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Xiu-Xia Song, Vice Director
World Journal of Gastrointestinal Endoscopy
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-85381891
Fax: +86-10-85381893
E-mail: editorialoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
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EDITORIAL

What is the current role of endoscopy in primary sclerosing cholangitis?

Benjamin Tharian, Nayana Elizabeth George, Tony Chiew Keong Tham

Benjamin Tharian, Center for Interventional Endoscopy, Florida Hospital, Orlando, FL 32803, United States

Nayana Elizabeth George, Western Hospital, Melbourne, Victoria 3011, Australia

Tony Chiew Keong Tham, Division of Gastroenterology, Ulster Hospital, N Ireland, BT16 1RH Belfast, United Kingdom

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Correspondence to: Dr. Benjamin Tharian, MD, MRCP (UK), Gastro FRACP, Advanced Endoscopy Fellow, Center for Interventional Endoscopy, Florida Hospital, 601 East Rollins Drive, Orlando, FL 32803,
United States. benjamintharian@yahoo.co.in
Telephone: +1-407-2270144
Fax: +1-407-3032585

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Abstract

Endoscopy has important roles in the management of primary sclerosing cholangitis (PSC), ranging from narrowing down the differential diagnoses, screening for complications, determining prognosis and therapy. While the need for a diagnostic endoscopic retrograde cholangiopancreatography (ERCP) may be obviated by a positive magnetic resonance cholangiopancreatography (MRCP), a negative MRCP does not exclude PSC and may therefore necessitate an ERCP, which is traditionally regarded as the gold standard. In this editorial we have not covered the endoscopic management of inflammatory bowel disease in the context of PSC nor of endoscopic surveillance and treatment of portal hypertension complicating PSC.

Key words: Sclerosing cholangitis; Endoscopic retrograde cholangiopancreatography; Endosonography; Cholangiocarcinoma; Stents; Fluorescence *in situ* hybridization technique; Biochemical markers

Core tip: Primary sclerosing cholangitis is a cholestatic disease of unclear etiopathogenesis, often seen in association with inflammatory bowel disease. It is characterized by fibrosis of the intra and extra hepatic bile ducts, resulting in stricturing disease, predisposing to cholangiocarcinoma. Diagnosis requires a high index of clinical suspicion and is often made by magnetic resonance cholangiopancreatography in the appropriate clinical context, although endoscopic retrograde cholangiopancreatography remains the gold standard. The latter being invasive is seldom used as a diagnostic modality and is reserved for management of complications including dilatation and stenting of dominant and anastomotic strictures, brush cytology and for SpyGlass Cholangioscopy.

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INTRODUCTION

Primary sclerosing cholangitis (PSC) is a chronic cholestatic disease characterized by inflammation and fibrosis that may involve the entire biliary tree. Inflammation and fibrosis results in diffuse narrowing of the intra and extra hepatic bile ducts causing persistent biliary stasis eventually leading to secondary biliary cirrhosis. It usually presents in the fourth decade of life with a variable disease progression[1].

Laboratory tests do not play a significant role as there is no definite test to confirm PSC. Non-invasive imaging modalities like trans abdominal ultrasound may pick up nonspecific abnormalities such as bile duct thickening, gall bladder enlargement or wall thickening. Contrast computed tomography (CT) scan and magnetic resonance cholangiopancreatography (MRCP) may detect inflammation, intrahepatic dilations as well as varices and splenomegaly indicative of portal hypertension. CT detects intraabdominal lymphadenopathy, suggestive of underlying cholangiocarcinoma. Even invasive tests like percutaneous transhepatic cholangiography have been used in the past. However none is confirmatory.

PSC recurs in about 10% of patients post orthotopic liver transplantation (OLT), with acute cellular rejection, need for maintenance steroids, HLA-DRB1*08 being positive predictors and pan colectomy being a negative predictor[2,3]. The diagnostic modalities for recurrent PSC (r-PSC) remain the same, with low threshold for biopsy to rule out rejection, which needs to be managed aggressively to prevent decompensation of the liver[2].

It is important to distinguish immunoglobulin (Ig) G4-associated cholangitis (IAC), also called IgG4-related sclerosing cholangitis, a recently described chronic cholangiopathy from PSC and other secondary sclerosing cholangitis, due to the excellent response of the former to steroid treatment. About 10% to 15% of patients with PSC also have elevated IgG4 levels. There is some evidence that the incorporation of IgG4/IgG1 ratio may be used in clinical practice to distinguish PSC from IAC[3,4]. Liver biopsy is rarely used these days, thought, might still be needed in the diagnosis of small duct PSC and when diagnosis is unclear.

Biliary IgG antineutrophilic cytoplasmic antibody and IgA against biliary epithelial cells correlates with the severity of bile duct strictures and may serve in the future as a diagnostic and prognostic marker of the disease progression and biliary complications[5,6]. Biliary protein biomarkers might help in distinguishing benign from malignant strictures, though further studies are warranted[7]. Novel biliary biomarkers like extracellular vesicles containing Micro-RNA's (miRs), U2 small nuclear RNA fragments (RNU2-1f) and oxidized phosphatidyl cholines (ON-PC and S-PC) have been proposed for the early diagnosis of cholangiocarcinoma in PSC, that is stable, reproducible, and has potential clinical utility[7-9].

ENDOSCOPIC DIAGNOSIS

Endoscopic retrograde cholangiopancreatography

Endoscopic retrograde cholangiopancreatography (ERCP) is the mainstay for accurate assessment of the hepatobiliary tree to establish a diagnosis of PSC. Typical cholangiographic findings include multifocal annular biliary strictures interspersed between dilated intra and extrahepatic bile ducts with alternating normal segments, creating the characteristic beaded pattern of PSC.

Even though MRCP is the preferred cholangiographic modality given the high sensitivity, non-invasive nature and lack of exposure to radiation, it has limited accuracy in early PSC, cirrhosis and in the differentiation of Caroli's disease, secondary sclerosing cholangitis and cholangiocarcinoma (CCA)[10]. A retrospective study by Moff *et al*[11] demonstrated that ERCP and MRCP were comparable for diagnosis of PSC. They recommended that MRCP be employed as the initial diagnostic modality given the safety profile as well as sensitivity and specificity of approximately 90% and 88% respectively, although ERCP with its higher specificity of nearly 96% would be necessary for confirmation[11].

Complications occur in about 4% to 16% of patients with PSC undergoing ERCP[12,13]. The complication risk was often dependent on the ease of cannulation, with post ERCP pancreatitis (PEP) reported in up to 7% of procedures[14]. Hence, we recommend routine sphincterotomy, especially in those who are likely to need further procedures, to minimise the risk of PEP[14]. PSC patients undergoing ERCP are routinely given antibiotic prophylaxis to reduce the risk of cholangitis, which is more so in the presence of strictures[12,14,15]. An extra attempt is made to clear the bile duct of all contrast by suctioning or irrigation. Overall, benefits of doing an ERCP outweighed the risks in PSC, when the indications were appropriate[14,15].

A confirmatory ERCP is warranted when clinical suspicion of PSC is moderately high, also in cases with inconclusive MRCP results and or cases being evaluated at centres where the technical expertise with MRCP is not well established[16]. A cost effectiveness analysis comparing ERCP with MRCP by Meagher *et al*[17] in the face of competing technologies revealed that initial MRCP, when negative, followed by subsequent ERCP was the most economic initial approach in the work-up of patients with suspected PSC.

It is crucial to distinguish dominant strictures (DS) in PSC from cholangiocarcinoma, which remains a challenge given that the former predisposes to CCA, which could be found in upto 25% of DS as per some studies[18]. The American Association for the Study of Liver Diseases (AASLD) guidelines recommend those with dominant strictures be assessed with CA 19-9, MRCP and ERCP for tissue acquisition. CCA is one of the major causes of mortality in PSC and

may be detected concurrently at the time of or within months of its diagnosis. However, cholangiocarcinoma related mortality does not diminish with early liver transplantation[19]. Due to the unpredictable natural history and lack of early predictors of cancer, there is no set guideline for surveillance of patients with PSC. Biliary tissue acquisition can be achieved by brush cytology and or intraductal biopsy (for histology using pediatric forceps) to distinguish benign from malignant strictures. Brush cytology being technically easy, safe and less time consuming is more commonly used[20]. The AASLD guidelines recommend performing the above to exclude superimposed malignancy prior to endoscopic therapy for dominant bile duct strictures[21]. A meta analysis by Navaneethan *et al*[7] demonstrated that biliary brush cytology has high specificity (97%) for the diagnosis of CCA, however the low sensitivity limited its role in detecting early CCA[22]. Most cases of malignant DS occur in the perihilar region and accessible to brush cytology[23]. Repeated brush cytology aids early detection of high grade dysplasia before manifest CCA, enabling pre-emptive liver transplantation[24]. A weighted scoring system, proposed by Witt *et al*[25], termed the Atypical Biliary Brushing Score (ABBS) helps to risk stratify the individuals with atypical brush cytology to identify those at high risk of CCA[25]. ABBS considers seven variables including age over 60, pancreatic mass as an indication, distal biliary stricture, CA 19-9 over 300 U/mL scoring one each, endoscopic impression of malignancy, common hepatic duct stricture and a definite diagnosis of PSC with the last three scoring two each. Patients with a score over 4 are considered to be at high risk of harboring malignancy despite atypical results on a biliary brush cytology[25].

There are now advanced techniques in cytology such as digital image analysis (DIA) and fluorescence in situ hybridization (FISH) that enhance the sensitivity and improves diagnostic yield of brush cytology, compared with routine cytology[26-28]. DIA is a method by which microscopic images of a cell are quantified by digital conversion and computer analysis of the image feature[29]. FISH allows fluorescent labeling of DNA probes to target chromosomal regions to detect numerical or structural chromosomal abnormalities, such as trisomy or polysomy which suggest malignant process. The ability of FISH to detect polysomic cells from pancreatobiliary brushings puts it ahead of other pathological or imaging modalities in detecting CCA[30]. FISH of the cytologic specimen has significantly greater sensitivity than conventional cytology for the identification of CCA in patients with PSC, however it has lower specificity compared to biliary brushings[26,31]. Combining FISH with routine cytology can markedly improve the odds of detecting CCA at an early stage[30,32]. By identifying chromosomal abnormalities, DIA and FISH highly improve sensitivity while maintaining specificity. A prospective study from Mayo clinic revealed that composite DIA and FISH yielded 100% specificity and improved sensitivity by fivefold in indeterminate biliary strictures[27]. Many of these techniques once widely available should be used routinely.

Cholangioscopy

In recent years, peroral cholangioscopy as an adjunct to ERCP has gained popularity as it helps overcome diagnostic inaccuracies in biliary diseases, initially described by Chen and Pleskow[33]. In the management of challenging indeterminate biliary strictures, cholangioscopy permits direct intra luminal view of the biliary tree, targeted tissue acquisition and allows endoscopic guidance for therapeutic interventions[34]. The dual operated cholangioscope, "mother-baby" system was the first to be introduced, however the "two scope system" was time consuming, expensive, had limited manoeuvrability, poor irrigation capacity, required two endoscopists, and was easily damaged[35,36] it is therefore seldom used in clinical practise. The single-operator peroral cholangioscopy using SpyGlass direct visualization system appears to have overcome some of the limitations of the conventional peroral cholangioscopy. In addition to having two independent irrigation channels, this provides a 70-degree field of view, though the single use SpyBite forceps has only a maximum jaw separation of 4.1 mm. Hence, negative findings on the mini-forceps biopsy cannot exclude CCA owing to small sample obtained[37]. SpyGlass system was shown to have a lower complication rate, with a potential to become a diagnostic standard for the assessment of indeterminate biliary lesions with further refinements[38]. In a single center prospective study of thirty six patients with indeterminate biliary stricture, Ramchandani *et al*[36] from the Hyderabad group, showed that SpyBite had an overall accuracy of 82% in differentiating malignant from benign ductal lesions on an intention-to-treat analysis. The sensitivity of SpyGlass to obtain adequate tissue from indeterminate strictures could be upto 88%, especially when atleast 3 bites are taken. Sensitivity of diagnosing CCA by visual impression is 78% and by biopsy alone is 49%[39].

Endoscopic ultrasound scan

Endoscopic ultrasound scan (EUS) is a safe, accurate and technically feasible approach for diagnosing extrahepatic PSC. Lutz *et al*[40] demonstrated it to be an efficient tool for confirming suspected PSC, which has eluded diagnosis by ERCP or other modalities. Sensitivity and specificity of EUS-FNA for evaluation of biliary strictures ranges from 43% to 86% and 95% to 100% respectively[40-42]. The specific sonographic features include duct wall thickening greater than 1.5 mm, irregular CBD wall/caliber (change of wall thickness by $\geqslant$ 1 mm over 5 mm and caliber $\geqslant$ 2 mm over 5 mm ductal length) and the presence of perihilar lymph nodes at least 1 cm diameter, with an EUS diagnosis of PSC when two or more of above

criteria positive[43]. EUS enables refinement in disease detection and diminishes need for high risk invasive procedures[40]. In patients with a high index of suspicion of PSC with an inconclusive MRCP and EUS, core biopsy of the liver could be done safely in the same sitting (less than 1% risk of major complication), to look for small duct PSC and also to rule out cirrhosis, which would have prognostic implications[44-47]. Tumour seeding has been rarely reported with the FNA and hence some authorities advocate FNA of only suspicious lymph nodes[48]. Hence, we do not advocate EUS-FNA of the bile duct in a patient with suspected cholangiocarcinoma, who is a possible OLT candidate, until discussion at the tumor meeting with transplant surgeons. Direct biopsy using a cholangioscope would certainly be the preferred modality of tissue acquisition. EUS guided FNA has a significant role in diagnosing CCA when standard modalities are inconclusive, as it allows assessment and aspiration of malignant appearing lymph nodes[49,50].

Intraductal ultrasound

Intraductal ultrasound (IDUS) utilises a standard duodenoscope to insert a high frequency ultrasound transducer over a wire into the biliary system under fluoroscopic guidance. IDUS allows visualisation of the wall layers of the biliary strictures thereby providing an estimate of the extend of potentially cancerous infiltration[51]. This information is valuable in deciding treatment options. IDUS as an adjunct to ERCP guided tissue sampling significantly enhances the ability to distinguish malignant from benign strictures, it however is not an efficient modality assessing lymph nodes associated with malignant strictures[52]. Biliary cannulation with IDUS can be performed with ease, thereby avoiding the need for sphincterotomy; it provides detailed images of ductal and peri ductal tissues with high resolution. Additionally, when CCA is identified, IDUS may be employed for local staging in candidates prior to surgical resection[53].

Confocal laser endomicroscopy

Probe-based confocal laser endomicroscopy (pCLE) is a novel diagnostic technique that provides a virtual biopsy to facilitate subepithelial evaluation of the pancreatobiliary mucosa. It delivers microscopic information in real time and also provides dynamic information such as blood flow, cellular architecture, contrast uptake and leakage[54].

In a small single centre study of pCLE, Heif *et al*[55], showed a high technical success rate in patients with PSC and DS. Sufficient visualization was achieved in 95%, with sensitivity, specificity, positive predictive value and negative predictive values of 100%, 61.1%, 22.2% and 100% respectively, in detecting neoplasia. If verified in larger prospective studies, this could be potentially utilized for risk stratification of dominant strictures in patients with PSC[55].

ENDOSCOPIC THERAPY

PSC is characterized by inflammation and fibrosis leading to bile duct strictures. DS is defined as stenosis with a diameter of 1.5 mm in the common bile duct or 1 mm in the hepatic duct[21,56]. They develop in about forty percent of patients with PSC leading to significant biliary obstruction[57]. These predispose to stone formation, recurrent cholangitis and secondary biliary cirrhosis; also it may be a marker for underlying malignancy.

Traditionally ERCP has been employed for the stone removal that is the main indication for biliary sphincterotomy in PSC; balloon dilation *via* ERCP reduces stenosis thereby improving biliary flow and potentially preventing recurrent cholangitis[58,59]. Current therapy for stricture in PSC including balloon dilation, biliary stent placement and often a combination of both have become the mainstay of treatment, at least as a first line intervention[43,60]. Studies have established that repeated endoscopic therapy in patients with PSC is safe, the prognosis however worse in the subgroup of patients with dominant strictures at increased risk for development of cholangiocarcinoma[56].

An average of 3.46 ERCP's were needed per patient over a 8 year follow up study, with an improved observed survival rate of 82.8% at 4 years compared to 71.3% predicted survival (as per the Mayo Clinic natural history model)[58]. Endoscopic dilatation with short-term stenting is effective in benign dominant strictures and does not have predilection for malignant transformation or complications after transplantation[23]. Gotthardt *et al*[61] in a 20 year follow up of 171 patients have shown that repeated endoscopic therapy helps preserve a functioning common bile duct for many years, improving transplant free survival to 81% at 5 years and 52% at 10 years after initial endoscopic therapy. In a small subset of patients with DS in the extra hepatic duct without signs of cirrhosis, resection or bypass surgery may be performed, especially when endoscopic treatment fails[62].

Biliary sphincterotomy done in PSC is often a limited one, to minimize the reflux of enteric contents and ascending cholangitis[63]. Sphincterotomy prior to stent placement minimizes the chance of post ERCP pancreatitis (PEP)[64]. Stricture dilation could also be done using tapered-tip dilators (Cotton graded dilator) over a guide wire as a stand-alone or in combination with balloon dilatation[65]. In difficult cases, where only the wire could be passed through, a screw-tip dilator (Soehendra screw) could be employed[66]. In high grade stenosis, a Terumo guide wire could be used, since it has the added advantage of a very flexible tip[63]. Following this, stiff dilatation upto 7F facilitates balloon dilatation upto a target of 24F in the common duct and 18F in the hepatic ducts. Stiehl *et al*[57,67] have shown that even long segment stenosis (over 2 cm) of the common bile duct and shorter-segment intrahepatic stenosis within 2 cm of the hilum could be successfully

treated endoscopically.

Although controversial, there are interventional endoscopists, who advocate routine placement of one or more stents with frequent stent exchanges (every 6 to 8 wk), after dilatation with any of the above modalities, to prevent the stricture from reforming immediately due to the underlying fibrosis and elasticity[43]. International bodies like AASLD however, do not endorse this above practice, since there is no strong evidence demonstrating additional benefit of stenting over endoscopic dilatation[68]. Though results have been conflicting, there is evidence from a recent study in favour of additional stenting when clinically appropriate[68]. In cases of hilar strictures, it is preferable to gain access into both ducts first, as dilatation of one system somehow makes access to the other side more challenging[69].

Stents used in PSC could be either plastic or self-expandable metallic stents (SEMS). Teflon (PTFE) stents are the most commonly used ones, with longer patency[70]. However, fully/partially covered SEMS (CSEMS) have also been used for management of dominant strictures, though there are no randomized trials to support this[71-73]. The possible reasons why SEMS has not become standard of care of dominant strictures in PSC, is the theoretical risk of ascending cholangitis in this high risk group due to the larger caliber of the metal stent, in addition to not being cost effective compared to plastic stents in this situation. This is in addition to the potential risk of cholecystitis from obstruction of the cystic duct (in individuals who have not undergone cholecystectomy) and of obstruction of bile flow from the other lobe of the liver in case of hilar lesions.

Uncovered SEMS has been successfully used for palliation of inoperable CCA[56,74,75]. SEMS is preferred over plastic stents for patients with life expectancy over 3 mo[76]. For hilar strictures, stenting of one or both lobes and use of plastic stent or metallic stents continues to be debated, with ongoing research into the design of specifically tailored stents including cross wired stents and new plastic inside stent with thread (IT) stent[77-79].

EUS-guided palliation of malignant obstructive jaundice, when ERCP access fails has been gaining grounds and when expertise available replacing percutaneous drainage, since the latter is less appealing cosmetically with the external bag and inconvenient. This is mostly used for drainage of the obstructed left system (though there have been initial attempts to drain the right duct) using EUS-guided hepaticogastrostomy and of the main duct by a choledochoduodenostomy. Although technically feasible, the challenge is in the controlled deployment of the fully CSEMS, preferably in a single step, to minimize the risk of perforation, biliary peritonitis and stent migration[80-85]. These risks are minimized by the availability of lumen apposing metal stents. Endoscopic placement of nasobiliary drains to decompress the non-atrophic lobe has been done in some centers especially in Japan, to bridge the gap to surgery[79].

Biliary complications can occur in as many as 10% to 35% of patients after orthotopic liver transplantation with PSC recurrence in around 10%[86-88]. The most common biliary complications after OLT include biliary strictures (anastomotic or ischemic), bile duct leaks, common bile duct stones, and biliary casts, sphincter of Oddi/ampullary muscle dysfunction/spasm and r-PSC. With the advances in biliary endoscopy, majority of the complications could be managed with ERCP using regular techniques and tools. ERCP directed brachytherapy for locoregional disease control in cholangiocarcinoma, using photodynamic therapy or radiofrequency ablation, is promising, though still in its early stages[89,90]. They have comparable efficacy for local disease control and safety profile.

APPROACH TO THE PATIENT WITH SUSPECTED PSC

We recommend MRCP to be done as the initial diagnostic modality in suspected patients with PSC. ERCP with brush cytology and or biopsy, to date, continues to be the gold standard for diagnosis especially if the former is inconclusive, due to the surveillance and prognostic implications of making a correct and early diagnosis. EUS, IDUS and cholangioscopy could be utilized in the evaluation of patients, especially those with indeterminate dominant strictures, to get better cytologic yields to exclude early biliary dysplasia and cholangiocarcinoma. With further evidence and validation of EUS criteria for PSC, it might be done before ERCP in the diagnostic algorithm, especially considering its safety profile. Advancements in cytology including DIA and FISH should be considered to improve the yield, when ever available. The role of molecular markers and proteomics in diagnosis is still evolving. ERCP with repeated biliary dilatation with or without stenting is our current practice in management of benign strictures, in addition to routine use of antibiotic prophylaxis, as per BSG and ASGE recommendations. EUS guided biliary drainage procedures could be attempted in cases of failed SEMS deployment by ERCP for palliation of CCA. There is some evidence that endoscopic therapy could delay the need for orthotopic liver transplantation in patients with PSC.

CONCLUSION

Endoscopy has a pivotal role in the diagnosis and management of the condition, both pre and post orthotopic liver transplantation. Advances in endoscopy (complimented by cross sectional imaging) and ancillary cytologic testing would enhance earlier diagnosis, facilitating a surveillance protocol that could be used, to improve survival rates by timely curative therapy.

REFERENCES

1 **Wiesner RH**, Grambsch PM, Dickson ER, Ludwig J, MacCarty RL, Hunter EB, Fleming TR, Fisher LD, Beaver SJ, LaRusso NF. Primary sclerosing cholangitis: natural history, prognostic factors and survival analysis. *Hepatology* 1989; **10**: 430-436 [PMID: 2777204]

2 **Graziadei IW**, Wiesner RH, Batts KP, Marotta PJ, LaRusso NF, Porayko MK, Hay JE, Gores GJ, Charlton MR, Ludwig J, Poterucha JJ, Steers JL, Krom RA. Recurrence of primary sclerosing cholangitis following liver transplantation. *Hepatology* 1999; **29**: 1050-1056 [PMID: 10094945]

3 **Boonstra K**, Culver EL, de Buy Wenniger LM, van Heerde MJ, van Erpecum KJ, Poen AC, van Nieuwkerk KM, Spanier BW, Witteman BJ, Tuynman HA, van Geloven N, van Buuren H, Chapman RW, Barnes E, Beuers U, Ponsioen CY. Serum immunoglobulin G4 and immunoglobulin G1 for distinguishing immunoglobulin G4-associated cholangitis from primary sclerosing cholangitis. *Hepatology* 2014; **59**: 1954-1963 [PMID: 24375491 DOI: 10.1002/hep.26977]

4 **Nakazawa T**, Naitoh I, Hayashi K, Miyabe K, Simizu S, Joh T. Diagnosis of IgG4-related sclerosing cholangitis. *World J Gastroenterol* 2013; **19**: 7661-7670 [PMID: 24282356 DOI: 10.3748/wjg.v19.i43.7661]

5 **Lenzen H**, Weismüller TJ, Negm AA, Wlecke J, Loges S, Strassburg CP, Manns MP, Lankisch TO. Antineutrophil cytoplasmic antibodies in bile are associated with disease activity in primary sclerosing cholangitis. *Scand J Gastroenterol* 2013; **48**: 1205-1212 [PMID: 23957616 DOI: 10.3109/00365521.2013.825313]

6 **Berglin L**, Björkström NK, Bergquist A. Primary sclerosing cholangitis is associated with autoreactive IgA antibodies against biliary epithelial cells. *Scand J Gastroenterol* 2013; **48**: 719-728 [PMID: 23713804 DOI: 10.3109/00365521.2013.786131]

7 **Navaneethan U**, Gutierrez NG, Venkatesh PG, Jegadeesan R, Zhang R, Jang S, Sanaka MR, Vargo JJ, Parsi MA, Feldstein AE, Stevens T. Lipidomic profiling of bile in distinguishing benign from malignant biliary strictures: a single-blinded pilot study. *Am J Gastroenterol* 2014; **109**: 895-902 [PMID: 24710507 DOI: 10.1038/ajg.2014.60]

8 **Li L**, Masica D, Ishida M, Tomuleasa C, Umegaki S, Kalloo AN, Georgiades C, Singh VK, Khashab M, Amateau S, Li Z, Okolo P, Lennon AM, Saxena P, Geschwind JF, Schlachter T, Hong K, Pawlik TM, Canto M, Law J, Sharaiha R, Weiss CR, Thuluvath P, Goggins M, Shin EJ, Peng H, Kumbhari V, Hutfless S, Zhou L, Mezey E, Meltzer SJ, Karchin R, Selaru FM. Human bile contains microRNA-laden extracellular vesicles that can be used for cholangiocarcinoma diagnosis. *Hepatology* 2014; **60**: 896-907 [PMID: 24497320 DOI: 10.1002/hep.27050]

9 **Baraniskin A**, Nöpel-Dünnebacke S, Schumacher B, Gerges C, Bracht T, Sitek B, Meyer HE, Gerken G, Dechene A, Schlaak JF, Schroers R, Pox C, Schmiegel W, Hahn SA. Analysis of U2 small nuclear RNA fragments in the bile differentiates cholangiocarcinoma from primary sclerosing cholangitis and other benign biliary disorders. *Dig Dis Sci* 2014; **59**: 1436-1441 [PMID: 24482036 DOI: 10.1007/s10620-014-3034-5]

10 **Weber C**, Kuhlencordt R, Grotelueschen R, Wedegaertner U, Ang TL, Adam G, Soehendra N, Seitz U. Magnetic resonance cholangiopancreatography in the diagnosis of primary sclerosing cholangitis. *Endoscopy* 2008; **40**: 739-745 [PMID: 18698533 DOI: 10.1055/s-2008-1077509]

11 **Moff SL**, Kamel IR, Eustace J, Lawler LP, Kantsevoy S, Kalloo AN, Thuluvath PJ. Diagnosis of primary sclerosing cholangitis: a blinded comparative study using magnetic resonance cholangiography and endoscopic retrograde cholangiography. *Gastrointest Endosc* 2006; **64**: 219-223 [PMID: 16860072]

12 **Bangarulingam SY**, Gossard AA, Petersen BT, Ott BJ, Lindor KD. Complications of endoscopic retrograde cholangiopancreatography in primary sclerosing cholangitis. *Am J Gastroenterol* 2009; **104**: 855-860 [PMID: 19259076 DOI: 10.1038/ajg.2008.161]

13 **Cotton PB**, Garrow DA, Gallagher J, Romagnuolo J. Risk factors for complications after ERCP: a multivariate analysis of 11,497 procedures over 12 years. *Gastrointest Endosc* 2009; **70**: 80-88 [PMID: 19286178 DOI: 10.1016/j.gie.2008.10.039]

14 **Ismail S**, Kylänpää L, Mustonen H, Halttunen J, Lindström O, Jokelainen K, Udd M, Färkkilä M. Risk factors for complications of ERCP in primary sclerosing cholangitis. *Endoscopy* 2012; **44**: 1133-1138 [PMID: 23108808 DOI: 10.1055/s-0032-1325677]

15 **Navaneethan U**, Jegadeesan R, Nayak S, Lourdusamy V, Sanaka MR, Vargo JJ, Parsi MA. ERCP-related adverse events in patients with primary sclerosing cholangitis. *Gastrointest Endosc* 2015; **81**: 410-419 [PMID: 25085336 DOI: 10.1016/j.gie.2014.06.030]

16 **Dave M**, Elmunzer BJ, Dwamena BA, Higgins PD. Primary sclerosing cholangitis: meta-analysis of diagnostic performance of MR cholangiopancreatography. *Radiology* 2010; **256**: 387-396 [PMID: 20656832 DOI: 10.1148/radiol.10091953]

17 **Meagher S**, Yusoff I, Kennedy W, Martel M, Adam V, Barkun A. The roles of magnetic resonance and endoscopic retrograde cholangiopancreatography (MRCP and ERCP) in the diagnosis of patients with suspected sclerosing cholangitis: a cost-effectiveness analysis. *Endoscopy* 2007; **39**: 222-228 [PMID: 17385107]

18 **Tischendorf JJ**, Hecker H, Krüger M, Manns MP, Meier PN. Characterization, outcome, and prognosis in 273 patients with primary sclerosing cholangitis: A single center study. *Am J Gastroenterol* 2007; **102**: 107-114 [PMID: 17037993]

19 **Ahrendt SA**, Pitt HA, Nakeeb A, Klein AS, Lillemoe KD, Kalloo AN, Cameron JL. Diagnosis and management of cholangiocarcinoma in primary sclerosing cholangitis. *J Gastrointest Surg* 1999; **3**: 357-367; discussion 367-368 [PMID: 10482687]

20 **Weber A**, von Weyhern C, Fend F, Schneider J, Neu B, Meining A, Weidenbach H, Schmid RM, Prinz C. Endoscopic transpapillary brush cytology and forceps biopsy in patients with hilar cholangiocarcinoma. *World J Gastroenterol* 2008; **14**: 1097-1101 [PMID: 18286693]

21 **Chapman R**, Fevery J, Kalloo A, Nagorney DM, Boberg KM, Shneider B, Gores GJ. Diagnosis and management of primary sclerosing cholangitis. *Hepatology* 2010; **51**: 660-678 [PMID: 20101749 DOI: 10.1002/hep.23294]

22 **Trikudanathan G**, Navaneethan U, Njei B, Vargo JJ, Parsi MA. Diagnostic yield of bile duct brushings for cholangiocarcinoma in primary sclerosing cholangitis: a systematic review and meta-analysis. *Gastrointest Endosc* 2014; **79**: 783-789 [PMID: 24140129 DOI: 10.1016/j.gie.2013.09.015]

23 **Aljiffry M**, Renfrew PD, Walsh MJ, Laryea M, Molinari M. Analytical review of diagnosis and treatment strategies for dominant bile duct strictures in patients with primary sclerosing cholangitis. *HPB* (Oxford) 2011; **13**: 79-90 [PMID: 21241424 DOI: 10.1111/j.1477-2574.2010.00268.x]

24 **Sangfelt P**, Sundin A, Wanders A, Rasmussen I, Karlson BM, Bergquist A, Rorsman F. Monitoring dominant strictures in primary sclerosing cholangitis with brush cytology and FDG-PET. *J Hepatol* 2014; **61**: 1352-1357 [PMID: 25111173 DOI: 10.1016/j.jhep.2014.07.032]

25 **Witt BL**, Kristen Hilden RN, Scaife C, Chadwick B, Layfield L, Cory Johnston W, Safaee M, Siddiqui A, Adler DG. Identification of factors predictive of malignancy in patients with atypical biliary brushing results obtained via ERCP. *Diagn Cytopathol* 2013; **41**: 682-688 [PMID: 23008113 DOI: 10.1002/dc.22924]

26 **Kipp BR**, Stadheim LM, Halling SA, Pochron NL, Harmsen S, Nagorney DM, Sebo TJ, Therneau TM, Gores GJ, de Groen PC, Baron TH, Levy MJ, Halling KC, Roberts LR. A comparison of routine cytology and fluorescence in situ hybridization for the detection of malignant bile duct strictures. *Am J Gastroenterol* 2004; **99**: 1675-1681 [PMID: 15330900]

27 **Levy MJ**, Baron TH, Clayton AC, Enders FB, Gostout CJ, Halling KC, Kipp BR, Petersen BT, Roberts LR, Rumalla A, Sebo TJ, Topazian MD, Wiersema MJ, Gores GJ. Prospective evaluation of advanced molecular markers and imaging techniques in patients with indeterminate bile duct strictures. *Am J Gastroenterol* 2008; **103**: 1263-1273 [PMID: 18477350 DOI: 10.1111/j.1572-0241.2007.01776.x]

28 **Baron TH**, Harewood GC, Rumalla A, Pochron NL, Stadheim LM, Gores GJ, Therneau TM, De Groen PC, Sebo TJ, Salomao DR,

Kipp BR. A prospective comparison of digital image analysis and routine cytology for the identification of malignancy in biliary tract strictures. *Clin Gastroenterol Hepatol* 2004; **2**: 214-219 [PMID: 15017605]
29 **Sebo TJ**. Digital image analysis. *Mayo Clin Proc* 1995; **70**: 81-82 [PMID: 7528866]
30 **Barr Fritcher EG**, Kipp BR, Voss JS, Clayton AC, Lindor KD, Halling KC, Gores GJ. Primary sclerosing cholangitis patients with serial polysomy fluorescence in situ hybridization results are at increased risk of cholangiocarcinoma. *Am J Gastroenterol* 2011; **106**: 2023-2028 [PMID: 21844920 DOI: 10.1038/ajg.2011.272]
31 **Layfield LJ**, Ehya H, Filie AC, Hruban RH, Jhala N, Joseph L, Vielh P, Pitman MB. Utilization of ancillary studies in the cytologic diagnosis of biliary and pancreatic lesions: The Papanicolaou Society of Cytopathology Guidelines. *Cytojournal* 2014; **11**: 4 [PMID: 25191518 DOI: 10.4103/1742-6413.133352]
32 **Smoczynski M**, Jablonska A, Matyskiel A, Lakomy J, Dubowik M, Marek I, Biernat W, Limon J. Routine brush cytology and fluorescence in situ hybridization for assessment of pancreatobiliary strictures. *Gastrointest Endosc* 2012; **75**: 65-73 [PMID: 22078103 DOI: 10.1016/j.gie.2011.08.040]
33 **Chen YK**, Pleskow DK. SpyGlass single-operator peroral cholangiopancreatoscopy system for the diagnosis and therapy of bile-duct disorders: a clinical feasibility study (with video). *Gastrointest Endosc* 2007; **65**: 832-841 [PMID: 17466202]
34 **Moon J**, Seo Y, Choi H. Diagnostic and therapeutic peroral cholangioscopy. *J Dig Endosc* 2012; **3**: 23 [DOI: 10.4103/0976-5042.95026]
35 **Kahaleh M**. Spyglass direct visualization system. *Clin Endosc* 2012; **45**: 316-318 [PMID: 22977826 DOI: 10.5946/ce.2012.45.3.316]
36 **Ramchandani M**, Reddy DN, Gupta R, Lakhtakia S, Tandan M, Darisetty S, Sekaran A, Rao GV. Role of single-operator peroral cholangioscopy in the diagnosis of indeterminate biliary lesions: a single-center, prospective study. *Gastrointest Endosc* 2011; **74**: 511-519 [PMID: 21737076 DOI: 10.1016/j.gie.2011.04.034]
37 **Draganov PV**, Chauhan S, Wagh MS, Gupte AR, Lin T, Hou W, Forsmark CE. Diagnostic accuracy of conventional and cholangioscopy-guided sampling of indeterminate biliary lesions at the time of ERCP: a prospective, long-term follow-up study. *Gastrointest Endosc* 2012; **75**: 347-353 [PMID: 22248602 DOI: 10.1016/j.gie.2011.09.020]
38 **Manta R**, Frazzoni M, Conigliaro R, Maccio L, Melotti G, Dabizzi E, Bertani H, Manno M, Castellani D, Villanacci V, Bassotti G. SpyGlass single-operator peroral cholangioscopy in the evaluation of indeterminate biliary lesions: a single-center, prospective, cohort study. *Surg Endosc* 2013; **27**: 1569-1572 [PMID: 23233008 DOI: 10.1007/s00464-012-2628-2]
39 **Chen YK**, Parsi MA, Binmoeller KF, Hawes RH, Pleskow DK, Slivka A, Haluszka O, Petersen BT, Sherman S, Devière J, Meisner S, Stevens PD, Costamagna G, Ponchon T, Peetermans JA, Neuhaus H. Single-operator cholangioscopy in patients requiring evaluation of bile duct disease or therapy of biliary stones (with videos). *Gastrointest Endosc* 2011; **74**: 805-814 [PMID: 21762903 DOI: 10.1016/j.gie.2011.04.016]
40 **Lutz HH**, Wasmuth HE, Streetz K, Tacke F, Koch A, Luedde T, Trautwein C, Tischendorf JJ. Endoscopic ultrasound as an early diagnostic tool for primary sclerosing cholangitis: a prospective pilot study. *Endoscopy* 2012; **44**: 934-939 [PMID: 22752890 DOI: 10.1055/s-0032-1309896]
41 **Rösch T**, Hofrichter K, Frimberger E, Meining A, Born P, Weigert N, Allescher HD, Classen M, Barbur M, Schenck U, Werner M. ERCP or EUS for tissue diagnosis of biliary strictures? A prospective comparative study. *Gastrointest Endosc* 2004; **60**: 390-396 [DOI: 10.1016/S0016-5107(04)01732-8]
42 **Eloubeidi MA**, Chen VK, Jhala NC, Eltoum IE, Jhala D, Chhieng DC, Syed SA, Vickers SM, Mel Wilcox C. Endoscopic ultrasound-guided fine needle aspiration biopsy of suspected cholangiocarcinoma. *Clin Gastroenterol Hepatol* 2004; **2**: 209-213 [PMID: 15017604]
43 **Law R**, Baron TH. Endoscopic management of primary sclerosing cholangitis. *Clin Liver Dis* 2014; **3**: 79–82 [DOI: 10.1002/cld.327]
44 **Burak KW**, Angulo P, Lindor KD. Is there a role for liver biopsy in primary sclerosing cholangitis? *Am J Gastroenterol* 2003; **98**: 1155-1158 [PMID: 12809842]
45 **Dewitt J**, McGreevy K, Cummings O, Sherman S, Leblanc JK, McHenry L, Al-Haddad M, Chalasani N. Initial experience with EUS-guided Tru-cut biopsy of benign liver disease. *Gastrointest Endosc* 2009; **69**: 535-542 [PMID: 19231495 DOI: 10.1016/j.gie.2008.09.056]
46 **Gor N**, Salem SB, Jakate S, Patel R, Shah N, Patil A. Histological adequacy of EUS-guided liver biopsy when using a 19-gauge non-Tru-Cut FNA needle. *Gastrointest Endosc* 2014; **79**: 170-172 [PMID: 23916397 DOI: 10.1016/j.gie.2013.06.031]
47 **Hammoud GM**, Ibdah JA. Utility of endoscopic ultrasound in patients with portal hypertension. *World J Gastroenterol* 2014; **20**: 14230-14236 [PMID: 25339809 DOI: 10.3748/wjg.v20.i39.14230]
48 **Paquin SC**, Gariépy G, Lepanto L, Bourdages R, Raymond G, Sahai AV. A first report of tumor seeding because of EUS-guided FNA of a pancreatic adenocarcinoma. *Gastrointest Endosc* 2005; **61**: 610-611 [PMID: 15812422]
49 **Fritscher-Ravens A**, Broering DC, Sriram PV, Topalidis T, Jaeckle S, Thonke F, Soehendra N. EUS-guided fine-needle aspiration cytodiagnosis of hilar cholangiocarcinoma: a case series. *Gastrointest Endosc* 2000; **52**: 534-540 [PMID: 11023576]
50 **Ohshima Y**, Yasuda I, Kawakami H, Kuwatani M, Mukai T, Iwashita T, Doi S, Nakashima M, Hirose Y, Asaka M, Moriwaki H. EUS-FNA for suspected malignant biliary strictures after negative endoscopic transpapillary brush cytology and forceps biopsy. *J Gastroenterol* 2011; **46**: 921-928 [PMID: 21526370 DOI: 10.1007/s00535-011-0404-z]
51 **Domagk D**, Poremba C, Dietl KH, Senninger N, Heinecke A, Domschke W, Menzel J. Endoscopic transpapillary biopsies and intraductal ultrasonography in the diagnostics of bile duct strictures: a prospective study. *Gut* 2002; **51**: 240-244 [PMID: 12117887]
52 **Farrell RJ**, Agarwal B, Brandwein SL, Underhill J, Chuttani R, Pleskow DK. Intraductal US is a useful adjunct to ERCP for distinguishing malignant from benign biliary strictures. *Gastrointest Endosc* 2002; **56**: 681-687 [PMID: 12397276]
53 **Victor DW**, Sherman S, Karakan T, Khashab MA. Current endoscopic approach to indeterminate biliary strictures. *World J Gastroenterol* 2012; **18**: 6197-6205 [PMID: 23180939 DOI: 10.3748/wjg.v18.i43.6197]
54 **Wani S**, Shah RJ. Probe-based confocal laser endomicroscopy for the diagnosis of indeterminate biliary strictures. *Curr Opin Gastroenterol* 2013; **29**: 319-323 [PMID: 23507916 DOI: 10.1097/MOG.0b013e32835fee9f]
55 **Heif M**, Yen RD, Shah RJ. ERCP with probe-based confocal laser endomicroscopy for the evaluation of dominant biliary stenoses in primary sclerosing cholangitis patients. *Dig Dis Sci* 2013; **58**: 2068-2074 [PMID: 23475187 DOI: 10.1007/s10620-013-2608-y]
56 **Chapman MH**, Webster GJ, Bannoo S, Johnson GJ, Wittmann J, Pereira SP. Cholangiocarcinoma and dominant strictures in patients with primary sclerosing cholangitis: a 25-year single-centre experience. *Eur J Gastroenterol Hepatol* 2012; **24**: 1051-1058 [PMID: 22653260 DOI: 10.1097/MEG.0b013e3283554bbf]
57 **Stiehl A**, Rudolph G, Klöters-Plachky P, Sauer P, Walker S. Development of dominant bile duct stenoses in patients with primary sclerosing cholangitis treated with ursodeoxycholic acid: outcome after endoscopic treatment. *J Hepatol* 2002; **36**: 151-156 [PMID: 11830325]
58 **Gluck M**, Cantone NR, Brandabur JJ, Patterson DJ, Bredfeldt JE, Kozarek RA. A twenty-year experience with endoscopic therapy for symptomatic primary sclerosing cholangitis. *J Clin Gastroenterol* 2008; **42**: 1032-1039 [PMID: 18580600 DOI: 10.1097/MCG.0b013e3181646713]
59 **Alkhatib AA**, Hilden K, Adler DG. Comorbidities, sphincterotomy, and balloon dilation predict post-ERCP adverse events in PSC patients: operator experience is protective. *Dig Dis Sci* 2011; **56**: 3685-3688 [PMID: 21789539 DOI: 10.1007/s10620-011-1830-8]
60 **Kaya M**, Petersen BT, Angulo P, Baron TH, Andrews JC, Gostout

CJ, Lindor KD. Balloon dilation compared to stenting of dominant strictures in primary sclerosing cholangitis. *Am J Gastroenterol* 2001; **96**: 1059-1066 [PMID: 11316147]
61 **Gotthardt DN**, Rudolph G, Klöters-Plachky P, Kulaksiz H, Stiehl A. Endoscopic dilation of dominant stenoses in primary sclerosing cholangitis: outcome after long-term treatment. *Gastrointest Endosc* 2010; **71**: 527-534 [PMID: 20189511 DOI: 10.1016/j.gie.2009.10.041]
62 **Tsai S**, Pawlik TM. Primary sclerosing cholangitis: the role of extrahepatic biliary resection. *Adv Surg* 2009; **43**: 175-188 [PMID: 19845177]
63 **Gotthardt D**, Stiehl A. Endoscopic retrograde cholangiopancreatography in diagnosis and treatment of primary sclerosing cholangitis. *Clin Liver Dis* 2010; **14**: 349-358 [PMID: 20682240 DOI: 10.1016/j.cld.2010.03.010]
64 **Cui PJ**, Yao J, Zhao YJ, Han HZ, Yang J. Biliary stenting with or without sphincterotomy for malignant biliary obstruction: a meta-analysis. *World J Gastroenterol* 2014; **20**: 14033-14039 [PMID: 25320543 DOI: 10.3748/wjg.v20.i38.14033]
65 **Siddiqui UD**, Banerjee S, Barth B, Chauhan SS, Gottlieb KT, Konda V, Maple JT, Murad FM, Pfau PR, Pleskow DK, Tokar JL, Wang A, Rodriguez SA. Tools for endoscopic stricture dilation. *Gastrointest Endosc* 2013; **78**: 391-404 [PMID: 23948186 DOI: 10.1016/j.gie.2013.04.170]
66 **Faigel DO**, Ginsberg GG, Kochman ML. Innovative use of the Soehendra stent retriever for biliary stricture recannalization. *Gastrointest Endosc* 1996; **44**: 635 [PMID: 8934187]
67 **Stiehl A**. Primary sclerosing cholangitis: the role of endoscopic therapy. *Semin Liver Dis* 2006; **26**: 62-68 [PMID: 16496234]
68 **Etzel JP**, Eng SC, Ko CW, Lee SD, Saunders MD, Tung BY, Kimmey MB, Kowdley KV. Complications after ERCP in patients with primary sclerosing cholangitis. *Gastrointest Endosc* 2008; **67**: 643-648 [PMID: 18061595]
69 **Koro NS**, Alkaade S. Role of endoscopy in primary sclerosing cholangitis. *Curr Gastroenterol Rep* 2013; **15**: 361 [PMID: 24258288 DOI: 10.1007/s11894-013-0361-1]
70 **van Berkel AM**, van Marle J, van Veen H, Groen AK, Huibregtse K. A scanning electron microscopic study of biliary stent materials. *Gastrointest Endosc* 2000; **51**: 19-22 [PMID: 10625789]
71 **Kahaleh M**, Behm B, Clarke BW, Brock A, Shami VM, De La Rue SA, Sundaram V, Tokar J, Adams RB, Yeaton P. Temporary placement of covered self-expandable metal stents in benign biliary strictures: a new paradigm? (with video). *Gastrointest Endosc* 2008; **67**: 446-454 [PMID: 18294506 DOI: 10.1016/j.gie.2007.06.057]
72 **Devière J**, Nageshwar Reddy D, Püspök A, Ponchon T, Bruno MJ, Bourke MJ, Neuhaus H, Roy A, González-Huix Lladó F, Barkun AN, Kortan PP, Navarrete C, Peetermans J, Blero D, Lakhtakia S, Dolak W, Lepilliez V, Poley JW, Tringali A, Costamagna G. Successful management of benign biliary strictures with fully covered self-expanding metal stents. *Gastroenterology* 2014; **147**: 385-395; quiz e15 [PMID: 24801350 DOI: 10.1053/j.gastro.2014.04.043]
73 **Mahajan A**, Ho H, Sauer B, Phillips MS, Shami VM, Ellen K, Rehan M, Schmitt TM, Kahaleh M. Temporary placement of fully covered self-expandable metal stents in benign biliary strictures: midterm evaluation (with video). *Gastrointest Endosc* 2009; **70**: 303-309 [PMID: 19523620 DOI: 10.1016/j.gie.2008.11.029]
74 **Kim JH**. Endoscopic stent placement in the palliation of malignant biliary obstruction. *Clin Endosc* 2011; **44**: 76-86 [PMID: 22741117 DOI: 10.5946/ce.2011.44.2.76]
75 **Irisawa A**, Katanuma A, Itoi T. Otaru consensus on biliary stenting for unresectable distal malignant biliary obstruction. *Dig Endosc* 2013; **25** Suppl 2: 52-57 [PMID: 23617650 DOI: 10.1111/den.12069]
76 **Lee TH**, Moon JH, Park SH. Bilateral metallic stenting in malignant hilar obstruction. *Clin Endosc* 2014; **47**: 440-446 [PMID: 25325005 DOI: 10.5946/ce.2014.47.5.440]
77 **Lee TH**, Lee SJ, Moon JH, Park SH. Technical tips and issues of biliary stenting, focusing on malignant hilar obstruction. *Minerva Gastroenterol Dietol* 2014; **60**: 135-149 [PMID: 24780948]
78 **Ishiwatari H**, Hayashi T, Ono M, Sato T, Kato J. Newly designed plastic stent for endoscopic placement above the sphincter of Oddi in patients with malignant hilar biliary obstruction. *Dig Endosc* 2013; **25** Suppl 2: 94-99 [PMID: 23617658 DOI: 10.1111/den.12080]
79 **Yasuda I**, Mukai T, Moriwaki H. Unilateral versus bilateral endoscopic biliary stenting for malignant hilar biliary strictures. *Dig Endosc* 2013; **25** Suppl 2: 81-85 [PMID: 23617655 DOI: 10.1111/den.12060]
80 **Park do H**, Jeong SU, Lee BU, Lee SS, Seo DW, Lee SK, Kim MH. Prospective evaluation of a treatment algorithm with enhanced guidewire manipulation protocol for EUS-guided biliary drainage after failed ERCP (with video). *Gastrointest Endosc* 2013; **78**: 91-101 [PMID: 23523301 DOI: 10.1016/j.gie.2013.01.042]
81 **Bories E**, Pesenti C, Caillol F, Lopes C, Giovannini M. Transgastric endoscopic ultrasonography-guided biliary drainage: results of a pilot study. *Endoscopy* 2007; **39**: 287-291 [PMID: 17357952]
82 **Iwashita T**, Doi S, Yasuda I. Endoscopic ultrasound-guided biliary drainage: a review. *Clin J Gastroenterol* 2014; **7**: 94-102 [PMID: 24765215]
83 **Kahaleh M**. Training the next generation of advanced endoscopists in EUS-guided biliary and pancreatic drainage: learning from master endoscopists. *Gastrointest Endosc* 2013; **78**: 638-641 [PMID: 24054742 DOI: 10.1016/j.gie.2013.05.034]
84 **Hawes RH**, Van Dam J, Varadarajulu S. EUS 2008 Working Group document: interventional EUS--a road map for the future. *Gastrointest Endosc* 2009; **69**: S1-S2 [PMID: 19179130 DOI: 10.1016/j.gie.2008.11.013]
85 **Savides TJ**, Varadarajulu S, Palazzo L. EUS 2008 Working Group document: evaluation of EUS-guided hepaticogastrostomy. *Gastrointest Endosc* 2009; **69**: S3-S7 [PMID: 19179166 DOI: 10.1016/j.gie.2008.10.060]
86 **Gopal DV**, Pfau PR, Lucey MR. Endoscopic Management of Biliary Complications After Orthotopic Liver Transplantation. *Curr Treat Options Gastroenterol* 2003; **6**: 509-515 [PMID: 14585240]
87 **Londoño MC**, Balderramo D, Cárdenas A. Management of biliary complications after orthotopic liver transplantation: the role of endoscopy. *World J Gastroenterol* 2008; **14**: 493-497 [PMID: 18203278]
88 **Cholongitas E**, Shusang V, Papatheodoridis GV, Marelli L, Manousou P, Rolando N, Patch D, Rolles K, Davidson B, Burroughs AK. Risk factors for recurrence of primary sclerosing cholangitis after liver transplantation. *Liver Transpl* 2008; **14**: 138-143 [PMID: 18236447 DOI: 10.1002/lt.21260]
89 **Cosgrove ND**, Al-Osaimi AM, Sanoff HK, Morris MM, Read PW, Cox DG, Mann JA, Argo CK, Berg CL, Pelletier SJ, Maluf DG, Wang AY. Photodynamic therapy provides local control of cholangiocarcinoma in patients awaiting liver transplantation. *Am J Transplant* 2014; **14**: 466-471 [PMID: 24373228 DOI: 10.1111/ajt.12597]
90 **Strand DS**, Cosgrove ND, Patrie JT, Cox DG, Bauer TW, Adams RB, Mann JA, Sauer BG, Shami VM, Wang AY. ERCP-directed radiofrequency ablation and photodynamic therapy are associated with comparable survival in the treatment of unresectable cholangiocarcinoma. *Gastrointest Endosc* 2014; **80**: 794-804 [PMID: 24836747 DOI: 10.1016/j.gie.2014.02.1030]

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REVIEW

Rare gastrointestinal lymphomas: The endoscopic investigation

Calogero Vetro, Giacomo Bonanno, Giorgio Giulietti, Alessandra Romano, Concetta Conticello, Annalisa Chiarenza, Paolo Spina, Francesco Coppolino, Rosario Cunsolo, Francesco Di Raimondo

Calogero Vetro, Alessandra Romano, Concetta Conticello, Annalisa Chiarenza, Paolo Spina, Francesco Di Raimondo, Division of Hematology, A.O. "Policlinico-Vittorio Emanuele", University of Catania, 95124 Catania, Italy

Giacomo Bonanno, Division of Gastroenterology, A.O. "Policlinico-Vittorio Emanuele", 95129 Catania, Italy

Giorgio Giulietti, Department of Diagnostic and Interventional Radiology, A.O. "Policlinico-Vittorio Emanuele", 95124 Catania, Italy

Francesco Coppolino, Department of Radiology, University of Palermo, 90141 Palermo, Italy

Rosario Cunsolo, Health Direction, A.O. "Policlinico-Vittorio Emanuele", 95129 Catania, Italy

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Correspondence to: Calogero Vetro, MD, Division of Hematology, A.O. "Policlinico-Vittorio Emanuele", University of Catania, Via Citelli 6, 95124 Catania, Italy. gerovetro@gmail.com
Telephone: +39-95-7435916
Fax: +39-95-365174

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Abstract

Gastrointestinal lymphomas represent up to 10% of gastrointestinal malignancies and about one third of non-Hodgkin lymphomas. The most prominent histologies are mucosa-associated lymphoid tissue lymphoma and diffuse large B-cell lymphoma. However, the gastrointestinal tract can be the site of rarer lymphoma subtypes as a primary or secondary localization. Due to their rarity and the multifaceted histology, an endoscopic classification has not been validated yet. This review aims to analyze the endoscopic presentation of rare gastrointestinal lymphomas from disease diagnosis to follow-up, according to the involved site and lymphoma subtype. Existing, new and emerging endoscopic technologies have been examined. In particular, we investigated the diagnostic, prognostic and follow-up endoscopic features of T-cell and natural killer lymphomas, lymphomatous polyposis and mantle cell lymphoma, follicular lymphoma, plasma cell related disease, gastrointestinal lymphomas in immunodeficiency and Hodgkin's lymphoma of the gastrointestinal tract. Contrarily to more frequent gastrointestinal lymphomas, data about rare lymphomas are mostly extracted from case series and case reports. Due to the data paucity, a synergism between gastroenterologists and hematologists is required in

order to better manage the disease. Indeed, clinical and prognostic features are different from nodal and extranodal or the bone marrow (in case of plasma cell disease) counterpart. Therefore, the approach should be based on the knowledge of the peculiar behavior and natural history of disease.

Key words: Endoscopy; Lymphoma; Endosonography; Stomach; Intestine

Core tip: The gastrointestinal tract can be the site of rare lymphomas as a primary or secondary localization. Their endoscopic behavior has been scantily evaluated but is emerging as a useful tool with prognostic and therapeutic implications. T-cell lymphomas present mainly with ulcerative lesions, while B-cell lymphomas (follicular or mantle cell lymphomas) present as a duodenal mass or multiple polyposis. Plasma cell-related disorders localize to the gastrointestinal tract, either as a neoplastic mass or as an amyloid deposition. Immunodeficits (primary or secondary) can lead to gastrointestinal localization of rare and seldom fatal high-grade lymphomas. More rarely, Hodgkin's lymphoma localizes to the gastrointestinal tract with an uncertain impact on prognosis.

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INTRODUCTION AND MAIN SECTION OF THE WORK

Gastrointestinal (GI) lymphomas represent 5%-10% of primary GI malignancies and almost two third of extranodal non Hodgkin's lymphomas (NHL), that in turn account for 24%-49% of all NHL[1,2]. The most common lymphomas are mucosa-associated lymphoid tissue (MALT) and diffuse large B-cell lymphoma (DLBCL), accounting for 70%-95% of GI lymphomas[3,4]. Apart from MALT and DLBCL, the GI tract can be the site of other lymphomas, either as a primary or secondary localization[5], and these lymphomas will be the subject of this report. The knowledge of their clinical and echo-endoscopic features would help in addressing clinical questions[3,6-8], sparing inappropriate evaluations[9-13]. Nonetheless, histology, together with immunohistochemistry and molecular biology, are mandatory for diagnosis[14].

While the endoscopic classification for MALT and DLBCL has been already validated[15,16], such an analysis on rare GI lymphomas is still under debate. In 2001 and 2003, the Taiwanese[17] and the South Korean group[18] respectively published a 3/5 item classification of ileocolonic GI lymphomas. Table 1 shows patterns analyzed in both classifications. Basically, the endoscopic appearance is classified according to the presence and depth of ulcerations and of fungating lesions. To date, these were the only attempts to classify rare GI lymphomas. After that, Kim *et al*[19] investigated the endoscopic differences between B- and T-cell lymphomas of the colon and they observed that B-cell lymphomas occur more often as fungating or ulcerofungating lesions, while T-cell lymphomas more frequently have an ulcerative or ulceroinfiltrative pattern (Figure 1). Notwithstanding, a clear prognostic implication based on the endoscopic pattern has not been validated yet.

Table 1 Endoscopic features of rare gastrointestinal lymphomas according to two classification systems

Ref.	Wang *et al*[18]		Myung *et al*[17]	
No. of patients	13		32	
Endoscopic pattern	Mucosal - ulcerative	30.7%	Fungating	39%
	Mucosal - erosive	15.3%	Ulcerative	6%
	Polypoid	23%	Infiltrative	14%
	Massive	31%	Ulcerofungating	31%
			Ulceroinfiltrative	11%

Newer techniques, *i.e.,* capsule endoscopy (CE) and double-balloon enteroscopy (DBE), are emerging as useful tools in detecting small bowel tumors (15% of them represented by lymphomas)[3,20-22]. Surely both techniques can augment the endoscopic diagnostic field (especially for follicular lymphomas[21]). Moreover, spiral enteroscopy has been also evaluated as a tool for revealing GI lymphomas of the small intestine. Boudiaf *et al*[23] reported that 4 out of 14 patients affected by refractory celiac sprue developed a small bowel mass that was confirmed to be an enteropathy-associated T-cell lymphoma (EATL) by histological evaluation. Although less widespread, single-balloon enteroscopy has been used in the definition of small bowel lesions and recently it has been implemented with the water exchange method in order to improve the visualization of the lumen to better define and sample the lesion[24]. However, such deep diagnostic tools have not been validated for routine use in GI lymphoma staging and follow-up since they do not induce a treatment change. Thus, their application in gastric or colonic lymphomas has not been fully validated[25]. Differently, faced with T-cell lymphomas with a jejunal tropism, DBE can lead to a definitive diagnosis coupling the endoscopic investigation with the bioptic evaluation[26,27]. However, not many publications related to the usage of these techniques are available to date.

A particular consideration should be given to the role of endoscopic ultrasonography (EUS). Its role has gained more and more importance in MALT lymphomas since the locoregional staging of the disease has a great

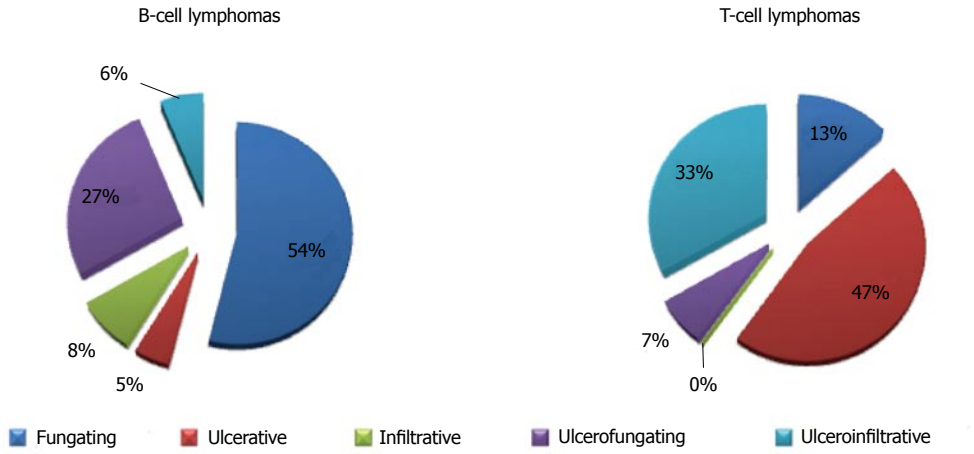

Figure 1 Differences in endoscopic pattern between B-cell and T-cell lymphomas of the gastrointestinal tract. Data extrapolated from Kim *et al*[19] 2005.

impact on the treatment approach[6]. Regarding DLBCL, the locoregional extension has significant prognostic implications, although its role in treatment definition is still under discussion[3]. In contrast, few data are available in rare GI lymphomas. In particular, they are more frequently regarded as general diseases so that the locoregional extension is not always evaluated, with some reports indicating just the EUS pattern without any clinical implication. Exceptional cases have indicated the role of EUS in defining the limited extension of the disease, thus leading to an endoscopic resection of the mass [see the paragraph "Extramedullary Plasmacytoma (EMP) and Plasma Cell-related Diseases"]. That notwithstanding, EUS information is gathered only for describing the behavior of these lesions in most cases without any significant clinical impact.

Definitively, a proper staging for GI lymphomas will include[28]: (1) physical examination: evaluation of superficial lymph nodes and Waldeyer ring inspection; abdomen palpation in order to detect liver enlargement, splenomegaly and abdominal masses; (2) endoscopic ultrasonography that is the golden standard in defining the locoregional GI involvement since it is able to distinguish the involvement of a specific layer and also of regional lymph nodes. However, as stated above, its role is under study and it is not strictly recommended in this setting; (3) computed tomography of the neck, chest and abdomen in order to detect involvement of nodes above and below the diaphragm and also other extranodal involvement not pertaining to the GI tract. In some cases, computed tomography can be of great help in defining the extension of a large bulky mass departing from the GI tract but exteriorizing outside the GI tract (see the paragraph "Plasma-cell related diseases"); (4) positron emission tomography is not generally indicated as a staging procedure, especially in MALT lymphomas, but it retains a role in defining the pre-treatment lymphomatous involvement and response to treatment; and (5) bone marrow biopsy: notwithstanding the low-grade, indolent diseases that tend to remain localized at the GI tract, bone marrow biopsy should be performed in order to exclude a marrow involvement that could influence treatment and follow-up management. However, the level of evidence on its utility is poor. A recent update of the staging recommendation in nodal lymphomas does not encourage the performance of bone marrow biopsy facing diffuse large B-cell lymphoma and Hodgkin's lymphoma, but this strategy has not been evaluated specifically for GI lymphomas[29].

