ISSN 1948-5190 (online)

World Journal of *Gastrointestinal Endoscopy*

World J Gastrointest Endosc 2022 March 16; 14(3): 106-190

Published by Baishideng Publishing Group Inc

World Journal of Gastrointestinal Endoscopy

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INDEXING/ABSTRACTING

The *WJGE* is now abstracted and indexed in Emerging Sources Citation Index (Web of Science), PubMed, PubMed Central, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2022 edition of Journal Citation Reports® cites the 2021 Journal Citation Indicator (JCI) for *WJGE* as 0.33.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Rui-Rui Wu*; **Production Department Director:** *Xu Guo*; **Editorial Office Director:** *Jia-Ping Yan.*

NAME OF JOURNAL
World Journal of Gastrointestinal Endoscopy

ISSN
ISSN 1948-5190 (online)

LAUNCH DATE
October 15, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Anastasios Koulaouzidis, Sang Chul Lee, Bing Hu, Joo Young Cho

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1948-5190/editorialboard.htm

PUBLICATION DATE
March 16, 2022

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

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https://www.wjgnet.com/bpg/GerInfo/287

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World J Gastrointest Endosc 2022 March 16; 14(3): 106-112

DOI: 10.4253/wjge.v14.i3.106

ISSN 1948-5190 (online)

MINIREVIEWS

Role of intraluminal brachytherapy in palliation of biliary obstruction in cholangiocarcinoma: A brief review

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Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Ricci AD, Italy; Tabibian JH, United States

Received: May 30, 2021
Peer-review started: May 30, 2021
First decision: October 18, 2021
Revised: November 24, 2021
Accepted: February 25, 2022
Article in press: February 25, 2022
Published online: March 16, 2022

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Abstract

Surgery is the only curative treatment for cholangiocarcinoma. However, most patients present with advanced disease, and hence are unresectable. Thus, the intent of treatment shifts from curative to palliative in the majority of cases. Biliary drainage with intraluminal brachytherapy is an effective means of relieving the malignant biliary obstruction. In this review, we discuss the role of brachytherapy in the palliation of obstructive symptoms in extrahepatic cholangiocarcinoma.

Key Words: Biliary tract; Cholangiocarcinoma; Extrahepatic; Intraluminal brachytherapy

Core Tip: Intraluminal brachytherapy (ILBT) is an effective means for palliation of biliary obstruction in patients with cholangiocarcinoma. It delivers a high dose of radiation to the tumor but spares surrounding normal tissues, thus avoiding many of the side effects seen with external beam radiation. The high dose *per* fraction in ILBT can have an ablative effect on the tumor and can lead to better symptom control and quality of life. ILBT, when combined with these drainage procedures, improves the stent patency rates by inhibiting tumor ingrowth.

Citation: Khosla D, Zaheer S, Gupta R, Madan R, Goyal S, Kumar N, Kapoor R. Role of intraluminal brachytherapy in palliation of biliary obstruction in cholangiocarcinoma: A brief review. *World J Gastrointest Endosc* 2022; 14(3): 106-112
URL: https://www.wjgnet.com/1948-5190/full/v14/i3/106.htm
DOI: https://dx.doi.org/10.4253/wjge.v14.i3.106

INTRODUCTION

Biliary tract carcinomas, also known as cholangiocarcinomas, may be intrahepatic or extrahepatic. Intrahepatic cholangiocarcinomas arise from the biliary duct epithelium within the liver parenchyma. Extrahepatic cholangiocarcinomas include hilar and distal cholangiocarcinomas. Among these variants, the hilar variety, also known as Klatskin tumor, is the most common. It arises at the junction of the right and the left hepatic ducts.

The Asian population is more susceptible to developing bile duct carcinomas. The disease is more frequently seen in Thailand, India, Japan, and Korea. The incidence varies from 0.3 to 6 *per* lakh population[1]. Surgery is the only curative treatment. However, the disease is resectable only in a minority of the cases. Biliary obstruction is common and results in symptoms such as jaundice, intense pruritis, or pain abdomen. The various means of palliation include biliary drainage procedures, which may be endoscopic or percutaneous, external beam radiation therapy (EBRT), palliative chemotherapy, and intraluminal brachytherapy (ILBT) with or without EBRT.

CLINICAL FEATURES AND PATHOLOGY

Cholangiocarcinoma is a disease of the elderly, mostly affecting those more than 60 years of age. It is seen more commonly in males as compared to females. The risk factors include parasitic infection by organisms such as *Clonorchis sinensis* and *Opisthorchis viverrini*, biliary stones, and smoking. Primary sclerosing cholangitis and hepatitis C are the other risk factors. Primary sclerosing cholangitis with or without cholangitis is the commonest risk factor in Western countries[2].

In the early stages, the patient is usually asymptomatic. The signs and symptoms are non-specific. These may include pain abdomen, fever, jaundice, loss of weight, loss of appetite, generalized itching, and other features of biliary obstruction. Distant metastasis is fairly common[3]. Most of the patients present with either locally advanced or metastatic disease.

Cholangiocarcinomas are histologically adenocarcinomas in 95% of cases[2]. These can be well-differentiated, moderately differentiated, or poorly differentiated[4].

DIAGNOSTIC WORK-UP

Ultrasonography (USG) is the baseline investigation done whenever a biliary obstruction is suspected. It may reveal dilated biliary channels, any mass, or the presence of gallstones. Contrast-enhanced computed tomography (CECT) is the standard imaging tool, especially for staging and preoperative assessment. The delayed scans are useful for diagnosing intrahepatic cholangiocarcinomas which may show contrast enhancement on delayed scans due to abundant fibrous stroma[5-7]. However, CECT may not show the true longitudinal extent of perihilar cholangiocarcinoma[8]. Magnetic resonance imaging (MRI) with magnetic resonance cholangiopancreatography (MRCP) is considered the imaging modality of choice. It allows the assessment of the entire biliary tree as well as the vascular anatomy[9].

Cancer antigen (CA) 19-9, carcinoembryonic antigen (CEA), and CA-125 are the non-specific tumor markers, which may help in establishing the diagnosis[10]. Tissue diagnosis is essential before a patient can be given chemotherapy or radiotherapy. This may be quite challenging, especially if the patient has primary sclerosing cholangitis or biliary strictures. The biopsy samples, collected by endoscopic imaging and tissue sampling, are usually inadequate for molecular typing. In this setting, liquid biopsy holds promise. It is mainly based on circulating free DNA and circulating tumour DNA[11]. Cholangiocarciomas exhibit specific RNA profiles in extra-cellular vesicles in a patient's serum and urine. It is one of the promising liquid biopsy markers[12].

MANAGEMENT

Surgery is the only curative treatment for cholangiocarcinomas. The disease is resectable in only 10%-15% of the patients[13,14]. The low resection rates may be due to invasion of the hepatic artery or portal

vein, lymph node involvement, or the invasion of the adjacent structures. Some patients may present with peritoneal or distant metastasis, so are inoperable, and need to be managed with palliative intent. Operative mortality has been reported to be 5%-10% in some studies[14-16]. The 5-year survival rates after surgery are 9%-18% for proximal bile duct lesions and 20%-30% for distal bile duct lesions[2]. Although phase 2 studies and some retrospective studies suggest the advantage of adding adjuvant therapy, there are no phase 3 studies to support this[17-20].

Bonet Beltrán *et al*[21] did a systematic review and meta-analysis in patients with extrahepatic bile duct cancer. The authors reported a significant benefit of adjuvant radiation, especially in patients with extrahepatic cholangiocarcinoma. This benefit was seen in terms of improved overall survival[21].

Sahai *et al*[22] reviewed the literature on the role of radiation in adjuvant, neoadjuvant, definitive, and palliative settings. They concluded that stenting with palliative radiotherapy, either external or brachytherapy, improves the stent patency rates and survival in unresectable cholangiocarcinoma[22].

There is no definite consensus on the role of adjuvant chemotherapy. The studies have reported variable results. A retrospective study on patients with hilar cholangiocarcinoma showed a significant improvement in survival in those who received adjuvant chemotherapy[23]. The greatest benefit of adjuvant chemotherapy is seen in those with lymph node positive or resection margin positive status [24]. After the BILCAP study, capecitabine is considered to be the standard treatment for biliary tract cancers in the adjuvant setting[25].

Neoadjuvant therapy has been explored in cholangiocarcinoma with the aim to achieve negative surgical margins and improve survival rates. Nelson *et al*[26] conducted a study in patients diagnosed with extra-hepatic cholangiocarcinoma. These patients received neoadjuvant chemo-radiotherapy with 5-flourouracil and EBRT with or without brachytherapy. They reported a R0 resection rate of 91.7%[26]. Similar results have been reported by Jung *et al*[27] and Sumiyoshi *et al*[28].

Novel treatment options are opening the doors of a new world. There is increasing interest in the use of targeted therapy and immunotherapy. Targeted therapies have demonstrated a role in mainly intrahepatic cholangiocarcinoma[29]. Fibroblast growth factor receptor (FGFR) aberrations and isocitrate dehydrogenase (IDH) mutations based therapy hold promise[30,31].

There are several ongoing trials on immunotherapy in advanced biliary tract cancers. Although monotherapy with immune check-point inhibitors or their combination with other anti-cancer agents shows only modest survival advantages and efficacy, there is a need to test these patients for deficiency in mismatch repair proteins (dMMR), high microsatellite instability (MSI-H), increased tumor mutational burden (TMB), and programmed death-ligand 1 (PD-L1) expression[32,33].

Due to low resectability, the goal of treatment is palliation in most of the patients. Endoscopic retrograde cholangiopancreaticography (ERCP) or percutaneous transhepatic biliary drainage (PTBD) are the initial procedures that may be used to relieve biliary obstruction resulting from cholangiocarcinoma. These procedures are only palliative with a median survival of around 6 mo[34]. This article provides a concise overview of the role of ILBT in the palliation of biliary obstruction. Biliary drainage, which is done either endoscopically or percutaneously, can palliate symptoms, but ILBT can decrease the tumor size and delay the tumor ingrowth.

ROLE OF BRACHYTHERAPY

ILBT can be used in cholangiocarcinomas with both palliative and curative intent. With curative intent, it can be used following chemoradiotherapy to escalate the tumor dose and thus increase the local control[35]. The main indication in the palliative setting is to relieve the biliary obstruction. The mechanism may be *via* preventing stent re-occlusion, which may occur due to tumor ingrowth[36,37].

When ILBT is combined with EBRT, usually 30-40 Gy are delivered *via* EBRT and 15-20 Gy in 2-3 fractions *via* high dose rate (HDR) brachytherapy. When pulsed dose rate brachytherapy (PDR) is used in the combined modality setting, a single course of 20 Gy is usually prescribed[3]. In the palliative setting, the HDR ILBT dose is usually 15-20 Gy in 3-4 Gy/fraction. When PDR brachytherapy is used, 1 or 2 fractions of 20-40 Gy may be prescribed[3].

ILBT techniques, dose, and response

ILBT can be performed using ERCP or PTBD. Whenever possible, percutaneous transhepatic technique is preferred. It is reported that when PTBD is combined with ILBT, the median survival time increases [38,39]. The feasibility of ILBT is better with PTBD. Lesions in the right and left hepatic duct, as well as the common bile duct, can be easily assessed. Before PTBD, imaging is done to know the exact site and extent of the obstruction. It can be assessed *via* USG, CT, or MRI. First, percutaneous transhepatic cholangiography is performed followed by biliary decompression. ILBT catheters are inserted when serum bilirubin levels decrease and the patient stabilizes. Jain *et al*[40] performed ILBT when the serum bilirubin levels decreased to 2 mg% or fell to 50% of the baseline. Other inclusion criteria reported by them included Eastern Cooperative Oncology Group (ECOG) performance status 0-2; absence of fever, signs of cholangitis, or any evidence of distant metastasis[40]. Aggarwal *et al*[34] did ILBT after biliary drainage *via* PTBD when the serum bilirubin levels were below 5 mg%[34]. They did PTBD under USG

Table 1 Some studies in which brachytherapy has been used with palliative intent

No.	No of patients	Diagnosis	PTBD	EBRT	Dose of ILBT	Survival	Stent patency	Ref.
1	18	Malignant biliary obstruction	Yes	-	16 Gy in 2 fractions	8.27 mo (median survival)	-	Aggarwal *et al* [34]
2	48	Bile duct and pancreatic cancer	Yes	-	25 pulses of 0.8 Gy hourly (total dose of 20 Gy PDR)	11.2 mo for bile duct carcinoma	-	Skowronek *et al*[36]
3	32	Non resectable biliary malignancy	Yes	-	5 Gy in 6 fractions	358 d in Klatskin-tumour	418 d	Bruha *et al*[37]
4	22	Malignant biliary obstruction	Yes	Yes	15-31 Gy (mean 25 Gy)	22.6 mo	19.5 mo	Eschelman *et al* [39]
5	12	Malignant obstructive jaundice	Yes	Yes (6 patients)	10-14 Gy	-	9.8 mo	Jain *et al*[40]
6	34	Malignant obstructive jaundice	Yes	-	14-21 Gy in 3-4 fractions	9.4 mo	12.6 mo	Chen *et al*[43]
7	14	Bile duct cancers	Yes	Yes (5 patients)	10 Gy, 2 fractions of 2.5 Gy 6 h apart for 2 d	6.5 mo (median survival)	-	Mayer *et al*[44]
8	8	Malignant obstruction of bile duct	Yes	-	2 fractions of 10 Gy each	7.5 mo	6.9 mo	Kocak *et al*[45]

PTBD: Percutaneous transhepatic biliary drainage; EBRT: External beam radiation therapy; ILBT: Intraluminal brachytherapy.

and fluoroscopic guidance. After biliary decompression, an internal-external drainage tube was inserted and left in place for 7-10 d to allow bilirubin levels to fall and the patient's general condition to improve. When ILBT was performed, the external–internal catheter was replaced with brachytherapy catheter. Its tip was placed 1.5-2 cm beyond the distal end of the stricture. These patients received a dose of 8 Gy in 2 fractions at an interval of 1 wk *via* HDR brachytherapy. Various brachytherapy doses and schedules are described in the literature. Jain *et al*[40] used a dose of 10-14 Gy at 1 cm from the central axis of the source, which was delivered *via* HDR microselectron[40].

Deufel *et al*[41] have described the HDR brachytherapy in patients with cholangiocarcinoma *via* a nasobiliary route[41]. They did the procedure using an 8.5 Fr or 10 Fr nasobiliary catheter inserted *via* ERCP technique. This was followed by insertion of a 4.7 Fr treatment catheter into the nasobiliary catheter. The dose schedules described are a single fraction of 9.3 Gy or fractionated regime using four fractions of 4 Gy delivered twice a day. For patients who are suitable for liver transplantation after neoadjuvant chemoradiation, the minimally invasive nasobiliary approach may be preferred as there is a higher risk of tumor seeding with transhepatic technique[42]. However, the nasobiliary route is technically more difficult and may not be preferred in the palliative setting.

Bruha *et al*[37] in their study on cholangiocarcinoma patients with malignant obstructive jaundice treated by HDR ILBT, showed that the mean stent patency was 418 d[37]. Jain *et al*[40] reported a mean stent patency duration of 9.4 mo in patients with cholangiocarcinoma treated by PTBD and ILBT[40].

Chen *et al*[43] showed a similar trend in their study. The stent patency rate in patients who underwent ILBT with PTBD was 45%. However, this rate was just 21%in the group of patients who had only stent placement. The dose of ILBT used was 14-21 Gy in 3-4 fractions. The duration of stent patency was also significantly greater in the ILBT group[43].

Aggarwal *et al*[34] reported an improvement in symptoms such as fatiguability, nausea, vomiting, pain, icterus, pruritis, dyspnea, insomnia, and loss of appetite after palliation with PTBD combined with ILBT[34]. Mayer *et al*[44] reported symptomatic improvement in pruritis and jaundice in all their patients with unresectable bile duct malignancy after biliary decompression with PTBD followed by ILBT. The dose of brachytherapy in their study was 2.5 Gy in 2 fractions *per* day for a total dose of 10 Gy. However, five of their patients also received EBRT[44]. Few of the studies in which brachytherapy has been used with palliative intent, mainly to relieve biliary obstruction, are presented in Table 1.

Complications

The most frequent complication of ILBT is cholangitis[45]. Other side effects of PTBD combined with ILBT include nausea, vomiting, and gastroduodenal ulceration[34].

Limitations

ILBT is not used frequently due to the lack of availability and expertise and patient's moribund condition due to disease. Also, there is paucity of literature, and a lack of survival benefit. But in patients with malignant biliary obstruction, it can be used as an adjunct to systemic therapies. It can be

used as an adjunct to biliary drainage in the palliative setting.

CONCLUSION

ILBT offers an effective means of palliating biliary obstruction in patients with cholangiocarcinoma. The article focuses mainly on the role of ILBT in the palliation of malignant biliary obstruction. ILBT delivers a high dose of radiation to the tumor with sparing of surrounding normal tissues, thus avoiding many of the side effects seen with external beam radiation. The high dose *per* fraction in ILBT can have an ablative effect on the tumor and can lead to better symptom control and quality of life. The transhepatic approach is preferred over the endoscopic technique as ILBT is easier to perform when combined with PTBD as compared to ERCP. ILBT, when combined with these drainage procedures, improves the stent patency rates by inhibiting tumor ingrowth. There is a need for prospective studies to compare the quality of life and outcome in such patients using ILBT.

FOOTNOTES

Author contributions: Khosla D contributed to conceptualization and manuscript preparation, writing, and editing and was responsible for the integrity of the article; Zaheer S and Gupta R contributed to literature search and manuscript writing and editing; Madan R contributed to literature search; Goyal S contributed to manuscript editing; Kumar N and Kapoor R reviewed and approved the manuscript.

Conflict-of-interest statement: The authors declare no conflicts of interest in the preparation of the manuscript.

Country/Territory of origin: India

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S-Editor: Fan JR
L-Editor: Wang TQ
P-Editor: Fan JR

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World Journal of Gastrointestinal Endoscopy

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World J Gastrointest Endosc 2022 March 16; 14(3): 113-128

DOI: 10.4253/wjge.v14.i3.113

ISSN 1948-5190 (online)

MINIREVIEWS

Endoscopic management of difficult laterally spreading tumors in colorectum

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Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Fiori E

Received: June 30, 2021
Peer-review started: June 30, 2021
First decision: October 18, 2021
Revised: November 1, 2021
Accepted: February 15, 2022
Article in press: February 15, 2022
Published online: March 16, 2022

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Abstract

Due to the advent of the screening programs for colorectal cancer and the era of quality assurance colonoscopy the number the polyps that can be considered difficult, including large (> 20 mm) laterally spreading tumors (LSTs), has increased in the last decade. All LSTs should be assessed carefully, looking for suspicious areas of submucosal invasion (SMI), such as nodules or depressed areas, describing the morphology according to the Paris classification, the pit pattern, and vascular pattern. The simplest, most appropriate and safest endoscopic treatment with curative intent should be selected. For LST-granular homogeneous type, piecemeal endoscopic mucosal resection should be the first option due to its biological low risk of SMI. LST-nongranular pseudodepressed type has an increased risk of SMI, and en bloc resection should be mandatory. Underwater endoscopic mucosal resection is useful in situations where submucosal injection alters the operative field, *e.g.*, for the resection of scar lesions, with no lifting, adjacent tattoo, incomplete resection attempts, lesions into a colonic diverticulum, in ileocecal valve and lesions with intra-appendicular involvement. Endoscopic full thickness resection is very useful for the treatment of difficult to resect lesions of less than 20 up to 25 mm. Among the indications, we highlight the treatment of polyps with suspected malignancy because the acquired tissue allows an exact histologic risk stratification to assign patients individually to the best treatment and avoid surgery for low-risk lesions. Endoscopic submucosal dissection is the only endoscopic procedure that allows completes en bloc resection regardless of the size of the lesion. It should therefore be indicated in the treatment of lesions with risk of SMI.

Key Words: Colorectal polyps; Laterally spreading tumors; Endoscopic mucosal resection; Underwater endoscopic mucosal resection; Endoscopic full thickness resection; Endo-

scopic submucosal dissection

Core Tip: The number of detected large laterally spreading tumors has increased in the last decade. Herein, we review the current landscape of different endoscopic techniques that allow us to resect difficult laterally spreading tumors. We also describe strategies in problematic situations such as scarred lesions or difficult areas and how to treat adverse events related to colonoscopy.

Citation: Castillo-Regalado E, Uchima H. Endoscopic management of difficult laterally spreading tumors in colorectum. *World J Gastrointest Endosc* 2022; 14(3): 113-128
URL: https://www.wjgnet.com/1948-5190/full/v14/i3/113.htm
DOI: https://dx.doi.org/10.4253/wjge.v14.i3.113

INTRODUCTION

Therapeutic endoscopy is nowadays a well consolidated area in the gastroenterology field, covering techniques such as gastroscopy, colonoscopy, enteroscopy, endoscopic retrograde cholangiopancreatography and therapeutic endoscopic ultrasound. In the last decade, techniques for resection of early gastrointestinal neoplasia have become widespread worldwide and gaining popularity among young endoscopists with special interests in learning endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). The main societies have published their statements[1-4].

On the other hand, with the advent of the screening programs for colorectal cancer and adopted in Europe, Australia, Asia and North America and the era of quality assurance and high-definition colonoscopy, the number of advanced mucosal neoplasia and early cancer in the colon, including the polyps that can be considered difficult, has increased in the last decade[5]. The definition of a difficult polyp is not well established. These polyps are typically defined by their size (generally considered as those greater than or equal to 20 mm), morphology, location, biology and previous manipulation (Figure 1).

Thus, the endoscopist should have the skills to detect and characterize all types of colorectal lesions and should be able to predict their risk of deep submucosal invasion (SMI) with high accuracy and proceed to endoscopic resection if it is indicated. The optical diagnosis with image-enhanced endoscopy is the key and mandatory first step before management of a colorectal polyp. First, morphology should be assessed and described according to the Paris Classification, including surface [granular or non-granular in cases of laterally spreading tumors (LSTs) or presence of ulcerations] and looking for demarcated areas (nodules, depressions or marked erythema). Then, virtual chromoendoscopy with blue light technology should be applied to investigate the surface and microvascular patterns. There are different classifications that help predict the risk of deep SMI, like Narrow Band Imaging (NBI) International Colorectal Endoscopic classification that does not need optical zoom or Japan NBI Expert Team (JNET) classification that uses optical zoom. The subclass JNET3 includes deep submucosal invasive lesions; JNET2a includes mostly intraepithelial lesions (*e.g.*, low-grade dysplasia), while that of JNET2b could be found in intramucosal lesions and lesions with SMI. In those cases, pit pattern evaluation with chromoendoscopy and optical zoom using crystal violet or indigo carmine should be recommended, especially in the demarcated areas that may have a higher risk of SMI[6].

The endoscopic treatment of colorectal lesions should be reserved to all early neoplastic lesions with low risk of SMI and thus ideally no risk of lymph node metastasis. If the lesion is considered to have risk of lymph node metastasis, surgery should be considered as a first option.

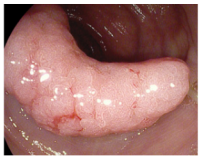
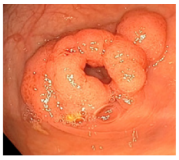
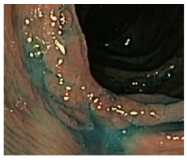
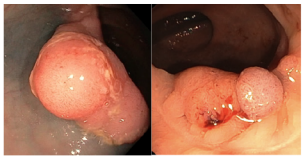
There is strong evidence now to recommend the EMR as the first-line therapy for non-invasive lesions. It has good results and lesser mortality compared to surgery, and the patients could be discharged the same day (even elderly patients or patients with a severe comorbidity)[7,8].

Herein, we review the techniques for endoscopic resection of the LST, including complex lesions.

LATERALLY SPREADING COLORECTAL TUMORS

The term LST, initially reported by Kudo *et al*[9], refers to flat lesions larger than 10 mm that grow laterally along the colonic wall, being classified as granular (LST-G) and non-granular (LST-NG).

The LST-G can be classified as LST-G homogeneous type (Paris Classification 0-IIa) if they show a granular homogeneous surface (usually < 3 mm) or as LST-G nodular mixed type (Paris Classification 0-

Morphology	Special location	Biology	Previous manipulation
Non-granular morphology; Large sessile; Depressed area	Appendicular orifice; Ileocecal valve; Diverticulum; Anal margin; Flexures	Poor/Non-lifting (Fibrosis, desmoplastic reaction); High impedance (fat); Easy bleeding (arterioles hiding in fat, high density of vessels)	Tattooing; Biopsies/"macrobiopsies;" Prior resection attempt
			

DOI: 10.4253/wjge.v14.i3.113

Figure 1 Characteristics that make a polyp difficult.

II + Is) if they have one or more sessile nodules, with those greater than 10 mm carrying an increasing risk of SMI. The LST-NG can be classified as LST-NG flat type (Paris Classification 0-IIa) or LST-NG pseudodepressed type (Paris Classification 0-IIa + IIc)[10].

Their characteristic growth (lateral rather than vertical) appear to be caused by adequate co-expression of β-catenin and E-cadherin in the basolateral membrane, type IV collagen along the basement membrane and expression of atypical protein kinase λ/ι (an essential cell polarity regulator) like normal colonic mucosa[11].

They also seem to overexpress lipocalin-2 and metallopeptidase-9 in a correlated manner to advanced stages (worse pathology grading), being both suggested as potential serum biomarkers for LST progression[12].

The types of LST have a different biology. For example, the LST-G type express CpG island methylator phenotype-high involving more than two loci and has a high prevalence of *K-ras* mutations (especially in the right colon), whereas the LST-NG type have less *K-ras* mutations and are CpG island methylator phenotype-low[13,14]. New non-invasive diagnostic biomarkers are being explored with the microbiome signature being one of them.

Clinically, the LST-NG type tend to be more aggressive with a higher incidence of advanced carcinoma, especially the pseudodepressed type, with incidences of 19.8%-43.4%. On the other hand, LST-G type tend to have less submucosal carcinoma, being rare in the LST-G homogeneous type (0.5%; 95%CI: 0.1%-1.0%) irrespective of the size of the lesion (Figure 2)[15].

Location is variable. Granular type is more often localized in the cecum and rectum and non-granular in the right colon[16].

For large LST-G homogeneous type, piecemeal EMR should be the first option irrespective of the size of the lesion most of the time due to its biological low risk of SMI. For LST-G nodular mixed type careful inspection of the surface and vascular patterns (specially in nodules > 10 mm) should be done to rule out signs of deep SMI prior to treatment.

For LST-NG type, en bloc resection should be considered as the first option in all cases due to its higher risk of SMI (especially for the pseudodepressed type). Thus, ESD or surgical treatment should be decided according to local expertise in case the lesion is too big for en bloc EMR. Endoscopic full thickness resection (EFTR) may be an alternative if the lesion is suitable.

In some cases, LST-NG flat type might be resected in piecemeal if the surface and vascular patterns show no signs of SMI. These considerations are summarized in Table 1.

ELECTROSURGICAL PRINCIPLES FOR EMR

Knowing the basic principles of diathermy is mandatory for endoscopists. Knowledge on the management of electrosurgery may be able to improve procedural outcomes and safety for our patients [17].

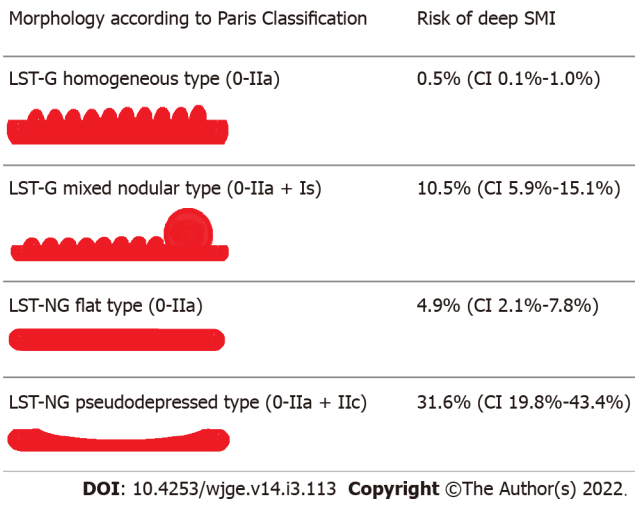
Electrosurgery uses radiofrequency electricity to generate heat in the tissue itself rather than applying heat from an outside source. The snares and most endoscopic knives commonly used in the west are monopolar [the electricity flows from the active electrode (snare) to the neutral electrode placed in the patient skin]. Fortunately, the electrosurgical units use high frequency alternating current (300 kHz to 5 MHz) to avoid neuromuscular stimulation. Thus, the risk of complications is mainly related to the amount of heat produced.

Power is the amount of energy consumed per unit time, and it is measured in watts. The energy dissipated as heat when the electric current (amperes) passes through the resistance (ohms) of the tissue held by the snare is measured in joules. There are two main clinical effects when the electric current is

Table 1 Considerations for endoscopic treatment in laterally spreading tumors

LST suitable for piecemeal EMR	Comments	LST not suitable for piecemeal EMR	Comments
LST-G homogeneous type	Very low risk for deep SMI, independent of size of the lesion	LST-NG pseudodepressed type	En bloc resection
LST-G mixed nodular type with no signs of SMI	Consider en bloc resection first. If not, careful inspection of surface/pit pattern and vascular pattern specially in the larger nodules (≥ 10 mm), resect the nodular area apart (*e.g.*, JNET2a)	LST-G mixed nodular or NG flat with risk of SMI	En bloc resection (*e.g.*, JNET2b, pit pattern V)
LST-NG flat with no demarcated area and no signs of SMI	Consider en bloc resection first. If not, careful inspection of surface/pit pattern and vascular pattern (*e.g.*, JNET2a)		

EMR: Endoscopic mucosal resection; G: Granular type; JNET: Japan Narrow Band Imaging Expert Team; LST: Laterally spreading tumor; NG: Non-granular type; SMI: Submucosal invasion.



DOI: 10.4253/wjge.v14.i3.113

Figure 2 Risk of submucosal invasion.

applied to the tissue by the snare: boiling (cells burst resulting in cutting tissue) and coagulation. If there is more current per unit of area (current density), then more heat is produced; therefore, the smaller the area of tissue trapped into the snare, a lesser amount of power is needed to heat the tissue.

Electrosurgical cutting is produced when a continuous alternating current with more than 200 voltage peaks is applied to the tissue, raising very rapidly the intracellular fluid temperature and boiling the cells (so they burst) with steam formation. Electrosurgical coagulation is produced if the tissue is heated slowly by an intermittent electric current. The temperature rises within cells, the cells shrink, and the cellular proteins coagulate, turning the tissue white (like the effect of heating the albumin of an egg). However, if current application to the tissue continues, then it produces carbon and smoke. This thermal damage may obscure the specimen margins on pathological evaluation.

If the current used has less than 200 voltage peaks, then the effect would be a superficial "pure coagulation" (*e.g.*, SOFT COAG mode in ICC 200 and VIO 300D; ERBE, Tüebingen, Germany). If the current used has more than 200 voltage peaks and is activated 10% or less of the time (of the duty cycle, the fraction of time current flows each second that the activating pedal is depressed), then it would produce a deep coagulation (FORCED COAG mode of ERBE has 4% duty cycle). Even the "purest" cutting current can have some coagulation effect in the tissue around the cutting area where there is not enough heating to boil the cells but to dehydrate and coagulate proteins. Thus, the more cutting or coagulating effect would depend on the duty cycle. The more time energy is delivered by pushing the pedal, the greater the heat is produced and the chances of having a thermal-related complication, such as deep muscle layer injury or perforation.

To perform an EMR, alternating cutting and coagulating output is very useful (*e.g.*, in the ENDOCUT mode of ERBE that alternates cutting current with SOFT COAG). For ERBE VIO 300, it would be recommended to use ENDO CUT Q effect 3 (cut duration 1, cut interval 6) for cutting and SOFT COAG Effect 4 (max. watts 80) for snare tip soft coagulation. The power settings (if they are not self-regulated by the electrosurgical units) should be adapted to the instrument used according to the manufacturer's recommendation, and it is recommended to use the lowest power that will allow the resection[18].

Once we have set the mode and power, we can control by closing the snare on the area of tissue to resect (smaller area, less current needed for tissue cell burst) and the time we deliver that power to the tissue by pressing the pedal. The timing of the pedal is also very important during ESD.

MATERIALS

Endoscope

Nowadays, endoscopes with optical narrow band technology using "blue light" to display the mucosa and vessels in high contrast, such as NBI (Olympus, Tokyo, Japan), Blue Light Imaging (Fujifilm, Tokyo, Japan) or i-scan Optical Enhancement (Pentax, Tokyo, Japan), should be used for endoscopic assessment of the lesion prior to resection, especially if there is optical magnification, to rule out signs of SMI[19].

