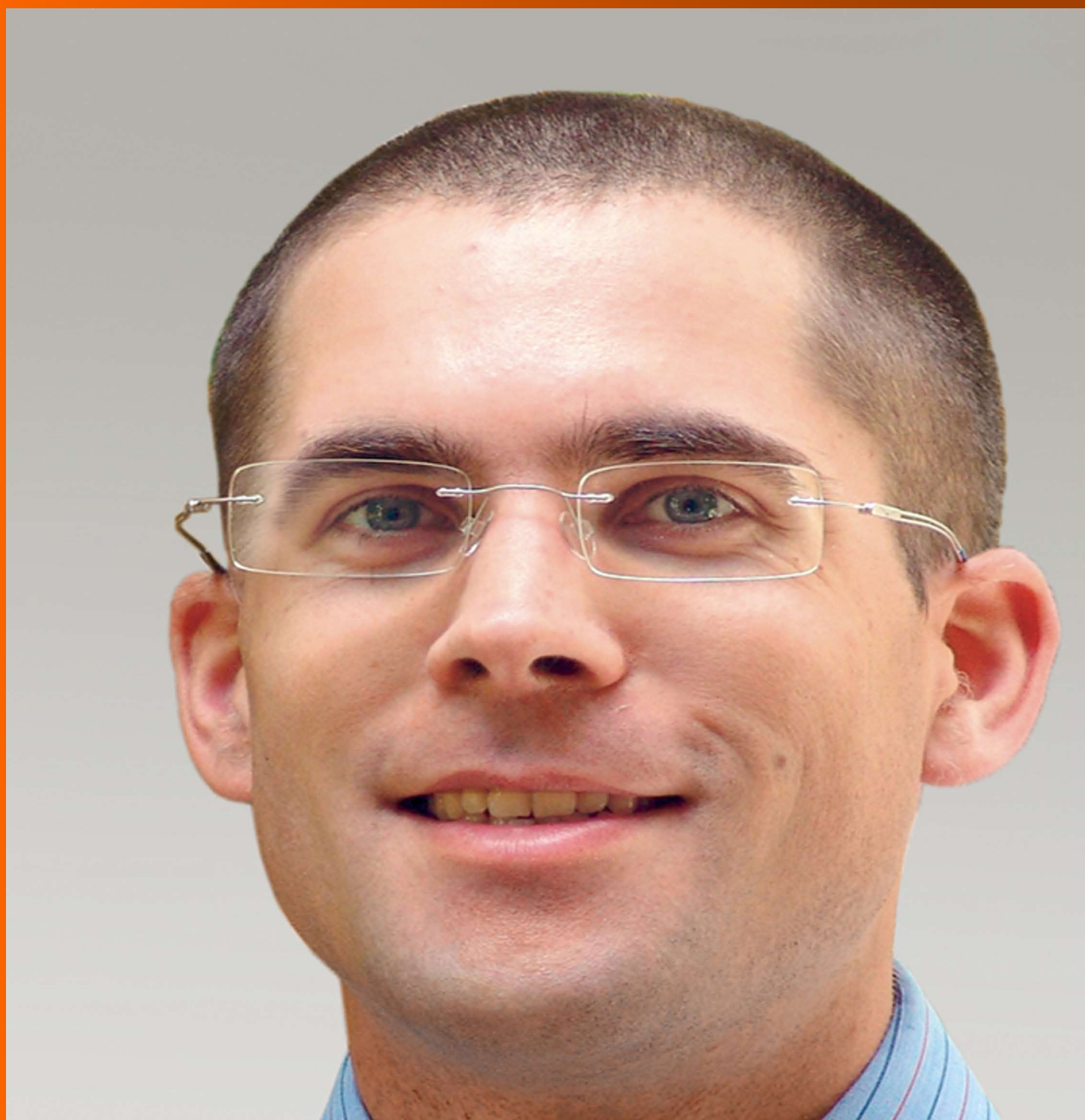


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Terahertz endoscopic imaging for colorectal cancer detection: Current status and future perspectives

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Abstract

Terahertz (THz) imaging is progressing as a robust

platform for myriad applications in the field of security, health, and material science. The THz regime, which comprises wavelengths spanning from microns to millimeters, is non-ionizing and has very low photon energy: Making it inherently safe for biological imaging. Colorectal cancer is one of the most common causes of death in the world, while the conventional screening and standard of care yet relies exclusively on the physician's experience. Researchers have been working on the development of a flexible THz endoscope, as a potential tool to aid in colorectal cancer screening. This involves building a single-channel THz endoscope, and profiling the THz response from colorectal tissue, and demonstrating endogenous contrast levels between normal and diseased tissue when imaging in reflection modality. The current level of contrast provided by the prototype THz endoscopic system represents a significant step towards clinical endoscopic application of THz technology for in-vivo colorectal cancer screening. The aim of this paper is to provide a short review of the recent advances in THz endoscopic technology and cancer imaging. In particular, the potential of single-channel THz endoscopic imaging for colonic cancer screening will be highlighted.

Key words: Endoscopy; Terahertz imaging; Colonoscopy; Colon; Cancer detection; Flexible waveguides; Metal-coated; Polarization-sensitive; Polarization; Cross-pol

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Core tip: Terahertz (THz) imaging is progressing as a robust platform for a myriad of applications in the field of medicine. The non-ionizing THz radiation associated with safe energy levels has the potential to achieve high-resolution images of an organ or tissue, effectively combining both macroscopic and microscopic information. THz reflection imaging provides an intrinsic contrast between normal and diseased tissues, in real-time. This review describes the design, development, and practical implication of flexible THz endoscopic system, while simultaneously obtaining an overview of the existing

technology. In addition to the state-of-art THz endoscopy, the feasibility study of a single-channel THz endoscopic system for colorectal cancer screening will be highlighted.

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INTRODUCTION

Colorectal cancer

Cancers represents the most common reason for death worldwide causing 8.2 million deaths each year with more than 14 million new diagnosed cases. Colorectal cancer (CRC) is the third most commonly diagnosed cancer in the world causing 0.7 million deaths per year (WHO Data and Statistics). The most effective method of bringing down the cancer risk is the early diagnosis. The current staging and treatment of CRC relies on the traditional imaging technologies; such as conventional colonoscopy^[1,2], optical coherence tomography (OCT)^[3,4], computed tomography (CT)^[5,6], magnetic resonance imaging (MRI)^[7,8], and positron emission tomography (PET)^[9,10]. The present method for CRC screening is colonoscopy, which relies exclusively on the physician's experience and judgment. During colonoscopy, the obtained abnormal tissue will be sent for pathological examination for diagnosis.

Besides colonoscopy, the aforementioned CT, MRI and PET are the conventional diagnostic imaging modalities for the detection of CRC. Optical coherence tomography offers micrometer resolution and is proved to be ideal for cancer imaging. However, it has the limitation due to unwanted high optical scattering in the tissue^[11]. Computed tomography is a noninvasive technique and provides 3D tomographic images of the entire colon. CT is better at detecting small lesions (less than 1 cm size) as compared with MRI. Despite of that CT cannot detect most common tumors, especially the lesions smaller than 0.5 cm diameter^[12]. Furthermore, CT uses harmful ionizing X-rays^[13] and cannot be used in renal failure patients^[14]. In contrast, magnetic resonance imaging relies on liquid enema for contrast and hence is expensive^[12]. On the other hand, positron emission tomography provides good sensitivity and specificity of 80%-90% and can differentiate tumors from scar tissue created by surgery. However, MRI provides very low resolution if the tumor is not metabolically active and also has less sensitivity for lymph node staging^[15].

Macroscopic information of the tissue can be attained using conventional CT and MRI techniques, but they provide low-resolution images with less specificity. The microscopic (structural and functional) information can

be extracted only from the biopsied samples. It is still not plausible to achieve *in-vivo* high-resolution images of an organ or tissue with microscopic information in real-time using conventional imaging methods. One can potentially bridge this gap between macroscopic and microscopic imaging using the terahertz (THz) wavelengths spanning from microns to millimeters. In addition, to ascertain the presence of cancer during conventional colonoscopy, a biopsy will be performed from the suspected regions or polyps^[16]. Since most of the CRCs, above 80%, are difficult to detect in the early stage; clinicians often schedule regular patient visits and perform biopsy excisions for pathological examination. If an imaging modality provides the ability of delineating the diseased or abnormal region of fresh tissue in real-time, without staining the tissue, it's not only time effective but also improves the screening capability of endoscopy. Since, THz is nonionizing and provide endogenous contrast within the tissue based on the abnormalities^[17], alternative to the conventional colonoscopy, a THz endoscope can potentially be used for the *in-vivo* cancer screening.

Tissue abnormality and cell disorder

Figure 1 displays the histology slides^[18-20] of hyperplastic, normal, and various stages of colon cancer tissues. Usually, a tumorous tissue contains larger size nuclei with irregular shapes. The structures are disorganized and crowded. Figure 1 (N) shows the enface section of normal mucosa with an inset showing normal mucus-secreting colon cell. In the enface direction, Figure 1 (HP) shows both normal and hyperplastic mucosa structures for comparison. Crypts are the columnar structures in the mucosa layer of the colon tissue, made up of goblet cells, with approximately 100 μm diameter. The hyperplastic crypts tend to be order of magnitude larger and elliptical in shape. The hyperplastic crypts shown in the Figure 1 (HP) are 4 times larger than normal crypts and oblong in shape. Figure 1 (P) shows an enface cut of a sporadic juvenile polyp (benign). The smooth eroded surface with numerous mucus retention cysts is typical of these polyps. Figure 1 (S1) shows a benign neoplasm of mucus-secreting colon cell. The Mu denoted in the figure is the mucin contained inside goblet cells. The benign tumor is characterized by crowded nuclei and shortage of mucin production in goblet cells. Figure 1 (S2) exhibits neoplasm of mucus-secreting colon cell. The characteristics shown are larger nuclei, nuclei that are no longer arranged at the bottom of goblet cells, and almost no mucin production.

The typical size of the nucleus is around 1 micron, whereas in neoplastic cells the nuclei tend to be larger and around 3 to 5 μm . Figure 1 (S3) shows a malignant neoplasm of mucus-secreting colon cell, which is characterized by the disorganization of cellular components such that it no longer resembles the normal colon tissue. The aggressive tumor cells are randomly arranged and contain large nuclei that vary

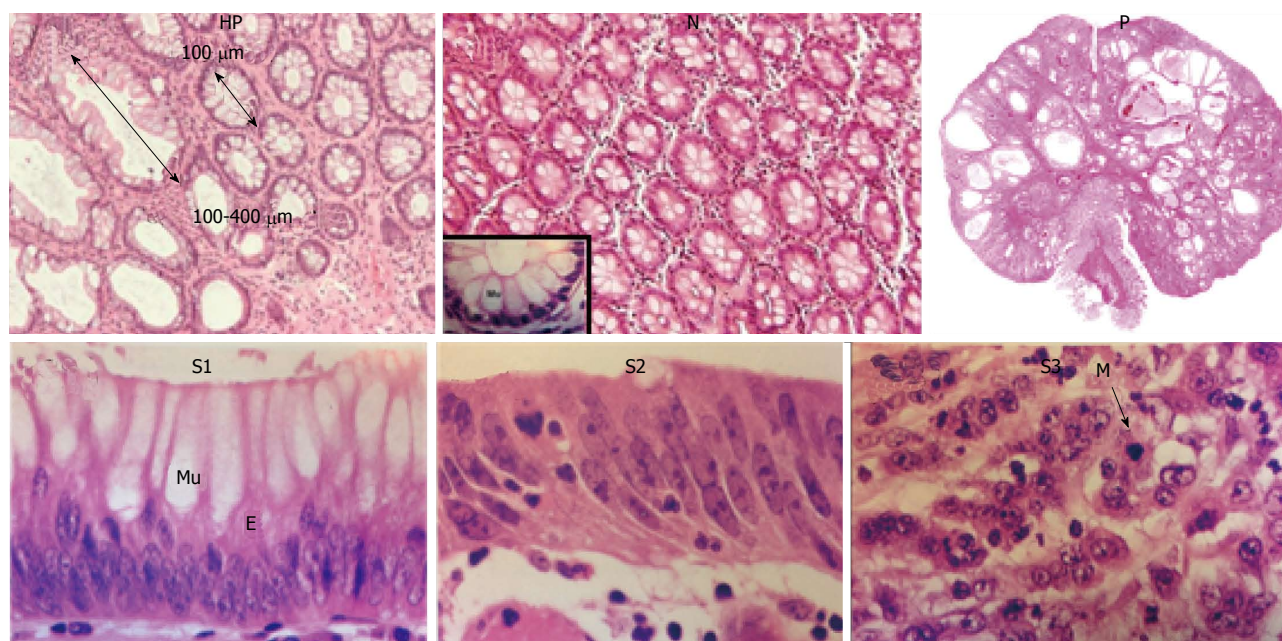


Figure 1 Enface histology^[19,20] sections of hyperplastic mucosa (HP), normal (inset: Mucus secreting colon cell) (N), sporadic juvenile benign polyp (P), low grade stage I (S1), intermediate stage II (S2), and high grade stage III colon (S3). Mu: Mucin; E: Epithelium; M: Mitoses.

in size and shape, dominating most of the cell volume. Therefore, the normal tissue is very homogenous at THz wavelengths while cancerous and dysplastic tissue has structures approaching the size of the wavelength. In addition, the dense structure of abnormal region can lead to higher refractive indices and can result in greater reflectance values. As a result, both of these mechanisms can engender an intrinsic contrast between normal and cancerous regions.

Screening techniques

CRC is one of the most common cancers across the world. The disease is slow to develop, but the early diagnosis and removal of abnormal growths is an effective method of reducing cancer risk. Expert groups recommend that people at average risk for CRC should start regular screening at the age of 50. Several tests can be used to screen CRCs^[21] and these tests were classified into two types; tests that can detect both polyps as well as cancer and tests that detect mainly cancer. The first kind looks at the structural information to recognize abnormal regions, which can be achieved with the insertion of scope into the rectum or by using a special X-ray imaging method. This test can prevent CRC, since the polyps found in the benign stage will be removed during the test. The second type diagnostics involve testing stools for the presence of cancer. These tests are less invasive and can be easily performed but are less likely to detect polyps. Although most expert groups generally recommend high sensitivity fecal occult blood test, sigmoidoscopy, and colonoscopy for cancer screening; several other tests such as virtual colonoscopy and barium enema are also used. Table 1 describes the merits and demerits of the techniques used for CRC screening.

THz endoscopy

The THz frequency region is situated between microwave and infrared regions of the electromagnetic spectrum with frequencies ranging from 10^{11} to 5×10^{12} Hz. THz imaging has shown a great potential for *in-vivo* and *ex-vivo* identification of tissue abnormalities, hydration and sub-layer probing^[22]. Since THz frequencies are sensitive to water content and they can penetrate deep into the tissue, THz was proven to be ideal for cancer^[23,24] imaging. Researchers have affirmed the use of THz wavelengths and in turn the potential of THz colonoscopic imaging by demonstrating positive results with dental^[25,26], skin^[17,27], breast^[28], liver^[29], oral^[30] and especially gastric cancer studies^[31].

Endoscopy is a less invasive medical procedure to diagnose the interior surfaces of an organ or cavity of body without the need for surgery. To address the physician's requirement in accessing different areas of the body^[32], endoscopes were traditionally designed in "rigid" and "flexible" configurations. Rigid endoscopes relay images from the tip of the scope to eyepieces with the help of arranged stack of lenses and provide high-quality images. These rigid endoscopes are surgical devices and have to be inserted through temporary access ports created by the physician. Unlike the rigid endoscope, flexible endoscope is more versatile and can be directly inserted through natural body cavities. Usually flexible endoscopes provide low quality images and typically contain either a fiber-optic or miniature video camera at the tip^[33]. Using conventional endoscopes, the cancer screening and decision to remove abnormal region solely depends on the visual inspection and experience of a physician. In contrast, a THz endoscope integrated into a conventional endoscopic system will suffice the *in-vivo* CRC screening requirement in real

Table 1 Merits and demerits of current conventional techniques used in colorectal cancer screening

Test	Advantages	Disadvantages
Flexible sigmoidoscopy	Quick and safe method Biopsy or polypectomy can be done Usually doesn't require full bowel preparation Sedation is not required	Bowel cleansing is required Can miss small polyps Views only the lower third of the colon Can't remove all polyps
Standard colonoscopy	Done every 5 yr Very sensitive Can view entire colon Can do biopsy and remove polyps Can diagnose other diseases	If an abnormality is found, colonoscopy will be required Full bowel preparation needed Can miss small polyps More expensive Minor sedation is required
Virtual colonoscopy	Done every 10 yr Quick and noninvasive Can view entire colon No sedation is needed Done every 5 yr	Small risk of bleeding, bowel tears, or infection Need full bowel preparation Cannot detect polyps < 5 mm Possibility of false positive test results Cannot remove polyps
Fecal occult blood test	Non-invasive No bowel preparation is required No sedation is required Inexpensive Sampling done at home	If an abnormality is found, colonoscopy will be required May miss polyps and cancers that doesn't cause bleeding Some false positive results Pre-test dietary limitations Should be done every year If an abnormality is found, colonoscopy will be required

time. The THz endoscope is a medical device consisting of a flexible THz waveguide instead of an optical fiber and uses a THz laser as light source and a THz detector in place of a video camera for examining the interior surface of an organ or cavity and detects abnormal regions.

THz endoscopic imaging has the potential to offer a safe, minimally invasive medical imaging modality for screening and detecting CRCs. To test this hypothesis, the experimental measurements have to be performed in four steps: Obtaining ideal system-imaging frequency, evaluating base contrast, testing flexible THz waveguides for use as an endoscope, and demonstrating THz waveguide based imaging of colorectal tissue. To confirm system-imaging frequency, the frequency dependent absorption coefficient and refractive index of colorectal tissues must be acquired using a traditional time domain pulsed THz system with frequency bandwidth of 0.1 to 5 THz. To evaluate the base contrast, THz reflectance images of human colonic tissues need to be obtained on *ex vivo* specimens and compared with the tissue histology. To test the flexible THz waveguides for use as an endoscope, waveguides should be characterized at the desired imaging frequency prior to the determination of waveguide operational parameters. Finally to demonstrate THz endoscopic imaging, the requirement is to integrate flexible waveguide with the transceiver system, implement waveguide based reflection modality imaging, and obtain sensitivity and specificity of the device from colorectal specimens.

Previously proposed THz endoscopes fall into two categories. The first category uses an uncoated polymer tube to transmit THz radiation and works in transmission modality. This study based on anti-resonant hollow core waveguides used a Teflon pipe to transmit THz radiation. However, the guiding capability is compromised due to the radiation not confining inside the bent tube and

results in high bending losses^[34]. Also, for endoscopic applications that require extensive bending, the guided field easily escapes into the air and interacts with the surrounding and ultimately contaminates the resultant image. In addition, a recent study that relied on a polymer tube to propagate the THz beam with an attached bull's-eye structure, works in transmission modality, to obtain near-field enhancement^[35]. However, in general, the high absorption associated with THz demands reflection based imaging for *in vivo* applications. The second category uses a mode locked femtosecond laser and relies on optical fibers for pulse propagation. It contains the THz source at the end of the optical fiber and is inserted into the patient^[36]. Consequently, electrical connections to drive the THz source must be inserted into the patient. Also it requires two channels, including a first channel for guiding radiation to the sample and a second channel for guiding the reflected light to a detector. In addition, the photoconductive antenna connected with the optical fiber necessitates high input voltage that is inadmissible for in-vivo imaging.

A recent study by Doradla *et al.*^[37] demonstrated a bendable prototype endoscopic system that relies on metal-coated THz waveguides for cancer imaging. The endoscopic system uses a single flexible waveguide channel to transmit the THz and collect the reflected signal from the tissue. The system is able to operate in both transmission and reflection configurations. Using a metal-coated THz waveguide provides 99% inner surface reflectivity at all THz wavelengths and confines the THz radiation. It preserves the linearly polarized launched mode and exhibits low bending loss even at larger bending angles. The hyper hemi spherical lens attached to the waveguide output end provides diffraction limited, approximately half the wavelength ($\lambda/2$) sized beam waist, which is free from lens aberrations. The resulting THz intensity images, attained

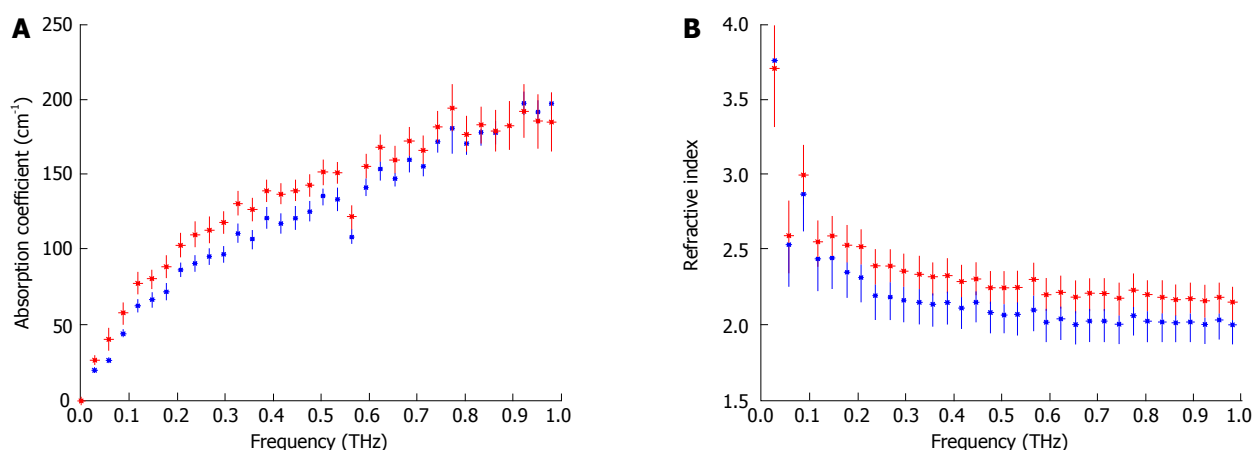


Figure 2 Terahertz spectroscopic results for the absorption coefficient (A) and refractive index (B) of fresh excisions of normal (blue) and cancerous (red) colon tissues^[38] (Printed with permission). THz: Terahertz.

using polarization sensitive detection, exhibited an endogenous natural contrast between normal and abnormal (cancer) regions of both formalin fixed and fresh tissues. Henceforth, this study shows the potential of THz endoscopic imaging for cancer screening and detection.

OVERVIEW OF EXPERIMENTAL WORK

THz spectroscopy of colorectal tissue

Intrinsic contrast observed in THz images of human colonic tissues is indicative of a change in the complex refractive index between cancer and normal tissue at THz frequencies. Thus the first step to develop an imaging system is to measure the THz spectroscopic response of colorectal tissues and determine frequency regimes for the contrast. Reid *et al.*^[38] and Faustino *et al.*^[39] performed THz time domain spectroscopy on cancerous and normal colon tissues, in this section we summarize their results.

Reid *et al.*^[38] used a conventional THz-TDS system to image cancer, dysplastic and healthy colon tissues from 30 patients. Their study was carried out in reflection mode and histopathological sections of the imaged tissues were used as the gold standard to classify tissue regions as cancer/dysplastic/normal and the corresponding optical properties were determined and averaged over different specimens. Their results for the frequency dependent absorption coefficient and refractive index are shown in Figure 2. As expected, the absorption increases with increasing frequency (this mimics how liquid water responds in this frequency region) and the refractive index (real part) is fairly steady in the region of interest. What is of interest for imaging applications, however, is the variation of these parameters between healthy and diseased tissue.

Faustino *et al.*^[39] investigated the THz reflectance and transmittance of specimens of paraffin embedded colon cancer and normal tissues. The samples investigated were cut to 2 mm thicknesses and the results are displayed in Figure 3.

As seen in Figure 3, there is a difference in the absorption coefficient of normal and cancerous colon in dehydrated formalin fixed samples. This result is extremely interesting as it indicates that water is not the sole contributor to THz contrast. Other studies^[40], have shown that while water does contribute to the observed contrast in fresh tissues, it is not the sole mechanism. Other factors such as tissue morphology leading to scattering might also measurably affect the tissue response. We discuss possible contrast mechanisms later in this review, however, at this point the complete mechanism for the intrinsic contrast seen in THz images of colon tissue is not completely understood.

When determining the exposure frequency for THz imaging of colon cancers, it is the difference in the complex refractive index that ultimately determines contrast. Transmission images rely primarily on differences in the absorption coefficient while sample reflectance is dominated by changes to the real part of the refractive index. As seen in Reid *et al.*^[38]'s data (Figure 3) while the absorption increases with increasing frequency, the difference in absorption decreases- thus frequencies above approximately 0.7 THz are not suited for transmittance based images. For reflection based imaging, however, the frequency region of interest spans 0.2-1 THz, as the difference in refractive index is equitably constant.

Different imaging approaches are discussed in later sections; however, there are other factors that also influence modality and frequency selection that we discuss below. *In vivo* applications require reflection based imaging-THz radiation is strongly absorbed by tissue, thus transmission through thick sections is not feasible. Lower frequencies correspond to longer wavelengths and thus lower resolution in the far field. However, higher frequencies experience stronger absorption, thus exhibit less penetration into tissue. Most single frequency systems used for imaging colon tissue thus far work at around 0.6 THz (500 μm) as a compromise between these two factors. A notable exception is the work done by Chen *et al.*^[41]

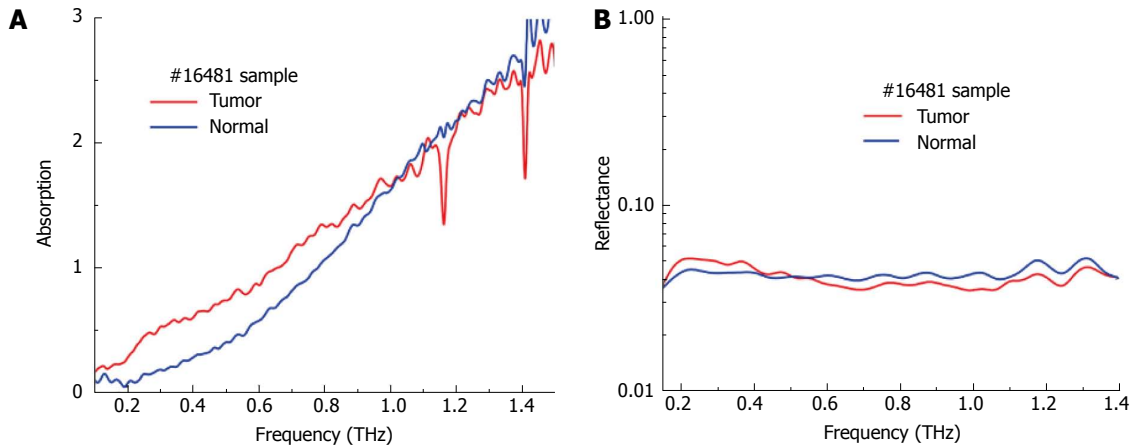


Figure 3 Absorption (A) and reflectance (B) measurements of paraffin embedded dehydrated fixed specimens of normal and cancerous colon tissue^[39] (printed with permission). THz: Terahertz.

