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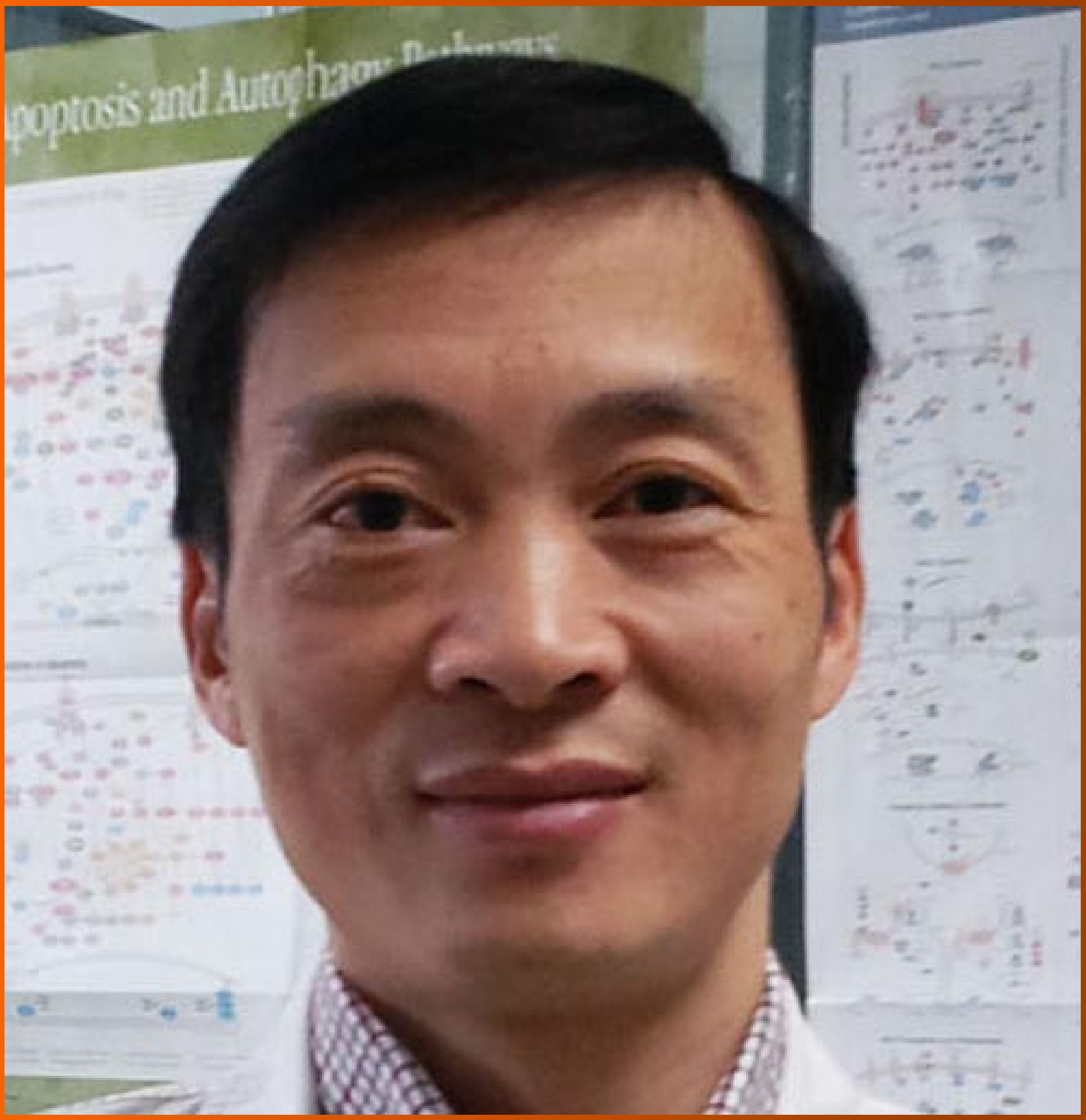

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TOPIC HIGHLIGHT

2016 Colorectal Cancer: Global view

New era of colorectal cancer screening

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Abstract

Colorectal cancer (CRC) is the 2nd most common cancer in women and 3rd most common cancer in men worldwide. Most CRCs develop from adenomatous polyps arising from glandular epithelium. Tumor growth is initiated by mutation of the tumor suppressor gene *APC* and involves other genetic mutations in a stepwise process over years. Both hereditary and environmental factors contribute to the development of CRC. Screening has been proven to reduce the incidence of CRC. Screening has also contributed to the decrease in CRC mortality in the United States. However, CRC incidence and/or mortality remain on the rise in some parts of the world (Eastern Europe, Asia, and South America), likely due to factors including westernized diet, lifestyle, and lack of healthcare infrastructure. Multiple screening options are available, ranging from direct radiologic or endoscopic visualization tests that primarily detect premalignant or malignant lesions such as flexible sigmoidoscopy, optical colonoscopy, colon capsule endoscopy, computed tomographic colonography, and double contrast barium enema - to stool based tests which primarily detect cancers, including fecal DNA, fecal immunochemical test, and fecal occult blood test. The availability of some of these tests is limited to areas with high economic resources. This article will discuss CRC epidemiology, pathogenesis, risk factors, and screening modalities with a particular focus on new technologies.

Key words: Colorectal neoplasm; Prevention and control; Guidelines; Epidemiology; Colonoscopy; Capsule endoscopy; Computed tomographic colonography; Occult blood

Core tip: Multiple societies have issued screening guidelines for colorectal cancer (CRC). However, global CRC screening implementation can be challenging due to wide variability in healthcare infrastructure and resources in different countries. The practical implementation of CRC screening in a given area depends mainly upon availability of endoscopic resources. In areas with the greatest healthcare resources, colonoscopy remains the gold standard, although technological advances have provided alternative screening methods including

computed tomographic colonography, fecal DNA testing, and colon capsule endoscopy. In areas with fewer healthcare resources, guaiac-based fecal occult blood testing is the predominant screening modality.

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INTRODUCTION

Colorectal cancer (CRC) is the second most common cancer in women and third most common cancer in men worldwide[1]. Globally, there is marked variation in CRC incidence and mortality[1,2]. Some countries in Eastern Europe and Asia have demonstrated increasing incidence rates (Slovakia, Czech Republic, Singapore, and Japan) which have been attributed to behavioral risk factors related to westernization of diet and lifestyle[3]. In addition, some countries (Brazil, Mexico, and Romania) have experienced increasing CRC mortality rates from CRC purportedly due to limited healthcare resources[4]. In the United States, CRC is the third leading cause of cancer death and accounts for approximately 7% and 9% of overall cancer deaths in females and males, respectively[5]. CRC incidence and mortality rates have been declining in the United States secondary to increased screening mainly *via* colonoscopy, which enables primary prevention and early detection[6,7]. In recent years, technological advances have led to the development of new, less invasive screening modalities including fecal immunochemical testing, computed tomographic colonography (CTC), stool DNA testing, and colon capsule endoscopy. This article will discuss CRC pathogenesis, risk factors, and screening with a particular focus on new screening methods.

PATHOGENESIS

Most colorectal carcinomas develop from adenomatous polyp arising from the glandular epithelium of the intestine[8]. Adenomas are initiated by somatic mutation of the tumor suppressor gene *APC*[9]. Additional genetic alterations of oncogenes and tumor suppressor genes are involved in a stepwise growth process that occurs over years[10-12]. The accumulation of genetic mutations in accordance with chromosomal instability, shifts the normal intestinal lining to an adenomatous polyp, then high-grade adenoma and finally to a carcinoma[13,14]. CRC can also arise from nonpolypoid and depressed lesions. Although these lesions are less common than that of the polypoid adenoma, they manifest more aggressive behavior and more rapid growth, and they are more difficult to diagnose[15,16].

SCREENING TESTS

Available tests for CRC screening are divided into 2 major types, stool-based tests or endoscopic and radiologic tests. The stool-based tests include the guaiac-based fecal occult blood test (gFOBT), fecal immunochemical test (FIT), and fecal DNA testing. These tests detect cell debris and blood shed by vascularized polyps, adenomas and cancers[17]. The endoscopic and radiologic examinations include optical colonoscopy, flexible sigmoidoscopy (FS or FSIG), double-contrast barium enema (DCBE), capsule endoscopy, and CTC and are based on direct or radiographic visualization of the polyp or cancer.

STOOL-BASED TESTS

gFOBT

gFOBT detects the presence of blood in feces through a chemical reaction dependent upon the peroxidase activity of heme. It is an inexpensive test that can be mailed to patients. Annual or biennial gFOBT have shown to decrease CRC mortality rates by 15%-33%[18-20]. In the Minnesota Colon Cancer Control Study, a 30-year follow-up of patients randomly assigned to annual/or biennial gFOBT *vs* usual care showed a 32% decrease in CRC mortality. Furthermore, mortality reduction was more pronounced in men compared to women[21].

A disadvantage of gFOBT is the requirement for 3 different stool samples[22]. This makes collection more cumbersome to the patient, which results in lowered adherence and thus decreases its effectiveness as a screening test[23,24]. gFOBT endorses a risk of false-positive results if patients ingest animal products or vegetables prior to testing, or if the patient is on anticoagulants or antiplatelet agents[25]. On the other hand, a risk of false negative test arises if patient is on ascorbic acid or any other form of antioxidants[26].

FIT

FIT is an antibody-based test that detects and binds to the globin component of hemoglobin. The FIT sampling technique is simpler and easier to collect compared to that of gFOBT. Only one or two fecal samples are required and no dietary or medication restrictions are needed prior to the test. The overall accuracy of FIT for detection of CRC was 95% with 79% sensitivity and 94% specificity as been shown in systematic review and meta-analysis including 19 qualified studied performed by Lee *et al*[27]. FIT has been shown to have a greater sensitivity in detecting advanced adenomas and CRC than gFOBT[28-31].

A disadvantage of FIT is its more expensive cost compared to FOBT. Although FIT is easier to collect, its sensitivity decreases with any delay in mailing or processing of the sample. Furthermore, similar to other non-invasive tests, if the test is positive, a follow-up colonoscopy would be needed.

Fecal DNA testing

Fecal DNA testing, or Cologuard (Exact Sciences), is a non-invasive, easy to perform test based on a single stool sample, and does not require dietary or medication restriction. It is a composite test that includes an immunochemical assay similar to the one used in FIT, methylated markers and molecular mutations markers associated with CRC. In 2014, this test was approved by the United States Food and Drug Administration as a screening test for CRC.