However, these are general guidelines adopted from MALT lymphoma since in more rare GI lymphomas these guidelines have not been fully validated.

The aim of the present review is to highlight macroscopic features of rare GI lymphomas using endoscopy and related techniques. In particular, we will focus on T-cell lymphomas, lymphomatous polyposis (LP) and mantle cell lymphoma (MCL), follicular lymphoma (FL), plasma cell-related diseases, gastrointestinal lymphomas in immunodeficiency and Hodgkin's lymphoma (HL). An outline on the endoscopic presentation will be given for the diagnostic aspect and follow-up assessment. As a whole, Table 2 summarizes the clinical and molecular characteristics and prognostic features of these lymphomas.

T-cell and natural killer lymphomas

GI T-cell lymphomas are rare, representing about 5% of GI lymphomas[14,30,31]. However, the incidence varies according to the geographical zones. European studies reported that 1.3% of primary GI lymphomas are of T-cell origin[32], while groups from eastern countries reported 7%-15%[33,34], reaching 41% in other series of intestinal lymphomas[35].

Ulcerated lesions are the main endoscopic features[30,36-38]. The first definition of this disease was "ulcerative jejunitis" by Isaacson and Du, given the always present ulcerative pattern[14]. Usually, symptoms are related to malabsorption[14], although perforation[39] or intestinal bleeding[40] can occur. Incidentally, GI perforation or bleeding can occur in cases of nodal T-cell lymphomas independently from GI localization and are an infective etiology, reflecting the immune impairment that characterizes these lymphomas[41,42].

Table 2 Table listing gastro-intestinal lymphoma with main gastro-intestinal organ involvement, typical presenting characteristics, typical immunophenotype and genotype and prognosis

Lymphoma histotype		Presenting characteristics	Main GI involvement	Main endoscopic pattern	Typical immunophenotype	Typical genotype	Prognosis
T and NK lymphomas	EATL	Celiac patients with abdominal pain and small intestine obstruction/ perforation	Duodenum and jejunum	Multiple erosions and ulcers	$CD3^+$, $CD4^-$, $CD8^{+/-}$, $CD7^+$, $CD5^-$, $CD2^+$, TIA^+, $GrBPer^+$, $CD30^{-/+}$, $CD25^{-/+}$, $CD56^{-/+}$, $CD16^-$, $CD57^-$, $BCL6^-$, $CD10^-$, EBV^-, $EMA^{-/+}$	TRB and TRG clonally rearranged +9q31.3 -16q12.1 +1q32.2-q41 +5q34-q35.2 +8q24 (MYC)	Poor
	PTCL	Poor performance status	Stomach and duodenum	Ulcerative	$CD3^+$, $CD4^+$, $CD8^-$, $CD7^+$, $CD5^+$, $CD2^+$, TIA^-, $GrBPer^-$, $CD30^{-/+}$, $CD25^-$, $CD56^-$, $CD16^-$, $CD57^-$, $BCL6^-$, $CD10^-$, EBV^-, EMA^-	[1]TCR clonally rearranged +7q/+8q/+17q/ +22q/-4q -5q/-6q/-9p/-10q/-12q/-13q	54% survival at five year Poor in case of high IPI score and stage III-IV disease
	Extranodal NK/T-cell lymphoma	Gastrointestinal bleeding and B symptoms	Small intestine	Multiple erosions and ulcers	$cyCD3^+$, $CD4^-$, $CD8^{-/+}$, $CD7^-$, $CD5^-$, $CD2^+$, TIA^+, $GrBPer^+$, $CD30^-$, $CD25^-$, $CD56^+$, $CD16^-$, $CD57^-$, $BCL6^-$, $CD10^-$, EBV^+, EMA^-	TCR in germinal configuration No specific cytogenetic studies on this specific subtype	Poor especially if perforation occurs
	Adult T-cell leukemia/ lymphoma	Abdominal pain, diarrhea, general fatigue, weight loss	No site preferences	Ulcers	$CD3^+$, $CD4^+$, $CD8^-$, $CD7^-$, $CD5^+$, $CD2^+$, TIA^-, $GrBPer^-$, $CD30^{-/+}$, $CD25^{++}$, $CD56^-$, $CD16^-$, $CD57^-$, $BCL6^-$, $CD10^-$, EBV^-, EMA^-	TCR clonally rearranged Monoclonal integration of HTLV-1	Poor[2] Good[3]
	Indolent lympho-prolipherative diseases of GI tract: T-LPD	Dyspepsia and mild diarrhea	Small intestine and colon	Unremarkable/ friable or erythematous mucosa	$CD3^+$, $CD4^-$, $CD8^+$, $CD7^{+/-}$, $CD5^{+/-}$, $CD2^+$, $TIA^{+/-}$, $GrBPer^{-/+}$, $CD30^-$, $CD56^-$, EBV^-	TCR-γ monoclonal	Indolent course
	NK-cell enteropathy	Vague symptoms (dyspepsia)	Stomach and small intestine	Lesions exhibit superficial ulceration, flat elevations with central depression and are associated with edema and local hemorrhage	$cCD3^+$, $CD4^-$, $CD8^-$, $CD7^+$, $CD5^-$, TIA^+, $GrBPer^+$, $CD56^+$, EBV^-	TRC polyclonal or oligoclonal	Indolent course
Mantle cell lymphoma		Vague symptoms (dyspepsia)	Colon	Multiple polyposis, seldom with ulcerations	$CD19^+$, $CD20^+$, $CD5^+$, $CD10^-$, $CD43^+$, sIg^+, $BCL6^-$, $IRF4/MUM1^-$, $Cyclin\ D1^+$	BCR rearranged t(11;14)(q13;q32)	Negative impact on prognosis
Follicular lymphoma		Vague symptoms (dyspepsia)	Second part of duodenum	Whitish polyps	$CD19^+$, $CD20^+$, $CD5^-$, $CD10^+$, $CD43^-$, sIg^+, $BCL6^+$, $IRF4/MUM1^{-/+}$, $Cyclin\ D1^-$, $\alpha4\beta7^+$	BCR rearranged t(14:18)(q32:q2 1)	Good
Extramedullary plasmacytoma		Alarm symptoms and obstruction	Stomach	Infiltrating mass	Plasmacells expressing $CD79a^+$, $CD38^+$, $CD19^-$, $CD138^+$, $CD56^+$, usually $CD20^-$	BCR rearranged t(11;14)(q32;q13)	Poor
PTLD		Alarm symptoms	Colon	Rubbery erythematous or ulcerated	Similar to DLBCL and Burkitt's lymphoma $CD19^+$, $CD20^+$, $CD5^{-/+}$, $CD10^{-/+}$, $CD43^{-/+}$, $sIg^{+/-}$, $BCL6^{-/+}$, $IRF4/MUM1^{-/+}$, $Cyclin\ D1^-$	Monoclonal BCR	Poor median survival 6 mo
Plasmablastic lymphoma		Alarm symptoms	Stomach	Large masses and exophitic processes	$CD79a^+$, $CD138^+$, $CD38^+$, $IRF4/MUM1$, $CD45^-$, $CD20$, $PAX5^-$, $CD56^-$	Clonal IgH chain gene rearranqement	Poor
Hodgkin's lymphoma		Obstruction	Colon	Protruding mass	$CD30^+$, $CD15^+$, $CD45^-$, $CD20^-$, $CD79a^-$, $PAX5^+$, Ig^-, $OCT2^-$, $BOB1^-$, $CD3^-$, $CD2^-$, $CD5^-$, ALK^-	Clonal immunoglobulin gene rearrangements	Prognostic impact not known

[1]Estrapolated from nodal counterpart but not explored in Primary GI lymphoma; [2]ATLL acute and lymphoma types; [3]ATLL chronic and smoldering types. TCR: T-cell receptor; BCR: B-cell receptor; EATL: Entheropathy–associated T-cell lymphoma; PTCL: Perypheral T-cell lymphoma; T-LPD: T-cell lymph-prolipferative disease; NK: Natural killer; DLBCL: Diffuse Large B-cell lymphoma; PTLD: Post-transplantation lymph-proliferative disease; GI: Gastro-intestinal.

Guidelines suggest that diagnostic work-up and follow-up should be done in synergism between hematologists and gastroenterologists in order to better define the staging and the treatment needed and to ensure the best nutritional guidance (evidence level Ⅲ grade B)[43].

In a study from the German group, the most frequent histotype of intestinal lymphoma was T-cell lymphomas[44]. The most commonly involved organs are the duodenum and jejunum, followed by the ileum and colon. Less frequent is the involvement of the stomach[45], also as part of composite lymphoma[46], *i.e.,* lymphoma with B- and T-cells origin. Regarding gastric involvement, in 30% of cases there is localization in the upper part of the stomach, in 20% the localization is in the middle part and diffuse in 40% of cases[47]. Due to the fact that the prognosis and treatment strategy depends on the lymphoma histotype, bioptic evaluation is a mandatory step. In addition, each subtype presents peculiar endoscopic behaviors that can drive diagnosis and treatment. GI T-cell lymphomas typically have a mature phenotype, while acute types of T-cell neoplasms do not classically involve the GI tract[48].

According to the 2008 WHO classification of hematological malignancies, the most prevalent histotypes are[48,49]: (1) enteropathy-associated T-cell lymphomas (EATL) (distinguished in type Ⅰ and Ⅱ); (2) peripheral T-cell lymphomas and extranodal natural killer (NK)/T-cell lymphoma; and (3) adult T-cell leukemia/lymphoma (ATLL).

In addition, very rare cases have been reported (mostly as singular events) of colorectal T-cell prolymphocytic leukemia/lymphoma[50] or anaplastic T-cell lymphoma (ALCL) ALK$^+$[51] or ALK$^-$[52]. Distinct entities not described in the WHO classification are indolent T-cell/NK diseases that will also be taken into account.

Although EUS findings are not usually reported except in peculiar cases, submucosal hypoechogenic lesions destroying the involved layer would be the main pattern[53]. Another proof of the sub-mucosal origin of the tumor is given by narrow band imaging that is able to show intact gastric pits elevated from the underlying mass[51]. Very rare and unusual is the GI involvement in Sezary syndrome where, despite unremarkable gastric mucosa, EUS can show the hyperechogenic submucosa layer at giant fold level[54].

Enteropathy-associated T-cell lymphoma

EATL can be divided into two forms[14]. The first variant is characterized by features of celiac disease with abdominal pain and small intestine obstruction/perforation. Usually there is a large mass with massive necrosis, while the neighboring mucosa shows villous atrophy and crypt hyperplasia as in typical enteropathy. Type II exhibits villous atrophy in the context of tumor mass with normal intestinal mucosa in uninvolved sites. Contrarily to type I EATL, type Ⅱ EATL does not progress from undiagnosed or refractory celiac disease[14,55]. Prognosis is poor with a median overall survival of 7-10 mo[56].

The exact incidence and lymphoma risk in celiac patients is still a debated issue[57]. Some studies indicate a 200-fold increased risk of developing EATL compared to the general population[58,59]. According to other studies, the risk of developing non-Hodgkin's lymphomas in celiac patients appears to be 6-fold higher than in the general population and this risk assumes a downward trend over years[60]. Nonetheless, it appears clear that the occurrence of complications in celiac patients, although infrequent, is an event that negatively impacts on patient survival[61]. In fact, the occurrence of intestinal perforation in a patient affected by celiac disease should lead to suspicion of lymphoma.

Usually, EATL patients tend to have a poorer performance status than B-cell lymphomas (even though tends to be localized), independent of the stage. Fever and diarrhea are the most frequent symptoms[44]. The duodenum and jejunum are the most involved sites, with secondary involvement of the gross intestine in 14% of cases[44]. The diagnosis of the disease in some cases is difficult since neoplastic lymphocytes can be present in a context of an inflammatory background.

Endoscopic features are aspecific, with multiple erosions and ulcers[31]. Nodularity and thickened folds can be seen at DBE[26,27]. Strictures and masses are less common[62]. In some cases, macroscopic findings together with the occurrence of an intense inflammatory reaction can lead to a mistaken diagnosis of Crohn's disease (CD)[31,63]. However, although it is not a general rule, CD ulcers are transversal, while, in the presence of T-cell lymphoma, ulcers are longitudinal[63].

Peripheral T-cell lymphomas and extranodal NK/T-cell lymphoma

Peripheral T-cell lymphomas (PTCL) and NK lymphomas are more frequent in South America and Asia. These entities are distinct from other GI T-cell lymphomas by morphological and immunohistochemistry criteria[62] and should be diagnosed when other more frequent T-cell lymphomas are excluded[48]. Korean and Japanese series indicated that these are the most frequent GI T-cell lymphoma subtype, accounting for 40% of primary T-cell GI lymphomas HTLV-1 negative[64]. PTCL arises frequently in extranodal sites, especially at the skin. However, the involvement of the gastrointestinal tract is a severe prognostic factor[65,66]. The stomach and duodenum accounts for 60% of GI localizations[52]. The most frequent findings are ulcerative (46% of cases), infiltrative (9%), ulceroinfiltrative (18%), ulcerofungating (18%) and erosive (9%)[52]. Multiple polyposis can also be detected[67]. In the literature, there are two reports indicating the involvement by T-cell lymphomas in the ileocolonic anastomosis for a previously resected right colon, presenting with polypoid lesions[68] or ulcerative lesions[69].

Extranodal NK/T-cell lymphoma usually arises in nasal cavities and rarely affects the GI tract. A strict relationship exists between ENKTCL and EBV infection,

with almost 70% of cases positive for Epstein–Barr virus-encoded small RNAs (EBER) detection[70]. The small intestine is the most involved organ, while the stomach is rarely involved[71]. The endoscopic pattern in the majority of cases is given by multifocal ulcers[72-75] and infiltrative lesions[52]. Sometimes the ulceration leads to intestine perforation and acute peritonitis (60% of the total complications)[52]. Additionally, perforation is more frequent in the infiltrative pattern compared to the non-infiltrative. Fungating lesions are not usually reported[76]. The most involved organ is the small intestine[77,78] and/or colon[72,76] (depending on the case series), followed by the small intestine, rectum and stomach[72]. However, the location at the GI tract does not seem to affect the prognosis[77]. Interestingly, since the perforation usually leads to the development of peritonitis, the Lugano staging system has been applied, resulting in the advanced stage of the disease being a prognostic factor at multivariate analysis[72]. Due to the high risk of perforation, many patients undergo surgery as a pre-emptive or curative strategy, rarely for diagnosis[79]. However, according to Kim *et al*[77], patients undergoing surgery followed by chemo/radiotherapy would show a better OS. However, as the authors themselves stated, this benefit would be ascribed to the fact that patients undergoing surgery had a better performance status and more limited disease which would have affected the outcome. Similarly, as Hong *et al*[78] reported in a multivariate analysis, surgery ensures a better survival compared to chemotherapy. Therefore, an appropriate locoregional staging is also useful to tailor treatment.

Adult T-cell leukemia/lymphoma

As for EATL, ATLL tends to present with ulcers with aggressive behavior. This is a specific variant of peripheral T-cell lymphoma that recognizes the HTLV-1 virus as an etiological agent[48]. This variant is mainly found in endemic areas of Japan[64]. In about one third of ATLL cases, GI involvement is secondary to a systemic disease[49]. According to the first data by Suzumiya, the stomach is involved in 40% of cases and the small and large intestine in 38% and 34% respectively[80]. Although four types of ATLL have been depicted (*i.e.,* smoldering, chronic, lymphoma, acute), no endoscopic pattern has been related to a peculiar histotype. HTLV-1 infection has no role in determining the macroscopic features[47]. Noteworthy, the detection of GI involvement has a prognostic impact[49], representing the aggressiveness of the disease[43]. In fact, smoldering or chronic ATLL subtypes do not typically show GI involvement[81]. However, primary GI smoldering ATLL have been described and show long term disease-free survival after chemotherapy[82]. Gastric involvement can be enhanced by *Helicobacter pylori* infection that creates an inflammatory state able to lead lymphocytes (also malignant) to migrate into gastric wall through the expression of specific adhesion molecules[83].

An ulcerative pattern is present in more than half of cases of gastric involvement[47]. Single or multiple yellow-whitish polyposis of the first or second loop are more frequent in the duodenum[49] and multiple polyposis is the recurrent lesion in cases of colon involvement[84]. Although a single or multiple polyps are the most frequent lesions, flat ulcerations/erosions can also be present[84]. Red flat or elevated lesions in the rectum have been also documented[85,86]. Rarely, there is the involvement of the ileum, where polyps are the main features[87]. It should be underlined that GI lesions are not always monotone but can be variegated. For examples, case reports indicate the occurrence of protruding masses with normal or eroded mucosa at the stomach and the occurrence of flat granular, friable lesions that bled on contact with mucosa at the colon[88] or reddish irregular flat lesions at the esophagus[89].

Narrow band imaging is able to document irregular microvascular architecture, dilated and destroyed gastric pits and dense aggregations between the pits with variegated irregular nuclei without interglandular infiltration (reflecting the absence of lymphoepithelial lesions)[90].

Indolent lymph-proliferative diseases of the GI tract

A new category of T-cell GI lymphoproliferative disease, namely T-cell lymphoproliferative disease (T-LPD), has been recently introduced[91]. The indolent course is the main clinical hallmark while this entity has been previously treated and managed as PTCL. Noteworthy, the etiology of the disease is unknown, although many patients present with a history of inflammatory bowel disease (IBD). Basically, the clinical picture is dyspepsia and mild diarrhea, while endoscopic features can vary from unremarkable mucosa to erythema. The small intestine and colon are the most frequently involved sites, followed by the oral cavity, stomach and esophagus. Usually, the gastric mucosa is normal despite a disease localization, while the duodenum can show thickened folds and an irregular pattern. In the colon, the occurrence of friable mucosa, erythematous mucosa and small polyps can be seen. Ulcerations are not described. At immunohistochemistry, lymphoid cells have a cytotoxic phenotype ($CD8^+$; $CD4^-$; TIA^+), clonal T-cell receptor (*TCR*) gene rearrangements, do not form masses, do not invade the intestinal crypts and do not cover the full thickness of the bowel[91]. Additionally, the lymphoid infiltrate is limited to the mucosa and sub-mucosa. The molecular study for TCR can show a monoclonal rearrangement of TCR-γ chain[91]. The recognition of this disease has many therapeutic implications since aggressive chemotherapy is excessive and an immunosuppressive treatment is virtually sufficient.

Indolent $CD4^+$ T-cell lymphoma has also been described and shows a good outcome and survival despite a persistence after immunomodulatory drug-based treatment[92]. Rarely, gastric mucosa can show multiple nodularities[93]. However, a clinical and endoscopic follow-up of these lesions is always

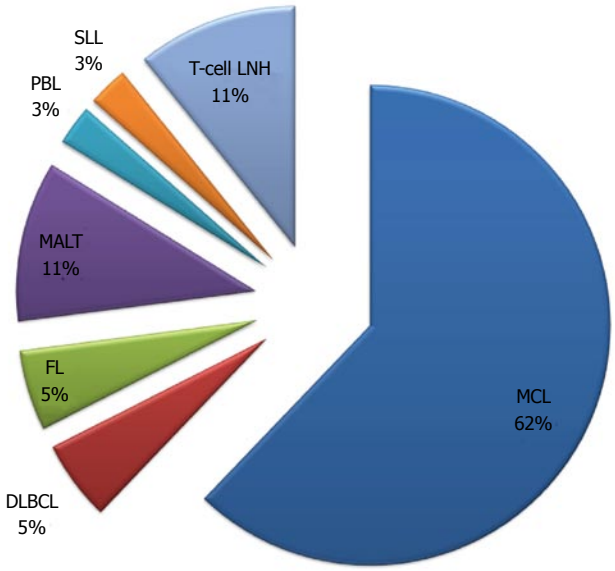

Figure 2 Pie chart describing the distribution of lymphomatous polyposis as a presenting gastrointestinal feature in gastrointestinal non-Hodgkin's lymphomas according to histotype. SLL: Small lymphocytic lymphoma; PBL: Plasmablastic B-cell lymphoma; DLBCL: Diffuse large B-cell lymphoma; MCL: Mantle cell lymphoma.

advisable[93], also for the risk of progression in the long term[92].

Similarly to T-LPD, NK cells can also give rise to an indolent form of lymphoid infiltrate in the context of the GI tract, *i.e.,* NK-cell enteropathy[94]. Usually the symptoms are vague and the GI lesions can be present in the stomach (more frequently), duodenum, small intestine and colon. At endoscopy, these lesions exhibit superficial ulceration, flat elevations with central depression and are associated with edema and local hemorrhage. Usually these ulcers are 1 cm in diameter and the surrounding mucosa is not abnormal. This disease is distinct from ENKTL since gastric involvement in the latter is really infrequent (and if present, the localization is not limited to the stomach) and EBER is positive. In addition, in the presence of NK-enteropathy, the epithelium can be invaded, showing a lymphoepithelial-like lesion[95]. Moreover, contrarily to T-LPD, the TCR rearrangement is polyclonal or oligoclonal[94].

Lymphomatous polyposis and mantle cell lymphoma

The pioneering study by Cornes *et al*[96] in 1961 first reported the term "lymphomatous polyposis (LP)". It is defined as the presence of diffuse proliferation of monotonous small-to-intermediate sized lymphocytes presenting as multiple polypoid tumors from 2 mm to several centimeters in different GI sites. Although the preferred site is the small intestine[14], other sites can be involved alone or at the same time[97-104]. Actually, LP is present in 4%-9% of all GI lymphomas[14], more frequently in western than eastern countries[105]. B-cell lymphomas are more frequent than T-cell lymphomas and this is due to the fact that histologically these polyps originate from the mantle zone of the lymphoid follicle of the mucosa-associated lymphoid tissue[106]. Additionally, this fact justifies the augmented frequency in the small intestine (rich in lymphatic tissue) compared to other GI tract sites. Additionally, multiple tumors or different kinds of lymphomas can be simultaneously present in a context of LP[107]. Therefore, the biopsy of more than one polyp and of different types of lesions is always advisable[108,109]. Additionally, it must be underlined that although the occurrence of multiple polyposis in a patient with nodal lymphoma is not a criterion to absolutely define the involvement of the GI tract, the histological evaluation is always mandatory[110].

Typical lymphoma presenting with LP is MCL[14,111], although other tumors can show this feature[98-100,112-114]. Among 37 case reports of LP since 2000[67,84,98-100,103,112-142], MCL was indeed the most frequent disease (more than 50% of cases) (Figure 2). The most involved site was the colon (Figure 3). In the case series by Saito *et al*[143], regarding patients affected by MALT lymphomas or MCL at the ileal site, it was underlined that LP was the most frequent presentation of MCL and the least common lesion in MALT lymphomas (Figure 4).

MCL can locate at the GI tract secondary to the generalized disease[102] and, although only 25% of patients with nodal mantle cell lymphoma suffer GI symptoms, 77%-88% have a localization at the gross intestine and 43%-77% in the upper GI tract, also in the absence of macroscopic lesions[14] (Figure 5). LP is the most frequent endoscopic pattern although other endoscopic features can be present[144], for example, a granular pattern associated with polyps (Figure 6) or ulcerated polyps[145] or masses[146]. In addition, the endoscopic pattern varies according to the part of the GI tract involved (Figure 7). EUS has been applied in this setting, giving the possibility of identifying submucosal lesions[115]. MCL appears echo-poor, usually departing from the second layer and remaining confined to the GI wall (Figure 8)[115,147,148]. In some cases, the diagnosis of MCL could be incidental during the endoscopic definition of gastric bleeding caused by gastric ulcers[149].

Contrarily to GI follicular lymphoma (discussed below), the GI tract involvement by MCL assumes a great prognostic implication and is useful to monitor patients after the treatment[14,101]. Indeed, the occurrence of LP designates a median survival of 3-4 years[14,101]. Due to the fact that the small intestine can be also involved by the tumor, the performance of CE or DBE would be advisable in order to correctly stage the patient and assess the follow-up evaluations[116,117].

Although the disease presentation has been well studied, there are no data about the management of LP during follow-up assessment. Our opinion is that endoscopic evaluation with mapping biopsies should be performed in these patients since in some cases the presence of aspecific abnormalities during follow-up can lead to the finding of lymphoma reappearance[146], sometimes many years after complete remission[103,119].

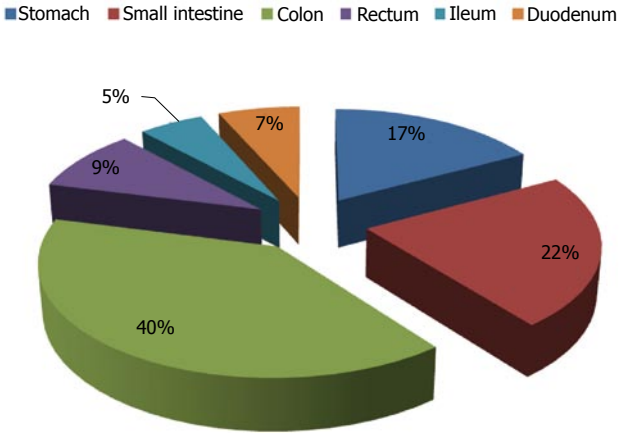

Figure 3 Pie chart describing the most involved gastrointestinal site in lymphomatous polyposis.

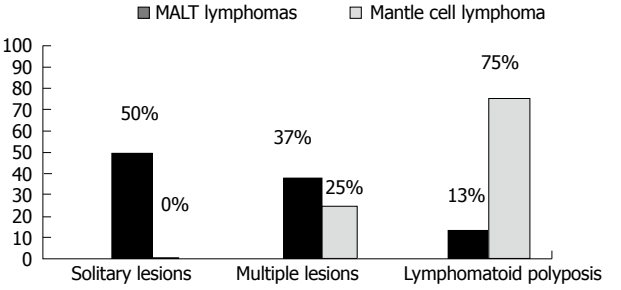

Figure 4 Frequency of lymphomatous polyposis at ileum in mucosa-associated lymphoid tissue lymphoma and mantle cell lymphoma. Adapted from Saito *et al*[143], 2005.

Follicular Lymphoma

GI FL is a rare entity, representing up to 3.6% of all GI NHL[150,151]. Primary GI FL was recognized as an histological variant of FL in the 2008 WHO classification of hematopoietic tumors[152]. Sites most frequently involved are the duodenum (55.6% of cases)[101], in particular the second part[152], and the terminal ileum (33.3% of cases)[151,153]. Since positron emission tomography and computed tomography have low sensitivity and specificity[154] in catching small intestine involvement, CE and DBE have acquired more and more importance[155,156]. Indeed, these techniques have shown that the small bowel can be involved in 70%-83% of cases[157,158], even in cases of duodenal lymphoma[152].

To date, a clear endoscopic classification of GI-FL has not been done, as for GI MALT lymphomas. However, Yamamoto *et al*[151], reviewing 249 GI-FL cases, reported a reliable endoscopic classification of the disease. Whitish polyps usually up to 2 mm[151,153] and/or white granules-nodular aggregates, with or without ulceration of the mucosa layer (Figure 9), are the typical endoscopic pattern[150,159,160]. This can be unifocal or multifocal and is mainly present in intestinal FL. A large mass with or without ulceration is less frequent and in half of cases can be associated with multifocal whitish polyps. The latter is the most frequent endoscopic pattern of primary gastric FL. Multiple lymphomatous polyposis can also be

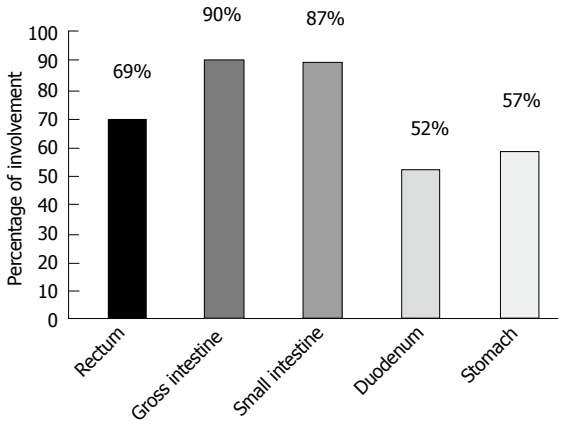

Figure 5 Frequency of the sites involved in mantle cell lymphoma. Adapted from Ruskoné-Fourmestraux *et al*[101], 2010.

found[30,101,150,158,161,162]. Interestingly, in the series of 48 patients with GI FL reported by Yanai *et al*[163], it was found that the LP was the most frequent endoscopic feature (more than 50% of cases), followed by polypoid or ulcerative lesions (Figure 10).

Recently, high-definition endoscopy, as well as magnifying endoscopy (ME), has been used to describe the surface microstructures of GI FL, such as enlarged whitish villi and tiny whitish depositions and an irregular microvascular pattern[164,165]. This fact indicates that the tumor is of non-epithelial origin and usually reflects the formation of lymphoid follicles[164,166-169]. EUS has not been widely applied. A few reports have indicated that the echoendoscopic pattern is given by second and third layer thickening, dotted by hypoechogenic nodules[170].

Capsule endoscopy and double-balloon enteroscopy are useful in the definition of small intestine involvement in a non-invasive way. The typical picture is a whitish submucosal elevation presenting as nodules or polyps[21], usually multifocal[171,172]. However, the limitation is the inability to perform a biopsy that is postponed until the enteroscopy and the risk of retention in cases of stenosis (unusual in cases of GI-FL).

Nodal spread is rare and GI FL tends to be localized in the gastrointestinal tract (stage IE according to Ann Arbor staging system)[173] and to have an indolent course[152,174]. However, transformation to aggressive lymphoma has been documented[175]. Different from other form of lymphomas, the GI involvement is not an adverse prognostic factor[176]. Lymphoma grading is low in the majority of cases, while in the nodal counterpart grade I-II FL is documented in 1 case out of 10[173]. Furthermore, in contrast to nodal FL, these cells do not acquire additional mutations and this justifies the absence of grade 3 GI FL and the very low rate of transformation[173,175].

Treatment strategies are not uniform, although GI FL are treated more frequently compared to the nodal counterpart[177]. Different case series have demonstrated that a watch and wait approach is as useful as the pharmacological approach, except for relieving clinical symptoms[163,178-180]. However, case series differ greatly

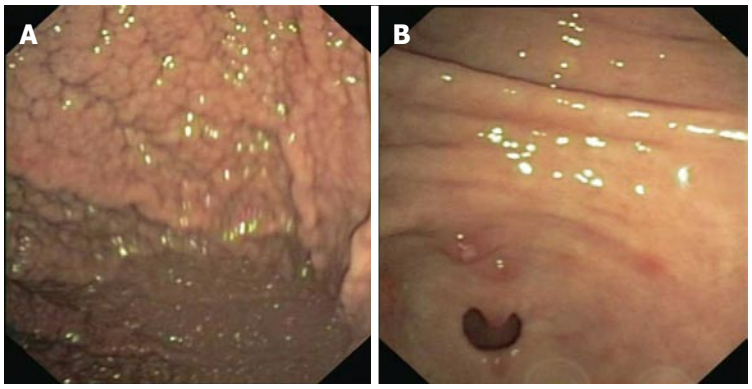

Figure 6 Endoscopy stomach: Granular pattern of the fundus and body of the stomach (A) and polyps in the antrum (B).

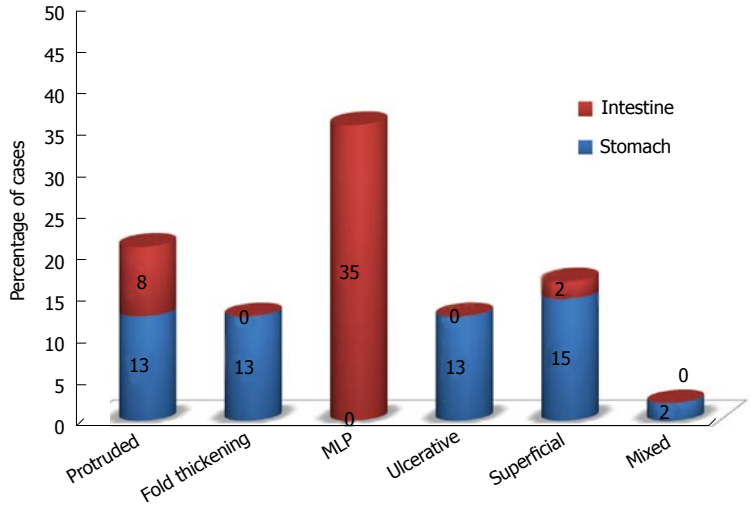

Figure 7 Endoscopic lesions in mantle cell lymphomas according to the gastric and intestinal localization. Adapted from Iwamuro *et al*[144], 2010.

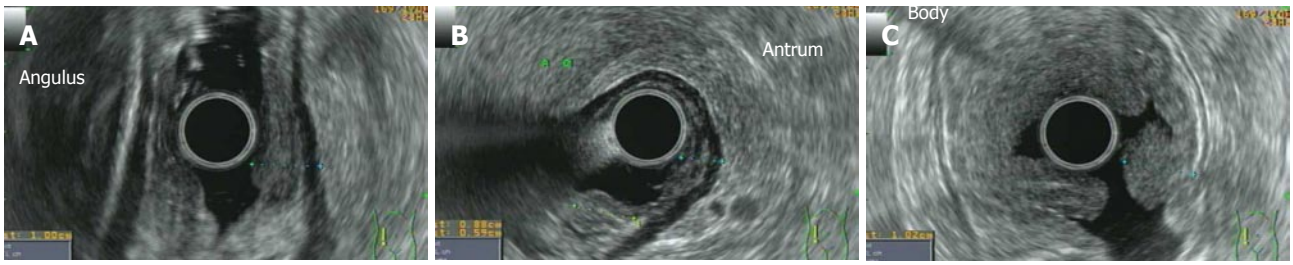

Figure 8 Endoscopic ultrasonography (radial scanning): Marked thickening of the muscularis propria and increased wall thickness (12 mm) in the angulus (A); antrum (B); body (C).

in identifying the correct treatment approach to be applied. Surgical resection is not recommended and chemoimmunotherapy is preferred[151,171]. It must also be considered that the introduction of anti CD20 antibodies has augmented the survival rate and in some series localized/low-grade GI FL have been treated with anti CD20 monoclonal antibody alone, without chemotherapy[151].

It is debatable whether CE and/or DBE are truly useful. Indeed, no studies have demonstrated that the detection of small bowel involvement (especially if duodenal lymphoma is present) would have changed the treatment needed. Surely, these procedures would change the treatment strategy in cases of radiation or surgical treatment and are needed in cases of obscure gastrointestinal bleeding[172,181]. Apart from these occurrences, the effectiveness of chemoimmunotherapy or immunotherapy alone would render these procedures less practical in patient management. However, since no clear data exists regarding survival and quality of life in dependence of small bowel involvement, clinician choice is the only way to proceed.

That notwithstanding, the diagnostic suspicion based on the endoscopic features, together with the patient history, is fundamental in addressing the pathological diagnosis. Indeed, in almost 20% of cases, FL can be misdiagnosed by endoscopic biopsy evaluation[182]. Therefore, multiple biopsies would be necessary. In particular, biopsies of the peripheral mucosa would be more informative than biopsies from the erosion/ulceration since the probability of catching necrotic tissue decreases significantly.

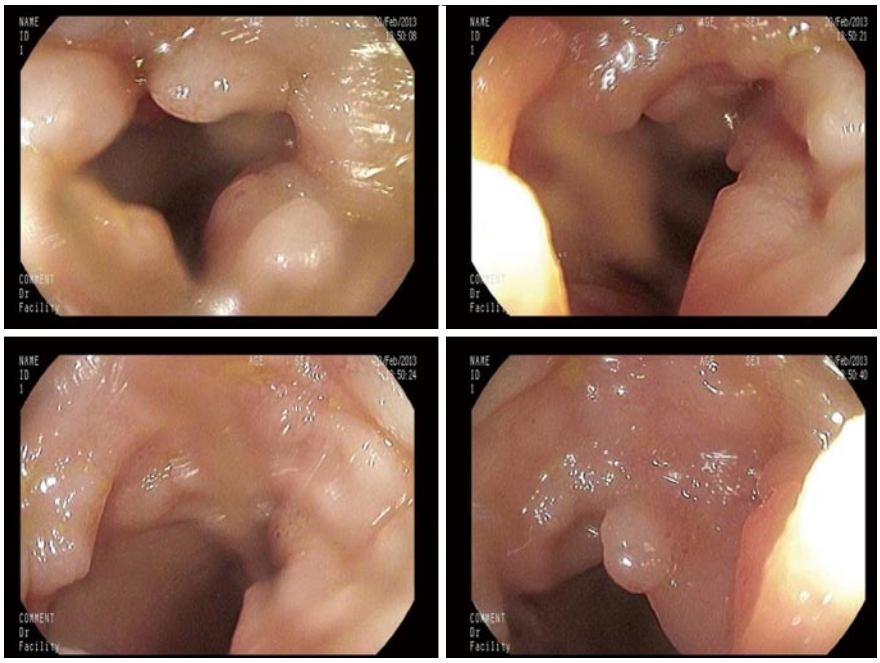

Figure 9 Ileoscopy revealing the presence of hyperemic mucosa with whitish polypoid nodularity. The subsequent diagnosis was a grade 2A follicular lymphoma.

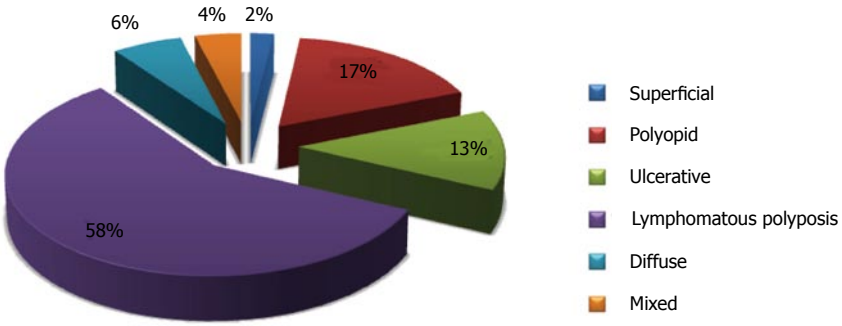

Figure 10 Endoscopic features of follicular gastrointestinal lymphomas. Adapted from Yanai *et al*[163], 2011.

EMP and plasma cell-related diseases

EMP belongs to a precise type of lymphoid malignancies, *i.e.,* plasma cell neoplasms, representing 3%-4% of cases[183]. It is important to distinguish this subtype from lymphomas with plasmacytic differentiation, particularly MALT lymphomas[48]. The upper respiratory tract is the most involved organ (almost 80% of cases), while GI localization is rare[48]. Among these cases, the stomach is the most involved site, followed by the liver, colon and the small intestine (duodenum, jejunum and ileum)[184].

Usually, gastric localization is secondary to a plasma cell myeloma (PCM) and often emerges through a clone selection process. Indeed, multiple myeloma treatment itself can select a particular chemoresistant PC clone able to migrate at extra-nodal organs. In these cases, an accurate endoscopic investigation is critical for the diagnostic assessment and disease monitoring[185]. Due to the strict relationship with plasma cell myeloma, the clinical course is poor. The most frequent endoscopic finding consists of an infiltrating mass or masses in the stomach and/or the duodenum[186,187] or well-demarcated, flat, yellow-whitish mucosal changes[188] or nodular lesion with central umbilication[189]. Endoscopic appearance as diffusely thickened mucosal folds simulating linitis plastica is rare[190]. Sometimes, large ulcerations can be seen[191,192]. However, the gastric mucosa can appear normal, while the extramural growth is incredibly vast (Figure 11). EUS could be of great help in defining the disease extension that appears as a large echo-poor mass infiltrating surrounding organs[186]. However, sometimes EUS can be useful to detect limited gastric wall involvement and in these cases, an endoscopic resection of the mass can be performed, resulting in safety for the patient and effective in the treatment of the disease[188,193,194]. Alternatively, patients with localized disease can be treated with radiation treatment[190,195].

Small intestine involvement is generally primary with a benign course. These lesions can be explored by enteroscopy and/or capsule endoscopy[196], paying attention to the cases in which obstructions or retention are expected. Differential diagnosis is other cases of

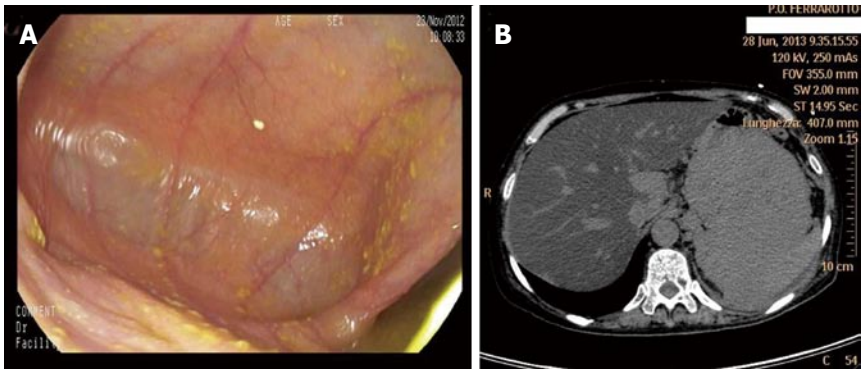

Figure 11 Extra-medullary plasmacytoma with gastric localization arising after treatment for multiple myeloma. A: Gastroscopy resulted negative for tumor detection; B: CT scan analysis of the upper abdomen showing a bulky mass departing from the stomach.

sub-mucosal masses in the small intestine, as reported by Lopes da Silva[196]. Colon involvement appears more frequently as stricture[197,198], in some cases difficult to differentiate from colon adenocarcinoma[199], returning to the differential diagnosis of sub-mucosal tumors[193]. Rarely it can determine rectal bleeding[200]. The localization at the rectum appears as a mild granularity as well as a reddish, protruded lesion[201]. Usually these lesions disappear after treatment and this is a confirmation of treatment efficacy[186], although mucosal atrophy and non-specific inflammation can be reinstated[195].

Apart from EMP, other plasma cell-related disorders can involve the GI tract. This is due to the production of amyloid protein in AL amyloidosis (light chain amyloidosis)[187]. The most involved organ is the small intestine. In some cases the amyloid deposition is synchronous with EMP[187,193,195] or other GI lymphomas[202]. Usually, the amyloid protein in AL amyloidosis involves the submucosa and the muscularis mucosae, resulting in thickened folds and valvulae conniventes and polypoid lesions in the GI tract. The typical deposition of AL amyloid proteins result in pseudo-obstruction, constipation and mechanical obstruction as the main symptoms[203]. Intestinal bleeding can also occur[204] and if this event occurs in a patient with multiple myeloma, the occurrence of aspecific elevated lesions at the endoscopic evaluations should lead to suspicion of systemic amyloidosis. More rarely, submucosal hematoma, ulcers and hemorrhagic bullous colitis can be seen[205]. On the other hand, nodularity, fine granular appearance and mucosal friability are more frequent in other types of amyloidosis, *i.e.,* AA amyloidosis (amyloidosis secondary to systemic disorders). This is due to the deposit of amyloid proteins into the lamina propria with impaired absorption and subsequent diarrhea[203].

Immunodeficiency and GI lymphomas

Immunodeficiency is defined as a state of impaired function of the immune system that can be congenital, acquired or iatrogenic. The reduced immune-surveillance can determine an augmented rate of lymphomas. Two conditions mainly determine the arising of lymphomas: human immunodeficiency virus (HIV) infection with the correlated acquired immunodeficiency syndrome (AIDS) and post-transplant immunosuppression. In both conditions, the GI tract is the most involved site[206]. Apart from HIV and PTLD, common variable immunodeficiency (CVID) has been associated with the development of gastrointestinal NHL, although this is a very rare finding[207,208].

In HIV patients, the rate of GI lymphomas was higher in the pre-HAART era before 1996[209] and the risk of gastric NHL was 353-fold compared with normal subjects, with aggressive lymphomas the most prevalent feature[59]. In cases of AIDS-related lymphoma, the GI tract is involved in 20% to 50% of cases[206,210]. However, the decrease of GI lymphoma incidence has not been as high as in central nervous system lymphomas[209]. A recent analysis of 243 HIV patients performed at the University of Sao Paolo revealed an incidence of gastric NHL of 2.5%[211]. Co-infection with EBV and/or CMV would complicate the prognosis[212], although the occurrence of viral infection is less pathogenetically important compared to PTLD[206]. The main histologies are B-cell lymphomas (67%) (DLBCL, Burkitt lymphoma, MALT lymphoma)[213], while T-cell lymphomas are less frequent (33%)[209] and other types of hematological malignancies are anecdotal[214,215]. In 5%-10% of cases, cMyc rearrangement is present and confers a poor prognosis[212]. Additionally, the prompt recognition of this lymphoma subtype has a great impact in patient management since the presenting symptoms are usually alarm symptoms in about half of patients. However, in the majority of patients, the lymphoma is diagnosed at Ann Arbor stage Ⅲ-Ⅳ[206]. The most frequent endoscopic features are multifocal ulcerations, followed by polypoid or a bulky mass together with bloody spots[206,212]. The most involved sites are the stomach and duodenum[216], followed by the small bowel and colon-rectum (Figure 12)[211]. However, unusual presentations can be seen more commonly than in immunocompetent patients[206]. At narrow-band, a honeycomb-like pattern is present without irregularity in the microvasculature[212]. The localization can also be perirectal and in these cases,

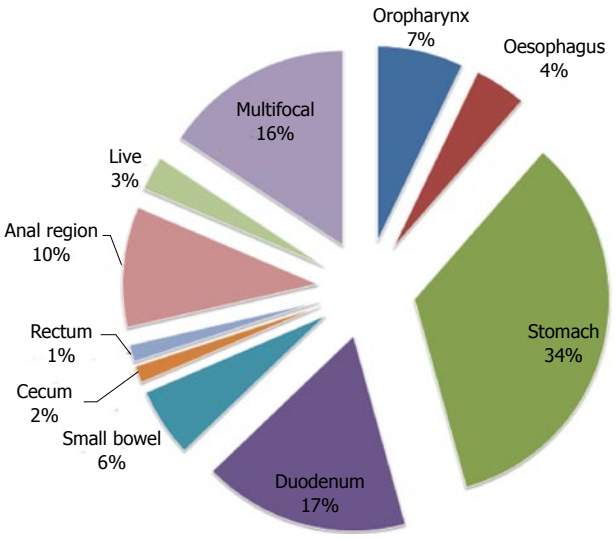

Figure 12 Frequency of the involved gastrointestinal tract in human immunodeficiency virus-related gastrointestinal lymphomas. Adapted from Heise[206], 2010.

EUS-guided fine needle biopsy would be a valid tool for diagnosis given the high grade nature of this kind of lymphomas[217]. Noteworthy, EUS appearance is of a hypoechoic poorly defined mass[217] and is important for the locoregional staging[206]. Prognosis is poor with a median survival of 6 mo and a rate of complete remission less than 40%[211]. Prognosis is also impaired by the occurrence of opportunistic infections[210]. Extremely suggestive is the development of EBV-related DLBCL in patients suffering other types of lymphomas that induce a state of immunosuppression, such as AITL[218]. In these peculiar cases, the outcome is really poor and alarm symptoms and perforation can occur with fatal implications[218].

GI lymphomas are also more frequent in solid organ transplant recipients, particularly after renal, heart and small bowel transplantation, encompassing the spectrum of PTLD (Table 3). The pathogenetic events seem to be different compared to HIV-related lymphomas since in this kind of lymphomas, Epstein-Barr virus reactivation due to immunosuppressants plays a pivotal role[219]. Apart from negative EBV serology prior to transplantation, length of immunosuppression is an overt risk factor[220,221]. EBV-positive lymphomas arise earlier than EBV-negative lymphomas[221]. In adults, the majority of cases arises over 12 mo from transplantation[222], at a median of 36 mo[223]. A second peak is after 5-10 years[206]. Median overall survival is 8 years and the principal histotype is B-cell lymphoma, although lymphomas of T-cell origin can also be present. Noteworthy, the GI tract is involved in one third of cases. Endoscopy is of great help in establishing the diagnosis. Especially in small bowel transplantation, endoscopic follow-up has gained a pivotal role in defining the transplant-related complications, including the onset of PTLD[224]. Typically, lesions are raised, rubbery, erythematous or ulcerated[222,225,226]. The most involved organ is the colon, followed by the small intestine and stomach[223]. However, the recognition of symptoms together with the patient history is of great help in driving the diagnosis. Additionally, endoscopic procedures are essential in order to follow the course of disease[225], also valid in the long-term[226]. Interestingly, early stage PTLD can be safely removed endoscopically and this would be a valid approach in the treatment of localized PTLD[224].

Table 3 Prevalence of gastrointestinal lymphomas among transplant recipients according to transplanted organ

Transplant	Prevalence
Bone marrow	0.50%
Liver	1%-2%
Kidney	0.7%-4%
Heart	2%-10%
Small bowel	up to 30%

The data extracted from Heise[206], 2010.

Plasmablastic lymphoma (PBL) is a rare and aggressive type of lymphoma characterized at histological evaluation by the presence of large immunoblasts with plasmacytic differentiation with an high replication index[227]. Usually, this lymphoma arises in the oral cavity in HIV-infected patients and in the literature there are few cases of GI localization (Table 4)[228-237]. The stomach is the most involved site (about 50% of cases), followed by the small intestine, anal region, cecum, colon and esophagus[237]. Large masses and exophytic processes are the main endoscopic appearance in the stomach and anal region. Intestinal localization is extremely rare and when present, the endoscopic appearance is of multiple nodularity[227]. Moreover, PBL can also arise in immunocompetent patients with ulcerated lesions at the stomach[236]. These patients are normally older than HIV^+ patients, tend to present with GI localizations more that HIV^+ patients and have a worse overall survival[236,237].

Additionally, CD has also been linked to the development of lymphomas of the gastrointestinal tract. Most of them are of B origin, comprising DLBCL and HL, although T-cell lymphomas can also arise. In the recent report by Kappelman *et al*[238], patients with CD showed a greater risk of developing hematological malignancies compared to the general population. This study confirmed the previous report by Askling *et al*[239], also showing an augmented rate of hematological malignancies compared to the general population and 10% of developed lymphomas were T-type. Probably, it would be related to the state of immunosuppression leading to infection of lymphotropic and oncogenic viruses, but the specific mechanism is still to be clarified. This predisposition seems to be unrelated to immunosuppressive treatment. In this setting, anti-TNFα treatment has been related to development of hepatosplenic T-cell lymphoma[240]. However, two years later, a meta-analysis by Siegel *et al*[241] indicated that

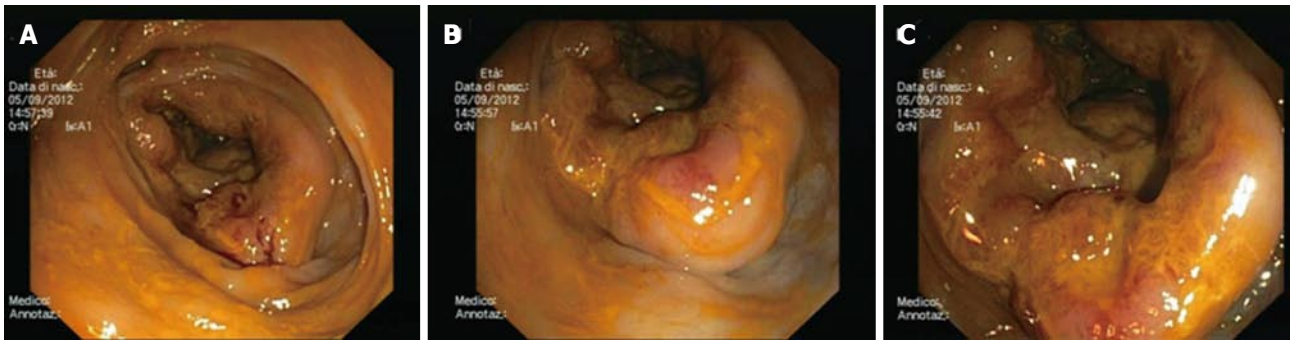

Figure 13 Exophytic erythematous circumferential non-ulcerated mass determining a stenosis of the ileocecal region. The mass arises from the deep layer and the mucosa presents reddish areas suggestive for lymphomatous infiltration of the cecum.

Table 4 Reports of gastrointestinal plasmablastic lymphoma from 1998

Manuscript	Year	localization	Endoscopic appearance	HIV
Pruneri *et al*[230]	1998	Stomach	Large polypoid mass	-
Colomo *et al*[231]	2004	Anal region	Mass	+
Dong *et al*[232]	2005	GI tract	Not reported	+
		Small Intestine	Not reported	+
Tavora *et al*[228]	2006	Anal region	Not reported	+
		Anal region	Exophytic mass	+
Taddesse-Heath *et al*[233]	2010	Small intestine/colon (2 cases)	Not reported	+
Brahmania *et al*[234]	2011	Ano-rectal junction	Hypervascular cauliflower-like mass	-
Mihaljevic *et al*[235]	2012	Stomach	Not reported	-
Hashimoto *et al*[236]	2012	Stomach	Not reported	-
Chapman-Fredricks *et al*[229]	2012	Stomach	Not reported	+
Luria *et al*[237]	2014	Anal region	Mass	+
		Sigma	Mass	-
		Small bowel	Not reported	-
		Ileum	Not reported	-

HIV: Human immunodeficiency virus; GI: Gastrointestinal.

immunosuppressive treatment is not a risk factor for the development of NHL in CD patients. However, it is still a matter of discussion since the augmented incidence of GI lymphomas in these patients is related to the more intensive examinations. Moreover, the histological evaluation is a crucial point since the inflammatory background can lead to a false positive result. That notwithstanding, anti-TNFα treatment seems to be safe regarding the incidence of NHL and should not be regarded as a risk factor. Therefore, more epidemiological studies will be needed in order to better define the link between CD and GI lymphomas.

Hodgkin's lymphoma

Lymphomatous GI involvement in HL appears as a stricture (Figure 13) or ulceration[242-245]. The abundant lymphoid tissue present at this site renders it one of the most involved regions[246]. HL rarely presents as a colonic localization (almost 1%-3% of extra-nodal HL cases[247] and less than 5% of gastrointestinal lymphomas[243]) and the prognostic impact is still obscure. Mixed-cellularity subtype is the most common feature[248]. As for the nodal counterpart, the inflammatory background is a key feature of HL[249]. In some cases, the endoscopic and histological presentation can resemble IBD, that in turn is seldom associated with colonic HL[244,250]. Additionally, immunodeficiency is a risk factor[251], although this type of lymphoma can also arise in immunocompetent patients[247].

Recently, a new entity has been proposed, *i.e.*, "EBV-associated mucocutaneous ulcer" (EBVMCU)[252]. This disease subtype resembles HL but there are peculiar clinical and histological differences. Indeed, the presence of "plasmacytoid" apoptotic cells and the confinement to mucosa and sub-mucosal layers are the histological hallmark that can lead to a differential diagnosis from cHL. However, EBV infection is always present, as in GI-HL.

CONCLUSION

Endoscopic features of GI lymphomas are variegated encompassing ulcers, erosions, polyps and so on. It is a fascinating matter of study for both hematologists and gastroenterologists. As stated in guidelines, a synergism between these two figures is fundamental. This is due to the lack of data and the fact that information regarding rare GI lymphomas are extrapolated from case series or

case reports. Actually, the scientific community is gaining more and more knowledge about the recognition and management of these lymphomas, with the creation of proper guidelines for specific lymphoma subtypes. In this setting, the collection of different case series and their analysis will assume a pivotal role in drawing general guidance on disease characterization. Certainly, as has emerged in the manuscript, the management of these lymphomas is different from the nodal or medullary counterparts and a proper understanding of the endoscopic features together with clinical and histological characteristics is crucial for better management of patients, with the ultimate goal of improving clinical outcome and quality of life for patients.