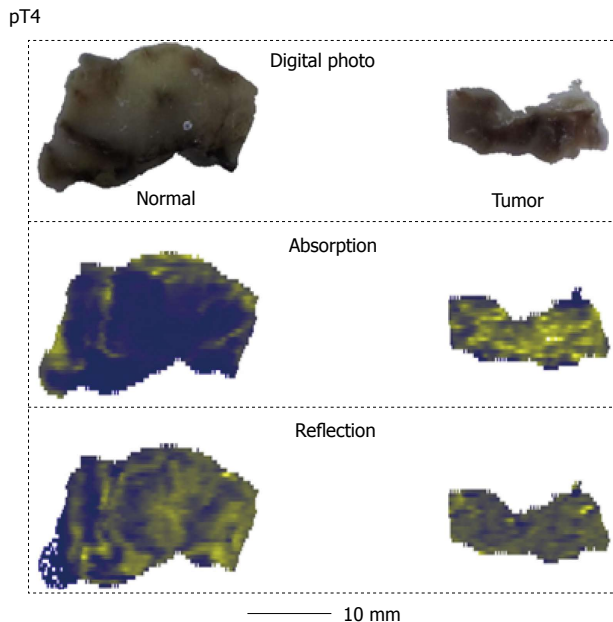


Figure 4 Photographs, absorption (transmittance) and reflection images of formalin fixed dehydrated colon tissue^[39] (printed with permission).

in transmission imaging at 0.3 THz (approximately 1 mm); they compensate for the lower far-field resolution by using a specially designed aperture which allows for significantly higher resolution in the near field.

THz imaging of human colorectal tissues

Continuous-Wave (CW), or single frequency imaging of *ex vivo* samples of normal and cancerous colon tissues has been demonstrated. Faustino *et al.*^[39] have imaged paraffin embedded, formalin fixed specimens of normal and cancerous colon in both transmission and reflection modalities. They used a solid-state multiplier/amplifier chain as their source (VDI systems) and a microbolometer array for detection. The frequency of the imaging system was 0.6 THz (500 μm). As can be seen in Figure 4, the transmittance images of dehydrated fixed tissue still show contrast between

normal and cancer, while the reflection images do not show any appreciable difference. This is expected based on the spectroscopy results for these tissues, which are discussed in prior section. The change in absorption persists in the imaging while the lack of difference in the real part of the refractive index shows up as no observable contrast in the reflectance images.

Reid *et al.*^[38] have imaged excised healthy, dysplastic, and cancerous colonic tissues obtained from 30 patients in reflection modality. They used a stand-alone portable THz imaging system TIP imaga1000. The frequency of the imaging system was 0.03-1 THz. The difference in the reflected waveforms and the ultimate contrast between normal, dysplastic, and cancerous tissue regions were depicted in Figure 5.

Doradla *et al.*^[42] measured the THz reflectance of thick, fresh excisions of cancerous and normal colon tissue using a CW THz imaging system operating at 0.584 THz (513 μm). They used far-infrared laser based on CO₂ gas and a silicon bolometer that runs with liquid helium as a detector. Figure 6, below shows a schematic of the imaging system. The beam is incident normal to the sample and the reflectance is measured using a beam-splitter. Wire-grid polarizers allow for the selection of specific polarizations and both images comprised of the co-polarized and cross-polarized remittance of the samples can be measured. The samples used in this study were thick fresh excisions of normal and cancerous colon tissues. The samples were measured the same day as the surgical procedure and were backed with saline soaked gauze during the measurement process to make sure that they did not dry out. Figure 7 shows some of the images collected alongside digital photographs of the sample.

As shown in Figure 7, the cross-polarized reflectance of normal colon is lower than the cross-polarized reflectance of cancerous colon. This result was found for all 4 sample sets (each sample set consisted of one normal and one cancerous tissue) measured in this study. The authors also computed the percent reflectivity difference between normal and cancerous

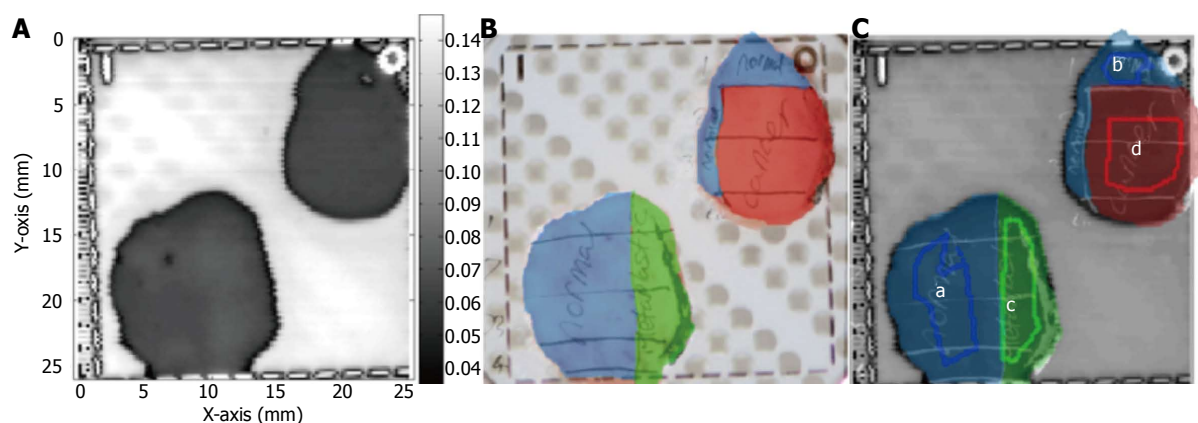


Figure 5 An example terahertz image of excised cancerous, dysplastic and healthy colonic tissues. A: Example terahertz (THz) image of tissue containing healthy regions, dysplasia and cancerous tissue; B: The histology results (drawn onto a photographic image of the tissue samples); C: The histology results are overlaid on the THz image. In this example, regions a and b are normal tissue, c is dysplastic tissue and d is cancerous tissue^[38] (printed with permission).

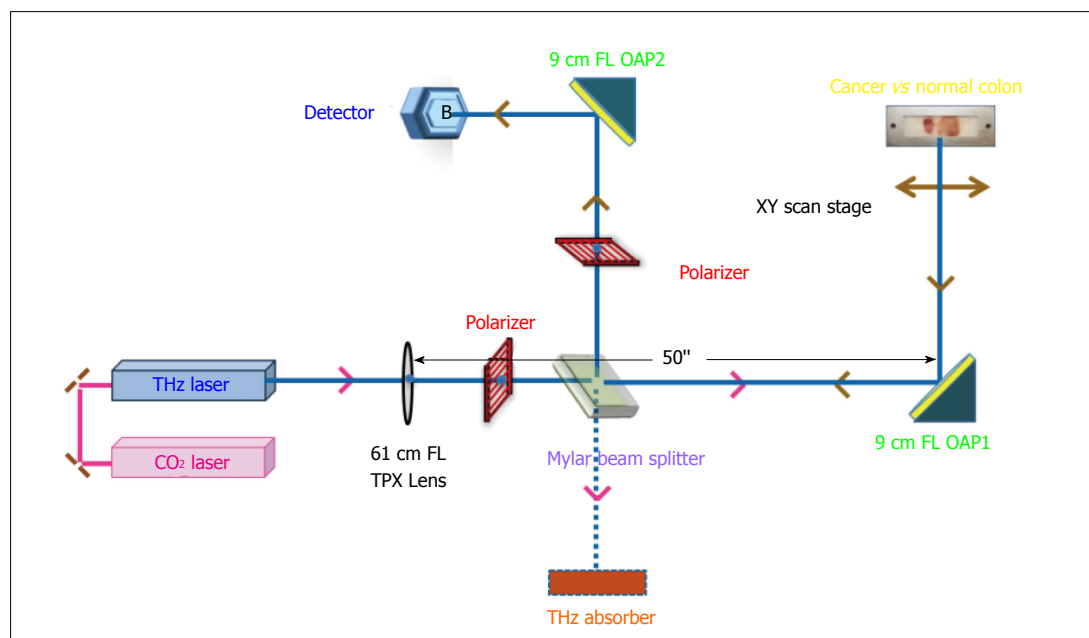


Figure 6 Schematic of continuous-wave terahertz reflection imaging system^[42].

colon tissue for both the cross-polarized and co-polarized data for each sample set while accounting for background.

As can be seen in Table 2, the cross-polarization channel exhibits a significantly larger reflectivity difference than the co-polarized channel. Moreover, the difference observed in cross-polarization is consistent across different sample sets (*i.e.*, it is consistent across samples from different patients), thus it presents a potential quantitative screening tool for cancer detection.

Waveguide based imaging

Biomedical imaging of organs or hollow cavities of human body often demands endoscopic access. Highly bendable waveguides with low transmission loss are inevitable for endoscopic applications. Therefore, flexible THz waveguides with good mode preservation

characteristics and low propagation and bending losses are essential for *in-vivo* THz imaging of CRC. Previously, THz waveguides were fabricated from various materials^[43-45] with multifarious cross sectional designs^[46-48]. Most of these waveguides are either rigid or not flexible at larger bore diameters^[49,50]. In addition the flexible THz waveguides suffered from excessive propagation losses^[51,52]. On the other hand, the fabrication technique used for the fabrication of the cylindrical waveguides is not applicable for waveguides with < 3 mm diameter^[53]. Doradla *et al.*^[54,55] reported the characteristics of hollow, flexible, cylindrical THz waveguides that were fabricated with inner metal and metal/dielectric coatings. They provide low loss (less than 1 dB/m) and are small enough in diameter and satisfy the criteria for endoscopic applications.

The three operational parameters of waveguides

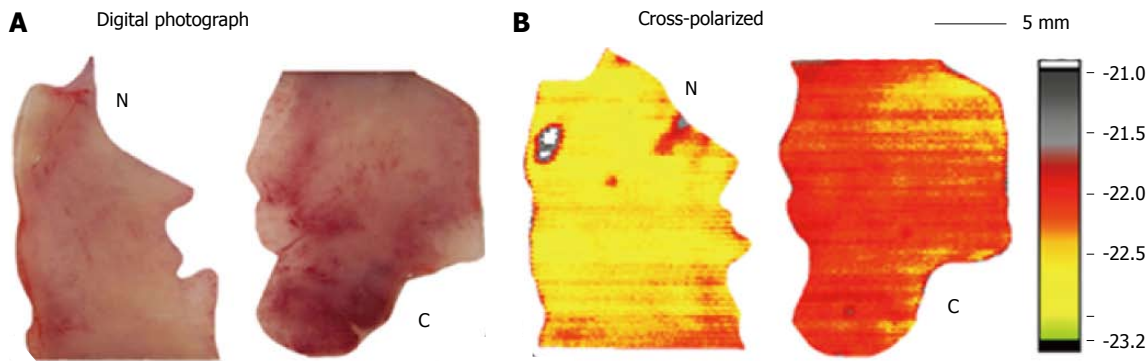


Figure 7 Digital photograph (A) and corresponding terahertz reflectance images (B) of normal (N) and cancerous (C) colon tissue^[42].

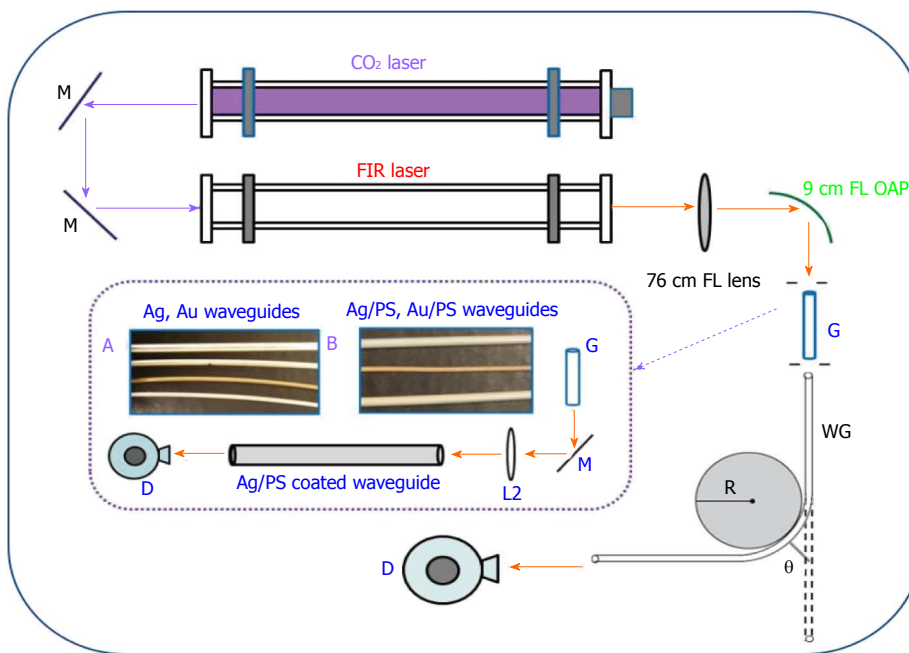


Figure 8 Experimental setup for the transmission loss measurement in metal and metal dielectric. Inset: A: 4 mm Ag (top), 3 mm Ag, 2 mm Au, and 2 mm Ag; B: 3 mm Ag/PS (top), 2 mm Au/PS, and 4 mm Ag/PS) coated terahertz waveguides^[54].

Table 2 The relative reflectance difference between normal and cancerous colonic tissue^[42]

Sample #	Co-pol ($\times 10^{-1}$ %)	Cross-pol (%)
Set 1	1.53	7.74
Set 2	3.03	7.74
Set 3	1.56	7.75
Set 4	2.44	7.30

that are crucial in determining the transmission losses and modal characteristics are waveguide inner diameter, coating material, and material thickness. Selection of coating materials such as silver and polystyrene were described in the preliminary investigation^[56]. Also, the optimal coating thicknesses and requisite fabrication processes were detailed^[55]. In order to choose a suitable candidate waveguide for THz endoscopic imaging, the characterization was done in three steps: Measuring propagation loss of the waveguide as a function of its

inner diameter and coating material, obtaining bending loss as a function of bend radius and bending angle, and acquiring modal characteristics as a function of bending angle, bend radius, waveguide inner diameter, and coating material. The transmission losses and modal characteristics for flexible waveguides can be obtained using the optical layout shown in Figure 8. Harrington *et al.*^[49] showed that when the waveguide bore size is about 17 times wavelength the guide is multimode, but when it is 12 times the wavelength or less then the waveguide becomes essentially single mode^[54]. The characterization of flexible waveguides at the selected frequency^[56], suitable for THz endoscopic system, is described in Ref 56.

Two groups so far have demonstrated waveguide based THz imaging. Chen *et al.*^[41] used a polymethylmethacrylate waveguide to demonstrate THz transmission imaging of human colon tissue and Doradla *et al.*^[37] demonstrated reflection modality imaging using a single channel THz waveguide.

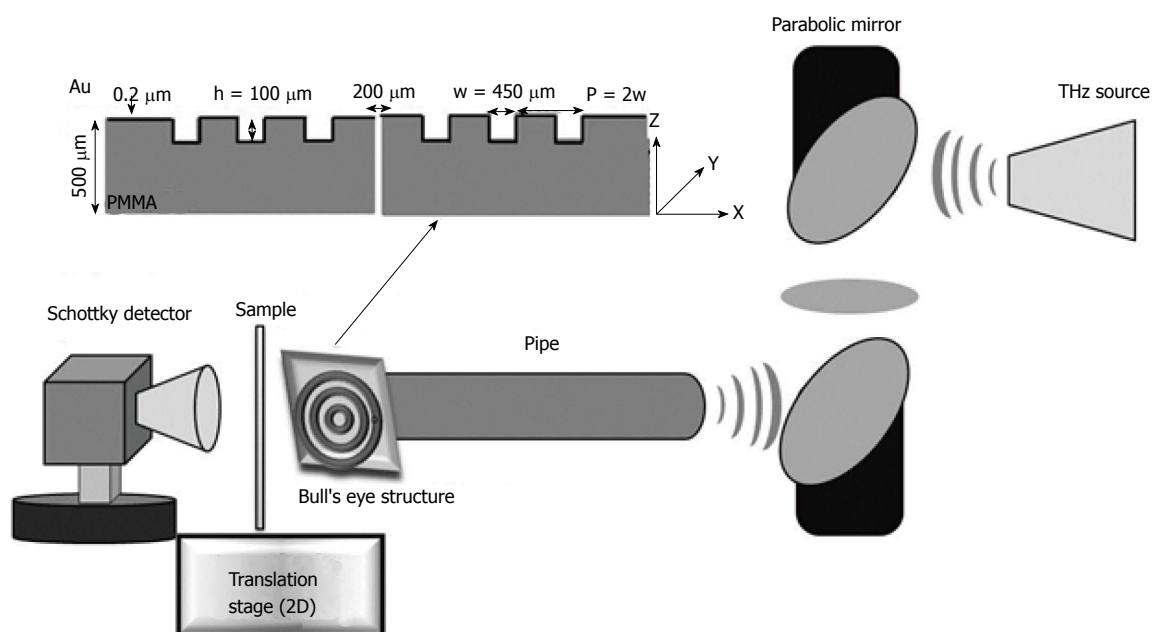


Figure 9 Schematic of waveguide based terahertz near-field transmission imaging system^[41] (printed with permission). PMMA: Polymethyl methacrylate.

The work by Chen *et al.*^[41] utilized a continuous-wave source (Gunn diode) centered at 0.3 THz. Figure 9 shows a schematic of their system. As mentioned in Section 2, while 0.3 THz offers contrast in absorption, the resolution is limited in the far-field by the relatively long wavelength (1 mm). Chen *et al.*^[41] overcome the resolution restriction by using a bull's eye structure with a sub-wavelength aperture to get a near field resolution of 0.2 mm.

Figure 10 shows THz transmission images at 0.3 THz of specimens of fresh normal and cancerous colon that have been sectioned into 30 μm thick slices. As expected, the cancerous specimens exhibit significantly higher absorption than normal tissue. Chen *et al.*^[41] investigated the response of 30 specimens and were able to demonstrate 100% sensitivity and specificity.

The work by Doradla *et al.*^[42,57,58] utilized a far-infrared gas laser operating at 513 μm wavelength (0.58 THz). The THz endoscopic system contains THz transceiver system, system optics and a low-loss flexible THz waveguide. The transceiver system is used for the generation and detection of the THz signal. System optics control and guide the THz beam based on the coupling requirements. Hollow metal-coated waveguide confines and transport the THz beam. Ultimately, to achieve the maximal coupling efficiency and transmission through the waveguide, off axis parabolic mirror (OAP1 of Figure 11) has been adjusted to maintain the ratio of beam size and waveguide diameter as 0.77. This prototype endoscopic system utilized a single-channel for the THz signal transmission, collection from the specimen and works in both transmission and reflection configurations to overcome the higher THz absorption associated with the tissue and satisfy the *in-vivo* imaging criteria. It uses a highly reflective flexible waveguide lens assembly to propagate THz beam.

Metal-coated waveguides provide 99% inner surface reflectivity at all THz wavelengths and confine the radiation inside the tube. Metal-coated waveguides preserve the linearly polarized launched mode and exhibits low bending loss even at larger bending angles. The hyper hemispherical lens attached to the waveguide output end provides an aberration free diffraction limited beam waist. The technique in accordance with the present work acquires both co- and cross-polarized THz images using polarization sensitive detection. The data analysis indicates utilizing the cross-polarized component not only helps in obtaining Fresnel reflection free volume sampling but also in achieving a reflectance parameter that doesn't vary with patient/individual^[42,58]. The THz endoscopic system doesn't need any conventional contrast agents to detect abnormal tissue as an intrinsic contrast was observed between normal and diseased tissue in fresh colonic specimens. Also, the device uses just one channel and hence can be easily integrated with the conventional optical endoscope. Moreover, the prototype THz endoscope is integrated with the flexible THz waveguides, which are small enough in diameter (2 mm to 100 μm). Therefore, based on the application and requirement, the dimensions of the THz probe can be reduced further.

This study^[37,58] demonstrated the first prototype continuous-wave THz endoscopic system for cancer detection. The 2D THz intensity images attained using polarization based detection scheme exhibited an endogenous natural contrast between normal and abnormal (cancerous) regions of both formalin fixed and fresh colorectal tissue (Figure 12). The imaging system demonstrated the capability of identifying cancerous colonic tissue based on the intrinsic reflectance difference. The optical layout evident the potential and the experimental manifestation confirms the feasibility

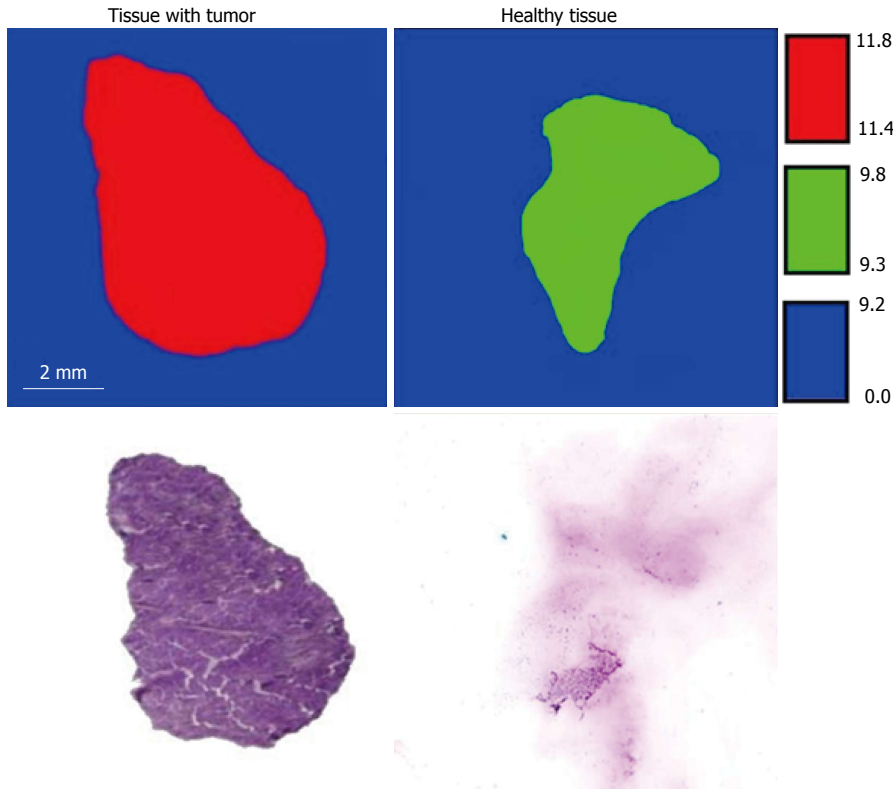


Figure 10 Terahertz transmittance images and stained histology sections showing cancerous and normal colon tissue^[41] (printed with permission).

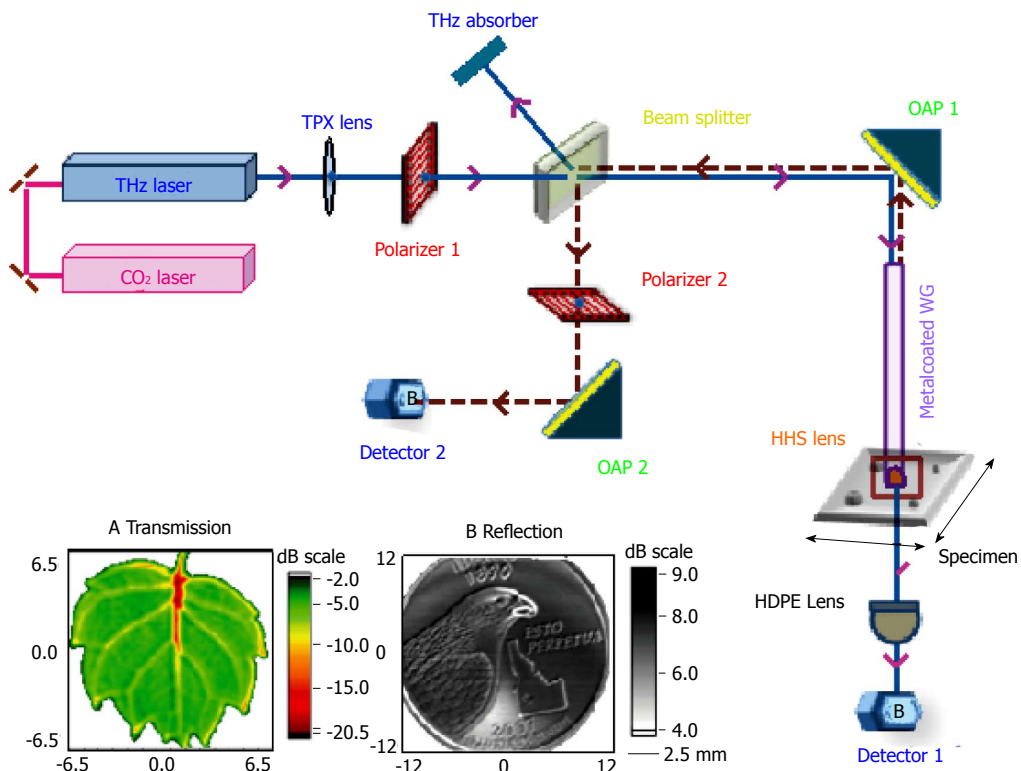


Figure 11 Schematic of single-channel prototype terahertz endoscopic imaging setup. Inset: Terahertz (A) transmission imaging of a small 10 mm leaf, and (B) reflection imaging of a 25-cent coin. THz: Terahertz.

of using THz endoscopic device in accessing data from previously inaccessible organs^[59]. Furthermore, this

study significantly increased and prevail the overall impact of THz imaging for biomedical detection/

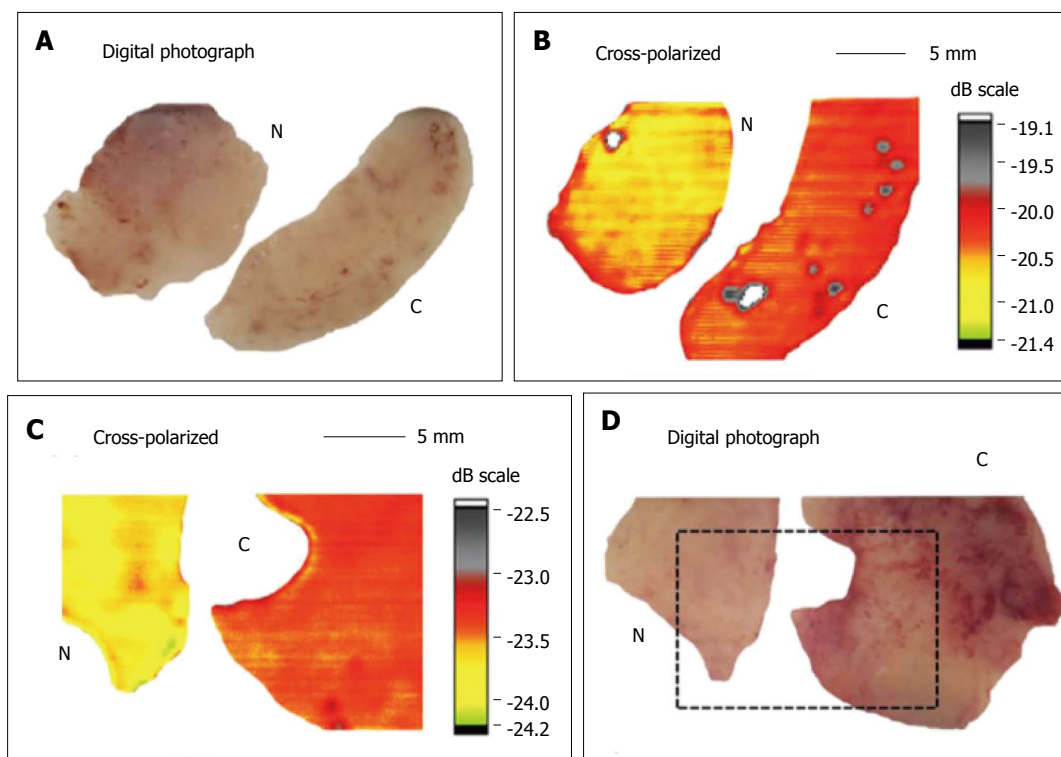


Figure 12 Digital photograph, cross-polarized terahertz reflection images of normal N vs cancerous C human colonic formalin fixed (A and B) and fresh (C and D) tissue sets^[58].

screening applications^[60].

