endoscopies and reading of the capsule by an endoscopy nurse. *J Gastroenterol* 2011; **46**: 138-142 [PMID: 20821237 DOI: 10.1007/s00535-010-0312-7]

10 **Yamada A**, Niikura R, Otani K, Aoki T, Koike K. Automatic detection of colorectal neoplasia in wireless colon capsule endoscopic images using a deep convolutional neural network. *Endoscopy* 2021; **53**: 832-836 [PMID: 32947623 DOI: 10.1055/a-1266-1066]

11 **Shaukat A**, Kahi CJ, Burke CA, Rabeneck L, Sauer BG, Rex DK. ACG Clinical Guidelines: Colorectal Cancer Screening 2021. *Am J Gastroenterol* 2021; **116**: 458-479 [PMID: 33657038 DOI: 10.14309/ajg.0000000000001122]

12 **Heisser T**, Peng L, Weigl K, Hoffmeister M, Brenner H. Outcomes at follow-up of negative colonoscopy in average risk population: systematic review and meta-analysis. *BMJ* 2019; **367**: l6109 [PMID: 31722884 DOI: 10.1136/bmj.l6109]

13 **Pickhardt PJ**, Pooler BD, Mbah I, Weiss JM, Kim DH. Colorectal Findings at Repeat CT Colonography Screening after Initial CT Colonography Screening Negative for Polyps Larger than 5 mm. *Radiology* 2017; **282**: 139-148 [PMID: 27552558 DOI: 10.1148/radiol.2016160582]

14 **Ohmiya N**, Hotta N, Mitsufuji S, Nakamura M, Omori T, Maeda K, Okuda K, Yatsuya H, Tajiri H. Multicenter feasibility study of bowel preparation with castor oil for colon capsule endoscopy. *Dig Endosc* 2019; **31**: 164-172 [PMID: 30102791 DOI: 10.1111/den.13259]

15 **Hasegawa R**, Yashima K, Ikebuchi Y, Sasaki S, Yoshida A, Kawaguchi K, Isomoto H. Characteristics of Advanced Colorectal Cancer Detected by Fecal Immunochemical Test Screening in Participants with a Negative Result the Previous Year. *Yonago Acta Med* 2020; **63**: 63-69 [PMID: 32158335 DOI: 10.33160/yam.2020.02.009]

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ORIGINAL ARTICLE

Retrospective Study

Safety of upper endoscopy in patients with active cocaine use

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Institutional review board statement: This study was reviewed and approved by the Ethics Committee of the John H. Stroger, Jr. Hospital of Cook County

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

Conflict-of-interest statement: We have no financial relationships to disclose.

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Abstract

BACKGROUND

Cocaine is a synthetic alkaloid initially viewed as a useful local anesthetic, but which eventually fell out of favor given its high addiction potential. Its predominantly sympathetic effects raise concern for cardiovascular, respiratory, and central nervous system complications in patients undergoing procedures. Peri-procedural cocaine use, often detected *via* a positive urine toxicology test, has been mostly addressed in the surgical and obstetrical literature. However, there are no clear guidelines on how to effectively risk stratify patients found to be positive for cocaine in the pre-operative setting, often leading to costly procedure cancellations. Within the field of gastroenterology, there is no current data available regarding safety of performing esophagogastroduodenoscopy (EGD) in patients with recent cocaine use.

AIM

To compare the prevalence of EGD related complications between active (≤ 5 d) and remote (> 5 d) users of cocaine.

METHODS
In total, 48 patients who underwent an EGD at John H. Stroger, Jr. Hospital of Cook County from October 2016 to October 2018 were found to have a positive urine drug screen for cocaine (23 recent and 25 remote). Descriptive statistics were compiled for patient demographics. Statistical tests used to analyze patient characteristics, procedure details, and preprocedural adverse events included *t*-test, chi-square, Wilcoxon rank sum, and Fisher exact test.

RESULTS
Overall, 20 periprocedural events were recorded with no statistically significant difference in distribution between the two groups (12 active *vs* 8 remote, $P = 0.09$). Pre- and post-procedure hemodynamics demonstrated only a statistically, but not clinically significant drop in systolic blood pressure and increase in heart rate in the active user group, as well as drop in diastolic blood pressure and oxygen saturation in the remote group ($P < 0.05$). There were no significant differences in overall hemodynamics between both groups.

CONCLUSION
Our study found no significant difference in the rate of periprocedural adverse events during EGD in patients with recent *vs* remote use of cocaine. Interestingly, there were significantly more patients (30%) with active use of cocaine that required general anesthesia as compared to remote users (0%).

Key Words: Gastrointestinal endoscopy; Cocaine-related disorders; General anesthesia; Risk factors; Local anesthetics; Retrospective studies

Core Tip: There is no data available regarding safety of performing an esophago-gastroduodenoscopy in patients with evidence of recent cocaine use. This study compared the prevalence of procedure complications between active and remote cocaine users and found no statistically significant difference between the two groups. Pre- and post-procedure hemodynamics demonstrated only statistically, but not clinically significant changes in blood pressure, heart rate, and oxygenation. Results suggest relative safety in performing this procedure on active cocaine users. Patients in the active group required more general anesthesia; however, given nature of study, the reasoning behind this sedation choice was difficult to determine.

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INTRODUCTION

Illicit drug abuse remains an ongoing public health crisis in the United States. As of 2018, 11.7% of the population over the age of 12 were illegal drug users. Of these, 2% reported regular use of cocaine[1]. Given the self-reporting nature of these statistics, there is reasonable concern that these values may be a significant underestimation of the actual number of active cocaine users in the population[2]. In the medical literature, cocaine's predominantly sympathetic effects have been linked to a myriad of cardiovascular, respiratory, and central nervous system complications that may compromise patient stability when undergoing a procedure. Major cardiac abnormalities such as tachycardias, hypertension, myocardial ischemia or infarction, and various arrhythmias are at the forefront of concern[3]. Pulmonary edema, pulmonary hemorrhages, and pulmonary barotrauma have been attributed to the use of smoked "crack" cocaine[4]. Lastly, cocaine has also been implicated in several neurological complications including hemorrhage, stroke, seizures, and coma[5,6].

additional data are available.

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Table 1 Patient characteristics

		Active cocaine users, *n* = 23	Remote cocaine users, *n* = 25	*P* value[3]
Age, yr, *n*[2]	(Avg. ± SD)	51.0 ± 9.5	54.8 ± 10.9	0.210[4]
Sex, *n*[1]	Male	19	11	0.006[5]
	Female	4	14	
Ethnicity, *n*[1]	White	1	2	0.889[6]
	African American	17	19	
	Hispanic	5	4	
EKG, *n*[1]	Normal	8	9	0.757[5]
	Abnormal	14	13	
	No EKG	1	3	
Comorbidities, *n*[1]	Pulmonary	8	8	0.838[5]
	Cardiac	4	4	1.000[6]
	Renal	1	3	0.610[6]
	Liver	4	12	0.025[5]
	Hypertension	7	12	0.214[5]
	Other drug abuse	12	17	0.263[5]
	Neurologic	0	1	1.000[6]
	Obesity	1	2	1.000[6]
	Infectious	1	13	0.0003[5]
	Malignancy	1	3	0.610[6]
	Diabetes	1	3	0.610[6]
	Other	3	3	1.000[6]

[1]Categorical value. Presented as frequency.
[2]Continuous variables. Presented as mean value and standard deviation.
[3]Compared to alpha value < 0.05 for significance.
[4]*t*-test.
[5]chi-SQ.
[6]Fisher exact test.
EKG: Electrocardiogram

Jeffcoat *et al*[7] published one of the first studies exploring the differences in common routes of administration of cocaine including intravenous injection, nasal insufflation, and smoke inhalation. From this paper, the elimination half-life of cocaine was calculated to range between 69-78 min depending on the mode of administration. Using more modern laboratory assays for detection, the plasma half-life of cocaine has been determined to range between 0.7–1.5 h while the urine detection window is typically less than 1 d[8]. Cocaine's main inactive metabolite, benzoylecgonine, has a plasma half-life of 5.5–7.5 h and a urine drug screen (UDS) window of 1–2 d[9]. These values can vary depending on differences in renal function, and frequency of cocaine use. In fact, benzoylecgonine has been detected in the urine up to 10-14 d after heavy cocaine use[10].

Pre-procedural management of a patient with recent cocaine use, typically determined *via* a positive urine toxicology test detecting benzoylecgonine, has been mostly addressed in the surgical and obstetrical literature. Within these fields, only a handful of cases have been published reporting cardiac arrhythmias, hypertension, and myocardial ischemia while intoxicated with cocaine and under general anesthesia [11]. In the setting of elective surgeries, larger studies such as Hill *et al*[12] demonstrated no greater risk for intraprocedural complications for non-toxic cocaine users when compared to drug-free patients. Baxter and Alexandrov[13] showed statistically significantly higher baseline systolic pressure, mean arterial pressure, and heart rate differences in the cocaine-positive cohort, but ultimately these were not deemed

clinically significant values. More recently, Moon *et al*[14] determined that cocaine positive patients did not demonstrate significantly different medication requirements as compared to cocaine-negative patients.

Despite the existence of this data, there remains no standard for practice on how to proceed with procedures this patient population. As such, practitioner preference is often used to determine the main course of action, leading to same day cancellations of procedures, resulting in waste of clinical time and resources[15]. There have been no direct published works addressing complications encountered during gastrointestinal endoscopies in patients with positive cocaine drug screens. This retrospective, single-center study aims to determine the safety of EGD with anesthesia support in patients who abuse cocaine, both actively and remotely.

MATERIALS AND METHODS

Records were reviewed from patients who underwent EGD at John H. Stroger, Jr. Hospital of Cook County from October 2016 to October 2018. Those with a cocaine positive UDS within less than 6 mo were identified. Remote cocaine users were classified as individuals with positive cocaine screen > 5 d, up to 6 mo from procedure, while active cocaine users had a positive UDS within 5 d. The study was approved by the institutional review board.

Demographic data including age, ethnicity, and comorbidities (pulmonary, cardiac, renal, liver, hypertension, other drug abuse, neurologic, obesity, infectious disease, malignancy, diabetes, and other medical conditions) were recorded. Procedural details such as American Society of Anesthesiologists Classification (ASA class), urgency level of procedure, type of anesthesia, location (inpatient *vs* outpatient), and length of stay, were also collected. Periprocedural adverse events such as hypotension, tachycardia, nausea/vomiting, and oxygen desaturation were recorded. The outcomes measured included hemodynamic changes in blood pressure, heart rate, respiratory rate, and oxygen saturation, pre- and post-procedure.

All patient data was analyzed using STATA/SE 12.0 and Excel version 365 (Microsoft). Several statistical tests were used to analyze patient characteristics, procedure details, and preprocedural adverse events including *t*-test, chi-square, Wilcoxon rank sum, and Fisher exact test. All *P*-values < 0.05 were considered statistically significant.

RESULTS

A total of 2122 patients were identified during the study period; 129 patients had a positive drug screen of which 48 were positive for cocaine. Active users (23) were predominately male (83%) and African American (74%). Remote users (25) were 44% female and predominantly African American (76%). There was a significant difference male gender predominance in the active group compared to the remote ($P = 0.006$). A substantial number of patients in both groups had abnormal admitting electrocardiogram (14 active *vs* 13 remote) and both were found to have concurrent drug abuse (12 active *vs* 17 remote) as their most prevalent comorbidity (Table 1). There was no significant difference between groups for both categories, although liver and infectious comorbidities were more prevalent in the remote group ($P = 0.025$, 0.0003).

Patients in both groups underwent urgent procedures (17 active *vs* 14 remote) with no statistical difference ($P = 0.195$); although the active group was treated more often in the inpatient setting ($P = 0.024$). ASA class III was most prevalent among the two groups (14 active *vs* 21 remote) although more predominant in the remote group ($P = 0.046$). Monitored anesthesia care (MAC) sedation was the preferred anesthesia support over general anesthesia (16 active *vs* 25 remote) ($P = 0.003$). Hospitalizations were longer for remote *vs* active patients ($P = 0.003$), (Table 2). Overall, 20 periprocedural adverse events occurred among the 48 patients. Although not statistically significant, active users had more events compared to remote users (12 *vs* 8, $P = 0.09$) defined as documented oxygen desaturation during the procedure, use of vasopressor, rate-controlling, or anti-nausea medications (Table 3).

Pre- and post-procedure hemodynamics demonstrated a statistically significant, but not clinically significant, drop in systolic blood pressure (136/77 pre-procedure *vs* 129/76 post-procedure, $P = 0.03/0.64$), as well as an increase in heart rate (73 pre-procedure *vs* 76 post-procedure, $P = 0.04$) in the active user group. In the remote user group, there was also a statistically significant, but not clinically significant, drop in

Table 2 Procedure details

		Active cocaine users, *n* = 23	Remote cocaine users, *n* = 25	*P* value[3]
Urgency, *n*[1]	Non-urgent	6	11	0.195[4]
	Urgent	17	14	
Location, *n*[1]	Inpatient	22	17	0.024[5]
	Outpatient	1	8	
ASA Class, *n*[1]	Class II	9	3	0.046[5]
	Class III	14	21	
	Class IV	0	1	
LOS, *n*2	(Avg day ± SD)	5.4 ± 3.6	5.6 ± 11.9	0.018[6]
Type of Anesthesia,	MAC	16	25	0.003[5]
n[1]	General	7	0	

[1]Categorical value. Presented as frequency.
[2]Continuous variables. Presented as mean value and standard deviation.
[3]Compared to alpha value < 0.05 for significance.
[4]chi-SQ.
[5]Fisher exact test.
[6]Wilcoxon rank sum test.
ASA Class: American Society of Anesthesiologists Classification; LOS: Length of stay; MAC: Monitored anesthesia care.

Table 3 Periprocedural adverse events

	Active cocaine users, *n* = 23	Remote cocaine users, *n* = 25	*P* value[2]
Cumulative complications, *n*[1]	12	8	0.09
Oxygen desaturation, *n*[1]	1	2	1.000[3]
Nausea/vomiting, *n*[1]	7	2	0.068[3]
Hypotension, *n*[1]	4	4	1.000[3]
Tachycardia, *n*[1]	0	0	NA

[1]Categorical value. Presented as frequency.
[2]Compared to alpha value < 0.05 for significance.
[3]Fisher exact test.

diastolic blood pressure (130/80 pre-procedure *vs* 124/74 post-procedure, P = 0.34/0.01) and oxygen saturation (98 pre-procedure *vs* 97 post-procedure, P = 0.04). There were no significant differences in overall hemodynamics between both groups when compared *via* two-sample *t*-test (Table 4).

DISCUSSION

To the best of our knowledge, our project is the first retrospective, single-center study aimed at determining the safety of EGD under anesthesia in patients who have recently abused cocaine with comparison to remote users. Although cumulatively there were more reported periprocedural adverse events in patients with active cocaine use compared to patients with remote cocaine use undergoing endoscopy, the primary result of this study was that ultimately this difference was statistically insignificant. Moreover, the statistically significant differences in preprocedural and postprocedural hemodynamics both within and across groups were, much like in the Baxter *et al*[13] study, not deemed clinically significant[14]. There was no reported mortality in any of the groups.

Table 4 Hemodynamic outcomes

	Active cocaine users, *n* = 23	Remote cocaine users, *n* = 25	*P* value[2,3]		
Blood pressure pre-procedure	136/77 (17/13)	130/80 (19/12)	0.14/0.38	Active: 0.03/0.64	Remote: 0.34/0.01
Blood pressure post-procedure (mmHg ± SD), *n*[1]	129/76 (15/11)	124/74 (27/12)	0.46/0.52		
Heart rate pre-procedure	73 (12)	78 (16)	0.16	0.04	0.27
Heart Rate post-procedure (BPM ± SD), *n*[1]	76 (13)	81 (16)	0.28		
Respiratory rate pre-procedure	19 (2)	19 (4)	0.95	0.11	0.42
Respiratory rate post-procedure (BPM ± SD), *n*[1]	18 (3)	20 (5)	0.10		
Oxygen saturation pre-procedure	98 (2)	98 (1)	0.43	0.74	0.04
Oxygen saturation post-procedure (% ± SD), *n*[1]	98 (2)	97 (3)	0.12		

[1]Continuous variables. Presented as mean value and standard deviation.
[2]Compared to alpha value < 0.05 for significance.
[3]*t*-test.

A unique component to our study, in contrast to much of the available literature, is the overwhelming preponderance of MAC used *vs* general anesthesia in both cohorts. MAC is a type of anesthesia commonly used in diagnostic or therapeutic procedures such as endoscopies as it can be titrated to maintain spontaneous breathing and airway reflexes[16]. For endoscopic procedures, especially in the ambulatory setting, the rapid recovery of MAC is ideal for high volume centers. In contrast, under general anesthesia, patients undergo a drug-induced loss of consciousness that prevents any ability to respond purposefully and often necessitate airway support[16]. Further analysis into the two cohorts of our study showed that active users were more likely to undergo the EGD under general anesthesia, 30%, *vs* remote users, 0%. Unfortunately, given the retrospective nature of the study and the small sample size, the reasoning behind this deviation in anesthesia type could not be further dissected. However, it may point to some component in the patient's clinical status that swayed the anesthesiologist to favor one form over the other.

As previously mentioned, given the retrospective nature of this study, there are several limitations that must be addressed. Despite the two-year timespan for chart review, our total sample population of cocaine positive patients, both active and remote, remained small. This was to be expected as UDS are not part of the standard pre-procedural work up of a patient undergoing an EGD. Additionally, similarly to what was mentioned in Moon *et al*[14], selection bias is likely at play in the sample population as individuals that undergo a procedure even after a positive cocaine UDS are more likely to need urgent intervention[14]. Lastly, despite the stratification of active *vs* remote users based off UDS timing, there are several unknown factors that could not be standardized such as the exact time span between the last drug use and the procedure date, quantity of cocaine consumed, and other confounding factors such as co-morbid polysubstance abuse. As such, the generalizability of the results of our current study is difficult to determine and larger studies are needed to corroborate our findings.

In summary, the findings of our study suggest that there are no significant differences in periprocedural adverse events or hemodynamic disturbances in active *vs* remote cocaine users undergoing an EGD with anesthesia support. Further investigation *via* larger prospective studies, containing a cocaine-negative control group, in which the type of anesthesia used can be standardized may elucidate any true difference in adverse events rates between MAC *vs* general anesthesia in this patient population. Additionally, given the wide range of drug agents used for MAC, other studies may be needed to identify which agents, if any, would be safer for use in cocaine positive patients or those suspected to have had recent cocaine abuse.

CONCLUSION

In conclusion, performing an EGD in patients with recent cocaine use, as evidenced by a positive UDS test, appears to be relatively safe, supporting forgoing procedure cancellation in this patient population.

ARTICLE HIGHLIGHTS

Research background

Procedure delay in patients with a recent history of cocaine use due to concerns of possible adverse events can compromise patient care and incur undue healthcare costs.

Research motivation

There is a paucity of literature available to risk stratify patients with recent cocaine use undergoing endoscopic procedures.

Research objectives

We endeavored in this study to evaluate the relative safety of performing an esophagogastroduodenoscopy (EGD) in this specific patient population.

Research methods

Pre- and post-procedure hemodynamics were recorded and as well as frequency of adverse events. Using statistical tests including *t*-test, chi-square, Wilcoxon rank sum, and Fisher exact test, our data analysis results suggested no statistically significant differences in periprocedural adverse events or clinically significant hemodynamic disturbances in active (< 5 d) *vs* remote cocaine users (> 5 d).

Research results

Our study found no significant difference in the rate of periprocedural adverse events during EGD in patients with recent *vs* remote use of cocaine.

Research conclusions

Performing an EGD in patients with recent cocaine use appears to be safe.

Research perspectives

Given the retrospective nature of this study, we hope our results generate more interest to explore this topic further in larger, prospective studies.