REFERENCES

1 **Zullo A**, Hassan C, Cristofari F, Perri F, Morini S. Gastric low-grade mucosal-associated lymphoid tissue-lymphoma: Helicobacter pylori and beyond. *World J Gastrointest Oncol* 2010; **2**: 181-186 [PMID: 21160595 DOI: 10.4251/wjgo.v2.i4.181]

2 **Vetro C**, Romano A, Palumbo GA, Bonanno G, Di Raimondo F. Role of the endoscopic ultrasonography in the management of gastric lymphomas: our experience and review of literature. Russian Federation: Novosibirsk State technical University: InTech, 2011: 235-258

3 **Vetro C**, Romano A, Amico I, Conticello C, Motta G, Figuera A, Chiarenza A, Di Raimondo C, Giulietti G, Bonanno G, Palumbo GA, Di Raimondo F. Endoscopic features of gastro-intestinal lymphomas: from diagnosis to follow-up. *World J Gastroenterol* 2014; **20**: 12993-13005 [PMID: 25278693 DOI: 10.3748/wjg.v20.i36.12993]

4 **Vetro C**, Romano A, Donnarumma D, La Fauci A, Fiumara P, Chiarenza A, Figuera A, Palumbo G, Bonanno G, Di Raimondo F. Role of the endoscopic ultrasonography in the management of gastric lymphomas: metanalysis of literature. *Haematologica* 2011; **96**: 567

5 **Ferry JA**. Extranodal Lymphomas. Publisher: Elsevier Health Sciences, 2011

6 **Vetro C**, Chiarenza A, Romano A, Amico I, Calafiore V, Di Raimondo C, Coppolino F, Di Raimondo F. Prognostic assessment and treatment of primary gastric lymphomas: how endoscopic ultrasonography can help in tailoring patient management. *Clin Lymphoma Myeloma Leuk* 2014; **14**: 179-185 [PMID: 24369919 DOI: 10.1016/j.clml.2013.10.010]

7 **Vetro C**, Romano A, Chiarenza A, Conticello C, Donnarumma D, Gorgone A, Coppolino F, Palumbo GA, Bonanno G, Di Raimondo F. Endoscopic ultrasonography in gastric lymphomas: appraisal on reliability in long-term follow-up. *Hematol Oncol* 2012; **30**: 180-185 [PMID: 22189677 DOI: 10.1002/hon.1022]

8 **O'Malley DP**, Goldstein NS, Banks PM. The recognition and classification of lymphoproliferative disorders of the gut. *Hum Pathol* 2014; **45**: 899-916 [PMID: 24613566 DOI: 10.1016/j.humpath.2013.12.001]

9 **Zullo A**, Esposito G, Ridola L, Hassan C, Lahner E, Perri F, Bianco MA, De Francesco V, Buscarini E, Di Giulio E, Annibale B. Prevalence of lesions detected at upper endoscopy: an Italian survey. *Eur J Intern Med* 2014; **25**: 772-776 [PMID: 25245606 DOI: 10.1016/j.ejim.2014.08.010]

10 **Di Giulio E**, Hassan C, Marmo R, Zullo A, Annibale B. Appropriateness of the indication for upper endoscopy: a meta-analysis. *Dig Liver Dis* 2010; **42**: 122-126 [PMID: 19497799 DOI: 10.1016/j.dld.2009.04.019]

11 **Faintuch JJ**, Silva FM, Navarro-Rodriguez T, Barbuti RC, Hashimoto CL, Rossini AR, Diniz MA, Eisig JN. Endoscopic findings in uninvestigated dyspepsia. *BMC Gastroenterol* 2014; **14**: 19 [PMID: 24499444 DOI: 10.1186/1471-230X-14-19]

12 **Hassan C**, Di Giulio E, Marmo R, Zullo A, Annibale B. Appropriateness of the indication for colonoscopy: systematic review and meta-analysis. *J Gastrointestin Liver Dis* 2011; **20**: 279-286 [PMID: 21961096]

13 **Buri L**, Bersani G, Hassan C, Anti M, Bianco MA, Cipolletta L, Di Giulio E, Di Matteo G, Familiari L, Ficano L, Loriga P, Morini S, Pietropaolo V, Zambelli A, Grossi E, Intraligi M, Tessari F, Buscema M. How to predict a high rate of inappropriateness for upper endoscopy in an endoscopic centre? *Dig Liver Dis* 2010; **42**: 624-628 [PMID: 20308024 DOI: 10.1016/j.dld.2010.02.012]

14 **Burke JS**. Lymphoproliferative disorders of the gastrointestinal tract: a review and pragmatic guide to diagnosis. *Arch Pathol Lab Med* 2011; **135**: 1283-1297 [PMID: 21970484 DOI: 10.5858/arpa.2011-0145-RA]

15 **Ahmad A**, Govil Y, Frank BB. Gastric mucosa-associated lymphoid tissue lymphoma. *Am J Gastroenterol* 2003; **98**: 975-986 [PMID: 12809817 DOI: 10.1111/j.1572-0241.2003.07424.x]

16 **Zullo A**, Hassan C, Andriani A, Cristofari F, Cardinale V, Spinelli GP, Tomao S, Morini S. Primary low-grade and high-grade gastric MALT-lymphoma presentation. *J Clin Gastroenterol* 2010; **44**: 340-344 [PMID: 19745757 DOI: 10.1097/MCG.0b013e3181b4b1ab]

17 **Myung SJ**, Joo KR, Yang SK, Jung HY, Chang HS, Lee HJ, Hong WS, Kim JH, Min YI, Kim HC, Yu CS, Kim JC, Kim JS. Clinicopathologic features of ileocolonic malignant lymphoma: analysis according to colonoscopic classification. *Gastrointest Endosc* 2003; **57**: 343-347 [PMID: 12612513 DOI: 10.1067/mge.2003.135]

18 **Wang MH**, Wong JM, Lien HC, Lin CW, Wang CY. Colonoscopic manifestations of primary colorectal lymphoma. *Endoscopy* 2001; **33**: 605-609 [PMID: 11473333 DOI: 10.1055/s-2001-15320]

19 **Kim YH**, Lee JH, Yang SK, Kim TI, Kim JS, Kim HJ, Kim JI, Kim SW, Kim JO, Jung IK, Jung SA, Jung MK, Kim HS, Myung SJ, Kim WH, Rhee JC, Choi KY, Song IS, Hyun JH, Min YI. Primary colon lymphoma in Korea: a KASID (Korean Association for the Study of Intestinal Diseases) Study. *Dig Dis Sci* 2005; **50**: 2243-2247 [PMID: 16416168 DOI: 10.1007/s10620-005-3041-7]

20 **Chen WG**, Shan GD, Zhang H, Li L, Yue M, Xiang Z, Cheng Y, Wu CJ, Fang Y, Chen LH. Double-balloon enteroscopy in small bowel tumors: a Chinese single-center study. *World J Gastroenterol* 2013; **19**: 3665-3671 [PMID: 23801870 DOI: 10.3748/wjg.v19.i23.3665]

21 **Egea-Valenzuela J**, Castillo-Espinosa JM, Sánchez-Torres A, Alberca-de-las-Parras F, Carballo-Álvarez F. Diagnosis of follicular lymphoma of the small bowel by video capsule endoscopy. *Rev Esp Enferm Dig* 2014; **106**: 51-52 [PMID: 24689716]

22 **Nakamura M**, Ohmiya N, Hirooka Y, Miyahara R, Ando T, Watanabe O, Itoh A, Kawashima H, Ohno E, Kinoshita T, Goto H. Endoscopic diagnosis of follicular lymphoma with small-bowel involvement using video capsule endoscopy and double-balloon endoscopy: a case series. *Endoscopy* 2013; **45**: 67-70 [PMID: 23208779 DOI: 10.1055/s-0032-1325867]

23 **Boudiaf M**, Jaff A, Soyer P, Bouhnik Y, Hamzi L, Rymer R. Small-bowel diseases: prospective evaluation of multi-detector row helical CT enteroclysis in 107 consecutive patients. *Radiology* 2004; **233**: 338-344 [PMID: 15459329 DOI: 10.1148/radiol.2332030308]

24 **Liang S**, Pan Y, Wang B, Luo H, Xue X, Qin J, Guo X, Wu K. Complete small-bowel examination by oral single-balloon enteroscopy using the water-exchange method. *Endoscopy* 2013; **45** Suppl 2 UCTN: E415-E417 [PMID: 24285078 DOI: 10.1055/s-0033-1358810]

25 **Al-Taie O**, Dietrich CG, Flieger D, Katzenberger T, Fischbach W. Is there a role for capsule endoscopy in the staging work-up of patients with gastric marginal zone B-cell lymphoma of MALT? *Z Gastroenterol* 2013; **51**: 727-732 [PMID: 23955137 DOI: 10.1055/s-0033-1335077]

26 **Yanai S**, Matsumoto T, Nakamura S, Fujisawa K, Ueki T, Hirahashi M, Yao T, Iida M. Endoscopic findings of enteropathy-type T-cell lymphoma. *Endoscopy* 2007; **39** Suppl 1: E339-E340 [PMID: 18273786 DOI: 10.1055/s-2007-967063]

27 **Matsumoto T**, Nakamura S, Esaki M, Yada S, Moriyama T, Yanai S, Hirahashi M, Yao T, Iida M. Double-balloon endoscopy depicts

diminutive small bowel lesions in gastrointestinal lymphoma. *Dig Dis Sci* 2010; **55**: 158-165 [PMID: 19241169 DOI: 10.1007/s10620-009-0713-8]
28 **Zucca E**, Copie-Bergman C, Ricardi U, Thieblemont C, Raderer M, Ladetto M , Ladetto M; ESMO Guidelines Working Group. Gastric marginal zone lymphoma of MALT type: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2013; **24** Suppl 6: vi144-vi148 [PMID: 24078657 DOI: 10.1093/annonc/mdt343]
29 **Cheson BD**, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, Lister TA. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol* 2014; **32**: 3059-3068 [PMID: 25113753 DOI: 10.1200/jco.2013.54.8800]
30 **Terada T**. Gastrointestinal malignant lymphoma: a pathologic study of 37 cases in a single Japanese institution. *Am J Blood Res* 2012; **2**: 194-200 [PMID: 23119230]
31 **Freeman HJ**. Malignancy in adult celiac disease. *World J Gastroenterol* 2009; **15**: 1581-1583 [PMID: 19340898]
32 **Koch P**, Probst A, Berdel WE, Willich NA, Reinartz G, Brockmann J, Liersch R, del Valle F, Clasen H, Hirt C, Breitsprecher R, Schmits R, Freund M, Fietkau R, Ketterer P, Freitag EM, Hinkelbein M, Heinecke A, Parwaresch R, Tiemann M. Treatment results in localized primary gastric lymphoma: data of patients registered within the German multicenter study (GIT NHL 02/96). *J Clin Oncol* 2005; **23**: 7050-7059 [PMID: 16129843 DOI: 10.1200/jco.2005.04.031]
33 **Park YH**, Kim WS, Bang SM, Lee SI, Uhm JE, Kang HJ, Na II, Yang SH, Lee SS, Kim K, Jung CW, Park K, Ko YH, Ryoo BY. Prognostic factor analysis and proposed prognostic model for conventional treatment of high-grade primary gastric lymphoma. *Eur J Haematol* 2006; **77**: 304-308 [PMID: 16879609 DOI: 10.1111/j.1600-0609.2006.00709.x]
34 **Kohno S**, Ohshima K, Yoneda S, Kodama T, Shirakusa T, Kikuchi M. Clinicopathological analysis of 143 primary malignant lymphomas in the small and large intestines based on the new WHO classification. *Histopathology* 2003; **43**: 135-143 [PMID: 12877728]
35 **Gou HF**, Zang J, Jiang M, Yang Y, Cao D, Chen XC. Clinical prognostic analysis of 116 patients with primary intestinal non-Hodgkin lymphoma. *Med Oncol* 2012; **29**: 227-234 [PMID: 21193968 DOI: 10.1007/s12032-010-9783-x]
36 **Ho HC**, Nagar AB, Hass DJ. Obscure gastrointestinal bleeding and video capsule retention due to enteropathy-associated T-cell lymphoma. *Gastroenterol Hepatol* (N Y) 2013; **9**: 536-538 [PMID: 24719605]
37 **Kawamoto K**, Nakamura S, Iwashita A, Watanabe J, Oshiro Y, Nakayama Y, Nimura S, Kimura N, Aoyagi K, Yao T, Kuramochi S, Matsuyama A, Kurihara K, Ohshima K, Takeshita M. Clinicopathological characteristics of primary gastric T-cell lymphoma. *Histopathology* 2009; **55**: 641-653 [PMID: 20002766 DOI: 10.1111/j.1365-2559.2009.03430.x]
38 **Radersma M**, Mulder CJ, Tushuizen ME. A rare cause of weight loss and night sweats. *Gastroenterology* 2014; **147**: e11-e12 [PMID: 25173784 DOI: 10.1053/j.gastro.2014.05.032]
39 **Dughayli MS**, Baidoun F, Lupovitch A. Synchronous perforation of non-Hodgkin's lymphoma of the small intestine and colon: a case report. *J Med Case Rep* 2011; **5**: 57 [PMID: 21310044 DOI: 10.1186/1752-1947-5-57]
40 **Kinaci E**, Gunes ME, Huq GE. An unusual presentation of EATL type 1: Emergency surgery due to life-threatening gastrointestinal bleeding. *Int J Surg Case Rep* 2013; **4**: 961-964 [PMID: 24055918 DOI: 10.1016/j.ijscr.2013.08.007]
41 **Saitoh T**, Matsushima T, Matsuo A, Yokohama A, Irisawa H, Handa H, Tsukamoto N, Karasawa M, Nojima Y, Murakami H. Small-bowel perforation accompanied by Aspergillus endocarditis in a patient with angioimmunoblastic T-cell lymphoma. *Ann Hematol* 2007; **86**: 71-73 [PMID: 17043778]
42 **Keiser PB**, Nutman TB. Strongyloides stercoralis in the Immunocompromised Population. *Clin Microbiol Rev* 2004; **17**: 208-217 [PMID: 14726461]
43 **Dearden CE**, Johnson R, Pettengell R, Devereux S, Cwynarski K, Whittaker S, McMillan A. Guidelines for the management of mature T-cell and NK-cell neoplasms (excluding cutaneous T-cell lymphoma). *Br J Haematol* 2011; **153**: 451-485 [PMID: 21480860 DOI: 10.1111/j.1365-2141.2011.08651.x]
44 **Daum S**, Ullrich R, Heise W, Dederke B, Foss HD, Stein H, Thiel E, Zeitz M, Riecken EO. Intestinal non-Hodgkin's lymphoma: a multicenter prospective clinical study from the German Study Group on Intestinal non-Hodgkin's Lymphoma. *J Clin Oncol* 2003; **21**: 2740-2746 [PMID: 12860953 DOI: 10.1200/JCO.2003.06.026]
45 **Sugita S**, Iijima T, Furuya S, Kano J, Yanaka A, Ohta K, Kojima H, Noguchi M. Gastric T-cell lymphoma with cytotoxic phenotype. *Pathol Int* 2007; **57**: 108-114 [PMID: 17300676 DOI: 10.1111/j.1440-1827.2006.02065.x]
46 **Tachikawa Y**, Shiratsuchi M, Sada E, Idutsu K, Kiyasu J, Karube K, Ohshima K, Nishimura J, Takayanagi R, Abe Y. Composite gastrointestinal lymphoma consisting of diffuse large B-cell lymphoma and peripheral T-cell lymphoma. *Int J Hematol* 2009; **90**: 275-277 [PMID: 19588220 DOI: 10.1007/s12185-009-0371-9]
47 **Hatano B**, Ohshima K, Katoh A, Kanda M, Kawasaki C, Tsuchiya T, Shimazaki K, Haraoka S, Sugihara M, Suzumiya J, Kikuchi M. Non-HTLV-1-associated primary gastric T-cell lymphomas show cytotoxic activity: clinicopathological, immunohistochemical characteristics and TIA-1 expression in 31 cases. *Histopathology* 2002; **41**: 421-436 [PMID: 12405910]
48 **Swerdlow SHCE**, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Vardimar JW. WHO classification of tumours of haematopoietic and lymphoid tissues: International Agency for Research on Cancer, 2008
49 **Isomoto H**, Ohnita K, Mizuta Y, Maeda T, Onizuka Y, Miyazaki M, Omagari K, Takeshima F, Murase K, Haraguchi M, Murata I, Kohno S. Clinical and endoscopic features of adult T-cell leukemia/lymphoma with duodenal involvement. *J Clin Gastroenterol* 2001; **33**: 241-246 [PMID: 11500618]
50 **Toyota S**, Nakamura N, Dan K. T-cell prolymphocytic leukemia with hemorrhagic gastrointestinal involvement and a new chromosomal abnormality. *Int J Hematol* 2002; **75**: 314-317 [PMID: 11999363]
51 **Ishii H**, Isomoto H, Taniguchi H, Kinoshita N, Matsushima K, Taguchi J, Miyazaki Y, Nakao K. Education and Imaging: Gastrointestinal: gastroduodenal involvement of ALK-positive anaplastic large cell lymphoma. *J Gastroenterol Hepatol* 2011; **26**: 933 [PMID: 21488949 DOI: 10.1111/j.1440-1746.2011.06665.x]
52 **Kim do H**, Lee D, Kim JW, Huh J, Park SH, Ha HK, Suh C, Yoon SM, Kim KJ, Choi KD, Ye BD, Byeon JS, Song HJ, Jung HY, Yang SK, Kim JH, Myung SJ. Endoscopic and clinical analysis of primary T-cell lymphoma of the gastrointestinal tract according to pathological subtype. *J Gastroenterol Hepatol* 2014; **29**: 934-943 [PMID: 24325295 DOI: 10.1111/jgh.12471]
53 **Okada M**, Maeda K, Suzumiya J, Hagimoto T, Wakamatsu S, Ohshima K, Kanda M, Sonoda T, Sakamoto A, Tamura K. Primary colorectal T-cell lymphoma. *J Gastroenterol* 2003; **38**: 376-384 [PMID: 12743779 DOI: 10.1007/s005350300067]
54 **Schuler MK**, Kroschinsky F, Schaich M, Kalauch A, Stroszczynski C, Kellermann S, Ehninger G, Benter T. Sézary syndrome: infiltration of the gastric wall--does it matter? *Ann Hematol* 2012; **91**: 1507-1509 [PMID: 22362119 DOI: 10.1007/s00277-012-1426-1]
55 **Okumura K**, Ikebe M, Shimokama T, Takeshita M, Kinjo N, Sugimachi K, Higashi H. An unusual enteropathy-associated T-cell lymphoma with MYC translocation arising in a Japanese patient: a case report. *World J Gastroenterol* 2012; **18**: 2434-2437 [PMID: 22654438 DOI: 10.3748/wjg.v18.i19.2434]
56 **Sieniawski MK**, Lennard AL. Enteropathy-associated T-cell lymphoma: epidemiology, clinical features, and current treatment strategies. *Curr Hematol Malig Rep* 2011; **6**: 231-240 [PMID: 21912848 DOI: 10.1007/s11899-011-0097-7]
57 **Rostami Nejad M**, Aldulaimi D, Ishaq S, Ehsani-Ardakani MJ, Zali MR, Malekzadeh R, Rostami K. Geographic trends and risk of gastrointestinal cancer among patients with celiac disease in Europe

and Asian-Pacific region. *Gastroenterol Hepatol Bed Bench* 2013; **6**: 170-177 [PMID: 24834268]

58 **d'Amore F**, Brincker H, Grønbaek K, Thorling K, Pedersen M, Jensen MK, Andersen E, Pedersen NT, Mortensen LS. Non-Hodgkin's lymphoma of the gastrointestinal tract: a population-based analysis of incidence, geographic distribution, clinicopathologic presentation features, and prognosis. Danish Lymphoma Study Group. *J Clin Oncol* 1994; **12**: 1673-1684 [PMID: 8040680]

59 **Chang ST**, Menias CO. Imaging of primary gastrointestinal lymphoma. *Semin Ultrasound CT MR* 2013; **34**: 558-565 [PMID: 24332207 DOI: 10.1053/j.sult.2013.05.008]

60 **Askling J**, Linet M, Gridley G, Halstensen TS, Ekström K, Ekbom A. Cancer incidence in a population-based cohort of individuals hospitalized with celiac disease or dermatitis herpetiformis. *Gastroenterology* 2002; **123**: 1428-1435 [PMID: 12404215]

61 **Biagi F**, Gobbi P, Marchese A, Borsotti E, Zingone F, Ciacci C, Volta U, Caio G, Carroccio A, Ambrosiano G, Mansueto P, Corazza GR. Low incidence but poor prognosis of complicated coeliac disease: a retrospective multicentre study. *Dig Liver Dis* 2014; **46**: 227-230 [PMID: 24268568 DOI: 10.1016/j.dld.2013.10.010]

62 **Arps DP**, Smith LB. Classic versus type II enteropathy-associated T-cell lymphoma: diagnostic considerations. *Arch Pathol Lab Med* 2013; **137**: 1227-1231 [PMID: 23991736 DOI: 10.5858/arpa.2013-0242-CR]

63 **Jiao G**, Zheng Z, Jiang K, Zhang J, Wang B. Enteropathy-associated T-cell lymphoma presenting with gastrointestinal tract symptoms: A report of two cases and review of diagnostic challenges and clinicopathological correlation. *Oncol Lett* 2014; **8**: 91-94 [PMID: 24959225 DOI: 10.3892/ol.2014.2105]

64 **Park YH**, Kim WS, Bang SM, Lee SI, Kang HJ, Na II, Yang SH, Lee SS, Uhm JE, Kwon JM, Kim K, Jung CW, Park K, Ko YH, Ryoo BY. Primary gastric lymphoma of T-cell origin: clinicopathologic features and treatment outcome. *Leuk Res* 2006; **30**: 1253-1258 [PMID: 16529813 DOI: 10.1016/j.leukres.2006.01.018]

65 **Bellei M**, Chiattone CS, Luminari S, Pesce EA, Cabrera ME, de Souza CA, Gabús R, Zoppegno L, Zoppegno L, Milone J, Pavlovsky A, Connors JM, Foss FM, Horwitz SM, Liang R, Montoto S, Pileri SA, Polliack A, Vose JM, Zinzani PL, Zucca E, Federico M. T-cell lymphomas in South america and europe. *Rev Bras Hematol Hemoter* 2012; **34**: 42-47 [PMID: 23049383 DOI: 10.5581/1516-8484.20120013]

66 **Velagapudi P**, Turagam M, Uzoaru I, Graham D. Small bowel obstruction due to mycosis fungoides: an unusual presentation. *Am J Med Sci* 2011; **341**: 508-509 [PMID: 21613936 DOI: 10.1097/MAJ.0b013e31821389da]

67 **Isomoto H**, Maeda T, Akashi T, Tsuchiya T, Kawaguchi Y, Sawayama Y, Koida S, Ohnita K, Kohno S, Tomonaga M. Multiple lymphomatous polyposis of the colon originating from T-cells: a case report. *Dig Liver Dis* 2004; **36**: 218-221 [PMID: 15046193 DOI: 10.1016/j.dld.2003.09.019]

68 **Cooperberg MR**, Fiedler PN. Ki-1 anaplastic large-cell lymphoma occurring at the site of ileocolonic anastomosis in a patient treated surgically for colonic adenocarcinoma: case report and review of the literature. *Ann Diagn Pathol* 2001; **5**: 162-167 [PMID: 11436170 DOI: 10.1053/adpa.2001.25408]

69 **Ikeda J**, Yamauchi A, Hoshida Y, Okamura S, Hashimoto K, Aozasa K, Morii E. Peripheral T-cell lymphoma developing at ileocolonic anastomosis site after colectomy for adenocarcinoma. *Pathol Res Pract* 2010; **206**: 376-378 [PMID: 19836149 DOI: 10.1016/j.prp.2009.08.001]

70 **Jung CK**, Lee KY, Kim Y, Han K, Shim SI, Kim BK, Kang CS. Epstein-Barr virus infection, drug resistance and prognosis in Korean T- and NK-cell lymphomas. *Pathol Int* 2001; **51**: 355-363 [PMID: 11422793]

71 **Zhang YC**, Sha Zhao JB, Lei Shi MX, Zhang HY, Liu WP. Gastric involvement of extranodal NK/T-cell lymphoma, nasal type: a report of 3 cases with literature review. *Int J Surg Pathol* 2008; **16**: 450-454 [PMID: 18492683 DOI: 10.1177/1066896908316068]

72 **Jiang M**, Chen X, Yi Z, Zhang X, Zhang B, Luo F, Jiang Y, Zou L. Prognostic characteristics of gastrointestinal tract NK/T-cell lymphoma: an analysis of 47 patients in China. *J Clin Gastroenterol* 2013; **47**: e74-e79 [PMID: 23948755 DOI: 10.1097/MCG.0b013e31829e444f]

73 **Wakabayashi S**, Arai A, Oshikawa G, Araki A, Watanabe M, Uchida N, Taniguchi S, Miura O. Extranodal NK/T cell lymphoma, nasal type, of the small intestine diagnosed by double-balloon endoscopy. *Int J Hematol* 2009; **90**: 605-610 [PMID: 19936878 DOI: 10.1007/s12185-009-0438-7]

74 **Li JZ**, Tao J, Ruan DY, Yang YD, Zhan YS, Wang X, Chen Y, Kuang SC, Shao CK, Wu B. Primary duodenal NK/T-cell lymphoma with massive bleeding: A case report. *World J Clin Oncol* 2012; **3**: 92-97 [PMID: 22724088 DOI: 10.5306/wjco.v3.i6.92]

75 **Kobold S**, Merz H, Tiemann M, Mahuad C, Bokemeyer C, Koop I, Fiedler W. Primary NK/T cell lymphoma nasal type of the stomach with skin involvement: a case report. *Rare Tumors* 2009; **1**: e58 [PMID: 21139937 DOI: 10.4081/rt.2009.e58]

76 **Kim JH**, Lee JH, Lee J, Oh SO, Chang DK, Rhee PL, Kim JJ, Rhee JC, Lee J, Kim WS, Ko YH. Primary NK-/T-cell lymphoma of the gastrointestinal tract: clinical characteristics and endoscopic findings. *Endoscopy* 2007; **39**: 156-160 [PMID: 17657701 DOI: 10.1055/s-2006-945114]

77 **Kim SJ**, Jung HA, Chuang SS, Hong H, Guo CC, Cao J, Hong XN, Suzuki R, Kang HJ, Won JH, Chng WJ, Kwong YL, Suh C, Song YQ, Zhu J, Tay K, Lim ST, Suzumiya J, Lin TY, Kim WS. Extranodal natural killer/T-cell lymphoma involving the gastrointestinal tract: analysis of clinical features and outcomes from the Asia Lymphoma Study Group. *J Hematol Oncol* 2013; **6**: 86 [PMID: 24238138 DOI: 10.1186/1756-8722-6-86]

78 **Hong H**, Liang C, Huang H, Guo C, Tian Y, Liu T, Zhang M, Li X, Wang Z, Fang X, Lin J, Lin T. Surgical resection followed by chemotherapy may be an effective treatment strategy for primary gastrointestinal natural killer/T-cell lymphoma: a single center experience. *Leuk Lymphoma* 2014; **55**: 2649-2651 [PMID: 24506468 DOI: 10.3109/10428194.2014.889829]

79 **Yang H**, Wu M, Yin W, Sun W, Zhang G. Diagnosis and treatment of a patient with primary gastric extranodal natural killer/T-cell lymphoma, nasal type. *Leuk Lymphoma* 2010; **51**: 2137-2140 [PMID: 20858103 DOI: 10.3109/10428194.2010.512964]

80 **Suzumiya J**, Marutsuka K, Nabeshima K, Nawa Y, Koono M, Tamura K, Kimura N, Hisano S, Tachibana N, Inoue S. Autopsy findings in 47 cases of adult T-cell leukemia/lymphoma in Miyazaki prefecture, Japan. *Leuk Lymphoma* 1993; **11**: 281-286 [PMID: 8260899 DOI: 10.3109/10428199309087005]

81 **Bazarbachi A**, Suarez F, Fields P, Hermine O. How I treat adult T-cell leukemia/lymphoma. *Blood* 2011; **118**: 1736-1745 [PMID: 21673346 DOI: 10.1182/blood-2011-03-345702]

82 **Tanaka K**, Nakamura S, Matsumoto T, Hirakawa K, Yanaru-Fujisawa R, Onoyama K, Sakata H, Ohshima K, Yao T, Iida M. Long-term remission of primary gastric T cell lymphoma associated with human T lymphotropic virus type 1: a report of two cases and review of the literature. *Intern Med* 2007; **46**: 1783-1787 [PMID: 17978535]

83 **Ohnita K**, Isomoto H, Mizuta Y, Maeda T, Haraguchi M, Miyazaki M, Murase K, Murata I, Tomonaga M, Kohno S. Helicobacter pylori infection in patients with gastric involvement by adult T-cell leukemia/lymphoma. *Cancer* 2002; **94**: 1507-1516 [PMID: 11920508]

84 **Hokama A**, Tomoyose T, Yamamoto Y, Watanabe T, Hirata T, Kinjo F, Kato S, Ohshima K, Uezato H, Takasu N, Fujita J. Adult T-cell leukemia/lymphoma presenting multiple lymphomatous polyposis. *World J Gastroenterol* 2008; **14**: 6584-6588 [PMID: 19030219]

85 **Asada Y**, Isomoto H, Shikuwa S, Ito M, Momita S, Matsumura N, Ohba K, Ohnita K, Nakamura T, Mizuta Y, Ishibashi H, Kohno S. Adult T-cell leukemia with colorectal involvement. *Gastrointest Endosc* 2004; **60**: 983-984 [PMID: 15605016]

86 **Onishi T**, Tamura S, Onishi S. A case of adult T-cell leukemia with colon involvement. *Gastrointest Endosc* 2007; **65**: 712-713 [PMID: 17383471 DOI: 10.1016/j.gie.2006.06.076]

87 **Ohnita K**, Isomoto H, Maeda T, Jubashi T, Nakamura H, Misuta

Y, Murase K, Tomonaga M, Kohno S. Two cases of adult T-cell leukemia/lymphoma involving the terminal ileum. *Leuk Lymphoma* 2003; **44**: 973-976 [PMID: 12854896 DOI: 10.1080/1042819031000063499]
88 **Isomoto H**, Furusu H, Onizuka Y, Kawaguchi Y, Mizuta Y, Maeda T, Kohno S. Colonic involvement by adult T-cell leukemia/lymphoma mimicking ulcerative colitis. *Gastrointest Endosc* 2003; **58**: 805-808 [PMID: 14997894]
89 **Isomoto H**, Ohnita K, Mizuta Y, Maeda T, Omagari K, Miyazaki M, Murase K, Hasui K, Murata I, Kohno S. Adult T-cell leukemia with an unusual esophageal lesion. *Gastrointest Endosc* 2001; **53**: 673-675 [PMID: 11323605]
90 **Isomoto H**, Matsushima K, Hayashi T, Imaizumi Y, Shiota J, Ishii H, Minami H, Ohnita K, Takeshima F, Shikuwa S, Miyazaki Y, Nakao K. Endocytoscopic findings of lymphomas of the stomach. *BMC Gastroenterol* 2013; **13**: 174 [PMID: 24369830 DOI: 10.1186/1471-230x-13-174]
91 **Perry AM**, Warnke RA, Hu Q, Gaulard P, Copie-Bergman C, Alkan S, Wang HY, Cheng JX, Bacon CM, Delabie J, Ranheim E, Kucuk C, Hu X, Weisenburger DD, Jaffe ES, Chan WC. Indolent T-cell lymphoproliferative disease of the gastrointestinal tract. *Blood* 2013; **122**: 3599-3606 [PMID: 24009234 DOI: 10.1182/blood-2013-07-512830]
92 **Margolskee E**, Jobanputra V, Lewis SK, Alobeid B, Green PH, Bhagat G. Indolent small intestinal CD4+ T-cell lymphoma is a distinct entity with unique biologic and clinical features. *PLoS One* 2013; **8**: e68343 [PMID: 23861889 DOI: 10.1371/journal.pone.0068343]
93 **Leventaki V**, Manning JT, Luthra R, Mehta P, Oki Y, Romaguera JE, Medeiros LJ, Vega F. Indolent peripheral T-cell lymphoma involving the gastrointestinal tract. *Hum Pathol* 2014; **45**: 421-426 [PMID: 24439229 DOI: 10.1016/j.humpath.2013.08.003]
94 **Mansoor A**, Pittaluga S, Beck PL, Wilson WH, Ferry JA, Jaffe ES. NK-cell enteropathy: a benign NK-cell lymphoproliferative disease mimicking intestinal lymphoma: clinicopathologic features and follow-up in a unique case series. *Blood* 2011; **117**: 1447-1452 [PMID: 20966166 DOI: 10.1182/blood-2010-08-302737]
95 **Takeuchi K**, Yokoyama M, Ishizawa S, Terui Y, Nomura K, Marutsuka K, Nunomura M, Fukushima N, Yagyuu T, Nakamine H, Akiyama F, Hoshi K, Matsue K, Hatake K, Oshimi K. Lymphomatoid gastropathy: a distinct clinicopathologic entity of self-limited pseudomalignant NK-cell proliferation. *Blood* 2010; **116**: 5631-5637 [PMID: 20829373 DOI: 10.1182/blood-2010-06-290650]
96 **Cornes JS**. Multiple lymphomatous polyposis of the gastrointestinal tract. *Cancer* 1961; **14**: 249-257 [PMID: 13695582]
97 **Shen KH**, Chen CJ, Yen HH. Multiple polyposis of the esophagus: mantle cell lymphoma. *Clin Gastroenterol Hepatol* 2012; **10**: e65 [PMID: 22516172 DOI: 10.1016/j.cgh.2012.04.009]
98 **Esteban JM**, Gutiérrez del Olmo A, Baki W, Fernández S, Soria MT, Díaz Mediavilla J, Ramírez Armengol JA. Colonic mucosa-associated lymphoid tissue lymphoma presenting as multiple polyposis. *Gastrointest Endosc* 2005; **61**: 928-930 [PMID: 15933708]
99 **Isomoto H**, Maeda T, Ohnita K, Nakayama T, Kohno S. Colonic lymphomatous polyposis. *Gastrointest Endosc* 2004; **59**: 261 [PMID: 14745401]
100 **Peters JH**, Rondonotti E, Weijmer MC, Mulder CJ, Jacobs MA. Lymphomatous polyposis of the small intestine. *Gastrointest Endosc* 2008; **67**: 763-765 [PMID: 18207144 DOI: 10.1016/j.gie.2007.09.035]
101 **Ruskoné-Fourmestraux A**, Audouin J. Primary gastrointestinal tract mantle cell lymphoma as multiple lymphomatous polyposis. *Best Pract Res Clin Gastroenterol* 2010; **24**: 35-42 [PMID: 20206107 DOI: 10.1016/j.bpg.2009.12.001]
102 **Moynihan MJ**, Bast MA, Chan WC, Delabie Jan RS, Wu G, Weisenburger DD. Lymphomatous polyposis. A neoplasm of either follicular mantle or germinal center cell origin. *Am J Surg Pathol* 1996; **20**: 442-452 [PMID: 8604811]
103 **Saito M**, Mori A, Irie T, Tanaka M, Morioka M, Ozasa M, Kobayashi T, Saga A, Miwa K, Tanaka S. Endoscopic follow-up of 3 cases with gastrointestinal tract involvement of mantle cell lymphoma. *Intern Med* 2010; **49**: 231-235 [PMID: 20118601]
104 **Chung R**, Peters AC, Armanious H, Anand M, Gelebart P, Lai R. Biological and clinical significance of GSK-3beta in mantle cell lymphoma--an immunohistochemical study. *Int J Clin Exp Pathol* 2010; **3**: 244-253 [PMID: 20224723]
105 **Chuang SS**, Chang ST, Liu H, Ye H, Sheu MJ, Chen MJ, Tsao CJ. Intramucosal follicular lymphoma in the terminal ileum with nodal involvement. *Pathol Res Pract* 2007; **203**: 691-694 [PMID: 17643847 DOI: 10.1016/j.prp.2007.05.006]
106 **Isaacson PG**, MacLennan KA, Subbuswamy SG. Multiple lymphomatous polyposis of the gastrointestinal tract. *Histopathology* 1984; **8**: 641-656 [PMID: 6479906]
107 **Kanehira K**, Braylan RC, Lauwers GY. Early phase of intestinal mantle cell lymphoma: a report of two cases associated with advanced colonic adenocarcinoma. *Mod Pathol* 2001; **14**: 811-817 [PMID: 11504842 DOI: 10.1038/modpathol.3880395]
108 **Chong Y**, Shin JJ, Cho MY, Cui Y, Kim HY, Park KH. Synchronous primary gastric mantle cell lymphoma and early gastric carcinoma: a case report. *Pathol Res Pract* 2008; **204**: 407-411 [PMID: 18282664 DOI: 10.1016/j.prp.2007.12.008]
109 **Okazaki K**. Multiple lymphomatous polyposis form is common but not specific for mantle cell lymphoma in the gastrointestinal tract. *J Gastroenterol* 2004; **39**: 1023-1024 [PMID: 15549463 DOI: 10.1007/s00535-004-1459-x]
110 **Au WY**, Lo SH, Law WL, Khong PL, Shek TW, Lau WH, Chau EM. Concomitant Eber-positive lymphomatoid papulosis and malignant transformation of colonic polyposis in a heart transplant recipient. *J Heart Lung Transplant* 2008; **27**: 575-576 [PMID: 18442728 DOI: 10.1016/j.healun.2008.01.024]
111 **Lee JA**, Taxier MS, Nicely CJ. Electronic clinical challenges and images in GI. Lymphomatous polyposis. *Gastroenterology* 2008; **135**: e1-e3 [PMID: 18619969 DOI: 10.1053/j.gastro.2008.06.041]
112 **Hirata N**, Tominaga K, Ohta K, Kadouchi K, Okazaki H, Tanigawa T, Shiba M, Watanabe T, Fujiwara Y, Nakamura S, Oshitani N, Higuchi K, Arakawa T. A case of mucosa-associated lymphoid tissue lymphoma forming multiple lymphomatous polyposis in the small intestine. *World J Gastroenterol* 2007; **13**: 1453-1457 [PMID: 17457982]
113 **Bahari A**, Jahantigh M, Mashhadi A, Bari Z, Bari A. Plasmablastic Lymphoma presenting as small intestinal polyposis: A case-report. *Iran Red Crescent Med J* 2012; **14**: 669-675 [PMID: 23285420]
114 **Khaled S**, Gotlieb V, Schuster IP, Saif MW. Multiple lymphomatous polyposis associated with small lymphocytic lymphoma: a unique presentation. *J Gastrointestin Liver Dis* 2008; **17**: 461-463 [PMID: 19104711]
115 **Songür Y**, Tezel A, Ensari A, Sahin B. EUS diagnosis of lymphomatous polyposis. *Gastrointest Endosc* 2000; **52**: 685-687 [PMID: 11060202 DOI: 10.1067/mge.2000.107713]
116 **Rodrigues S**, Cardoso H, Macedo G. Mantle cell lymphoma presenting as multiple lymphomatous polyposis of the small bowel. *Clin Gastroenterol Hepatol* 2013; **11**: e71 [PMID: 23466713 DOI: 10.1016/j.cgh.2013.02.018]
117 **Hotta K**, Oyama T, Kitamura Y, Tomori A, Miyata Y, Mitsuishi T. Mantle cell lymphoma presenting as multiple lymphomatous polyposis spreading widely to the small intestine and diagnosed by double-balloon endoscopy. *Endoscopy* 2007; **39** Suppl 1: E347-E348 [PMID: 18273791 DOI: 10.1055/s-2007-995331]
118 **Han EJ**, Yang SA, Sohn HS, Kim JI, Kang CS, Cho SG. Successful treatment with tandem consolidation using 90yttrium-ibritumomab tiuxetan (Zevalin) and high-dose therapy with autologous PBSCT in a patient with relapsed mantle cell lymphoma presenting as multiple lymphomatous polyposis. *Bone Marrow Transplant* 2012; **47**: 877-879 [PMID: 21946384 DOI: 10.1038/bmt.2011.193]
119 **Tanțău M**, Tanțău A, Zaharia T, Cucuianu A. Gastrointestinal lymphomatous polyposis--clinical, endoscopical and evolution features. A case report. *Rom J Gastroenterol* 2005; **14**: 273-278 [PMID: 16200239]
120 **Chung HH**, Kim YH, Kim JH, Cha SH, Kim BH, Kim TK, Kim

AR, Cho SJ. Imaging findings of mantle cell lymphoma involving gastrointestinal tract. *Yonsei Med J* 2003; **44**: 49-57 [PMID: 12619175]

121 **Yu SC**, Liu KL, Chang LC. Lymphomatous polyposis as primary manifestation of mantle cell lymphoma. *Eur J Haematol* 2012; **89**: 185-186 [PMID: 22563740 DOI: 10.1111/j.1600-0609.2012.01791.x]

122 **Christopoulos C**, Stathakis S, Theodoropoulos I, Papavassiliou E, Savva S. Multiple lymphomatous polyposis. *Br J Haematol* 2004; **125**: 544 [PMID: 15147367 DOI: 10.1111/j.1365-2141.2004.04915.x]

123 **Chim CS**, Shek TW, Chung LP, Liang R. Unusual abdominal tumors: case 3. Multiple lymphomatous polyposis in lymphoma of colon. *J Clin Oncol* 2003; **21**: 953-955 [PMID: 12610202]

124 **Watanabe T**, Homma N, Ogata N, Saito H, Kanefuji T, Hasegawa K, Soga K, Shibasaki K, Endo T, Ajioka Y. Complete response in a patient with colonic mantle cell lymphoma with multiple lymphomatous polyposis treated with combination chemotherapy using anti-CD20 antibody and cladribine. *Gut* 2007; **56**: 449-450 [PMID: 17339260 DOI: 10.1136/gut.2006.114207]

125 **Meral M**, Demirpençe M, Gönen C, Akarsu M, Kayahan H, Demirkan F, Kargi A, Akpinar H. Diffuse gastrointestinal involvement of mantle cell lymphoma. *Turk J Gastroenterol* 2008; **19**: 117-120 [PMID: 19110668]

126 **Alvarez-Martínez P**, Pipa-Muñiz M, Ordieres-Díaz C, Fernández-Vega I, Palacio-Galán MA, Granero-Castro P, Suárez-González A. Multiple lymphomatous polyposis of intestine as presentation of mantle cell lymphoma. *Rev Esp Enferm Dig* 2012; **104**: 491-492 [PMID: 23130858]

127 **Kyung Shin B**, Lee H, Choi J, Kim A, Kim H, Park J, Kim I. Primary marginal zone B-cell lymphoma of gastrointestinal tract presenting as multiple lymphomatoid polyposis. *Int J Colorectal Dis* 2007; **22**: 991-992 [PMID: 16586077 DOI: 10.1007/s00384-006-0125-6]

128 **Wolfsen HC**, Achem SR. Diffuse colonic polyposis detected at screening colonoscopy: mantle-cell lymphoma. *Endoscopy* 2004; **36**: 471 [PMID: 15100973 DOI: 10.1055/s-2004-814418]

129 **Lam KC**, Yeo W, Lee JF, Chow J, Mok TS. Unusual abdominal tumors: case 4. Multiple lymphomatous polyposis in mantle cell lymphoma. *J Clin Oncol* 2003; **21**: 955-956 [PMID: 12610203]

130 **Michopoulos S**, Petraki K, Matsouka C, Kastritis E, Chrysanthopoulou H, Dimopoulos MA. Mantle-cell lymphoma (multiple lymphomatous polyposis) of the entire GI tract. *J Clin Oncol* 2008; **26**: 1555-1557 [PMID: 18349408 DOI: 10.1200/JCO.2007.14.9856]

131 **Xu XJ**, Wu SM. Multiple lymphomatous polyposis of the gastrointestinal tract: report of three cases and literature review. *J Dig Dis* 2012; **13**: 649-653 [PMID: 23134448 DOI: 10.1111/j.1751-2980.2012.00635.x]

132 **Barut F**, Kandemır NO, Karakaya K, Kökten N, Ozdamar SO. Primary intestinal diffuse large B-cell lymphoma forming multiple lymphomatous polyposis. *Turk J Gastroenterol* 2011; **22**: 324-328 [PMID: 21805425]

133 **Cestaro G**, De Rosa M, Vitiello C, Galloro G, Gentile M. Multiple lymphomatous polyposis with diffuse involvement of the gastrointestinal tract. Case report. *G Chir* 2013; **34**: 173-175 [PMID: 23837958]

134 **Murase K**, Matsunaga T, Sato T, Kuribayashi K, Kogawa K, Kawano Y, Okamoto T, Takayama T, Watanabe H, Niitsu Y, Hirayama Y. Allogeneic bone marrow transplantation in a patient with T-prolymphocytic leukemia with small-intestinal involvement. *Int J Clin Oncol* 2003; **8**: 391-394 [PMID: 14663643 DOI: 10.1007/s10147-003-0349-1]

135 **Chen CY**, Wu CC, Hsiao CW, Lee TY, Jao SW. Colonic manifestation of mantle cell lymphoma with multiple lymphomatous polyposis. *Int J Colorectal Dis* 2009; **24**: 729-730 [PMID: 19172280 DOI: 10.1007/s00384-009-0649-7]

136 **Franco MI**, Waisberg J, Lopes LS. Multiple lymphomatous polyposis of the gastrointestinal tract. *Sao Paulo Med J* 2004; **122**: 131-133 [PMID: 15448813]

137 **Kella VK**, Constantine R, Parikh NS, Reed M, Cosgrove JM, Abo SM, King S. Mantle cell lymphoma of the gastrointestinal tract presenting with multiple intussusceptions--case report and review of literature. *World J Surg Oncol* 2009; **7**: 60 [PMID: 19646237 DOI: 10.1186/1477-7819-7-60]

138 **Remes-Troche JM**, De-Anda J, Ochoa V, Barreto-Zuñiga R, Arista-Nasr J, Valdovinos MA. A rare case of multiple lymphomatous polyposis with widespread involvement of the gastrointestinal tract. *Arch Pathol Lab Med* 2003; **127**: 1028-1030 [PMID: 12873180 DOI: 10.1043/1543-2165(2003)127<1028]

139 **Mar N**, Khaled S, Kencana F, Gergis U, Khattak F, Brodsky N, Gotlieb V. Multiple lymphomatous polyposis as a sole presentation of mantle cell lymphoma. *J Clin Gastroenterol* 2006; **40**: 653-654 [PMID: 16917415]

140 **Tomita S**, Kojima M, Imura J, Hori H, Ueda Y, Koitabashi A, Suzuki Y, Nakamura T, Nakamura Y, Mitani K, Terano A, Ohkura Y, Kawamata H, Fujimori T. Extranodal diffuse follicular center lymphoma mimicking mantle cell lymphoma of the intestine. *Am J Hematol* 2003; **74**: 287-289 [PMID: 14635213 DOI: 10.1002/ajh.10437]

141 **Sciaudone G**, Pellino G, Selvaggi F. Diagnostic pitfalls: cancerization in IBD versus mantle cell lymphoma presenting with multiple lymphomatous polyposis. *Inflamm Bowel Dis* 2011; **17**: E28-E30 [PMID: 21287677 DOI: 10.1002/ibd.21642]

142 **Yang SF**, Liao YL, Kuo SY, Ye H, Lin SF, Chen FM, Chen CY, Chuang SS. Primary intestinal diffuse large B-cell lymphoma presenting as multiple lymphomatous polyposis. *Leuk Lymphoma* 2009; **50**: 1219-1222 [PMID: 19557644 DOI: 10.1080/10428190902974247]

143 **Saito T**, Toyoda H, Yamaguchi M, Nakamura T, Nakamura S, Mukai K, Fuke H, Wakita Y, Iwata M, Adachi Y, Shiku H. Ileocolonic lymphomas: a series of 16 cases. *Endoscopy* 2005; **37**: 466-469 [PMID: 15844027 DOI: 10.1055/s-2005-861093]

144 **Iwamuro M**, Okada H, Kawahara Y, Shinagawa K, Morito T, Yoshino T, Yamamoto K. Endoscopic features and prognoses of mantle cell lymphoma with gastrointestinal involvement. *World J Gastroenterol* 2010; **16**: 4661-4669 [PMID: 20872966]

145 **Yilmaz B**, Posul E, Col C, Uyeturk U, Boran C, Aktas G, Kurt M. Diffuse gastric mantle cell lymphoma resembling gastrointestinal stromal tumors. *Gastrointest Endosc* 2014; **79**: 375 [PMID: 24368075 DOI: 10.1016/j.gie.2013.11.008]

146 **Kelkitli E**, Atay H, Yıldız L, Bektaş A, Turgut M. Mantle cell lymphoma mimicking rectal carcinoma. *Case Rep Hematol* 2014; **2014**: 621017 [PMID: 24822134 DOI: 10.1155/2014/621017]

147 **Raderer M**, Püspök A, Birkner T, Streubel B, Chott A. Primary gastric mantle cell lymphoma in a patient with long standing history of Crohn's disease. *Leuk Lymphoma* 2004; **45**: 1459-1462 [PMID: 15359648 DOI: 10.1080/10428190310001645915]

148 **Viana HL**, Henrique RM, Ferreira ES, Correia AM, Silva RA, Dias LM, Viana RL. Endoscopic ultrasonography in multiple lymphomatous polyposis. *J Clin Gastroenterol* 2002; **34**: 150-154 [PMID: 11782610]

149 **Zheng W**, Song Y, Lin N, Tu M, Liu W, Zhu J. Primary gastrointestinal mantle lymphoma with massive bleeding: a case report and literature review. *Chin J Cancer Res* 2013; **25**: 250-253 [PMID: 23592907 DOI: 10.3978/j.issn.1000-9604.2012.12.05]

150 **Yoshino T**, Miyake K, Ichimura K, Mannami T, Ohara N, Hamazaki S, Akagi T. Increased incidence of follicular lymphoma in the duodenum. *Am J Surg Pathol* 2000; **24**: 688-693 [PMID: 10800987]

151 **Yamamoto S**, Nakase H, Yamashita K, Matsuura M, Takada M, Kawanami C, Chiba T. Gastrointestinal follicular lymphoma: review of the literature. *J Gastroenterol* 2010; **45**: 370-388 [PMID: 20084529 DOI: 10.1007/s00535-009-0182-z]

152 **Takata K**, Miyata-Takata T, Sato Y, Yoshino T. Pathology of follicular lymphoma. *J Clin Exp Hematop* 2014; **54**: 3-9 [PMID: 24942941]

153 **Shia J**, Teruya-Feldstein J, Pan D, Hegde A, Klimstra DS, Chaganti RS, Qin J, Portlock CS, Filippa DA. Primary follicular lymphoma of the gastrointestinal tract: a clinical and pathologic study of 26 cases. *Am J Surg Pathol* 2002; **26**: 216-224 [PMID: 11812943]

154 **Iwamuro M**, Okada H, Takata K, Shinagawa K, Fujiki S, Shiode J, Imagawa A, Araki M, Morito T, Nishimura M, Mizuno M, Inaba T, Suzuki S, Kawai Y, Yoshino T, Kawahara Y, Takaki A,

Yamamoto K. Diagnostic role of 18F-fluorodeoxyglucose positron emission tomography for follicular lymphoma with gastrointestinal involvement. *World J Gastroenterol* 2012; **18**: 6427-6436; discussion p.6434 [PMID: 23197888 DOI: 10.3748/wjg.v18.i44.6427]

155 **Higuchi N**, Sumida Y, Nakamura K, Itaba S, Yoshinaga S, Mizutani T, Honda K, Taki K, Murao H, Ogino H, Kanayama K, Akiho H, Goto A, Segawa Y, Yao T, Takayanagi R. Impact of double-balloon endoscopy on the diagnosis of jejunoileal involvement in primary intestinal follicular lymphomas: a case series. *Endoscopy* 2009; **41**: 175-178 [PMID: 19214900 DOI: 10.1055/s-0028-1119467]

156 **Hoffmann M**, Chott A, Püspök A, Jäger U, Kletter K, Raderer M. 18F-fluorodeoxyglucose positron emission tomography (18F-FDG-PET) does not visualize follicular lymphoma of the duodenum. *Ann Hematol* 2004; **83**: 276-278 [PMID: 15060746 DOI: 10.1007/s00277-003-0827-6]

157 **Chowdhury M**, Endo M, Chiba T, Kudara N, Oana S, Sato K, Akasaka R, Tomita K, Fujiwara S, Mizutani T, Sugai T, Takikawa Y, Suzuki K. Characterization of follicular lymphoma in the small intestine using double-balloon endoscopy. *Gastroenterol Res Pract* 2009; **2009**: 835258 [PMID: 19901998 DOI: 10.1155/2009/835258]

158 **Wright DH**. Pathology of extra-nodal non Hodgkin lymphomas. *Clin Oncol* (R Coll Radiol) 2012; **24**: 319-328 [PMID: 22480571 DOI: 10.1016/j.clon.2012.02.004]

159 **Matsumoto H**, Haruma K, Akiyama T. An unusual case of multiple small ulcerations throughout the GI tract. *Gastroenterology* 2011; **141**: e11-e12 [PMID: 21959077 DOI: 10.1053/j.gastro.2010.10.054]

160 **Hayashi H**, Onishi Y, Mitsuoka H, Ogura T, Maeda M, Nishigami T, Harada M. Regression of follicular lymphoma of the duodenum following eradication of H. pylori infection. *Intern Med* 2013; **52**: 2611-2614 [PMID: 24292749]

161 **Ruskoné-Fourmestraux A**, Delmer A, Lavergne A, Molina T, Brousse N, Audouin J, Rambaud JC. Multiple lymphomatous polyposis of the gastrointestinal tract: prospective clinicopathologic study of 31 cases. Groupe D'étude des Lymphomes Digestifs. *Gastroenterology* 1997; **112**: 7-16 [PMID: 8978336]

162 **Matsuura M**, Nakase H, Mochizuki N. Ileal polyposis caused by follicular lymphoma. *Clin Gastroenterol Hepatol* 2007; **5**: e30 [PMID: 17625984 DOI: 10.1016/j.cgh.2007.05.005]

163 **Yanai S**, Nakamura S, Takeshita M, Fujita K, Hirahashi M, Kawasaki K, Kurahara K, Sakai Y, Matsumoto T. Translocation t(14; 18)/IGH-BCL2 in gastrointestinal follicular lymphoma: correlation with clinicopathologic features in 48 patients. *Cancer* 2011; **117**: 2467-2477 [PMID: 24048795 DOI: 10.1002/cncr.25811]

164 **Nakase H**, Matsuura M, Mikami S, Chiba T. Magnified endoscopic view of primary follicular lymphoma at the duodenal papilla. *Intern Med* 2007; **46**: 141-142 [PMID: 17268132]

165 **Nakazuru S**, Yoshio T, Suemura S, Iwasaki R, Hasegawa H, Sakakibara Y, Mita E, Ikeda H, Mori K, Mano M. Education and Imaging. Gastrointestinal: Unusual duodenal follicular lymphoma observed by magnifying endoscopy with narrow-band imaging. *J Gastroenterol Hepatol* 2013; **28**: 1255 [PMID: 23875635 DOI: 10.1111/jgh.12297]

166 **Iwamuro M**, Kawai Y, Takata K, Kawano S, Yoshino T, Okada H, Yamamoto K. Primary intestinal follicular lymphoma: How to identify follicular lymphoma by routine endoscopy. *World J Gastrointest Endosc* 2013; **5**: 34-38 [PMID: 23330052 DOI: 10.4253/wjge.v5.i1.34]

167 **Iwamuro M**, Okuda M, Yumoto E, Suzuki S, Shirakawa A, Takata K, Yoshino T, Okada H, Yamamoto K. Magnifying endoscopy for intestinal follicular lymphoma is helpful for prompt diagnosis. *Gut Liver* 2013; **7**: 258-261 [PMID: 23560166 DOI: 10.5009/gnl.2013.7.2.258]

168 **Inoue N**, Isomoto H, Shikuwa S, Mizuta Y, Hayashi T, Kohno S. Magnifying endoscopic observation of primary follicular lymphoma of the duodenum by using the narrow-band imaging system. *Gastrointest Endosc* 2009; **69**: 158-159; discussion 159 [PMID: 19111697 DOI: 10.1016/j.gie.2008.06.055]

169 **Norimura D**, Isomoto H, Imaizumi Y, Akazawa Y, Matsushima K, Inoue N, Yamaguchi N, Ohnita K, Shikuwa S, Arima T, Hayashi T, Takeshima F, Miyazaki Y, Nakao K. Case series of duodenal follicular lymphoma, observed by magnified endoscopy with narrow-band imaging. *Gastrointest Endosc* 2011; **74**: 428-434 [PMID: 21620398 DOI: 10.1016/j.gie.2011.03.1237]

170 **Higuchi K**, Komatsu K, Wakamatsu H, Kawasaki H, Murata M, Miyazaki K, Oikawa K, Ohwada M, Nanjo H, Otaka M, Watanabe S, Komatsu K. Small intestinal follicular lymphoma with multiple tumor formations diagnosed by double-balloon enteroscopy. *Intern Med* 2007; **46**: 705-709 [PMID: 17541220]

171 **Akamatsu T**, Kaneko Y, Ota H, Miyabayashi H, Arakura N, Tanaka E. Usefulness of double balloon enteroscopy and video capsule endoscopy for the diagnosis and management of primary follicular lymphoma of the gastrointestinal tract in its early stages. *Dig Endosc* 2010; **22**: 33-38 [PMID: 20078662 DOI: 10.1111/j.1443-1661.2009.00915.x]

172 **Nakamura M**, Ohmiya N, Hirooka Y, Miyahara R, Ando T, Watanabe O, Itoh A, Kawashima H, Ohno E, Kinoshita T. Endoscopic diagnosis of follicular lymphoma with small-bowel involvement using video capsule endoscopy and double-balloon endoscopy: a case series. *Endoscopy* 2013; **45**: 67-70

173 **Schmatz AI**, Streubel B, Kretschmer-Chott E, Püspök A, Jäger U, Mannhalter C, Tiemann M, Ott G, Fischbach W, Herzog P, Seitz G, Stolte M, Raderer M, Chott A. Primary follicular lymphoma of the duodenum is a distinct mucosal/submucosal variant of follicular lymphoma: a retrospective study of 63 cases. *J Clin Oncol* 2011; **29**: 1445-1451 [PMID: 21383289 DOI: 10.1200/JCO.2010.32.9193]

174 **Sagaert X**, Tousseyn T, Yantiss RK. Gastrointestinal B-cell lymphomas: From understanding B-cell physiology to classification and molecular pathology. *World J Gastrointest Oncol* 2012; **4**: 238-249 [PMID: 23443141 DOI: 10.4251/wjgo.v4.i12.238]

175 **Miyata-Takata T**, Takata K, Sato Y, Taniguchi K, Takahashi Y, Ohara N, Yoshino T. A case of diffuse large B-cell lymphoma transformed from primary duodenal follicular lymphoma. *Pathol Int* 2014; **64**: 527-532 [PMID: 25186289 DOI: 10.1111/pin.12197]

176 **Hawkes EA**, Wotherspoon A, Cunningham D. Diagnosis and management of rare gastrointestinal lymphomas. *Leuk Lymphoma* 2012; **53**: 2341-2350 [PMID: 22616672 DOI: 10.3109/10428194.2012.695780]

177 **Watanabe T**. Treatment strategies for nodal and gastrointestinal follicular lymphoma: current status and future development. *World J Gastroenterol* 2010; **16**: 5543-5554 [PMID: 21105187]

178 **Damaj G**, Verkarre V, Delmer A, Solal-Celigny P, Yakoub-Agha I, Cellier C, Maurschhauser F, Bouabdallah R, Leblond V, Lefrère F, Bouscary D, Audouin J, Coiffier B, Varet B, Molina T, Brousse N, Hermine O. Primary follicular lymphoma of the gastrointestinal tract: a study of 25 cases and a literature review. *Ann Oncol* 2003; **14**: 623-629 [PMID: 12649111]

179 **Huang WT**, Hsu YH, Yang SF, Chuang SS. Primary gastrointestinal follicular lymphoma: a clinicopathologic study of 13 cases from Taiwan. *J Clin Gastroenterol* 2008; **42**: 997-1002 [PMID: 18719510 DOI: 10.1097/MCG.0b013e3180f62b12]

180 **Mori M**, Kobayashi Y, Maeshima AM, Gotoda T, Oda I, Kagami Y, Bennett S, Nomoto J, Azuma T, Yokoyama H, Maruyama D, Kim SW, Watanabe T, Matsuno Y, Tobinai K. The indolent course and high incidence of t(14; 18) in primary duodenal follicular lymphoma. *Ann Oncol* 2010; **21**: 1500-1505 [PMID: 20022910 DOI: 10.1093/annonc/mdp557]

181 **Rondonotti E**, Pennazio M, Toth E, Menchen P, Riccioni ME, De Palma GD, Scotto F, De Looze D, Pachofsky T, Tacheci I, Havelund T, Couto G, Trifan A, Kofokotsios A, Cannizzaro R, Perez-Quadrado E, de Franchis R. Small-bowel neoplasms in patients undergoing video capsule endoscopy: a multicenter European study. *Endoscopy* 2008; **40**: 488-495 [PMID: 18464193 DOI: 10.1055/s-2007-995783]

182 **Iwamuro M**, Okada H, Takata K, Nose S, Miyatani K, Yoshino T, Yamamoto K. Diagnostic accuracy of endoscopic biopsies for the diagnosis of gastrointestinal follicular lymphoma: a clinicopathologic study of 48 patients. *Ann Diagn Pathol* 2014; **18**: 99-103 [PMID: 24513028 DOI: 10.1016/j.anndiagpath.2013]

183 **Nolan KD**, Mone MC, Nelson EW. Plasma cell neoplasms. Review

of disease progression and report of a new variant. *Surg Oncol* 2005; **14**: 85-90 [PMID: 15993050 DOI: 10.1016/j.suronc.2005.05.001]

184 **Hu K**, Yahalom J. Radiotherapy in the management of plasma cell tumors. *Oncology* (Williston Park) 2000; **14**: 101-108, 111; discussion 101-108, 115 [PMID: 10680152]

185 **Terpos E**, Rezvani K, Basu S, Milne AE, Rose PE, Scott GL, Rahemtulla A, Samson D, Apperley JF. Plasmacytoma relapses in the absence of systemic progression post-high-dose therapy for multiple myeloma. *Eur J Haematol* 2005; **75**: 376-383 [PMID: 16191086 DOI: 10.1111/j.1600-0609.2005.00531.x]

186 **Katodritou E**, Kartsios C, Gastari V, Verrou E, Mihou D, Banti A, Lazaraki G, Lazaridou A, Kaloutsi V, Zervas K. Successful treatment of extramedullary gastric plasmacytoma with the combination of bortezomib and dexamethasone: first reported case. *Leuk Res* 2008; **32**: 339-341 [PMID: 17560647 DOI: 10.1016/j.leukres.2007.04.016]

187 **Carneiro FP**, Sobreira MN, Maia LB, Sartorelli AC, Franceschi LE, Brandão MB, Calaça BW, Lustosa FS, Lopes JV. Extramedullary plasmocytoma associated with a massive deposit of amyloid in the duodenum. *World J Gastroenterol* 2009; **15**: 3565-3568 [PMID: 19630116]

188 **Park CH**, Lee SM, Kim TO, Kim DU, Jung WJ, Kim GH, Song GA. Treatment of solitary extramedullary plasmacytoma of the stomach with endoscopic submucosal dissection. *Gut Liver* 2009; **3**: 334-337 [PMID: 20431772 DOI: 10.5009/gnl.2009.3.4.334]

189 **Krishnamoorthy N**, Bal MM, Ramadwar M, Deodhar K, Mohandas KM. A rare case of primary gastric plasmacytoma: an unforeseen surprise. *J Cancer Res Ther* 2010; **6**: 549-551 [PMID: 21358099 DOI: 10.4103/0973-1482.77067]

190 **Chim CS**, Wong WM, Nicholls J, Chung LP, Liang R. Extramedullary sites of involvement in hematologic malignancies: case 3. Hemorrhagic gastric plasmacytoma as the primary presentation in multiple myeloma. *J Clin Oncol* 2002; **20**: 344-347 [PMID: 11773190]

191 **Matsumoto Y**, Matsumoto T, Nakamura S, Kawasaki A, Aso M, Aoyagi K, Sadoshima S, Onoyama K, Fujishima M. Primary ileal plasmacytoma arising in mixed low- and high-grade B-cell lymphoma of mucosa-associated lymphoid tissue type. *Abdom Imaging* 2000; **25**: 139-141 [PMID: 10675454]

192 **Ammar T**, Kreisel F, Ciorba MA. Primary antral duodenal extramedullary plasmacytoma presenting with melena. *Clin Gastroenterol Hepatol* 2010; **8**: A32 [PMID: 19286477 DOI: 10.1016/j.cgh.2009.03.005]

193 **Kodani T**, Osada T, Terai T, Ohkusa T, Shibuya T, Sakamoto N, Beppu K, Kato J, Nagahara A, Watanabe H, Watanabe S. Successful endoscopic mucosal resection of a solitary extramedullary plasmacytoma in the sigmoid colon. *Endoscopy* 2011; **43** Suppl 2 UCTN: E298-E299 [PMID: 21915836 DOI: 10.1055/s-0030-1256451]

194 **Nakagawa Y**, Nagai T, Okawara H, Nakashima H, Hisamatsu A, Syutou M, Yamauchi M, Kai S, Nakayama T, Yokoyama S, Murakami K, Fujioka T. Minute primary extramedullary plasmacytomas of the large intestine. *Endoscopy* 2011; **43** Suppl 2 UCTN: E105-E106 [PMID: 21424997 DOI: 10.1055/s-0030-1256138]

195 **Tan J**, Lade S, Harrison S, Opat S, Mac Manus MP. Complete remission of localised gastric plasmacytomas following definitive radiotherapy. *J Med Imaging Radiat Oncol* 2012; **56**: 328-331 [PMID: 22697332 DOI: 10.1111/j.1754-9485.2012.02369.x]

196 **Lopes da Silva R**. Extramedullary plasmacytoma of the small intestine: clinical features, diagnosis and treatment. *J Dig Dis* 2012; **13**: 10-18 [PMID: 22188911 DOI: 10.1111/j.1751-2980.2011.00544.x]

197 **Lattuneddu A**, Farneti F, Lucci E, Garcea D, Ronconi S, Saragoni L. A case of primary extramedullary plasmacytoma of the colon. *Int J Colorectal Dis* 2004; **19**: 289-291 [PMID: 14689207 DOI: 10.1007/s00384-003-0560-6]

198 **Doki T**, Takeuchi O, Kaiho T, Tsuchiya S, Matsuzaki O, Miyazaki M. Primary isolated extramedullary plasmacytoma of the colon. *Int J Colorectal Dis* 2008; **23**: 719-720 [PMID: 18239923 DOI: 10.1007/s00384-008-0439-7]

199 **Makis W**, Ciarallo A, Hickeson M, Lisbona R. Gastric recurrence of a primary colon plasmacytoma: staging and evaluating response to therapy with 18F-FDG PET/CT. *Br J Radiol* 2012; **85**: e4-e9 [PMID: 22190759 DOI: 10.1259/bjr/37953406]

200 **Pacheco DC**, de Solórzano MM, Lázaro EQ, Alvarez CI, Torre LR. Extramedullary plasmacytoma of the colon: a rare cause of gastrointestinal bleeding. *Endoscopy* 2009; **41** Suppl 2: E306-E307 [PMID: 19921603 DOI: 10.1055/s-0029-1215225]

201 **Hashiguchi K**, Iwai A, Inoue T, Okudaira K, Miyazaki J, Matsuzaki K, Tsuzuki Y, Kawaguchi A, Nagao S, Itoh K, Sato K, Miura S. Extramedullary plasmacytoma of the rectum arising in ulcerative colitis: case report and review. *Gastrointest Endosc* 2004; **59**: 304-307 [PMID: 14745413]

202 **Yaita H**, Nakamura S, Kurahara K, Nagasue T, Kochi S, Oshiro Y, Ohshima K, Ikeda Y, Fuchigami T. Primary small-bowel adult T-cell leukemia/lymphoma with gastric AL amyloidosis. *Endoscopy* 2014; **46** Suppl 1 UCTN: E613-E614 [PMID: 25502266 DOI: 10.1055/s-0034-1390757]

203 **Hokama A**, Kishimoto K, Nakamoto M, Kobashigawa C, Hirata T, Kinjo N, Kinjo F, Kato S, Fujita J. Endoscopic and histopathological features of gastrointestinal amyloidosis. *World J Gastrointest Endosc* 2011; **3**: 157-161 [PMID: 21954412 DOI: 10.4253/wjge.v3.i8.157]

204 **Chang SS**, Lu CL, Tsay SH, Chang FY, Lee SD. Amyloidosis-induced gastrointestinal bleeding in a patient with multiple myeloma. *J Clin Gastroenterol* 2001; **32**: 161-163 [PMID: 11205655]

205 **Sattianayagam PT**, Hawkins PN, Gillmore JD. Systemic amyloidosis and the gastrointestinal tract. *Nat Rev Gastroenterol Hepatol* 2009; **6**: 608-617 [PMID: 19724253 DOI: 10.1038/nrgastro.2009.147]

206 **Heise W**. GI-lymphomas in immunosuppressed patients (organ transplantation; HIV). *Best Pract Res Clin Gastroenterol* 2010; **24**: 57-69 [PMID: 20206109 DOI: 10.1016/j.bpg.2010.01.001]