CONCLUSION

CRC is the third most commonly diagnosed cancer in the world. Early detection and treatment of CRC can significantly reduce the number of deaths. Current standard of care for CRC screening is an optical endoscopy, which relies on physician's visual inspection and experience followed by histological analysis of biopsied specimens. Thus, an *in vivo* imaging modality capable of measuring quantitative differences between diseased (cancerous) and normal colon can significantly improve the screening of CRCs. THz imaging, which is non-ionizing and highly sensitive to tissue water content can potentially fill this niche.

This review article has outlined the steps required for clinical application of THz imaging of CRC and provided an update on the current status of the technology. The first step was to measure the refractive indices and absorption coefficients of normal and diseased colon tissue in the THz region. This has been accomplished by several groups using both fresh and formalin fixed dehydrated colon tissue. The results indicate a measurable difference in specific frequency ranges for both fresh and fixed tissue. The second step was to image normal and cancerous colon at desired frequencies to confirm the contrast can be imaged. This has also been accomplished for both fresh and fixed tissue in both transmission and reflection imaging modalities using THz imaging systems. In order to

proceed to clinical systems, the next step was to develop thin, flexible waveguides capable of endoscopic applications. This step has also been accomplished by multiple groups postulating a variety of endoscopic setups. The fourth step was to integrate the waveguide with a THz imaging system and test if waveguide enabled image acquisition was feasible. This was also demonstrated by different groups in both transmission and reflection modalities on fresh colon tissues. There is considerable evidence that THz imaging can potentially screen for colon cancers. A lot of the technological barriers have been overcome and the next step for the field is the development and testing of an *in vivo* THz endoscopy system capable of providing sensitivity and specificity numbers for the technique in identifying multiple stages of colon cancer.

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Use and barriers to chromoendoscopy for dysplasia surveillance in inflammatory bowel disease

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Abstract

Traditionally, patients with inflammatory bowel disease (IBD) have been thought to be at increased risk of developing colitis-associated colorectal cancer. Although there are recent data suggesting that rates of colitis-associated cancer in IBD patients is declining, current guidelines still recommend regular dysplasia surveillance for early detection and prevention of neoplasia in patients with IBD. White-light endoscopy with random biopsies has been the traditional approach for dysplasia detection; however, newer technologies and approaches have emerged. One method, dye-based chromoendoscopy, has the potential to detect more dysplasia. However, longitudinal data to showing a benefit in morbidity or mortality from the use of chromoendoscopy are still lacking. Many societies have included recommendation on the use of chromoendoscopy with targeted biopsies as a method of surveillance for colitis - associated colorectal cancer. This narrative review seeks to outline data on dysplasia detection as well as barriers to the implementation of dye-based chromoendoscopy for the prevention and early detection of colitis-associated colorectal cancer.

Key words: Chromoendoscopy; Inflammatory bowel disease; Dysplasia surveillance

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Core tip: Patients with inflammatory bowel disease (IBD) are at an increased risk of developing colorectal cancer. Current guidelines recommend surveillance for early of neoplasia in patients with IBD. White-light endoscopy with random biopsies has been the traditional approach for dysplasia detection. Dye-based chromoendoscopy has the potential to detect more dysplasia. Many societies have endorsed the use of chromoendoscopy with targeted biopsies as a method of surveillance for colitis associated colorectal cancer. This review seeks to outline

data on dysplasia detection as well as barriers to the implementation of chromoendoscopy for the prevention and early detection of colitis associated colorectal cancer.

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INTRODUCTION

Inflammatory bowel disease (IBD), which includes ulcerative colitis (UC) and Crohn's disease (CD), is a chronic inflammatory disease of the GI tract. Both ulcerative colitis and Crohn's colitis have historically been thought to be associated with an increased risk of developing colorectal cancer (CRC)^[1-3]. Current guidelines provide various permutations of surveillance colonoscopy to detect and remove precursor lesions at an early stage^[4-7]. Over the last several years, dye-based chromoendoscopy (CE) with targeted biopsies has emerged as an option to improve the ability to detect these early, subtle lesions. CE is a technique using absorptive stains or contrast stains dye such as methylene blue and indigo carmine that can aid in the early detection of malignant changes in the gastrointestinal tract. In this technique, 0.4% indigo carmine or 0.1% methylene blue is sprayed directly onto the colonic mucosa to help detect subtle mucosal irregularities that aid in the detection of changes indicative of dysplasia as well as help in differentiation of neoplastic and non-neoplastic lesions by assessing crypt architecture and modified pit patterns^[8]. The technique of colonic CE was first described by Tada in 1976 with work two decades later indicating a role for CE with high resolution video endoscopy in increasing the detection of small flat neoplastic lesions in UC patients^[9,10]. In this review, we will review current guidelines for the surveillance of colitis-associated colorectal cancer (CAC), barriers to implementation, and areas that require further study.

CRC RISK AMONG PATIENTS WITH IBD

The concept of carcinoma arising as a complication of chronic inflammation from IBD was first described by Crohn and Rosenberg in 1925, with later reports expanding on this observation^[1-3]. A review of the literature in 1961 by Goldgraber and Kirsner^[2] made the observation of increased risk of carcinoma of the colon in patients with UC with pancolonic disease and in those with disease duration greater than 10 years. The presence of dysplastic lesions in the colon of patients with UC was recognized as early as 1949 with the recommendation to search for precancerous lesions

which often were flat (non-polypoid) with rectal biopsies annually as an aid to the detection of early colon cancer being made in 1969^[11,12]. It was not until 1983 that a standardized terminology and grading system were established to help guide surveillance protocols. In the landmark paper by Riddell *et al.*^[13] in 1983, dysplasia was defined as an unequivocal neoplastic alteration of the colonic epithelium that may represent a precursor of carcinoma or itself be malignant and associated with direct invasion into the underlying tissue. The classification for dysplasia was further categorized into either negative, indefinite or positive for dysplasia.

In a landmark meta-analysis conducted by Eaden *et al.*^[14] in 2001, the authors assessed 116 studies and found that the cumulative risk of developing CAC was 2% by 10 years of disease, 8% by 20 years, and 18% by 30 years. Subsequent studies investigating the CAC risk in IBD patients have shown considerable variability, depending on the population studied, with cumulative risk ranging between 2.1% to 33.2%^[15-18]. Remarkably, more recent studies have actually shown that the risk of CAC in IBD patients may actually be declining and nearing the risk of the general population^[19]. In a meta-analysis by Jess *et al.*^[20] assessing 47374 Danish patients with IBD over 30 years, the authors found that the relative risk of developing CAC in UC patients was comparable to non-IBD controls (RR = 1.07, 95%CI: 0.95-1.21) as was the risk of CAC in patients with Crohn's colitis (RR = 0.80, 95%CI: 0.43-1.49). This study also found that the overall risk of CAC was declining in UC patients where the overall RR for CAC decreased from 1.34 (95%CI: 1.13-1.58) in 1979-1988 to 0.57 (95%CI: 0.41-0.80) in 1999-2008. This decline potentially may be attributed to improvement in therapies to reduce intestinal inflammation in IBD or to improved surveillance programs to promote early detection of neoplastic lesions.

Despite the decline in overall risk, there is still consistent information across many studies that there is a particularly higher risk of developing CAC in a subset of patients - those with extensive and long standing UC or CD^[20-22]. Rutter *et al.*^[23] evaluated 68 patients in a case-control study at St. Mark's Hospital in England and found that severity of colonic inflammation is also an important predictor for development of neoplasia. Moreover, in the aforementioned study by Jess *et al.*^[20], despite an overall decline in incidence of CAC in IBD patients, there are particular subsets of patients- those with a diagnosis of UC in childhood or adolescence, those with long standing UC and those with concurrent primary sclerosing cholangitis (PSC)-who were at a notably increased risk of developing CAC during the study period.

CURRENT GUIDELINES FOR CAC SURVEILLANCE

While CAC may only represent a small proportion of

Table 1 Colorectal cancer surveillance guidelines for inflammatory bowel disease patients

Guideline (year of publication)	Timing of initiating surveillance	Surveillance interval	Biopsy protocol
AGA (2003) ^[4]	After 8 yr of disease (pancolitis) After 15 yr of disease (left-sided colitis)	1-2 yr	Random biopsy
BSG (2010) ^[46]	10 yr after onset of colitic symptoms	5 yr (lower risk) ¹ 2-3 yr (intermediate risk) 1 yr (higher risk)	Targeted biopsy with CE (preferred) otherwise random biopsy
ECCO (2013) ^[6]	8 yr after onset of colitic symptoms	5 yr (lower risk) ² 2-3 yr (intermediate risk) 1 yr (higher risk)	Targeted biopsy with CE (preferred), random biopsies if CE expertise unavailable
ASGE (2015) ^[7]	8 yr after symptom onset	1-3 yr (1 yr if any risk factor) ³	Targeted biopsy with CE recommended with SD-WLE (preferred with HD-WLE as well); random biopsies with targeted biopsies of suspicious lesions is alternative

¹Higher risk group: Dysplasia in the past 5 years declining surgery, PSC/liver transplantation for PSC, family history of CRC in a first degree relative < 50 years, or extensive colitis with moderate/severe active endoscopic/histological inflammation; intermediate risk group: Post-inflammatory polyps, family history of CRC in a first degree relative > 50 years, extensive colitis with mild active endoscopic/histologic inflammation; lower risk group: Left sided colitis, Crohn's colitis with less than 50% of the colonic mucosal surface affected by the disease, or extensive colitis with no active endoscopic/histologic inflammation; ²Higher risk group: Stricture or dysplasia in the past 5 years, PSC, extensive colitis with severe active inflammation, or family history of CRC in a first degree relative < 50 years; intermediate risk group: extensive colitis with mild or moderate active inflammation post-inflammatory polyps, or family history of CRC in a first degree relative > 50 years; lower risk group: Patients with neither intermediate nor higher risk features; ³Risk factors: Active inflammation, anatomic abnormality (stricture or multiple pseudopolyps), history of dysplasia, family history of CRC in a first degree relative, PSC. AGA: American gastroenterological association; BSG: British society of gastroenterology; ECCO: European crohn's and colitis organisation; ASGE: American society of gastrointestinal endoscopy; PSC: Primary sclerosing cholangitis; CRC: Colorectal cancer; CE: Chromoendoscopy; SD-WLE: Standard definition white light endoscopy; HD-WLE: High definition white light endoscopy.

all CRC cases (1%-2%), CRC is responsible for one in six deaths of IBD patients^[24]. As such, colonoscopy has been the test of choice for early detection and prevention of CAC in IBD patients. The major United States gastroenterology societies have endorsed colonoscopy for prevention of early CAC^[25-27]. There are limited data on the benefit of the recommended surveillance programs. Some studies have found that patients with IBD undergoing surveillance colonoscopies may have reduced rates of CAC or detection of CAC at an earlier stage^[28].

Choi *et al.*^[29] examined 41 UC patients who developed CAC. The authors found that CAC was detected at a significantly earlier Dukes' stage in patients taking part in an endoscopic surveillance program ($P = 0.039$). Furthermore, the 5-year survival rate was 77.2% for the surveillance group and 36.3% for the no-surveillance group ($P = 0.026$). Though this study is promising evidence in favor of CRC surveillance, other studies have not shown a similar benefit. Lynch *et al.*^[30] prospectively examined 160 UC patients and found no mortality benefit in patients undergoing CRC surveillance. More recently, Ananthakrishnan *et al.*^[31] studied 6823 established patients (following for at least 3 years) with IBD of which 2764 had undergone recent colonoscopy. They found that the incidence of CAC among patients without a recent colonoscopy (2.7%) was significantly higher than among patients with a recent colonoscopy (1.6%) (OR = 0.56, 95%CI: 0.39-0.80). This was one of the few studies which specifically addressed the risk of CAC in IBD patients undergoing surveillance.

Current society guidelines recommend regular dysplasia surveillance in patients with long-standing colitis. Several major GI societies guidelines, including

those published by the American Gastroenterological Association in 2003, recommend initiating a surveillance program to evaluate for dysplasia in patients who have had colitis for at least 8 years^[4,5]. After starting a surveillance program, colonoscopy should continue every 1-2 years. The consensus of the expert panel formulating these guidelines is that random biopsy specimens should be taken every 10 cm in all 4 quadrants and that additional biopsies should be taken of any endoscopically abnormal appearing lesions (strictures, mass lesions, etc.). This results in a minimum of 33 biopsies to meet the threshold for neoplasia detection - a process that can be quite cumbersome and time consuming. Newer society guidelines, such as those issued by the American Society for Gastrointestinal Endoscopy (ASGE) and the European Crohn's and Colitis Organization (ECCO)^[6,7], have now updated their guidelines to incorporate the use of chromoendoscopy for dysplasia surveillance. A summary of the current guidelines from the major GI societies is outlined in Table 1.

There have been many criticisms of the random biopsy strategy as less than 1% of the entire mucosal surface was sampled and low dysplasia detection rates as well as high sampling-error^[32]. There are also no prospective studies that have determined the optimal number of biopsies that should be taken to detect dysplasia reliably though one study has recommended a minimum of 33 biopsy specimens to be taken in patients with pancolitis^[33]. It has also been estimated that this surveillance method provides only 80% confidence that dysplasia involving $\geq 5\%$ of the colon can be detected^[34]. There have also been several studies showing poor adherence of gastroenterologists

in taking the recommended number of biopsies along with practice variability in surveillance^[35-37]. These initial recommendations were made at time prior to high-definition colonoscopy and lesions previously considered “invisible” or flat may be visualized with modern day high-definition equipment. It is now understood that most dysplasia can be visualized endoscopically and have led some to question the added value of random biopsies^[26]. Recent studies have supported the strategy of targeted biopsies of abnormal lesions without random biopsies only when high definition white light endoscopy (HD-WLE) is used. A clinical practice cohort of 454 IBD patients undergoing surveillance colonoscopy between 2011-2014 using standard definition white light endoscopy (SD-WLE), HD-WLE, virtual electronic CE, or CE found that most lesions were visible and of the four dysplastic lesions and one adenocarcinoma identified all were visible with HD-WLE and biopsied in a targeted manner. No dysplasia was identified on random biopsies^[38]. A recent randomized controlled trial of 256 of patients with UC performed in Japan comparing surveillance with either a targeted biopsy protocol vs a random biopsy protocol with white light endoscopy found neoplasia was detected in 11.4% of patients in the targeted biopsy group vs 9.3% in the random biopsy group ($P = 0.617$) with less biopsies specimens being required per neoplasia diagnosis, suggesting a targeted biopsy approach as being more cost-effective and more efficient without missing dysplasia^[39].

SCENIC CONSENSUS STATEMENT

In March of 2015, the SCENIC (Surveillance for Colorectal Endoscopic Neoplasia Detection and Management in Inflammatory Bowel Disease Patients: International Consensus Recommendations) consensus statement^[40] regarding use of chromoendoscopy for dysplasia surveillance was released. In this statement, the authors made several updates regarding the approach to dysplasia surveillance among which they suggested that endoscopists consider the use of CE, when utilizing high definition colonoscopy, to enhance dysplasia detection. A commentary by Marion and Sands^[41] accompanying the publication of the SCENIC statement propounded an important argument: The lack of longitudinal data regarding CE limits the ability to accept this as the standard of care in dysplasia surveillance. More specifically, while there is certainly evidence that CE increases dysplasia detection, it remains unclear what the long-term management of these patients should be. While pursuing the goal of cancer prevention, the accompanying risk profile of increased dysplasia detection including onerous surveillance schedules, possibly unnecessary colectomies or post-surgical complications also increases. This risk/benefit profile, along with the limited evidence to support use of CE, must all be considered when deciding to employ this technique.

EVIDENCE FOR CHROMOENDOSCOPY

Two studies increased the attention on CE as a means to more efficiently detect dysplasia in IBD compared to random biopsies. In one study of 100 patients with long-standing UC using a tandem colonoscopy design, random biopsies along with targeted biopsies using standard white light was compared to CE with targeted biopsies only using indigo carmine. This study demonstrated a 3.5-fold increase in diagnostic yield of dysplasia along with a 4.5-fold increase in dysplasia detection, with no dysplasia being detected on random biopsies^[42]. In the first randomized prospective trial using CE for IBD-associated colonic dysplasia, methylene blue was compared to conventional colonoscopy in patients with long-standing UC. Chromoendoscopy was associated with an increased diagnostic yield for total number of detected intraepithelial neoplasia compared to conventional colonoscopy (32 vs 10, $P = 0.003$). The CE group also required less biopsies and using the modified pit pattern demonstrated a sensitivity and specificity for differentiation between neoplastic and non-neoplastic lesions of 93%^[43]. Subsequent studies also have shown an increased detection yield of CE over standard white light endoscopy (WLE), which was highlighted by a meta-analysis evaluating prospective studies comparing CE to WLE. Six prospective studies were included in the analysis and concluded that CE resulted in a 7% higher yield in detection of neoplasia as well as a pooled increase in targeted dysplastic (low or high grade) lesion detection of CE over standard definition WLE of 44% (95%CI: 28.6-59.1)^[44]. Mounting data of the effectiveness in dysplasia detection with CE lead to the 2010 position statement from the American Gastroenterological Association recommending CE as an alternative to analyses of random biopsies for endoscopists experienced with the technique^[45]. The British Society of Gastroenterology also recommended CE with targeted biopsies with a grade A recommendation as the preferred method of surveillance^[46].

Though clinical trials demonstrated a benefit of CE over WLE for dysplasia detection, a large retrospective study covering 13 years did not confirm this conclusion in the clinical practice setting. This multicenter study from the Netherlands including 401 patients undergoing CE and 772 patients undergoing WLE found no difference in the detection of dysplasia between the two groups (11% vs 10%, $P = 0.80$)^[47]. This conclusion was in accordance with a previous study using narrow-band imaging showing no difference in dysplasia yield between CE and HD WLE^[48]. Of note, the authors of this study highlighted that prior studies assessing outcomes in chromoendoscopy had a “back-to-back” design where WLE was performed first followed by CE (as WLE cannot be performed after dye spraying). They postulated that such a design may have overestimated the yield of CE in detecting neoplasia and generated potential bias. To try and fill the discrepancy in the

data, Carballal *et al.*^[49] conducted the first randomized prospective trial evaluating the real-life experience of CE for dysplasia detection in long-standing IBD. In this prospective, multicenter cohort study from Spain, 350 patients with long-standing IBD underwent surveillance using a tandem colonoscopy method with each colonic segment being evaluated with WLE followed by CE using 0.4% indigo carmine with targeted biopsies of suspicious lesions. This study found a 57.4% incremental yield in dysplasia detection with CE vs WLE which was comparable in standard WLE vs HD WLE. The dysplasia miss rate was 40 of 94 lesions for white-light examination. Overall dysplasia detection rate was 15.7% in this real-life setting which is in line with previous estimates^[50]. This study also demonstrated no significant difference in dysplasia detection between CE-expert and non-expert endoscopists with no significant learning curve being observed. Though it has been concluded that CE improves dysplasia detection and is the most effective modality for surveillance, data regarding the effect on patient outcomes and cancer-related morbidity and mortality are still lacking.

BARRIERS TO PERFORMING CHROMOENDOSCOPY

While CE may provide some benefit with regards to increased dysplasia detection, there are several barriers to performing CE that must be considered when deciding whether to implement this technique.

Does expertise affect outcomes?

Much of the existing data, especially data demonstrating positive results, on CE arises from centers where gastroenterologists have particular expertise in performing CE^[42,43,50-53]. In the article by Mooiweer *et al.*^[47], the neoplasia detection rate for CE-based surveillance procedures was 11% compared with an average rate of 14% over several prior randomized trials examining neoplasia detection using CE. The authors of the study postulated that the lower neoplasia detection rate could be due to the inexperience of the endoscopists who had no dedicated training prior to performing the CE procedures. Conversely, Carballal *et al.*^[49] prospectively examined a cohort of IBD patients undergoing dysplasia surveillance between 2012-2014. The study protocol required that each colonic segment was evaluated with white light followed by 0.4% indigo carmine CE. When assessing for differences between expert (endoscopists who had performed > 20 CE-based dysplasia surveillance procedures) and non-expert endoscopists, the dysplasia detection rate was not found to be significantly different between the two groups (18.5% vs 13.1%, $P = 0.20$).

Cost concerns and technical disadvantages associated with CE

The equipment required to perform chromoendoscopy

usually includes one of the absorptive, contrast or reactive stains; these stains are generally inexpensive but have had issues with availability at times. Additionally, when performing chromoendoscopy, a spray catheter may be used to apply a uniform mist of the staining agent. The cost of these spray catheters is between approximately \$50-200. The equipment used to perform chromoendoscopy is compatible with most commonly used colonoscopies and the staining dyes are thought to add no additional risk to the patient^[54]. While the equipment may only add a small amount of cost to the procedure, the cost of additional time to perform high quality chromoendoscopy harder to quantify. The data on cost-effectiveness of this technique is quite limited. One formal cost effectiveness study has been conducted by Konijeti *et al.*^[55]. The authors utilized a Markov model to analyze the cost effectiveness of CE relative to WLE or no endoscopy for CRC surveillance in UC patients. This study design was chosen to better analyze need for surveillance and optimal surveillance intervals given increasing data about decreasing rates of CRC in patients with IBD. CE was found to be more effective and less costly than WLE at all surveillance intervals. However, compared with no surveillance, CE was cost effective only at surveillance intervals of at least 7 years, with an incremental cost-effectiveness ratio of \$77176. While this study suggests that CE may be more cost effective than white-light endoscopy, it only demonstrates a cost benefit over no surveillance if intervals are stretched out to greater than every 7 years. Overall, the question on whether chromoendoscopy offers a cost savings when used in a real-world surveillance program remains unanswered and more studies are required to truly clarify this.

One additional barrier that may prevent gastroenterologists in implementing CE is the additional procedure time. In the meta-analysis conducted by Subramanian *et al.*^[44], taking data from experienced centers, CE increased procedure time by 11 min overall. In the previously mentioned study by Kiesslich *et al.*^[43], procedure time was increased from 35 to 44 min (with CE) overall. However, this procedure time also included time dedicated for random biopsies. If a practice of conducting only targeted biopsies of suspicious lesion were employed, the additional procedure time added by using CE would likely be less. Additionally, increasing experience with CE may translate into shorter procedure times. In an implementation study by Leong *et al.*^[56], the authors observed that withdrawal time decreased with experience, ranging from 31 min for fewer than 5 procedures to 19 min for more than 15 procedures completed.

CLINICAL IMPACT OF CHROMOENDOSCOPY

CE is highlighted as a more effective modality than high definition white light endoscopy for detecting "invisible

dysplasia". However, it is important to consider whether there is truly a significant clinical impact of missed, "invisible" dysplastic lesions on CAC-related outcomes. To answer this question, Rubin *et al.*^[25] conducted a retrospective review of all cases of dysplasia or CRC in UC between November 1994 and October 2004. There were 1339 surveillance examinations in 622 patients with UC; forty-six patients were found to have dysplasia or CRC. seventy-five separate dysplastic or cancerous lesions were identified, 38 of 65 dysplastic lesions (58.5%) and 8 of 10 cancers (80.0%) were visible to the endoscopist as 23 polyps and masses, 1 stricture, and 22 irregular mucosa. Moreover, van den Broek *et al.*^[57] conducted a retrospective analysis of 1010 colonoscopies from 1998-2008. In total, 475 patients with UC were included in the study. Of all colonoscopies, 466 were performed for surveillance (in 167 patients) during which 11772 random biopsies were taken (median 29). Dysplasia was detected in random biopsy specimens alone in 5 colonoscopies (0.5%) in 4 patients (0.8%). Of these 4 patients, 2 had had visible dysplasia in previous colonoscopies, 1 had unifocal low-grade dysplasia that was not confirmed in 3 subsequent colonoscopies, and 1 had multifocal low-grade dysplasia and suspicious appearing ulcerations and underwent proctocolectomy, which confirmed the presence of neoplasia. Thus, dysplasia uncovered *via* random biopsy changed the management of only 1 of 475 patients (0.2%). In comparison, targeted biopsy specimens were positive for neoplasia in 83 colonoscopies (8.2%), and major therapeutic decisions (endoscopic resection or colectomy) were made in 61 of these cases (73%). This data suggests that "invisible dysplasia" detected on random biopsy is infrequent and of unclear clinical relevance. Though recent published data has shown promising results for a targeted biopsy approach to dysplasia surveillance^[38], the issue of invisible dysplasia likely remains an open issue that requires future investigation before eliminating random biopsy protocols altogether.

Does dysplasia detection affect long-term outcomes?

In a meta-analysis by Subramanian *et al.*^[44], the authors assessed the diagnostic yield, for detection of dysplasia between white light endoscopy and CE. In 6 studies involving 1277 patients, the difference in yield of dysplasia between CE and white light endoscopy was 7% (95%CI: 3.2-11.3) with a number needed to treat of 14.3. The difference in proportion of lesions detected by targeted biopsies was 44% (95%CI: 28.6-59.1) and flat lesions was 27% (95%CI: 11.2-41.9) in favor of CE. The aforementioned prospective studies, derived from expert centers, have demonstrated a significant difference in dysplasia detection with the utilization of CE^[42,43,50-53]. It must be noted, however, that most of these studies follow a cross-sectional design in which the number of detected lesions using CE is compared with the number of lesions detected using standard definition white-light endoscopy.