REFERENCES

1 **Substance Abuse and Mental Health Services Administration**. Key Substance Use and Mental Health Indicators in the United States: Results from the 2019 National Survey on Drug Use and Health. 2020 Sep [cited 10 November 2020]. Available from: https://www.samhsa.gov/data/

2 The Validity of Self-Reported Drug Use: Improving the Accuracy of Survey Estimates. Harrison L, Hughes A, editors. Rockville (MD): National Institute on Drug Abuse, 1997

3 **Schwartz BG**, Rezkalla S, Kloner RA. Cardiovascular effects of cocaine. *Circulation* 2010; **122**: 2558-2569 [PMID: 21156654 DOI: 10.1161/CIRCULATIONAHA.110.940569]

4 **Perper JA**, Van Thiel DH. Respiratory complications of cocaine abuse. *Recent Dev Alcohol* 1992; **10**: 363-377 [PMID: 1589607 DOI: 10.1007/978-1-4899-1648-8_18]

5 **Marasco CC**, Goodwin CR, Winder DG, Schramm-Sapyta NL, McLean JA, Wikswo JP. Systems-level view of cocaine addiction: the interconnection of the immune and nervous systems. *Exp Biol Med (Maywood)* 2014; **239**: 1433-1442 [PMID: 24903164 DOI: 10.1177/1535370214537747]

6 **Richards JR**, Jacqueline KL. Cocaine Toxicity. 2020 Oct 21 [cited 4 February 2021]. In: StatPearls [Internet]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK430976/

7 **Jeffcoat AR**, Perez-Reyes M, Hill JM, Sadler BM, Cook CE. Cocaine disposition in humans after intravenous injection, nasal insufflation (snorting), or smoking. *Drug Metab Dispos* 1989; **17**: 153-159 [PMID: 2565204]

8 **Drug plasma half-life and urine detection window**. ARUP Laboratories. [cited 4 February 2021]. Available from: https://www.aruplab.com/files/resources/pain-management/DrugAnalytesPlasmaUrine.pdf

9 **Nickley J**, Pesce AJ, Krock K. A sensitive assay for urinary cocaine metabolite benzoylecgonine

shows more positive results and longer half-lives than those using traditional cut-offs. *Drug Test Anal* 2017; **9**: 1214-1216 [PMID: 28024167 DOI: 10.1002/dta.2153]

10 **Weiss RD**, Gawin FH. Protracted elimination of cocaine metabolites in long-term high-dose cocaine abusers. *Am J Med* 1988; **85**: 879-880 [PMID: 3195611 DOI: 10.1016/s0002-9343(88)80042-1]

11 **Kuczkowski KM**. The cocaine abusing parturient: a review of anesthetic considerations. *Can J Anaesth* 2004; **51**: 145-154 [PMID: 14766691 DOI: 10.1007/BF03018774]

12 **Hill GE**, Ogunnaike BO, Johnson ER. General anaesthesia for the cocaine abusing patient. Is it safe? *Br J Anaesth* 2006; **97**: 654-657 [PMID: 16914461 DOI: 10.1093/bja/ael221]

13 **Baxter JL**, Alexandrov AW. Utility of cocaine drug screens to predict safe delivery of general anesthesia for elective surgical patients. *AANA J* 2012; **80**: S33-S36 [PMID: 23248828]

14 **Moon TS**, Gonzales MX, Sun JJ, Kim A, Fox PE, Minhajuddin AT, Pak TJ, Ogunnaike B. Recent cocaine use and the incidence of hemodynamic events during general anesthesia: A retrospective cohort study. *J Clin Anesth* 2019; **55**: 146-150 [PMID: 30660093 DOI: 10.1016/j.jclinane.2018.12.028]

15 **Elkassabany N**, Speck RM, Oslin D, Hawn M, Chaichana K, Sum-Ping J, Sepulveda J, Whitley M, Sakawi Y. Preoperative screening and case cancellation in cocaine-abusing veterans scheduled for elective surgery. *Anesthesiol Res Pract* 2013; **2013**: 149892 [PMID: 24069030 DOI: 10.1155/2013/149892]

16 **Das S**, Ghosh S. Monitored anesthesia care: An overview. *J Anaesthesiol Clin Pharmacol* 2015; **31**: 27-29 [PMID: 25788769 DOI: 10.4103/0970-9185.150525]

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ORIGINAL ARTICLE

Observational Study

Association between mucosal surface pattern under near focus technology and *Helicobacter pylori* infection

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Institutional review board statement: The study was reviewed and approved by the ethical committee of Hospital

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Abstract

BACKGROUND

Many studies evaluated magnification endoscopy (ME) to correlate changes on the gastric mucosal surface with *Helicobacter pylori* (*H. pylori*) infection. However, few studies validated these concepts with high-definition endoscopy without ME.

AIM

To access the association between mucosal surface pattern under near focus technology and *H. pylori* infection status in a western population.

METHODS

Cross-sectional study including all patients referred to routine upper endoscopy. Endoscopic exams were performed using standard high definition (S-HD) followed by near focus (NF-HD) examination. Presence of erythema, erosion, atrophy, and nodularity were recorded during S-HD, and surface mucosal pattern was classified using NF-HD in the gastric body. Biopsies were taken for rapid urease test and histology.

RESULTS

One hundred and eighty-seven patients were analyzed from August to November 2019. Of those, 47 (25.1%) were *H. pylori*+, and 42 (22.5%) had a previous *H. pylori* treatment. In the examination with S-HD, erythema had the best sensitivity for *H. pylori* detection (80.9%). Exudate (99.3%), nodularity (97.1%), and atrophy (95.7%) demonstrated better specificity values, but with low sensitivity (6.4%-19.1%). On the other hand, the absence of erythema was strongly associated with *H. pylori*- (negative predictive value = 92%). With NF-HD, 56.2% of patients presented type

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1 pattern (regular arrangement of collecting venules, RAC), and only 5.7% of RAC+ patients were *H. pylori*+. The loss of RAC presented 87.2% sensitivity for *H. pylori* detection, 70.7% specificity, 50% positive predictive value, and 94.3% negative predictive value, indicating that loss of RAC was suboptimal to confirm *H. pylori* infection, but when RAC was seen, *H. pylori* infection was unlikely.

CONCLUSION

The presence of RAC at the NF-HD exam and the absence of erythema at S-HD were highly predictive of *H. pylori* negative status. On the other hand, the loss of RAC had a suboptimal correlation with the presence of *H. pylori*.

Key Words: Diagnosis; Endoscopy; Gastric infection; Gastritis; *Helicobacter pylori*; Sensitivity and specificity

Core Tip: Imaging advances in endoscopy significantly improved our diagnostic capability. While magnification endoscopy is well incorporated in Asian countries, in Western countries most upper endoscopes devices are not equipped with this feature. In this study, we evaluated the near focus technology to access mucosal surface pattern and correlate with *Helicobacter pylori* infection. We believe this article will be of great interest to endoscopist in the Western, as there is still a room for better understanding gastric mucosal surface pattern and near focus technology.

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INTRODUCTION

The relationship between *Helicobacter pylori* (*H. pylori*) infection, chronic gastritis, and the development of gastric cancer is well established[1-4]. Eradication of *H. pylori* in patients with non-atrophic chronic gastritis could lead to regeneration of normal mucosa and interruption of Correa's cascade[1,5,6]. In this sense, a technology that helps with diagnosis of *H. pylori*-associated gastritis is useful.

In recent years, many advances in endoscopic imaging have surged, allowing for better characterization of gastric mucosal patterns. High definition (HD) magnification endoscopy (ME) can increase the image view from 1.5× to 150× and allow the visualization of objects that are 10-71 μm in diameter[7]. In 2001, Yao and Oishi[8] described the characteristics of normal gastric mucosa with image magnification. In the following year, Yagi *et al*[9] described the differences between the magnified view of normal gastric mucosa from the pattern seen in patients with *H. pylori*-associated gastritis. A more detailed classification was used by Anagnostopoulos *et al*[10] to distinguish normal gastric mucosa, *H. pylori*-associated gastritis, and gastric atrophy in a Western population. Since then, several articles have studied the association between ME and histological findings[9,11,12].

However, endoscopes with magnification are scarce in Western countries. In 2016, Olympus launched the Near Focus (or Dual Focus) technology on conventional 190 endoscopes for the Western market, which consists of a variable focus lens system, allowing for close examination of the mucosa (2-6 mm) without definition loss[13].

Although there are many studies correlating the findings of ME and *H. pylori* status, only a few validated these findings with HD endoscopes without ME[14-18]. Moreover, most of these studies were conducted in Asian countries, in centers with high expertise with magnifying images[9,12].

The aim of this study is to access the association between mucosal surface pattern under near focus high-definition (NF-HD) technology and *H. pylori* infection status in

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a western population.

MATERIALS AND METHODS

This was a cross-sectional study conducted from August to November 2019 at the Endoscopy Center of the Hospital Alemao Oswaldo Cruz (São Paulo, Brazil). The ethical committee of our institution (approval number 3.577.527) approved this research. It is in accordance with the Declaration of Helsinki.

Inclusion criteria were patients referred to routine diagnostic upper gastrointestinal endoscopy for dyspepsia symptoms who agreed to sign the informed consent form. Exclusion criteria were patients using proton pump inhibitors (PPIs) or H2 inhibitors in the last 10 d prior to endoscopy, patients with previous gastric surgeries (gastroplasty or gastrectomy), gastric stasis, hypertensive gastropathy, patients under 18 years of age, and non-elective indications (upper gastrointestinal bleeding, foreign body, *etc.*).

Baseline data that included age, gender, symptoms, medications, and previous *H. pylori* treatment were recorded.

Primary and secondary endpoints

The primary endpoint was to assess if NF-HD examination of gastric mucosal surface patterns could predict *H. pylori* status. The secondary endpoint was to assess if any other features observed with standard focus high definition (S-HD) white light examination was associated with *H. pylori* status.

Endoscopic procedures and near focus classification

All procedures were performed under anesthesiologist-assisted sedation with propofol. Before the procedures, every patient received a solution containing 200 mL of water and simethicone to help clean the stomach and improve visualization of the gastric mucosa. All examinations were performed with an Olympus CV-190 gastroscope. The images were captured by the BSCap™ system with a minimum of 10 photos, according to the European standard[19].

The examinations were performed by nine senior endoscopists (over 10 years of experience). Subsequently, two other endoscopists (Fiuza F and Martins BC), who had training on magnification imaging, reviewed all images and standardized the responses. Endoscopists who performed the exams had information about previous *H. pylori* infection. Fiuza F and Martins BC were blinded for previous and present *H. pylori* infection.

Initially, a complete exam was performed using S-HD white light view, and the characteristics of gastric mucosa were recorded: erythema, erosion, exudate, atrophy, and nodularity (Figure 1). Next, the near focus (NF-HD) exam was performed (Figure 2), with particular attention to the greater curvature and anterior wall of the medium gastric body, according to Yagi *et al*[9].

The gastric mucosal surface pattern was classified based on the classification proposed by Anagnostopoulos *et al*[10]: Type 1: Honeycomb-type subepithelial capillary network (SECN) with regular arrangement of collecting venules (RAC) and regular round pits; Type 2: Honeycomb-type SECN with regular round pits, with or without sulci but with loss of collecting venules; Type 3: Loss of normal SECN and collecting venules and with white enlarged pits surrounded by erythema; and Type 4: Loss of normal SECN and round pits, with irregular arrangement of collecting venules.

Gastric biopsies and histological examination

Gastric biopsies were collected for evaluation with the rapid urease test (RUT-Uretest®, RenyLab): One sample in the lesser curvature of the antrum close to the *incisura angularis* and the other in the greater curvature of the medium body. Next, gastric biopsies were collected for anatomopathological (AP) study: Two samples from the body and two from the antrum (greater and lesser curvature in each region), as oriented by the IV Brazilian Consensus on *Helicobacter pylori* Infection[3]. *H. pylori* infection was considered positive when at least one of the methods was positive.

Gastric biopsies were sent for histologic evaluation by a senior pathologist who was blinded from the endoscopic findings related to inflammation of gastric mucosa. Hematoxylin eosin staining was used for assessment of gastritis and Giemsa for *H. pylori* status. When gastritis was present at histology, but *H. pylori* was negative, immunohistochemical analysis for *H. pylori* antigen was performed.

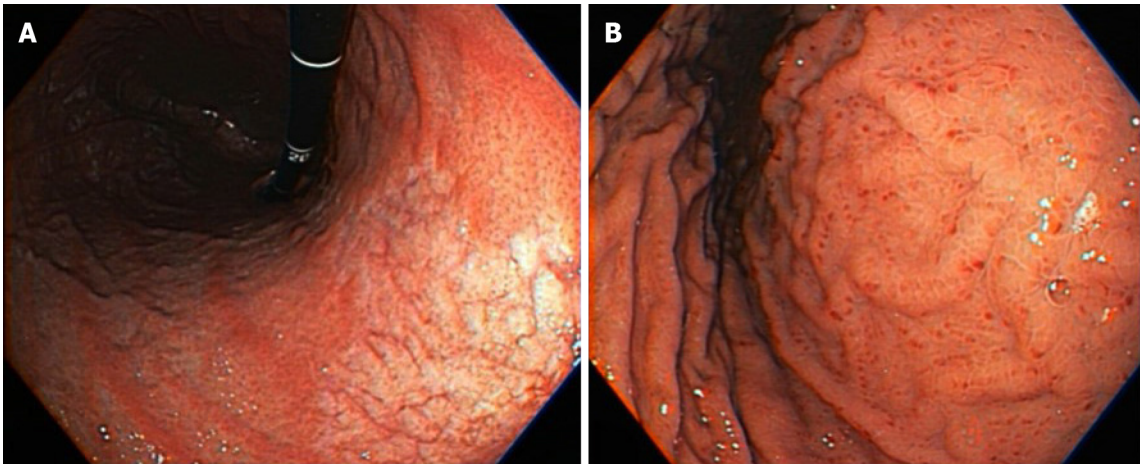

Figure 1 Standard high definition examination. A: Atrophy in the lesser curvature of the gastric body; B: Erythema of gastric body.

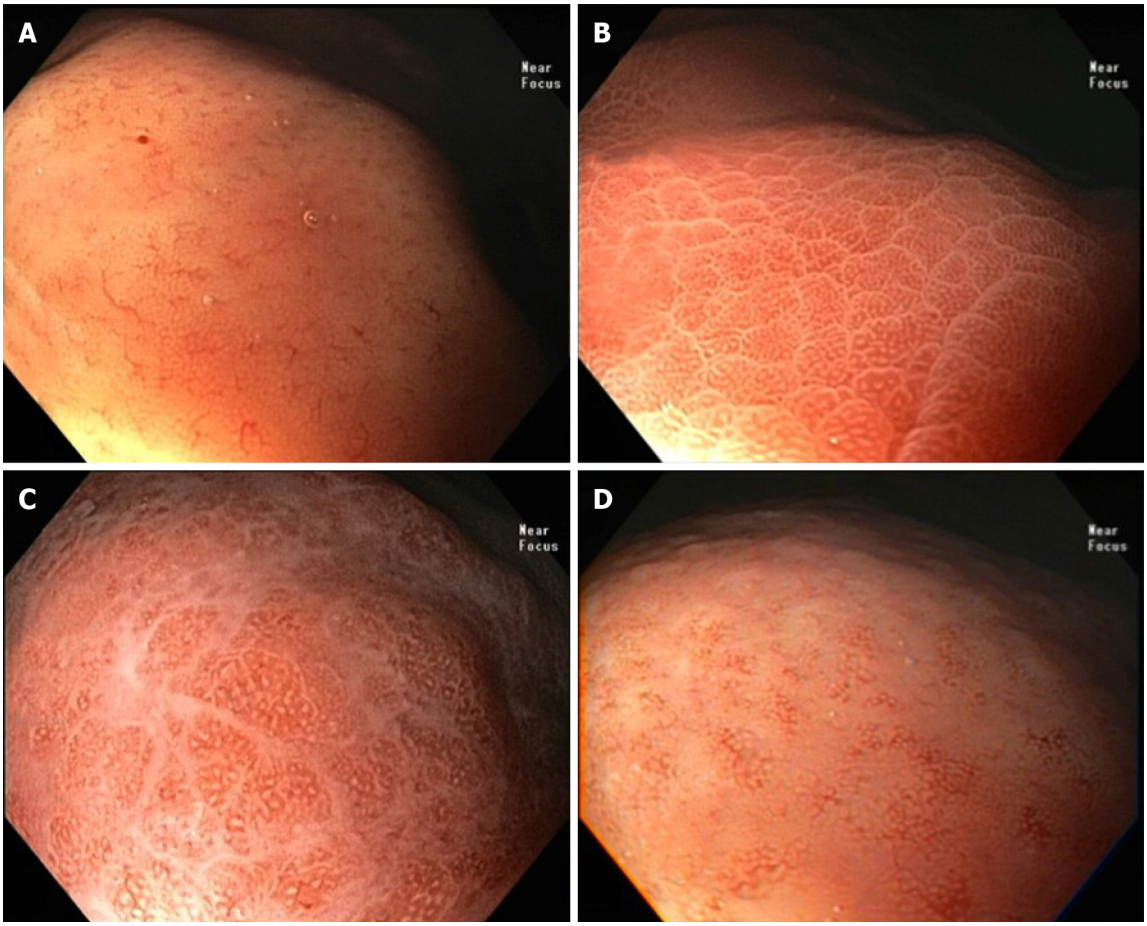

Figure 2 Near focus examination of gastric body. A: Type 1: regular arrangement of collecting venules and regular round pits; B: Type 2: regular round pits, with erythema, sulci and loss of collecting venules; C: Type 3: loss of normal subepithelial capillary network (SECN) and collecting venules and with white enlarged pits surrounded by erythema and exudate; D: Type 4: loss of normal SECN and round pits, with irregular arrangement of collecting venules.

Statistical analysis and sample size calculation

Based on the results of previous studies[10,11,20], expecting a sensitivity of 94%, specificity of 95%, and a prevalence of infection of 40%, using an error margin of ± 6% and an alpha error of 5%, we estimated a sample size of 150 patients. Assuming a drop-out rate of 25%, the sample size was increased to 180 patients.

Measures of central tendency and dispersion were calculated for quantitative variables, as well as absolute and relative frequencies for categorical variables. The association between categorical variables was assessed using the chi-square test.

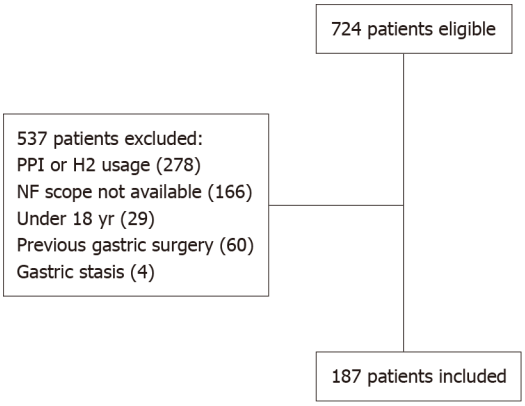

Figure 3 Study flowchart. PPI: Proton pump inhibitor; NF: Near focus.

For the evaluation of the endoscopic diagnostic value, we estimated the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), area under the ROC curve and their respective 95% confidence intervals (CI) for the findings at S-HD and NF-HD. For all statistical tests, an alpha error of 5% was established, that is, the results were considered statistically significant when $P < 0.05$. All analyses were performed with Stata Software version 15.1.

RESULTS

A total of 724 patients met the inclusion criteria and were eligible for this study. Five hundred thirty-seven patients were excluded: 278 due to PPI or H2 inhibitors usage in the previous 10 d, 166 due to NF endoscopes not available at the time of exam, 29 patients were under 18 years old, 60 due to previous gastric surgery, and 4 due to gastric stasis. Finally, 187 patients were included in the study (Figure 3). The majority of patients were female (60.5%), with a mean age of 50.1 years. Forty-two patients (22.5%) had been previously treated for *H. pylori* infection with an average interval of 48.2 mo (range 3-180 mo). The most prevalent symptom was epigastric pain (44.4%), followed by heartburn (21.4%). *H. pylori* was positive in 47 patients (25.1%), of which 42 were positive by both methods, four only by AP and one only by RUT (Table 1).

Endoscopic findings with standard focus

Upon initial examination of the gastric body with S-HD (Table 2), the finding with the best sensitivity for *H. pylori* detection was erythema (80.9%), present in 75 patients. Exudate (99.3%), nodularity (97.1%), and atrophy (95.7%) demonstrated better specificity values, but with low sensitivity (6.4%-19.1%). On the other hand, the absence of erythema on the gastric body was strongly associated with the absence of *H. pylori* infection (NPV = 92.0%).

In the antrum, all findings showed sensitivity below 75% (Table 2). Nodularity (98.6%) and atrophy (96.4%) had the best values for specificity, but both had low sensitivities (10.6%-23.4%). Exudate, although presenting with 100% specificity, was found in only one patient.

Endoscopic findings with near focus

With the use of NF (Table 3), the majority of patients presented with a type 1 pattern (56.2%), followed by type 2 (30.5%), type 3 (9.6%), and type 4 (3.7%). Type 1 pattern is the only one in which RAC is seen. Only six patients (5.7%) with RAC + were *H. pylori* positive. The loss of RAC presented with a sensitivity of 87.2% for *H. pylori* detection and a NPV of 94.3%, indicating that *H. pylori* infection was less likely when RAC was seen. All patients with type 4 pattern were *H. pylori* positive (PPV of 100%), albeit only seven patients presented with this pattern. Among patients with successful previous *H. pylori* treatment ($n = 25$), 21 (91.3%) were RAC positive (Table 4). Loss of RAC had a NPV of 91.3%, specificity of 84%, and an accuracy of 85.7% (Table 5).