Olympus has recently incorporated new postprocessing functions in the EVIS X1 system that includes extended depth of field and texture and color enhancement imaging that improves the visibility using white light endoscopy and red dichromatic imaging that enhances the visibility of deep blood vessels and bleeding. These functions could help diagnose and manage complications.

To facilitate resection for polyps in the rectosigmoid area and proximal colon, a gastroscope and a pediatric colonoscope or a short colonoscope may be used, respectively[20]. New colonoscopes like the RetroView™ EC34-i10T, PCF-H190TL/I EVIS EXERA III (Olympus) and Eluxeo EC-740TM/TL [Treier Endoscopie (part of the Duomed Group), Beromünster, Switzerland] provide excellent maneuverability due to a smaller bending radius of the distal tip, and 210° deflection is ideal for the detection and treatment of hard-to-reach lesions.

CO_2

CO_2 insufflation is highly recommended for therapeutic colonoscopy. It reduces pain after EMR of LSTs, which might be a cause of admission, especially in patients with a long duration of polypectomy[21].

Injection solution

A solution mixed with a blue dye is commonly used. The submucosal solution could be a crystalloid like normal saline solution or a colloid solution like glycerol or a succinylated gelatin. The inexpensive succinylated gelatin (gelafusine, gelafundin) was shown to be superior to saline solution requiring fewer injections, resections and an overall reduced EMR time[22]. A meta-analysis showed that use of viscous solutions during EMR leads to higher rates of en bloc resection and lower rates of residual lesions compared with normal saline solution especially with colonic polyp greater than 2 cm[23]. Nonetheless, research to determine the ideal submucosal injection is still ongoing.

Eleview® (Cosmo Pharmaceuticals, Dublin, Ireland), ORISE™ gel (Boston Scientific, Marlborough, MA, United States) and LiftUp® (Endotherapuetics, Australia) are synthetic solutions that were specifically designed to provide a submucosal cushion of optimal height and duration[24,25]. When compared to normal saline solution, Eleview® has demonstrated better cushion-forming ability and a duration of lift of up to 45 min. A double-blind randomized controlled trial comparing Eleview® with saline showed that the mean injected volume was significantly lower, and there was a trend towards shorter procedure and a lower number of resection pieces with this new solution. Despite all these advantages, larger, multicenter, prospective controlled trials are required to compare performance of Eleview®, ORISE™ gel and LiftUp® to other available viscous submucosal solutions for EMR and ESD.

An inert dye such as indigo carmine (or alternatively methylene blue) is added to stain the submucosal layer blue and facilitate the delineation of the lesion margins. The authors do not use adrenaline for submucosal injection, but diluted adrenaline (1/100000-1/300000) could be added according to the preferences of the endoscopist[26].

Transparent cap

The distal cap attachment may contribute to stabilize the tip of the scope, improve visualization of the operative field and facilitate resecting lesions in difficult locations[27]. They are especially useful to create tension of submucosal fibers during ESD. Conic shaped short ST hood may be useful for non-lifting and other complex lesions when access to submucosal space could be difficult.

Premedication

Deep sedation is preferred by the authors for EMR or underwater EMR (UEMR). Prophylactic antibiotics should be considered in cases of EMR or ESD of LST in the distal rectum (as drainage bypasses the liver) especially when a large resection defect ($\geq$ 4 cm) is expected[28]. Consider buscopan or glucagon to reduce bowel peristalsis during the procedure.

Snares

The choice of a specific snare may rely on size and morphology of the lesion, its location, the endoscopist technique and preference or what type of snare is familiar. There are some snares that

combine different sizes and shapes, but no clear benefit of one shape over the other has been demonstrated[2]. In cases of cold EMR, a dedicated cold snare is recommended. For hot EMR and UEMR, the authors' preference is a rounded stiff snare 15 mm for most cases.

ESD knives

Like the choice of snare, it may depend on the lesion and the endoscopist preference. There are many types of ESD knives, but it is highly recommended to have water-jet or water injection capability to save time during dissection.

APPROACH

Endoscopic preoperative optical diagnosis

The most important step is to provide a good endoscopic diagnosis of the lesion, to be sure that the endoscopic resection would have a curative intention. The only way the endoscopic resection will be curative is if all the neoplastic cells are within the lesion we resect, even if they are malignant cells. But if there is a distant spread of the neoplastic tissue (*e.g.*, lymphatics), then the treatment will not be curative. By endoscopic inspection we can predict the risk of deep SMI, telling us that there could be a risk of lymph node metastases. That is why during preoperative evaluation the endoscopist should rule out signs of deep SMI.

The endoscopist should use the best scope (better if there is magnification or dual focus with optical narrow band "blue light" technology), use Paris classification to describe the morphology of the lesion and assess demarcated areas of risk of SMI, such as the nodular and depressed areas. This assessment should focus on pit pattern and vascular pattern.

The JNET Classification was proposed in 2016 according to NBI magnifying endoscopy[6]. It consists of the following four categories, combining vessel and surface patterns: Type 1, the hyperplastic polyp or sessile serrated adenoma/polyp with "invisible" vessel pattern with regular dark or white spots similar to surrounding normal mucosa; Type 2A, the adenoma with low grade dysplasia, with regular vessels (in caliber and distribution) and surface pattern (corresponding to pit pattern III or IV); Type 2B, the adenoma with high grade dysplasia, or sometimes shallow submucosal cancer, with moderately distorted vessels and irregular or obscure surface pattern (corresponding to pit pattern Vi); and Type 3, an invasive cancer with amorphous areas with markedly distorted vessels or avascular areas.

However, in a retrospective study from prospectively collected records (n = 1402 lesions), Type 2B presented low sensitivity (42%) even among expert Japanese endoscopists. Therefore, some authors have suggested that Type 2B requires further investigation using pit pattern diagnosis to differentiate the Vi (irregular; superficial SMI) and Vn (non-structural; deep SMI)[29].

If there is a high suspicion of deep SMI, the patient should undergo a surgical procedure or an endoscopic technique for en bloc resection. It is also very important to delimitate the margins of the lesion, especially if it is a serrated adenoma.

In the LST-G homogeneous type (Paris 0-IIa) of any size, the risk of deep SMI is very low, which makes EMR almost always suitable[2-4,15].

EMR

"Classic" EMR is based on inject and resect technique (Table 2). It may be helpful for en bloc resection of lesions up to 2 cm and for piecemeal resection in bigger LSTs. For piecemeal resection 10 mm to 15 mm snares are usually recommended. For cold EMR, a specific cold snare is recommended. For a successful piecemeal EMR the resection should be performed in a systematic manner, sequentially from the first point of resection or entry in the submucosal plane, including 2-3 mm of apparently normal mucosa at the borders and including the edge of the advancing mucosal defect to avoid islands and bridges of neoplastic tissue.

The final mucosal defect should be checked for signs of injury or residual tissue. It is useful to use a topical submucosal chromoendoscopy with indigo carmine to rule out deep injury. It can be injected or sprayed superficially over the defect with the needle catheter close. The submucosa would pick up the blue color. If there is muscle layer exposed, then it would remain unstained[4,30].

After finishing piecemeal EMR, snare tip coagulation of the normal appearing margins and mucosal defect using SOFT COAG 80W is beneficial as it can reduce 4-fold the rate of residual or recurrent adenoma[4,30,31] even after en bloc EMR.

UEMR

UEMR, described by Nett *et al*[32] in 2012, has been shown to enable safe resection of LST. UEMR is performed by aspirating all the gas from the colonic lumen and instilling water or saline to fill the cavity. The colonic lesion "floats" in a lumen filled with fluid, and the muscularis propria retains a circular configuration and does not follow involutions of the mucosa and submucosa even during peristaltic contractions (Figure 3), making it easier to snare the lesion[33] (Table 2).

Table 2 Steps for endoscopic mucosal resection of laterally spreading tumors

Steps for endoscopic resection	
(1) Endoscopic evaluation	Using Paris classification, pit pattern and vascular pattern to characterize the lesions and define the risk of deep SMI
(2) Strategy	Decide en bloc *vs* piecemeal resection according to risk of SMI. Consider patient position and gravity
(3) EMR technique	
Injection	Needle tangential to the plane. Inject whilst "stabbing" the mucosa helps accurately find the SM plane. Use a dynamic injection technique
Resection	Put the area to resect ideally between 5-6 o'clock (with colonoscope); accommodate the snare over the lesion and push "down," aspirate to decrease tension and maximize tissue capture; close the snare tightly; check for mobility and degree of closure of the snare handle (usually < 1 cm distance between thumb and fingers), be sure there is no muscle trapped, otherwise release the tissue (in case of doubt, open and close the snare to "drop out" possible muscular entrapment); press the pedal to resect
Wash and check mucosal defect	Check the mucosal defect produced to rule out signs of muscle layer damage or perforation
Hemostasis	If there is mild intraprocedural bleeding, try first snare tip soft coagulation. If necessary, coagulating forceps or clips can be helpful
Systematic inject and resect	Continue resection injecting when necessary to maintain submucosal cushion. Resect 2-3 mm of normal mucosa to ensure margins. Try not to leave islands or bridges between resections
(4) UEMR technique	
Water filling	Aspirate all the gas and fill the lumen of the working space with water or saline (turning off insufflation may help) to create a gravity-free environment
Resection	Put the area to resect ideally between 5-6 o'clock (with colonoscope); accommodate the snare over the lesion "torque and crimp" and push "down" to get the floating lesion inside the snare; aspirate and irrigate more water to help the capture of the tissue; close the snare tightly and separate the tissue from the wall. Press the pedal to resect. Underwater, higher outputs might be needed for resection/coagulation due to the heat sink effect
Wash and check mucosal defect	Check the mucosal defect produced to rule out signs of muscle layer damage or perforation. As no dye is used to stain the submucosa, the operator should become familiarized with the aspect of the "transparent" fibers
Hemostasis	In cases of jet bleeding gas insufflation might be needed to find the bleeding point
Systematic gas aspiration water irrigation and resection	Continue resection aspirating gas or irrigating water when necessary. Resect 2-3 mm of normal mucosa to ensure margins. Try not to leave islands or bridges between resections
(5) Final inspection	Check the scar to rule out residual neoplastic tissue or signs of deep injury. In cases of piecemeal resection, thermal ablation with the tip of the snare (Soft COAG 80 W) to coagulate the mucosal borders of the scar reduces risk of recurrence
(6) Specimen retrieval and assessment	Consider using a net for retrieval. Big nodules should be sent separately if it was piecemeal resection

EMR: Endoscopic mucosal resection; SM; Submucosal; SMI: Submucosal invasion; UEMR: Underwater endoscopic mucosal resection

In recent years, meta-analysis has supported that UEMR resection achieves a higher en bloc resection rate and less post-endoscopic resection recurrence compared to conventional EMR, especially when polyps greater than or equal to 20 mm are resected. In contrast, no significant differences were detected with respect to the occurrence of adverse events[34,35].

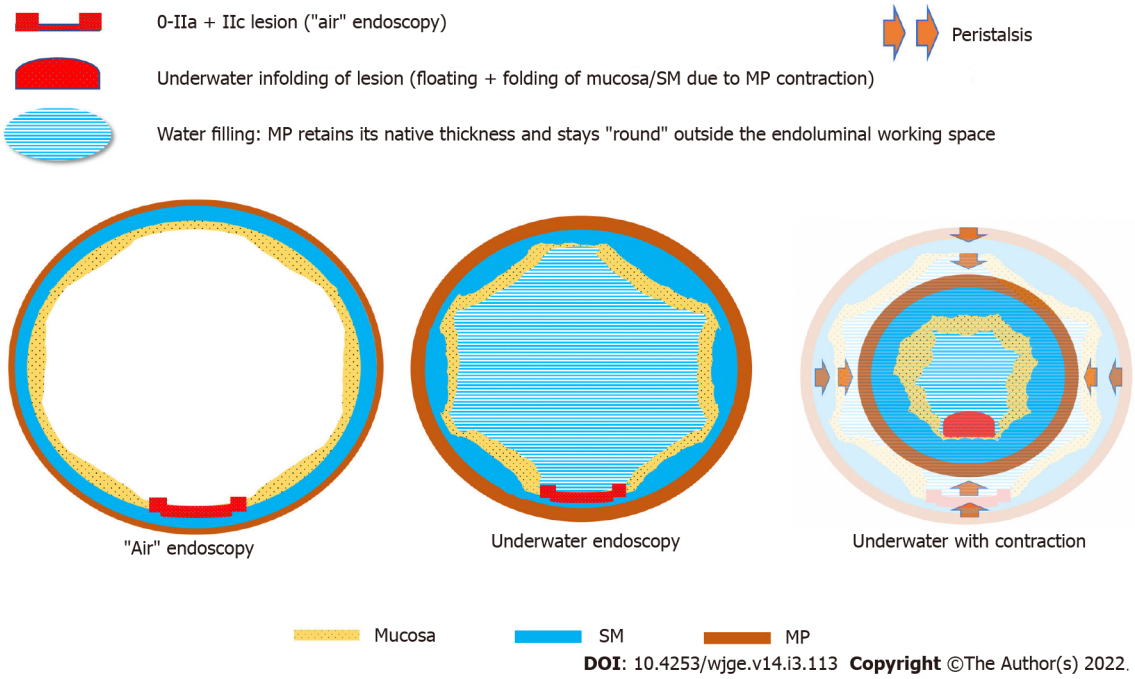
In daily clinical practice, UEMR is very useful due to its effectiveness, safety and easy learning. This technique can be used for the resection of scar lesions with no lifting, adjacent tattoo, incomplete resection attempts, lesions into a colonic diverticulum, in the ileocecal valve with ileal component and lesions with intra-appendicular involvement[36].

UEMR may also be useful for en bloc resection of pseudodepressed less than or equal to 2 cm LST-NG in which en bloc resection is mandatory due to the high risk of SMI[33].

Another advantage of UEMR is that it is a "reversible" technique. In the case that en bloc resection of a high-risk lesion does not seem feasible, all the water can be aspirated, and the technique can be changed either to ESD or EFTR.

EFTR

EFTR is an emerging technique for removal of complex colorectal lesions. Since the introduction of the full thickness resection device (FTRD; Ovesco Endoscopy AG, Tübingen, Germany) in Germany in 2014 [37] several studies have reported encouraging results on the short-term safety and efficacy of EFTR[38, 39].



DOI: 10.4253/wjge.v14.i3.113

Figure 3 During muscularis propria contraction, infolding of the 0-IIa + IIc lesion occurs. Citation: Uchima H, Colán-Hernández J, Binmoeller KF. Peristaltic contractions help snaring during underwater endoscopic mucosal resection of colonic non-granular pseudodepressed laterally spreading tumor. *Dig Endosc* 2021; 33: e74–6. Copyright ©The Author(s) 2021. Published by John Wiley & Sons Australia, Ltd[33].

To perform an EFTR, the lateral margins of the lesion are first marked with the probe that is part of the set or by other means (*e.g.*, snare tip coagulation or argon plasma). Thereafter, the colonoscope is retracted, and the FTRD is mounted and advanced to the target lesion. The lesion is then pulled into the resection cap with the grasping forceps. After deployment of the clip, the snare is closed, and the tissue is cut. To avoid unintended incorporation of organs next to the colonic wall, traction of the target lesion without suction is recommended, and when necessary, suction should be performed very gently and with caution. After resection, the specimen is recovered, and inspection of the resection site to check for the correct position of the over-the-scope clip is mandatory. For colonic lesions, prOVECAP (Ovesco Endoscopy, Tübingen, Germany), a cap similar in size to the FTRD cap, can be mounted on the instrument tip to evaluate accessibility to the target lesion. The keys to technical success are the right size of the lesion, performing correct traction and coordinated teamwork[40].

General indications for EFTR are residual adenoma after endoscopic resection, non-lifting sign adenoma, histological R1 resection (deep and lateral positive margins at histology), suspected T1 carcinoma, adenomas at difficult anatomic locations (appendiceal orifice, diverticulum, folds) and subepithelial lesions[38,39].

Among the indications for EFTR, we highlight the treatment of polyps with suspected malignancy due to its clinical impact because in most cases the acquired tissue allows an exact histologic risk stratification to assign patients individually to the best treatment and avoid surgery for low-risk lesions. In a retrospective multicenter study that included 64 patients with incomplete resection of malignant polyps, the performance of EFTR obviated the need for surgery in most of these patients (84%) by classifying them as low risk and therefore may be the method of choice for this indication[41].

A recent meta-analysis including nine studies conducted in European countries with 469 Lesions showed a pooled rate of technical success, full thickness resection and R0 resection of 94.0% (95%CI: 89.8%-97.3%), 89.5% (95%CI: 83.9%-94.2%) and 84.9% (95%CI: 75.1%-92.8%), respectively; a pooled estimate of bleeding, perforation and post-polypectomy syndrome of 2.2% (95%CI: 0.4%-4.9%), 0.19% (95%CI: 0.00-1.25%) and 2.3% (95%CI: 0.1%-6.3%), respectively and pooled rates of residual/recurrent adenoma and surgery for any reason of 8.5% (95%CI: 4.1%-14.0%) and 6.3% (2.4%-11.7%), respectively. These results show that EFTR with an FTRD system is efficient and safe for treating non-lifting and invasive colorectal lesions with conventional EMR and ESD criteria[42]. Nonetheless, future studies are needed to investigate the role of EFTR in large colorectal lesions and specify its indications.

ESD

ESD was first described in Japan for the treatment of early gastric cancer and adopted for the treatment of colonic lesions. It is the only procedure that allows complete en bloc resection regardless of the size of the lesion.

It is a technically demanding procedure, requires a long learning curve and requires a longer procedure time than EMR[43]. Adverse events are more common for ESD than for EMR, with published perforation rates of about 5%[44]. Nevertheless, the safety profile is adequate because almost all ESD complications can be managed endoscopically, and the risk of surgery related to post-ESD complications (2%) is low[45].

It basically consists of entering the submucosal space, which is a virtual space that we will create with a solution injected into the submucosa. The classic technique includes marking the lesion to be resected and injecting a lifting agent into the submucosa at its periphery. Using the endoscopic knife, the mucosa is incised circumferentially, and the lesion is separated from the muscularis propria. Additional submucosal injections are performed as necessary to lift the central portion of the lesion to allow for complete resection. Other strategies for ESD have been described, such as pocket-creation method or tunnel[46]. Traction is recommended for colonic lesions, *e.g.*, using rubber band-clip technique because it can significantly decrease the procedure time, increase the en bloc resection rate and the R0 resection rate[47].

There are several tips thoroughly commented on elsewhere in the literature[48].

Post-procedural care

If there is no complication during the procedure and there are no special risk factors, then the patient could be discharge within 1-3 h after EMR/UEMR or ESD of small lesions, or 24 h or less after EFTR. If there are symptoms, risk factors for complications or special situations (very large lesion), then a longer period of observation might be consider. If there is any sign of complication (pain with abdominal distension, vomiting, rectal bleeding, fever) perform a blood test and or computed tomography scan according to the clinical suspicion and act according to the results. If perforation with peritonitis is suspected, then surgery should be evaluated[49].

COMPLICATIONS

Deep mural injury and perforation

It is very important to differentiate post-polypectomy syndrome, a benign complication with a good prognosis in most cases that can be treated medically[50], secondary to excess coagulation and thermal injury of the colonic wall in which computed tomography scan may show a severe mural thickening with stratified enhancement pattern with surrounding infiltration but no air[51]. It is extremely important to recognize deep mural injury (DMI) signs such as the target sign during or immediately after finishing the EMR using the Sydney Classification of DMI (Table 3)[52].

The right colon (and cecum) is the thinner part of colon and might be more prone to complications such as perforation, but in one study it seemed that the transverse colon might have more incidence of DMI. The transverse colon is highly mobile, and it has a long mesentery. It is possible that the muscular propria could be more mobile and be trapped easily without "feeling" that we snare the muscular layer.

If there are signs of DMI, then an endoscopic treatment could be offered according to the experience of the endoscopist by using through-the-scope clips for iatrogenic perforations less than 1 cm and the use of the over-the-scope clip could be considered for defects 1-2 cm[53]. For larger iatrogenic perforations, endoscopic treatments with endoscopic suturing or a polyloop and clips method using a double-channel or single-channel endoscope have been described[54,55].

Prophylactic clipping of muscular injury (target signs) might protect against delayed clinical perforation. If the perforation had leakage of colonic fluid, then a surgical approach might be a better option.

Bleeding

Bleeding is a frequent complication of EMR and ESD. Intraprocedural bleeding (IPB) is relatively common, being most of the time an auto limited event from cutting small capillary vessels or vessels that may require coagulation. The IPB rate in the literature is over 10%. In an observational multicenter study that analyzed data from EMR of sessile colorectal polyps greater than or equal to 20 mm in size (mean size: 35.5 mm) of 1172 patients, IPB was observed in 133 (11.3%)[56].

The small bleeding during procedure could be minimized by adding diluted adrenaline to the submucosal injection solution and could be treated with coagulating current using the tip of the snare (*e.g.*, ERBE soft coagulation 80 W, snare tip soft coagulation), coagulating forceps or hemostatic clips[17].

IPB that requires endoscopic treatment is associated with a longer procedure time, higher risk of clinically significant post procedural bleeding and recurrence at first surveillance after piecemeal EMR [56].

Post procedural bleeding is also relatively frequent. In a prospective study involving 1039 patients after EMR, 6% had a clinically significant delayed post-polypectomy bleeding, 21% of them (13 patients) being unstable and 26% (16 patients) requiring blood transfusion. Most of the patients (55%) were managed conservatively, 44% underwent colonoscopy, and 1 patient required primary embolization and surgery[57].

Table 3 Sydney Classification of deep mural injury

Sydney Classification of deep mural injury	
Type 0	Normal defect. Blue mat appearance of obliquely oriented intersecting submucosal connective tissue fibers (with a blue dye such as indigo carmine or methylene blue)
Type 1	MP visible but no mechanical injury ("Whale" sign)
Type 2	Focal loss of the submucosal plane raising concern for MP injury or rendering the MP defect uninterpretable
Type 3	MP injured, specimen target sign or defect mirror target sign identified
Type 4	Actual hole within a white cautery ring, no observed contamination
Type 5	Actual hole within a white cautery ring, observed contamination

MP: Muscular propria.

To control the active bleeding after EMR or ESD, mechanical therapy (*e.g.*, through-the-scope/cap-mounted clips) and/or contact thermal coagulation are helpful. In cases of inadequate or failed hemostasis with ongoing bleeding, hemostatic topical agents can be used as a secondary treatment option[58].

The risk factors for clinically significant delayed post procedural bleeding include lesions larger than 3 or 4 cm, located in the proximal colon, elderly patients, patients with major comorbidities, taking antiplatelets and absence of use of epinephrine. Two scores have been published to predict the risk of delayed bleeding in two different populations, with similar results summarized in Table 4[59,60].

Prophylactic endoscopic coagulation with a coagulating forceps (with low-power coagulation) does not seem to significantly decrease the incidence of clinically significant post-EMR bleeding. Nonetheless, a recent meta-analysis has shown benefit when clipping polyps measuring greater than or equal to 20 mm, especially in the proximal colon[61].

In recent years, coverage agents have been developed to cover large mucosal defects that appear to be effective in the prevention of late complications, but randomized controlled trials and head-to-head comparative studies of shielding products are still needed[62].

RECURRENCE OR RESIDUAL NEOPLASTIC TISSUE AND SURVEILLANCE

Recurrence or residual neoplastic tissue after EMR can be easily solved endoscopically in most of cases during surveillance since treatment after first revision is usually successful.

Early recurrence of large conventional adenomas seems to be around 16% at first surveillance colonoscopy (SC), with a cumulative recurrence around 20% after second SC 1 year after and around 28% after 2 years. Large sessile serrated adenomas/polyp recurrence seems to be lower, at about 7% from 12 mo onwards[7].

First SC at 3-6 mo after piecemeal EMR of polyps greater than or equal to 20 mm is recommended for scar assessment and the intervals to the next colonoscopy at 1 year and then 3 years[4,30]. It has been published that after EMR of lesions smaller than 4 cm without significant intraprocedural bleeding (not requiring endoscopic treatment) and with low-grade dysplasia, the first SC can be safely scheduled at 18 mo. The Sydney EMR recurrence tool (Table 5) was developed to help predict the risk of recurrence after piecemeal EMR, with a 92% negative predictive value for recurrence at first SC, for Sydney EMR recurrence tool 0 lesions[63]. It is also very important to treat other synchronic lesions, clear the rest of the colon or rule out a serrated polyposis in cases of resection of large serrated lesions.

It is very important to carefully inspect the scar. The scar might be identified as a pale area with disruption of vascular pattern or fold convergence. All the edges and center of the scar should be interrogated, looking for a transition point where a non-neoplastic pit or vascular pattern turns into a neoplastic pattern (Kudo pit pattern, NBI International Colorectal Endoscopic and JNET classification) and being aware of post-EMR scar clip artifact using a high-definition endoscope with optical narrow band technology[64].

In surveillance cases with local recurrence, endoscopic resection with repeat EMR, snare or avulsion method can be performed, and ablation of the perimeter of the post-treatment site may be considered. If there is a retained clip in the scar, the procedure should be the same. In case there is a suspicious area of residual polyp, the retained clip should not prevent endoscopic resection of the residual tissue[4,30].

Table 4 Spanish Score for risk of bleeding after endoscopic mucosal resection

	Age ≥ 75-yr-old	Lesion ≥ 40 mm	ASA III-IV	Location proximal to transverse colon	Aspirin	Clips
Yes	1	1	1	3	2	0
No	0	0	0	0	0	2
Risk of bleeding after EMR						
Low risk 0.6% (0.2%-1.8%)	0-3 points					
Medium risk 5.5% (3.8%-7.9%)	4-7 points					
Elevated risk 40% (21.8%-61.1%)	8-10 points					

ASA: American Society of Anesthesiologists classification of physical health; EMR: Endoscopic mucosal resection.

Table 5 Sydney endoscopic mucosal resection recurrence tool

Risk factor	Score
LST size ≥ 40 mm	2
IPB requiring endoscopic control	1
High-grade dysplasia	1
Total	4
Cumulative incidence of EDR% (standard error)	
SERT = 0	9.8% (2.2); 6 mo FU
	11.6% (2.5); 18 mo FU
SERT = 1-4	23.0% (2.5); 6 mo FU
	36.3% (3.2); 18 mo FU

EDR: Endoscopically determined recurrence; FU: Follow-up; IBP: Intraprocedural bleeding; LST: Laterally spreading tumor; SERT: Sydney endoscopic mucosal resection recurrence tool.

SPECIAL AND PROBLEMATIC SITUATIONS

The actual problems of EMR are the treatment of fibrotic tissues or non-lifting tissues as well as difficult areas for endoscopic resection.

Peri/intra-appendicular orifice lesions

In this scenario, EMR is a technical challenge because of difficult endoscopic access due to the narrow lumen of the appendix and thin colonic wall at the base of the cecum, which means a high risk of perforation. Nonetheless in expert hands, it is a safe and effective treatment, but if more than 50% of the circumference of the appendicular orifice (AO) is involved, then surgery should be considered[65]. As it is a narrow area, injection must be small to avoid narrowing the working field, and use of mini snares is helpful.

UEMR has been shown to enable safe resection of AO lesions, especially those limited to the rim. In a series of 27 consecutive patients with AO adenomas (median size 15 mm, range 8-50 mm), 89% successful resection was achieved, with 59% of lesions being resected en bloc. Post-polypectomy syndrome occurred in 7% of cases. No other complications occurred, and over a median follow-up of 29 wk only 10% of patients (n = 2) had residual adenoma present[66].

With underwater submersion, the appendix can partially evert into the cecal lumen, and the colonic lesion "floats" in a lumen filled with water. This allows endoscopic resection without previous submucosal injection, which makes lesions that affect the AO more accessible to endoscopic resection. To maximize tissue capture, contraction of the muscularis propria followed by the torque-and-crimp technique can be expected with the open loop[32]. In cases of residual tissue deep in the AO, a combination of air suction and more water infusion can help to evert residual tissue, making it accessible for snare resection[36].

ESD for lesions located in close proximity to the AO remains a challenging technique. In a retrospective study that included 76 lesions, en bloc resection was achieved in 72 (94.7%) and median tumor size was 36 mm (10-110 mm). One patient experienced intraoperative perforation, was treated by

clip closure, later developed appendicitis and underwent emergency ileocecal surgical resection; another patient experienced postoperative appendicitis and recovered with antibiotic treatment. Despite the challenges of working in the region of the cecum and AO, this study demonstrates that ESD performed by skilled and experienced endoscopists can be a safe and effective technique[67].

EFTR is another endoscopic treatment option. In a multicenter study in Germany that included 50 lesions, with mean size of 18 mm, EFTR was technically successful in 48 (96%), and R0 resection was achieved in 32 patients (64%). Post interventional appendicitis occurred in 7 patients (14%) during follow-up, and conservative treatment was sufficient in half of the cases[68]. The authors believe that the EFTR of appendicular lesions is a promising modality in a certain group of patients, but further studies are required to prospectively evaluate the feasibility and safety of this technique.

Islands or bridges of neoplastic tissue during EMR

A new injection and a mini/small snare should be tried. If it is not possible to snare, then sometimes the suction pseudopolyp technique or precutting with the tip of the snare around the non-lifting area may help. Otherwise, cold avulsion with forceps and snare tip soft coagulation/ablation of the scar area seems to be helpful in small areas of benign residual tissue. In this situation, UEMR and band ligation with or without resection can also be performed.

Scarred lesions

If it is not possible to resect with the inject and resect technique, then the non-lifting part of the lesion could be resected by cold avulsion (forceps), pre-cutting EMR[69], UEMR, ESD, EFTR[42] or surgery (the latter especially if there are suspicious areas of SMI). The same recommendation would apply to fibrotic lesions secondary to tattoo, multiple biopsies, the biology of the lesion or SMI, showing non-lifting sign, "jet sign" or canyoning. The authors find UEMR especially useful in this situation for benign lesions. As it is a "reversible" technique, if it is not suitable, then another technique like ESD or EFTR could be performed during the same session. If there is suspicion of malignancy, then surgery or EFTR might be preferable.

LST at the ileocecal valve

It is very important to define the borders of the lesion and if the ileum is involved, then sometimes a cap is helpful[27]. In cases of classic EMR, the amount of submucosal injection should be small if there is a flat lesion over the ileocecal valve to avoid excessive tension in the submucosal cushion since it is very easy that the snare slips while closing in this situation. A mini snare may be helpful when the ileum is involved. It is a safe procedure, and stenosis after EMR seems to be rare. Although it is complex, successful EMR seems to be greater than 90% in experienced hands. Extensive involvement of the terminal ileum or both ileocecal valve lips are associated with EMR failure[70]. UEMR is a good option, and the one preferred by the authors at this location.

Anorectal lesions

Because of the innervation in distal rectum, the use of long-acting local anesthetic (ropivacaine or bupivacaine) in the submucosal injectate (avoiding intravascular injection and requiring cardiac monitoring) for submucosal injection around the anorectal region and prophylactic antibiotics should be considered[28]. The use of a gastroscope for increased mobility and retroflexion may be helpful. It is safe to perform the endoscopic resection over the dentate line and hemorrhoidal columns. When performing ESD at this location, the operator should be aware that there could be muscular fibers on the submucosal layer on this location (it is the exception in the gastrointestinal tract).

Tough colonoscopy

It is a subjective term, which covers different situations, such as scope instability. Working using retroversion (easier with a gastroscope or a pediatric colonoscope) might stabilize the endoscope facilitating the resection sometimes. In the proximal colon, a distal attachment such as Endocuff or using a balloon enteroscope or a double balloon platform (Dilumen, Lumendi, Westport, Conn, United States) might help to stabilize the scope.

CONCLUSION

There are different endoscopic techniques for the resection of complex colorectal LST that the therapeutic colonoscopist should be aware of. EMR (inject and resect) is useful for most colorectal benign lesions. UEMR is a very useful technique since it avoids the need for submucosal injection. It might be a very good alternative in non-lifting lesions or in difficult locations like ileocecal valve, AO, narrow sigmoid or peridiverticular area where there is a narrow space where injection could make the access more difficult. ESD is the only technique that allows en bloc resection regardless of the size of the lesion, being especially useful for large LSTs that harbor risk for SMI, for example large LST with big

nodules in the rectosigmoid area. EFTR on the other hand is the technique that allows the deepest margins and because of that might be the best choice for endoscopic resection of less than 2.5 cm suspected malignant LST.

FOOTNOTES

Author contributions: Castillo-Regalado E wrote the paper; Uchima H wrote and reviewed the paper.