The intended goal of surveillance strategies is to detect early lesions that would lead to decreased colon cancer morbidity and mortality as well as unnecessary colectomies. Although chromoendoscopy may help to increase dysplasia detection compared to white light endoscopy, the clinical implications of this increased detection yield are largely unknown. In a follow-up^[58] to an initial index study^[50] looking at 102 high-risk IBD patients undergoing surveillance comparing CE and SD-WLE with random biopsy, 68 patients were longitudinally followed over a median of 27.8 mo to compare the techniques for dysplasia detection. CE was found to be more likely to detect dysplasia compared to targeted WLE (OR = 2.4, 95%CI: 1.4-4.0) and random biopsy (OR = 5.4, 95%CI: 2.9-9.9) Furthermore, in the 10 patients who underwent colectomy, CE was found to have better overall agreement between endoscopy and colectomy findings regarding the presence or absence of dysplasia which was 80% in CE, 20% for random biopsy and 10% in targeted WLE. Furthermore, a negative result from CE was the best indicator of dysplasia free outcome which may play a role in future decisions regarding recommended screening intervals. There is recent data with conflicting results regarding the impact of lesions detected with CE compared to WLE. In a retrospective study evaluating the implications of LGD found during surveillance in a Dutch cohort, 159/1065 patients evaluated were found to have LGD (133 visible lesions and 26 invisible lesions) for an overall incidence rate of 1.34 per 100 patient-years for all LGD lesions. There was a total of 10 cases which advanced to either HGD (5/10) or CRC (5/10) with no significant difference in the risk of advanced neoplasia during follow-up for index lesions detected with either WLE or CE^[59]. Though there was no difference in advancement in lesions detected by HD-WLE vs CE, this may have been limited by the overall low number of neoplastic lesions.

Finally, these findings are supported by a recent systematic review that demonstrated a superiority of CE over WLE in dysplasia detection when compared to SD-WLE only with no direct evidence of prevention of cancer-related mortality and time to interval cancer in patients who received CE^[60]. As described in this paper, there have been consistent data suggesting increased dysplasia detection with CE, however data showing an impact in cancer related outcomes are still lacking. More longitudinal head to head studies comparing CE with HD-WLE are needed to compare the outcomes of surveillance techniques and to confirm whether the clinical significance of these lesions are indeed comparable.

FUTURE DIRECTIONS

CE appears to increase the rate of colonic dysplasia detection in IBD patients undergoing CAC surveillance. CE with targeted biopsies is now an alternative to random biopsies for CAC surveillance. However, we currently do not have sufficient data to suggest that

there is a clear “real-world” benefit of CE including reduction in cancer rates or improved survival. As such, further studies are required to assess the effect on CAC outcomes, not only dysplasia detection rates. Patients are likely to seek answers from their gastroenterologist regarding the “best” way to prevent CRC. It is important that we are prepared to explain to patients how CE fits into their care.

It is likely that the future of CAC will be increasingly complex as our understanding of dysplasia in IBD and technologies available to detect and treat dysplasia evolve. Risk stratification will likely play a larger role in identifying patients most at risk for CAC who would most likely benefit from aggressive CAC surveillance, including CE.

It is imperative that more studies, particularly longitudinal studies should be done to clarify the role of CE in achieving the ultimate goal of reducing patient morbidity and mortality from CAC while also reducing unnecessary colectomies in patients with clinically insignificant lesions.

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Evolution of stereoscopic imaging in surgery and recent advances

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Abstract

In the late 1980s the first laparoscopic cholecystectomies were performed prompting a sudden rise in technological innovations as the benefits and feasibility of minimal access surgery became recognised. Monocular laparoscopes provided only two-dimensional (2D) viewing with reduced depth perception and contributed to an extended learning curve. Attention turned to producing a usable three-dimensional (3D) endoscopic view for surgeons; utilising different technologies for image capture and image projection. These evolving visual systems have been assessed in various research environments with conflicting outcomes of success and usability, and no overall consensus to their benefit. This review article aims to provide an explanation of the different types of technologies, summarise the published literature evaluating 3D vs 2D laparoscopy, to explain the conflicting outcomes, and discuss the current consensus view.

Key words: Three-dimensional laparoscopy; Endoscopy; Three-dimensional displays; Minimally invasive surgery; Stereoscopic

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Core tip: Capture of true stereopsis from the operative field is crucial for the subsequent projection of a high quality stereoscopic image. The latest three-dimensional (3D) systems using dual channel stereoendoscopes and passive polarizing stereoscopic projection generate high quality 3D images for minimally invasive surgery. There is subjective and objective laboratory based evidence supporting use of 3D vs two-dimensional for surgeons of all experience. However, their clinical application has yet to be addressed with Level 1 evidence.

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of stereoscopic imaging in surgery and recent advances. *World J Gastrointest Endosc* 2017; 9(8): 368-377 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v9/i8/368.htm> DOI: <http://dx.doi.org/10.4253/wjge.v9.i8.368>

INTRODUCTION

When Phillippe Bozzini first designed and used his "Lichtleiter" in 1803 to peer into the human body, the medical world unwittingly became reliant on observing the endoscopic view of the human body in only two-dimensions (2D).

In 1838 Charles Wheatstone^[1] was the first to accurately describe and publish the phenomenon of stereopsis - "... the mind perceives an object of three dimensions by means of the two dissimilar pictures projected by it on the two retinae ...". He described in his paper how the illusion of light projecting outwards from the surface of a metal plate that had been turned on a lathe had brought him to this realisation. He demonstrated the validity of his proposed mechanism of stereopsis by creating the "Wheatstone Stereoscope". This created an illusion of stereopsis simply by projecting different images to each eye of the viewer. By adjusting each image to give an impression of the perspective that would have been seen by that eye the viewer was left with a sense of a three-dimensional (3D) image.

The first endoscopic procedures were performed with single eyepiece rigid scopes which provided a monocular view for the operating surgeon. In the 1970s these images were relayed *via* a camera to a video monitor. Thus was born the modern era of "off screen" videoscopic operating. In the late 1980s the first laparoscopic cholecystectomies were performed and popularity for laparoscopic surgery began to increase exponentially. This prompted a sudden rise in surgical and technological innovations as the benefits and feasibility of minimal access surgery became more universally recognised. As minimal access surgery became more widely adopted the steepness of the learning curve for surgeons became more apparent. In particular the monocular laparoscopic view providing two-dimensional viewing, and associated reduced depth perception, became the focus of technological advances. Attention therefore turned to producing a usable 3D endoscopic view for surgeons, utilising different technologies for image capture and image projection. These evolving visual systems have been assessed in various research environments with conflicting outcomes of success and usability, and no overall consensus to their benefit.

This review article aims to provide an explanation of the different types of technologies, summarise the published literature evaluating 3D vs 2D laparoscopy, to explain the conflicting outcomes, and discuss the current consensus view.

First stereoptic views

Binocular microscopes were first used in 1922 in

otolaryngology to overcome the lack of depth perception associated with monocular operating microscopes by surgeon Gunnar Holmgren (1875-1954), Head of the University Clinic of Stockholm^[2]. These provided a stereoptic magnified view of the operating field and were quickly adopted by Otolaryngology, Neurosurgery and Orthodontics. In the 1980s, a German surgeon, Dr. Gerhard Buess^[3], pioneered Transanal Endoscopic Microsurgery (TEMS) utilising the first "stereoendoscope" with two optical channels, viewed through binocular eye pieces. In 1992, his team trialed the first prototype laparoscopic stereoendoscope in animal studies and clinically during laparoscopic cholecystectomies, and concluded the stereopsis facilitated complex laparoscopy^[4].

Image capture

In the laparoscopic setting, an image of the operative field may be captured in one of two ways. A traditional rod-lens laparoscope may be used to transmit the light from the image to outside the patient where a video camera then captures the image and sends it as an electrical signal to an image processor. Rod lens technology is now being superseded by "chip on the tip" technology utilizing small camera chips which capture the image at the tip of the laparoscope and then transmit the electrical signal along the laparoscope to an image processor.

The technology used to capture the 3D characteristics of the operating field includes the laparoscope, the camera and the image processor. Various systems have been developed and trialed in the literature. Single channel systems attempt to extract two perspectives of the operative field from a single point of view by splitting the image either with a prism or filter. The result is therefore not a true binocular image^[5]. Dual channel systems provide two horizontally separated images and thus produce two truly different perspectives of the operative field. "Insect eye" scopes allow for multi images to be captured and processed simultaneously. There is significant variety in the design of the video capture systems, which results in differences in the quality of the perceived image.

Projection systems

Projection systems aim to deliver the 3D view to the observer. Early systems used active shuttering projection, where alternate left and right views are displayed at high frequency on a display. With these systems the operator wears active shuttering glasses so that each eye receives only the corresponding right or left eye image. Robotic systems evolved to use a fixed viewing environment, where, like in a microscope, the observer has a separate image displayed to each eye. This concept was used in Head Mounted Displays (HMDs) where each eye was provided with its own screen to achieve stereopsis. The latest commercial projection systems use passive polarizing technology, which allows for two images to be projected simultaneously in different polarized waveforms. A high definition image is made

up of 1080 horizontal pixel lines. For passive polarizing projection the image projected has odd horizontal pixel lines emitting light polarized vertically and even lines emitting light polarized horizontally. The user then wears lightweight polarizing glasses to separate the correct image to each eye. The horizontal resolution of the image is therefore reduced by half to 540 pixels but the vertical resolution remains at 1080 pixels and the resulting image therefore remains high quality. When this technology was transferred from cinema projection systems to home television monitors the opportunity to use this system in the operating theatre became a possibility.

More recently there has been the experimental development of complex waveform projection systems (advanced systems based on anaglyph separation), autostereoscopic "glass-free" displays and holographic displays.

LITERATURE REVIEW

We aimed to identify from the literature, all published work evaluating 3D laparoscopic systems compared to 2D standard "classical laparoscopic" systems. PubMed, EMBASE, Ovid and Medline were used as search engines to identify any published full English language papers since 1996 which referenced stereopsis, 3D, vs two-dimensional or 2D, laparoscopy, endoscopic surgery, imaging and 3D. Overall, 361 titles were identified and 275 were discounted on further review of their titles. Of the 86 abstracts reviewed, 45 were further discounted as they didn't compare 3D with 2D. Review of these 41 papers acknowledged another six papers not identified by the original search. In total, 47 papers reported assessing 3D imaging systems against 2D systems in laparoscopic surgery. A further four titles were discounted on reading the whole paper, leaving 43 to be assessed. Ninety-six percent of the studies describe laboratory based experiments, involving a variety of laparoscopic skills tasks, some from validated curriculum programmes and others designed to mimic advanced laparoscopic skills. The studies also use a variety of subjects from non-surgical participants to those with a variety of experience in laparoscopic surgery.

The number of tasks, repetitions, cross over in visual systems, assessment of a learning curve and number of individual subjects involved varied in each study. Universally, the common themes assessed in the majority of studies were the time for task completion and performance, either by clearly defined errors or by other assessment defined scoring systems.

There has been speculation for the last 18 years over the benefit of 3D operating visual systems, largely based on conflicting reports in the literature and the ongoing evolution of the system technology. We separated data by the type of optical or projection system in order to clarify the results and explain the conflicting outcomes observed by different researchers.

Single channel endoscope studies

We identified 13 studies which used single channelled scopes to capture the laparoscopic view (Table 1). Seven of these studies^[6-12] utilised active shuttering projection systems with only one study^[7] identifying a significant improvement in outcomes using the 3D system compared to the 2D standard. All of these studies also reported poor subjective outcomes associated with the 3D systems, including visual strain, headaches and nausea as well as an awareness of flickering of the screen. Four studies^[13-16] assessed a second-generation 3D system, which used a single channel scope and projected left and right images to head mounted display systems, allowing individual eye projection without loss of light or image quality. Three of the studies reported significant improvement in performance for novices. The HMDs, although bulky, did not cause any of the cortical disturbances reported by the active shuttering systems. The final two studies^[17,18] used single channel scopes and the latest passive polarizing systems. Neither identified a significant difference in respective outcomes with the 3D systems. Both studies reported that a period of adaptation was required to overcome any higher processing symptoms that the 3D visual system induced^[17].

Dual channel endoscope studies

Robotic "fixed screen" studies: Nine studies investigated the effect of stereopsis in laparoscopic surgery utilising the Da Vinci robotic system (Intuitive, California United States) (Table 2)^[19-27]. Stereopsis is achieved with a binocular endoscope and two camera heads for separate left and right image capture. Each image is received by the respective eye, simultaneously using a fixed console, alleviating the need for shuttering, polarizing or head mounted projection. All studies reported significant improvement in performance with the Da Vinci system in 3D mode over 2D mode. Notably, performance advantages were independent of participant experience^[27].

Studies using screen projection and eye-glass technology

Five studies reported outcomes with binocular stereo-endoscopes (Table 3), alternating screen image and active shuttering glasses^[28-32]. Four of the five studies reported significant improvements in performance with 3D systems^[28-32]. In the one study (Wentink *et al.*^[30], 2002) the screen was placed very close to the surgeon while the working environment from the stereoendoscope was 12 cm. This produces conflict between convergence and focus for the operating surgeon, and it is therefore unsurprising that the 3D system showed poorer performance.

Eight studies evaluated passive polarizing screen and glass technology (Table 3)^[33-40]. Two of these studies retrospectively compared a series of operations (laparoscopic cholecystectomies and laparoscopic

Table 1 Single channelled scopes

Ref.	Year	Projection system for 3D	Who and what assessed	Objective outcomes	Subjective outcomes
McDougall <i>et al</i> ^[6]	1996	Active shuttering screen and glasses	22 urological and gynaecological surgeons, non-novice Pig-lab, laparoscopic vessel dissection and securing, suturing and knot tying	Time for completion. No significant difference found	3D not felt to enhance image quality or enhance performance. Blurred vision and eye fatigue with 3D
Dion <i>et al</i> ^[7]	1997	Active shuttering screen and glasses	Surgeons and non-surgeons. Lab visual ($n = 8$) and motor skills ($n = 9$)	Time and errors. Improvement in both with 3D	Glasses bothersome and dizziness reported
Chan <i>et al</i> ^[8]	1997	Active shuttering screen and glasses	32 surgeons, 11 with and 21 without laparoscopic experience 1 × lab based skills task	Time for completion in 2D and 3D (1 repetition). No significant difference	50% felt no improved performance although 66% felt depth perception improved 40% felt reduced image quality and dimmer; 10% reported dizziness and eyestrain
Hanna <i>et al</i> ^[9]	1998	Active shuttering screen and glasses (A/S)	4 surgical SpRs performing 60 laparoscopic cholecystectomies	Time for completion and errors No significant difference	Visual strain, headache and facial discomfort with 3D system
Mueller <i>et al</i> ^[10]	1999	Active shuttering screen and glasses	30 subjects (10 with and 20 without laparoscopic experience) 4 × lab based skills tasks for all, then experienced did suturing tasks	Time for attempts, and success/failure of attempt No significant difference	Reported loss of concentration, headaches and distraction with 3D system
Herron <i>et al</i> ^[11]	1999	3D (active shuttering screen and glasses) and 3D HMD	50 laparoscopic novices 3 × lab based skills tasks	Time to completion of 3 skills tasks in each visual system (2 × repetitions) No significant difference	Although 48% preferred 3D A/S screen over all, 7% and 25% respectively reported headaches with 3D screen and 3D HMD. 82% found HMD uncomfortable
Mueller-Richter <i>et al</i> ^[12]	2003	3D (active shuttering screen and polarising glasses) and 3D Autostereoscopic screen	59 laparoscopic novices 3 × lab based skills tasks	Number of completions in time limit and subjective difficulty No significant difference	Flickering reported with both 3D systems
Bhayani <i>et al</i> ^[13]	2005	HMD	24 surgical residents, minimal laparoscopic experience. 1 × lab based skills task	Time for completion in 2D and 3D (1 repetition) Significant reduction in time	> 50% preferred the 3D system and found task easier in 3D No subjective assessment on physical symptoms
Patel <i>et al</i> ^[14]	2007	HMD	15 novices and 2 experts 5 × lab based skills tasks	Time and accuracy in 2D and 3D (1 repetition) of the novices compared to the experts Significant difference in both for novices only in 3D	NA
Bittner <i>et al</i> ^[15]	2008	HMD	2 novices, 2 intermediate and 2 experts 2 × lab based suturing tasks (based on handedness, visual system and articulating needle holder)	Time and accuracy in 2D and 3D (multi repetitions with each variable) No significant difference	83% felt improved depth perception. No reported physical symptoms
Votanopoulos <i>et al</i> ^[16]	2008	HMD	36 surgical residents and medical students (11 with and 25 without laparoscopic experience) 6 × lab based skills tasks (rpt 3/12 later)	Time and errors in 2D and 3D (1 repetition) Significant improvement in time and errors in novice group only	NA
Kong <i>et al</i> ^[17]	2009	Passive polarising screen and glasses	21 novices and 6 experienced surgeons 2 × lab based skills tasks	Time and errors in 2D and 3D (4 repetitions of each over 4 d) Significant reduction in errors in 3D novices, no other significant difference noted	Dizziness and eye fatigue in novice with 3D system which improved with time
Mistry <i>et al</i> ^[18]	2013	Passive polarising screen and glasses	31 medical students (novices) 4 × lab based skills tasks (MISTELS)	Task Performance in 2D and 3D as per MISTELS scoring system No significant difference	No detrimental symptoms with 3D

NA: Not available; 3D: Three-dimensional; 2D: Two-dimensional; HMD: Head mounted display.

Table 2 Dual channel laparoscopes - Robotic fixed screen

Ref.	Year	Projection system for 3D	Who and what assessed	Objective outcomes	Subjective outcomes
Falk <i>et al</i> ^[19]	2001	Da Vinci	15 experienced laparoscopic surgeons 6 × lab based skills tasks (increasing difficulty)	Time and errors in 2D and 3D and 2DHD (1 repetition in each view) Significant differences in time and errors in 3D	Only 33% felt 3D better view No detrimental symptoms reported
Munz <i>et al</i> ^[20]	2004	Da Vinci	11 experienced laparoscopic surgeons 4 × lab based skills tasks	Errors and performance (ICSAD assessment - time, no. movements and distance moved) Significant difference in both in 3D	NA
Moorthy <i>et al</i> ^[21]	2004	Da Vinci	10 surgeons of varying experience Lab based suturing task	Time and distance travelled of instruments in 2D and 3D Significant difference in both in 3D	NA
Badani <i>et al</i> ^[22]	2005	Da Vinci	7 surgeons (3 experienced with Da Vinci, 4 not)	Time and errors	NA
Blavier <i>et al</i> ^[23]	2007	Da Vinci	2 × lab based suturing tasks 40 medical students Lab based skills task	Significant difference in 3D in all areas Errors, performance and learning curve Significant difference in 3D	No detrimental symptoms reported
Byrn <i>et al</i> ^[24]	2007	Da Vinci	12 surgeons of varying experience 4 × lab based skills tasks	Time and errors in 2D and 3D Significant difference in 3D	No detrimental symptoms reported
Blavier <i>et al</i> ^[25]	2007	Da Vinci	60 medical students 4 × lab based skills task (increasing difficulty)	Specific performance metric score Significant difference in 3D in all tasks	No detrimental symptoms reported
Fishman <i>et al</i> ^[27]	2008	Da Vinci and prototype Ames stereoscopic camera	12 subjects of varying exposure to stereoptic systems	Time for completion while altering binocular disparity of stereoptic camera until 0% (matching 2D vision)	NA
Blavier <i>et al</i> ^[28]	2009	Da Vinci	Lab based skills task using Da Vinci manipulator 80 subjects (60 novice individuals and 20 expert laparoscopic surgeons) Lab based task	Significant difference with 3D from binocular disparity Time for task completion and estimation of time in 2D or 3D not both Significant difference in 3D for novices, similar results for experts	NA

NA: Not available; 3D: Three-dimensional; 2D: Two-dimensional.

Table 3 Dual channel laparoscopes - Screen projection and glasses

Ref.	Year	Projection system for 3D	Who and what assessed	Objective outcomes	Subjective outcomes
Birkett <i>et al</i> ^[26]	1994	Active shuttering screen and Active glasses then polarised glasses <i>vs</i> 2D	10 Subjects? experience 2 × lab based skills tasks	Time take for repetitive cycles; No difference in simples task, reduced time in complex task	NA
Peitgen <i>et al</i> ^[29]	1996	Active shuttering screen and glasses	60 subjects (20 novices, 20 beginners, 20 advanced laparoscopic surgeons) 2 × lab based skills tasks	Time and accuracy of tasks Both significantly improved in 3D, independent of experience	NA
Wentink <i>et al</i> ^[30]	2002	Active shuttering screen and polarised glasses <i>vs</i> TFT display <i>vs</i> projection <i>vs</i> standard (2D)	8 surgeons with laparoscopic experience Lab based skills task	Time for task completion, 10 repetitions but only 2 surgeons per visual system No improvement with 3D	Felt image quality poorer with 3D
Jourdan <i>et al</i> ^[31]	2004	Active shuttering screen and glasses	8 experienced laparoscopic surgeons 5 × lab based skills tasks	Time and errors, 10 repetitions each, in each visual system Significant improvement in both in 3D	NA
Feng <i>et al</i> ^[32]	2010	Active shuttering screen and polarised glasses (SD <i>vs</i> 2D SD <i>vs</i> 2D HD)	27 subjects (16 novices, 11 with varying laparoscopic experience) Lab based skills task	Time and economy of movement Time significantly improved over both 2D systems in 3D, economy of movement improved in 3D <i>vs</i> HD, not SD 2D	Felt improved depth perception in 3D
Hubber <i>et al</i> ^[33]	2003	Prototype passive polarising screen and glasses	16 Medical Students (novices) Lab based skills tasks	Time and performance (ICSAD) Improvements in 3D significant over 2D	NA
Honeck <i>et al</i> ^[34]	2012	Passive polarising screen and glassed	10 novices and 10 experienced laparoscopic surgeons 5 × lab based skills tasks	Time and errors (1 × repetition, in only 1 of the visual systems) No significant improvement in time, reduction in errors significant in both groups in 3D	No impairment felt in subjective feedback when using the 3D system
Smith <i>et al</i> ^[35]	2012	Passive polarising screen and glassed	20 novices 4 × lab based skills tasks	Time and errors (10 repetitions of each task in each visual condition) Significant improvement in time and errors in 3D	NA

Bilgen <i>et al</i> ^[36]	2013	Passive polarising screen and glassed	3 surgeons Clinical - 11 laparoscopic cholecystectomies performed in 3D (compared to 11 performed retrospectively in 2D)	Time Significant reduction in time when performed in 3D, compared to case matched lap choles performed previously in 2D	NA
Sinha <i>et al</i> ^[37]	2013	Passive polarising screen and glassed	Retrospective analysis of 451 clinical gynaecological surgery performed in 3D Case matched assessment of 200 hysterectomies performed in 3D vs 2D	Time Significant reduction in operating time and morcellation time when performed in 3D	NA
Cicione <i>et al</i> ^[38]	2013	Passive polarising screen and glassed	33 subjects (10 experts and 23 novices) 5 × lab based skills tasks (Basic Laparoscopic Urological Skills)	Time and errors Overall, significant improvement in time and errors (although experts only improved time in 1 task in 3D)	Subjective Questionnaire - felt tasks were easier in 3D universally
Lusch <i>et al</i> ^[39]	2014	Passive polarising screen and glassed	24 subjects (10 medical students, 7 residents, 7 expert surgeons) 6 × lab based skills tasks	Time and errors 4 out of 5 skills tasks had significantly improved time and errors when done in 3D, independent on experience	Optical resolution and depth perception improved in 3D
Smith <i>et al</i> ^[40]	2014	Passive polarising screen and glassed	20 experienced surgeons 4 × lab based skills tasks	Time and errors (10 repetitions of each task in each visual condition) Significant improvement in time and errors in 3D	Subjective assessments using NASA Task Load Index - improvements with 3D all sections

NA: Not available; 3D: Three-dimensional; 2D: Two-dimensional; HMD: Head mounted display.

gynaecological operations) with case matched procedures in standard 2DHD systems^[36,37]. Both reported a significant reduction in operating times for case matched procedures. Six laboratory based studies identified significant improvements in most of the tested parameters when tasks were performed in 3D^[33-35,38-40]. Two other studies (Honeck *et al*^[34], 2012, and Cicione *et al*^[38], 2013) found varied performance improvements in 3D. Honeck found reduced errors but no significant time improvements, while Cicione *et al*^[38] (2013) found an overall significant improvement with 3D over 2D. These advantages were only observed in the expert subgroup when performing one task, the "Peg Transfer". However both studies only allowed for a single repetition of tasks in 3D and 2D before comparison. In studies which allowed for repetitions and plateauing of the learning curve in both visual environments before comparison, there was a universal improvement when comparing 3D over 2D, independent of experience^[33,35,39,40].

Comparing different scopes and projection systems

Four papers described using more than one type of 3D system in their comparison of 3D vs 2D (Table 4)^[41-44]. Hanna *et al*^[42] (2000) assessed single-channel scope and dual-channel scope systems, both using active shuttering screen/glasses systems compared to a standard 2D system when performing laboratory based bowel anastomosis. The 3D systems were evaluated together, rather than separately and showed no significant difference in time or precision compared to 2D. However, closer analysis of the data implies the dual channel scope demonstrated a trend of improved time and precision compared to its single channel

counterpart. Visual strain was reported using both stereoendoscopes. Wilhelm *et al*^[43] (2014) reported all performance parameters were superior in 3D over 2D using a variety of experimental and commercially available systems, although visual disturbance related to the autostereoscopic screen only. Finally, Wagner *et al*^[44] (2012), compared single channel scope with HMD technology (in 3D and 2D settings) with robotic dual channel fixed screen technology (2D and 3D settings) and demonstrated significant time reductions with robotic 3D across all other laparoscopic outcomes.

Other prototype projection systems

Four publications assessed prototype projection systems (Table 5)^[45-48]. Three used autostereoscopic screen technology with binocular scopes thus negating the need for eyewear^[45,46,48]. Improvements in all outcomes were seen with the 3D group. Storz *et al*^[47] (2011) used a novel projection system with a wavelength multiplex camera and monitor with wavelength polarizing eyewear (a technology based on original anaglyph systems). This again returned a true sense of stereopsis and improvements in outcomes were significant in 3D over 2D.

DISCUSSION

There is subjective and objective laboratory based evidence supporting use of 3D vs 2D for surgeons of all experiences as it provides the most realistic view of the operating field. It is also evident that stereoscopic imaging technology is continuing to evolve to generate higher quality 3D images.

Table 4 Comparing multisystems

Ref.	Year	Projection system for 3D	Who and what assessed	Objective outcomes	Subjective outcomes
van Bergen <i>et al</i> ^[441]	1998	2 × single channelled and 2 × dual channelled scopes + active shuttering screen <i>vs</i> 2D	40 subjects - novices Variety of different models and skills tasks	Times and errors Objectively - significant improvement in 3D throughout	Subjectively - all tasks judged easier in 3D
Hanna <i>et al</i> ^[442]	2000	Single-channel scope + active shuttering screen and glasses; double-channel scope + active	10 experienced surgeons Lab based endoscopic anastomotic suturing	Time, precision of suture placement and pressure leakage score of anastomosis (2 × repetitions in each visual system) 3D systems evaluated together, no significant difference noted in 3D	Visual strain reported with 3D systems
Wilhelm <i>et al</i> ^[443]	2014	Dual channel scope + passive polarising screen and glasses <i>vs</i> 2D <i>vs</i> autostereoscopic screen	48 subjects, varying experience Lab based suturing task	Time, economy of movement (electromagnetic tracking) and workload assessments (using NASA Task Index Score) All performance parameters were superior in 3D	No symptoms in 3D PP system, visual disturbance reported with autostereoscopic display
Wagner <i>et al</i> ^[444]	2012	Single-channel scope + HMD <i>vs</i> robotic dual channel scope + fixed head view	34 subjects (18 novices) 3 × lab based skills tasks	Time 3D robotic performance faster than all others, significantly	NA

NA: Not available; 3D: Three-dimensional; 2D: Two-dimensional; HMD: Head mounted display.