Rapid urease test results

Four patients had RUT negative, but AP positive, and one patient had RUT positive and AP negative. Thus, RUT presented with a sensitivity of 91.5%, specificity of 100%,

Table 1 Patient's characteristics

Characteristics	Total (%)	*H. pylori* + (%) 47 (25.1%)	*H. pylori*-(%) 140 (74.9%)	*P* value
Age, yr				0.580
< 50	85 (45.5)	23 (48.9)	62 (44.3)	
> 50	102 (54.5)	24 (51.1)	78 (55.7)	
Gender				0.629
Male	74 (39.5)	20 (42.5)	54 (38.6)	
Female	113 (60.5)	27 (57.5)	86 (61.4)	
Symptoms				
Epigastric pain	83 (44.4)	26 (55.3)	57 (40.7)	0.081
Heartburn	40 (21.4)	9 (19.1)	31 (22.1)	0.665
Previous treated *H. pylori* infection	42 (22.5)	17 (36.2)	25 (17.9)	0.009

Chi-square test. *Helicobacter pylori*: *H. pylori*.

Table 2 Endoscopic findings with standard focus high definition white light and association with *Helicobacter pylori* infection

Location	Feature	Patients	Sensitivity % (95%CI)	Specificity % (95%CI)	PPV % (95%CI)	NPV % (95%CI)	AUC % (95%CI)	Accuracy % (95%CI)
Body	Erythema	75	80.9 (66.7-90.9)	73.6 (65.5-80.7)	50.7 (38.9-62.4)	92.0 (85.3-62.4)	0.77 (0.70-0.84)	75.4 (68.6-81.4)
	Erosion	16	10.6 (3.6-23.1)	92.1 (86.4-96.0)	31.3 (11.0-58.7)	75.4 (68.3-81.7)	0.51 (0.46-0.56)	71.7 (64.6-78.0)
	Exudate	4	6.4 (1.3-17.5)	99.3 (96.1-100)	75.0 (19.4-99.4)	76.0 (69.1-82.0)	0.53 (0.49-0.56)	75.9 (69.2-81.9)
	Atrophy	15	19.1 (9.1-33.3)	95.7 (90.9-98.4)	60.0 (71.0-83.9)	77.9 (71.0-83.9)	0.57 (0.52-0.63)	76.5 (69.7-82.3)
	Nodularity	7	6.4 (1.3-17.5)	97.1 (92.8-99.2)	42.9 (9.9-81.6)	75.6 (68.6-81.6)	0.52 (0.48-0.56)	74.3 (67.4-80.4)
Antrum	Erythema	87	72.3 (57.4-84.4)	62.1 (53.6-70.2)	39.1 (28.8-50.1)	87.0 (78.8-92.9)	0.67 (0.60-0.75)	64.7 (57.4-71.5)
	Erosion	38	21.3 (10.7-35.7)	80.0 (72.4-86.3)	26.3 (13.4-43.1)	75.2 (67.4-81.9)	0.51 (0.44-0.57)	65.2 (57.9-72.0)
	Exudate	1	2.1 (0.5-11.3)	100 (97.4-100)	100 (2.5-100)	75.3 (68.4-81.3)	0.51 (0.49-0.53)	75.4 (68.6-81.4)
	Atrophy	16	23.4 (12.3-38.0)	96.4 (91.9-98.8)	68.8 (41.3-89.0)	78.9 (72.1-84.8)	0.60 (0.54-0.66)	78.1 (71.4-83.8)
	Nodularity	7	10.6 (3.5-23.1)	98.6 (94.9-99.8)	71.4 (29.0-96.3)	76.7 (69.8-82.6)	0.55 (0.50-0.59)	76.5 (69.7-82.3)

CI: Confidence interval; PPV: Positive predictive value; NPV: Negative predictive value; AUC: Area under receiver operating characteristic curve.

PPV of 100%, NPV of 97.2%, and accuracy of 97.9%.

DISCUSSION

An endoscopic mucosal sample is the most common method used for *H. pylori* detection. However, it generates costs associated with biopsy forceps, reagent agents, vials, and pathologists, in addition to the risk of bleeding and other complications. Thus, a diagnostic method that excludes the need for large-scale biopsies with good cost-effectiveness is welcome both economically and logistically.

In 2002, Yagi *et al*[11] described the magnified view of *H. pylori* negative gastric mucosa and showed that the identification of collecting venules and capillaries forming a network with gastric pits in the center is indicative of *H. pylori*-negative normal mucosa. This pattern was named RAC. In a study with 557 patients submitted to endoscopy, the same authors demonstrated that the presence of RAC had a sensitivity of 93.6% and specificity of 96.2% as an indicator of a normal stomach without *H. pylori*[11]. Similar findings were reported by Anagnostopoulos *et al*[10], in a study including 95 patients in a Western population. The authors applied ME in the gastric body and showed that type 1 pattern predicted normal gastric mucosa with a

Table 3 Association between classifications and *Helicobacter pylori* infection of the gastric body

RAC	Classification	*Helicobacter pylori* status (%)		Total (%)
		Negative	Positive	
RAC +				
	Type 1	99 (94.3)	6.0 (5.7)	105 (56.2)
RAC -				
	Type 2	35 (61.4)	22 (38.6)	57 (30.5)
	Type 3	6 (33.3)	12 (66.7)	18 (9.6)
	Type 4	0 (0.0)	7 (100.0)	7 (3.7)
	Types 2, 3 and 4	41 (50)	41 (50)	82 (43.8)
Total		140 (74.9)	47 (25.1)	187 (100)

Chi-square test; $P < 0.001$. RAC: Regular arrangement of collecting venules.

Table 4 Association between regular arrangement of collecting venules and *Helicobacter pylori* infection in patients with previous *Helicobacter pylori* treatment

Classification	*Helicobacter pylori* status (%)		Total (%)
	Negative	Positive	
RAC +	21 (91.3)	2 (8.7)	23 (54.8)
RAC -	4 (21.1)	15 (78.9)	19 (45.2)
Total	25 (59.5)	17 (40.5)	42 (100)

RAC: Regular arrangement of collecting venules.

Table 5 Loss of regular arrangement of collecting venules with near focus high-definition examination in the gastric body and correlation with *Helicobacter pylori* infection

Loss of RAC	Sensitivity% (95%CI)	Specificity% (95%CI)	PPV % (95%CI)	NPV % (95%CI)	AUC % (95%CI)	Accuracy % (95%CI)
Overall (n = 187)	87.2 (74.3-95.2)	70.7 (62.4-78.1)	50.0 (38.7-61.3)	94.3 (88.0-97.9)	0.79 (0.73-0.85)	74.5 (67.6-80.5)
Patients without previous *Helicobacter pylori* treatment (n = 145)	86.7 (69.3-96.2)	67.8 (58.5-76.2)	41.3 (29.0-54.4)	95.1 (88.0-98.7)	0.77 (0.69-0.85)	71.7 (63.6-78.9)
Patients with previous *Helicobacter pylori* treatment (n = 42)	88.2 (63.6-98.5)	84.0 (63.9-95.5)	78.9 (54.4-93.9)	91.3 (72.0-98.9)	0.86 (0.73-0.97)	85.7 (71.5-94.6)

CI: Confidence interval; PPV: Positive predictive value; NPV: Negative predictive value; AUC: Area under receiver operating characteristic curve.

sensitivity of 92.7%, specificity of 100%, PPV of 100%, and NPV of 83.8%. However, magnification is time-consuming, requires training, and is not widely available in western centers. Therefore, the use of NF becomes an alternative due to its feasibility and availability.

In this study, we evaluated near-focus imaging for the diagnosis of *H. pylori* status of gastric mucosa. We showed that the loss of RAC had a sensitivity of 87% for detection of *H. pylori* and a NPV of 94.3%. Only six patients with RAC + were positive for *H. pylori*. In other words, if RAC was present, the probability of a *H. pylori* negative mucosa was 94.3%. In a prospective study with 140 patients, Garcés-Durán *et al*[14] used Olympus 190 gastroscopes to evaluate if the presence of RAC could rule out *H. pylori* infection in a western population. The authors did not mention if they applied NF to examine the gastric mucosa, so it is assumed that only S-HD exam was performed. The authors found a sensitivity and NPV of 100% for the exclusion of *H.*

pylori infection in RAC+ patients. In a congress report communication, Jang *et al*[18] compared NF + NBI with SD-WL for predicting *H. pylori* status. The sensitivity, specificity, PPV, and NPV were 86.5%, 84.1%, 84.1%, and 88.3% for NF + NBI and 57.7%, 92.1%, 53.0%, and 72.5% for SD-WL endoscopy, respectively. In a pediatric population (children and adolescents) using standard endoscopes, Machado *et al*[16] demonstrated that the absence of RAC had a sensitivity of 96.9% and a specificity of 88.1% in predicting *H. pylori* infection. Glover *et al*[21] showed that RAC becomes less visible with increasing age, presenting NVP of 93.0% for patients below 50 years and NVP of 90.7% for all ages. Table 6 shows a comparison between studies that addressed the association of RAC with *H. pylori* status. On the other hand, loss of RAC was present in 49/96 (51%) *H. pylori* negative patients in the study of Garcés-Durán *et al* [14], while in our study, loss of RAC was present in 41/140 (29%) *H. pylori* negative patients. This difference could be explained by the use of NF in our study. NF increased the sensitivity to identify capillary venules. Therefore, NF-HD resulted in increased specificity but decreased sensitivity for *H. pylori* detection applying the "loss of RAC" signal.

Although RAC identification with HD endoscopes has good accuracy to screen *H. pylori* negative patients, it seems that the loss of RAC is not so specific to confirm *H. pylori* infection. In this study, the loss of RAC was associated with *H. pylori* infection in only 50.6% (41/81) of the cases, with a PPV of 50%. These findings are in accordance with other studies where RAC negative patients presented *H. pylori* infection in 40-47.3% of patients[14,21,22]. With ME, Anagnostopoulos *et al*[10] presented that types 2 and 3 together had a specificity of 92.7% and PPV of 83.8% for predicting *H. pylori* infection.

Taken together, sensitivity of "loss of RAC" to predict *H. pylori* infection varied from 66% to 100% and specificity varied from 48% to 100%. Excluding the studies that used ME, the one with higher sensitivity was also the one with lower specificity[14]. The wide variability of sensitivity and specificity of RAC identification and *H. pylori* status among studies might be explained by different technology applied and different endoscopists' expertise. Apparently, there is lower variability of NPV among studies, meaning that the presence of RAC is a good indicator of *H. pylori* negative status.

Besides RAC, the best S-HD criteria to screen for *H. pylori* negative patients in this study was erythema, with NPV of 92%. The sensitivity of erythema for *H. pylori* detection was 80.9%, specificity 73.6%, and PPV 50.7%. Exudate, atrophy, and nodularity were the most specific findings. In a multicenter study including 24 facilities in Japan, Kato *et al*[23] studied the association of body erythema and *H. pylori* infection with S-HD. Spotty redness had sensitivity of 70.3%, specificity of 73.8, PPV of 75%, and NPV of 69.1%; diffuse redness, sensitivity of 83.4%, specificity of 66.9, PPV of 73.8%, and NPV of 78.4%. Machado *et al*[16] highlighted nodularity in children and adolescents as a strong predictor of *H. pylori* infection (98.5%). Absence of nodularity was associated with the presence of RAC, virtually excluding the probability of *H. pylori* (post-test probability 0.78%). In a series of 200 gastroscopic examination with S-HD[22], the presence of RAC and the Kimura-Takemoto classification grade C1 were predictive of *H. pylori* negative status, while atrophic changes and diffuse redness without RAC were significantly associated with *H. pylori* infection.

The awareness of these findings may lead endoscopists to change some practices during elective routine endoscopy. For example, many patients may be referred to endoscopy while using continuous PPI, which is known to decrease sensitivity of RUT and AP tests[3]. In this sense, findings of diffuse erythema, atrophy, or exudate on white light examination, as well as loss of RAC on NF exam, may lead the endoscopist to use more resources to increase the yield of *H. pylori* detection. This may include collecting more fragments and/or performing biopsies for histopathological analysis besides RUT. We also believe that a closer look at the mucosa must be routinely incorporated in elective upper endoscopy in order to look for the mucosal surface pattern. It is quick and easy to apply.

The reversal of mucosal changes after *H. pylori* eradication is still poorly understood. In this study, the accuracy of RAC pattern to predict *H. pylori* status in the group of patients with previous *H. pylori* treatment was 85.7% (95%CI: 71.5-94.6) compared with 71.1% (95%CI: 63.6-78.9) to the non-treated group. PPV was higher (78.9%; 95%CI: 54.4-93.9 *vs* 41.3%; 95%CI: 29.0-54.4), and NPV was similar (91.3; 95%CI: 72.0-98.9 *vs* 95.1%; 95%CI: 88.0-98.7). These findings could indicate that mucosal changes might be reversible in some cases.

Our study has some limitations. First, it is a single-institution study. It would be important to evaluate the interobserver agreement and to validate these findings in a multicenter study. On the other hand, our study supports the concept of first screening patients for the presence of RAC and deferring biopsy in patients positive for RAC.

Table 6 Studies associating loss of regular arrangement of collecting venules with the presence of *Helicobacter pylori*

Ref.	Country	*n*	RAC +	Technology	Sensitivity	Specificity	PPV	NPV
Machado *et al*[16], 2008	Brazil	99	60	SD	96.9	88.1	-	-
Cho *et al*[15], 2013	Korea	617	254	S-HD	93.3	89.1	92.	90.6
Yagi *et al*[17], 2014	Japan	38	26	S-HD	79	52	70	63
Garcés-Durán *et al*[14], 2019	Spain	140	47	S-HD	100	48.9	47.3	100
Ebigbo *et al*[22], 2021	German	200	-	S-HD	80.7	57.4	40.0	89.4
Glover *et al*[21], 2021	United Kingdom	153	108	S-HD	78.4	64.3	40.0	90.7
Jang *et al*[18], 2020	Korea	115	-	NF + NBI	86.5	84.1	84.1	88.3
Yagi *et al*[11], 2002	Japan	557	161	ME	93.8	96.2	-	-
Nakagawa *et al*[12], 2003	Japan	92	23	ME	66.7	100	100	82.4
Anagnostopoulos *et al*[10], 2007	United Kingdom	95	64	ME	100	92.7	83.8	100
Yagi *et al*[17], 2014	Japan	49	30	ME + NBI	91	83	88	86
This study	Brazil	187	105	NF	87.2	70.7	50.0	94.3

RAC: Regular arrangement of collecting venules; S-HD: Standard high definition; ME: Magnification endoscopy; SD: Standard definition; NF: Near focus; PPV: Positive predictive value; NPV: Negative predictive value.

CONCLUSION

In conclusion, the presence of RAC at the NF-HD exam and the absence of erythema in the gastric body at S-HD were predictive of *H. pylori* negative status. On the other hand, the loss of RAC had a poor association with the presence of *H. pylori*.

ARTICLE HIGHLIGHTS

Research background

In recent years, many advances in endoscopic imaging have surged, allowing for better characterization of gastric mucosal patterns. In 2001, Yao and Oishi described the characteristics of normal gastric mucosa with image magnification (ME). In the following year, Yagi *et al* described the differences between the magnified view of normal gastric mucosa from the pattern seen in patients with *Helicobacter pylori* (*H. pylori*)-associated gastritis. Although there are many studies correlating the findings of ME and *H. pylori* status, only a few validated these findings with high definition (HD) endoscopes without ME. Moreover, most of these studies were conducted in Asian countries, in centers with high expertise with magnifying images.

Research motivation

While magnification endoscopy is well incorporated in Asian countries, in Western countries most upper endoscopes devices are not equipped with this feature.

Research objectives

The aim of this study is to access the association between mucosal surface pattern under near focus HD (NF-HD) technology and *H. pylori* infection status in a western population.

Research methods

This was a cross-sectional study including all patients referred to routine upper endoscopy. Endoscopic exams were performed using standard HD (S-HD) followed by NF-HD examination. Presence of erythema , erosion, atrophy, and nodularity were recorded during S-HD, and surface mucosal pattern was classified using NF-HD in the gastric body, based on the classification proposed by Anagnostopoulos *et al*. Biopsies were taken for rapid urease test and histology.

Research results

One hundred and eighty-seven patients were included in the study, of those, 47 (25.1%) were *H. pylori* +. In the examination with S-HD, erythema had the best sensitivity for *H. pylori* detection (80.9%). On the other hand, the absence of erythema was strongly associated with *H. pylori*- (negative predictive value = 92%). With NF-HD, the loss of the regular arrangement of collecting venules (RAC) presented 87.2% sensitivity for *H. pylori* detection and 94.3% negative predictive value, indicating that loss of RAC was suboptimal to confirm *H. pylori* infection, but when RAC was seen, *H. pylori* infection was unlikely.

Research conclusions

Presence of RAC at the NF-HD exam and the absence of erythema in the gastric body at S-HD were predictive of *H. pylori* negative status. The loss of RAC had a poor association with the presence of *H. pylori*.

Research perspectives

Our study supports the concept of first screening patients for the presence of RAC and deferring biopsy in patients positive for RAC.

REFERENCES

1 **Correa P**, Piazuelo MB. The gastric precancerous cascade. *J Dig Dis* 2012; **13**: 2-9 [PMID: 22188910 DOI: 10.1111/j.1751-2980.2011.00550.x]

2 **Dinis-Ribeiro M**, Areia M, de Vries AC, Marcos-Pinto R, Monteiro-Soares M, O'Connor A, Pereira C, Pimentel-Nunes P, Correia R, Ensari A, Dumonceau JM, Machado JC, Macedo G, Malfertheiner P, Matysiak-Budnik T, Megraud F, Miki K, O'Morain C, Peek RM, Ponchon T, Ristimaki A, Rembacken B, Carneiro F, Kuipers EJ; European Society of Gastrointestinal Endoscopy; European Helicobacter Study Group; European Society of Pathology; Sociedade Portuguesa de Endoscopia Digestiva. Management of precancerous conditions and lesions in the stomach (MAPS): guideline from the European Society of Gastrointestinal Endoscopy (ESGE), European Helicobacter Study Group (EHSG), European Society of Pathology (ESP), and the Sociedade Portuguesa de Endoscopia Digestiva (SPED). *Endoscopy* 2012; **44**: 74-94 [PMID: 22198778 DOI: 10.1055/s-0031-1291491]

3 **Coelho LGV**, Marinho JR, Genta R, Ribeiro LT, Passos MDCF, Zaterka S, Assumpção PP, Barbosa AJA, Barbuti R, Braga LL, Breyer H, Carvalhaes A, Chinzon D, Cury M, Domingues G, Jorge JL, Maguilnik I, Marinho FP, Moraes-Filho JP, Parente JML, Paula-E-Silva CM, Pedrazzoli-Júnior J, Ramos AFP, Seidler H, Spinelli JN, Zir JV. IVTH brazilian consensus conference on helicobacter pylori infection. *Arq Gastroenterol* 2018; **55**: 97-121 [PMID: 30043876 DOI: 10.1590/S0004-2803.201800000-20]

4 **Uemura N**, Okamoto S, Yamamoto S, Matsumura N, Yamaguchi S, Yamakido M, Taniyama K, Sasaki N, Schlemper RJ. Helicobacter pylori infection and the development of gastric cancer. *N Engl J Med* 2001; **345**: 784-789 [PMID: 11556297 DOI: 10.1056/NEJMoa001999]

5 **Ford AC**, Forman D, Hunt RH, Yuan Y, Moayyedi P. Helicobacter pylori eradication therapy to prevent gastric cancer in healthy asymptomatic infected individuals: systematic review and meta-analysis of randomised controlled trials. *BMJ* 2014; **348**: g3174 [PMID: 24846275 DOI: 10.1136/bmj.g3174]

6 **Chen HN**, Wang Z, Li X, Zhou ZG. Helicobacter pylori eradication cannot reduce the risk of gastric cancer in patients with intestinal metaplasia and dysplasia: evidence from a meta-analysis. *Gastric Cancer* 2016; **19**: 166-175 [PMID: 25609452 DOI: 10.1007/s10120-015-0462-7]

7 **Chai NL**, Ling-Hu EQ, Morita Y, Obata D, Toyonaga T, Azuma T, Wu BY. Magnifying endoscopy in upper gastroenterology for assessing lesions before completing endoscopic removal. *World J Gastroenterol* 2012; **18**: 1295-1307 [PMID: 22493543 DOI: 10.3748/wjg.v18.i12.1295]

8 **Yao K**, Oishi T. Microgastroscopic findings of mucosal microvascular architecture as visualized by magnifyin endoscopy. *Dig Endosc* 2001; **13**: 27-33 [DOI: 10.1111/j.1443-1661.2001.00114.x]

9 **Yagi K**, Nakamura A, Sekine A. Comparison between magnifying endoscopy and histological, culture and urease test findings from the gastric mucosa of the corpus. *Endoscopy* 2002; **34**: 376-381 [PMID: 11972268 DOI: 10.1055/s-2002-25281]