207 **Delia M**, Liso V, Capalbo S, Napoli A, Ricco R, Semenzato G, Liso A. Common variable immunodeficiency patient with large granular lymphocytosis developing extranodal diffuse large B-cell lymphoma: a case report. *Haematologica* 2006; **91**: ECR61 [PMID: 17194667]

208 **Castellano G**, Moreno D, Galvao O, Ballestín C, Colina F, Mollejo M, Morillas JD, Solís Herruzo JA. Malignant lymphoma of jejunum with common variable hypogammaglobulinemia and diffuse nodular hyperplasia of the small intestine. A case study and literature review. *J Clin Gastroenterol* 1992; **15**: 128-135 [PMID: 1401824]

209 **Persson EC**, Shiels MS, Dawsey SM, Bhatia K, Anderson LA, Engels EA. Increased risk of stomach and esophageal malignancies in people with AIDS. *Gastroenterology* 2012; **143**: 943-950.e2 [PMID: 22796240 DOI: 10.1053/j.gastro.2012.07.013]

210 **Gao GJ**, Yang D, Lin KK, Xiao J, Li X, Liang HY, Liu L, Han N, Zhao HX. Clinical analysis of 10 AIDS patients with malignant lymphoma. *Cancer Biol Med* 2012; **9**: 115-119 [PMID: 23691465 DOI: 10.3969/j.issn.2095-3941.2012.02.006]

211 **Rezende RE**, Mantelmacher M, Ferreira Sda C, Hyppólito EB, Machado AA, Ardengh JC, Módena JL. Clinical, endoscopic and prognostic aspects of primary gastric non-hodgkin's lymphoma associated with acquired immunodeficiency syndrome. *Braz J Infect Dis* 2009; **13**: 2-4 [PMID: 19578621]

212 **Tanaka S**, Nagata N, Mine S, Igari T, Kobayashi T, Sugihara J, Honda H, Teruya K, Kikuchi Y, Oka S, Uemura N. Endoscopic appearance of AIDS-related gastrointestinal lymphoma with c-MYC rearrangements: case report and literature review. *World J Gastroenterol* 2013; **19**: 4827-4831 [PMID: 23922484 DOI: 10.3748/wjg.v19.i29.4827]

213 **Kim Y**, Leventaki V, Bhaijee F, Jackson CC, Medeiros LJ, Vega F. Extracavitary/solid variant of primary effusion lymphoma. *Ann Diagn Pathol* 2012; **16**: 441-446 [PMID: 22497739 DOI: 10.1016/j.anndiagpath.2012.03.004]

214 **Flanagan PK**, Coupland SE, Arumainathan A, Probert CS. A rare cause of weight loss. *Gut* 2014; **63**: 1024, 1027 [PMID: 24277727 DOI: 10.1136/gutjnl-2013-306299]

215 **Manley K**, Dunning J, Nelson M, Bower M. HIV-associated gastric natural killer/T-cell lymphoma. *Int J STD AIDS* 2012; **23**: 66-67

[PMID: 22362696 DOI: 10.1258/ijsa.2009.009121]
216 **Smith G**, Crocker J, Nar P, Chesner I, Leyland MJ. Immunogold-silver technique applied to showing malignant B cell infiltration of gastrointestinal tract in patients with chronic lymphocytic leukaemia and non-Hodgkin's lymphoma. *J Clin Pathol* 1987; **40**: 756-759 [PMID: 3114328]
217 **Palakodeti S**, Hoda K, Munroe CA. Perirectal Burkitt lymphoma presenting as an uncommon cause of lower gastrointestinal bleeding. *Clin Gastroenterol Hepatol* 2014; **12**: A23-A24 [PMID: 24135467 DOI: 10.1016/j.cgh.2013.10.006]
218 **Takahashi T**, Maruyama R, Mishima S, Inoue M, Kawakami K, Onishi C, Miyake T, Tanaka J, Nabika T, Ishikura H. Small bowel perforation caused by Epstein-Barr virus-associated B cell lymphoma in a patient with angioimmunoblastic T-cell lymphoma. *J Clin Exp Hematop* 2010; **50**: 59-63 [PMID: 20505277]
219 **Ghobrial IM**, Habermann TM, Maurer MJ, Geyer SM, Ristow KM, Larson TS, Walker RC, Ansell SM, Macon WR, Gores GG, Stegall MD, McGregor CG. Prognostic analysis for survival in adult solid organ transplant recipients with post-transplantation lymphoproliferative disorders. *J Clin Oncol* 2005; **23**: 7574-7582 [PMID: 16186599 DOI: 10.1200/JCO.2005.01.0934]
220 **Shroff R**, Rees L. The post-transplant lymphoproliferative disorder-a literature review. *Pediatr Nephrol* 2004; **19**: 369-377 [PMID: 14986084 DOI: 10.1007/s00467-003-1392-x]
221 **Knight JS**, Tsodikov A, Cibrik DM, Ross CW, Kaminski MS, Blayney DW. Lymphoma after solid organ transplantation: risk, response to therapy, and survival at a transplantation center. *J Clin Oncol* 2009; **27**: 3354-3362 [PMID: 19451438 DOI: 10.1200/jco.2008.20.0857]
222 **Haverkos BM**, Oza VM, Johnson A, Walker J, Shana'ah A. Rare presentation of post-transplant lymphoproliferative disorder isolated to gastroesophageal junction. *World J Gastrointest Oncol* 2013; **5**: 230-234 [PMID: 24363831 DOI: 10.4251/wjgo.v5.i12.230]
223 **Shitrit D**, Shitrit AB, Dickman R, Sahar G, Saute M, Kramer MR. Gastrointestinal involvement of posttransplant lymphoproliferative disorder in lung transplant recipients: report of a case. *Dis Colon Rectum* 2005; **48**: 2144-2147 [PMID: 16086224 DOI: 10.1007/s10350-005-0116-7]
224 **Lauro A**, Di Simone M, Zanfi C, Pironi L, D'Errico A, Pinna AD. Operative endoscopy for treatment of native rectal post-transplantation lymphoproliferative disease after adult small bowel transplantation: a case report. *Transplant Proc* 2013; **45**: 3442-3443 [PMID: 24182833 DOI: 10.1016/j.transproceed.2013.07.066]
225 **Sharma S**, Gurakar A, Camci C, Jabbour N. Avoiding pitfalls: what an endoscopist should know in liver transplantation--part II. *Dig Dis Sci* 2009; **54**: 1386-1402 [PMID: 19085103 DOI: 10.1007/s10620-008-0520-7]
226 **Lauro A**, Pinna AD, Pellegrini S, Bagni A, Zanfi C, Dazzi A, Pironi L, Di Simone MP. Long-term endoscopic follow-up in small bowel transplant recipients: single-center series. *Transplant Proc* 2014; **46**: 2325-2328 [PMID: 25242780 DOI: 10.1016/j.transproceed.2014.07.025]
227 **Wang HW**, Yang W, Sun JZ, Lu JY, Li M, Sun L. Plasmablastic lymphoma of the small intestine: case report and literature review. *World J Gastroenterol* 2012; **18**: 6677-6681 [PMID: 23236245 DOI: 10.3748/wjg.v18.i45.6677]
228 **Tavora F**, Gonzalez-Cuyar LF, Sun CC, Burke A, Zhao XF. Extra-oral plasmablastic lymphoma: report of a case and review of literature. *Hum Pathol* 2006; **37**: 1233-1236 [PMID: 16938530 DOI: 10.1016/j.humpath.2006.04.009]
229 **Chapman-Fredricks J**, Montague N, Akunyili I, Ikpatt O. Extraoral plasmablastic lymphoma with intravascular component and MYC translocation. *Ann Diagn Pathol* 2012; **16**: 48-53 [PMID: 21239197 DOI: 10.1016/j.anndiagpath.2010.11.002]
230 **Pruneri G**, Graziadei G, Ermellino L, Baldini L, Neri A, Buffa R. Plasmablastic lymphoma of the stomach. A case report. *Haematologica* 1998; **83**: 87-89 [PMID: 9542326]
231 **Colomo L**, Loong F, Rives S, Pittaluga S, Martínez A, López-Guillermo A, Ojanguren J, Romagosa V, Jaffe ES, Campo E. Diffuse large B-cell lymphomas with plasmablastic differentiation represent a heterogeneous group of disease entities. *Am J Surg Pathol* 2004; **28**: 736-747 [PMID: 15166665]
232 **Dong HY**, Scadden DT, de Leval L, Tang Z, Isaacson PG, Harris NL. Plasmablastic lymphoma in HIV-positive patients: an aggressive Epstein-Barr virus-associated extramedullary plasmacytic neoplasm. *Am J Surg Pathol* 2005; **29**: 1633-1641 [PMID: 16327436]
233 **Taddesse-Heath L**, Meloni-Ehrig A, Scheerle J, Kelly JC, Jaffe ES. Plasmablastic lymphoma with MYC translocation: evidence for a common pathway in the generation of plasmablastic features. *Mod Pathol* 2010; **23**: 991-999 [PMID: 20348882 DOI: 10.1038/modpathol.2010.72]
234 **Brahmania M**, Sylwesterowic T, Leitch H. Plasmablastic lymphoma in the ano-rectal junction presenting in an immunocompetent man: a case report. *J Med Case Rep* 2011; **5**: 168 [PMID: 21539737 DOI: 10.1186/1752-1947-5-168]
235 **Mihaljevic BS**, Todorovic MR, Andjelic BM, Antic DA, Perunicic Jovanovic MD. Unusual presentation of gastric plasmablastic lymphoma in HIV-negative patient. *Med Oncol* 2012; **29**: 1186-1189 [PMID: 21476144 DOI: 10.1007/s12032-011-9930-z]
236 **Hashimoto M**, Inaguma S, Kasai K, Kuwabara K, Noda N, Hayakawa M, Fujino M, Ito M, Ikeda H. Plasmablastic lymphoma of the stomach in an HIV-negative patient. *Pathol Int* 2012; **62**: 763-770 [PMID: 23121609 DOI: 10.1111/pin.12005]
237 **Luria L**, Nguyen J, Zhou J, Jaglal M, Sokol L, Messina JL, Coppola D, Zhang L. Manifestations of gastrointestinal plasmablastic lymphoma: a case series with literature review. *World J Gastroenterol* 2014; **20**: 11894-11903 [PMID: 25206297 DOI: 10.3748/wjg.v20.i33.11894]
238 **Kappelman MD**, Farkas DK, Long MD, Erichsen R, Sandler RS, Sørensen HT, Baron JA. Risk of cancer in patients with inflammatory bowel diseases: a nationwide population-based cohort study with 30 years of follow-up evaluation. *Clin Gastroenterol Hepatol* 2014; **12**: 265-73.e1 [PMID: 23602821 DOI: 10.1016/j.cgh.2013.03.034]
239 **Askling J**, Brandt L, Lapidus A, Karlén P, Björkholm M, Löfberg R, Ekbom A. Risk of haematopoietic cancer in patients with inflammatory bowel disease. *Gut* 2005; **54**: 617-622 [PMID: 15831904 DOI: 10.1136/gut.2004.051771]
240 **Mackey AC**, Green L, Liang LC, Dinndorf P, Avigan M. Hepatosplenic T cell lymphoma associated with infliximab use in young patients treated for inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2007; **44**: 265-267 [PMID: 17255842 DOI: 10.1097/MPG.0b013e31802f6424]
241 **Siegel CA**, Marden SM, Persing SM, Larson RJ, Sands BE. Risk of lymphoma associated with combination anti-tumor necrosis factor and immunomodulator therapy for the treatment of Crohn's disease: a meta-analysis. *Clin Gastroenterol Hepatol* 2009; **7**: 874-881 [PMID: 19558997 DOI: 10.1016/j.cgh.2009.01.004]
242 **Venizelos I**, Tamiolakis D, Bolioti S, Nikolaidou S, Lambropoulou M, Alexiadis G, Manavis J, Papadopoulos N. Primary gastric Hodgkin's lymphoma: a case report and review of the literature. *Leuk Lymphoma* 2005; **46**: 147-150 [PMID: 15621794 DOI: 10.1080/10428190400012037]
243 **Sharma S**, Rana S, Kapur S, Jairajpuri ZS. Primary Intestinal Hodgkin's Lymphoma: An Uncommon Presentation. *J Lab Physicians* 2013; **5**: 124-126 [PMID: 24701107 DOI: 10.4103/0974-2727.119866]
244 **Kashi MR**, Belayev L, Parker A. Primary extranodal Hodgkin lymphoma of the colon masquerading as new diagnosis of Crohn's disease. *Clin Gastroenterol Hepatol* 2010; **8**: A20 [PMID: 20601139 DOI: 10.1016/j.cgh.2010.06.007]
245 **Hossain FS**, Koak Y, Khan FH. Primary gastric Hodgkin's lymphoma. *World J Surg Oncol* 2007; **5**: 119 [PMID: 17949508 DOI: 10.1186/1477-7819-5-119]
246 **Ghimire P**, Wu GY, Zhu L. Primary gastrointestinal lymphoma. *World J Gastroenterol* 2011; **17**: 697-707 [PMID: 21390139 DOI: 10.3748/wjg.v17.i6.697]
247 **da Costa AA**, Flora AC, Stroher M, Soares FA, de Lima VC. Primary Hodgkin's lymphoma of the rectum: an unusual presentation. *J Clin Oncol* 2011; **29**: e268-e270 [PMID: 21220602 DOI: 10.1200/JCO.2010.32.2073]

248 **Gupta D**, Sharma A, Dwary A, Kark AK. Hodgkin lymphoma involving ascending colon and mesenteric lymphnodes: A rare entity. *Indian J Cancer* 2009; **46**: 175-176 [PMID: 19346657]
249 **Romano A**, Vetro C, Caocci G, Greco M, Parrinello NL, Di Raimondo F, La Nasa G. Immunological deregulation in classic hodgkin lymphoma. *Mediterr J Hematol Infect Dis* 2014; **6**: e2014039 [PMID: 24959336 DOI: 10.4084/MJHID.2014.039]
250 **Bautista-Quach MA**, Ake CD, Chen M, Wang J. Gastrointestinal lymphomas: Morphology, immunophenotype and molecular features. *J Gastrointest Oncol* 2012; **3**: 209-225 [PMID: 22943012 DOI: 10.3978/j.issn.2078-6891.2012.024]
251 **Vadmal MS**, LaValle GP, DeYoung BR, Frankel WL, Marsh WL. Primary localized extranodal hodgkin disease of the transverse colon. *Arch Pathol Lab Med* 2000; **124**: 1824-1827 [PMID: 11100066 DOI: 10.1043/0003-9985(2000)124<1824]
252 **Dojcinov SD**, Venkataraman G, Raffeld M, Pittaluga S, Jaffe ES. EBV positive mucocutaneous ulcer--a study of 26 cases associated with various sources of immunosuppression. *Am J Surg Pathol* 2010; **34**: 405-417 [PMID: 20154586 DOI: 10.1097/PAS.0b013e3181cf8622]

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REVIEW

Duodenal adenoma surveillance in patients with familial adenomatous polyposis

Fábio Guilherme Campos, Marianny Sulbaran, Adriana Vaz Safatle-Ribeiro, Carlos Augusto Real Martinez

Fábio Guilherme Campos, Adriana Vaz Safatle-Ribeiro, Gastroenterology Department, Hospital das Clínicas, University of São Paulo Medical School, São Paulo, PC 01411-000, Brazil

Marianny Sulbaran, Gastroenterology Department, University of São Paulo Medical School, São Paulo, PC 01411-000, Brazil

Carlos Augusto Real Martinez, Colorectal Division, State University of Campinas (UNICAMP, São Paulo), Postgraduate Program in Health Sciences at San Francisco University, Bragança Paulista, PC 12916-350, Brazil

Author contributions: Campos FG performed research and wrote the paper; Martinez CAR also performed research and wrote the paper; Sulbaran M and Safatle-Ribeiro AV contributed with photo documentation and endoscopic examinations.

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Correspondence to: Carlos Augusto Real Martinez, MD, PhD, Colorectal Division, State University of Campinas (UNICAMP, São Paulo), Postgraduate Program in Health Sciences at San Francisco University, Av. São Francisco de Assis, 218, Bragança Paulista, PC 12916-350,
Brazil. caomartinez@uol.com.br
Telephone: +55-11-44389203
Fax: +55-11-44389203

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Abstract

Familial adenomatous polyposis (FAP) is a hereditary disorder caused by Adenomatous Polyposis Gene mutations that lead to the development of colorectal polyps with great malignant risk throughout life. Moreover, numerous extracolonic manifestations incorporate different clinical features to produce varied individual phenotypes. Among them, the occurrence of duodenal adenomatous polyps is considered an almost inevitable event, and their incidence rates increase as a patient's age advances. Although the majority of patients exhibit different grades of duodenal adenomatosis as they age, only a small proportion (1%-5%) of patients will ultimately develop duodenal carcinoma. Within this context, the aim of the present study was to review the data regarding the epidemiology, classification, genetic features, endoscopic features, carcinogenesis, surveillance and management of duodenal polyps in patients with FAP.

Key words: Familial adenomatous polyposis; Adenoma; Duodenum; Surveillance; Endoscopy; Digestive system

Core tip: The development of duodenal adenomas is considered a very common and important extracolonic manifestation in patients with familial adenomatous polyposis. Results from recently published studies have indicated the need for life-long surveillance of patients presenting with this condition due to a risk of malignization, especially in patients with severe adenomatosis. The present study discusses the incidence, endoscopic features and management of duodenal adenomas and reviews the published data regarding cancer prevention and surveillance.

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INTRODUCTION

Familial adenomatous polyposis (FAP) is an inherited autosomal dominant syndrome that is caused by germline mutations in one copy of the adenomatous polyposis coli (*APC*) gene. These mutations lead to the development of a variable number of colorectal polyps during the second and third decade of life[1,2]. *APC* is a tumor suppressor gene that is located on the long arm of chromosome 5 (5q21-22) and is composed of 15 exons. Exons 1-14 are small compared to the large exon 15, which has 6571 base pairs and accounts for over 70% of the coding portion of the gene[3,4].

As the disease is associated with an almost 100% risk of developing colorectal cancer (CRC) in untreated patients, prophylactic colectomy is considered the cornerstone of FAP management[1,5]. Performing a proctocolectomy before a patient reaches adulthood is associated with a substantial reduction in the incidence of CRC and a better prognosis. Consequently, the extracolonic manifestations (ECM) of the disease have been reported to lead to a relative increase in death[6]. Survival effects associated with screening and prophylactic surgery, life expectancy remains lower than that observed in the general population[7,8].

The majority of ECM have little clinical significance, but some of them may cause serious complications and even lead to death[9-11]. The majority of FAP patients (over 70%) present with some level of ECM during the course of the disease, such as cutaneous lesions (lipomas, fibromas, sebaceous and epidermoid cysts), desmoids tumors, osteomas, dental abnormalities, congenital hypertrophy of retinal pigment epithelium lesions (CHRPE) or upper-gastrointestinal polyps[1]. Moreover, patients with PAF are also at an increased risk for several malignancies, including hepatoblastoma, pancreatic, thyroid, biliary-tree, brain and duodenal cancers[12].

Gastric fundic gland polyps, gastric adenomas, duodenal adenomas and carcinoma represent the most common upper digestive lesions that are diagnosed in FAP patients (Figure 1)[13,14]. As they are an important potential cause of morbidity in FAP patients, duodenal polyps require diagnosis, follow-up and preventive measures to avoid carcinogenesis. Thus, the aim of the present study was to review the data regarding the epidemiology, classification, genetic features, endoscopic features, carcinogenesis, surveillance and management of duodenal polyps in patients with FAP.

CHARACTERIZATION OF DUODENAL POLYPS IN FAP

Historical aspects

After the colon and rectum, the duodenum is the second most common site of polyp development in patients with FAP[12-14]. The existence of gastric and duodenal polyps in these patients was established more than a century ago, and Cabot described the first case of duodenal cancer in 1935[12-17]. In a different study, it was found that a considerable number of stomach and duodenum polyps develop at an early age in the majority of pediatric patients, which led to the recommendation of periodic screening of the upper gastrointestinal in the 1960s[18]. The malignant potential of duodenal lesions was gradually established over the next decade, primarily following the introduction of flexible endoscopes during the 1970s[18-21]. During the 1970s and 1980s, numerous additional studies described high numbers of gastroduodenal polyps being identified during endoscopic screenings, providing definitive support for the inclusion of upper digestive endoscopy during routine evaluation and surveillance of FAP patients[22,23].

Epidemiology

Duodenal adenomas tend to occur approximately 15 years after the appearance of colonic adenomas[20,21,24]. Duodenal adenomas have been found in 30%-92% of FAP patients, with a lifetime risk approaching 100%[7,14,22-24]. The frequency of detecting duodenal adenomas in FAP patients may vary depending on endoscopic technique and the method of tissue sampling[7,23-27]. Employing side-viewing endoscopes and random biopsies, exceptional detection rates of 70% and above may be achieved for duodenal and periampullary adenomas[22,26,28]. Biopsies of periampullary regions and duodenal papilla revealed numerous microadenomas that were not detected in normal duodenal mucosa[22,26,27].

Polyp distribution and histology

The macroscopic appearance of duodenal adenomas in patients with FAP varies widely[21,29-31]. These lesions are usually white, numerous and sessile flat. Due to their small size, they may easily be missed or even entirely overlooked during upper endoscopy. With the aid of chromoscopic techniques, such as sprinkling indigo-carmine or methylene blue over the mucosa, the number of detected polyps may increase considerably. In any given patient, using such techniques can identify anywhere from no visible microadenomas to the existence of over 100 microadenomas of varying diameters (1-10 mm)[7,21,22]. The use of side-viewing endoscopes may eventually enable the detection of a prominent papilla of Vater within a solitary adenoma (Figure 2).

The distribution pattern throughout the duodenum

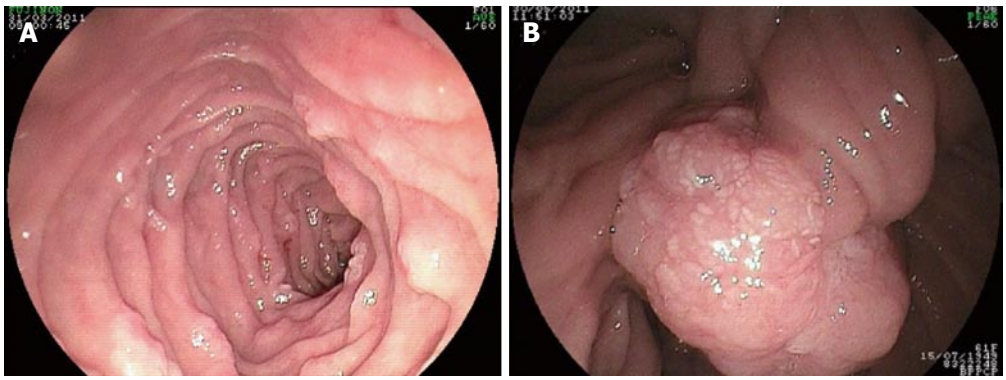

Figure 1 Endoscopic view showing a stage II disease (10-20 small duodenal adenomas with tubular histology) in A, and a large papilla lesion which biopsy revealed a well-moderated carcinoma in B.

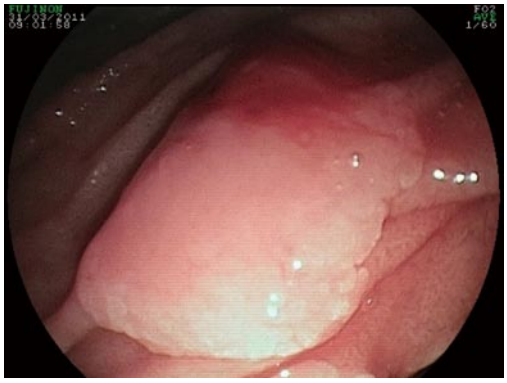

Figure 2 Detection of a prominent papilla of Vater with a solitary adenoma with the help of a side-viewing endoscope.

and the upper part of the small bowel reveals that the majority of polyps are found in clusters around and mainly distal to the ampulla of Vater (second and third part of the duodenum)[32,33].

In 1989, Spigelman *et al*[22] proposed a five-stage classification (0-IV) system to evaluate polyp severity that has become widely adopted. Classification is based on points that are accumulated according to the number, size, histology and dysplasia of polyps. Following this, disease stages are categorized as mild (I), moderate (II), or severe (III and IV) (Table 1).

Previous reports have indicated that approximately 70%-80% of FAP patients have stage II or III duodenal disease and 20%-30% have stage I or IV disease[22,33] (Figure 3). In a retrospective Swedish study that evaluated 180 patients with FAP, 134 (74%) of the patients exhibited duodenal adenomas, of which only 14 (7.8%) were classified as stage IV periampullary adenomas. The authors estimated a time course of 7.1 (range: 5.3-9.8) years for the development of stage IV periampullary adenomas from normal duodenum. Periampullary adenocarcinomas were diagnosed in 5 (2.7%) patients, of whom 3 had a previous diagnosis of stage IV disease based on endoscopic screening and 2 had less severe periampullary adenomatosis[34].

In an interesting, large multicentric study that analyzed 368 upper endoscopies, Bülow *et al*[14] detected duodenal polyps in 228 (61.9%) patients, with adenomas in 209 (91%) and normal mucosa in 19 (9%). Moreover, random duodenal biopsies revealed adenomatous tissue in 28 patients who did not have visible polyps at endoscopy. Based on Spigelman classification, 34%, 15%, 27%, 17% and 7% of patients had stage I, II, III, IV and V disease, respectively. Two of the patients in this series presented with duodenal carcinoma during screening. The estimated cumulative lifetime risks were 88% for duodenal adenomatosis and 35% for stage IV disease. The authors also measured a cumulative cancer incidence of 18% at 75 years of age. Groves *et al*[33] followed 99 patients over a course of 10 years and reported a progression in the incidence of stage IV disease from 9.6% to 14% in patients with a mean age of 42 years. These prospective studies showed that adenomas progress slowly in the duodenum and that adenomatosis is usually diagnosed at a premalignant stage.

In addition to the above, it must be emphasized that although Spigelman classification correlates well with duodenal cancer risk, it focuses primarily on non-ampullary duodenal disease. Therefore, a separate evaluation of ampullary disease is required to establish an accurate individual risk assessment[35].

Duodenal carcinogenesis and cancer risk

The distribution of adenomas within the duodenum probably reflects the exposure of duodenal mucosa to bile acids, suggesting a role for these compounds in duodenal carcinogenesis[22]. Duodenal cancer is one of the two leading causes of death (the other being desmoid tumors) in patients with FAP after they receive prophylactic colectomy[10,12]. When compared to the general population (in whom duodenal carcinoma is rare), the relative risks of developing duodenal adenocarcinoma and ampullary carcinoma were respectively 331 and 124 times higher in FAP patients[36]. Similarly, another study estimated these risks as being 100- to 330-fold higher[27]. The absolute lifetime risk was estimated to be approximately 3%-5%[32-35].

In contrast to colorectal polyps, duodenal polyps

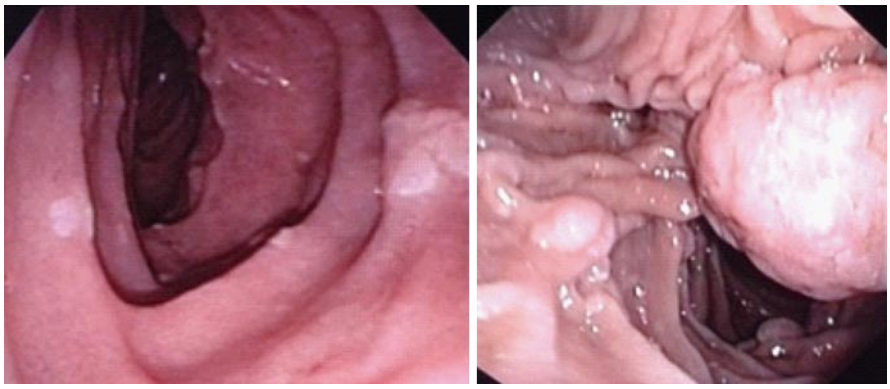

Figure 3 Endoscopic aspect of a stage Ⅰ patient exhibiting 3 adenomatous-tubular polyps with low-grade dysplasia (left); on the right, one may observe a 6 mm tubulo-villous polyp with severe dysplasia, along with other smaller adenomas diagnosed in another patient (stage Ⅳ disease).

do not inevitably transform into cancer[14]. Dysplastic duodenal polyps in FAP patients generally occur 10-20 years after the development of colorectal polyps, and the risk of malignant transformation ranges from 1% to 5%[14,33,37,38].

Stage Ⅳ patients have the greatest risk of developing duodenal cancer, with rates of 7%-36% having been described in 7.6- to 10-year follow-up periods[14,33]. Alternatively, this risk is low (0.7%) among stage 0 to stage Ⅲ patients[12] . Mortality rates from duodenal cancer vary from 1.7% to 8.2%[10,39-43].

Genotype-phenotype correlation

Several genotype-phenotype correlations have been described for colonic polyposis and ECM in FAP patients, including those related to CHRPE and desmoids[44-46]. Aside from the identification of genetic hot spots that are associated with the severity of duodenal adenomatosis, a genotype-phenotype correlation for the disease has not been well defined[12,47].

In a study conducted by Friedl *et al*[48], no correlation was detected between the locations of mutations and the severity of duodenal polyposis. Conversely, Soravia *et al*[49] described severe duodenal polyposis in patients with 5′ mutations. Additional reports have suggested that mutations in the central part of the APC gene and in exon 15 (particularly distal to codon 1400) may predispose an individual to a severe duodenal phenotype[50].

SURVEILLANCE AND MANAGEMENT

Why is surveillance necessary?

In patients with FAP, small bowel polyps are predominantly found in the duodenum and ampulla, although they may also develop in ileostomies and ileal pouches[51]. Within the duodenum, the cumulative incidence of polyp development increases with age (65% at 38 years and 90%-95% by 70 years)[14].

Recognition of the problem is essential toward establishing recommendations for surveillance of the upper gastrointestinal tract. The risk of malignancy increases with size, location (ampullary) and adenomatosis severity[35,52]. Thus, between the existence of an almost 100% lifetime risk of developing duodenal adenomatosis and the cumulative incidence rates of Spigelman stage Ⅳ disease and carcinoma (4% to 10%), there is a clear need for careful follow-up and surveillance of this population[14,52-54].

Improving prognosis through early detection of neoplastic changes is the basis for endoscopic surveillance, and decision analysis has shown that surveillance increases life expectancy by seven months[40]. Moreover, a surveillance program that was based on endoscopic/histological findings and associated with early diagnosis and resection of cancer was shown to improve the prognosis of selected patients[55].

How much and how often?

Adequate evaluation of the duodenum can be obtained with the use of frontal and side viewing (lateral) endoscopes, which facilitate evaluation of the Vater Papilla. Additionally, indigo carmine chromoendoscopy and electronic imaging techniques may improve the efficacy of detecting lesions. As periampullary carcinomas represent a leading cause of death in FAP patients, biopsies of this region should be performed regardless of whether mucosa appears normal, as approximately 7.6% of patients with normal endoscopic results exhibit adenomatous tissue on random biopsy[10,14,33].

When to begin surveillance of FAP patients is a controversial issue, with some clinicians supporting that surveillance begin when FAP is diagnosed and others proposing that it should not begin until patients reach 25-30 years in age, as a diagnosis of duodenal cancer before age 30 is rare[12,33,56,57]. Post-baseline evaluations should be planned according to Spigelman disease stage. This classification is widely accepted as the best option for stratifying the risk of duodenal cancer[54]. Surveillance is the most advantageous in stage Ⅳ patients, as their risk of duodenal carcinoma ranges from 7%-36% compared to non-stage Ⅳ patients, who have an overall risk of 5%.

Although published recommendations differ, in

Table 1 Spigelman classification for duodenal polyposis in patients with familial adenomatous polyposis

Criterion	Points		
	1	2	3
Polyp number	1-4	5-20	> 20
Polyp size (mm)	1-4	5-10	> 10
Histology	Tubular	Tubulo-villous	Villous
Dysplasia	Mild	Moderate	Severe

Stage 0: 0 points; stage I: 1-4 points; stage II: 5-6 points; stage III: 7-8 points; stage IV: 9-12 points

Table 2 Recommendations for surveillance and management of duodenal polyposis in familial adenomatous polyposis patients[11,12,28]

Spigelman stage	Suggested interval (yr) to next duodenoscopy	Conservative therapy	Surgical treatment
0 (0 points)	4 (maximum 5 yr)	No	No
I (1-4 points)	3 (maximum 5 yr)	No	No
II (5-6 points)	2-3	Chemoprevention with or without endoscopic therapy	No
III (7-8 points)	6-12 (maximum 1-2 yr)	Chemoprevention with or without endoscopic therapy[1]	Acceptable
IV (9-12 ponits)	6-12 (maximum 1-2 yr)	Endoscopic therapy and endoscopic ultrasonography	Duodenectomy with pancreas/ pylorus preservation

[1]Consider endoscopy general anesthesia.

general, early stage patients are advised to undergo endoscopy either every 4-5 years (stages 0-I) or every 3-5 years (stage II)[33,57-60]. In stage II patients, Groves *et al*[33] have suggested that endoscopic therapy include endoscopic mucosal resection (EMR). However, the above intervals may be reduced to 1-3 years for patients with mild polyposis (stage III) or to 6-12 mo for patients with severe polyposis, large adenomas or dysplasia[12,14,58]. It has been suggested that stage III patients undergo EMR to reduce duodenal adenomatosis[33,57]. As one third of stage IV patients may experience malignant transformation if they are not treated, these patients should also undergo endoscopic ultrasonography and computed tomography for staging during initial evaluation[14,61].

For patients with periampullary lesions, a different protocol has been proposed due to the greater associated risks[35,62]. This protocol recommends that patients with ampullary polyposis should be examined annually, irrespective of disease severity in other regions of the duodenum. Progression of the disease may be evaluated with magnetic resonance imaging and/or endoscopic ultrasound.

The majority of large studies have shown that the risk of advanced duodenal adenomatosis (stage IV) increases with age. Bulow *et al*[63] found a 52% cumulative risk at 70 years, which was similar to the 50% risk reported by *Saurin* et al[14] and the 20%-30% risk found by studies conducted in Sweden and Finland[14,34,63,64].

Therefore, endoscopic surveillance programs should be performed according to the following published recommendations (Table 2).

Endoscopic treatment

Ideally, treatment should include complete removal or destruction of adenomas and minimal morbid risk. Endoscopic management may be performed with standard polipectomy and local ablation techniques (thermal ablation, argon plasma coagulation or photodynamic therapy)[12,35]. Endoscopic therapy with argon plasma coagulation and Nd-YAG lasers has been attempted with varying results.

The plaque-like morphology of the majority of duodenal adenomas may pose some technical difficulties in performing endoscopic polipectomy, and new techniques of mucosal elevation/resection and hemostasis using different tools may reduce the risks of bleeding, pancreatitis and perforation. Another possible advantage of endoscopic treatment is the postponement of major operations such as duodenopancreatectomy. Although polipectomy or polyp destruction in stage II and stage III patients may be useful, long-term results have demonstrated adenoma recurrence rates of 50%-100%, and complications are not rare[26,49,65]. Thus, endoscopy generally does not affect disease course and follow-up remains necessary.

In this context, low-risk lesions (small, tubular, low-grade adenomas) should be biopsied and observed. Conversely, high-risk lesions (adenomas greater than 1 cm and those with villous patterns or high-grade dysplasia) may be treated *via* transduodenal resection[61]. Endoscopic or surgical ampullectomy should be used on lesions that have developed in the ampulla of Vater (mainly those with severe dysplasia, Tis or T1), despite the associated morbidity[66].

Patients with large stage III polyps (or stage IV, for which surgical treatment is not appropriate) may be candidates for endoscopic polipectomy. The use of general anesthesia may optimize therapeutic maneuvers by allowing the introduction of front and lateral endoscopes to evaluate the papilla, and third and fourth portions of duodenum. Such a strategy aims to avoid progression to stage IV disease, as this results in a greater risk (1 in 3 patients) of duodenal cancer[33]. The management of stage IV patients with desmoids disease, unfavorable clinical conditions or diffuse involvement of duodenal mucosa remains a significant problem.

Surgical treatment

Surgical management includes local procedures (duodenotomy with polypectomy and/or ampullectomy),

pancreas- and pylorus-sparing duodenectomies, and pancreatico-duodenectomy (Whipple's operation). The specific choice of which procedure to use appears to be related to technical expertise, local features (size and site of polyp) and disease severity. In the final analysis, the morbidity and mortality of these procedures must be weighed against the risk of developing duodenal adenocarcinoma.

Whereas radical resection is the obvious option for patients with carcinomas, a prophylactic operation (pancreas and pylorus sparing duodenectomy) to avoid cancer is also justified in cases of severe adenomatosis (Spigelman Ⅳ) or after a failed attempt at local resection (endoscopic or surgical)[33,67]. Even patients with stage Ⅲ polyposis have been considered for surgery[49,68,69]. However, no randomized studies to help guide surgical selection have been published thus far.

Duodenotomy with local resection may be indicated in selected patients who present with one or two dominant duodenal lesions and in whom endoscopic resection would be considered dangerous. In a recent review on this subject, Brosens *et al*[12] indicated that this approach might be useful for delaying major procedures in young patients. Otherwise, high recurrence rates have been reported after local surgical resection, similarly to what occurs after endoscopic resection. Moreover, patients who have previously undergone prophylactic colectomy and present with desmoids tumors have a significant risk of developing complications from duodenectomy[37,57].

Pancreatico-duodenectomy remains a last resort for advanced duodenal and ampullary adenomatosis, despite the risks of this complex procedure and the possibility of inducing desmoid tumor formation[58].

Pharmacological treatment

Chemoprevention is defined as the use of pharmaceutical drugs, natural agents or dietary supplements to reduce the incidence or delay the onset of diseases, including cancer[70]. In FAP patients, the colorectum, ileal pouch and duodenum represent the most clinically relevant sites of carcinogenesis[71]. Consequently, FAP patients constitute an ideal group for assessing the efficacy of various chemopreventive strategies at delaying polyp progression, postponing prophylactic colectomy and preventing the recurrence of adenoma following colectomy with IRA. These effects have also been evaluated in the upper gastrointestinal tract, particularly in the duodenum[72].

As prophylactic surgical resection of an ampulla and/or duodenum may be accompanied by significant morbidity, duodenal resection is currently reserved for only severe cases of duodenal polyposis or duodenal carcinoma. In this context, chemoprevention should be the strategy employed to control premalignant lesions[72]. Secondary chemoprevention has been attempted with the use of agents such as non-steroidal anti-inflammatory drugs (NSAIDs)[73-75]. The use of the cyclooxygenase (COX) non-selective inhibitor sulindac and of the selective COX-2 inhibitors celecoxib and rofecoxib may be beneficial when duodenal polyposis develops by inducing polyposis regression or stabilization.

Studies using sulindac have revealed the drug to have a statistically significant effect on small (2 mm) duodenal polyps, whereas larger (> 3 mm) polyps were unaffected[76,77]. In a different study, the administration of 300 mg/d of sulindac for 10 mo resulted in a 30% discontinuation rate due to side effects and no regression of polyps; furthermore, three patients developed large polyps and one developed an infiltrating carcinoma while on this drug[78].

In a large randomized trial, the use of celecoxib resulted in a 14%-31% reduction in the regions of the duodenum that were affected by adenomatosis and therefore this drug may be recommended as a therapeutic alternative to patients with moderate adenomatosis[33,79]. However, the promising use of coxibs in chemoprevention must be weighed against their potential cardiovascular and renal side effects[80,81]. In addition to the fact that celecoxib may delay worsening of polyposis, there have not been sufficient long-term results or evidence from controlled studies on cancer protection to routinely recommend these agents during follow-up[14,51,58].

In conclusion, although they may reduce the progression and even lead to regression of small adenomas, the role of NSAIDs and other compounds in duodenal polyposis regression remains unclear, and thus far the results have primarily been ambiguous[12]. The evidence must prove to be reproducible, and potential cardiovascular and renal side effects, in addition to the risk of gastrointestinal bleeding, must be taken into account[24]. Moreover, duodenal adenomas are less likely to degenerate compared to colonic polyps, and they also appear to be less responsive to chemoprevention with NSAIDs[12,82].

To date, no medical therapy has demonstrated long-term effectiveness and safety in the management of duodenal adenomatosis. There has been a single report indicating an apparent disappearance of duodenal polyposis in a patient who was treated with FOLFOX chemotherapy for an ileal pouch adenocarcinoma[83].

As dietary chemoprevention has shown no effective results, a new line of interventions focus on the role of the estrogen receptor (ER) in reducing polyp numbers and sizes, based on the supposed preventive effects of CRC. In an interesting study, Calabrese *et al*[84] evaluated whether dietary supplementation with phytoestrogens, which are selective agonists of the estrogen receptor, was able to prevent the progression of duodenal polyps. They demonstrated that short-term (90 d) supplementation with Eviendep® in FAP patients with recurrent adenomas in the duodenal mucosa resulted in a 32% reduction of polyp numbers and 51% reduction in polyp size.

This study clearly demonstrates that researches with FAP patients will always have a lead role in the testing

of new agents, favoring their own interests and those of non-familial adenomas, a problem with even greater social impact. For the next future, the role of NSAIDs in chemoprevention has gained renewed interest in sporadic adenoma prevention, although the long-term risks associated with its use have always been a source of concern[85,86].

As chemoprevention may eventually avoid surgical resection of at-risk duodenal adenomas, it would desirable to identify patients important to select advanced adenomas that would be candidates. In an interesting research, it was reported that mRNA levels of glutathione S-transferase A1 (28.16% *vs* 38.24%, P = 0.008) and caspase-3 (3.30% *vs* 5.31%, P = 0.001) were significantly lower in patients with FAP *vs* non-FAP patient controls, respectively[87]. This finding points at a lower capacity to detoxify toxins and carcinogens, with subsequent increased susceptibility for malignant degeneration[88]. Previous studies have already found lower GDT enzyme activity in colonic mucosa but no differences in duodenal mucosa when compared to patient controls[89,90]. Other eventual risk factors include the development of small intestinal adenomas and location of APC mutation[91-93].

All of these findings indicate that routine gastroduodenal endoscopy in FAP patients is necessary[94-96]. In this setting of surveillance, both endoscopy and EUS are extremely important to select advanced adenomas that are candidates for endoscopic intervention instead of surgical resection[97,98]. Moreover, although these lesions progress in severity (size and degree of dysplasia), their progression rate to carcinoma is slow[96,99].

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REFERENCES

1 **Nieuwenhuis MH**, Vasen HF. Correlations between mutation site in APC and phenotype of familial adenomatous polyposis (FAP): a review of the literature. *Crit Rev Oncol Hematol* 2007; **61**: 153-161 [PMID: 17064931]

2 **Leoz ML**, Carballal S, Moreira L, Ocaña T, Balaguer F. The genetic basis of familial adenomatous polyposis and its implications for clinical practice and risk management. *Appl Clin Genet* 2015; **8**: 95-107 [PMID: 25931827 DOI: 10.2147/TACG.S51484]

3 **Kinzler KW**, Nilbert MC, Su LK, Vogelstein B, Bryan TM, Levy DB, Smith KJ, Preisinger AC, Hedge P, McKechnie D. Identification of FAP locus genes from chromosome 5q21. *Science* 1991; **253**: 661-665 [PMID: 1651562]

4 **Bertario L**, Russo A, Sala P, Varesco L, Giarola M, Mondini P, Pierotti M, Spinelli P, Radice P. Multiple approach to the exploration of genotype-phenotype correlations in familial adenomatous polyposis. *J Clin Oncol* 2003; **21**: 1698-1707 [PMID: 12721244]

5 **Campos FG**. Surgical treatment of familial adenomatous polyposis: dilemmas and current recommendations. *World J Gastroenterol* 2014; **20**: 16620-16629 [PMID: 25469031 DOI: 10.3748/wjg.v20.i44.16620]

6 **van Heumen BW**, Nieuwenhuis MH, van Goor H, Mathus-Vliegen LE, Dekker E, Gouma DJ, Dees J, van Eijck CH, Vasen HF, Nagengast FM. Surgical management for advanced duodenal adenomatosis and duodenal cancer in Dutch patients with familial adenomatous polyposis: a nationwide retrospective cohort study. *Surgery* 2012; **151**: 681-690 [PMID: 22265391 DOI: 10.1016/j.surg.2011.12.008]

7 **Bülow S**, Bülow C, Nielsen TF, Karlsen L, Moesgaard F. Centralized registration, prophylactic examination, and treatment results in improved prognosis in familial adenomatous polyposis. Results from the Danish Polyposis Register. *Scand J Gastroenterol* 1995; **30**: 989-993 [PMID: 8545620]

8 **Björk J**, Akerbrant H, Iselius L, Alm T, Hultcrantz R. Epidemiology of familial adenomatous polyposis in Sweden: changes over time and differences in phenotype between males and females. *Scand J Gastroenterol* 1999; **34**: 1230-1235 [PMID: 10636071]

9 **Ficari F**, Cama A, Valanzano R, Curia MC, Palmirotta R, Aceto G, Esposito DL, Crognale S, Lombardi A, Messerini L, Mariani-Costantini R, Tonelli F, Battista P. APC gene mutations and colorectal adenomatosis in familial adenomatous polyposis. *Br J Cancer* 2000; **82**: 348-353 [PMID: 10646887]

10 **de Campos FG**, Perez RO, Imperiale AR, Seid VE, Nahas SC, Cecconello I. Evaluating causes of death in familial adenomatous polyposis. *J Gastrointest Surg* 2010; **14**: 1943-1949 [PMID: 20676788 DOI: 10.1007/s11605-010-1288-6]

11 **Campos FG**, Martinez CA, Novaes M, Nahas SC, Cecconello I. Desmoid tumors: clinical features and outcome of an unpredictable and challenging manifestation of familial adenomatous polyposis. *Fam Cancer* 2015; **14**: 211-219 [PMID: 25480728 DOI: 10.1007/s10689-014-9772-x]

12 **Brosens LA**, Keller JJ, Offerhaus GJ, Goggins M, Giardiello FM. Prevention and management of duodenal polyps in familial adenomatous polyposis. *Gut* 2005; **54**: 1034-1043 [PMID: 15951555]

13 **Hashimoto T**, Ogawa R, Matsubara A, Taniguchi H, Sugano K, Ushiama M, Yoshida T, Kanai Y, Sekine S. Familial adenomatous polyposis-associated and sporadic pyloric gland adenomas of the upper gastrointestinal tract share common genetic features. *Histopathology* 2015 Mar 31; Epub ahead of print [PMID: 25832318 DOI: 10.1111/his.12705]

14 **Bülow S**, Björk J, Christensen IJ, Fausa O, Järvinen H, Moesgaard F, Vasen HF. Duodenal adenomatosis in familial adenomatous polyposis. *Gut* 2004; **53**: 381-386 [PMID: 14960520 DOI: 10.1136/gut.2003.027771]

15 **Hauser G**. Ueber Polyposis intestinalis adenomatosa und deren Beziehungen zur Krebsentwicklung. *Deutsche Archive Klinische Medizinische* 1895; **55**: 429-448

16 **Funkenstein O**. Über Polyposis intestinalis. *Z Med Lab Diagn* 1904; **55**: 236-248

17 **Cabot RC**, Harris NL, Shepard JA, Rosenberg ES, Cort AM, Ebeling SH, Peters CC, Misra M, Parangi S, Ross DS, Shailam R, Sadow PM. Case records of the Massachusetts General Hospital: Case 38-2010: a 13-year-old girl with an enlarging neck mass. *N Engl J Med* 2010; **363**: 2445-2454 [PMID: 21158661 DOI: 10.1056/NEJMcpc1004361]

18 **Duncan BR**, Dohner VA, Priest JH. The Gardner syndrome: need for early diagnosis. *J Pediatr* 1968; **72**: 497-505 [PMID: 5647292]

19 **Macdonald JM**, Davis WC, Crago HR, Berk AD. Gardner's syndrome and periampullary malignancy. *Am J Surg* 1967; **113**: 425-430 [PMID: 6018692]

20 **Jones TR**, Nance FC. Periampullary malignancy in Gardner's syndrome. *Ann Surg* 1977; **185**: 565-573 [PMID: 856075]

21 **Wallace MH**, Phillips RK. Upper gastrointestinal disease in patients with familial adenomatous polyposis. *Br J Surg* 1998; **85**: 742-750 [PMID: 9667698]

22 **Spigelman AD**, Williams CB, Talbot IC, Domizio P, Phillips RK. Upper gastrointestinal cancer in patients with familial adenomatous polyposis. *Lancet* 1989; **2**: 783-785 [PMID: 2571019]

23 **Church JM**, McGannon E, Hull-Boiner S, Sivak MV, Van Stolk

R, Jagelman DG, Fazio VW, Oakley JR, Lavery IC, Milsom JW. Gastroduodenal polyps in patients with familial adenomatous polyposis. *Dis Colon Rectum* 1992; **35**: 1170-1173 [PMID: 1335405]
24 **Sarre RG**, Frost AG, Jagelman DG, Petras RE, Sivak MV, McGannon E. Gastric and duodenal polyps in familial adenomatous polyposis: a prospective study of the nature and prevalence of upper gastrointestinal polyps. *Gut* 1987; **28**: 306-314 [PMID: 3032754]
25 **Burke CA**, Beck GJ, Church JM, van Stolk RU. The natural history of untreated duodenal and ampullary adenomas in patients with familial adenomatous polyposis followed in an endoscopic surveillance program. *Gastrointest Endosc* 1999; **49**: 358-364 [PMID: 10049420]
26 **Bertoni G**, Sassatelli R, Nigrisoli E, Pennazio M, Tansini P, Arrigoni A, Ponz de Leon M, Rossini FP, Bedogni G. High prevalence of adenomas and microadenomas of the duodenal papilla and periampullary region in patients with familial adenomatous polyposis. *Eur J Gastroenterol Hepatol* 1996; **8**: 1201-1206 [PMID: 8980941]
27 **Kadmon M**, Tandara A, Herfarth C. Duodenal adenomatosis in familial adenomatous polyposis coli. A review of the literature and results from the Heidelberg Polyposis Register. *Int J Colorectal Dis* 2001; **16**: 63-75 [PMID: 11355321]
28 **Iida M**, Aoyagi K, Fujimura Y, Matsumoto T, Hizawa K, Nakamura S. Nonpolypoid adenomas of the duodenum in patients with familial adenomatous polyposis (Gardner's syndrome). *Gastrointest Endosc* 1996; **44**: 305-308 [PMID: 8885351]
29 **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]
30 **Fatemi SR**, Safaee A, Pasha S, Pourhoseingholi MA, Bahrainei R, Molaei M. Evaluation of endoscopic characteristics of upper gastrointestinal polyps in patients with familial adenomatous polyposis. *Asian Pac J Cancer Prev* 2014; **15**: 6945-6948 [PMID: 25169551]
31 **Moussata D**, Napoleon B, Lepilliez V, Klich A, Ecochard R, Lapalus MG, Nancey S, Cenni JC, Ponchon T, Chayvialle JA, Saurin JC. Endoscopic treatment of severe duodenal polyposis as an alternative to surgery for patients with familial adenomatous polyposis. *Gastrointest Endosc* 2014; **80**: 817-825 [PMID: 24814771 DOI: 10.1016/j.gie.2014.03.012]
32 **Debinski HS**, Spigelman AD, Hatfield A, Williams CB, Phillips RK. Upper intestinal surveillance in familial adenomatous polyposis. *Eur J Cancer* 1995; **31A**: 1149-1153 [PMID: 7577011]
33 **Groves CJ**, Saunders BP, Spigelman AD, Phillips RK. Duodenal cancer in patients with familial adenomatous polyposis (FAP): results of a 10 year prospective study. *Gut* 2002; **50**: 636-641 [PMID: 11950808]
34 **Björk J**, Akerbrant H, Iselius L, Bergman A, Engwall Y, Wahlström J, Martinsson T, Nordling M, Hultcrantz R. Periampullary adenomas and adenocarcinomas in familial adenomatous polyposis: cumulative risks and APC gene mutations. *Gastroenterology* 2001; **121**: 1127-1135 [PMID: 11677205]
35 **Latchford AR**, Neale KF, Spigelman AD, Phillips RK, Clark SK. Features of duodenal cancer in patients with familial adenomatous polyposis. *Clin Gastroenterol Hepatol* 2009; **7**: 659-663 [PMID: 19281862 DOI: 10.1016/j.cgh.2009.02.028]
36 **Offerhaus GJ**, Giardiello FM, Krush AJ, Booker SV, Tersmette AC, Kelley NC, Hamilton SR. The risk of upper gastrointestinal cancer in familial adenomatous polyposis. *Gastroenterology* 1992; **102**: 1980-1982 [PMID: 1316858]
37 **Basford PJ**, Bhandari P. Endoscopic management of nonampullary duodenal polyps. *Therap Adv Gastroenterol* 2012; **5**: 127-138 [PMID: 22423261 DOI: 10.1177/1756283X11429590]
38 **Eswaran SL**, Sanders M, Bernadino KP, Ansari A, Lawrence C, Stefan A, Mattia A, Howell DA. Success and complications of endoscopic removal of giant duodenal and ampullary polyps: a comparative series. *Gastrointest Endosc* 2006; **64**: 925-932 [PMID: 17140900]
39 **Lepistö A**, Kiviluoto T, Halttunen J, Järvinen HJ. Surveillance and treatment of duodenal adenomatosis in familial adenomatous polyposis. *Endoscopy* 2009; **41**: 504-509 [PMID: 19533554 DOI: 10.1055/s-0029-1214719]
40 **Vasen HF**, Bülow S, Myrhøj T, Mathus-Vliegen L, Griffioen G, Buskens E, Taal BG, Nagengast F, Slors JF, de Ruiter P. Decision analysis in the management of duodenal adenomatosis in familial adenomatous polyposis. *Gut* 1997; **40**: 716-719 [PMID: 9245923]
41 **Lal G**, Gallinger S. Familial adenomatous polyposis. *Semin Surg Oncol* 2000; **18**: 314-323 [PMID: 10805953]
42 **Bertario L**, Presciuttini S, Sala P, Rossetti C, Pietroiusti M. Causes of death and postsurgical survival in familial adenomatous polyposis: results from the Italian Registry. Italian Registry of Familial Polyposis Writing Committee. *Semin Surg Oncol* 1994; **10**: 225-234 [PMID: 8085100]
43 **Belchetz LA**, Berk T, Bapat BV, Cohen Z, Gallinger S. Changing causes of mortality in patients with familial adenomatous polyposis. *Dis Colon Rectum* 1996; **39**: 384-387 [PMID: 8878496]
44 **Church J**, Xhaja X, LaGuardia L, O'Malley M, Burke C, Kalady M. Desmoids and genotype in familial adenomatous polyposis. *Dis Colon Rectum* 2015; **58**: 444-448 [PMID: 25751801 DOI: 10.1097/DCR.0000000000000316]
45 **Schiessling S**, Kihm M, Ganschow P, Kadmon G, Büchler MW, Kadmon M. Desmoid tumour biology in patients with familial adenomatous polyposis coli. *Br J Surg* 2013; **100**: 694-703 [PMID: 23334997 DOI: 10.1002/bjs.9053]
46 **de Leon MP**, Urso ED, Pucciarelli S, Agostini M, Nitti D, Roncucci L, Benatti P, Pedroni M, Kaleci S, Balsamo A, Laudi C, Di Gregorio C, Viel A, Rossi G, Venesio T. Clinical and molecular features of attenuated adenomatous polyposis in northern Italy. *Tech Coloproctol* 2013; **17**: 79-87 [PMID: 22976915 DOI: 10.1007/s10151-012-0887-5]
47 **Groves C**, Lamlum H, Crabtree M, Williamson J, Taylor C, Bass S, Cuthbert-Heavens D, Hodgson S, Phillips R, Tomlinson I. Mutation cluster region, association between germline and somatic mutations and genotype-phenotype correlation in upper gastrointestinal familial adenomatous polyposis. *Am J Pathol* 2002; **160**: 2055-2061 [PMID: 12057910]
48 **Friedl W**, Caspari R, Sengteller M, Uhlhaas S, Lamberti C, Jungck M, Kadmon M, Wolf M, Fahnenstich J, Gebert J, Möslein G, Mangold E, Propping P. Can APC mutation analysis contribute to therapeutic decisions in familial adenomatous polyposis? Experience from 680 FAP families. *Gut* 2001; **48**: 515-521 [PMID: 11247896]
49 **Soravia C**, Berk T, Madlensky L, Mitri A, Cheng H, Gallinger S, Cohen Z, Bapat B. Genotype-phenotype correlations in attenuated adenomatous polyposis coli. *Am J Hum Genet* 1998; **62**: 1290-1301 [PMID: 9585611]
50 **Matsumoto T**, Lida M, Kobori Y, Mizuno M, Nakamura S, Hizawa K, Yao T. Genetic predisposition to clinical manifestations in familial adenomatous polyposis with special reference to duodenal lesions. *Am J Gastroenterol* 2002; **97**: 180-185 [PMID: 11808944]
51 **Skipworth JR**, Morkane C, Raptis DA, Vyas S, Olde Damink SW, Imber CJ, Pereira SP, Malago M, West N, Phillips RK, Clark SK, Shankar A. Pancreaticoduodenectomy for advanced duodenal and ampullary adenomatosis in familial adenomatous polyposis. *HPB* (Oxford) 2011; **13**: 342-349 [PMID: 21492334 DOI: 10.1111/j.1477-2574.2011.00292.x]
52 **Half E**, Bercovich D, Rozen P. Familial adenomatous polyposis. *Orphanet J Rare Dis* 2009; **4**: 22 [PMID: 19822006 DOI: 10.1186/1750-1172-4-22]
53 **King JE**, Dozois RR, Lindor NM, Ahlquist DA. Care of patients and their families with familial adenomatous polyposis. *Mayo Clin Proc* 2000; **75**: 57-67 [PMID: 10630758]
54 **Mathus-Vliegen EM**, Boparai KS, Dekker E, van Geloven N. Progression of duodenal adenomatosis in familial adenomatous polyposis: due to ageing of subjects and advances in technology. *Fam Cancer* 2011; **10**: 491-499 [PMID: 21416262 DOI: 10.1007/s10689-011-9433-2]

55 **Bülow S**, Christensen IJ, Højen H, Björk J, Elmberg M, Järvinen H, Lepistö A, Nieuwenhuis M, Vasen H. Duodenal surveillance improves the prognosis after duodenal cancer in familial adenomatous polyposis. *Colorectal Dis* 2012; **14**: 947-952 [PMID: 21973191 DOI: 10.1111/j.1463-1318.2011.02844.x]

56 **Cairns SR**, Scholefield JH, Steele RJ, Dunlop MG, Thomas HJ, Evans GD, Eaden JA, Rutter MD, Atkin WP, Saunders BP, Lucassen A, Jenkins P, Fairclough PD, Woodhouse CR. Guidelines for colorectal cancer screening and surveillance in moderate and high risk groups (update from 2002). *Gut* 2010; **59**: 666-689 [PMID: 20427401 DOI: 10.1136/gut.2009.179804]

57 **Gallagher MC**, Phillips RK, Bulow S. Surveillance and management of upper gastrointestinal disease in Familial Adenomatous Polyposis. *Fam Cancer* 2006; **5**: 263-273 [PMID: 16998672]

58 **Johnson JC**, DiSario JA, Grady WM. Surveillance and Treatment of Periampullary and Duodenal Adenomas in Familial Adenomatous Polyposis. *Curr Treat Options Gastroenterol* 2004; **7**: 79-89 [PMID: 15010021]

59 **Vasen HF**, Möslein G, Alonso A, Aretz S, Bernstein I, Bertario L, Blanco I, Bülow S, Burn J, Capella G, Colas C, Engel C, Frayling I, Friedl W, Hes FJ, Hodgson S, Järvinen H, Mecklin JP, Møller P, Myrhøi T, Nagengast FM, Parc Y, Phillips R, Clark SK, de Leon MP, Renkonen-Sinisalo L, Sampson JR, Stormorken A, Tejpar S, Thomas HJ, Wijnen J. Guidelines for the clinical management of familial adenomatous polyposis (FAP). *Gut* 2008; **57**: 704-713 [PMID: 18194984 DOI: 10.1136/gut.2007.136127]

60 **Al-Kawas FH**. The significance and management of nonampullary duodenal polyps. *Gastroenterol Hepatol* (N Y) 2011; **7**: 329-332 [PMID: 21857835]

61 **Shibata C**, Ogawa H, Miura K, Naitoh T, Yamauchi J, Unno M. Clinical characteristics of gastric cancer in patients with familial adenomatous polyposis. *Tohoku J Exp Med* 2013; **229**: 143-146 [PMID: 23343691]

62 **Gallagher MC**, Shankar A, Groves CJ, Russell RC, Phillips RK. Pylorus-preserving pancreaticoduodenectomy for advanced duodenal disease in familial adenomatous polyposis. *Br J Surg* 2004; **91**: 1157-1164 [PMID: 15449267]

63 **Saurin JC**, Ligneau B, Ponchon T, Leprêtre J, Chavaillon A, Napoléon B, Chayvialle JA. The influence of mutation site and age on the severity of duodenal polyposis in patients with familial adenomatous polyposis. *Gastrointest Endosc* 2002; **55**: 342-347 [PMID: 11868006]

64 **Heiskanen I**, Kellokumpu I, Järvinen H. Management of duodenal adenomas in 98 patients with familial adenomatous polyposis. *Endoscopy* 1999; **31**: 412-416 [PMID: 10494676]

65 **Morpurgo E**, Vitale GC, Galandiuk S, Kimberling J, Ziegler C, Polk HC. Clinical characteristics of familial adenomatous polyposis and management of duodenal adenomas. *J Gastrointest Surg* 2004; **8**: 559-564 [PMID: 15239991]

66 **Mantas D**, Charalampoudis P, Nikiteas N. FAP related periampullary adenocarcinoma. *Int J Surg Case Rep* 2013; **4**: 684-686 [PMID: 23792481 DOI: 10.1016/j.ijscr.2013.05.006]

67 **Mackey R**, Walsh RM, Chung R, Brown N, Smith A, Church J, Burke C. Pancreas-sparing duodenectomy is effective management for familial adenomatous polyposis. *J Gastrointest Surg* 2005; **9**: 1088-1093; discussion 1093 [PMID: 16269379]

68 **de Vos tot Nederveen Cappel WH**, Järvinen HJ, Björk J, Berk T, Griffioen G, Vasen HF. Worldwide survey among polyposis registries of surgical management of severe duodenal adenomatosis in familial adenomatous polyposis. *Br J Surg* 2003; **90**: 705-710 [PMID: 12808618]

69 **Kalady MF**, Clary BM, Tyler DS, Pappas TN. Pancreas-preserving duodenectomy in the management of duodenal familial adenomatous polyposis. *J Gastrointest Surg* 2002; **6**: 82-87 [PMID: 11986022]