Table 5 Other prototype projection systems

Ref.	Year	Projection system for 3D	Who and what assessed	Objective outcomes	Subjective outcomes
Taffinder <i>et al</i> ^[445]	1999	Dual channel scope with autostereoscopic/glass free screen	28 subjects (16 novices and 12 experienced laparoscopic surgeons) Novices = basic grasping and cutting lab based skills Experienced = suturing and complex cutting lab based skills	Time and performance score (ICSAD assessment tool) Significant improvement in 3D over 2D laparoscopy	No side effects reported with 3D
Ohuchida <i>et al</i> ^[446]	2009	Dual channel scope with "Cyberdome" projection system	23 novices 6 × lab based skills tasks	Time, errors and performance Significant improvement in all parameters in 3D with cyberdome over 2D	NA
Storz <i>et al</i> ^[447]	2011	Dual-channel scope + wavelength multiplex camera and monitor with polarising glasses	30 subjects (20 medical students and 10 experienced laparoscopic surgeons) 5 × lab based skills tasks	Time and errors In 4 out 5 tasks, significant reduction in time in 3D, in 4 out of 5 tasks, significant reduction in errors	NA
Khoshabeh <i>et al</i> ^[448]	2012	Dual-channel scope + Multiview autostereoscopic display/glass free screen	3 experienced laparoscopic surgeons 2 × lab based skills tasks	Time and errors Reduced time and errors using 3D	NA

NA: Not available; 3D: Three-dimensional; 2D: Two-dimensional.

Capture of true stereopsis from the operative field is crucial for the subsequent projection of a true stereoptic image. However, with such focus on producing an effective projection system, the acquisition and true stereopsis of the image has sometimes been overlooked. It is clear from this review that in systems that compromised on the capture of two truly separate images of the operative field, they yielded no advantage for the participants using 3D over 2D. In studies using dual channel stereoendoscopes, the separate lenses within the laparoscope provided a greater spatial impression of stereopsis^[449-51]. Consequently, for the operator, there is a more accurate appreciation of depth. Fishman *et al*^[27] (2008) concluded there was deterioration in laparoscopic performance by reducing

horizontal lens separation in an experimental dual channel scope (thereby reducing stereopsis impression). However single channel systems produce images of greater clarity and resolution due to the greater size of the single optic channel for light transfer^[52]. Single channel optics can produce convincing stereopsis only at close operating distances, whereas dual channel systems provide significant stereopsis in larger cavities, where there is greater distance from the end of the stereoendoscope to the operating site^[51]. Close operating or near field objects with dual channel systems can cause visual discomfort due to the fixed focal point of the two lenses and our natural convergence conflicting. Therefore it is not surprising that the majority of studies which utilised single channel

laparoscopes did not show a benefit of 3D laparoscopy as all used target operating points distant to the scopes key stereoptic capabilities, irrespective of the projection system employed.

Modern projection systems attempt to provide as true a representation of the natural 3D view as possible, whilst balancing comfort and visual ease for the observer(s) and maintaining the brightness and resolution quality of the image. Active systems caused visual disturbances, headaches and symptoms of nausea due to the conflict of convergence and accommodation, as well as flickering and discomfort for the viewer due to the cumbersome battery powered glasses.

Early 3D images had poor resolution and luminosity as early cameras could not cope with low light levels or capture at high resolution. Projection systems were equally constrained by low refresh rates, low resolution and brightness. This added to discomfort and degraded the early 3D view^[51]. Falk *et al.*^[19], 2001, demonstrated that image quality is vital for precision and surgical performance, as 2DHD systems produced better results when compared with standard view 2D and 3D. The use of polarizing glasses and filters over the shuttering screen provides a more comfortable wear experience for the observer but this is at the expense of image brightness.

Head-mounted displays provide good quality images with no degradation in quality or light and preserve the normal hand-eye axis^[53]. However open sided head units, which do not block surrounding visual stimuli, can cause headaches and dizziness due to conflicting information from visual input and body position whilst with sealed units the surgeons are isolated from their surroundings and unable to react to unforeseen environmental incidents^[42].

The Da Vinci robotic system (intuitive, United States) allows for fixed console viewing and so provides an unparalleled quality of stereopsis for the surgeon. All the studies which assessed binocular and biocular (same view through each eye, therefore 2D view)^[51], showed statistically significant advantages with 3D performance for time and errors, reduced motion, and all other comparative markers for surgical performance. There can be no doubt that the advantages noted were purely due to the improvement in view provided by reintroduction of natural stereoptic depth cues. However use of the robot is limited to a relatively small number of procedures where advantage of the robotic platform over standard laparoscopic techniques has been established.

Later studies (Table 3), which used binocular endoscopes and the latest passive polarizing projection systems, identified no subjective impairment or "side effects" to using the 3D systems. The majority identified significant differences in their respective markers of surgical performance when comparing classical laparoscopy to 3D systems. Whilst surgeon experience does affect outcomes, it must be appreciated that

experience in classical laparoscopy leads to the development of techniques to overcome the lack of stereopsis. This therefore favours poorer outcomes with the 3D system in studies where the assessment was made after short exposure times and single repetition of skills^[34,38,39]. Studies which accounted for learning curves by allowing familiarisation with the system with multiple repetitions and well powered sample sizes demonstrate clearly the benefits in performance achievable with 3D laparoscopy^[31,33,35,40].

High quality experimental studies have shown that the latest 3D systems using dual channel stereo-endoscopes and passive polarizing technology provide a "near natural" view, almost comparable to that observed by the Da Vinci. However, their clinical application has yet to be addressed with Level 1 evidence. The only randomised clinical trial assessing 3D systems^[9], and addressed by Cochrane review^[54], showed no discernible difference for laparoscopic cholecystectomy performance. However, this study is over ten years old and the system assessed used a single channel scope and active shuttering projection, which was unlikely to have provided a true spatial impression of the operating field throughout. Studies that investigated the clinical application of the latest 3D systems identify performance advantages but are underpowered^[36,37]. Establishing the benefits of these systems can only truly be addressed within randomised clinical trials, using appropriately powered sample sizes.

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Endoscopic ultrasonography - emerging applications in hepatology

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Abstract

The inspection of the liver is a valuable part of the upper endoscopic ultrasonography (EUS) studies, regardless of the primary indication for the examination. The detailed images of the liver segments provided by EUS allows the use of this technique in the study of parenchymal liver disease and even in the diagnosis and classification of focal liver lesions. EUS has also emerged as an important tool in understanding the complex collateral circulation in patients with portal hypertension and their clinical and prognostic value. Recently, EUS-guided portal vein catheterization has been performed for direct portal pressure measurement as an alternative method to evaluate portal hemodynamics. In this review, the authors summarize the available evidence regarding the application of EUS to patients with liver diseases and how we can apply it in our current clinical practice.

Key words: Endoscopic ultrasonography; Portal hypertension; Gastroesophageal varices; Focal liver lesions; Liver biopsy

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Core tip: This review summarizes the current status of the available evidence regarding the application of endoscopic ultrasonography (EUS) to patients with liver diseases, focusing on recent breakthroughs and its potential application on clinical practice. We highlight the

emerging role of EUS in the study of parenchymal liver disease as well as in the diagnosis and classification of focal liver lesions. Finally, we emphasise the crucial role of EUS in the understanding of the complex collateral circulation in patients with portal hypertension.

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INTRODUCTION

In the recent years, there has been remarkable improvement in hepatology, with new treatments for viral hepatitis, recommendations for the follow-up of cirrhotic patients and treatment of portal hypertension complications. These advances have brought an increased need for the assessment of liver function and liver histologic characterization.

Endoscopic ultrasonography (EUS) has become an important tool, not only in the diagnosis of several gastrointestinal lesions, but also in performing various therapeutic manoeuvres^[1]. Due to the close proximity of the transducer to the liver, from the transgastric and transduodenal routes, EUS allows a clear visualization of the liver anatomy and its vasculature providing accurate and detailed images^[2,3] (Figure 1). As experience grows with this technique new indications for EUS continue to emerge, and endosonographers have made an effort to define a clinical role for EUS in liver diseases.

This review summarizes the available evidence regarding the application of EUS to patients with liver diseases and how it can be applied in a current clinical practice.

EUS AND LIVER PARENCHYMAL DISEASE

Although non-invasive tests, such as elastography or serologic markers for liver fibrosis, have been developed, the liver biopsy remains an important part of the liver disease evaluation and management^[4].

Liver biopsy has been commonly performed by percutaneously image-guided. A transjugular fluoroscopy-guided approach is used when the percutaneous route is not safe, because of coagulopathy or ascites^[5,6].

EUS-guidance represents an emerging method of liver biopsy. EUS provides images of both lobes of the liver; moreover biopsy needle can be safely directed into the liver under image guidance, and intervening vessels and organs can be avoided.

EUS-guided liver biopsy (EUS-LB) for studying parenchymal liver disease has largely been studied with the use of different needles. Since a tissue core biopsy with a preserved architecture is crucial to diagnosis and fully characterization of the hepatic diseases,

needles specifically designed for core biopsy have been used. The ability to obtain specimens of liver tissue for histologic examination with a Tru-Cut biopsy needle dedicated for EUS-guided biopsy, the Quick-Core® needle (Cook® Medical), were demonstrated in some published studies^[7,8]. In a study by DeWitt *et al*^[8], 21 consecutive patients underwent liver biopsy by using a Quick-Core® needle. Liver biopsy specimens were able to provide diagnostic clinical information in only 15 of 21 patients (71%), the total specimen length was a median of 9 mm, with a median of 2 complete portal tracts. The technique was safe and feasible. However the samples were smaller than those traditionally considered adequate for histologic assessment.

The Tru-Cut biopsy needle failed to reach widespread use due to technical difficulties with its utilization. To overcome the main limitations of a Tru-Cut biopsy needle, the same manufacture developed a new needle, the ProCore® needle (Cook® Medical). Sey *et al*^[9] compared the diagnostic yield of a 19-gauge ProCore® needle with a Quick-Core® needle. A total of 45 patients underwent liver biopsy by using the Quick-Core® and 30 patients the ProCore® needle. The ProCore® needle group required fewer passes (median 2 vs 3, $P < 0.0001$), produced a longer median specimen length (median 20 mm vs 9 mm, $P < 0.0001$) with more complete portal tracts (median 5 vs 2, $P = 0.0003$) and also allowed a histologic diagnosis more frequently (97% vs 73%).

Other studies have also been published demonstrating the adequacy of liver tissue sampling by a 19-gauge FNA needle. Stavropoulos *et al*^[10] presented a study in which patients underwent a EUS-LB with a 19-gauge FNA needle. All patients underwent EUS with a 7.5-MHz linear echoendoscope (Olympus GF-UC140P-AL5; Olympus, Tokyo, Japan) as the initial procedure. Twenty-two patients underwent a EUS-LB of the left lobe of the liver, a median of 2 passes (range 1-3) yielded a median specimen length of 36.9 mm, with a median of 9 complete portal tracts and a diagnostic yield of 91%, without post-procedure complications. The authors concluded that EUS-LB by using a 19-gauge FNA needle was feasible, safe, with an excellent diagnostic yield and sample adequacy for histologic examination.

To evaluate the diagnostic yield of EUS-LB in a large patient cohort, Diehl *et al*^[11] recently presented a prospective, multicentre study with 110 patients who underwent EUS-LB at eight centres. EUS examination was performed with a linear echoendoscope (GF-UC140P, Olympus America, Center Valley, PA, United States). The biopsy was performed using a 19-gauge FNA needle, with or without a stylet, 7-10 to-and-fro motions of the needle were made per pass (1-2 pass were made), using the fanning technique and almost all endoscopists preferred to use full suction for the needle aspiration. Adequate liver biopsy specimens for pathological diagnosis were obtained in 98% of patients, with a median specimen length of 38 mm, with median of 14 complete portal tracts. There were five patients whose tissue yield was

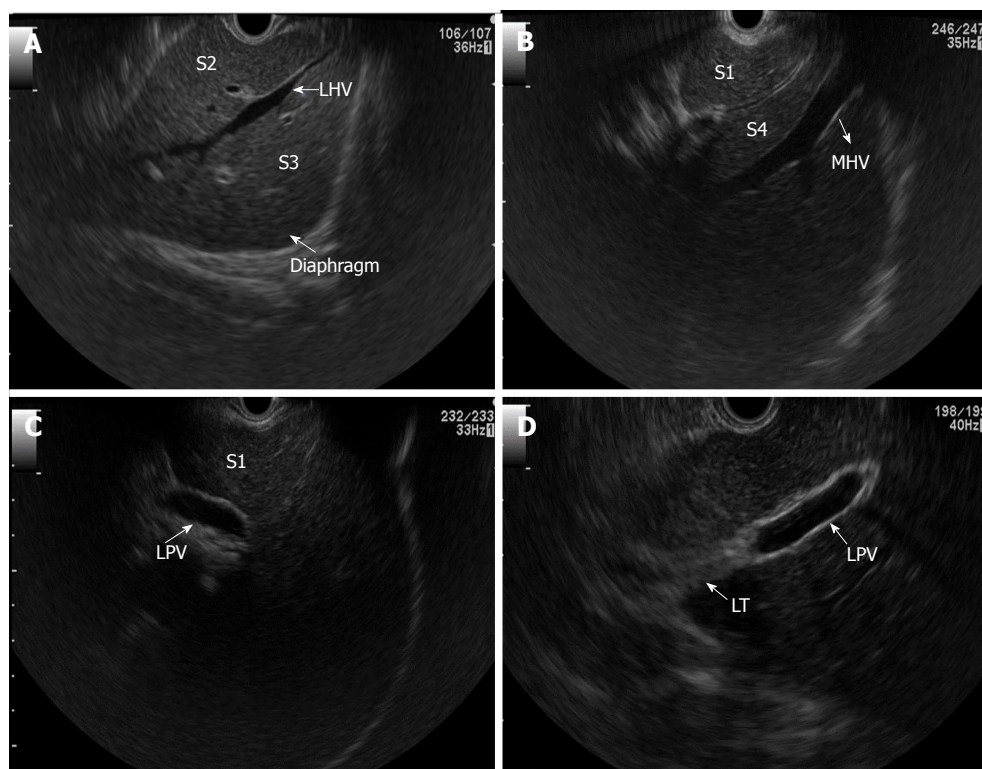


Figure 1 Endoscopic ultrasonography images of the hepatic structures from the proximal stomach: The left lateral segments (S2 and S3) (A); S1 (caudate lobe) and segment 4 (S4) (B); S1 with portal vein behind it (C); Umbilical part of the left portal vein (D). Images recorded using the curved linear scanning echoendoscope (GF-UCT 180; Olympus Medical Systems, Tokyo, Japan) coupled with a ProSound Alpha 10 processor (Aloka, Tokyo, Japan). LHV: Left hepatic vein; MHV: Middle hepatic vein; LPV: Left portal vein; LT: Ligamentum teres.

less than 6 complete portal tracts with aggregate length less than 15 mm. Nevertheless it has been possible to obtain a histological diagnosis in samples from four patients. There was no statistical difference in the yield between bilobar, left lobe only, or right lobe only biopsies. There was, however, one complication, where self-limited bleeding (pericapsular hematoma) occurred in a patient with coagulopathy and thrombocytopenia (platelets, 64000; INR, 1.42), evaluated for abnormal transaminases.

In a recent study by Pineda *et al.*^[12] the EUS-LB was for the first time compared with the other methods of liver biopsy (percutaneous and transjugular). The EUS-LB was obtained in widely separated regions of the liver or one single region only using a 19-gauge FNA needle. There were 68 EUS-LB cases when both lobes were biopsied, the left lobe only in 34 cases and transduodenal liver biopsy only in 8 cases. A sample of 27 percutaneous liver biopsies and 38 transjugular liver biopsies were selected. EUS-LB of both liver regions produced significantly more tissue in terms of both total specimen length (40 mm vs 25 mm, $P < 0.001$) and complete portal tracts (17 vs 10, $P < 0.001$) compared to a percutaneous liver biopsy. EUS-LB produced significantly longer total specimen length than transjugular liver biopsy (40 mm vs 34 mm, $P = 0.01$) and similar complete portal triads (17 vs 15.5, $P = 0.22$). Those EUS-LB cases in which the left lobe only was sampled were not statistically different compared

to percutaneous and transjugular liver biopsy.

Nowadays the EUS-LB could be considered a procedure with several advantages. The liver can be sampled under ultrasonographic visualization, which is important to avoid vessels and organs. The biopsy of both left and right lobes of the liver can overcome the concerns about sampling error, since a more accurate representation of liver histology can be provided. Another potential advantage is that the patient is sedated for the EUS procedure, making the experience less uncomfortable.

All previous reports excluded patients with international normalized ratio (INR) > 1.5 , thrombocytopenia (platelets $< 50000/\mu\text{L}$) and antiplatelet agents within 5 d of the procedure. Although the needle puncture occurs under ultrasonographic guidance, Glisson's capsule is punctured, and bleeding remains a concern, thus the use of EUS for these patients is not recommended. The Table 1 summarizes the data from the main studies of EUS-LB.

EUS AND FOCAL LIVER LESIONS

Focal liver lesions are frequently incidentally discovered during an imaging test, such as ultrasonography (US) or computed tomography (CT). Other times they are found in patients with risk factors for hepatic malignancy or even during a preoperative staging of extra-hepatic malignancies. Accurate characterization of these lesions remains an integral part of patients' evaluation, as the

Table 1 Data from the main studies of endoscopic ultrasonography-guided liver biopsy

Ref.	Study design	Needle	Passes	Specimen length (median)	Complete portal tracts (median)	Histological diagnosis
DeWitt <i>et al</i> ^[8]	Prospective unicentre study <i>n</i> = 21	Quick-Core ¹	1-4	9 mm	2	71%
Diehl <i>et al</i> ^[11]	Prospective multicentre study <i>n</i> = 110	19G (FNA) Expect ¹	1-2	38 mm	14	98%
Stavropoulos <i>et al</i> ^[10]	Prospective unicentre study <i>n</i> = 22	19G (FNA) Echotip ²	1-3	36.9 mm	9	91%
Sey <i>et al</i> ^[9]	Prospective unicentre study <i>n</i> = 75	Quick-Core ¹	1-7	9 mm	2	73%
		ProCore 19G ¹	1-3	20 mm	5	97%

¹Cook® Medical; ²Boston Scientific. FNA: Fine needle aspiration.

extent of liver involvement may change clinical stage and management.

The inspection of the liver is a valuable part of the upper EUS studies, regardless of the primary indication for the examination. Recently, EUS and EUS-guided fine needle aspiration (EUS-FNA) has emerged as an important tool in the diagnosis and classification of liver lesions. Most of the liver segments can be visualized with the echoendoscope^[3] and the proximity of the ultrasound probe to the liver parenchyma provides exceptional images of the liver parenchyma, which may have a key role in the detection, characterization and even in the definitive diagnosis of liver lesions.

Awad *et al*^[13] evaluated the feasibility of EUS for the detection and diagnosis of liver lesions in 14 patients with known or suspected hepatocellular carcinoma (HCC) and metastatic liver lesions. Consecutive patients referred for EUS with suspected liver lesions were evaluated. EUS not only successfully identified all previously hepatic lesions described by CT scan, but also identified new or additional lesions in 4 patients (28%), all less than 0.5 cm in size. Nine patients underwent EUS-FNA of hepatic lesions, with a 22-gauge needle and two passes for each lesion, and all FNA yielded adequate specimens. The authors suggested that EUS is an adequate pre-operative staging tool for liver lesions suspected to be HCC or metastatic lesions, as EUS can detect small hepatic lesions previously undetected by dynamic CT scans.

Singh *et al*^[14] have conducted a prospective trial to compare the accuracy of EUS and EUS-FNA with other imaging modalities for the detection of primary liver tumors in subjects at high risk of HCC. Seventeen subjects were enrolled in the study. The EUS has detected more HCC lesions than US (8 vs 2, $P = 0.06$), CT (19 vs 8, $P = 0.06$) or magnetic resonance imaging (MRI) (14 vs 7, $P = 0.25$), although not statistically significant. Moreover, EUS has detected small HCC lesions that has been missed by CT and MRI, with the smallest lesion visualized by EUS and confirmed by FNA having 4 mm in size. Thus, EUS-FNA helped in the determination of the cytological nature of liver nodular lesions that were

indeterminate on CT and MRI. A diagnostic algorithm has been proposed in which EUS could be used for high-risk patients with inconclusive CT, or poorly accessible lesions requiring tissue confirmation.

In a study by DeWitt *et al*^[15], the sensitivity of EUS features and EUS-FNA for benign and malignant solid liver lesions was described. The EUS-FNA was performed on 77 different liver lesions, a total of 45 aspirates (58%) were diagnostic for malignancy (true positives), of these, 44 were metastatic and one was a HCC. In 25 patients (55%), the FNA provided both the primary diagnosis and upstaged the malignancy and in nine subjects (20%) the EUS-FNA made the initial diagnosis, upstaged the tumor, and prevented surgery. Three lesions previously classified as benign were lately, by intraoperative findings or percutaneous-FNA, reclassified as malignant (false negatives). The EUS features predictive of malignant hepatic lesions were the presence of regular outer margins (60% vs 27%, $P = 0.02$) and the detection of two or more lesions (38% vs 9%, $P = 0.03$). EUS-FNA was performed using a 22-gauge needle and no complications were reported. This study concluded that EUS is a safe and sensitive procedure that can have a significant impact on patient management. The Table 2 summarizes the reported data from the studies of EUS of Focal liver lesions.

The diagnosis of portal vein thrombosis (PVT) secondary to HCC invasion is of paramount importance since it preclude a therapeutic approach^[16]. Non-tumor PVT has usually a similar appearance to portal vein tumor thrombosis, the last could enhance with contrast or have Doppler sign, however sometimes this differentiation is difficult and the diagnosis remains doubtful until proven otherwise. Although percutaneous US-guided FNA of a PVT has been well documented^[17], this technique presents some difficulties, especially in accessing thrombus in the centrally located main portal vein. The EUS-FNA could overcome some limitations of a percutaneous US-guided FNA, as it provides an excellent view of the liver hilum which facilitates the puncture of a PVT. Some case reports have been published which the EUS-FNA was used to diagnose

Table 2 Reported diagnostic yields of endoscopic ultrasonography of focal liver lesions

Ref./ study design	Study population	Patient number/ EUS-FNA	EUS diagnostic yield	EUS-FNA diagnostic yield
Awad <i>et al</i> ^[13] Prospective unicenter study	Suspected HCC or metastatic liver carcinoma	14/9	EUS identified all hepatic lesions (<i>n</i> = 14) previously reported by CT 4 new/additional lesions identified by EUS	All FNA passes yielded adequate specimens (malignant: <i>n</i> = 8; benign: <i>n</i> = 1)
Singh <i>et al</i> ^[14] Prospective unicenter study	High risk for HCC	17/16	The diagnostic accuracy of US, CT, MRI, and EUS/EUS-FNA were 38%, 69%, 92%, and 94%	Cytologic diagnosis of primary liver tumor was established in 8 cases (HCC = 7; cholangiocarcinoma = 1)
DeWitt <i>et al</i> ^[15] Retrospective unicenter study	Staging EUS examinations for known or suspected malignancy	77/77	EUS features predictive of malignant hepatic lesions were the presence of regular outer margins and the detection of two or more lesions	45 aspirates were diagnostic for malignancy (metastasis: <i>n</i> = 44; HCC = 1)

HCC: Hepatocellular carcinoma; EUS: Endoscopic ultrasonography; FNA: Fine needle aspiration; US: Ultrasonography; CT: Computed tomography; MRI: Magnetic resonance imaging.

HCC in patients with portal vein thrombosis^[18-21]. In two cases the procedure was performed with a 25-gauge needle^[18,19], while the other cases were performed with a 22-gauge needle^[20,21] and all patient have tolerated the procedure well, without any immediate or delayed complications.

After a careful study and analysis of these articles we can easily conclude that the EUS and EUS-FNA may be helpful in the management of a subset of patients with a high suspicion for small liver lesions and to approach lesions that remain difficult to sample by percutaneous US-guided techniques. However some important issues remain unanswered^[22,23], the risk of needle track spread of HCC from EUS-FNA remains undefined and the quality of the visualization of peripheral lesions, such as the areas under the dome of the diaphragm and the inferior-posterior portion of the right lobe of the liver.

Other potential concerns are related to the risks associated with EUS-FNA. In a large international survey^[24], in which centres with large experience participated, the EUS-FNA of the liver lesions, in expert hands, proved to be a safe procedure. The complication rate was 4%, although this included one major complication (death) and several minor complications (bleeding, infection, abdominal pain). The death occurred in a patient with a pancreatic mass. The patient was suspected to have an occluded biliary stent at the time of the EUS and a cholangitis resulted from the introduction of bacteria into an obstructed bile duct by the needle. For this reason it is recommended that antibiotics are administered prophylactically and biliary drainage is established rapidly if fine needle aspiration of the liver is to be performed in the setting of obstructive jaundice. Despite these results more information about the risks and complications in specific groups is necessary, especially in patients with a particular propensity for liver lesions, such as patients with cirrhosis or portal hypertension. Prospective studies comparing the accuracy and complication rate of the EUS-FNA and percutaneous FNA techniques for the diagnosis of liver tumors are also still needed.

The therapy of HCC guided by EUS has also been

reported in some case reports. In 2011, Di Matteo *et al*^[25] reported a case of a hepatocellular carcinoma located in the caudate lobe unsuitable for surgical resection, liver transplant and percutaneous treatment. The embolization failed and an EUS-guided neodymium: Yttrium-aluminium-garnet (Nd: YAG) laser ablation was performed. The ablation of hepatocellular carcinoma was effective without adverse events. Nakaji *et al*^[26] reported another case of EUS-guided hepatocellular carcinoma treatment this time with ethanol injection. These two cases have shown the significant innovative options to treat lesions that are difficult to reach by conventional methods.

EUS AND ENDOSCOPIC THERAPY OF GASTROESOPHAGEAL VARICES

Gastroesophageal varices are the most important portosystemic collaterals that can be developed as a consequence of portal hypertension^[27]. The venous anatomy of the lower esophagus and stomach in patients with portosystemic collaterals is complex. The dilated submucosal veins can be readily seen during an upper endoscopy. This superficial venous plexus is connected, through the perforating vessels, with the deep venous plexus, periesophageal and paraesophageal veins^[28].