10 **Anagnostopoulos GK**, Yao K, Kaye P, Fogden E, Fortun P, Shonde A, Foley S, Sunil S, Atherton JJ, Hawkey C, Ragunath K. High-resolution magnification endoscopy can reliably identify normal gastric mucosa, Helicobacter pylori-associated gastritis, and gastric atrophy. *Endoscopy* 2007; **39**: 202-207 [PMID: 17273960 DOI: 10.1055/s-2006-945056]

11 **Yagi K**, Nakamura A, Sekine A. Characteristic endoscopic and magnified endoscopic findings in the normal stomach without Helicobacter pylori infection. *J Gastroenterol Hepatol* 2002; **17**: 39-45 [PMID: 11895551 DOI: 10.1046/j.1440-1746.2002.02665.x]

12 **Nakagawa S**, Kato M, Shimizu Y, Nakagawa M, Yamamoto J, Luis PA, Kodaira J, Kawarasaki M, Takeda H, Sugiyama T, Asaka M. Relationship between histopathologic gastritis and mucosal microvascularity: observations with magnifying endoscopy. *Gastrointest Endosc* 2003; **58**: 71-75

[PMID: 12838224 DOI: 10.1067/mge.2003.316]
13 **Jang HY**, Hong SJ, Han JP, Park SK, Yun HK, Ko BJ. Comparison of the Diagnostic Usefulness of Conventional Magnification and Near-focus Methods with Narrow-band Imaging for Gastric Epithelial Tumors. *Korean J Helicobacter Up Gastrointest Res* 2015; **15**: 39 [DOI: 10.7704/kjhugr.2015.15.1.39]
14 **Garcés-Durán R**, García-Rodríguez A, Córdova H, Cuatrecasas M, Ginès À, González-Suárez B, Araujo I, Llach J, Fernández-Esparrach G. Association between a regular arrangement of collecting venules and absence of Helicobacter pylori infection in a European population. *Gastrointest Endosc* 2019; **90**: 461-466 [PMID: 31108089 DOI: 10.1016/j.gie.2019.05.027]
15 **Cho JH**, Chang YW, Jang JY, Shim JJ, Lee CK, Dong SH, Kim HJ, Kim BH, Lee TH, Cho JY. Close observation of gastric mucosal pattern by standard endoscopy can predict Helicobacter pylori infection status. *J Gastroenterol Hepatol* 2013; **28**: 279-284 [PMID: 23189930 DOI: 10.1111/jgh.12046]
16 **Machado RS**, Viriato A, Kawakami E, Patrício FR. The regular arrangement of collecting venules pattern evaluated by standard endoscope and the absence of antrum nodularity are highly indicative of Helicobacter pylori uninfected gastric mucosa. *Dig Liver Dis* 2008; **40**: 68-72 [PMID: 17988964 DOI: 10.1016/j.dld.2007.08.003]
17 **Yagi K**, Saka A, Nozawa Y, Nakamura A. Prediction of Helicobacter pylori status by conventional endoscopy, narrow-band imaging magnifying endoscopy in stomach after endoscopic resection of gastric cancer. *Helicobacter* 2014; **19**: 111-115 [PMID: 24372729 DOI: 10.1111/hel.12104]
18 **Jang JY**, Baek S, Ryu B, Park YM, Oh CH, Kim JW. Usefulness of Near-Focus magnification with Narrow-Band Imaging in the prediction of helicobacter pylori infection: a prospective trial. *Gastrointest Endosc* 2020; **91**: AB242-AB243 [DOI: 10.1016/j.gie.2020.03.1789]
19 **Bisschops R**, Areia M, Coron E, Dobru D, Kaskas B, Kuvaev R, Pech O, Ragunath K, Weusten B, Familiari P, Domagk D, Valori R, Kaminski MF, Spada C, Bretthauer M, Bennett C, Senore C, Dinis-Ribeiro M, Rutter MD. Performance measures for upper gastrointestinal endoscopy: a European Society of Gastrointestinal Endoscopy (ESGE) Quality Improvement Initiative. *Endoscopy* 2016; **48**: 843-864 [PMID: 27548885 DOI: 10.1055/s-0042-113128]
20 **Gonen C**, Simsek I, Sarioglu S, Akpinar H. Comparison of high resolution magnifying endoscopy and standard videoendoscopy for the diagnosis of Helicobacter pylori gastritis in routine clinical practice: a prospective study. *Helicobacter* 2009; **14**: 12-21 [PMID: 19191891 DOI: 10.1111/j.1523-5378.2009.00650.x]
21 **Glover B**, Teare J, Patel N. Assessment of *Helicobacter pylori* status by examination of gastric mucosal patterns: diagnostic accuracy of white-light endoscopy and narrow-band imaging. *BMJ Open Gastroenterol* 2021; **8** [PMID: 34353822 DOI: 10.1136/bmjgast-2021-000608]
22 **Ebigbo A**, Marienhagen J, Messmann H. Regular arrangement of collecting venules and the Kimura-Takemoto classification for the endoscopic diagnosis of Helicobacter pylori infection: Evaluation in a Western setting. *Dig Endosc* 2021; **33**: 587-591 [PMID: 32767790 DOI: 10.1111/den.13808]
23 **Kato T**, Yagi N, Kamada T, Shimbo T, Watanabe H, Ida K; Study Group for Establishing Endoscopic Diagnosis of Chronic Gastritis. Diagnosis of Helicobacter pylori infection in gastric mucosa by endoscopic features: a multicenter prospective study. *Dig Endosc* 2013; **25**: 508-518 [PMID: 23369058 DOI: 10.1111/den.12031]

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CASE REPORT

Endoscopic treatment of periampullary duodenal duplication cysts in children: Four case reports and review of the literature

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Author contributions: Bulotta AL, Stern MV and Alberti D conceptualized and designed the study; Bulotta AL, Stern MV, Parolini F, Boroni G and Alberti D were involved in medical care of the patients; Bondioni MP performed radiological investigations; Missale G and Moneghini D performed endoscopic treatment; Stern MV, Bulotta AL and Parolini F collected the clinical data from patients and from literature; All authors contributed equally to preparation of the manuscript and reviewed and approved the final manuscript as submitted.

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Abstract

BACKGROUND

Duodenal duplications are rare congenital anomalies of the gastrointestinal tract. As the periampullary variant is much rarer, literature is scant and only few authors have reported their experience in diagnosis and treatment, particularly with operative endoscopy.

CASE SUMARY

To report our experience with the endoscopic treatment in a series of children with periampullary duodenal duplication cysts, focusing on the importance of obtaining an accurate preoperative anatomic assessment of the malformations. The pediatric periampullary duodenal duplication cyst literature is reviewed. We conducted a systematic review according to the PRISMA guidelines. The PubMed database was searched for original studies on "duodenal duplication", "periampullary duplication" or "endoscopic management" published since 1990, involving patients younger than 18 years of age. Eligible study designs were case report, case series and reviews. We analyzed the data and reported the results in table and text. Fifteen eligible articles met the inclusion criteria with 16 patients, and analysis was extended to our additional 4 cases. Median age at diagnosis was 13.5 years. Endoscopic treatment was performed in 10 (50%) patients, with only 2 registered complications.

CONCLUSION

Periampullary duodenal duplication cysts in pediatric patients are very rare. Our

according to the PRISMA 2009 Checklist.

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experience suggests that an accurate preoperative assessment is critical. In the presence of sludge or stones inside the duplication, endoscopic retrograde cholangio-pancreatography is mandatory to demonstrate a communication with the biliary tree. Endoscopic treatment resulted in a safe, minimally invasive and effective treatment. In periampullary duodenal duplication cyst endoscopically treated children, long-term follow-up is still necessary considering the potential malignant transformation at the duplication site.

Key Words: Periampullary duodenal duplication cyst; Duodenal duplication; Endoscopic ultrasound; Endoscopic treatment; Double wall sign; Case report

Core Tip: Periampullary duodenal duplications are extremely uncommon in children. The authors report a series of 4 patients and provide a detailed literature review.

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INTRODUCTION

Duodenal duplications (DD) are rare congenital anomalies of the gastrointestinal tract, which usually arise during the first decade of life[1-3]. Due to variability of location and size, DD do not display pathognomonic clinical presentation, but they can manifest with a variety of complications including pancreatitis, bleeding, perforation and duodenal obstruction[1]. Unfortunately, little is reported about the anatomical details of DD, which can be divided into two groups: periampullary and non-periampullary duplication cyst. Periampullary duodenal duplication cysts (PADDC) are defined as cysts located near the major papilla and the biliary-pancreatic ampulla, sometimes with a small aberrant pancreatic duct drained into the cyst[4]. As the periampullary variant is much rarer, literature is scant and only few authors have reported their experience in diagnosis and treatment. Moreover, the recent introduction of operative endoscopy for DD treatment in adults has also been extended to the pediatric population with promising results[5-10].

The aim of this paper is to report our experience with the endoscopic treatment (ET) in a series of children with PADDC, focusing on the importance of obtaining an accurate preoperative anatomic assessment of the malformations. The pediatric PADDC literature is reviewed.

CASE PRESENTATION

All consecutive children with PADDC managed at our tertiary-level institution from 2015 to 2020 were retrospectively reviewed. A written consent was obtained from all patients. All data were retrospectively collected and recorded according to the Declaration of Helsinki.

Chief complaints

Case 1, 2 and 4: Abdominal pain.

Case 3: Abdominal pain and vomiting.

History of present illness

Case 1: A 14-year-old boy was admitted with a 1-year history of recurrent pancreatitis. The abdominal computed tomography (CT) scan, previously performed at another

center, showed a cyst within the duodenal lumen.

Case 2: A 16-year-old girl was admitted to our emergency room with abdominal pain.

Case 3: A Chinese 11-year-old girl was admitted for 1-year history of epigastric pain with vomiting and weight loss.

Case 4: An 11-year-old girl was admitted to our unit with abdominal pain and vomiting.

History of past illness

Case 1: His previous history was unremarkable.

Case 2: In the past 2 years she had suffered from recurrent abdominal pain due to pancreatitis.

Case 3: The girl was previously examined in her country, and a CT scan showed a cyst in the second part of the duodenum.

Case 4: Unremarkable.

Personal and family history

Unremarkable.

Physical examination upon admission

Case 1: On inspection, the abdomen was distended with tenderness in epigastrium upon superficial and deep palpation.

Case 2: Physical examination at admission showed a mild distended abdomen and diffuse tenderness upon superficial and deep palpation.

Case 3: Physical examination showed mild diffuse abdominal tenderness upon superficial and deep palpation.

Case 4: Physical examination showed severe tenderness upon superficial and deep palpation of the upper abdomen.

Laboratory examination

Case 1: Laboratory values revealed an increased serum levels of lipase (1077 UI/L; normal value (n.v.) 70-280 UI/L), amylase 514 UI/L (n.v. 15-53 UI/L) and C-reactive protein 168 mg/dL (n.v. < 5 mg/L), while gamma glutamyl transferase 69 U/L (n.v. 6-42 UI/L), count of blood cells, white cell count, total and conjugated bilirubin, alkaline phosphatase level, aspartate aminotransferase and alanine aminotransferase were normal.

Case 2: Blood samples revealed increased serum levels of lipase (2365 UI/L; n.v. 70-280 UI/L); the full panel of liver tests including cholestasis indexes were normal. US showed the presence of an anechoic cystic lesion within the pancreatic head. Intrahepatic and extrahepatic biliary ducts were normal.

Case 3: Laboratory values revealed increased serum levels of lipase (43440 UI/L; n.v. 70-280 UI/L). The full panel of liver tests was normal.

Case 4: Biochemical investigation revealed hyperlipasemia (5497 UI/L; n.v. 70-280 UI/L) and increased levels of aspartate aminotransferase (5.3 x n.v.), alanine aminotransferase (9.2 x n.v.) and gamma-glutamyl transferase (169 UI/L, n.v. 6-42).

Imaging examination

Case 1: The radiological workup first included an abdominal ultrasound (US) that showed a heterogeneous hyperechogenicity of the whole pancreas and an intraluminal duodenal cyst (5.8 cm x 4.5 cm x 4.0 cm in size) near the pancreas head. An 8.5 mm dilatation of the main common bile duct (CBD) was also detected. Intrahepatic biliary ducts and gallbladder were normal.

A magnetic resonance imaging (MRI) on HASTE T2-w sequence showed a homogeneously hyperintense cyst below the pancreatic head, located within a partially occluded duodenum (Figure 1A). On cholangiographic reconstruction the intrahepatic bile ducts were normal, the cystic duct appeared dilated with a tortuous course and the common hepatic duct presented saccular dilation. CBD had a caliber at

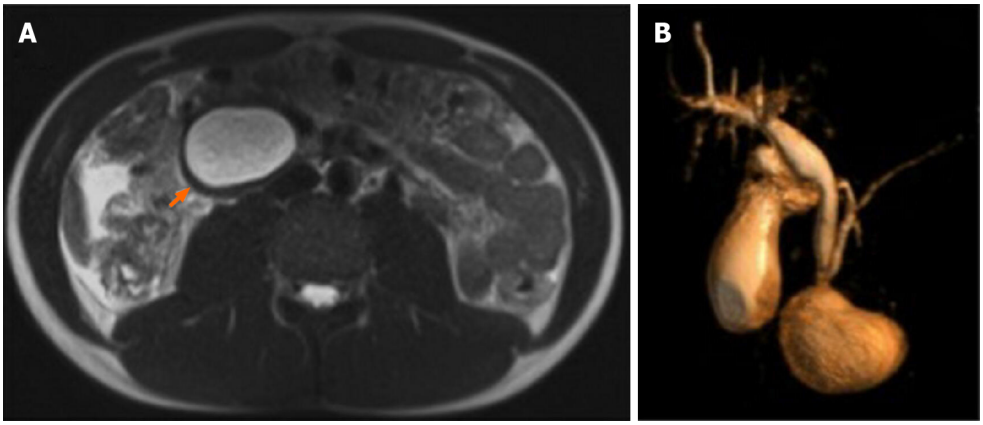

Figure 1 Magnetic resonance imaging on HASTE T2 w sequence. A: Homogeneously hyperintense cyst located within the duodenum, which was partially occluded (arrow); B: On 3D cholangiographic reconstruction, intrahepatic bile ducts were normal, cystic duct was dilated with tortuous course and common hepatic duct presented saccular dilation. Common bile duct had a caliber at the upper limits of the normal range with a regular course and was in communication with periampullary duodenal duplication cysts.

the upper limits of the normal range with a regular course; the Wirsung duct was normal (Figure 1B).

Case 2: An MRI on HASTE T2 w sequence revealed (Figure 2) a round homogeneous hyperintense lesion on the pancreas uncinate process, determining a major compression of the second portion of the duodenum. At cholangiographic reconstruction, the intra- and extrahepatic biliary tree along with the pancreatic ductal system were normal (Figure 2B).

Case 3: An MRI on HASTE T2 w sequence showed an oval heterogeneous hyperintense lesion, measuring 4.5 cm x 3.5 cm, containing multiple stones and located in the second part of the duodenum. Cholangiographic reconstruction indicated a normal/physiologic gallbladder as well as intra- and extrahepatic bile ducts. The lesion, irregularly hyperintense, was located below the gallbladder and laterally to the CBD and pancreatic duct (Figures 3 and 4).

Case 4: US examination found a cyst (2.5 cm × 2.5 cm × 1.6 cm) sharing bowel wall stratification with the second part of the duodenum and full of hyperechogenic debris. An MRI on HASTE T2 sequence detected an oval mass, located below the gallbladder and laterally to the CBD and pancreatic duct (Figure 5), adjacent to the pancreatic head. The cyst was filled with fluid and multiple stones. Cholangiographic reconstruction indicated a normal gallbladder and intra- and extrahepatic bile ducts.

FINAL DIAGNOSIS

Case 1

Endoscopic ultrasound (EUS) showed a bulging in the second duodenal portion, covered with normal mucosa, next to the Vater's papilla and filled with biliary sludge (Figure 6). The lesion preserved a five-layer wall consisting with the typical echoendoscopic feature for the gastrointestinal wall consistent with a PADDC, and ET was proposed to parents.

Case 2

A EUS showed an anechoic cystic lesion within the second duodenal portion, characterized by normal echographic bowel wall stratification and containing multiple hyperechoic stones; the cyst was not in communication with the CBD, and thereby PADDC was diagnosed.

Case 3

A EUS revealed an anechoic cystic lesion characterized by a normal echographic bowel wall stratification and containing biliary sludge.

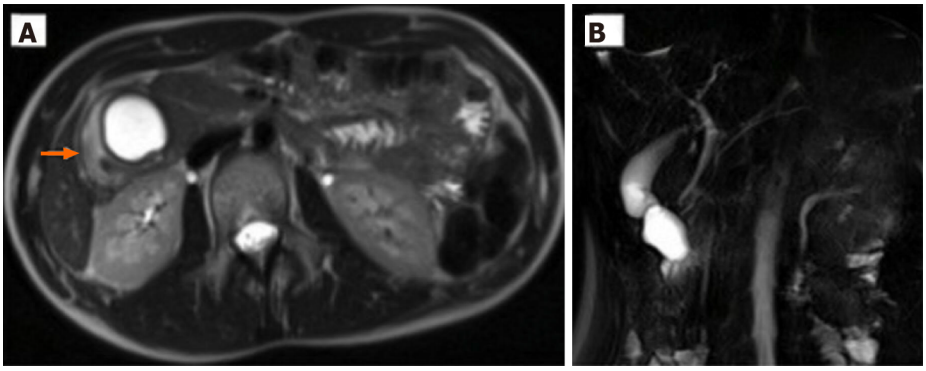

Figure 2 Magnetic resonance imaging of case 2. A: Round homogeneously hyperintense lesion at the level of uncinate process of the pancreas determined a major compression on the second portion of duodenum (arrow); B: At cholangiographic reconstruction, the intra- and extrahepatic biliary tree and pancreatic ductal system were normal.

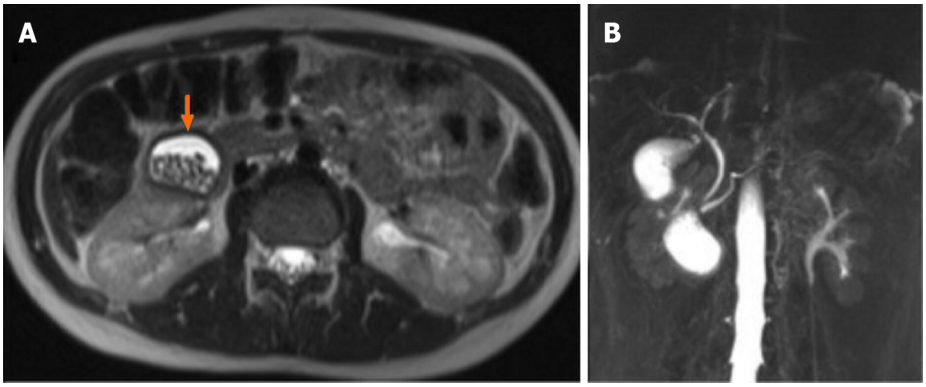

Figure 3 Magnetic resonance imaging of case 3. A: An oval heterogeneously hyperintense lesion containing multiple stones and located in the second part of the duodenum; B: Cholangiographic reconstruction showed normal gallbladder and intra- and extrahepatic bile ducts.

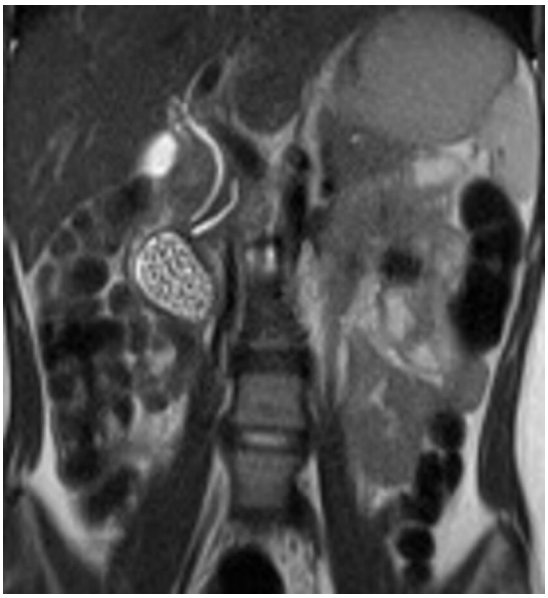

Figure 4 Magnetic resonance imaging showed periampullary duodenal duplication cysts filled with stones.

Case 4

Duodenoscopy revealed an intraduodenal cyst, next to the papilla of Vater and not in communication with the duodenal lumen.