70 **Schönthal AH**, Chen TC, Hofman FM, Louie SG, Petasis NA. Celecoxib analogs that lack COX-2 inhibitory function: preclinical development of novel anticancer drugs. *Expert Opin Investig Drugs* 2008; **17**: 197-208 [PMID: 18230053 DOI: 10.1517/13543784.17.2.197]

71 **Laukaitis CM**, Erdman SH, Gerner EW. Chemoprevention in patients with genetic risk of colorectal cancers. *Colorectal Cancer* 2012; **1**: 225-240 [PMID: 25221625]

72 **Kim B**, Giardiello FM. Chemoprevention in familial adenomatous polyposis. *Best Pract Res Clin Gastroenterol* 2011; **25**: 607-622 [PMID: 22122775 DOI: 10.1016/j.bpg.2011.08.002]

73 **Chan AT**. Aspirin and familial adenomatous polyposis: coming full circle. *Cancer Prev Res* (Phila) 2011; **4**: 623-627 [PMID: 21543340 DOI: 10.1158/1940-6207.CAPR-11-0157]

74 **Matsumoto T**, Nakamura S, Esaki M, Yao T, Iida M. Effect of the non-steroidal anti-inflammatory drug sulindac on colorectal adenomas of uncolectomized familial adenomatous polyposis. *J Gastroenterol Hepatol* 2006; **21**: 251-257 [PMID: 16460482]

75 **Koornstra JJ**, Rijcken FE, Oldenhuis CN, Zwart N, van der Sluis T, Hollema H, deVries EG, Keller JJ, Offerhaus JA, Giardiello FM, Kleibeuker JH. Sulindac inhibits beta-catenin expression in normal-appearing colon of hereditary nonpolyposis colorectal cancer and familial adenomatous polyposis patients. *Cancer Epidemiol Biomarkers Prev* 2005; **14**: 1608-1612 [PMID: 16030090]

76 **Debinski HS**, Trojan J, Nugent KP, Spigelman AD, Phillips RK. Effect of sulindac on small polyps in familial adenomatous polyposis. *Lancet* 1995; **345**: 855-856 [PMID: 7898240]

77 **Kim KY**, Jeon SW, Park JG, Yu CH, Jang SY, Lee JK, Hwang HY. Regression of Colonic Adenomas After Treatment With Sulindac in Familial Adenomatous Polyposis: A Case With a 2-Year Follow-up Without a Prophylactic Colectomy. *Ann Coloproctol* 2014; **30**: 201-204 [PMID: 25210691 DOI: 10.3393/ac.2014.30.4.201]

78 **Richard CS**, Berk T, Bapat BV, Haber G, Cohen Z, Gallinger S. Sulindac for periampullary polyps in FAP patients. *Int J Colorectal Dis* 1997; **12**: 14-18 [PMID: 9112144]

79 **Phillips RK**, Wallace MH, Lynch PM, Hawk E, Gordon GB, Saunders BP, Wakabayashi N, Shen Y, Zimmerman S, Godio L, Rodrigues-Bigas M, Su LK, Sherman J, Kelloff G, Levin B, Steinbach G. A randomised, double blind, placebo controlled study of celecoxib, a selective cyclooxygenase 2 inhibitor, on duodenal polyposis in familial adenomatous polyposis. *Gut* 2002; **50**: 857-860 [PMID: 12010890]

80 **Giardiello FM**, Hamilton SR, Krush AJ, Piantadosi S, Hylind LM, Celano P, Booker SV, Robinson CR, Offerhaus GJ. Treatment of colonic and rectal adenomas with sulindac in familial adenomatous polyposis. *N Engl J Med* 1993; **328**: 1313-1316 [PMID: 8385741]

81 **Steinbach G**, Lynch PM, Phillips RK, Wallace MH, Hawk E, Gordon GB, Wakabayashi N, Saunders B, Shen Y, Fujimura T, Su LK, Levin B, Godio L, Patterson S, Rodriguez-Bigas MA, Jester SL, King KL, Schumacher M, Abbruzzese J, DuBois RN, Hittelman WN, Zimmerman S, Sherman JW, Kelloff G. The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis. *N Engl J Med* 2000; **342**: 1946-1952 [PMID: 10874062]

82 **Asano TK**, McLeod RS. Non steroidal anti-inflammatory drugs (NSAID) and Aspirin for preventing colorectal adenomas and carcinomas. *Cochrane Database Syst Rev* 2004; **(2)**: CD004079 [PMID: 15106236]

83 **Pioche M**, Aguero Garcete G, Forestier J, Lépilliez V, Nozières C, Lombard-Bohas C, Saurin JC. Macroscopic and histologic regression of duodenal polyposis with FOLFOX4 chemotherapy for an ileal pouch adenocarcinoma in a patient with familial adenomatous polyposis. *Endoscopy* 2012; **44**: 1165-1167 [PMID: 23188666 DOI: 10.1055/s-0032-1325674]

84 **Calabrese C**, Praticò C, Calafiore A, Coscia M, Gentilini L, Poggioli G, Gionchetti P, Campieri M, Rizzello F. Eviendep® reduces number and size of duodenal polyps in familial adenomatous polyposis patients with ileal pouch-anal anastomosis. *World J Gastroenterol* 2013; **19**: 5671-5677 [PMID: 24039360 DOI: 10.3748/wjg.v19.i34.5671]

85 **Lynch PM**. Chemoprevention with special reference to inherited colorectal cancer. *Fam Cancer* 2008; **7**: 59-64 [PMID: 17680350]

86 **Garcia Rodriguez LA**, Cea-Soriano L, Tacconelli S, Patrignani P. Coxibs: pharmacology, toxicity and efficacy in cancer clinical trials. *Recent Results Cancer Res* 2013; **191**: 67-93 [PMID: 22893200 DOI: 10.1007/978-3-642-30331-9_4]

87 **van Heumen BW**, Roelofs HM, te Morsche RH, Nagengast FM, Peters WH. Duodenal mucosal risk markers in patients with familial adenomatous polyposis: effects of celecoxib/ursodeoxycholic acid co-treatment and comparison with patient controls. *Orphanet J Rare Dis* 2013; **8**: 181 [PMID: 24245549 DOI: 10.1186/1750-1172-8-181]

88 **Hayes JD**, Flanagan JU, Jowsey IR. Glutathione transferases. *Annu Rev Pharmacol Toxicol* 2005; **45**: 51-88 [PMID: 15822171 DOI: 10.1146/annurev.pharmtox.45.120403.095857]

89 **Grubben MJ**, van den Braak CC, Nagengast FM, Peters WH. Low colonic glutathione detoxification capacity in patients at risk for colon cancer. *Eur J Clin Invest* 2006; **36**: 188-192 [PMID: 16506964 DOI: 10.1111/j.1365-2362.2006.01618.x]

90 **Berkhout M**, Roelofs HM, Friederich P, van Krieken JH, Nagengast FM, Peters WH. Detoxification enzymes in the duodenal mucosa of patients with familial adenomatous polyposis. *Br J Surg* 2005; **92**: 754-755 [PMID: 15856485 DOI: 10.1002/bjs.4996]

91 **Jaganmohan S**, Lynch PM, Raju RP, Ross WA, Lee JE, Raju GS, Bhutani MS, Fleming JB, Lee JH. Endoscopic management of duodenal adenomas in familial adenomatous polyposis--a single-center experience. *Dig Dis Sci* 2012; **57**: 732-737 [PMID: 21960285 DOI: 10.1007/s10620-011-1917-2]

92 **Matsumoto T**, Esaki M, Yanaru-Fujisawa R, Moriyama T, Yada S, Nakamura S, Yao T, Iida M. Small-intestinal involvement in familial adenomatous polyposis: evaluation by double-balloon endoscopy and intraoperative enteroscopy. *Gastrointest Endosc* 2008; **68**: 911-919 [PMID: 18561922 DOI: 10.1016/j.gie.2008.02.067]

93 **Park SY**, Ryu JK, Park JH, Yoon H, Kim JY, Yoon YB, Park JG, Lee SH, Kang SB, Park JW, Oh JH. Prevalence of gastric and duodenal polyps and risk factors for duodenal neoplasm in korean patients with familial adenomatous polyposis. *Gut Liver* 2011; **5**: 46-51 [PMID: 21461071 DOI: 10.5009/gnl.2011.5.1.46]

94 **Freeman HJ**. Appearance of attenuated intestinal polyposis during chronic non-steroidal anti-inflammatory drugs use. *World J Gastrointest Pharmacol Ther* 2012; **3**: 100-102 [PMID: 23494537 DOI: 10.4292/wjgpt.v3.i6.100]

95 **Wood LD**, Salaria SN, Cruise MW, Giardiello FM, Montgomery EA. Upper GI tract lesions in familial adenomatous polyposis (FAP): enrichment of pyloric gland adenomas and other gastric and duodenal neoplasms. *Am J Surg Pathol* 2014; **38**: 389-393 [PMID: 24525509 DOI: 10.1097/PAS.0000000000000146]

96 **Drini M**, Speer A, Dow C, Collier N, Bhathal P, Macrae FA. Management of duodenal adenomatosis in FAP: single centre experience. *Fam Cancer* 2012; **11**: 167-173 [PMID: 22131053 DOI: 10.1007/s10689-011-9496-0]

97 **Gluck N**, Strul H, Rozner G, Leshno M, Santo E. Endoscopy and EUS are key for effective surveillance and management of duodenal adenomas in familial adenomatous polyposis. *Gastrointest Endosc* 2015; **81**: 960-966 [PMID: 25440680 DOI: 10.1016/j.gie.2014.08.029]

98 **Samadder NJ**, Jasperson K, Burt RW. Hereditary and common familial colorectal cancer: evidence for colorectal screening. *Dig Dis Sci* 2015; **60**: 734-747 [PMID: 25501924 DOI: 10.1007/s10620-014-3465-z]

99 **Serrano PE**, Grant RC, Berk TC, Kim D, Al-Ali H, Cohen Z, Pollett A, Riddell R, Silverberg MS, Kortan P, May GR, Gallinger S. Progression and Management of Duodenal Neoplasia in Familial Adenomatous Polyposis: A Cohort Study. *Ann Surg* 2014 Jun 19; Epub ahead of print [PMID: 24950262]

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REVIEW

Uncommon complications of therapeutic endoscopic ultrasonography: What, why, and how to prevent

Tanyaporn Chantarojanasiri, Pitulak Aswakul, Varayu Prachayakul

Tanyaporn Chantarojanasiri, Division of Gastroenterology, Department of Internal Medicine, Police General Hospital, Bangkok 10330, Thailand

Pitulak Aswakul, Liver and Digestive Institute, Samitivej Sukhumvit Hospital, Bangkok 10120, Thailand

Varayu Prachayakul, Siriraj GI Endoscopy Center, Division of Gastroenterology, Department of Internal Medicine, Siriraj Hospital, Faculty of Medicine, Mahidol University, Bangkok 10700, Thailand

Author contributions: Prachayakul V conceived of and designed the article; Chantarojanasiri T reviewed the literature and drafted the article; all the authors revised and approved the final version to be published.

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Correspondence to: Varayu Prachayakul, Associate Professor, Siriraj GI Endoscopy Center, Division of Gastroenterology, Department of Internal Medicine, Siriraj Hospital, Faculty of Medicine, Mahidol University, Bangkok 10700, Thailand. kaiyjr@gmail.com
Telephone: +66-841-8654646
Fax: +66-2-4115013

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Abstract

There is an increasing role for endoscopic ultrasound (EUS)-guided interventions in the treatment of many conditions. Although it has been shown that these types of interventions are effective and safe, they continue to be considered only as alternative treatments in some situations. This is in part due to the occurrence of complications with these techniques, which can occur even when performed by experienced endosonographers. Although common complications have been described for many procedures, it is also crucial to be aware of uncommon complications. This review describes rare complications that have been reported with several EUS-guided interventions. EUS-guided biliary drainage is accepted as an alternative treatment for malignant biliary obstruction. Most of the uncommon complications related to this procedure involve stent malfunction, such as the migration or malposition of stents. Rare complications of EUS-guided pancreatic pseudocyst drainage can result from air embolism and infection. Finally, a range of uncommon complications has been reported for EUS-guided celiac plexus neurolysis, involving neural and vascular injuries that can be fatal. The goal of this review is to identify possible complications and promote an understanding of how they occur in order to increase general awareness of these adverse events with the hope that they can be avoided in the future.

Key words: Complications; Endoscopic ultrasonography; Rare; Therapeutic; Uncommon

Core tip: This article reviews the rare complications that occur with endoscopic ultrasound-guided interventions, including those for biliary and pancreatic pseudocyst drainage and celiac plexus neurolysis. Knowledge

of the types of rare complications will promote an understanding of their causes, and help to reduce their occurrence.

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INTRODUCTION

Endoscopic ultrasound (EUS)-guided interventions have recently been accepted as an alternative to percutaneous or radiologic-guided treatments, as well as for more invasive treatments such as surgery, for many conditions. Accumulating evidence continues to demonstrate the feasibility, efficacy, and safety of these novel procedures. Although such methods are less invasive, there are reports of adverse events with EUS-guided transluminal therapies. It is important for endosonographers to have adequate knowledge of the indications, techniques, and potential risks before performing any given procedure. Indeed, many reviews have been published describing common complications related to EUS-guided procedures. However, only a limited number of studies report on rare complications. Thus, the purpose of this review was to identify the uncommon complications related to these interventions, evaluate how they occurred, and ascertain how to prevent them. To achieve this, a search was made of English-language human studies listed in the PubMed database that were published between1991 and December 2014. The following keywords were used alone or in combination with EUS: therapeutic complication, drainage, guidewire, celiac plexus neurolysis, tumor ablation, ethanol ablation, pancreatic fluid collection, pancreatic drainage, fiducial, cystogastrostomy, abscess drainage, antibiotics, endoscopy, vascular, glue injection, oncolytic virus, and cryotherapy. References of identified articles were also searched for potentially relevant studies.

EUS-GUIDED BILIARY DRAINAGE

EUS-guided procedures have recently gained popularity for performing biliary drainage in patients for whom endoscopic retrograde cholangiopancreatography (ERCP) has failed. The initial report of EUS-guided cholangiography in 1996 was followed by a description of EUS-guided choledochoduodenostomy in 2001[1]. Since then, additional techniques for EUS-guided transluminal biliary drainage have been described, including creating a bilo-enteric fistula, using an EUS-antegrade approach, and a rendezvous technique to assist transpapillary cannulation[2]. Fistula tracts can be created either between the intrahepatic bile duct and stomach, as in EUS-guided hepaticogastrostomy, or between the extrahepatic bile duct and duodenum, as in EUS-guided choledochoduodenostomy[3]. These procedures have become a rescue therapy[4]. Although small case series of no more than five patients describe successful procedures with no complications[5-7], larger series report complication rates ranging from 9.5% to 40%[3,8-14]. The most common complications were bile leakage, stent misplacement, bleeding, and pneumoperitoneum, which accounted for 5.2%, 3.1%, 2.1%, and 1.0% of cases, respectively[3,15].Other rare complications such as biloma, cholangitis and perforation were also reported, all of which were related to the use of needle knife cautery in the multivariate analysis[15].

Most complications can be treated conservatively[15,16]. For example, bilomaas a result of stent migration can be treated with a variety of methods[8,11], including percutaneous[3] or EUS-guided[17] drainage. Only one fatality was reported, which involved severe peritonitis[18]. A case of retrogastric fluid collection was successfully treated with antibiotics and percutaneous drainage[19]. Several series reported cholangitis as an early or late complication resulting from reflux of gastrointestinal (GI) contents or stent migration[11,14,15,20]. In other cases, shortening of the metallic stent after deployment caused misplacement into to the abdominal cavity or gastroduodenal perforation, which required surgical intervention[3,19,21]. Cases of bleeding from the puncture site[3,9,19] or from a hepatic artery aneurysm, which was treated by angiographic embolization[22], were also reported. One technical concern involving guidewire shearing by the EUS-needle bevel was reported, which was treated by radiologic intervention[23].

Preventative measures

When inserting stents into the bilo-enteric tract, the membrane from fully/partially covered or specially designed metal stents prevents leakage of bile from the newly created tract. As stent shortening was related to cases of biloma, perforation, and peritonitis, an appropriate-length stent should be carefully selected and placed in the optimal position. Stent dislocation can be prevented by placing clips at the endoluminal stent margins[9], or, as we have observed, by placing a double-pigtail plastic stent inside the fully covered self-expanding metal stent. In addition, the maneuver applied during stent deployment is critical, and it is recommended that the endoscopist perform the initial stent deployment under fluoroscopic monitoring, before switching to endoscopic monitoring.

Infectious complications were reported[3], including a case of cholecystitis due to previous ERCP contamination of the obstructed biliary system[20]. Although the role of antibiotic prophylaxis in such procedures has not been established[24], it has been used by several authors who found that 4-5 d (nil per mouth) of antibiotic treatment was essential for preventing minor leakage and perito-

neum contamination[4,10,20].

Although guidewire shearing during the procedure is not common during EUS-guided biliary drainage, the risk could be eliminated by avoiding acute angles during needle retraction and by retracting slowly with a lot of caution for any resistance. If any resistance is felt, the needle and the wire should be retracted concurrently[25]. Other authors recommend changing the EUS needle after puncture to a 4 Fr cannula for guidewire manipulation[26], or using a blunt-ended needle with a sharp needle-tip stylet (Access needle®; Wilson Cook Inc., Winston-Salem, NC, United States) for biliary access[23,27]. In one case, guidewire knotting occurred in an EUS-guided rendezvous procedure as a result of guidewire loop formation during endoscopic–catheter exchange[28]. In this report, the guidewire was untangled with rat-toothed forceps using a gastroscope, and the author suggested that, to prevent looping, constant tension on the wire should be maintained during exchanges. A summary of uncommon complications from EUS-guided biliary drainage is presented in Table 1.

EUS-GUIDED PANCREATIC DRAINAGE

EUS-guided pancreatic drainage can be performed to remove accumulated fluid due to acute pancreatitis or pancreatic duct obstruction. This procedure is typically performed *via* transpapillary, transluminal, or transanastomotic approaches with neotract formation or by the rendezvous technique in patients for whom ERCP has failed or who have surgically altered anatomy[25,29,30]. EUS-guided pancreatic drainage is effective with a lower morbidity compared to the other platforms[31]. The success rate depends on the type of fluid collection, and ranges from 50.0%-63.2% up to 100%[32,33]. The common complications of pancreatic duct drainage are pancreatitis, bleeding, perforation, and stent migration, with overall complication rates ranging from 0% to 52%[25,30,34]. In some case series, the complication rate was significantly higher in patients with necrosis compared to those with pseudocysts[34].

Less common complications that have been reported with EUS-guided pancreatic drainage include peri-pancreatic abscesses, fluid collection, and shearing of the guidewire during diagnostic pancreatography and therapeutic drainage[29,35-37]. In these reports, peri-pancreatic collection was the result of pancreatic fluid or pseudocyst leakage. To prevent bacterial peritonitis, some endoscopists recommend antibiotic prophylaxis[37]. Guidewire shearing occurred more frequently than was reported for EUS-guided biliary drainage, likely due to the greater angle between the EUS needle and the desired direction of the pancreatic duct[29,36], with similar remedies for prevention. A splenic artery aneurysm within the pancreatic pseudocyst was the cause of bleeding in one case, which was treated by selective angiographic embolization[38]. A summary of uncommon complications from EUS-guided pancreatic drainage is presented in Table 2.

The rare but fatal complication of air embolism was also reported, occurring in one patient who had previously undergone ERCP, and in one case of EUS with fine-needle aspiration of an accessory spleen[39]. A fatal case occurred in a patient who underwent EUS-guided pancreatic pseudocyst drainage[40]. Hikichi *et al*[41] reported a case of gallbladder puncture and drainage following misdiagnosis of a pancreatic pseudocyst, which was treated with nasocystic-tube drainage and antibiotic administration. The authors strongly recommended that every endosonographer should verify the location of the puncture site *via* EUS-scanning before initiating any drainage intervention.

EUS-GUIDED CELIAC PLEXUS NEUROLYSIS AND CELIAC PLEXUS BLOCK

Celiac plexus neurolysis (CPN) and celiac plexus block (CPB) have been performed for more than five decades in patients with upper abdominal pain of pancreatic origin and from stomach, intestinal, and intra-abdominal metastases. CPB has been performed under guidance of radiography, fluoroscopy, CT, and ultrasonography. Common complications with this procedure include local pain, diarrhea, and hypotension, whereas lower extremity weakness, paresthesia, lumbar puncture, pneumothorax, pleuritic pain, hiccups, and hematuria occur in only 1% of patients[42]. EUS-guided CPB has gained in popularity since the 1990sas it enables the endoscopist to easily and accurately determine the location for injection[43]. For EUS-guided CPN, the complications are similar, with hypotension, pain, and diarrhea occurring in 3.4%-20.0%, 6.8%-9.0%, and 10.3%-17.0% of cases, respectively[44-46].

Uncommon complications, which occurred less than 1%, from EUS-guided CPN have primarily been described within case reports. Despite the improved injection-site localization, there were reports of anterior spinal cord infarction due to alcohol-induced injury to the lumbar artery and prolonged hypotension[44-48]. Nevertheless, the occurrence is much more infrequent than is observed with other approaches[49-54]. It is possible that spinal arterial spasm or thrombosis due to the chemical agent or the direct injection into the cerebrospinal fluid in cases of percutaneous injection caused the infarctions[49,55]. Other reports describe celiac artery thrombosis resulting in gastric ulceration with hepatosplenic infarction[42,56,57] or fatal multiple organ ischemia[58]. In two of these cases[56,58], color Doppler was performed either before or after the procedure to ensure celiac artery patency. Aspiration tests were also conducted after needle puncture in two cases[56,57]. The cause of arterial thrombosis was attributed to a vasospasm of affected vessels from alcohol irritation, as the amount of alcohol was similar among the cases. There was one case of peri-pancreatic collection after absolute alcohol injection that was treated by EUS-

Table 1 Uncommon complications of endoscopic ultrasound-guided biliary drainage

Ref.	Procedure	Stent	Complications (*n*/total successful cases)	Postulated causes	Treatment	Prevention recommendation
Püspök *et al*[20]	EUS-CDS, EUS-HGS, rendezvous	Plastic stent, FCSEMS, UCSEMS	Cholangitis (1/6), cholecystitis from previous ERCP (1/6)	Cholangitis may result from previous ERCP attempt	Antibiotics, PTBD, surgery	Consider antibiotic prophylaxis
Bories *et al*[11]	EUS-HGS, rendezvous	FCSEMS	Biloma (1/11), cholangitis (1/11)	Stent shortening	Percutaneous drainage (biloma), second stent insertion (cholangitis)	Select a stent of appropriate length Observe stent position during deployment (both endoscopic and fluoroscopic views)
Attasaranya *et al*[19]	EUS-CDS, EUS-HGS, cholecystoduodenostomy, transduodenal FCSEMS insertion	Plastic stent, FCSEMS	Duodenal perforation (1/31), retrogastric collection (1/31), cholangitis (1/31)	Stent shortening	Surgery (duodenal perforation), percutaneous drainage (retrogastric collection)	Keep at least 2 cm length of stent at the mural site
Martin *et al*[18]	EUS-HGS	PCSEMS	Stent migration and biloma	Stent migration	(Dead)	
Siddiqui *et al*[21]	EUS-CDS	FCSEMS	Duodenal perforation (1/8)	Stent shortening	Surgery	
Khashab *et al*[23]	EUS-HGS	Not mentioned	Wire shearing (1/1)	Injury from EUS needle	Percutaneous intervention	Avoid acute angulation of guidewire and retract it gently Change needle to a small-size cannula during guidewire manipulation
Prachayakul *et al*[8]	EUS-CDS, EUS-HGS	FCSEMS	Biloma (1/21)	Malpositioned stent	Percutaneous drainage[17]	Observe stent position during deployment (both endoscopic and fluoroscopic views)
Prachayakul *et al*[22]	EUS-HGS	FCSEMS	Bleeding from hepatic artery aneurysm (1/1)	Iatrogenic trauma during EUS-HGS	Angiographic embolization	Puncture site should be away from major vascular structure
Kawakubo *et al*[3]	EUS-CDS, EUS-HGS	Plastic stents, FCSEMS	Cholangitis (1/61), biloma (1/61), perforation (1/61)	Stent misplacement	Percutaneous drainage (biloma), surgery (perforation)	Observe stent position during deployment (both endoscopic and fluoroscopic views)
Saxena *et al*[28]	Rendezvous	FCSEMS	Guidewire knot	Guidewire formed a knot during exchanges	Untangled using forceps	Maintain constant pressure on the guidewire during exchanges

ERCP: Endoscopic retrograde cholangiopancreatography; EUS-CDS: Endoscopic ultrasound-guided choledochoduodenostomy; EUS-HGS: Endoscopic ultrasound-guided hepaticogastrostomy; FCSEMS: Fully covered self-expandable metallic stent; PCSEMS: Partially covered self-expandable metallic stent; PTBD: Percutaneous transhepatic biliary drainage; UCSEMS: Uncovered self-expandable metallic stent.

guided drainage and intravenous antibiotics[59]. Another case involved a mixed fungal and bacterial brain abscess as a result of hematogenous spread[60]. As with the other EUS-guided procedures, the use of antibiotic prophylaxis has not been established for these rare infectious complications[24]. A summary of uncommon complications from EUS-guided CPN is presented in Table 3.

EUS-GUIDED INTRA-ABDOMINAL INTERVENTIONS

Intra-abdominalabscess drainage

Only a limited number of cases using EUS-guided intra-abdominal drainage for liver abscesses have been reported, which were performed without complications[61-65]. In addition, several reports involving 4-25 cases each of pelvic abscess drainage using a transrectal approach with or without an irrigation tube to prevent stent occlusion by fecal material have been described, also without complications[66-70]. One case series describes abscess drainage in nine patients through the esophagus, stomach, and colon[64]. Mediastinitis and pneumothorax developed in one patient who underwent transesophageal drainage of a pancreatic pseudocyst, and was treated conservatively. Stent migration occurred in another patient undergoing transcolonic drainage, which was treated endoscopically.

Vascular therapy

EUS-guided interventions have been used for creating portosystemic shunts to treat GI bleeding (both variceal and non-variceal bleeding)[71]. In addition, EUS-guided injection of cyanoacrylate or coil embolization has

Table 2 Uncommon complications of endoscopic ultrasound-guided pancreatic drainage

Ref.	Procedure	Stent	Complication (*n*/total successful cases)	Postulated causes	Treatment	Prevention recommendation
Hikishi *et al*[41]	EUS-cystogastrostomy drainage	Plastic stent, nasobiliary drainage	Gallbladder puncture and drainage	Marked distension of gallbladder with debris, overlapping location between pseudocyst and gallbladder in fluoroscopy	Conservative with antibiotics	EUS scanning prior to initiating drainage intervention
Barkay *et al*[29]	EUS-PD rendezvous, dye injection	Plastic stent	Peripancreatic abscess (1/10), wire shearing (1/10)	Failed to inject PD (peripancreatic abscess), repeated to-and-fro movements of wire	Percutaneous drainage (abscess), transluminal removal (wire)	Carefully manipulate the guidewire, avoid acute angles
Jows *et al*[40]	EUS-cystogastrostomy drainage	Not mentioned	Air emboli	Prolonged high pressure air sufflation, inflammation, mechanical injury	(Dead)	Use CO_2 inflation instead of air
Fujii *et al*[36]	EUS-PD stent (antegrade and retrograde)	Plastic stents	Peripancreatic abscess (1/32), wire shearing (1/32)	Balloon dilation? Multiple devices (peripancreatic abscess), injury from EUS needle (wire shearing)	EUS-guided transmural drainage (abscess)	Carefully manipulate the guidewire
Kurihara *et al*[38]	EUS-PD rendezvous, and PD stenting	Plastic stents, UCSEMS	Pancreatic pseudocyst with splenic artery aneurysm	Pancreatic juice leakage	Angiographic embolization	Avoid major vascular structures

EUS-PD: Endoscopic ultrasound-guided pancreatic duct drainage; PD: Pancreatic duct; UCSEMS: Uncovered self-expandable metallic stent.

Table 3 Uncommon complications of endoscopic ultrasound-guided celiac plexus neurolysis

Ref.	Composition of injection solution	Complication	Treatment and outcome	Prevention recommendation
Fujii *et al*[47]	0.25% bupivacaine in 99% alcohol (ganglia: 1 mL; plexus: 23 mL)	Paraplegia	Remained paraplegic until death	Use color Doppler to avoid intravascular injection
Mittal *et al*[48]	0.25% bupivacaine and epinephrine with alcohol (1:5) (ganglia: 5 mL; around the celiac artery: 19 mL)	Paraplegia	Lumbar drainage but no improvement	Minimize the volume of absolute alcohol
Jang *et al*[56]	0.25% bupivacaine (5 mL), 98% ethanol (10 mL), triamcinolone (1 mL)	Hepatosplenic, stomach, and small bowel infarctions, gastroduodenal ulcers	Supportive treatment, died 27 d later	
Ahmed *et al*[57]	0.25% bupivacaine (20 mL), 98% ethanol (20 mL)	Pancreaticosplenic infarction, gastric ischemia and stenosis	Subtotal gastrectomy with Roux-en-Y gastrojejunostomy	
Gimeno-García *et al*[58]	0.5% bupivacaine (5 mL), absolute alcohol (10 mL) on each side of the celiac takeoff	Thrombosis of celiac artery, pneumatosis of the stomach andsmall and large intestines, and liver, kidney, and spleen infarctions	Conservative treatment, died 8 d later	
Muscatiello *et al*[59]	Not mentioned	Peripancreatic abscess	EUS-guided aspiration of abscess and ceftazidime injection	Consider antibiotic prophylaxis
Lalueza *et al*[60]	Not mentioned	Brain abscess by *Cladosporium macrocarpum* and *Streptococcus constellatus*	Surgery, antibiotics, and antifungal	

EUS: Endoscopic ultrasound.

emerged for treatment of refractory variceal bleeding. Numerous studies have reported on the feasibility, efficacy, and safety of such methods with the aid of EUS Doppler for treatment of esophagogastric[72-75] and ectopic varices[76-78]. EUS-guidance allows for optimization of the obliteration rate as well as reduction of cyanoacrylate to lower the risk of embolization, which, though not completely eliminated, is not fatal[73]. Sclerotherapy and cyanoacrylate injections have also been used for non-variceal bleeding from duodenal

ulcers, aneurysms, and Dieulafoy's lesion[79,80]. EUS-guided injection of cyanoacrylate and polidocanol for treatment of upper GI bleeding had a success rate of 87.5%, with only one of these eight cases experiencing asymptomatic cyanoacrylate diffusion into the hepatic artery[79].

Tumor-ablative therapy

EUS-guided procedures have also shown promise for the treatment of intra-abdominal tumors and cystic lesions, such as pancreatic cystic neoplasms. Currently, there are only a few reports of ethanol ablation with or without paclitaxel lavage for pancreatic cystic lesions[81-86]. Common complications with these procedures included acute pancreatitis, abdominal pain, and hyperamylasemia. One case experienced asymptomatic splenic vein obliteration with collateral formations after 27 mo[86]. Ethanol ablation has also been described for solid tumors in the abdomen, including pancreatic neuroendocrine tumors[87-90], a GI stromal tumor[91], metastatic lymph nodes[92], and metastatic tumors in the liver[93,94] and adrenal glands[95]. The majority of these cases were treated successfully without complications, except for low-grade fever and hematomas following liver tumor ablation[94].

There are a few reports describing EUS-guided injection of biologic agents[96] and oncolytic virus therapy[97], and insertion of radioactive seed, cryotherapy, and fiducial placement for stereotactic body radiotherapy[98-103] to treat pancreatic adenocarcinoma, a deadly cancer for which only 15%-20% of patients are candidates for curative resection[96]. Adverse events were rare for these procedures, consisting of duodenal perforations due to the EUS tip, effects from the injected agents[97], mild pancreatitis, cholangitis, bleeding and fever[99-101]. Antibiotic prophylaxis was utilized in one study[100], in order to prevent cholangitis.

CONCLUSION

Therapeutic EUS is becoming more prominent in the treatment of many diseases due to the increased accuracy afforded by real-time high-resolution imaging. As a result, information regarding possible complications is greatly needed. The review presented here describes some of the less common complications that have been reported in various EUS-guided applications. By acknowledging the adverse events that occur, we can gain a better understanding of their causes and preventative actions to increase the safety of these techniques. EUS-guided interventions have been utilized for procedures of biliary and pancreatic drainage and CPN, as well as for various intra-abdominal conditions. Potential complications and preventive strategies will become clearer in the future as the number of patients treated and procedures reported increase. The authors recommended that endosonographers apply this knowledge in routine endoscopic practice for monitoring and early detection (including treatment) of these uncommon adverse events for the best clinical outcomes.

REFERENCES

1 **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]

2 **Iwashita T**, Doi S, Yasuda I. Endoscopic ultrasound-guided biliary drainage: a review. *Clin J Gastroenterol* 2014; **7**: 94-102 [PMID: 24765215 DOI: 10.1007/s12328-014-0467-5]

3 **Kawakubo K**, Isayama H, Kato H, Itoi T, Kawakami H, Hanada K, Ishiwatari H, Yasuda I, Kawamoto H, Itokawa F, Kuwatani M, Iiboshi T, Hayashi T, Doi S, Nakai Y. Multicenter retrospective study of endoscopic ultrasound-guided biliary drainage for malignant biliary obstruction in Japan. *J Hepatobiliary Pancreat Sci* 2014; **21**: 328-334 [PMID: 24026963 DOI: 10.1002/jhbp.27]

4 **Takada J**, Carmo AM, Artifon EL. EUS-guided biliary drainage for malignant biliary obstruction in patients with failed ERCP. *J Intervent Gastroenterol* 2013; **3**: 76-81 [DOI: 10.7178/jig.128]

5 **Ang TL**, Teo EK, Fock KM. EUS-guided transduodenal biliary drainage in unresectable pancreatic cancer with obstructive jaundice. *JOP* 2007; **8**: 438-443 [PMID: 17625296]

6 **Artifon EL**, Takada J, Okawa L, Moura EG, Sakai P. EUS-guided choledochoduodenostomy for biliary drainage in unresectable pancreatic cancer: a case series. *JOP* 2010; **11**: 597-600 [PMID: 21068493]

7 **Hanada K**, Iiboshi T, Ishii Y. Endoscopic ultrasound-guided choledochoduodenostomy for palliative biliary drainage in cases with inoperable pancreas head carcinoma. *Dig Endosc* 2009; **21** Suppl 1: S75-S78 [PMID: 19691742 DOI: 10.1111/j.1443-1661.2009.00855.x]

8 **Prachayakul V**, Aswakul P. A novel technique for endoscopic ultrasound-guided biliary drainage. *World J Gastroenterol* 2013; **19**: 4758-4763 [PMID: 23922474 DOI: 10.3748/wjg.v19.i29.4758]

9 **Will U,** Fueldner F, Kern C, Meyer F. EUS-Guided Bile Duct Drainage (EUBD) in 95 Patients. *Ultraschall Med* 2015; **36**: 276-283 [PMID: 24854133 DOI: 10.1055/s-0034-1366557]

10 **Kim TH**, Kim SH, Oh HJ, Sohn YW, Lee SO. Endoscopic ultrasound-guided biliary drainage with placement of a fully covered metal stent for malignant biliary obstruction. *World J Gastroenterol* 2012; **18**: 2526-2532 [PMID: 22654450 DOI: 10.3748/wjg.v18.i20.2526]

11 **Bories E**, Pesenti C, Caillol F, Lopes C, Giovannini M. Transgastric endoscopic ultrasonography-guided biliary drainage: results of a pilot study. *Endoscopy* 2007; **39**: 287-291 [PMID: 17357952 DOI: 10.1055/s-2007-966212]

12 **Mallery S**, Matlock J, Freeman ML. EUS-guided rendezvous drainage of obstructed biliary and pancreatic ducts: Report of 6 cases. *Gastrointest Endosc* 2004; **59**: 100-107 [PMID: 14722561 DOI: 10.1016/S0016-5107(03)02300-9]

13 **Hara K**, Yamao K, Niwa Y, Sawaki A, Mizuno N, Hijioka S, Tajika M, Kawai H, Kondo S, Kobayashi Y, Matumoto K, Bhatia V, Shimizu Y, Ito A, Hirooka Y, Goto H. Prospective clinical study of EUS-guided choledochoduodenostomy for malignant lower biliary tract obstruction. *Am J Gastroenterol* 2011; **106**: 1239-1245 [PMID: 21448148 DOI: 10.1038/ajg.2011.84]

14 **Horaguchi J**, Fujita N, Noda Y, Kobayashi G, Ito K, Koshita S, Kanno Y, Ogawa T, Masu K, Hashimoto S, Ishii S. Metallic stent deployment in endosonography-guided biliary drainage: long-term follow-up results in patients with bilio-enteric anastomosis. *Dig Endosc* 2012; **24**: 457-461 [PMID: 23078440 DOI: 10.1111/j.1443-1661.2012.01316.x]

15 **Park do H**, Jang JW, Lee SS, Seo DW, Lee SK, Kim MH. EUS-guided biliary drainage with transluminal stenting after failed ERCP: predictors of adverse events and long-term results. *Gastrointest Endosc* 2011; **74**: 1276-1284 [PMID: 21963067 DOI: 10.1016/j.gie.2011.07.054]

16 **Komaki T**, Kitano M, Sakamoto H, Kudo M. Endoscopic

ultrasonography-guided biliary drainage: evaluation of a choledochoduodenostomy technique. *Pancreatology* 2011; **11** Suppl 2: 47-51 [PMID: 21464587 DOI: 10.1159/000323508]
17 **Prachayakul V,** Aswakul P. Successful endoscopic treatment of iatrogenic biloma as a complication of endosonography-guided hepaticogastrostomy: The first case report. *J Interv Gastroenterol* 2012; **2**: 202-204 [PMID: 23687611 DOI: 10.4161/jig.23750]
18 **Martins FP**, Rossini LG, Ferrari AP. Migration of a covered metallic stent following endoscopic ultrasound-guided hepaticogastrostomy: fatal complication. *Endoscopy* 2010; **42** Suppl 2: E126-E127 [PMID: 20405376 DOI: 10.1055/s-0029-1243911]
19 **Attasaranya S**, Netinasunton N, Jongboonyanuparp T, Sottisuporn J, Witeerungrot T, Pirathvisuth T, Ovartlarnporn B. The Spectrum of Endoscopic Ultrasound Intervention in Biliary Diseases: A Single Center's Experience in 31 Cases. *Gastroenterol Res Pract* 2012; **2012**: 680753 [PMID: 22654900 DOI: 10.1155/2012/680753]
20 **Püspök A**, Lomoschitz F, Dejaco C, Hejna M, Sautner T, Gangl A. Endoscopic ultrasound guided therapy of benign and malignant biliary obstruction: a case series. *Am J Gastroenterol* 2005; **100**: 1743-1747 [PMID: 16086710 DOI: 10.1111/j.1572-0241.2005.41806.x]
21 **Siddiqui AA**, Sreenarasimhaiah J, Lara LF, Harford W, Lee C, Eloubeidi MA. Endoscopic ultrasound-guided transduodenal placement of a fully covered metal stent for palliative biliary drainage in patients with malignant biliary obstruction. *Surg Endosc* 2011; **25**: 549-555 [PMID: 20632191 DOI: 10.1007/s00464-010-1216-6]
22 **Prachayakul V**, Thamtorawat S, Siripipattanamongkol C, Thanathanee P. Bleeding left hepatic artery pseudoaneurysm: a complication of endoscopic ultrasound-guided hepaticogastrostomy. *Endoscopy* 2013; **45** Suppl 2 UCTN: E223-E224 [PMID: 23939431 DOI: 10.1055/s-0033-1344064]
23 **Khashab MA**, Dewitt J. Treatment and prevention of wire shearing during EUS-guided biliary drainage. *Gastrointest Endosc* 2012; **76**: 921-923 [PMID: 22985651 DOI: 10.1016/j.gie.2012.05.018]
24 **Khashab MA**, Chithadi KV, Acosta RD, Bruining DH, Chandrasekhara V, Eloubeidi MA, Fanelli RD, Faulx AL, Fonkalsrud L, Lightdale JR, Muthusamy VR, Pasha SF, Saltzman JR, Shaukat A, Wang A, Cash BD. Antibiotic prophylaxis for GI endoscopy. *Gastrointest Endosc* 2015; **81**: 81-89 [PMID: 25442089 DOI: 10.1016/j.gie.2014.08.008]
25 **Fujii-Lau LL**, Levy MJ. Endoscopic ultrasound-guided pancreatic duct drainage. *J Hepatobiliary Pancreat Sci* 2015; **22**: 51-57 [PMID: 25385528 DOI: 10.1002/jhbp.187]
26 **Park do H**, Jeong SU, Lee BU, Lee SS, Seo DW, Lee SK, Kim MH. Prospective evaluation of a treatment algorithm with enhanced guidewire manipulation protocol for EUS-guided biliary drainage after failed ERCP (with video). *Gastrointest Endosc* 2013; **78**: 91-101 [PMID: 23523301 DOI: 10.1016/j.gie.2013.01.042]
27 **Romagnuolo J**. Endoscopic choledochoenterostomy using a new blunt-ended endoscopic ultrasound-guided access device. *Endoscopy* 2011; **43** Suppl 2 UCTN: E356-E357 [PMID: 22020725 DOI: 10.1055/s-0030-1256859]
28 **Saxena P**, Aguila G, Kumbhari V, Khashab MA. Untying the knot: technique of unraveling a guidewire knot created during EUS-guided biliary drainage. *Endoscopy* 2014; **46** Suppl 1 UCTN: E140-E141 [PMID: 24756263 DOI: 10.1055/s-0033-1359240]
29 **Barkay O**, Sherman S, McHenry L, Yoo BM, Fogel EL, Watkins JL, DeWitt J, Al-Haddad MA, Lehman GA. Therapeutic EUS-assisted endoscopic retrograde pancreatography after failed pancreatic duct cannulation at ERCP. *Gastrointest Endosc* 2010; **71**: 1166-1173 [PMID: 20303489 DOI: 10.1016/j.gie.2009.10.048]
30 **Tessier G**, Bories E, Arvanitakis M, Hittelet A, Pesenti C, Le Moine O, Giovannini M, Devière J. EUS-guided pancreatogastrostomy and pancreatobulbostomy for the treatment of pain in patients with pancreatic ductal dilatation inaccessible for transpapillary endoscopic therapy. *Gastrointest Endosc* 2007; **65**: 233-241 [PMID: 17258981 DOI: 10.1016/j.gie.2006.06.029]
31 **Seewald S**, Ang TL, Kida M, Teng KY, Soehendra N. EUS 2008 Working Group document: evaluation of EUS-guided drainage of pancreatic-fluid collections (with video). *Gastrointest Endosc* 2009; **69**: S13-S21 [PMID: 19179137 DOI: 10.1016/j.gie.2008.10.061]
32 **Fabbri C**, Luigiano C, Maimone A, Polifemo AM, Tarantino I, Cennamo V. Endoscopic ultrasound-guided drainage of pancreatic fluid collections. *World J Gastrointest Endosc* 2012; **4**: 479-488 [PMID: 23189219 DOI: 10.4253/wjge.v4.i11.479]
33 **Varadarajulu S**, Bang JY, Phadnis MA, Christein JD, Wilcox CM. Endoscopic transmural drainage of peripancreatic fluid collections: outcomes and predictors of treatment success in 211 consecutive patients. *J Gastrointest Surg* 2011; **15**: 2080-2088 [PMID: 21786063 DOI: 10.1007/s11605-011-1621-8]
34 **Fabbri C**, Luigiano C, Lisotti A, Cennamo V, Virgilio C, Caletti G, Fusaroli P. Endoscopic ultrasound-guided treatments: are we getting evidence based--a systematic review. *World J Gastroenterol* 2014; **20**: 8424-8448 [PMID: 25024600 DOI: 10.3748/wjg.v20.i26.8424]
35 **Ergun M**, Aouattah T, Gillain C, Gigot JF, Hubert C, Deprez PH. Endoscopic ultrasound-guided transluminal drainage of pancreatic duct obstruction: long-term outcome. *Endoscopy* 2011; **43**: 518-525 [PMID: 21437853 DOI: 10.1055/s-0030-1256333]
36 **Fujii LL**, Topazian MD, Abu Dayyeh BK, Baron TH, Chari ST, Farnell MB, Gleeson FC, Gostout CJ, Kendrick ML, Pearson RK, Petersen BT, Truty MJ, Vege SS, Levy MJ. EUS-guided pancreatic duct intervention: outcomes of a single tertiary-care referral center experience. *Gastrointest Endosc* 2013; **78**: 854-864.e1 [PMID: 23891418 DOI: 10.1016/j.gie.2013.05.016]
37 **Itoi T**, Kasuya K, Sofuni A, Itokawa F, Kurihara T, Yasuda I, Nakai Y, Isayama H, Moriyasu F. Endoscopic ultrasonography-guided pancreatic duct access: techniques and literature review of pancreatography, transmural drainage and rendezvous techniques. *Dig Endosc* 2013; **25**: 241-252 [PMID: 23490022 DOI: 10.1111/den.12048]
38 **Kurihara T**, Itoi T, Sofuni A, Itokawa F, Moriyasu F. Endoscopic ultrasonography-guided pancreatic duct drainage after failed endoscopic retrograde cholangiopancreatography in patients with malignant and benign pancreatic duct obstructions. *Dig Endosc* 2013; **25** Suppl 2: 109-116 [PMID: 23617660 DOI: 10.1111/den.12100]
39 **Donepudi S**, Chavalitdhamrong D, Pu L, Draganov PV. Air embolism complicating gastrointestinal endoscopy: A systematic review. *World J Gastrointest Endosc* 2013; **5**: 359-365 [PMID: 23951390 DOI: 10.4253/wjge.v5.i8.359]
40 **Jow AZ**, Wan D. Complication of cardiac air embolism during ERCP and EUS-assisted cyst-gastrostomy for pancreatic pseudocyst. *Gastrointest Endosc* 2012; **75**: 220-221 [PMID: 21492848 DOI: 10.1016/j.gie.2011.01.047]
41 **Hikichi T**, Irisawa A, Takagi T, Shibukawa G, Wakatsuki T, Imamura H, Takahashi Y, Sato A, Sato M, Oyama H, Sato N, Yamamoto G, Mokonuma T, Obara K, Ohira H. A case of transgastric gallbladder puncture as a complication during endoscopic ultrasound-guided drainage of a pancreatic pseudocyst. *Fukushima J Med Sci* 2007; **53**: 11-18 [PMID: 17957961 DOI: 10.5387/fms.53.11]
42 **Eisenberg E**, Carr DB, Chalmers TC. Neurolytic celiac plexus block for treatment of cancer pain: a meta-analysis. *Anesth Analg* 1995; **80**: 290-295 [PMID: 7818115 DOI: 10.1213/00000539-199502000-00015]
43 **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]
44 **O'Toole TM**, Schmulewitz N. Complication rates of EUS-guided celiac plexus blockade and neurolysis: results of a large case series. *Endoscopy* 2009; **41**: 593-597 [PMID: 19588286 DOI: 10.1055/s-0029-1214868]
45 **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]
46 **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]
47 **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]
48 **Mittal MK**, Rabinstein AA, Wijdicks EF. Pearls & amp; 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]
49 **van Dongen RT**, Crul BJ. Paraplegia following coeliac plexus block. *Anaesthesia* 1991; **46**: 862-863 [PMID: 1952003 DOI: 10.1111/j.1365-2044.1991.tb09603.x]
50 **Kumar A**, Tripathi SS, Dhar D, Bhattacharya A. A case of reversible paraparesis following celiac plexus block. *Reg Anesth Pain Med* 2001; **26**: 75-78 [PMID: 11172517 DOI: 10.1053/rapm.2001.20090]
51 **Kinoshita H**, Denda S, Shimoji K, Ohtake M, Shirai Y. Paraplegia following coeliac plexus block by anterior approach under direct vision. *Masui* 1996; **45**: 1244-1246 [PMID: 8937021]
52 **Abdalla EK**, Schell SR. Paraplegia following intraoperative celiac plexus injection. *J Gastrointest Surg* 2001; **3**: 668-671 [PMID: 10554376]
53 **Galizia EJ**, Lahiri SK. Paraplegia following coeliac plexus block with phenol. Case report. *Br J Anaesth* 1974; **46**: 539-540 [PMID: 4458776 DOI: 10.1093/bja/46.7.539]
54 **Wong GY**, Brown DL. Transient paraplegia following alcohol celiac plexus block. *Reg Anesth* 1995; **20**: 352-355 [PMID: 7577786]
55 **Davies DD**. Incidence of major complications of neurolytic coeliac plexus block. *J R Soc Med* 1993; **86**: 264-266 [PMID: 8505748]
56 **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]
57 **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]
58 **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]
59 **Muscatiello N**, Panella C, Pietrini L, Tonti P, Ierardi E. Complication of endoscopic ultrasound-guided celiac plexus neurolysis. *Endoscopy* 2006; **38**: 858 [PMID: 17001583 DOI: 10.1055/s-2006-925382]
60 **Lalueza A**, López-Medrano F, del Palacio A, Alhambra A, Alvarez E, Ramos A, Pérez A, Lizasoain M, Meije Y, García-Reyne A, Aguado JM. Cladosporium macrocarpum brain abscess after endoscopic ultrasound-guided celiac plexus block. *Endoscopy* 2011; **43** Suppl 2 UCTN: E9-10 [PMID: 21271535 DOI: 10.1055/s-0030-1255804]
61 **Singhal S**, Changela K, Lane D, Anand S, Duddempudi S. Endoscopic ultrasound-guided hepatic and perihepatic abscess drainage: an evolving technique. *Therap Adv Gastroenterol* 2014; **7**: 93-98 [PMID: 24587822 DOI: 10.1177/1756283X13506178]
62 **Noh SH**, Park do H, Kim YR, Chun Y, Lee HC, Lee SO, Lee SS, Seo DW, Lee SK, Kim MH. EUS-guided drainage of hepatic abscesses not accessible to percutaneous drainage (with videos). *Gastrointest Endosc* 2010; **71**: 1314-1319 [PMID: 20400078 DOI: 10.1016/j.gie.2009.12.045]
63 **Seewald S**, Imazu H, Omar S, Groth S, Seitz U, Brand B, Zhong Y, Sikka S, Thonke F, Soehendra N. EUS-guided drainage of hepatic abscess. *Gastrointest Endosc* 2005; **61**: 495-498 [PMID: 15758937 DOI: 10.1016/S0016-5107(04)02848-2]
64 **Itoi T**, Ang TL, Seewald S, Tsuji S, Kurihara T, Tanaka R, Itokawa F. Endoscopic ultrasonography-guided drainage for tuberculous liver abscess drainage. *Dig Endosc* 2011; **23** Suppl 1: 158-161 [PMID: 21535224 DOI: 10.1111/j.1443-1661.2011.01115.x]
65 **Ang TL**, Seewald S, Teo EK, Fock KM, Soehendra N. EUS-guided drainage of ruptured liver abscess. *Endoscopy* 2009; **41** Suppl 2: E21-E22 [PMID: 19219764 DOI: 10.1055/s-0028-1103468]
66 **Hadithi M**, Bruno MJ. Endoscopic ultrasound-guided drainage of pelvic abscess: A case series of 8 patients. *World J Gastrointest Endosc* 2014; **6**: 373-378 [PMID: 25132921 DOI: 10.4253/wjge.v6.i8.373]
67 **Trevino JM**, Drelichman ER, Varadarajulu S. Modified technique for EUS-guided drainage of pelvic abscess (with video). *Gastrointest Endosc* 2008; **68**: 1215-1219 [PMID: 19028235 DOI: 10.1016/j.gie.2008.07.016]
68 **Varadarajulu S**, Drelichman ER. Effectiveness of EUS in drainage of pelvic abscesses in 25 consecutive patients (with video). *Gastrointest Endosc* 2009; **70**: 1121-1127 [PMID: 19962502 DOI: 10.1016/j.gie.2009.08.034]
69 **Varadarajulu S**, Drelichman ER. EUS-guided drainage of pelvic abscess (with video). *Gastrointest Endosc* 2007; **66**: 372-376 [PMID: 17643716 DOI: 10.1016/j.gie.2007.02.054]
70 **Holt B**, Varadarajulu S. Endoscopic ultrasound-guided pelvic abscess drainage (with video). *J Hepatobiliary Pancreat Sci* 2015; **22**: 12-15 [PMID: 25159523 DOI: 10.1002/jhbp.150]
71 **Bokun T**, Grgurevic I, Kujundzic M, Banic M. EUS-Guided Vascular Procedures: A Literature Review. *Gastroenterol Res Pract* 2013; **2013**: 865945 [PMID: 23737766 DOI: 10.1155/2013/865945]
72 **Romero-Castro R**, Pellicer-Bautista FJ, Jimenez-Saenz M, Marcos-Sanchez F, Caunedo-Alvarez A, Ortiz-Moyano C, Gomez-Parra M, Herrerias-Gutierrez JM. EUS-guided injection of cyanoacrylate in perforating feeding veins in gastric varices: results in 5 cases. *Gastrointest Endosc* 2007; **66**: 402-407 [PMID: 17643723 DOI: 10.1016/j.gie.2007.03.008]
73 **Romero-Castro R**, Ellrichmann M, Ortiz-Moyano C, Subtil-Inigo JC, Junquera-Florez F, Gornals JB, Repiso-Ortega A, Vila-Costas J, Marcos-Sanchez F, Muñoz-Navas M, Romero-Gomez M, Brullet-Benedi E, Romero-Vazquez J, Caunedo-Alvarez A, Pellicer-Bautista F, Herrerias-Gutierrez JM, Fritscher-Ravens A. EUS-guided coil versus cyanoacrylate therapy for the treatment of gastric varices: a multicenter study (with videos). *Gastrointest Endosc* 2013; **78**: 711-721 [PMID: 23891417 DOI: 10.1016/j.gie.2013.05.009]
74 **Binmoeller KF**, Weilert F, Shah JN, Kim J. EUS-guided transesophageal treatment of gastric fundal varices with combined coiling and cyanoacrylate glue injection (with videos). *Gastrointest Endosc* 2011; **74**: 1019-1025 [PMID: 21889139 DOI: 10.1016/j.gie.2011.06.030]
75 **Lee YT**, Chan FK, Ng EK, Leung VK, Law KB, Yung MY, Chung SC, Sung JJ. EUS-guided injection of cyanoacrylate for bleeding gastric varices. *Gastrointest Endosc* 2000; **52**: 168-174 [PMID: 10922086 DOI: 10.1067/mge.2000.107911]
76 **Levy MJ**, Wong Kee Song LM, Kendrick ML, Misra S, Gostout CJ. EUS-guided coil embolization for refractory ectopic variceal bleeding (with videos). *Gastrointest Endosc* 2008; **67**: 572-574 [PMID: 17997404 DOI: 10.1016/j.gie.2007.06.063]
77 **Weilert F**, Shah JN, Marson FP, Binmoeller KF. EUS-guided coil and glue for bleeding rectal varix. *Gastrointest Endosc* 2012; **76**: 915-916 [PMID: 22172480 DOI: 10.1016/j.gie.2011.09.027]
78 **Kinzel J**, Pichetshote N, Dredar S, Aslanian H, Nagar A. Bleeding from a duodenal varix: a unique case of variceal hemostasis achieved using EUS-guided placement of an embolization coil and cyanoacrylate. *J Clin Gastroenterol* 2014; **48**: 362-364 [PMID: 24518801 DOI: 10.1097/MCG.0000000000000004]
79 **Gonzalez JM**, Giacino C, Pioche M, Vanbiervliet G, Brardjanian S, Ah-Soune P, Vitton V, Grimaud JC, Barthet M. Endoscopic ultrasound-guided vascular therapy: is it safe and effective? *Endoscopy* 2012; **44**: 539-542 [PMID: 22389233 DOI: 10.1055/s-0031-1291609]
80 **Levy MJ**, Wong Kee Song LM, Farnell MB, Misra S, Sarr MG, Gostout CJ. Endoscopic ultrasound (EUS)-guided angiotherapy of refractory gastrointestinal bleeding. *Am J Gastroenterol* 2008; **103**: 352-359 [PMID: 17986314 DOI: 10.1111/j.1572-0241.2007.01616.x]
81 **Gan SI**, Thompson CC, Lauwers GY, Bounds BC, Brugge WR. Ethanol lavage of pancreatic cystic lesions: initial pilot study. *Gastrointest Endosc* 2005; **61**: 746-752 [PMID: 15855986 DOI:

10.1016/S0016-5107(05)00320-2]
82 **DeWitt J**, McGreevy K, Schmidt CM, Brugge WR. EUS-guided ethanol versus saline solution lavage for pancreatic cysts: a randomized, double-blind study. *Gastrointest Endosc* 2009; **70**: 710-723 [PMID: 19577745 DOI: 10.1016/j.gie.2009.03.1173]
83 **Oh HC**, Seo DW, Lee TY, Kim JY, Lee SS, Lee SK, Kim MH. New treatment for cystic tumors of the pancreas: EUS-guided ethanol lavage with paclitaxel injection. *Gastrointest Endosc* 2008; **67**: 636-642 [PMID: 18262182 DOI: 10.1016/j.gie.2007.09.038]
84 **Oh HC**, Seo DW, Kim SC, Yu E, Kim K, Moon SH, Park do H, Lee SS, Lee SK, Kim MH. Septated cystic tumors of the pancreas: is it possible to treat them by endoscopic ultrasonography-guided intervention? *Scand J Gastroenterol* 2009; **44**: 242-247 [PMID: 18949629 DOI: 10.1080/00365520802495537]
85 **DiMaio CJ**, DeWitt JM, Brugge WR. Ablation of pancreatic cystic lesions: the use of multiple endoscopic ultrasound-guided ethanol lavage sessions. *Pancreas* 2011; **40**: 664-668 [PMID: 21562447 DOI: 10.1097/MPA.0b013e3182128d06]
86 **Oh HC**, Seo DW, Song TJ, Moon SH, Park do H, Soo Lee S, Lee SK, Kim MH, Kim J. Endoscopic ultrasonography-guided ethanol lavage with paclitaxel injection treats patients with pancreatic cysts. *Gastroenterology* 2011; **140**: 172-179 [PMID: 20950614 DOI: 10.1053/j.gastro.2010.10.001]
87 **Muscatiello N**, Nacchiero M, Della Valle N, Di Terlizzi F, Verderosa G, Salcuni A, Macarini L, Cignarelli M, Castriota M, D'Agnessa V, Ierardi E. Treatment of a pancreatic endocrine tumor by ethanol injection (PEI) guided by endoscopic ultrasound. *Endoscopy* 2008; **40** Suppl 2: E83 [PMID: 18633893 DOI: 10.1055/s-2007-995540]
88 **Jürgensen C**, Schuppan D, Neser F, Ernstberger J, Junghans U, Stölzel U. EUS-guided alcohol ablation of an insulinoma. *Gastrointest Endosc* 2006; **63**: 1059-1062 [PMID: 16733126 DOI: 10.1016/j.gie.2005.10.034]
89 **Deprez PH**, Claessens A, Borbath I, Gigot JF, Maiter D. Successful endoscopic ultrasound-guided ethanol ablation of a sporadic insulinoma. *Acta Gastroenterol Belg* 2008; **71**: 333-337 [PMID: 19198582]
90 **Levy MJ**, Thompson GB, Topazian MD, Callstrom MR, Grant CS, Vella A. US-guided ethanol ablation of insulinomas: a new treatment option. *Gastrointest Endosc* 2012; **75**: 200-206 [PMID: 22078104 DOI: 10.1016/j.gie.2011.09.019]
91 **Günter E**, Lingenfelser T, Eitelbach F, Müller H, Ell C. EUS-guided ethanol injection for treatment of a GI stromal tumor. *Gastrointest Endosc* 2003; **57**: 113-115 [PMID: 12518147 DOI: 10.1067/mge.2003.39]
92 **DeWitt J**, Mohamadnejad M. EUS-guided alcohol ablation of metastatic pelvic lymph nodes after endoscopic resection of polypoid rectal cancer: the need for long-term surveillance. *Gastrointest Endosc* 2011; **74**: 446-447 [PMID: 21481867 DOI: 10.1016/j.gie.2011.01.064]
93 **Barclay RL**, Perez-Miranda M, Giovannini M. EUS-guided treatment of a solid hepatic metastasis. *Gastrointest Endosc* 2002; **55**: 266-270 [PMID: 11818938 DOI: 10.1067/mge.2002.120784]
94 **Hu YH**, Tuo XP, Jin ZD, Liu Y, Guo Y, Luo L. Endoscopic ultrasound (EUS)-guided ethanol injection in hepatic metastatic carcinoma: a case report. *Endoscopy* 2010; **42** Suppl 2: E256-E257 [PMID: 20931470 DOI: 10.1055/s-0030-1255653]
95 **Artifon EL**, Lucon AM, Sakai P, Gerhardt R, Srougi M, Takagaki T, Ishioka S, Bhutani MS. EUS-guided alcohol ablation of left adrenal metastasis from non-small-cell lung carcinoma. *Gastrointest Endosc* 2007; **66**: 1201-1205 [PMID: 18061721 DOI: 10.1016/j.gie.2007.05.051]
96 **Hecht JR**, Farrell JJ, Senzer N, Nemunaitis J, Rosemurgy A, Chung T, Hanna N, Chang KJ, Javle M, Posner M, Waxman I, Reid A, Erickson R, Canto M, Chak A, Blatner G, Kovacevic M, Thornton M. EUS or percutaneously guided intratumoral TNFerade biologic with 5-fluorouracil and radiotherapy for first-line treatment of locally advanced pancreatic cancer: a phase I/II study. *Gastrointest Endosc* 2012; **75**: 332-338 [PMID: 22248601 DOI: 10.1016/j.gie.2011.10.007]
97 **Hecht JR**, Bedford R, Abbruzzese JL, Lahoti S, Reid TR, Soetikno RM, Kirn DH, Freeman SM. A phase I/II trial of intratumoral endoscopic ultrasound injection of ONYX-015 with intravenous gemcitabine in unresectable pancreatic carcinoma. *Clin Cancer Res* 2003; **9**: 555-561 [PMID: 12576418]
98 **Ryan DP**, Hong TS, Bardeesy N. Pancreatic adenocarcinoma. *N Engl J Med* 2014; **371**: 1039-1049 [PMID: 25207767 DOI: 10.1056/NEJMra1404198]
99 **Sanders MK**, Moser AJ, Khalid A, Fasanella KE, Zeh HJ, Burton S, McGrath K. EUS-guided fiducial placement for stereotactic body radiotherapy in locally advanced and recurrent pancreatic cancer. *Gastrointest Endosc* 2010; **71**: 1178-1184 [PMID: 20362284 DOI: 10.1016/j.gie.2009.12.020]
100 **Choi JH**, Seo DW, Park do H, Lee SK, Kim MH. Fiducial placement for stereotactic body radiation therapy under only endoscopic ultrasonography guidance in pancreatic and hepatic malignancy: practical feasibility and safety. *Gut Liver* 2014; **8**: 88-93 [PMID: 24516706 DOI: 10.5009/gnl.2014.8.1.88]
101 **Pishvaian AC**, Collins B, Gagnon G, Ahlawat S, Haddad NG. EUS-guided fiducial placement for CyberKnife radiotherapy of mediastinal and abdominal malignancies. *Gastrointest Endosc* 2006; **64**: 412-417 [PMID: 16923491 DOI: 10.1016/j.gie.2006.01.048]
102 **DiMaio CJ**, Nagula S, Goodman KA, Ho AY, Markowitz AJ, Schattner MA, Gerdes H. EUS-guided fiducial placement for image-guided radiation therapy in GI malignancies by using a 22-gauge needle (with videos). *Gastrointest Endosc* 2010; **71**: 1204-1210 [PMID: 20598247 DOI: 10.1016/j.gie.2010.01.003]
103 **Park WG**, Yan BM, Schellenberg D, Kim J, Chang DT, Koong A, Patalano C, Van Dam J. EUS-guided gold fiducial insertion for image-guided radiation therapy of pancreatic cancer: 50 successful cases without fluoroscopy. *Gastrointest Endosc* 2010; **71**: 513-518 [PMID: 20189509 DOI: 10.1016/j.gie.2009.10.030]

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New technologies and techniques to improve adenoma detection in colonoscopy

Ashley Bond, Sanchoy Sarkar

Ashley Bond, Sanchoy Sarkar, Department of Gastroenterology and Hepatology, Royal Liverpool and Broadgreen University Hospital Trust, Liverpool L7 8XP, United Kingdom

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Correspondence to: Dr. Sanchoy Sarkar, PhD, FRCP, BSc, Department of Gastroenterology and Hepatology, Royal Liverpool and Broadgreen University Hospital Trust, 5Z link, Prescot Street, Liverpool L7 8XP,
United Kingdom. sanchoy@aol.com
Telephone: +44-151-7063554
Fax: +44-151-7065832

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Abstract

Adenoma detection rate (ADR) is a key component of colonoscopy quality assessment, with a direct link between itself and future mortality from colorectal cancer. There are a number of potential factors, both modifiable and non-modifiable that can impact upon ADR. As methods, understanding and technologies advance, so should our ability to improve ADRs, and thus, reduce colorectal cancer mortality. This article will review new technologies and techniques that improve ADR, both in terms of the endoscopes themselves and adjuncts to current systems. In particular it focuses on effective techniques and behaviours, developments in image enhancement, advancement in endoscope design and developments in accessories that may improve ADR. It also highlights the key role that continued medical education plays in improving the quality of colonoscopy and thus ADR. The review aims to present a balanced summary of the evidence currently available and does not propose to serve as a guideline.