One multicenter study on 9989 patients comparing fecal DNA test to FIT using colonoscopy as the gold standard showed that the fecal DNA test had a higher sensitivity than FIT for detecting CRC, (92% *vs* 74%), adenomas with high-grade dysplasia (69% *vs* 46%), and serrated sessile polyps (42% *vs* 5%). However, specificity was lower with fecal DNA test at 87%-90% compared to FIT at 95%-96%[32].

In a large multicenter case-control study, automated fecal DNA testing accurately detected CRC regardless of the site or the stage of the lesion with an overall sensitivity of more than 98%. Sensitivity for precancerous lesions increased in proportion to lesion size from 57% for lesions > 1 cm to 83% for those > 3 cm[33].

Disadvantages of fecal DNA testing include its expensive cost; the inconvenience stool sampling and shipment to the lab; and the need for colonoscopy if the test is positive.

ENDOSCOPIC AND RADIOLOGIC TESTS

DCBE

DCBE is a non-invasive radiological test, which provides a complete evaluation of the large intestine. The sensitivity and specificity of barium enema for polyps of any size is 38% and 86%, respectively[34]. One study comparing barium enema to CT colonography and colonoscopy showed that DCBE has the lowest sensitivity and specificity with sensitivity of 41% for lesions ⩾ 6 mm and sensitivity and specificity of 48% and 90% respectively for lesions ⩾ 10 mm[35]. These results are consistent with a meta-analysis comparing the performance of barium enema to that of CTC showing CTC is more sensitive and more specific than barium enema for large polyps (⩾ 10 mm) and small polyps (6-9 mm) in average-risk and high-risk populations[36]. In the United States, CT colonography has largely replaced DCBE as a radiographic option for CRC screening. A disadvantage of DCBE is that the test must be followed by colonoscopy if abnormalities are found.

Colonoscopy

Optical colonoscopy entails direct visualization of the colonic mucosa from the cecum to the rectum with a flexible endoscope. Insufflation, irrigation, and suction facilitate careful inspection of the mucosa. Colonoscopy allows both detection and removal of polyps, which can be submitted for histopathological examination. Colonoscopy is routinely performed in some countries with sedation, whereas in others sedation is rarely used. Colonoscopy requires a bowel preparation with a laxative and clear liquid diet prior to the procedure. Split-dose protocols, in which patients ingest half the bowel preparation the day of the procedure, may encourage compliance and are now recommended for optimal bowel cleansing[37]. Procedural risks include cardiopulmonary complications due to sedation, the possibility of missed lesions, bleeding, and a 0.08% rate of perforation, which is typically related to polypectomy[38]. Although traditionally colonoscopy has been considered to be the gold standard for CRC screening, the miss rate for adenomas ⩾ 1 cm was 6% in a tandem colonoscopy study[39]. Moreover, colonoscopy is less effective at reducing proximal compared with distal CRCs[40-43]. This finding may result from a combination of factors including inadequate bowel preparation, which is more likely to affect the right colon; incomplete colonoscopy; and a higher prevalence in the proximal colon of non-polypoid colorectal neoplasms, which are often more difficult to detect than traditional polypoid neoplasms[44]. Based on pooled data from several large North American studies, 0.6% of patients with adenomas developed CRC within an average of 4 years after clearing colonoscopy[45]. Fifty-two percent of these cancers were felt to be missed lesions, 19% were thought to be potentially incompletely resected lesions, and 24% were thought to be new lesions. These statistics reflect the fact that colonoscopy is operator dependent. Indeed, the development of interval cancers within 3 years after colonoscopy has been associated with performance of colonoscopy by non-gastroenterologists[46].

FS

FS is used to visualize the left-sided or descending colon and the rectum where approximately 60% of all CRCs develop. Compared to colonoscopy, FS is safer, faster, and more easily tolerated procedure. Sedation is not required, and self-administered enemas are usually used in bowel preparation[47,48].

Screening with FS decreases the incidence and overall mortality of CRC[48,49]. A large randomized control trial involving 34272 participants between the ages of 55 and 64 years with a median follow-up of around 11 years showed a 31% decrease in the incidence of CRC and a 38% decrease in CRC mortality after one-time screening with FS, compared with no screening[49].

A disadvantage of FS is that follow-up colonoscopy is required given that about 3%-5% of patients with CRC in the distal colon will have lesions in the proximal colon[50]. In the United States, colonoscopy has largely replaced FS for CRC screening.

Colon capsule endoscopy

With capsule endoscopy (Pillcam COLON, Given Imaging Ltd, Yoqneam, Israel) the patient swallows a capsule which records digital images on 2 camera heads at a rate ranging from 4 to 35 frames per second for appro-

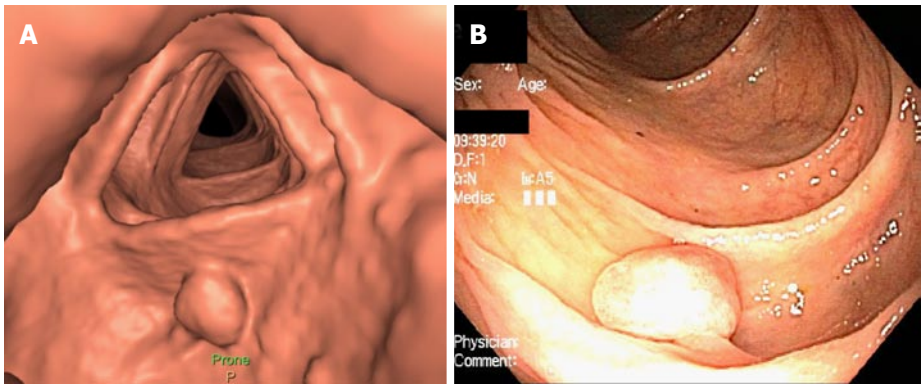

Figure 1 Visualization of a colonic polyp by computed tomographic colonography and optical colonoscopy. A: Three dimensional view of a splenic flexure colonic polyp on computed tomographic colonography; B: View of the same polyp on optical colonoscopy.

ximately 10 h. These images are then transmitted wirelessly to a recording device carried by the patient. The data are transferred from the device to a computer that uses a software (RAPID) to compile the video to be analyzed then by an experienced gastroenterologist[51]. Indications for colon capsule endoscopy have not been standardized; the use of CE is recommended in cases of colonoscopy contraindication, colonoscopy failure, or in patients unwilling to perform colonoscopy. In the United States, the Food and Drug Administration has approved Pillcam COLON 2 (second generation) for patients who have had an incomplete colonoscopy.

A recent prospective study conducted by Doug Rex on 884 patients comparing accuracy of PillCam COLON 2 to that of optical colonoscopy demonstrated 88% sensitivity and 82% specificity in detecting adenoma $\geqslant$ 6 mm in average risk screening population[52].

An advantage of capsule endoscopy compared to other non-invasive methods is the lack of radiation exposure. Disadvantages of capsule endoscopy include the need for a complex bowel preparation regimen and the risk, albeit low, of capsule retention, which may necessitate surgical removal.

CTC

CTC, or virtual colonoscopy, is a radiographic imaging test in which two-dimensional or three-dimensional images of the colon and rectum are generated using specialized computer software and abdominal computed tomography scanning. It is offered to the patient if colonoscopy is incomplete or in the event of patients' refusal or has additional risk factors. CT colonography every 5 years is a screening option according to some CRC screening guidelines (see below). Multiple steps are involved in completing CTC. The first step is the bowel preparation, which includes a fiber-free diet and ingestion of a laxative and contrast medium prior to the test. The second step is colonic insufflation, which is done by insufflation of CO_2 *via* a rectal catheter and bulb in a gradual manner with a controlled pressure to prevent perforation. The third step is acquisition of the radiographic images. An adjusted scout-view is obtained so that the entire colon is covered. Images are obtained in 2 positions, supine and prone; decubitus lateral positions are performed if patient is overweight.

The final step is interpretation of images; two dimensional interpretation identifies any lesion that is larger than a centimeter. The infracentimetric lesions are identified *via* three dimensional interpretation. After identification of a polyp-like lesion, its density should be determined. The lipoma or an inverted tumor is fatty, fecal residue is dense, and tumor tissue's density is similar to that of the colonic wall. Each lesion is then classified by C-RAD, which specifies the site, the shape, type of density, and the largest diameter of the head of the polyp. A colonoscopy is indicated for lesions that are $\geqslant$ 10 mm or more than 3 lesions > 5 mm[53]. Figure 1 displays a polyp visualized on CT colonography and subsequent colonoscopy.

A multicenter trial enrolling 845 patients who underwent screening with CTC followed by colonoscopy showed 69% sensitivity and 91% specificity in detecting polyps > 6 mm[54]. CTC was found to accurately detect 90% of lesions > 10 mm in diameter[55]. The detection rate for advanced neoplasm was found to be similar for patients undergoing CTC compared to colonoscopy, while the rate of polypectomies and complications was considerably smaller in the CTC group compared to that of colonoscopy[56]. Radiation exposure is one of disadvantage of CTC[57]. In addition, perforation is still a risk, although it is less than that with colonoscopy[36].

SCREENING GUIDELINES

In the United States, the two major guidelines for CRC screening are: (1) joint guidelines from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology; and (2) the US Preventive Services Task Force (USPSTF) guidelines. Other organizations have issued their own guidelines as well, such as the American College of Gastroenterology and the American College of Physicians. Table 1 summarizes the varying

Table 1 Summary of colorectal cancer screening guidelines from various organizations in the United States

	Joint guidelines	USPSTF	ACG	ACP
Flexible sigmoidoscopy	Every 5 yr	Every 5 yr, with high sensitivity FOBT every 3 yr	Every 5-10 yr	Every 5 yr
Colonoscopy	Every 10 yr	Every 10 yr	Every 10 yr	Every 10 yr
Barium enema	Every 5 yr	Not recommended	Not recommended	Every 5 yr
CT colonography	Every 5 yr	Insufficient evidence to recommend	Every 5 yr	Every 5 yr
gFOBT	Annual	Annual	Annual	Annual
FIT	Annual	Every year	Annual	Annual
sDNA	Uncertain	Insufficient evidence to recommend	Every 3 yr	Uncertain

USPSTF: United States Preventive Services Task Force; ACG: American College of Gastroenterology; ACP: American College of Physicians; FOBT: Fecal occult blood testing; CT: Computed tomographic; gFOBT: Guaiac-based fecal occult blood testing; FIT: Fecal immunochemical test; sDNA: Stool deoxyribonucleic acid.

recommendations from these different sets of guidelines for average risk individuals. USPSTF guidelines were issued in 2008 and are in the process of being updated. On a global level, CRC screening can be challenging to implement due to wide variability in healthcare infrastructure and resources in different countries. The World Gastroenterology Organization practice guidelines on CRC screening provide differing recommendations for average risk screening depending upon the availability of endoscopic resources[58]. In areas with the lowest access to FS and colonoscopy, for example, biennial gFOBT or FIT is recommended, while colonoscopy every 10 years is recommended in areas with greater healthcare and endoscopic resources.

