ISSN 1948-5190 (online)

World Journal of *Gastrointestinal Endoscopy*

World J Gastrointest Endosc 2022 February 16; 14(2): 63-105

Published by Baishideng Publishing Group Inc

World Journal of Gastrointestinal Endoscopy

Contents

Monthly Volume 14 Number 2 February 16, 2022

FRONTIER

MINIREVIEWS

ORIGINAL ARTICLE

Retrospective Study

World Journal of Gastrointestinal Endoscopy

Monthly Volume 14 Number 2 February 16, 2022

Contents

ABOUT COVER

Editorial Board Member of *World Journal of Gastrointestinal Endoscopy*, Diogo Turiani Hourneaux de Moura, MD, MSc, PhD, Associate Professor, Postdoc, Department of Gastroenterology, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo 05403900, Brazil. dthmoura@hotmail.com

AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Endoscopy* (*WJGE*, *World J Gastrointest Endosc*) is to provide scholars and readers from various fields of gastrointestinal endoscopy with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGE mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal endoscopy and covering a wide range of topics including capsule endoscopy, colonoscopy, double-balloon enteroscopy, duodenoscopy, endoscopic retrograde cholangiopancreatography, endosonography, esophagoscopy, gastrointestinal endoscopy, gastroscopy, laparoscopy, natural orifice endoscopic surgery, proctoscopy, and sigmoidoscopy.

INDEXING/ABSTRACTING

The *WJGE* is now abstracted and indexed in Emerging Sources Citation Index (Web of Science), PubMed, PubMed Central, China National Knowledge Infrastructure (CNKI), and Superstar Journals Database. The 2021 edition of Journal Citation Reports® cites the 2020 Journal Citation Indicator (JCI) for *WJGE* as 0.36.

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, Bing Hu, Sang Chul Lee, Joo Young Cho

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

PUBLICATION DATE
February 16, 2022

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

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

World Journal of Gastrointestinal Endoscopy

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

World J Gastrointest Endosc 2022 February 16; 14(2): 63-76

DOI: 10.4253/wjge.v14.i2.63

ISSN 1948-5190 (online)

FRONTIER

Peroral cholangioscopy: Update on the state-of-the-art

Amith Subhash, James L Buxbaum, James H Tabibian

ORCID number: Amith Subhash 0000-0002-8039-119X; James L Buxbaum 0000-0003-0868-5238; James H Tabibian 0000-0001-9104-1702.

Author contributions: Subhash A, Buxbaum JL, and Tabibian JH have all been involved in drafting the manuscript and/or making critical revisions; Subhash A, Buxbaum JL, and Tabibian JH meet the criteria for authorship established by the International Committee of Medical Journal Editors and approve the final manuscript for publication.

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

Country/Territory of origin: United States

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): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Open-Access: This article is an

Amith Subhash, Department of Gastroenterology, Kirk Kerkorian School of Medicine at UNLV, Las Vegas, NV 89102, United States

James L Buxbaum, Division of Gastrointestinal and Liver Diseases, Keck School of Medicine of USC, Los Angeles, NV 90033, United States

James H Tabibian, David Geffen School of Medicine at UCLA, Division of Gastroenterology, Department of Medicine, Olive View-UCLA Medical Center, Sylmar, CA 91342, United States

James H Tabibian, Vatche and Tamar Manoukian Division of Digestive Diseases, David Geffen School of Medicine at UCLA, Los Angeles, NV 90095, United States

Corresponding author: James H Tabibian, MD, PhD, Associate Professor, David Geffen School of Medicine at UCLA, Division of Gastroenterology, Department of Medicine, Olive View-UCLA Medical Center, 2B-182 Olive View Dr, Sylmar, CA 91342, United States. jtabibian@dhs.lacounty.gov

Abstract

Peroral cholangioscopy (POC) is an endoscopic procedure that allows direct intraductal visualization of the biliary tract. POC has emerged as a vital tool for indeterminate biliary stricture evaluation and treatment of difficult biliary stones. Over several generations of devices, POC has fulfilled additional clinical needs where other diagnostic or therapeutic modalities have been inadequate. With adverse event rates comparable to standard endoscopic retrograde cholangioscopy and unique technical attributes, the role of POC is likely to continue expand. In this frontiers article, we highlight the existing and growing clinical applications of POC as well as areas of ongoing research.

Key Words: Peroral cholangioscopy; SpyGlass™; Difficult bile duct stones; Indeterminate biliary strictures; Cholangioscope-guided biopsy; Cholangioscope-guided lithotripsy

Core Tip: Cholangioscopy is an endoscopic technique that was first developed in the 1970s as a minimally-invasive modality for the evaluation of various biliopancreatic pathologies. Since the advent of the digital single-operator cholangioscopy (D-SOC) in 2015 as well as other, complementary advancements in the field, diagnostic and therapeutic applications have further expanded. Herein, we discuss the various current

Received: June 30, 2021
Peer-review started: June 30, 2021
First decision: July 29, 2021
Revised: August 25, 2021
Accepted: January 17, 2022
Article in press: January 17, 2022
Published online: February 16, 2022

P-Reviewer: Maetani I
S-Editor: Fan JR
L-Editor: A
P-Editor: Fan JR

applications of cholangioscopy, with a focus on D-SOC, and areas of ongoing research to better understand potential future directions.

Citation: Subhash A, Buxbaum JL, Tabibian JH. Peroral cholangioscopy: Update on the state-of-the-art. *World J Gastrointest Endosc* 2022; 14(2): 63-76
URL: https://www.wjgnet.com/1948-5190/full/v14/i2/63.htm
DOI: https://dx.doi.org/10.4253/wjge.v14.i2.63

INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) was first reported in 1968 as a method to cannulate the major duodenal papilla[1]. It is now widely utilized as the primary interventional modality for many biliopancreatic disorders. Despite its vast utility, ERCP technique relies on indirect visualization of the biliary tree *via* fluoroscopy; this can be limiting for certain diagnostic and/or therapeutic applications (*e.g.* evaluation of biliary strictures, mapping of intraductal tumors for operative planning, tumor-directed ablative therapy, *etc.*).

In order to provide direct visualization of the biliopancreatic tree, peroral cholangioscopy (POC) was introduced in the 1970s[2,3]. POC was originally designed as a "mother-baby" system that required two endoscopists to operate the "mother" duodenoscope and "baby" cholangioscope[2]. In addition to the multi-operator requirement, there was a notable deficiency in this setup in the ability to acquire tissue following visualization, thus further limiting its use. Moreover, the initial scopes provided only two-way tip deflection, were fragile, and costly[4].

Over the past several decades, technologic improvements in the equipment utilized for POC has led to more widespread adoption and a growing number of applications (Figure 1). In the early 2000s, a new single-operator duodenoscope-assisted cholangioscopy technique utilizing a Pentax cholangioscope (FCP-8P/FCP-9P, Pentax Precision Instruments, Orangeburg, New York, United States) was introduced. However, this technique required the use of an endoscopist-worn breastplate to mount the cholangioscope, which allowed for manipulation of the duodenoscope with the left hand and the cholangioscope with the right hand[5]. In 2005, Boston Scientific released the first commercially available single-operator cholangioscopy (SOC) system (SpyGlass™, Boston Scientific Corporation, Natick, MA, United States), a catheter-based system that utilizes an optical probe inserted through the duodenoscope working channel[6]. Ten years later, a digital SOC (D-SOC) system was introduced (SpyGlass™ DS, Boston Scientific Corporation)[6]; this updated digital system brought improvements in image size and quality, a wider field of view, and a redesigned working channel allowing for larger diameter cholangioscopic accessories, among other changes[4,7]. In 2018, a third generation SpyScope™ DSII Catheter (Boston Scientific Corporation) featuring increased resolution and improved lighting was introduced alongside new cholangioscopic accessories. Alternatively, direct POC (DPOC) can be performed utilizing a modern ultraslim upper endoscope that can be advanced into the biliary tree following endoscopic sphincterotomy, a technique first published in a pilot study in 2006[8-10]; however, this setup is primarily used outside the United States and available in only select markets[7].

Given the recent technologic advancements in POC, its array of accessories (Figure 2), and improved training of advanced endoscopists, there has been wide propagation of this technique across most large medical centers. In this Frontiers article, we aim to underscore the major developments in the growing body of literature on POC, with particular emphasis on SOC and D-SOC, including diagnostic and therapeutic applications as well as established and investigational indications.

COMMON APPLICATIONS OF CHOLANGIOSCOPY

Management of difficult biliary stones

Approximately 10%-18% of patients with symptomatic cholelithiasis will have concomitant choledocholithiasis[11]. The standard of care for these patients is ERCP

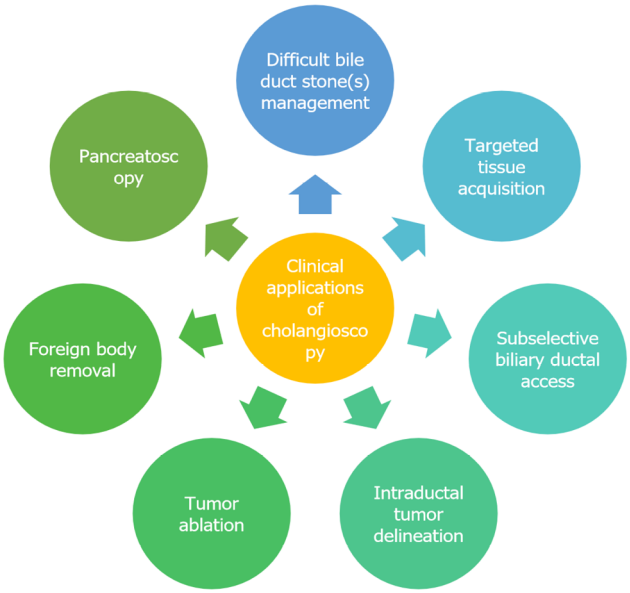

Figure 1 Common diagnostic and therapeutic applications of cholangioscopy.

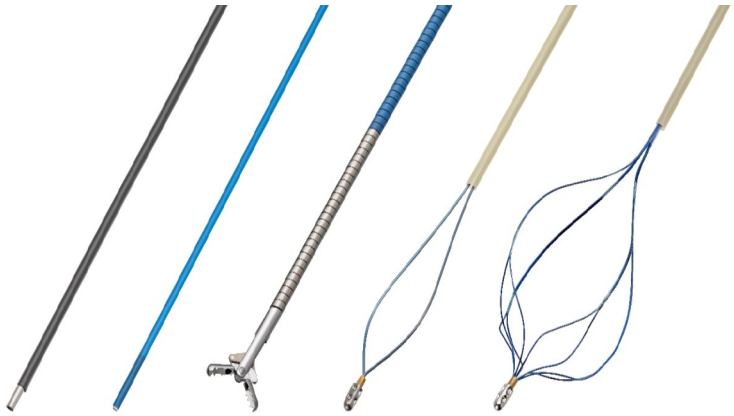

Figure 2 SpyGlass™ DS accessories including: Autolith™ Touch biliary electrohydraulic lithotripsy probe, Lumenis SlimLine™ SIS GI™ holmium laser lithotripsy probe, SpyBite™ Max biopsy forceps, SpyGlass retrieval snare, and SpyGlass retrieval basket (left to right). Additional accessories are expected to be developed over time[83]. Image adapted with permission from Dr. Isaac Raijman and Boston Scientific. Citation: **Boston Scientific Corporation.** An Expanding Suite of Compatible Accessories and Applications. [cited June 23, 2021]. Available from: https://www.bostonscientific.com/en-EU/products/direct-visualization-systems/spyglass-ds-direct-visualization-system/accessories-and-applications.html. Copyright© 2022. Published by SpyGlass™ DS.

with endoscopic sphincterotomy followed by stone extraction with a balloon or basket [4,11]. In a minority of cases, bile duct stones may be more difficult to extract, requiring additional measures[12]. Difficult bile duct stones have been previously defined as large size (> 1.5 cm in diameter), impacted stones in the bile or cystic duct, intrahepatic location, hard stone consistency, stricture distal to stones, and/or anatomical variants (*e.g.* unusual size/shape of bile duct) posing technical challenges [12,13].

POC allows for direct visualization and decreased risk of bile duct injury and is a vital addition to the ERCP armamentarium for stone disease. Indeed, a recent meta-analysis found the estimated success rate for difficult bile duct stone clearance to be 88% [95% confidence interval (CI): 85%-91%] across 820 patients (n = 31 studies)[14]. Furthermore, POC was found to have a low adverse event (AE) rate of 7% (95%CI: 6%-95%), comparable to ERCP[14,15]. Thus, POC is a valuable modality in addition to or in lieu of conventional ERCP methods such as mechanical lithotripsy (ML) and endoscopic papillary large balloon dilation (EPLBD).

Since the time of publication of the aforementioned meta-analysis, three randomized controlled trials (RCTs) comparing POC-guided electrohydraulic lithotripsy (EHL) or holmium laser lithotripsy (LL) *vs* conventional therapy (*i.e.* ML,

EPLBD, and balloon extraction) have been published. In the first study, the investigators randomized patients with bile duct stones > 1 cm in diameter in a 2:1 ratio to SOC-guided LL *vs* conventional therapy. Stone clearance was achieved in 39 of 42 (93%) patients treated with SOC-guided LL compared to 12 of 18 (67%) treated with conventional therapy (P = 0.009). AE rates were similar in the two treatment groups [16]. In the second study, successful stone removal did not differ in the SOC-guided EHL arm (37 of 48) *vs* conventional therapy arm (36 of 50) (P > 0.05); similarly, crossover yielded non-statistically significant differences in the two groups (successful stone removal in 40 of 47 patients *vs* 42 of 44 patients, P > 0.05)[17]. In the final study, the investigators randomized 32 patients with large CBD stones in whom sphincterotomy and/or EPLBD had failed into ML or D-SOC-guided LL treatment arms. Crossover was permitted as a rescue treatment if the primarily assigned technique failed to achieve stone clearance. Stone clearance rates for ML and D-SOC-guided LL groups were 63% and 100%, respectively (P < 0.01). In six patients, ML was considered a failure; when crossed over to LL, four of these patients achieved stone clearance in the same session, and the remaining two patients achieved stone clearance in subsequent LL sessions. AEs were reported at similar rates, 13% in the ML group and 6% in the LL group (P = 0.76). The median length of hospital stay following the respective procedures was 1 d in both groups (P = 0.27). At six months follow-up, neither group had recurrent cholangitis or evidence of recurrent CBD stones[18]. While the RCT data presented above may appear mixed or only partially in favor of POC in the management of difficult bile duct stones, it is important to note that only the last of the three studies discussed above utilized the newer generation of D-SOC. Thus, additional RCT data using the contemporary D-SOC system is needed.

POC can also be utilized to confirm stone clearance in cases of choledocholithiasis. In a retrospective study of 36 patients who underwent ERCP with EPLBD for difficult biliary stones, DPOC was performed immediately after a negative balloon-occluded cholangiography[19]. In 31 of 36 patients (86%), technical success was achieved with hepatic hilum visualization. Residual stones were found in 7 of these 31 patients (22.5%) upon DPOC, among which 4 patients underwent successful stone extraction during the same DPOC session. The remaining 3 patients underwent secondary ERCP for residual stone removal. There were no reported AEs in the study.

Indeterminate biliary strictures

Visual evaluation: Another major indication for POC is the evaluation of indeterminate biliary strictures (IDBSs). IDBSs are defined as biliary strictures of persistent unclear etiology following cross-sectional imaging and evaluation by ERCP with brush cytology or intraductal biopsies[20]. In a meta-analysis of 16 studies including 1556 patients, the overall sensitivity of conventional cytology from ERCP was found to be 41.6% (99%CI: 38.4%-44.8%), with a negative predictive value of 58.0% (99%CI: 54.8%-61.2%)[21]. This study and others, as well as widespread clinical experience, attest to the need for improved diagnostic capability for IDBSs.

The visual diagnosis of intraductal lesions can be aided by direct visualization during POC (Figure 3). Currently, there is no widely accepted classification system for visual diagnosis; however, some cholangioscopic findings are highly suggestive of malignancy in the appropriate clinical context. These findings include the presence of neovascularization, mucosal changes and projections, and intraductal nodules, among others[22-24]. Historically, neovascularization, also termed "tumor vessels," has had the most consensus regarding its description and malignant implications[24]. It has been described as irregularly dilated, tortuous, and abnormally proliferating vessels on the mucosa adjacent to a stricture.

In a recent systematic review and meta-analysis of 21 studies examining the diagnostic performance characteristics of POC-based visual assessments of IDBSs, the pooled sensitivity and specificity for establishing a malignancy diagnosis were 88% (95%CI: 83%-91%) and 95% (95%CI: 89-98%), respectively[25]. Subgroup analysis of studies that utilized D-SOC found a higher sensitivity for visual diagnosis [94% (95%CI: 89%-97%)] compared to D-SOC-guided biopsy [79% (95%CI: 72%-84%), P < 0.001] while also showing a higher specificity for D-SOC-guided biopsy [100% (95%CI: 97%-100%)] compared to D-SOC visual impression [86% (95%CI: 76%-92%), P < 0.001] [25]. Subgroup analysis of studies that utilized DPOC did not reveal statistically significant differences in performance characteristics of visual impression *vs* DPOC-guided biopsy (possibly suggesting superior optical performance of DPOC compared to D-SOC), though power was limited[25]. Overall, performance characteristics of visual impression utilizing modern POC (both D-SOC and DPOC) appears promising.

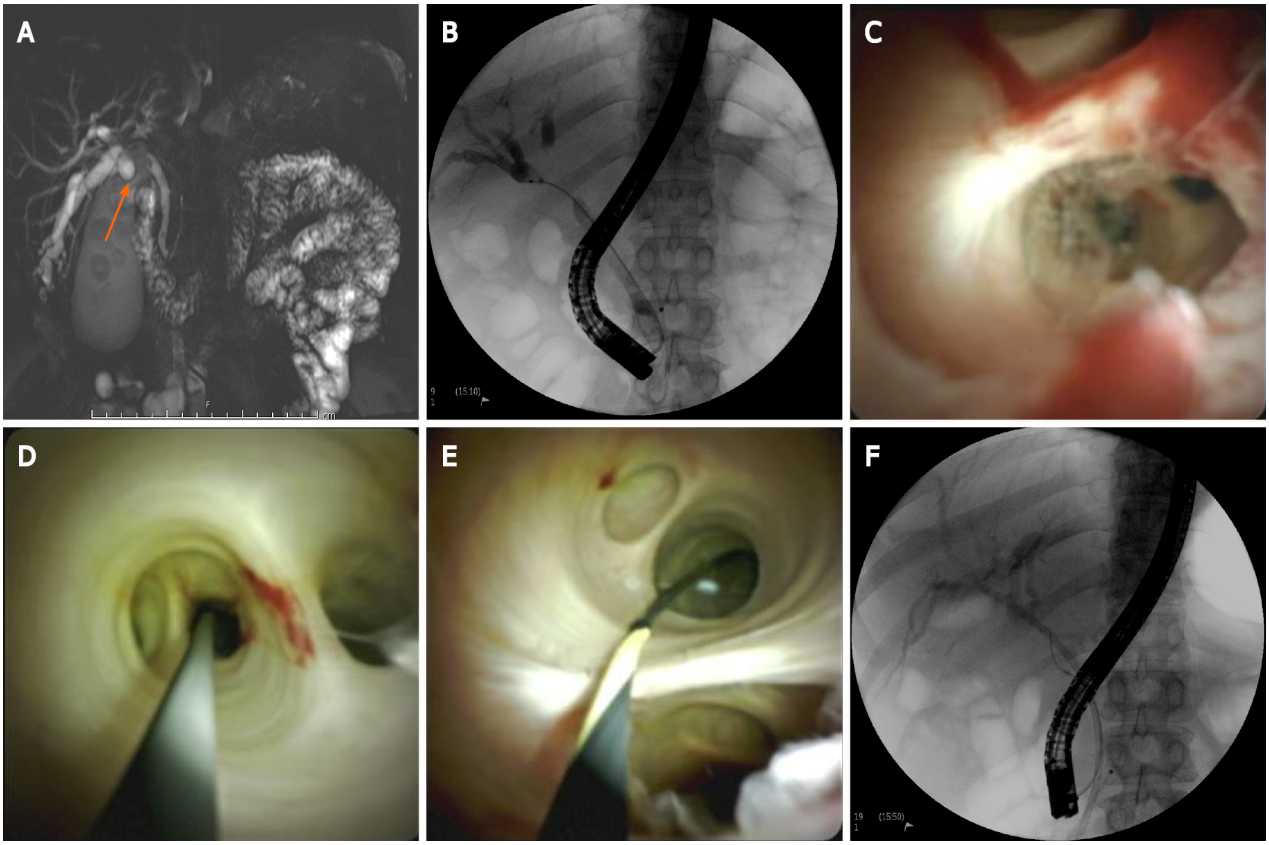

Figure 3 Example of an indeterminate biliary stricture further evaluated by cholangioscopy, initially thought to be Mirizzi syndrome secondary to chronic choledocholithiasis. A: Magnetic resonance cholangiopancreatography (T2 HASTE, coronal projection) demonstrating cholelithiasis, choledocholithiasis, and right hepatic ductal dilation as well as possible common hepatic duct (CHD) obstruction (arrow); B: Endoscopic retrograde cholangiopancreatography (ERCP) showing 1.5 cm CHD stricture suspicious for perihilar cholangiocarcinoma (CCA); C: Frond-like growth and neovascularization suggestive of neoplasm involving the CHD, later confirmed as perihilar CCA following SpyBite™ Max biopsy (previously with negative cytology on initial ERCP); D and E: Multiple views of the hepatic ducts that demonstrate scant reactive changes (from prior plastic biliary stent) and proximal limit of disease extension/tumor mapping; F: ERCP confirming successful deployment of plastic biliary stent across CHD stricture and subsequent decompression of right hepatic duct.

A recent group of researchers have produced a new schema, the "Monaco Classification," in order to attempt to standardize visual criteria in evaluating IDBSs as malignant *vs* benign. Twelve expert biliary endoscopists from around the world reviewed 40 video clips (13 benign pathology, 27 malignant) in order to consolidate visual criteria into the following: (1) Presence of stricture (symmetric or asymmetric); (2) Presence of lesion (with associated mass, nodule, or polypoid in appearance); (3) Smooth or granular mucosal features; (4) Papillary projections; (5) Ulceration; (6) Abnormal vessels; (7) Scarring (local or diffuse); and (8) Pronounced pit pattern[26]. Thereafter, 21 D-SOC video clips were reviewed by 14 interventional endoscopists utilizing these criteria, ranging from slight to moderate in interobserver agreement [26]. Diagnostic accuracy of visual interpretation of malignant *vs* benign pathology was 70% based on the new criteria, compared to an average accuracy less than 50% on prior attempts to establish visual criteria[26,27]. While the Monaco Classification has taken a crucial step in a forward direction, it would benefit from further refinement and validation.

Cytopathologic evaluation: In addition to the visual diagnosis of IDBSs, POC-guided biopsy can provide further histopathologic interpretation of IDBSs. In a systematic review with meta-analysis of 10 studies evaluating the use of SOC-guided biopsy for the diagnosis of malignant biliary strictures, the overall pooled sensitivity and specificity were 60.1% (95%CI: 54.9%-65.2%) and 98.0% (95%CI: 96.0%-99.0%), respectively[28]. In a subset of four studies, patients (n = 148) had previously undergone ERCP with benign or non-diagnostic brushing/biopsy results (with strong suspicion for malignancy); in this specific cohort, the pooled sensitivity and specificity of SOC-guided biopsy were 74.7% (95%CI: 63.3%-84.0%) and 93.3% (95%CI: 85.1%-97.8%), respectively[28]. More recently, a systematic review with meta-analysis of 11 studies examined the use of D-SOC-guided biopsy for evaluation of IDBSs. The pooled

sensitivity and specificity were 74% (95%CI: 67%-80%) and 98% (95%CI: 95%-100%), respectively[29]. These data suggest that POC-guided biopsy, in particular D-SOC-guided biopsy, yields improved diagnostic sensitivity when evaluating IDBSs.

POC-guided biopsies can be useful in cases where prior ERCP biopsies/brushings return benign or non-diagnostic results (when a strong suspicion for malignancy nevertheless remains) (Figure 3). In addition, a retrospective study of 40 patients found that biliary lavage cytology can be combined with POC-guided biopsy to further improve diagnostic sensitivity and accuracy when compared to POC-guided biopsy alone (sensitivity 88% *vs* 70% and accuracy 90% *vs* 75%, respectively)[30]. Of note, the data presented above predates the advent of the SpyBite™ Max biopsy forceps, which has increased tissue capacity compared to the first-generation SpyBite (legacy) forceps. This, along with other improvements, is expected to further improve the diagnostic performance of POC-guided intraductal biopsy.