Key words: Colorectal cancer; Adenoma detection; New technology; Techniques; Colonoscopy

Core tip: The most important quality indicator in colonoscopy is Adenoma detection rate. It is associated with outcomes from colorectal cancer, with low detection rates being associated with increased mortality and poor outcomes. Whilst a number of technologies are emerging to improve adenoma detection rate (ADR), at present, it seems that education, team work and optimising current practice will provide the biggest gains in ADR whilst maintaining financial acceptability.

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INTRODUCTION

Colorectal cancer is the third most common cancer in men and the second in women. Worldwide, an estimated 1.2 million cases of colorectal cancer occur annually[1]. The highest incidence rates have previously been in North America, Australia, New Zealand, Europe, and Japan. In recent years some of these incidences has stabilised and even began to reduce, *e.g.*, United States and this may, in some part, be related to the introduction of national screening programmes (Figure 1).

Worldwide, colonoscopy forms the basis of colorectal cancer screening programmes and has been shown to reduce the risk of death from colorectal cancer through detection of tumours at an earlier, more treatable stage and through removal of precancerous adenomas[2]. There are a number of quality assurance measures for colonoscopy in screening programmes include caecal intubation rate, bowel preparation quality, complications, cancer detection and adenoma detection rate (ADR, the proportion of colonoscopies performed by a physician that detect at least one histologically confirmed colorectal adenoma). However, ADR is now established as the most important quality indicator due to 2 landmark studies. The first demonstrated increased risk of interval cancer when the colonoscopy is performed by an endoscopist with a ADR below 20%[3]. As a result professional societies recommend a detection rate of > 25% in order to be deemed adequate[4]. The second demonstrated an inverse relationship between ADR and the risks of interval colorectal cancer, advanced-stage interval cancer, and fatal interval cancer. With each 1.0% increase in ADR was associated with a 3.0% decrease in the risk of cancer[2].

There are a number of techniques and technologies, both established and emerging that provide an exciting and promising potential to improve ADR. This article will discuss effective technique and behaviours, developments in image enhancement, advancement in endoscope design and developments in accessories that may improve ADR.

EFFECTIVE TECHNIQUE AND BEHAVIOURS

Bowel preparation

Good bowel preparation is vital for effective lesion recognition at colonoscopy. Consequently, guidance from the United States multi-society task force for colorectal cancer recently published strong recommendations for adequate bowel preparation with split-dose regimes in order to optimise ADR[5]. Poor bowel preparation has been associated with a adenoma miss rate of 43%[6]. Studies have demonstrated a clear improvement in ADR (35%) with split dose preparation ($P \leqslant 0.001$). They also showed a clear improvement in caecal intubation rate (95.5%) and preparation quality[7]. Attempts to implement further measures to improve bowel preparation have also been studied. One such scheme studied telephone education relating to the bowel preparation prior to colonoscopy. There was a improvement in compliance, preparation quality and ADR[8].

Insertion and withdrawal polypectomy

Colonic configuration during insertion phase and withdrawal phase is different and some polyps seen during insertion are difficult to find during withdrawal and vice versa[9]. It is typical practice to perform the formal mucosal examination and polypectomy on withdrawal, noting any pathology on insertion for subsequent intervention. One study suggested this may not be preferable, finding that polyp < 10 mm identified during insertion are frequently missed on withdrawal, suggesting polypectomy during insertion[10]. A more recent study compared 610 colonoscopies where patients were randomised to either polypectomy during insertion and withdrawal or just withdrawal. In both arms, mean number of adenomas detected per patient were similar. With the only significant difference being that of insertion time[9]. Overall, the evidence suggests neither technique is superior over the other.

Retroflexion in the caecum

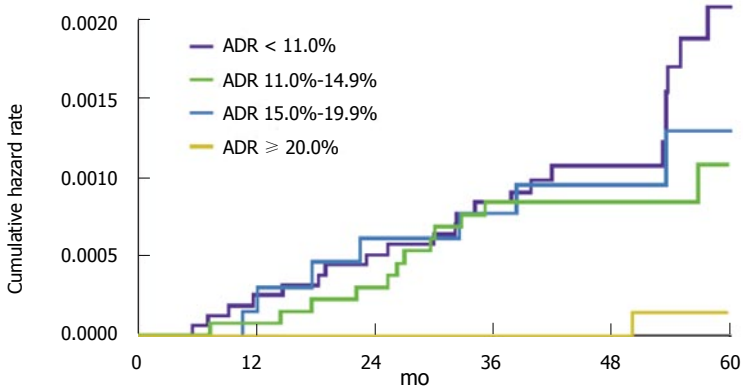
Rectal retroflexion forms part of the required standards for colonoscopy completion. Retroflexion in the right colon is not routinely performed but has been reported to improve ADR. A prospective cohort study conducted in the United States examined the potential impact of caecal retroflexion on ADR. One thousand consecutive adults undergoing colonoscopy were studied. A standard forward viewing colonoscopy of the right colon was performed and polyps were removed. There was then repeated examination in retroflexion from the caecum to the hepatic flexure. Retroflexion was successful in 94.4% of the patients. The subsequent examination in retroflexion demonstrated a 9.3% miss rate for the forward viewing method[11]. However, safety concerns have been raised due to the risk of perforation of using this technique.

Dynamic position change

Randomised controlled trials examining dynamic position changes have produced conflicting results regarding ADR, but predominate positive findings. It is clear that position change aids caecal intubation rate and patient comfort. Such position changes result in better distension with less insufflation of air, shifting of fluids and residues, and opening tight angles at flexures[12]. Specifically during withdrawal, such position changes have repeatedly been shown to improve ADR[13,14].

Antispasmodics

Hyoscine butylbromide is a relatively safe antispasmodic anticholinergic agent that blunts the response of colonic neurons to muscarinic and nicotinic stimulation which leads to inhibition of smooth muscle contraction in the



No. at risk

ADR < 11.0%	15883	15805	15744	15669	9355	4717
ADR 11.0%-14.9%	13281	13223	13182	13120	7571	4003
ADR 15.0%-19.9%	6607	6582	6562	6539	4022	2529
ADR ⩾ 20.0%	9255	9235	9202	9166	7155	5548

Figure 1 Cumulative hazard rates for interval colorectal cancer, according to the endoscopists adenoma detection rate. The graph shows cumulative hazard rates for interval colorectal cancer among subjects who underwent screening colonoscopy that was performed by an endoscopist with an ADR in one of the following categories: less than 11.0%, 11.0% to 14.9%, 15.0% to 19.9%, and 20.0% or more. ADR: Adenoma detection rate.

colon[15]. A recent meta-analysis assessed the results of 8 Randomised control trials (RCTs) conducted in Europe, Asia and Australia concluded hyoscine use in patients undergoing colonoscopy does not appear to significantly increase the detection of adenomas[16]. However, a recent study has shown that within the bowel cancer screening programme (BCSP) in England, it does improve ADR when used[17]. Recently, another antispasmodic topically applied: L-menthol (an organic compound found in peppermint oil, has been shown to improve ADR when sprayed on to the colonic mucosa during colonoscopy[18]. Whilst promising further studies are need to corroborate these findings.

Procedural factors-withdrawal time, use of sedation, colonoscopist and time of day

Variable factors inherent to colonoscopy have been shown to affect ADR. Time spent during the withdrawal phase is one such factor. A recent study within the BCSP in England demonstrated a plateau effect after approximately ten minutes. The lowest ADR was demonstrated if the withdrawal was less than 7 min, with the maximum ADR, seen with a withdrawal time of 9-11 min[17]. A multi centred RCT assessed multiple factors that may affect ADR, namely, bowel cleansing, sedation, withdrawal time in normal colonoscopies, and caecal intubation rates. They concluded a mean withdrawal time of > 8 min was the only modifiable factor related to the ADR in colorectal cancer screening colonoscopies[19].

Sedation use in one study found that larger amounts of sedation improved many aspects of colonoscopy quality. ADR increased (25.9% to 35%), early complications rate decreased (3.4% to 0.3%) and completion rates increased (88.3% to 96.4%)[20]. The mode of sedation that is used also appears to influence the quality of colonoscopy and particularly ADR. Again the literature reports conflicting results. A study which compared 843 colonoscopies found that deep sedation was associated with improved caecal intubation rates, and increased ADR. There were more immediate complications reported in the deep sedation group[21]. Another study suggested the type of sedation used during colonoscopy does not affect the number of patients in whom adenomatous polyps are detected. This followed a retrospective study that examined 3252 colonoscopies across two centres. ADR was the comparable for those receiving propofol and conscious sedation (midazolam and fentanyl)[22].

A variety of different studies have questioned whether the individual colonoscopist, *i.e.*, the person performing the examination, influences ADR. A study that assessed factors that influence the quality of 12000 screening colonoscopy found that annual case volume and life experience did not affect ADR but continued medical education (CME) was found to be most influential, with those who attended most CME meetings having the highest ADR[23]. These findings were supported by a study from the Mayo clinic that formally assessed the impact of a colonoscopy education program. An additional training program, known as Endoscopic Quality Improvement Program (EQUIP) was used. ADRs were measured at baseline, then half of the 15 colonoscopist were randomly assigned to EQUIP. Baseline and post training ADRs were then compared, a total of 1200 procedures were completed in each of the two study phases. In the post-training phase, the group of endoscopists randomized to EQUIP training had an increase in ADR to 47%, whereas the ADR for the group of endoscopists who were not trained remained unchanged at 35%[24].

The procedural start time may also affect ADRs

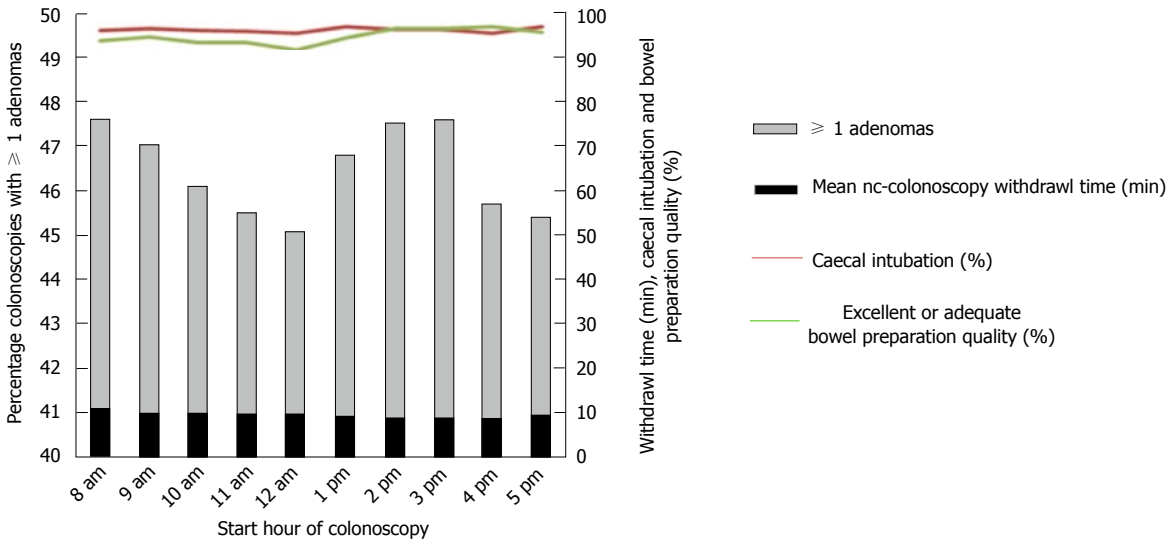


Figure 2 Relationship between start time of colonoscopy and adenoma detection, withdrawal time, caecal intubation, and bowel preparation quality.

as suggested by a study of > 31000 colonoscopies. Procedures starting in the second half of a session (11:00-14:00 or 16:00-18:00) were associated with a reduction in detection of adenomas and advanced adenomas compared with procedures starting between 08:00 and 11:00 or 14:00 and 16:00[17]. Having assistance from the entire technical team to spot abnormalities during the examination has also been shown to improve ADR. In one such study the process was termed "all eyes on screen", increasing ADR from 34% to 51% in 2 years[25]. A central visual gaze pattern on the colonoscopist has also been shown to improve ADR[26] (Figure 2).

Water infusion techniques

The original goal of this novel technique was to facilitate caecal intubation, reduce colonic spasms, lower patient discomfort and need for sedation, for which it performs well[27,28]. It works by combining or replacing air-insufflation with water infusion. Concerns have been raised about an impaired ability to detect lesions due to contaminated water impairing visibility[27]. A systematic review performed in 2012 reported no difference in ADR when comparing water infusion to conventional insufflations[29]. A similar technique is known as Water Exchange. The water-exchange method is a technique in which water containing residual faeces is removed and "exchanged" for clean water in lieu of air-insufflation. The exchange of large volumes of water during the insertion of the colonoscope results in additional cleansing of the mucosa[27]. A study in 2009 exploring this technique failed to reach statistical significance for an improved ADR[30]. Improved ADR was demonstrated in one study when they combined the water exchange technique with cap-assisted colonoscopy (P = 0.002)[31].

The prolonged insertion time, colonoscopist experience and general technicalities of these techniques including expense are likely to limit their introduction into routine practice.

IMAGE ENHANCEMENT TECHNIQUES AND TECHNOLOGY

Standard white light, high definition and zoom endoscopy

There is conflicting evidence when assessing the superiority of high definition colonoscopy *vs* standard white light. A meta-analysis involving 4422 patients provided data on ADR. There was no significant difference in detection of high risk ADR. The detection of small adenomas was slightly better in the high definition group, but overall the analysis concluded here were marginal differences between high definition colonoscopy and SVE for the detection of colonic polyps/adenomas[32]. A more recent study showed improved ADR with high definition colonoscopy, when used by endoscopists with a low ADR (< 20%). For those with an ADR already > 20% there was no improvement in detection of high risk polyps, flat polyps or proximal lesions[33]. In contrast, other studies that have directly compared high definition colonoscopy to standard video endoscopy have shown significant improvements in ADR. On such study did so without compromising procedure duration, caecal intubation or levels of sedation. The additional polyps detected were mainly flat and sessile[34]. A further study with similar design also showed a lower adenoma miss rate with high definition colonoscopy[35]. Interestingly, a study assessing the multiple factors that influence the quality of colonoscopy identified advancing generations of colonoscope technology as a positive effector over ADR[23].

In summary, it would appear there are gains to be made from the use of high definition colonoscopy, but these may be limited, but the use of new generation colonoscopes (compared to older ones) may be the important factor.

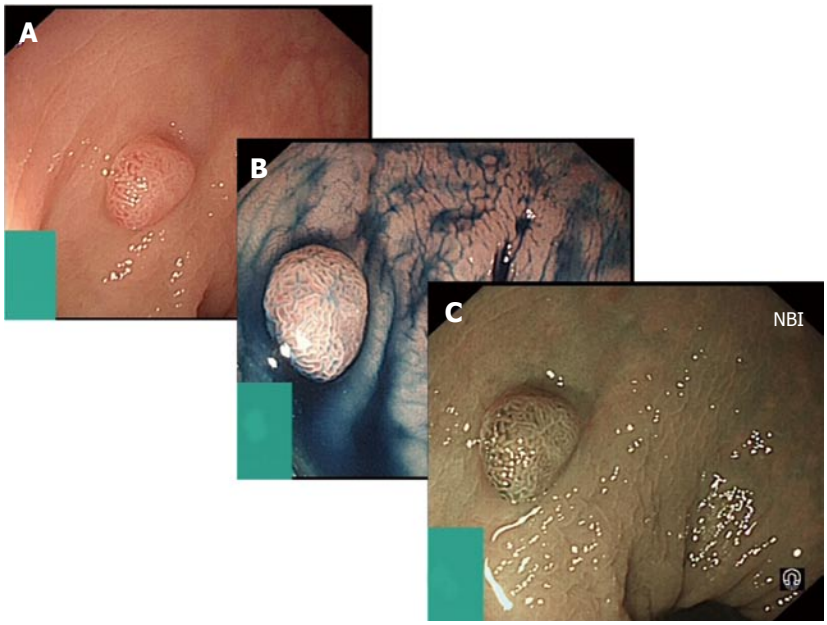


Figure 3 Digital chromoendoscopy. A: Represents sessile adenoma seen in standard white light; B: Shows the same adenoma after the use of indigo carmine applied for chromoendoscopy; C: Shows further assessment of the adenoma using narrow band imaging (NBI).

Chromoendoscopy

Chromoendoscopy refers to the topical application of stains or dyes at the time of endoscopy in an effort to enhance tissue characterization, differentiation, or diagnosis[36]. The stains that are used for chromoendoscopy are classified as absorptive, contrast, or reactive. Indigo carmine is an example of a contrast stain and is most commonly used to improve ADR. Indigo carmine staining combined with magnification endoscopy appears to be a useful technique for the detection of aberrant crypt foci in the rectum, a potential biomarker for proximal flat colonic neoplasia[36,37].

A number of studies have examined whether the use of chromoendoscopy can improve ADR when compared to conventional white light colonoscopy, many of which have demonstrated an increase in the yield of neoplasia detection[38-40]. Many of these studies examine its use in high risk groups[37], One study compared high-definition chromocolonoscopy with high-definition white light colonoscopy for the detection of colorectal adenomas in average-risk United States persons undergoing screening colonoscopy. They compared the colonoscopy results of 660 patients, finding no significant difference in the number of small adenomas, advanced adenoma or carcinoma. Concluding that their results do not support the routine use of high-definition chromocolonoscopy for colorectal screening in average-risk patients[41]. These conflicting results and the time consuming nature of dye spray may limit its adoption into routine screening of average risk patients.

New promising techniques are emerging, with stains incorporated into bowel preparation. One such formulation uses methylene blue (MB MMX, Cosmos Technolgies). This has been designed as a modified release device which ensures colonic release. The methylene blue is taken up by normal mucosa and poorly by neoplasia resulting in unstained areas where the lesions are present. A preliminary study has been promising on the efficacy of MB MMX 25 mg for the detection of polyps involved 96 patients undergoing routine colonoscopy. Polyps were detected in 61 patients, resulting in a 63.5% polyp detection rate[42].

Digital chromoendoscopy

Digital chromoendoscopy refers to advances in endoscope technology that manipulate wavelengths of the light source to create an effect similar to chromoendoscopy by accentuating lesion characteristics (Figure 3).

Narrow band imaging (NBI) is available on Olympus endoscopes. When used in colonoscopy, it allows potential improvement in ADR due to the enhanced appearance of certain mucosal and vascular features. A filter leads to the use of ambient light of wavelengths of 440 to 460 nm (blue) and 540 to 560 nm (green). Because the peak light absorption of haemoglobin occurs at these wavelengths, blood vessels will appear very dark, allowing for their improved visibility and the improved identification of other surface structures[43]. Compared with chromoendoscopy, classification of colorectal polyps by NBI appears to have a shorter learning curve. However, there is still substantial inter-observer variability, and classification of colorectal lesions based on vascular patterns is not objectively standardized yet[44]. A meta-analysis of 7 studies in 2936 patients showed no statistically significant difference in the overall adenoma detection rate with the use of NBI or white light (36% *vs* 34%, P = 0.4). They also showed no difference in the number of polyps detected between the two modalities (P = 0.2). A second met-analysis performed again failed

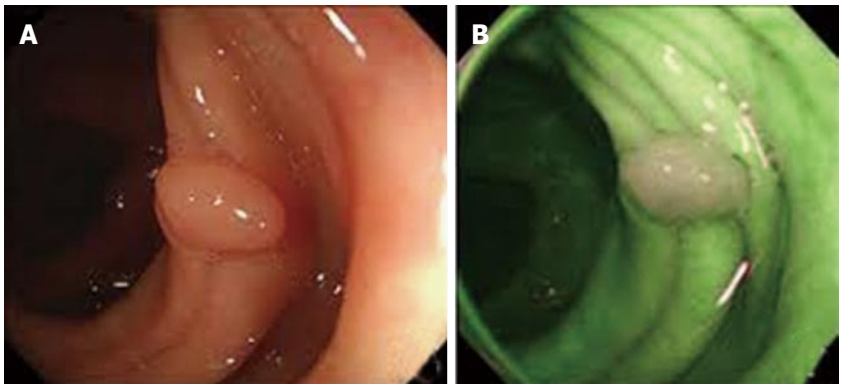


Figure 4 Digital-auto-fluorescence. A demonstrates polyp in white light, whilst B represents the same area in digital-auto-fluorescence. The normal mucosa appears green, with the adenoma appearing white.

show a significant difference in ADR between NBI and conventional white light. Concluding, NBI does not increase the yield of colon polyps, adenomas, or flat adenomas, nor does it decrease the miss rate of colon polyps or adenomas in patients undergoing screening/surveillance colonoscopy[45]. A further, larger, meta-analysis examined 11 RCTs evaluated NBI and ADR in a screening population of average- and higher-risk individuals and found limited benefit compared with white light colonoscopy[46]. These results were supported by a recent Cochrane review of 3673 patients in 8 randomized trials [relative risk (RR), 0.94; 95%CI: 0.87-1.02][47].

As with narrow-band imaging, the Fujinon intelligent colour enhancement (FICE) also narrows the bandwidth of conventional white-light colonoscopy to improve visualization, but it creates this effect electronically. Dedicated computer algorithms are used to generate the image. FICE enables the endoscopist to choose between different wavelengths for optimal examination of the colon mucosa[48]. It is reported to allow inspection of microvascular patterns as well as pit patterns and circumvents some limitations in conventional chromo-endoscopy[49]. Back to back studies have examined FICE and its impact upon ADR. Neither study demonstrated an improvement in ADR or adenoma miss rate when compared to NBI and white light[50,51].

The Pentax technology equivalent is i-Scan, for which there are limited RCT with most of the literature focusing on lesion characterisation. Some studies have compared high definition scopes coupled with i-Scan against standard resolution scopes. One such study demonstrated significantly more neoplastic lesions and more flat adenomas could be detected using high definition endoscopy with surface enhancement. Histology could be predicted with high accuracy (98.6%) within the HD+ group[52].

Digital-auto-fluorescence

Digital-auto-fluorescence (AFI) is technology available only in Olympus endoscopes where rotating filter wheel in front of the light source sequentially generates blue light (390-470 nm) and green light (540-560 nm)[53]. The exposure of tissue to this specific light leads to the excitation of some endogenous substances and subsequently the emission of fluorescent light. The reflected blue light is blocked by a second filter while the reflected red light and the emitted green autofluorescence from the tissue are used to obtain an image. AFI colonoscopy colours neoplastic lesions red-purple while non-neoplastic mucosa appears green[27] (Figure 4).

Three of the most widely reported studies comparing AFI and white light describe a lower adenoma miss rate with AFI, with up to a 20% difference[54-56]. One study reported that the detection rate of flat and depressed adenoma, but not elevated adenoma; by AFI is significantly higher than that by white light. In less experienced hands, AFI dramatically increased the detection rate (30.3%) and reduced miss rate (0%) of colorectal adenoma in comparison to white light (7.7%, 50.0%); this was not seen with more experienced endoscopists. They did describe a significantly longer duration time in the AFI group[54]. Another study explored the use of AFI in those undergoing colonoscopy for Lynch syndrome surveillance or those with a family history of colorectal cancer (one first-degree relative with colorectal cancer diagnosed at a young age (< 50 years) or two first-degree relatives regardless of age). This study reported a significantly higher sensitivity of AFI compared with white light (92% *vs* 68%; $P = 0.001$). The additionally detected adenomas with AFI were significantly smaller than the adenomas detected by white light (mean 3.0 mm *vs* 4.9 mm, $P < 0.01$)[55]. AFI also achieved better diagnostic accuracy (77%) than white light (57%) or NBI (63%) for polyp differentiation in the evaluation of still images by inexperienced endoscopists (accuracy compared with white light, $P = 0.001$; with NBI, $P = 0.016$)[57].

At present, whilst evidence exists that digital chromoendoscopic techniques (NBI, FICE and i-Scan) aide's lesion recognition, the evidence does not currently support that it improves ADR. There is some evidence to support of the positive effects of AFI, however, it is associated with added expense and poor image resolution, which are practical concerns for the

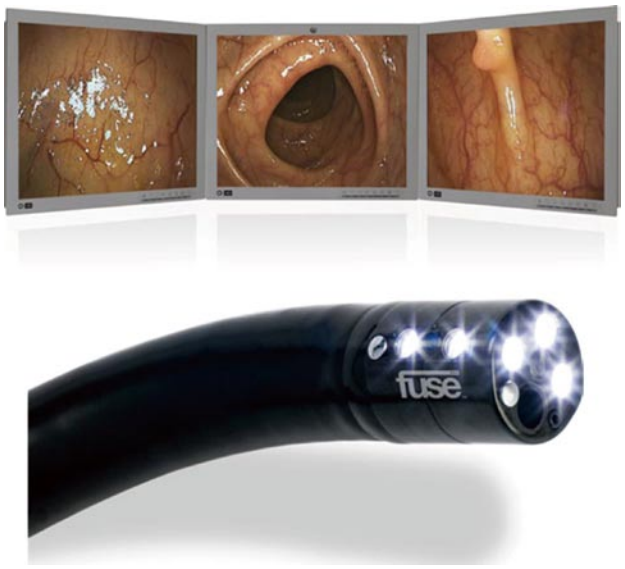


Figure 5 Example of the display module of the full spectrum endoscopy system and the 330° view (top). Bottom image is the full spectrum endoscopy scope demonstrating the side mounted camera and lights[27].

widespread introduction of this technology.

ADVANCEMENTS IN ENDOSCOPE DESIGN

Extra-wide angle view colonoscopes

This may represent one of the few recent developments in the design of the colonoscope that aide ADR. The full spectrum endoscopy (FUSE) system (EndoChoice) is currently on the market. It allows for full-spectrum views of the colon lumen, comprising 330 degrees. The colonoscope in the Fuse system has 2 additional cameras, on the left and right side of the scope's tip, to supplement the front camera. The video images transmitted from the cameras are displayed on 3 contiguous monitors corresponding to each camera. This array provides a comprehensive view of the total colonic lumen, including imaging of the traditionally encountered blind spots at the flexures or proximal edges of the mucosal folds (Figure 5).

During its initial development, trials revolved around anatomical models with simulated polyps, some of which were purposely placed in the tradition blind spot, *e.g.*, behind folds. In one such study 37 endoscopists performed colonoscopy by using the forward-viewing camera scope, followed by a colonoscopy with all 3 camera on; this increases the field of view to previously described 330 degrees. In total, 85.7% of the polyps were detected with the three cameras compared to 52.9% with only forward-viewing colonoscopy ($P \leqslant 0.001$). Particularly polyps that were "hidden" behind flexures and folds were more frequently detected with FUSE colonoscopy than with forward-viewing colonoscopy (81.9% *vs* 31.9%)[58]. An international, multicentre, randomised trial, the results of which were published in 2014 examined the use of FUSE further. Patients aged 18-70 years referred for colorectal cancer screening, polyp surveillance, or diagnostic assessment, were included. One hundred and eighty-five participants were assessed. The adenoma miss rate was significantly lower in patients in the FUSE group than in those in the standard forward-viewing procedure group: (7%) *vs* (41%) ($P = 0.0001$). In those who underwent standard colonoscopy first ($n = 88$), the FUSA system detected 39 additional polyps[59]. The authors reported a significantly longer withdrawal time ($P \leqslant 0.01$), however in real-time this was only a median time of 30 s. There certainly appears to be promise for ADR improvement with the FUSE system, more numerous and larger RCT's will be required to confirm this.

The findings from a study examining the effectiveness of a prototype wide angled colonoscopy were recently reported. The prototype colonoscope has a extra-wide angle of view has a 144°-232°-angle lateral-backward viewing lens in addition to a standard 140°-angle forward-viewing lens. Views from both lenses are simultaneously constructed and displayed on a video monitor as a single image. The ADR reported from this study was 57.1%, achieved whilst maintaining appropriate caecal intubation rate, completion times and no adverse event[60].

Balloon assisted colonoscopy

The NaviAid G-EYE colonoscope (SMART Medical Systems) is one such system. With this there is an integrated balloon on the flexible tip of the scope. The balloon can be reprocessed and reinflated by the endoscopist upon withdrawal of the scope. The mechanical flattening and straightening of haustral folds with the inflated balloon permit visualization of hidden anatomic areas, thus increasing the ADR[28]. Only simulated studies on anatomical models exist for this device. One such study showed a significantly greater ADR in the balloon assisted group ($P \leqslant 0.0001$)[61]. Clearly larger scale human studies are required to more about the utility of this device.

Real-time histology and confocal microscopy

Confocal laser endomicroscopy (CLE) is an emerging technology, which allows *in vivo* imaging of cellular and subcellular details of the gut mucosa and vessels during ongoing endoscopy. The most commonly used contrast agents are acriflavine hydrochloride and fluorescein sodium. For colon pathology assessment, the administration of fluorescein intravenously produces a strong staining of both surface epithelium and deeper layers of lamina propria[62,63]. Mounted into the end of a regular colonoscope is a miniature confocal microscope. When the tip of the scope is placed in direct contact with the mucosa and an argon ion laser excites the tissue a grayscale image can be produced, with a 7 μm thickness and a lateral resolution of 0.7 μm, the field of view being 475 μm × 475 μm[63] (Figure 6).

A number of studies have demonstrated the ability of confocal microendosocopy to perform real time

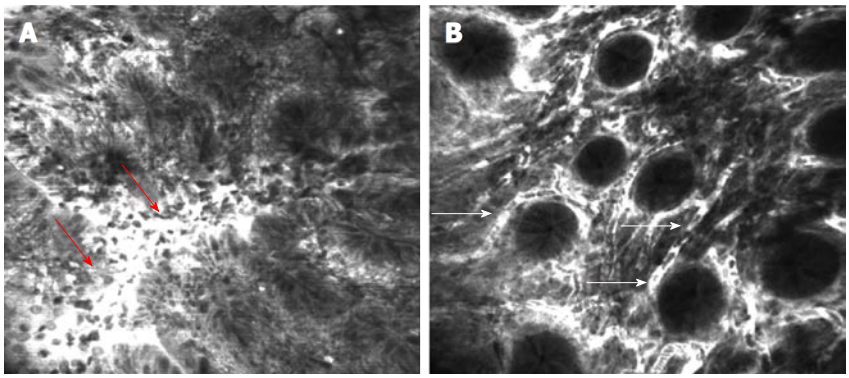


Figure 6 Confocal laser endomicroscopy of the colon using intravenous fluorescein. A: Colon carcinoma with total disorganization of cell architecture, invasion and destruction of the vessels with leakage of fluorescein (arrows); B: Severe inflammatory changes in ulcerative colitis with cellular infiltrate causing an increase in the distance between crypts and excessive vascularity (arrows)[63].

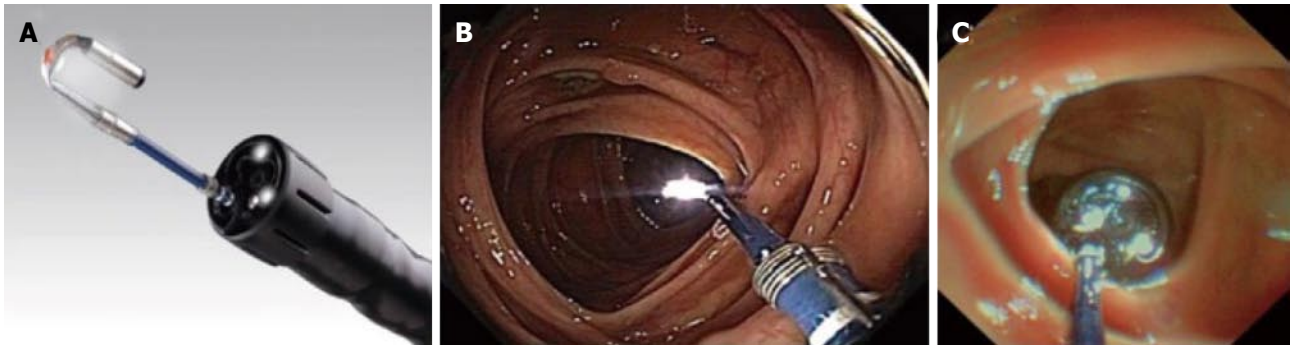


Figure 7 Third eye retroscope®. A: Image of the third eye retroscope® protruding from the working channel of the colonoscope; B: Forward view of third-eye retroscope®; C: View from lens of third-eye retroscope®[27].

histological analysis. Showing its ability to separate hyperplastic and adenomatous polyps, whilst identifying malignant features also[62-64]. The application of confocal is somewhat in its infancy, however as things develop real-time microendoscopy may become mainstream for endoscopist. There is little evidence to suggest that confocal can improve ADR, but it can improve decision making once the adenoma is detected.

DEVELOPMENTS IN ACCESSORIES

Third eye retroscope®

Third eye retroscope® (Avantis Medical Systems, Inc) consists of a video processor, a single-use polarizing filter cap for the colonoscope light source, and a 3.5 mm flexible single-use catheter with a camera and diode light source at the tip. The retroscope is retroflexed 180 degrees after being advanced through the working channel of the colonoscope and provides a 135 degrees retrograde view of the colon[27]. The system has been quoted to increase mucosal visualisation from 87% to 99%[65]. Like the FUSE system, initial studies of the third-eye system used anatomical models with simulated polyps. Standard colonoscopy detected 12% of the polyps located on the proximal aspects of folds, while 81% of these polyps were detected with the third eye retroscope[66]. A study demonstrated a 14.8% increase in polyp detection and a 16.0% increase in adenoma detection in their study that included 298 patients[67]. A further study reported similar result with a 13.2% increase in polyp detection and a 11.0% increase in adenoma detection[68]. The largest study for Third eye was the TERRACE study. TERRACE was a multi-centred study that included 349 patients. A net additional detection rate with the third eye retroscope of 29.8% for polyps and 23.2% for adenomas was reported. The study was criticised as the withdrawal time for the Third eye scopes were on average 2 min longer, however post-hoc analysis found withdrawal time to be independent of ADR[69] (Figure 7).

Despite the apparent improved ADR and reduced miss rate, third eye endoscopy has some significant flaws. It results in a 50% reduction in suction capacity; it needs to be removed from the working channel as another device is required and is very expensive[27].

Cap assistance

Transparent caps attached to the distal tip of the colonoscope were first designed to assist during endoscopic mucosal resection but they have also been suggested to be of help in depressing colonic folds to improve visualization of their proximal aspects[27]. Particularly in the hands of trainees and less-experienced colonoscopist they have been shown to improve

caecal intubation times and rates[70]. Most recently, a study, assessed ADR using cap-assisted colonoscopy *vs* normal colonoscopy. A total of 1380 patients were randomly allocated cap-assisted or normal, these consisted of asymptomatic participants (aged 50-75 years) in a primary colonoscopy screening programme. There was no significant difference in the type, location, size or number of polyps detected between the two groups. Caecal intubation time and Gloucester Comfort Scores were lower in the cap-assisted group[71]. A further study had similar finding, only demonstrated a superior ADR for polyps < 5 mm in the cap-assisted group[72]. Such finding have been persistent in other studies over the last decade with one of the original cap-assisted studies that examined 684 patients failing to demonstrate a significant difference in ADR[70]. This has been supported further by a meta-analysis performed in 2012 that concluded cap-assisted colonoscopy does not significantly improve ADR[73]. It would appear that cap-assisted colonoscopy may be of benefit in reducing caecal intubation time, but has limited or no benefit on polyp detection.

A similar device is Endocuff (Arc Medical, United States). Endocuff has been introduced as a means of enhancing visualization and scope stability during endoscopic mucosal resection of large or flat polyps of the sigmoid colon[74]. The Endocuff is a 2-cm long, flexible cuff with 2 rows of small flexible, hinged wings that help flatten large mucosal folds during withdrawal of the instrument. A prospective randomized trial in 498 patients undergoing screening colonoscopy showed Endocuff-assisted colonoscopy increased the absolute rate of polyp detection by 14% over unassisted colonoscopy from 42% to 56% (P = 0.001). The increase was particularly marked for polyps in the sigmoid colon 32% *vs* 15% (P = 0.0001) and caecum 4% *vs* 7% (P = 0.019)[75].

CONCLUSION

Novel and refinement of existing techniques, together with advancements in technologies can improve ADRs, and thus, potentially reduce cancer mortality. The use of chromoendoscopy in high risk groups such as colitis or HNPCC is becoming standard practice, but remains unsubstantiated for general use and is impractical. However, the development oral preparation given with the bowel preparation is a promising development. Increased ADR is yet to be proven with NBI, FICE and AFI beyond the use of high quality colonoscopes, and the marginal gains of using water exchange endoscopy are negated by time constraints, expense and further technical points for widespread application. Extra-wide angle colonoscopes such has FUSE has additional cost but its significant ADR may in the long-term make this economically viable, but more studies investigating the diagnostic before this device can be recommended for routine practice. The third-eye retroscope may be prohibited by cost, despite the apparent benefit, In contrast, cap-assistance is relatively inexpensive and further studies may show such devices as the Endo-cuff to be cost effective in improving ADR. However, at present, it seems that education, team work and optimising current practice will provide the biggest gains in ADR whilst maintaining financial acceptability.

REFERENCES

1 **Ferlay J**, Shin HR BF, Bray F, Forman D, Mathers C, Parkin DM. GLOBOCAN 2008 v2.0. Cancer Incidence and Mortality Worldwide: IARC Cancer Base No. 10 2010. 2008

2 **Corley DA**, Jensen CD, Marks AR, Zhao WK, Lee JK, Doubeni CA, Zauber AG, de Boer J, Fireman BH, Schottinger JE, Quinn VP, Ghai NR, Levin TR, Quesenberry CP. Adenoma detection rate and risk of colorectal cancer and death. *N Engl J Med* 2014; **370**: 1298-1306 [PMID: 24693890 DOI: 10.1056/NEJMoa1309086]

3 **Kaminski MF**, Regula J, Kraszewska E, Polkowski M, Wojciechowska U, Didkowska J, Zwierko M, Rupinski M, Nowacki MP, Butruk E. Quality indicators for colonoscopy and the risk of interval cancer. *N Engl J Med* 2010; **362**: 1795-1803 [PMID: 20463339 DOI: 10.5217/ir.2010.8.1.91]

4 **Rex DK**, Petrini JL, Baron TH, Chak A, Cohen J, Deal SE, Hoffman B, Jacobson BC, Mergener K, Petersen BT, Safdi MA, Faigel DO, Pike IM. Quality indicators for colonoscopy. *Am J Gastroenterol* 2006; **101**: 873-885 [PMID: 16635231 DOI: 10.1016/j.gie.2006.02.021]

5 **Johnson DA**, Barkun AN, Cohen LB, Dominitz JA, Kaltenbach T, Martel M, Robertson DJ, Richard Boland C, Giardello FM, Lieberman DA, Levin TR, Rex DK. Optimizing adequacy of bowel cleansing for colonoscopy: recommendations from the US Multi-Society Task Force on Colorectal Cancer. *Am J Gastroenterol* 2014; **109**: 1528-1545 [PMID: 25223578 DOI: 10.1053/j.gastro.2014.07.002]

6 **Lebwohl B,** Kastrinos F, Michael Glick AJ, Rosenbaum BA, Wang T, Alfred I. Neugut M. The Impact of Suboptimal Preparation on Adenoma Miss Rates and the Factors Associated with Early Repeat Colonoscopy. *Gastrointest Endosc* 2011; **73**: 1207-1214 [DOI: 110.1016/j.gie.2011.01.051]

7 **Gurudu SR**, Ramirez FC, Harrison ME, Leighton JA, Crowell MD. Increased adenoma detection rate with system-wide implementation of a split-dose preparation for colonoscopy. *Gastrointest Endosc* 2012; **76**: 603-8.e1 [PMID: 22732876 DOI: 10.1016/j.gie.2012.04.456]

8 **Liu X**, Luo H, Zhang L, Leung FW, Liu Z, Wang X, Huang R, Hui N, Wu K, Fan D, Pan Y, Guo X. Telephone-based re-education on the day before colonoscopy improves the quality of bowel preparation and the polyp detection rate: a prospective, colonoscopist-blinded, randomised, controlled study. *Gut* 2014; **63**: 125-130 [PMID: 23503044 DOI: 10.1136/gutjnl-2012-304292]

9 **Sanaka MR**, Parsi MA, Burke CA, Barnes D, Church J, Rizk M, Zein N, Joseph R, Thota PN, Lopez R, Kiran RP. Adenoma detection at colonoscopy by polypectomy in withdrawal only versus both insertion and withdrawal: a randomized controlled trial. *Surg Endosc* 2015; **29**: 692-699 [PMID: 25037727 DOI: 10.1007/s00464-014-3723-3]

10 **Wildi SM**, Schoepfer AM, Vavricka SR, Fruehauf H, Safroneeva E, Wiegand N, Bauerfeind P, Fried M. Colorectal polypectomy during insertion and withdrawal or only during withdrawal? A randomized controlled trial. *Endoscopy* 2012; **44**: 1019-1023 [PMID: 22930173 DOI: 10.1055/s-0032-1310237]

11 **Hewett DG**, Rex DK. Miss rate of right-sided colon examination during colonoscopy defined by retroflexion: an observational study. *Gastrointest Endosc* 2011; **74**: 246-252 [PMID: 21679946 DOI: 10.1016/j.gie.2011.04.005]

12 **Ghosh S**, Iacucci M. Dynamic position change at colonoscopy improves adenoma detection. *Can J Gastroenterol* 2013; **27**: 508 [PMID: 24078933]

13 **East JE**, Bassett P, Arebi N, Thomas-Gibson S, Guenther T, Saunders BP. Dynamic patient position changes during colonoscope withdrawal increase adenoma detection: a randomized, crossover

trial. *Gastrointest Endosc* 2011; **73**: 456-463 [PMID: 20950801 DOI: 10.1016/j.gie.2010.07.046]
14 **Köksal AŞ**, Kalkan IH, Torun S, Taşkıran I, Öztaş E, Kayaçetin E, Şaşmaz N. A simple method to improve adenoma detection rate during colonoscopy: altering patient position. *Can J Gastroenterol* 2013; **27**: 509-512 [PMID: 24078934]
15 **Krueger D**, Michel K, Allam S, Weiser T, Demir IE, Ceyhan GO, Zeller F, Schemann M. Effect of hyoscine butylbromide (Buscopan®) on cholinergic pathways in the human intestine. *Neurogastroenterol Motil* 2013; **25**: e530-e539 [PMID: 23682729 DOI: 10.1111/nmo.12156]
16 **Ashraf I**, Ashraf S, Siddique S, Nguyen DL, Choudhary A, Bechtold ML. Hyoscine for polyp detection during colonoscopy: A meta-analysis and systematic review. *World J Gastrointest Endosc* 2014; **6**: 549-554 [PMID: 25400869 DOI: 10.4253/wjge.v6.i11.549]
17 **Lee TJ**, Rees CJ, Blanks RG, Moss SM, Nickerson C, Wright KC, James PW, McNally RJ, Patnick J, Rutter MD. Colonoscopic factors associated with adenoma detection in a national colorectal cancer screening program. *Endoscopy* 2014; **46**: 203-211 [PMID: 24473907 DOI: 10.1055/s-0033-1358831]
18 **Inoue K**, Dohi O, Gen Y, Jo M, Mazaki T, Tokita K, Yoshida N, Okayama T, Kamada K, Katada K, Uchiyama K, Ishikawa T, Handa O, Takagi T, Konishi H, Wakabayashi N, Yagi N, Naito Y, Itoh Y. L-menthol improves adenoma detection rate during colonoscopy: a randomized trial. *Endoscopy* 2014; **46**: 196-202 [PMID: 24573731 DOI: 10.1055/s-0034-1365035]
19 **Jover R**, Zapater P, Polanía E, Bujanda L, Lanas A, Hermo JA, Cubiella J, Ono A, González-Méndez Y, Peris A, Pellisé M, Seoane A, Herreros-de-Tejada A, Ponce M, Marín-Gabriel JC, Chaparro M, Cacho G, Fernández-Díez S, Arenas J, Sopeña F, de-Castro L, Vega-Villaamil P, Rodríguez-Soler M, Carballo F, Salas D, Morillas JD, Andreu M, Quintero E, Castells A. Modifiable endoscopic factors that influence the adenoma detection rate in colorectal cancer screening colonoscopies. *Gastrointest Endosc* 2013; **77**: 381-389.e1 [PMID: 23218945 DOI: 10.1016/j.gie.2012.09.027]
20 **Triantafyllou K**, Sioulas AD, Kalli T, Misailidis N, Polymeros D, Papanikolaou IS, Karamanolis G, Ladas SD. Optimized sedation improves colonoscopy quality long-term. *Gastroenterol Res Pract* 2015; **2015**: 195093 [PMID: 25648556 DOI: 10.1155/2015/195093]
21 **Parra V**, Watanabe J, Nago A, Astete M, Rodríguez C, Valladares G, Nuñez N, Yoza M, Gargurevich T, Pinto J. Sedation used during colonoscopies at the Peruvian-Japanese policlinic. Their relationship with quality indicators. *Rev Gastroenterol Peru* 2010; **30**: 40-45 [PMID: 20445723]
22 **Metwally M**, Agresti N, Hale WB, Ciofoaia V, O'Connor R, Wallace MB, Fine J, Wang Y, Gross SA. Conscious or unconscious: the impact of sedation choice on colon adenoma detection. *World J Gastroenterol* 2011; **17**: 3912-3915 [PMID: 22025879 DOI: 10.3748/wjg.v17.i34.3912]
23 **Adler A**, Wegscheider K, Lieberman D, Aminalai A, Aschenbeck J, Drossel R, Mayr M, Mroß M, Scheel M, Schröder A, Gerber K, Stange G, Roll S, Gauger U, Wiedenmann B, Altenhofen L, Rosch T. Factors determining the quality of screening colonoscopy: a prospective study on adenoma detection rates, from 12,134 examinations (Berlin colonoscopy project 3, BECOP-3). *Gut* 2013; **62**: 236-241 [PMID: 22442161 DOI: 10.1136/gutjnl-2011-300167]
24 **Coe SG**, Crook JE, Diehl NN, Wallace MB. An endoscopic quality improvement program improves detection of colorectal adenomas. *Am J Gastroenterol* 2013; **108**: 219-226; quiz 227 [PMID: 23295274 DOI: 10.1038/ajg.2012.417]
25 **Saunders F**, Allegretti P SD. Adenoma Detection Rate (ADR) as a Quality Standard in a Privately Operated Community Surgical Center. *Am J Gastroenterol* 2012; **107**: S796–S797
26 **Almansa C**, Shahid MW, Heckman MG, Preissler S, Wallace MB. Association between visual gaze patterns and adenoma detection rate during colonoscopy: a preliminary investigation. *Am J Gastroenterol* 2011; **106**: 1070-1074 [PMID: 21326224 DOI: 10.1016/j.gie.2010.03.178]
27 **Dik VK**, Moons LM, Siersema PD. Endoscopic innovations to increase the adenoma detection rate during colonoscopy. *World J Gastroenterol* 2014; **20**: 2200-2211 [PMID: 24605019 DOI: 10.3748/wjg.v20.i9.2200]
28 **Titi M**, Gupta GSP. Advanced Colonoscopic Imaging: Do New Technologies Improve Adenoma Detection? *Gastroenterol Endosc News* 2014; **12**
29 **Leung FW**, Amato A, Ell C, Friedland S, Harker JO, Hsieh YH, Leung JW, Mann SK, Paggi S, Pohl J, Radaelli F, Ramirez FC, Siao-Salera R, Terruzzi V. Water-aided colonoscopy: a systematic review. *Gastrointest Endosc* 2012; **76**: 657-666 [PMID: 22898423 DOI: 10.1016/j.gie.2012.04.467]
30 **Leung FW**, Aharonian HS, Leung JW, Guth PH, Jackson G. Impact of a novel water method on scheduled unsedated colonoscopy in U.S. veterans. *Gastrointest Endosc* 2009; **69**: 546-550 [PMID: 19231497 DOI: 10.1016/j.gie.2008.08.014]
31 **Yen AW**, Leung JW, Leung FW. A new method for screening and surveillance colonoscopy: Combined water-exchange and cap-assisted colonoscopy. *J Interv Gastroenterol* 2012; **2**: 114-119 [PMID: 23805389 DOI: 10.4161/jig.23730]
32 **Subramanian V**, Mannath J, Hawkey CJ, Ragunath K. High definition colonoscopy vs. standard video endoscopy for the detection of colonic polyps: a meta-analysis. *Endoscopy* 2011; **43**: 499-505 [PMID: 21360420 DOI: 10.1055/s-0030-1256207]
33 **Waldmann E**, Britto-Arias M, Gessl I, Heinze G, Salzl P, Sallinger D, Trauner M, Weiss W, Ferlitsch A, Ferlitsch M. Endoscopists with low adenoma detection rates benefit from high-definition endoscopy. *Surg Endosc* 2015; **29**: 466-473 [PMID: 25005016 DOI: 10.1007/s00464-014-3688-2]
34 **Banks MR**, Haidry R, Butt MA, Whitley L, Stein J, Langmead L, Bloom SL, O'Bichere A, McCartney S, Basherdas K, Rodriguez-Justo M, Lovat LB. High resolution colonoscopy in a bowel cancer screening program improves polyp detection. *World J Gastroenterol* 2011; **17**: 4308-4313 [PMID: 22090787 DOI: 10.3748/wjg.v17.i38.4308]
35 **Gross SA**, Buchner AM, Crook JE, Cangemi JR, Picco MF, Wolfsen HC, DeVault KR, Loeb DS, Raimondo M, Woodward TA, Wallace MB. A comparison of high definition-image enhanced colonoscopy and standard white-light colonoscopy for colorectal polyp detection. *Endoscopy* 2011; **43**: 1045-1051 [PMID: 21971929 DOI: 10.1055/s-0030-1256894]
36 **Wong Kee Song LM**, Adler DG, Chand B, Conway JD, Croffie JM, Disario JA, Mishkin DS, Shah RJ, Somogyi L, Tierney WM, Petersen BT. Chromoendoscopy. *Gastrointest Endosc* 2007; **66**: 639-649 [PMID: 17643437 DOI: 10.1016/j.gie.2007.05.029]
37 **Hurlstone DP**, Karajeh M, Sanders DS, Drew SK, Cross SS. Rectal aberrant crypt foci identified using high-magnification-chromoscopic colonoscopy: biomarkers for flat and depressed neoplasia. *Am J Gastroenterol* 2005; **100**: 1283-1289 [PMID: 15929758 DOI: 10.1111/j.1572-0241.2005.40891.x]
38 **Fujii T**, Rembacken BJ, Dixon MF, Yoshida S, Axon AT. Flat adenomas in the United Kingdom: are treatable cancers being missed? *Endoscopy* 1998; **30**: 437-443 [PMID: 9693889 DOI: 10.1055/s-2007-1001304]
39 **Kiesslich R**, von Bergh M, Hahn M, Hermann G, Jung M. Chromoendoscopy with indigocarmine improves the detection of adenomatous and nonadenomatous lesions in the colon. *Endoscopy* 2001; **33**: 1001-1006 [PMID: 11740641 DOI: 10.1055/s-2001-18932]
40 **Jaramillo E**, Watanabe M, Slezak P, Rubio C. Flat neoplastic lesions of the colon and rectum detected by high-resolution video endoscopy and chromoscopy. *Gastrointest Endosc* 1995; **42**: 114-122 [PMID: 7590045 DOI: 10.1016/S0016-5107(95)70066-8]
41 **Kahi CJ**, Anderson JC, Waxman I, Kessler WR, Imperiale TF, Li X, Rex DK. High-definition chromocolonoscopy vs. high-definition white light colonoscopy for average-risk colorectal cancer screening. *Am J Gastroenterol* 2010; **105**: 1301-1307 [PMID: 20179689 DOI: 10.1038/ajg.2010.51]
42 **Repici A**, Di Stefano AF, Radicioni MM, Jas V, Moro L, Danese S. Methylene blue MMX tablets for chromoendoscopy. Safety tolerability and bioavailability in healthy volunteers. *Contemp Clin Trials* 2012; **33**: 260-267 [PMID: 22101227 DOI: 10.1016/

j.cct.2011.11.006]
43 **Singh R**, Mei SC, Sethi S. Advanced endoscopic imaging in Barrett's oesophagus: a review on current practice. *World J Gastroenterol* 2011; **17**: 4271-4276 [PMID: 22090782 DOI: 10.3748/wjg.v17.i38.4271]
44 **Gross S**, Trautwein C, Behrens A, Winograd R, Palm S, Lutz HH, Schirin-Sokhan R, Hecker H, Aach T, Tischendorf JJ. Computer-based classification of small colorectal polyps by using narrow-band imaging with optical magnification. *Gastrointest Endosc* 2011; **74**: 1354-1359 [PMID: 22000791 DOI: 10.1016/j.gie.2011.08.001]
45 **Pasha SF**, Leighton J a., Das A, Gurudu S, Sharma VK. Narrow Band Imaging (NBI) and White Light Endoscopy (WLE) Have a Comparable Yield for Detection of Colon Polyps in Patients Undergoing Screening or Surveillance Colonoscopy: A Meta-Analysis. *Gastrointest Endosc* 2009; **69**: AB363 [DOI: 10.1016/j.gie.2009.03.1079]
46 **Sabbagh LC**, Reveiz L, Aponte D, de Aguiar S. Narrow-band imaging does not improve detection of colorectal polyps when compared to conventional colonoscopy: a randomized controlled trial and meta-analysis of published studies. *BMC Gastroenterol* 2011; **11**: 100 [PMID: 21943365 DOI: 10.1186/1471-230X-11-100]
47 **Nagorni A**, Bjelakovic G, Petrovic B. Narrow band imaging versus conventional white light colonoscopy for the detection of colorectal polyps. *Cochrane Database Syst Rev* 2012; **1**: CD008361 [PMID: 22258983 DOI: 10.1002/14651858.cd008361.pub2]
48 **Pohl J**, May A, Rabenstein T, Pech O, Ell C. Computed virtual chromoendoscopy: a new tool for enhancing tissue surface structures. *Endoscopy* 2007; **39**: 80-83 [PMID: 17252465 DOI: 10.1055/s-2006-945045]
49 **Kaltenbach T**, Sano Y, Friedland S, Soetikno R. American Gastroenterological Association (AGA) Institute technology assessment on image-enhanced endoscopy. *Gastroenterology* 2008; **134**: 327-340 [PMID: 18061178 DOI: 10.1053/j.gastro.2007.10.062]
50 **Chung SJ**, Kim D, Song JH, Kang HY, Chung GE, Choi J, Kim YS, Park MJ, Kim JS. Comparison of detection and miss rates of narrow band imaging, flexible spectral imaging chromoendoscopy and white light at screening colonoscopy: a randomised controlled back-to-back study. *Gut* 2014; **63**: 785-791 [PMID: 23853211 DOI: 10.1136/gutjnl-2013-304578]
51 **Chung SJ**, Kim D, Song JH, Park MJ, Kim YS, Kim JS, Jung HC, Song IS. Efficacy of computed virtual chromoendoscopy on colorectal cancer screening: a prospective, randomized, back-to-back trial of Fuji Intelligent Color Enhancement versus conventional colonoscopy to compare adenoma miss rates. *Gastrointest Endosc* 2010; **72**: 136-142 [PMID: 20493487 DOI: 10.1016/j.gie.2010.01.055]
52 **Hoffman A**, Sar F, Goetz M, Tresch A, Mudter J, Biesterfeld S, Galle PR, Neurath MF, Kiesslich R. High definition colonoscopy combined with i-Scan is superior in the detection of colorectal neoplasias compared with standard video colonoscopy: a prospective randomized controlled trial. *Endoscopy* 2010; **42**: 827-833 [PMID: 20803419 DOI: 10.1055/s-0030-1255713]
53 **Song LM**, Banerjee S, Desilets D, Diehl DL, Farraye FA, Kaul V, Kethu SR, Kwon RS, Mamula P, Pedrosa MC, Rodriguez SA, Tierney WM. Autofluorescence imaging. *Gastrointest Endosc* 2011; **73**: 647-650 [PMID: 21296349 DOI: 10.1016/j.gie.2010.11.006]
54 **Moriichi K**, Fujiya M, Sato R, Watari J, Nomura Y, Nata T, Ueno N, Maeda S, Kashima S, Itabashi K, Ishikawa C, Inaba Y, Ito T, Okamoto K, Tanabe H, Mizukami Y, Saitoh Y, Kohgo Y. Back-to-back comparison of auto-fluorescence imaging (AFI) versus high resolution white light colonoscopy for adenoma detection. *BMC Gastroenterol* 2012; **12**: 75 [PMID: 22726319 DOI: 10.1186/1471-230X-12-75]
55 **Ramsoekh D**, Haringsma J, Poley JW, van Putten P, van Dekken H, Steyerberg EW, van Leerdam ME, Kuipers EJ. A back-to-back comparison of white light video endoscopy with autofluorescence endoscopy for adenoma detection in high-risk subjects. *Gut* 2010; **59**: 785-793 [PMID: 20551463 DOI: 10.1136/gut.2008.151589]
56 **Matsuda T**, Saito Y, Fu KI, Uraoka T, Kobayashi N, Nakajima T, Ikehara H, Mashimo Y, Shimoda T, Murakami Y, Parra-Blanco A, Fujimori T, Saito D. Does autofluorescence imaging videoendoscopy system improve the colonoscopic polyp detection rate?--a pilot study. *Am J Gastroenterol* 2008; **103**: 1926-1932 [PMID: 18647285 DOI: 10.1111/j.1572-0241.2008.01931.x]
57 **van den Broek FJ**, van Soest EJ, Naber AH, van Oijen AH, Mallant-Hent RCh, Böhmer CJ, Scholten P, Stokkers PC, Marsman WA, Mathus-Vliegen EM, Curvers WL, Bergman JJ, van Eeden S, Hardwick JC, Fockens P, Reitsma JB, Dekker E. Combining autofluorescence imaging and narrow-band imaging for the differentiation of adenomas from non-neoplastic colonic polyps among experienced and non-experienced endoscopists. *Am J Gastroenterol* 2009; **104**: 1498-1507 [PMID: 19491863 DOI: 10.1038/ajg.2009.161]
58 **Gralnek IM**, Carr-Locke DL, Segol O, Halpern Z, Siersema PD, Sloyer A, Fenster J, Lewis BS, Santo E, Suissa A, Segev M. Comparison of standard forward-viewing mode versus ultrawide-viewing mode of a novel colonoscopy platform: a prospective, multicenter study in the detection of simulated polyps in an in vitro colon model (with video). *Gastrointest Endosc* 2013; **77**: 472-479 [PMID: 23410700 DOI: 10.1016/j.gie.2012.12.011]
59 **Gralnek IM**, Siersema PD, Halpern Z, Segol O, Melhem A, Suissa A, Santo E, Sloyer A, Fenster J, Moons LM, Dik VK, D'Agostino RB, Rex DK. Standard forward-viewing colonoscopy versus full-spectrum endoscopy: an international, multicentre, randomised, tandem colonoscopy trial. *Lancet Oncol* 2014; **15**: 353-360 [PMID: 24560453 DOI: 10.1016/S1470-2045(14)70020-8]
60 **Uraoka T**, Tanaka S, Oka S, Matsuda T, Saito Y, Moriyama T, Higashi R, Matsumoto T. Feasibility of a novel colonoscope with extra-wide angle of view: a clinical study. *Endoscopy* 2015; **47**: 444-448 [PMID: 25412088]
61 **Hasan N**, Gross SA, Gralnek IM, Pochapin M, Kiesslich R, Halpern Z. A novel balloon colonoscope detects significantly more simulated polyps than a standard colonoscope in a colon model. *Gastrointest Endosc* 2014; **80**: 1135-1140 [PMID: 24929483 DOI: 10.1016/j.gie.2014.04.024]
62 **Gheonea DI**, Saftoiu A, Ciurea T, Popescu C, Georgescu CV, Malos A. Confocal laser endomicroscopy of the colon. *J Gastrointestin Liver Dis* 2010; **19**: 207-211 [PMID: 20593059]
63 **Gheonea DI**, Cârțână T, Ciurea T, Popescu C, Bădărău A, Săftoiu A. Confocal laser endomicroscopy and immunoendoscopy for real-time assessment of vascularization in gastrointestinal malignancies. *World J Gastroenterol* 2011; **17**: 21-27 [PMID: 21218080 DOI: 10.3748/wjg.v17.i1.21]
64 **Shukla R**, Abidi WM, Richards-Kortum R, Anandasabapathy S. Endoscopic imaging: How far are we from real-time histology? *World J Gastrointest Endosc* 2011; **3**: 183-194 [PMID: 22013499]
65 **East JE**, Saunders BP, Burling D, Boone D, Halligan S, Taylor SA. Surface visualization at CT colonography simulated colonoscopy: effect of varying field of view and retrograde view. *Am J Gastroenterol* 2007; **102**: 2529-2535 [PMID: 17640320 DOI: 10.1111/j.1572-0241.2007.01429.x]
66 **Triadafilopoulos G**, Watts HD, Higgins J, Van Dam J. A novel retrograde-viewing auxiliary imaging device (Third Eye Retroscope) improves the detection of simulated polyps in anatomic models of the colon. *Gastrointest Endosc* 2007; **65**: 139-144 [PMID: 17185094 DOI: 10.1016/j.gie.2006.07.044]
67 **DeMarco DC**, Odstrcil E, Lara LF, Bass D, Herdman C, Kinney T, Gupta K, Wolf L, Dewar T, Deas TM, Mehta MK, Anwer MB, Pellish R, Hamilton JK, Polter D, Reddy KG, Hanan I. Impact of experience with a retrograde-viewing device on adenoma detection rates and withdrawal times during colonoscopy: the Third Eye Retroscope study group. *Gastrointest Endosc* 2010; **71**: 542-550 [PMID: 20189513 DOI: 10.1016/j.gie.2009.12.021]
68 **Waye JD**, Heigh RI, Fleischer DE, Leighton JA, Gurudu S, Aldrich LB, Li J, Ramrakhiani S, Edmundowicz SA, Early DS, Jonnalagadda S, Bresalier RS, Kessler WR, Rex DK. A retrograde-viewing device improves detection of adenomas in the colon: a prospective efficacy evaluation (with videos). *Gastrointest Endosc* 2010; **71**: 551-556 [PMID: 20018280 DOI: 10.1016/j.gie.2009.09.043]
69 **Leufkens AM**, DeMarco DC, Rastogi A, Akerman PA, Azzouzi K, Rothstein RI, Vleggaar FP, Repici A, Rando G, Okolo PI, Dewit O, Ignjatovic A, Odstrcil E, East J, Deprez PH, Saunders BP,

Kalloo AN, Creel B, Singh V, Lennon AM, Siersema PD. Effect of a retrograde-viewing device on adenoma detection rate during colonoscopy: the TERRACE study. *Gastrointest Endosc* 2011; **73**: 480-489 [PMID: 21067735 DOI: 10.1016/j.gie.2010.09.004]

70 **Kondo S**, Yamaji Y, Watabe H, Yamada A, Sugimoto T, Ohta M, Ogura K, Okamoto M, Yoshida H, Kawabe T, Omata M. A randomized controlled trial evaluating the usefulness of a transparent hood attached to the tip of the colonoscope. *Am J Gastroenterol* 2007; **102**: 75-81 [PMID: 17100978 DOI: 10.1111/j.1572-0241.2006.00897.x]

71 **de Wijkerslooth TR**, Stoop EM, Bossuyt PM, Mathus-Vliegen EM, Dees J, Tytgat KM, van Leerdam ME, Fockens P, Kuipers EJ, Dekker E. Adenoma detection with cap-assisted colonoscopy versus regular colonoscopy: a randomised controlled trial. *Gut* 2012; **61**: 1426-1434 [PMID: 22187070 DOI: 10.1136/gutjnl-2011-301327]

72 **Rastogi A**, Bansal A, Rao DS, Gupta N, Wani SB, Shipe T, Gaddam S, Singh V, Sharma P. Higher adenoma detection rates with cap-assisted colonoscopy: a randomised controlled trial. *Gut* 2012; **61**: 402-408 [PMID: 21997547 DOI: 10.1136/gutjnl-2011-300187]

73 **Ng SC**, Tsoi KK, Hirai HW, Lee YT, Wu JC, Sung JJ, Chan FK, Lau JY. The efficacy of cap-assisted colonoscopy in polyp detection and cecal intubation: a meta-analysis of randomized controlled trials. *Am J Gastroenterol* 2012; **107**: 1165-1173 [PMID: 22664471 DOI: 10.1038/ajg.2012.135]

74 **Tsiamoulos ZP**, Saunders BP. A new accessory, endoscopic cuff, improves colonoscopic access for complex polyp resection and scar assessment in the sigmoid colon (with video). *Gastrointest Endosc* 2012; **76**: 1242-1245 [PMID: 23164515 DOI: 10.1016/j.gie.2012.08.019]

75 **Biecker E**, Floer M, Heinecke A, Ströbel P, Böhme R, Schepke M, Meister T. Novel endocuff-assisted colonoscopy significantly increases the polyp detection rate: a randomized controlled trial. *J Clin Gastroenterol* 2015; **49**: 413-418 [PMID: 24921209 DOI: 10.1097/MCG.0000000000000166]

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Current role of non-anesthesiologist administered propofol sedation in advanced interventional endoscopy

Daniela Elena Burtea, Anca Dimitriu, Anca Elena Maloş, Adrian Săftoiu

Daniela Elena Burtea, Adrian Săftoiu, Research Center of Gastroenterology and Hepatology Craiova, University of Medicine and Pharmacy Craiova, 200639 Craiova, Romania

Daniela Elena Burtea, Endoscopy Department, Clinical County Emergency Hospital Craiova, 200639 Craiova, Romania

Anca Dimitriu, Anca Elena Maloş, Anesthesiology Department, Clinical County Emergency Hospital Craiova, 200639 Craiova, Romania

Adrian Săftoiu, Endoscopy Department, Gastrointestinal Unit, Copenhagen University Hospital Herlev, 2730 Herlev, Denmark

Author contributions: Burtea DE retrieved the references, carefully reviewed the literature and wrote the initial manuscript; Dimitriu A and Maloş AE contributed to the reviewing of the manuscript; Săftoiu A designed the content of the mini-review and wrote parts of the manuscript.