CONCLUSION

CRC screening is associated with decreased CRC incidence and mortality. CRC screening modalities include radiographic or endoscopic methods (colonoscopy, FS, CT colonography, double contrast barium enema, colon capsule endoscopy) and stool-based tests (fecal DNA test, gFOBT, and FIT). Options for screening also depend upon the healthcare infrastructure of the country including the availability of endoscopic resources. In offering CRC screening, the physician should discuss with the patient the advantages and disadvantages of each test and ascertain the patient's preferences for better adherence.

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Endoscopic imaging of Barrett's esophagus

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Abstract

The incidence of esophageal adenocarcinoma (EAC) has dramatically increased in the United States as well as Western European countries. The majority of esophageal adenocarcinomas arise from a backdrop of Barrett's esophagus (BE), a premalignant lesion that can lead to dysplasia and cancer. Because of the increased risk of EAC, GI society guidelines recommend endoscopic surveillance of patients with BE. The emphasis on early detection of dysplasia in BE through surveillance endoscopy has led to the development of advanced endoscopic imaging technologies. These techniques have the potential to both improve mucosal visualization and characterization and to detect small mucosal abnormalities which are difficult to identify with standard endoscopy. This review summarizes the advanced imaging technologies used in evaluation of BE.

Key words: Esophageal adenocarcinoma; Barrett's esophagus; Dysplasia; Intestinal metaplasia; Advanced endoscopic imaging; Narrow band imaging; Confocal laser endomicroscopy

Core tip: The majority of esophageal adenocarcinomas (EAC) arise from a backdrop of Barrett's esophagus (BE), a premalignant lesion that can lead to dysplasia and cancer. Because of the increased risk of EAC, GI society guidelines recommend endoscopic surveillance of patients with BE. The emphasis on early detection of dysplasia in BE through surveillance endoscopy has led to the development of advanced endoscopic imaging technologies. These techniques have the potential to both improve mucosal visualization and characterization and to detect small abnormalities which are difficult to identify with standard endoscopy. This review summarizes the advanced imaging technologies used in evaluation of BE.

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INTRODUCTION

The incidence of esophageal adenocarcinoma (EAC) has been steadily rising over the last three decades, with population-based cohort studies suggestive of a 300%-500% increase during this time[1]. The majority of esophageal adenocarcinomas arise from a backdrop of Barrett's esophagus (BE), a premalignant lesion which progresses through several stages of dysplasia to cancer. The prevalence and incidence of BE have increased over time, parallel to the increase in frequency of EAC[2]. There are various estimates (ranging from 0.1%-2.0%) of the annual rate of progression from BE to cancer, with higher rates of progression to cancer reported for patients with low grade dysplasia (0.54% to 1.8% per year) and high grade dysplasia (6.6% per year)[3-6]. Because of the increased risk of EAC, GI society guidelines recommend that patients with BE undergo endoscopic surveillance[7-10]. The aim of endoscopic surveillance is to identify areas of dysplasia which can subsequently be treated with endoscopic eradication therapy before progression to cancer. In patients with BE undergoing surveillance, biopsies are collected from areas with visible mucosal abnormalities and at random in four quadrants every 1-2 cm along the BE segment[11]. This protocol, however, is labor intensive and can still miss neoplasia despite multiple biopsies.

The emphasis on early detection of pre-cancerous lesions has led to the development of advanced imaging technologies to improve care of patients with BE. These techniques have the potential to improve mucosal visualization and detection of abnormal tissue, such as with high-definition white light endoscopy (HD-WLE), while other techniques such as dye-based or electronic chromoendoscopy enhance and adjust the color of the endoscopic images to improve lesion detection and tissue characterization. There are also techniques that allow histological evaluation such as confocal laser endoscopy (CLE). This review summarizes the currently available advanced imaging technologies used in evaluation of BE.

CONVENTIONAL (WHITE LIGHT) ENDOSCOPY

HD-WLE

Over the past decade, high resolution endoscopes using high definition (HD) systems have largely replaced the original low-resolution or standard definition (SD) white light video-endoscopes in most if not all endoscopic units. Capable of producing images with higher magnification and an image resolution of more than 1 million pixels (compared to the 100000-400000 pixels of standard-definition endoscopes), HD-WLE has enhanced the endoscopists' ability to inspect and visualize subtle mucosal abnormalities[12,13]. Many research studies using HD-WLE combine it with another advanced endoscopic imaging technique, such as narrow band imaging (NBI) or chromoendoscopy[14,15]. There are few studies comparing standard endoscopy with HD-WLE, but one study did show improved detection of dysplasia using HD-WLE[16]. In some studies, addition of additional imaging techniques does not significantly improve detection of BE and neoplasia above HD-WLE alone on a per-patient basis, although additional lesions may be detected and fewer biopsies may be acquired[17-19]. Though high resolution endoscopes have higher sensitivity for detection of neoplasia than standard endoscopes, targeted biopsies using high resolution endoscopy (HRE) alone may still miss dysplasia that is found using random biopsies[15].

Magnification endoscopy

Magnifying or zoom endoscopes permit better visualization of mucosal details by enabling the images to be magnified from 1.5 times to 150 times without loss of resolution[20]. While magnification endoscopy alone allows for visualization of mucosal surface patterns and vessels, this technique has most often been studied in combination with chromoendoscopy. In one study, magnification chromoendoscopy improved the detection of intestinal metaplasia (IM) and HGD in patients BE compared to standard endoscopy[21]. Magnification endoscopy is not widely used for patients with BE and some studies have shown a high level of inter-observer variability in identifying dysplastic lesions[22].

ENHANCING COLOR DURING ENDOSCOPY

Chromoendoscopy

Chromoendoscopy involves endoscopic evaluation of gastrointestinal mucosa following the topical application of dyes or contrast agents. The goal of chromoendoscopy is to improve the detection and characterization of abnormalities and facilitate targeted biopsy sampling of suspicious areas. While it can be used with standard endoscopy, chromoendoscopy is most often performed with another advanced imaging modality, such as HD-WLE, magnification endoscopy, or confocal endomicroscopy. There are several types of chromoendoscopy agents, some of which are absorbed by cells, while others highlight the mucosal surface. Absorptive stains, such as methylene blue (MB) and Lugol's iodine, are absorbed across cell membranes while contrast agents such as indigo carmine are not absorbed by the mucosa but highlight the surface topography and mucosal irregularities.

Methylene blue has been used in several studies of patients undergoing chromoendoscopy for evaluation of BE and BE-associated neoplasia. Several studies suggested that MB could discern areas of IM

and dysplasia with high accuracy and with fewer biopsies compared to traditional surveillance techniques[23-26]. However, other studies have found that chromoendoscopy was not better than conventional four quadrant random biopsies for detection of BE and neoplasia[27,28]. Further limiting the widespread use of methylene blue chromoendoscopy is the potential risk of DNA damage and carcinogenesis[29].

Indigo carmine has been used in conjunction with magnification endoscopy to identify the mucosal pit patterns within segments of BE[21,30]. The presence of villiform pit patterns and irregular mucosal patterns have been shown to correlate with presence of IM and dysplasia[30].

Acetic acid chromoendoscopy has been used in several recent studies for evaluation of patients with BE. Targeted biopsies following staining with acetic acid has been associated with increased yield for detecting BE as well as dysplasia and early cancer within an area of BE[31]. One retrospective cohort study evaluated the yield for neoplasia in patients with BE, comparing acetic acid chromoendoscopy and a standard random biopsy protocol. Acetic acid chromoendoscopy detected more neoplasia than conventional protocol-guided mapping biopsies and required significantly fewer biopsies per neoplasia detected[32]. Another randomized crossover study of acetic acid magnification endoscopy found a higher yield for detection of BE (78%) compared to standard endoscopy with biopsy (57%)[33].

In comparison to other endoscopic imaging modalities, chromoendoscopy is relatively inexpensive, requiring only a spray catheter and contrast agent, many of which are readily available. On the other hand, chromoendoscopy can be cumbersome requiring a significant increase in endoscopy time and image interpretation is operator dependent, with high interobserver variability reported in some studies[22]. These factors and the mixed results of research studies have limited the widespread use of chromoendoscopy in patients with BE.

Electronic chromoendoscopy: Narrow band imaging

First described in 2004 by Gono *et al*[34], NBI enhances the resolution of the mucosal surface and is the most-investigated image-enhanced endoscopy technique[34,35]. NBI restricts the wavelengths of light used for endoscopic imaging. Shorter wavelength blue light (440-460 nm) highlights the superficial capillary network, while longer wavelength green light (540 nm) highlights the subepithelial vessels, allowing identification of subtle mucosal abnormalities. Furthermore, as blue light is absorbed by hemoglobin, the alterations in vascular patterns associated with neoplasia may be detected.

NBI has shown promise in the detection of BE-associated dysplasia[36,37]. In a recent meta-analysis of eight studies including 446 patients and 2194 lesions, NBI demonstrated a pooled sensitivity and specificity of 95% and 65%, respectively, for the detection of BE. The sensitivity and specificity of NBI in detecting HGD was 96% and 94%[38]. Additional studies have demonstrated NBI's superiority in identifying higher grades of dysplasia in comparison to WLE using significantly fewer biopsies per patient[14,17,37]. However, not all studies have shown an improvement in detection of neoplasia using NBI. Kara *et al*[15] found no difference in the detection of HGD and intra-mucosal cancer (IMC) in a tandem study comparing HD-WLE and NBI, although NBI did detect additional lesions in some patients who had neoplasia identified by HD-WLE.