One limiting factor that has been thought to potentially hamper the utility of SOC-guided biopsy is the absence of on-site cytopathology for real-time tissue processing, a concern recently addressed by the SOCRATES (single-operator cholangioscopy randomized trial evaluating specimens) trial[31]. In this RCT, patients (n = 62) with IDBSs were randomized to an off-site tissue processing cohort (n = 30) and an on-site cohort (n = 32) in order to compare diagnostic accuracy. The study found a diagnostic accuracy of 90% (95%CI: 73.5%-97.9%) versus 84.4% (95%CI: 67.2%-94.7%) when comparing off-site tissue processing *vs* on-site, respectively (P = 0.86). Additionally, the overall treatment costs of D-SOC based on the Medicare reimbursement fee structure (including anesthesia, hospital fees, laboratory fees, medications, supplies, and radiologic fees) was found to be $14423 for the off-site cohort compared to $13015 for the on-site cohort (P = 0.60). Thus, this RCT suggests that D-SOC is a cost-effective option for the evaluation of IDBSs, even in centers without on-site cytopathology.

Primary sclerosing cholangitis

Primary sclerosing cholangitis (PSC) is a chronic, progressive disease that causes inflammation and fibrosis of the biliary tract, often leading to end-stage liver disease and/or cholangiocarcinoma (CCA)[32]. Patients with PSC can develop "dominant strictures," or focal narrowing defined at ERCP as stenosis with diameter ≤ 1.5 mm in the CBD and/or ≤ 1.0 mm in a hepatic duct within 2 cm of the ductal confluence[20,32-34]. Dominant strictures are clinically significant in light of their higher propensity for bacterial cholangitis and for underlying dysplasia or carcinoma[32,35]. A recent systematic review and meta-analysis of 21 studies found the that the pooled sensitivity and specificity of POC for diagnosis of CCA was 65% (95%CI: 35%-87%) and 97% (95%CI: 87%-99%), respectively[36]. POC-guided biopsy also had the highest diagnostic accuracy (96%), compared to bile duct brushings (87%), fluorescence *in situ* hybridization (FISH) (69% for polysomy and 47% for trisomy), and probe-based confocal laser endomicroscopy (75%)[36].

However, not all data to date support the use of POC in patients with PSC. For example, a prospective study of 47 patients with PSC evaluating the use of POC-guided biopsy of strictures found a significantly lower sensitivity (33%) than previously reported[37]. Additionally, a retrospective study of 92 patients, both with (n = 36) and without (n = 56) PSC, examined the performance characteristics of ERCP with brush cytology, FISH, POC-guided biopsy, transpapillary biopsy and each possible combination of the aforementioned for the detection of CCA. When combining all diagnostic modalities, patients without PSC showed a trend towards improved sensitivity compared to brush cytology alone (75% *vs* 40.9%, P = 0.06)[38]. However, the PSC group did not show a similar trend towards improved sensitivity when comparing all four diagnostic modalities to cytology alone (60% *vs* 50%, P = 1)[38].

Overall, the precise role of POC in the diagnostic evaluation of dominant strictures in PSC remains unclear. POC can potentially play an important role in studying the natural history and progression of PSC and in general facilitate better characterization and sampling of dominant strictures. For instance, with the newly proposed cholangioscopy-based "Edmonton Classification" system for phenotypic classification, dominant strictures can be classified into one of the three following phenotypes: Inflammatory, fibro-stenotic, or nodular or mass-forming. One theory is that these and other POC findings may differ by disease stage/pathobiological involvement (*e.g.* nodular or mass forming may be indicative of developing or nascent CCA)[39]. It is proposed that combining phenotypic data with histopathology, biochemical markers, and cholangiography scores over time could lead to improved management algorithms[40]. For now, validation of this classification system remains the initial step

prior to determining its ultimate clinical utility.

Evaluation of intraductal neoplasms

POC is becoming increasingly useful in the mapping of biliopancreatic neoplasms such as CCA and intraductal papillary mucinous neoplasms (IPMNs). With improved visual delineation of neoplastic margins in the biliary tree and pancreatic ducts, staging can be more precise, and thus a better-informed therapeutic plan can be formulated (Figure 3). A multicenter prospective cohort study of 118 patients evaluated the impact of cholangiopancreatoscopy on preoperative assessment of biliopancreatic neoplasms. Following cholangiopancreatoscopy, the initial therapeutic plan was altered in 34% of patients[41]. Of these patients, more extensive surgery was required in 10%, less extensive surgery was required in 65%, and surgery was avoided in the remaining 25%[41]. Additionally, the study reported a 88% correlation in histology between the surgical specimens and cholangiopancreatoscopy specimens [41].

Cholangiopancreatoscopy is also being utilized to directly examine pancreatic duct abnormalities, such as distinguishing between pancreatic duct dilation secondary to chronic pancreatitis *vs* IPMNs[42]. When used in conjunction with non-invasive imaging, POC/cholangiopancreatoscopy improves diagnostic and therapeutic ability. As has been discussed in prior sections, this is mainly from direct visual tissue inspection and the ability to obtain targeted biopsies. Simultaneously, it also offers the opportunity for facilitate therapeutic intervention (*e.g.* management of pancreatolithiasis).

Selective guidewire placement

Numerous case reports, series, and a retrospective study have all demonstrated the potential benefits of POC-guided guidewire placement across strictures of varying causes (malignant, post-OLT, PSC, *etc.*)[43-45]. In the retrospective study, a total of 23 patients with known biliary strictures in whom endoscopic guidewire placement had previously failed underwent 30 procedures; technical success (guidewire placement) was achieved in 70%[43]. Subgroup analysis demonstrated a higher technical success rate among benign biliary strictures *vs* malignant strictures (88% *vs* 46%, $P = 0.02$). Of the 23 patients, 7 underwent repeat procedures, both in patients with previous failure of guidewire placement ($n = 3$) and prior success of guidewire placement ($n = 4$). A higher technical success rate was demonstrated on initial exam compared to subsequent exams (78% *vs* 43%, $P = 0.15$)[43]. While data are limited, POC-guided guidewire placement can be an effective alternative option, though traditional ERCP approaches should be attempted primarily given the significantly higher costs associated with POC and the ability to potentially troubleshoot successfully with varying guidewire diameters, tip designs, tip core materials, *etc.* during ERCP.

Biliary tumor ablation

The use of POC-guided radiofrequency ablation (RFA) to provide locoregional cancer-directed therapy for the management of extrahepatic CCA or other intraductal malignancies has been presented in various case reports[46,47]. Historically, percutaneous RFA has been well studied, though this technique has demonstrated an association with various AEs[48]. ERCP-RFA (without POC) has thus been explored as a possible alternative in porcine models, yielding similar concerns for high AE rates [49]. In a review article, the pooled data from 12 studies evaluating endoscopic RFA treatment for the management of patients with unresectable malignant biliary strictures showed similarly high AE rates (16%) across 318 total patients[50]. In a retrospective study of 12 patients, POC-guided RFA was both technically (RFA probe insertion into stricture site) and clinically successful (tumor ablation with POC imaging) while demonstrating safety (1 AE in study population) and efficacy in maintaining stent patency (median of 154 d) following POC-guided RFA. Though data are limited, POC-guided RFA could be explored in further studies as a potentially viable, safer (compared to percutaneous RFA and endoscopic RFA) palliative treatment option for select patients with unresectable malignant biliary strictures.

POC-guided photodynamic therapy (PDT) has also been suggested to improve symptoms and prolong survival in cases of unresectable biliary tumors, with relatively few complications[51]. PDT begins with the administration of intravenous photosensitizer, which is preferentially retained by malignant tissue, approximately 24 h prior to POC. Subsequently, light energy can be delivered under POC guidance to the target tissue at a photoactivating wavelength, resulting in a photochemical reaction inducing ischemia and necrosis of tumor cells[52]. RCT data is limited to ERCP-based studies, in which PDT plus endoscopic stenting ($n = 20$) *vs* endoscopic stenting alone

(n = 19) found improvement in median survival (493 d *vs* 98 d, P < 0.0001)[53]. However, a retrospective case series (n = 45) demonstrated similar absolute increases in median survival time when comparing SOC-guided PDT *vs* PDT-only, though not statistically significant (386 d *vs* 200 d, P = 0.45)[51]. This may suggest that larger cohorts need to be studied to better understand whether the effect of SOC-guided PDT truly plays an essential role compared to PDT therapy alone.

Post-liver transplant biliary complications

One AE orthotopic liver transplantation (OLT) patients face is the development of biliary strictures, either anastomotic (more common) or nonanstomotic (less common). Biliary strictures affect up to nearly 40% of post-OLT patients[54]. In these cases, POC can be utilized for visual assessment of the biliary epithelium and/or targeted biopsy, if needed[55]. Additionally, some strictures are not amenable to guidewire insertion or cannulation with standard ERCP (*e.g.* angulated strictures)[56]; the addition of POC can facilitate guidewire insertion and possibly obviate the need for biliary drainage or surgical intervention[55,56].

In a recent observational study of 26 patients who underwent ERCP followed by POC for suspected biliary complications post-OLT, 33 biliary complications were found in 22 patients. The remaining 4 patients were found to have normal bile ducts. Of the biliary complications, anastomotic strictures were the most common (14), followed by nonastomotic strictures (7), biliary stones (6), and lastly biliary casts (3). In 12 patients (46%), POC demonstrated a clear benefit: Selective guidewire placement, identification of biliary cast and/or stones not previously found on ERCP, or epithelial changes (*e.g.* ulceration or inflammation) secondary to infection[44]. Additional case series have shown the potential benefits of POC-guided steroid injections for management of anastomotic strictures and POC-guided guidewire placement across strictures (previously failed under fluoroscopic guidance)[56,57]. All of these observational studies suggest low rates of AEs, even in the post-OLT population[44,56,57]. Of note, in immunocompromised post-OLT patients, it is important to provide a prophylactic course of antibiotics given the potential increased risk of bacterial translocation with POC[58].

Radiation-free management

One of the disadvantages of conventional ERCP therapy is radiation exposure to patients and medical staff from the use of fluoroscopy. In particular, there can be teratogenic risk posed to pregnant patients in the first trimester[59]. While ERCP remains the standard of care and every effort should be made to use fluoroscopy selectively and with proper safety measures, POC can be utilized as an alternative management strategy to minimize or obviate the use of radiation[60]. A recent retrospective, multicenter study demonstrated 100% success rate in achieving bile duct cannulation without the use of fluoroscopy in the study population of pregnant patients (n = 10) with a mean gestational age of 23 wk. Indications for intervention included: Choledocholithiasis (7), stent removal (1), biliary stricture (1), and combined choledocholithiasis/stent removal (1). Fifty-percent of patients were able to undergo a completely radiation-free procedure, while an additional 30% received a dose minimized below the recommended amount. AEs (pancreatitis[1], mild bleeding[1]) occurred in two patients (20%)[61]. The data remain limited in this cohort, but this application of POC can certainly be considered as a possibly safer alternative in select cases[61-63].

EMERGING AND MISCELLANEOUS APPLICATIONS OF CHOLANGIOSCOPY

Novel applications of POC continue to emerge. One area of demonstrated utility has been in the removal of migrated stents and other foreign bodies. Following failed retrieval attempts with ERCP, POC can provide better visualization and/or access for successful extraction, thereby avoiding more invasive procedures[64-67]. Additionally, POC can aid in the evaluation and management of hemobilia. After magnetic resonance cholangiopancreatography (MRCP) or ERCP demonstrates the presence of blood in the bile duct, POC can facilitate determining the source and etiology of bleeding. In one case report, POC was utilized to confirm hemobilia arising from the gallbladder, and ultimately a diagnosis of diffusely infiltrative gallbladder cancer was made[68]. Another case report describes the detection of biliary angiodysplasia during

POC following an unrevealing MRCP[69]. There have also been reports of the use of POC in select cases of cholecystitis, where patients may not otherwise be surgical candidates and/or in the presence of anatomical challenges. In these instances, POC can be utilized to access and traverse the cystic duct with subsequent deployment of metal or plastic stents as a means of minimally-invasive management[70-72]. Finally, there has been a reported case of POC-guided EHL for the removal of a calcified stool bezoar in an elderly patient with chronic, severe constipation[73].

DRAWBACKS OF CHOLANGIOSCOPY: ECONOMIC CONSIDERATIONS AND AEs

Though the clinical applications of POC continue to expand, several factors hinder further widespread use. In particular, the financial implications of POC *vs* conventional ERCP, owing to the high cumulative costs of the POC processor, cholangioscopes, and cholangioscopic accessories, are major hindering factors. Overall, start-up costs have been estimated to range between 50000 to $90000, though they can vary substantially by institutional contract[74]. Additionally, cholangioscopes (D-SOC) and their accessories are both single-use, and each one costs on the order of thousands and hundreds of dollars, respectively. Based on a micro-costing approach, one European study suggested that POC could be cost-effective for both treatment of difficult bile duct stones and diagnosis of IDBSs when compared to conventional ERCP[75]. However, robust economic data are lacking in the United States. Moreover, procedure times are often longer with POC when compared to conventional ERCP; thus, this may deter performance of POC due to the ability to generate more revenue with conventional ERCP *per* unit of time.

The overall AE rate associated with POC has been reported to be between 4% and 22%[76]. The major AEs include: Cholangitis, bacteremia, liver abscess, pancreatitis, and bleeding[77]. In a nationwide study in Sweden analyzing 36352 ERCP procedures and 408 cholangioscopy procedures between 2007 and 2012, reported post-procedural AEs were higher with POC when compared to ERCP (19.1% *vs* 14.0%)[78]. Pancreatitis (7.4% *vs* 3.9%) and cholangitis (4.4% *vs* 2.7%) showed similar increases, though multivariate analysis did not demonstrate a statistically significant difference when adjusted for confounders[78]. While higher rates of AEs with POC remain a concern, one group found that administration of peri-interventional antibiotics can substantially reduce rates of cholangitis[79]. With ongoing evolution of POC technology, its safety profile when directly compared to conventional ERCP will need continued assessment.

RECENT AND FUTURE DEVICE DEVELOPMENT

In May 2019, a next generation "mother-baby" videocholangioscope system (CHF-B290, Olympus Medical Systems Corporation, Tokyo, Japan) was introduced[80,81]. Despite being a newer iteration with notable improvements, some previously known limitations (*e.g.* two endoscopist operators and two equipment towers) remain, while others, such as scope fragility and accessory channel diameter, have been reported to be improved[80]. Currently, this system is only available for use in certain markets in Asia and Europe[80].

In July 2020, Ambu Inc. received FDA approval for the Ambu® aScope™ (Ambu Inc, Columbia, MD United States) Duodeno, a single-use duodenoscope. It is anticipated that a single-use cholangioscope and additional accessories will follow in the next 1-2 years, with the potential for new clinical applications. It will be interesting to compare these developments to existing scopes and accessories.

CONCLUSION

With growing evidence to support its use, POC has evolved into an important tool in the biliopancreatic armamentarium. It is an important therapeutic option for difficult biliary stones and a core part of the evaluation of indeterminate strictures. Outcomes from the use of D-SOC for other ongoing and investigational indications (*e.g.* radiation-free intervention in pregnant patients, migrated stent/foreign body extraction, post-OLT biliary complication management, and selective guidewire

placement) appear promising. Still, as discussed in this review, there are constraining factors and limitations to consider, *e.g.* device costs, paucity of standardized cholangioscopic visual classification systems, anatomical challenges, *etc.*[82].

In the future, further research and data are needed to solidify the evidence for POC and clarify the outcomes of its investigational applications. For now, endoscopists may continue to explore additional frontiers of clinical application, particularly with the advent of new accessories and further technologic enhancements that may be on the horizon.

REFERENCES

1 **McCune WS**, Shorb PE, Moscovitz H. Endoscopic cannulation of the ampulla of vater: a preliminary report. *Ann Surg* 1968; **167**: 752-756 [PMID: 5646296 DOI: 10.1016/S0016-5107(88)71332-2]

2 **Urakami Y**, Seifert E, Butke H. Peroral direct cholangioscopy (PDCS) using routine straight-view endoscope: first report. *Endoscopy* 1977; **9**: 27-30 [PMID: 862583 DOI: 10.1055/s-0028-1098481]

3 **Choi JH**, Lee SK. Percutaneous transhepatic cholangioscopy: does its role still exist? *Clin Endosc* 2013; **46**: 529-536 [PMID: 24143316 DOI: 10.5946/ce.2013.46.5.529]

4 **Ayoub F**, Yang D, Draganov PV. Cholangioscopy in the digital era. *Transl Gastroenterol Hepatol* 2018; **3**: 82 [PMID: 30505969 DOI: 10.21037/tgh.2018.10.08]

5 **Farrell JJ**, Bounds BC, Al-Shalabi S, Jacobson BC, Brugge WR, Schapiro RH, Kelsey PB. Single-operator duodenoscope-assisted cholangioscopy is an effective alternative in the management of choledocholithiasis not removed by conventional methods, including mechanical lithotripsy. *Endoscopy* 2005; **37**: 542-547 [PMID: 15933927 DOI: 10.1055/s-2005-861306]

6 **Hoffman A**, Rey JW, Kiesslich R. Single operator choledochoscopy and its role in daily endoscopy routine. *World J Gastrointest Endosc* 2013; **5**: 203-210 [PMID: 23678372 DOI: 10.4253/wjge.v5.i5.203]

7 **Ghersi S**, Fuccio L, Bassi M, Fabbri C, Cennamo V. Current status of peroral cholangioscopy in biliary tract diseases. *World J Gastrointest Endosc* 2015; **7**: 510-517 [PMID: 25992189 DOI: 10.4253/wjge.v7.i5.510]

8 **Larghi A**, Waxman I. Endoscopic direct cholangioscopy by using an ultra-slim upper endoscope: a feasibility study. *Gastrointest Endosc* 2006; **63**: 853-857 [PMID: 16650553 DOI: 10.1016/j.gie.2005.07.050]

9 **Parsi MA**. Direct peroral cholangioscopy. *World J Gastrointest Endosc* 2014; **6**: 1-5 [PMID: 24527174 DOI: 10.4253/wjge.v6.i1.1]

10 **Moon JH**, Choi HJ. The role of direct peroral cholangioscopy using an ultraslim endoscope for biliary lesions: indications, limitations, and complications. *Clin Endosc* 2013; **46**: 537-539 [PMID: 24143317 DOI: 10.5946/ce.2013.46.5.537]

11 **Dasari BV**, Tan CJ, Gurusamy KS, Martin DJ, Kirk G, McKie L, Diamond T, Taylor MA. Surgical *vs* endoscopic treatment of bile duct stones. *Cochrane Database Syst Rev* 2013; CD003327 [PMID: 23999986 DOI: 10.1002/14651858.CD003327.pub3]

12 **Carr-Locke DL**. Difficult bile-duct stones: cut, dilate, or both? *Gastrointest Endosc* 2008; **67**: 1053-1055 [PMID: 18513548 DOI: 10.1016/j.gie.2008.02.003]

13 **McHenry L**, Lehman G. Difficult bile duct stones. *Curr Treat Options Gastroenterol* 2006; **9**: 123-132 [PMID: 16539873 DOI: 10.1007/s11938-006-0031-6]

14 **Korrapati P**, Ciolino J, Wani S, Shah J, Watson R, Muthusamy VR, Klapman J, Komanduri S. The efficacy of peroral cholangioscopy for difficult bile duct stones and indeterminate strictures: a systematic review and meta-analysis. *Endosc Int Open* 2016; **4**: E263-E275 [PMID: 27004242 DOI: 10.1055/s-0042-100194]

15 **Andriulli A**, Loperfido S, Napolitano G, Niro G, Valvano MR, Spirito F, Pilotto A, Forlano R. Incidence rates of post-ERCP complications: a systematic survey of prospective studies. *Am J Gastroenterol* 2007; **102**: 1781-1788 [PMID: 17509029 DOI: 10.1111/j.1572-0241.2007.01279.x]

16 **Buxbaum J**, Sahakian A, Ko C, Jayaram P, Lane C, Yu CY, Kankotia R, Laine L. Randomized trial of cholangioscopy-guided laser lithotripsy versus conventional therapy for large bile duct stones (with videos). *Gastrointest Endosc* 2018; **87**: 1050-1060 [PMID: 28866457 DOI: 10.1016/j.gie.2017.08.021]

17 **Franzini T**, Moura RN, Bonifácio P, Luz GO, de Souza TF, Dos Santos MEL, Rodela GL, Ide E, Herman P, Montagnini AL, D'Albuquerque LAC, Sakai P, de Moura EGH. Complex biliary stones management: cholangioscopy *vs* papillary large balloon dilation - a randomized controlled trial. *Endosc Int Open* 2018; **6**: E131-E138 [PMID: 29399609 DOI: 10.1055/s-0043-122493]

18 **Angsuwatcharakon P**, Kulpatcharapong S, Ridtitid W, Boonmee C, Piyachaturawat P, Kongkam P, Pareesri W, Rerknimitr R. Digital cholangioscopy-guided laser *vs* mechanical lithotripsy for large bile duct stone removal after failed papillary large-balloon dilation: a randomized study. *Endoscopy* 2019; **51**: 1066-1073 [PMID: 30786315 DOI: 10.1055/a-0848-8373]

19 **Anderloni A**, Auriemma F, Fugazza A, Troncone E, Maia L, Maselli R, Carrara S, D'Amico F, Belletrutti PJ, Repici A. Direct peroral cholangioscopy in the management of difficult biliary stones: a new tool to confirm common bile duct clearance. Results of a preliminary study. *J Gastrointestin Liver Dis* 2019; **28**: 89-94 [PMID: 30851177 DOI: 10.15403/jgld.2014.1121.281.bil]

20 **Hilscher MB**, Tabibian JH, Carey EJ, Gostout CJ, Lindor KD. Dominant strictures in primary sclerosing cholangitis: A multicenter survey of clinical definitions and practices. *Hepatol Commun* 2018; **2**: 836-844 [PMID: 30027141 DOI: 10.1002/hep4.1194]

21 **Burnett AS**, Calvert TJ, Chokshi RJ. Sensitivity of endoscopic retrograde cholangiopancreatography standard cytology: 10-y review of the literature. *J Surg Res* 2013; **184**: 304-311 [PMID: 23866788 DOI: 10.1016/j.jss.2013.06.028]

22 **Seo DW**, Lee SK, Yoo KS, Kang GH, Kim MH, Suh DJ, Min YI. Cholangioscopic findings in bile duct tumors. *Gastrointest Endosc* 2000; **52**: 630-634 [PMID: 11060187 DOI: 10.1067/mge.2000.108667]

23 **Shah RJ**, Raijman I, Brauer B, Gumustop B, Pleskow DK. Performance of a fully disposable, digital, single-operator cholangiopancreatoscope. *Endoscopy* 2017; **49**: 651-658 [PMID: 28511237 DOI: 10.1055/s-0043-106295]

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

25 **Kulpatcharapong S**, Pittayanon R, Kerr SJ, Rerknimitr R. Diagnostic performance of digital and video cholangioscopes in patients with suspected malignant biliary strictures: a systematic review and meta-analysis. *Surg Endosc* 2021 [PMID: 34076761 DOI: 10.1007/s00464-021-08571-2]

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

27 **Sethi A**, Doukides T, Sejpal DV, Pleskow DK, Slivka A, Adler DG, Shah RJ, Edmundowicz SA, Itoi T, Petersen BT, Gress FG, Gaidhane M, Kahaleh M. Interobserver agreement for single operator choledochoscopy imaging: can we do better? *Diagn Ther Endosc* 2014; **2014**: 730731 [PMID: 25400494 DOI: 10.1155/2014/730731]

28 **Navaneethan U**, Hasan MK, Lourdusamy V, Njei B, Varadarajulu S, Hawes RH. Single-operator cholangioscopy and targeted biopsies in the diagnosis of indeterminate biliary strictures: a systematic review. *Gastrointest Endosc* 2015; **82**: 608-14.e2 [PMID: 26071061 DOI: 10.1016/j.gie.2015.04.030]

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

30 **Motomura Y**, Akahoshi K, Kajiyama K. Utility of lavage cytology plus targeted biopsy during cholangioscopy for the diagnosis of indeterminate biliary lesions. *Gastroenterol Hepatol Endosc* 2017; **2**: 1-4 [DOI: 10.15761/ghe.1000142]

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

32 **Fung BM**, Tabibian JH. Biliary endoscopy in the management of primary sclerosing cholangitis and its complications. *Liver Res* 2019; **3**: 106-117 [PMID: 31341699 DOI: 10.1016/j.livres.2019.03.004]

33 **Stiehl A**, Rudolph G, Klöters-Plachky P, Sauer P, Walker S. Development of dominant bile duct stenoses in patients with primary sclerosing cholangitis treated with ursodeoxycholic acid: outcome after endoscopic treatment. *J Hepatol* 2002; **36**: 151-156 [PMID: 11830325 DOI: 10.1016/s0168-8278(01)00251-3]