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Correspondence to: Adrian Săftoiu, MD, PhD, MSc, FASGE, Visiting Clinical Professor, Research Center of Gastroenterology and Hepatology Craiova, University of Medicine and Pharmacy Craiova, 2 Petru Rares str., 200639 Craiova, Romania. adrian.saftoiu@umfcv.ro
Telephone: +40-744-823355
Fax: +40-251-310287

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Abstract

Complex and lengthy endoscopic examinations like endoscopic ultrasonography and/or endoscopic retrograde cholangiopancreatography benefit from deep sedation, due to an enhanced quality of examinations, reduced discomfort and anxiety of patients, as well as increased satisfaction for both the patients and medical personnel. Current guidelines support the use of propofol sedation, which has the same rate of adverse effects as traditional sedation with benzodiazepines and/or opioids, but decreases the procedural and recovery time. Non-anesthesiologist administered propofol sedation has become an option in most of the countries, due to limited anesthesiology resources and the increasing evidence from prospective studies and meta-analyses that the procedure is safe with a similar rate of adverse events with traditional sedation. The advantages include a high quality of endoscopic examination, improved satisfaction for patients and doctors, as well as decreased recovery and discharge time. Despite the advantages of non-anesthesiologist administered propofol, there is still a continuous debate related to the successful generalization of the procedures.

Key words: Non-anesthesiologist administered propofol sedation; Advanced interventional endoscopy; Endoscopic ultrasound; Endoscopic retrograde cholangiopancreatography

Core tip: A large amount of clinical research data demonstrated that propofol provides significant advantages over traditional sedation techniques during advanced endoscopic procedures like endoscopic retrograde cholangiopancreatography and/or endoscopic ultrasonography. Thus, propofol is more effective and safer than the combination of midazolam and meperidine to maintain an adequate level of sedation during advanced endoscopic procedures, with shorter recovery times and increased patient and endoscopist satisfaction. The trend of an increased usage of propofol and generalization of non-anesthesiologist administered propofol sedation in both hospital and private practice settings will certainly increase in the years to come.

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INTRODUCTION

Most of the endoscopic procedures, either diagnostic or therapeutic, are nowadays performed under sedation, used as a standard practice in most of the centers[1]. Non-complex endoscopic examinations can be performed safely without any sedation, but with thorough psychological preparation and pre-procedural care, which might be good enough for patients to decrease procedure related anxiety[2]. However, the number and complexity of endoscopic procedures increased due to the generalized usage of sedation, which diminishes anxiety, discomfort and/or pain for the patients, thus improving patient acceptance and satisfaction[3-7]. Sedation is also important to medical practitioners as it improves the quality of endoscopic examinations and completion rate, but also treatment outcomes in therapeutic endoscopy, thus increasing endoscopist's satisfaction[3]. Sedation levels and medication types depend on a variety of factors, related to both patient characteristics (age, comorbidities, preference, *etc.*), as well as procedure types (simple diagnostic gastroscopy or colonoscopy, as opposed to prolonged complex therapeutic procedures)[4].

Sedation levels are variable and include a continuum of states ranging from minimal and moderate sedation to deep sedation and general anesthesia[4]. Conscious sedation assumes an *iv* administration of pharmacologic agents that lower the level of consciousness up to a state of drowsiness, relaxation, but the patient stays awake during the procedure retaining its ability to maintain an open airway and to breath spontaneously (patients do not require intubation and mechanical ventilation as with general anesthesia). Conscious sedation also helps to ensure adequate cardiac output, to communicate with the medical team and to respond to verbal commands[8,9]. Nevertheless, complex and lengthy procedures like endoscopic ultrasound (EUS) and endoscopic retrograde cholangiopancreatography (ERCP) usually require a deeper sedation level[10]. Consequently, deep sedation makes the pain more tolerable, minimizes patient anxiety and/or discomfort, and has no memory effect (the patient will never recall any negative emotions) and thereby facilitates the procedure performance by the endoscopist[4]. Current guidelines also support the use of propofol-based sedation as compared with traditional (conventional) sedation with benzodiazepines and/or opioids, thus offering higher patient and endoscopist satisfaction, decreasing procedure-related time, as well as recovery time, without increasing the rate of adverse events[11].

On the other hand, the use of intravenous sedation has increased the demand of qualified medical providers to assess and intervene on behalf of the patient, before serious adverse events occur[6].

Due to limited anesthesiology resources in most countries, non-anesthesiologist administered propofol (NAAP) sedation has started to be used extensively[6]. Registered nurses have responded to this demand through implementation of educational programs, definition of clinical competencies and promulgation of recommended practice guidelines by professional practice organizations and nursing position statements[12].

The aim of this article was to critically review the available evidence on deep sedation procedures necessary for complex therapeutic EUS and/or ERCP procedures, highlighting the controversies that still concern sedation by non-anesthesiologists (either endoscopists or nurses) based on structured multisociety sedation curriculum programs.

METHODS OF SEDATION

Sedation methods differ widely from one country to another, from one health system to another and, of course, they depend on local circumstances and both patient's and endoscopist's preferences that all increased the threshold on quality[2]. On the other hand, the differences between various hospitals/departments, university/community hospitals, as well as public/private endoscopy units, and other systematic differences of practice, might influence a particular endoscopy unit concerning its own sedation practices. Various types and degrees of sedation techniques are thus used during gastrointestinal (GI) endoscopic procedures, although the optimal sedation is tailored according to the individual patient, based on the balance between clinical risks and type of procedure performed[13]. Even nowadays, there is no standard system of sedation, while in the private institutions the choice of sedation depends on endoscopist and/or anesthesiologist preference, as well as the complexity of procedures to be performed.

Recent pharmacological researches and progresses have also contributed to the increased use of conscious sedation for specific patient populations. The introduction of "non-barbituric" intravenous anesthetics (propofol, remifentanil, ketamine, etomidate) with shorter half-lives and having minimum cumulative active metabolites, have increased the safety and efficacy associated with the administration of sedation. Nevertheless, both propofol (alone or in combination with other agents), but also conventional/traditional sedation techniques (using benzodiazepines and/or opioids) can induce deep sedation, even though only moderate sedation is desired[5].

Benzodiazepines

Benzodiazepines, such as midazolam, alprazolam, bromazepam, diazepam, *etc.*, are among the most commonly prescribed drugs[2]. These drugs act as anxiolytics, sedatives, hypnotics, anesthetics, antiepileptic and muscle relaxants. Moderate sedation using midazolam and an opioid is still considered the standard method of sedation, although propofol is increasingly used in many countries, mainly because both the endoscopists', as well as patients' satisfaction are higher than for conventional sedation. Midazolam is currently considered the benzodiazepine of choice because of its shorter duration of action and better pharmacokinetic profile compared with diazepam. The duration of action of midazolam is dependent on the duration of its administration. Mental function returns to normal after approximately 4 h after administration, the drug being very useful for short procedures. One published meta-analysis reported that midazolam provided better patient satisfaction as compared to diazepam, and less frequent memory of procedures[9]. The recovery time can be shortened after midazolam usage by using the benzodiazepine antagonist flumazenil[14].

Opioids

Among the opioids, fentanyl and meperidine/pethidine and are the most popular[2]. Fentanyl is a synthetic narcotic analgesic characterized by a rapid onset and short duration of action. At the level of respiratory system, higher doses can cause respiratory depression, immediately, as well as late. It can induce chest muscle rigidity followed by a difficult or even impossible intubation. Also, the combination of fentanyl and midazolam that is used quite often in some endoscopy departments can produce apnea and cardiac arrest[9]. Pethidine/meperidine is a weak opioid (7-10 times weaker than morphine) which relaxes smooth muscles, produces sedation and mild euphoria. The combination between midazolam and meperidine is safe and effective for GI endoscopy[15]. Ketamine is also a suitable sedative for GI endoscopy[16], although it might stimulate salivary and tracheobronchial secretion, while it sometimes gives a dissociative anesthesia that can produce hallucinations and delirium awakening[17].

Propofol

Propofol is an ultra-short-acting, sedative-hypnotic agent that has multiple potential advantages compared with "traditional sedation" based upon administration of an opioid and benzodiazepine agents for endoscopic procedures[18]. Propofol is a highly soluble phenol derivative, consisting of an *iv* emulsion for injection or infusion (1% concentration, 10 mg/mL) containing also 10% soybean oil, 2.25% glycerol and 1.2% purified egg phosphatide[2]. Propofol has become undoubtedly the induction agent of choice in GI endoscopy, as it is really easy to administer and provides prompt awakening, with fewer side effects[19]. Postprocedure, propofol reduces nausea and vomiting as well as the time required for the ability to walk, as compared with thiopental and methohexital. The pain on injection of propofol may be reduced by injecting it into large veins or by mixing with 20-40 mL of lidocaine anesthetic agents. Co-induction with midazolam reduces the dose of propofol, produce sedation and amnesia without prolonging hospitalization time[20]. Nevertheless, recovery is slower, which for outpatient endoscopy cabinets can be an impediment.

ADVANCED ENDOSCOPY

Compared to standard diagnostic upper or lower GI endoscopy, advanced therapeutic procedures (EUS and/or ERCP) are often longer and complicated, thus requiring higher doses of sedatives for corresponding patient compliance, without recall of the procedure[10].

ERCP

ERCP is a technically demanding, but highly important modality to diagnose and treat pancreaticobiliary disorders. ERCP has progressed from an initial diagnostic technique to an exclusively therapeutic procedure used for the management of common bile duct stones, as well as biliary strictures. Pancreatic stones, strictures or even pseudocysts can be also managed by ERCP in highly specialized tertiary centers[21]. Traditional conscious (moderate) sedation with the combination between a benzodiazepine and an opiate is challenged nowadays by the use of propofol sedation. A Cochrane review on individual studies concluded that patients have a better recovery profile after propofol sedation, as compared to the combination midazolam - meperidine, with no difference in complication rate[22]. The same conclusion has been reached by several meta-analyses that indicated clear advantages for propofol sedation, without increased risk of cardiopulmonary adverse events[18,23]. In order to obtain the desired deep sedation effects, balanced propofol sedation (propofol in combination with midazolam and fentanyl) has been used showing a longer recovery time without any other difference in term of complications[24]. The conclusion was that non-anesthesiologists propofol sedation can also be administered safely by trained, registered sedation nurses, with the same being

valid also in emergency ERCP[25]. Although propofol is nowadays preferred, in high doses it induces a risk of cardiopulmonary complications (bradycardia, hypotension, apnea, hypoxemia, *etc.*), consequently various methods of administration have been designed. Target propofol infusion (TPI) consists of an initial bolus, followed by a rate of constant infusion controlled by a computer, and has been compared to self-administration of propofol through patient controlled sedation (PCS)[26]. The later technique showed a reduced consumption of propofol and a faster recovery, but no significant benefits over TPI.

EUS

EUS is a state-of-the-art method for the assessment of GI pathology, especially for pancreaticobiliary lesions, but also GI tract or lung cancers. Moreover, the procedure allows the performance of EUS-guided fine needle aspiration (FNA) used to obtain a final diagnosis through cytology or histology exams of the obtained samples[27]. While routine diagnostic or staging EUS carries a relatively low risk, it is usually more time consuming and more uncomfortable than a simple diagnostic upper GI tract endoscopy. Likewise, EUS-FNA procedures are more difficult and lengthier, therefore a deeper sedation is necessary. The same thing is valid for therapeutic procedures which start with the initial placement of a needle through EUS-guidance, for, *e.g.,* celiac plexus neurolysis or pancreatic pseudocyst drainage. Other therapeutic procedures performed under EUS-guidance or assistance, like hepaticogastrostomies, choledocoduodenostomies or cholecystogastrostomies, are also performed under deep sedation or general anesthesia, even in high risk patients [American Society of Anesthesiologists (ASA) Ⅲ-Ⅳ][28]. A large prospective study including 500 patients showed that administration of propofol by qualified persons, other than endoscopist, is safe and effective for patients with ASA less than 2, during upper GI EUS[29]. Balanced propofol sedation techniques have been used also during EUS-FNA procedures without any major complications[30]. Likewise, TCI during monitored anesthesia has been proven useful for safe sedation during EUS, without major complications[31].

NAAP

NAAP propofol sedation caused major debates due to limited anesthesiology resources that determined administration of NAAP by trained nurses or endoscopists in selected endoscopy procedures[6]. A comprehensive guideline endorsed by the European Society of Gastrointestinal Endoscopy (ESGE) and European Society of Gastroenterology and Endoscopy Nurses and Associates established the role of NAAP in clinical endoscopy. Thus, trained registered nurses or endoscopists can safely administer propofol during ongoing endoscopy, with a very low rate of respiratory events requiring endotracheal intubation[32]. The recommendations from the ESGE guidelines are clear, indicating that propofol sedation has a similar rate of adverse events compared to conventional sedation (based on benzodiazepines ± opioids), with a high post-procedural satisfaction for both the patients, but also endoscopists. Moreover, the time for sedation decreases, with a higher quality of the endoscopic examination, while the recovery and discharge time will decrease[6]. Even psychomotor ability after the procedure seems to be improved leading to a possible continuation of daily routine (including driving after recovery in the medical suites)[33]. Because higher category of ASA physical status classification system leads to higher complication rate, an anesthesiologist is usually required on-site or for all patients with ASA category equal to or more than Ⅲ[34].

A dedicated person (usually a trained registered nurse) should be used for propofol administration, based on a clear protocol and adequate monitoring of the patient. An intravenous access should be maintained based on catheter with continuous supplemental oxygen, with careful continuous pulse oximetry and automated non-invasive blood pressure monitoring at 3-5 min intervals[6]. While simple endoscopic procedures can be performed with moderate sedation, complex procedures like EUS and/or ERCP are usually performed with deep sedation[10]. Currently, there is insufficient evidence that balanced propofol sedation with combination of drugs, beside propofol, has more beneficial effects[35,36]. The preferred mode of administration is with intermittent bolus administration or PCS in a minority of patients, if available[37]. Nevertheless, one large study from Germany showed that the combination of propofol and midazolam has a significantly lower sensation of pain, as well as reduced symptoms of dizziness, nausea and vomiting as compared to patients that received only propofol mono-sedation[38]. There is a lot of data to support the usage of patient-selected music during the procedures, which can decrease the dosage of propofol administered[39].

Both endoscopists and nurses should undergo a specific training program, which includes theoretical and practical parts on both basic life support and advanced cardiac life support[6]. A structured training program followed by an implementation phase documented a low incidence of adverse events, while the independent risk factors were: type of intervention and level of staff experience[40]. Thus, the patients had short duration hypoxia (4.7%), needed suction (2.4%) or bag-mask ventilation (0.9%), with only 0.3% of procedures that had to be discontinued[12]. Anesthetic assistance was necessary for only 0.4% of patients. A recent meta-analysis compared pooled results for NAAP and AAP studies, and showed the same rates of hypoxia (oxygen saturation less than 90%) and airway intervention in both arms[41]. Respiratory complications after endoscopist directed sedation were also shown to be important, with coughing or vomiting resulting in an increased risk of respiratory infections, thus requiring antibiotic treatment[42]. However, pooled patient satisfaction and

pooled endoscopist satisfaction rate, as well as the dose of propofol administered were lower in the NAAP group, as compared to the AAP group. In order to generalize this approach there are important legal issues that may arise if sedation complications occur during NAAP procedures, while these legal implications usually have country or even hospital specificities and particularities.

Nevertheless, cautious opinions on NAAP still exist, with more data required before transition of procedures from major hospitals to community practice[43,44]. Retraction of endorsement for the NAAP guideline by the European Society of Anesthesiology (ESA) came in line with the concerns of using NAAP by trained nurses or endoscopists, mainly in view with the possible complications and their proper management[45]. Our own approach for the patients with advanced interventional endoscopic procedures (EUS and/or ERCP) consists of exclusive use of propofol sedation in the presence of an anesthesiologist, as required by the current national and local legislation practices. Based on a total number of 192 patients examined during one year in the Research Center of Gastroenterology and Hepatology Craiova, Romania, we have encountered no severe adverse events, with drowsiness, nausea, vomiting, dizziness, headache, coughing or shivers being the most frequent, while less than 2% of patients had mild braycardia.

CONCLUSION

In conclusion, several large prospective studies and meta-analyses demonstrated that propofol provides significant advantages over benzodiazepine and opioid agents for deep patient sedation during advanced endoscopic procedures like ERCP and/or EUS: propofol was more effective and safer than the combination of midazolam and meperidine for achieving and maintaining an adequate level of sedation during endoscopic procedures, with better titration of the level of sedation and shorter recovery times. The trend of an increased usage of propofol and generalization of NAAP sedation in both hospital and private practice settings will certainly increase in the years to come.

REFERENCES

1 **Ferreira AO**, Cravo M. Sedation in gastrointestinal endoscopy: Where are we at in 2014? *World J Gastrointest Endosc* 2015; **7**: 102-109 [PMID: 25685266 DOI: 10.4253/wjge.v7.i2.102]

2 **Triantafillidis JK**, Merikas E, Nikolakis D, Papalois AE. Sedation in gastrointestinal endoscopy: current issues. *World J Gastroenterol* 2013; **19**: 463-481 [PMID: 23382625 DOI: 10.3748/wjg.v19.i4.463]

3 **Obara K**, Haruma K, Irisawa A, Kaise M, Gotoda T, Sugiyama M, Tanabe S, Horiuchi A, Fujita N, Ozaki M, Yoshida M, Matsui T, Ichinose M, Kaminishi M. Guidelines for sedation in gastroenterological endoscopy. *Dig Endosc* 2015; **27**: 435-449 [PMID: 25677012 DOI: 10.1111/den.12464]

4 **Igea F**, Casellas JA, González-Huix F, Gómez-Oliva C, Baudet JS, Cacho G, Simón MA, De la Morena E, Lucendo A, Vida F. Sedation for gastrointestinal endoscopy. *Endoscopy* 2014; **46**: 720-731 [PMID: 25061964 DOI: 10.1055/s-0034-1377561]

5 **Vargo JJ**, DeLegge MH, Feld AD, Gerstenberger PD, Kwo PY, Lightdale JR, Nuccio S, Rex DK, Schiller LR. Multisociety sedation curriculum for gastrointestinal endoscopy. *Gastroenterology* 2012; **143**: e18-e41 [PMID: 22624720 DOI: 10.1053/j.gastro.2012.05.001]

6 **Dumonceau JM**, Riphaus A, Aparicio JR, Beilenhoff U, Knape JT, Ortmann M, Paspatis G, Ponsioen CY, Racz I, Schreiber F, Vilmann P, Wehrmann T, Wientjes C, Walder B. European Society of Gastrointestinal Endoscopy, European Society of Gastroenterology and Endoscopy Nurses and Associates, and the European Society of Anaesthesiology Guideline: Non-anesthesiologist administration of propofol for GI endoscopy. *Endoscopy* 2010; **42**: 960-974 [PMID: 21072716 DOI: 10.1055/s-0030-1255728]

7 **Riphaus A**, Wehrmann T, Weber B, Arnold J, Beilenhoff U, Bitter H, von Delius S, Domagk D, Ehlers AF, Faiss S, Hartmann D, Heinrichs W, Hermans ML, Hofmann C, In der Smitten S, Jung M, Kähler G, Kraus M, Martin J, Meining A, Radke J, Rösch T, Seifert H, Sieg A, Wigginghaus B, Kopp I. S3-guidelines--sedation in gastrointestinal endoscopy. *Z Gastroenterol* 2008; **46**: 1298-1330 [PMID: 19012203 DOI: 10.1055/s-2008-1027850]

8 **Müller M**, Wehrmann T. How best to approach endoscopic sedation? *Nat Rev Gastroenterol Hepatol* 2011; **8**: 481-490 [PMID: 21750516 DOI: 10.1038/nrgastro.2011.122]

9 **McQuaid KR**, Laine L. A systematic review and meta-analysis of randomized, controlled trials of moderate sedation for routine endoscopic procedures. *Gastrointest Endosc* 2008; **67**: 910-923 [PMID: 18440381 DOI: 10.1016/j.gie.2007.12.046]

10 **Cheriyan DG**, Byrne MF. Propofol use in endoscopic retrograde cholangiopancreatography and endoscopic ultrasound. *World J Gastroenterol* 2014; **20**: 5171-5176 [PMID: 24833847 DOI: 10.3748/wjg.v20.i18.5171]

11 **Ellett ML**. A literature review of the safety and efficacy of using propofol for sedation in endoscopy. *Gastroenterol Nurs* 2010; **33**: 111-117 [PMID: 20389224 DOI: 10.1097/SGA.0b013e3181d601fb]

12 **Slagelse C**, Vilmann P, Hornslet P, Hammering A, Mantoni T. Nurse-administered propofol sedation for gastrointestinal endoscopic procedures: first Nordic results from implementation of a structured training program. *Scand J Gastroenterol* 2011; **46**: 1503-1509 [PMID: 22050137 DOI: 10.3109/00365521.2011.619274]

13 **Fanti L**, Testoni PA. Sedation and analgesia in gastrointestinal endoscopy: what's new? *World J Gastroenterol* 2010; **16**: 2451-2457 [PMID: 20503443 DOI: 10.3748/wjg.v16.i20.2451]

14 **Mathus-Vliegen EM**, de Jong L, Kos-Foekema HA. Significant and safe shortening of the recovery time after flumazenil-reversed midazolam sedation. *Dig Dis Sci* 2014; **59**: 1717-1725 [PMID: 24563235 DOI: 10.1007/s10620-014-3061-2]

15 **Lee BS**, Ryu J, Lee SH, Lee MG, Jang SE, Hwang JH, Ryu JK, Do SH, Kim YT. Midazolam with meperidine and dexmedetomidine vs. midazolam with meperidine for sedation during ERCP: prospective, randomized, double-blinded trial. *Endoscopy* 2014; **46**: 291-298 [PMID: 24671858 DOI: 10.1055/s-0033-1358909]

16 **Varadarajulu S**, Eloubeidi MA, Tamhane A, Wilcox CM. Prospective randomized trial evaluating ketamine for advanced endoscopic procedures in difficult to sedate patients. *Aliment Pharmacol Ther* 2007; **25**: 987-997 [PMID: 17403003 DOI: 10.1111/j.1365-2036.2007.03285.x]

17 **Chudnofsky CR**, Weber JE, Stoyanoff PJ, Colone PD, Wilkerson MD, Hallinen DL, Jaggi FM, Boczar ME, Perry MA. A combination of midazolam and ketamine for procedural sedation and analgesia in adult emergency department patients. *Acad Emerg Med* 2000; **7**: 228-235 [PMID: 10730829 DOI: 10.1111/j.1553-2712.2000.tb01064.x]

18 **Sethi S**, Wadhwa V, Thaker A, Chuttani R, Pleskow DK, Barnett SR, Leffler DA, Berzin TM, Sethi N, Sawhney MS. Propofol versus traditional sedative agents for advanced endoscopic procedures: a meta-analysis. *Dig Endosc* 2014; **26**: 515-524 [PMID: 24354404 DOI: 10.1111/den.12219]

19 **Vargo JJ**, Zuccaro G, Dumot JA, Shermock KM, Morrow JB, Conwell DL, Trolli PA, Maurer WG. Gastroenterologist-administered propofol versus meperidine and midazolam for advanced upper endoscopy: a prospective, randomized trial.

Gastroenterology 2002; **123**: 8-16 [PMID: 12105827 DOI: 10.1053/gast.2002.34232]

20 **Molina-Infante J**, Dueñas-Sadornil C, Mateos-Rodriguez JM, Perez-Gallardo B, Vinagre-Rodríguez G, Hernandez-Alonso M, Fernandez-Bermejo M, Gonzalez-Huix F. Nonanesthesiologist-administered propofol versus midazolam and propofol, titrated to moderate sedation, for colonoscopy: a randomized controlled trial. *Dig Dis Sci* 2012; **57**: 2385-2393 [PMID: 22615015 DOI: 10.1007/s10620-012-2222-4]

21 **Bakman Y**, Freeman ML. Update on biliary and pancreatic sphincterotomy. *Curr Opin Gastroenterol* 2012; **28**: 420-426 [PMID: 22782017 DOI: 10.1097/MOG.0b013e32835672f3]

22 **Garewal D**, Powell S, Milan SJ, Nordmeyer J, Waikar P. Sedative techniques for endoscopic retrograde cholangiopancreatography. *Cochrane Database Syst Rev* 2012; **6**: CD007274 [PMID: 22696368 DOI: 10.1002/14651858.CD007274]

23 **Bo LL**, Bai Y, Bian JJ, Wen PS, Li JB, Deng XM. Propofol vs traditional sedative agents for endoscopic retrograde cholangiopancreatography: a meta-analysis. *World J Gastroenterol* 2011; **17**: 3538-3543 [PMID: 21941422 DOI: 10.3748/wjg.v17.i30.3538]

24 **Lee TH**, Lee CK, Park SH, Lee SH, Chung IK, Choi HJ, Cha SW, Moon JH, Cho YD, Hwangbo Y, Kim SJ. Balanced propofol sedation versus propofol monosedation in therapeutic pancreaticobiliary endoscopic procedures. *Dig Dis Sci* 2012; **57**: 2113-2121 [PMID: 22615018 DOI: 10.1007/s10620-012-2234-0]

25 **Ikeuchi N**, Itoi T, Gotoda T, Kusano C, Kono S, Kamada K, Tsuchiya T, Tominaga N, Mukai S, Moriyasu F. Feasibility of non-anesthesiologist-administered propofol sedation for emergency endoscopic retrograde cholangiopancreatography. *Gastroenterol Res Pract* 2015; **2015**: 685476 [PMID: 25883644 DOI: 10.1155/2015/685476]

26 **Mazanikov M**, Udd M, Kylänpää L, Mustonen H, Lindström O, Färkkilä M, Halttunen J, Pöyhiä R. A randomized comparison of target-controlled propofol infusion and patient-controlled sedation during ERCP. *Endoscopy* 2013; **45**: 915-919 [PMID: 24104763 DOI: 10.1055/s-0033-1344712]

27 **Vilmann P**, Săftoiu A. Endoscopic ultrasound-guided fine needle aspiration biopsy: equipment and technique. *J Gastroenterol Hepatol* 2006; **21**: 1646-1655 [PMID: 16984583 DOI: 10.1111/j.1440-1746.2006.04475.x]

28 **Redondo-Cerezo E**, Sánchez-Robaina A, Martínez Cara JG, Ojeda-Hinojosa M, Matas-Cobos A, Sánchez Capilla AD, López de Hierro Ruíz M, Pleguezuelo-Díaz J, de Teresa J. Gastroenterologist-guided sedation with propofol for endoscopic ultrasonography in average-risk and high-risk patients: a prospective series. *Eur J Gastroenterol Hepatol* 2012; **24**: 506-512 [PMID: 22330236 DOI: 10.1097/MEG.0b013e328350fcbd]

29 **Yusoff IF**, Raymond G, Sahai AV. Endoscopist administered propofol for upper-GI EUS is safe and effective: a prospective study in 500 patients. *Gastrointest Endosc* 2004; **60**: 356-360 [PMID: 15332023 DOI: 10.1016/S0016-5107(04)01711-0]

30 **Pagano N**, Arosio M, Romeo F, Rando G, Del Conte G, Carlino A, Strangio G, Vitetta E, Malesci A, Repici A. Balanced Propofol Sedation in Patients Undergoing EUS-FNA: A Pilot Study to Assess Feasibility and Safety. *Diagn Ther Endosc* 2011; **2011**: 542159 [PMID: 21785561 DOI: 10.1155/2011/542159]

31 **Fanti L**, Agostoni M, Arcidiacono PG, Albertin A, Strini G, Carrara S, Guslandi M, Torri G, Testoni PA. Target-controlled infusion during monitored anesthesia care in patients undergoing EUS: propofol alone versus midazolam plus propofol. A prospective double-blind randomised controlled trial. *Dig Liver Dis* 2007; **39**: 81-86 [PMID: 17049322 DOI: 10.1016/j.dld.2006.09.004]

32 **Rex DK**, Heuss LT, Walker JA, Qi R. Trained registered nurses/endoscopy teams can administer propofol safely for endoscopy. *Gastroenterology* 2005; **129**: 1384-1391 [PMID: 16285939 DOI: 10.1053/j.gastro.2005.08.014]

33 **Vargo JJ**. Doc, can I drive home? *Am J Gastroenterol* 2009; **104**: 1656-1657 [PMID: 19574969 DOI: 10.1038/ajg.2009.262]

34 **Frieling T**, Heise J, Kreysel C, Kuhlen R, Schepke M. Sedation-associated complications in endoscopy--prospective multicentre survey of 191142 patients. *Z Gastroenterol* 2013; **51**: 568-572 [PMID: 23740356 DOI: 10.1055/s-0032-1330441]

35 **Lee SH**. Non-anesthesiologist administered propofol with or without midazolam for moderate sedation-the problem is not "which regimen" but "who's regimen". *Dig Dis Sci* 2012; **57**: 2243-2245 [PMID: 22833381 DOI: 10.1007/s10620-012-2268-3]

36 **González-Santiago JM**, Martín-Noguerol E, Vinagre-Rodríguez G, Hernández-Alonso M, Dueñas-Sadornil C, Pérez-Gallardo B, Mateos-Rodríguez JM, Fernández-Bermejo M, Robledo-Andrés P, Molina-Infante J. Intermittent boluses versus pump continuous infusion for endoscopist-directed propofol administration in colonoscopy. *Rev Esp Enferm Dig* 2013; **105**: 378-384 [PMID: 24206547 DOI: 10.4321/S1130-01082013000700002]

37 **Repici A**, Pagano N, Hassan C, Carlino A, Rando G, Strangio G, Romeo F, Zullo A, Ferrara E, Vitetta E, Ferreira Dde P, Danese S, Arosio M, Malesci A. Balanced propofol sedation administered by nonanesthesiologists: The first Italian experience. *World J Gastroenterol* 2011; **17**: 3818-3823 [PMID: 21987624 DOI: 10.3748/wjg.v17.i33.3818]

38 **Sieg A**, Beck S, Scholl SG, Heil FJ, Gotthardt DN, Stremmel W, Rex DK, Friedrich K. Safety analysis of endoscopist-directed propofol sedation: a prospective, national multicenter study of 24441 patients in German outpatient practices. *J Gastroenterol Hepatol* 2014; **29**: 517-523 [PMID: 24716213 DOI: 10.1111/jgh.12458]

39 **Lee DW**, Chan KW, Poon CM, Ko CW, Chan KH, Sin KS, Sze TS, Chan AC. Relaxation music decreases the dose of patient-controlled sedation during colonoscopy: a prospective randomized controlled trial. *Gastrointest Endosc* 2002; **55**: 33-36 [PMID: 11756911 DOI: 10.1067/mge.2002.120387]

40 **Jensen JT**, Vilmann P, Horsted T, Hornslet P, Bodtger U, Banning A, Hammering A. Nurse-administered propofol sedation for endoscopy: a risk analysis during an implementation phase. *Endoscopy* 2011; **43**: 716-722 [PMID: 21811940 DOI: 10.1055/s-0030-1256515]

41 **Goudra BG,** Singh PM, Gouda G, Borle A, Gouda D, Dravida A, Chandrashakhara V. Safety of Non-anesthesia Provider-Administered Propofol (NAAP) Sedation in Advanced Gastrointestinal Endoscopic Procedures: Comparative Meta-Analysis of Pooled Results. *Dig Dis Sci* 2015 Mar 3; Epub ahead of print [PMID: 25732719]

42 **Friedrich K**, Scholl SG, Beck S, Gotthardt D, Stremmel W, Rex DK, Sieg A. Respiratory complications in outpatient endoscopy with endoscopist-directed sedation. *J Gastrointestin Liver Dis* 2014; **23**: 255-259 [PMID: 25267952 DOI: 10.15403/jgld.2014.1121.233.kf1]

43 **Cohen LB**. Nurse-administered propofol sedation for upper endoscopic ultrasonography: not yet ready for prime time. *Nat Clin Pract Gastroenterol Hepatol* 2009; **6**: 76-77 [PMID: 19092792 DOI: 10.1038/ncpgasthep1332]

44 **Vargo JJ**. Big NAPS, little NAPS, mixed NAPS, computerized NAPS: what is your flavor of propofol? *Gastrointest Endosc* 2007; **66**: 457-459 [PMID: 17725935 DOI: 10.1016/j.gie.2007.03.1035]

45 **Perel A**. Non-anaesthesiologists should not be allowed to administer propofol for procedural sedation: a Consensus Statement of 21 European National Societies of Anaesthesia. *Eur J Anaesthesiol* 2011; **28**: 580-584 [PMID: 21705907 DOI: 10.1097/EJA.0b013e328348a977]

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Endoscopic papillectomy: The limits of the indication, technique and results

José Celso Ardengh, Rafael Kemp, Éder Rios Lima-Filho, José Sebastião dos Santos

José Celso Ardengh, Rafael Kemp, José Sebastião dos Santos, Division of Digestive and Endoscopic Surgery, Department of Surgery and Anatomy, Ribeirão Preto School of Medicine, University of São Paulo, Ribeirão Preto 14049-900, São Paulo, Brazil

Éder Rios Lima-Filho, Department of Surgery, Hospital Federal dos Servidores do Estado, Rua Sacadura Cabral, Rio de Janeiro 20221-903, Brazil

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Correspondence to: José Sebastião dos Santos, MD, PhD, Professor, Division of Digestive and Endoscopic Surgery, Department of Surgery and Anatomy, Ribeirão Preto School of Medicine, University of São Paulo, Av. Bandeirantes, 3900 - 9º andar do Hospital das Clínicas de Ribeirão Preto, Ribeirão Preto 14049-900, Brazil. jsdsanto@fmrp.usp.br
Telephone: +55-16-36022508
Fax: +55-16-36330836

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Abstract

In the majority of cases, duodenal papillary tumors are adenomas or adenocarcinomas, but the endoscopy biopsy shows low accuracy to make the correct differentiation. Endoscopic ultrasonography and endoscopic retrograde cholangiopancreatography are important tools for the diagnosis, staging and management of ampullary lesions. Although the endoscopic papillectomy (EP) represent higher risk endoscopic interventions, it has successfully replaced surgical treatment for benign or malignant papillary tumors. The authors review the epidemiology and discuss the current evidence for the use of endoscopic procedures for resection, the selection of the patient and the preventive maneuvers that can minimize the probability of persistent or recurrent lesions and to avoid complications after the procedure. The accurate staging of ampullary tumors is important for selecting patients to EP or surgical treatment. Compared to surgery, EP is associated with lower morbidity and mortality, and seems to be a preferable modality of treatment for small benign ampullary tumors with no intraductal extension. The EP procedure, when performed by an experienced endoscopist, leads to successful eradication in up to 85% of patients with ampullary adenomas. EP is a safe and effective therapy and should be established as the first-line therapy for ampullary adenomas.

Key words: Epidemiology; Ampullary tumors; Endoscopic resection; Endoscopic ultrasound; Staging; Endoscopic papillectomy; Surgical ampullectomy

Core tip: Although the endoscopic papillectomy (EP) represent higher risk endoscopic interventions, it has successfully replaced surgical treatment for benign or malignant papillary tumors. The accurate staging of ampullary tumors is important for selecting patients to EP or surgical treatment. Compared to surgery, EP is associated with lower morbidity and mortality, and seems to be a preferable modality of treatment for small benign ampullary tumors with no intraductal extension.

The EP procedure, when performed by an experienced endoscopist, leads to successful eradication in up to 85% of patients with ampullary adenomas. EP is a safe and effective therapy and should be established as the first-line therapy for ampullary adenomas.

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INTRODUCTION

Ampullomas represent an uncommon group of gastrointestinal malignancies. Advances in endoscopic ultrasound (EUS) and endoscopic retrograde cholangiopancreatography (ERCP) have significantly impacted the clinical approach to patients with suspected premalignant or malignant lesions of the duodenal papilla[1]. The present review leads us to the discussion of numerous current issues related to the epidemiology of ampullary tumors, the role of the endoscopy biopsy, EUS, and ERCP, as well as indications, optimal technique, complications and outcomes in patients with benign or malignant tumor.

The term "endoscopic papillectomy" refers to the duodenal mucosa and submucosa resection, including all the anatomic attachments of the ampulla of Vater, and the tissues around the bile and pancreatic ducts. In turn, the term ampullectomy should be used to define this surgical procedure, which consists in the resection of the ampulla of Vater, through a duodenotomy including the cephalic pancreatic tissue resection, followed by reinsertion of common bile duct (CBD) and main pancreatic duct (MPD) in the duodenal wall[2].

The endoscopic papillectomy (EP) was first reported as a route of access to the biliary tract[3]. Years later, it was used as a treatment modality for two cases of duodenal papilla cancer[4], and today it is accepted as a viable alternative therapy to surgery in patients with sporadic adenoma of the major or minor duodenal papilla due to its high success rate and low recurrence[2].

EPIDEMIOLOGY

Tumors of the duodenal papilla may be classified as benign, premalignant, and malignant[5]. The annual incidence of ampullary lesions in the United States is 3000, with reported prevalence rates of 0.04%-0.12% in autopsy series[6,7]. Ampullary adenomas may occur sporadically or in the setting of hereditary polyposis syndromes, including familial adenomatous polyposis (FAP) with adenomatous polyposis coli gene mutations. In patients with FAP, ampullary adenomas occur in up to 80% of individuals during their lifetime and progress to malignancy in 4%[8]. Ampullary adenomas are likely to follow an adenoma-to-carcinoma sequence similar to colorectal adenocarcinoma[9]. These lesions are considered premalignant, with an incidence of transformation to carcinoma ranging from 25%-85% for sporadic adenomas. As with all neoplasms, tumor stage dictates the appropriate therapy[10].

DETERMINANT FACTORS IN THE RESECTION OF NON-INVASIVE NEOPLASMS OF THE VATER´S AMPULLA

It seems that the knowledge of the histological and immunohistochemical characteristics is useful for precisely indicate an EP. In this context, the study of such characteristics is useful for selecting the appropriate surgical or endoscopic procedure. To corroborate this fact, japanese authors reported the results of this analysis in 56 noninvasive ampullary tumors. They demonstrated that the intestinal type cancer of intra-ampullary location shows lower CK20 expression than tumors of the periampullary location, and besides that, the intestinal type tumors without CDX2 expression, that included extended and intra-ampullary location types, tend to show a compromised vertical margin after EP. This suggests that periampullary tumors, intestinal histology and high CK20-positive rate can be regarded as good indications for the EP procedure. On the other hand, this study shows that tumors that are either pancreatobiliary or intestinal type without CDX2 expression have a higher chance of involvement of the common channel inside duodenal papilla, CBD and MPD[11].

INDICATIONS

The indications for EP are based on features that can predict a complete tumor removal, while minimizing complications related to the procedure[1]. Currently the indications are not fully established and are far from a consensus.

The main criteria for EP include the lesion size (up to 5 cm), no evidence of intraductal tumor growth or malignancy in endoscopic findings, such as ulceration, spontaneous bleeding and friability[1,12-18]. However, the indications for EP are expanding[10,19-24]. For example, the endoscopic piecemeal resection technique, is used to removing tumors that can't be removed "*en bloc*", and provided increasing resections, when properly performed[25]. The clinical results of this technique are very good, but the chance of recurrence is higher.

The ductal invasion in an extension less than 1 cm does not seem to be an absolute contraindication for EP, because the tumor can be exposed by endoscopic maneuvers, such as the use of an extractor balloon into the lumen, and thus it can be completely resected with a polypectomy snare[26-28].

The cancer arising within an adenoma without

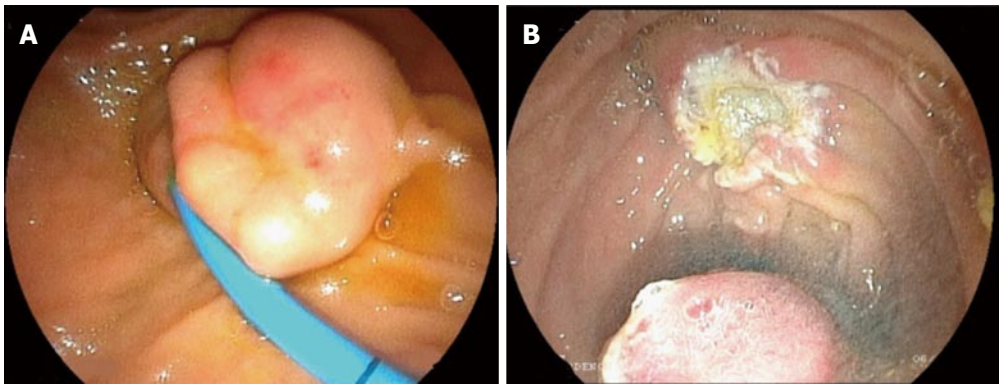

Figure 1 Endoscopic view of neuroendocrine tumor of the papilla with Fujinon intelligent chromo endoscopy. A: This picture show the depression in the center of the lesion; B: The picture shows the aspect of the papillary region after the "*en bloc*" resection.

invasion of duodenal muscularis propria and pancreas, or CBD and MPD, are liable to resection by EP[29-33]. However, in some situations, EP can be used as a macrobiopsy procedure for a simple local tumoral staging, if the resection margins are compromised[34].

PREOPERATIVE ENDOSCOPIC EVALUATION

The most common preoperative concern is to define if a papillary tumor is benign or malignant. The endoscopic aspect alone cannot always distinguish adenomas from carcinomas and even from adenomatous polyps, carcinoids, gangliocytic paraganglioma, and other tumors that may occur in this region[35,36]. Some endoscopic aspects like ulceration, friability, spontaneous bleeding are usually relate to malignant lesions. The use of endoscopic tools such as NBI, FICE and magnifying endoscopy are useful to select patients for EP (Figure 1)[37].

A definitive histological diagnosis is a basic prerequisite for adequate management of these patients, but we must remember that endoscopic biopsy of the duodenal papilla misses 30% of malignant tumors[38]. Moreover, the coexistence of carcinoma and adenoma cannot be excluded by endoscopic biopsy. Some authors advocate deep biopsy after sphincterotomy, to increase diagnostic accuracy of endoscopic biopsy[39]. We do not recommend this procedure, because endoscopic sphincterotomy eliminates the possibility of endoscopic *en bloc* resection of ampullary tumors, impeding a possible curative resection.

Favoring our impression, a prospective study showed that endoscopic biopsy is not reliable for preoperative diagnosis of tumors of the duodenal papilla (sensitivity of 21% before and 37% after sphincterotomy)[40]. Thus, in some cases, EP can be recommended as a technique for preoperative diagnosis because a high false negative rate of endoscopic biopsy[34].

PREOPERATIVE STAGING

EUS is the imaging modality of choice for local staging (T). EUS is superior to helical computed tomography (CT) for preoperative evaluation of tumor size, detection of regional lymph node metastasis, vascular invasion in patients with periampullary neoplasms and also to detect tumor infiltration of biliary and pancreatic ducts (Figure 2A)[40].

Many experts believe that EUS is not useful in lesions less than 1 cm in diameter, with no suspicious signs of malignancy (ulceration, induration, bleeding and/or biopsies with high-grade dysplasia or carcinoma)[12]. Our experience shows that, when EUS is performed for staging ampullary tumor prior to EP, it allows deciding for EP, because it shows the relationship between CBD and MPD, as well their diameter. EUS allows the verification of the relationship of the borders of the tumor in the duodenal wall, CBD and MPD, regardless of the size of the tumor. However, prospective studies are needed to evaluate the accuracy of these findings.

The use of intraductal ultrasound (IDUS), with a 20 MHz probe can be more accurate in visualizing mucosa layers compared to conventional EUS[41]. According to literature, EUS and IDUS accuracy before surgical resection or diagnostic EP was 97% and 94% for pTis, 73% and 73% for pT1, 50% and 50% for pT2 and 50% and 100% for pT3-4 respectively. The overall EUS and IDUS accuracy was 85% and 80% for T stage[42]. In our experience with this type of technology, the interpretation is more difficult, especially when the mini-probe is placed within the biliary or pancreatic ducts. If this is not done, the sensitivity is lower when compared with the conventional EUS[41].

From a technical standpoint, EUS and IDUS are able to detect, with high precision, tumoral infiltration of the common bile duct and main pancreatic duct (Figure 2B). Despite ERCP can detect CBD invasion, we believe that it should only be performed after EUS, if EP is indicated. EUS and IDUS can provide high precision diagnostic information for staging ampullary tumors, and are useful in identifying lesions selected for EP. However, these tools have limitations, because the occurrence of super and understating and the difficulty in assessing focal infiltration are relevant. The improvement of endoscopic procedures is necessary for an accurate assessment of

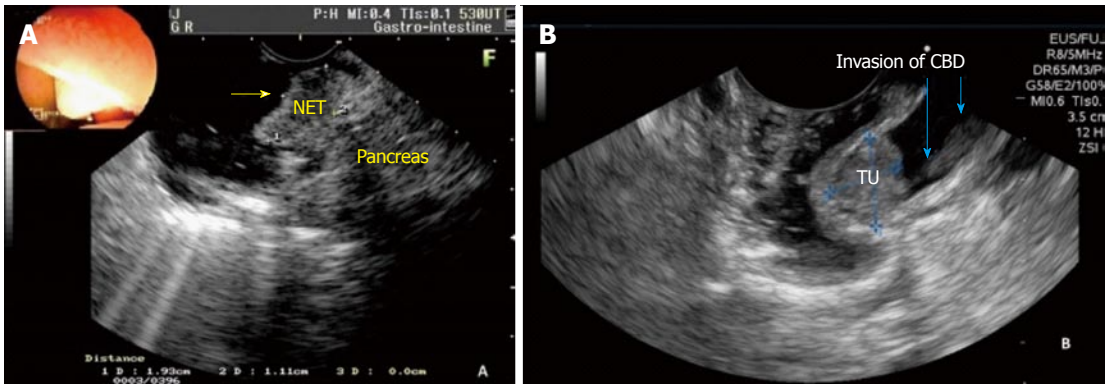

Figure 2 Endoscopic ultrasound staging of the duodenal papilla. A: Patient of the Figure 1. Endoscopic ultrasound staging shows the regular and hypoechoic nodule (1.93 cm) in the papilla without infiltration of the duodenal wall and pancreatic gland. The staging was uT1N0Mx; B: This picture shows the papillary tumor with 1.72 cm with invasion of the common bile duct wall (blue arrows). NET: Neuroendocrine tumor; TU: Tumor; CBD: Common bile duct.

ampullary tumors[43].

From a practical standpoint, ERCP should be performed before EP, if EUS is not available or inconclusive as to ductal involvement. Although intraductal invasion is usually an indication for surgery, it has been demonstrated that, when tumoral infiltration reaches ± 1 cm into CBD and MPD, tumor is amenable to endoscopic resection[26,27,44].

Positron computerized tomography (PET/CT) and magnetic resonance imaging (MRI) are highly sensitive for detection of distant metastases. MRI and CT was superior to EUS for assessment of nodal involvement[45].

ENDOSCOPIC PAPILLECTOMY TECHNIQUE

EP is performed after EUS staging confirming a less than 5.0 cm tumor confined to mucosa and/or submucosal (uT1), with intraductal tumoral infiltration less than 1 cm. It can be performed using the EUS device itself or a duodenoscope. With the duodenoscope rectified, a preferable monofilament polypectomy snare is used for grasping the tumor, always in the craniocaudal direction, *i.e.,* the snare tip is positioned on cranial tumor apex.

The snare is widely opened, duodenoscope is pushed in a craniocaudal direction, and tumor is grasped for en bloc resection (Figure 3). The papillary tumor is grasped at its base, always respecting a limit, up to 0.5 cm below the lesion border identified by FICE. Thereafter a constant tension is applied to the ring handle while using an electrocautery until tumor en bloc resection is completed. There are no specific equipment or a standard technique for EP.

There is also no guidance on the potency and mode of electronic current (cutting or coagulation). The authors prefer to use only cutting current (40 to 50 J) and the endocutter. Some authors recommend performing submucosal injection, ablative therapy after EP, and placement of a prophylactic pancreatic stent. The use of antibiotic prophylaxis before EP is not established[46]. The authors do not advocate its use.

Some experts use injection of contrast with methylene blue into MPD to identify the pancreatic orifice after tumor resection. This is not our practice. After complete removal of the lesion, which sometimes takes a few minutes, depending on its size and extension, a whitish rough area can be seen, which in some cases reveals the muscular layer of duodenal wall, as well two holes (biliary and pancreatic ducts).

Efforts should be exhaustive and mandatory to recover all resected tissue in all patients, for histopathological evaluation. Then CBD and MPD catheterization is performed, with contrast injection, to ensure easy recanalization after ampullary resection.

When *en bloc* resection is not feasible, a piecemeal resection is recommended. However, it should be noted that the en bloc resection is essential for the treatment of preneoplastic and/or malignant lesions, because this allows accurate histopathologic evaluation after tumoral resection[26].

The submucosal injection of diluted epinephrine is suggested as a means to lift the tumor from the wall, which at least theoretically may reduce the risk of bleeding. However, it is uncertain and questionable whether injection of adrenaline reduces the risk of bleeding and/or perforation[20,27,47]. The authors dismiss the submucosal injection of pharmacological agents, due to distortion of tumoral anatomy and its periphery, hindering an adequate grasping by the polypectomy snare. Moreover, a perforation following tumor resection may occur, due to a short distance between duodenal wall and pancreas, as seen by EUS.

If residual tumor tissue remains after resection, it should be destroyed! The use of coagulation with argon gas is the most widely used modality; it is safe because it is a non-contact technique, acting in tumor surface[12,46-48].

The use of stent in MPD, in order to reduce the risk of acute pancreatitis (AP) associated to EP, seems to be a consensus because it minimizes the risk of MPD stenosis, allowing the use of safer coagulation therapies. Anyway we must emphasize that this theory is unproven. Others advocate pancreatic stent placement only if MPD drainage is not sufficient after EP[49-52]. The only

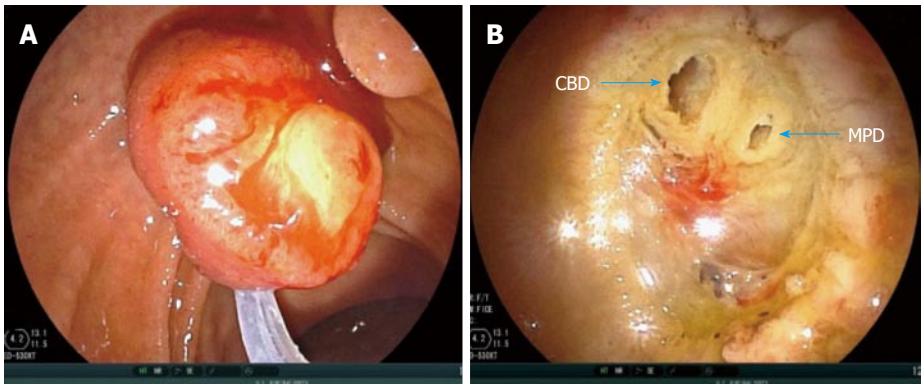

Figure 3 Endoscopic papillectomy immediately after endoscopic ultrasound for staging. A: *En bloc* resection of the tumor, after the snare is widely opened, duodenoscope is pushed in a craniocaudal direction; B: The endoscopic view of the common bile duct and main pancreatic duct (blue arrows) after a complete *en bloc* resection of the papillary tumor. CBD: Common bile duct; MPD: Main pancreatic duct.

Table 1 Result after endoscopic papilectomy

Ref.	Patients	Success/(%)	Complications/(%)	Mortality/(%)	Recidive/(%)	Surgery/(%)
Binmoeller *et al*[13]	25	23/92	5/20	0/0	6/24	3/12
Vogt *et al*[64]	18	12/67	4/22	0/0	6/33	NA
Zádorová *et al*[18]	16	13/81	4/25	0/0	3/19	1/6.2
Desilets *et al*[47]	13	12/92	1/7.7	0/0	0/0	1/7.7
Norton *et al*[48]	26	12/46	5/19	0/0	2/7.7	1/3.8
Bohnacker *et al*[20]	87	74/85	29/33	0/0	15/17	17/19
Catalano *et al*[14]	103	83/80	10/9.7	0/0	10/9.7	16/15.5
Cheng *et al*[15]	55	39/71	12/22	0/0	9/16.3	4/7.2
Han *et al*[21]	33	20/60.6	11/33.3	0/0	2/6	2/6
Ismail *et al*[65]	61	56/92	15/24.5	0/0	12/19.6	9/14.7
Napoleon *et al*[66]	93	84/90	39/42	1/1	5/5.3	NA
Ridtitid *et al*[67]	182	134/73.6	34/18.6	0/0	16/8.7	NA
Ardengh *et al*[58]	41	38/92	11/26.8	0/0	3/7.3	4/9.7

NA: Not available.

prospective, randomized, controlled study, to evaluate the role of prophylactic stent in MPD, to reduce AP after EP, showed a statistically significant decrease in the rate of AP after stent procedure[53].

Otherwise, the adequate MPD diameter and length for stenting are uncertain. In other work, for example, the authors suggests that routine use of prophylactic pancreatic stent in all patients is unnecessary and efforts should be directed to know which groups of patients actually benefit from its insertion[54]. Most pancreatic stents migrate spontaneously from MPD within 2 wk after insertion. Abdominal X-ray after 2 wk can confirm this finding. A stent, which remains "*in situ*" for more than 2 wk, should be removed endoscopically. The placement of a prophylactic plastic biliary stent, to reduce the risk of cholangitis, has not been widely performed and cannot be uniformly recommended at the present moment, unless there is concern about inadequate biliary drainage after EP.

COMPLICATIONS

The EP is a "high risk" procedure, due to complications inherent to the method. They can be classified as early: AP, bleeding, perforation and cholangitis or late: papillary stenosis. The overall complication rate reported by major centers of tertiary care varies between 8% and 35%, and the most common complications are AP (5%-15%) and bleeding (2%-16%)[10,25,48,55]. Most episodes of bleeding can be controlled immediately by conservative treatment and endoscopic hemostasis and most episodes of AP are mild and resolve with conservative treatment only. The rate of pancreatic and/or biliary ductal stenosis varies between 0%-8%, and can be treated by sphincterotomy, stent placement, and balloon dilation.

The use of pancreatic stent can prevent an episode of AP and papillary stenosis[49-54]. Another interesting fact reported by a recent randomized study showed that prophylactic rectal indomethacin significantly reduced the incidence and severity of AP post-ERCP, providing an additional benefit in pancreatic temporary stenting[56]. The mortality after-EP is rare, but it has been reported to be 0.4% (range 0% to 7%)[57].

RESULTS

The results of the endoscopic treatment of ampullary

tumors reported in the literature are shown in Table 1. The EP results are based on retrospective case series studies with heterogeneous groups. As there is no consensus on the definition of "success" after EP, it is difficult to compare the results of the reported studies. Conventionally, "success" can be defined as a complete tumor resection (as the proven absence of visible residual adenoma by endoscopy and histological analysis during a 3-6 mo follow up). In the literature the rate of the success varies between 46% to 92% in the different series. The complication rate after EP varies between 8% to 42% and the major problems are acute pancreatitis, perforation and bleeding. The most important complication after EP is the acute pancreatitis that could be diminished with the insertion of the plastic pancreatic stent. This is a controversial point, because in our experience if you have a dilated main pancreatic duct the use of the PPS is unnecessary[58].

Recurrence of benign lesions occur in up to 33% of patients depending on the tumor size, final histology, presence of intraductal tumor, coexistence of FAP and endoscopist experience[21,57,59-64]. If you use the endoscopic ultrasound before the EP you could find with precision the presence of intraductal tumor. In this case there are contraindication to submitted the patient to EP. Recurrent lesions are usually benign and most can be removed endoscopically.

CONCLUSION

EP is a safe and effective therapy and should be established as the first-line therapy for ampullary adenomas. The accurate staging of ampullary tumors is important for selecting patients to EP or surgical treatment. Compared to surgery, EP is associated with lower morbidity and mortality, and seems to be a preferable modality of treatment for small benign ampullary tumors with no intraductal extension. The EP procedure, when performed by an experienced endoscopist, leads to successful eradication in up to 85% of patients with ampullary adenomas.