Several studies have focused on the specific mucosal patterns, or pit patterns, associated with BE and BE-associated neoplasia. Hamamoto *et al*[39] described the use of NBI and a pit pattern classification system in BE and reported superior results when magnifying endoscopy was combined with NBI. Several studies of NBI combined with magnification endoscopy have identified irregular microvascular and microstructural patterns with a high sensitivity, specificity and positive predictive value for identification of HGD and cancer[36,37,40]. Singh *et al*[41] demonstrated that presence of a villous or ridged with regular microvasculature was suggestive of IM, while a distorted pit pattern and irregular microvasculature was highly suggestive of dysplasia. A meta-analysis of the various NBI pit pattern classification schemes for BE found a high sensitivity (96%) and specificity (94%) for detection of BE neoplasia when irregular pit patterns and/or microvasculature were identified using NBI with magnification[38].

The advantages of NBI include the ability to study both mucosal and vascular patterns, the ease of use, and integration into standard endoscopic equipment. Limiting the widespread implementation of NBI-targeted biopsies has been the lack of a universal classification system for the mucosal and vascular patterns observed and some studies have shown only moderate interobserver agreement with interpretation of NBI images[40,42].

Electronic chromoendoscopy: Flexible intelligent chromoendoscopy and i-scan

Similar to the principle behind NBI, Flexible Intelligent Chromoendoscopy (FICE) and i-scan are electronic chromoendoscopy techniques that manipulate the red, green, and blue components of light to create an image that enhances the superficial mucosal and vascular structures. FICE has been used in several studies, including one that showed FICE was able to clearly demarcate the junction between Barrett's mucosa and gastric mucosa[43]. In one study comparing FICE and acetic acid chromoendoscopy, FICE was found to have comparable sensitivity to acetic acid chromoendoscopy for detection of BE neoplasia[44]. I-scan has also been used in patient with BE, most recently in a randomized trial comparing the efficacy of endoscopy with 4-quadrant random biopsies and targeted biopsies using i-scan or acetic acid chromoendoscopy[45]. Use of i-scan or acetic acid-guided biopsies produced a significantly

higher diagnostic yield for IM compared to endoscopy with random biopsies. Acetic acid and i-scan showed comparable results for diagnosis of BE.

Autofluorescence imaging

Endogenous tissue fluorophores are biological substances in mucosa that emit fluorescent light when exposed to a light of a shorter wavelength. Autofluorescence imaging (AFI) is based on the principle that different tissue types differ in their fluorescence emission, with normal mucosa appearing green under fluorescence excitation, while dysplasia and neoplasia appears magenta or purple[46]. Differences in fluorescence emission can be examined using a fluorescence-detecting endoscope and these differences in fluorescence can be used for lesion detection and characterization.

AFI is a sensitive but poorly specific tool for the detection HGD and early cancer in BE[47-49]. Studies comparing AFI to white light endoscopy (WLE) found that AFI increased the detection of HGD and IMC compared with WLE, but was associated with a high false positive rate[49]. Subsequent studies have attempted to reduce this false positive rate by combining AFI with NBI, with improvement in one study of patients with BE and suspected neoplasia from false positive rate of 40% to 10% using NBI[48]. The combination of high resolution WLE, AFI and NBI is known as endoscopic trimodal imaging (ETMI), and is not currently available in the United States. An international multicenter study by Curvers *et al*[50] compared ETMI with standard video endoscopy and demonstrated that addition of AFI to HRE increased detection rate of HGD and IMC compared to WLE alone (90% *vs* 53%), but did so at the expense of a high false-positive rate of 81%, which was reduced to 26% with the addition of NBI. Two subsequent large randomized studies from the same group comparing ETMI and WLE failed to show superiority of ETMI over endoscopy with a 4 quadrant random biopsy protocol[19,51]. Furthermore, in these studies random four quadrant biopsies with WLE identified more areas of high grade dysplasia (HGD) and EAC than targeted biopsies after ETMI inspection. The addition of NBI to AFI and HRE reduced the false positive rate in one of the studies, although 17% of dysplastic lesions were re-classified as being normal[51]. While AFI may be useful as an adjunctive technique to WLE, due to its decreased sensitivity and high false positive rate, AFI as a solo method of detection is not suitable to replace the standard BE surveillance biopsy protocol.

MICROSCOPIC ENDOSCOPY

Several advanced endoscopic imaging techniques are available for *in vivo* histological evaluation of the esophageal mucosa, and are used in conjunction with WLE and other advanced endoscopic imaging techniques to identify suspicious lesions that require further evaluation.

Confocal laser endomicroscopy

Confocal laser endomicroscopy (CLE) magnifies the mucosa up to 1000-fold and up to 250 μm below the mucosal surface allowing for real-time histological assessment of the GI mucosa during endoscopy. When evaluating patients with BE, this level of magnification allows for visualization of the specialized IM and goblet cells. Two endomicroscopy platforms have been used for most of the CLE studies of BE, an endoscope based confocal system (eCLE) in which a confocal microscope is integrated into the tip of a standard endoscope and a probe-based system (pCLE), in which a probe is passed through the accessory channel of the endoscope. Both systems use blue laser light and require administration of either topical or intravenous fluorescent contrast agents.

The initial study of eCLE found that BE and BE-associated neoplasia could be identified with a sensitivity of 98.1% and 92.9% and a specificity of 94.1% and 98.4%, respectively[52]. A subsequent prospective randomized controlled crossover trial of eCLE found that CLE with targeted biopsies almost doubled the diagnostic yield for neoplasia compared to a standard biopsy protocol for BE (33% *vs* 17%), with a significant reduction in the number of mucosal biopsies needed for diagnosis. Two thirds of patients in this study undergoing routine surveillance of BE were able to avoid any mucosal biopsies during their CLE procedures[53]. In a subsequent multicenter randomized, controlled trial of eCLE, 192 patients with BE were randomized to either HD-WLE with random biopsies or HD-WLE and CLE with targeted biopsies. In this study, CLE with targeted biopsies outperformed HD-WLE with standard biopsies for detection of neoplasia (22% *vs* 6%) and impacted clinical decision-making (such as the decision to perform endoscopic mucosal resection) in almost 1/3 of patients[54]. Multiple studies have evaluated use of pCLE in patients with BE with promising results. Bertani *et al*[55] found the use of pCLE in addition to WLE enhanced the detection of dysplasia compared with WLE alone (28% *vs* 10%). A multi-center study of 101 patients found the addition of pCLE to HD-WLE improved the diagnostic yield and detection of neoplasia[56]. This study examined the pCLE for *in vivo* prediction of HGD and EAC and found that the addition of pCLE to WLE and NBI increased sensitivity for neoplasia from 45% to 76% and allowed for a reduction in number of biopsies needed for diagnosis[56]. The advantages of CLE, such as the potential for real-time histological diagnosis during an endoscopic procedure, may be offset by the increased procedure length, equipment costs, and the training necessary to interpret the images.

Endocytoscopy

Endocytoscopy allows for real time microscopic imaging of the mucosa using white light and special lenses for

magnification. Images are acquired on the surface of the mucosa after application of a contrast agent, most commonly methylene blue. Surface magnification during endocytoscopy is up to 1400-fold, depending on the endocytoscopy system used and has been used in several studies of squamous esophageal cancer and squamous dysplasia[57]. Studies have reported variable accuracy of endocytoscopy for the detection of neoplasia in a backdrop of BE and the technique has been limited in BE patients by inadequate image quality. In one study evaluating patients undergoing surveillance for BE, image quality was found to be inadequate in 49% of sites imaged at 450-fold magnification and inadequate in 22% of images using 1125-fold magnification[58]. Another study has examined *ex vivo* EMR specimens with endocytoscopy to develop a classification system which showed good accuracy and interobserver agreement. At this time, endocytoscopy is not widely used in management of patients with BE[59].

OTHER LIGHT-BASED TEHCNIQUES

Optical coherence tomography

Optical coherence tomography (OCT) is similar to ultrasound in acquiring tissue images but uses light waves rather than acoustic waves to generate cross-sectional images of epithelial and sub-epithelial tissues based on differences in optical scattering of the tissue structures. OCT does not require tissue contact and images are obtained *via* a catheter introduced through a standard endoscope. One prospective clinical study assessed the presence of dysplasia in BE in 55 patients using 177 biopsy correlated images and found that OCT could detect HGD and EAC with 83% sensitivity and 75% specificity[60]. Several other studies have evaluated a variety of OCT systems and found variable sensitivity, specificity, and accuracy for detection of dysplasia in Barrett's esophagus[61-63].

Optical frequency domain imaging and volumetric laser endomicroscopy

Optical frequency domain imaging (OFDI), also known as volumetric laser endomicroscopy (VLE), allows for high resolution, high-speed acquisition of larger areas of the luminal surface than standard OCT. Preliminary studies with both OFDI/VLE have suggested that differences between normal squamous mucosa, BE, and BE neoplasia can be identified using this technique[64,65]. Recent studies of VLE have focused on interobserver agreement with image interpretation and correlation of VLE images with histology findings[66,67].

Spectroscopy

Spectroscopy uses variation in scattered light across a full spectrum to obtain information about nuclear size, crowding, vascularity and tissue structure and organization. Several types of spectroscopy have been used to study BE, including light-scattering, reflectance and Raman spectroscopy. Light-scattering spectroscopy provides information about cell nuclei characteristics and has demonstrated the ability to detect dysplasia in patients with BE[68,69]. Reflectance spectroscopy measures the color and intensity of reflected light after tissue illumination to help differentiate normal from neoplastic tissue and has also been used in studies of BE[70,71]. Raman spectroscopy detects scattered light that has been changed in wavelength (termed inelastic scattering) and results in characteristic peaks and bands that are correspond with normal *vs* abnormal mucosa. One study reported an accuracy of 96% when using Raman spectroscopy for detecting EAC[72]. In a large study of 373 BE patients, Raman spectroscopy was used for real-time detection of BE and neoplasia with good success[73]. At this time, spectroscopy remains an interesting research technique for patients with BE.

CONCLUSION

In the last decade there have been many advances in the field of endoscopic imaging for the detection of early dysplastic changes and neoplasia in patients with BE. While many of these modalities have demonstrated high sensitivity and specificity in detecting dysplasia and EAC, some limitations to widespread adoption exist. The need for training in image interpretation, inter-observer variability in image interpretation, expensive equipment, and potential increases in procedure length have limited use of these technologies. Technological improvements could make several of these novel endoscopic imaging techniques easier to use, and in time endoscopists may become more comfortable with advanced endoscopic imaging options. In the future, advanced endoscopic imaging techniques could improve care for patients with BE and BE-associated neoplasia by providing more accurate detection of dysplasia and providing real-time histology.