34 **Aabakken L**, Karlsen TH, Albert J, Arvanitakis M, Chazouilleres O, Dumonceau JM, Färkkilä M, Fickert P, Hirschfield GM, Laghi A, Marzioni M, Fernandez M, Pereira SP, Pohl J, Poley JW, Ponsioen CY, Schramm C, Swahn F, Tringali A, Hassan C. Role of endoscopy in primary sclerosing cholangitis: European Society of Gastrointestinal Endoscopy (ESGE) and European Association for the Study of the Liver (EASL) Clinical Guideline. *Endoscopy* 2017; **49**: 588-608 [PMID: 28420030 DOI: 10.1055/s-0043-107029]

35 **Waldthaler A**, Schramm C, Bergquist A. Present and future role of endoscopic retrograde cholangiography in primary sclerosing cholangitis. *Eur J Med Genet* 2021; **64**: 104231 [PMID: 33905896 DOI: 10.1016/j.ejmg.2021.104231]

36 **Njei B**, McCarty TR, Varadarajulu S, Navaneethan U. Systematic review with meta-analysis: endoscopic retrograde cholangiopancreatography-based modalities for the diagnosis of cholangiocarcinoma in primary sclerosing cholangitis. *Aliment Pharmacol Ther* 2016; **44**: 1139-1151 [PMID: 27696456 DOI: 10.1111/apt.13817]

37 **Arnelo U**, von Seth E, Bergquist A. Prospective evaluation of the clinical utility of single-operator peroral cholangioscopy in patients with primary sclerosing cholangitis. *Endoscopy* 2015; **47**: 696-702 [PMID: 25826274 DOI: 10.1055/s-0034-1391845]

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

39 **Fujisawa T**, Ushio M, Takahashi S, Yamagata W, Takasaki Y, Suzuki A, Okawa Y, Ochiai K, Tomishima K, Ishii S, Saito H, Isayama H. Role of Peroral Cholangioscopy in the Diagnosis of

Primary Sclerosing Cholangitis. *Diagnostics (Basel)* 2020; **10** [PMID: 32365686 DOI: 10.3390/diagnostics10050268]

40 **Sandha G**, D'Souza P, Halloran B, Montano-Loza AJ. A Cholangioscopy-Based Novel Classification System for the Phenotypic Stratification of Dominant Bile Duct Strictures in Primary Sclerosing Cholangitis-the Edmonton Classification. *J Can Assoc Gastroenterol* 2018; **1**: 174-180 [PMID: 31294358 DOI: 10.1093/jcag/gwy020]

41 **Tyberg A**, Raijman I, Siddiqui A, Arnelo U, Adler DG, Xu MM, Nassani N, Sejpal DV, Kedia P, Nah Lee Y, Gress FG, Ho S, Gaidhane M, Kahaleh M. Digital Pancreaticocholangioscopy for Mapping of Pancreaticobiliary Neoplasia: Can We Alter the Surgical Resection Margin? *J Clin Gastroenterol* 2019; **53**: 71-75 [PMID: 29517713 DOI: 10.1097/MCG.0000000000001008]

42 **De Luca L**, Repici A, Koçollari A, Auriemma F, Bianchetti M, Mangiavillano B. Pancreatoscopy: An update. *World J Gastrointest Endosc* 2019; **11**: 22-30 [PMID: 30705729 DOI: 10.4253/wjge.v11.i1.22]

43 **Bokemeyer A**, Gross D, Brückner M, Nowacki T, Bettenworth D, Schmidt H, Heinzow H, Kabar I, Ullerich H, Lenze F. Digital single-operator cholangioscopy: a useful tool for selective guidewire placements across complex biliary strictures. *Surg Endosc* 2019; **33**: 731-737 [PMID: 30006839 DOI: 10.1007/s00464-018-6334-6]

44 **Pillai S**, Zhou GX, Arnaud P, Jiang H, Butler WJ, Zhang H. Antibodies to endometrial transferrin and alpha 2-Heremans Schmidt (HS) glycoprotein in patients with endometriosis. *Am J Reprod Immunol* 1996; **35**: 483-494 [PMID: 8738720 DOI: 10.3748/wjg.v23.i22.4064]

45 **Imanishi M**, Ogura T, Kurisu Y, Onda S, Takagi W, Okuda A, Miyano A, Amano M, Nishioka N, Masuda D, Higuchi K. A feasibility study of digital single-operator cholangioscopy for diagnostic and therapeutic procedure (with videos). *Medicine (Baltimore)* 2017; **96**: e6619 [PMID: 28403110 DOI: 10.1097/MD.0000000000006619]

46 **Natov NS**, Horton LC, Hegde SR. Successful endoscopic treatment of an intraductal papillary neoplasm of the bile duct. *World J Gastrointest Endosc* 2017; **9**: 238-242 [PMID: 28572878 DOI: 10.4253/wjge.v9.i5.238]

47 **Gunasingam N**, Craig PI. Cholangioscopy-directed radiofrequency ablation of complex biliary cholangiocarcinoma. *VideoGIE* 2019; **4**: 211-213 [PMID: 31061941 DOI: 10.1016/j.vgie.2018.12.017]

48 **Livraghi T**, Solbiati L, Meloni MF, Gazelle GS, Halpern EF, Goldberg SN. Treatment of focal liver tumors with percutaneous radio-frequency ablation: complications encountered in a multicenter study. *Radiology* 2003; **226**: 441-451 [PMID: 12563138 DOI: 10.1148/radiol.2262012198]

49 **Wadsworth CA**, Westaby D, Khan SA. Endoscopic radiofrequency ablation for cholangiocarcinoma. *Curr Opin Gastroenterol* 2013; **29**: 305-311 [PMID: 23449026 DOI: 10.1097/MOG.0b013e32835faacc]

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

51 **Talreja JP**, DeGaetani M, Sauer BG, Kahaleh M. Photodynamic therapy for unresectable cholangiocarcinoma: contribution of single operator cholangioscopy for targeted treatment. *Photochem Photobiol Sci* 2011; **10**: 1233-1238 [PMID: 21512706 DOI: 10.1039/c0pp00259c]

52 **Chahal P**, Baron TH. Endoscopic palliation of cholangiocarcinoma. *Curr Opin Gastroenterol* 2006; **22**: 551-560 [PMID: 16891889 DOI: 10.1097/01.mog.0000239872.12081.a4]

53 **Ortner ME**, Caca K, Berr F, Liebetruth J, Mansmann U, Huster D, Voderholzer W, Schachschal G, Mössner J, Lochs H. Successful photodynamic therapy for nonresectable cholangiocarcinoma: a randomized prospective study. *Gastroenterology* 2003; **125**: 1355-1363 [PMID: 14598251 DOI: 10.1016/j.gastro.2003.07.015]

54 **Greif F**, Bronsther OL, Van Thiel DH, Casavilla A, Iwatsuki S, Tzakis A, Todo S, Fung JJ, Starzl TE. The incidence, timing, and management of biliary tract complications after orthotopic liver transplantation. *Ann Surg* 1994; **219**: 40-45 [PMID: 8297175 DOI: 10.1097/00000658-199401000-00007]

55 **Boeva I**, Karagyozov PI, Tishkov I. Post-liver transplant biliary complications: Current knowledge and therapeutic advances. *World J Hepatol* 2021; **13**: 66-79 [PMID: 33584987 DOI: 10.4254/wjh.v13.i1.66]

56 **Martins FP**, Ferrari AP. Cholangioscopy-assisted guidewire placement in post-liver transplant anastomotic biliary stricture: efficient and potentially also cost-effective. *Endoscopy* 2017; **49**: E283-E284 [PMID: 28905337 DOI: 10.1055/s-0043-117940]

57 **Franzini T**, Sagae VMT, Guedes HG, Sakai P, Waisberg DR, Andraus W, D'Albuquerque LAC, Sethi A, de Moura EGH. Cholangioscopy-guided steroid injection for refractory post liver transplant anastomotic strictures: a rescue case series. *Ther Adv Gastrointest Endosc* 2019; **12**: 2631774519867786 [PMID: 31489404 DOI: 10.1177/2631774519867786]

58 **Moy BT**, Birk JW. A Review on the Management of Biliary Complications after Orthotopic Liver Transplantation. *J Clin Transl Hepatol* 2019; **7**: 61-71 [PMID: 30944822 DOI: 10.14218/JCTH.2018.00028]

59 **Wu W**, Faigel DO, Sun G, Yang Y. Non-radiation endoscopic retrograde cholangiopancreatography in the management of choledocholithiasis during pregnancy. *Dig Endosc* 2014; **26**: 691-700 [PMID: 24861135 DOI: 10.1111/den.12307]

60 **Barakat MT**, Girotra M, Choudhary A, Huang RJ, Sethi S, Banerjee S. A prospective evaluation of

radiation-free direct solitary cholangioscopy for the management of choledocholithiasis. *Gastrointest Endosc* 2018; **87**: 584-589.e1 [PMID: 28797911 DOI: 10.1016/j.gie.2017.07.042]

61 **Brewer Gutierrez OI**, Godoy Brewer G, Zulli C, Tejaswi S, Pawa R, Jamidar P, Robles-Medranda C, Pawa S, Camilion JV, Oleas R, Parsa N, Runge T, Miaw D, Ichkhanian Y, Khashab MA. Multicenter experience with digital single-operator cholangioscopy in pregnant patients. *Endosc Int Open* 2021; **9**: E116-E121 [PMID: 33532547 DOI: 10.1055/a-1320-0084]

62 **Achanta CR**. Radiation-free removal of common bile duct stones in pregnancy facilitated by endoscopic ultrasound and single-operator cholangioscopy. *Endoscopy* 2021; **53**: E100-E101 [PMID: 32659801 DOI: 10.1055/a-1202-1248]

63 **Uradomo L**, Pandolfe F, Aragon G, Borum ML. SpyGlass cholangioscopy for management of choledocholithiasis during pregnancy. *Hepatobiliary Pancreat Dis Int* 2011; **10**: 107 [PMID: 21269945 DOI: 10.1016/s1499-3872(11)60017-9]

64 **Sanaka MR**, Wadhwa V, Patel M. Retrieval of proximally migrated biliary stent with direct peroral cholangioscopy with an ultraslim endoscope. *Gastrointest Endosc* 2015; **81**: 1483-1484 [PMID: 25865384 DOI: 10.1016/j.gie.2015.01.029]

65 **Ogura T**, Okuda A, Miyano A, Nishioka N, Higuchi K. Migrated endoclip removal after cholecystectomy under digital single-operator cholangioscopy guidance. *Endoscopy* 2018; **50**: E74-E75 [PMID: 29329478 DOI: 10.1055/s-0043-124758]

66 **Al Lehibi A**, Al Mtawa A, Almasoudi T, Al Ghamdi A, Al Otaibi N, Al Balkhi A. Removal of proximally migrated biliary stents by using single-operator cholangioscopy. *VideoGIE* 2020; **5**: 213-216 [PMID: 32426574 DOI: 10.1016/j.vgie.2020.01.001]

67 **Bas-Cutrina F**, Garcia-Sumalla A, Velasquez J, Consiglieri CF, Lladó L, Gornals JB. Removal of a migrated biliary stent using new digital cholangioscopy retrieval devices in a transplant patient. *Endoscopy* 2019; **51**: E323-E324 [PMID: 31163480 DOI: 10.1055/a-0916-8490]

68 **Zhang L**, Craig PI. A case of hemobilia secondary to cancer of the gallbladder confirmed by cholangioscopy and treated with a fully covered self-expanding metal stent. *VideoGIE* 2018; **3**: 381-383 [PMID: 30506001 DOI: 10.1016/j.vgie.2018.08.013]

69 **Sum Foong K**, Lee A, Kudakachira S, Ramberan H. Hemobilia from Biliary Angiodysplasia Diagnosed with Cholangioscopy. *ACG Case Rep J* 2016; **3**: e132 [PMID: 27807584 DOI: 10.14309/crj.2016.105]

70 **Kedia P**, Kuo V, Tarnasky P. Digital cholangioscopy-assisted endoscopic gallbladder drainage. *Gastrointest Endosc* 2017; **85**: 257-258 [PMID: 27449190 DOI: 10.1016/j.gie.2016.07.016]

71 **Gutkin E**, Hussain SA, Kim SH. The Successful Treatment of Chronic Cholecystitis with SpyGlass Cholangioscopy-Assisted Gallbladder Drainage and Irrigation through Self-Expandable Metal Stents. *Gut Liver* 2012; **6**: 136-138 [PMID: 22375186 DOI: 10.5009/gnl.2012.6.1.136]

72 **Tyberg A**, Zerbo S, Kahaleh M, Sharaiha RZ. Digital cholangioscopy-assisted gallbladder drainage: seeing is accessing. *Endoscopy* 2015; **47** Suppl 1 UCTN: E417 [PMID: 26397847 DOI: 10.1055/s-0034-1392655]

73 **Shi L**, Lin S, Yao J, Li F. A novel endoscopic method for removal of giant calcified stool bezoar by cholangioscopy-guided electric hydraulic lithotripsy. *Gastrointest Endosc* 2019; **90**: 531-532 [PMID: 31077703 DOI: 10.1016/j.gie.2019.05.002]

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

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

76 **Karagyozov P**, Boeva I, Tishkov I. Role of digital single-operator cholangioscopy in the diagnosis and treatment of biliary disorders. *World J Gastrointest Endosc* 2019; **11**: 31-40 [PMID: 30705730 DOI: 10.4253/wjge.v11.i1.31]

77 **Gravito-Soares M**, Almeida N. Peroral Cholangiopancreatoscopy: New Advances Bring New Concerns. *GE Port J Gastroenterol* 2018; **25**: 112-114 [PMID: 29761145 DOI: 10.1159/000486019]

78 **Lübbe J**, Arnelo U, Lundell L, Swahn F, Törnqvist B, Jonas E, Löhr JM, Enochsson L. ERCP-guided cholangioscopy using a single-use system: nationwide register-based study of its use in clinical practice. *Endoscopy* 2015; **47**: 802-807 [PMID: 25910063 DOI: 10.1055/s-0034-1391990]

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

80 **Murabayashi T**, Ogawa T, Koshita S, Kanno Y, Kusunose H, Sakai T, Masu K, Yonamine K, Miyamoto K, Kozakai F, Endo K, Noda Y, Ito K. Peroral Cholangioscopy-guided Electrohydraulic Lithotripsy with a SpyGlass DS Versus a Conventional Digital Cholangioscope for Difficult Bile Duct Stones. *Intern Med* 2020; **59**: 1925-1930 [PMID: 32389946 DOI: 10.2169/internalmedicine.4463-20]

81 **Xu MM**, Kahaleh M. Recent developments in choledochoscopy: technical and clinical advances. *Clin Exp Gastroenterol* 2016; **9**: 119-124 [PMID: 27274300 DOI: 10.2147/CEG.S84020]

82 **Subhash A**, Abadir A, Iskander JM, Tabibian JH. Applications, Limitations, and Expansion of

Cholangioscopy in Clinical Practice. *Gastroenterol Hepatol (N Y)* 2021; **17**: 110-120 [PMID: 34035770]

83 **Boston Scientific Corporation**. An Expanding Suite of Compatible Accessories and Applications. [cited June 23, 2021]. Available from: https://www.bostonscientific.com/en-EU/products/direct-visualization-systems/spyglass-ds-direct-visualization-system/accessories-and-applications.html

World Journal of Gastrointestinal Endoscopy

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

World J Gastrointest Endosc 2022 February 16; 14(2): 77-84

DOI: 10.4253/wjge.v14.i2.77

ISSN 1948-5190 (online)

MINIREVIEWS

Exposed endoscopic full-thickness resection for duodenal submucosal tumors: Current status and future perspectives

Antonino Granata, Alberto Martino, Francesco Paolo Zito, Dario Ligresti, Michele Amata, Giovanni Lombardi, Mario Traina

ORCID number: Antonino Granata 0000-0001-5377-3304; Alberto Martino 0000-0002-8759-6518; Francesco Paolo Zito 0000-0002-1084-3373; Dario Ligresti 0000-0002-4213-0482; Michele Amata 0000-0001-6743-7520; Giovanni Lombardi 0000-0002-5957-3132; Mario Traina 0000-0001-5041-0858.

Author contributions: Granata A, Martino A, Zito FP and Ligresti D designed the research and wrote, edited and finalized the text; Martino A, Ligresti D and Amata M performed literature search and analyzed the data; Lombardi G and Traina M reviewed the paper for important intellectual content.

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

Country/Territory of origin: Italy

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): 0
Grade C (Good): C

Antonino Granata, Dario Ligresti, Michele Amata, Mario Traina, Endoscopy Service, Department of Diagnostic and Therapeutic Services, IRCCS–ISMETT, Palermo 90127, Italy

Alberto Martino, Francesco Paolo Zito, Giovanni Lombardi, Department of Gastroenterology and Digestive Endoscopy, AORN "Antonio Cardarelli", Napoli 80131, Italy

Corresponding author: Alberto Martino, MD, Staff Physician, Department of Gastroenterology and Digestive Endoscopy, AORN "Antonio Cardarelli", Via Antonio Cardarelli 9, Napoli 80131, Italy. alberto-martino@libero.it

Abstract

Exposed endoscopic full-thickness resection (EFTR), with or without laparoscopic assistance, is an emergent natural orifice transluminal endoscopic surgery technique with promising safety and efficacy for the management of gastrointestinal submucosal tumors (SMTs) arising from the muscularis propria (MP), especially of the gastric wall. To date, evidence concerning duodenal exposed EFTR is lacking, mainly due to both the technical difficulty involved because of the special duodenal anatomy and concerns about safety and effectiveness of transmural wall defect closure. However, given the non-negligible morbidity and mortality associated with duodenal surgery, the recent availability of dedicated endoscopic tools for tissue-approximation capable to realize full-thickness defect closure could help in promoting the adoption of this endosurgical technique among referral centers. The aim of our study was to review the current evidence concerning exposed EFTR with or without laparoscopic assistance for the treatment of MP-arising duodenal SMTs.

Key Words: Endoscopic full-thickness resection; Exposed endoscopic full-thickness resection; Laparoscopy-assisted endoscopic full-thickness resection; Duodenal submucosal tumors; Novel oral transluminal endoscopic surgery

Core Tip: Exposed endoscopic full-thickness resection (EFTR) is a promising minimally invasive alternative to surgery for the removal of gastrointestinal

Grade D (Fair): 0
Grade E (Poor): 0

Received: March 20, 2021
Peer-review started: March 20, 2021
First decision: July 17, 2021
Revised: July 31, 2021
Accepted: January 13, 2022
Article in press: January 13, 2022
Published online: February 16, 2022

P-Reviewer: Libânio D
S-Editor: Fan JR
L-Editor: A
P-Editor: Fan JR

submucosal tumors (SMTs) originating from the muscularis propria. To date, evidence concerning duodenal exposed EFTR is lacking, mainly due to both the technical difficulty and concerns about an effective closure of the transmural defect. However, given the non-negligible morbidity and mortality associated with duodenal surgery, the recent availability of dedicated endoscopic devices able to achieve a full-thickness defect closure could help in overcoming these concerns. Our study aimed to review the current evidence regarding exposed EFTR for deep duodenal SMTs.

Citation: Granata A, Martino A, Zito FP, Ligresti D, Amata M, Lombardi G, Traina M. Exposed endoscopic full-thickness resection for duodenal submucosal tumors: Current status and future perspectives. *World J Gastrointest Endosc* 2022; 14(2): 77-84
URL: https://www.wjgnet.com/1948-5190/full/v14/i2/77.htm
DOI: https://dx.doi.org/10.4253/wjge.v14.i2.77

INTRODUCTION

Though relatively infrequent, the diagnosis of duodenal submucosal tumors (D-SMTs) has increased due to the widespread use of gastrointestinal endoscopy[1,2]. D-SMTs originating from the submucosa and from the muscularis propria (MP) include lesions with malignant potential, such as gastrointestinal stromal tumors (GISTs) and neuroendocrine tumors (NETs)[3,4].

According to current guidelines, either suspected or histologically proven GISTs larger than 20 mm in diameter or with high-risk endoscopic ultrasonography (EUS) features (*i.e.*, irregular borders, cystic spaces, ulcerations, echogenic foci and heterogeneity) should be removed with histologically negative margins. Given the limited intramural extension of GISTs and their rare lymph node involvement, surgical local resection without additional lymphadenectomy is currently regarded as the gold standard of treatment[4-6]. Furthermore, resection of gastric NETs ≥ 10 mm in diameter is recommended, while all duodenal NETs should be excised, regardless of their size[7]. However, traditional duodenal surgery, such as open pancreaticoduodenectomy (PD), carries a significantly higher risk of morbidity and mortality compared to that for other gastrointestinal (GI) sites[8]. Moreover, various types of laparoscopic limited resection of the duodenum have been reported, including laparoscopic wedge resection, laparoscopic and endoscopic cooperative surgery, and laparoscopic segmental duodenectomy[9,10]. Though less invasive, they are technically challenging due to the retroperitoneal anatomical location of the duodenum and its intimate relationship with the pancreas, ampulla of Vater, and distal common bile duct. Thus, conversion to PD may be required[11].

In this setting, endoscopy may offer the chance for a minimally invasive curative approach for D-SMTs. Safe and effective removal of small D-SMT without involvement of the MP by means of endoscopic mucosal resection (EMR) has been reported [4]. Furthermore, though endoscopic submucosal dissection (ESD) within the duodenum is not routinely recommended due to high risk of perforation, its adoption for the treatment of duodenal lesions has been reported, with good outcomes across referral centers[12-14]. However, MP-originating D-SMTs cannot be completely removed by means of EMR or ESD, due to both MP layer involvement and adherence to serosa. ESD-assisted exposed endoscopic full-thickness resection (EFTR) is a scarless natural orifice transluminal endoscopic surgery (NOTES) procedure with a reported good safety and efficacy profile, particularly for the treatment of MP-originating gastric submucosal tumors (G-SMTs)[15,16]. However, there is a lack of evidence regarding duodenal exposed EFTR, due to technical difficulty related to the complex duodenal anatomy and concerns about a safe and effective closure of the transmural defect[17]. Nevertheless, duodenal perforation is associated with higher morbidity and mortality compared with those occurring within other GI sites[18].

The aim of our study was to review the current evidence concerning exposed EFTR with or without laparoscopic assistance for the treatment of MP-originating D-SMTs.

LITERATURE SEARCH

A literature search by using PubMed (MEDLINE) and EMBASE for the period January 1998 (the year EFTR was first reported) to February 2021 was undertaken in order to identify relevant studies on duodenal ESD-assisted exposed EFTR, with or without laparoscopic assistance. The search strategy usedthe following terms: "Endoscopic full-thickness resection," "EFTR," "exposed endoscopic full-thickness resection," "laparoscopy assisted endoscopic full-thickness resection," and "LAEFR." The literature search was limited to human studies and English language. Meeting abstracts were excluded. Articles reporting on both LECS procedures, in which tumor resection is mainly performed surgically, and non ESD-assisted EFTR were also excluded from the current review. The references of review articles and relevant papers were hand-searched to identify any additional studies.

ROLE OF EXPOSED EFTR IN THE MANAGEMENT OF MP-ORIGINATING D-SMTS

Technique

Exposed EFTR is a "cut then close" technique carrying out full-thickness excision with the creation of an intentionalperforation, followed by wall defect suture. Thus, the term "exposed" is derived from the temporary peritoneal exposure to the GI contents [19].

The exposed EFTR technique was first described by Ikeda *et al*[20] in a porcine stomach in 2006[20], and finally translated into clinical practice by Zhou *et al*[21] a few years later[21]. The principal procedures of ESD-assisted exposed EFTR are as follows [4]: (1) Circumferential mucosal and submucosal incision around the lesion by means of typical ESD technique; (2) Muscular and serosal incision, pursuing an active perforation; and (3) Endoscopic closure of the resulting transmural wall defect. Alternatively, post-EFTR defect closure by means of laparoscopic hand-suturing has been reported in the laparoscopy-assisted endoscopic full-thickness resection (LAEFR)[22].

The exposed ESD-assisted EFTR without laparoscopic assistance technique is illustrated in Figure 1.

Evidence

In 2012, Abe *et al*[22] reported the first case of LAEFR for a 10 mm carcinoid tumor of the duodenal bulb. Resection with histologically negative margins was accomplished, and the duodenal post-EFTR wall defect was sutured laparoscopically by means of an Albert anastomosis. No major adverse events were reported. Of note, during the same operative session laparoscopic lymphadenectomy was done before the EFTR, with intra-operative histological examination showing the absence of metastatic tumor cells [23].

In a multicenter prospective cohort study enrolling 42 patients undergoing gastrointestinal exposed EFTR, five procedures performed for SMTs located in the duodenal bulb were also included. The resulting post-EFTR transmural defect was effectively closed by the application of pursestring sutures with nylon loops and clips in all cases, and no major adverse events were observed[24].