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

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S-Editor: Zhang H
L-Editor: A
P-Editor: Zhang H

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World Journal of Gastrointestinal Endoscopy

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World J Gastrointest Endosc 2022 March 16; 14(3): 129-141

DOI: 10.4253/wjge.v14.i3.129

ISSN 1948-5190 (online)

ORIGINAL ARTICLE

Retrospective Cohort Study

Endoscopic ultrasound-guided through-the-needle microforceps biopsy and needle-based confocal laser-endomicroscopy increase detection of potentially malignant pancreatic cystic lesions: A single-center study

Carlos Robles-Medranda, Juan I Olmos, Miguel Puga-Tejada, Roberto Oleas, Jorge Baquerizo-Burgos, Martha Arevalo-Mora, Raquel Del Valle Zavala, Joao Autran Nebel, Daniel Calle Loffredo, Hannah Pitanga-Lukashok

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): E

P-Reviewer: Altonbary AY, Egypt; Ryozawa S, Japan; Sugimoto M, Japan

Received: July 27, 2021
Peer-review started: July 27, 2021
First decision: November 11, 2021
Revised: December 15, 2021
Accepted: February 27, 2022
Article in press: February 27, 2022
Published online: March 16, 2022

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Abstract

BACKGROUND

Currently, there is insufficient data about the accuracy in the diagnosing of pancreatic cystic lesions (PCLs), especially with novel endoscopic techniques such as with direct intracystic micro-forceps biopsy (mFB) and needle-based confocal laser-endomicroscopy (nCLE).

AIM

To compare the accuracy of endoscopic ultrasound (EUS) and associated techniques for the detection of potentially malignant PCLs: EUS-guided fine needle aspiration (EUS-FNA), contrast-enhanced EUS (CE-EUS), EUS-guided fiberoptic probe cystoscopy (cystoscopy), mFB, and nCLE.

METHODS

This was a single-center, retrospective study. We identified patients who had undergone EUS, with or without additional diagnostic techniques, and had been diagnosed with PCLs. We determined agreement among malignancy after 24-mo follow-up findings with detection of potentially malignant PCLs *via* the EUS-guided techniques and/or EUS-guided biopsy when available (EUS malignancy detection).

RESULTS

A total of 129 patients were included, with EUS performed alone in 47/129. In 82/129 patients, EUS procedures were performed with additional EUS-FNA (21/82), CE-EUS (20/82), cystoscopy (27/82), mFB (36/82), nCLE (44/82). Agreement between EUS malignancy detection and the 24-mo follow-up findings was higher when associated with additional diagnostic techniques than EUS alone [62/82 (75.6%) *vs* 8/47 (17%); OR 4.35, 95%CI: 2.70-7.37; $P < 0.001$]. The highest malignancy detection accuracy was reached when nCLE and direct intracystic mFB were both performed, with a sensitivity, specificity, positive predictive value, negative predictive value and observed agreement of 100%, 89.4%, 77.8%, 100% and 92.3%, respectively ($P < 0.001$ compared with EUS-alone).

CONCLUSION

The combined use of EUS-guided mFB and nCLE improves detection of potentially malignant PCLs compared with EUS-alone, EUS-FNA, CE-EUS or cystoscopy.

Key Words: Pancreatic cysts; Endoscopic ultrasound-guided fine-needle aspiration; Confocal microscopy; Image-guided biopsy

Core Tip: This retrospective study compared the accuracy of endoscopic ultrasound (EUS) and associated techniques such as EUS-guided fine needle aspiration (EUS-FNA), contrast-enhanced EUS (CE-EUS), EUS-guided fiberoptic probe cystoscopy (cystoscopy), EUS-guided direct intracystic micro-forceps biopsy (mFB), and EUS-guided needle-based confocal laser-endomicroscopy (nCLE) for the detection of potentially malignant pancreatic cystic lesions (PCLs) in 129 patients. Patients were allocated to three cohorts: those evaluated *via* EUS alone; *via* EUS-FNA, CE-EUS and/or cystoscopy; and with mFB plus nCLE. We observed that combining EUS, mFB, and nCLE had a statistically significant improved detection of potentially malignant PCLs compared to any of the evaluated techniques alone.

Citation: Robles-Medranda C, Olmos JI, Puga-Tejada M, Oleas R, Baquerizo-Burgos J, Arevalo-Mora M, Del Valle Zavala R, Nebel JA, Calle Loffredo D, Pitanga-Lukashok H. Endoscopic ultrasound-guided through-the-needle microforceps biopsy and needle-based confocal laser-endomicroscopy increase detection of potentially malignant pancreatic cystic lesions: A single-center study. *World J Gastrointest Endosc* 2022; 14(3): 129-141
URL: https://www.wjgnet.com/1948-5190/full/v14/i3/129.htm
DOI: https://dx.doi.org/10.4253/wjge.v14.i3.129

INTRODUCTION

The incidence of pancreatic cystic lesions (PCLs) is rising mainly in elderly patients[1]. Therefore, early detection of potentially malignant PCLs increases the possibility of a curative approach. Current American Gastroenterological Association guideline recommends magnetic resonance imaging (MRI) or magnetic resonance cholangiopancreatography (MRCP) to assess PCLs[2]. For the same purpose, the revised Fukuoka guideline recommend computerized tomography (CT), MRI or MRCP, keeping endoscopic ultrasound guided fine-needle aspiration (EUS-FNA) for intraductal papillary mucinous neoplasm (IPMN) evaluation[3]. Nevertheless, both guidelines showed an unsatisfactory pooled sensitivity for malignant PCLs of 64% and 59%, respectively[4].

EUS is the most sensitive diagnostic method for detecting potentially malignant pancreatic lesions with an 88.5% sensitivity; yet it holds a 52.9% specificity and a higher inter-observer variability. Thus, EUS alone has very low diagnosability capacity[5-7]. Similarly, a considerable number of PCLs cannot be characterized by CT, MRI or MRCP alone[8,9]. EUS-guided diagnostics techniques increase EUS accuracy for differentiating PCLs, namely: (1) EUS-FNA; (2) Contrast-enhanced EUS (CE-EUS); (3) Fiberoptic probe cystoscopy (cystoscopy); (4) EUS-guided through-the-needle direct intracystic micro forceps biopsy (mFB); and (5) EUS-guided confocal laser endomicroscopy (nCLE)[9].

EUS-FNA allows biopsy of suspicious lesions and cytological and biochemical cystic fluid analysis [7]. Whereas, CE-EUS help to differentiate between solid *vs* PCLs, by detecting enhanced septa or nodules present within cystic lesions[10]. Through-the-needle fiberoptic probe cystoscopy requires a 19-gauge needle guided by EUS to locate and enter the PCL. Then, the preloaded fiberoptic probe is advanced, allowing visualization of the cyst content as cystic wall features[11]. The microforceps device samples tissue from the cyst's wall, septations, and/or mural nodules and thus increase cellular yield [12]. Furthermore, nCLE characterizes PCLs type by imaging the intact cyst architecture, targeting

abnormal areas and reducing unnecessary sampling of surrounding tissue, with a diagnostic accuracy of 80% to 95%[8].

Given the poor prognosis of malignant pancreatic lesions, determining the best diagnostic approach for early detection of potential malignancy among the variety of newly available EUS-related technology is essential. Therefore, we aimed to compare the accuracy of EUS for detection of potentially malignant PCLs when it is performed alone, EUS-FNA, CE-EUS or cystoscopy and associated with novel EUS-related techniques: mFB and nCLE. We hypothesize that EUS-guided through-the-needle mFB and nCLE may increase malignancy detection during EUS assessment of pancreatic cysts.

MATERIALS AND METHODS

Study design

The following is an observational, analytic, longitudinal, retrospective cohort and single-center study performed at the Instituto Ecuatoriano de Enfermedades Digestivas (IECED), a tertiary center in Ecuador. The study protocol and informed consent documents were approved by the institutional review board, and the study was conducted in accordance with the Declaration of Helsinki. Selected patients signed corresponding informed written consent for healthcare purposes.

Population selection

Records from patients older than 18 years of age who underwent EUS at IECED from January 2013 to March 2018 were extracted from the institutional database. Cases with non-pancreatic lesions were excluded. Patients were allocated to three cohorts: (1) Patients who had been evaluated *via* EUS alone; (2) Patients who had been evaluated with EUS-FNA, CE-EUS and/or cystoscopy; and (3) Those evaluated with novel EUS-related techniques: mFB and nCLE.

Endoscopic techniques malignancy criterion for pancreatic cystic lesions

Due to sparse cellularity of acquired specimens, several complementary clinical, radiological, and imaging techniques are required to achieve PCLs definitive diagnosis. PCLs with potential to progress to malignancy mainly IPMN, mucinous cystic neoplasms (MCN), and neuroendocrine tumors (c-NET) with cystic degeneration. Identifying malignancy features for these lesions with EUS, CE-EUS, cystoscopy, nCLE, FNA, and mFB include the following:

EUS: Presenting two out of the three following characteristics was considered as increased risk for malignancy criteria: main pancreatic duct dilation between 5-9 mm (10 mm high risk stigmata for malignancy), PCLs size > 3 cm, and mural nodules presence[3,13].

CE-EUS: A thick/hyper-enhancing wall/septum, enhancing solid component within a cyst, or an enhancing mural nodule favors malignancy criterion. Furthermore, there is a radiological correlation between pancreatic duct communication and IPMN diagnosis, but not MCN. Also, main duct type IPMNs hold a higher risk of malignancy transformation than branch duct type IPMNs (up to 68% *vs* 22%, respectively). MCN may show peripheral calcifications within multilocular septate lesions[3,14].

Cystoscopy: Cloudy fluid and a smooth cyst wall identify MCN, while finger-like projections and a mucin cloud are perceived with IPMN through single-operator cholangioscopy (SOC)[11,14].

nCLE: Prone to malignancy lesions may depict epithelial or vascular patterns in nCLE[5,8,11,13,15]. nCLE Epithelial patterns: MCN show epithelial borders with a flat mosaic appearance (single or multiple layers of epithelial bands). IPMN exhibit dark rings and papillary projections. c-NET portray a trabecular pattern (fibrous bands separating cells nests). nCLE Vascular patterns: MCN, IPMN and cystic-NET may show a branched pattern; IPMN and MCN may also display a rope-ladder pattern[5].

EUS-FNA and EUS-mFB are resources for tissue sample extraction. For these techniques, cytology should be assessed in the context of radiological and clinical findings[3,11,14]. Low and high-grade IPMN dysplasia should be distinguished as the latter may easily become invasive. Low-grade IPMN: may resemble normal gastric epithelium. High-grade IPMN may show a cell size ≤ 12 μm, hypo/hyperchromasia, background necrosis, nuclear irregularity, large single vacuolated cells, and increased nuclear to cytoplasmic ratio[14].

IPMNs histologic examinations exhibit four possible morphologies: gastric (columnar cells lining papillae with basally located nuclei rich in apical mucin), intestinal (similar morphology to colonic villous adenomas with cigar shaped nuclei and variable apical mucin amount), pancreaticobiliary (more complex papillae composed of rounded nuclei cuboidal cells with some prominent nucleoli), and oncocytic (complex papillae lined with round cells with granular eosinophilic cytoplasm and prominent central nucleoli)[3,14].

MCNs also display low and high-grade dysplasia features. While bland mucin-containing epithelium honeycomb sheets are seen with low-grade MCNs, a complex papillary structure with smooth nuclear contour mucin-containing cells, inconspicuous nucleoli, and fine chromatin is found in high-grade

MCNs. On histologic examination, MCNs show focally flat o cuboidal lining and tall mucin-containing epithelium, with a densely ovarian-type stroma wall that positively stains for progesterone/estrogen receptors, calretinin, and inhibin[3,14].

C-NET aspirate display classic endocrine morphology (pseudorosettes, isolated, and loosely cohesive groups of round/polygonal cells with finely stippled chromatin round nucleus)[5,11,14,15]. Immunostains (chromogranin, CD10, vimectin, and β-catenin cytoplasmic expression) provide a definitive diagnosis[14].

Endoscopic techniques methods

Three experienced endosonographers (C.R-M., J.O., R.V.) performed all EUS evaluations, under general anesthesia with patients in the supine position and use of antibiotic prophylaxis. EUS procedures were performed with a linear-array video echoendoscope (EG-3870 UTK, Pentax Medical, Montalve, NJ, United States) attached to an ultrasound console (HI VISION Avius®, Hitachi Medical Systems, Steinhaus, Switzerland). Indication of EUS-related techniques was based on endosonographers discretion. Although more techniques are available to perform on larger cysts (> 3 cm).

Endoscopic ultrasound fine needle aspiration: EUS-FNA was performed with a 19-gauge needle (Expect™ Slimline, Boston Scientific, Malborough, United States) (Figure 1A). The cystic fluid was examined for tumor markers (amylase, lipase, carcinoembryonic antigen levels).

Contrast enhanced endoscopic ultrasound: To display cystic wall and nodule vascularization, 4.8 mL of SonoVue® (Braccio, Milan, Italy) was used for CE-EUS. Cystic wall and nodule vascularization were defined as visible contrast enhancer bubble movement within the cystic wall, septum, and nodules (Figure 1B), and were referred for further diagnosis with EUS-FNA.

Cystoscopy: Examinations were performed by using a linear-array video echoendoscope attached to an ultrasound console, as previously described. A SOC fiber optic probe (Legacy SpyGlass® fiber optic, Boston Scientific, Marlborough, United States) was inserted through the 19-gauge needle into the cystic cavity to observe the intracystic wall and contents (Figure 1C).

EUS-guided through-the-needle direct intracystic micro forceps biopsy: The target lesion was identified under EUS and punctured with a 19-gauge FNA needle. With the needle inside the lesion, the stylet was removed, and the micro forceps (Moray™ micro forceps, STERIS, Mentor, United States) were inserted through the needle for tissue sampling. Two to three bites of biopsy specimens were taken with each pass of the micro forceps. The tissue acquisition was visually confirmed and directly placed on formalin containers for pathologic evaluation.

EUS-guided confocal laser endomicroscopy: After EUS examination, patients were intravenously injected with 5 mL of 10% fluorescein (BioGlo®, Sofar Productos, Bogota, Colombia) 2 to 3 min before nCLE imaging. CLE was performed using the AQ-Flex nCLE miniprobe (Cellvizio, Mauna Kea Technologies, Paris, France). The probe was advanced through the locking device into the 19-gauge needle. The preloaded needle was advanced under EUS guidance into the PCL. The tip of the nCLE probe was placed in contact with the intracystic epithelium, and intracystic endomicroscopic images were captured (Video 1and Video 2). After image acquisition, the nCLE probe was withdrawn, and the PCL was aspirated.

Data abstraction

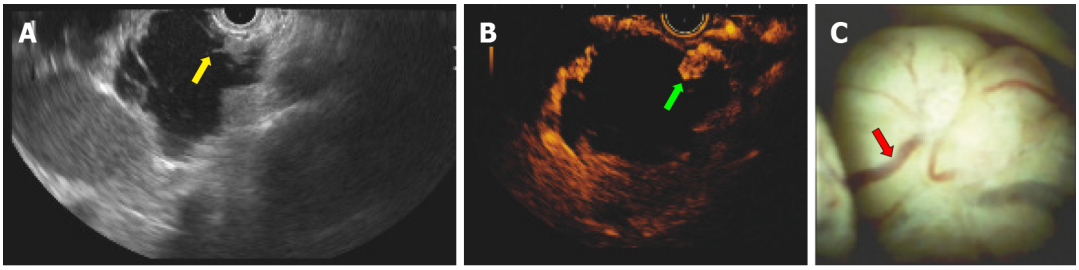
Demographic, clinic, endoscopic and histopathological and 24-mo follow-up data were obtained from the institutional database and phone calls when necessary. The study endpoint was to determine agreement between detection of potentially malignant in PCLs (EUS malignancy detection) and malignancy after 24-mo follow-up. EUS malignancy detection was defined based on procedure findings (EUS-alone, CE-EUS, cystoscopy and/or nCLE) reported on endoscopic records, as well as EUS-FNA and/or EUS-mFB aquired biopsy results when available. PCLs were classified as malignant (MCN, IPMN and c-NET) according to Fukuoka criteria. This data was recovered by two endoscopists (C.R.M. and H.P-L.). Malignancy after 24-mo follow-up was based on clinical outcomes, endoscopic surveillance, or surgical specimen histopathology when available. This data was recovered by two general practitioners (R.O. and J.B-B.) and a general surgeon (D.C-L.) who were blinded to information concerning to EUS malignancy detection.

Interobserver agreement

An offline interobserver analysis (IOA) of the EUS criteria (EUS borders, lobularity, wall, microcyst component, diagnosis, and level of confidence) was performed by three endoscopists (J.O., R.V. and J.N.) using a randomly selected EUS image set (n = 111 cases) collected by C.R-M.

Statistical analysis

Technical considerations: Final database was consolidated and encrypted by M.A-M. Data analysis was performed by IECED Institutional Biostatistician (M.P-T.) using R v.4.0 (R Foundation for Statistical



DOI: 10.4253/wjge.v14.i3.129

Figure 1 Case No. 13: A 77 years old woman with a pancreatic cyst lesion corresponding to an intraductal papillary mucinous neoplasm. The lesion exhibited malignancy criteria at endoscopic ultrasound (EUS) and related techniques. A: EUS identifying a 4 cm pancreatic cyst lesion with mural nodules (yellow arrow); B: Mural nodule with hyper-enhancing at EUS (green arrow) shown in contrast-enhanced EUS; C: EUS-guided cystoscopy using a digital probe showing vascularity (red arrow) of a pancreatic macrocystic lesion filled with clear fluid.

Computing, Vienna, Austria). A *P*-value <0.05 was considered statistically significant.

Sample size calculation: We considered a 100% specificity of EUS + nCLE for the prediction of potentially malignant PCLs, with a 35% disease prevalence (6/31 mucinous cystic neoplasm and 5/31 IPMNs) for defining the sample size (16). We estimated a sample size of 25 patients for each cohort, with an α and β-error of 5% and 20% respectively, and an 80% statistical power.

Descriptive analysis: Numeric variables were described through the mean ± SD or median (minimum-maximun range) in accordance with statistical distribution (Kolmógorov-Smirnov test). Categorical variables were described with frequency (%), and 95%CI when corresponding. Descriptions about techniques combination was summarized on a Venn Diagram (17).

Inferential analysis: Observed agreement between EUS malignancy detection and malignancy after 24-mo follow-up was established. The statistical association between EUS alone or EUS with an additional endoscopic technique *vs* the positive observed agreement described above was determined by binary logistic regression [odds ratio (OR)]. A univariate analysis was performed for each individual technique. Those with a significant association were entered into the multivariate analysis. The overall diagnostic accuracy for malignancy detection was determined for each diagnostic procedure which shown significance on multivariate analysis, considering a 24-mo follow-up as gold standard. Overall diagnostic accuracy comprehended calculation of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio, negative likelihood ratio, and observed agreement. For multivariate analysis discrimination, we estimated the corresponding area under the receiver operating characteristics (AUROC) curves and contrasting using the DeLong's test for two ROC curves. The IOA of the EUS criteria was performed using Fleiss' kappa score (κ) calculation and interpreted based on Landis and Koch criteria.

RESULTS

Patient selection

A total of 2812 patients were referred to our unit for diagnostic EUS along study period. Of these, 856 had pancreatic lesions, of which 129 patients with PCLs were included for analysis (n = 129) (Figure 2).

Baseline characteristics

The median age of the 129 patients with PCLs was 69 years, and 69.8% patients were female. The most frequent pancreatic cyst location was the head of the pancreas (35.7%). Younger patients were significantly evaluated with EUS and an additional novel technique (mFB and/or nCLE) in comparison to those evaluated with EUS alone, EUS-FNA, CE-EUS or cystoscopy (P < 0.001). Cysts size above 30 mm were reported among patients evaluated with EUS and an additional novel technique (46.3%) compared with general cohort (27.1%; P < 0.001). There were no statistically significant differences when comparing gender and PCLs location between patients evaluated with EUS alone and those evaluated with EUS plus additional diagnostic techniques (Table 1).

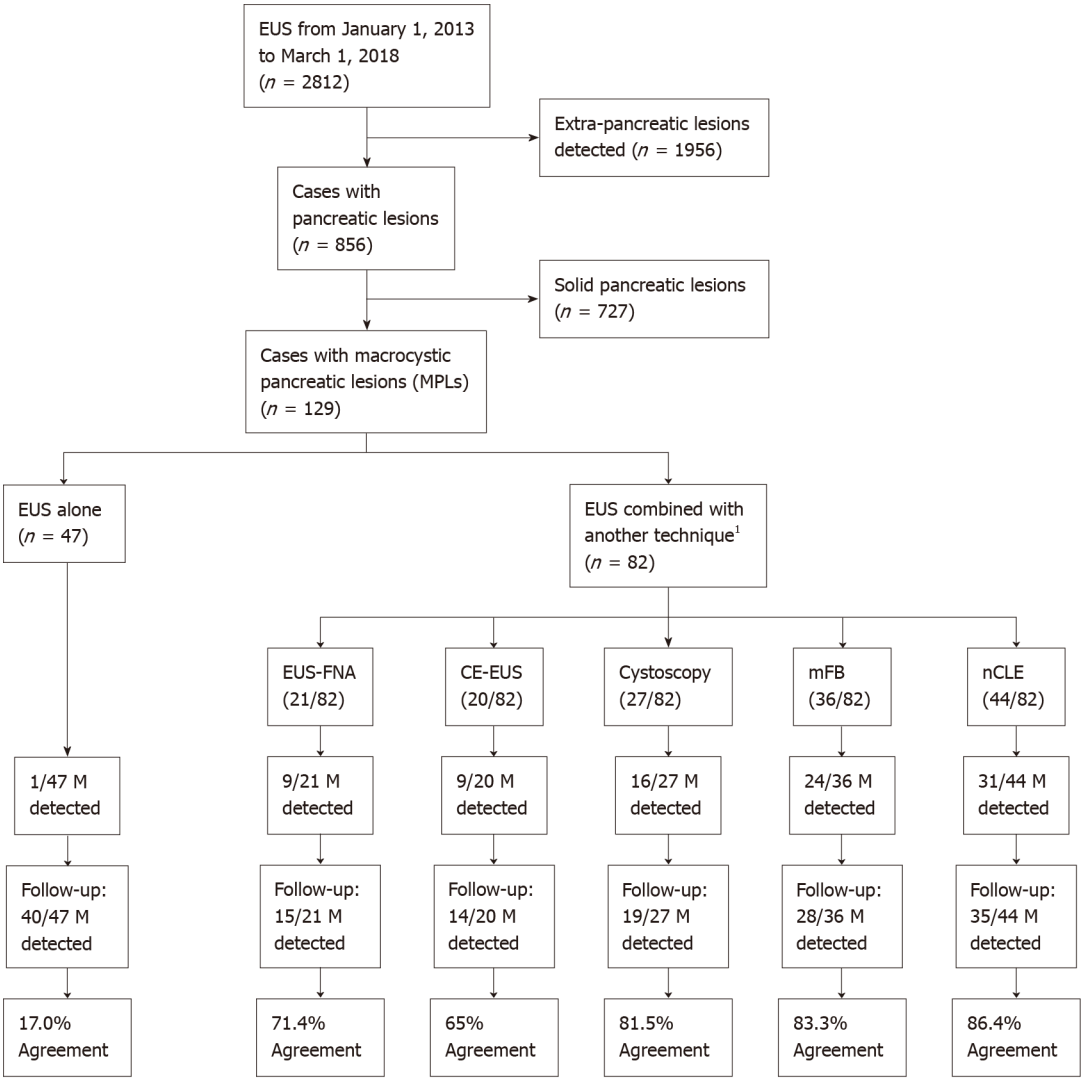
EUS was performed with an additional diagnostic technique in 82/129 patients: EUS-FNA [21/82 (25.6%)], CE-EUS [20/82 (24.4%)], cystoscopy [27/82 (32.9%)], mFB [36/82 (43.9%)], and nCLE [44/82 (53.7%)]. More than one diagnostic technique was performed in a sample proportion (Figure 3). A 100% technical success was reached, with no documented adverse events for any of the performed procedures.

Table 1 Baseline characteristics and clinical 24-mo follow-up outcome of included patients

	Total (*n* = 129)	EUS alone (*n* = 47)	EUS + FNA/CE/ Cystoscopy (*n* = 28)	EUS + mFB/nCLE (novel techniques) (*n* = 54)	*P* value
Age (yr), median (range)	69 (26-97)	71 (29-97)	78 (49-92)	59 (27-97)	< 0.001[a]
Sex (female), *n* (%)	90 (69.8)	33 (70.2)	19 (67.0)	38 (70.4)	0.9694[b]
Pancreatic cyst location, *n* (%)					0.6258[b]
Uncinate process	3 (2.3)			3 (5.6)	
Head	46 (35.7)	17 (36.2)	9 (32.1)	20 (37.0)	
Neck	13 (10.1)	3 (6.4)	4 (14.3)	6 (11.1)	
Body	36 (27.9)	14 (29.8)	8 (28.6)	14 (25.9)	
Tail	31 (24.0)	13 (27.7)	7 (25.20)	11 (20.4)	
Cyst size (mm), *n* (%)					
< 10 mm	33 (25.6)	29 (61.7)	1 (3.6)	3 (5.6)	< 0.001[b]
10-30 mm	61 (47.3)	16 (34.0)	19 (67.9)	26 (48.1)	
> 30 mm	35 (27.1)	2 (4.3)	8 (28.6)	25 (46.3)	
Additional endoscopic procedure used for diagnosis[1], *n* (%)					-
EUS-FNA	21 (16.3)		17 (60.7)	4 (7.4)	
CE-EUS	20 (15.5)		11 (39.3)	9 (16.7)	
Cystoscopy	27 (20.9)		1 (3.6)	26 (48.1)	
mFB	36 (27.9)			36 (66.7)	
nCLE	44 (34.1)			44 (81.5)	
Pancreatic cyst diagnosis, *n* (%)					< 0.001[b]
Malignant[2]	81 (62.8)	46 (97.9)	19 (67.9)	16 (29.6)	
Mucinous cystadenocarcinoma	6 (4.7)	1 (2.1)	4 (14.3)	1 (1.9)	
Mucinous cystadenoma	4 (3.1)		1 (3.6)	3 (5.6)	
Intraductal papillary mucinous neoplasm	70 (54.3)	45 (95.7)	14 (50.0)	11 (20.4)	
Neuroendocrine	1 (0.8)			1 (1.9)	
Non-malignant[2]	48 (37.2)	1 (2.1)	9 (32.1)	38 (70.4)	
Serous cystadenoma	46 (35.7)	1 (2.1)	9 (32.1)	36 (66.7)	
Pseudocysts	2 (1.6)			2 (3.7)	
24-mo follow-up, *n* (%)					0.0351[b]
Malignant	28 (21.7)	7 (14.9)	11 (39.3)	10 (18.5)	
Non-malignant	101 (78.3)	40 (85.1)	17 (60.7)	44 (81.5)	
Positive observed agreement between EUS-guided biopsy *vs* 24-mo follow-up for malignancy detection, *n* (%)	70 (54.3)	8 (17.0)	18 (64.3)	44 (81.5)	< 0.001[b]

[a]Kruskal-Wallis rank sum test.
[b]Pearson's Chi-squared test.
[1]Additional endoscopic procedures are not mutually exclusive.
[2]Cases with histopathological confirmation met the Fukuoka criteria.
EUS: Endoscopic ultrasound; EUS-FNA: Endoscopic ultrasound-guided fine needle aspiration; Cystoscopy: Fiberoptic probe cystoscopy; nCLE: Endoscopic ultrasound-guided needle-based confocal laser-endomicroscopy; mFB: Endoscopic ultrasound-guided through-the-needle direct intracystic micro forceps biopsy; CE-EUS: Contrast-enhanced endoscopic ultrasound.

According to the PCLs EUS findings and guided biopsy when available (*n* = 53), potentially malignant PCLs were detected in 81/129 (62.8%) patients, and the most frequent lesion among this group was IPMN [70/129 (54.3%)]. In the nonmalignant group [48/129 (37.2%)], 46 cases were serous cystadenomas (Table 1). Observed agreement between EUS malignancy detection and malignancy after



DOI: 10.4253/wjge.v14.i3.129

Figure 2 Population study flowchart. [1]Numbers of techniques were not mutually exclusive. Endoscopic ultrasound could be combined with more than one other technique, as shown on the illustrated Venn diagram in Figure 3. EUS: Endoscopic ultrasound; EUS-FNA: Endoscopic ultrasound-guided fine needle aspiration; Cystoscopy: Fiberoptic probe cystoscopy; nCLE: Endoscopic ultrasound-guided needle-based confocal laser-endomicroscopy; mFB: Endoscopic ultrasound-guided through-the-needle direct intracystic micro forceps biopsy; CE-EUS: Contrast-enhanced endoscopic ultrasound; M: Malignancy.

24-mo follow-up was higher in patients evaluated with EUS plus at least one additional novel technique (mFB and/or nCLE), followed by EUS-FNA, CE-EUS and or cystoscopy; than in patients evaluated with EUS alone [42/55 (80.0%) *vs* 18/27 (66.7%) *vs* 8/47 (17%), respectively; OR 4.35, 95%CI: 2.70-7.37; $P < 0.001$].

Univariable and multivariable analysis

Independently, there was a positive statistical association and observed agreement for EUS malignancy detection with cystoscopy, mFB or nCLE, and 24-mo follow-up. EUS-FNA and CE-EUS exhibited a positive but nonsignificant association; whereas EUS alone only presented a negative significantly association [OR 0.066 (0.025-0.157; $P < 0.001$)] when considering the agreement between EUS malignancy detection and malignancy after 24-mo follow-up as an outcome.

Through multivariate analysis, we confirmed that malignancy detection was significantly more accurate with nCLE [OR 8.441 (2.698-33.081; $P < 0.001$)] and mFB [OR 3.425 (1.104-11.682; $P = 0.038$)] than cystoscopy [OR 0.622 (0.125-2.813; $P = 0.541$)] (Table 2).

Diagnostic accuracy for determining malignancy

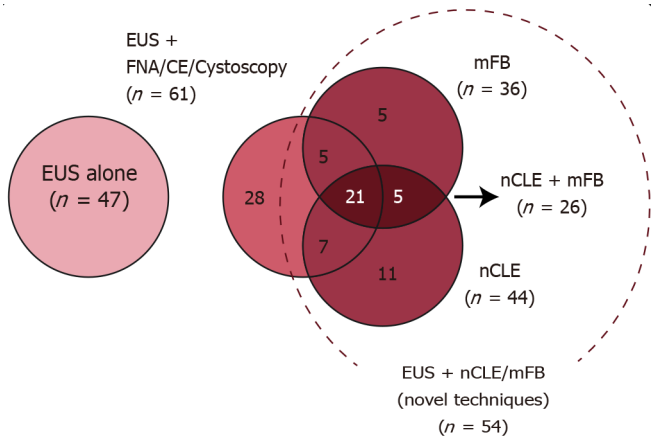
EUS alone was performed in 47 cases and had a sensitivity, specificity, PPV, and NPV of 100%, 3%, 15%, and 100%, respectively. EUS-FNA, CE-EUS, and/or cystoscopy was performed in 28 cases and had a sensitivity, specificity, PPV, and NPV of 91%, 47% 53% and 89%, respectively. EUS with nCLE and mFB yielded similar results for sensitivity (89% *vs* 88%), specificity (86% *vs* 82%), PPV (62% *vs* 58%) and NPV (97% *vs* 96%). When the three techniques were simultaneously performed (EUS with nCLE and mFB, *n*

Table 2 Association between different additional performed techniques *vs* a positive observed agreement for malignancy diagnosis among endoscopic ultrasound and endoscopic ultrasound-related techniques *vs* 24-mo follow-up [OR (95%CI; *P* value)]

	Univariate analysis[1]	Multivariate analysis[1]
EUS alone (*n* = 47)	0.066 (0.025-0.157; < 0.001)	
EUS-FNA (*n* = 21)	2.409 (0.905-7.182; 0.091)	
CE-EUS (*n* = 20)	1.694 (0.642-4.811; 0.298)	
Cystoscopy (*n* = 27)	4.950 (1.862-15.695; 0.003)	0.622 (0.125-2.813; 0.541)
mFB (*n* = 36)	6.625 (2.667-19.024; < 0.001)	3.425 (1.104-11.682; 0.038)
nCLE (*n* = 44)	10.489 (4.242-30.125; < 0.001)	8.441 (2.698-33.081; < 0.001)

[1]Positive observed agreement: In 70/129 (54.3%) there was a positive agreement between endoscopic ultrasound *vs* 24-mo follow-up for a malignant and non-malignant diagnosis.

EUS: Endoscopic ultrasound; EUS-FNA: Endoscopic ultrasound-guided fine needle aspiration; Cystoscopy: Fiberoptic probe cystoscopy; nCLE: Endoscopic ultrasound-guided needle-based confocal laser-endomicroscopy; mFB: Endoscopic ultrasound-guided through-the-needle direct intracystic micro forceps biopsy; CE-EUS: Contrast-enhanced endoscopic ultrasound.



DOI: 10.4253/wjge.v14.i3.129

Figure 3 Venn diagram describing distribution of additional diagnostic techniques performed in the studied population. EUS: Endoscopic ultrasound; EUS-FNA: Endoscopic ultrasound-guided fine needle aspiration; Cystoscopy: Fiberoptic probe cystoscopy; nCLE: Endoscopic ultrasound-guided needle-based confocal laser-endomicroscopy; mFB: Endoscopic ultrasound-guided through-the-needle direct intracystic micro forceps biopsy; CE-EUS: Contrast-enhanced endoscopic ultrasound.