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MINIREVIEWS

Efforts to increase image quality during endoscopy: The role of pronase

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Abstract

Clear visualization of the gastrointestinal mucosal surface is essential for thorough endoscopy. An unobstructed assessment can reduce the need for additional time-consuming manipulations such as frequent washing and suction, which tend to prolong total procedure time. However, mucus, foam, and bubbles often hinder clear visibility during endoscopy. Premedication with pronase, a compound of mixed proteolytic enzymes, has been studied in order to improve mucosal visibility during endoscopy. Although its effects differ according to the location in the stomach, premedication with pronase 10 to 20 min before endoscopy significantly improves mucosal visibility without affecting the accuracy of *Helicobacter pylori* identification. The effects of pronase as premedication also extend to chromoendoscopy, narrow-band imaging, magnifying endoscopy, and endoscopic ultrasonography. In addition, endoscopic flushing with pronase during endoscopy may improve the quantity and the quality of a biopsy to some degree. Although improved mucosal visibility does not necessarily improve clinical outcomes, premedication with pronase may be helpful for increasing the detection rate of early cancers.

Key words: Endoscopy; Premedication; Pronase

Core tip: The present review discusses the role of

pronase in increasing image quality during endoscopy. Premedication with pronase 10 to 20 min before endoscopy significantly improves mucosal visibility without affecting the accuracy of *Helicobacter pylori* identification. The effects of pronase as premedication are also applicable in advanced endoscopic procedures such as narrow-band imaging, magnifying endoscopy, or endoscopic ultrasonography. Although improved mucosal visibility does not necessarily improve clinical outcomes, premedication with pronase may be helpful for increasing the detection rate of early cancers.

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INTRODUCTION

Esophagogastroduodenoscopy (EGD) is commonly performed to diagnose and treat benign and malignant diseases, especially early gastric cancer in the upper gastrointestinal tract. Clear visualization of the gastrointestinal mucosal surface is essential for thorough EGD, particularly when using advanced endoscopic methods such as narrow-band imaging (NBI) or magnifying endoscopy (ME). Furthermore, clear visualization can decrease the need for additional time-consuming manipulations such as frequent washing and suction, which may prolong the total procedure time. In other words, proper premedication before EGD is important to obtain satisfactory visualization of the gastrointestinal mucosa. However, mucus, foam, and bubbles often hinder clear visibility during EGD[1]. To overcome these problems, mucolytic and defoaming agents have been applied in EGD.

In most endoscopic centers, simethicone or dimethylpolysiloxane (DMPS) is commonly used to eliminate bubbles and foam during EGD[1,2]. Simethicone is a mixture of polydimethylsiloxanes that reduces the surface tension of air bubbles and results in the coalescence of small bubbles into larger ones, which may then pass more easily with belching or flatulence[3]. DMPS, which is similar to simethicone, also has the effect of eliminating foam and bubbles. Several studies have shown that simethicone is a suitable premedication to improve the endoscopic view of EGD[4,5]. However, despite premedication with these deforming agents, great deal of mucus can still be encountered during EGD[6].

Pronase, a compound of mixed proteolytic enzymes, was isolated from the culture filtrate of *Streptomyces griseus* in 1962, and has been used as a base material in the preparation of anti-inflammatory and digestive enzymes[7]. Because of its mucolytic effects[8], pronase was used to remove gastric mucus for roentgenographic examination in 1964[9]. It has also been applied as a premedication for endoscopy since 1991[10]. However, the effectiveness of premedication with pronase for improving mucosal visibility during EGD has been the subject of a few clinical trials. Similarly, a limited number of systematic reviews have been performed to address its efficacy in improving mucosal visibility during advanced endoscopy such as NBI or ME as well as conventional endoscopy. Therefore, the aim of this review is to evaluate the role of pronase in increasing imaging quality of various endoscopic examinations based on the published literature.

METHODS TO IDENTIFY STUDIES

Two reviewers (Kim GH and Chung IK) performed a literature search using PubMed and Embase databases. Key words included pronase, premedication, and endoscopy. Relevant review articles were also investigated and additional studies were identified by searching the bibliography of published articles. We focused on studies that described premedication with pronase to increase imaging quality during endoscopy.

THE EFFECTS OF PRONASE ON MUCOSAL VISIBILITY DURING CONVENTIONAL ENDOSCOPY

Table 1 summarizes studies of the effects of pronase as premedication for conventional endoscopy. In most studies, the mucosal visibility score was classified from 1 to 4 (1, no adherent mucus; 2, mild mucus, but not obscuring vision; 3, large amount of mucus obscuring vision; and 4, heavy adherent mucus). All studies showed the superior effects of pronase for improving mucosal visibility in the stomach, but this effect differed according to the location in the stomach. In a recent meta-analysis that included three studies until 2012[11], significant improvement in mucosal visibility was noted only with pronase use in the antrum and fundus. Mucosal visibility in the greater curvature of the upper body did not improve despite pronase premedication, which suggests that this area needs to be cautiously observed[12,13]. In our study, even though the grade of mucosal visibility in the upper body and fundus was high compared to other sites, a significant difference in mucosal visibility grade during EGD was observed in the fundus and upper body of the stomach[7].

Improving visibility can also lead to reduce the need of additional manipulation for washing to clear the surface of the gastrointestinal mucosa, which results in shortening the total EGD procedure time[8,10,13]. However, pronase only induces mucolysis, but itself does not have a defoaming effect. Therefore, if a defoaming agent is used simultaneously as premedication in addition to pronase, it is expected that mucosal visibility will be improved *vs* using pronase alone. In fact, many studies have reported a combination of pronase

Table 1 Summary of studies about premedication with pronase for visualization of the mucosa during conventional endoscopy

Ref.	Year	Study design	Premedication group (*n*)	Mucosal visibility
Fujii *et al*[8]	1998	Prospective	A: DMPS (34) B: DMPS + SB (32) C: DMPS + SB + pronase (34)	C > A, B
Kuo *et al*[6]	2002	Prospective	A: DMPS (34) B: DMPS + water (30) C: Pronase + water (31) D: Pronase + SB + water (32) E: Pronase + SB + DMPS + water (33)	E > A, B, C, D
Chang *et al*[12]	2007	Prospective	A: DMPS (39) B: DMPS + water (35) C: Pronase + SB + DMPS + water (34) D: N-acetylcystein + DMPS + water (39)	C = D > A, B
Bhandari *et al*[30]	2010	Prospective	A: Drinking of simethicone + pronase + water (35) B: Endoscopic flushing of simethicone + water (37) C: Endoscopic flushing of simethicone + pronase + water (40)	A > B, C
Lee *et al*[13]	2012	Prospective	A: DMPS + SB + pronase within 10 min (100) B: DMPS + SB within 10 min (100) C: DMPS + SB + pronase within 20 min (100) D: DMPS + SB within 20 min (100)	A = C > B, D
Woo *et al*[26]	2013	Prospective	A: Pronase + SB + DMPS within 10 min (98) B: Pronase + SB + DMPS between 10-30 min (97) C: Pronase + SB + DMPS at 30 min (99)	A = B > C
Kim *et al*[7]	2015	Prospective	A: Simethicone + SB + pronase (71) B: Simethicone (72)	A > B

DMPS: Dimethylpolysiloxane; SB: Sodium bicarbonate.

with defoaming agents such as DMPS significantly improves visibility during conventional endoscopy or chromoendoscopy[6,8,10]. Therefore, when pronase is used to improve visibility during EGD, we recommend the concurrent use of a defoaming agent.

THE EFFECTS OF PRONASE ON MUCOSAL VISIBILITY DURING ADVANCED ENDOSCOPY

Table 2 summarizes studies that explored the effects of pronase as premedication for advanced endoscopy.

Chromoendoscopy

Chromoendoscopy requires a clear field in order for the dye to bind to the targeted mucosa rather than the overlying mucus[14,15]. Gastric mucus prevents the dye from spraying onto the gastric mucosa and is a frequent source of artifacts during endoscopic imaging. The mucolytic effect of pronase during conventional endoscopy is sustained during chromoendoscopy. In a randomized controlled trial of chromoendoscopy with methylene blue, premedication with pronase came to significantly improve the visibility of the gastric wall both before and after methylene blue spraying and also to significantly shorten the time of the chromoendoscopic examination[8].

NBI and ME

Recently, NBI has been reported to improve the visibility of mucosal structure and the accuracy of detection for precancerous conditions[16]. Like conventional endoscopy, the presence of foam, bubbles, or mucus on the gastric mucosa can obstruct mucosal visualization during NBI endoscopy. Therefore, a premedication with defoaming and mucolytic agents can be an effective method to improve visibility and possibly the diagnostic performance of NBI endoscopy. In our study comparing the visibility score and diagnostic performance of NBI endoscopy for patients with precancerous conditions with or without pronase premedication, a combination of pronase with simethicone significantly improved visibility during NBI endoscopy in the proximal part of the stomach, and it also improved the negative predictive value of NBI endoscopy compared with that of white light endoscopy[17].

ME with NBI (ME-NBI) is reported to have high accuracy for diagnosing corpus gastritis, intestinal metaplasia and early gastric cancer[18-21]. In particular, the microvascular and microsurface patterns observed during ME-NBI are clinically helpful for distinguishing cancerous from noncancerous lesions. As mucosal visibility during EGD is essential in finding subtle mucosal abnormalities associated with early neoplasia, mucosal visibility is especially important during ME-NBI in that this procedure has time-consuming and complicated nature. In a randomized study, we showed that premedication with pronase improved mucosal visibility during ME-NBI of the stomach and reduced the frequency of water flushing needed to clear the mucosa[7].