A large retrospective study evaluated the efficacy and safety of exposed EFTR without laparoscopic assistance in 32 patients with non-ampullary MP-arising duodenal SMTs. With regard to post-EFTR defect closure, various endoscopic techniques were adopted (Table 1). In one case, endoscopic closure of a 2.5 cm post-EFTR defect located at the anterior wall of the bulb-descending junction appeared technically unfeasible; thus, conversion to open surgery was undertaken, with successful defect suture. Complete resection was achieved in all cases, and no recurrence was observed during a mean follow-up period of 38 mo. The occurrence of major adverse events was reported in two of 32 procedures. A case of EFTR performed for a 2.5 cm lesion in the anterior wall of the bulb-descending junction with defect closure by means of endoloops and clips was complicated by delayed perforation. Laparoscopic exploration with drainage tube placement was performed, and the patient was discharged on post-operative day 6. Finally, in a male patient aged 81, with a history of chronic obstructive pulmonary disease post-operative decline in blood oxygen saturation was observed. The patient was transferred to the intensive care unit and successfully treated conservatively[25].

Table 1 Summary of studies reporting on duodenal endoscopic submucosal dissection-assisted exposed endoscopic full-thickness resection

Ref.	Study design	Lesions, *n*	Mean size (range), cm	Site	R0	Histology	Surgical conversion	Closure method	Mean operation time (range), min	Major AEs	Mean poLOS (range), days	Mean follow-up (range), months	Recurrence
Abe *et al* [23], 2012	CR	1	1.0	Bulb: Anterior wall		Carcinoid	0	Laparoscopic hand-suturing	200	0	7	-	-
Qiao *et al* [24], 2018	R	5	-	Bulb	-	-	0	EPSS	-	0	4.5	12	0
Ren *et al* [25], 2019	R	32	1.2 (0.5–3.0)	Bulb: Anterior wall (*n* = 21); posterior wall *via* (*n* = 1); Bulb-D2 junction: Anterior wall (*n* = 8); D2 (*n* = 2)	32	GIST (*n* = 14); NET (*n* = 4); Heterotopic pancreas (*n* = 11); Leiomyoma (*n* = 2); Lipoma (*n* = 1)	2	Clips (*n* = 6); Clips + endoloops (*n* = 20). Clips + endoloops + fibrin glue (*n* = 4); ESS (*n* = 1)	-	Delayed perforation (*n* = 1); SO2 decline (*n* = 1)	6.2 (2–19)	38 (14–73)	0
Yuan *et al* [26], 2019	CR	1	2.0	Bulb	1	GIST	0	EPSS	55	0	4	3	0
Granata *et al*[27], 2021	R	2	2.4 (1.8–3.0)	Bulb: Anterior wall (*n* = 1); inferior wall (*n* = 1)	2	GIST (*n* = 1); NET (*n* = 1)	0	ESS	293 (145–148)	0	3.5 (3–4)	15 (12–18)	0

AEs: Adverse events; poLOS: Post-operative length of stay; CR: Case report; R: Retrospective; D2: Descending duodenum; GIST: Gastrointestinal stromal tumor; NET: Neuroendocrine tumor; SO2: Oxygen saturation; EPSS: Endoscopic purse-string suture; ESS: Endoscopic suturing system.

In 2019, Yuan *et al*[26] reported a case of successful exposed EFTR without laparoscopic assistance performed for a 20 mm duodenal bulb low-grade GIST. The resulting transmural wall defect was effectively closed with endoloops and endoclips using the purse-string suture technique. R0 resection was achieved, no major adverse events were observed, and the patient was discharged home on post-operative day 4[26].

Finally, in a recent retrospective case series from Italy, two exposed EFTR procedures of the duodenal bulb were reported. Wall defect closure was successfully performed by means of the OverStitch Endoscopic Suturing System (Apollo Endosurgery, Austin, Texas, United States). Histological examination showed free resection margins in both cases (1 NET, 1 GIST) and no major adverse events were encountered[27].

Results of the included studies in which duodenal ESD-assisted exposed EFTR was performed are summarized in Table 1.

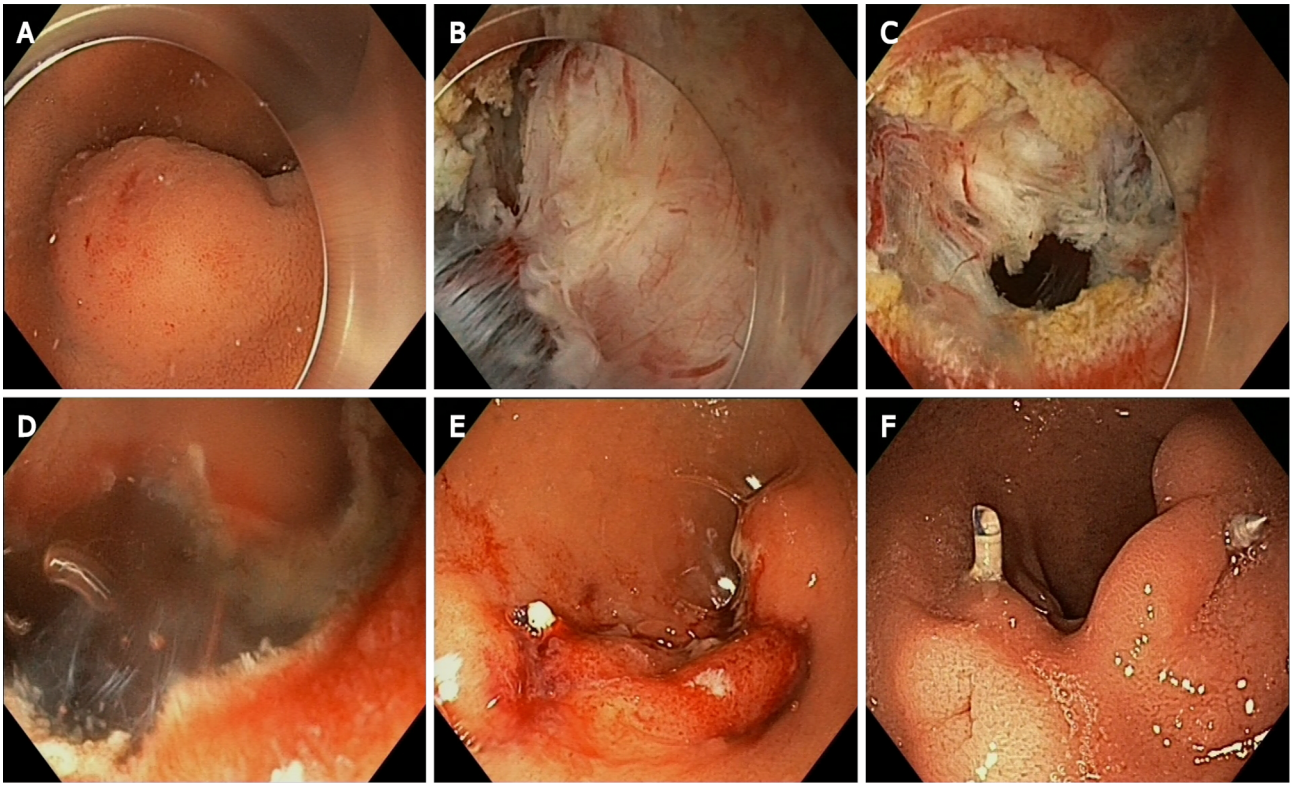

Figure 1 Duodenal exposed endoscopic full-thickness resection without laparoscopic assistance with defect closure using endoscopic suturing system. A: Endoscopic view of a submucosal lesion located in the duodenal bulb; B: Circumferential mucosal and submucosal incision; C: Exposed endoscopic full-thickness resection of the tumor and creation of "active perforation"; D: Transmural defect of the duodenal bulb; E: Full-thickness defect closure by means of OverStitch endoscopic suturing system; F: Endoscopic view of the resection site on post-operative day 60.

CONCLUSION

To date, the optimal resection modality for the treatment of MP-originating D-SMTs has not been established. PD carries a high rate of morbidity[8,11], while pancreas-preserving limited duodenal resection techniques are technically challenging, with a non-negligible rate of conversion to PD[9,11]. Furthermore, both EMR and ESD techniques are technically unsuitable for the complete resection of D-SMTs arising from the MP and adhering to the serosa layer, being limited to mucosal and submucosal layer, respectively. Intriguingly, non-exposed EFTR have been proposed for the resection of deep D-SMTs, with promising outcomes[28]. With the use of this "close then cut" technique, the lesion is resected after the GI wall patency is secured by creation of full-thickness wall duplication. Non-exposed EFTR can be realized with the use of a dedicated full-thickness resection device (FTRD; Ovesco Endoscopy, Tuebingen, Germany), consisting of an over-the-scope clip (OTSC) preloaded into a cap with an integrated snare. Alternatively, the application of an OTSC (OTSC, Ovesco Endoscopy GmbH, Tuebingen, Germany; Padlock Clip, Aponos Medical, Kingston, NH, United States) is followed by excision of the created pseudopolyp by the use of a snare or a needle knife. Non-exposed EFTR provides the potential avoidance of both peritoneal dissemination of tumor cells and extraluminal spillage of gastrointestinal content. In addition, this approach is technically much easier and faster to perform. However, this technique has a lower R0 resection rate than exposed EFTR. This is probably due to the technical unfeasibility of a "real-time" and direct visualization of the circumferential cutting margins. Furthermore, OTSC cannot be repositioned after its deployment, and non-exposed EFTR is reserved for smaller lesions (< 25 mm)[19,28].

In this scenario, ESD-assisted exposed EFTR with or without laparoscopic assistance could replace traditional surgery for the radical treatment of select cases of deep D-SMTs. However, evidence concerning the use of this NOTES procedure for D-SMTs is lacking. Traditionally, the duodenum has been considered a "forbidden" zone for exposed EFTR mainly due to technical difficulties related to complex anatomic relationships with surrounding organs and vessels, a narrow lumen, and a "C-loop," resulting in troublesome maintenance of the desired endoscope position. Hence,

concerns about an effective and reliable post-EFTR transmural defect closure must be raised.

Delayed perforation of the duodenum is associated with higher morbidity and mortality than other GI sites[8]. However, the recent development of dedicated endoscopic devices for tissue-approximation capable of achieving a full-thickness "surgical-quality" defect closure, such as the OverStitch Endoscopic Suturing System and OTSC systems, could help in overcoming these concerns[29,30].

In our opinion, a step-up approach with exposed EFTR as the first-line of treatment for selected deep D-SMTs appears particularly intriguing. Its adoption should be reserved for non-periampullary MP-originating D-SMTs up to 30 mm in diameter and without predominant extraluminal growth pattern, and limited to highly experienced centers. Full-thickness closure of the post-EFTR wall defect is strongly advised.

High morbidity and mortality associated with duodenal surgery justify active research in this field. Further large prospective studies in high-volume referral centers are needed to better clarify the role of exposed EFTR with or without laparoscopic assistance for the treatment of MP-arising D-SMTs.

REFERENCES

1 **Caletti G**, Fusaroli P, Bocus P. Endoscopic ultrasonography. *Digestion* 1998; **59**: 509-529 [PMID: 9705536 DOI: 10.1159/000007528]

2 **Rösch T**, Lorenz R, Dancygier H, von Wickert A, Classen M. Endosonographic diagnosis of submucosal upper gastrointestinal tract tumors. *Scand J Gastroenterol* 1992; **27**: 1-8 [PMID: 1736335 DOI: 10.3109/00365529209011157]

3 **Miettinen M**, Sobin LH, Lasota J. Gastrointestinal stromal tumors of the stomach: a clinicopathologic, immunohistochemical, and molecular genetic study of 1765 cases with long-term follow-up. *Am J Surg Pathol* 2005; **29**: 52-68 [PMID: 15613856 DOI: 10.1097/01.pas.0000146010.92933.de]

4 **Standards of Practice Committee**, Faulx AL, Kothari S, Acosta RD, Agrawal D, Bruining DH, Chandrasekhara V, Eloubeidi MA, Fanelli RD, Gurudu SR, Khashab MA, Lightdale JR, Muthusamy VR, Shaukat A, Qumseya BJ, Wang A, Wani SB, Yang J, DeWitt JM. The role of endoscopy in subepithelial lesions of the GI tract. *Gastrointest Endosc* 2017; **85**: 1117-1132 [PMID: 28385194 DOI: 10.1016/j.gie.2017.02.022]

5 **von Mehren M**, Randall RL, Benjamin RS, Boles S, Bui MM, Ganjoo KN, George S, Gonzalez RJ, Heslin MJ, Kane JM, Keedy V, Kim E, Koon H, Mayerson J, McCarter M, McGarry SV, Meyer C, Morris ZS, O'Donnell RJ, Pappo AS, Paz IB, Petersen IA, Pfeifer JD, Riedel RF, Ruo B, Schuetze S, Tap WD, Wayne JD, Bergman MA, Scavone JL. Soft Tissue Sarcoma, Version 2.2018, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 2018; **16**: 536-563 [PMID: 29752328 DOI: 10.6004/jnccn.2018.0025]

6 **Casali PG**, Abecassis N, Aro HT, Bauer S, Biagini R, Bielack S, Bonvalot S, Boukovinas I, Bovee JVMG, Brodowicz T, Broto JM, Buonadonna A, De Álava E, Dei Tos AP, Del Muro XG, Dileo P, Eriksson M, Fedenko A, Ferraresi V, Ferrari A, Ferrari S, Frezza AM, Gasperoni S, Gelderblom H, Gil T, Grignani G, Gronchi A, Haas RL, Hassan B, Hohenberger P, Issels R, Joensuu H, Jones RL, Judson I, Jutte P, Kaal S, Kasper B, Kopeckova K, Krákorová DA, Le Cesne A, Lugowska I, Merimsky O, Montemurro M, Pantaleo MA, Piana R, Picci P, Piperno-Neumann S, Pousa AL, Reichardt P, Robinson MH, Rutkowski P, Safwat AA, Schöffski P, Sleijfer S, Stacchiotti S, Sundby Hall K, Unk M, Van Coevorden F, van der Graaf WTA, Whelan J, Wardelmann E, Zaikova O, Blay JY; ESMO Guidelines Committee and EURACAN. Gastrointestinal stromal tumours: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2018; **29**: iv68-iv78 [PMID: 29846513 DOI: 10.1093/annonc/mdy095]

7 **Delle Fave G**, O'Toole D, Sundin A, Taal B, Ferolla P, Ramage JK, Ferone D, Ito T, Weber W, Zheng-Pei Z, De Herder WW, Pascher A, Ruszniewski P; Vienna Consensus Conference participants. ENETS Consensus Guidelines Update for Gastroduodenal Neuroendocrine Neoplasms. *Neuroendocrinology* 2016; **103**: 119-124 [PMID: 26784901 DOI: 10.1159/000443168]

8 **Tien YW**, Lee CY, Huang CC, Hu RH, Lee PH. Surgery for gastrointestinal stromal tumors of the duodenum. *Ann Surg Oncol* 2010; **17**: 109-114 [PMID: 19841981 DOI: 10.1245/s10434-009-0761-5]

9 **Hashimoto D**, Arima K, Chikamoto A, Taki K, Inoue R, Kaida T, Higashi T, Imai K, Beppu T, Baba H. Limited Resection of the Duodenum for Nonampullary Duodenal Tumors, with Review of the Literature. *Am Surg* 2016; **82**: 1126-1132 [PMID: 28206943]

10 **Ojima T**, Nakamura M, Hayata K, Kitadani J, Katsuda M, Takeuchi A, Tominaga S, Yamaue H. Laparoscopic Limited Resection for Duodenal Gastrointestinal Stromal Tumors. *J Gastrointest Surg* 2020; **24**: 2404-2408 [PMID: 32542555 DOI: 10.1007/s11605-020-04692-6]

11 **Yang F**, Jin C, Du Z, Subedi S, Jiang Y, Li J, Di Y, Zhou Z, Tang F, Fu D. Duodenal gastrointestinal stromal tumor: clinicopathological characteristics, surgical outcomes, long term survival and predictors for adverse outcomes. *Am J Surg* 2013; **206**: 360-367 [PMID: 23673012 DOI: 10.1016/j.amjsurg.2012.11.010]

12 **Pimentel-Nunes P**, Dinis-Ribeiro M, Ponchon T, Repici A, Vieth M, De Ceglie A, Amato A, Berr F, Bhandari P, Bialek A, Conio M, Haringsma J, Langner C, Meisner S, Messmann H, Morino M, Neuhaus H, Piessevaux H, Rugge M, Saunders BP, Robaszkiewicz M, Seewald S, Kashin S, Dumonceau JM, Hassan C, Deprez PH. Endoscopic submucosal dissection: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. *Endoscopy* 2015; **47**: 829-854 [PMID: 26317585 DOI: 10.1055/s-0034-1392882]

13 **Vanbiervliet G**, Moss A, Arvanitakis M, Arnelo U, Beyna T, Busch O, Deprez PH, Kunovsky L, Larghi A, Manes G, Napoleon B, Nalankilli K, Nayar M, Pérez-Cuadrado-Robles E, Seewald S, Strijker M, Barthet M, van Hooft JE. Endoscopic management of superficial nonampullary duodenal tumors: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. *Endoscopy* 2021; **53**: 522-534 [PMID: 33822331 DOI: 10.1055/a-1442-2395]

14 **Pérez-Cuadrado-Robles E**, Quénéhervé L, Margos W, Moreels TG, Yeung R, Piessevaux H, Coron E, Jouret-Mourin A, Deprez PH. ESD *vs* EMR in non-ampullary superficial duodenal tumors: a systematic review and meta-analysis. *Endosc Int Open* 2018; **6**: E998-E1007 [PMID: 30083591 DOI: 10.1055/a-0579-9050]

15 **Granata A**, Martino A, Amata M, Ligresti D, Tuzzolino F, Traina M. Erratum: Efficacy and safety of gastric exposed endoscopic full-thickness resection without laparoscopic assistance: a systematic review. *Endosc Int Open* 2020; **8**: C4 [PMID: 34150984 DOI: 10.1055/a-1527-7164]

16 **Wang C**, Gao Z, Shen K, Cao J, Shen Z, Jiang K, Wang S, Ye Y. Safety and efficiency of endoscopic resection *vs* laparoscopic resection in gastric gastrointestinal stromal tumours: A systematic review and meta-analysis. *Eur J Surg Oncol* 2020; **46**: 667-674 [PMID: 31864827 DOI: 10.1016/j.ejso.2019.10.030]

17 **Gaspar JP**, Stelow EB, Wang AY. Approach to the endoscopic resection of duodenal lesions. *World J Gastroenterol* 2016; **22**: 600-617 [PMID: 26811610 DOI: 10.3748/wjg.v22.i2.600]

18 **Paspatis GA**, Arvanitakis M, Dumonceau JM, Barthet M, Saunders B, Turino SY, Dhillon A, Fragaki M, Gonzalez JM, Repici A, van Wanrooij RLJ, van Hooft JE. Diagnosis and management of iatrogenic endoscopic perforations: European Society of Gastrointestinal Endoscopy (ESGE) Position Statement - Update 2020. *Endoscopy* 2020; **52**: 792-810 [PMID: 32781470 DOI: 10.1055/a-1222-3191]

19 **ASGE Technology Committee**, Aslanian HR, Sethi A, Bhutani MS, Goodman AJ, Krishnan K, Lichtenstein DR, Melson J, Navaneethan U, Pannala R, Parsi MA, Schulman AR, Sullivan SA, Thosani N, Trikudanathan G, Trindade AJ, Watson RR, Maple JT. ASGE guideline for endoscopic full-thickness resection and submucosal tunnel endoscopic resection. *VideoGIE* 2019; **4**: 343-350 [PMID: 31388606 DOI: 10.1016/j.vgie.2019.03.010]

20 **Ikeda K**, Mosse CA, Park PO, Fritscher-Ravens A, Bergström M, Mills T, Tajiri H, Swain CP. Endoscopic full-thickness resection: circumferential cutting method. *Gastrointest Endosc* 2006; **64**: 82-89 [PMID: 16813808 DOI: 10.1016/j.gie.2005.12.039]

21 **Zhou PH**, Yao LQ, Qin XY, Cai MY, Xu MD, Zhong YS, Chen WF, Zhang YQ, Qin WZ, Hu JW, Liu JZ. Endoscopic full-thickness resection without laparoscopic assistance for gastric submucosal tumors originated from the muscularis propria. *Surg Endosc* 2011; **25**: 2926-2931 [PMID: 21424195 DOI: 10.1007/s00464-011-1644-y]

22 **Abe N**, Takeuchi H, Yanagida O, Masaki T, Mori T, Sugiyama M, Atomi Y. Endoscopic full-thickness resection with laparoscopic assistance as hybrid NOTES for gastric submucosal tumor. *Surg Endosc* 2009; **23**: 1908-1913 [PMID: 19184206 DOI: 10.1007/s00464-008-0317-y]

23 **Abe N**, Takeuchi H, Shibuya M, Ohki A, Yanagida O, Masaki T, Mori T, Sugiyama M. Successful treatment of duodenal carcinoid tumor by laparoscopy-assisted endoscopic full-thickness resection with lymphadenectomy. *Asian J Endosc Surg* 2012; **5**: 81-85 [PMID: 22776369 DOI: 10.1111/j.1758-5910.2011.00120.x]

24 **Qiao Z**, Ling X, Zhu J, Ying G, Xu L, Zhu H, Tang J. Therapeutic application of purse-string sutures with nylon loops and metal clips under single-channel endoscopy for repair of gastrointestinal wall defects. *Exp Ther Med* 2018; **15**: 4356-4360 [PMID: 29849777 DOI: 10.3892/etm.2018.5956]

25 **Ren Z**, Lin SL, Zhou PH, Cai SL, Qi ZP, Li J, Yao LQ. Endoscopic full-thickness resection (EFTR) without laparoscopic assistance for nonampullary duodenal subepithelial lesions: our clinical experience of 32 cases. *Surg Endosc* 2019; **33**: 3605-3611 [PMID: 31240477 DOI: 10.1007/s00464-018-06644-3]

26 **Yuan XL**, Liu XW, Hu B. Endoscopic full-thickness resection for a duodenal gastrointestinal stromal tumour. *Arab J Gastroenterol* 2019; **20**: 211-212 [PMID: 31813741 DOI: 10.1016/j.ajg.2019.12.001]

27 **Granata A**, Martino A, Amata M, Ligresti D, Traina M. Gastrointestinal exposed endoscopic full-thickness resection in the era of endoscopic suturing: a retrospective single-center case series. *Wideochir Inne Tech Maloinwazyjne* 2021; **16**: 321-328 [PMID: 34136027 DOI: 10.5114/wiitm.2021.104496]

28 **Brewer Gutierrez OI**, Akshintala VS, Ichkhanian Y, Brewer GG, Hanada Y, Truskey MP, Agarwal A, Hajiyeva G, Kumbhari V, Kalloo AN, Khashab MA, Ngamruengphong S. Endoscopic full-thickness resection using a clip non-exposed method for gastrointestinal tract lesions: a meta-analysis. *Endosc Int Open* 2020; **8**: E313-E325 [PMID: 32118105 DOI: 10.1055/a-1073-7593]

29 **Ge PS**, Thompson CC. The Use of the Overstitch to Close Perforations and Fistulas. *Gastrointest Endosc Clin N Am* 2020; **30**: 147-161 [PMID: 31739961 DOI: 10.1016/j.giec.2019.08.010]

30 **Weiland T**, Rohrer S, Schmidt A, Wedi E, Bauerfeind P, Caca K, Khashab MA, Hochberger J, Baur F, Gottwald T, Schurr MO. Efficacy of the OTSC System in the treatment of GI bleeding and wall

defects: a PMCF meta-analysis. *Minim Invasive Ther Allied Technol* 2020; **29**: 121-139 [PMID: 30957599 DOI: 10.1080/13645706.2019.1590418]

World Journal of Gastrointestinal Endoscopy

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

World J Gastrointest Endosc 2022 February 16; 14(2): 85-95

DOI: 10.4253/wjge.v14.i2.85

ISSN 1948-5190 (online)

MINIREVIEWS

Endoscopic colorectal cancer surveillance in inflammatory bowel disease: Considerations that we must not forget

Paulina Núñez F, Rodrigo Quera, David T Rubin

ORCID number: Paulina Núñez F 0000-0003-3727-1851; Rodrigo Quera 0000-0001-5854-0526; David T Rubin 0000-0001-5647-1723.

Author contributions: All authors equally contributed to this review with the conception and design of the study, literature review and analysis, drafting and critical revision and editing, and approval of the final version.

Conflict-of-interest statement: Rubin DT has received grant support from Takeda; and has served as a consultant for Abbvie, Altrubio, Allergan Inc., Arena Pharmaceuticals, Bellatrix Pharmaceuticals, Boehringer Ingelheim Ltd., Bristol-Myers Squibb, Celgene Corp/Syneos, Connect BioPharma, GalenPharma/Atlantica, Genentech/Roche, Gilead Sciences, InDex Pharmaceuticals, Ironwood Pharmaceuticals, Iterative Scopes, Janssen Pharmaceuticals, Lilly, Materia Prima, Pfizer, Prometheus Biosciences, Reistone, Takeda, and Techlab Inc. Quera R has received grant support from Janssen and Nu ñez F P has received support for attending meetings from Janssen.