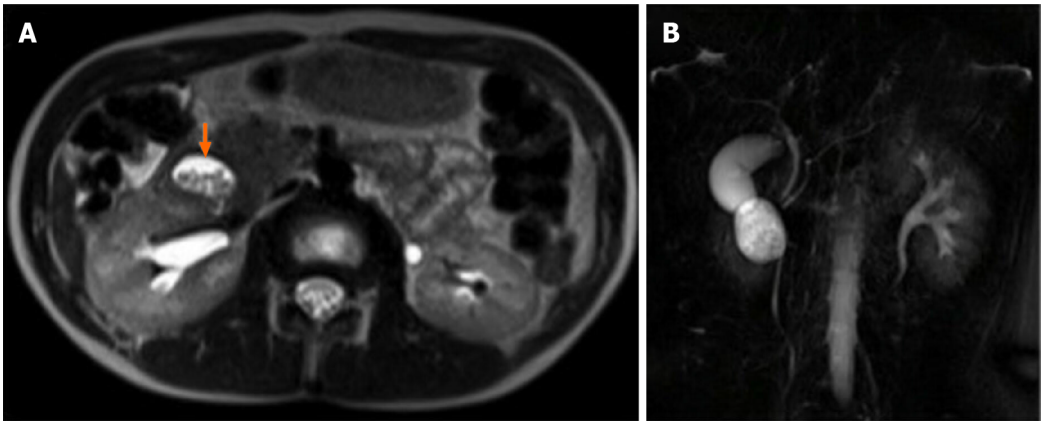

Figure 5 Magnetic resonance imaging. A: Oval mass is located below the gallbladder and lateral to the common bile duct and pancreatic duct, adjacent to the pancreatic head. The cyst was filled with fluid and multiple stones; B: Cholangiographic reconstruction showed normal gallbladder and intra- and extrahepatic bile ducts.

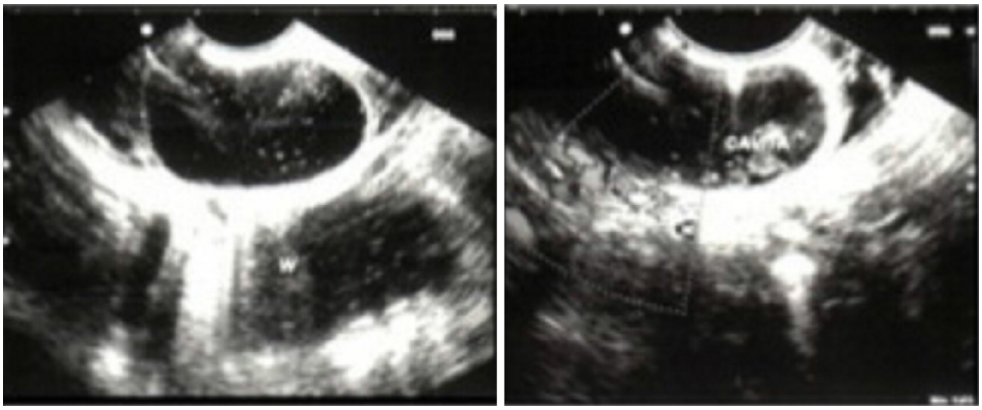

Figure 6 Endoscopic ultrasound. The probe is inside the duodenum, and the common wall separates the duodenum and the duodenal duplication.

TREATMENT

Case 1

Upon endoscopic retrograde cholangio-pancreatography (ERCP), elective cannulation of the CBD showed a direct communication with the cyst and multiple stones in its lumen. A sphincterotome incision of the wall cyst, laterally to the papilla, was performed, and the stones were removed.

Case 2

Upon ERCP, a small orifice on the lateral surface of the cyst was cannulated; a contrast injection failed to demonstrate any communication with the CBD. Intracystic stones were confirmed. The DD wall was incised with sphincterotome,, and stones were removed.

Case 3

ERCP showed a regular main pancreatic duct; after distal papillotomy, contrast was injected, and it filled the PADDC (Figure 7). Marsupialization of the cyst with sphincterotome was then performed.

Case 4

ERCP showed a normal pancreatic duct, dilation of CBD (20 mm diameter) without a detectable communication with the cyst. Cyst marsupialization was performed with subsequent extraction of biliary microstones (Figure 8).

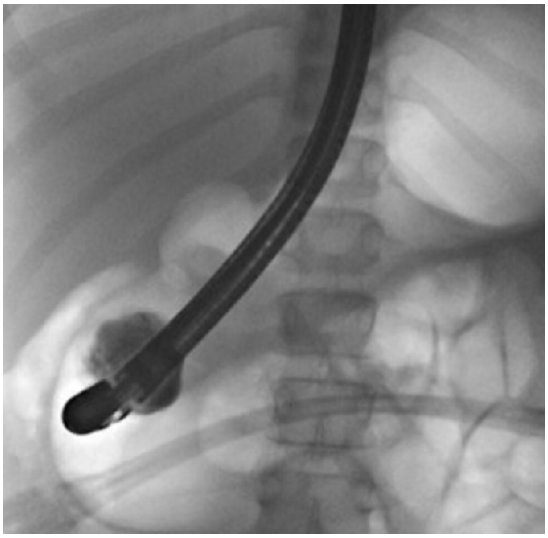

Figure 7 Endoscopic retrograde cholangio-pancreatography. After distal papillotomy, contrast filled the periampullary duodenal duplication cysts.

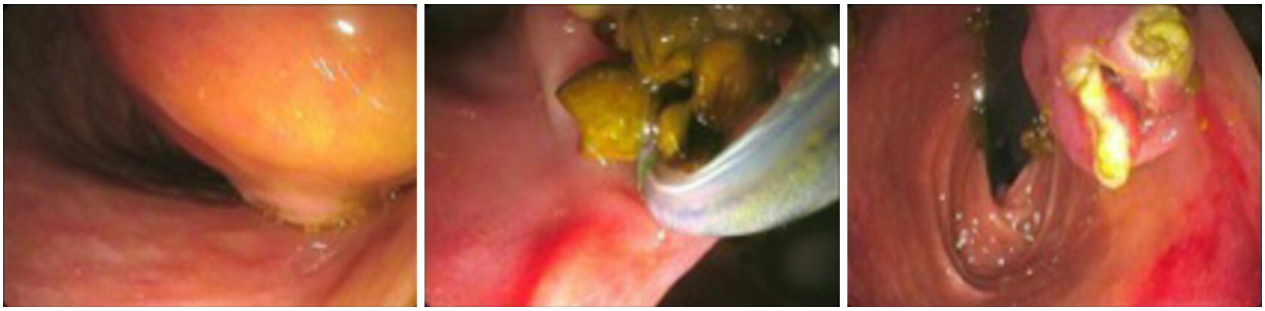

Figure 8 Cyst marsupialization was performed with subsequent extraction of biliary microstones.

OUTCOME AND FOLLOW-UP

Case 1

The patient had an uneventful postoperative course and was discharged home 8 d later with a quick resolution of the abdominal pain and normalization of serum pancreatic enzymes. Ursodeoxycholic acid therapy and a hypolipic diet were continued until the next follow-up. At the 3 mo follow-up, magnetic resonance cholangiopancreatography (MRCP) control after ET, PADDC was no longer detected (Figure 9). At the 10-year follow-up the patient is doing well, without any therapy or further episodes of pancreatitis.

Case 2

The patient had an uneventful recovery and was discharged home 2 d after the procedure with low fat meals. The 9 mo follow-up MRCP did not show any residual duplication (Figure 10), and at 8 years follow-up no further pancreatitis episodes were reported.

Case 3

The postoperative course was complicated by severe melena on day 3, which required packed red cell transfusion. Esophagogastroduodenoscopy detected bleeding at the cyst section site. Endoscopic metallic clip placement was effective for bleeding control. The patient showed a progressive normalization of the serum lipase, and she was discharged home with ursodeoxycholic acid therapy and a low-fat diet. MRCP, done 2 mo later, did not show any duodenal cyst or intra- or extrahepatic bile and pancreatic duct dilatation. At the 4-year follow-up, she was well, and no further episodes of abdominal pain were reported.

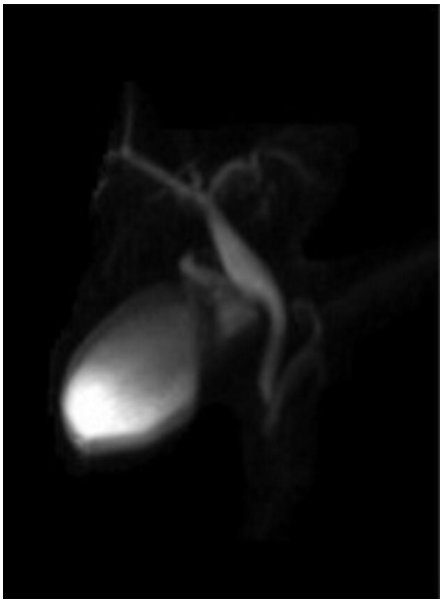

Figure 9 Magnetic resonance cholangiopancreatography performed 3 months after the endoscopic treatment did not show periampullary duodenal duplication cysts.

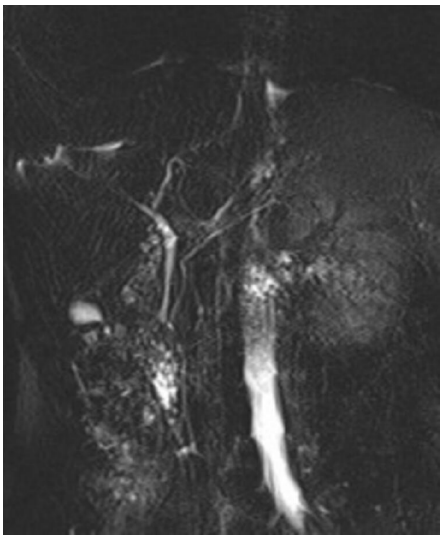

Figure 10 Magnetic resonance cholangiopancreatography performed after 9 mo endoscopic treatment did not show periampullary duodenal duplication cysts.

Case 4

The patient had an uneventful recovery and was discharged home 10 d after the procedure, with an ursodeoxycholic acid therapy and low-fat meals for 3 mo.

At the 2-year follow-up, she was totally asymptomatic, abdominal US was normal, and she eats a free diet.

Literature search

This literature review was performed according to preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines[11] (Figure 11). The PubMed database was searched for original studies on "duodenal duplication," "periampullary duplication" or "endoscopic management" published since 1990, involving patients younger than 18 years of age. Eligible study designs were case reports, case series and reviews. We omitted reports in which abstracts indicated an adult population (> 18 years) and improper reporting of the diagnosis and treatment methods. We then evaluated the full text of the selected articles and consider PADDC only where that diagnosis was confirmed by authors.

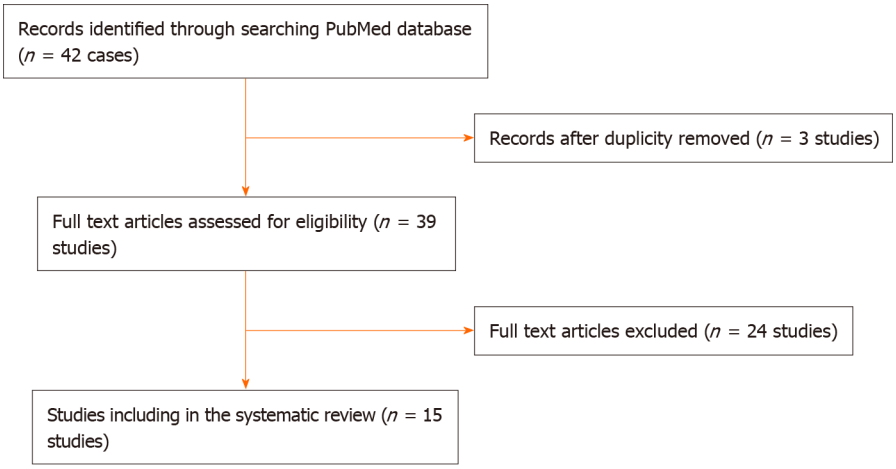

Figure 11 PRISMA 2009 flow diagram.

According to Tröbs *et al*[4], PADDC were defined as cysts located near the major papilla and the biliary-pancreatic ampulla that can have a small aberrant pancreatic duct drained into the cyst. We excluded all patients with a diagnosis of biliary/gallbladder disease (including acute acalculous cholecystitis) or with a diagnosis of duodenal duplication not located near the major papilla.

The date of the last search was December 2020. For each study, data were extracted for two primary outcomes (diagnostic assessment and type of treatment) and several secondary outcomes (including sex and age at presentation, clinical presentation, pathological examination and outcome). Analysis was extended to our additional 4 cases.

Research results

The initial PubMed search yielded 42 potentially relevant studies. Eventually, 16 eligible articles met the inclusion criteria, involving a total of 17 children with PADDC [1,3,4,6-9,12-20] (Table 1 and Figure 11). All selected studies were case reports (class of evidence III and rating scale of evidence E) and clearly reported the two primary outcomes.

The patients' median age at diagnosis was 14 years (range: 3-18 years), and PADDC was reported in 10 males and 8 females. For 3 patients, data were not available. Clinical presentation was unspecific, with abdominal pain reported in all cases. Recurrent pancreatitis was the most common complication and was observed in 14 cases (70%), followed by cholestasis, jaundice and intussusception.

All patients underwent abdominal ultrasound, followed by abdominal CT scan in 18 cases (90%), ERCP in 13 (65%), MRCP in 7 (35%) and EUS in 8 (4%); 1 patient was only examined with ERCP (5%) (Table 1).

Endoscopic treatment was performed in 10 patients (50%), with two reported complications, namely bleeding at the duplication incision site, which were treated with packed red cell transfusion and endoscopic clipping of the bleeding site in one case and with local injection of epinephrine in the other case (Table 1) [9]. The median follow-up was 22.5 mo (range: 4-108 mo); all endoscopically treated patients are doing well with disappearance of the duplication on imaging. No case of malignancy was reported.

DISCUSSION

Duodenal duplications are uncommon congenital anomalies of the gastrointestinal tract, which usually present during the first decade of life[4,5]. They represent 5%-7% of all gastrointestinal duplications and result from disturbances in the embryonic development, probably due to duodenal epithelial pinching during the outgrowth of the dorsal pancreatic bud or secondary to an epithelial sequestration[4]. The majority of them are cystic, adherent and located on the mesenteric side of the second or third portion of the duodenum, with an epithelial mucosal lining and a smooth muscle layer [10,21]. A communication with the duodenal lumen has been reported in up to 25% of cases[1], and some authors have also described the possibility of a pancreato-biliary

Table 1 Data of included studies

Ref.	Year	Age	Sex	Clinical	Laboratory data	US	MR/CT	EUS	ERCP	Description	Treatment and complications
Mattioli *et al* [13]	1999	11 yr	F	Abdominal pain	NA	Yes	Yes (CT)	No	Yes	Periampullary duplication	Surgical resection
Zamir *et al*[16]	1999	17 yr	M	Abdominal pain, duodeno-jejunal intussusception	AST/ALT, 50/140; ALP 250, GGT 400	Yes	Yes (CT)	No	No	Periampullary duplication	Surgical cyst marsupialization
Niehues *et al* [18]	2005	16 yr	M	Abdominal pain, jaundice	Lipase 3343	Yes	Yes (CT and MRCP)	No	Yes	Periampullary duplication	Surgical resection and cholecystectomy
Guarise *et al* [2]	2006	18 yr	M	Abdominal pain, pancreatitis	NA	Yes	Yes (CT and MRCP)	Yes	Yes	Periampullary duplication	Surgical resection
Chryssostalis *et al*[8]	2007	17 yr	-	Abdominal pain Recurrent pancreatitis	NA	Yes	Yes (CT)	No	Yes	Periampullary duplication	Endoscopic excision of the cyst
Ozel *et al*[14]	2008	8 yr	F	Abdominal pain, pancreatitis	Amylase 1287	Yes	Yes (CT)	No	No	Periampullary duplications	Surgical resection
Chen *et al*[3]	2009	8 yr	F	Abdominal pain, pancreatitis	Amylase 155; lipase 109	Yes	Yes (CT and MRCP)	No	Yes	Periampullary duplication	Surgical cyst marsupialization
Tröbs *et al*[4]	2009	8 yr	M	Abdominal pain, pancreatitis, hepatitis	Lipase 3000	Yes	Yes (CT and MRCP)	No	No	Periampullary duplication	Surgicalcyst marsupialization
Tekin *et al*[7]	2009	18 yr	F	Abdominal pain, pancreatitis	NA	Yes	Yes (CT)	No	Yes	Periampullary duplication	Endoscopic sphincterotomy and stent implantation
Criblez *et al* [17]	2011	17 yr	M	Abdominal pain	Lipase 5400	Yes	Yes (CT)	No	Yes	Periampullary duplication	Endoscopic cyst marsupialization and sphincterotomy
Romeo *et al*[9]	2011	-	-	Recurrent pancreatitis	NA	Yes	Yes (CT and MRCP)	Yes	Yes	Periampullary duplication	Surgical resection of common wall
		-	-	Recurrent pancreatitis	NA	Yes	Yes (CT and MRCP)	Yes	No	Periampullary duplication	Endoscopic cyst wall resection
Meier *et al*[6]	2012	9 yr	M	Abdominal pain	Amylase 270 U/ml; Lipase 824 U/ml	Yes	Yes (CT and MRCP)	No	Yes	Periampullary duplication	Endoscopic opening of cyst wall
Koffie *et al*[12]	2012	13 yr	M	Abdominal pain, hepatitis and pancreatitis	Lipase 1363; Amylase 401, direct bilirubin 9.1	Yes	Yes (CT and MRCP)	No	No	Periampullary duplication	Surgical resection
Taghavi *et al* [15]	2017	17 yr	M	Recurrent pancreatitis	NA	Yes	Yes (MRCP)	No	No	Periampullary duplication	Surgical resection, sphincteroplasty of terminal pancreatic duct and stent positioning.
Salazar *et al* [19]	2018	3 yr	M	Abdominal pain, pancreatitis	NA	Yes	Yes (MRCP)	Yes	No	Periampullary duplication	Endoscopic cyst marsupialization
This case	2019	14 yr	M	Recurrent pancreatitis and abdominal pain	Lipase 1077, Amylase 514 GGT 69	Yes	Yes (CT in another center, MRCP)	Yes	Yes	Periampullary duplication	Endoscopic distal papillotomy and cyst incision
		16 yr	F	Recurrent pancreatitis and abdominal pain	Lipase 2365	Yes	Yes (CT in another center, MRCP)	Yes	Yes	Periampullary duplication	Endoscopic cyst incision
		11 yr	F	Recurrent pancreatitis, abdominal pain	Lipase 43440	Yes	Yes (CT in another center,	Yes	Yes	Periampullary duplication	Endoscopic cyst incision (bleeding treated with metallic

			and weight loss			MRCP)				clips placement and blood transfusion)
	11 yr	F	Pancreatitis	Lipase 5497, AST/ALT 315/532; GGT 169	Yes	Yes (MRCP)	Yes	Yes	Periampullary duplication	Sphincterotomy

Unit used were as follows: amylase (UI/L), lipase (UI/L), bilirubin (mg/dL), alkaline phosphatase (UI/L), aspartate aminotransferase (UI/L), alanine aminotransferase (UI/L) and gamma-glutamyl transferase (UI/L). US: Ultrasound; CT: Computed tomography; EUS: Endoscopic ultrasound; ERCP: Endoscopic retrograde cholangio-pancreatography; NA: Not available; ALP: Alkaline phosphatase level; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; MRCP: Magnetic resonance cholangiopancreatography; GGT: Gamma-glutamyl transpeptidase; MR: Magnetic resonance; F: Female; M: Male.

involvement in 30% of patients, although this cannot always be the only explanation of pancreatitis[5,6].

Three different mechanisms have been reported as responsible for pancreatitis: (1) External papilla obstruction by duplication enlargement; (2) Presence of an aberrant pancreatic duct within the duplication, which can become obstructed by mucus and debris; and (3) Migration of biliary sludge and/or microstones from the cyst into the bilio-pancreatic duct[3,4]. Migration of biliary sludge and/or microstones from the cyst to the bilio-pancreatic duct is possible only due to a communication between the duplication and the bilio-pancreatic duct with stone formation due to the bile stasis within the duplication seeing as its peristalsis is intermittent[2]. For this reason, the presence of stones or biliary sludge inside a duodenal mass do not ruled out the possibility of a DD.

DD can be divided into two subgroups: periampullary (PADDC) and non-periampullary duplication cyst. According to Tröbs *et al*[4] periampullary duodenal duplication is defined as a duplication cyst located near the major papilla and the biliary-pancreatic ampulla, sometimes with a small aberrant pancreatic duct drained into the cyst[4].

Our experience suggests the possibility of communication between PADDC and the CBD and pancreatic duct, which explains both the possibility of observing sludge or calculi in the cyst and the pancreatitis. Unfortunately, detailed descriptions of the relationships between duplication and major papilla and/or pancreatic ampulla are lacking, and our review found that only 17 out of 49 pediatric patients reported a detailed description of the DD that can be classified as periampullary type (Table 1).

PADDC cases have been reported in childhood with a median age of diagnosis of 14 years (range: 3-18 years); this was consistent also in our series (Table 1).