Endoscopic ultrasonography

Endoscopic ultrasonography (EUS) plays an important

Table 2 Summary of studies about premedication with pronase for visualization of the mucosa during advanced endoscopy

Examination	Ref.	Year	Study design	Premedication group (*n*)	Mucosal visibility
Chromoendoscopy	Fujii *et al*[8]	1998	Prospective	A: DMPS (34) B: DMPS + SB (32) C: DMPS + SB + pronase (34)	C > A, B
NBI endoscopy	Cha *et al*[17]	2014	Prospective	A: Pronase + SB (28) B: Simethicone (27)	A > B
ME-NBI	Kim *et al*[7]	2015	Prospective	A: Simethicone + SB + pronase (71) B: Simethicone (72)	A > B
EUS	Sakai *et al*[24]	2003	Prospective	A: DMPS (29) B: DMPS + SB (29) C: DMPS + SB + pronase (29)	C > A, B
	Han *et al*[25]	2011	Prospective	A: Saline (60) B: Pronase + SB (62) C: Pronase + SB + simethicone (61)	B > A > C

NBI: Narrow-band imaging; ME-NBI: Magnifying endoscopy with narrow-band imaging; EUS: Endoscopic ultrasonography; DMPS: Dimethylpolysiloxane; SB: Sodium bicarbonate.

role in assessing benign and malignant gastrointestinal diseases. It is especially useful for diagnosing subepithelial lesions and the staging of early gastric cancer[22,23]. However, artifacts caused by gastric mucus can potentially affect visibility during EUS, which inhibits the ability to evaluate superficial mucosal lesions. Reducing gastric cavity and mucosal surface artifacts caused by mucus may be helpful in improving EUS performance. A randomized study evaluating the effect of pronase in improving EUS images showed that premedication with pronase reduced artifacts during EUS *via* a mucolytic effect that disrupts the surface mucus gel layer of the stomach[24]. In another similar randomized controlled study, premedication with pronase decreased the number of gastric wall and lumen hyperechoic artifacts observed in patients given either saline solution or pronase/simethicone[25]. Unlike pronase, the use of simethicone led to turbidity and echogenicity, which did not improve visibility during EUS. Although a more accurate diagnosis is not necessarily gleaned from better-quality images, obtaining good EUS images through premedication with pronase may lead to improve the diagnostic accuracy for superficial mucosal lesions during EUS.

CONSIDERATIONS IN USING PRONASE AS PREMEDICATION

To improve the effect of pronase on removing gastric mucus, several factors must be considered[10]. First is intragastric pH. Mucolysis by pronase is found to be maximal at pH 6 to 8. Therefore, it is necessary to neutralize the acidity of the gastric juice with a neutralizer such as sodium bicarbonate and to prevent subsequent hypersecretion of gastric juice with an anticholinergic agents such as scopolamine butylbromide[8]. The second consideration is the amount of pronase and the volume of oral solution. Based on previous findings[6,8,10,13], 2000 units or more (usually 20000 units) of pronase and 80 mL to 100 mL of oral solution are needed to achieve adequate effects. The third consideration relates to position change of the patient. Rotation from supine, left or right lateral, to prone position several times is helpful for completely removing gastric mucus[8]. However, in two recent studies, similar effects of pronase were shown without position changes before EGD[12,13]. The argument for not changing position before EGD stems from the fact that the ingested solution flows into the gastric fundus, then gradually into the gastric antrum by the way of the gastric body after premedication with pronase.

When is the optimal time for taking pronase to maximize its mucolytic effect before EGD? In previous studies, premedication with pronase was administered 10 to 20 min before EGD[8,12]. In a recent study comparing premedication times of 10 min and 20 min before EGD, mucosal visibility score did not differ between the two groups[13]. In another recent study evaluating the optimal time of medication with pronase, administration of pronase within 30 min before EGD significantly improved endoscopic visualization compared to administration at 30 min before EGD[26]. These results suggest that if pronase is given within 30 min before EGD, the duration of premedication does not play a significant role in satisfactory mucosa visualization.

OTHER ADDITIVE EFFECTS OF PRONASE

Effect of pronase on Helicobacter pylori

Because *Helicobacter pylori* (*H. pylori*) strains reside in the surface mucous gel layer as well as on the surface of gastric epithelial cells, premedication with pronase could reduce the accuracy of *H. pylori* identification in biopsy specimens *via* its mucolytic effect. However, the use of pronase seems not to influence the identification of *H. pylori* by culture and rapid urease test of biopsy specimens in many studies[6,8,12].

Pronase can disrupt gastric mucus and so reduce the thickness of the surface mucous gel layer, which enhances drug delivery to improve the eradication

rate of *H. pylori*[6,27,28]. Therefore, it is assumed that supplements of pronase in addition to anti-*H. pylori* regimen could increase the eradication rate of *H. pylori*. Earlier randomized controlled studies showed the additive effect of pronase in improvement of *H. pylori* eradication rates[27,28], but a recent randomized controlled study did not confirm this effect[29].

Effect of pronase on gastric biopsy

Although pronase improves visibility, a patient's positioning may prevent it from reaching some portions of the stomach in sufficient quantity. In these situations, the endoscopist aid distribution to the target lesion through endoscopic flushing of pronase. Although endoscopic flushing is not able to provide equivalent improvements in mucosal visibility during EGD when compared with the oral administration of pronase[30], it can be helpful for improving the visibility of a target lesion. Furthermore, patients receiving endoscopic flushing with pronase in a limited area exhibited decrease in thickness of mucus, increase in depth of biopsy, improved anatomical orientation, and improved overall diagnostic assessment of the second biopsy specimens compared with a control group[31]. Therefore, endoscopic flushing with pronase during EGD can be recommended in order to improve the quantity and quality of endoscopic biopsies.

CONCLUSION

During EGD, foam, bubbles, and mucus often obstruct visibility. Premedication is therefore usually administered prior to an endoscopic procedure in order to remove foam and mucus. Satisfactory visibility achieved through premedication with proper agents can reduce the need to carry out flushing during the procedure, thus shortening the duration of an endoscopy. The use of pronase as premedication improves mucosal visualization in advanced endoscopy as well as in conventional endoscopy without affecting the accuracy of *H. pylori* identification. Although the use of pronase does not necessarily result in a higher detection rate of early cancers or improve clinical outcomes, improved mucosal visibility may be helpful for increasing the detection rate of early cancers. Large randomized clinical trials will be needed to confirm the utility of pronase for identifying early cancers.

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MINIREVIEWS

Raman spectroscopy for early real-time endoscopic optical diagnosis based on biochemical changes during the carcinogenesis of Barrett's esophagus

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Author contributions: Shi H and Chen SY were responsible for the study concept and design; all authors conducted endoscopic operations together; Chen SY and Lin K drafted the manuscript; Shi H revised and finalized the manuscript.

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Abstract

Raman spectroscopy is a spectroscopic technique based on the inelastic scattering of monochromatic light that represents the molecular composition of the interrogated volume to provide a direct molecular fingerprint. Several investigations have revealed that confocal Raman spectroscopy can differentiate non-dysplastic Barrett's esophagus from esophageal high-grade dysplasia and adenocarcinoma with high sensitivity and specificity. An automated on-line Raman spectral diagnostic system has made it possible to use Raman spectroscopy to guide accurate target biopsy instead of multiple random forceps-biopsies, this novel system is expected to improve *in vivo* precancerous diagnosis and tissue characterization of Barrett's esophagus.

Key words: Raman spectroscopy; Barrett's esophagus; Confocal; High-grade dysplasia; Diagnosis

Core tip: Raman spectroscopy is a very sensitive tool to detect subtle biochemical and molecular changes, which is crucial for differentiating nondysplastic from high-grade dysplastic Barrett's esophagus. With an increased accuracy of updated algorithms and a real time automatic analysis system, Raman spectroscopy is expected to improve *in vivo* precancerous diagnosis and tissue characterization of Barrett's esophagus.

Shi H, Chen SY, Lin K. Raman spectroscopy for early real-time endoscopic optical diagnosis based on biochemical changes during the carcinogenesis of Barrett's esophagus. *World J Gastrointest Endosc* 2016; 8(5): 273-275 Available from: URL: http://www.wjgnet.com/1948-5190/full/v8/i5/273.htm DOI: http://dx.doi.org/10.4253/wjge.v8.i5.273

INTRODUCTION

Confirmed by the presence of intestinal metaplasia with or without goblet cells from a squamous to a columnar-lined esophageal epithelium[1,2], Barrett's esophagus is a metaplastic precursor of esophageal adenocarcinoma. Given the poor prognosis that has remained relatively constant, with current 5-year survival rates of only 8% to 15%[3], early identification of Barrett's esophagus associated with high-grade dysplasia followed by targeted endoscopic resection is the most critical measure to prevent progression to invasive esophageal malignancy[4]. According to the current diagnostic guidelines, patients with Barrett's esophagus are recommended to undergo strict biopsy samplings (typically 4-quadrant random samplings) for every 2 cm of Barrett's mucosa during endoscopic surveys at intervals of 3 to 5 years. This approach may produce a large number of negative biopsies and increase the risk of bleeding. Considering the elevated incidence of esophageal adenocarcinoma, the need for new advanced endoscopic technologies that can transition standard Barrett's esophagus surveillance from random biopsies to a real-time "optical biopsy" is imperative.

Optical spectroscopy is a technique that utilizes microstructural information contained in light-tissue interactions to enhance suspicious tissue recognition during standard endoscopy[5], including fluorescence, elastic scattering, and inelastic (Raman) scattering.

Principle of raman spectroscopy

Raman spectroscopy represents a unique optical vibrational technique based on the inelastic scattering of a monochromatic laser light source. Inelastic scattering is a phenomenon in which the frequency of the scattered photon is shifted up or down with respect to the incident excitation light depending on the specific vibrational motions of the molecules in the tissue being interrogated, which is called the Raman effect. This shift of frequency provides unique information on the scattering molecules.

Taking the unique advantage of the ability of Raman spectroscopy to harvest a wealth of direct molecular fingerprint information from inter and/or intracellular components such as proteins, lipids, carbohydrates and DNA in cells and tissue, Raman spectroscopy has shown great promise for histo-pathologic assessments at the biochemical and molecular levels[6]. Because the progression from non-dysplastic Barrett's esophagus to esophagus adenocarcinoma manifests a progressive series of molecular and biochemical changes, Raman spectroscopy may provide the capability to analyze the carcinogenesis process. Furthermore, the majority of biological molecules are Raman active, each with its own unique fingerprint. As a result, Raman spectroscopy is a very sensitive tool to detect subtle biochemical and molecular changes, which is crucial for differentiating nondysplastic from high-grade dysplastic Barrett's esophagus.

Overall configuration of the raman spectroscopy system

Briefly, the Raman spectroscopy system consists of four major components[6]: A light generator (near-infrared diode laser); light collection optics; a wavelength selector (filter or spectrophotometer); and a detector (photodiode array, charge coupled device or photomultiplier tube). Compared with an ultraviolet ray illumination source, near infrared excitation not only minimizes spectral disruption from tissue fluorescence but also produces reduced mutagenic effects and deeper penetration capability.