= 26), the diagnostic accuracy analysis showed that the sensitivity, specificity, PPV, and NPV were 100%, 89%, 78%, and 100%, respectively. MCC identified a good correlation between EUS malignancy detection and malignancy after the 24-mo follow-up through different techniques. Nonetheless, EUS paired with nCLE and mFB showed the highest agreement (MCC = 0.83) (Table 3).

Detection of potentially malignant PCLs using EUS alone reached a 51.3% AUROC (P = 0.3599; moderate agreement). Meanwhile, EUS-guided mFB, nCLE or/and mFB reached an 87.3% AUROC (P < 0.001), 84.8% (P < 0.001) and 94.7% (P < 0.001), respectively. In addition, nCLE reached a greater AUROC in comparison to EUS alone (P < 0.001) (Figure 4A). Moreover, a significantly higher AUROC was described for combined EUS-guided nCLE and mFB in comparison to EUS-FNA/CE-EUS/cystoscopy (94.7% *vs* 69%, P = 0.044) (Figure 4B).

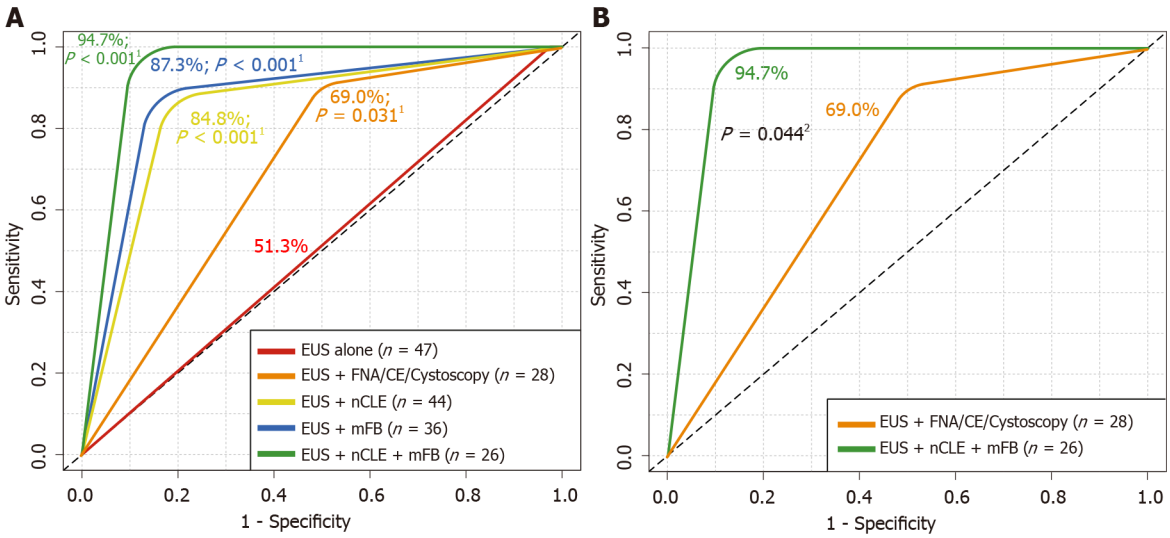
Interobserver agreement

In the secondary IOA performed by three experienced endoscopists, the κ values in EUS borders, lobularity, wall, microcyst component, diagnosis, and level of confidence were as follows: 0.12 (poor agreement), 0.08 (poor agreement), 0.04 (poor agreement), 0.29 (fair agreement), 0.21 (fair agreement), and 0.06 (poor agreement) respectively.

Table 3 Overall diagnostic accuracy for determining malignancy [% (95%CI)]

	EUS alone (*n* = 47)	EUS + FNA/CE/ Cystoscopy (*n* = 28)	EUS + mFB (*n* = 36)	EUS + nCLE (*n* = 44)	EUS + nCLE + mFB (*n* = 26)
Sensitivity	7/7; 100.0% (59.3-100.0)	10/11; 90.9% (58.7-99.8)	7/8; 87.5% (47.3-99.7)	8/9; 88.8%; (51.8-99.7)	7/7; 100.0% (59.0-100.0)
Specificity	1/40; 2.5% (0.1-13.2)	8/17; 47.1% (22.9-72.3)	23/28; 82.1% (63.1-93.9)	30/35; 85.7% (69.7-95.2)	17/19; 89.4% (66.9-98.7)
PPV	7/46; 15.2% (6.3-28.9)	10/19; 52.6% (28.9-75.6)	7/12; 58.3% (27.7-84.8)	8/13; 61.5% (31.6-86.1)	7/9; 77.8% (40.0-97.1)
NPV	1/1; 100.0% (2.5-100.0)	8/9; 88.9% (51.8-99.7)	23/24; 95.8% (78.9-99.8)	30/31; 97% (83-100)	17/17; 100.0% (80.5-100.0)
PLR	1.03 (0.98-1.08)	1.72 (1.06-2.79)	4.90 (2.12-11.31)	6.22 (2.68-14.47)	9.50 (2.56-35.24)
NLR	n/a	0.19 (0.03-1.34)	0.15 (0.02-0.96)	0.13 (0.02-0.83)	n/a
Observed agreement	8/47 (17%); *P* = 0.672[a]	18/28 (64.3%); *P* = 0.049[a]	30/36 (83.3%); *P* < 0.001[a]	38/44 (86.4%); *P* < 0.001[a]	24/26 (92.3%); *P* < 0.001[a]
MCC	+ 0.06	+ 0.40	+ 0.61	+ 0.66	+ 0.83
AU-ROC	51.3%; *P* = 0.359[b]	69.0%; *P* = 0.02[b]	84.8%; *P* < 0.001[b]	87.3%; *P* < 0.001[b]	94.7%; *P* < 0.001[b]

[a]Fisher's exact test for count data.
[b]Mann–Whitney U test.
EUS: Endoscopic ultrasound; nCLE: Confocal laser endomicroscopy; mFB: Endoscopic ultrasound-guided through-the-needle direct intracystic micro forceps biopsy; PPV: Positive predictive value; NPV: Negative predictive value; PLR: Positive likelihood ratio; NLR: Negative likelihood ratio; MCC: Matthews correlation coefficient; AU-ROC: Area under the receiver operating characteristics curve; n/a: Not available.



DOI: 10.4253/wjge.v14.i3.129

Figure 4 Received operating characteristics describing overall diagnostic accuracy of endoscopic ultrasound alone and in addition with fine needle aspiration or contrast-enhanced endoscopic ultrasound, needle-based confocal laser-endomicroscopy and/or with direct intracystic micro forceps biopsy for detecting malignancy. A: Comparison among endoscopic ultrasound (EUS) alone *vs* additional diagnostic techniques; B: Comparison among EUS alone *vs* EUS + EUS-guided needle-based confocal laser-endomicroscopy (nCLE) + EUS-guided through-the-needle direct intracystic micro forceps biopsy (mFB). [1]DeLong's test for two received operating characteristics (ROC) curves comparing EUS-alone area under the ROC curve (red line) with EUS + fine needle aspiration (FNA)/contrast-enhanced (CE) (orange line), EUS + nCLE (yellow line), EUS + mFB (blue line) and EUS + nCLE + mFB (green line). [2]DeLong's test for two ROC curves comparing EUS + FNA/CE (orange line) with EUS + nCLE + mFB (green line). EUS: Endoscopic ultrasound; FNA: Fine needle aspiration; Cystoscopy: Fiberoptic probe cystoscopy; nCLE: Endoscopic ultrasound-guided needle-based confocal laser-endomicroscopy; mFB: Endoscopic ultrasound-guided through-the-needle direct intracystic micro forceps biopsy; CE: Contrast-enhanced.

DISCUSSION

Various clinically-available advanced EUS-guided diagnostic techniques have improved the accuracy of malignancy detection among PCLs; however, these techniques are not referenced in current guidelines, with unsatisfactory diagnostic accuracy in the risk stratification of potentially malignant PCLs[4].

To provide guidance on the relative accuracy and effectiveness of these new EUS-related techniques, we compared various additional endoscopic techniques during the EUS evaluation of PCLs. We evaluated the accuracy of EUS alone with more recent EUS-related techniques, namely EUS-FNA, cystoscopy, nCLE, mFB, and CE-EUS and found that the highest level of malignancy detection can be achieved when EUS is combined with both nCLE and direct intracystic mFB.

An increasing number of PCLs have been identified due to the growing use of complementary diagnostic techniques, such as CT and MRI; moreover, the malignancy potential of PCLs vary, and current diagnostic techniques cannot characterize the lesions with precision by their self[18-20]. Due to the malignancy potential, patients with pancreatic neoplasms are recommended to undergo resection therapy; however, for patients with a high risk of postsurgical complications, preoperative determination of malignancy is critical for management guidance.

In our study, EUS alone had a low agreement in comparison to the 24-mo follow-up. Also, in an offline interobserver agreement between three endosonographers, endoscopic criteria showed low agreement between operators, as previously described. Therefore, EUS itself should be complemented with additional endoscopic techniques for a more accurate detection of malignancy in PCLs.

Wang *et al*[21] demonstrated that EUS-FNA can accurately confirm the presence of malignancy but does not perform well at excluding malignant or premalignant pancreatic lesions. This procedure achieved a pooled sensitivity and specificity of 51%, 94%, respectively, for differentiating malignant lesions. In our study, which included 21/129 patients with pancreatic lesions for whom FNA was performed, we found that EUS-FNA did not achieve statistical significance in detecting malignancy with a modest agreement with the 24-mo follow-up; however, this may be due a limited number of cases in our cohort.

The DETECT trial revealed that a combination of through-the-needle cystoscopy and nCLE for PCLs under EUS was feasible, with a sensitivity of 90% for cystoscopy in the clinical diagnosis of MCNs, an 80%sensitivity for nCLE, and a 100% sensitivity for the combination of both[11]. In our study, we analyzed both techniques (separately and then combined) and obtained similar results – we obtained a sensitivity of 89% for EUS-guided-nCLE and 88% for EUS-guided through-the-needle cystoscopy; however, the sensitivity of EUS-guided nCLE combined with mFB was 78%. Additionally, in our cohort, we had more heterogenic lesions than in the DETECT trial, which was limited to mucinous lesions.

Haghighi *et al*[8] compared the diagnostic accuracy of nCLE and EUS-FNA, where nCLE was found to have a higher accuracy (87.5%), sensitivity (91.7%), and NPV (93.3%). In our cohort, 44/129 patients underwent nCLE, obtaining similar results (an 86.0% accuracy, an 89% sensitivity, and an NPV of 96%). Konda *et al*[22] reviewed 31 PCLs that were examined using nCLE, and showed a high specificity (100%) and PPV (100%); and an overall accuracy of 71%. In our study, we obtained a higher sensitivity (89%), NPV (96%) and accuracy (86%) probably owing to a higher number of cases.

EUS-nCLE and mFB exhibited an 86.4% and an 83.3% agreement for PCLs malignancy detection, probably due to a better *in vivo* cyst component evaluation and guided tissue acquisition. EUS combined with nCLE and mFB reached the highest AUROC (94.7%), in comparison to independent nCLE (87.3%) and mFB (84.8%). We propose that these techniques should be considered for the diagnostic workup of PCLs.

The main limitation of our study lies in its retrospective design and in establishing an agreement of different endoscopic techniques for determining potential malignancy among different types of PCLs. This resulted in a difficulty in the recovery of different size cysts, where the smaller the cyst, the fewer the diagnostic methods at our disposal for use. On the other hand, larger cysts (specially over 30 mm), allowed us to perform a wider array of diagnostic procedures, including novel techniques. Moreover, these novel endoscopic techniques (*i.e,* nCLE), are costly, limiting their widespread use. Furthermore, these tools require training, which increase the procedure's startup cost. Despite these limitations, we compared these endoscopic techniques in terms of their ability to detect potential malignancy in patients with PCLs, and not only pancreatic lesions, as with other studies. Finally, as this study was designed in the context of PCLs assessment with EUS, to estimate EUS (and eventual used related techniques) diagnosability of malignancy considering a 24-mo follow-up as gold standard, a prospective diagnostic trial to re-analyse histopathological samples of PCLs after discarding malignancy during follow-up may be warranted to further asses the accuracy in diagnosing high-grade dysplasia/adenocarcinoma in non-malignant PCLs (MCN, IPMN) using the studied endoscopic techniques.

CONCLUSION

In conclusion, new EUS technologies such as through-the-needle techniques (direct intracystic mFB combined with nCLE), improve malignancy detection in patients with PCLs. However, multicenter, and cost-benefit studies are recommended to validate these findings.

ARTICLE HIGHLIGHTS

Research background

Pancreatic cystic lesions (PCLs) incidence is rising mainly in elderly patients. Accurate diagnosing and appropriate management of patients with malignant PCLs, have a positive impact in regards of healthcare expenses and in patients' quality of life.

Research motivation

Currently, there is insufficient data about the accuracy in the diagnosing of PCLs, especially with novel endoscopic techniques. Furthermore, the early detection of potentially malignant PCLs, increases the possibility of a curative approach in said patients.

Research objectives

Given the poor prognosis of malignant PCLs, attaining early detection, an accurate diagnosis, and determining the best diagnostic approach with newly available endoscopic techniques, was essential to this study.

Research methods

This was a retrospective, single-center study. Patients were allocated to three evaluation cohorts: (1) Endoscopic ultrasound (EUS) alone; (2) EUS- fine needle aspiration, contrast-enhanced-EUS and/or EUS-guided fiberoptic probe cystoscopy (cystoscopy); and (3) EUS-guided direct intracystic micro-forceps biopsy (mFB) and EUS-guided needle-based confocal laser-endomicroscopy (nCLE); and compared the accuracy of these techniques for the detection of potentially malignant PCLs.

Research results

We described that pairing EUS, mFB, and nCLE, had a statistically significant improved detection of potentially malignant PCLs compared to any of the evaluated techniques alone. No adverse events were documented, and a 100% technical success rate was achieved.

Research conclusions

In our study, EUS-guided mFB combined with nCLE, improve malignancy detection in patients with PCLs.

Research perspectives

To define formal diagnostic and therapeutical guidelines, we encourage researchers to conduct long-term follow-up randomized multicenter and cost-benefit studies, comparing newly available endoscopic techniques for the assessment of PCLs.

FOOTNOTES

Author contributions: Robles-Medranda C contributed to study conception, design, drafting; Olmos JI, Del Valle Zavala R, Nebel JA, Calle Loffredo D and Pitanga-Lukashok H contributed to study design, acquisition of data; Puga-Tejada M and Oleas R contributed to study design; Baquerizo-Burgos J, Puga-Tejada M and Oleas R contributed to study drafting, acquisition/analysis of data; Arevalo-Mora M did final database study consolidation and encryption, data acquisition; Robles-Medranda C, Olmos JI, Del Valle Zavala R, Nebel JA, Calle Loffredo D, Pitanga-Lukashok H, Puga-Tejada M, Oleas R and Arevalo-Mora M contributed to critical revision of important intellectual content; all authors did final approval of the version to be published.

Institutional review board statement: The study was approved by the Institutional Review Board of Instituto Ecuatoriano de Enfermedades Digestivas.

Informed consent statement: All study participants, and their legal guardians, provided informed written consent prior to study enrolment.

Conflict-of-interest statement: Robles-Medranda C reports other from Pentax Medical, other from Boston Scientific, other from Steris, other from Medtronic, other from Motus, other from Micro-tech, other from G-Tech Medical Supply, other from CREO Medical, other from Mdconsgroup, outside the submitted work; The other authors declare no conflicts of interest.

Data sharing statement: The data that support the findings of this study are openly available by contacting the corresponding author.

STROBE statement: The authors have read the STROBE Statement-checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.

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S-Editor: Zhang H
L-Editor: A
P-Editor: Zhang H

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World Journal of Gastrointestinal Endoscopy

Submit a Manuscript: https://www.f6publishing.com

World J Gastrointest Endosc 2022 March 16; 14(3): 142-152

DOI: 10.4253/wjge.v14.i3.142

ISSN 1948-5190 (online)

ORIGINAL ARTICLE

Observational Study

Ergonomics of gastrointestinal endoscopies: Musculoskeletal injury among endoscopy physicians, nurses, and technicians

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Specialty type: Gastroenterology and hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C, C, C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Arslan M, Costache RS, Mestrovic A, Patel D

Received: April 21, 2021
Peer-review started: April 21, 2021
First decision: June 25, 2021
Revised: July 17, 2021
Accepted: February 11, 2022
Article in press: February 11, 2022
Published online: March 16, 2022

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Abstract

BACKGROUND

Musculoskeletal injuries (MSI) have plagued endoscopists and ancillary staff for decades without any innovative and strong ergonomic guidelines. It has placed a physical and mental strain on our endoscopists and ancillary staff. We have very have limited data supporting this claim in our region and most data is supported by western literature.

AIM

To document the prevalence of MSI, and awareness and practices of ergonomics by endoscopists and ancillary staff.

METHODS

This is an observational cross-sectional study, conducted in Karachi, a city that boasts the maximum number of daily endoscopies in the country. An eleven-point self-administered questionnaire was distributed and used to evaluate MSI and ergonomic adjustments amongst three tertiary care setups in Karachi. An onsite survey *via* a 13-point checklist for endoscopy suite facilities was used to assess the ergonomically friendly conveniences at five tertiary care setups in Karachi. A total of 56 participants replied with a filled survey.

RESULTS

There were 56 participants in total with 39 (69.6%) males. Pain and numbness were documented by 75% of the patients, with pain in the neck (41.1%), lower back (32.1%), shoulder (21.4%), thumb (12.5%), hand (23.2%), elbow (8.9%), and carpal tunnel syndrome (CTS) (7.1%). Of those, 33.3% attributed their symptoms

to endoscopy, 14.2% said that symptoms were not caused by endoscopy, and 52.4% were not certain whether endoscopy had caused their symptoms. Twenty-one point four percent of patients had to take time off their work, while 33.9% took medications for pain. Ergonomic modifications to prevent musculoskeletal injury, including placement of endoscopic monitor at eye level and the cardiac monitor in front, stopping the procedure to move patients, sitting while performing colonoscopy, and navigating height-adjustable bed were used by 21.4%. Nine out of 13 ergonomic facilities were not present in all five tertiary care hospitals. Conveniences, such as anti-fatigue mats, height-adjustable computer stations, and time out between patients were not present.

CONCLUSION
Three-fourth of our endoscopists reported MSI, of which more than half were not sure or attributed this problem to endoscopy. The prevalence of MSI warrants urgent attention.

Key Words: Endoscopy; Ergonomics; Injury; Musculoskeletal; Endoscopists; Gastroenterologist

Core Tip: Musculoskeletal injuries (MSI) have impacted gastroenterologists and ancillary staff involved in endoscopy. Maneuvers, time duration, and failure of ergonomic practices and provision of facilities have led to the prevalence of MSI. This has resulted in stress, chronic pain management, office leaves, and consumption of analgesics. We found three-fourth of our endoscopists reported MSI, of which more than half were not sure or attributed this problem to endoscopy. The high prevalence of MSI and lack of awareness among endoscopists and ancillary staff needs to be addressed urgently.

Citation: Shah SZ, Rehman ST, Khan A, Hussain MM, Ali M, Sarwar S, Abid S. Ergonomics of gastrointestinal endoscopies: Musculoskeletal injury among endoscopy physicians, nurses, and technicians. *World J Gastrointest Endosc* 2022; 14(3): 142-152
URL: https://www.wjgnet.com/1948-5190/full/v14/i3/142.htm
DOI: https://dx.doi.org/10.4253/wjge.v14.i3.142

INTRODUCTION

Several studies have suggested a high prevalence of musculoskeletal injuries (MSI) among endoscopists and ancillary staff. Survey-based studies estimate a 29% to 89% prevalence of musculoskeletal pain among gastroenterologists[1], which directly translates to a loss of productivity. Rigorous training and increased demand for endoscopies make a gastroenterologist an asset in the workplace, especially in the developing world. A work-related injury can greatly affect the quality and longevity of the gastroenterologist, which can ultimately exacerbate the shortage of specialists[2]. Improving ergonomic conditions will ensure maximum utilization of this scarce human resource. MSI are widespread and are strongly correlated with high procedure volume and procedure duration[3]. Endoscopists are at risk for overuse syndromes and overuse injuries, such as carpal tunnel syndrome (CTS), De Quervain's tenosynovitis, and lateral epicondylitis because of the repetitive movements, pinching and gripping of the endoscope, pushing, pulling, torquing of the insertion tube and potentially awkward posture associated with endoscopic procedures[1,3]. However, institutional changes minimizing MSI are limited, which can be an important contributory factor of lack of awareness[1].

Limited documented data, especially in the eastern population, and lack of awareness are contributory factors to the lack of widespread change. Additionally, a robust analysis to identify risk factors associated with endoscopy-related injury is lacking. Creating awareness about the importance of ergonomics in endoscopy may prevent future injury. There is no standardized curriculum for learning endoscopic techniques, and most endoscopists learn their skills during their fellowship training through their faculty mentor, which creates great variability in the level of skill among trainees. This variability and lack of emphasis on ergonomics during teaching propagate the risk of MSI. Strategies for the management of the risk of MSI related to the practice of endoscopy include compliance with currently recommended ergonomic practices, standardized education of trainees in ergonomic technique when practicing endoscopy, research toward the modification and development of more ergonomic endoscopes and procedure spaces, and institutional emphasis[4]. This study aims to document the prevalence of MSI, awareness and practice of ergonomics by endoscopists and ancillary staff.

MATERIALS AND METHODS

Questionnaires were tendered to endoscopists and ancillary staff. The questionnaire was designed and informed consent was implied by a completed response to the survey. The survey was handed out following June 2019 onwards with a collection on follow-up from respondents. Ethical approval was obtained from Ethics Review Committee Aga Khan University (5357-Med-ERC-18).

Study subjects

Participants were endoscopists and ancillary staff found in the endoscopy suites in three tertiary care hospitals namely, Aga Khan University Hospital, Liaquat National Hospital, and Dr. Ruth K. M. Pfau Civil Hospital, all located in Karachi, Pakistan. All endoscopy physicians, nurses, and technicians approached. There was no monetary compensation for participation.

Evaluation of MSI

An eleven-point, self-administered, paper-based survey was devised by an endoscopist and a member of the ancillary staff (Supplementary Material 1). Items in the questionnaire were generated based on literature review[2,3,5] and multidisciplinary discussions on the topic. These questions focused on demographics, average physical activity, location of the injury. It also questioned the subject's perception of work/endoscopy-related MSI, and further intrigued on their remedies, the need for skipping work, and the use of ergonomic techniques to facilitate themselves.

Initially, the survey was pilot-tested by handing it over to endoscopists and ancillary staff members from the Department of Gastroenterology at Aga Khan University Hospital. The purpose was to evaluate its language, content clarity, and to deduce an approximate time to complete, although trained researchers were present during data collection to clarify any ambiguities. The final survey evaluated the respondent's general demographic, characteristics, workload, type, treatment, and impact of severity of MSI on a daily professional capacity. The survey took approximately 6 min to be filled out.

Assessment of facilities to prevent MSI

A 13-point checklist (Supplementary Material 2) was adapted and devised from a literature search[6-9]. The endoscopic suites at five tertiary care hospitals, namely, Aga Khan University Hospital, Ziauddin University Hospital, Liaquat National Hospital, Dr. Ruth K. M. Pfau Civil Hospital, Sindh Institute of Urology and Transplant, all placed within Karachi, Pakistan were evaluated. The checklist was used to assess measures employed by these 5 major tertiary care hospitals in this metropolis to reduce MSI.

Ergonomic conditions were evaluated by the investigators. These 13 points briefly assessed the suite for endoscopic monitor, monitor height adjustability, booms, and stands. It also assessed time out between two consecutive patients, support stands, anti-fatigue mats, tiltable examination beds, cardiac monitor adjustability, and having the endoscopic retrograde cholangiopancreatography (ERCP) room in the same suite (Supplementary Material 2).

Statistical analysis

This observational cross-sectional study had its statistical review performed by a biomedical statistician present at the Department of Medicine at Aga Khan University. Analysis was performed using SPSS (Statistical Package of Social Sciences) version 19. Continuous variables were reported as mean ± SD. Prevalence (%) of demographic and clinical factors were assessed. All participants were divided into four groups: endoscopists, trainees, nurses, and technicians, and had their frequency of MSI compared in different groups by chi-square test. This data was stratified by gender and evaluated. All *P* values were based on two-sided tests and significance was set at a *P* value less than 0.05.

RESULTS

Demographics

Data from 56 participants were collected, of which 39 (69.6%) were male (Table 1). Eighty-seven point five percent had right-hand dominance. There were 23.2% endoscopists, 16.1% gastroenterology residents, 26.8% endoscopy nurses, and 33.9% endoscopy technicians.

The level of physical activity was appraised. No regular exercise was seen in 41.1%, 23.2% exercised less than 150 min/wk, 8.9% exercised 150 min/wk, and 26.8% exercised more than 150 min/wk.

MSI

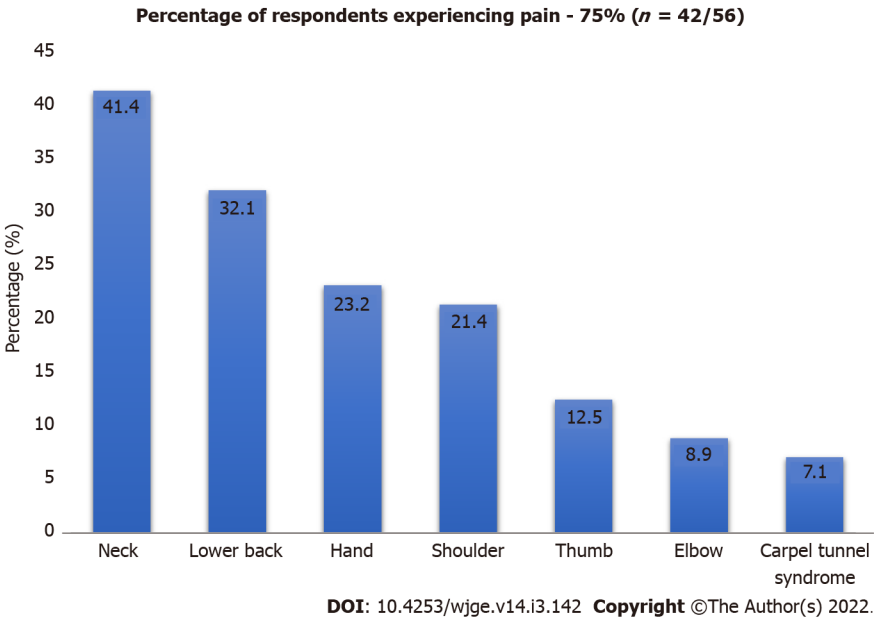
Participants who had been doing endoscopies for up to 5 years accounted for 48.9%, while 51% had been involved in endoscopy for more than 5 years.

Pain and numbness were reported by 75% of total respondents with anatomical regions specified as neck (41.1%) lower back pain (32.1%) shoulder pain (21.4%), thumb pain (12.5%) hand pain (23.2%), elbow pain (8.9%) and CTS (7.1%), being the most affected with pain (Figure 1).

Table 1 Demographics

Demographics	*n* = 56 (%)
Mean age, yr	35.09 (18-62)
Male	39 (69.6)
Female	17 (30.3)
Endoscopist	13 (23.2)
GI resident	9 (16.1)
Endoscopy nurse	15 (26.8)
Endoscopy technician	19 (33.9)
Mean number of endoscopies performed per week	63.85

Table 1 shows the demographic representation of our respondents out of n = 56. We stratified our data based on gender and profession to analyze musculoskeletal injuries. GI: Gastrointestinal.



DOI: 10.4253/wjge.v14.i3.142

Figure 1 The percentage of respondents experiencing a particular type of pain.

On an individual basis, out of endoscopists, residents, nurses, and technicians, we found endoscopists reporting the least to experience pain (53.8%) (Table 2). This was followed by residents at 77.8%, technicians at 78.9%, and finally with nurses reporting the most pain at 86.7%. Overall, there is not much distribution amongst the subgroups of the endoscopy team; however, we saw four cases of CTS. All four belonged to endoscopy nurses or endoscopy technicians.

We found a majority of the male and female technicians (66% and 100%) (Table 3) agreeing to neck pain which is the most common area affected overall while most nurses, both in males (100%) and females (53.8%) said to experience no pain in their neck. This does have real-time value as we found nurses using and performing hand and wrist-based actions and movements more frequently, and likewise, the nurses in our setup play a major role in holding the mouth guard. Table 3 can be seen showing a sub-analysis of gender-based data of male *vs* females in their respective professions of endoscopists, residents, nurses, and technicians.

Of all the total respondents only 33.3% of those having pain attributed it to endoscopy while, 52.4% were not certain whether the symptoms had been caused by endoscopy and 14.3% said that symptoms were not caused by endoscopy.

Thirty-two point one percent of respondents indicated evident pain during endoscopy, with 33.3% of those were bothered by this symptom.

Thirty point five percent of the participants indicated that the duration of their symptoms was more than 6 mo, and of those, 57.1% indicated that their symptoms were static and 10.7% indicated they were increasing. Around 21.4% of respondents had to take time off from work and 33.9% took medications

Table 2 Spectrum of musculoskeletal injuries amongst subgroups of endoscopic team

	Endoscopist	GI resident	Endoscopy nurse	E. technician	*P* value
Pain or numbness (%)					0.22
Yes	7 (53.8)	7 (77.8)	13 (86.7)	15 (78.9)	
No	6 (46.2)	2 (22.2)	2 (13.3)	4 (21.1)	
Left thumb pain (%)					0.02
Yes	2 (15.4)	0	2 (13.3)	0	
No	11 (84.6)	9 (100)	13 (86.7)	19 (100)	
Right thumb pain (%)					
Yes	0	3 (33.3)	0	0	
No	13 (100)	6 (66.7)	15 (100)	19 (100)	
Left shoulder pain (%)					0.48
Yes	0	0	1 (6.6)	0	
No	13 (100)	9 (100)	14 (93.4)	19 (100)	
Right shoulder pain (%)					
Yes	0	1 (11.1)	0	0	
No	13 (100)	8 (88.9)	15 (100)	19 (100)	
Both shoulder pain (%)					
Yes	2 (15.4)	2 (22.2)	3 (20)	3 (15.7)	
No	11 (84.6)	7 (77.8)	12 (80)	16 (84.)	
Left hand pain (%)					0.06
Yes	0	0	2 (13.3)	0	
No	13 (100)	9 (100)	13 (86.7)	19 (100)	
Right hand pain (%)					
Yes	0	2 (22.2)	1 (6.6)	1 (5.3)	
No	13 (100)	7 (77.8)	14 (93.4)	18 (94.7)	
Both hand pain (%)					
Yes	0	0	2 (13.3)	5 (26.3)	
No	13 (100)	9 (100)	13 (86.7)	14 (73.7)	
Neck/upper back (%)					0.004
Yes	3 (23.1)	5 (55.5)	6 (40)	9 (47.3)	
No	10 (76.9)	4 (44.5)	9 (60)	10 (52.7)	
Lower back (%)					
Yes	2 (15.4)	1 (11.1)	8 (53.3)	7 (36.8)	
No	11 (84.6)	8 (88.9)	7 (46.7)	12 (63.2)	
Left elbow pain (%)					0.57
Yes	0	0	1 (6.6)	0	
No	13 (100)	9 (100)	14 (93.4)	19 (100)	
Right elbow pain (%)					
Yes	1 (7.6)	1 (11.8)	1 (6.6)	0	
No	12 (92.4)	8 (88.2)	14 (93.4)	19 (100)	
Both elbow pain (%)					
Yes	0	0	1 (6.6)	0	

No	13 (100)	9 (100)	14 (93.4)	19 (100)	
L hand numbness (%)					0.59
Yes	1 (7.6)	0	1 (6.6)	0	
No	12 (92.4)	9 (100)	14 (93.4)	19 (100)	
R hand numbness (%)					
Yes	0	1 (11.1)	0	1 (5.2)	
No	13 (100)	8 (88.9)	15 (100)	18 (94.8)	
B/l hand numbness (%)					
Yes	0	0	1 (6.6)	0	
No	13 (100)	9 (100)	14 (93.4)	19 (100)	
Carpal tunnel (%)					0.00
Yes	0	0	2 (13.3)	2 (10.5)	
No	13 (100)	9 (100)	13 (86.6)	17 (89.5)	

GI: Gastrointestinal.

for resolution of pain.

Assessment of facilities and awareness of ergonomics

The responders were asked if they used some modifications to prevent these injuries (Supplementary Material 1). Specific modifications that were assessed were placing the endoscopic monitor at eye level (21.4%) or cardiac monitor in front (12.5%), stopping the procedure to move patients (8.9%), sitting while performing a colonoscopy (12.5%), and using height-adjustable patient beds (23.2%).