REFERENCES

1 **El Hajj II**, Coté GA. Endoscopic diagnosis and management of ampullary lesions. *Gastrointest Endosc Clin N Am* 2013; **23**: 95-109 [PMID: 23168121 DOI: 10.1016/j.giec.2012.10.004]

2 **De Palma GD**. Endoscopic papillectomy: indications, techniques, and results. *World J Gastroenterol* 2014; **20**: 1537-1543 [PMID: 24587629 DOI: 10.3748/wjg.v20.i6.1537]

3 **Fujita R**, Satake Y, Sugata F, Ono K, Soma S. Endoscopic papillectomy--excision of biliary calculi. *Nihon Rinsho* 1978; Suppl: 2190-2191 [PMID: 691690]

4 **Suzuki K**, Kantou U, Murakami Y. Two cases with ampullary cancer who underwent endoscopic excision. *Prog Dig Endosc* 1983; **23**: 236-239

5 **Ohike N**, Kim GE, Tajiri T, Krasinskas A, Basturk O, Coban I, Bandyopadhyay S, Morohoshi T, Goodman M, Kooby DA, Sarmiento JM, Adsay NV. Intra-ampullary papillary-tubular neoplasm (IAPN): characterization of tumoral intraepithelial neoplasia occurring within the ampulla: a clinicopathologic analysis of 82 cases. *Am J Surg Pathol* 2010; **34**: 1731-1748 [PMID: 21084962 DOI: 10.1097/PAS.0b013e3181f8ff05]

6 **Grobmyer SR**, Stasik CN, Draganov P, Hemming AW, Dixon LR, Vogel SB, Hochwald SN. Contemporary results with ampullectomy for 29 "benign" neoplasms of the ampulla. *J Am Coll Surg* 2008; **206**: 466-471 [PMID: 18308217 DOI: 10.1016/j.jamcollsurg.2007.09.005]

7 **Martin JA**, Haber GB. Ampullary adenoma: clinical manifestations, diagnosis, and treatment. *Gastrointest Endosc Clin N Am* 2003; **13**: 649-669 [PMID: 14986792 DOI: 10.1016/S1052-5157(03)00101-6]

8 **Burke CA**, Beck GJ, Church JM, van Stolk RU. The natural history of untreated duodenal and ampullary adenomas in patients with familial adenomatous polyposis followed in an endoscopic surveillance program. *Gastrointest Endosc* 1999; **49**: 358-364 [PMID: 10049420 DOI: 10.1016/S0016-5107(99)70013-1]

9 **Fischer HP**, Zhou H. Pathogenesis of carcinoma of the papilla of Vater. *J Hepatobiliary Pancreat Surg* 2004; **11**: 301-309 [PMID: 15549428]

10 **Patel R**, Varadarajulu S, Wilcox CM. Endoscopic ampullectomy: techniques and outcomes. *J Clin Gastroenterol* 2012; **46**: 8-15 [PMID: 22064552 DOI: 10.1097/MCG.0b013e318233a844]

11 **Yamamoto Y**, Nemoto T, Okubo Y, Nihonyanagi Y, Ishiwatari T, Takuma K, Tochigi N, Okano N, Wakayama M, Igarashi Y, Shibuya K. Comparison between the location and the histomorphological/immunohistochemical characteristics of noninvasive neoplasms of the ampulla of Vater. *Hum Pathol* 2014; **45**: 1910-1917 [PMID: 25081540 DOI: 10.1016/j.humpath.2014.05.013]

12 **Baillie J**. Endoscopic ampullectomy. *Am J Gastroenterol* 2005; **100**: 2379-2381 [PMID: 16279887 DOI: 10.1111/j.1572-0241.2005.00332.x]

13 **Binmoeller KF**, Boaventura S, Ramsperger K, Soehendra N. Endoscopic snare excision of benign adenomas of the papilla of Vater. *Gastrointest Endosc* 1993; **39**: 127-131 [PMID: 8495831 DOI: 10.1016/S0016-5107(93)70051-6]

14 **Catalano MF**, Linder JD, Chak A, Sivak MV, Raijman I, Geenen JE, Howell DA. Endoscopic management of adenoma of the major duodenal papilla. *Gastrointest Endosc* 2004; **59**: 225-232 [PMID: 14745396 DOI: 10.1016/S0016-5107(03)02366-6]

15 **Cheng CL**, Sherman S, Fogel EL, McHenry L, Watkins JL, Fukushima T, Howard TJ, Lazzell-Pannell L, Lehman GA. Endoscopic snare papillectomy for tumors of the duodenal papillae. *Gastrointest Endosc* 2004; **60**: 757-764 [PMID: 15557951 DOI: 10.1016/S0016-5107(04)02029-2]

16 **Silvis SE**. Endoscopic snare papillectomy. *Gastrointest Endosc* 1993; **39**: 205-207 [PMID: 8495850 DOI: 10.1016/S0016-5107(93)70074-7]

17 **Wong RF**, DiSario JA. Approaches to endoscopic ampullectomy. *Curr Opin Gastroenterol* 2004; **20**: 460-467 [PMID: 15689680 DOI: 10.1097/00001574-200409000-00008]

18 **Zádorová Z**, Dvofák M, Hajer J. Endoscopic therapy of benign tumors of the papilla of Vater. *Endoscopy* 2001; **33**: 345-347 [PMID: 11315897 DOI: 10.1055/s-2001-13693]

19 **Bassan M,** Bourke M. Endoscopic ampullectomy: a practical guide. *J Interv Gastroenterol* 2012; **2**: 23-30 [PMID: 22586547 DOI: 10.4161/jig.20131]

20 **Bohnacker S**, Soehendra N, Maguchi H, Chung JB, Howell DA. Endoscopic resection of benign tumors of the papilla of vater. *Endoscopy* 2006; **38**: 521-525 [PMID: 16767591 DOI: 10.1055/s-2006-925263]

21 **Han J**, Kim MH. Endoscopic papillectomy for adenomas of the major duodenal papilla (with video). *Gastrointest Endosc* 2006; **63**: 292-301 [PMID: 16427938 DOI: 10.1016/j.gie.2005.07.022]

22 **Hernandez LV**, Catalano MF. Endoscopic papillectomy. *Curr Opin Gastroenterol* 2008; **24**: 617-622 [PMID: 19122504 DOI: 10.1097/MOG.0b013e3283088e12]

23 **Ito K**, Fujita N, Noda Y. Endoscopic diagnosis and treatment of ampullary neoplasm (with video). *Dig Endosc* 2011; **23**: 113-117 [PMID: 21429014 DOI: 10.1111/j.1443-1661.2010.01101.x]

24 **Rattner DW**, Fernandez-del Castillo C, Brugge WR, Warshaw AL. Defining the criteria for local resection of ampullary neoplasms.

Arch Surg 1996; **131**: 366-371 [PMID: 8615720 DOI: 10.1001/archsurg.1996.01430160024003]

25 **Ito K**, Fujita N, Noda Y, Kobayashi G, Obana T, Horaguchi J, Koshita S, Kanno Y, Ogawa T, Kato Y, Yamashita Y. Impact of technical modification of endoscopic papillectomy for ampullary neoplasm on the occurrence of complications. *Dig Endosc* 2012; **24**: 30-35 [PMID: 22211409 DOI: 10.1111/j.1443-1661.2011.01161.x]

26 **Aiura K**, Imaeda H, Kitajima M, Kumai K. Balloon-catheter-assisted endoscopic snare papillectomy for benign tumors of the major duodenal papilla. *Gastrointest Endosc* 2003; **57**: 743-747 [PMID: 12709713 DOI: 10.1067/mge.2003.213]

27 **Bohnacker S**, Seitz U, Nguyen D, Thonke F, Seewald S, deWeerth A, Ponnudurai R, Omar S, Soehendra N. Endoscopic resection of benign tumors of the duodenal papilla without and with intraductal growth. *Gastrointest Endosc* 2005; **62**: 551-560 [PMID: 16185970 DOI: 10.1016/j.gie.2005.04.053]

28 **Kim JH**, Kim JH, Han JH, Yoo BM, Kim MW, Kim WH. Is endoscopic papillectomy safe for ampullary adenomas with high-grade dysplasia? *Ann Surg Oncol* 2009; **16**: 2547-2554 [PMID: 19568817 DOI: 10.1245/s10434-009-0509-2]

29 **Kim HK**, Lo SK. Endoscopic approach to the patient with benign or malignant ampullary lesions. *Gastrointest Endosc Clin N Am* 2013; **23**: 347-383 [PMID: 23540965 DOI: 10.1016/j.giec.2013.01.003]

30 **Petrone G**, Ricci R, Familiari P, Inzani F, Matsuoka M, Mutignani M, Delle Fave G, Costamagna G, Rindi G. Endoscopic snare papillectomy: a possible radical treatment for a subgroup of T1 ampullary adenocarcinomas. *Endoscopy* 2013; **45**: 401-404 [PMID: 23616129 DOI: 10.1055/s-0032-1326213]

31 **Salmi S**, Ezzedine S, Vitton V, Ménard C, Gonzales JM, Desjeux A, Grimaud JC, Barthet M. Can papillary carcinomas be treated by endoscopic ampullectomy? *Surg Endosc* 2012; **26**: 920-925 [PMID: 22011948 DOI: 10.1007/s00464-011-1968-7]

32 **Woo SM**, Ryu JK, Lee SH, Lee WJ, Hwang JH, Yoo JW, Park JK, Kang GH, Kim YT, Yoon YB. Feasibility of endoscopic papillectomy in early stage ampulla of Vater cancer. *J Gastroenterol Hepatol* 2009; **24**: 120-124 [PMID: 19032444 DOI: 10.1111/j.1440-1746.2008.05578.x]

33 **Yoon LY**, Moon JH, Choi HJ, Min SK, Cha SW, Cheon YK, Cho YD, Lee MS, Kim JS. Wire-guided endoscopic snare retrieval of proximally migrated pancreatic stents after endoscopic papillectomy for ampullary adenoma. *Gut Liver* 2011; **5**: 532-535 [PMID: 22195255 DOI: 10.5009/gnl.2011.5.4.532]

34 **Ogawa T**, Ito K, Fujita N, Noda Y, Kobayashi G, Horaguchi J, Koshita S, Kanno Y, Masu K, Ishii S. Endoscopic papillectomy as a method of total biopsy for possible early ampullary cancer. *Dig Endosc* 2012; **24**: 291 [PMID: 22725127 DOI: 10.1111/j.1443-1661.2011.01214.x]

35 **Kwon J**, Lee SE, Kang MJ, Jang JY, Kim SW. A case of gangliocytic paraganglioma in the ampulla of Vater. *World J Surg Oncol* 2010; **8**: 42 [PMID: 20497533 DOI: 10.1186/1477-7819-8-42]

36 **Niido T**, Itoi T, Harada Y, Haruyama K, Ebihara Y, Tsuchida A, Kasuya K. Carcinoid of major duodenal papilla. *Gastrointest Endosc* 2005; **61**: 106-107 [PMID: 15672069 DOI: 10.1016/S0016-5107(04)02384-3]

37 **Itoi T**, Tsuji S, Sofuni A, Itokawa F, Kurihara T, Tsuchiya T, Ishii K, Ikeuchi N, Igarashi M, Gotoda T, Moriyasu F. A novel approach emphasizing preoperative margin enhancement of tumor of the major duodenal papilla with narrow-band imaging in comparison to indigo carmine chromoendoscopy (with videos). *Gastrointest Endosc* 2009; **69**: 136-141 [PMID: 19026411 DOI: 10.1016/j.gie.2008.07.036]

38 **Elek G**, Gyôri S, Tóth B, Pap A. Histological evaluation of preoperative biopsies from ampulla vateri. *Pathol Oncol Res* 2003; **9**: 32-41 [PMID: 12704445 DOI: 10.1007/BF03033712]

39 **Bourgeois N**, Dunham F, Verhest A, Cremer M. Endoscopic biopsies of the papilla of Vater at the time of endoscopic sphincterotomy: difficulties in interpretation. *Gastrointest Endosc* 1984; **30**: 163-166 [PMID: 6735092 DOI: 10.1016/S0016-5107(84)72357-1]

40 **Ito K**, Fujita N, Noda Y, Kobayashi G, Horaguchi J, Takasawa O, Obana T. Preoperative evaluation of ampullary neoplasm with EUS and transpapillary intraductal US: a prospective and histopathologically controlled study. *Gastrointest Endosc* 2007; **66**: 740-747 [PMID: 17905017 DOI: 10.1016/j.gie.2007.03.1081]

41 **Menzel J**, Hoepffner N, Sulkowski U, Reimer P, Heinecke A, Poremba C, Domschke W. Polypoid tumors of the major duodenal papilla: preoperative staging with intraductal US, EUS, and CT--a prospective, histopathologically controlled study. *Gastrointest Endosc* 1999; **49**: 349-357 [PMID: 10049419 DOI: 10.1016/S0016-5107(99)70012-X]

42 **Okano N**, Igarashi Y, Hara S, Takuma K, Kamata I, Kishimoto Y, Mimura T, Ito K, Sumino Y. Endosonographic preoperative evaluation for tumors of the ampulla of vater using endoscopic ultrasonography and intraductal ultrasonography. *Clin Endosc* 2014; **47**: 174-177 [PMID: 24765600 DOI: 10.5946/ce.2014.47.2.174]

43 **Moon JH**. Endoscopic diagnosis of ampullary tumors using conventional endoscopic ultrasonography and intraductal ultrasonography in the era of endoscopic papillectomy: advantages and limitations. *Clin Endosc* 2014; **47**: 127-128 [PMID: 24765593 DOI: 10.5946/ce.2014.47.2.127]

44 **Kim JH**, Moon JH, Choi HJ, Lee HS, Kim HK, Cheon YK, Cho YD, Lee JS, Lee MS, Shim CS. Endoscopic snare papillectomy by using a balloon catheter for an unexposed ampullary adenoma with intraductal extension (with videos). *Gastrointest Endosc* 2009; **69**: 1404-1406 [PMID: 19152886 DOI: 10.1016/j.gie.2008.07.049]

45 **Cannon ME**, Carpenter SL, Elta GH, Nostrant TT, Kochman ML, Ginsberg GG, Stotland B, Rosato EF, Morris JB, Eckhauser F, Scheiman JM. EUS compared with CT, magnetic resonance imaging, and angiography and the influence of biliary stenting on staging accuracy of ampullary neoplasms. *Gastrointest Endosc* 1999; **50**: 27-33 [PMID: 10385718 DOI: 10.1016/S0016-5107(99)70340-8]

46 **Menees SB**, Schoenfeld P, Kim HM, Elta GH. A survey of ampullectomy practices. *World J Gastroenterol* 2009; **15**: 3486-3492 [PMID: 19630102 DOI: 10.3748/wjg.15.3486]

47 **Desilets DJ**, Dy RM, Ku PM, Hanson BL, Elton E, Mattia A, Howell DA. Endoscopic management of tumors of the major duodenal papilla: Refined techniques to improve outcome and avoid complications. *Gastrointest Endosc* 2001; **54**: 202-208 [PMID: 11474391 DOI: 10.1067/mge.2001.116564]

48 **Norton ID**, Gostout CJ, Baron TH, Geller A, Petersen BT, Wiersema MJ. Safety and outcome of endoscopic snare excision of the major duodenal papilla. *Gastrointest Endosc* 2002; **56**: 239-243 [PMID: 12145603 DOI: 10.1016/S0016-5107(02)70184-3]

49 **Baillie J**. Endoscopic ampullectomy: does pancreatic stent placement make it safer? *Gastrointest Endosc* 2005; **62**: 371-373 [PMID: 16111954 DOI: 10.1016/j.gie.2005.04.021]

50 **Lee SK**, Kim MH, Seo DW, Lee SS, Park JS. Endoscopic sphincterotomy and pancreatic duct stent placement before endoscopic papillectomy: are they necessary and safe procedures? *Gastrointest Endosc* 2002; **55**: 302-304 [PMID: 11818948 DOI: 10.1067/mge.2002.120885]

51 **Napoléon B**, Alvarez-Sanchez MV, Leclercq P, Mion F, Pialat J, Gincul R, Ribeiro D, Cambou M, Lefort C, Rodríguez-Girondo M, Scoazec JY. Systematic pancreatic stenting after endoscopic snare papillectomy may reduce the risk of postinterventional pancreatitis. *Surg Endosc* 2013; **27**: 3377-3387 [PMID: 23549765 DOI: 10.1007/s00464-013-2920-9]

52 **Yamao T**, Isomoto H, Kohno S, Mizuta Y, Yamakawa M, Nakao K, Irie J. Endoscopic snare papillectomy with biliary and pancreatic stent placement for tumors of the major duodenal papilla. *Surg Endosc* 2010; **24**: 119-124 [PMID: 19517183 DOI: 10.1007/s00464-009-0538-8]

53 **Harewood GC**, Pochron NL, Gostout CJ. Prospective, randomized, controlled trial of prophylactic pancreatic stent placement for endoscopic snare excision of the duodenal ampulla. *Gastrointest Endosc* 2005; **62**: 367-370 [PMID: 16111953 DOI: 10.1016/j.gie.2005.04.020]

54 **Chang WI**, Min YW, Yun HS, Lee KH, Lee JK, Lee KT, Rhee PL. Prophylactic pancreatic stent placement for endoscopic duodenal ampullectomy: a single-center retrospective study. *Gut Liver* 2014; **8**: 306-312 [PMID: 24827628 DOI: 10.5009/gnl.2014.8.3.306]

55 **Jun DW**, Choi HS. Is the endoscopic papillectomy safe procedure in periampullary tumors?. *Korean J Gastroenterol* 2005; **46**: 247-250 [PMID: 16179847]

56 **Elmunzer BJ**, Scheiman JM, Lehman GA, Chak A, Mosler P, Higgins PD, Hayward RA, Romagnuolo J, Elta GH, Sherman S, Waljee AK, Repaka A, Atkinson MR, Cote GA, Kwon RS, McHenry L, Piraka CR, Wamsteker EJ, Watkins JL, Korsnes SJ, Schmidt SE, Turner SM, Nicholson S, Fogel EL. A randomized trial of rectal indomethacin to prevent post-ERCP pancreatitis. *N Engl J Med* 2012; **366**: 1414-1422 [PMID: 22494121 DOI: 10.1056/NEJMoa1111103]

57 **Heinzow HS**, Lenz P, Lenze F, Domagk D, Domschke W, Meister T. Feasibility of snare papillectomy in ampulla of Vater tumors: meta-analysis and study results from a tertiary referral center. *Hepatogastroenterology* 2012; **59**: 332-335 [PMID: 21940377 DOI: 10.5754/hge11414]

58 **Ardengh JC**, Baron TH, Kemp PR, Mota GA, Taglieri E, Micelli-Neto O, Orsini ET, Santos JS. Impact of technical modification of EUS-guided endoscopic papillectomy for ampullary neoplasm on the rate of post- resection acute pancreatitis. *Gastrointest Endosc* 2013; **77**: AB 374

59 **Ahn DW**, Ryu JK, Kim J, Yoon WJ, Lee SH, Kim YT, Yoon YB. Endoscopic papillectomy for benign ampullary neoplasms: how can treatment outcome be predicted? *Gut Liver* 2013; **7**: 239-245 [PMID: 23560162 DOI: 10.5009/gnl.2013.7.2.239]

60 **Boix J**, Lorenzo-Zúñiga V, Moreno de Vega V, Domènech E, Gassull MA. Endoscopic resection of ampullary tumors: 12-year review of 21 cases. *Surg Endosc* 2009; **23**: 45-49 [PMID: 18398649 DOI: 10.1007/s00464-008-9866-3]

61 **Irani S**, Arai A, Ayub K, Biehl T, Brandabur JJ, Dorer R, Gluck M, Jiranek G, Patterson D, Schembre D, Traverso LW, Kozarek RA. Papillectomy for ampullary neoplasm: results of a single referral center over a 10-year period. *Gastrointest Endosc* 2009; **70**: 923-932 [PMID: 19608181 DOI: 10.1016/j.gie.2009.04.015]

62 **Jung MK**, Cho CM, Park SY, Jeon SW, Tak WY, Kweon YO, Kim SK, Choi YH. Endoscopic resection of ampullary neoplasms: a single-center experience. *Surg Endosc* 2009; **23**: 2568-2574 [PMID: 19360365 DOI: 10.1007/s00464-009-0464-9]

63 **Kim SH**, Moon JH, Choi HJ, Kim DC, Lee TH, Cheon YK, Cho YD, Park SH, Kim SJ. Usefulness of pancreatic duct wire-guided endoscopic papillectomy for ampullary adenoma for preventing post-procedure pancreatitis. *Endoscopy* 2013; **45**: 838-841 [PMID: 23918619 DOI: 10.1055/s-0033-1344392]

64 **Vogt M**, Jakobs R, Benz C, Arnold JC, Adamek HE, Riemann JF. Endoscopic therapy of adenomas of the papilla of Vater. A retrospective analysis with long-term follow-up. *Dig Liver Dis* 2000; **32**: 339-345 [PMID: 11515633 DOI: 10.1016/S1590-8658(00)80028-6]

65 **Ismail S**, Marianne U, Heikki J, Jorma H, Leena K. Endoscopic papillectomy, single-centre experience. *Surg Endosc* 2014; **28**: 3234-3239 [PMID: 24928230 DOI: 10.1007/s00464-014-3596-5]

66 **Napoleon B**, Gincul R, Ponchon T, Berthiller J, Escourrou J, Canard JM, Boyer J, Barthet M, Ponsot P, Laugier R, Helbert T, Coumaros D, Scoazec JY, Mion F, Saurin JC. Endoscopic papillectomy for early ampullary tumors: long-term results from a large multicenter prospective study. *Endoscopy* 2014; **46**: 127-134 [PMID: 24477368 DOI: 10.1055/s-0034-1364875]

67 **Ridtitid W**, Tan D, Schmidt SE, Fogel EL, McHenry L, Watkins JL, Lehman GA, Sherman S, Coté GA. Endoscopic papillectomy: risk factors for incomplete resection and recurrence during long-term follow-up. *Gastrointest Endosc* 2014; **79**: 289-296 [PMID: 24094466 DOI: 10.1016/j.gie.2013.08.006]

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ORIGINAL ARTICLE

Retrospective Study

Gastric polyps: Association with *Helicobacter pylori* status and the pathology of the surrounding mucosa, a cross sectional study

Sherif Elhanafi, Mohammed Saadi, Wynee Lou, Indika Mallawaarachchi, Alok Dwivedi, Marc Zuckerman, Mohamed O Othman

Sherif Elhanafi, Mohammed Saadi, Wynee Lou, Marc Zuckerman, Division of Gastroenterology, Department of Internal Medicine, Paul L. Foster School of Medicine, Texas Tech University Health Sciences Center, El Paso, TX 77030, United States

Indika Mallawaarachchi, Alok Dwivedi, Division of Biostatistics and Epidemiology, Department of Biomedical Sciences, Paul L. Foster School of Medicine, Texas Tech University Health Sciences Center, El Paso, TX 77030, United States

Mohamed O Othman, Gastroenterology and Hepatology Section, Department of Internal Medicine, Baylor College of Medicine, Houston, TX 77030, United States

Author contributions: Elhanafi S contributed to the study concept and design, acquisition of data, analysis and interpretation of data and drafting of the manuscript; Saadi M and Lou W acquired of data; Mallawaarachchi I and Dwivedi A made the contributed to the analysis and interpretation of data and drafting of the manuscript and statistical analysis; Zuckerman M made the study concept and critical revision of the manuscript for important intellectual content; Othman MO performed the study concept and design critical revision of the manuscript for important intellectual content, statistical analysis and study supervision.

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Correspondence to: Mohamed O Othman, MD, Assistant Professor, Gastroenterology and Hepatology Section, Department of Internal Medicine, Baylor College of Medicine, 7200 Cambridge Street, Houston, TX 77030, United States. mohamed.othman@bcm.edu
Telephone: +1-713-7980950

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Abstract

AIM: To assess the endoscopic characteristics of gastric polyps and their association with *Helicobacter pylori* (*H. pylori*) status in a predominantly Hispanic population.

METHODS: We conducted a retrospective study of all esophagogastroduodenoscopies performed at our institution. Demographic, endoscopic and histopathological data were reviewed. Categorization of patients into Hispanic and Non-Hispanic was based on self-identification. Patients without resection/biopsy were not included in the analysis. Identification of polyps type was based on histological examination. One way analysis of variance was used to compare continuous

variables among different polyp types and Fisher's exact test was used compare categorical variables among polyp types. Unadjusted and adjusted comparisons of demographic and clinical characteristics were performed according to the *H. pylori* status and polyp type using logistic regressions.

RESULTS: Of 7090 patients who had upper endoscopy, 335 patients had gastric polyps (4.7%). Resection or biopsy of gastric polyps was performed in 296 patients (88.4%) with a total of 442 polyps removed or biopsied. Of 296 patients, 87 (29%) had hyperplastic polyps, 82 (28%) had fundic gland polyps and 5 (1.7%) had adenomatous polyps. Hyperplastic polyps were significantly associated with positive *H. pylori* status compared with fundic gland polyps (OR = 4.621; 95%CI: 1.92-11.13, *P* = 0.001). Hyperplastic polyps were also found to be significantly associated with portal hypertensive gastropathy compared with fundic gland polyps (OR = 6.903; 95%CI: 1.41-33.93, *P* = 0.0174). Out of 296 patients, 30 (10.1%) had a follow-up endoscopy with a mean duration of 26 ± 16.3 mo. Interval development of cancer was not noted in any of the patients during follow up period.

CONCLUSION: Gastric hyperplastic polyps were significantly associated with positive *H. pylori* status and portal hypertensive gastropathy as compared with fundic gland polyps.

Key words: Gastric polyps; Fundic gland polyp; Hyperplastic polyp; Adenomatous polyps; Chronic gastritis; *Helicobacter pylori*

Core tip: In a predominantly Hispanic population, the most common gastric polyps were hyperplastic and fundic gland polyps (more than half of gastric polyps). Gastric hyperplastic polyps were significantly associated with positive *Helicobacter pylori* status and portal hypertensive gastropathy as compared with fundic gland polyps. Hyperplastic polyps and fundic gland polyps were more prevalent in chronic gastritis, while adenomatous polyps were associated with intestinal metaplasia.

Elhanafi S, Saadi M, Lou W, Mallawaarachchi I, Dwivedi A, Zuckerman M, Othman MO. Gastric polyps: Association with *Helicobacter pylori* status and the pathology of the surrounding mucosa, a cross sectional study. *World J Gastrointest Endosc* 2015; 7(10): 995-1002 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i10/995.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i10.995

INTRODUCTION

Gastric polyps can be defined as abnormal luminal growths projecting above the plane of the mucosal surface. The incidence of gastric polyps has been estimated to be between 2% and 6%. The incidence of gastric polyps is gradually increasing due to expanded indications and widespread use of endoscopic examinations[1-4]. Gastric polyps are usually asymptomatic and discovered incidentally during endoscopic examination, but on rare occasions they can present with nonspecific symptoms such as abdominal pain, gastrointestinal bleeding, anemia, or symptoms of gastric outlet obstruction[5-8]. Determination of gastric polyp type is important as the risk for malignant transformation depends on the histopathological nature of the polyp[9-12]. The frequency of different types of gastric polyps varies widely depending on the population studied. It has been reported that hyperplastic polyps are relatively more frequent than fundic gland polyps in regions where *Helicobacter pylori* (*H. pylori*) infection is common[1,13]. A higher prevalence of *H. pylori* infection has been documented in Hispanics living in United States regions bordering Mexico compared with non-border areas[14,15]. There is a paucity of published data from the United States regarding the nature and various characteristics of gastric polyps, especially in Hispanics and other immigrant groups. The aim of this study is to assess the prevalence of gastric polyps and their endoscopic and histological characteristics in a predominantly Hispanic population on the United States-Mexico border.

MATERIALS AND METHODS

Study design

After receiving approval from Texas Tech University Institutional Review Board, we retrospectively reviewed all esophagogastroduodenoscopies (EGDs) performed at the University Medical Center, El Paso, TX for all indications. The review period of the study was from November 1, 2007 to July 30, 2013. The electronic database system (ProVation®, Minneapolis, MN) was used to identify the patient's demographic data, the indication for the procedure and gastric polyp characteristics. Categorization of patients into Hispanic and Non-Hispanic was based on self-identification. Patients without resection/biopsy were not included in the analysis. Identification of polyps type was based on histological examination.

Statistical analysis

Quantitative variables were described using the mean ± SD, whereas categorical variables were described using the frequency and proportion. One way analysis of variance was used to compare continuous variables among different polyp types and Fisher's exact test was used compare categorical variables among polyp types. Unadjusted and adjusted comparisons of demographic and clinical characteristics were performed according to the *H. pylori* status and polyp type using logistic regressions. The logistic regression analysis for *H. pylori* status was conducted after removing *H. pylori*

Table 1 Patient level summary of polyp histology

Polyp's type	Total patients (n = 296)	Percentage
Hyperplastic polyp	87	29.39
Fundic gland polyp	82	27.7
Chronic gastritis	41	13.85
Mixed	13	4.39
Intestinal metaplasia	12	4.05
Foveolar hyperplasia	10	3.38
Adenoma	5	1.69
Carcinoid tumor	4	1.35
Granulation tissue polyp	4	1.35
Adenocarcinoma	2	0.68
Gastric xanthelasma	2	0.68
Hamartomatous polyp	2	0.68
Lymphoid follicles	2	0.68
Submucosal Brunner glands	2	0.68
Lipoma	1	0.34
Normal	27	9.12

not tested patients. The logistic regression was used to find out factors associated with hyperplastic polyp type as compared with fundic polyp type after removing patients with adenoma, mixed polyps, and others. The results of logistic regression analysis were reported using odds ratio (OR), 95%CI and *P* values. Stepwise selection method using probability to enter = 0.10 and probability to stay = 0.05 was used to obtain the final model. All the statistical analyses were carried out using statistical analysis software (SAS) 9.3. Results were considered significant at the 5% level of significance. The statistical methods of this study were reviewed by Dr. Alok Dwivedi from the department of Biostatistics at Texas Tech University HSC at El Paso.

RESULTS

Demographic and clinical characteristics

A total of 7090 patients underwent 9450 EGD procedures. Of these, 335 patients had gastric polyps (4.7%). Resection or biopsy of 442 gastric polyps was done in 296 patients (88.4%). 39 patients did not undergo resection or biopsy of their gastric polyps because of the high risk of bleeding or obvious endoscopic diagnosis of fundic gland polyps (FGPs). The mean age of the patients was 58 years (SD: ± 12 years). The majority of the patients were females (74%) and most were Hispanics (85%). Portal hypertensive gastropathy was seen in 20 patients (7%).

Endoscopic and histopathological features

Polyps' histology: Of 296 patients, 87 (29%) patients had hyperplastic polyps and 82 (28%) patients had fundic gland polyps. There were 5 (1.7%) patients with adenomatous polyps while 13 (4.4%) patients had mixed types of polyps. Histology results of the remaining polyps revealed chronic gastritis in 41 patients (14%), intestinal metaplasia in 12 patients (4.1%), faveolar hyperplasia in 10 patients (3.4%), carcinoid tumor in 4 patients (1.4%) and granulation tissue polyps in 4 patients (1.4%). Adenocarcinoma, gastric xanthelasma, hamartomatous polyps, lymphoid follicles and submucosal brunner glands were each found in 2 patients (0.68%). There was one patient with lipoma. The histology of resected or biopsied polyp was normal in 27 patients (9.1%).

Pathology of the surrounding mucosa: Out of 296 patients, 266 (89.8%) patients had biopsies of the surrounding mucosa (Table 1).

Of these, 190 (64%) patients had chronic gastritis while 25 (8%) patients had intestinal metaplasia. Thirty (10%) patients were not biopsied. In regards to *H. pylori status, H. pylori* were positive in 71 (24%) patients, and negative in 211 (71%) patients, while 14 patients were not tested.

Clinical characteristics of gastric polyps: Table 2 shows the distribution of patient and clinical characteristics according to five categories (Adenoma, Hyperplastic, Fundic gland, Mixed and other) of polyps. The gender and ethnicity distributions were not found to be significantly different among different polyp types. The distribution of age, pathology of surrounding gastric mucosa, and *H. pylori* status were found to be associated with different polyp types. Adenomatous polyps were more common in advanced age ($P < 0.0013$). Fundic, hyperplastic and mixed polyps were more frequent in chronic gastritis while adenomatous polyps were more common (60%) in intestinal metaplasia ($P < 0.001$). Thirty-one percent of the patients with hyperplastic polyps tested positive for *H. pylori* status while 9.8% of the patients with fundic gland polyps tested positive for *H. pylori.* Portal hypertensive gastropathy was seen in 11.5% of patients with hyperplastic polyps compared to 2.4% of patients with fundic gland polyps.

Associations of *H. pylori* status and gastric pathology: The prevalence of hyperplastic polyps was 34% in the *H. pylori* positive group while the prevalence of fundic polyps was 10% in the *H. pylori* positive group. Table 3 shows the unadjusted and adjusted associations of cofactors with *H. pylori* status. Only the polyp type and the pathology of surrounding gastric mucosa were associated with *H. pylori* in unadjusted and adjusted models. Hyperplastic polyps have a 4.6 times higher odds of having a positive *H. pylori* status compared to fundic gland polyps (OR = 4.621; 95%CI: 1.92-11.13, $P = 0.001$).

Cofactors association of hyperlastic and fundic gland polyps: Table 4 shows the unadjusted and adjusted associations of cofactors with hyperplastic polyps as compared with fundic polyps. In the unadjusted analysis, age, *H. pylori* status and portal hypertension were found to be associated with hyperplastic polyps. Per unit increase in age increased the odds of hyperplastic polyp type by 3% as compared

Table 2 Distribution of patient and clinical characteristics according to different polyp types *n* (%)

Cofactor	Adenoma *n* = 5	Fundic *n* = 82	Hyperplastic *n* = 87	Mixed *n* = 13	Other *n* = 109	*P* value
Age (yr), mean ± SD	75.4 (3.3)	54.7 (13.0)	58.4 (10.8)	62.2 (14.0)	57.7 (11.9)	0.0013
Gender						0.2086
Female	5 (100.0)	67 (81.71)	64 (73.56)	9 (69.23)	75 (68.81)	
Male	0 (0.00)	15 (18.29)	23 (26.44)	4 (30.77)	34 (31.19)	
Ethnicity						0.7427
Hispanic	5 (100.0)	66 (80.49)	77 (88.51)	11 (84.62)	93 (85.32)	
Non-Hispanic White	0 (0.00)	5 (6.10)	4 (4.60)	0 (0.00)	8 (7.34)	
Other	0 (0.00)	11 (13.41)	6 (6.90)	2 (15.38)	8 (7.34)	
Pathology of surrounding gastric						< 0.0001[1]
Chronic gastritis	0 (0.00)	51 (62.20)	52 (59.77)	9 (69.23)	78 (41.05)	
Intestinal metaplasia	3 (60.00)	1 (1.22)	6 (6.90)	1 (7.69)	14 (56.00)	
Other	0 (0.00)	22 (26.83)	15 (17.24)	2 (15.38)	5 (16.67)	
Not biopsied	2 (40.00)	8 (9.76)	14 (16.09)	1 (7.69)	12 (23.53)	
Helicobacter pylori status						0.0006[1]
Negative	4 (80.00)	70 (85.37)	52 (59.77)	11 (84.62)	74 (35.07)	
Positive	0 (0.00)	8 (9.76)	27 (31.03)	2 (15.38)	34 (47.89)	
Not tested	1 (20.00)	4 (4.88)	8 (9.20)	0 (0.00)	1 (7.14)	
Portal hypertensive gastropathy						0.1821
No	5 (100.0)	80 (97.56)	77 (88.51)	12 (92.31)	102 (93.58)	
Yes	0 (0.00)	2 (2.44)	10 (11.49)	1 (7.69)	7 (6.42)	

[1]*P* value was obtained using χ^2 test.

Table 3 Unadjusted and adjusted associations of cofactors with *Helicobacter pylori* positive status (*n* = 262)

Cofactor	Unadjusted OR (95%CI), *P* value	Adjusted OR (95%CI), *P* value
Age (yr)	1.011 (0.988-1.034), 0.3686	
Polyp type		
Fundic (referent)	1	1
Hyperplastic	4.621 (1.918-11.133), 0.0006	4.621 (1.861-11.479), 0.0010
Other	3.469 (1.509-7.976), 0.0034	2.952 (1.250-6.972), 0.0136
Gender		
Female (referent)	1	
Male	0.891 (0.460-1.726), 0.7321	
Ethnicity		
Hispanic (referent)	1	
Non-hispanic White	0.205 (0.026-1.605), 0.1311	
Other	0.409 (0.117-1.435), 0.1629	
Pathology of surrounding gastric		
Chronic gastritis (referent)	1	1
Intestinal metaplasia	0.996 (0.407-2.437), 0.9931	0.827 (0.331-2.065), 0.6848
Other	0.088 (0.021-0.375), 0.0010	0.090 (0.021-0.390), 0.0013
Portal hypertension		
No (referent)	1	
Yes	0.569 (0.159-2.044), 0.3877	

Table 4 Unadjusted and adjusted associations of cofactors with hyperplastic polyps as compared with fundic polyps (*n* = 143)

Cofactor	Unadjusted OR (95%CI), *P* value	Adjusted OR (95%CI), *P* value
Age (yr)	1.031 (1.001-1.062), 0.0419	
H. pylori status		
Negative (referent)	1	1
Positive	4.622 (1.918-11.137), 0.0006	5.285 (2.166-12.892), 0.0003
Gender		
Female (referent)	1	
Male	1.804 (0.756-4.303), 0.1837	
Ethnicity		
Hispanic (referent)	1	
Non-Hispanic White	0.469 (0.083-2.655), 0.3922	
Other	0. 536 (0.150-1.923), 0.3390	
Pathology of surrounding gastric		
Chronic gastritis (referent)	1	
Intestinal metaplasia	5.997 (0.697-51.614), 0.1029	
Other	0.714 (0.331-1.542), 0.3917	
Portal hypertension		
No (referent)	1	1
Yes	5.080 (1.057-24.414), 0.0424	6.903, 0.0174

with fundic gland polyp. After adjusting for all other factors, *H. pylori* status and portal hypertensive gastropathy were the only remained significant factors in the final adjusted model. Positive *H. pylori* status has 5.3 times higher odds to have hyperplastic polyps compared with negative *H. pylori* status (OR = 5.285; 95%CI: 2.17-12.89, *P* = 0.0003) after adjusting for portal hypertensive gastropathy. Patients with portal hypertensive gastropathy are 6.4 times more likely to have hyperplastic polyps after adjusting for *H. pylori*

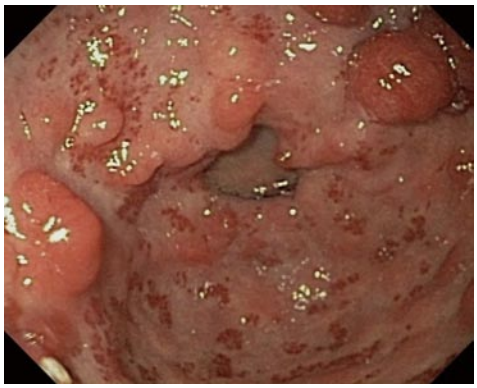

Figure 1 Multiple hyperplastic polyps in the setting of portal hypertensive gastropathy.

status (OR = 6.903; 95%CI: 1.40-33.93, *P* = 0.0174).

Long term follow-up

Out of 296 patients, 30 (10.1%) had a follow-up endoscopy with a mean duration of 26 ± 16.3 mo. Out of these 30 patients, 11 (36.6%) had hyperplastic polyps, 5 had chronic gastritis polyp, 4 had fundic gland polyp, two had intestinal metaplasia, two had carcinoid tumor, two had faveloar hyperplasia, one had adenomatous polyp and 3 patients were classified as other (gastric adenocarcinoma, brunner gland hyperplasia and normal pathology). Polyp's recurrence was noted in five out of eleven hyperplastic polyps and one out of four fundic gland polyps surveyed.

All Five adenomatous polyps were polypectomized during the initial endoscopy session. Four out of the five patients with adenomatous polyps were lost to follow-up in our system. Recurrence of the adenomatous polyp was noted in the one patient who had surveillance endoscopy.

Interval development of cancer was not noted in any of the patients during follow up period.

DISCUSSION

In this study, we found the prevalence of gastric polyps to be 4.7% in a predominantly Hispanic population, which is similar to the reported spectrum in previous series[1,13,16,17]. However, there is wide variation in the reported frequencies of different histological subtypes. Fundic gland polyps and hyperplastic polyps are the most prevalent types of gastric polyps in the current literature[1,2,16]. This was found in our study as well. We found 29% prevalence of hyperplastic polyps and 28% prevalence of fundic polyps. In addition, our data confirmed the positive association between *H. pylori* infection and hyperplastic polyps compared to fundic gland polyps.

There are several subtypes of gastric polyps which can be classified based on their endoscopic appearance or histopathological features. One of the most popular classifications is dividing the gastric polyps into two categories; epithelial and subepithelial. Epithelial polyps include fundic gland polyps, hyperplastic polyps, adenomatous polyps, polyps associated with familial adenomatous polyposis (FAP) and Peutz-Jeghers syndrome. Subepithelial polyps include gastrointestinal stromal tumors (GISTs]), inflammatory fibroid polyps, pancreatic heterotopia, leiomyomas, neuroendocrine tumors and granular cell tumors[17].

In our study, hyperplastic polyps were the most frequent subtype of polyps. We found a strong association between hyperplastic polyps, chronic gastritis and *H. pylori* infection which confirms what was reported in other studies[18,19]. A higher prevalence of *H. pylori* infection has been documented in Hispanics living in United States-Mexico border regions compared with non-border areas, which may explain the relatively high prevalence of hyperplastic polyps in our study population[14,15,20,21]. The risk of dysplasia and neoplastic progression of hyperplastic polyps is controversial with wide discrepancy between the reported rates (1.9% to 19%)[19,22-24]. However, this type of polyp has been reported to have an increased risk of neoplasia in the surrounding abnormal mucosa and is associated with higher incidence of synchronous gastric cancer[3,25]. In our series, 11 out of 87 patients who were found to have hyperplastic polyps, had follow-up endoscopy with a mean duration of 30 ± 18 mo. Five (45%) of these 11 patients were found to have residual polyps in follow up endoscopy and none (0%) of them developed dysplasia or cancer. Given this higher risk of developing adenocarcinoma in the surrounding mucosa of hyperplastic polyp, the guidelines recommend obtaining multiple biopsies of the intervening mucosa[26]. Polyp resection has been recommended for any hyperplastic polyp greater than 0.5 cm in size. Repeat surveillance endoscopy is recommended at 1 year after endoscopic resection[22,27,28]. Regression of hyperplastic polyps has been reported in many studies after effective treatment of *H. pylori* infection, it is thus essential to treat the patients with active *H. pylori* infection before entertaining any further management[18,19,29,30] (Figure 1).

FGPs were found to be the second most frequent type of polyp in our study population. The highest prevalence of fundic gland polyps was reported by Carmack *et al*[1] in a nationwide United States population from 2007-2008 in which FGP constituted 77% of the study cohort. FGP can be found sporadically or in patients with FAP syndrome[31,32]. Sporadic FGP has been reported in many studies to have a positive association with prolonged use of proton pump inhibitors (PPI)[33-36]. However, in other series this correlation was not confirmed[37,38]. Jalving *et al*[36] reported up to 4-times increased risk of fundic gland polyps with long-term proton pump inhibitor, and Ally *et al*[33] reported that the duration of PPI therapy greater than 4 years is an independent predictor for FGP development regardless of the used dosage. Due to the retrospective nature of our study, we were unable to obtain accurate data regarding PPI use among the study population. FGPs

have been reported to have a negative association with the presence of *H. pylori* infection[39]. This was found in our study as well. The risk of dysplasia in sporadic FGPs is rare, while it occurs in 25%-41% of FAP-associated polyps[31,40]. Biopsy of FGPs is recommended to exclude dysplasia or adenocarcinoma. Polyp resection is recommended for FGPs more than 1 cm in size to eliminate sampling error by missing any neoplastic foci within the polyp[26,41]. Further workup is recommended to exclude FAP in patients who are less than 40 years of age with numerous FGPs, or if the initial polyp biopsy showed dysplasia[26].

Raised Intraepithelial Neoplasia is the recent nomenclature for gastric adenomas as they are at increased risk for malignant transformation[3,42,43]. Three (60%) of the gastric adenomas in our study were associated with underlying atrophic gastritis and intestinal metaplasia which confirms what was reported in other studies[42,44]. The malignant potential of adenomatous polyps correlates with the polyp size and the age of the patient[3,24,45-47]. Polyps more than 2 cm in size had been reported to have higher risk of development of adenocarcinoma[3,45]. The guidelines recommend complete endoscopic removal of gastric adenomas or referral for surgical resection if lesions are not amenable to endoscopic resection or if they contain invasive carcinoma[26,27]. In addition, careful examination of the rest of the gastric mucosa and obtaining multiple biopsies is recommended to rule out any synchronous neoplastic process. In 2006, the American Society of Gastrointestinal Endoscopy guideline recommended endoscopic surveillance at 1 year for adenomatous polyps. The 2010 British Society of Gastroenterology guidelines recommended to repeat the endoscopic examination at 6 mo for incompletely resected adenomatous polyps or those with high grade dysplasia[26,27].

In our series, 20 (6.76%) patients were found to have portal hypertensive gastropathy. Half of these patients were found to have hyperplastic polyps. However, it has been reported that hyperplastic polyps in portal hypertensive patients are pathologically distinct from the typical hyperplastic polyps seen in nonportal hypertensive patients with uncertain malignant potential[48-52]. Management of portal hypertensive polyps is difficult as patients are at increased risk of post-polypectomy bleeding due to associated thrombocytopenia and coagulopathy. Conservative management and follow up endoscopy has been suggested as a safer strategy than multiple polypectomies[49,52].

There are some limitations to our study. One of the main drawbacks in our study is the lack of information on PPI use for the study cohort. As a result, we were unable to study the correlation between the various types of gastric polyps and PPI use. Second, this study was designed as a retrospective study with its obvious drawbacks. Although this study was performed in a unique practice setting on the United States-Mexico international border and the database used is significantly large, our results may not be applicable to all settings as our study is single-center study. However, one of the significant strengths of this study is the fact that the majority of the study population is Hispanic (85%) which may give more insight about the characteristics and the histopathologic features of gastric polyps in Hispanics.

In conclusion, the prevalence of gastric polyps in a predominantly Hispanic population is similar to what has been reported in the literature for other populations. Hyperplastic polyps were significantly associated with positive *H. pylori* status and portal hypersensitive gastropathy. Hyperplastic polyps and FGPs were more prevalent in chronic gastritis, while adenomatous polyps were associated with intestinal metaplasia.

COMMENTS

Background

Gastric polyps are usually asymptomatic and incidentally discovered during endoscopic examination. Determination of gastric polyp type is important as the risk for malignant transformation depends on the histopathological type.

Research frontiers

The relationship between *Helicobacter pylori* (*H. pylori*) and the different types of gastric polyps is not well studied.

Innovations and breakthroughs

This is one of a few studies focused on the prevalence and distribution of gastric polyps in Hispanic populations. Hyperplastic and fundic gland polyps accounted for more than half of the resected polyps in this study. Gastric hyperplastic polyps were significantly associated with positive *H. pylori* status and portal hypertensive gastropathy as compared with fundic gland polyps. Hyperplastic polyps and fundic gland polyps were more prevalent in chronic gastritis, while adenomatous polyps were associated with intestinal metaplasia.

Applications

When Hyperplastic polyp is suspected, biopsy of the surrounding mucosa should be done to rule out *H. pylori* infection. In case of an adenomatous polyp, biopsy of the surrounding mucosa should be done to rule out intestinal metaplasia.

Terminology

FGPs: Fundic Galnd Polyps; EGDs: Esophagogastroduodenoscopies.

Peer-review

The manuscript is concise, fluent and well-written. Strengths are the number of cases and the ethnicity orientation of the study group. The main drawback is that there is no new knowledge added, apart from ethnicity-targeted results. However, this is still of notice.

REFERENCES

1 **Carmack SW**, Genta RM, Schuler CM, Saboorian MH. The current spectrum of gastric polyps: a 1-year national study of over 120,000 patients. *Am J Gastroenterol* 2009; **104**: 1524-1532 [PMID: 19491866 DOI: 10.1038/ajg.2009.139]

2 **García-Alonso FJ**, Martín-Mateos RM, González Martín JA, Foruny JR, Vázquez-Sequeiros E, Boixeda de Miquel D. Gastric polyps: analysis of endoscopic and histological features in our center. *Rev Esp Enferm Dig* 2011; **103**: 416-420 [PMID: 21867351 DOI: 10.4321/S1130-01082011000800005]

3 **Laxén F**, Sipponen P, Ihamäki T, Hakkiluoto A, Dortscheva Z. Gastric polyps; their morphological and endoscopical characteristics and relation to gastric carcinoma. *Acta Pathol Microbiol Immunol*

Scand A 1982; **90**: 221-228 [PMID: 7102316 DOI: 10.1111/j.1699-0463.1982.tb00085_90a.x]
4 **Carmack SW**, Genta RM, Graham DY, Lauwers GY. Management of gastric polyps: a pathology-based guide for gastroenterologists. *Nat Rev Gastroenterol Hepatol* 2009; **6**: 331-341 [PMID: 19421245 DOI: 10.1038/nrgastro.2009.70]
5 **Oberhuber G**, Stolte M. Gastric polyps: an update of their pathology and biological significance. *Virchows Arch* 2000; **437**: 581-590 [PMID: 11193468 DOI: 10.1007/s004280000330]
6 **Secemsky BJ**, Robinson KR, Krishnan K, Matkowskyj KA, Jung BH. Gastric hyperplastic polyps causing upper gastrointestinal hemorrhage in a young adult. *World J Clin Cases* 2013; **1**: 25-27 [PMID: 24303456 DOI: 10.12998/wjcc.v1.i1.25]
7 **Aydin I**, Ozer E, Rakici H, Sehitoglu I, Yucel AF, Pergel A, Sahin DA. Antral hyperplastic polyp: A rare cause of gastric outlet obstruction. *Int J Surg Case Rep* 2014; **5**: 287-289 [PMID: 24747755 DOI: 10.1016/j.ijscr.2014.03.016]
8 **Nayudu SK**, Niazi M, Balar B, Kumbum K. A rare complication of hyperplastic gastric polyp. *Case Rep Gastrointest Med* 2013; **2013**: 631975 [PMID: 23401808 DOI: 10.1155/2013/631975]
9 **Tomasulo J**. Gastric polyps. Histologic types and their relationship to gastric carcinoma. *Cancer* 1971; **27**: 1346-1355 [PMID: 5088211 DOI: 10.1002/1097-0142(197106)27]
10 **Eichhorn K**, Kratzsch KH, Stibenz J, Waller H, Winkelvoss H. Relations between stomach polyps and stomach cancer--results of follow-up after endoscopic polypectomy. *Z Gesamte Inn Med* 1986; **41**: 433-435 [PMID: 3765746]
11 **Nechipaĭ AM**, Poddubnyĭ BK, Kuvshinov IuP, Efimov ON, Rottenberg VI. The probability of malignant degeneration of stomach polyps. *Vopr Onkol* 1989; **35**: 1044-1049 [PMID: 2815691]
12 **Orlowska J**, Jarosz D, Pachlewski J, Butruk E. Malignant transformation of benign epithelial gastric polyps. *Am J Gastroenterol* 1995; **90**: 2152-2159 [PMID: 8540506]
13 **Archimandritis A**, Spiliadis C, Tzivras M, Vamvakousis B, Davaris P, Manika Z, Scandalis N. Gastric epithelial polyps: a retrospective endoscopic study of 12974 symptomatic patients. *Ital J Gastroenterol* 1996; **28**: 387-390 [PMID: 8937940]
14 **Cardenas VM**, Mena KD, Ortiz M, Karri S, Variyam E, Behravesh CB, Snowden KF, Flisser A, Bristol JR, Mayberry LF, Ortega YR, Fukuda Y, Campos A, Graham DY. Hyperendemic H. pylori and tapeworm infections in a U.S.-Mexico border population. *Public Health Rep* 2010; **125**: 441-447 [PMID: 20433039]
15 **Mapel D**, Roberts M, Overhiser A, Mason A. The epidemiology, diagnosis, and cost of dyspepsia and Helicobacter pylori gastritis: a case-control analysis in the Southwestern United States. *Helicobacter* 2013; **18**: 54-65 [PMID: 23067108 DOI: 10.1111/j.1523-5378.2012.00988.x]
16 **Csontos AA**, Fekete B, Lőrinczy K, Terjék O, Berczi L, Juhász M, Miheller P, Tulassay Z. Prevalence of gastric polypoid lesions at an endoscopic facility. *Orv Hetil* 2013; **154**: 770-774 [PMID: 23666023 DOI: 10.1556/OH.2013.29617]
17 **Cao H**, Wang B, Zhang Z, Zhang H, Qu R. Distribution trends of gastric polyps: an endoscopy database analysis of 24 121 northern Chinese patients. *J Gastroenterol Hepatol* 2012; **27**: 1175-1180 [PMID: 22414211 DOI: 10.1111/j.1440-1746.2012.07116.x]
18 **Ljubicić N**, Banić M, Kujundzić M, Antić Z, Vrkljan M, Kovacević I, Hrabar D, Doko M, Zovak M, Mihatov S. The effect of eradicating Helicobacter pylori infection on the course of adenomatous and hyperplastic gastric polyps. *Eur J Gastroenterol Hepatol* 1999; **11**: 727-730 [PMID: 10445791 DOI: 10.1097/00042737-199907000-00008]
19 **Dirschmid K**, Platz-Baudin C, Stolte M. Why is the hyperplastic polyp a marker for the precancerous condition of the gastric mucosa? *Virchows Arch* 2006; **448**: 80-84 [PMID: 16189701 DOI: 10.1007/s00428-005-0068-2]
20 **Goodman KJ**, Correa P. The transmission of Helicobacter pylori. A critical review of the evidence. *Int J Epidemiol* 1995; **24**: 875-887 [PMID: 8557443 DOI: 10.1093/ije/24.5.875]
21 **Graham D**. Public health issues relating to Helicobacter pylori infection and global eradication. Gastritis Philadelphia: Lippincott Williams and Wilkins, 1999: 241-246
22 **Daibo M**, Itabashi M, Hirota T. Malignant transformation of gastric hyperplastic polyps. *Am J Gastroenterol* 1987; **82**: 1016-1025 [PMID: 3661508]
23 **Hizawa K**, Fuchigami T, Iida M, Aoyagi K, Iwashita A, Daimaru Y, Fujishima M. Possible neoplastic transformation within gastric hyperplastic polyp. Application of endoscopic polypectomy. *Surg Endosc* 1995; **9**: 714-718 [PMID: 7482172 DOI: 10.1007/BF00187948]
24 **Cristallini EG**, Ascani S, Bolis GB. Association between histologic type of polyp and carcinoma in the stomach. *Gastrointest Endosc* 1992; **38**: 481-484 [PMID: 1511825 DOI: 10.1016/S0016-5107(92)70481-7]
25 **Hattori T**. Morphological range of hyperplastic polyps and carcinomas arising in hyperplastic polyps of the stomach. *J Clin Pathol* 1985; **38**: 622-630 [PMID: 4008664]
26 **Goddard AF**, Badreldin R, Pritchard DM, Walker MM, Warren B. The management of gastric polyps. *Gut* 2010; **59**: 1270-1276 [PMID: 20675692 DOI: 10.1136/gut.2009.182089]
27 **Hirota WK**, Zuckerman MJ, Adler DG, Davila RE, Egan J, Leighton JA, Qureshi WA, Rajan E, Fanelli R, Wheeler-Harbaugh J, Baron TH, Faigel DO. ASGE guideline: the role of endoscopy in the surveillance of premalignant conditions of the upper GI tract. *Gastrointest Endosc* 2006; **63**: 570-580 [PMID: 16564854 DOI: 10.1016/j.gie.2006.02.004]
28 **Ginsberg GG**, Al-Kawas FH, Fleischer DE, Reilly HF, Benjamin SB. Gastric polyps: relationship of size and histology to cancer risk. *Am J Gastroenterol* 1996; **91**: 714-717 [PMID: 8677935]
29 **Ohkusa T**, Takashimizu I, Fujiki K, Suzuki S, Shimoi K, Horiuchi T, Sakurazawa T, Ariake K, Ishii K, Kumagai J, Tanizawa T. Disappearance of hyperplastic polyps in the stomach after eradication of Helicobacter pylori. A randomized, clinical trial. *Ann Intern Med* 1998; **129**: 712-715 [PMID: 9841603 DOI: 10.7326/0003-4819-129-9-199811010-00006]
30 **Tokunaga K**, Tanaka A, Takahashi S. [Gastric hyperplastic polyps and H. pylori infection, their relationship and effects of eradication therapy]. *Nihon Rinsho* 2013; **71**: 1449-1452 [PMID: 23967678]
31 **Burt RW**. Gastric fundic gland polyps. *Gastroenterology* 2003; **125**: 1462-1469 [PMID: 14598262 DOI: 10.1016/j.gastro.2003.07.017]
32 **Attard TM**, Cuffari C, Tajouri T, Stoner JA, Eisenberg MT, Yardley JH, Abraham SC, Perry D, Vanderhoof J, Lynch H. Multicenter experience with upper gastrointestinal polyps in pediatric patients with familial adenomatous polyposis. *Am J Gastroenterol* 2004; **99**: 681-686 [PMID: 15089902 DOI: 10.1111/j.1572-0241.2004.04115.x]
33 **Ally MR**, Veerappan GR, Maydonovitch CL, Duncan TJ, Perry JL, Osgard EM, Wong RK. Chronic proton pump inhibitor therapy associated with increased development of fundic gland polyps. *Dig Dis Sci* 2009; **54**: 2617-2622 [PMID: 19830554 DOI: 10.1007/s10620-009-0993-z]
34 **Hegedus I**, Csizmadia C, Lomb Z, Cseke L, Enkh-Amar Y, Pajor L, Bogner B. [Massive fundic gland polyposis caused by chronic proton pump inhibitor therapy]. *Orv Hetil* 2012; **153**: 351-356 [PMID: 22348851 DOI: 10.1556/OH.2012.29313]
35 **Zelter A**, Fernández JL, Bilder C, Rodríguez P, Wonaga A, Dorado F, Galich M, Viola LA. Fundic gland polyps and association with proton pump inhibitor intake: a prospective study in 1,780 endoscopies. *Dig Dis Sci* 2011; **56**: 1743-1748 [PMID: 21127978 DOI: 10.1007/s10620-010-1493-x]
36 **Jalving M**, Koornstra JJ, Wesseling J, Boezen HM, DE Jong S, Kleibeuker JH. Increased risk of fundic gland polyps during long-term proton pump inhibitor therapy. *Aliment Pharmacol Ther* 2006; **24**: 1341-1348 [PMID: 17059515 DOI: 10.1111/j.1365-2036.2006.03127.x]
37 **Vieth M**, Stolte M. Fundic gland polyps are not induced by proton pump inhibitor therapy. *Am J Clin Pathol* 2001; **116**: 716-720 [PMID: 11710689 DOI: 10.1309/XFWR-LXA7-7TK1-N3Q8]
38 **Declich P**, Ambrosiani L, Bellone S, Tavani E, Prada A, Bortoli A, Gozzini C. Fundic gland polyps under omeprazole treatment. *Am J Clin Pathol* 1999; **112**: 576-577 [PMID: 10510676]

39 **Watanabe N**, Seno H, Nakajima T, Yazumi S, Miyamoto S, Matsumoto S, Itoh T, Kawanami C, Okazaki K, Chiba T. Regression of fundic gland polyps following acquisition of Helicobacter pylori. *Gut* 2002; **51**: 742-745 [PMID: 12377817]

40 **Bianchi LK**, Burke CA, Bennett AE, Lopez R, Hasson H, Church JM. Fundic gland polyp dysplasia is common in familial adenomatous polyposis. *Clin Gastroenterol Hepatol* 2008; **6**: 180-185 [PMID: 18237868 DOI: 10.1016/j.cgh.2007.11.018]

41 **Chandrasekhara V**, Ginsberg GG. Endoscopic management of gastrointestinal stromal tumors. *Curr Gastroenterol Rep* 2011; **13**: 532-539 [PMID: 21931997 DOI: 10.1007/s11894-011-0224-6]

42 **Kamiya T**, Morishita T, Asakura H, Miura S, Munakata Y, Tsuchiya M. Long-term follow-up study on gastric adenoma and its relation to gastric protruded carcinoma. *Cancer* 1982; **50**: 2496-2503 [PMID: 7139542 DOI: 10.1002/1097-0142(19821201)50]

43 **Nakamura K**, Sakaguchi H, Enjoji M. Depressed adenoma of the stomach. *Cancer* 1988; **62**: 2197-2202 [PMID: 3179932 DOI: 10.1002/1097-0142(19881115)62]

44 **Ito H**, Hata J, Yokozaki H, Nakatani H, Oda N, Tahara E. Tubular adenoma of the human stomach. An immunohistochemical analysis of gut hormones, serotonin, carcinoembryonic antigen, secretory component, and lysozyme. *Cancer* 1986; **58**: 2264-2272 [PMID: 3530427 DOI: 10.1002/1097-0142(19861115)58]

45 **Abraham SC**, Park SJ, Lee JH, Mugartegui L, Wu TT. Genetic alterations in gastric adenomas of intestinal and foveolar phenotypes. *Mod Pathol* 2003; **16**: 786-795 [PMID: 12920223 DOI: 10.1097/01.MP.0000080349.37658.5E]

46 **Park do Y**, Lauwers GY. Gastric polyps: classification and management. *Arch Pathol Lab Med* 2008; **132**: 633-640 [PMID: 18384215 DOI: 10.1043/1543-2165[2008]132[633]

47 **Nakamura T**, Nakano G. Histopathological classification and malignant change in gastric polyps. *J Clin Pathol* 1985; **38**: 754-764 [PMID: 4019798]

48 **Amarapurkar AD**, Amarapurkar D, Choksi M, Bhatt N, Amarapurkar P. Portal hypertensive polyps: distinct entity. *Indian J Gastroenterol* 2013; **32**: 195-199 [PMID: 23512212 DOI: 10.1007/s12664-013-0324-3]

49 **Lam MC**, Tha S, Owen D, Haque M, Chatur N, Gray JR, Yoshida EM. Gastric polyps in patients with portal hypertension. *Eur J Gastroenterol Hepatol* 2011; **23**: 1245-1249 [PMID: 22002002 DOI: 10.1097/MEG.0b013e32834c15cf]

50 **Pai CG**. Portal hypertensive polyp--what is in a name? *Indian J Gastroenterol* 2013; **32**: 163-164 [PMID: 23475552 DOI: 10.1007/s12664-013-0331-4]

51 **Lee TH**, Jang JY, Jeong SW, Jin SY. Gastric polyposis associated with portal hypertension. *Korean J Intern Med* 2013; **28**: 261 [PMID: 23526873 DOI: 10.3904/kjim.2013.28.2.261]

52 **Boyd JT**, Lee L. Portal hypertension-associated gastric polyps. *BMJ Case Rep* 2014; **2014**: [PMID: 24403387 DOI: 10.1136/bcr-2013-202312]

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