The combination of Raman spectroscopy and an endoscopic system is realized by a Raman probe, which is coupled to an optical cable containing the excitation and collection fibers, with an outer diameter enabling easy passage through the instrument channel of an endoscope. Currently, the two novel confocal Raman probes[3,4] have the following advantages: They ensure the precise interrogation of the epithelium (with a volume of < 0.02 mm^3), which is closely related to early onset of Barrett's carcinogenesis, because the ratio of the epithelium to stromal Raman photons collected is 19-fold higher than that collected using previous volume-type Raman probes; and they provide the capacity for reproducible and objective Raman measurements achieved in a direct contact mode.

Clinical application

Water molecules, the predominant constituents of living tissue, have a negligible influence on Raman signals due to the limited change in the polarity of the -OH bond, which enables Raman spectroscopic analysis of fresh, unprepared tissue, both *ex vivo* and *in vivo*.

Robles[5] summarized some clinical research on Raman spectroscopic technology for classification of malignant changes in Barrett's esophagus, carried out by two groups, from Gloucestershire Royal Hospital[3], United Kingdom and the National University of Singapore[4], Singapore. The latter demonstrated for the first time that confocal Raman spectroscopy can be used to target dysplasia identification and subsequent biopsy in Barrett's esophagus in real-time, which has also been used to diagnose gastric[7] and colorectal[8] lesions. The characteristics of the two abovementioned confocal probes were compared and listed in Table 1.

At present, most biomedical Raman research on pre-cancer and early cancer diagnosis remain focused on the fingerprint (FP) Raman spectra, which contain rich biochemical information regarding the tissue; however, some extremely weak tissue Raman signals in certain organ sites may be overwhelmed by the tissue autofluorescence (AF) background. Because the high-wavenumber (HW) Raman spectral range exhibits stronger tissue Raman signals with less AF interference, it has been integrated with the FP Raman spectra to improve the real-time *in vivo* diagnosis of esophageal squamous cell carcinoma (ESCC) during endoscopic examination, resulting in a predictive diagnostic sensitivity of 92.7% and specificity of 93.6% for ESCC

Table 1 Comparison of two endoscopic confocal raman spectroscopic systems

Technical parameters	Developed by Almond *et al*[3]	Developed by Bergholt *et al*[4]
λex	830 nm	785 nm
Diameter of probe	2.7 mm	1.8 mm
Range of Raman spectra	400-1850 cm^{-1}	800-1800 cm^{-1}
Acquisition times	1 s	0.2 s
Classification model	Principal component fed linear discriminant analysis	Partial least-squares discriminant analysis[9]
Diagnostic way	*Ex vivo*	Real-time *in vivo*
Sensitivity and specificity for detecting HGD in BE	86% and 88%	87.0% and 84.7%

HGD: High grade dysplasia; BE: Barrett's esophagus.

identification[10].

CONCLUSION

Despite some limitations, such as only identifying molecular features, susceptibility to interference of fluorescence from impurities or from the sample itself, and thermal damage to tissues, confocal Raman spectroscopy uncovers the biochemical and molecular changes occurring in the epithelium during Barrett's carcinogenesis. This technique is expected to improve *in vivo* precancerous diagnosis and tissue characterization of Barrett's esophagus with increased accuracy based upon updated algorithms and the on-line real time automatic analysis system.

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ORIGINAL ARTICLE

Retrospective Study

Endoscopic mucosal resection of colorectal adenomas > 20 mm: Risk factors for recurrence

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Author contributions: Briedigkeit A collected and analyzed the data, and drafted the manuscript; Sultanie O and Sido B provided analytical oversight; Dumoulin FL performed EMRs and designed and supervised the study; all authors have read and approved the final version to be published.

Institutional review board statement: The study was approved by the Institutional Review Board of the Gemeinschaftskrankenhaus Bonn (Chair Bremekamp C). A formal ethical approval is not required for retrospective studies by German Federal Law. This statement may be verified by contacting the chairman of the Ethics Committee of the University of Bonn (Professor Racké K, email: ethik@uni-bonn.de).

Informed consent statement: All patients gave informed consent for an anonymized data analysis along with the informed consent for interventional endoscopy. According to German Federal Law informed consent of patients is not required for retrospective data analysis.

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Data sharing statement: An anonymized dataset is available from the corresponding author at the email address given below.

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Abstract

AIM: To evaluate risk factors for local recurrence after endoscopic mucosal resection of colorectal adenomas > 20 mm.

METHODS: Retrospective data analysis of 216 endoscopic mucosal resections for colorectal adenomas > 20 mm in 179 patients (40.3% female; median age 68 years; range 35-91 years). All patients had at least 1 follow-up endoscopy with a minimum control interval of 2 mo (mean follow-up 6 mo/2.0-43.4 mo). Possible factors associated with local recurrence were analyzed by univariate and multivariate analysis.

RESULTS: Median size of the lesions was 30 mm (20-70 mm), 69.0% were localized in the right-sided (cecum, ascending and transverse) colon. Most of the lesions (85.6%) showed a non-pedunculated morphology and the majority of resections was in piecemeal technique (78.7%). Histology showed carcinoma or high-grade intraepithelial neoplasia in 51/216 (23.6%) lesions including 4 low risk carcinomas (pT1a, L0, V0, R0 - G1/G2). Histologically proven recurrence was observed in 33/216 patients (15.3%). Patient age > 65 years, polyp size > 30 mm, non-

pedunculated morphology, localization in the right-sided colon, piecemeal resection and tubular-villous histology were found as associated factors in univariate analysis. On multivariate analysis, only localization in the right-sided colon (HR = 6.842/95%CI: 1.540-30.394; *P* = 0.011), tubular-villous histology (HR = 3.713/95%CI: 1.617-8.528; *P* = 0.002) and polyp size > 30 mm (HR = 2.563/95%CI: 1.179-5.570; *P* = 0.017) were significantly associated risk factors for adenoma recurrence.

CONCLUSION: Meticulous endoscopic follow-up is warranted after endoscopic mucosal resection of adenomas localized in the right-sided colon larger than > 30 mm, with tubular-villous histology.

Key words: Colorectal adenoma; Endoscopic mucosal resection; Piecemeal resection; Local recurrence rate; Tubular-villous adenoma

Core tip: Endoscopic mucosal resection of larger adenomas is burdened with relatively high rates of local recurrence. In this retrospective analysis, size > 30 mm, non-pedunculated morphology, right-sided localization, piecemeal resection and histology were all associated with local recurrence. In addition, right-sided localization, tubular-villous histology and size > 30 mm were independently associated with local recurrence. These findings emphasize the necessity of meticulous endoscopic follow-up, they might also argue in favor of *en bloc* resection of larger colorectal lesions, in particular in the right-sided colon.

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INTRODUCTION

Screening colonoscopy and removal of detected adenomas is now recognized as an effective measure to prevent colorectal cancer[1-3]. However, efficacy of screening endoscopy is hampered not only by a low adenoma detection rate but also by incomplete removal of advanced adenomas[4].

Endoscopic mucosal resection (EMR) is the current standard for the treatment of colorectal adenomas in Western countries[5-7]. While widely used, EMR is burdened by incomplete adenoma resections even for smaller lesions up to 20 mm[8]. The technique is also used for lesions > 20 mm where it is performed in piecemeal technique, *i.e.*, the adenoma is removed in fragments. As a consequence of fragmentation it is impossible to histologically confirm the completeness of resection. Endoscopic control is therefore recommended after 2-6 mo by current guidelines[9-12]. Reported recurrence rates during endoscopic follow-up vary from 5%-27% in retrospective studies[13-23]. In a recently published well-conducted prospective study the recurrence rate was 32%[24]. Since the majority of colorectal lesions harbors only low-grade intraepithelial neoplasia, local recurrence is usually not viewed as a treatment failure[22,25]. Nevertheless, all patients need close endoscopic observation and those with recurrences often need several EMR interventions during follow-up[26]. Moreover, there is a concern about late local recurrences and even subsequent cancer after a negative first control endoscopy[13,22,24,27]. Many of these problems could be overcome by the use endoscopic submucosal dissection (ESD) - which allows *en bloc* resection of larger adenomas, but colorectal ESD is still largely considered an experimental therapy in the Western world[11].

Several risk factors for local recurrence after EMR (*e.g.*, lesion size, localization, morphology, resection in piecemeal technique, histological features) have been reported in retrospective studies[18,22,28-30]. The purpose of this study was to analyze risk factors in a cohort of larger colorectal adenomas with preferentially right-sided localization. The results of this study should have an impact on the choice of the resection strategy (*e.g.*, EMR *vs* ESD *vs* laparoscopic surgery) as well as on the intensity of endoscopic follow-up.

MATERIALS AND METHODS

Patients and data collection

A single experienced interventional endoscopist (FLD) performed 688 EMRs over a five-year period (03/2008-03/2013). Of these, 216 EMRs in 179 patients, 87 female (40.3%) and 129 male (59.7%), with a median age of 68 years (35-91) met the inclusion criteria of polyp size > 20 mm, at least one endoscopic control 2-6 mo after EMR and sufficient data of follow-up examinations. The median follow-up time was 6 mo (range: 2-43.4 mo).

EMR procedure

EMRs were carried out under conscious sedation with propofol (B Braun Melsungen, Melsungen, German) and occasionally midazolam (Roche Pharma AG, Basel, Switzerland) using standard endoscopes (GIF 1-TQ160, CF-H180 AL, PCF 180 AL; Olympus Europe, Hamburg Germany). After detailed endoscopic inspection, lesions were classified according to the Paris classification[31] and the size of the lesion was estimated by comparison to an opened snare. Submucosal injection of normal saline with 0.01% indigo carmine (Novaplus, Lake Forrest, IL, United States) was performed with a small bore injector needle (25G, Olympus Europe, Hamburg, Germany). EMR was then carried out with different snare types according to the size and shape of the lesions (Snaremaster®, Olympus Europe, Hamburg,

Table 1 Characteristics of the resected lesions *n* (%)

No. of polyps	*n* = 216
Size (median/range)	30 mm (20.0-70.0)
Localization	
Right-sided colon (cecum, ascending, transverse)	149 (69.0)
Left-sided colon (descending, sigmoid) or rectum	67 (31.0)
Morphology of polyps (Paris classification[31])	
Pedunculated (0-Ip)	31 (14.4)
Non-pedunculated (0-Is; 0-IIa/b/c)	185 (85.6)
Resection in piecemeal technique	170 (78.7)
Final histology	
Low-risk invasive adeno-carcinoma	4 (1.9)
Tubular-villous adenoma	102 (47.2)
Tubular adenoma	65 (30.1)
Serrated adenoma	45 (20.8)

Germany; Acusnare®, Cook Medical Germany, Mönchengladbach, Germany) using standard power settings on an Erbe VAIO 200S electrosurgical unit (Erbe Elektromedizin, Tübingen, Germany). Careful APC coagulation of resection bed or margins was performed if deemed necessary. Resected specimens were retrieved and fixed in phosphate buffered formaldehyde solution for histopathology. To prevent delayed bleeding hemoclips (EZ clip; Olympus Europe, Hamburg, Germany) were used in most procedures.