The first radiological tool for diagnosis was US, which is highly suggestive for a DD when peristalsis and pathognomonic "double wall sign," consisting of an outer hypoechoic muscular layer, an internal echogenic mucosal layer and corpuscular fluid inside the lesion, are found[22]. However, this finding should be confirmed with a more exhaustive radiological work-up by abdominal CT scan or preferably by MRCP [23], which provides more information about the location, size, enhancement and multilayered duplication cyst wall as well as anatomical details of the biliary and pancreatic ductal system. Furthermore, ionizing radiation should be limited as much as possible in childhood.

Moreover, we suggest performing an EUS in children with a cystic lesion next to the papilla. In our experience, EUS offered two major advantages: (1) Endoscopic vision allowed a better definition of the intraluminal duodenal lesion and an accurate localization of the papilla; and (2) US vision highlighted the presence of an anechoic structure surrounded by a five layer wall, consisting with the typical echo-endoscopic feature for the gastrointestinal wall, distinguishing DD from the other cystic and neoplastic duodenal or pancreatic masses, including cystic dystrophy of the duodenal wall, pseudocysts, cystic lymphangiomas, mesenteric cysts and choledochocele[4,24].

In particular, the performance of EUS to identify the presence of normal echographic bowel wall stratification at the DD allowed us to make differential diagnosis with choledochocele, where that hallmark is absent, but which represents the most frequent and challenging differential diagnosis. Furthermore, although many authors consider biopsy as the gold standard for the differential diagnosis between DD and choledochocele, duodenal type mucosa has been reported in choledochocele[25-27]. Sarris and Tsang reported 15 cases of choledochocele with duodenal mucosa at pathological examination[27,28].

Eventually, EUS can well indicate the relationships between the duplication and biliary-pancreatic duct. Therefore, when a PADDC is suspected, we suggest considering radiological (EUS) and anatomic criteria appropriate to confirm the diagnosis. Only 4 out of the 16 patients (25%) that were included in our literature review, underwent a preoperative EUS evaluation (Table 1), but this is partly explainable by the recent EUS availability in pediatrics.

Despite having carried out the EUS, before proceeding with the endoscopic duplication unroofing, ERCP would have to be mandatory in order to obtain a detailed anatomic view of the bilio-pancreatic system and to detect a possible communication between the duplication and the biliary and/or pancreatic duct, particularly in patients with stones or sludge inside the cyst.

Endoscopic treatment of children with PADDC was first described in 2007[8], and a later meta-analysis of the pediatric population confirmed the safety, feasibility and effectiveness of this approach in this population[10]. Our review revealed that 10/20 patients with PADDC (50%) underwent ET[6-9,17,19].

Two postoperative complications occurred (bleeding) and were both endoscopically treated; this point stresses the importance of ensuring a careful coagulation of the severed edges of the duplication. When planning an ET we thereby advise that a thorough preoperative radiological imaging encompassing EUS be mandatory, and our experience suggests that the real incidence of PADDC is underestimated because of incomplete preoperative imaging.

The anatomic location of the PADD and the possible communication with the biliary and/or pancreatic ductal system makes an open surgical approach highly demanding and not necessarily safer than ET. Furthermore, surgery has several disadvantages over ET, including worse postoperative pain, higher risk of postoperative complications, visible scars and longer hospitalization time.

Endoscopic cyst marsupialization was highly effective in relieving symptoms and cyst disappearance even at long-term follow-up.

Undoubtedly endoscopic management of PADDC requires a skilled multidisciplinary team, and the still limited use of the endoscopic strategy in a pediatric setting is probably explained, other than the rarity of PADDC, by the unavailability of a trained ERCP endoscopic team.

We suggest considering ET as a first line approach after a complete EUS study and reserving a surgical approach only when it is impossible to understand the relationship between PADDC and the pancreato-biliary tree.

ET provides marsupialization or incision of PADDC, therefore it is rare, but possible, to leave ectopic gastric or pancreatic tissue with potential risk of malignant degeneration.

Eventually, although DD (PADDC included) are generally benign lesions and only a few cases of malignant transformation have been reported in literature[5,29,30], a long-term follow up is mandatory in endoscopically treated patients, even in asymptomatic ones.

CONCLUSION

PADDC in pediatric patients are very rare. Our experience suggests that an accurate preoperative assessment with EUS is essential to differentiating the duplication from other duodenal lesions. In the presence of sludge or stones inside the duplication, ERCP is mandatory to demonstrate a communication with the biliary tree. ET is a safe, minimally invasive and effective treatment in children with PADDC. Long-term follow-up of this population throughout adulthood is mandatory and necessary considering that malignant degeneration of duodenal duplication has been described [5,29,30].

REFERENCES

1 **Rockx MA**, McAlister VC. Endoscopic fenestration of a duodenal duplication cyst to resolve recurrent pancreatitis. *JOP* 2007; **8**: 795-798 [PMID: 17993733]

2 **Guarise A**, Faccioli N, Ferrari M, Romano L, Parisi A, Falconi M. Duodenal duplication cyst causing severe pancreatitis: imaging findings and pathological correlation. *World J Gastroenterol* 2006; **12**: 1630-1633 [PMID: 16570360 DOI: 10.3748/wjg.v12.i10.1630]

3 **Chen JJ**, Lee HC, Yeung CY, Chan WT, Jiang CB, Sheu JC. Meta-analysis: the clinical features of the duodenal duplication cyst. *J Pediatr Surg* 2010; **45**: 1598-1606 [PMID: 20713206 DOI:

10.1016/j.jpedsurg.2010.01.010]
4 **Tröbs RB**, Hemminghaus M, Cernaianu G, Liermann D. Stone-containing periampullary duodenal duplication cyst with aberrant pancreatic duct. *J Pediatr Surg* 2009; **44**: e33-e35 [PMID: 19159708 DOI: 10.1016/j.jpedsurg.2008.10.106]
5 **Gjeorgjievski M**, Manickam P, Ghaith G, Cappell MS. Safety and Efficacy of Endoscopic Therapy for Nonmalignant Duodenal Duplication Cysts: Case Report and Comprehensive Review of 28 Cases Reported in the Literature. *Medicine (Baltimore)* 2016; **95**: e3799 [PMID: 27258515 DOI: 10.1097/MD.0000000000003799]
6 **Meier AH**, Mellinger JD. Endoscopic management of a duodenal duplication cyst. *J Pediatr Surg* 2012; **47**: e33-e35 [PMID: 23164028 DOI: 10.1016/j.jpedsurg.2012.07.035]
7 **Tekin F**, Ozutemiz O, Ersoz G, Tekesin O. A new endoscopic treatment method for a symptomatic duodenal duplication cyst. *Endoscopy* 2009; **41** Suppl 2: E32-E33 [PMID: 19288421 DOI: 10.1055/s-2008-1077337]
8 **Chryssostalis A**, Ribiere O, Prat F. Endoscopic management of a duodenal duplication cyst filled with stones and revealed by recurrent pancreatitis. *Clin Gastroenterol Hepatol* 2007; **5**: e31-e32 [PMID: 17678837 DOI: 10.1016/j.cgh.2007.05.028]
9 **Romeo E**, Torroni F, Foschia F, De Angelis P, Caldaro T, Santi MR, di Abriola GF, Caccamo R, Monti L, Dall'Oglio L. Surgery or endoscopy to treat duodenal duplications in children. *J Pediatr Surg* 2011; **46**: 874-878 [PMID: 21616244 DOI: 10.1016/j.jpedsurg.2011.02.022]
10 **Wada S**, Higashizawa T, Tamada K, Tomiyama T, Ohashi A, Satoh Y, Sugano K, Nagai H. Endoscopic partial resection of a duodenal duplication cyst. *Endoscopy* 2001; **33**: 808-810 [PMID: 11558037 DOI: 10.1055/s-2001-16528]
11 **Moher D**, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg* 2010; **8**: 336-341 [PMID: 20171303 DOI: 10.1016/j.ijsu.2010.02.007]
12 **Koffie RM**, Lee S, Perez-Atayde A, Mooney DP. Periampullary duodenal duplication cyst masquerading as a choledochocele. *Pediatr Surg Int* 2012; **28**: 1035-1039 [PMID: 22752148 DOI: 10.1007/s00383-012-3116-4]
13 **Mattioli G**, Buffa P, Pesce F, Barabino A, Ganduglia P, Fratino G, Granata C, Torre M, Magnano G, Gambini C, Ivani G, Jasonni V. Pancreatitis caused by duodenal duplication. *J Pediatr Surg* 1999; **34**: 645-648 [PMID: 10235345 DOI: 10.1016/s0022-3468(99)90096-9]
14 **Ozel A**, Uysal E, Tufaner O, Erturk SM, Yalcin M, Basak M. Duodenal duplication cyst: a rare cause of acute pancreatitis in children. *J Clin Ultrasound* 2008; **36**: 584-586 [PMID: 18393380 DOI: 10.1002/jcu.20475]
15 **Taghavi K**, Wilms H, Bann S, Stringer MD. Duodenal duplication cyst causing recurrent pancreatitis. *J Paediatr Child Health* 2017; **53**: 814-816 [PMID: 28695671 DOI: 10.1111/jpc.13592]
16 **Zamir G**, Gross E, Shmushkevich A, Bar-Ziv J, Durst AL, Jurim O. Duodenal duplication cyst manifested by duodeno-jejunal intussusception and hyperbilirubinemia. *J Pediatr Surg* 1999; **34**: 1297-1299 [PMID: 10466620 DOI: 10.1016/s0022-3468(99)90176-8]
17 **Criblez D**, Mitschele T, Scheiwiller A. A rare cause of acute pancreatitis in an adolescent. Juxtapapillary duodenal duplication cyst as a rare cause of acute pancreatitis in an adolescent. *Gastroenterology* 2011; **140**: 783, 1110 [PMID: 21266208 DOI: 10.1053/j.gastro.2010.02.063]
18 **Niehues R**, Dietl KH, Bettendorf O, Domschke W, Pohle T. Duodenal duplication cyst mimicking pancreatic cyst in a patient with pancreatitis. *Gastrointest Endosc* 2005; **62**: 190-192 [PMID: 15990852 DOI: 10.1016/s0016-5107(04)02846-9]
19 **Salazar E**, Sin EI, Low Y, Khor CJL. Insulated-tip knife: an alternative method of marsupializing a symptomatic duodenal duplication cyst in a 3-year-old child. *VideoGIE* 2018; **3**: 356-357 [PMID: 30402584 DOI: 10.1016/j.vgie.2018.08.006]
20 **Alatas FS**, Masumoto K, Matsuura T, Pudjiadi AH, Taguchi T. Modified Puestow Procedure for Chronic Pancreatitis in a Child Due to Annular Pancreas and Duodenal Duplication: A Case Report. *Pediatr Gastroenterol Hepatol Nutr* 2020; **23**: 304-309 [PMID: 32483552 DOI: 10.5223/pghn.2020.23.3.304]
21 **Merrot T**, Anastasescu R, Pankevych T, Tercier S, Garcia S, Alessandrini P, Guys JM. Duodenal duplications. Clinical characteristics, embryological hypotheses, histological findings, treatment. *Eur J Pediatr Surg* 2006; **16**: 18-23 [PMID: 16544221 DOI: 10.1055/s-2006-923798]
22 **Cheng G**, Soboleski D, Daneman A, Poenaru D, Hurlbut D. Sonographic pitfalls in the diagnosis of enteric duplication cysts. *AJR Am J Roentgenol* 2005; **184**: 521-525 [PMID: 15671373 DOI: 10.2214/ajr.184.2.01840521]
23 **Wong AM**, Wong HF, Cheung YC, Wan YL, Ng KK, Kong MS. Duodenal duplication cyst: MRI features and the role of MR cholangiopancreatography in diagnosis. *Pediatr Radiol* 2002; **32**: 124-125 [PMID: 11819082 DOI: 10.1007/s00247-001-0600-8]
24 **Ko SY**, Ko SH, Ha S, Kim MS, Shin HM, Baeg MK. A case of a duodenal duplication cyst presenting as melena. *World J Gastroenterol* 2013; **19**: 6490-6493 [PMID: 24151370 DOI: 10.3748/wjg.v19.i38.6490]
25 **Ghazi A**, Slone E. Endoscopic management of choledochocele. A case report and review of the English literature. *Surg Endosc* 1987; **1**: 151-154 [PMID: 3332475 DOI: 10.1007/BF00590921]
26 **Schimpl G**, Sauer H, Goriupp U, Becker H. Choledochocele: importance of histological evaluation. *J Pediatr Surg* 1993; **28**: 1562-1565 [PMID: 8301491 DOI: 10.1016/0022-3468(93)90097-5]
27 **Sarris GE**, Tsang D. Choledochocele: case report, literature review, and a proposed classification.

Surgery 1989; **105**: 408-414 [PMID: 2646745]
28 **Zhu L**, Lv Z, Liu J, Xu W. Choledochocele: A Case Report and Discussion of Diagnosis Criteria. *European J Pediatr Surg Rep* 2015; **3**: 85-89 [PMID: 26788455 DOI: 10.1055/s-0035-1563601]
29 **Seeliger B**, Piardi T, Marzano E, Mutter D, Marescaux J, Pessaux P. Duodenal duplication cyst: a potentially malignant disease. *Ann Surg Oncol* 2012; **19**: 3753-3754 [PMID: 22832999 DOI: 10.1245/s10434-012-2502-4]
30 **Rai BK**, Zaman S, Mirza B, Hanif G, Sheikh A. Duodenal Duplication Cyst having Ectopic Gastric and Pancreatic Tissues. *APSP J Case Rep* 2012; **3**: 15 [PMID: 22953309]

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CASE REPORT

Small bowel perforation from a migrated biliary stent: A case report and review of literature

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Abstract

BACKGROUND

Bowel perforation from biliary stent migration is a serious potential complication of biliary stents, but fortunately has an incidence of less than 1%.

CASE SUMMARY

We report a case of a 54-year-old Caucasian woman with a history of Human Immunodeficiency virus with acquired immunodeficiency syndrome, chronic obstructive pulmonary disease, alcoholic liver cirrhosis, portal vein thrombosis and extensive past surgical history who presented with acute abdominal pain and local peritonitis. On further evaluation she was diagnosed with small bowel perforation secondary to migrated biliary stents and underwent exploratory laparotomy with therapeutic intervention.

CONCLUSION

This case presentation reports on the unusual finding of two migrated biliary stents, with one causing perforation. In addition, we review the relevant literature on migrated stents.

Key Words: Biliary stent; Biliary stent migration; Small bowel perforation; Endoscopic retrograde cholangiopancreatography; Case report

Core Tip: Bowel perforation from biliary stent migration is a serious potential complication of biliary stents, but fortunately has an incidence of less than 1%. From this review of literature, we can see that most common types of migrated stents entailing bowel perforation are the plastic stents and the most common site of perforation is duodenum. A significant finding is the mortality after bowel perforation

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from biliary stent which is as high as 10.3%. The main treatment is surgical stent removal, but a growing body of literature shows that endoscopic removal and mucosal repair is feasible in select cases. This has still not been accomplished in the mid portion of the bowel.

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INTRODUCTION

Endoscopic biliary stents placement is a well-established therapeutic intervention in the era of modern medicine. It has been used either for temporary or permanent decompression of biliary system, for benign or malignant diseases. Biliary stents are classified by material into two categories: plastic and metallic stents, with the former being less expensive and easier to remove or change[1]. However, this technologically advanced treatment has not been free from complications. The complication rate ranges between 8% and 10% and serious common complications are stent occlusion, cholangitis, bleeding, pancreatitis, duodenal perforation and stent migration[2]. Biliary stent migration is well known with a rate of 5%-10% and can be either proximal or distal[2].

A serious potential consequence of stent migration is bowel perforation which can happen at any part of the small or large bowel, but fortunately has an incidence of less than 1%[3,4]. The majority of the case reports with bowel perforation secondary to migrated biliary stent describe duodenal or colonic perforations, with very few cases of small bowel perforations. Herein we report a case of a patient with multiple comorbidities and surgical interventions, who presents with two migrated biliary stents, one of which was perforating through the small bowel. Both stents were removed uneventfully with laparotomy and a single small bowel resection.

CASE PRESENTATION

Chief complaints

Diffuse abdominal pain.

History of present illness

We present the case of a 54-year-old Caucasian female, who presented in the emergency department of our hospital with diffuse abdominal pain for one week, which had become severe in the last day.

History of past illness

She initially presented in October 2019 with hyperbilirubinemia. At the time she had an ultrasound that showed gallstones as well as a dilated common bile duct of 10 mm. She underwent an magnetic resonance cholangiopacreatography (MRCP) which showed an 8mm duct, but no definite filling defects. Following this she underwent a diagnostic ERCP, at which time a distal stricture was noted, and a plastic stent [7 French (Fr) 7 cm single external and single internal flap] was placed. A second ERCP was done in February 2020, at which time choledocholithiasis was identified and felt to be the cause of the stricture. At that time a new plastic stent was placed (8.5 Fr 7 cm). The original stent was not seen at that time. In August 2020 she went for another ERCP at which time she had a normal cholangiogram, and the stent was not seen at that time. She presented to our Emergency Department in November 2020.

Personal and family history

Her past medical history was significant for human immunodeficiency virus (HIV) infection with acquired immunodeficiency syndrome, chronic obstructive pulmonary

disease, alcoholic liver cirrhosis, and portal vein thrombosis. Her past surgical history was significant for colectomy with end ileostomy for toxic megacolon from Clostridium difficile, followed later by a re-exploration and ileorectal anastomosis with proximal diverting loop ileostomy, which was still in place.

Physical examination

On initial evaluation the patient had temperature 98.2 °F (36.7 °C), pulse 87 per minute, blood pressure 115/83 mmHg. Her clinical examination revealed diffuse abdominal tenderness and focal peritonitis in the left lower quadrant of the abdomen.

Laboratory examinations

From laboratory evaluation the patient had WBC 6.1 k/μL and total bilirubin 0.7 mg/dL.

Imaging examinations

Computed tomography (CT) scan of the abdomen and pelvis with intravenous contrast showed two migrated biliary stents. The first was in an ileal loop and was perforating through the bowel wall into the mesentery (Figure 1A) and a second stent within a mid-jejunal loop (Figure 1B, C). The CT scan showed significant surrounding inflammatory phlegmon, but no free air or focal abscess was noted. After discussion with the patient, it was decided to proceed with surgical treatment of the bowel perforation and removal of both biliary stents.

MULTIDISCIPLINARY EXPERT CONSULTATION

The gastroenterology team was consulted, and they agreed with surgical exploration.

FINAL DIAGNOSIS

Small bowel perforation from a migrated biliary stent.

TREATMENT

The patient underwent a laparotomy at which time extensive adhesions were noted. The bowel was cocooned in most of the abdomen, with multiple interloop adhesions, as well as adhesions to the abdominal wall. The segment of bowel with the perforation was planned for resection due to the extensive inflammation. The second stent was milked within the bowel lumen to the area of the first stent, and both stents were removed in a single resection, after which a primary anastomosis was done. As a result of the extensive adhesions, and the urgent nature of the surgery, the right upper quadrant was not explored at this time. On detailed examination of the specimen, the resected small bowel had hypertrophic changes of the luminal mucosa at the internal opening of the perforation track (Figures 2, 3).

OUTCOME AND FOLLOW-UP

The patient had an uneventful recovery and she was discharged eight days later to a rehab facility.