The endoscopic and ultrasound images provided by the EUS allows the visualization of the collateral vessels within and outside the esophageal wall^[29-31] (Figure 2), and its role in the diagnosis and management of gastroesophageal varices is now well established.

In a study by Faigel *et al*^[32] the presence and diameter of varices surrounding the esophagus and proximal stomach (paraesophageal and paragastric varices) were correlated with the presence and degree of liver disease and portal hypertension and represented a risk factor for variceal bleeding.

Since the previous reports about the role of collaterals in patients with portal hypertension and its clinical significance, some studies have analyzed the role of the EUS in the evaluation of the outcome of endoscopic

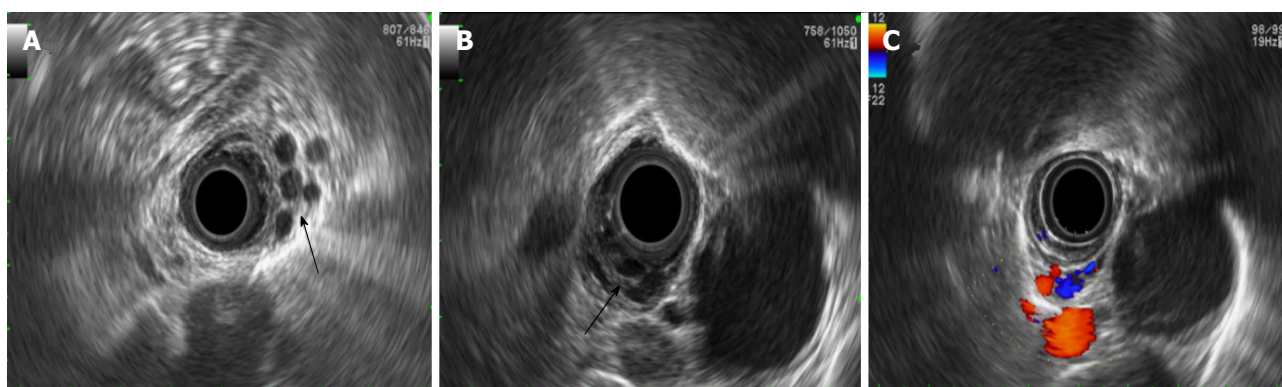


Figure 2 Esophageal collateral vessels (arrow) (A), esophageal varices seen as hypoechoic structures inside the esophageal wall (arrows) (B); and paraesophageal varices and perforating veins (C). Images recorded using the radial scanning echoendoscope (GF-UE160-AL5; Olympus Medical Systems, Tokyo, Japan) coupled with a ProSound Alpha 10 processor (Aloka, Tokyo, Japan).

therapeutics for esophageal varices, thereby allowing the selection of these patients for more intensive therapy or follow-up^[33].

Endoscopic band ligation (EBL) has become the preferred method of treatment for esophageal varices, as it has proved to be as effective as injection sclerotherapy with fewer serious adverse events^[34], however the risks of recurrence and rebleeding still remain a concern.

Recently, Masalaite *et al.*^[35] have assessed the role of the EUS in predicting the recurrence of esophageal varices following EBL. The study has shown that the presence of severe or multiple periesophageal collateral veins were independent prognostic factors for variceal recurrence. Similar results have been previously reported^[36-38].

The effects of sclerotherapy and EBL on esophageal varices are considered to be different, which might be explained by different results of each technique in the ablation of collateral veins.

Lo *et al.*^[39] conducted a study to assess the correlation between paraesophageal varices and esophageal variceal recurrence/rebleeding in patients who underwent sclerotherapy and EBL. Patients with more severe paraesophageal varices have presented a significantly higher rate of variceal recurrence and rebleeding. The prevalence of paraesophageal varices was 86% in the EBL group compared to 51% in the sclerotherapy group ($P = 0.002$).

In a study by de Paulo *et al.*^[40], the EUS was used to guide sclerotherapy for esophageal varices and although no significant benefit was found in the EUS-guided sclerotherapy in relation to the mean number of sessions necessary for eradication, the presence of collateral vessels, associated with bleeding recurrence, was less frequent in the EUS-guided group.

A possible explanation for these results could be appointed as the sclerotherapy causes fibrosis and obliteration of the perforating veins, while during EBL collateral vessels, in deeper layers, could remain untouched.

In order to identify factors that contributed to recurrence of varices and bleeding after endoscopic treatment some authors have also used color Doppler EUS. The

association of Doppler to ultrasound images obtained by EUS allows both the visualization of varices and its collaterals and the understanding of the hemodynamics of the portal venous system and even the effects of endoscopic and pharmacological therapeutics for esophageal varices^[41]. In a study by Hino *et al.*^[42] the color Doppler EUS was used to study the hemodynamics changes and morphology pattern of the left gastric vein (the main feeder vessel of esophageal varices). The hepatofugal flow velocity in the left gastric vein was studied in 31 patients with high risk esophageal varices. This study has demonstrated that patients showing anterior branch dominant pattern of left gastric vein and high hepatofugal flow velocity may present a high risk of an early recurrence of esophageal varices. Posteriorly, these results were validated by the same authors in a larger study of 68 patients^[43].

The Table 3 summarizes the reports about the role of EUS in the evaluation of the outcome of endoscopic therapeutics for esophageal varices.

Currently, there are no specific recommendations for the EUS in the diagnosis or treatment management of patients with esophageal varices. However, the previously reported studies report information that may be important for the selection of optimal treatment for esophageal varices. The identification of collateral veins after endoscopic treatment would allow us to identify patients who are at higher risk of variceal recurrence and rebleeding and to select those who require a closer follow-up and even a more aggressive endoscopic approach.

Gastric varices occur in approximately 17% of patients with portal hypertension^[44]. The endoscopic diagnosis of high risk for bleeding of gastric varices is not always easy to assess, and sometimes they are mistaken for large gastric folds or submucosal tumors. The magnetic resonance and CT allow the visualization of the entire portal venous system, however the accuracy of these techniques in distinguishing between submucosal gastric varices and perigastric collateral veins remains limited^[41].

The EUS equipped with Doppler can significantly

Table 3 Role of endoscopic ultrasonography in the evaluation of the outcome of endoscopic therapeutics for esophageal varices

Ref.	Study design	Endoscopic findings	EUS findings
Masalaite <i>et al</i> ^[35]	Prospective The role of EUS in predicting the recurrence/ rebleeding of esophageal varices: EBL (<i>n</i> = 40)	Recurrence of esophageal varices: 19 (47.5%) within 12 mo of EBL	EUS independent prognostic factors for variceal recurrence: Severe esophageal collaterals (OR= 24.39) multiple esophageal collaterals (OR = 24.39)
Lo <i>et al</i> ^[39]	Prospective The role of EUS in predicting the recurrence of esophageal varices: ES (<i>n</i> = 35) <i>vs</i> EBL (<i>n</i> = 44)	Recurrence of esophageal varices: 43% ES <i>vs</i> 70% EBL	Paraesophageal varices: 51% ES <i>vs</i> 86% EBL
de Paulo <i>et al</i> ^[40]	Prospective The role of EUS-guided ES: ES (<i>n</i> = 25) <i>vs</i> EUS- guided ES (<i>n</i> = 25) of esophageal collateral vessels	Mean number of sessions until eradication: 4.3 ES group <i>vs</i> 4.1 for the EUS-ES Recurrence of esophageal varices: 16.7% ES <i>vs</i> 8.3% EUS-ES	Esophageal collaterals at the end of the sclerotherapy program: 8 patients in ES <i>vs</i> 0 patients in EUS-ES

EUS: Endoscopic ultrasonography; EBL: Endoscopic band ligation; ES: Endoscopic sclerotherapy.

improve the detection of gastric varices and the understanding of the feeding vein, according to each type and the evaluation of vascular blood flow, which could be important in defining the therapeutic strategy^[45,46]. With EUS-Color Doppler, Iwase *et al*^[47] visualized small gastric varices that were difficult to detect by endoscopic observation, and were able to identify the feeding vein for each type of gastric varices. In a recent study by Imamura *et al*^[48] the gastric varices diameter, which was independent from endoscopic view, Child-Pugh classification and the presence of hepatocellular carcinoma, have been correlated with flow volume measured by the EUS.

Sato *et al*^[49] have also studied the role of the EUS-Color Doppler in the diagnosis and prediction of bleeding risk of gastric varices. The EUS-Color Doppler has allowed a clear sonographic visualization of the gastric varices and the evaluation of its morphology. In addition, the authors have showed that a smaller thickness of the gastric wall was a significant predictor of a high bleeding risk.

The presence of isolated gastric varices without esophageal varices can also be observed in patients with non-cirrhotic portal hypertension, which can occur in patients with splenic vein obstruction (left-sided portal hypertension). The role of the EUS color Doppler in patients with isolated gastric varices related to splenic vein occlusion has also been studied by Sato *et al*^[50]. In this study the authors have provide specific findings that may be regarded as hallmarks of gastric varices due to splenic vein occlusion, namely a flow clearly depicted a round fundal region at the centre, with varices expanding to the curvatura major of the gastric body.

Endoscopic procedures, mainly the injection of tissue adhesives, such as cyanoacrylate (CYA), have become the therapy of choice for the treatment of gastric varices^[51], although it is known to be associated with risk of clinical adverse events^[52]. An innovative endoscopic option for the management of gastric varices includes the EUS-guided therapy.

The EUS can not only provide a clear image of the

varix lumen, but also of the main feeding vein, and thus guiding the treatment directly to the perforating feeder vessel, which may theoretically minimize the amount of CYA needed to achieve the obliteration of gastric varices.

In a small study conducted by Romero-Castro *et al*^[53] the EUS was used to guide the CYA injection in gastric varices. The EUS-guided CYA injection at the entrance of the perforating veins was successful in eradicating gastric varices in all the 5 patients treated, without recurrent bleeding or other subsequent complications. The authors have reported that the most difficult and time-consuming issue was the identification of the perforating vein of gastric varices and rule out what would be the outflowing vein. To be sure that the targeted vessel was the perforator, they carefully displayed the vascular anatomy by EUS and checked by fluoroscopy that the CYA-lipiodol mixture would not go downstream if an outflowing vein was mistakenly punctured.

Despite the reported success of the EUS-guided CYA injection, the concerns about the risks of embolization still remain. In a study by Binmoeller *et al*^[54], coils, that are currently used for intravascular embolization treatments, were delivered into the varix under the EUS-guidance and previous to CYA injection, in order to reduce or eliminate the risk of glue embolization. The procedure was successful in all patients (thirty patients) with immediate hemostasis achieved in patients with active gastric varices bleeding (two patients). There was no damage to the echoendoscope, related to glue injections and non-procedure-related complications

In a multicentre study by Romero-Castro *et al*^[55], EUS-guided coil application *vs* cyanoacrylate for the embolization of feeding gastric varices was studied. Thirty patients, 11 patients in the coil group and 19 patients in cyanoacrylate group, were included. Both techniques were effective in the gastric variceal obliteration. However coil application required fewer endoscopies and tended to have fewer adverse events.

An advantage of the EUS-guided treatment is the lack of dependency on direct varix visualization. In a case study reported by Tang *et al*^[56] the point

of rebleeding of a fundal gastric varices, which was persistently obscured due to ongoing bleeding and blood clots, was identified by the EUS, followed by CYA injection and real-time Doppler confirmation of vascular signal loss in gastric varices.

Transesophageal EUS-guided coil or CYA injection of gastric varices is feasible and deserves further studies to determine whether these approaches can improve safety and efficiency over standard endoscopic injection of CYA alone. Although the EUS-guided gastric variceal therapy offers many potential advantages, a review by Fujii-Lau *et al.*^[46] lists several pitfalls that should be considered before applying the technique, such as the risk of damage the echoendoscope if glue lodged within the channel, the smaller aspiration channel, compared to a therapeutic endoscope, which could be important in cases of active bleeding, the limited retroflexion of the echoendoscope making the approximation to the fundal mucosa difficult, the importance of a fluoroscopy guidance to monitor for the immediate embolization and the complexity of the entire procedure making it time-consuming.

EUS FOR THE EVALUATION OF HEMODYNAMIC CHANGES IN PORTAL HYPERTENSION

Portal hypertension is a common adverse event of liver cirrhosis as this syndrome develops in the majority of patients with cirrhosis being responsible for severe complications such as gastrointestinal variceal bleeding, ascites, hepatorenal syndrome and hepatic encephalopathy^[57]. The hepatic venous pressure gradient, an acceptable indirect measurement of portal pressure, predicts the development of complications of portal hypertension^[58], whilst its use has also been proposed in the evaluation of the efficacy of pharmacological therapeutics in patients with portal hypertension^[59]. Hepatic venous pressure gradient is traditionally measured by a transjugular approach, an invasive procedure, with radiation and intravenous contrast exposure and not readily available in all centres. The EUS-Guided portal vein catheterization for direct portal pressure measurement has been reported in some studies.

The possibility of direct EUS-guided portal vein catheterization using a 25-gauge needle and accurate pressure measurement has been demonstrated in animal models. In a study by Huang *et al.*^[60] a novel EUS-guided system using a 25-gauge FNA needle (Cook® Medical, Winston-Salem, NC, United States), and a compact manometer with non-compressible tubing (Cook® Medical, Bloomington, Ind, United States) has been used to directly measure portal pressure gradient and to evaluate its performance and clinical feasibility. Under the EUS guidance a 25-gauge FNA needle with attached manometer has been used to puncture (transgastric-transhepatic approach) and to measure pressures in the portal vein, right hepatic vein, inferior vena cava, and

aorta in 3 animal models and the results were correlated with the standard transjugular approach. There has been an excellent correlation between the two methods and no adverse events have been reported. Recently, the same group^[61] has presented the first human pilot study of the EUS-guided portal pressure gradient measurement (EUS-PPGM) in patients with liver disease. The procedure has been performed with a linear echoendoscope and the same equipment previously described. Twenty-eight patients underwent EUS-PPGM, 15 of 28 (57.1%) had evidence of portal hypertension based on portal pressure gradient of which 10 of 15 (66.7%) had clinical significant portal hypertension. There has been an excellent association between portal pressure gradient and clinical evidence of cirrhosis, presence of varices, portal hypertensive gastropathy and thrombocytopenia. There have not been technical failures or reported intraprocedural or post-procedural adverse events. This was the first study demonstrating that the EUS-PPGM can be safe and accurate in humans, even in the context of suspected cirrhosis.

The EUS-guided measurements of portal pressure gradient provide an alternative method to evaluate portal hemodynamics. More studies are still needed, mainly in cirrhotic patients with impaired hemostasis, and therefore there is a possibility to use this new method to evaluate the effect of pharmacological therapy on portal hypertension.

CONCLUSION

There is evidence to suggest that the EUS alone or with FNA represent a significant advance in the evaluation and treatment of liver diseases and its complications. The EUS is able to provide an early detection and the biopsy of small focal liver lesions that are either not visualized by other imaging modalities or visualized during routine staging procedures of gastrointestinal malignancies. Thus, the EUS is another potential method for a guided liver biopsy for study parenchymal liver disease.

The EUS proves to be really helpful in managing portal hypertension being used to stratify patients who are at risk of recurrence and rebleeding of gastroesophageal varices and providing support for more aggressive therapy with frequent endoscopic treatments including direct treatment to the perforating veins. Concerning gastric varices, it can be used to guide cyanoacrylate injection in an effort to achieve total occlusion of the varices and decrease the recurrence rate and complications.

More recently, the EUS has been described as a method for guiding interventions such as portal vein catheterization for direct portal pressure measurement. However most of the studies in this field are performed in animal models, and safety data in humans, mainly cirrhotic patients, are still lacking.

The diagnostic and therapeutic role of EUS in hepatology is emerging and the available evidence suggests that the EUS has the potential to be a valuable

alternative imaging modality in the study of liver diseases and its complications. Several methods are still under development and need to be validated, but the authors expect that in the near future applications of the EUS in hepatology will become an integral part of the evaluation of patients with liver diseases.

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Retrospective Cohort Study

Clinical impact of confocal laser endomicroscopy in the management of gastrointestinal lesions with an uncertain diagnosis

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Abstract

AIM

To evaluate the clinical impact of confocal laser endomicroscopy (CLE) in the diagnosis and management of patients with an uncertain diagnosis.

METHODS

A retrospective chart review was performed. Patients who underwent CLE between November 2013 and October 2015 and exhibited a poor correlation between endoscopic and histological findings were included. Baseline characteristics, indications, previous diagnostic studies, findings at the time of CLE, clinical management and histological results were analyzed. Interventions based on CLE findings were also analyzed. We compared the diagnostic accuracy of CLE and target biopsies of surgical specimens.

RESULTS

A total of 144 patients were included. Of these, 51% (74/144) were female. The mean age was 51 years old.

In all, 41/144 (28.4%) lesions were neoplastic (13 bile duct, 10 gastric, 8 esophageal, 6 colonic, 1 duodenal, 1 rectal, 1 ampulloma and 1 pancreatic). The sensitivity, specificity, positive predictive value, negative predictive value, and observed agreement when CLE was used to detect N-lesions were 85.37%, 87.38%, 72.92%, 93.75% and 86.81%, respectively. Cohen's Kappa was 69.20%, thus indicating good agreement. Changes in management were observed in 54% of the cases.

CONCLUSION

CLE is a new diagnostic tool that has a significant clinical impact on the diagnosis and treatment of patients with uncertain diagnosis.

Key words: Confocal laser endomicroscopy; *In vivo* microscopy; Barret esophagus; Gastrointestinal cancer; Pancreatic cyst; Biliary strictures

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Core tip: Endoscopic and histopathological findings are not always certain, thus potentially leading to inaccurate diagnoses and inappropriate therapeutics. The use of confocal laser endomicroscopy has a significant clinical impact on the diagnosis and treatment of patients with uncertain diagnoses.

Robles-Medranda C, Vargas M, Ospina J, Puga-Tejada M, Valero M, Soria M, Bravo G, Robles-Jara C, Lukashok HP. Clinical impact of confocal laser endomicroscopy in the management of gastrointestinal lesions with an uncertain diagnosis. *World J Gastrointest Endosc* 2017; 9(8): 389-395 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v9/i8/389.htm> DOI: <http://dx.doi.org/10.4253/wjge.v9.i8.389>

INTRODUCTION

Conventional histology is the gold standard procedure in evaluating lesions in the gastrointestinal tract. However, endoscopic and histological findings are sometimes poorly correlated, thus hindering accurate diagnosis and subsequent clinical management^[1-5]. The probability of sampling error has been found to be 20%-30% and is affected by several factors, such as inadequate macroscopic interpretation and minimal biopsy acquisition^[6].

Confocal laser endomicroscopy (CLE) is a technique that is used *in vivo* during endoscopy to evaluate the mucosal epithelium of the gastrointestinal tract, the bile duct and pancreatic cysts^[5,7]. Furthermore, it provides dynamic information including blood flow and contrast up-take^[8].

Multiple studies have shown that CLE has a diagnostic accuracy above 90% when standardized parameters are used to evaluate specific lesion features^[9-17]. However, there is minimal information in the literature regarding

the influence of CLE on the evaluation and management of patients with GI lesions of uncertain diagnosis. The aim of this study was to evaluate the clinical impact of CLE in this group of patients.

MATERIALS AND METHODS

Study design

This study was an observational, analytical, retrospective, cross-sectional single-center study. Prospective data from November 2013 to September 2015 were collected at the Ecuadorian Institute of Digestive Diseases (IECED) Omni Hospital Academic Tertiary Care Center, Guayaquil, Ecuador. The study protocol was approved by the Institutional Ethical and Review Board and conducted according to the guidelines in the declaration of Helsinki.

Demographic data, indications, previous diagnostic findings, CLE findings, clinical management and histological results are described. Records from previous endoscopies [*i.e.*, upper endoscopy (UE), colonoscopy with high definition magnification and digital chromoendoscopy, endoscopic retrograde cholangiopancreatography (ERCP) with brushing sample and endoscopic ultrasound (EUS)], computed tomography (CT), magnetic resonance imaging (MRI) cholangiopancreatography and tests for tumor markers were analyzed.

Population selection

Inclusion criteria: Patients who underwent CLE (Cellvizio®, Mauna Kea Technology, France) as a result of an uncertain diagnosis (an absence of correlation between endoscopic and histological findings) in gastrointestinal diseases, including neoplastic (N) or non-neoplastic (NN) lesions (Table 1). Patients ≥ 18 years old; Patients who agreed to participate; Patients with no previous p-CLE.

Exclusion criteria: Pregnant patients and patients with allergies and/or contraindication to fluorescein.

Endoscopy and CLE procedures

All participants underwent CLE according to the standard protocol. Sedation was accomplished with propofol in UE and colonoscopy and general anesthesia in ERCP and EUS. In UE and colonoscopy, the CLE was performed with Gastroflex® and Coloflex® probes (Cellvizio®, Mauna Kea Technology, France) through the working channel of a standard video-endoscope. In ERCP procedures, CLE was performed through cholangioscopy (SpyGlass® system, Boston Scientific®), and in EUS, CLE was performed through a 19G needle (Expect® needle, Boston Scientific) with Cholangioflex® and AQ-flex® probes (Cellvizio®, Mauna Kea Technology, France).

After the GI mucosa was inspected, the areas with suspected pathology were further examined. The probe was carefully advanced to the mucosa, and *in vivo* microscopy images were scanned at 1000 ×

Table 1 Baseline characteristics *n* (%)

	Biopsy/surgical specimen diagnosis			<i>P</i> value
	Total (<i>n</i> = 144)	Neoplastic lesions (<i>n</i> = 41)	Non-neoplastic lesions (<i>n</i> = 103)	
Sex (female)	74 (51.4)	19 (46.3)	55 (53.4)	0.445
Age, yr, mean ± SD	51.33 ± 16.5	56.73 ± 17.1	49.19 ± 15.8	0.014
Initial endoscopy indication				< 0.001
Suspected tumor	70 (48.6)	32 (78.0)	38 (36.9)	
Other	74 (51.4)	9 (22.0)	65 (63.1)	
Location				0.187
Vater ampulla	2 (1.4)	1 (2.4)	1 (1.0)	
Colon	14 (9.7)	6 (14.6)	8 (7.8)	
Duodenum	4 (2.8)	1 (2.4)	3 (2.9)	
Esophagus	24 (16.7)	8 (19.5)	16 (15.5)	
Stomach	59 (41.0)	10 (24.4)	49 (47.6)	
Ileum	1 (0.7)	0 (0.0)	1 (1.0)	
Pancreas	8 (5.6)	1 (2.4)	7 (6.8)	
Rectum	3 (2.1)	1 (2.4)	2 (1.9)	
Bile duct	29 (20.1)	13 (31.7)	16 (15.5)	

SD: Standard deviation.

magnification by using CLE. These video images were transmitted in a real-time onto a screen situated next to the endoscopy monitor. For tissue contrast, 5 mL of 10% fluorescein was injected in all patients.

All lesions were analyzed in real-time after an endoscopic assessment. Micrographs and videos obtained during CLE were stored for further examination. The images were interpreted according to methods previously published in esophageal^[18,19], gastric^[14,20,21] and colonic^[22-24] lesions. The Miami^[25,26], Paris^[13], and CONTACT^[11] study criteria for using CLE were used in bilio-pancreatic tract and cystic pancreatic lesions.

Definitions

An uncertain diagnosis in a case of gastrointestinal lesions was defined as a lack of correlation between a histological report and findings on initial endoscopy (*e.g.*, UE, colonoscopy, ERCP, EUS). Neoplastic (N) lesions included dysplasia, adenomas and carcinomas that were located at any level of the GI tract, pancreas or biliary duct. Any other lesion was defined as a non-neoplastic (NN) lesion (Figures 1 and 2).

We defined a "change in management" resulting from CLE in cases of uncertain diagnosis when the results of CLE changed the management strategy that was initially based on the original biopsy or when no further diagnostic methods were used.

Statistical analysis

Baseline characteristics, including demographic data, indications, CLE findings, histological results and changes in management, were described as percentages and ranges or means and standard deviations, as appropriate. The overall diagnostic accuracy of CLE in an N-lesion was determined by comparing the CLE findings to the final post-CLE histopathological report (*e.g.*, biopsy or surgical specimen). The following measurements were used for this purpose: Sensitivity, specificity, positive predictive value (PPV), negative

predictive value (NPV), simple percentage agreement (observed agreement) and inter-rater agreement (Cohen's Kappa). Cohen's Kappa was interpreted by using Landis and Koch-Kappa's Benchmark Scale. Changes in management and redirected biopsy samples were described as percentages. The characteristics of N-lesions and NN-lesions groups were compared using Student's *t*-test for continuing variables and χ^2 and Fisher's test for categorical variables. A *P* value < 0.05 was considered to be statistically significant. The statistical methodology used in this study was reviewed by the IECED institutional Biostatistician. Statistical calculations were performed in SPSS software suite v.22.

RESULTS

A total of 144 patients were included. The mean age of the patients was 51.33 years old (range 18-86), and 51.4% (74/144) were female. There were 41/144 N-lesions, including 13 bile duct, 10 gastric, 8 esophageal, 6 colonic, 1 duodenal, 1 rectal, 1 ampulloma and 1 pancreatic lesion (Table 1). The findings included Barrett's esophagus with or without dysplasia, adenocarcinomas and mucosal inflammation in different segments of the digestive tract, gastric metaplasia and dysplasia, carcinoid tumors, ampulloma, mucinous and serous pancreatic cysts, pseudocysts, adenoma and adenocarcinoma of the biliary tract and inflammation related to parasites.

The sensitivity, specificity, PPV and NPV for detecting N-lesions between CLE and target biopsies or surgical specimens were 85.37%, 87.38%, 72.92% and 93.75%, respectively. The observed agreement was 86.81%, and Cohen's Kappa value was 69.20%, thus indicating good agreement (Table 2). Changes in management were noted in 78/144 (54.2) cases (Table 3). These changes resulted from the improved ability of CLE to acquire targeted biopsies, which avoided the need for further diagnostic methods.