All 5 tertiary care institutions ensured that the endoscopist monitor was located directly in front of the endoscopist and monitor boom, mobile stands, and endoscope support stands were available (Figure 2). All 5 hospitals also ensured that the patient examination table was height adjustable. Four out of the 5 hospitals had a tiltable examination table. Three out of 5 tertiary setups had adjustable monitor height, adjustable cardiac monitor, 2-piece lead aprons, non-slip flooring, and covered bundled wires. Three of 5 hospitals also had an ERCP room in the endoscopy suite.

One hospital provided an adjustable computer station and none of the institutions provided anti-fatigue mats/gel floor pads or had a time-out session of 10 min or more in between two consecutive endoscopy patients.

DISCUSSION

In this study, we tried to shed light on challenges affecting MSI in endoscopists and their ancillary staff. Numerous studies have identified procedure volume and number of years in practice to be a risk factors for injury[10]. In this study, we documenting the prevalence of such injuries, the awareness and practice of ergonomic intervention by current endoscopists and the ancillary staff, as well as the availability and use of ergonomic facilities in our tertiary care institutions.

Prevalence and awareness of musculoskeletal injury

Workplace injury has undoubtedly put an additional strain on the already chronic shortage of specialists. It can harm the productivity of healthcare workers and cause long-term pain and disability.

The overall prevalence of pain or has been reported among reporting endoscopists to be as high as 29% to 89% in numerous literature[1,5,11,12]. Our study confirmed these results, with our respondents acknowledging the prevalence of such pain and injury in 75% of our subjects, similar to Hansel *et al*[5] at 74%. In the largest survey done, examining endoscopy-related MSI, which targeted members of the American Society for Gastrointestinal Endoscopy (ASGE), 53% of endoscopists had reported injuries [13]. Similarly, in a study involving 190 endoscopists in Japan, 43% reported musculoskeletal pain[14].

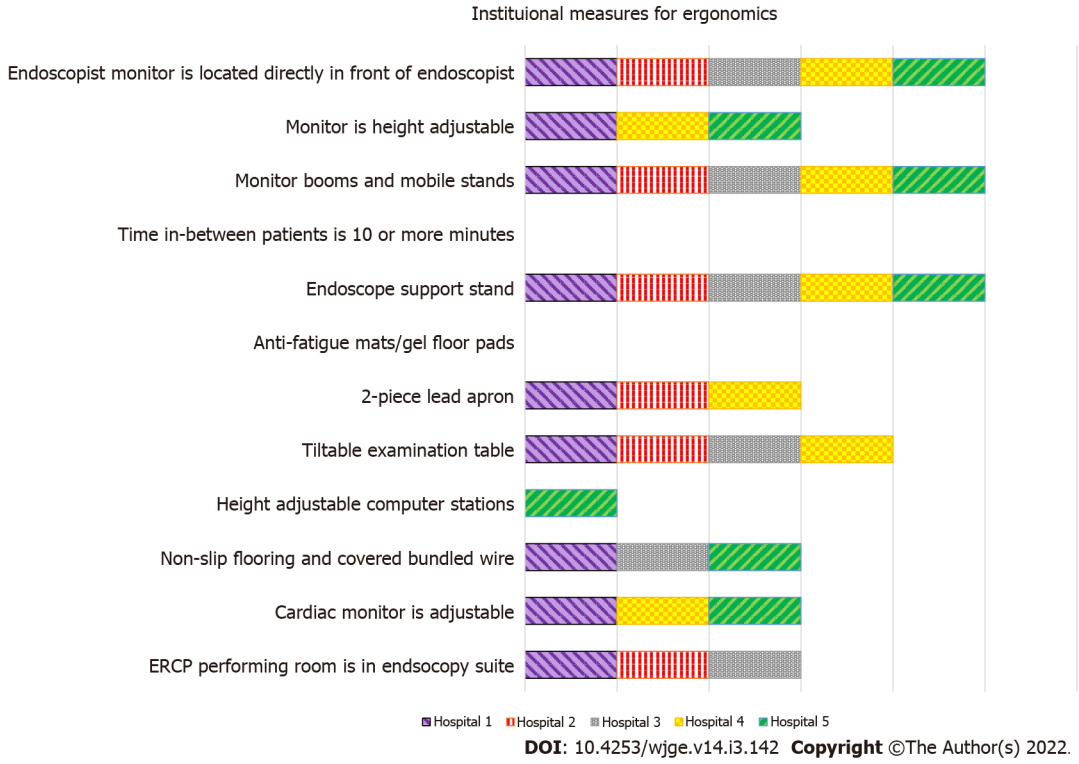
The site of injury plays an important role in the hindrance of an endoscopist's work. The three most commonly affected anatomical regions in our series were the neck, lower back, and shoulders, at 41.1%, 32.1%, and 21.4%, respectively. These numbers were partially contradictory to most articles we found, such as Han *et al*[15] quoting shoulders and back at approximately 42% and 38%, respectively, and Villa *et al*[3] signifying the right wrist and left thumb being the most affected at 53% and 48%, respectively.

Table 3 Spectrum of musculoskeletal injuries according to gender amongst various subgroups in the endoscopic team

	Male				*P* value	Female				*P* value
	Endoscopist (%)	GI resident (%)	Nurse (%)	Technicians (%)		Endoscopist (%)	GI resident (%)	Nurse (%)	Technicians (%)	
Pain					0.536					0.148
Yes	7 (58.3)	5 (71.4)	2 (100)	14 (77.8)		0 (0)	2 (100)	11 (84.6)	1 (100)	
No	5 (41.7)	2 (28.6)	0	4 (22.2)		1 (100)	0	2 (15.4)	0	
Thumb pain					0.028					0.207
Left	2 (16.7)	0	0	0		0	0	2 (15.4)	0	
Right	0	2 (28.6)	0	0		0	1 (50)	0	0	
No	10 (83.3)	5 (71.4)	2 (100)	18 (100)		1 (100)	1 (50)	11 (84.6)	18	
Shoulder pain					0.472					0.152
Yes	2 (16.7)	2 (28.6)	1 (50)	2 (11.1)		0	1 (50)	3 (23.1)	1 (100)	
No	10 (83.3)	5 (71.4)	1 (50)	16 (88.9)		1 (100)	1 (50)	13 (76.9)	0	
Hand					0.001					0.898
Left	0	0	1 (50)	0		0	0	1 (7.7)	0	
Right	0	1 (14.2)	0	1 (5.55)		0	1 (50)	1 (7.7)	0	
Both	0	0	0	5 (27.7)		0	0	2 (15.4)	0	
No	12 (100)	6 (85.7)	1 (50)	12 (66.6)		1 (100)	1 (50)	9 (69.2)	1 (100)	
Neck pain					0.029					0.258
Yes	3 (25)	3 (42.9)	0 (0)	8 (66)		0 (0)	2 (100)	6 (46.2)	1 (100)	
No	9 (75)	4 (57.1)	2 (100)	4 (44)		1 (100)	0 (0)	7 (53.8)	0	
Lower back pain					0.003					0.3
Yes	2 (16.7)	1 (14.3)	2 (100)	6 (54.5)		0 (0)	0 (0)	6 (46.2)	1 (100)	
No	10 (83.3)	6 (85.7)	0	5 (45.5)		1 (100)	2 (100)	7 (53.8)	0	
Elbow pain					0.468					0.99
Yes	1 (8.3)	1 (14.3)	0	0		0 (0)	0 (0)	3 (23.1)	0	
No	11 (91.7)	6 (85.7)	2 (100)	18 (100)		1 (100)	2 (100)	10 (76.9)	1	
Hand numbness					0.75					0.489
Left	1 (8.3)	0	0 (0)	1 (5.6)		0 (0)	1 (50)	2 (15.4)	0	
Right	11 (91.7)	7	2 (100)	17 (94.4)		1 (100)	1 (50)	11 (84.6)	1	
Both										
No										
Carpal tunnel					0.007					0.874
Yes	0	0	0	2 (22)		0 (0)	0	2 (15.4)	0	
No	12	7	2	7 (78)		1 (100)	2	11 (84.6)	1	

Although literature such as Villa *et al*[3] reported almost half of their subjects, 47%, acknowledging pain related to that of endoscopies, our study reflected one-third (33.3%) of our respondents attributing their symptoms due to such procedures. This could be identified as a lack of awareness or as a reluctance to practice ergonomic activities in the endoscopy suites.

Although three-quarters of our respondents acknowledging the presence of pain, surprisingly, 52.4% stated that they could not be certain whether endoscopy was a cause of their symptoms, and 14.3% said their symptoms were not caused by performing these procedures.



DOI: 10.4253/wjge.v14.i3.142

Figure 2 An individual hospital representation of ergonomic-based facilities present. ERCP: Endoscopic retrograde cholangiopancreatography.

Some of the most important factors are repetitive movements, overuse of muscles, and prolonged standing, all of which are important parts of conducting an endoscopy. Some studies even go as far as quoting more than 16 h or 20 cases per week can lead to an increase in the risk of MSI[10,12]. Although factors leading to these injuries were not directly studied in our numbers, previous literature shed some light as stated above.

Arguably, gender does play a role according to a study conducted in ASGE fellows, which reported female gender as the only significant risk factor for MSI based on factors pertaining to their hand size and grip strength[13]. However, in our study, with only 30.3% females, a relative comparison showed no gender-related difference in MSI (Table 3).

Most literature on the prevalence of endoscopic MSI did not evaluate the impact of regular activity and work. Alarmingly, we noted 21.4% of our respondents had to take time off from work due to endoscopy-related pain. This number was an increase from other literature we found and can be subjectively linked to limited specialists and ancillary staff in this field in the city and long working hours this entails[2,5]. Morais *et al*[2] recently conducted a study amongst Portuguese endoscopists, and found that 10.1% of their respondents took time off on account of endoscopy-related injuries, with a median of 30 d. This number contrasts with previous literature in which only a few endoscopists reported missing work and only for a few days[5].

In regards to our study, this significant loss of productivity needs to be properly addressed. This will ensure avoidable time off and lead to a decreased load on fellow endoscopists and ancillary staff.

Awareness and implementation of facilities for ergonomics

Our study further investigated what measures are being taken by the endoscopists at an institutional level to decrease MSI. For example, the availability and use of portable and/or flexible endoscopy and cardiac/vital monitors can play a vital role in preventing injuries[8].

Documentation of injuries is the first step in improving and promoting discussion on workplace ergonomics as indicated in a national survey by Austin *et al*[13], where gastroenterology trainees and program directors were approached pre- and post- ergonomic training, and 90% of participants reportedly agreed that the ergonomic training sessions had a positive impact. These trainings eventually led to a decrease in the number of injuries and the creation a more ergonomic friendly work environment for endoscopists. Such practices are uncommon in our institutions.

Multiple factors were questioned in our survey that we compiled based on the current literature search and the proven adjustments and maneuvers that played a role in ergonomics[8]. Out of the total, 23.2% adjusted the height-adjustable-bed, 12.5% placed a cardiac monitor in front, 8.9% stopped to move patients, and 8.9% sat while performing the procedure. Such low numbers speak volumes on the limited awareness of ergonomics, despite the availability of these possibilities, and also shed light on why ergonomic sessions must be undertaken in the initial training months of endoscopy. Regional pain

as described above could all be caused due to poor posture. Lack of posture and ergonomic timeouts play a vital role in such context. Effective strategies to ensure good posture can significantly improve endoscopists' pain.

To avoid improper positioning, endoscopy units should consider having an "ergonomic timeout" before starting a procedure to ensure proper bed height, patient position, and monitor location[3,11]. There is a clear role for widespread education and the implementation of guidelines for the best clinical practice of ergonomics[6,7,11,16]. It is easy to see the need for more training to ensure a higher percentage of respondents take preventive measures to improve their quality of life.

Assessment of facilities at endoscopy suite

To elucidate this aspect, our 13-point checklist was studied at five tertiary care hospitals, where we examined the accessibility to basic endoscopy suite ergonomic capabilities in the devices used for every endoscopic procedure. Out of the five hospitals, none of them had a time out of ten mins or more between two patients, which could lead to patient identification errors and would give insufficient time for the endoscopist to complete individualized patient reports. A 10-min time-out would also support decreased muscle fatigue levels.

Height-adjustable examination beds, endoscopy support stand, monitor booms, and having the accessibility of the main endoscopic camera screen in front were available in all five tertiary care facilities.

None of the hospitals had any form of anti-fatigue mats or gel floor pads, however, three of them did have anti-slip flooring with wires being covered for protection against tripping over. Three of the hospitals also had movable cardiac/vital monitors alongside height-adjustable monitors for the endoscopist. One of the tertiary care hospitals had an adjustable computer station, while three of the hospitals had the ERCP procedure room within the reaches of the endoscopic procedure room.

Limitations

Our respondents were limited to 56 participants. For ergonomic evaluations, only five units in a geographic area limit the generalizability of the findings. An analysis of the pre- and post- ergonomic training with quantitative and qualitative analysis on our subjects would have added to the reliability of our findings.

CONCLUSION

This is the first study to be conducted in Pakistan for injuries caused by endoscopy. Our endoscopists had a significant prevalence of MSI leading to hindrance in their day-to-day activities and professional continuity.

Lack of knowledge and awareness of such injuries, both at a personal and institutional level, need to be addressed. Multiple areas need to be addressed in a strategic approach. We must increase awareness of these injuries among endoscopists and staff and standardized curricula to educate fellows on ergonomic practices to reduce the early development of overuse injuries. Institutions should also have standardized ergonomic protocols in place in endoscopy suites.

More research is needed to document the efficacy of an intervention in improving quality of life and productivity.

ARTICLE HIGHLIGHTS

Research background

Ergonomics in the field of gastroenterology with regards to musculoskeletal injuries (MSI) among endoscopists and ancillary staff have been highlighted in studies from the western world. MSI affect the quality and longevity of the gastroenterologist, which can lead to a shortage of specialists. There has been a dearth of literature on the topic from our region.

Research motivation

The goal of this research was to create awareness about the importance of ergonomics in endoscopy that may prevent future injuries. Research would lead towards the modification and development of more ergonomic endoscopes and techniques. Furthermore, procedure rooms and spaces with institutional emphasis would promote strategies for the management of musculoskeletal injury.

Research objectives

Our objective is to document the prevalence of MSI, awareness, and practice of ergonomics by endoscopists, ancillary staff, and institutions.

Research methods

An observational cross-sectional study in Karachi. An eleven-point self-administered questionnaire was distributed and used to evaluate MSI and ergonomic adjustments amongst three tertiary care setups in Karachi. An onsite survey *via* a 13-point checklist for endoscopy suite facilities was used to assess the ergonomically friendly conveniences at five tertiary care setups.

Research results

There were 56 participants in total with 39 (69.6%) males. Pain and numbness were documented by 75% of the respondents, with the neck (41.1%) and lower back (32.1%) being the most commonly affected regions. Twenty one point four percent had to take time off their work, while 33.9% took medications for pain. Ergonomic modifications to prevent musculoskeletal injury were used by 21.4%. Institutions lacked sufficient ergonomic facilities.

Research conclusions

Three-fourth of our endoscopists reported MSI, of which more than half are not sure or attributed this problem to endoscopy. The prevalence of MSI warrants urgent attention.

Research perspectives

It would be interesting to see interventions to improve the ergonomics among participants, such as pre- and post-intervention improvement and the impact of creating awareness. Research can be directed towards the development of curriculum and guidelines addressing ergonomics and modifications to prevent MSI.

ACKNOWLEDGEMENTS

We thank all the respondents for taking out their time to fill in our questionnaire and also thank the following five hospitals for allowing us to examine their endoscopy suites: Aga Khan University Hospital, Liaquat National Hospital, Ziauddin University Hospital, Dr. Ruth K. M. Pfau Civil Hospital and Sindh Institute of Urology and Transplant.

FOOTNOTES

Author contributions: Shah SZ designed the study and methodology for the study and contributed to the finalized article writing; Abid S conceptualized the idea, edited and revised the manuscript and oversaw the entire project; Rehman ST and Hussain MM contributed to initial and finalized article writing and analysis alongside literature search; Ali M, Khan A and Sarwar S contributed in data collection and analysis.

Institutional review board statement: The study was reviewed and approved by the Ethics Review Committees (ERC) at the Aga Khan University (Karachi, Pakistan).

Informed consent statement: All study participants provided informed written consent prior to study enrollment.

Conflict-of-interest statement: There are no conflicts of interest to report.

Data sharing statement: No additional data are available.

STROBE statement: The authors have read the STROBE Statement-checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.

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S-Editor: Gao CC
L-Editor: Filipodia

P-Editor: Gao CC

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World Journal of Gastrointestinal Endoscopy

Submit a Manuscript: https://www.f6publishing.com

World J Gastrointest Endosc 2022 March 16; 14(3): 153-162

DOI: 10.4253/wjge.v14.i3.153

ISSN 1948-5190 (online)

ORIGINAL ARTICLE

Observational Study

SARS-CoV-2 in inflammatory bowel disease population: Antibodies, disease and correlation with therapy

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Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Jin X, Zhang H

Received: October 11, 2021
Peer-review started: October 11, 2021
First decision: December 3, 2021
Revised: December 14, 2021
Accepted: February 16, 2022
Article in press: February 16, 2022
Published online: March 16, 2022

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Abstract

BACKGROUND

Guidelines recommend to cease inflammatory bowel disease (IBD) biologic therapy during coronavirus disease 2019 (COVID-19).

AIM

To investigate severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibody positivity in an IBD cohort, COVID-19 disease severity and to evaluate the correlation with clinical/therapeutic variables.

METHODS

Prospective observational cohort study. IBD patients were tested for SARS-CoV-2 IgG. Data on COVID-19 disease, demographics/therapeutics and clinical features of the IBD population were collected. IgG ≥ 7 was set for SARS-CoV-2 antibody positivity. Throat swab was performed in cases of IgG positivity. Correlations between antibody positivity or COVID-19 symptoms and therapeutic/clinical data were assessed.

RESULTS

In total, 103 IBD patients were enrolled. Among them, 18.4% had IgG ≥ 7. Multivariate analysis of antibody positivity correlated only with IBD treatment. For IgG ≥ 7, the odds ratio was 1.44 and 0.16 for azathioprine and mesalazine, respectively, *vs* biologic drugs (P = 0.0157 between them). COVID-19 related symptoms were reported in 63% of patients with IgG positivity. All but one

patient with COVID-19 symptoms did not require ceasing IBD treatment or hospitalization. IBD treatment and body mass index correlated with COVID-19 disease development with symptoms.

CONCLUSION

The IBD population does not have a higher risk of severe COVID-19. The relative risk of having SARS-CoV-2 antibodies and symptoms was higher for patients taking azathioprine, then biologic therapy and lastly mesalazine. None of the patients under biologic therapy developed severe COVID-19.

Key Words: Inflammatory bowel disease; SARS-CoV-2; COVID-19; Biologic treatment; SARS-CoV-2 antibody; Inflammatory bowel disease therapy

Core Tip: Guidelines recommend ceasing inflammatory bowel disease (IBD) biologic therapy during coronavirus disease 2019 (COVID-19). IBD patients were prospectively tested for severe acute respiratory syndrome coronavirus 2 IgG. In total, 103 IBD patients were enrolled. We found that 18.4% had IgG positivity, and 63% developed COVID-19 disease with symptoms. However, all but one patient with symptoms did not require ceasing IBD treatment no hospitalization. None of the patients under biologic therapy developed severe COVID-19. Therefore, the IBD population does not seem to have a high risk of severe COVID-19, particularly if under biological treatment or mesalazine.

Citation: Conti CB, Mainardi E, Soro S, Testa S, De Silvestri A, Drago A, Cereatti F, Grassia R. SARS-CoV-2 in inflammatory bowel disease population: Antibodies, disease and correlation with therapy. *World J Gastrointest Endosc* 2022; 14(3): 153-162

URL: https://www.wjgnet.com/1948-5190/full/v14/i3/153.htm

DOI: https://dx.doi.org/10.4253/wjge.v14.i3.153

INTRODUCTION

A new β-coronavirus (SARS-CoV-2) spread in November 2019 in China and then worldwide, becoming a pandemic. The related disease, known as coronavirus disease 2019 (COVID-19), mainly involves the respiratory system. The elderly and patients affected by chronic diseases seem to be at a higher risk to develop severe pneumonia and acute distress syndrome[1]. In this scenario, the patients affected by inflammatory bowel diseases (IBD) appeared to be an at-risk population for severe COVID-19, considering the possible gastrointestinal system involvement[2-6]. Indeed, it seems that the high expression of angiotensin-converting enzyme 2 in the intestinal tract, above all in the absorptive enterocytes of the ileum and colon and in the epithelial cells of the esophagus, makes these tissues highly susceptible to SARS-CoV-2 infection. Mucosal damage was observed in the esophagus, stomach, duodenum and rectum by histological examinations as plasma cells and lymphocytes infiltrated the lamina propria. Approximately 3% of COVID-19 cases have only digestive symptoms. Moreover, the detection of SARS-CoV-2 in the stool suggested that the virus could replicate in the digestive tract[6].

Initial indications from an IBD center in Wuhan, China was to discontinue all biological and immunosuppressive treatments. They reported that among 318 registered IBD patients, none developed COVID-19[7]. Nevertheless, scientific societies suggested that IBD patients should continue the ongoing treatment to avoid relapse, including the biological therapies[1]. However, regarding IBD patients affected by COVID-19, guidelines suggest handling the treatments with more caution. In particular, the American Gastroenterological Association guidelines divided them into three different categories: IBD patients without SARS-CoV-2 infection; IBD patients with SARS-CoV-2 infection but no symptoms of COVID-19; and IBD patients with COVID-19 symptoms. The first category should continue all treatments. The second category should discontinue thiopurines, methotrexate and tofacitinib and delay biological therapies for 2 wk while monitoring symptoms of COVID-19. The third category should discontinue thiopurines, methotrexate, tofacitinib and biological therapy during the illness[1].

Since the scientific community had to develop new guidelines in a short time with a new and unknown disease, the recommendations carry a low grade of evidence. In an Italian cohort of 522 IBD patients, none were hospitalized for SARS-CoV-2 infection, and 16% of the patients were under biologic treatment. However, 11% of the patients were children, a population with an unclear susceptibility to the virus[8]. Moreover, some interesting observational studies report COVID-19 prevalence and symptoms/outcomes in IBD cohorts[9,10]. However, little is known about the possible role of IBD treatments in the development of severe COVID-19 disease. Importantly, it remains unclear whether

IBD patients are at a higher or lower risk of severe COVID-19.

Systemic inflammation is a crucial target for the treatment of COVID-19 pneumonia, as the severity of the respiratory disease seems to be linked to the upregulation of inflammatory cytokines by creating a "cytokine storm," producing interleukin (IL)-6, IL-1, tumor necrosis factor (TNF) and interferon-γ. The exaggerated synthesis of IL-6 can lead to an acute severe systemic inflammatory response. It should be noted that cytokine blockers and Jak inhibitors were considered for clinical therapy of COVID-19 acute respiratory distress syndrome[11-13]. Interestingly, TNF inhibition has also been suggested in selected patients with high IL-6 levels. Indeed, when TNF is blocked, there is a serial decrease of IL-6 and IL-1 within 12 h in patients with active rheumatoid arthritis. A reduction of adhesion molecules and vascular endothelial growth factor was observed as well[14]. Nevertheless, no definitive treatment has been approved. Therefore, many hypotheses but few certainties are present. In particular, COVID-19 outcomes in patients with IBD immunomodulant/immunosuppressive treatments remains under debate.

The present study aimed to investigate the prevalence of SARS-CoV-2 antibody positivity and COVID-19 disease severity in an IBD cohort, in both symptomatic and asymptomatic patients and to evaluate the correlation with clinical/therapeutic variables.

MATERIALS AND METHODS

Study design

We conducted a prospective cohort study. The informed consent for the study was obtained from all the patients in accordance with the World Medical Association's 2008 Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. The privacy rights of patients were always observed. All authors had access to the study data and reviewed and approved the final manuscript.

Patients

Cohort of patients affected by IBD (Crohn's disease or ulcerative colitis). From April 22, 2020 to May 31, 2020, each IBD patient followed-up at ASST Cremona was offered to participate in the study. The patients were consecutively enrolled.

Data collection

Each IBD patient was asked about his/her recent clinical history (respiratory and gastrointestinal symptoms) from the beginning of the COVID-19 pandemic in Europe (February 21, 2020) by completing a questionnaire, and all the information was validated with the doctor who conducted the interview. Data collected in the questionnaire were summarized in the Supplementary Material.

Age, sex, body mass index (BMI), IBD type, treatments and clinical activity and other comorbidities were anonymously collected in a database. Charlson Comorbidity Index was calculated for each patient.

Antibody testing

A single blood test was performed for each patient to search for anti-SARS-CoV-2 IgG. The LIAISON® SARS-CoV-2 S1/S2 IgG test [Diasorin S.p.A, Saluggia (VC) – Italy] was used according to manufacturer's instructions. S1 and S2 are subunits of the spike protein and are responsible for binding (S1) and fusion (S2) of the virus to cells. The spike protein is the target of neutralizing antibodies. They are defined as antibodies that protect cells from pathogens or infectious particles by neutralizing their biological effects. The manufacturer reports a positive agreement of 94.4% [95% confidence interval (CI): 88.8%-97.2%] with the plaque reduction neutralization test. The IgG test has diagnostic specificity of 98.5% (95%CI: 97.5%-99.2%) in blood donors and 98.9% in presumably SARS-Cov-2 negative diagnostic routine samples. The IgG values are considered negative when < 12.0 kAU/L, equivocal from 12 kAU/L to 15.0 kAU/L and positive when ≥ 15.0 kAU/L. When applying a cutoff of >15 kAU/L, the reported test's sensitivity is time-dependent: 25% (14.6%-39.4%) ≤ 5 d after reverse transcriptase-PCR-confirmed diagnosis; 90.4% (79.4%-95.8%) from day 5 to day 15; and 97.4% (86.8%-99.5%) after > 15 d from PCR diagnosis[15]. However, Plebani *et al*[16] found that 6.2 kAU/L was the appropriate cutoff for the DiaSorin method to reach a sensitivity of 97.1% and a specificity of 88.9%. Moreover, in our hospital, all health care workers (HCW) were tested for serology immediately after the first 2 mo of pandemic (between April and May 2020). Among the HCW who were previously confirmed ill, only the 85% of them resulted having IgG value > 15, whereas 14% of them had values between 7 and 15 (data from National Institute of Heath, 2020).

Thus, in the present study we decided to perform the analysis using both 15 and 7 as cutoffs, considering 7 as the most reliable value.

Swab throat test

All patients who resulted positive for SARS-CoV-2 IgG were tested with a SARS-CoV-2 swab throat test during the same week using the Allplex 2019-nCoV assay (Arrow Diagnostics S.r.l., Genova, Italy),

which is a single-tube assay able to detect the three target genes (*E* gene, *RdRP* gene and *N* gene) as recommended by the World Health Organization.

Statistical analysis

Categorical variables were described as count and percentage and compared between groups with the χ^2 test. Continuous variables were described as mean and standard deviation or median and interquartile range if not normally distributed (Shapiro-Wilks test) and compared with independent *t*-test or Mann-Whitney.

Univariate and multivariate logistic regression models were used to assess: (1) Association between age, sex, BMI, IBD type, IBD treatments, IBD clinical activity, Charlson Comorbidity Index and SARS-CoV-2 IgG positivity; and (2) Association between age, sex, BMI, IBD type, IBD treatments, IBD clinical activity, Charlson Comorbidity Index and presence of COVID-19 symptoms.

The analysis was performed using SARS-CoV-2 IgG value cutoff of > 7 kAU/L (15-16).

RESULTS

In total, 103 IBD patients were consecutively enrolled; 54 had Crohn's disease and 49 ulcerative colitis. Among these, 36 patients (35.0%) were treated with biologic treatment, 14 (13.6%) with azathioprine (AZA) and 53 (51.4%) with mesalazine. Demographic, clinical and therapeutic characteristics of the cohort were summarized in Table 1**.** The survey's results were summarized in Table 2.

Prevalence of SARS-CoV-2 IgG positivity in IBD cohort

SARS-CoV-2 IgG positivity with value > 7 was found in 19 out of 103 patients (18.4%). Among them: 10 were under biological treatment; 5 under AZA; and 4 under mesalazine. Symptoms related to COVID-19 disease were reported in 12 out of 19 patients (63%). Among them, 2 were treated with mesalazine, 4 with AZA and 6 with biologic treatment. Among the 7 out of 19 patients without a history of COVID-19-related symptoms but positive for antibodies, 2 were treated with mesalazine, 1 with AZA and 4 with biologic therapy. All but one patient, who had pneumonia and was under AZA treatment, did not require hospitalization. Data regarding the patients with IgG > 7 were summarized in Table 3.

Swab throat test

All the patients with IgG > 7 were tested with a swab throat test. All of them were negative. The patient with a history of COVID-19 pneumonia had tested positive before the enrollment and tested negative after enrollment.

Correlation between SARS-CoV-2 IgG positivity and clinical/therapeutic variables in the IBD cohort

SARS-CoV-2 IgG value ≥ 7 correlated at multivariate analysis only with IBD treatment. In detail, stratifying the population for treatment, the relative risk of having SARS-COV-2 IgG ≥ 7 was higher for patients treated with AZA and lower with mesalazine. The odds ratios for AZA was 1.44 (95%CI: 0.27-7.56) and 0.16 (95%CI: 0.03-0.71) for mesalazine *vs* biologic drug (P = 0.0157 between them). The relative risk for patients under mesalazine was lower than for those under biologic therapy (P = 0.016).

Correlation between the presence of COVID-19-related symptoms and clinical/therapeutic variables in IBD cohort

The presence of COVID-19-related symptoms were correlated after multivariate analysis with BMI (P = 0.05) and with IBD therapy. The relative risk of having symptoms was higher for patients treated with AZA and lower with mesalazine *vs* biologic drug: odds ratios 7.47 (95%CI: 1.22-45.73) and 0.52 (95%CI: 0.17-1.72, P = 0.03) for AZA and mesalazine, respectively (P = 0.004 between them).

DISCUSSION

The use of SARS-Cov-2 antibodies to monitor the immunity against COVID-19 remains a matter of debate in the general population. However, the presence of SARS-CoV-2 IgG antibodies certify the previous or recent infection[17]. In our hospital, all health care workers (HCW) were tested for serology immediately after the first 2 mo of pandemic, in the same week of the start of our study on IBD cohort. 364 out of 1600 operators were diagnosed as affected by COVID-19 between February 21 and April 22 and all of them tested positive for SARS-CoV-2 swab throat test. Among the HCWs who were previously confirmed ill, the 99% resulted having IgG3 value > 7. Interestingly, 20% of operators who did not report symptoms suggestive for COVID-19 resulted having SARS-CoV-2 antibodies ≥ 7. (data from National Institute of Health, 2020). This observation confirms the presence of an unknown number of asymptomatic infected people[18]. The available studies on the serum concentration of IgG after

Table 1 Demographic, clinical and therapeutic characteristics of the inflammatory bowel disease cohort

Therapy	Characteristics (*n*, %)	Disease		Total (*n*)
		CD (*n*)	UC (*n*)	
Biologic treatment	Male (15, 41.6)	13	3	36
	Woman (20, 55.5)	15	5	
	BMI > 30 (5, 13.8)	3	2	
	BMI < 30 (31, 82.2)	25	6	
	Comorbidities yes (14, 38.8)	11	3	
	Comorbidities no (22, 61.2)	17	5	
	Age > 65 (5, 13.8)	2	3	
	Age < 65 (31, 86.2)	26	5	
Azathioprine	Male (9, 64.2)	3	6	14
	Woman (5, 35.7)	2	3	
	BMI > 30 (1, 7.1)	1	0	
	BMI < 30 (13, 92.8)	4	9	
	Comorbidities yes (6, 42.8)	2	4	
	Comorbidities no (8, 57.1)	3	5	
	Age > 65 (3, 21.4)	1	2	
	Age < 65 (11, 78.6)	4	7	
Mesalazine	Male (23, 43.4)	10	13	53
	Woman (30, 56.6)	11	19	
	BMI > 30 (6, 11.3)	2	4	
	BMI < 30 (47, 88.7)	19	28	
	Comorbidities yes (30, 56.6)	10	20	
	Comorbidities no (23, 43.3)	11	12	
	Age > 65 (19, 35.8)	10	9	
	Age < 65 (34, 64.2)	11	23	
		54	49	103

BMI: Body mass index; CD: Crohn's disease; UC: Ulcerative colitis.