Country/Territory of origin: United States

Specialty type: Gastroenterology and hepatology

Paulina Núñez F, Rodrigo Quera, Universidad de los Andes, Digestive Disease Center, Inflammatory Bowel Disease Program, Clinica, Santiago 7620157, RM, Chile

Paulina Núñez F, Department of Gastroenterology, Hospital San Juan de Dios. Universidad de Chile, Santiago 7701230, RM, Chile

David T Rubin, Medicine Inflammatory Bowel Disease Center, University of Chicago, Chicago, IL 60637, United States

Corresponding author: David T Rubin, AGAF, FACG, MD, Chief Doctor, Medicine Inflammatory Bowel Disease Center, University of Chicago, 5841 S. Maryland Ave, MC4076, Room M410, Chicago, IL 60637, United States. drubin@medicine.bsd.uchicago.edu

Abstract

Inflammatory bowel disease (IBD), encompassing Crohn's disease and ulcerative colitis, is a chronic immune-mediated inflammatory disease that primarily affects the gastrointestinal tract and is characterized by periods of activity and remission. The inflammatory activity of the disease involving the colon and rectum increases the risk of colorectal cancer (CRC) over the years. Although prevention strategies are evolving, regular surveillance for early detection of neoplasia as a secondary prevention strategy is paramount in the care of IBD patients. In this review article, we discuss the current evidence of the risks of developing CRC and evaluate the best available strategies for screening and surveillance, as well as future opportunities for cancer prevention.

Key Words: Inflammatory bowel disease; Endoscopy; Crohn's disease; Ulcerative colitis; Surveillance; Colorectal cancer

Core Tip: Colorectal cancer (CRC) is one of the leading causes of death in inflammatory bowel disease (IBD) today. However, subsequent reports have shown lower rates of CRC. The expanding medical options in IBD have substantially improved our ability to control severe inflammation and likely to reduce the risk of CRC in this setting. We discuss the current evidence of the risks of developing CRC, and evaluate

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, B, B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Received: June 14, 2021
Peer-review started: June 14, 2021
First decision: July 27, 2021
Revised: August 2, 2021
Accepted: January 22, 2022
Article in press: January 22, 2022
Published online: February 16, 2022

P-Reviewer: Batyrbekov K, KAMADA Y, Triantafillidis J, Yoshimatsu K
S-Editor: Wang LL
L-Editor: A
P-Editor: Wang LL

the best available strategies for detection and surveillance, as well as future opportunities for cancer prevention.

Citation: Núñez F P, Quera R, Rubin DT. Endoscopic colorectal cancer surveillance in inflammatory bowel disease: Considerations that we must not forget. *World J Gastrointest Endosc* 2022; 14(2): 85-95
URL: https://www.wjgnet.com/1948-5190/full/v14/i2/85.htm
DOI: https://dx.doi.org/10.4253/wjge.v14.i2.85

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic, progressive or relapsing and remitting immune-mediated condition of the intestines[1,2]. While the pathogenesis has not been fully elucidated, it is generally considered a consequence of a dysregulated immune response to environmental triggers in genetically predisposed subjects[3,4]. CRC is a major cause of death in IBD, accounting for 10 to 15% of death in IBD[5,6]. CRC risk increases over time after IBD diagnosis. In ulcerative colitis (UC), a prior meta-analysis estimated the CRC risk to be 2%, 8%, and 18% at 10, 20, and 30 years, respectively, after disease diagnosis[7]. This risk is also higher in patients with long-standing and diffuse colonic CD [relative risk (RR) of 4.5 (95%CI: 1.3-4.9)][8]. However, later reports have shown lower rates of left-sided CRC of 2.5%, 7.6%, and 10.8% at 20, 30, and 40 years after diagnosis, respectively[9]. This lower risk may be explained due to successful CRC surveillance programs and better control of mucosal inflammation from early disease stages[10]. The more recent 40-year surveillance experience in the United Kingdom demonstrated decreasing rates of advanced CRC and interval CRC with cumulative incidences of 0.1%, 6.7%, and 10% in the first, third, and fourth decade after diagnosis, respectively[11]. The reasons for decreasing incidences are thought to reflect effective surveillance, access to surgery, and more effective therapies.

Endoscopic surveillance is the primary recommended CRC prevention strategy, with an active search of early-stage cancer or pre-cancerous (dysplastic) lesions[12]. Endoscopic surveillance has been previously suggested to start 8-10 years after IBD diagnosis based on a historical analysis by Eaden *et al* that showed a CRC risk of 2% 10 years after diagnosis[7]. However, earlier surveillance starting 8 years after diagnosis is modeled to capture an additional 6% of patients developing CRC[13], so newer guidelines embrace this earlier starting time, which may also reflect the emergence of earlier age colorectal cancers described in the population.

Historically, CRC surveillance in patients with IBD has been characterized by extensive four-quadrant non-targeted (random) biopsies to improve the detection of dysplastic mucosa. However, a newer technology that enhances digital mucosal images as high-definition white-light endoscopy (HD-WLE) and dye-assisted chromoendoscopy (CE) with magnification have improved the visualization and detection of early neoplastic lesions, and therefore have increased the diagnostic yield for dysplasia[14,15].

CRC PATHOGENESIS IN IBD

Although the pathogenesis of IBD-related CRC is believed to be different from the pathogenesis of sporadic CRC and CRC that is associated with polyposis and non-polyposis hereditary syndromes, their molecular pathways are similar[16], involving DNA methylation, microsatellite instability, aneuploidy, activation of oncogene Kras, alteration of COX-2 enzymes, and mutation of tumour suppressor genes, with loss of p53 function[17]. One well-known molecular link between cancer and inflammation is the nuclear factor Kappa B (NF-kB)[18]. It can be activated by pro-inflammatory cytokines like interleukin-1 (IL-1), IL-6, and tumor necrosis factor α(TNF-α), ultimately producing reactive oxygen species damaging the DNA and favoring tumor development[19] in Figure 1.

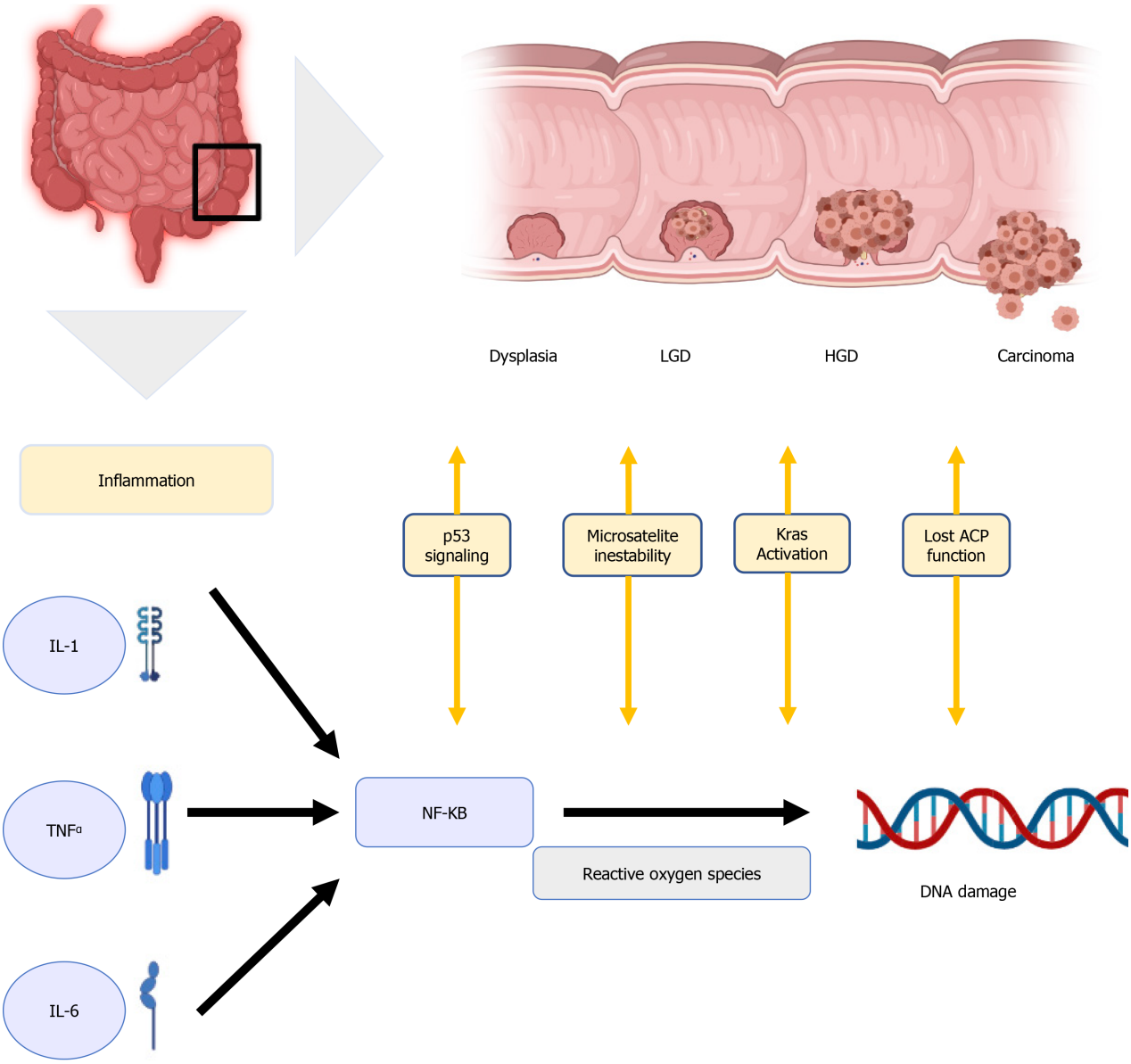

Figure 1 Physiological mechanism. IBD: Inflammatory bowel disease; LGD: Low-grade dysplasia; HGD: High-grade dysplasia.

Inflammation plays a central role in carcinogenesis; as a consequence, the severity of flare-ups with accumulated inflammatory damage (persistence of inflammation) predisposes to the development of CCR. Choi *et al* observed that the accumulative inflammatory burden had a 2-fold increase in the risk of CCR, (95%CI: 1.5 to 2.9; $P <$ 0.001 for endoscopic and 95%CI: 1.4 to 3.0; $P < 0.001$ for histological) for every 10 years of mild, 5 years of moderate o 3.3 years of severe activity disease[20]. The importance of this finding is that it is based not only on the most recent colonoscopy but also on several colonoscopies in a given time to assess the cumulative effect of inflammation. This persistent inflammation mechanism would explain the predominance of right-sided neoplasia that has been described in PSC patients. In a recent study, UC PSC patients who remain in clinical remission have greater endoscopic and histological activity in the right colon compared to UC patients without PSC[21].

Moreover, chronic inflammation may lead to the development of dysplastic changes in colonic mucosa. These changes can be classified as low-grade dysplasia (LGD), high-grade dysplasia (HGD), or indefinite for dysplasia[22]. LGD is characterized by hyperchromatic enlarged nuclei with preserved cell polarity, decreased mucinous differentiation, and dystrophic goblet cells[23,24]. In contrast, HGD presents as atypical cells with prominent nuclear pleomorphism, hyperchromatic stratified nuclei, and loss of cell polarity, and whenever pathologists cannot distinguish between inflammatory-associated and dysplastic changes, the sample is defined as indefinite for dysplasia[23,24]. This should be distinguished from indeterminate findings, which

are usually due to the presence of confounding amounts of histologic inflammation. Given the high inter-observer variability in grading dysplastic changes, guidelines recommend that all cases of suspected dysplasia should be evaluated by two expert pathologists[25,26].

Neoplastic progression can occur multifocally so that dysplasia can be associated with an increased risk of synchronous (simultaneous) or metachronous (six months after diagnosis) dysplasia or carcinoma[25,27].

RISK FACTORS FOR DYSPLASIA AND CRC

Most relevant CRC risk factors in IBD include longer disease duration, greater disease extent (extensive-pancolitis) and degree of inflammation over time[28,29], family history of CRC[30], personal history of dysplasia or colonic stricture, and diagnosis of primary sclerosing cholangitis (PSC) Table 1[31,32].

Younger age at diagnosis and disease duration have been shown as risk factors for CRC in IBD patients, possibly related to more aggressive phenotypes and longer exposure to mucosal inflammation[33]. A previous meta-analysis showed that patients diagnosed before the age of 30 had a CRC standardized incidence ratio (SIR) of 8.2 (95%CI: 1.8-14.6, I2 82%) compared to patients diagnosed after 30-years-old with an SIR of 1.8 (95%CI: 0.9-2.7, I2 81%)[34]. Also, disease extension in UC has been related to a higher risk of CRC, with SIR of 6.9 (95%CI: 1.9-11.9, I2 84%) for extensive colitis and only 1.7 (CI 95% 0.6-4.5 I2 47%) for left-sided colitis; furthermore, in patients with segmental colitis in CD, there was no higher risk of CRC, with a SIR of 1.7 (95%CI: 0.9-2.6, I2 0%)[35]. There is evidence that IBD patients with a prior family history of CRC have at least a two-fold higher risk of IBD-related CRC (adjusted RR = 2.5; 95%CI: 1.4-4.4); moreover, when CRC family history is associated to first-degree relatives, diagnosed under the age of 50, the risk is even higher (RR = 9.2; 95%CI: 3.7-23)[25,35]. There are some cases of Lynch Syndrome with IBD who develop CRC at a younger age, which are more accelerated and significantly compare with patients without IBD. In this scenario, a colectomy would be necessary due to the high risk of recurrence and multiple CRC[36]. This risk has been seen in UC, and only a few cases in CD, so it does not allow conclusions to be drawn about the risk of CRC[37].

The presence of prior dysplasia or stricture is also associated with an increased risk of neoplasia in IBD[38,39]. Furthermore, colonic strictures in any setting should be considered malignant until proven otherwise.[40] Previous studies have reported variable risk of dysplasia or CRC associated with colonic strictures in UC (from 0% to 86%)[41,42] and there is insufficient data for this risk in CD[43]. Regarding the presence of inflammatory polyps, it is debated if they are related to the development of dysplasia. Historically, case-control studies have reported that patients with inflammatory polyps have 1.9-to-2.5-fold increased risk of CRC[29,44], but recent retrospective cohort studies have suggested that they do not independently predict the development of CRC, nor do they predict progression from LGD to HGD or CRC[20,45].

One major risk factor for CRC in IBD is the presence of concomitant PSC. A previous meta-analysis by Soetikno *et al*[46] showed that patients with PSC and UC had a higher risk for development of CRC [odds ratio (OR) of 4.09 (95%CI: 2.89-5.76)]. An observational longitudinal cohort study also reported an increased risk for CRC in patients with PSC and UC compared to patients with UC and no PSC with a SIR of 9.8 (95%CI: 1.9-96.6)[47]. Additionally, patients who are in clinical remission have a higher chance of endoscopic and histological inflammation in the right colon compared to UC patients without PSC, being the place where the CCR is most frequently found[21] in Figure 2.

CRC SURVEILLANCE IN IBD

Recommendations for CRC surveillance in IBD vary according to the type of IBD, comorbidities, and previous family history of CRC. According to the current SCENIC consensus statements and ACG guidelines, surveillance colonoscopies should start 8 years after diagnosis in patients with left-sided or extensive UC, and in patients with a colonic CD that comprise more than 30% of the colonic surface or > 1 colonic segment [48,49]. Patients with a first-degree family history of CRC should start surveillance colonoscopies 10 years before the age their relative was diagnosed with CRC or 8 years after IBD diagnosis, whichever occurs first[50]. In patients with IBD and PSC,

Table 1 Risk factors

Clinical risk factors	Endoscopic risk factors
Disease duration, extension, and severity	Active disease
Personal history of dysplasia	Colonic stricture
Primary sclerosing cholangitis	Pseudopolys (post-inflammatory polyps)
Family history of CRC /dysplasia	Tubular appearance of colon

IBD: Inflammatory bowel disease; UC: Ulcerative colitis; CD: Crohn disease.

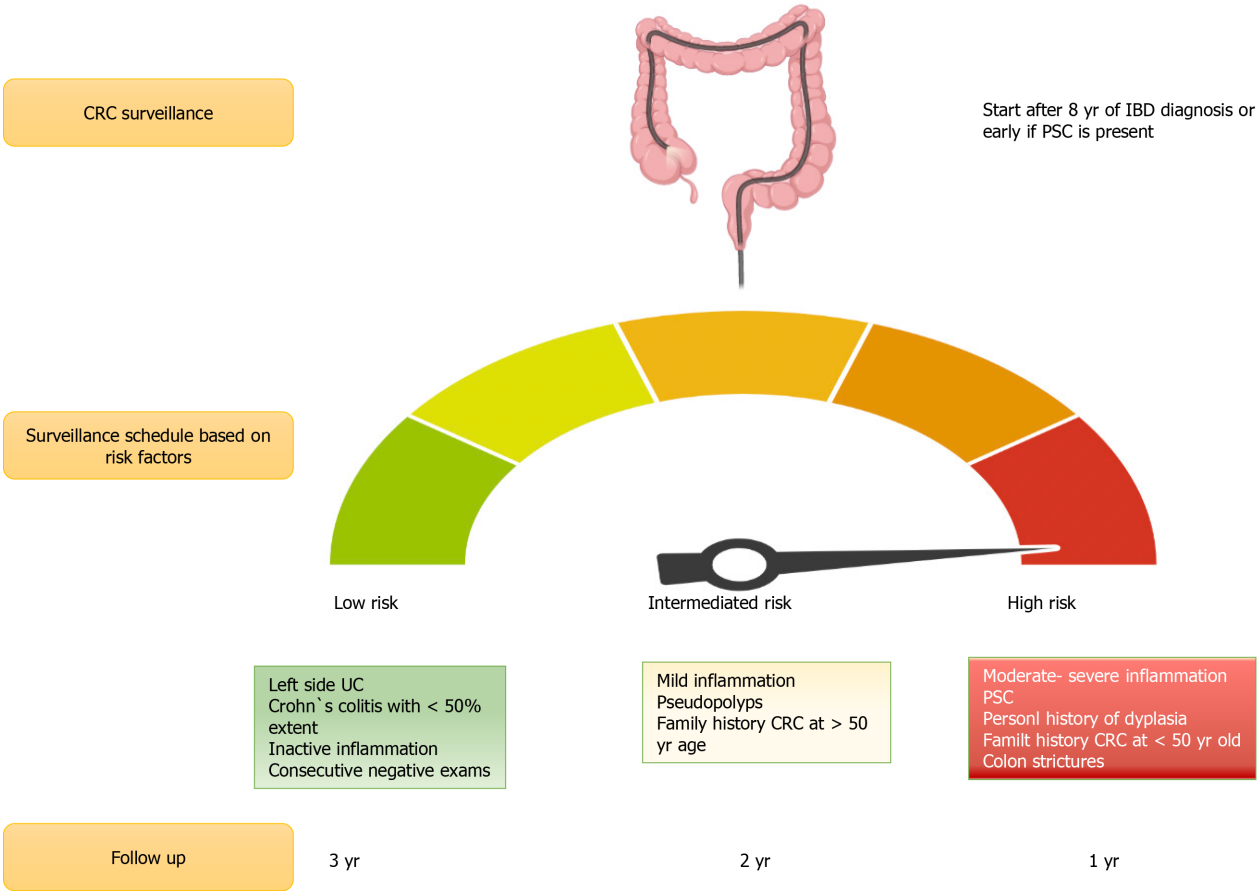

Figure 2 Colorectal cancer risk. CRC: Colorectal cancer; UC: Ulcerative colitis; CD: Crohn disease; PSC: Primary sclerosing cholangitis.

surveillance colonoscopies should start at diagnosis and be repeated on an annual basis[51]. Surveillance colonoscopy intervals are every 1-3 years, according to each patient risk-stratification[27,52]. Patients with isolated proctitis do not need surveillance colonoscopies[51].

ENDOSCOPIC TECHNIQUES FOR DETECTION OF DYSPLASIA

Despite the greater surveillance efforts for early detection of CRC in IBD patients, CRC risk remains significant, and the incidence of interval cases may be due to rapid progression and unclear pathogenesis[53]. In order to perform an optimal evaluation of the colonic mucosa, optimum bowel preparation is essential[54,55].

Several advanced imaging techniques have been developed to improve visualization of mucosal defects, enhancing dysplasia and early CRC detection. High-definition white light endoscopy (HD-WLE) has demonstrated higher adenoma detection than standard definition colonoscopy in patients undergoing screening colonoscopy in non-IBD patients[56]. Chromoendoscopy uses optical or computer/bas

-ed techniques to enhance mucosal details in order to improve lesion detection and characterization[57,58]. This technique can be assisted by different dye agents applied as sprays during colonoscopy, which can be classified as contrast agents (i.e., indigo carmine)[59], absorptive agents (i.e., methylene blue), and reactive staining agents (i.e., Congo red); being the first two, the most commonly used[60]. Among dye-less chromoendoscopy, there are different optical CE techniques. Narrow-band imaging (NBI) is a type of optical CE, based in the use of blue-light technology improving characterization of detected lesions, but has shown no further benefit in primary detection of dysplasia when compared to HD-WLE[61]. Unlike NBI, other dye-less CE methods, such as flexible spectral imaging color enhancement (FICE), visualizes mucosal structures without using optical filters but capturing mucosal imaging and performing digital software-based processing of the captured images. The adequate examination requires a clean mucosa, as stools and blood can obscure interpretation of the images. DCE was more effective in identifying dysplasia compared to white light endoscopy (WLE), but without reaching significant differences compared to HD WLE [62]. Recently, a retrospective analysis also showed no differences in the detection of dysplasia with these techniques, but longer examination time using DCE (24.6 min *vs* 15.4, $P < 0.001$)[63].

The National Institute for Health and Care Excellence (NICE) and the European Crohn's and Colitis Organization (ECCO) have recommended the routine use of CE with targeted biopsies in IBD-CRC surveillance in their society guidelines[49]. In 2015 an international expert consensus, SCENIC (Surveillance for Colorectal Endoscopic Neoplasia Detection and Management in Inflammatory Bowel Disease Patients: International Consensus) recommended a surveillance study with high-definition colonoscopy or else the use of dye spray chromoendoscopy if a standard definition white-light exam is performed[20]. Prior to HD- WLE, the standard of care for CRC surveillance included four-quadrant non-targeted (random) biopsies every 10 cm from the cecum to the rectum, with a minimum of 32 biopsies, with the goal of detecting "invisible" dysplasia[64]. This technique intended to sample the mucosa in order to identify "invisible" lesions; we now understand that newer imaging technology, if used by experienced endoscopists, has likely made this approach unnecessary in many patients[65].

Virtual chromoendoscopy (VCE) is an optical imaging technique that uses filters to enhance the contrast of both the mucosa and the superficial vasculature, allowing a better evaluation. In a multicenter study with UC patients comparing DCE *vs* NBI, no significant difference was reported between these techniques in detecting neoplastic lesions (OR: 1.02 (95%CI: 0.44-2.35, $P = 0.964$)[66]. A recent randomized controlled trial comparing DCE, VCE, and HD-WLE found that both techniques were non-inferior to DCE[67]. The 2019 ACG guidelines recommend the use of DCE or NBI for the surveillance of dysplasia (conditional recommendation, low quality of evidence)[50].

Despite their low yield, random biopsies may have a role when performed in association with CE in IBD patients with a personal history of neoplasia, an appearing tubular colon, or concomitant PSC. A French multicenter study performed quadrantic random biopsies every 10 cm in patients with a personal history of neoplasia, showing that 12.8% of neoplasia can be detected[68]. Saravia *et al*[69] consider that random biopsies should be performed when CE is not available or when WLE is used in the presence of inflammation or high-risk factors.

NEW TECHNOLOGIES IN CRC DETECTION

Artificial intelligence (AI) is evolving as a topic of interest in the field of gastrointestinal endoscopy. AI has been used in endoscopic polyp detection; no studies on AI in IBD surveillance have been published so far[70].

MANAGEMENT OF DYSPLASIA

It is important to distinguishing polypoid from non-polypoid lesions, due to their different management, prognosis, and follow-up[71]. A meta-analysis performed by Wanders *et al* showed that patients with polypoid lesions had a lower incidence of CRC compared to patients with non-polypoid lesions, which was attributed to the complete endoscopic resection of the first type of lesions[72].