DISCUSSION

Endoscopic placement of stents in common bile duct of pancreatic duct has been an important scientific achievement of modern medicine and is a frequently employed method to relieve either benign or malignant stenosis/obstruction of biliary or pancreatic tract. It was first described in 1980 by Soehandra *et al*[5] as an alternative method of decompressing the biliary system for high risk or inoperable cases instead of surgical choledochoduodenostomy. After the first description of endoscopic biliary

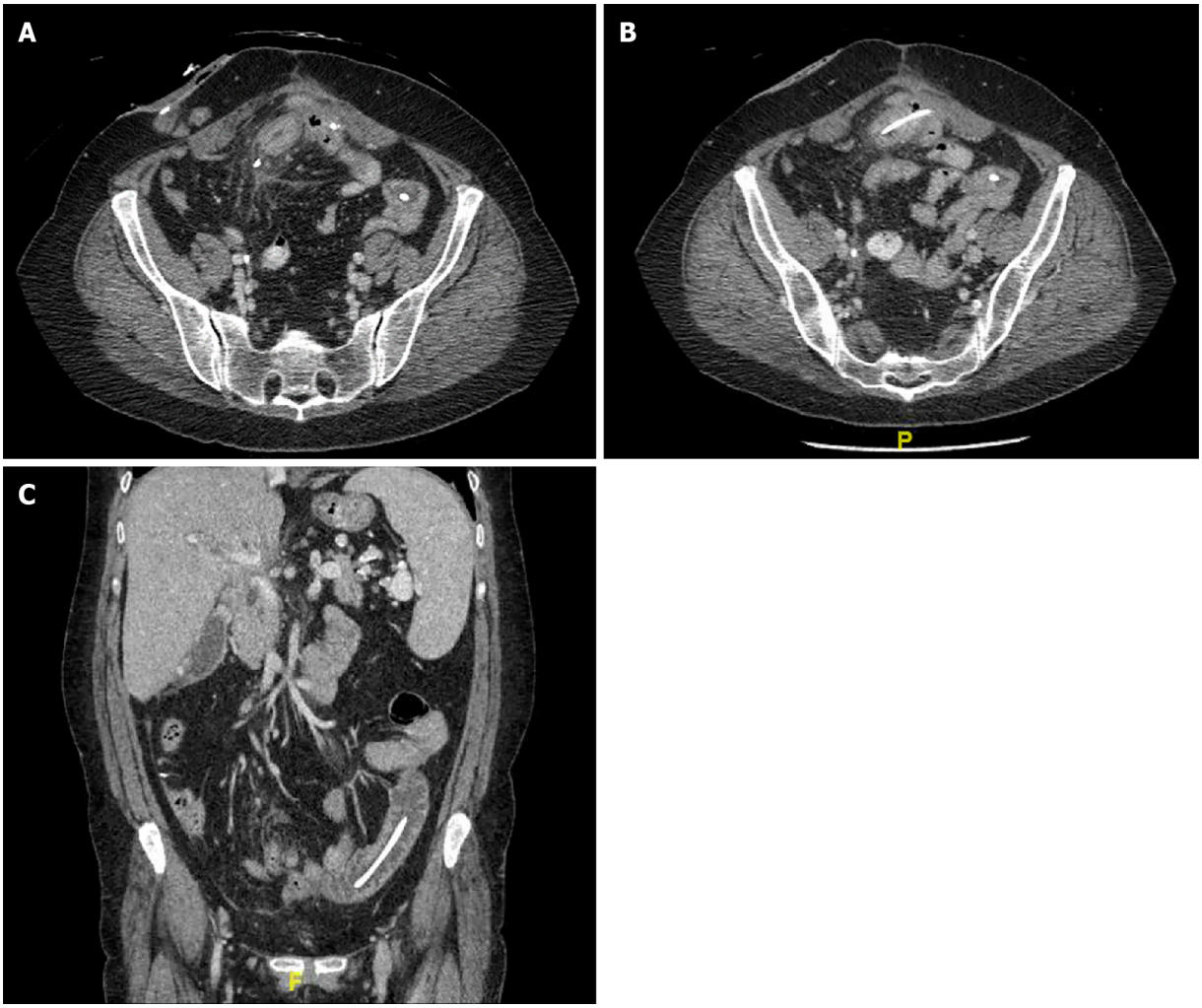

Figure 1 Computed tomography scan. A: Small bowel perforation by migrated biliary stent (Axial view); B: Second migrated biliary stent (Axial view); C: Second migrated biliary stent (Coronal view).

stent placement, the whole procedure and the available stents have been significantly improved and the popularity of this technique is gradually increasing as it constitutes a less morbid intervention comparing to a surgical operation[6]. Despite its clear benefit and the significant improvements in this field, there is always the risk of significant complications during or after endoscopic procedures like upper endoscopy and biliary tract cannulation.

Well described complications of biliary stent placement include stent occlusion by clogging with possible subsequent cholecystitis or cholangitis, pancreatitis from duct manipulation, hemorrhage, stent fracture and stent migration[1,2,6,7]. The total rate of biliary stent complications varies among different institutes because of different level of experience, different available equipment and different etiologic reasons for the intervention. According to Arhan *et al*[2] the complication rete for biliary stents is between 8% and 10%. Stent migration rate ranges from 5% to 10%, with the migration rates in plastic stents higher compared to others[2,7,8]. Biliary stent migration can be further categorized into proximal and distal migration. Distally migrated stents usually pass through the bowel without any complication[1,9]. In our case the patient had multiple previous laparotomies which led to adhesions, thereby making the bowel less mobile. This led to an increased likelihood that the stent would get impacted and not pass. In general, most institutions have policies in place to make sure all stent patients are called back for stent removal, including our own. At the last ERCP there was a normal cholangiogram and the stent was no longer in place. It was felt to have migrated, but without symptoms the impression was that it had completely passed through and eliminated from the GI tract safely. In retrospect an X-ray or further imaging at that time would have been helpful.

Bowel perforation from a migrated stent is a serious complication, which can occur in any part of the small or large bowel. The vast majority of reported cases with bowel

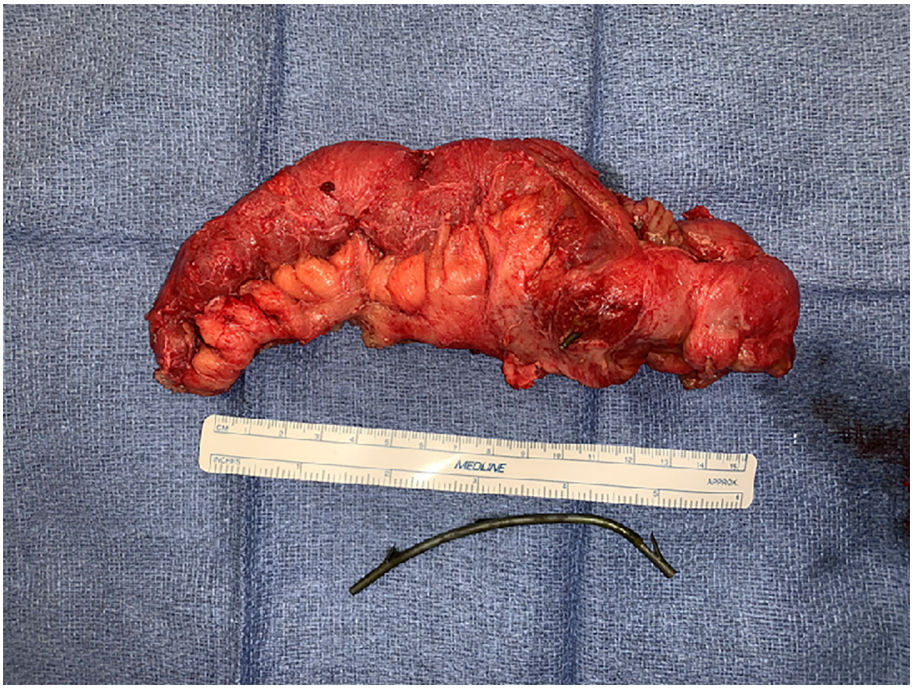

Figure 2 Small bowel segment with stent perforating through it, together with second migrated stent.

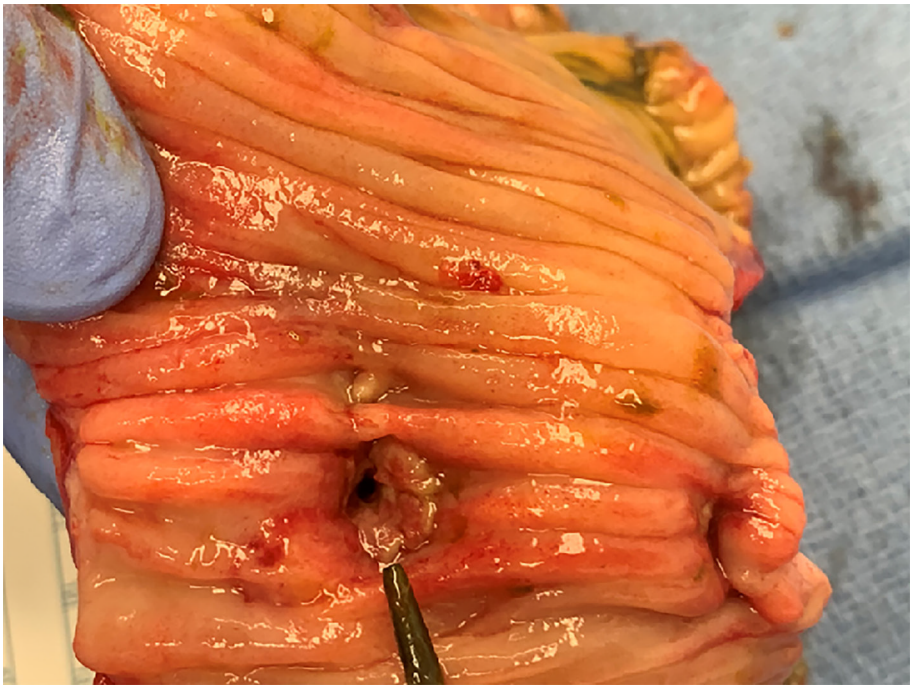

Figure 3 Internal opening of perforation.

perforation from migrated biliary stent describe either duodenal perforation or large bowel perforation, with very few cases of small bowel perforation. Most patients with perforation will present with diffuse peritonitis and signs of sepsis. In our patient, we believe the amount of infection was limited by the perforation happening slowly over time, and her septic response was also blunted by her HIV with a low CD4 count.A growing body of literature exists on this topic and different treatment approaches have been proposed. Diller *et al*[10] reported a case series of stent migration necessitating surgical intervention in 2003. The size of the stents varied between 7 and 14 Fr and the lengths ranged from 7 to 12 cm. Two patients had Polyurethane stents, one patient had Teflon stent placement and the other two patients had metallic stents. The diagnosis was biliary obstruction from acute pancreatitis in 4 patients and the fifth patient

received a prophylactic stent after liver transplantation. One of those five patients died from postoperative respiratory failure. In this study they reported a stent migration rate of 3.7% among 987 patients. Namdar *et al*[1] reported a case of rectal perforation from migrated biliary stent and review of literature with 12 cases in total and 7 cases from 2000. Several studies have shown that downstream migration is more frequent in benign than in malignant biliary disease, with the possible explanation being the resolution of the stenosis after regression of inflammation[1]. In addition, they state that any migrated biliary stent should be removed immediately regardless of the patient's clinical status[1]. An early growing body of literature describes endoscopic techniques for treatment of bowel perforation from migrated stent, but the majority focus on duodenal perforation or distal large bowel perforation. Bureau *et al*[11] recently described a case series of six patients with lateral duodenal wall perforation from displaced plastic biliary stent that were treated with over-the-scope clip. Given that in our case the bowel perforation was in a mid-jejunal loop, the endoscopic approach was less feasible. In addition, there was already significant inflammation seen around the bowel on CT scan, and we were concerned that an endoscopic mucosal repair would not hold. As such, we proceeded directly to surgery.

We performed a systematic review of literature from 2000 until 2020 for bowel perforation from migrated biliary stents and we found 81 cases (Table 1). Eligible articles were identified by a search of MEDLINE bibliographical database (last search: July 4th, 2021) using the following search algorithm: (("intestinal perforation"[MeSH Terms] OR ("intestinal"[All Fields] AND "perforation"[All Fields]) OR "intestinal perforation"[All Fields] OR ("bowel"[All Fields] AND "perforation"[All Fields]) OR "bowel perforation"[All Fields]) AND ("migrate"[All Fields] OR "migrated"[All Fields] OR "migrates"[All Fields] OR "migrating"[All Fields] OR "migration"[All Fields] OR "migrational"[All Fields] OR "migrations"[All Fields] OR "migrator"[All Fields] OR "migrators"[All Fields]) AND "biliary"[All Fields] AND ("stent s"[All Fields] OR "stentings"[All Fields] OR "stents"[MeSH Terms] OR "stents"[All Fields] OR "stent"[All Fields] OR "stented"[All Fields] OR "stenting"[All Fields])) AND (2000:2020[pdat]). Further search was performed in the references of related articles and relative articles with our topic were included. Manuscripts with full text available online were used and E-Videos, E-pictures and not English manuscripts were excluded. Cases were also excluded if there was not full text available online. Wang *et al*[3] in 2020 reported three cases of duodenal perforation due to biliary stent migration and performed a review of literature of duodenal perforation from migrated stents. In this study they reported that duodenal perforation from migrated biliary stents are mainly caused by distal stent migration[3]. Kawaguchi *et al*[12] studied 396 patients with bile duct stenosis between June 2003 and March 2009, retrospectively examined the frequency of stent migration and analyzed the patient factors and stent characteristics. They found that potential risk factors for stent migration are stent with large diameter, straight-type stents, stent duration > 1 mo, and common bile duct diameter > 10 mm[12].

In our review of literature (Table 1) there were 39 (50%) of male gender, 35 (44.9%) of female gender and 4 (5.1%) patients with missing data. The mean age of the total population was 66 (± 15.5) and the median 67 (IQR-56-77.5). The majority of patients had a plastic stent (93.6%). The stent length ranged from 5 to 15 cm and the stent size from 5 to 14 Fr. However, the majority of patients (50%) had a stent of 10 Fr or 12 Fr size. From the total population 35 patients (44.9%) had duodenal perforation, 23 patients (29.5%) had large bowel perforation, 18 patients (23.1%) had small bowel perforation, one patient had bile duct perforation and the last patient had no available information regarding the site of perforation. From the whole cohort, 47 patients (60.3%) had surgical intervention, 27 patients (34.6%) had endoscopic removal of the stent and 3 patients (3.8) had percutaneous removal of the stent. The overall mortality among the 54 patients was 8 patients (10.1%). Finally, the distribution of case reports was 38 (48.7%) from Europe, 21 (26.9%) from Asia-Middle East, 12 (15.4%) from the United States, 5 (6.4%) from Australia and 2 (2.6%) from South America.

CONCLUSION

From this review of literature, we can see that most common types of migrated stents entailing bowel perforation are the plastic stents and the most common site of perforation is duodenum. A significant finding is the mortality after bowel perforation from biliary stent which is as high as 10.3%. The main treatment is surgical stent removal, but a growing body of literature shows that endoscopic removal and mucosal repair is feasible in select cases. This has still not been accomplished in the mid portion

Table 1 Systematic review of literature from 2000 until 2020 for bowel perforation from migrated biliary stents

No	Year	Age, yr	Gender	Type of stent[1]	Site of perforation	Treatment	Country	Mortality	Stent length	Stent size	Ref.
1	2000	81	M	P	SB	ST	Norway	Y	6.5	10 Fr	[13]
2	2000	86	M	P	LB	ST	Norway	N	5	7 Fr	[13]
3	2000	74	M	P	DU	ET	Spain	N	15	10 Fr	[14]
4	2001	58	M	P	DU	ET	Italy	N	12	10 Fr	[15]
5	2001	43	F	P	DU	ET	India	N	NA	10 Fr	[16]
6	2001	NA	NA	P	SB	ST	United States	N	12	11.5 Fr	[17]
7	2001	88	F	P	DU	ST	Germany	N	10	7 Fr	[18]
9	2001	31	F	NA	BD	ST	Denmark	N	NA	NA	[19]
10	2001	47	M	P	LB	ST	Spain	N	10	10 Fr	[20]
11	2002	72	F	P	SB	ST	Italy	N	NA	12 Fr	[21]
12	2002	NA	NA	P	SB	ST	United States	N	7	8.5 Fr	[22]
13	2003	85	F	P	LB	ST	Germany	N	NA	NA	[23]
14	2003	86	M	P	DU	ET	Italy	Y	15	10 Fr	[24]
15	2003	27	F	P	SB	ST	Germany	N	12	12 Fr	[10]
16	2003	58	M	P	LB	ET-ST	Germany	N	10	7 Fr	[10]
17	2003	60	F	P	SB	ST	Germany	N	12	14 Fr	[10]
18	2003	64	M	M	LB	ST	Germany	Y	7	10 Fr	[10]
19	2003	65	M	M	NA	ST	Germany	N	7	10 Fr	[10]
20	2003	62	F	P	LB	ST	Argentina	N	NA	8 Fr	[25]
21	2003	62	F	P	SB	ST	Argentina	N	NA	5.5/10 Fr	[25]
22	2003	80	F	P	LB	ST	Australia	N	10	10 Fr	[26]
23	2004	65	F	P	LB	ST	United States	N	NA	NA	[27]
24	2005	69	M	M	DU	ST	United States	N	NA	NA	[28]
25	2006	55	M	P	DU	ET	Greece	Y	NA	NA	[29]
26	2006	74	M	P	DU	ST	India	NA	10	7 Fr	[30]
27	2006	54	F	P	SB	ST	United Kingdom	N	7	10 Fr	[31]
28	2006	85	M	P	DU	ST	Italy	N	10	9 Fr	[32]
29	2007	65	F	P	LB	ST	Germany	N	10	12 Fr	[1]
30	2008	75	M	P	DU	ST	Taiwan	N	NA	NA	[33]
31	2008	52	F	P	DU	ST	Turkey	N	10	8.5 Fr	[34]
32	2008	67	M	P	DU	ST	Australia	Y	NA	5/10 Fr	[35]
33	2008	43	M	P	DU	ET	Belgium	N	NA	NA	[36]
34	2008	71	F	P	SB	ST	Belgium	N	NA	NA	[36]
35	2009	77	M	P	LB	PI	United States	N	12	10 Fr	[37]
36	2009	76	F	P	SB	PI	United States	N	NA	10 Fr	[38]
37	2009	59	F	P	SB	ST	Turkey	N	7	11 Fr	[39]
38	2011	58	M	P	DU	PI	United Kingdom	N	10	8.5 Fr	[40]
39	2011	65	F	P	LB	ST	Germany	N	10	10 F Fr	[41]
40	2011	73	NA	P	LB	ST	France	N	5	10 Fr	[42]

41	2011	75	M	P	SB	ST	United Kingdom	N	NA	NA	[43]
42	2011	70	M	P	DU	ET	China	N	NA	8.5 Fr	[44]
43	2011	82	F	P	LB	ET	United Kingdom	N	7	7 Fr	[45]
44	2012	55	M	P	DU	ET	South Korea	N	7/5	5 Fr	[46]
45	2012	27	F	P	DU	ST	United Kingdom	N	12	7 Fr	[47]
46	2012	87	F	P	DU	ET	United States	N	15	8.5 Fr	[48]
47	2012	73	M	P	LB	ET	Spain	N	12	10 Fr	[49]
48	2012	50	NA	P	LB	ET	Belgium	N	NA	NA	[50]
49	2013	51	M	P	DU	ST	S. Arabia	N	10	10 Fr	[51]
50	2013	66	M	P	LB	ET	United Kingdom	N	NA	NA	[52]
51	2013	50	M	M	SB	ST	India	N	NA	NA	[53]
52	2014	67	M	P	DU	ST	United States	Y	12	10 Fr	[54]
53	2014	73	M	P	LB	ST	Australia	N	5	10 Fr	[55]
54	2014	66	F	P	DU	ET	The Netherlands	N	15	NA	[56]
55	2015	48	M	P	DU	ET	United States	N	NA	NA	[57]
56	2015	NA	F	P	LB	ST	Italy	N	12	12 Fr	[58]
57	2015	NA	F	P	LB	ET	Italy	N	12	12 Fr	[58]
58	2015	52	F	P	SB	ST	Turkey	N	NA	NA	[7]
59	2015	NA	M	P	LB	ST	United Kingdom	Y	NA	NA	[59]
60	2016	85	F	P	SB	NA	Turkey	Y	NA	NA	[6]
61	2017	75	F	P	LB	ST	Greece	N	NA	NA	[60]
62	2018	57	M	P	DU	ET	United States	N	15	8.5 Fr	[61]
63	2018	79	F	P	DU	ET	United States	N	12+15	7+10 Fr	[62]
64	2018	87	M	P	DU	ST	Greece	N	15	10F	[63]
65	2018	20	M	P	SB	ST	Turkey	N	NA	NA	[64]
66	2019	71	M	P	DU	ET	France	N	12	8.5 Fr	[65]
67	2019	50	M	P	DU	ET	South Korea	N	10	10F	[66]
68	2019	78	M	P	DU	ET	South Korea	N	10	7 Fr	[66]
69	2019	72	M	P	DU	ET	South Korea	N	12	10 Fr	[66]
70	2019	84	F	P	DU	ET	South Korea	N	12	10 Fr	[66]
71	2019	73	F	P	DU	ET	South Korea	N	15	10 Fr	[66]
72	2019	63	F	P	DU	ST	Jordan	N	10	10 Fr	[67]
73	2019	65	F	P	LB	ST	Portugal	N	5	10 Fr	[68]
74	2019	79	F	P	LB	ST	United States	N	10	7+10 Fr	[69]
75	2020	90	F	P	SB	ST	Australia	N	9	10 Fr	[70]
76	2020	84	F	P	SB	ST	Australia	N	7	10 Fr	[71]
77	2020	72	M	P	DU	ET	China	N	9	8.5 Fr	[3]
78	2020	84	M	P	DU	ET	China	N	12	7 Fr	[3]
79	2020	52	M	P	DU	ET	China	N	9	8.5 Fr	[3]

[1]Time interval from stent placement to complication in days.
P: Plastic; M: Metallic; BD: Bile duct; DU: Duodenum; SB: Small bowel; LB: Large bowel; ST: Surgical treatment; ET: Endoscopic treatment; PI: Percutaneous intervention; NA: Not available.

of the bowel, however this might be an area for future innovation and research.