COVID-19 infection revealed conflicting results and the duration of antibodies rises is currently unknown, but is estimated around 9 mo (data from National Institute of Health, 2021). There is a possible decrease of IgG title after the first two wk of infection and it is unclear whether the test is able to detect lower antibody levels in milder and asymptomatic COVID-19 disease[17-20]. Plebani group tried to harmonize the thresholds to allow a larger agreement on IgG anti Sars-Cov-2 antibodies determination. They found 6.2 KAU/L as the cut off for Diasorin method to reach a sensitivity of 97.1% and a specificity of 88.9% for the diagnosis of SARS-CoV-2 infection[16]. Our data are thus in line with this latter observation. The COVID-19 symptoms occurred in IBD patients at least 1 mo before the interview. During the time between the symptoms and the enrollment, they lived the complete lock down, established in Italy from March 9 to May 18. They tested all negative at the swab test performed at the enrollment. This is in line with the overall sensitivity of the test, ranging from 56 to 83%: 66.7% in the first week of the infection and lower in the following wk observation that the SARS-CoV-2 positivity in the swab[21].

Prevalence of patients with SARS-CoV-2 IgG positivity in our cohort was 18.4%. This means that those patients got infected with SARS-CoV-2 virus in the previous period, but only 63% of them developed the disease, reporting symptoms. Moreover, only one patient required hospitalization for pneumonia. The patients with history of COVID-19 related symptoms mainly had mild respiratory symptoms or minor manifestations. None but one patient (5%) required hospitalization, but without the need of intensive care unit. Conversely, in the general population, during both the first and the second

Table 2 Survey responses of 103 inflammatory bowel disease patients

Survey answers					
Close contacts with positive patients (*n*, %)		Yes	17, 16.5		
		No	85, 82.5		
		Nd	1, 1		
Tested for swab (*n*, %)		Yes	13, 12.5	Positive	1, 1
				Negative	12, 11.5
		No	90, 87.5		
Symptoms (*n*, %)	No symptoms		49, 47.5		
	Mild	Cough	19, 18.4		
		Changes in taste/smell	6, 5.8		
		Muscle and joint pain	12, 11.6		
		Asthenia	11, 10.6		
		Fever	18, 17.4		
		GI symptoms	23, 22.3		
	Severe	Mild dyspnea	4, 3.8		
		Pneumonia	1, 0.9		
Total number of patients (*n*)					103

GI: Gastrointestinal; Nd: Not determined.

Table 3 Severe acute respiratory syndrome coronavirus 2 IgG positive inflammatory bowel disease patients divided by presence or absence of COVID-19 symptoms and ongoing therapy

SARS-CoV-2 IgG value > 7				
SARS-CoV-2 IgG positive patients (*n*, %)	**Therapy (patients, *n*, %)**	**Disease**		**Total *n* (%)**
		CD (*n*)	**UC (*n*)**	
COVID-19 symptoms yes (12, 63.2)	Biologic drug (6, 50.0)	5	1	6
	Azathioprine (4, 33.3)	1	3	4
	Mesalazine (2, 16.6)	0	2	2
COVID-19 symptoms no (7, 36.8)	Biologic treatment (4, 57.1)	4	0	4
	Azathioprine (1, 14.3)	0	1	1
	Mesalazine (2, 28.6)	0	2	2
		12	7	19

CD: Crohn' s disease; COVID-19: Coronavirus disease 2019; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; UC: Ulcerative colitis.

wave of the pandemic, 10% of people required hospitalization in intensive care unit (data from the National Institute of Health, 2021). Half of the IBD patients that resulted positive to antibody test remained asymptomatic and in 48% of cases they developed only mild symptoms. We can thus conclude that the IBD population does not seem at higher risk to develop severe COVID-19 disease in comparison with the general population, confirming the observation of Bezzio *et al*[9]. Only the patient with pneumonia hold the IBD treatment. This happened because, due to the mildness of the disease, the patients informed the general practitioner but not the IBD center about the symptoms. These data, even if do not confirm the American Gastroenterological Association guidelines strategy, gave us the opportunity to evaluate the cohort[1]. The results obtained are encouraging, as it seems that IBD patients with COVID-19 ongoing disease with symptoms could continue any treatments both avoiding IBD relapse and without a significant higher risk of developing severe COVID-19 requiring hospitalization. Differently from Bezzio *et al*[9], nobody died in our cohort; moreover, nor age neither active IBD

were significantly associated with a COVID-19 worse prognosis.

SARS-coV-2 serology resulted associated only with the ongoing IBD treatment. Among the patients having a positive serology there was a prevalence of biologic therapy. The presence of COVID-19 disease was associated with both IBD therapy and BMI. The patients who reported previous symptoms were treated with mesalazine in 2 cases, with AZA in 4 and with biological treatment in 6; the only patient with pneumonia was treated with AZA. The calculated relative risk of being infected was higher for patients treated with AZA, then for patients treated with biologic drugs and the lowest risk was found for patients treated with mesalazine. We decided to separate the different treatments in the analysis, as the AZA and the biologic therapy have a different mechanism of action: AZA is an immunosuppressive agent, whereas the biologic therapies are known as immunomodulating agents. None of the patients treated with biologic therapy developed a severe COVID-19 disease. Our results show that the use of biologic therapy does not seem to expose the patients to higher risk of severe COVID-19 disease, even when the infection is present. We did not perform a sub-analysis of the different type of biologic treatment for the small sample size. However, we report that the 80% of patients was treated with anti-TNF agents. More studies are needed to confirm whether it is appropriate to continue biological drugs for IBD patients who are affected with Sars-cov-2. The other variable associated with the presence of COVID-19 related symptoms was the BMI. This data is supported by the literature, as obesity is a factor associated with bad prognosis in the patients with COVID-19 pneumonia [22]. Interestingly, nor the old age neither the comorbidities or the type of IBD were associated with the antibody positivity or the development of COVID-19 symptoms in our study. This could be explained by the fact that these variables were associated in literature to death or very bad outcome, and none of our patients reported such complication[23].

All the 103 patients of the study had been clinically followed up for 10 mo after the beginning of the study. None of them hold the IBD treatments or developed new symptoms of COVID-19 until April 2021. After this period of time all our IBD patients had been received the vaccine against COVID-19.

The main limitation of the study is the small sample. Therefore, further studies with larger populations are needed to confirm our observations.

CONCLUSION

We investigated both the SARS-CoV-2 IgG positivity in symptomatic and asymptomatic IBD patients and the relationship between IBD therapy and COVID-19 disease severity. The results are interesting and seem encouraging for the patients treated with biologic therapy, since they don't seem to carry a high risk of developing severe COVID-19. However, further and larger studies are needed to confirm these observations.

ARTICLE HIGHLIGHTS

Research background

Guidelines recommend to hold inflammatory bowel diseases (IBD) biologic therapy during coronavirus disease 2019 (COVID-19). It is still not clear if the IBD patients carry a high risk of developing severe COVID-19.

Research motivation

IBD patients could carry a high risk of relapse or worsening of the intestinal disease in holding the therapy.

Research objectives

To investigate the prevalence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibodies positivity and COVID-19 disease severity in IBD patients. Evaluate the correlation with clinical/therapeutic variables.

Research methods

Prospective cohort study. Patients with IBD were consecutively enrolled from April 22nd to May 31st 2020. Age, sex, BMI, IBD type, treatments and clinical activity and other comorbidities were anonymously collected in a Database. Charlson Comorbidity Index was calculated for each patient. A single blood test was performed to each patient to search for Immunoglobulin IgG anti SARS-Cov-2. The LIAISON® SARS-CoV-2 S1/S2 IgG test [DiasorinS.p.A, Saluggia (VC) – Italy] was used according to manufacturers' instructions. The analysis was performed using SARS-CoV-2 IgG value cut off of > 7 kAU/L. All patients who resulted positive to SARS-CoV-2 IgG were tested with SARS-CoV-2 swab throat test during the same week, using the Allplex 2019-nCoV assay (Arrow Diagnostics S.r.l., Genova,

Italy) a single-tube assay able to detect the three target genes (E gene, RdRP gene and N gene) as in the WHO recommended protocols. Categorical variables were described as count and percentage and compared between groups with chi square test; continuous variables were described as mean and standard deviation or median and inter-quartile range if not normally distributed (Shapiro-Wilks test) and compared with independent t- test or Mann-Whitney. Through univariate and multivariate logistic regression models were assessed: association between age, sex, BMI, IBD type, IBD treatments, IBD clinical activity, Charlson Comorbidity Index and SARS-CoV-2 IgG positivity or the presence of COVID-19 symptoms.

Research results

103 IBD consecutive patients were enrolled: 54 with Crohn's disease and 49 ulcerative colitis. 36 patients (35%) were treated with biologic treatment, 14 (13.6%) with azathioprine (AZA) and 53 (51.4%) with mesalazine. 19 out of 103 patients (18.4%) had SARS-CoV-2 IgG positivity, with value > 7. Among them: 10 were under biological treatment, 5 under AZA and 4 under mesalazine. 12 out of 19 (63%) reported symptoms related to COVID-19 disease. Among them, 2 were treated with mesalazine, 4 with AZA and 6 with biologic treatment. Among the 7 out 19 patients without history of COVID-19 related symptoms, but positive for antibodies, 2 were treated with mesalazine, one with AZA and 4 with biologic therapy. All but one patient, who had pneumonia and was under AZA treatment, did not require hospitalization. All the patients with IgG > 7 were tested for swab throat test. All of them resulted negative at the enrollment. SARS-CoV-2 IgG value ≥ 7 correlated at multivariate analysis only with IBD treatment. The relative risk of having SARS-COV-2 IgG ≥ 7 was higher for patients treated with AZA and lower with mesalazine: odds ratio (OR) 1.44 (95%CI: 0.27-7.56) and 0.16 (95%CI: 0.03-0.71), for AZA and mesalazine, respectively, *vs* biologic drug (P = 0.0157 between them). The relative risk for patients under mesalazine was lower than for those under biologic therapy, P = 0.016. The presence of COVID-19 related symptoms resulted correlated at multivariate analysis with Body Mass Index (BMI), P = 0.05 and with IBD therapy. The relative risk of having symptoms was strongly higher for patients treated with AZA and lower with mesalazine *vs* biologic drug: odds ratio (OR) 7.47 (95%CI: 1.22-45.73) and 0.52 (95%CI: 0.17-1.72, P = 0.03), for AZA and mesalazine, respectively (P = 0.004 between them).

Research conclusions

The patients treated with biologic therapy don't seem to carry a high risk of developing severe COVID-19.

Research perspectives

The patients treated with biologic therapy don't seem to carry a high risk of developing severe COVID-19. Therefore, further and larger studies are needed to confirm these observations and to understand if the strategy to hold the IBD treatment during COVID-19 disease could be modified.

FOOTNOTES

Author contributions: Conti CB and Grassia R conceived and planned the study; Mainardi E, Grassia R, Drago A, Cereatti F, Soro S and Testa S carried out the tests and collected the data; Testa S and Mainardi E contributed to the interpretation of the results; De Silvestri A performed the statistical analysis; Conti CB wrote the manuscript; all authors provided critical feedback and helped the research and analysis of the manuscript.

Institutional review board statement: The study was reviewed and approved by the Institutional Review Board Comitato EticoVal Padana.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: No conflict of interest.

Data sharing statement: Technical appendix, statistical code, and data set available from the corresponding author at benedetta.conti1@gmail.com. Participants gave informed consent for data collection and data are recorded anonymized. Risk of identification is very low.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

Country/Territory of origin: Italy

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S-Editor: Wang LL
L-Editor: Filipodia
P-Editor: Wang LL

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World Journal of Gastrointestinal Endoscopy

Submit a Manuscript: https://www.f6publishing.com

World J Gastrointest Endosc 2022 March 16; 14(3): 163-175

DOI: 10.4253/wjge.v14.i3.163

ISSN 1948-5190 (online)

SYSTEMATIC REVIEWS

Endoscopic management and outcome of non-variceal bleeding in patients with liver cirrhosis: A systematic review

Georgios Demetriou, Aikaterini Augoustaki, Evangelos Kalaitzakis

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A, A
Grade B (Very good): 0
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Cheng L, Gadour E

Received: June 30, 2021
Peer-review started: June 30, 2021
First decision: September 29, 2021
Revised: October 8, 2021
Accepted: February 10, 2022
Article in press: February 10, 2022
Published online: March 16, 2022

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Abstract

BACKGROUND

Acute non-variceal bleeding accounts for approximately 20% of all-cause bleeding episodes in patients with liver cirrhosis. It is associated with high morbidity and mortality therefore prompt diagnosis and endoscopic management are crucial.

AIM

To evaluate available data on the efficacy of endoscopic treatment modalities used to control acute non-variceal gastrointestinal bleeding (GIB) in cirrhotic patients as well as to assess treatment outcomes.

METHODS

Employing PRISMA methodology, the MEDLINE was searched through PubMed using appropriate MeSH terms. Data are reported in a summative manner and separately for each major non-variceal cause of bleeding.

RESULTS

Overall, 23 studies were identified with a total of 1288 cirrhotic patients of whom 958/1288 underwent endoscopic therapy for acute non-variceal GIB. Peptic ulcer bleeding was the most common cause of acute non-variceal bleeding, followed by portal hypertensive gastropathy, gastric antral vascular ectasia, Mallory-Weiss syndrome, Dieaulafoy lesions, portal hypertensive colopathy, and hemorrhoids. Failure to control bleeding from all-causes of non-variceal GIB accounted for less than 3.5% of cirrhotic patients. Rebleeding (range 2%-25%) and mortality (range 3%-40%) rates varied, presumably due to study heterogeneity. Rebleeding was usually managed endoscopically and salvage therapy using arterial embolisation or surgery was undertaken in very few cases. Mortality was usually associated with liver function deterioration and other organ failure or infections rather than uncontrolled bleeding. Endoscopic treatment-related complications were extremely rare. Lower acute non-variceal bleeding was examined in two studies (197/1288 patients) achieving initial hemostasis in all patients using argon plasma coagulation for portal hypertensive colopathy and endoscopic band ligation or

sclerotherapy for bleeding hemorrhoids (rebleeding range 10%-13%). Data on the efficacy of endoscopic therapy of cirrhotic patients *vs* non-cirrhotic controls with acute GIB are very scarce.

CONCLUSION

Endotherapy seems to be efficient as a means to control non-variceal hemorrhage in cirrhosis, although published data are very limited, particularly those comparing cirrhotics with non-cirrhotics and those regarding acute bleeding from the lower gastrointestinal tract. Rebleeding and mortality rates appear to be relatively high, although firm conclusions may not be drawn due to study heterogeneity. Hopefully this review may stimulate further research on this subject and help clinicians administer optimal endoscopic therapy for cirrhotic patients.

Key Words: Liver cirrhosis; Non-variceal gastrointestinal hemorrhage; Gastrointestinal endoscopy; Endoscopic therapy; Patient outcomes; Peptic ulcer; Mallory Weiss syndrome; Gastric antral vascular ectasia

Core Tip: Acute non-variceal gastrointestinal bleeding (ANVGIB) is not uncommon in cirrhotic patients. Survival of these patients has improved in recent years due to the evolution of both endoscopic and pharmacologic treatment. However data on most sources of ANVGIB and the efficacy of endoscopic therapy in cirrhosis are very limited, while similar data on acute bleeding from the lower gastrointestinal tract are almost non-existent in this group of patients. We herein present endoscopic modalities used to control ANVGIB and post-treatment outcomes in patients with liver cirrhosis. Our review highlights that endoscopic therapy seems to be effective in these patients, although comparative data with non-cirrhotic patients are very few.

Citation: Demetriou G, Augoustaki A, Kalaitzakis E. Endoscopic management and outcome of non-variceal bleeding in patients with liver cirrhosis: A systematic review. *World J Gastrointest Endosc* 2022; 14(3): 163-175
URL: https://www.wjgnet.com/1948-5190/full/v14/i3/163.htm
DOI: https://dx.doi.org/10.4253/wjge.v14.i3.163

INTRODUCTION

Acute upper gastrointestinal bleeding (AUGIB) in patients with cirrhosis is a detrimental complication resulting in high morbidity and mortality[1-3]. The source of AUGIB is most commonly related to portal hypertension and occurs mainly from gastroesophageal varices (60%-75%). However, a non-negligible number (20%-30%) of cirrhotic patients present with non-variceal gastrointestinal bleeding (NVGIB) with peptic ulcer being the leading cause[2,4-7]. Other sources of NVGIB in this group of patients are gastric antral vascular ectasia (GAVE), portal hypertensive gastropathy (PHG), portal hypertensive colopathy (PHC), Dieulafoy's lesions (DL), Mallory-Weiss syndrome (MWS), and hemorrhoids[8].

Regardless of the bleeding source, treatment and endoscopic control of haemorrhage can be really challenging due to the fragility of these patients and coagulopathy disorders in cirrhosis[9,10]. Albeit mortality rates have been declining in recent years due to advances in pharmaceutical and endoscopic management, the death burden remains high ranging from 15%-25% following an episode of AUGIB[3,11-14]. Although variceal bleeding in cirrhosis has been well studied, published data on outcomes of acute non-variceal upper and lower GIB are limited, with only few studies reporting the endoscopic modalities and efficacy of endoscopic therapy in patients with cirrhosis and acute NVGIB.

The aim of this systematic review was to evaluate available data on the efficacy of endoscopic treatment modalities used to control acute NVGIB in cirrhotic patients as well as to assess the treatment outcomes.

MATERIALS AND METHODS

A systematic review was conducted according to the PRISMA statement for reporting systematic reviews and meta-analyses[15]. The MEDLINE was searched through PubMed by two authors (Demetriou G, Augoustaki A) independently for relevant studies (start date: 01/01/1980, end date: 01/01/2021) using the following query: "Liver Cirrhosis" AND "Gastrointestinal Hemorrhage/therapy". All studies were eligible for inclusion except: (1) Studies in languages other than English; (2) Animal studies; (3) Cohort studies focused only on variceal bleeding; (4) Case reports (< 3 patients) or

reviews, meta-analyses, and letters; (5) Pediatric studies; (6) Iatrogenic induced haemorrhage; and (7) Studies conducted before 1980.

Our search strategy revealed 2002 relevant studies that were screened by Demetriou G and Augoustaki A according to their titles and abstracts. Following application of the exclusion criteria, 51 studies were chosen for full-text screening (Figure 1). Any disagreement was resolved by means of consensus with a third author (Kalaitzakis E). These studies were further subjected for eligibility and were excluded if: (1) Series with < 3 patients; (2) No numerical data for cirrhotic patients; (3) Not overt bleeding (overt bleeding was defined as the presence of melena and/or hematemesis and/or hematochezia or active bleeding on endoscopy); (4) No endoscopic treatment; and (5) Not at least one treatment outcome.

The list of references of all included studies and relevant review articles were checked and additional studies were included according to the eligibility criteria. A total of 23 studies were finally included for this review (Figure 1).

RESULTS

Study characteristics

The majority of the included studies (Table 1) were retrospective (15/23, 65%) while 8 (35%) were prospective. Except for two multi-center studies (9%) the remaining were single-centre (21/23, 91%). Most studies evaluated outcomes of AUGIB from a single source of bleeding, *i.e.* 7 studies from GAVE, four from peptic ulcer, four from MWS, two from PHC, two from Dieulafoy's lesion and one each from PHG and hemorrhoids. Three studies evaluated more than one sources of AUGIB.

Endoscopic treatment modalities applied to control bleeding (either as single or combination treatment) were epinephrine injection (10 studies), argon plasma coagulation (APC) (9 studies), electrocoagulation (6 studies), hemocliping (5 studies), injection sclerotherapy (polidocanol, N-butyl-cyanoacrylate, histoacryl) (5 studies), endoscopic band ligation (EBL) (4 studies), heater probe coagulation (3 studies), laser coagulation (1 study), and hemospray (1 study). The most common outcomes in the majority of the studies were success in control of bleeding, rebleeding, and mortality.

Overall, 1288 cirrhotic patients were included in the 23 studies identified by means of our search and 958/1288 underwent endoscopic therapy for non-variceal acute gastrointestinal bleeding (NVAGIB) (Tables 1-4). Failure to control bleeding from all-causes of NVAGIB was not common and accounted for 3.5% of cirrhotic patients who underwent endoscopic therapy[16,17]. Rebleeding (usually within 30 d or 6 wk following the index endoscopy) ranged between 2%-25% (Tables 2 and 4). Rebleeding was usually managed endoscopically and salvage therapy using arterial embolisation or surgery was undertaken in very few cases (n = 8). Mortality ranged between 3%-40%, although follow-up was variable, and it was usually associated with liver function deterioration and other organ failure or infections rather than uncontrolled bleeding. Endoscopic treatment-related complications were extremely rare (n = 1).

Peptic ulcer disease

Overall, 7 studies including a total of 947 (range 29-235) patients with cirrhosis and NVAUGIB were identified (Table 2)[18-24]. Peptic ulcer disease (PUD) was the aetiology of NVAUGIB in 799 patients (311 with duodenal ulcer, 438 with gastric ulcer, 39 with both duodenal and gastric ulcers, 8 with oesophageal ulcer and 3 with stomal ulcer). Most patients (686/947) required endoscopic therapy. The most common endoscopic modality used to control bleeding was combination of epinephrine injection with coagulation or hemoclips (198 patients). Data for failure to control bleeding at the index endoscopy were available in 4 studies (30 patients) and ranged between 1.3% and 10% (median 7.5%) (Table 2). Rescue therapy was not common (Table 2). Rebleeding rates were examined in all studies and occurred in a total of 121/947 (12.7%) patients (range 1.9%-22.4%). In-hospital mortality data were available in 4 studies and reached a total of 112/698 (16%) patients (range 13.8%-17.6%). Three studies examined 6-wk or 30-d mortality which was found to be 14.5% (36/249 patients) (range 3%-17%).

GAVE

Seven studies were identified reporting the outcomes and endoscopic modalities used in a total of 128 patients with AUGIB due to GAVE of whom 47 were cirrhotics (Table 3). The most common endoscopic modality used was APC in a total of 86/128 patients. Regardless of the endoscopic modality, sessions needed to achieve eradication of GAVE and/or improvement of symptoms ranged between 1 and 10, although recurrence of GAVE was documented in most patients (Table 3). The most common outcomes reported were need for blood transfusions before and after endoscopic treatment, eradication of GAVE and treatment complications as well as mortality. Four studies reported reduction in transfusion units needed after endoscopic treatment[25-28]. Three studies reported no treatment-related complications whereas Fuccio *et al*[28] reported abdominal discomfort or pain in almost all patients which ceased spontaneously and Sato *et al*[29] a post-treatment bleeding ulcer. Mortality during follow-up was available in four studies (ranged between a mean/median of 6 and 25 mo) and reached a total of 26/74 (35%) patients of whom 4 died due to uncontrolled bleeding[25,27-29].

Table 1 Main characteristics of all included studies

Ref.	Type of study	Period of enrolment, years	Number of patients[1]	Number of cirrhotic patients with acute NVGIB	Non-variceal bleeding source	Endoscopic treatment modality	Main outcomes
Paquet *et al* [30]	Retrospective	1985-1987	339	53	MWS	EIS (polidocanol)	CoB
Baettig *et al* [35]	Retrospective	1984-1991	480 (28 with Dieulafoy's lesion)	3	DL	EI + EIS (polidocanol)	CoB; Rebleeding; Mortality
Labenz *et al* [25]	Retrospective, case series	NR	5	3	GAVE	Nd-YAG LC	CoB; Post treatment TU (median f/up 8 mo)
Schuman *et al*[31]	Retrospective	1985-1990	42	14	MWS	BICAP electrocoagulation, Epinephrine injection	CoB; Severity of bleeding in relation to liver disease and/or PH[2]
Ikeda *et al* [16]	Retrospective	1993-1996	5	4	GAVE	EC or HPC	CoB; Eradication of GAVE; Endoscopic pattern and development of GAVE
Dulai *et al* [26]	Prospective	1991-1999	744 (26 with GAVE)	7	GAVE	Bipolar EC, HPC, APC	Hct pre- and post-treatment; TU needed; Number of hospitalizations pre- and post-treatment (median f/up 6 mo)
Cheng *et al* [36]	Retrospective	1999-2001	1393 (29 with DL)	5	DL	EI, EIS, HPC	CoB; Rebleeding; Mortality
Sato *et al*[17]	Retrospective	2001-2003	8	5	GAVE	APC	Recurrence of GAVE (mean f/up 28 mo); CoT (mean f/up 28 mo)
Higuchi *et al* [32]	Prospective	1998-2005	37	11	MWS	EBL	CoB; Rebleeding (28 d)
Lecleire *et al* [27]	Retrospective	2001-2005	30	11	GAVE	APC	CoB; GAVE pattern; Recurrence of symptoms (median f/up 20 mo); CoT (median f/up 20 mo)
Seo *et al*[18]	Retrospective multicenter	May-October 2005	464	76	GU, DU, OS	EC	CoB; Rebleeding (42 d); Mortality (42 d)
Lecleire *et al* [33]	Prospective	2001-2008	218	7	MWS	EBL or EI + HC	CoB; Rebleeding; TU needed; Mortality
Fuccio *et al* [28]	Prospective	2002-2006	20	4	GAVE	APC	Resolution of transfusion dependent anemia (mean f/up 25 mo); CoT (mean f/up 25 mo)
González-González *et al*[22]	Prospective	2000-2009	160	160	GU, DU, OS	BICAP EC, EI	CoB; Rebleeding; Mortality (in-hospital)
Gad *et al*[37]	Retrospective	2007-2011	77	77	PHC, OS	APC	CoB; PHC prevalence; PHC endoscopic pattern
Awad *et al* [38]	Prospective	2009-2010	120	120	Hemorrhoids	EBL, EIS (ethanolamine or N-butyl cyanoacrylate)	CoB; HR; Rebleeding; Pain relief; Patient's satisfaction
Rudler *et al* [23]	Prospective	2008-2011	203	29	PU	EI, HC	CoB; Rebleeding; Mortality (30 d); RT
Sato *et al*[29]	Retrospective	NR	34	13	GAVE	APC, EBL	CoB; Rebleeding; Mortality; GAVE recurrence
Smith *et al* [34]	Retrospective, case series	NR	4	4	PHG, PHC	Hemospray	CoB; CoT

Morsy *et al* [24]	Prospective	2011-2012	532	93	GU, DU, OS	EI, APC	Early rebleeding (24 h after stabilising patient); Mortality (in-hospital)
Yang *et al* [19]	Retrospective	2007-2013	210	210	PU	EI, APC, HC	CoB; Rebleeding; Mortality (in-hospital); Infection (in-hospital); Length of hospital stay
Kuo *et al*[20]	Retrospective	2008-2014	235	235	PU	EI, APC, HC	CoB; Rebleeding; Mortality (in-hospital); Infection (in-hospital); Length of hospital stay
Ardevol *et al* [21]	Retrospective multicenter	2005-2012	790	144	PU	EI, Multipolar EC, HC, EIS	CoB; Rebleeding (1-45 d); Mortality (45 d, 1 year); RT

[1]Including cirrhotics and non-cirrhotics with acute non-variceal gastrointestinal bleeding and cirrhotics with obscure gastrointestinal bleeding;
NR: Not reported; MWS: Mallory-Weiss syndrome; DL: Dieaulafoy's lesion; GAVE: Gastric antral vascular ectasia; PHC: Portal hypertensive colopathy; PHG: Portal hypertensive gastropathy; LC: Lasercoagulation; APC: Argon plasma coagulation; EBL: Endoscopic band ligation; EIS: Endoscopic injection sclerotherapy; EI: Epineprhine injection, HPC: Heater probe coagulation; CoB: Control of bleeding; TU: Transfusion units; PH: Portal hypertension; Hct: Hematocrit; CoT: Complications of treatment; PU: Peptic ulcer; GU: Gastric ulcer; DU: Duodenal ulcer; OS: Other sources; HR: Hemorrhoids recurrence; RT: Rescue therapies.

Table 2 Main characteristics of studies including patients with cirrhosis and acute upper gastrointestinal bleeding due to peptic ulcers

Ref.	Patients (*n*)	Cirrhotic patients with NVAGIB (*n*)	Non-variceal bleeding source: peptic ulcer/other (*n*)	Patients received endoscopic treatment (*n*)	Endoscopic treatment modality (*n*)	Failure to control bleeding, *n* (%)	Rebleeding, *n* (%)	Mortality, *n* (%)	Rescue therapy
Seo *et al* [18]	464	76	GU: 48; DU: 16; OL: 12	48	EC: 20[1]	1/76 (1.3%)	2/76 (2.6%)	42 d: 11/76 (14.5%)	NR
González-González *et al*[22]	160	160	GU: 39; DU: 33; GU + DU: 9; EU: 3	43	EI: 7; BICAP EC: 6; CT: 30	NR	3/160 (1.9%)	In-hospital: 22 (13.8%)	S: 0
Rudler *et al*[23]	203	29	DU: 19; GU: 7; MU: 3	20	EI: 9; EI + HC: 11	NR	2/29 (7%)	30 d: 1/29 (3%)	AE: 3; S: 0
Morsy *et al*[24]	532	93	DU: 25; EU: 5; GU: 3	42	EI: 23; APC: 19	NR	4/93 (4.3%)	In-hospital: 13/93 (14%)	NR
Yang *et al* [19]	210	210	GU: 133; DU: 66; GU + DU: 11	210	EI: 80; APC: 41; HC: 13; EI + APC: 36; EI + HC: 40	7 (3.3%)	47 (22.4%)	In-hospital: 37/210 (17.6%)	NR
Kuo *et al* [20]	235	235	GU:146; DU: 73; GU + DU: 16	235	EI: 84; APC: 50; HC: 20; CT: 81	8 (3.4%)	48 (20.4%)	In-hospital: 40/235 (17%)	NR
Ardevol *et al*[21]	790	144	DU: 79; GU: 62; SU: 3	88	EI: NR; Multipolar EC: NR; HC: NR; EIS: NR	14 (10%)	15 (10%)	6 wk: 24/144 (17%)	SET: 11; AE: 3; S: 2

[1]Endoscopic treatment modality only mentioned for 20/48 patients;
NVAGIB: Non-variceal acute gastrointestinal bleeding; GU: Gastric ulcer; DU: Duodenal ulcer; EU: Esophageal ulcer; OL: Other lesions; MU: Multiple ulcers; EC: Electrocoagulation; EI: Epinephrine injection; HC: Hemoclips; CT: Combination therapy; APC: Argon plasma coagulation; EIS: Endoscopic injection sclerotherapy; NR: Not reported; S: Surgery; AE: Arterial embolisation; SET: Second endoscopic treatment.

The largest study by Sato *et al*[29] retrospectively compared APC and EBL for the treatment of GAVE (Table 3). On endoscopy, eight active bleeders were identified in the APC group and five in the EBL group and they were all successfully managed. Recurrence rates of GAVE were significantly higher in the APC group ($P < 0.05$). No endoscopy-related complications were observed apart from one patient in the EBL group who had a bleeding ulcer successfully treated with APC.

MWS

Information regarding endoscopic management in cirrhotic patients with AUGIB due to MWS is scanty.

Table 3 Main characteristics of studies including patients with cirrhosis and acute upper gastrointestinal bleeding due to gastric antral vascular ectasia

Ref.	Patients (*n*)	Cirrhotic patients with overt bleeding (*n*)	Patients received endoscopic treatment (*n*)	Endoscopic treatment modality (*n*)	Failure to control initial overt bleeding, *n* (%)	Endoscopic sessions needed (*n*)	GAVE eradication, *n* (%)	Mortality during follow-up, *n* (%)	Follow-up period (mo)
Labenz *et al*[25]	5	3	5	NA-YAG LC	0	2-8	0	0	2-12 (median = 6)
Ikeda *et al*[16]	5	4	5	EC: NR; HPC: NR	0	NR	0	NR	64.8 (mean)
Dulai *et al*[26]	744 (26 with GAVE)	7	26	Bipolar EC: 13; HPC: 7; APC: 6	0	Median = 3 (2-5)	0	NR	3-10 (median = 6)
Sato *et al*[17]	8	5	8	APC	0	Mean = 1.8 (1-3)	6/8 (75%)	NR	28 (mean)
Lecleire *et al*[27]	30 (17 cirrhotics)	11	30	APC	0	Mean = 2.2	NR	9/17 (53%)	Cirrhotics: 20 (median); Non-cirrhotics: 24 (median)
Fuccio *et al*[28]	20	4	20	APC	0	Median = 3 (1-10)	14/20 (70%)	8/20 (40%)	1-47 (mean = 25)
Sato *et al*[29]	34 (32 cirrohtics)	13	34	APC (22); EBL (12)	0	APC: Mean = 2.3 (1-3); EBL: Mean = 3 (2-4)	APC: 7/22 (32%); EBL 11/12 (92%)	9/34 (26%)	APC: 16.6 (mean); EBL: 14.6 (mean)

GAVE: Gastric antral vascular ectasia; LC: Lasercoagulation; EC: Electrocoagulation; NR: Not reported; HPC: Heater probe coagulation; APC: Argon plasma coagulation; EBL: Endoscopic band ligation.