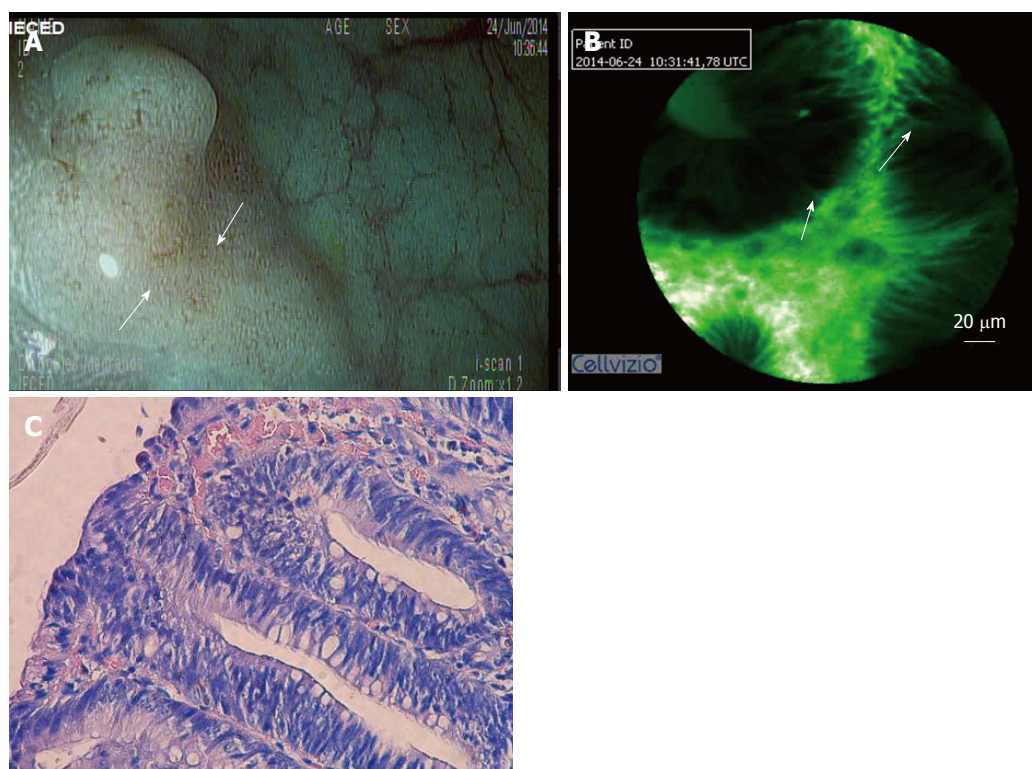


Figure 1 Colonic polyp. A: A sigmoid flat polyp was viewed using digital chromoendoscopy with high definition by i-scan, which revealed a pit pattern suggestive of a hyperplastic lesion in a patient with cirrhosis and important coagulation disorders; B: CLE showing dysplasia (image optimized by using a green-white image color palette in Cellvizio® viewer software); C: A histological analysis of the specimen confirmed the dysplasia. CLE: Confocal laser endomicroscopy.

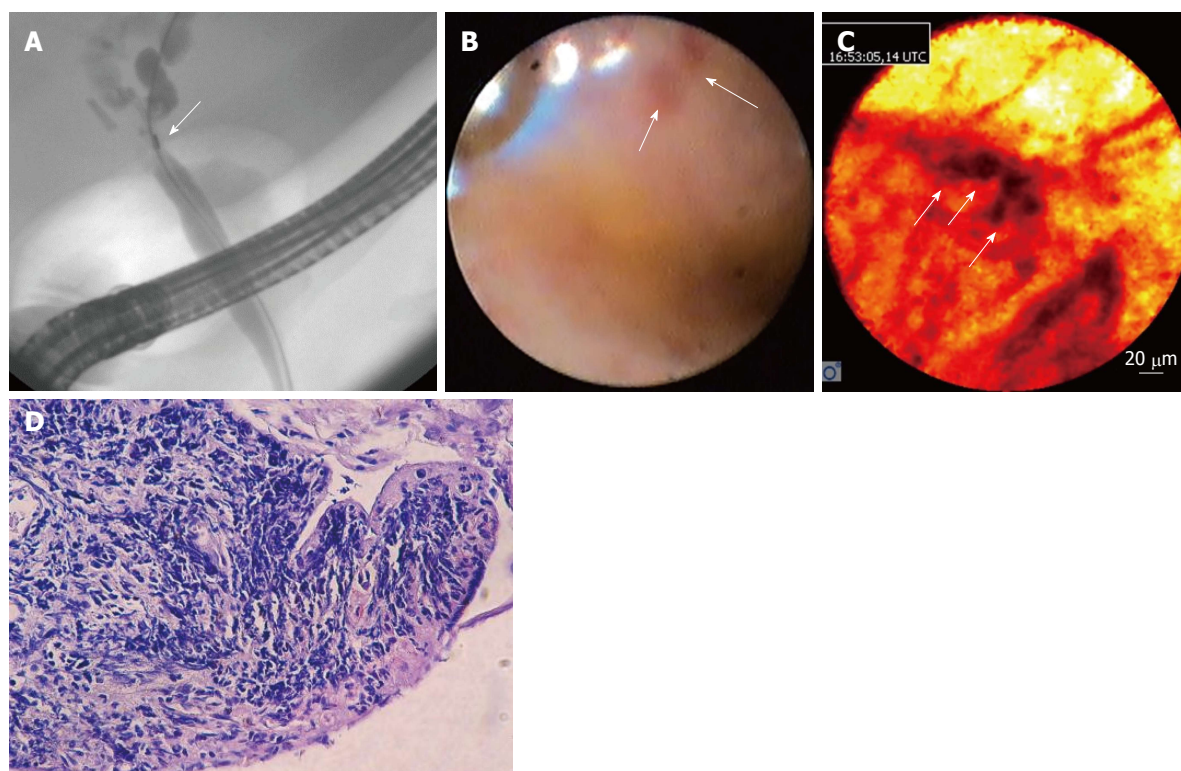


Figure 2 Undetermined stenosis of the biliary tract. A: ERCP was performed in a patient with undetermined stenosis who was cytobrush-negative for malignancy; B: Spyglass cholangioscopy showing a reddish area that was not suspected of malignancy; C: CLE showing dark clumps that were suspected of malignancy (image optimized using the "black-red-yellow" image color palette in Cellvizio® viewer software); D: The histological results of a target biopsy confirmed a diagnosis of cholangiocarcinoma. CLE: Confocal laser endomicroscopy; ERCP: Endoscopic retrograde cholangiopancreatography.

Table 2 Confocal laser endomicroscopy overall diagnostic accuracy with either confocal laser endomicroscopy target biopsy or surgical specimens as the Gold Standard *n* (%)

	Biopsy/surgical specimen diagnosis			<i>P</i> value
	Total (<i>n</i> = 144)	Neoplastic lesions (<i>n</i> = 41)	Non-neoplastic lesions (<i>n</i> = 103)	
CLE diagnosis				< 0.001
Neoplastic lesion	48 (33.3)	35 (85.4)	13 (12.6)	
Non-Neoplastic lesion	96 (66.7)	6 (14.6)	90 (87.4)	
CLE overall diagnostic accuracy				
Sensitivity, <i>n</i> /T (%; 95%CI)		35/41	(85.37; 70.83-94.43)	
Specificity, <i>n</i> /T (%; 95%CI)		90/103	(87.38; 79.38-93.11)	
PPV, <i>n</i> /T (%; 95%CI)		35/48	(72.92; 61.46-81.97)	
NPV, <i>n</i> /T (%; 95%CI)		90/96	(93.75; 87.71-96.93)	
Observed agreement, <i>n</i> /T (%)		125/144	-86.81	
Cohen's Kappa, % (95%CI)		69.2	(56.50-81.90)	

PPV: Positive predictive value; NPV: Negative predictive value; CI: Confidence interval; CLE: Confocal laser endomicroscopy.

Table 3 Patients with changes in management following biopsy/surgical specimen diagnosis, listed according to organ *n* (%)

	Biopsy/surgical specimen diagnosis			<i>P</i> value
	Total (<i>n</i> = 78)	Neoplastic lesions (<i>n</i> = 30)	Non-neoplastic lesions (<i>n</i> = 48)	
Location				0.707
Vater ampulla	1 (1.3)	1 (3.3)	0	
Colon	9 (11.5)	4 (13.3)	5 (10.4)	
Duodenum	4 (5.1)	1 (3.3)	3 (6.3)	
Esophagus	10 (12.8)	5 (16.7)	5 (10.4)	
Stomach	17 (21.8)	5 (16.7)	12 (25)	
Ileum	1 (1.3)	0	1 (2.1)	
Pancreas	6 (7.7)	1 (3.3)	5 (10.4)	
Rectum	3 (3.8)	1 (3.3)	2 (4.2)	
Bile duct	27 (34.6)	12 (40)	15 (31.3)	

DISCUSSION

CLE is an imaging method that has demonstrated substantial benefit for diagnosing GI tract, bile duct and pancreatic lesions. Several previous reports have supported CLE's efficacy by showing CLE and histological findings are well correlated^[15-17]. Recent studies^[11,18] have demonstrated that CLE has high accuracy in differentiating benign from malignant lesions in bile duct and pancreas pathology (mean accuracy, 81%)^[21], malignant gastric lesions (94%-96%)^[20] and polyps (82%)^[22]. In addition, the American Society for Gastrointestinal Endoscopy has reported that CLE has at least 90% sensitivity and 98% NPV when it is used to detect Barrett's esophagus-associated dysplasia^[18]. The Miami classification criteria for bile duct lesions have been demonstrated to have a higher accuracy when they are used to diagnose malignant strictures rather than biopsy samples (81% vs 75%, respectively)^[12]. However, these criteria have some limitations when they are used to differentiate inflammatory from malignant strictures, thus leading to false positives. On the basis of this finding, Caillol *et al.*^[13] have developed the Paris Classification, which has increased sensitivity and specificity in characterizing indeterminate bile duct strictures^[13,27]. Additionally, in colonoscopy, CLE has been demonstrated to be very useful. Neumann *et al.*^[23,24] have found that CLE, when used in inflammatory

bowel disease (IBD) surveillance, is a simple technique that facilitates the accurate and early detection of related lesions.

Our study focused on the clinical impact and management changes resulting from the use of CLE to evaluate GI (upper and lower) lesions, including bile duct pathology and pancreatic cysts, in a subgroup of patients with uncertain diagnoses due to non-conclusive previous tests.

CLE was found to have a high accuracy in detecting neoplastic bilio-pancreatic lesions, which accounted for 80% of all lesions found in the bile ducts and pancreas. In 54% of such cases, the use of CLE resulted in a change in the diagnostic and therapeutic approach. However, 71% of all lesions in patients with an inconclusive diagnosis were NN benign lesions, and CLE resulted in an observed agreement, PPV and NPV of 86%, 72% and 93%, respectively. These results were similar to those reported in previous publications that have explored lesions in the upper and lower portions of the gastrointestinal tract^[1,22-30].

The main advantages of using CLE include its ability to differentiate *in vivo* lesions and guide targeted biopsies, thereby avoiding the potential complications associated with endoscopic mucosal resections (*e.g.*, perforation or bleeding). Additionally, using CLE prevents a need for further unnecessary invasive and noninvasive diagnostic methods (*e.g.*, repeated endo-

scopy, ERCP, EUS, or other imaging modalities, such as CT and MRI), thus decreasing patient risk and economic burden associated with such procedures. However, our study has limitations, including its single-center retrospective design and lack of randomization.

Conclusion

The results of this study suggest that CLE is a valuable diagnostic tool for patients with an uncertain diagnosis (neoplastic or non-neoplastic). CLE can be used to perform real-time evaluation of the GI mucosa, thus allowing endoscopists to target biopsies and having a significant clinical impact when it is used to improve and modify diagnoses and treatment strategies.

COMMENTS

Background

Confocal laser endomicroscopy (CLE) is a technique that can be used *in vivo* during endoscopy to evaluate the mucosal epithelium of the gastrointestinal tract, the bile duct and pancreatic cysts.

Research frontiers

The authors evaluated the clinical impact of CLE in patients with an uncertain diagnosis in gastrointestinal lesions.

Innovations and breakthroughs

The observed agreement was 86.81% and had a Cohen's Kappa value of 69.20%, thus indicating good agreement. Changes in management were noted in 78/144 (54.2) cases and were associated with the improved acquisition of targeted biopsies, thus avoiding the need for further diagnostic tests.

Applications

CLE is a new diagnostic tool that can be used in patients with uncertain diagnosis, in whom it has a significant clinical impact on diagnosis and treatment.

Terminology

Confocal laser endomicroscopy; *in vivo* microscopy.

Peer-review

Overall the paper is interesting and points out discrepancy between endoscopic and histopathologic findings.

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Retrospective Cohort Study

Impact of laparoscopic liver resection on bleeding complications in patients receiving antithrombotics

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Data sharing statement: No additional data are available. Collected data under the form of Excel tables will be available on request. The authors are not responsible of any concern issued from external use of these files.

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Abstract**AIM**

To assess the impact of laparoscopic liver resection (LLR) on surgical blood loss (SBL), especially in patients with antithrombotics for thromboembolic risks.

METHODS

Consecutive 258 patients receiving liver resection at our institution between 2010 and 2016 were retrospectively reviewed. Preoperative antithrombotic therapy (ATT; antiplatelets and/or anticoagulation) was regularly used in 100 patients (ATT group, 38.8%) whereas not used in 158 (non-ATT group, 61.2%). Our perioperative management of high thromboembolic risk patients included maintenance of preoperative aspirin monotherapy for patients with antiplatelet therapy and bridging heparin for patients with anticoagulation. In both ATT and non-ATT groups, outcome variables of patients undergoing LLR were compared with those of patients receiving open liver resection (OLR), and the independent risk factors for increased SBL were determined by multivariate analysis.

RESULTS

This series included 77 LLR and 181 OLR. There were 3 thromboembolic events (1.2%) in a whole cohort, whereas increased SBL (≥ 500 mL) and postoperative bleeding complications (BCs) occurred in 66 patients (25.6%) and 8 (3.1%), respectively. Both in the ATT and non-ATT groups, LLR was significantly related to reduced SBL and low incidence of BCs, although LLR was less performed as anatomical resection. Multivariate analysis showed that anatomical liver resection was the most

significant risk factor for increased SBL [risk ratio (RR) = 6.54, $P < 0.001$] in the whole cohort, and LLR also had the significant negative impact (RR = 1/10.0, $P < 0.001$). The same effects of anatomical resection (RR = 15.77, $P < 0.001$) and LLR (RR = 1/5.88, $P = 0.019$) were observed when analyzing the patients in the ATT group.

CONCLUSION

LLR using the two-surgeon technique is feasible and safely performed even in the ATT-burdened patients with thromboembolic risks. Independent from the extent of liver resection, LLR is significantly associated with reduced SBL, both in the ATT and non-ATT groups.

Key words: Laparoscopic liver resection; Two-surgeon technique; Antithrombotic therapy; Increased surgical blood loss; Bleeding complication

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Core tip: Analyzing consecutive 258 patients undergoing liver resection using the two-surgeon technique, we showed that laparoscopic liver resection is significantly associated with reduced surgical blood loss and low postoperative bleeding complications even in antithrombotic-burdened patients with thromboembolic risks.

Fujikawa T, Kawamoto H, Kawamura Y, Emoto N, Sakamoto Y, Tanaka A. Impact of laparoscopic liver resection on bleeding complications in patients receiving antithrombotics. *World J Gastrointest Endosc* 2017; 9(8): 396-404 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v9/i8/396.htm> DOI: <http://dx.doi.org/10.4253/wjge.v9.i8.396>

INTRODUCTION

In recent years, with the arrival of an aging society, surgical cases with heart disease and cerebrovascular disease have become more common, and most of them are undergoing antithrombotic therapy [ATT; antiplatelet therapy (APT) and/or anticoagulation therapy (ACT)] to prevent thromboembolism. Although the indication for ATT is expanding, perioperative management of antithrombotic drugs during gastroenterological surgery is often at high risk of hemorrhagic and thromboembolic complications and can become difficult^[1-4].

In our institution, a protocol of risk stratification and perioperative antithrombotic management has been established for patients receiving ATT ("Kokura Protocol")^[5,6]. So far, the feasibility and safety of the Kokura Protocol during laparoscopic and/or open abdominal surgery have been reported^[5,6]. Moreover, our recent paper demonstrated that laparoscopic liver resection (LLR) using the "two-surgeon technique" is safely performed without critical intraoperative or postoperative bleeding even in patients receiving APT^[7]. But the effect of LLR on increased surgical blood loss

(SBL) and postoperative bleeding complications (BCs), especially in patients undergoing ATT, still remains unclear.

The aim of the current research is to investigate the impact of LLR on increased SBL and BCs with special reference to the presence or absence of ATT.

MATERIALS AND METHODS

Patients

Following institutional review board approval, we searched potentially relevant cases from the single institution prospectively collected surgery database. After excluding cases with emergency surgery or other types of surgery, we included 258 consecutive liver resections performed from January 2010 to October 2016 in the current study (Figure 1). ATT was regularly used in 100 patients (ATT group, 38.8%) whereas not used in 158 patients (non-ATT group, 61.2%). Background, perioperative and outcome variables of the patients were collected through the surgery database as well as hospital and clinic charts.

The status of patients' symptoms and functions regarding ambulatory status was described according to the ECOG scale of performance status (PS)^[8]. Postoperative complications were assessed and categorized by Clavien-Dindo classification (CDC)^[9] and CDC class II or higher was considered significant. Postoperative bleeding and thromboembolic complications were defined as previously described^[5,6]. BCs included luminal bleeding, abdominal bleeding, and abdominal wall hematoma; thromboembolic complications included myocardial infarction, cerebral infarction, mesenteric infarction, and pulmonary thromboembolism. Operative mortality included death within 30 d after surgery.

Surgical procedures in this cohort included 163 partial liver resection and 95 anatomical liver resection. All procedures were performed by or under the guidance of one of the board-certified attending surgeons at our institution. We have adopted the "two-surgeon technique" during open liver resection (OLR)^[10], and also introduced and maintained this procedure even in LLR, in order to perform safe liver parenchymal transection without critical intraoperative bleeding^[7]. The indications for LLR at our institution were initially limited to the lesions in S2, S3, S5, S6 and the ventral side of S4, but were later expanded to almost all areas including S1. Patients having a large tumor more than 10 cm in diameter, those requiring bile duct resection or lymph node dissection, those with tumors involving major hepatic veins or inferior vena cava were excluded. We currently perform both pure and hybrid LLR and select the procedure depending on the tumor location and patient condition. Especially, if the ATT-burdened patients with high thromboembolic risks require major anatomical resection, we definitely choose hybrid LLR or open hepatectomy to avoid elevation of thromboembolic risks due to reduced central venous pressure.

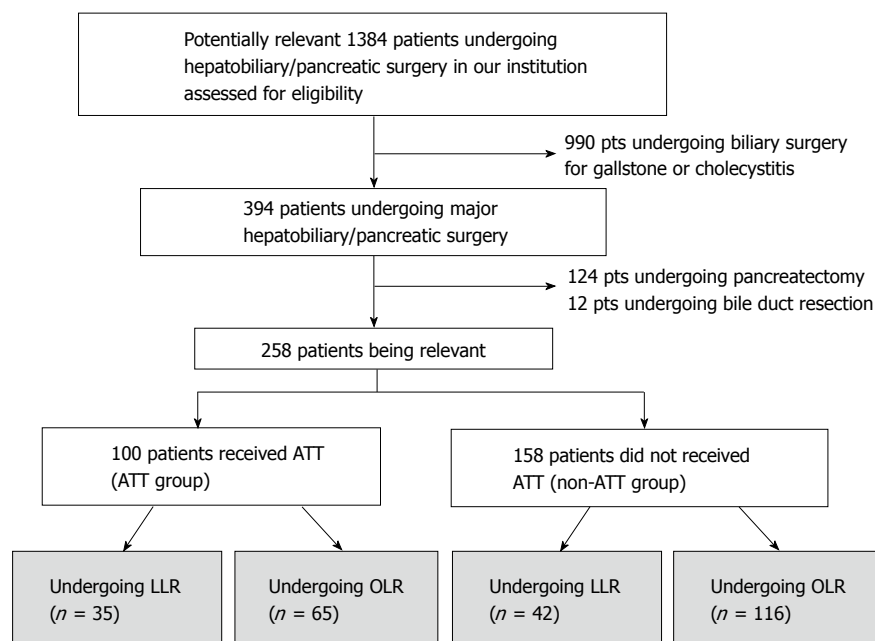


Figure 1 Consort diagram in the current study. Pts: Patients; ATT: Antithrombotic therapy; LLR: Laparoscopic liver resection; OLR: Open liver resection.

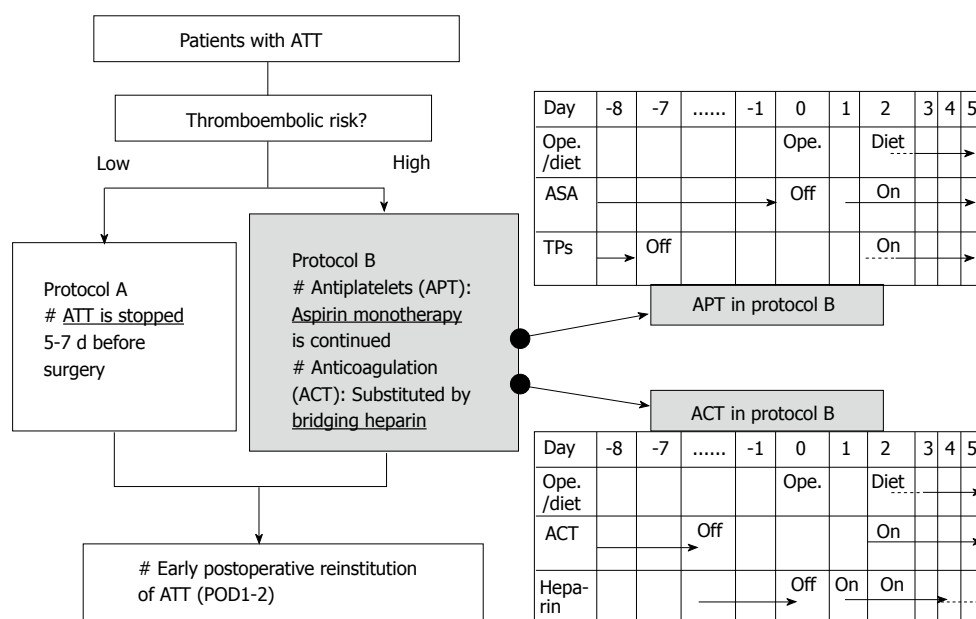


Figure 2 Perioperative management protocol ("Kokura Protocol") for patients undergoing antithrombotic therapy in case of elective surgery. The management generally consists of interrupting ATT 5 to 7 d before surgery and early postoperative reinstatement in low thromboembolic risk patients. In patients with high thromboembolic risks, aspirin monotherapy is continued in patients with APT, and/or ACT was substituted by bridging heparin. ATT: Antithrombotic therapy; APT: Antiplatelet therapy; ACT: Anticoagulation therapy; Ope.: Operation; ASA: Aspirin; TPs: Thienopyridines.

The primary outcome included increased SBL (500 mL or more) and BCs. Both in the ATT and non-ATT groups, background characteristics, perioperative factors, and outcome variables of patients undergoing LLR were compared with those of patients receiving OLR, and the independent risk factors for increased SBL were determined by multivariate analysis.

Perioperative management of antithrombotic drugs

We have established our perioperative antithrombotic

management system including thromboembolic risk stratification and perioperative antithrombotic management protocol ("Kokura Protocol"), and have shown that both open and laparoscopic abdominal surgeries in patients with antithrombotic therapy can be performed safely under Kokura Protocol^[5,6]. Figure 2 demonstrated perioperative flowchart of patients with ATT in the Kokura Protocol. The management generally consisted of interrupting ATT 5 to 7 d before surgery and early postoperative reinstatement in low thromboembolic risk

Table 1 Background characteristics of patients in the cohort *n* (%)

Variables	Total (<i>n</i> = 258)	ATT (<i>n</i> = 100)			Non-ATT (<i>n</i> = 158)		
		LLR (<i>n</i> = 35)	OLR (<i>n</i> = 65)	<i>P</i> value	LLR (<i>n</i> = 42)	OLR (<i>n</i> = 116)	<i>P</i> value
Age, yr, median (range)	69 (36-89)	78 (59-90)	76 (52-92)	0.067	71 (45-89)	69 (36-86)	0.106
Gender				0.312			1
Female	80 (31.0)	10 (28.6)	12 (18.5)		15 (35.7)	43 (37.1)	
Male	178 (69.0)	25 (71.4)	53 (81.6)		27 (64.3)	73 (62.9)	
BMI				0.662			1
< 30 kg/m ²	247 (95.7)	34 (97.1)	60 (92.3)		41 (97.6)	112 (96.6)	
≥ 30 kg/m ²	11 (4.3)	1 (2.9)	5 (7.7)		1 (2.4)	4 (3.4)	
Performance status				0.124			1
0, 1	242 (93.8)	30 (85.7)	62 (95.4)		40 (95.2)	110 (94.8)	
2, 3	16 (6.2)	5 (14.3)	3 (4.6)		2 (4.8)	6 (5.2)	
Concurrent diseases							
Diabetes mellitus	58 (22.5)	10 (28.6)	17 (26.2)	0.817	7 (16.7)	24 (20.7)	0.656
Hx of congestive heart failure	21 (8.1)	8 (22.9)	11 (16.9)	0.594	1 (2.4)	1 (0.9)	0.462
Coronary artery disease							
Hx of PCI	49 (19.0)	17 (48.6)	31 (47.7)	1	1 (2.4)	0 (0.0)	0.266
Hx of CABG	7 (2.7)	4 (11.4)	3 (4.6)	0.236	0 (0.0)	0 (0.0)	-
Hx of cerebral infarction	26 (10.1)	5 (14.3)	17 (26.2)	0.212	0 (0.0)	4 (3.4)	0.574
Current hemo-/peritoneal dialysis	11 (4.3)	2 (5.7)	5 (7.7)	1	1 (2.4)	3 (2.6)	1
Anticoagulation therapy	30 (11.6)	8 (22.9)	22 (33.8)	0.360	-	-	-
Periop. heparin bridging	26 (10.1)	7 (20.0)	19 (29.2)	0.350	-	-	-
Preop. aspirin continuation	35 (13.6)	14 (40.0)	21 (32.3)	0.382	-	-	-

ATT: Antithrombotic therapy; LLR: Laparoscopic liver resection; OLR: Open liver resection; BMI: Body mass index; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass graft; periop.: Perioperative; preop.: Preoperative.

patients. However, in case of high thromboembolic risks, single aspirin therapy is continued for APT patients, and ACT was substituted by bridging heparin; early reinstitution of the antithrombotic drugs is executed. In patients using both APT and ACT, perioperative management of APT was also combined with those of ACT.

Statistical analysis

The collected data were checked and statistically analyzed by using the package of SPSS software. The categorized variables between the groups were compared by Fisher's exact probability test. The continuous data, expressed as a median with range, and non-parametric variables were compared by Kruskal-Wallis test or Student's *t* test. The analytic method of multivariable logistic regression model was performed to assess significant risk factors affecting increased SBL and BC. Statistical significance was determined at the level of *P* < 0.05.

RESULTS

The current cohort included 77 LLR and 181 OLR. Table 1 demonstrates various characteristics of patient background in the both groups. The type of patient race in the present cohort was exclusively Asian. Both in the ATT and non-ATT groups, age, gender, the rate of high body mass index, and PS class were identical between LLR and OLR. Also, there were no differences between LLR and OLR groups in the occurrence of underlying diseases including history of coronary artery

disease, congestive heart failure, cerebral infarction, or diabetes mellitus. Among the ATT group, the rates of APT and ACT were 32.6% (84/258) and 11.6% (30/258), respectively. Totally, 57 (22.1%) of patients, including 35 (13.6%) of APT patients and 26 (10.1%) of ACT patients, were regarded as high thromboembolic risk and required to continue preoperative aspirin monotherapy and/or bridging heparin.