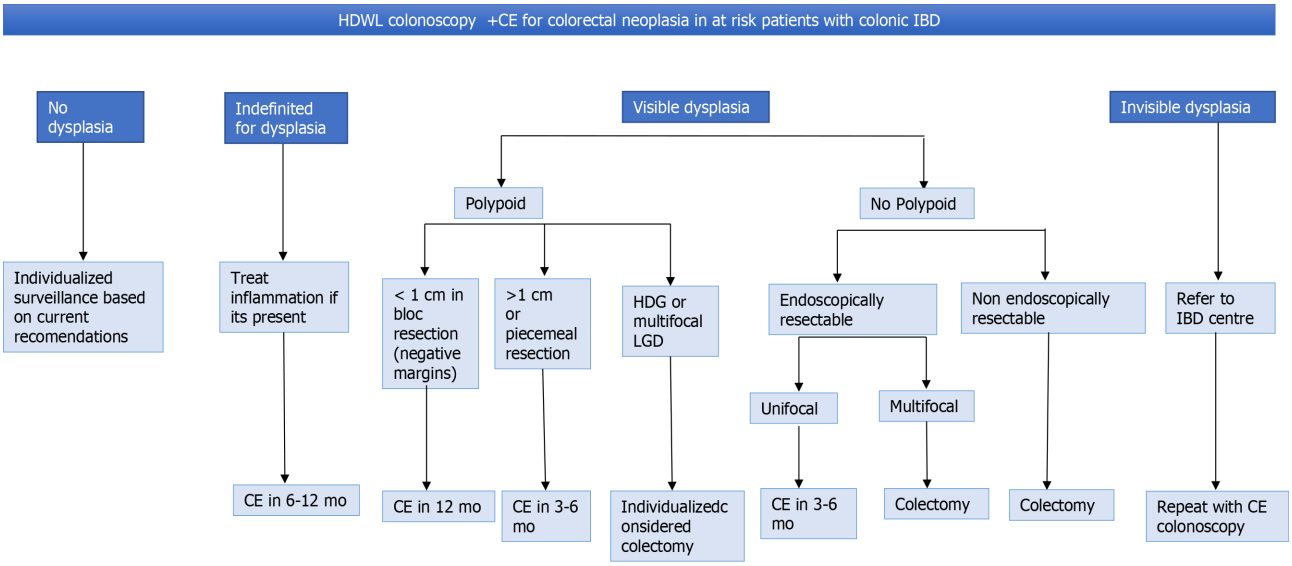

Figure 3 Algorithm for the management of dysplasia. Review all dysplasia with 2 experienced GI pathology. LDG: Low-grade dysplasia; HGD: High-grade dysplasia.

Less than 1 cm polypoid lesions (with negative margins) should be followed up with colonoscopy at 12 mo. For lesions greater than 1 cm or lesions that have been removed piecemeal, surveillance colonoscopy should be performed within 3-6 mo[49]. LGD had a low risk of progression to HGD or CRC from an incomplete resection if it is unifocal. In contrast, multifocal LGD carries substantial risk[73]. The rate of progression from LGD *vs* HGD to adenocarcinoma was significantly greater for HGD ($P < 0.001$)[74]. Although most dysplasias were found in the right colon, being higher in UC, the rate of progression of LGD and HGD dysplasia or adenocarcinoma was not significantly different in CD *vs* UC[75]. A Dutch nationwide cohort study observed that the cumulative incidence of advanced neoplasia was 21.7% after 15 years of follow-up. Male sex, older age at LDG (> 55 years), and follow-up by a tertiary IBD referral center were independent risk factors for advanced neoplasia[76]. The management of HGD in a visible lesion with complete resection is controversial. The decision should be made case by case between colectomy *vs* shorter follow-up[77].

In cases of non-polypoid dysplasia, classically, these were sent to colectomy. However, if there is complete resection, it can be followed up instead of colectomy but, always evaluating progression factors[78].

For endoscopically invisible LGD (found only on random biopsy), it should be referred to an IBD Centre or endoscopist with experience at high-risk surveillance. Surveillance endoscopy using CE with HD-WLE is required in an attempt to identify the neoplastic lesion (or others) and to remove it endoscopically[79]. In Figure 3, the management of dysplasia/LGD and HGD is summarized.

CONCLUSION

It is essential to know which risk factors affect the CRC risk in every IBD patient, allowing to identify the subgroups of patients who need closer surveillance and more intensive treatment. The risk of CRC is increased in IBD but not as high as previously reported. The expanding medical options in IBD have substantially improved our ability to control severe inflammation and likely to reduce the risk of CRC. The advance of new technologies allows us a better characterization of lesions and treat them on time.

Prospective studies to monitor the rate of interval cancer, the cost-effectiveness of surveillance programs are needed.

REFERENCES

1 **Ungaro R**, Mehandru S, Allen PB, Peyrin-Birolet L, Colombel JF. Ulcerative colitis. *Lancet* 2017;

389: 1756-1770 [DOI: 10.1016/S0140-6736(16)32126-2]
2 **Loftus EV Jr**. Crohn's Disease: Etiology, Complications, Assessment, Therapy, and Management. *Gastroenterol Clin North Am* 2017; **46**: xiii-xixv [PMID: 28838422 DOI: 10.1016/j.gtc.2017.06.001]
3 **Ananthakrishnan AN**. Epidemiology and risk factors for IBD. *Nat Rev Gastroenterol Hepatol* 2015; **12**: 205-217 [PMID: 25732745 DOI: 10.1038/nrgastro.2015.34]
4 **Cosnes J**, Beaugerie L, Carbonnel F, Gendre JP. Smoking cessation and the course of Crohn's disease: an intervention study. *Gastroenterology* 2001; **120**: 1093-1099 [PMID: 11266373 DOI: 10.1053/gast.2001.23231]
5 **Dyson JK**, Rutter MD. Colorectal cancer in inflammatory bowel disease: what is the real magnitude of the risk? *World J Gastroenterol* 2012; **18**: 3839-3848 [PMID: 22876036 DOI: 10.3748/wjg.v18.i29.3839]
6 **Munkholm P**. Review article: the incidence and prevalence of colorectal cancer in inflammatory bowel disease. *Aliment Pharmacol Ther* 2003; **18** Suppl 2: 1-5 [PMID: 12950413 DOI: 10.1046/j.1365-2036.18.s2.2.x]
7 **Eaden JA**, Abrams KR, Mayberry JF. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. *Gut* 2001; **48**: 526-535 [PMID: 11247898 DOI: 10.1136/gut.48.4.526]
8 **Canavan C**, Abrams KR, Mayberry J. Meta-analysis: colorectal and small bowel cancer risk in patients with Crohn's disease. *Aliment Pharmacol Ther* 2006; **23**: 1097-1104 [PMID: 16611269 DOI: 10.1111/j.1365-2036.2006.02854.x]
9 **Rutter MD**, Saunders BP, Wilkinson KH, Rumbles S, Schofield G, Kamm MA, Williams CB, Price AB, Talbot IC, Forbes A. Thirty-year analysis of a colonoscopic surveillance program for neoplasia in ulcerative colitis. *Gastroenterology* 2006; **130**: 1030-1038 [PMID: 16618396 DOI: 10.1053/j.gastro.2005.12.035]
10 **Herrinton LJ**, Liu L, Levin TR, Allison JE, Lewis JD, Velayos F. Incidence and mortality of colorectal adenocarcinoma in persons with inflammatory bowel disease from 1998 to 2010. *Gastroenterology* 2012; **143**: 382-389 [PMID: 22609382 DOI: 10.1053/j.gastro.2012.04.054]
11 **Choi CH**, Rutter MD, Askari A, Lee GH, Warusavitarne J, Moorghen M, Thomas-Gibson S, Saunders BP, Graham TA, Hart AL. Forty-Year Analysis of Colonoscopic Surveillance Program for Neoplasia in Ulcerative Colitis: An Updated Overview. *Am J Gastroenterol* 2015; **110**: 1022-1034 [PMID: 25823771 DOI: 10.1038/ajg.2015.65]
12 **Bye WA**, Ma C, Nguyen TM, Parker CE, Jairath V, East JE. Strategies for Detecting Colorectal Cancer in Patients with Inflammatory Bowel Disease: A Cochrane Systematic Review and Meta-Analysis. *Am J Gastroenterol* 2018; **113**: 1801-1809 [PMID: 30353058 DOI: 10.1038/s41395-018-0354-7]
13 **Lutgens MW**, Vleggaar FP, Schipper ME, Stokkers PC, van der Woude CJ, Hommes DW, de Jong DJ, Dijkstra G, van Bodegraven AA, Oldenburg B, Samsom M. High frequency of early colorectal cancer in inflammatory bowel disease. *Gut* 2008; **57**: 1246-1251 [PMID: 18337322 DOI: 10.1136/gut.2007.143453]
14 **Gasia MF**, Ghosh S, Panaccione R, Ferraz JG, Kaplan GG, Leung Y, Novak KL, Seow CH, Iacucci M. Targeted Biopsies Identify Larger Proportions of Patients With Colonic Neoplasia Undergoing High-Definition Colonoscopy, Dye Chromoendoscopy, or Electronic Virtual Chromoendoscopy. *Clin Gastroenterol Hepatol* 2016; **14**: 704-12.e4 [PMID: 26804384 DOI: 10.1016/j.cgh.2015.12.047]
15 **Ananthakrishnan AN**. Chromoendoscopy Is Better: So Why Am I Not (yet) Using it for Routine Inflammatory Bowel Disease Surveillance? *Clin Gastroenterol Hepatol* 2016; **14**: 720-722 [DOI: 10.1016/j.cgh.2015.09.016]
16 **Fogt F**, Vortmeyer AO, Goldman H, Giordano TJ, Merino MJ, Zhuang Z. Comparison of genetic alterations in colonic adenoma and ulcerative colitis-associated dysplasia and carcinoma. *Hum Pathol* 1998; **29**: 131-136 [PMID: 9490271 DOI: 10.1016/s0046-8177(98)90222-2]
17 **Axelrad JE**, Lichtiger S, Yajnik V. Inflammatory bowel disease and cancer: The role of inflammation, immunosuppression, and cancer treatment. *World J Gastroenterol* 2016; **22**: 4794-4801 [PMID: 27239106 DOI: 10.3748/wjg.v22.i20.4794]
18 **Kosinsky RL**, Chua RL, Qui M, Saul D, Mehlich D, Ströbel P, Schildhaus HU, Wegwitz F, Faubion WA, Johnsen SA. Loss of RNF40 Decreases NF-κB Activity in Colorectal Cancer Cells and Reduces Colitis Burden in Mice. *J Crohns Colitis* 2019; **13**: 362-373 [PMID: 30321325 DOI: 10.1093/ecco-jcc/jjy165]
19 **Nadeem MS**, Kumar V, Al-Abbasi FA, Kamal MA, Anwar F. Risk of colorectal cancer in inflammatory bowel diseases. *Semin Cancer Biol* 2020; **64**: 51-60 [PMID: 31112753 DOI: 10.1016/j.semcancer.2019.05.001]
20 **Choi CR**, Al Bakir I, Ding NJ, Lee GH, Askari A, Warusavitarne J, Moorghen M, Humphries A, Ignjatovic-Wilson A, Thomas-Gibson S, Saunders BP, Rutter MD, Graham TA, Hart AL. Cumulative burden of inflammation predicts colorectal neoplasia risk in ulcerative colitis: a large single-centre study. *Gut* 2019; **68**: 414-422 [PMID: 29150489 DOI: 10.1136/gutjnl-2017-314190]
21 **Krugliak Cleveland N**, Rubin DT, Hart J, Weber CR, Meckel K, Tran AL, Aelvoet AS, Pan I, Gonsalves A, Gaetano JN, Williams KM, Wroblewski K, Jabri B, Pekow J. Patients With Ulcerative Colitis and Primary Sclerosing Cholangitis Frequently Have Subclinical Inflammation in the Proximal Colon. *Clin Gastroenterol Hepatol* 2018; **16**: 68-74 [PMID: 28756053 DOI: 10.1016/j.cgh.2017.07.023]
22 **Greenson JK**. Dysplasia in inflammatory bowel disease. *Semin Diagn Pathol* 2002; **19**: 31-37 [PMID: 11936264]

23 **Itzkowitz SH**, Harpaz N. Diagnosis and management of dysplasia in patients with inflammatory bowel diseases. *Gastroenterology* 2004; **126**: 1634-1648 [PMID: 15168373 DOI: 10.1053/j.gastro.2004.03.025]

24 **Feakins RM**; British Society of Gastroenterology. Inflammatory bowel disease biopsies: updated British Society of Gastroenterology reporting guidelines. *J Clin Pathol* 2013; **66**: 1005-1026 [PMID: 23999270 DOI: 10.1136/jclinpath-2013-201885]

25 **Mattar MC**, Lough D, Pishvaian MJ, Charabaty A. Current management of inflammatory bowel disease and colorectal cancer. *Gastrointest Cancer Res* 2011; **4**: 53-61 [PMID: 21673876]

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

27 **Ibraheim H**, Dhillon AS, Koumoutsos I, Gulati S, Hayee B. Curriculum review: colorectal cancer surveillance and management of dysplasia in IBD. *Frontline Gastroenterol* 2018; **9**: 271-277 [PMID: 30245789 DOI: 10.1136/flgastro-2017-100919]

28 **Rubin DT**, Turner JR. Surveillance of dysplasia in inflammatory bowel disease: The gastroenterologist-pathologist partnership. *Clin Gastroenterol Hepatol* 2006; **4**: 1309-1313 [PMID: 17110299 DOI: 10.1016/j.cgh.2006.09.010]

29 **Jess T**, Rungoe C, Peyrin-Biroulet L. Risk of colorectal cancer in patients with ulcerative colitis: a meta-analysis of population-based cohort studies. *Clin Gastroenterol Hepatol* 2012; **10**: 639-645 [PMID: 22289873 DOI: 10.1016/j.cgh.2012.01.010]

30 **Jess T**, Horváth-Puhó E, Fallingborg J, Rasmussen HH, Jacobsen BA. Cancer risk in inflammatory bowel disease according to patient phenotype and treatment: a Danish population-based cohort study. *Am J Gastroenterol* 2013; **108**: 1869-1876 [PMID: 23978954 DOI: 10.1038/ajg.2013.249]

31 **Velayos FS**, Loftus EV Jr, Jess T, Harmsen WS, Bida J, Zinsmeister AR, Tremaine WJ, Sandborn WJ. Predictive and protective factors associated with colorectal cancer in ulcerative colitis: A case-control study. *Gastroenterology* 2006; **130**: 1941-1949 [PMID: 16762617 DOI: 10.1053/j.gastro.2006.03.028]

32 **Wang R**, Leong RW. Primary sclerosing cholangitis as an independent risk factor for colorectal cancer in the context of inflammatory bowel disease: a review of the literature. *World J Gastroenterol* 2014; **20**: 8783-8789 [PMID: 25083052 DOI: 10.3748/wjg.v20.i27.8783]

33 **Loftus EV Jr**, Harewood GC, Loftus CG, Tremaine WJ, Harmsen WS, Zinsmeister AR, Jewell DA, Sandborn WJ. PSC-IBD: a unique form of inflammatory bowel disease associated with primary sclerosing cholangitis. *Gut* 2005; **54**: 91-96 [PMID: 15591511 DOI: 10.1136/gut.2004.046615]

34 **Wijnands AM**, de Jong ME, Lutgens MWMD, Hoentjen F, Elias SG, Oldenburg B; Dutch Initiative on Crohn and Colitis (ICC). Prognostic Factors for Advanced Colorectal Neoplasia in Inflammatory Bowel Disease: Systematic Review and Meta-analysis. *Gastroenterology* 2021; **160**: 1584-1598 [PMID: 33385426 DOI: 10.1053/j.gastro.2020.12.036]

35 **Lutgens MW**, van Oijen MG, van der Heijden GJ, Vleggaar FP, Siersema PD, Oldenburg B. Declining risk of colorectal cancer in inflammatory bowel disease: an updated meta-analysis of population-based cohort studies. *Inflamm Bowel Dis* 2013; **19**: 789-799 [PMID: 23448792 DOI: 10.1097/MIB.0b013e31828029c0]

36 **Askling J**, Dickman PW, Karlén P, Broström O, Lapidus A, Löfberg R, Ekbom A. Family history as a risk factor for colorectal cancer in inflammatory bowel disease. *Gastroenterology* 2001; **120**: 1356-1362 [PMID: 11313305 DOI: 10.1053/gast.2001.24052]

37 **McNamara KL**, Aronson MD, Cohen Z. Is there a role for prophylactic colectomy in Lynch syndrome patients with inflammatory bowel disease? *Int J Colorectal Dis* 2016; **31**: 9-13 [PMID: 26412249 DOI: 10.1007/s00384-015-2398-0]

38 **Derikx LAAP**, Simits LJT, van Vliet S, Dekker E, Aalf CM, van Kouwen MCA, Nagengast FM, Nagtegaal ID, Hoogerbrugge N, Hoentjen F. Colorectal Cancer risk in patients with Lynch Syndrome and Inflamatory bowel disease. *Clin Gastroenterol Hepatol* 2017; **15**: 454-458 [PMID: 27521512 DOI: 10.1016/j.cgh.2016.08.005]

39 **Coviello LC**, Stein SL. Surgical management of nonpolypoid colorectal lesions and strictures in colonic inflammatory bowel disease. *Gastrointest Endosc Clin N Am* 2014; **24**: 447-454 [PMID: 24975535 DOI: 10.1016/j.giec.2014.04.002]

40 **Kristo I**, Riss S, Argeny S, Maschke S, Chitsabesan P, Stift A. Incidental adenocarcinoma in patients undergoing surgery for structuring Crohn`s disease. *World J Gastroenterol* 2017; **23**: 472-477 [DOI: 10.3748/wjg.v23.i3.472]

41 **Gumaste V**, Sachar DB, Greenstein AJ. Benign and malignant colorectal strictures in ulcerative colitis. *Gut* 1992; **33**: 938-941 [PMID: 1644333 DOI: 10.1136/gut.33.7.938]

42 **Rutter MD**, Saunders BP, Wilkinson KH, Rumbles S, Schofield G, Kamm MA, Williams CB, Price AB, Talbot IC, Forbes A. Cancer surveillance in longstanding ulcerative colitis: endoscopic appearances help predict cancer risk. *Gut* 2004; **53**: 1813-1816 [PMID: 15542520 DOI: 10.1136/gut.2003.038505]

43 **Lashner BA**, Turner BC, Bostwick DG, Frank PH, Hanauer SB. Dysplasia and cancer complicating strictures in ulcerative colitis. *Dig Dis Sci* 1990; **35**: 349-352 [PMID: 2307080 DOI: 10.1007/BF01537413]

44 **Yamazaki Y**, Ribeiro MB, Sachar DB, Aufses AH Jr, Greenstein AJ. Malignant colorectal strictures

in Crohn's disease. *Am J Gastroenterol* 1991; **86**: 882-885 [PMID: 2058631]
45 **Baars JE**, Looman CW, Steyerberg EW, Beukers R, Tan AC, Weusten BL, Kuipers EJ, van der Woude CJ. The risk of inflammatory bowel disease-related colorectal carcinoma is limited: results from a nationwide nested case-control study. *Am J Gastroenterol* 2011; **106**: 319-328 [PMID: 21045815 DOI: 10.1038/ajg.2010.428]
46 **Mahmoud R**, Shah SC, Ten Hove JR, Torres J, Mooiweer E, Castaneda D, Glass J, Elman J, Kumar A, Axelrad J, Ullman T, Colombel JF, Oldenburg B, Itzkowitz SH; Dutch Initiative on Crohn and Colitis. No Association Between Pseudopolyps and Colorectal Neoplasia in Patients With Inflammatory Bowel Diseases. *Gastroenterology* 2019; **156**: 1333-1344.e3 [PMID: 30529584 DOI: 10.1053/j.gastro.2018.11.067]
47 **Soetikno RM**, Lin OS, Heidenreich PA, Young HS, Blackstone MO. Increased risk of colorectal neoplasia in patients with primary sclerosing cholangitis and ulcerative colitis: a meta-analysis. *Gastrointest Endosc* 2002; **56**: 48-54 [PMID: 12085034 DOI: 10.1067/mge.2002.125367]
48 **Boonstra K**, Weersma RK, van Erpecum KJ, Rauws EA, Spanier BW, Poen AC, van Nieuwkerk KM, Drenth JP, Witteman BJ, Tuynman HA, Naber AH, Kingma PJ, van Buuren HR, van Hoek B, Vleggaar FP, van Geloven N, Beuers U, Ponsioen CY; EpiPSCPBC Study Group. Population-based epidemiology, malignancy risk, and outcome of primary sclerosing cholangitis. *Hepatology* 2013; **58**: 2045-2055 [PMID: 23775876 DOI: 10.1002/hep.26565]
49 **Laine L**, Kaltenbach T, Barkun A, McQuaid KR, Subramanian V, Soetikno R; SCENIC Guideline Development Panel. SCENIC international consensus statement on surveillance and management of dysplasia in inflammatory bowel disease. *Gastroenterology* 2015; **148**: 639-651.e28 [PMID: 25702852]
50 **Rubin DT**, Ananthakrishnan AN, Siegel CA, Sauer BG, Long MD. ACG Clinical Guideline: Ulcerative Colitis in Adults. *Am J Gastroenterol* 2019; **114**: 384-413 [PMID: 30840605 DOI: 10.14309/ajg.0000000000000152]
51 **Axelrad JE**, Shah SC. Diagnosis and management of inflammatory bowel disease-associated neoplasia: considerations in the modern era. *Therap Adv Gastroenterol* 2020; **13**: 1756284820920779 [PMID: 32523622 DOI: 10.1177/1756284820920779]
52 **Eaden JA**, Mayberry JF; British Society for Gastroenterology; Association of Coloproctology for Great Britain and Ireland. Guidelines for screening and surveillance of asymptomatic colorectal cancer in patients with inflammatory bowel disease. *Gut* 2002; **51** Suppl 5: V10-V12 [PMID: 12221032 DOI: 10.1136/gut.51.supp_5.v10]
53 **Magro F**, Gionchetti P, Eliakim R, Ardizzone S, Armuzzi A, Barreiro-de Acosta M, Burisch J, Gecse KB, Hart AL, Hindryckx P, Langner C, Limdi JK, Pellino G, Zagórowicz E, Raine T, Harbord M, Rieder F; European Crohn's and Colitis Organisation [ECCO]. Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. Part 1: Definitions, Diagnosis, Extra-intestinal Manifestations, Pregnancy, Cancer Surveillance, Surgery, and Ileo-anal Pouch Disorders. *J Crohns Colitis* 2017; **11**: 649-670 [PMID: 28158501 DOI: 10.1093/ecco-jcc/jjx008]
54 **Wang YR**, Cangemi JR, Loftus EV Jr, Picco Michael F. Rate of early/missed colorectal cancers after colonoscopy in older patients with or without inflammatory bowel disease in the United States. *Am J Gastroenterol* 2013; **108**: 444-449 [PMID: 23295277 DOI: 10.1038/ajg.2012.429]
55 **Megna B**, Weiss J, Ley D, Saha S, Pfau P, Grimes I, Li Z, Caldera F. Clear liquid diet before bowel preparation predicts successful chromoendoscopy in patients with inflammatory bowel disease. *Gastrointest Endosc* 2019; **89**: 373-379.e2 [PMID: 30339950 DOI: 10.1016/j.gie.2018.09.039]
56 **Sanduleanu S**, Kaltenbach T, Barkun A, McCabe RP, Velayos F, Picco MF, Laine L, Soetikno R, McQuaid KR. A roadmap to the implementation of chromoendoscopy in inflammatory bowel disease colonoscopy surveillance practice. *Gastrointest Endosc* 2016; **83**: 213-222 [PMID: 26364967 DOI: 10.1016/j.gie.2015.08.076]
57 **Buchner AM**, Shahid MW, Heckman MG, McNeil RB, Cleveland P, Gill KR, Schore A, Ghabril M, Raimondo M, Gross SA, Wallace MB. High-definition colonoscopy detects colorectal polyps at a higher rate than standard white-light colonoscopy. *Clin Gastroenterol Hepatol* 2010; **8**: 364-370 [PMID: 19932768 DOI: 10.1016/j.cgh.2009.11.009]
58 **American Society for Gastrointestinal Endoscopy Standards of Practice Committee**. , Shergill AK, Lightdale JR, Bruining DH, Acosta RD, Chandrasekhara V, Chathadi KV, Decker GA, Early DS, Evans JA, Fanelli RD, Fisher DA, Fonkalsrud L, Foley K, Hwang JH, Jue TL, Khashab MA, Muthusamy VR, Pasha SF, Saltzman JR, Sharaf R, Cash BD, DeWitt JM. The role of endoscopy in inflammatory bowel disease. *Gastrointest Endosc* 2015; **81**: 1101-21.e1 [PMID: 25800660 DOI: 10.1016/j.gie.2014.10.030]
59 **Mooiweer E**, van der Meulen-de Jong AE, Ponsioen CY, Fidder HH, Siersema PD, Dekker E, Oldenburg B. Chromoendoscopy for Surveillance in Inflammatory Bowel Disease Does Not Increase Neoplasia Detection Compared With Conventional Colonoscopy With Random Biopsies: Results From a Large Retrospective Study. *Am J Gastroenterol* 2015; **110**: 1014-1021 [PMID: 25823770 DOI: 10.1038/ajg.2015.63]
60 **Tontini GE**, Rath T, Neumann H. Advanced gastrointestinal endoscopic imaging for inflammatory bowel diseases. *World J Gastroenterol* 2016; **22**: 1246-1259 [PMID: 26811662 DOI: 10.3748/wjg.v22.i3.1246]
61 **Mönkemüller K**, Fry LC, Zimmermann L, Mania A, Zabielski M, Jovanovic I. Advanced endoscopic imaging methods for colon neoplasia. *Dig Dis* 2010; **28**: 629-640 [PMID: 21088415 DOI: 10.1159/000320065]