Table 4 Main characteristics of studies including patients with cirrhosis and acute upper gastrointestinal bleeding

Ref.	Patients (*n*)	Patients with MWS bleeding (*n*)	Cirrhotic patients with MWS bleeding (*n*)	Patients with MWS received endoscopic treatment (*n*)	Endoscopic treatment modalities (*n*)	Failure to control initial overt bleeding, *n* (%)	Rebleeding, *n* (%)	Mortality during follow-up, *n* (%)
Paquet *et al* [30]	339	55	53	53	ES (polidocanol)	0	NR	NR
Schuman *et al*[31]	79	42	14	4	EI; BICAP EC	0	NR	3/42 (7%)
Higuchi *et al*[32]	37	37	11	37	EBL	0	1/37 (2.7%)	1/37 (2.7%)
Lecleire *et al* [33]	218	218	7	56	EBL: 27; EI + HC: 29	0	5/56 (9%) (Hemoclips + Epinephrine)	0
González-González *et al*[22]	160	18	18	0	EI: 0; BICAP EC : 0	NR	NR	22/160 (13.8%)

ES: Esophageal sclerotherapy; EI: Epinephrine injection; EC: Electrocoagulation; NR: Not reported; EBL: Endoscopic band ligation; HC: Hemoclips.

Four studies exclusively examined MWS as the source of bleeding and included a total of 103 cirrhotic patients[30-33] (Table 4). Paquet *et al*[30] examined 55 patients with MWS of whom 53 cirrhotics and successfully applied sclerotherapy with polidocanol into the oesophageal wall to control bleeding. In a prospective study Higuchi *et al*[32] included 37 patients with MWS of c 11 cirrhotics. They achieved initial hemostasis in all patients using endoscopic band ligation. One cirrhotic patient experienced rebleeding within 24 h and died. No other complications during or after endoscopic treatment were reported and no further bleeding during follow up period (1-24 mo). In a comparative prospective study

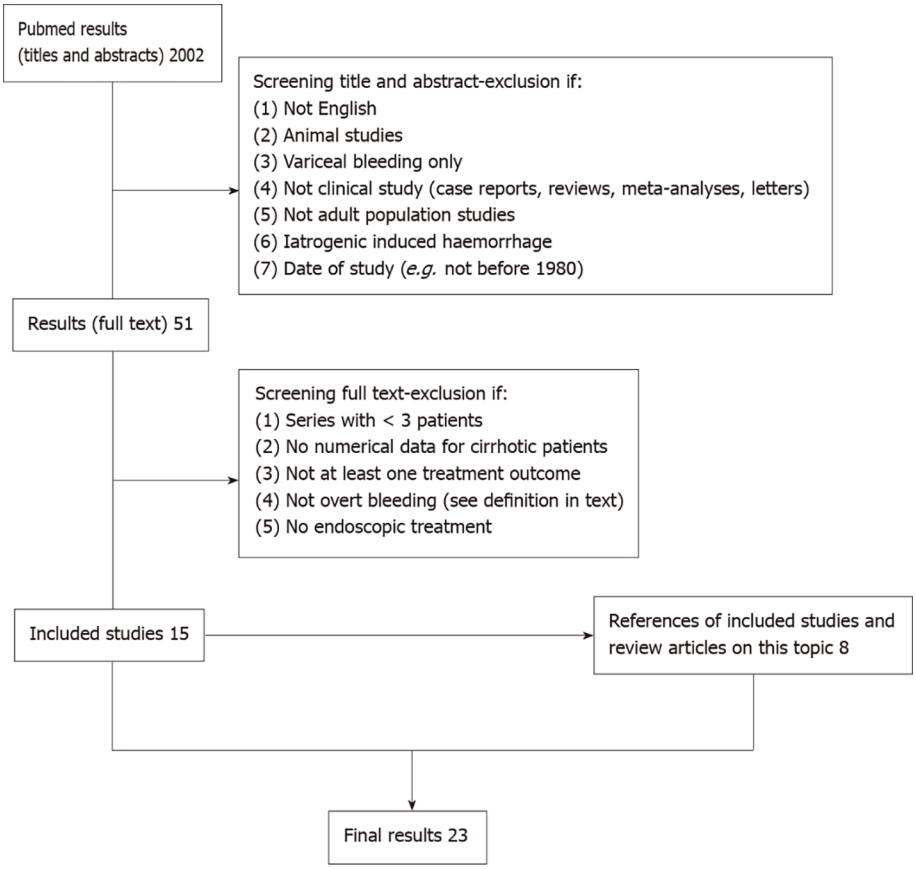

Figure 1 Flow chart of the selection of studies eligible for data extraction.

Lecleire *et al*[33] examined the efficacy of endoscopic band ligation *vs* epinephrine injection plus hemoclip and observed higher rebleeding rates in the latter group (0% *vs* 18%, $P = 0.02$).

PHG

Data on acute bleeding due to PHG and endoscopic therapy are limited. Three studies were identified including a total of 50 cirrhotic patients with acute PHG bleeding[22,24,34]. In one of them, all patients were managed conservatively but outcomes for these patients were not extractable[22]. Morsy *et al*[24] included 93 cirrhotic patients with AUGIB of whom 24 patients with acute bleeding due to PHG. They used epinephrine injection or APC in 42/93 patients with rebleeding rates reaching 4% and in-hospital mortality 14%. In a case series Smith *et al*[34] succesfully used hemospray to control acute bleeding from PHG in 3 patients of whom one had perforation and died 4 d after endoscopy.

DL

AUGIB due to DL is not common and therefore available data are extremely limited. From the studies included in this review González-González *et al*[22] reported one patient with DL who did not receive endoscopic treatment. Two studies fulfilled the inclusion criteria for our review with a total of 57 patients with bleeding DL of whom only 8 cirrhotics[35,36]. Four received epinephrine plus polidocanol injection[35] with the remaining receiving epinephrine injection plus heater probe ($n = 1$[36]), epinephrine injection monotherapy ($n = 1$[36]) or histoacryl injection ($n = 3$[36]) in all cases with initial success and without any reported rebleeding from the same lesion.

Lower acute GIB

Data with regard to lower acute GIB in cirrhotic patients are very scanty. Only two studies that investigated endoscopic therapy of acute bleeding from the lower gastrointestinal tract in patients with cirrhosis were identified[37,38]. In a retrospective series of cirrhotics with hematochezia[37], 7/77 (10%) had PHC-related bleeding. All received endotherapy with APC, achieving initial hemostasis. Moreover 12/77 (16%) patients had polyp-associated bleeding which was controlled with excision polypectomy. Other sources of LAGIB were non-specific (12%) and infectious colitis (34%), ulcerative colitis (9%), hemorrhoids (13%), rectal cancer (4%), colonic adenocarcinoma (4%) and diverticulosis (4%), and patients did not receive any specific endoscopic treatment.

Awad *et al*[38] prospectively compared endoscopic injection sclerotherapy (EIS) with endoscopic endoscopic band ligation (EBL) for the management of bleeding hemorrhoids in 120 cirrhotic patients equally divided into the two groups. Both techniques were effective in the control of bleeding with rebleeding rates reaching 10% and 13% respectively. Rebleeding was successfully managed with repeated sessions of the initial therapy (in total, 13 patients had 2 sessions while another needed 3 sessions). On average 3 bands were used for obliteration of hemorrhoids (range 2-4 bands). Recurrence of hemorrhoids did not differ significantly and occurred in 27% for the EIS group *vs* 18% in the EBL group. EBL seemed to be safer than EIS for patients with advanced cirrhosis as higher Child-Pugh score in the EIS group was correlated with rebleeding, recurrence and abscess formation. The EIS was subdivided into two groups comparing ethanolamine oleate (30 patients) and cyanoacrylate (30 patients). The former was significantly associated with lower rebleeding rates but higher pain score[38].

DISCUSSION

The main finding of the current systematic review is that endotherapy seems to be an efficient means to control hemorrhage in cirrhotics, although data especially with regard to lower bleeding, are limited. Failure to control bleeding from all-causes of NVAGIB was not frequent and accounted for approximately 3.5% of cirrhotic patients. Rebleeding (range 2%-25%) and mortality (range 3%-40%) rates were heterogenous between the studies which may be due to the different case mix, in terms of source of bleeding, endoscopic modality used, duration of follow-up patient age, cirrhosis severity *etc.*

Although variceal bleeding is the main cause of AUGIB in cirrhotic patients, published data have shown that NVGIB is not uncommon and is responsible for almost one fifth of all-cause bleeding episodes in these patients[4-7]. To our knowledge, this is the first systematic review focusing on all-cause of acute gastrointestinal bleeding in cirrhosis. A single previous review performed in 2012 including not only acute but also chronic obscure bleeding[8] while another non-systematic review from 1996 focused on NVAGIB and did not include data on lower gastrointestinal bleeding in these patients [39].

Comparative data on the utility of endoscopic therapy in AUGIB between cirrhotics and non-cirrhotics are scarce. In a prospective study Rudler *et al*[23] examined the aetiology of PUD and outcomes between cirrhotics and non-cirrhotics admitted in the intensive care unit due to PUB. Prognosis, in terms of rebleeding, need for salvage therapy, and mortality, was not different between the groups. Lecleire *et al*[27] compared cirrhotics and non-cirrhotics treated with APC due to bleeding GAVE. Patients with liver cirrhosis had overt bleeding more often (P = 0.01) and a honeycomb appearance of GAVE compared to non-cirrhotics who had a watermelon appearance. On the other hand non-cirrhotic patients required more APC sessions to achieve a stable haemoglobin level (P = 0.04). GAVE related bleeding was also examined by Dulai *et al*[26] in 26 patients of whom 7 cirrhotics and observed that portal hypertension was related to more diffuse gastric lesions and a higher chance of active bleeding during endoscopy. Obliteration of GAVE lesions was not achieved in any patient whether cirrhotic or not. Schuman *et al*[31] retrospectively compared cirrhotics and non-cirrhotics with bleeding MWS. Fourteen cirrhotic patients were identified of whom three with active bleeding during endoscopy and were successfully managed with epinephrine injection and/or BICAP electrocoagulation. Cirrhotics needed more transfusion units than non-cirrhotics whereas no correlation between MWS and the severity of portal hypertension was observed. They experienced 3/42 deaths, none related to MWS bleeding. Thus, it is clear that further studies with appropriate non-cirrhotic controls are warranted to clarify whether endoscopic therapy outcomes are comparable between cirrhotics and non-cirrhotics with acute gastrointestinal bleeding.

Studies that included unselected patients with cirrhosis and AUGIB, *i.e.*, with various causes of bleeding, showed that the most common non-variceal cause was PUD[18,22,24]. This is in accordance with other large studies which demonstrated that PUD accounts for 40%-50% of NVAUGIB in cirrhotic patients[4-7]. PUD have a higher prevalence in patients with cirrhosis compared to non-cirrhotics; in a large Swedish study[40] the overall prevalence of PUD in the general population was 4.1%, whereas in the cirrhotic population there is a significantly higher prevalence of PUD ranging from 20% to almost 50%[41-44]. Moreover, the prevalence of helicobacter pylori is similar between cirrhotics and non-cirrhotics however it does not seem to play a significant role in the development of PUD and its eradication does not seem to decrease the recurrence rate of PUD in these patients[43-47]. It has also been proposed that the more severe liver cirrhosis is, the more increased is the risk for development, recurrence, and complications of PUD[41]. Thus, it has been proposed that physiopathologic mechanisms implicated in the development of peptic ulceration in cirrhosis may differ from those in non-cirrhotic patients; congestive gastropathy and decreased gastric mucosal blood flow, impaired gastric mucus-bicarbonate barrier and epithelial renewal as well as low prostaglandin levels are some of the proposed mechanisms[45,48]. Treatment of PUB in cirrhosis is the same as in the general population. Combination of pharmacologic and endoscopic therapy namely intravenous proton pump inhibitors combined with endoscopic epinephrine injection plus a second hemostasis modality (contact thermal, mechanical or sclerosant therapy) is used to control active bleeding ulcers[49]. Notwithstanding the

same therapeutic management there are important differences compared to the general population as cirrhotics have a four-fold risk of PUB compared to controls and require endoscopic hemostasis more frequently than non-cirrhotics[4,50]. Furthermore, the risk for recurrence of PUB in the long-term and the 90-d mortality after hospitalisation for PUB are increased compared to the general population[51,52].

Published data on the comparative utility of endoscopic therapy in cirrhotics with variceal *vs* with non-variceal bleeding are also very few and somewhat conflicting. A retrospective multicenter study from Korea[18] showed that 6-wk rebleeding rate for NVAUGIB (9.3%) as well as six-week mortality rate (14.5%) were not significantly different from variceal bleeding in cirrhosis. However, comparative data between only PUB and variceal bleeding in these patients available in another retrospective multicenter study[20], demonstrated that rebleeding rates were significantly lower for PUB (10%) than variceal (26%) bleeding, but the 6-wk and 1-year risk of mortality were similar between the two groups.

Published data on the occurrence and endoscopic management of lower acute gastrointestinal bleeding in cirrhosis are very limited, based mainly on case reports, without any multicentre or comparative studies with non-cirrhotics available. Moreover in order to offer the optimal endoscopic and pharmacologic management in this group of patients it is imperative to understand the possible relation of portal hypertension with the cause of bleeding. Although PHC is a well-recognised condition that may be related to lower gastrointestinal bleeding, there is controversy in the literature concerning the relation of portal hypertension with PHC, hemorrhoids and rectal varices[53-57]. A relation between PHC and higher Child-Pugh class as well as history of esophageal band ligation or sclerotherapy has been demonstrated[37]. Hemorrhoids on the other hand seem to be more common in the absence of PHC[37]. Awad *et al*[38] reported that 75/120 (62%) of cirrhotic patients with bleeding hemorroids also had grade II or III oesophageal varices but they do not report how many of their patients had rectal varices or PHC.

One of the major limitations of our review is that data regarding cirrhotics with acute gastrointestinal bleeding are often extracted from cohorts which include non-cirrhotics, therefore cirrhosis-specific outcomes may not be readily available. Furthermore, most studies identified by the current research strategy were retrospective and single-centre and they usually included only few cirrhotic patients. Moreover, most studies did not have a non-cirrhotic control group, while rebleeding and mortality cases could frequently not be traced back to the bleeding source and endoscopic modality used. Last but not least, follow-up times and definitions of events, such as rebleeding, were heterogenous among studies.

CONCLUSION

NVAGIB is a non-negligible cause of morbidity and mortality in patients with cirrhosis and early recognition and endoscopic management are of pivotal importance. However data on most sources of NVAGIB and the efficacy of endoscopic therapy in cirrhosis are very limited, while similar data on acute bleeding from the lower gastrointestinal tract are almost non-existent in this group of patients. Our review highlights that endoscopic therapy seems to be effective in these patients, although comparative data with non-cirrhotic patients are very few. Furthermore, it is conceivable that NVAGIB may be related to decompensation of liver cirrhosis but outcomes such as hepatic encephalopathy, new-onset of ascites, and jaundice, were not available in most included studies. Although variceal bleeding is a well-investigated event in the natural history of liver cirrhosis, it is somewhat unclear whether, and to which extent, non-variceal bleeding may signify worse prognosis of these patients. Hopefully this review may stimulate further research on this subject and help clinicians administer optimal endoscopic therapy for cirrhotic patients.

ARTICLE HIGHLIGHTS

Research background

Non-variceal acute gastrointestinal bleeding (NVAGIB) accounts for approximately one fifth of the bleeding episodes in cirrhotic patients and can lead to catastrophic consequences with high morbidity and mortality. Available data and trials addressing the efficacy of endoscopic modalities used to treat NVAGIB are very limited.

Research motivation

Variceal bleeding is a well-known cause of decompensation in cirrhotic patients and endoscopic treatment and outcomes after such an episode have been well studied. Whether NVAGIB is related to decompensation and if it indicates worse prognosis in the natural history of cirrhotics still needs to be clarified. Knowledge of endoscopic treatment efficacy and outcomes is a prerequisite in answering these challenging questions. Addressing these issues can lead to future changes in treatment and follow up of these patients.

Research objectives

To analyse the different causes of NVAGIB and their frequency as well as the endoscopic modalities used to achieve haemostasis. To investigate if NVAGIB denotes worse prognosis in the natural history of cirrhotic patients, if endoscopic treatment is efficient and what are the rebleeding and failure rates of endotherapy. Data on these issues may stimulate future research, and assist clinicians in choosing the best endoscopic modality to treat NVAGIB in cirrhotics.

Research methods

A systematic review using the PRISMA statement for reporting systematic reviews and meta-analyses was conducted. The MEDLINE was searched through PubMed by two authors (Demetriou G, Augoustaki A) independently for relevant studies from 01/01/1980 until 01/01/2021 using the following query: "Liver Cirrhosis" AND "Gastrointestinal Hemorrhage/therapy". After applying exclusion/inclusion criteria 23 studies out of 2002 were chosen to be analyzed.

Research results

A total of 23 studies (15 retrospective and 8 prospective) included a total of 1288 patients with liver cirrhosis and NVAGIB of whom 958 underwent endoscopic treatment. Causes of NVAGIB in a decreasing frequency order were as follows; peptic ulcers, portal hypertensive gastropathy, gastric antral vascular ectasia, Mallory-Weiss syndrome, Dieaulafoy lesions, portal hypertensive colopathy, and hemorrhoids. Failure to control bleeding from all-causes of NVAGIB accounted for 3.5% of cirrhotic patients who underwent endoscopic therapy while rebleeding and mortality rates varied among studies (2%-25% and 3%-40% respectively). Endoscopic treatment related complications were rare (n = 1).

Research conclusions

NVAGIB is an important cause of morbidity and mortality in patients with cirrhosis and prompt diagnosis and endoscopic management affect prognosis. Despite limited data it seems that endoscopic management for upper-and lower-NVAGIB is safe and efficacious. The relatively high rebleeding and mortality rates are probably due to study heterogeneity but firm conclusions may not be drawn.

Research perspectives

The assumption that NVAGIB may be related to decompensation of liver cirrhosis and poor prognosis still need to be addressed. Expectantly this review will motivate further research on this subject and assist in administering optimal endoscopic therapy to patients with liver cirrhosis.

FOOTNOTES

Author contributions: Kalaitzakis E conceived the idea of the topic and designed the project with Demetriou G; Demetriou G and Augoustaki A searched and screened the titles and abstracts of all relative studies and then full text of the most relevant ones for eligibility criteria; any disagreement was resolved by means of consensus with all authors; all authors contributed to the selection of the studies and interpretation of the results; Demetriou G and Kalaitzakis E wrote the manuscript while Augoustaki A aided in revision; all authors discussed the results and made comments on the manuscript.

Conflict-of-interest statement: Authors declare no conflict of interests for this article.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

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S-Editor: Zhang H
L-Editor: A
P-Editor: Zhang H

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World Journal of Gastrointestinal Endoscopy

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World J Gastrointest Endosc 2022 March 16; 14(3): 176-182

DOI: 10.4253/wjge.v14.i3.176

ISSN 1948-5190 (online)

CASE REPORT

Mucosa-associated lymphoid tissue lymphoma in the terminal ileum: A case report

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Specialty type: Gastroenterology and hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): D, D
Grade E (Poor): 0

P-Reviewer: Batyrbekov K, Jin ZD, Chi T

Received: July 31, 2021
Peer-review started: July 31, 2021
First decision: September 29, 2021
Revised: October 5, 2021
Accepted: February 10, 2022
Article in press: February 10, 2022
Published online: March 16, 2022

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Abstract

BACKGROUND

The lymphoma of the mucosa-associated lymphoid tissue (MALT) is predominantly found in the stomach. The few cases reported in the literature of MALT lymphomas affecting the ileum are in patients who are already symptomatic and with clear advanced endoscopic findings. We present the first case of an asymptomatic female patient who underwent colonoscopy as a routine examination with the findings of an ulcer in the distal ileum region, which histopathological examination and associated immunohistochemistry revealed the diagnosis of MALT lymphoma.

CASE SUMMARY

A 57-year-old asymptomatic female patient underwent a colonoscopy exam for screening. The examination revealed an ulcer of medium depth with well-defined borders covered by a thin layer of fibrin and a halo of hyperemia in the distal ileum portion. Findings are nonspecific but may signal infections by viruses, protozoa, and parasites or inflammatory diseases such as Crohn's disease. Biopsies of the ulcer were taken. The anatomopathological result revealed an atypical diffuse lymphocytic infiltrate of small cells with a characteristic cytoplasmic halo of marginal zone cells. The immunohistochemical study was performed and the results demonstrated a negative neoplastic infiltrate for the

expression of cyclin D1 and cytokeratin AE1/AE3 and a positive for BCL60 in the germinal center. The test also revealed CD10 positivity in the glandular epithelium and germinal center of a reactive follicle with dual-labeling of CD20 and CD3 demonstrating the B lymphocyte nature of the neoplastic infiltrate. In BCL2 protein labeling, the neoplastic infiltrate is strongly positive with a negative germinal center. The findings are consistent with immunophenotype B non-Hodgkin's lymphoma, better classified as extranodal MALT. The patient was treated with chemotherapy and showed complete regression of the disease, as evidenced by colonoscopy performed after treatment.

CONCLUSION
MALT lymphomas in the terminal ileum are extremely rare and only 4 cases have been reported in the literature. Given the low sensitivity and specificity of endoscopic images in these cases, the pathology can be confused with other important differential diagnoses such as inflammatory diseases or infectious diseases and which makes the biopsy important, even in asymptomatic patients, paired with anatomopathological analysis and immunohistochemistry which is the gold standard for correct diagnosis.

Key Words: Mucosa-associated lymphoid tissue lymphoma; Ileum; Colonoscopy; Diagnosis; Biopsy; Case report

Core Tip: Mucosa-associated lymphoid tissue (MALT) lymphoma is predominantly found in the stomach. Only a few cases of MALT lymphomas affecting the ileum have been published in the literature and these patients already had clear symptoms and endoscopic findings. We present a rare case of MALT lymphoma in the terminal ileum in an asymptomatic patient who underwent the examination for age screening.

Citation: de Figueiredo VLP, Ribeiro IB, de Moura DTH, Oliveira CC, de Moura EGH. Mucosa-associated lymphoid tissue lymphoma in the terminal ileum: A case report. *World J Gastrointest Endosc* 2022; 14(3): 176-182
URL: https://www.wjgnet.com/1948-5190/full/v14/i3/176.htm
DOI: https://dx.doi.org/10.4253/wjge.v14.i3.176

INTRODUCTION

Mucosa-associated lymphoid tissue (MALT) lymphoma is a low-grade B-cell neoplasm of the extranodal marginal zone characterized by a lymphoid infiltrate in the mucous layer of hollow organs and glandular tissues[1,2]. The gastrointestinal tract is involved in about 50% of the cases[2,3] with the stomach accounting for 85% of all cases and strongly related to the presence and infection by *Helicobacter pylori* (*H. pylori*)[1,4]. Other, less usual regions can also be affected, such as salivary glands, lungs (14%), head and neck (15%), ocular attachments (12%) and skin (11%)[5].

MALT lymphomas in the ileum are extremely rare and few cases have been reported in the literature [5-9]. In these, all patients had already presented with an advanced degree of involvement with notable symptoms and with lesions dispersed throughout the ileocecal region[5,6].

This is the first reported case of a terminal ileum MALT lymphoma in an asymptomatic patient reported in the literature.

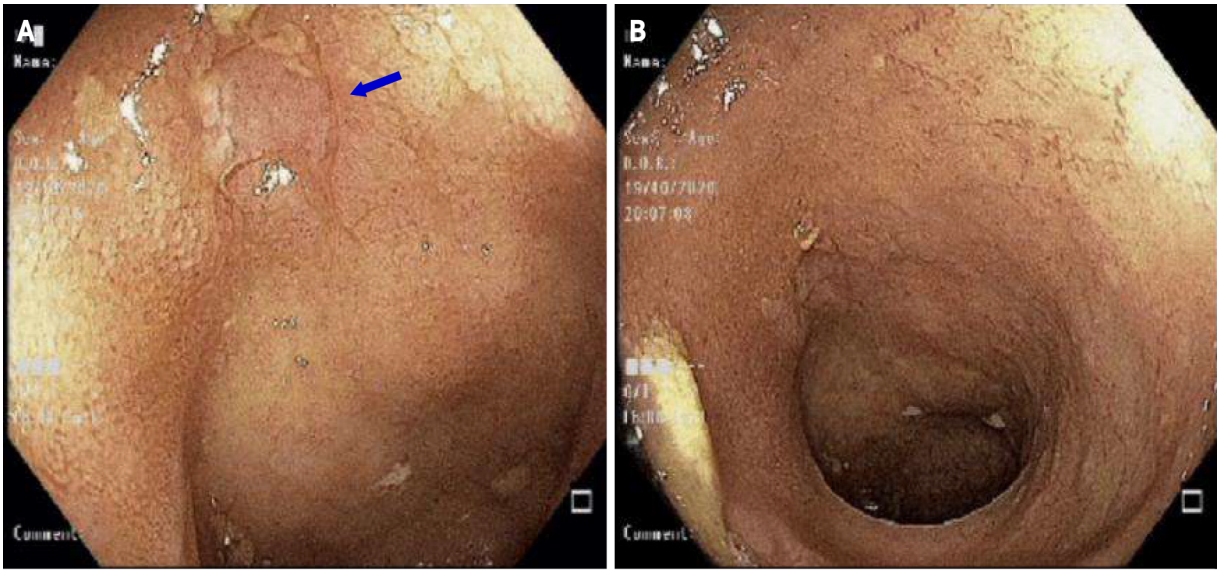
CASE PRESENTATION

Chief complaints

Asymptomatic.

History of present illness

A 57-year-old asymptomatic female patient underwent a colonoscopy exam for screening. The examination revealed an ulcer of medium depth with well-defined borders covered by a thin layer of fibrin and a halo of hyperemia in the distal ileum portion (Figure 1). Findings are nonspecific but may signal infections by viruses, protozoa and parasites or inflammatory diseases such as Crohn's disease.



DOI: 10.4253/wjge.v14.i3.176

Figure 1 Colonoscopy exam. A: Ulcer in the terminal ileum; B: Mild ulcer in terminal ileum.

Biopsies of the ulcer were taken.

The anatomopathological result revealed an atypical diffuse lymphocytic infiltrate of small cells with a characteristic cytoplasmic halo of marginal zone cells. The infiltrate presented with nodular and poorly delimited areas with dissection of collagen fibers and the muscular layer of the mucosa. There was no clear distinction regarding germinal centers. Signs of cellular atypia were also observed with enlarged nuclei. In the most superficial portion there was focal erosion, epithelial reactivity and eosinophilia (above 15 *per* high-power field) (Figure 2). No granulomas were found and there were no signs of infection by parasitic agents. An immunohistochemical study was requested to investigate lymphoproliferative disease.

The immunohistochemical study was performed by the EnVision FLEX Visualization System kit AGILENT (DAKO) method, which the results demonstrated a negative neoplastic infiltrate for the expression of cyclin D1 (Figure 2B) and cytokeratin AE1/AE3 (Figure 2C) and positive for BCL60 in the germinal center (Figure 2D). The test also revealed CD10 positivity in the glandular epithelium and germinal center of a reactive follicle (Figure 3A and B) with dual labeling of CD20 and CD3 demonstrating the B lymphocyte nature of the neoplastic infiltrate (Figure 3C and D). In BCL2 protein labeling, the neoplastic infiltrate is strongly positive with a negative germinal center (Figure 3E and F).

FINAL DIAGNOSIS

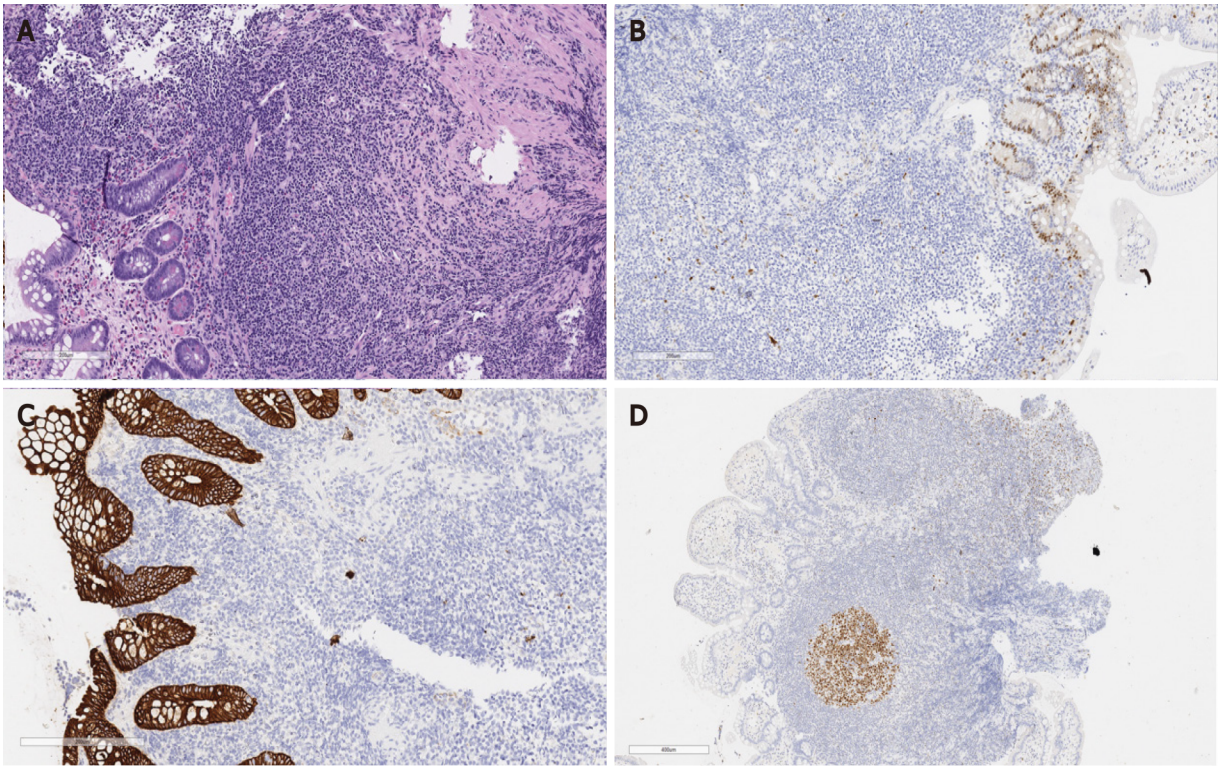
The findings are consistent with immunophenotype B non-Hodgkin's lymphoma, better classified as extranodal MALT. The identification of lymphoid proliferation with atypical limits in a nodular and infiltrative pattern with foci of epithelial aggression was crucial for the diagnosis. Since MALT lymphomas are always negative for BCL6 and CD10 and positive for BCL2 with a negative germinal center, it was possible to rule out the differential diagnosis of follicular lymphoma.

TREATMENT

The patient was referred to the oncology team and treated with chemotherapy.

OUTCOME AND FOLLOW-UP

Upon completion of treatment, the patient showed complete regression of the disease as evidenced by colonoscopy performed after treatment (Figure 4).



DOI: 10.4253/wjge.v14.i3.176

Figure 2 Biopsy of terminal ileum showing. A: Hematoxylin & eosin-dense lymphocytic infiltrate composed of small cells, with a cytoplasmic halo, characteristic of cells in the marginal zone; B: Cyclin D1-Negative neoplastic infiltrate for protein expression of cyclin D1. Observe the positive control in the glandular epithelium; C: Cytokeratin cocktail AE1/AE3-negative neoplastic infiltrate for protein expression of cytokeratin. Observe the positive control in the glandular epithelium; D: BCL6-Protein label for BCL60. Note the negativity of the neoplastic infiltrate, and the positive internal controls in the germinal center of a reactional follicle.