REFERENCES

1 **Namdar T**, Raffel AM, Topp SA, Namdar L, Alldinger I, Schmitt M, Knoefel WT, Eisenberger CF. Complications and treatment of migrated biliary endoprostheses: a review of the literature. *World J Gastroenterol* 2007; **13**: 5397-5399 [PMID: 17879415 DOI: 10.3748/wjg.v13.i40.5397]
2 **Arhan M**, Odemiş B, Parlak E, Ertuğrul I, Başar O. Migration of biliary plastic stents: experience of a tertiary center. *Surg Endosc* 2009; **23**: 769-775 [PMID: 18649099 DOI: 10.1007/s00464-008-0067-x]
3 **Wang X**, Qu J, Li K. Duodenal perforations secondary to a migrated biliary plastic stent successfully treated by endoscope: case-report and review of the literature. *BMC Gastroenterol* 2020; **20**: 149 [PMID: 32398025 DOI: 10.1186/s12876-020-01294-z]
4 **Johanson JF**, Schmalz MJ, Geenen JE. Incidence and risk factors for biliary and pancreatic stent migration. *Gastrointest Endosc* 1992; **38**: 341-346 [PMID: 1607087 DOI: 10.1016/s0016-5107(92)70429-5]
5 **Soehendra N**, Reynders-Frederix V. Palliative bile duct drainage - a new endoscopic method of introducing a transpapillary drain. *Endoscopy* 1980; **12**: 8-11 [PMID: 7353562 DOI: 10.1055/s-2007-1021702]
6 **Güngör G**, Okur N. A Fatal Complication: Intestinal Perforation Secondary to Migration of a Biliary Stent. *Pol J Radiol* 2016; **81**: 170-172 [PMID: 27141238 DOI: 10.12659/PJR.896231]
7 **Yilmaz Ö**, Kiziltan R, Aydin O, Bayrak V, Kotan Ç. A Rare Complication of Biliary Stent Migration: Small Bowel Perforation in a Patient with Incisional Hernia. *Case Rep Surg* 2015; **2015**: 860286 [PMID: 26273488 DOI: 10.1155/2015/860286]
8 **Görich J**, Rilinger N, Krämer S, Aschoff AJ, Vogel J, Brambs HJ, Sokiranski R. Displaced metallic biliary stents: technique and rationale for interventional radiologic retrieval. *AJR Am J Roentgenol* 1997; **169**: 1529-1533 [PMID: 9393158 DOI: 10.2214/ajr.169.6.9393158]
9 **Garg K**, Zagzag J, Khaykis I, Liang H. Surgical relief of small bowel obstruction by migrated biliary stent: extraction without enterotomy. *JSLS* 2011; **15**: 232-235 [PMID: 21902982 DOI: 10.4293/108680811X13071180406998]
10 **Diller R**, Senninger N, Kautz G, Tübergen D. Stent migration necessitating surgical intervention. *Surg Endosc* 2003; **17**: 1803-1807 [PMID: 14508668 DOI: 10.1007/s00464-002-9163-5]
11 **Bureau MA**, Gkolfakis P, Blero D, Pezzullo M, Devière J, Lemmers A. Lateral duodenal wall perforation due to plastic biliary stent migration: a case series of endoscopic closure. *Endosc Int Open* 2020; **8**: E573-E577 [PMID: 32355873 DOI: 10.1055/a-1123-7782]
12 **Kawaguchi Y**, Ogawa M, Kawashima Y, Mizukami H, Maruno A, Ito H, Mine T. Risk factors for proximal migration of biliary tube stents. *World J Gastroenterol* 2014; **20**: 1318-1324 [PMID: 24574806 DOI: 10.3748/wjg.v20.i5.1318]
13 **Størkson RH**, Edwin B, Reiertsen O, Faerden AE, Sortland O, Rosseland AR. Gut perforation caused by biliary endoprosthesis. *Endoscopy* 2000; **32**: 87-89 [PMID: 10691280 DOI: 10.1055/s-2000-87]
14 **Rosés LL**, Ramirez AG, Seco AL, Blanco ES, Alonso DI, Avila S, Lopez BU. Clip closure of a duodenal perforation secondary to a biliary stent. *Gastrointest Endosc* 2000; **51**: 487-489 [PMID: 10744829 DOI: 10.1016/s0016-5107(00)70454-8]
15 **Distefano M**, Bonanno G, Russo A. Biliocutaneous fistula following biliary stent migration. *Endoscopy* 2001; **33**: 97 [PMID: 11204999 DOI: 10.1055/s-2001-17404]
16 **Pathak KA**, de Souza LJ. Duodenocolic fistula: an unusual sequela of stent migration. *Endoscopy* 2001; **33**: 731 [PMID: 11490393 DOI: 10.1055/s-2001-16220]
17 **Mistry BM**, Memon MA, Silverman R, Burton FR, Varma CR, Solomon H, Garvin PJ. Small bowel perforation from a migrated biliary stent. *Surg Endosc* 2001; **15**: 1043 [PMID: 11443435 DOI: 10.1007/s004640041008]
18 **Liebich-Bartholain L**, Kleinau U, Elsbernd H, Büchsel R. Biliary pneumonitis after proximal stent migration. *Gastrointest Endosc* 2001; **54**: 382-384 [PMID: 11522987 DOI: 10.1067/mge.2001.113646]
19 **Jendresen MB**, Svendsen LB. Proximal displacement of biliary stent with distal perforation and impaction in the pancreas. *Endoscopy* 2001; **33**: 195 [PMID: 11272227 DOI: 10.1055/s-2001-11920]
20 **Figueiras RG**, Echart MO, Figueiras AG, González GP. Colocutaneous fistula relating to the migration of a biliary stent. *Eur J Gastroenterol Hepatol* 2001; **13**: 1251-1253 [PMID: 11711785 DOI: 10.1097/00042737-200110000-00021]
21 **Fiori E**, Mazzoni G, Galati G, Lutzu SE, Cesare A, Bononi M, Bolognese A, Tocchi A. Unusual breakage of a plastic biliary endoprosthesis causing an enterocutaneous fistula. *Surg Endosc* 2002; **16**: 870 [PMID: 11997843 DOI: 10.1007/s004640042021]

22 **Levey JM**. Intestinal perforation in a parastomal hernia by a migrated plastic biliary stent. *Surg Endosc* 2002; **16**: 1636-1637 [PMID: 12085152 DOI: 10.1007/s00464-002-4506-9]

23 **Wilhelm A**, Langer C, Zoeller G, Nustede R, Becker H. Complex colovesicular fistula: A severe complication caused by biliary stent migration. *Gastrointest Endosc* 2003; **57**: 124-126 [PMID: 12518151 DOI: 10.1067/mge.2003.71]

24 **Basile A**, Macri' A, Lamberto S, Caloggero S, Versaci A, Famulari C. Duodenoscrotal fistula secondary to retroperitoneal migration of an endoscopically placed plastic biliary stent. *Gastrointest Endosc* 2003; **57**: 136-138 [PMID: 12518156 DOI: 10.1067/mge.2003.37]

25 **Cerisoli C**, Diez J, Giménez M, Oria M, Pardo R, Pujato M. Implantation of migrated biliary stents in the digestive tract. *HPB (Oxford)* 2003; **5**: 180-182 [PMID: 18332981 DOI: 10.1080/13651820310015301]

26 **Elliott M**, Boland S. Sigmoid colon perforation following a migrated biliary stent. *ANZ J Surg* 2003; **73**: 669-670 [PMID: 12887548 DOI: 10.1046/j.1445-2197.2003.02698.x]

27 **Blake AM**, Monga N, Dunn EM. Biliary stent causing colovaginal fistula: case report. *JSLS* 2004; **8**: 73-75 [PMID: 14974669]

28 **Miller G**, Yim D, Macari M, Harris M, Shamamian P. Retroperitoneal perforation of the duodenum from biliary stent erosion. *Curr Surg* 2005; **62**: 512-515 [PMID: 16125609 DOI: 10.1016/j.cursur.2005.03.011]

29 **Paikos D**, Gatopoulou A, Moschos J, Soufleris K, Tarpagos A, Katsos I. Migrated biliary stent predisposing to fatal ERCP-related perforation of the duodenum. *J Gastrointestin Liver Dis* 2006; **15**: 387-388 [PMID: 17205153]

30 **Bharathi RS**, Rao PP, Ghosh K. Intra-peritoneal duodenal perforation caused by delayed migration of endobiliary stent: a case report. *Int J Surg* 2008; **6**: 478-480 [PMID: 19059151 DOI: 10.1016/j.ijsu.2006.06.012]

31 **Akimboye F**, Lloyd T, Hobson S, Garcea G. Migration of endoscopic biliary stent and small bowel perforation within an incisional hernia. *Surg Laparosc Endosc Percutan Tech* 2006; **16**: 39-40 [PMID: 16552378 DOI: 10.1097/01.sle.0000202198.74569.5a]

32 **Lanteri R**, Naso P, Rapisarda C, Santangelo M, Di Cataldo A, Licata A. Jejunal perforation for biliary stent dislocation. *Am J Gastroenterol* 2006; **101**: 908-909 [PMID: 16635240 DOI: 10.1111/j.1572-0241.2006.00509.x]

33 **Hsu YC**, Wu YM, Wang HP. Education of imaging. Hepatobiliary and pancreatic: biliary stent causing imminent duodenal perforation. *J Gastroenterol Hepatol* 2008; **23**: 817 [PMID: 18410612 DOI: 10.1111/j.1440-1746.2008.05335.x]

34 **Yaprak M**, Mesci A, Colak T, Yildirim B. Biliary stent migration with duodenal perforation. *Eurasian J Med* 2008; **40**: 154-156 [PMID: 25610053]

35 **Lo CH**, Chung S, Bohmer RD. A devastating complication: duodenal perforation due to biliary stent migration. *Surg Laparosc Endosc Percutan Tech* 2008; **18**: 608-610 [PMID: 19098671 DOI: 10.1097/SLE.0b013e318185a07a]

36 **Seerden TC**, Moreels TG, Salgado RA, Francque SM, Michielsen PP, Parizel PM, Pelckmans PA. Intestinal bowel perforation and bacterial peritonitis secondary to migrated biliary and pancreatic stents. *Endoscopy* 2008; **40** Suppl 2: E25 [PMID: 18278716 DOI: 10.1055/s-2007-966961]

37 **Brinkley M**, Wible BC, Hong K, Georgiades C. Colonic perforation by a percutaneously displaced biliary stent: report of a case and a review of current practice. *J Vasc Interv Radiol* 2009; **20**: 680-683 [PMID: 19339202 DOI: 10.1016/j.jvir.2009.02.005]

38 **Culnan DM**, Cicuto BJ, Singh H, Cherry RA. Percutaneous retrieval of a biliary stent after migration and ileal perforation. *World J Emerg Surg* 2009; **4**: 6 [PMID: 19183489 DOI: 10.1186/1749-7922-4-6]

39 **Akbulut S**, Cakabay B, Ozmen CA, Sezgin A, Sevinc MM. An unusual cause of ileal perforation: report of a case and literature review. *World J Gastroenterol* 2009; **15**: 2672-2674 [PMID: 19496201 DOI: 10.3748/wjg.15.2672]

40 **Papadopoulou I**, Fotiadis NI, Ahmed I, Thurley P, Hutchins RR, Fotheringham T. Perforation and abscess formation after radiological placement of a retrievable plastic biliary stent. *J Med Case Rep* 2011; **5**: 103 [PMID: 21401933 DOI: 10.1186/1752-1947-5-103]

41 **Lankisch TO**, Alten TA, Lehner F, Knitsch W. Biliary stent migration with colonic perforation: a very rare complication and the lesson that should be learned from it. *Gastrointest Endosc* 2011; **74**: 924-5; discussion 925 [PMID: 21951480 DOI: 10.1016/j.gie.2011.06.011]

42 **Malgras B**, Pierret C, Tourtier JP, Olagui G, Nizou C, Duverger V. Double Sigmoid colon perforation due to migration of a biliary stent. *J Visc Sur***148**: e397-e399 [PMID: 22075561 DOI: 10.1016/j.jviscsurg.2011.09.011]

43 **Abela JE**, Anderson JE, Whalen HR, Mitchell KG. Endo-biliary stents for benign disease: not always benign after all! *Clin Pract* 2011; **1**: e102 [PMID: 24765343 DOI: 10.4081/cp.2011.e102]

44 **Lin H**, Li ZS, Zhan XB. Asymptomatic duodenal perforation from obstructed and migrated biliary stent. *Endoscopy* 2011; **43** Suppl 2 UCTN: E40-E41 [PMID: 21287443 DOI: 10.1055/s-0029-1244037]

45 **Jafferbhoy SF**, Scriven P, Bannister J, Shiwani MH, Hurlstone P. Endoscopic management of migrated biliary stent causing sigmoid perforation. *BMJ Case Rep* 2011; 2011 [PMID: 22696699 DOI: 10.1136/bcr.04.2011.4078]

46 **Oh HC**, Kim SW, Do JH, Kim G. Duodenal perforation caused by a cutting-induced sharp-edged plastic stent (with video). *Gastrointest Endosc* 2012; **76**: 1050; discussion 1050-1050; discussion

1051 [PMID: 22902144 DOI: 10.1016/j.gie.2012.06.024]
47 **Smart P**, Keenan D, Campbell W, Morris-Stiff G. Duodenal perforation secondary to migration of endobiliary prosthesis. *BMJ Case Rep* 2012; 2012 [PMID: 23008374 DOI: 10.1136/bcr-2012-006711]
48 **O'Connor R**, Agrawal S, Aoun E, Kulkarni A. Biliary stent migration presenting with leg pain. *BMJ Case Rep* 2012; 2012 [PMID: 23162034 DOI: 10.1136/bcr-2012-007588]
49 **Alcaide N**, Lorenzo-Pelayo S, Herranz-Bachiller MT, de la Serna-Higuera C, Barrio J, Perez-Miranda M. Sigmoid perforation caused by a migrated biliary stent and closed with clips. *Endoscopy* 2012; **44** Suppl 2 UCTN: E274 [PMID: 22814918 DOI: 10.1055/s-0032-1309719]
50 **Depuydt P**, Aerts R, Van Steenbergen W, Verslype C, Laleman W, Cassiman D, Nevens F, Pirenne J, Monbaliu D. An unusual case of rectal perforation after liver transplantation. *Acta Chir Belg* 2012; **112**: 232-233 [PMID: 22808766]
51 **Issa H**, Nahawi M, Bseiso B, Al-Salem A. Migration of a biliary stent causing duodenal perforation and biliary peritonitis. *World J Gastrointest Endosc* 2013; **5**: 523-526 [PMID: 24147198 DOI: 10.4253/wjge.v5.i10.523]
52 **Jones M**, George B, Jameson J, Garcea G. Biliary stent migration causing perforation of the caecum and chronic abdominal pain. *BMJ Case Rep* 2013; 2013 [PMID: 24022897 DOI: 10.1136/bcr-2013-009124]
53 **Saravanan MN**, Mathai V, Kapoor D, Singh B. Fractured metallic biliary stent causing obstruction and jejunal perforation. *Asian J Endosc Surg* 2013; **6**: 234-236 [PMID: 23879419 DOI: 10.1111/ases.12033]
54 **El Zein MH**, Kumbhari V, Tieu A, Saxena P, Messallam AA, Azola A, Li Z, Weiss M, Khashab MA. Duodenal perforation as a consequence of biliary stent migration can occur regardless of stent type or duration. *Endoscopy* 2014; 46 Suppl 1 UCTN: E281-E282 [PMID: 24906101 DOI: 10.1055/s-0034-1365790]
55 **Chittleborough TJ**, Mgaieth S, Kirkby B, Zakon J. Remove the migrated stent: sigmoid colon perforation from migrated biliary stent. *ANZ J Surg* 2016; **86**: 947-948 [PMID: 25078878 DOI: 10.1111/ans.12796]
56 **Kusters PJ**, Keulen ET, Peters FP. Duodenal perforation following bile duct endoprosthesis placement. *Endoscopy* 2014; **46** Suppl 1 UCTN: E646-E647 [PMID: 25526406 DOI: 10.1055/s-0034-1390849]
57 **Kriss M**, Yen R, Fukami N, Bambha K, Wani S. Duodenal perforation secondary to migrated biliary stent in a liver transplant patient: successful endoscopic closure with an over-the-scope clip. *Gastrointest Endosc* 2015; **81**: 1258-1259 [PMID: 25293828 DOI: 10.1016/j.gie.2014.08.003]
58 **Virgilio E**, Pascarella G, Scandavini CM, Frezza B, Bocchetti T, Balducci G. Colonic perforations caused by migrated plastic biliary stents. *Korean J Radiol* 2015; **16**: 444-445 [PMID: 25741207 DOI: 10.3348/kjr.2015.16.2.444]
59 **Mady RF**, Niaz OS, Assal MM. Migrated biliary stent causing perforation of sigmoid colon and pelvic abscess. *BMJ Case Rep* 2015; 2015 [PMID: 25870211 DOI: 10.1136/bcr-2014-206805]
60 **Siaperas P**, Ioannidis A, Skarpas A, Angelopoulos A, Drikos I, Karanikas I. A rare cause for Hartmann's procedure due to biliary stent migration: A case report. *Int J Surg Case Rep* 2017; **31**: 83-85 [PMID: 28122319 DOI: 10.1016/j.ijscr.2017.01.016]
61 **Barakat MT**, Kothari S, Banerjee S. Cut and Paste: Endoscopic Management of a Perforating Biliary Stent Utilizing Scissors and Clips. *Dig Dis Sci* 2018; **63**: 2202-2205 [PMID: 29127608 DOI: 10.1007/s10620-017-4837-y]
62 **Ferm S**, Fisher C, Hassam A, Rubin M, Kim SH, Hussain SA. Primary Endoscopic Closure of Duodenal Perforation Secondary to Biliary Stent Migration: A Case Report and Review of the Literature. *J Investig Med High Impact Case Rep* 2018; **6**: 2324709618792031 [PMID: 30116760 DOI: 10.1177/2324709618792031]
63 **Ekmektzoglou K**, Nikou E, Apostolopoulos P, Grigoraki D, Manesis K, Alexandrakis G. Size does matter: when a large plastic biliary stent ends up in the root of the mesentery. *Clin J Gastroenterol* 2019; **12**: 102-105 [PMID: 30284196 DOI: 10.1007/s12328-018-0914-9]
64 **Topal U**, Ülkü A, Sarıtaş AG, Akçam AT. A rare complication in a liver transplant patient: Meckel diverticulum perforation due to biliary stent. *Int J Surg Case Rep* 2018; **53**: 35-38 [PMID: 30368122 DOI: 10.1016/j.ijscr.2018.09.034]
65 **Le Mouel JP**, Hakim S, Thiebault H. Duodenal Perforation Caused by Early Migration of a Biliary Plastic Stent: Closure With Over-the-Scope Clip. *Clin Gastroenterol Hepatol* 2019; **17**: e6-e7 [PMID: 29307844 DOI: 10.1016/j.cgh.2017.12.047]
66 **Kim HS**, Moon HJ, Lee NY, Lee HT, Woo MS, Lee JW, Jang IS, Lee KD. Endoscopic management of duodenal perforations caused by migrated biliary plastic stents. *Endosc Int Open* 2019; **7**: E792-E795 [PMID: 31198841 DOI: 10.1055/a-0887-4200]
67 **Jadallah K**, Alzubi B, Sweidan A, Almanasra AR. Intraperitoneal duodenal perforation secondary to early migration of biliary stent: closure with through-the-scope clip. *BMJ Case Rep* 2019; **12** [PMID: 31488444 DOI: 10.1136/bcr-2019-230324]
68 **Marcos P**, Capelão G, Atalaia-Martins C, Clara P, Eliseu L, Vasconcelos H. Sigmoid Perforation by a Migrated Plastic Biliary Stent. *GE Port J Gastroenterol* 2020; **27**: 215-218 [PMID: 32509931 DOI: 10.1159/000503076]
69 **Riccardi M**, Deters K, Jabbar F. Sigmoid Diverticulitis and Perforation Secondary to Biliary Stent Migration. *Case Rep Surg* 2019; **2019**: 2549170 [PMID: 31236301 DOI: 10.1155/2019/2549170]
70 **Tsang CLN**, O'Neill RS, Joseph CM, Palasovski T. Small Bowel Perforation Secondary to Biliary

Stent Migration in an Incarcerated Inguinal Hernia. *Cureus* 2020; **12**: e7268 [PMID: 32292679 DOI: 10.7759/cureus.7268]

71 **Ip CCK**, Hong M. Small bowel perforation from migrated biliary stent: why did it happen? *ANZ J Surg* 2020; **90**: 1779-1780 [PMID: 32011769 DOI: 10.1111/ans.15646]

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