Endoscopic follow-up after EMR

According to the German S3 guideline on colorectal carcinoma[11] control endoscopies were done 2-6 mo after EMR. If longer follow-up endoscopies without signs of recurrence were available the longest follow-up interval was counted.

Statistical analysis

Univariate (Kaplan Meier) analysis was carried out to describe the distributions of baseline variables. Cox regression analysis was then used to evaluate various combinations and interactions of prognostic variables in a multivariate manner. Data analysis was done using the SPSS package (student's edition; SPSS Inc. Somers, NY, United States). A P value < 0.05 was considered statistically significant.

RESULTS

A total of 216 adenomas with a median size of 30 mm (range 20-70 mm) were resected. Most adenomas were localized in the right-sided colon (69%), had a flat or sessile morphology (85.6%) and were resected in piecemeal technique (78.7%). Histological analysis revealed tubular adenoma (30.1%), tubular-villous adenoma (47.2%), serrated adenoma (20.8%) and invasive cancer in four lesions (1.9%). High-grade intraepithelial neoplasia was detected in 47 lesions (21.8%). While piecemeal fragments did show lateral margins with adenoma tissue, positive vertical margins were not detected. All four colorectal cancers were low risk (pT1a, L0, V0, R0 - G1/G2) and did not recur during follow-up (Tables 1 and 2).

Table 2 Histology by localization of the lesions *n* (%)

Histology	Right-sided colon (*n* = 149)	Left-sided colon (*n* = 67)
Low-risk invasive adeno-carcinoma	1 (0.7)	3 (4.5)
Tubular-villous adenoma	63 (42.3)	39 (58.2)
Tubular adenoma	42 (28.2)	23 (34.3)
Serrated adenoma	43 (28.9)	2 (3.0)

After a median follow-up interval of 6 mo (range 2-43.4) a total number of 33 recurrences were detected, resulting in a local recurrence rate of 15.3%. All recurrences showed the same histology as the initially resected lesion and by the time of writing all patients with recurrences had been treated endoscopically by EMR and/or argon plasma coagulation. Univariate (Kaplan-Meier) analysis (Table 3) detected significant differences in the recurrence rates for age group (< 65 years: 11.4%/> 65 years: 19.2%), adenoma size (< 30 mm: 12.4%/> 30 mm: 22.2%), localization (left-sided colon: 3.0%/right-sided colon: 20.8%), morphology (pedunculated: 0%/non-pedunculated: 17.8%), resection technique (*en bloc*: 6.5%/piecemeal: 17.6%) and histology (tubular, serrated, carcinoma: 7.1%/ tubular-villous 24.3%) but not for time interval of follow-up or histology of serrated adenoma. On multivariate (Cox regression) analysis only localization in the right-sided colon (HR = 6.842), histology of tubular-villous adenoma (HR = 3.713) and size > 30 mm (HR = 2.563) were independently associated with local recurrence. We did not detect an association of recurrence with high-grade intraepithelial neoplasia (OR = 0.549/95%CI: 0.193-1.562; P = 0.279) (Table 4).

DISCUSSION

In this retrospective analysis of EMRs for 216 large colorectal adenomas (median size 30 mm) with preferential proximal localization (69% right-sided colon) we observed a recurrence rate of 15.3% after a median follow-up of 6 mo. Univariate analysis showed significantly higher recurrence rates for patient age > 65 years, adenoma size > 30 mm, proximal localization, non-pedunculated morphology, resection in piecemeal technique and tubular-villous histology. Multivariate analysis revealed only adenoma size > 30 mm, right-sided localization and tubular-villous histology as risk factors independently associated with local recurrence.

Many of the above mentioned factors have been described in the literature (Table 5). Interestingly, and in contrast to most other reports, the strongest risk factor for adenoma recurrence identified in this study was a right-sided localization (HR = 6.842). These findings are in line with data from Cipolletta *et al*[30] who reported a similar association for lesions with predominantly right-sided localization. In the present study, 69% of the lesions were located in the right-sided colon and the

Table 3 Risk factors for recurrence (univariate analysis)[1]

Variable	Recurrence (fraction/%)	OR (95%CI)	*P* value[2]
Age			
< 65 yr	10/96 (11.4%)	2.492	0.011
> 65 yr	23/120 (19.2%)	(1.182-5.252)	
Size			
< 30 mm	19/153 (12.4%)	2.472	0.005
> 30 mm	14/63 (22.2%)	(1.233-4.957)	
Morphology			
Paris 0-Ip (pedunculated)	0/31 (0%)	26.386	0.018
Paris 0-Is, 0-II a, b, c (sessile/flat)	33/185 (17.8%)	(0.473-1472.565)	
Localization			
Right-sided colon	31/149 (20.8%)	7.475	0.002
Left-sided colon or rectum	2/67 (3.0%)	(1.787-31.264)	
Resection technique			
Piecemeal (fragmented)	30/170 (17.6%)	3.741	0.01
En bloc	3/46 (6.5%)	(1.139-12.292)	
Histology			
Tubular-villous adenoma	25/103 (24.3%)	3.417	0.002
Tubular, serrated, carcinoma	8/113 (7.1%)	(1.533-7.614)	

[1]The overall recurrence rate was 33/216 (15.3%); [2]As calculated with the Kaplan-Meier method.

Table 4 Risk factors for recurrence (multivariate analysis)[1]

Variabel	HR (95%CI)	*P* value
Size > 30 mm	2.563 (1.179-5.570)	0.017
Localization right-sided colon	6.842 (1.540-30.394)	0.011
Histology tubular-villous adenoma	3.713 (1.617-8.528)	0.002

[1]The factors age, morphology, resection technique were not significant in multivariate analysis.

Table 5 Reported associations with adenoma recurrence from the literature

Ref.	Lesions (*n*)	Size	Localization	Piecemeal resection
Luigiano *et al*[14]	148	> 40 mm		
Lim *et al*[28]	239		Left-sided	
Mannath *et al*[29]	121			Yes
Sakamoto *et al*[18]	222			Yes (> 5 pieces)
Woodward *et al*[19]	423			Yes
Cipolletta *et al*[30]	1012	> 30 mm	Right-sided	Yes
Moss *et al*[22]	799	> 40 mm		
Oka *et al*[23]	1029	> 40 mm		Yes
Briedigkeit *et al* (this study)	216	> 30 mm	Right-sided	Yes (univariate only)

recurrence rate was 20.9% (*vs* 3.0% for localization in left-sided colon or rectum). Our interpretation is, that this association is driven by the higher technical difficulty for the treatment of right-sided lesions, resulting in lower complete resection rates, in particular since all pedunculated lesions were localized in the left-sided colon. Since relatively high recurrence rates have been reported after resection of serrated lesions[8] it is tempting to speculate on a correlation of a serrated histology with local recurrence rates but in the current study we did not find any statistically significant association. Interestingly, contradictory findings with higher recurrence rates for left-sided rather than right-sided localization have been reported from a retrospective study with predominantly left-sided adenomas[28]. Thus, the diverging findings most probably reflect a difference in the study population, in particular with respect to adenoma characteristics (size, localization, morphology, *en bloc* resection rate), rather than true differences.

In addition, a larger size of the lesion[14,22,23,30] and resection in piecemeal technique[19,23,29,30] or a resection in more than 5 fragments[18] have been reported as risk factors for recurrence. Our findings of a significant association of piecemeal resection (univariate analysis only) and of adenoma size > 30 mm (multivariate) with local recurrence after EMR are in complete agreement with the aforementioned studies.

Finally, we identified tubular-villous histology as a risk factor for local recurrence. Since tubular-villous adenoma represents a more advanced neoplastic lesion these data are in line with Lim *et al*[28] who reported an association of recurrence with high-grade intraepithelial neoplasia (not significantly associated in our dataset). Such associations could reflect biological differences between the different types of histology (serrated *vs* tubular *vs* tubular-villous) but the study size was probably to small to definitively address such differences in greater detail. The same holds true for age, morphology and resection technique with significant associations only on univariate but not on multivariate analysis.

The presented study has several limits. In particular, the retrospective design and the relatively short follow up interval (which results from the current guideline in our country[11]) might have underestimated the true recurrence rate. In addition, the relatively low number of adenoma recurrences could have reduced the probability of correctly identifying associated risk factors. Nevertheless, the data underscore the necessity of meticulous endoscopic follow-up, in particular after EMR of larger adenomas with right-sided localization and tubular-villous histology, and probably also for adenomas resected in piecemeal technique. In these situations alternative procedures with higher *en bloc* resection rates such as colorectal ESD[23,32] or laparoscopic surgery should be considered.

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COMMENTS

Background

Endoscopic mucosal resection of colorectal adenomas is the standard treatment in the Western world. However, the effectiveness for endoscopic mucosal resection (EMR) is limited for larger adenomas with reported recurrence rates of more than 30%.

Research frontiers

The identification of risk factors associated with local adenoma recurrence may be useful to identify patients in need for a more intensive follow-up and - possibly - to guide treatment methods.

Innovations and breakthroughs

This study shows an increased risk for recurrence after EMR of adenomas with proximal localization, lager size (> 30 mm) and tubular-villous histology.

Applications

The results can be used to determine the follow-up strategy, which should be more stringent for adenomas with the above-mentioned criteria. Moreover, resection strategy for colorectal adenomas with particular high recurrence risk should preferably be an *en bloc* resection (either by endoscopic submucosal dissection or laparoscopic surgery).

Peer-review

The study is a well written paper, addressing an important issue regarding treatment of these borderline lesions.

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