DISCUSSION

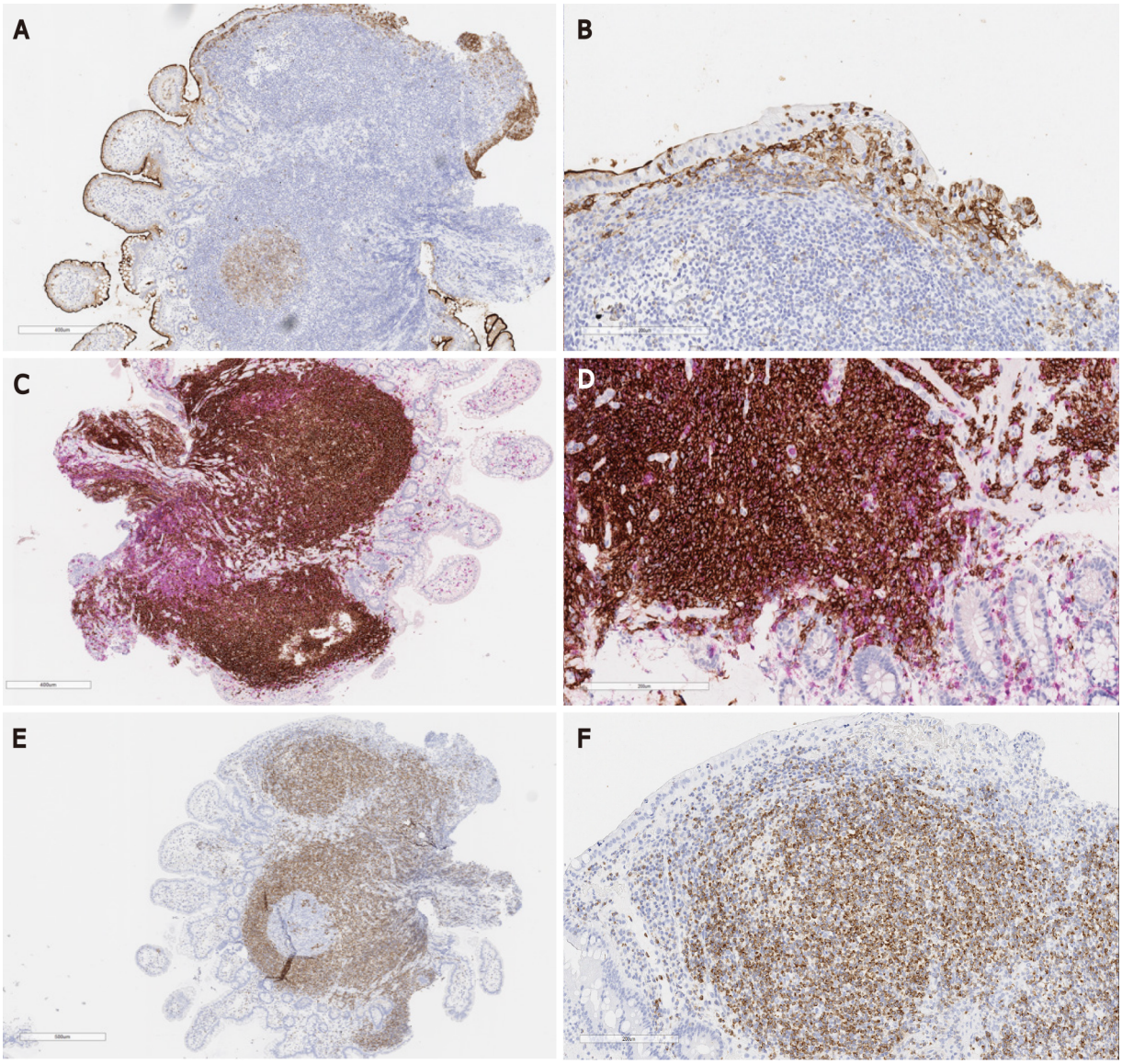
Extranodal marginal zone lymphoma (MALT lymphoma) is characterized by the proliferation of small B lymphocytes[10]. The stomach is the most common site of involvement where the main etiology is *H. pylori* infection[1]. In these cases, the endoscopic findings are varied and involve polyps, ulcerations, erythematous lesions, nodules and other non-specific findings[11]. Extranodal marginal zone lymphomas that affect the ileum region are extremely rare and only a few cases have been reported in the literature[5-9]. None of the previous studies showed *H. pylori* infections so the etiology of the disease remains unknown.

Endoscopic findings of primary small bowel lymphoma can be classified into 5 patterns: Mucosal fold thickening; nodular pattern, defined by the presence of nodules and micronodules of variable sizes; infiltrative pattern, where the bowel wall is immobile, not distended by insufflation, and firm over forceps; ulcerative pattern with ulcers of variable sizes and depths, and mosaic pattern[12].

Among the four cases published in the literature on ileum MALT lymphomas, all presented endoscopic findings with multiple protuberances: Two[5,7] cases with ulcerations and two[6,8] cases with smooth mucosa. In one case, the presence of a single mass in the intestine was demonstrated without erosions in the mucosa[6].

The treatment of MALT lymphoma is initially made with the eradication of *H. pylori*, in cases with involvement of the bacteria. If there is no concomitant *H. pylori* infection or no tumor remission after *H. pylori* treatment, radiotherapy, chemotherapy, or immunotherapy with anti-CD20 monoclonal antibodies should be considered. Radiotherapy has an excellent prognosis when used in cases where the disease is localized. In the presence of disseminated or more advanced disease, the use of radiotherapy or immunotherapy is indicated. Treatment must be individualized according to the stage of the disease and symptoms, as well as the patient's preference[13]. Although MALT lymphoma has a favorable prognosis and is responsive to systematic therapy, especially when identified early, when patients are symptomatic, unfortunately they already have a more advanced degree of involvement.

Terada[5] reported the case of a 34-year-old patient with abdominal pain and melena whose colonoscopy revealed multiple nodules and ulcers scattered throughout the ileum. Endoscopic images were suggestive of ileitis, mesenchymal tumor, or lymphoma.



DOI: 10.4253/wjge.v14.i3.176

Figure 3 Terminal ileum biopsy showing. A: Protein labeling for CD10. Note the negativity of the neoplastic infiltrate, and the positive internal controls of the glandular epithelium and germinal center of a reactional follicle; B: Protein labeling for CD10. Note the negativity of the neoplastic infiltrate and the positive internal controls of the glandular epithelium; C and D: Double labeling of CD20 (brown) and CD3 (red) demonstrating the nature of B lymphocytes of the neoplastic infiltrate. Note that T cells border the neoplastic infiltrate and preferably the epithelium, attesting to its reaction nature; E: Protein labeling for BCL2. Note that the neoplastic infiltrate expresses strongly and the internal negative control in the germinal center of a reactional follicle; F: Strong protein labeling of the neoplastic infiltrate for BCL2

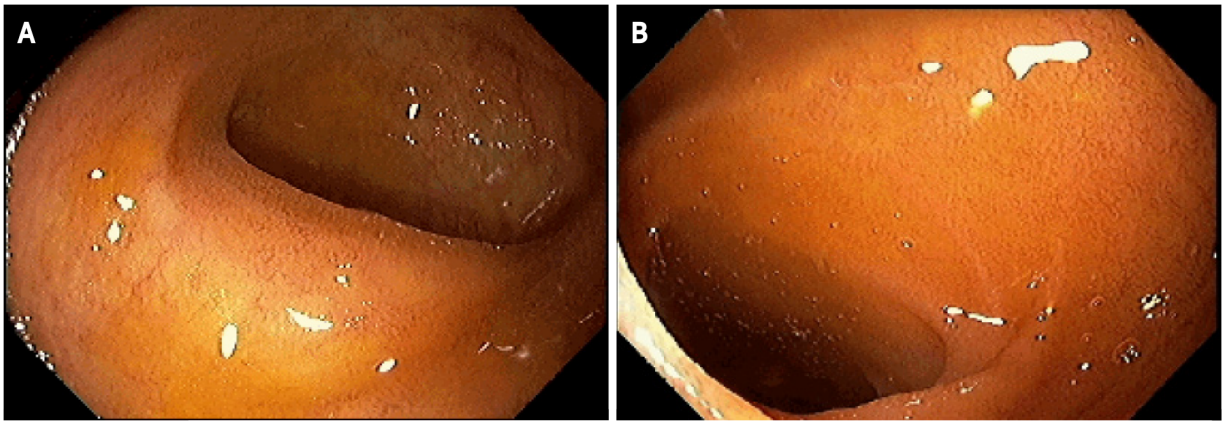
Hasegawa *et al*[6] described two cases of oligosymptomatic patients with abdominal pain being a common symptom. Colonoscopy in the first case found multiple whitish nodules in the region close to the ileocecal valve, which had a smooth and polished appearance. In the second case, a colonoscopy revealed an ileocecal valve with an enlarged, soft appearance and areas of enanthema.

Makino *et al*[7] discussed a case of a patient with initial complaints of postprandial epigastric pain. Colonoscopy examination revealed multiple protruding lesions in the terminal ileum with an erosive surface covered by swollen mucosa.

In the report by Ohashi *et al*[8] colonoscopy identified multiple polyposis lesions in the terminal ileum with an absence of villi.

In all cases, biopsy with histological evaluation concurrently with immunohistochemical analysis was crucial for the diagnosis of MALT lymphoma.

The uniqueness of the case presented in this study is due to the fact that the patient was asymptomatic and her endoscopic findings had a more discrete and nonspecific pattern compared to other studies which made the diagnosis even more challenging.



DOI: 10.4253/wjge.v14.i3.176

Figure 4 Colonoscopy after treatment. A: Disease-free mucosa; B: Ulcer-free terminal ileum.

CONCLUSION

Given the low sensitivity and specificity of endoscopic images in these cases the pathology can be confused with other important differential diagnoses such as inflammatory diseases (such as Crohn's disease) or infectious diseases, which makes the biopsy, even in asymptomatic patients, with anatomo-pathological analysis and performing immunohistochemistry, the gold standard for correct diagnosis [14].

FOOTNOTES

Author contributions: de Figueiredo VLP, Ribeiro IB, and de Moura EGH performed the data curation; Ribeiro IB and de Moura DTH contributed to the formal analysis; Ribeiro IB and de Moura EGH performed the investigation; de Moura EGH contributed to the supervision; de Figueiredo VLP and Ribeiro IB contributed to the writing of the original draft; Ribeiro IB contributed to the writing of the review and editing.

Informed consent statement: The work described has been conducted in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). Informed consent for publication of this case was obtained from the patient's daughter (witnessed by two physicians).

Conflict-of-interest statement: All other authors declare that they have no conflict of interest.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Country/Territory of origin: Brazil

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S-Editor: Fan JR
L-Editor: Filipodia
P-Editor: Fan JR

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World Journal of Gastrointestinal Endoscopy

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World J Gastrointest Endosc 2022 March 16; 14(3): 183-190

DOI: 10.4253/wjge.v14.i3.183

ISSN 1948-5190 (online)

CASE REPORT

Z-per-oral endoscopic myotomy as definitive prevention of a bleeding ulcer in Zenker's diverticulum: A case report

Chonlada Krutsri, Pitichote Hiranyatheb, Preeda Sumritpradit, Pongsasit Singhatas, Pattawia Choikrua

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Hu B, Ribeiro IB

Received: October 12, 2021
Peer-review started: October 12, 2021
First decision: November 17, 2021
Revised: November 18, 2021
Accepted: February 12, 2022
Article in press: February 12, 2022
Published online: March 16, 2022

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Abstract

BACKGROUND

Bleeding from Zenker's diverticulum is extremely rare. At present, there are no guidelines for the management of bleeding Zenker's diverticulum because of its rarity. Per-oral endoscopic myotomy (Z-POEM) is a precision myotomy technique and minimally invasive procedure for the treatment of Zenker's diverticulum. We present a systematic review and a rare case of bleeding Zenker's diverticulum that was effectively treated using Z-POEM.

CASE SUMMARY

A 72-year-old presented after 3 d of hematemesis. He had a 2-year history of progressive dysphagia and reported no antiplatelet, anticoagulant, or non-steroidal anti-inflammatory drug use. His vital signs were stable, and the hematocrit was 36%. Previous gastroscopy and barium swallow had revealed Zenker's diverticulum before the bleeding occurred. We performed gastroscopy and found a 5-mm ulcer with a minimal blood clot and spontaneously resolved bleeding. Z-POEM for definitive treatment was performed to reduce accumulation of food and promote ulcer healing. He had no complications and no bleeding; at the follow-up 6 mo later, the ulcer was healed.

CONCLUSION

Z-POEM can be definitive prevention for bleeding ulcer in Zenker's diverticulum that promotes ulcer healing, reducing the risk of recurrent bleeding. Z-POEM is also a definitive endoscopic surgery for treatment of Zenker's diverticulum.

Key Words: Zenker's diverticulum; Bleeding Zenker's diverticulum; Ulcer; Upper gastrointestinal bleed; Peroral endoscopic myotomy for Zenker's diverticulum; Peroral endoscopic myotomy

Core Tip: Bleeding from ulcers in a Zenker's diverticulum is extremely rare. Elderly patients with early symptoms of progressive dysphagia should be treated with a high index of suspicion. Risk factors include acidic pills, such as aspirin and non-steroidal anti-inflammatory drugs, that lodge themselves in the diverticulum creating an ulcer, and accumulation of food in the bottom of diverticulum leads to inflammation and subsequent ulcers. Per-oral endoscopic myotomy is a new definitive treatment for Zenker's diverticulum that can promote ulcer healing, decrease recurrent bleeding, and decrease dysphagia.

Citation: Krutsri C, Hiranyatheb P, Sumritpradit P, Singhatas P, Choikrua P. Z-per-oral endoscopic myotomy as definitive prevention of a bleeding ulcer in Zenker's diverticulum: A case report. *World J Gastrointest Endosc* 2022; 14(3): 183-190
URL: https://www.wjgnet.com/1948-5190/full/v14/i3/183.htm
DOI: https://dx.doi.org/10.4253/wjge.v14.i3.183

INTRODUCTION

Zenker's diverticulum is a pouch of false diverticulum that forms at a point of weakness in the posterior pharyngeal wall, known as Killian's triangle, within the upper esophageal sphincter[1,2]. The overall prevalence of Zenker's diverticulum in general population is 0.10%-0.11%[3]. The typical presentation is progressive dysphagia of solid and liquid food, regurgitation, and aspiration in elderly patients. The average age of patients with Zenker's diverticulum is 70-80 years old[4]. Complications of Zenker's diverticulum include choking and aspiration pneumonia; a large diverticulum more than 4 cm in size can compress the trachea or esophagus and cause obstruction[5]. Rare complications include ulceration, bleeding, and malignant transformation (squamous cell carcinoma)[2,6]. Bleeding from a Zenker's diverticulum is rare and only six cases have been reported in the last 20 years[7-12]. Patients typically present with hematemesis and/or sometimes hemoptysis. This can be fatal as result of hemodynamic instability following massive bleeding. The ulcer is one of the risk factors of bleeding Zenker's diverticulum. To the best of our knowledge, this is the seventh reported case of a bleeding Zenker's diverticulum in the past 20 years, and no standard treatment has been established for this condition. To date, minimally invasive third-space endoscopic surgery per-oral endoscopic myotomy (Z-POEM) plays an important role in the treatment of Zenker's diverticulum[13]. We present a case report of a patient who developed upper gastrointestinal bleeding (UGIB) from a rare Zenker's diverticulum who was treated definitively using third-space endoscopic surgery, Z-POEM, and provide a systematic review of the available literature.

This case report follows the SCARE 2016 criteria. The systematic review of the literature followed the PRISMA guidelines (Figure 1). We searched the PUBMED and SCOPUS databases for articles published between 2000 and 2020 published in the English language, including case reports and original article. The search terms were "Zenker's diverticulum" OR "esophageal diverticulum" AND "bleeding." The first author screened the titles and abstracts of the identified studies to identify potentially relevant studies; full-text assessment was then performed to assess eligibility to be included. If the first author was uncertain whether a given study should be included, the corresponding author was consulted to reach a conclusion. The data were extracted and patient characteristics, such as the size of the Zenker's diverticulum, management of bleeding, definitive management of Zenker's diverticulum, follow-up length, and outcome, were collected.

CASE PRESENTATION

Chief complaints

A 72-year-old man was admitted to our hospital with a 3-day history of hematemesis.

History of present illness

The patient developed hematemesis 3 d before presenting at our hospital. The hematemesis was approximately 200 mL in volume 2 times. He was admitted to the nearest private hospital. His hematocrits was 25%. Esophagogastroduodenoscopy (EGD) under local anesthesia was performed on the first day in the previous hospital but failed because the patient choked and resisted scope insertion. He was reported to have anemia with a hematocrit 25% at the previous hospital, he received a 1-unit transfusion of red blood cells, intravenous fluids, and pantoprazole. On day 3 after admission, the patient had no

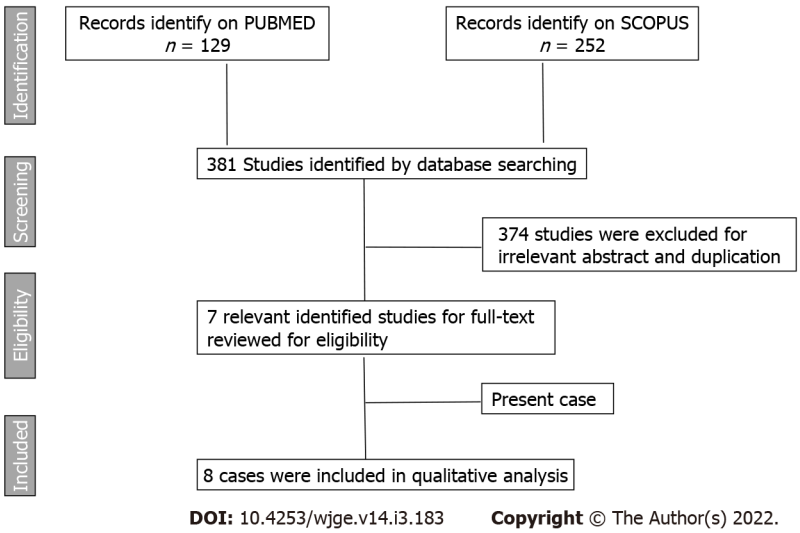


Figure 1 A study flowchart according to Preferred Reporting Items for Systematic reviews and Meta-analysis guidelines (PRISMA).

hematemesis or anemia and had a hematocrit of 36%. He was then referred to our hospital. We performed gastroscopy and found a 5-mm ulcer with minimal blood clot.

History of past illness

The patient had diabetes mellitus and primary hypertension; he took 81 mg aspirin until almost 8 mo before he developed hematemesis. He had an approximately 2-year history of progressive dysphagia, which manifest as difficulty in swallowing solid foods then liquid foods, sometimes choking, and a non-significant decrease in body weight; there was no evidence of aspiration pneumonia. Barium swallow was performed and revealed a Zenker's diverticulum that was 4 cm wide and 7.1 cm long, with a 1.1-cm-wide neck (Figure 2). Gastroscopy was performed and confirmed a large diverticulum 20 cm from the incisors without any ulcer in the diverticulum. He was diagnosed with Zenker's diverticulum and put on the waiting list for Z-POEM before developing hematemesis.

Personal and family history

No family history of Zenker's diverticulum.

Physical examination

On the day of admission, the patient was not pale and had a stable blood pressure of 146/70 mmHg and heart rate of 62 beats per minute. On physical examination, the abdomen was soft with no tenderness. Rectal examination found an empty rectum without any gross masses.

Laboratory examinations

Laboratory investigation revealed a hematocrit of 36%.

Imaging examinations

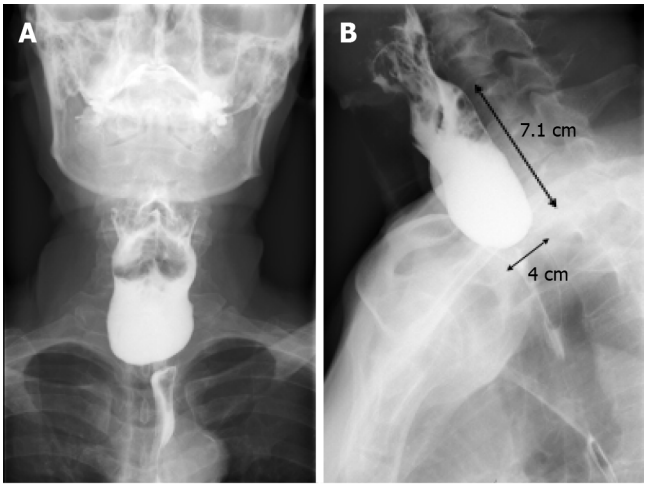
Barium swallow was performed and revealed a Zenker's diverticulum that was 4 cm wide and 7.1 cm long, with a 1.1-cm-wide neck (Figure 2B).

FINAL DIAGNOSIS

The final diagnosis was Zenker's diverticulum with a bleeding ulcer that spontaneously resolved.

TREATMENT

Because the bleeding ulcer spontaneously resolved, we decided therapeutic endoscopy of the ulcer was not necessary; however, we performed Z-POEM as definitive treatment of Zenker's diverticulum. This procedure aimed to improve dysphagia and to decrease food and drug retention in the diverticulum to reduce inflammation of the healed ulcer and prevent recurrent bleeding. Informed consent for the procedure was obtained from the patient after explaining the prognosis, results, and potential complic-



DOI: 10.4253/wjge.v14.i3.183

Figure 2 Preoperative barium swallow. A: Zenker's diverticulum; B: Size 4 cm × 7.1 cm, widening 1.1 cm before develop upper gastrointestinal bleeding.

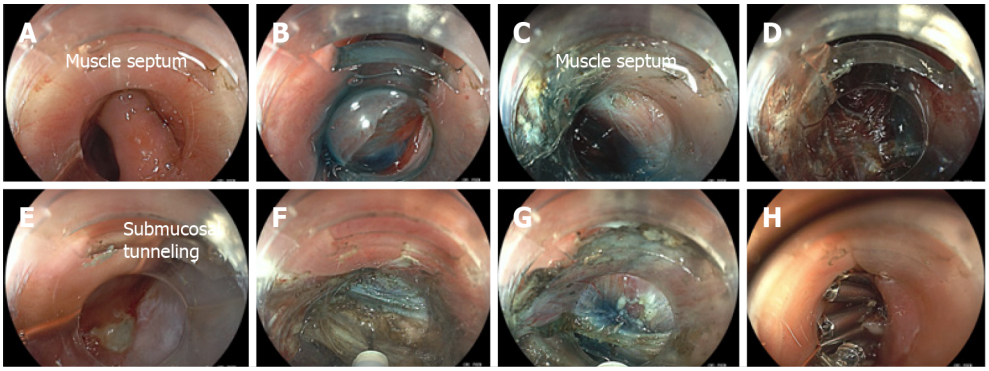
ations of the procedure, such as perforation. The Z-POEM technical process is shown in Figure 3. The operator was a surgical endoscopist in a university hospital. The patients underwent Z-POEM under general anesthesia with an endotracheal tube to prevent aspiration and end tidal CO_2 monitoring. CO_2 gas insufflation through the endoscope was required. The Z-POEM procedure was performed using a single-channel gastroscope (EG-760CT; Fuji-film Medical Co., Ltd. Tokyo, Japan). A triangle-tipped knife (KD-645; Olympus Corporation) was used for the mucosal incision, submucosal dissection, and myotomy. A small-caliber-tip transparent hood (ST hood) (DH-28GR; Fuji-film Medical Co., Ltd. Tokyo, Japan) was used to maintain and stabilize the operative field. Glycerol with a few drops of indigo carmine was used to lift the submucosal layer. The surgery was performed using a high-frequency electrosurgical energy generator (VIO 300 D; Erbe Elektromedizin, Tubingen, Germany) in endo cut mode (effect, 2.3 W) and spray coagulation mode (effect, 1,100 W). The procedure time was defined as the time from the insertion of the endoscope to application of the last through-the-scope clip (TTC). The septal muscle of Zenker's diverticulum was located 20 cm from the incisors and was 1.1 cm wide (Figure 3A). The submucosa was lifted using glycerol and indigo carmine at the septum level, and a mucosal incision was made above the septal muscle using a triangle-tipped knife in endo cut mode (effect 2.3 W) (Figure 3B). Submucosal tunneling was performed with transparent hood assistance, and submucosal dissection was performed with coagulation along both sides of the septal wall using the spray coagulation mode (effect, 1,100 W) up to behind the ulcer (Figure 3C). The submucosal layer behind the ulcer had numerous inflamed small vessels; partial coagulation of these small vessels was achieved using a Coagrasper (Figure 3D). The picture 3E shows ulcer while checking mucosal integrity after performed submucosal tunneling before undergo myotomy. After checking the integrity of the mucosa in the ulcer region, myotomy of the septal muscle was performed using endo cut mode (effect, 2.3 W) to achieve complete septal myotomy (Figure 3E-G). TTCs were applied to achieve mucosal apposition (Figure 3H). Neither patient developed bleeding or perforation. The total procedure time was 65 min.

OUTCOME AND FOLLOW-UP

Water soluble contrast esophagography was performed on postoperative day 1 to confirm the absence of leakage, and the patients were able to resume an oral diet thereafter. He had no recurrent bleeding. EGD was repeated 6 mo postoperatively because inflammation might be subside to confirm that the ulcer had resolved and that there was no food retention as shown in Figure 4. He was better able to swallow soft foods but still had some degree of difficulty with solid food; he also reported a sensation of a foreign body in his neck but no pain, hematemesis, melena, or choking. Moreover, he had a 6-kg weight gain.

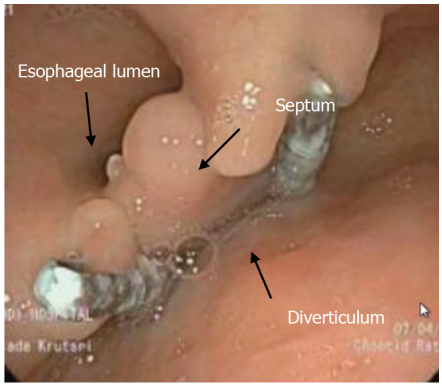
DISCUSSION

Our literature search only identified six published English language case reports[7-12]. Including our present case, the average age of patients was 77.86 years, which is consistent with the average age of patients with Zenker's diverticulum[2]. The average size of Zenker's diverticulum associated with UGIB



DOI: 10.4253/wjge.v14.i3.183

Figure 3 Per-oral endoscopic myotomy for Zenker's diverticulum. A: Endoscopic view of the Zenker's diverticulum with muscle septum, located 20 cm from the incisors; B: The mucosal incision was performed after lifted submucosa by using glycerol with a few drops of indigo carmine injected at the septum; C: Submucosal tunneling and dissection was performed along both sides of the septal wall; D: A submucosal tunnel behind the ulcer contain many small vessel, we partially coagulate by coagrasper to stop bleeding and also avoid mucosal perforation; E: The ulcer after submucosal tunneling: The picture shows ulcer while checking mucosal integrity after performed submucosal tunneling before undergo myotomy; F and G: The myotomy was performed until the last fibers of septal muscle; H: The mucosal defect closed by through-the-scope clip.



DOI: 10.4253/wjge.v14.i3.183

Figure 4 The esophagogastroduodenoscopy show no recurrent ulcer and no food retention after 6 mo follow up.

is 6.325 cm as shown in Table 1. Nowaday, there was not well established whether diverticulum size is related to the occurrence of UGIB but more bigger size is prone to have pills and food accumulation then more risk development of ulcer formation and UGIB. While the pathophysiology of a bleeding diverticulum is unclear, in our review, most cases were associated with chronic inflammation and ulceration of the diverticulum[7-10,12]. Common causes of ulcer formation in the diverticulum include aspirin and non-steroidal anti-inflammatory drug tablets, which are acidic and can become lodged or trapped in the diverticulum; the prolonged contact induces direct and indirect mucosal injury. Chronic alcohol consumption, gastroesophageal reflux disease (GERD), and stimulation of acid secretion also induce ulcer formation[10,14]. Anticoagulant use induces coagulopathy, which can lead to bleeding from diverticula, with or without ulceration, similar to other types of GI bleeding. Another assumed cause of bleeding Zenker's diverticulum is chronic inflammation from food accumulation in the diverticulum inducing inflammation or infection, with or without ulceration. This assumption was confirmed by Sardana *et al*, who reported a case of bleeding Zenker's diverticulum treated using diverticulectomy with a pathology report identifying chronic inflammation as the cause of mucosal bleeding[11]. Therefore, larger diverticula are more likely to ulcerate and bleed, especially those larger than 4 cm.

Bleeding from Zenker's diverticulum is rare and can be fatal, like other causes of UGIB. Elderly patients with previous progressive or intermittent dysphagia and regurgitation must be treated with a high index of suspicion. Currently, there are no guidelines regarding the management of bleeding Zenker's diverticulum because of its rarity. Flicker *et al* and Eaton *et al* reported successfully stopping bleeding from the diverticulum using an endoscopic hemoclip[8,9]. There are two case reports of failed endoscopic treatment due to blood pooling and hemodynamic instability, which prevented insertion of the endoscope; in this emergency setting, urgent open diverticulectomy was used as treatment[7,10]. For successful endoscopic management, the neck of the diverticulum should be more than 1 cm wide so the endoscope can pass into the diverticulum for therapeutic management of bleeding at the bottom of

Table 1 Summary of previous case reports of bleeding Zenker's diverticulum, including present case

Ref.	Age (yr)	Antiplatelet or coagulant use	NSAIDs	Ulcer in diverticulum	Diverticulum size (cm)	Technique to stop bleeding	Definitive surgical treatment	Follow up (months)	Recurrent bleeding
Haas *et al* [7], 2008	71	Aspirin	No	Yes	Large	Urgent diverticulectomy Stop aspirin	Diverticulectomy	N/A	No
Flicker *et al*[8], 2010	83	Aspirin Clopidogrel	No	Yes	Large	Hemoclip	Diverticulectomy	N/A	No
Eaton *et al*[9], 2011	85	Aspirin	No	Yes	5.2	Hemoclip	Died after discharge home from heart failure	N/A	No
Bălălău *et al*[10], 2013	75	No	No	Yes	4	Diverticulectomy	Diverticulectomy	12	No
Sardana *et al*[11], 2014	89	Aspirin Warfarin	No	No	9	FFP; Stop aspirin and warfarin	Diverticulectomy and cricopharyngeal myotomy	N/A	No
House *et al*[12], 2016	70	Aspirin, Clopidogrel	No	Yes	Large	IV pantoprazole; Stop aspirin and clopidogrel	Diverticulectomy	N/A	No
Present case	72	Aspirin	No	Yes	7.1	IV pantoprazole	Z-POEM	12	No

N/A: Not available data; POEM: Per-oral endoscopic myotomy.

diverticulum. There were two case reports of bleeding stopping spontaneously after withholding anticoagulant and aspirin treatment[11,12]. As in our case, the bleeding from the ulcer in the diverticulum can stop spontaneously. Based on this evidence, endoscopic treatment may be the first choice, but if there is hemodynamic instable or endoscopic treatment fails or cannot identify the esophageal lumen, open diverticulectomy in an emergency setting is mandatory. Insertion of an endotracheal tube is recommended when endoscopic treatment is performed due to the high resistance and pooling of blood in the diverticulum leading to aspiration of blood into the pulmonary system.

After endoscopic treatment successfully stops the bleeding, definitive treatment of Zenker's diverticulum is necessary to treat the ulcer and prevent rebleeding. In emergency situations when the patient is hemodynamically unstable or endoscopic treatment fails, open diverticulectomy is mandatory *via* left lateral neck incision to excise the bleeding diverticulum immediately. Therefore, patients and their relatives should be informed of the double set-up for endoscopic management and open surgery. Open diverticulectomy leads to a good outcome in 93% of cases, but there is a high rate of complications (10.5%-30%) and mortality (3%), respectively[15-17]. Potential complications include pharyngocutaneous fistulas, mediastinitis, perforation, vocal cord paralysis, and transient recurrent laryngeal nerve paralysis[18,19].

A comparison of definitive treatment of Zenker's diverticulum with per-oral endoscopic myotomy (Z-POEM), flexible endoscopic septostomy, stapler-assisted Zenker's diverticulectomy, endoscopic harmonic scalpel, and standard open diverticulectomy found that Z-POEM allows the most precise myotomy because the operator can see until the last fiber of septal muscle[13]. Z-POEM also has a lower complication rate (6.17%) because of the postoperative intact mucosal integrity, and with precision myotomy, the bottom of the diverticulum can be seen so perforation rarely occurs[3,13]. While other procedure of treatment Zenker's diverticulum such as standard open neck diverticulectomy and flexible endoscopic septotomy had more complication rate 10.5% and 11.3%, respectively[13]. The recurrence rate following Z-POEM can be as low as 1.23%, compared with a recurrence rate of 11%-20% for other techniques[13,20-22]. In our present case, Z-POEM was a minimally invasive definitive treatment that aimed to promote ulcer healing by decreasing the accumulation of food in the diverticulum. During Z-POEM, submucosal tunnelling can identify small vessels behind the ulcer and coagulate these vessels to stop the bleeding without any perforation. This patient experienced no perforation or rebleeding. After 6 mo of follow-up, the ulcer was healed.

In summary, bleeding Zenker's diverticulum is rare and may be caused by ulceration due to acidic medications such as aspirin, NSAIDs or food retention-induced inflammation. Elderly patients with progressive dysphagia should be treated with a high index of suspicion. Therapeutic endoscopy is the

first choice to manage bleeding Zenker's diverticulum under general anesthesia with endotracheal intubation to prevent aspiration. Z-POEM is a definitive for Zenker's diverticulum treatment that allows precision myotomy, which promotes ulcer healing and reduce the risk of rebleeding by decreasing the accumulation of drugs or food in the diverticulum with a low rate of complications.

CONCLUSION

Z-POEM can be definitive prevention for bleeding ulcer in Zenker's diverticulum that promotes ulcer healing, reducing the risk of recurrent bleeding. Z-POEM is also a definitive endoscopic surgery for treatment of Zenker's diverticulum.

FOOTNOTES

Author contributions: Krutsri C and Hiranyatheb P designed, performed and wrote the paper; Sumritpradit P and Singhatas P wrote the paper and analysed the data; Choikrau P contributed analytic tools and analysed the data.

Informed consent statement: Informed written consent was obtained from the patient for publication of this report and any accompanying images.

Conflict-of-interest statement: The authors declare that they have no conflict of interest.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Country/Territory of origin: Thailand

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S-Editor: Wang LL
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