62 **East JE**, Vleugels JL, Roelandt P, Bhandari P, Bisschops R, Dekker E, Hassan C, Horgan G, Kiesslich R, Longcroft-Wheaton G, Wilson A, Dumonceau JM. Advanced endoscopic imaging: European Society of Gastrointestinal Endoscopy (ESGE) Technology Review. *Endoscopy* 2016; **48**: 1029-1045 [PMID: 27711949 DOI: 10.1055/s-0042-118087]

63 **Feuerstein JD**, Rakowsky S, Sattler L, Yadav A, Foromera J, Grossberg L, Cheifetz AS. Meta-analysis of dye-based chromoendoscopy compared with standard- and high-definition white-light endoscopy in patients with inflammatory bowel disease at increased risk of colon cancer. *Gastrointest Endosc* 2019; **90**: 186-195.e1 [PMID: 31009609 DOI: 10.1016/j.gie.2019.04.219]

64 **Clarke K**, Kang M, Gorrepati VS, Stine JG, Tinsley A, Williams E, Moyer M, Coates M. Dysplasia detection is similar between chromoendoscopy and high-definition white-light colonoscopy in inflammatory bowel disease patients: a US-matched case-control study. *Int J Colorectal Dis* 2020; **35**: 2301-2307 [PMID: 32812090 DOI: 10.1007/s00384-020-03719-3]

65 **Eaden JA**, Ward BA, Mayberry JF. How gastroenterologists screen for colonic cancer in ulcerative colitis: an analysis of performance. *Gastrointest Endosc* 2000; **51**: 123-128 [PMID: 10650251 DOI: 10.1016/s0016-5107(00)70405-6]

66 **Kabir M**, Fofaria R, Arebi N, Bassett P, Tozer PJ, Hart AL, Thomas-Gibson S, Humphries A, Suzuki N, Saunders B, Warusavitarne J, Faiz O, Wilson A. Systematic review with meta-analysis: IBD-associated colonic dysplasia prognosis in the videoendoscopic era (1990 to present). *Aliment Pharmacol Ther* 2020; **52**: 5-19 [PMID: 32432797 DOI: 10.1111/apt.15778]

67 **Iacucci M**, Furfaro F, Matsumoto T, Uraoka T, Smith S, Gosh S, Kliesslich. Advanced endoscopic techniques in the assessment of inflammatory bowel disease: new technology, new era. *Gut* 2019; **68**: 562-572. [PMID: 30580249 DOI: 10.1136/gutjnl-2017-315235]

68 **Bisschops R**, Bessissow T, Joseph JA, Baert F, Ferrante M, Ballet V, Willekens H, Demedts I, Geboes K, De Hertogh G, Vermeire S, Rutgeerts P, Van Assche G. Chromoendoscopy vs narrow band imaging in UC: a prospective randomised controlled trial. *Gut* 2018; **67**: 1087-1094 [DOI: 10.1136/gutjnl-2016-313213]

69 **Moussata D**, Allez M, Cazals-Hatem D, Treton X, Laharie D, Reimund JM, Bertheau P, Bourreille A, Lavergne-Slove A, Brixi H, Branche J, Gornet JM, Stefanescu C, Moreau J, Marteau P, Pelletier AL, Carbonnel F, Seksik P, Simon M, Fléjou JF, Colombel JF, Charlois AL, Roblin X, Nancey S, Bouhnik Y, Berger F, Flourié B; the GETAID. Are random biopsies still useful for the detection of neoplasia in patients with IBD undergoing surveillance colonoscopy with chromoendoscopy? *Gut* 2018; **67**: 616-624 [PMID: 28115492 DOI: 10.1136/gutjnl-2016-311892]

70 **Saraiva S**, Rosa I, Moleiro J, Pereira da Silva J, Fonseca R, Dias Pereira A. Dysplasia Surveillance in Inflammatory Bowel Disease: A Cohort Study. *GE Port J Gastroenterol* 2021; **28**: 97-105 [PMID: 33791396 DOI: 10.1159/000510728]

71 **van der Laan JJH**, van der Waaij AM, Gabriëls RY, Festen EAM, Dijkstra G, Nagengast WB. Endoscopic imaging in inflammatory bowel disease: current developments and emerging strategies. *Expert Rev Gastroenterol Hepatol* 2021; **15**: 115-126 [PMID: 33094654 DOI: 10.1080/17474124.2021.1840352]

72 **Voorham QJ**, Rondagh EJ, Knol DL, van Engeland M, Carvalho B, Meijer GA, Sanduleanu S. Tracking the molecular features of nonpolypoid colorectal neoplasms: a systematic review and meta-analysis. *Am J Gastroenterol* 2013; **108**: 1042-1056 [PMID: 23649184 DOI: 10.1038/ajg.2013.126]

73 **Wanders LK**, Dekker E, Pullens B, Bassett P, Travis SP, East JE. Cancer risk after resection of polypoid dysplasia in patients with longstanding ulcerative colitis: a meta-analysis. *Clin Gastroenterol Hepatol* 2014; **12**: 756-764 [PMID: 23920032 DOI: 10.1016/j.cgh.2013.07.024]

74 **Zisman TL**, Bronner MP, Rulyak S, Kowdley KV, Saunders M, Lee SD, Ko C, Kimmey MB, Stevens A, Maurer J, Brentnall TA. Prospective study of the progression of low-grade dysplasia in ulcerative colitis using current cancer surveillance guidelines. *Inflamm Bowel Dis* 2012; **18**: 2240-2246 [PMID: 22508402 DOI: 10.1002/ibd.22912]

75 **Lightner AL**, Vogler S, McMichael J, Jia X, Regueiro M, Qazi T, Steele SR. Dysplastic Progression to Adenocarcinoma is Equivalent in Ulcerative Colitis and Crohn's Disease. *J Crohns Colitis* 2021; **15**: 24-34 [PMID: 32592468 DOI: 10.1093/ecco-jcc/jjaa133]

76 **De Jong ME**, Van Tilburg SB, Nissen LHC, Kievit W, Nagtegaal ID, Horjus CS, Römkens TEH, Drenth JPH, Hoentjen F, Derikx LAAP. Long-term Risk of Advanced Neoplasia After Colonic Low-grade Dysplasia in Patients With Inflammatory Bowel Disease: A Nationwide Cohort Study. *J Crohns Colitis* 2019; **13**: 1485-1491 [PMID: 31175827 DOI: 10.1093/ecco-jcc/jjz114]

77 **Krugliak Cleveland N**, Ollech JE, Colman RJ, Rodriquez D, Hirsch A, Cohen RD, Hanauer SB, Hart J, Hurst R, Rubin DT. Efficacy and Follow-up of Segmental or Subtotal Colectomy in Patients With Colitis-Associated Neoplasia. *Clin Gastroenterol Hepatol* 2019; **17**: 205-206 [PMID: 29751167 DOI: 10.1016/j.cgh.2018.04.061]

78 **Melcher AH**, Chan J. The relationship between section thickness and the ultrastructural visualization of collagen fibrils: importance in studies on resorption of collagen. *Arch Oral Biol* 1978; **23**: 231-233 [PMID: 278557 DOI: 10.1016/0003-9969(78)90222-4]

79 **Rubin DT**, Krugliak Cleveland N, Rodriquez DM. Outcomes of colitis-associated dysplasia after referral from the community to a tertiary center. *Gastrointest Endosc* 2016; **84**: 1078-1079 [PMID: 27855794 DOI: 10.1016/j.gie.2016.04.026]

World Journal of Gastrointestinal Endoscopy

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

World J Gastrointest Endosc 2022 February 16; 14(2): 96-105

DOI: 10.4253/wjge.v14.i2.96

ISSN 1948-5190 (online)

ORIGINAL ARTICLE

Retrospective Study

Texture and color enhancement imaging in magnifying endoscopic evaluation of colorectal adenomas

Osamu Toyoshima, Toshihiro Nishizawa, Shuntaro Yoshida, Tomoharu Yamada, Nariaki Odawara, Tatsuya Matsuno, Miho Obata, Ken Kurokawa, Chie Uekura, Mitsuhiro Fujishiro

ORCID number: Osamu Toyoshima 0000-0002-6953-6079; Toshihiro Nishizawa 0000-0003-4876-3384; Shuntaro Yoshida 0000-0002-9437-9132; Tomoharu Yamada 0000-0001-6312-5706; Nariaki Odawara 0000-0002-9839-4700; Tatsuya Matsuno 0000-0002-1935-3506; Miho Obata 0000-0002-2564-1504; Ken Kurokawa 0000-0001-8389-3315; Chie Uekura 0000-0002-6709-2662; Mitsuhiro Fujishiro 0000-0002-4074-1140.

Author contributions: Toyoshima O contributed to conception of article, drafted the article, took endoscopic images, reviewed the endoscopic images, did statistical analysis, and approved final manuscript; Nishizawa T contributed to conception of article, drafted the article, reviewed the endoscopic images, and approved final manuscript; Yoshida S, Yamada T, Matsuno T, and Odawara N reviewed the endoscopic images, critically reviewed, and approved final manuscript; Obata M, Kurokawa K, Uekura C, and Fujishiro M contributed to critical review and approved final manuscript.

Institutional review board statement: This study was reviewed and approved by the Certificated Review Board, Yoyogi Mental Clinic on July 16, 2021

Osamu Toyoshima, Toshihiro Nishizawa, Shuntaro Yoshida, Tomoharu Yamada, Nariaki Odawara, Tatsuya Matsuno, Miho Obata, Ken Kurokawa, Chie Uekura, Gastroenterology, Toyoshima Endoscopy Clinic, Tokyo 157-0066, Japan

Toshihiro Nishizawa, Department of Gastroenterology and Hepatology, International University of Health and Welfare, Narita Hospital, Narita 286-8520, Chiba, Japan

Tomoharu Yamada, Nariaki Odawara, Tatsuya Matsuno, Miho Obata, Ken Kurokawa, Chie Uekura, Mitsuhiro Fujishiro, Department of Gastroenterology, Graduate School of Medicine, The University of Tokyo, Tokyo 113-8655, Japan

Corresponding author: Toshihiro Nishizawa, MD, PhD, Professor, Department of Gastroenterology and Hepatology, International University of Health and Welfare, Narita Hospital, 852 Hatakeda, Narita 286-8520, Chiba, Japan. nisizawa@kf7.so-net.ne.jp

Abstract

BACKGROUND

Olympus Corporation has developed texture and color enhancement imaging (TXI) as a novel image-enhancing endoscopic technique.

AIM

To investigate the effectiveness of TXI in identifying colorectal adenomas using magnifying observation.

METHODS

Colorectal adenomas were observed by magnified endoscopy using white light imaging (WLI), TXI, narrow band imaging (NBI), and chromoendoscopy (CE). This study adopted mode 1 of TXI. Adenomas were confirmed by histological examination. TXI visibility was compared with the visibility of WLI, NBI, and CE for tumor margin, and vessel and surface patterns of the Japan NBI expert team (JNET) classification. Three expert endoscopists and three non-expert endoscopists evaluated the visibility scores, which were classified as 1, 2, 3, and 4.

RESULTS

Sixty-one consecutive adenomas were evaluated. The visibility score for tumor margin of TXI (3.47 ± 0.79) was significantly higher than that of WLI (2.86 ± 1.02, $P < 0.001$), but lower than that of NBI (3.76 ± 0.52, $P < 0.001$), regardless of the

endoscopist's expertise. TXI (3.05 ± 0.79) had a higher visibility score for the vessel pattern of JNET classification than WLI (2.17 ± 0.90, $P < 0.001$) and CE (2.47 ± 0.87, $P < 0.001$), but lower visibility score than NBI (3.79 ± 0.47, $P < 0.001$), regardless of the experience of endoscopists. For the visibility score for the surface pattern of JNET classification, TXI (2.89 ± 0.85) was superior to WLI (1.95 ± 0.79, $P < 0.01$) and CE (2.75 ± 0.90, $P = 0.002$), but inferior to NBI (3.67 ± 0.55, $P < 0.001$).

CONCLUSION

TXI provided higher visibility than WLI, lower than NBI, and comparable to or higher than CE in the magnified observation of colorectal adenomas.

Key Words: Texture and color enhancement imaging; Adenoma; Colonoscopy; Narrow band imaging; Japan NBI Expert Team; Olympus

Core Tip: Texture and color enhancement imaging (TXI) has been developed as a novel image-enhancing endoscopy. Colorectal adenomas were observed by magnified endoscopy using white light imaging (WLI), TXI, narrow band imaging (NBI), and chromoendoscopy (CE). TXI visibility was compared with the visibility of WLI, NBI, and CE for tumor margin, and vessel and surface patterns of the Japan NBI Expert Team (JNET) classification. TXI provided higher visibility than WLI and lower than NBI for tumor margin. TXI showed higher visibility than WLI and CE, and lower than NBI for the vessel and surface patterns of the JNET classification.

Citation: Toyoshima O, Nishizawa T, Yoshida S, Yamada T, Odawara N, Matsuno T, Obata M, Kurokawa K, Uekura C, Fujishiro M. Texture and color enhancement imaging in magnifying endoscopic evaluation of colorectal adenomas. *World J Gastrointest Endosc* 2022; 14(2): 96-105

URL: https://www.wjgnet.com/1948-5190/full/v14/i2/96.htm

DOI: https://dx.doi.org/10.4253/wjge.v14.i2.96

INTRODUCTION

Colorectal adenomas are precursors to colorectal cancer and their removal prevents occurrence of cancer in this region. Endoscopists with higher adenoma detection rates have lower colorectal cancer incidence and mortality in their patients than those with lower adenoma detection rates[1,2]. Currently, adenomas are a common finding. Hilsden *et al*[3] reported the following benchmarks of adenoma detection rates: minimally acceptable, 25%; standard of care, 30%; and aspirational, 39%. It is recommended that the endoscopists overcome the "minimally acceptable" threshold[3,4]. Therefore, accurate diagnosis of colorectal adenomas is crucial in clinical practice[5-7].

Recent advances in endoscopic technology have improved the accuracy of endoscopy using image-enhanced endoscopy (IEE) for lesions that are difficult to observe using conventional white light imaging (WLI). Since narrow band imaging (NBI) was developed as an IEE modality, evidence on the usefulness of IEE has been accumulated and IEE is commonly used in daily practice. NBI selects blue and green wavelengths using optical filters with the elimination of red light, thus emphasizing mucosal surface structures and blood vessels[8]. NBI has been reported to be effective in detecting[9] and characterizing lesions[10-12]. Following NBI, blue light imaging (BLI) and linked color imaging (LCI) have become available as new IEE modalities. BLI and LCI irradiate mucosa with a short wavelength, narrow-band light, which includes light amplification by stimulated emission of radiation or light emitting diode, without an optical filter. Furthermore, the acquired color information is reallocated to different colors that are similar to the mucosal color, resulting in improved performance in depicting blood vessels. In addition, image processing that enhances color separation for red color permits clear visualization of red blood vessels and white pits in LCI[13]. The efficacy of BLI and LCI has also been extensively

(approval no. RKK227).

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent. For full disclosure, the details of the study are published on the home page of Toyoshima Endoscopy Clinic.

Conflict-of-interest statement: Fujishiro M received research grant and honoraria from Olympus Corporation.

Data sharing statement: No additional data are available.

Country/Territory of origin: Japan

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
Grade D (Fair): 0
Grade E (Poor): 0

Received: August 15, 2021
Peer-review started: August 15, 2021
First decision: September 12, 2021

Revised: September 18, 2021
Accepted: January 6, 2022
Article in press: January 6, 2022
Published online: February 16, 2022

P-Reviewer: Shaikh DH
S-Editor: Chang KL
L-Editor: A
P-Editor: Chang KL

reported[14]. Texture and color enhancement imaging (TXI), which is a novel method to enhance images, was developed in the new endoscopy system EVIS X1 (Olympus Corporation, Tokyo, Japan) in 2020.

TXI is designed to enhance three image factors, including texture, brightness, and color, in WLI to clearly define subtle tissue differences by applying the retinex theory [15,16]. Retinex is based on the theory of "color constancy" and "brightness constancy", in which the human eye can perceive color and brightness regardless of the illumination light. TXI consists of the following six processes. First, the input image is split into two layers, base and detail. Next, the brightness in the dark regions of the base layer is adjusted. Tone-mapping is applied to the corrected base layer in step three. Fourth, texture enhancement is applied to the detail layer to enhance the subtle contrast. In step five, the base layer after tone-mapping and the detail layer after texture enhancement are recombined. A TXI image produced in the fifth step is immediately displayed in TXI mode 2. In the final step, color enhancement is applied to the output of TXI mode 1 to more clearly define the slight color contrast. The color enhancement algorithm of TXI was designed to expand the color difference between red and white hues in the image[16].

The Japan NBI Expert Team (JNET) classification is a standard for diagnosing the histology of a neoplasm by observing the surface structure (vessel pattern and surface pattern) of the neoplasm using magnified NBI. The JNET classification is widely used in clinical practice for the diagnosis of adenoma. It has proven to be useful for the diagnosis of superficial colorectal neoplasms in a clinical setting by both expert and non-expert endoscopists[12]. A meta-analysis suggested that the diagnostic efficacy of the JNET classification may be equivalent to that of the Pit pattern classification[17]. Furthermore, the algorithm for the treatment of colorectal polyps using the JNET classification was reported to be valid[18]. Meanwhile, evidence supports that chromoendoscopy (CE) increases colorectal polyp detection and contributes to accurate polyp diagnosis[6,19-22].

Currently, the only clinical studies on TXI that have already been published are those by Ishikawa *et al*[23] and Abe *et al*[24], wherein TXI was used for imaging the stomach. Some clinical trials on the efficacy of TXI in colorectal polyp observation are ongoing; however, no published reports on colonoscopy are available in PubMed or the Cochrane Library. Therefore, the aim of this study was to investigate the effectiveness of TXI for colorectal adenomas. The visibility of TXI was compared with the visibility of WLI, NBI, and CE for the tumor margin and JNET classification pattern using magnifying observation.

MATERIALS AND METHODS

Patients

Patients who underwent colonoscopy at Toyoshima Endoscopy Clinic (Tokyo, Japan), which is a representative clinic in Japan, from April to May 2021, were enrolled. Patients with removed adenomas were eligible for the study. When patients had multiple adenomas, they were treated individually. Adenomas were diagnosed histopathologically. Indications for colonoscopy included screening, examination of symptoms, investigation for a positive fecal immunochemical test, and polyp surveillance. Patients with inflammatory bowel disease were excluded.

Ethics

This study was conducted in accordance with the ethical guidelines for medical studies in Japan. Written informed consent was obtained from the patients at the time of colonoscopy to use their data for research purposes. The study design was described in a protocol prepared by Toyoshima Endoscopy Clinic and was approved by the Certificated Review Board, Yoyogi Mental Clinic on July 16, 2021 (approval No. RKK227). We published this study's protocol on our institute's website (http://www.ichou.com) so that patients could opt out of the study if they did not wish to participate. All clinical investigations were conducted in accordance with the ethical guidelines of the Declaration of Helsinki.

Endoscopy

EVIS X1 video system center (CV-1500), 4 K resolution ultra-high-definition liquid crystal display monitor (OEV321UH), and colonoscope CF-HQ290Z (Olympus Corporation, Tokyo, Japan) were used in this study setting. TXI has two methods, namely modes 1 and 2, and the enhancement of brightness and texture is similar

between them. Because the enhancement of the color contrast of mode 1 is superior to that of mode 2[16], this study adopted mode 1. For the enhanced structure level, A8 was selected for WLI, NBI, and CE. The type A mode is ideal for observation of larger mucosal tissues with high contrast, whereas the type B mode is suitable for observation of vascular tissues. There are eight levels among the type A mode, of which A8 is the most emphasized, and A1 is the least emphasized mode. A 0.05% indigo carmine was used for the CE. The T-File System (STS-Medic Inc., Tokyo, Japan) was used to file the endoscopic images and document the endoscopic findings.

One expert endoscopist performed colonoscopy and magnified observation using the WLI, TXI, NBI, and CE modalities. Lesions were first washed carefully with water to remove the mucus and dye from the mucosal surface; then, images were obtained through WL, TXI, and NBI. The lesions were subsequently stained for CE. The endoscopist took an image within 15 s for each modality.

Visibility scoring

We investigated the visibility of the tumor margin, and the vessel and surface patterns according to the JNET classification. The vessel pattern shows the pattern of superficial microvessels, which appear red in WLI, TXI, and CE, and brown in NBI. The surface pattern indicates the pattern of superficial crypts, which appear whitish in all modalities. JNET type 2A corresponds to the histopathological classification of low-grade intramucosal neoplasia, including adenoma. The vessel pattern of type 2A is of a regular caliber and distribution (meshed and/or spiral pattern). The surface pattern of type 2A is defined as regular (tubular, branched, and/or papillary)[10-12].

As in previous reports, the visibility score was defined as follows: score 4, excellent (easily detectable); score 3, good (detectable with careful observation); score 2, fair (hardly detectable without careful examination); score 1, poor (not detectable without repeated careful examination)[12,14]. Representative images of each score are shown in Figures 1, 2, and 3.

Three expert endoscopists and three non-expert endoscopists evaluated the visibility score. The images studied were observed without zooming. The endoscopist assessed all images at the same size and magnification. A physician with more than 5000 experiences in colonoscopy was defined as an expert endoscopist and one with less than 5000 experiences was considered a non-expert[12].

Outcomes

The main outcomes of this study were the mean visibility scores for tumor margin, vessel pattern of JNET classification, and surface pattern of JNET classification based on WLI, TXI, NBI, and CE observations. We collected data on age and sex of the patients, the location of adenomas, size of adenomas, morphology of adenomas based on the Paris endoscopic classification of neoplastic lesions[25], histological subtype (*i.e.*, tubular or villous) of adenomas, and atypia of adenomas as clinicopathological characteristics.

Statistical analysis

The visibility scores of TXI and other modalities were compared using the Wilcoxon signed-rank test. Statistical significance was defined as a P value less than 0.05. All statistical data were analyzed using the statistical software Ekuseru-Toukei 2015 (Social Survey Research Information Co., Ltd., Tokyo, Japan).

RESULTS

Patients

The clinicopathological characteristics of the 37 consecutive patients with 61 adenomas evaluated in this study are shown in Table 1. The mean age was 59.1 years, and men accounted for 51.4%. Of the adenomas with an average size of 4.2 mm, 78.7% were located on the right side, 86.9% had a flat morphology, and all were tubular subtype with low-grade dysplasia.

Visibility score for tumor margin

The visibility score for the tumor margin of TXI was higher than that of WLI, but lower than that of NBI. Similar tendencies were obtained regardless of the endoscopist's expertise (Table 2).

Table 1 Clinicopathological characteristics of patients and adenomas

Patients, *n*	37
Age, mean (range, SD), yr	59.1 (41-79, 9.0)
Sex, male/female, *n*	19/18
Adenomas, *n*	61
Location,cecum/ascending/transverse/descending/sigmoid/rectum, *n*	5/8/35/3/10/0
Size, mean (range, SD), mm	4.2 (1-12, 2.3)
Morphology[1], Ip/Is/IIa/IIb, *n*	2/6/48/5
Histological subtype, tubular/villous, *n*	61/0
Dysplasia, low-grade/high-grade, *n*	61/0

[1]Morphology was performed according to the Paris endoscopic classification of neoplastic lesions.

Table 2 Visibility scores of tumor margin, vessel pattern of Japan narrow band imaging Expert Team classification, and surface pattern of Japan narrow band imaging Expert Team classification for white light imaging, texture and color enhancement imaging, narrow band imaging, and chromoendoscopy

	WLI	TXI	NBI	CE	WLI *vs* TXI, *P* value	TXI *vs* NBI, *P* value	TXI *vs* CE, *P* value
Tumor margin							
All, mean (SD)	2.86 (1.02)	3.47 (0.79)	3.76 (0.52)	3.52 (0.84)	< 0.001	< 0.001	0.21
Expert, mean (SD)	2.85 (0.96)	3.57 (0.66)	3.81 (0.43)	3.64 (0.70)	< 0.001	< 0.001	0.14
Nonexpert, mean (SD)	2.86 (1.08)	3.37 (0.90)	3.72 (0.59)	3.39 (0.94)	< 0.001	< 0.001	0.73
Vessel pattern							
All, mean (SD)	2.17 (0.90)	3.05 (0.79)	3.79 (0.47)	2.47 (0.87)	< 0.001	< 0.001	< 0.001
Expert, mean (SD)	2.31 (0.87)	3.24 (0.67)	3.80 (0.41)	2.57 (0.85)	< 0.001	< 0.001	< 0.001
Nonexpert, mean (SD)	2.03 (0.90)	2.86 (0.85)	3.78 (0.52)	2.37 (0.88)	< 0.001	< 0.001	< 0.001
Surface pattern							
All, mean (SD)	1.95 (0.79)	2.89 (0.85)	3.67 (0.55)	2.75 (0.90)	< 0.001	< 0.001	0.002
Expert, mean (SD)	1.92 (0.74)	2.96 (0.78)	3.70 (0.47)	2.67 (0.81)	< 0.001	< 0.001	< 0.001
Nonexpert, mean (SD)	1.97 (0.83)	2.83 (0.92)	3.64 (0.61)	2.83 (0.97)	< 0.001	< 0.001	0.94

The visibility score was defined as follows: score 4, excellent (easily detectable); score 3, good (detectable with careful observation); score 2, fair (hardly detectable without careful examination); score 1, poor (not detectable without repeated careful examination). NBI: Narrow band imaging; JNET: Japan NBI Expert Team; WLI: White light imaging; TXI: Texture and color enhancement imaging; CE: Chromoendoscopy.

Visibility score for vessel pattern of JNET classification

TXI had a higher visibility score for vessel pattern of JNET classification than WLI and CE, but lower visibility score than NBI. Similar tendencies were observed regardless of the endoscopist's experience (Table 2).

Visibility score for surface pattern of JNET classification

The visibility score of TXI for surface pattern of JNET classification was higher than those of WLI or CE, but lower than that of NBI. However, no difference was observed in the visibility scores between TXI and CE for non-expert endoscopists (Table 2).

DISCUSSION

This study showed that TXI provided higher visibility than WLI, but lower visibility

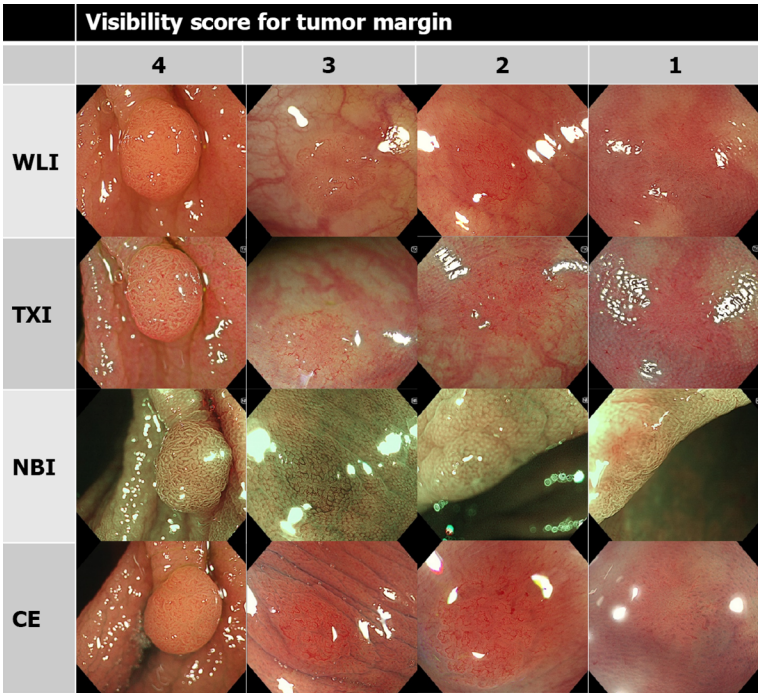

Figure 1 Representative images of visibility score for tumor margin. Visibility score was defined as following: score 4, excellent (easily detectable); score 3, good (detectable with careful observation); score 2, fair (hardly detectable without careful examination); score 1, poor (not detectable without repeated careful examination). WLI: White light imaging; TXI: Texture and color enhancement imaging; NBI: Narrow band imaging; CE: Chromoendoscopy.

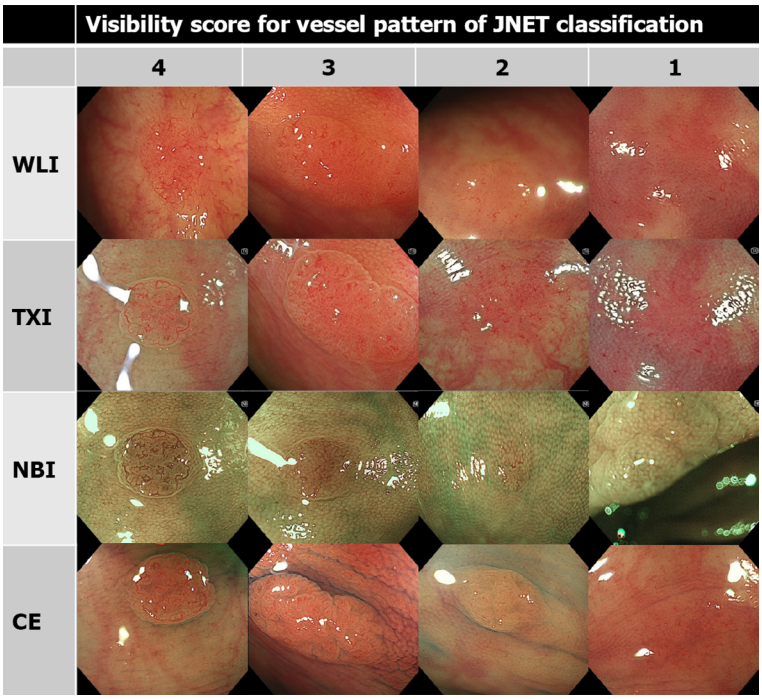

Figure 2 Representative images of visibility score for vessel pattern of Japan narrow band imaging Expert Team classification. Visibility score was defined as following: score 4, excellent (easily detectable); score 3, good (detectable with careful observation); score 2, fair (hardly detectable without careful examination); score 1, poor (not detectable without repeated careful examination). NBI: Narrow band imaging; JNET: Japan NBI Expert Team; WLI: White light imaging; TXI: Texture and color enhancement imaging; CE: Chromoendoscopy.

than NBI for margin and surface structure (*i.e.*, JNET patterns) of adenoma. Moreover, TXI had superior visibility for the surface structure of adenoma to CE. TXI is designed to enhance the three image components (*i.e.*, texture, brightness, and color) of WLI because it clearly defines subtle tissue differences and minimizes gross changes that negatively impact familiarity.

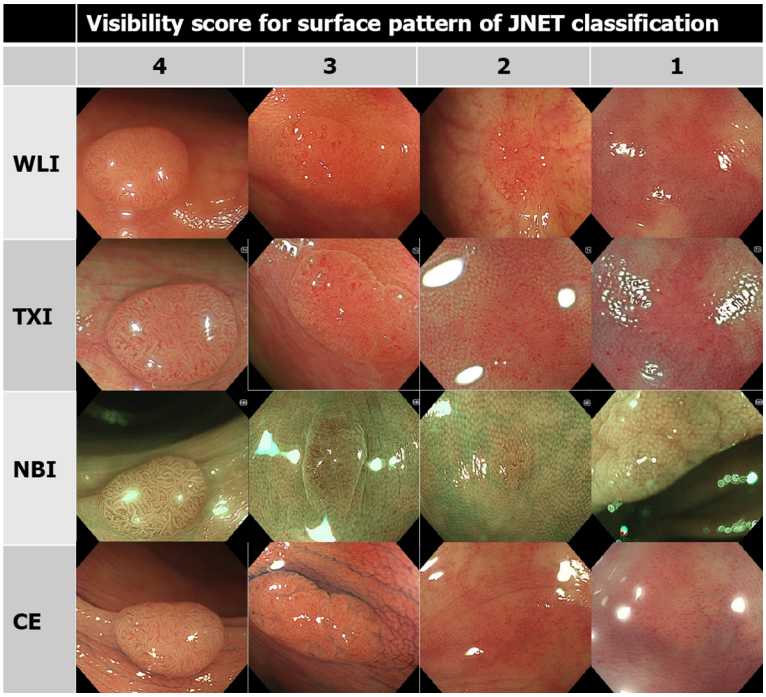

Figure 3 Representative images of visibility score for surface pattern of Japan narrow band imaging Expert Team classification. Visibility score was defined as following: score 4, excellent (easily detectable); score 3, good (detectable with careful observation); score 2, fair (hardly detectable without careful examination); score 1, poor (not detectable without repeated careful examination). NBI: Narrow band imaging; JNET: Japan NBI Expert Team; WLI: White light imaging; TXI: Texture and color enhancement imaging; CE: Chromoendoscopy.

Although TXI was inferior to NBI in a detailed observation of the lesions, many endoscopists prefer to maintain consistency regarding the brightness and color in the original WLI because WLI is used as the standard practice for observation of the entire mucosa. As shown in this study, TXI may improve the balance of image features vital to an endoscopist searching for abnormalities, with texture enhancement, color enhancement, and selectively increased brightness.

Olympus Corporation first developed the NBI in 2007. Fujifilm Corporation developed a similar BLI product. NBI uses ambient light with wavelengths of 415 nm and 540 nm, whereas BLI uses wavelengths of 410 and 450 nm. The images of NBI and BLI are similar. The diagnostic performances of NBI and BLI were also similar for colorectal and esophageal lesions[26]. Fujifilm Corporation developed the LCI. A randomized controlled trial showed that LCI was significantly superior to standard WLI colonoscopy for polyp detection[13]. Currently, LCI-based observations are becoming mainstream. However, Olympus did not have a mode corresponding to that of LCI until recently. Recently, Olympus released TXI as a mode similar to that of LCI.

Although LCI and TXI have similar images, there are several differences in their principles. LCI uses the same illumination as BLI-bright, the images are converted to resemble those of WLI, and color is enhanced such that red is changed to vivid red and white to clear white. On the other hand, TXI uses white light, brightness is adjusted, and texture and color are enhanced. In this study, TXI showed improved tumor margin visibility than WLI. Similar to LCI, TXI may contribute to the improvement in adenoma detection rate; however, future studies are warranted.

In this study, the magnified TXI was inferior to the magnified NBI. Several reports have shown that magnified LCI with CE is superior to magnified BLI. Sakamoto *et al* [27] reported that magnified LCI with crystal violet staining provided more diagnostic information than magnified BLI and WLI. Kitagawa *et al*[28] reported that magnified LCI with indigo carmine was superior to magnified BLI. Magnified TXI with CE needs to be further investigated in future studies.

Strengths and limitations

The strength of this study is that it is the first report on the efficacy of TXI in colonoscopy. Second, this study targeted colorectal adenomas, which are common in daily practice; however, evaluation of visibility of malignant tumors is required. Artificial intelligence (AI) has made remarkable progress in the field of endoscopy [29], and we have shown the possible usefulness of TXI for AI endoscopy in the future.

The present study has some limitations. This was a single-center, retrospective study. However, since our institution specializes in endoscopy, the endoscopic environment is well managed. Multicenter randomized control trials are required in the future. Since this study is only for magnified observation, it is desirable to study non-magnified observations as well. TXI has two modes: mode 1 and mode 2. Mode 2 includes brightness adjustment and texture enhancement, and mode 1 adds color enhancement to mode 2. Mode 2 is more natural than mode 1. Since TXI mode 1 was shown to be superior to TXI mode 2 in visibility for gastric neoplasms[23], only mode 1 was investigated in this study. However, comparative studies of visibility between modes 1 and 2 in colonoscopy should be conducted in the future. Additionally, since this study only used CF-HQ290Z, evaluation in various other scopes is necessary. Finally, colorectal adenomas that we investigated were as small as 4.2 mm, and most of them were morphologically flat (86.9%) and located in the proximal colon (78.7%), compared with the adenomas in previous Japanese studies[12]. Our previous study showed that an expert endoscopist with a high adenoma detection rate frequently detected diminutive and flat adenomas in the proximal colon[22]. In the present study, one expert endoscopist conducted all colonoscopies; hence, the adenomas investigated cannot be generalized. In the future, studies with a larger number of cases evaluated by non-expert endoscopists are warranted.

CONCLUSION

TXI provided higher visibility than WLI, lower than NBI, and comparable to or higher than CE in the magnified observation of colorectal adenomas. Further accumulation of evidence on the performance of TXI is required in the future.

ARTICLE HIGHLIGHTS

Research background

Olympus Corporation has developed texture and color enhancement imaging (TXI) as a novel image-enhancing endoscopic technique.

Research motivation

There are no reports on the use of TXI in the colon.

Research objectives

To investigated the effectiveness of TXI in identifying colorectal adenomas using magnifying observation.

Research methods

Colorectal adenomas were observed by magnified endoscopy using white light imaging (WLI), TXI, narrow band imaging (NBI), and chromoendoscopy (CE). TXI visibility was compared with the visibility of WLI, NBI, and CE for tumor margin, and vessel and surface patterns of the Japan NBI Expert Team (JNET) classification. The visibility scores were classified as 1, 2, 3, and 4.

Research results

Sixty-one consecutive adenomas were evaluated. The visibility score for tumor margin of TXI was significantly higher than that of WLI, but lower than that of NBI. TXI had a higher visibility score for the vessel pattern of JNET classification than WLI and CE, but lower visibility score than NBI. For the visibility score for the surface pattern of JNET classification, TXI was superior to WLI and CE, but inferior to NBI.

Research conclusions

TXI provided higher visibility than WLI, lower than NBI, and comparable to or higher than CE in the magnified observation of colorectal adenomas.

Research perspectives

TXI may contribute to the improvement in adenoma detection rate. Further accumulation of evidence on the performance of TXI is required in the future.

REFERENCES

1 **Nishihara R**, Wu K, Lochhead P, Morikawa T, Liao X, Qian ZR, Inamura K, Kim SA, Kuchiba A, Yamauchi M, Imamura Y, Willett WC, Rosner BA, Fuchs CS, Giovannucci E, Ogino S, Chan AT. Long-term colorectal-cancer incidence and mortality after lower endoscopy. *N Engl J Med* 2013; **369**: 1095-1105 [PMID: 24047059 DOI: 10.1056/NEJMoa1301969]

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

3 **Hilsden RJ**, Rose SM, Dube C, Rostom A, Bridges R, McGregor SE, Brenner DR, Heitman SJ. Defining and Applying Locally Relevant Benchmarks for the Adenoma Detection Rate. *Am J Gastroenterol* 2019; **114**: 1315-1321 [PMID: 30848731 DOI: 10.14309/ajg.0000000000000120]

4 **Toyoshima O**, Yoshida S, Nishizawa T, Yamakawa T, Arano T, Isomura Y, Kanazawa T, Ando H, Tsuji Y, Koike K. Simple feedback of colonoscopy performance improved the number of adenomas per colonoscopy and serrated polyp detection rate. *Endosc Int Open* 2021; **9**: E1032-E1038 [PMID: 34222627 DOI: 10.1055/a-1393-5469]

5 **Ignjatovic A**, East JE, Suzuki N, Vance M, Guenther T, Saunders BP. Optical diagnosis of small colorectal polyps at routine colonoscopy (Detect InSpect ChAracterise Resect and Discard; DISCARD trial): a prospective cohort study. *Lancet Oncol* 2009; **10**: 1171-1178 [PMID: 19910250 DOI: 10.1016/S1470-2045(09)70329-8]

6 **Toyoshima O**, Hata K, Yoshida S, Arita M. New-generation chromoendoscopy may increase confidence in the DISCARD2 study. *Gut* 2017 [DOI: 10.1136/gutjnl-2017-314999]

7 **Karsenti D**, Tharsis G, Burtin P, Venezia F, Tordjman G, Gillet A, Samama J, Nahon-Uzan K, Cattan P, Cavicchi M. Adenoma and advanced neoplasia detection rates increase from 45 years of age. *World J Gastroenterol* 2019; **25**: 447-456 [PMID: 30700941 DOI: 10.3748/wjg.v25.i4.447]

8 **Boeriu A**, Boeriu C, Drasovean S, Pascarenco O, Mocan S, Stoian M, Dobru D. Narrow-band imaging with magnifying endoscopy for the evaluation of gastrointestinal lesions. *World J Gastrointest Endosc* 2015; **7**: 110-120 [PMID: 25685267 DOI: 10.4253/wjge.v7.i2.110]

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

10 **Sano Y**, Tanaka S, Kudo SE, Saito S, Matsuda T, Wada Y, Fujii T, Ikematsu H, Uraoka T, Kobayashi N, Nakamura H, Hotta K, Horimatsu T, Sakamoto N, Fu KI, Tsuruta O, Kawano H, Kashida H, Takeuchi Y, Machida H, Kusaka T, Yoshida N, Hirata I, Terai T, Yamano HO, Kaneko K, Nakajima T, Sakamoto T, Yamaguchi Y, Tamai N, Nakano N, Hayashi N, Oka S, Iwatate M, Ishikawa H, Murakami Y, Yoshida S, Saito Y. Narrow-band imaging (NBI) magnifying endoscopic classification of colorectal tumors proposed by the Japan NBI Expert Team. *Dig Endosc* 2016; **28**: 526-533 [PMID: 26927367 DOI: 10.1111/den.12644]

11 **Iwatate M**, Sano Y, Tanaka S, Kudo SE, Saito S, Matsuda T, Wada Y, Fujii T, Ikematsu H, Uraoka T, Kobayashi N, Nakamura H, Hotta K, Horimatsu T, Sakamoto N, Fu KI, Tsuruta O, Kawano H, Kashida H, Takeuchi Y, Machida H, Kusaka T, Yoshida N, Hirata I, Terai T, Yamano HO, Nakajima T, Sakamoto T, Yamaguchi Y, Tamai N, Nakano N, Hayashi N, Oka S, Ishikawa H, Murakami Y, Yoshida S, Saito Y; Japan NBI Expert Team (JNET). Validation study for development of the Japan NBI Expert Team classification of colorectal lesions. *Dig Endosc* 2018; **30**: 642-651 [PMID: 29603399 DOI: 10.1111/den.13065]

12 **Kobayashi S**, Yamada M, Takamaru H, Sakamoto T, Matsuda T, Sekine S, Igarashi Y, Saito Y. Diagnostic yield of the Japan NBI Expert Team (JNET) classification for endoscopic diagnosis of superficial colorectal neoplasms in a large-scale clinical practice database. *United European Gastroenterol J* 2019; **7**: 914-923 [PMID: 31428416 DOI: 10.1177/2050640619845987]

13 **Min M**, Deng P, Zhang W, Sun X, Liu Y, Nong B. Comparison of linked color imaging and white-light colonoscopy for detection of colorectal polyps: a multicenter, randomized, crossover trial. *Gastrointest Endosc* 2017; **86**: 724-730 [PMID: 28286095 DOI: 10.1016/j.gie.2017.02.035]

14 **Suzuki T**, Hara T, Kitagawa Y, Takashiro H, Nankinzan R, Sugita O, Yamaguchi T. Linked-color imaging improves endoscopic visibility of colorectal nongranular flat lesions. *Gastrointest Endosc* 2017; **86**: 692-697 [PMID: 28193491 DOI: 10.1016/j.gie.2017.01.044]

15 **Meylan L**, Süsstrunk S. High dynamic range image rendering with a Retinex-based adaptive filter. *IEEE Trans Image Process* 2006; **15**: 2820-2830 [PMID: 16948325 DOI: 10.1109/tip.2006.877312]

16 **Sato T**. TXI: Texture and Color Enhancement Imaging for Endoscopic Image Enhancement. *J Healthc Eng* 2021; **2021**: 5518948 [PMID: 33880168 DOI: 10.1155/2021/5518948]

17 **Zhang Y**, Chen HY, Zhou XL, Pan WS, Zhou XX, Pan HH. Diagnostic efficacy of the Japan Narrow-band-imaging Expert Team and Pit pattern classifications for colorectal lesions: A meta-analysis. *World J Gastroenterol* 2020; **26**: 6279-6294 [PMID: 33177800 DOI: 10.3748/wjg.v26.i40.6279]

18 **Kato M**, Abe K, Kubosawa Y, Sunata Y, Hirai Y, Hirata T, Takada Y, Wada M, Takatori Y, Banno S, Kinoshita S, Mori H, Takabayashi K, Kikuchi M, Shiraishi J, Uraoka T. Validation of treatment algorithm based on the Japan narrow-band imaging expert team classification for sub-centimeter

colorectal polyps. *Endosc Int Open* 2018; **6**: E934-E940 [PMID: 30083581 DOI: 10.1055/a-0621-4445]

19 **Rahmi G**, Lecomte T, Malka D, Maniere T, Le Rhun M, Guimbaud R, Lapalus MG, Le Sidaner A, Moussata D, Caron O, Barbieux JP, Gaudric M, Coron E, Barange K, Ponchon T, Sautereau D, Samaha E, Saurin JC, Chaussade S, Laurent-Puig P, Chatellier G, Cellier C. Impact of chromoscopy on adenoma detection in patients with Lynch syndrome: a prospective, multicenter, blinded, tandem colonoscopy study. *Am J Gastroenterol* 2015; **110**: 288-298 [PMID: 25601014 DOI: 10.1038/ajg.2014.423]

20 **Buchner AM**. The Role of Chromoendoscopy in Evaluating Colorectal Dysplasia. *Gastroenterol Hepatol (N Y)* 2017; **13**: 336-347 [PMID: 28690450]

21 **Hurt C**, Ramaraj R, Farr A, Morgan M, Williams N, Philips CJ, Williams GT, Gardner G, Porter C, Sampson J, Hillier S, Heard H, Dolwani S; CONSCOP Clinical Research Consortium. Feasibility and economic assessment of chromocolonoscopy for detection of proximal serrated neoplasia within a population-based colorectal cancer screening programme (CONSCOP): an open-label, randomised controlled non-inferiority trial. *Lancet Gastroenterol Hepatol* 2019; **4**: 364-375 [PMID: 30885505 DOI: 10.1016/S2468-1253(19)30035-4]

22 **Toyoshima O**, Nishizawa T, Yoshida S, Sekiba K, Kataoka Y, Hata K, Watanabe H, Tsuji Y, Koike K. Expert endoscopists with high adenoma detection rates frequently detect diminutive adenomas in proximal colon. *Endosc Int Open* 2020; **8**: E775-E782 [PMID: 32490163 DOI: 10.1055/a-1136-9971]

23 **Ishikawa T**, Matsumura T, Okimoto K, Nagashima A, Shiratori W, Kaneko T, Oura H, Tokunaga M, Akizue N, Ohta Y, Saito K, Arai M, Kato J, Kato N. Efficacy of Texture and Color Enhancement Imaging in visualizing gastric mucosal atrophy and gastric neoplasms. *Sci Rep* 2021; **11**: 6910 [PMID: 33767278 DOI: 10.1038/s41598-021-86296-x]

24 **Abe S**, Yamazaki T, Hisada IT, Makiguchi ME, Yoshinaga S, Sato T, Nonaka S, Suzuki H, Oda I, Saito Y. Visibility of early gastric cancer in texture and color enhancement imaging. *DEN Open* 2022; **2**: e46 [DOI: 10.1002/deo2.46]

25 **Participants in the Paris Workshop**. The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon: November 30 to December 1, 2002. *Gastrointest Endosc* 2003; **58**: S3-43 [PMID: 14652541 DOI: 10.1016/s0016-5107(03)02159-x]

26 **Ueda T**, Dohi O, Naito Y, Yoshida T, Azuma Y, Ishida T, Matsumura S, Kitae H, Takayama S, Mizuno N, Nakano T, Iwai N, Hirose R, Inoue K, Yoshida N, Kamada K, Uchiyama K, Ishikawa T, Takagi T, Konishi H, Nishimura A, Kishimoto M, Itoh Y. Diagnostic performance of magnifying blue laser imaging *vs* magnifying narrow-band imaging for identifying the depth of invasion of superficial esophageal squamous cell carcinoma. *Dis Esophagus* 2021; **34** [PMID: 32691042 DOI: 10.1093/dote/doaa078]

27 **Sakamoto T**, Inoki K, Takamaru H, Sekiguchi M, Yamada M, Nakajima T, Matsuda T, Saito Y. Efficacy of linked colour imaging in magnifying chromoendoscopy with crystal violet staining: a pilot study. *Int J Colorectal Dis* 2019; **34**: 1341-1344 [PMID: 31168654 DOI: 10.1007/s00384-019-03323-0]

28 **Kitagawa Y**, Hara T, Ikebe D, Nankinzan R, Takashiro H, Kobayashi R, Nakamura K, Yamaguchi T, Suzuki T. Magnified endoscopic observation of small depressed gastric lesions using linked color imaging with indigo carmine dye. *Endoscopy* 2018; **50**: 142-147 [PMID: 28954304 DOI: 10.1055/s-0043-119212]

29 **Sinagra E**, Badalamenti M, Maida M, Spadaccini M, Maselli R, Rossi F, Conoscenti G, Raimondo D, Pallio S, Repici A, Anderloni A. Use of artificial intelligence in improving adenoma detection rate during colonoscopy: Might both endoscopists and pathologists be further helped. *World J Gastroenterol* 2020; **26**: 5911-5918 [PMID: 33132644 DOI: 10.3748/wjg.v26.i39.5911]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com