Table 2 shows factors concerning operative procedures and postoperative morbidity in the both groups. Totally, the diagnoses of the diseases were hepatocellular carcinoma (HCC) in 97 (37.6%) and other diseases in 161 (62.4%), including liver metastases from gastrointestinal malignancy and benign diseases. Type of operation consisted of partial resection in 163 (63.2%), sub-sectionectomy (S5, S6 or S8) in 9 (3.5%), left lateral sectionectomy in 19 (7.4%), and other anatomical hepatectomy (mono-/bi-/tri-sectionectomy) in 67 (26.0%). Both in the ATT and non-ATT groups, there was no difference in the type of liver diseases, although LLR comprised less anatomical resections (ATT, *P* < 0.001; non-ATT, *P* = 0.004), shorter duration of operations (ATT, *P* = 0.011; non-ATT, *P* = 0.049), and less SBL (ATT, *P* < 0.001; non-ATT, *P* = 0.007). Increased SBL (≥ 500 mL) was more frequently observed in OLR compared to LLR in the whole cohort [34.3% (62/181) vs 5.2% (4/77), *P* < 0.001]. One patient (0.4%) undergoing LLR in the non-ATT group was converted to open surgery due to massive bleeding but none was converted in the ATT group.

An overall rate of postoperative complication was

Table 2 Factors concerning operative procedures and postoperative morbidity *n* (%)

Variables	Total (<i>n</i> = 258)	ATT (<i>n</i> = 100)			Non-ATT (<i>n</i> = 158)		
		LLR (<i>n</i> = 35)	OLR (<i>n</i> = 65)	<i>P</i> value	LLR (<i>n</i> = 42)	OLR (<i>n</i> = 116)	<i>P</i> value
Liver diseases				0.393			0.271
HCC	97 (37.6)	15 (42.9)	22 (33.8)		19 (45.2)	41 (35.3)	
Non HCC	161 (62.4)	20 (57.1)	43 (66.2)		23 (54.8)	75 (64.7)	
Type of operation				< 0.001			0.004
Partial resection	163 (63.2)	24 (68.6)	38 (58.5)		31 (73.8)	70 (60.3)	
Sub-sectionectomy (S5, 6, 8)	9 (3.5)	0 (0.0)	2 (3.1)		4 (9.5)	3 (2.6)	
Lateral sectionectomy	19 (7.4)	9 (25.7)	1 (1.5)		4 (9.5)	5 (4.3)	
Other anatomical hepatectomy	67 (26.0)	2 (5.7)	24 (36.9)		3 (7.1)	38 (32.8)	
Duration of ope., min, median (range)	230 (74-705)	198 (98-418)	257 (86-587)	0.011	204 (104-420)	242 (74-705)	0.049
Surgical blood loss, mL, median (range)	200 (1-11070)	80 (1-850)	310 (5-2100)	< 0.001	50 (1-530)	265 (2-11070)	0.007
Intraoperative RBC transfusion	45 (17.4)	4 (11.4)	12 (18.5)	0.408	3 (7.1)	26 (22.4)	0.035
Postop. complication							
None	217 (84.1)	34 (97.1)	50 (76.9)	0.009	41 (97.6)	92 (79.3)	0.005
Superficial SSI	8 (3.1)	0 (0.0)	2 (3.1)		1 (2.4)	7 (6.0)	
Deep SSI	5 (1.9)	0 (0.0)	3 (4.6)		0 (0.0)	2 (1.7)	
Bile leakage	11 (4.3)	0 (0.0)	4 (6.2)		0 (0.0)	7 (6.0)	
Bleeding complication	8 (3.1)	0 (0.0)	3 (4.6)		0 (0.0)	5 (4.3)	
Major bleeding	6 (2.3)	0 (0.0)	3 (4.6)		0 (0.0)	3 (2.6)	
Minor bleeding	2 (0.8)	0 (0.0)	0 (0.0)		0 (0.0)	2 (1.7)	
Thromboembolic complication	3 (1.2)	0 (0.0)	1 (1.5)		0 (0.0)	2 (1.7)	
Cerebral infarction	2 (0.8)	0 (0.0)	0 (0.0)		0 (0.0)	2 (1.7)	
Coronary stent thrombosis	1 (0.4)	0 (0.0)	1 (1.5)		0 (0.0)	0 (0.0)	
Cardiopulmonary arrest	1 (0.4)	1 (2.9)	0 (0.0)		0 (0.0)	0 (0.0)	
Operative mortality	1 (0.4)	1 (2.9)	0 (0.0)	0.350	0 (0.0)	0 (0.0)	-
Length of postop. stay, d, median (range)	14 (4-103)	12 (7-23)	15 (8-103)	0.174	11 (6-19)	15 (4-92)	0.321

ATT: Antithrombotic therapy; LLR: Laparoscopic liver resection; OLR: Open liver resection; HCC: Hepatocellular carcinoma; RBC: Red blood cell; ope.: Operation; postop.; Postoperative; SSI: Surgical site infection.

15.9% (41/258), and LLR included less complications both in the ATT group (2.9% vs 23.1%, $P = 0.009$) and non-ATT group (2.4% vs 20.7%, $P = 0.005$). The most common complication was bile leakage (8/258, 4.3%), all of which were experienced after OLR. Only 3 thromboembolic complications (1.2%) occurred after OLR (cerebral infarction in 2 and coronary stent thrombosis in 1), but LLR was free from these events. Eight BCs were experienced only after OLR (3.1%), including 6 major and 2 minor bleedings, although there was no postoperative BC after LLR. One case of operative mortality was experienced in the ATT group. This patient had high thromboembolic risks, including long-term treatment of hemodialysis and history of multiple DES implantation, underwent partial LLR for HCC under continuation of aspirin monotherapy, and had a good postoperative course, but just the day before discharge (10 d after surgery), suddenly developed cardiopulmonary arrest (pulmonary embolism or coronary thrombosis were denied by urgent cardiopulmonary catheterization) and expired. The cause of arrest was unknown, but may not be related to surgical procedures.

Table 3 shows potential factors affecting increased SBL in the whole cohort ($n = 258$) and in the ATT group ($n = 100$). In the whole cohort, male gender ($P = 0.009$), HCC ($P = 0.008$), OLR ($P < 0.001$), and anatomical liver resection ($P < 0.001$) were the factors affecting increased SBL. When the analysis target was narrowed

down to the ATT group, however, not only OLR ($P = 0.013$) and anatomical liver resection ($P < 0.001$) but also use of multiple APT ($P = 0.035$) and preoperative aspirin continuation ($P = 0.046$) were significantly associated with increased SBL. To control potential confounding and interaction, multivariate analyses for increased SBL in the whole cohort and in the ATT group were performed and shown in Figure 3 as forest plots. In the whole cohort, anatomical liver resection was the most significant risk factor for increased SBL [risk ratio (RR) = 6.54, $P < 0.001$] and LLR also had the significant negative impact (RR = 1/10.0, $P < 0.001$). The same effects of anatomical resection (RR = 15.77, $P < 0.001$) and LLR (RR = 1/5.88, $P = 0.019$) were observed when analyzing the patients in the ATT group.

DISCUSSION

Various types of abdominal surgery are currently being performed laparoscopically thanks to development of many energy devices and techniques. Compared to OLR, many reports have demonstrated advantages of LLR, such as minimal degree of body wall damage, fewer intra- and post-operative complications, and decreased SBL^[11-14]. However, the impact of LLR on SBL and BC in patients receiving ATT has not been investigated and is still largely unknown. Our study demonstrates that the cohort comprised 258 liver resection, including 77 LLR and 181 OLR, among

Table 3 Univariate analysis of increased surgical blood loss (≥ 500 mL) in the whole cohort ($n = 258$) and in the antithrombotic therapy group ($n = 100$, %)

Variables	Increased surgical blood loss (≥ 500 mL)			
	The whole cohort ($n = 258$)		ATT group ($n = 100$)	
	Present/total	<i>P</i> value	Present/total	<i>P</i> value
Total	66/258 (25.6)		23/100 (23.0)	
Age		0.664		0.811
≥ 75 yr	25/105 (23.8)		14/57 (24.6)	
< 75 yr	41/153 (26.8)		9/43 (20.9)	
Gender		0.009		0.389
Female	12/80 (15.0)		3/22 (13.6)	
Male	54/178 (30.3)		20/78 (25.6)	
BMI		0.734		0.332
< 30 kg/m ²	64/247 (25.9)		23/94 (24.5)	
≥ 30 kg/m ²	2/11 (18.2)		0/6 (0.0)	
Performance status		1		0.192
0, 1	62/242 (25.6)		23/92 (25.0)	
2-4	4/16 (25.0)		0/8 (0.0)	
ASA class		0.148		0.789
I, II	34/153 (22.2)		5/25 (20.0)	
III, IV	32/105 (30.5)		18/75 (24.0)	
Diabetes mellitus		0.733		1
Yes	16/58 (27.6)		6/27 (22.2)	
No	50/200 (25.0)		17/73 (23.3)	
Hx of PCI		0.589		0.234
Yes	14/49 (28.6)		14/48 (29.2)	
No	52/209 (24.9)		9/52 (17.3)	
ATT used		0.468		-
Yes	23/100 (23.0)		-	
No	43/158 (27.2)		-	
Multiple APT used		0.117		0.035
Yes	11/29 (37.9)		11/29 (37.9)	
No	55/229 (24.0)		12/71 (16.9)	
Preop. aspirin continuation		0.215		0.046
Yes	12/35 (34.3)		12/34 (35.3)	
No	54/223 (24.2)		11/66 (16.7)	
Liver diseases		0.008		0.138
HCC	34/97 (35.1)		12/37 (32.4)	
Non HCC	32/161 (19.9)		11/63 (17.5)	
Laparoscopic liver resection		< 0.001		0.013
Yes	4/77 (5.2)		3/35 (8.6)	
No	62/181 (34.3)		20/65 (30.8)	
Anatomical liver resection		< 0.001		< 0.001
Yes	46/95 (48.4)		19/38 (50.0)	
No	20/163 (12.3)		4/62 (6.5)	

ATT: Antithrombotic therapy; BMI: Body mass index; ASA: American Society of Anesthesiologists; PCI: Percutaneous coronary intervention; APT: Antiplatelet therapy; HCC: Hepatocellular carcinoma; Preop.: Preoperative.

which 38% of patients received ATT regularly. LLR was significantly related to reduced SBL and low incidence of BC. Multivariate analyses also showed that both in the whole cohort and in the ATT group, not only anatomical liver resection was significantly associated with increased SBL, but also LLR independently had the impact on reduction of SBL. This is the first study to elucidate the effect of LLR on reduced SBL in patients receiving ATT. Using the two-surgeon technique, LLR is feasible and safely performed without increase of SBL or thromboembolic events even in the ATT-burdened patients with thromboembolic risks.

Minimizing intraoperative SBL during liver resection is one of the most important tasks, and improvement of several technical aspects has been reported, such

as the liver hanging manoeuvre, Pringle manoeuvre, and the two-surgeon technique^[10,15,16]. The two-surgeon technique during liver surgery, which was first recommended by Aloia, is a novel technique for decreasing SBL and postoperative bile leakage as well as shortening operative time by allowing two surgeons to simultaneously participate in the parenchymal transection^[10]. The primary surgeon dissects the liver parenchyma by ultrasonic dissection device; the assistant surgeon performs meticulous hemostasis using the saline-linked electrocautery. We also applied this manoeuvre during both conventional OLR and LLR.

In our hospital, the occurrence of ATT-received patients who need to undergo major hepatobiliary/pancreatic surgery is as many as 40%, and the number

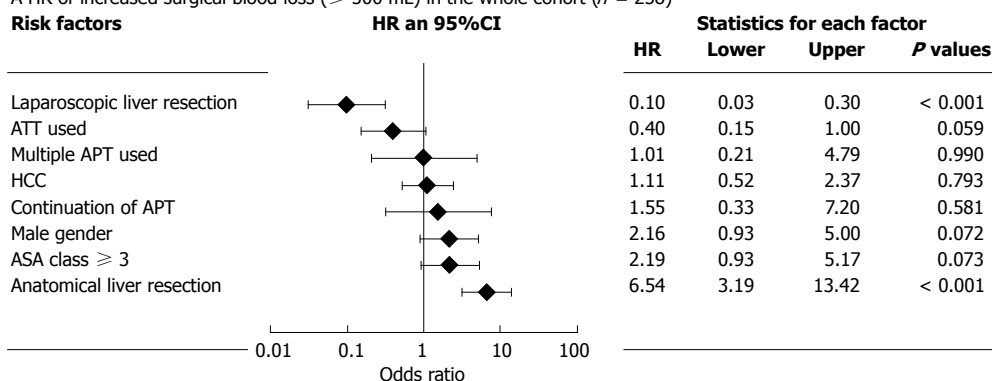
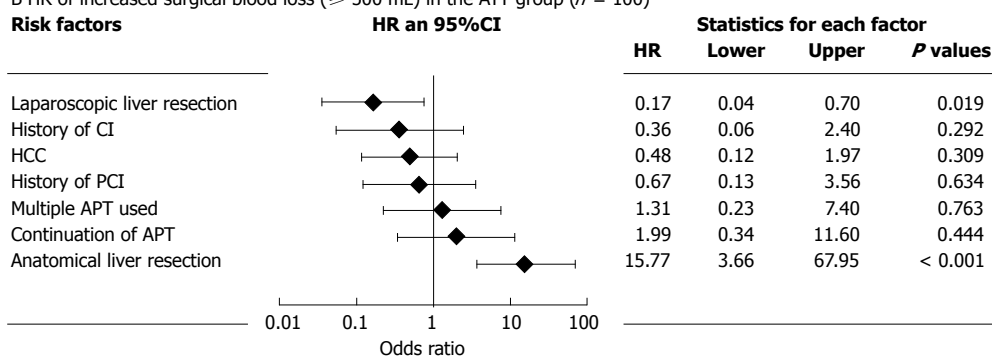
A HR of increased surgical blood loss (≥ 500 mL) in the whole cohort ($n = 258$)B HR of increased surgical blood loss (≥ 500 mL) in the ATT group ($n = 100$)

Figure 3 Forest plots showing hazard ratios of increased surgical blood loss. A: Hazard ratios in the whole cohort ($n = 258$); B: Hazard ratios in the ATT group ($n = 100$). HR: Hazard ratio; ATT: Antithrombotic therapy; APT: Antiplatelet therapy; HCC: Hepatocellular carcinoma; ASA: American Society of Anesthesiologists; CI: Cerebral infarction.

is increasing further in the future. In ATT-burdened patients undergoing major hepatobiliary/pancreatic surgery, both excessive surgical stress and inappropriate antithrombotic management are considered to affect bad postoperative outcome. The surgical stress has been demonstrated to make an inflammatory response which generates plaque fissure and subsequently causes acute thrombosis^[17,18]. Therefore, we should consider an application of LLR to even more troublesome ATT-burdened patients. If the patient has high thromboembolic risks and preoperative ATT cannot be stopped, the intraoperative and postoperative bleeding risks will increase. To minimize SBL especially in this critical patient population, we thought that the appropriate devices and techniques for rigid hemostasis must be applied during LLR. As shown in our previous report, LLR using the two-surgeon technique is safe and feasible, and can be applied to even ATT-burdened patients^[7].

Minimizing SBL to maintain a dry operative field is extremely crucial especially during pure LLR. To control hepatic inflow, Pringle maneuver (intermittent hepatic vascular inflow occlusion) is usually employed during liver parenchymal transection. To control backflow bleeding from the hepatic vein, the maintenance of low central venous pressure (CVP) is commonly used, and decreasing CVP combined with the maintenance of low airway pressure and high pneumoperitoneum pressure (PPP) is also reported to be useful^[19-22].

However, maintenance of low CVP and high PPP during liver parenchymal transection in pure LLR may expose the ATT-burdened patients to the elevated risks of thromboembolism. Therefore, if the patients with high thromboembolic risks require major anatomical resection, we definitely choose and perform "hybrid LLR" (in which the parenchymal transection is performed through mini-laparotomy) or OLR under the maintenance of normal CVP levels to avoid low CVP-induced thromboembolic events. Our data demonstrated that even though the procedures were associated with increased bleeding tendency due to normal CVP levels, hybrid LLR using the two-surgeon technique was performed safely without increase of SBL or thromboembolic complications.

Concerning perioperative thromboembolic complications including cerebrovascular stroke, pulmonary embolism, or major adverse cardiovascular event (MACE), the rates of perioperative thromboembolisms vary depending on differences in target patient population, study design, and changing of clinical practices. The reported incidence of stroke following noncardiac, nonneurosurgical surgery ranges between 0.1%-0.4% overall, and 2.9%-3.5% in patients at risk of perioperative stroke^[23-26]. In consideration of thromboembolic events after liver resection, the prevalence of thromboembolism seems to be higher. Schroeder *et al.*^[27] reported that analyzing 587 patients undergoing liver resection from ACS-National Surgical Quality Improvement Program (NSQIP) database, rates

of MACE and overall thromboembolic complications after liver resection were at 4.4% and 3.6%, respectively. Another research of 5227 liver resections from ACS-NSQIP database showed that the rate of critical cardiac complications including myocardial infarction and cardiac arrest after liver resection was at 4.8% in patients with underlying cardiac disease and at 1.6% in those without^[28]. The present study demonstrated that the incidence of perioperative thromboembolic complication was maintained at 1.2%, a relatively low rate compared to the previous report. Hence, it is suggested that liver resections including both OLR and LLR can be performed safely under the Kokura Protocol, the rigorous perioperative antithrombotic management protocol, with successful inhibition of thromboembolic events even in high thromboembolic risk patients.

There are limitations to the present study. This single-center retrospective observational design of the current study has inherent potential for bias, which lessens the effect of the statistical analysis. This restriction will be alleviated by follow-up investigation, or by multi-institutional prospective studies. Since we continuously manage ATT-received cases that are required to undergo liver resection using the Kokura Protocol and the same surgical policies, we are going to analyze more cases to investigate the safety and feasibility of LLR on this high-risk patient population.

Conclusion

LLR using the two-surgeon technique is feasible and safely performed without increase of SBL or thromboembolic events even in the ATT-burdened patients with thromboembolic risks. Independent from the extent of liver resection, LLR is significantly associated with reduced SBL, both in the ATT and non-ATT groups.

COMMENTS

Background

Nowadays, patients who have histories of cardiovascular or cerebrovascular diseases have been seen more often with aging of patients, and those patients frequently receive antithrombotic therapy (ATT) for the purpose of primary and secondary prevention of thromboembolic diseases. While indications for ATT use have expanded, antithrombotic management during gastrointestinal and/or hepatobiliary-pancreatic surgery is difficult and always bothersome because of high risks of perioperative bleeding or thromboembolic events. Recently, laparoscopic liver resection (LLR) using the "two-surgeon technique" is safely performed without critical intraoperative or postoperative bleeding even in patients receiving ATT, but the effect of LLR on increased surgical blood loss (SBL) and postoperative bleeding complications (BCs), especially in patients undergoing ATT, still remains unclear.

Research frontiers

In the authors' institution, a protocol of risk stratification and perioperative antithrombotic management has been established for patients receiving ATT ("Kokura Protocol"). So far, the feasibility and safety of both open and laparoscopic abdominal surgeries under the Kokura Protocol have been reported. Moreover, the authors' recent paper demonstrated that LLR using the "two-surgeon technique" is safely performed without critical intraoperative or postoperative bleeding even in patients receiving ATT.

Innovations and breakthroughs

The impact of LLR on BCs in patients receiving ATT has not been investigated

and is still largely unknown. The authors' study demonstrates that the cohort comprised 258 liver resection, including 77 LLR and 181 OLR, among which 38% of patients received ATT regularly. LLR was significantly related to reduced SBL and low incidence of postoperative BCs. Multivariate analyses also showed that both in the whole cohort and in the ATT group, LLR independently had the impact on reduction of SBL. This is the first study to elucidate the effect of LLR on reduced SBL in patients receiving ATT.

Applications

Using the two-surgeon technique, LLR is feasible and safely performed without increase of SBL or thromboembolic events even in the ATT-burdened patients with thromboembolic risks.

Terminology

ATT includes antiplatelet therapy (APT) and/or anticoagulation therapy (ACT) for the purpose of primary and secondary prevention of thromboembolic diseases. LLR has been innovated and currently accepted as minimally-invasive procedures for both hepatocellular carcinoma and metastatic liver diseases in selected patients. LLR is reportedly related to reduced degree of body wall damage, fewer intraoperative and postoperative complications, and decreased SBL.

Peer-review

It is an interesting work.

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Retrospective Study

Correlation of abnormal histology with endoscopic findings among mycophenolate mofetil treated patients

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Abstract**AIM**

To describe all abnormal histological findings and their associated endoscopic presentation in patients using mycophenolate mofetil (MMF).

METHODS

A retrospective review of all individuals prescribed MMF within 6 mo of a colonoscopy or flexible sigmoidoscopy between 07/2009 and 09/2015 was performed within Northwell Health system. Records were analyzed for age, gender, procedure indication, MMF indication, and both gross and microscopic findings. Only reports with abnormal histology were included.

RESULTS

One hundred and eighty-four procedures from 170

patients were found, of which 39 met inclusion criteria. Fifty-one point three percent were female. MMF was used for solid organ transplant in 71.8%. Diarrhea was the indication for 71.8% of colonoscopies. Fifty-nine percent of reports revealed gross and microscopic abnormalities while 41.0% had only microscopic findings. Only 11 patients' reports (28.2%) indicated a specific histopathology of MMF colitis. Among the entire group, only 23.1% of abnormal histology was isolated proximal to the splenic flexure.

CONCLUSION

Our results demonstrate a high rate of left sided disease and microscopic findings without gross mucosal abnormalities among patients using MMF. Also, a broader definition of MMF-colonopathy may be appropriate, with a majority of our abnormal histology falling outside of the more narrowly defined MMF-colitis category. Given the high frequency of isolated microscopic abnormalities and distal disease, sigmoidoscopy with random biopsies may be an appropriate, less invasive initial endoscopic examination in selected MMF patients.

Key words: Mycophenolate mofetil; Colitis; Colonoscopy; Diarrhea

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Core tip: Gastrointestinal complaints are common among patients using mycophenolate mofetil (MMF). Little information exists to guide an effective endoscopic workup in this population. A retrospective review of all patients prescribed mycophenolate within 6 mo of an endoscopic procedure was performed. Our results demonstrate a high rate of left sided disease and microscopic findings without gross mucosal abnormalities among patients using mycophenolate. A broader definition of MMF-colonopathy may be appropriate, with a majority of our abnormal histology falling outside of the more narrowly defined MMF-colitis category. Our findings suggest sigmoidoscopy with random biopsies may be an appropriate initial evaluation.

Izower MA, Rahman M, Molmenti EP, Bhaskaran MC, Amin VG, Khan S, Sultan K. Correlation of abnormal histology with endoscopic findings among mycophenolate mofetil treated patients. *World J Gastrointest Endosc* 2017; 9(8): 405-410 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v9/i8/405.htm> DOI: <http://dx.doi.org/10.4253/wjge.v9.i8.405>

INTRODUCTION

Mycophenolate mofetil (MMF) is an immunosuppressive agent that is used mainly for the prevention of organ transplant rejection, but is increasingly used for autoimmune and hematologic disorders^[1,2]. Mycophenolic acid (MPA) is the active metabolite of MMF. MPA prevents the proliferation of lymphocytes by inhibiting

inosine monophosphate dehydrogenase, an enzyme in the *de novo* pathway of purine synthesis^[3]. Other mechanisms of MPA immunosuppression have been reported, including apoptosis of activated T-lymphocytes, decreased recruitment of lymphocytes to sites of inflammation, and decreased nitric oxide-mediated tissue damage^[4]. Enterocytes are also dependent on the *de novo* pathway of purine synthesis and become potential targets for MPA^[1,4]. This can lead to gastrointestinal toxicity, which typically manifests as diarrhea, and can occur in up to 36% of patients^[1].

For many patients using MMF who develop diarrhea, the severity of complaints may prompt a formal workup. In cases with negative stool studies for infectious causes, endoscopic examination either with flexible sigmoidoscopy or colonoscopy may be performed^[5]. In those individuals with abnormal histology, it is then critical to differentiate MMF-related colitis from colitis of other etiologies such as new onset inflammatory bowel disease (IBD) or atypical infection. Accurate diagnosis is critical to proper use of MMF, as dose modification and/or discontinuation of MMF risks organ rejection or reactivation of autoimmune disease^[2,6].

Prototypical histopathology of MMF colitis has been described as "prominent crypt cell apoptosis and reactive/reparative changes including enterocyte cytologic atypia, increased neuroendocrine cells, and glandular architectural distortion"^[7]. While a pathologist informed of MMF usage may identify a typical pattern of MMF related injury^[1,2,4], and specify a finding as "MMF colitis", a broader spectrum of abnormal histology associated with MMF appears to exist^[2]. In addition, the endoscopic findings related to MMF colitis, and other MMF associated abnormal histology, are not well described - including the gross nature of lesions and typical distribution within the colon. Most prior studies have been limited to case reports and retrospective studies and have focused on abnormal histopathology associated with MMF usage without addressing the endoscopic appearance or patterns of distribution within the GI tract^[4].

As with other disorders such as Crohn's disease and microscopic colitis, knowledge of anatomic disease distribution and associated presence or absence of gross mucosal abnormalities are critical to guide an effective work up. Our aim was to describe all abnormal histological findings and their associated endoscopic presentation in all patients undergoing colonoscopy while using MMF.

MATERIALS AND METHODS

We conducted a retrospective review of all patients who were 18 years of age and older and had documented use of MMF within 6 mo of undergoing a colonoscopy or flexible sigmoidoscopy from July 2009 to September 2015. The study was conducted within the North Shore-LIJ Health System (now Northwell Health) after obtaining institutional review board approval. Only

Table 1 Demographic of mycophenolate mofetil treated patients and procedures (170 patients, 184 procedures) (%)

Characteristic	
mean age	57.05
Female	89 (48.4)
Indication for procedure ²	
Screening	72 (39.1)
Diarrhea	51 (27.7)
Bleeding	24 (13.0)
Anemia	20 (10.9)
Abdominal pain	14 (7.7)
Constipation	3 (1.6)
Weight loss	3 (1.6)
Abnormal imaging	3 (1.6)
Bloating	1 (0.52)
Other (history of IBD, amyloid, stricture)	9 (4.9)
Indication for MMF	
Organ transplant (kidney, liver, lung)	116
Autoimmune	35
Blood disorder	7
Unknown indication	26
Abnormal mucosa (gross)	40
With normal biopsies	10
With abnormal biopsies	25 (2 duplicates)
Without biopsies ¹	5
Normal mucosa (gross)	144
With normal biopsies	44 (normal biopsy or polypectomy, 1 for mass)
With abnormal biopsies	17 (1 duplicate)
Without biopsies ¹	83

¹Without biopsies done or with reports unavailable; ²Some procedures with multiple indications documented. MMF: Mycophenolate mofetil; IBD: Inflammatory bowel disease.

sigmoidoscopy or colonoscopy reports with abnormal histology described on the official pathology report were included in the review. Sigmoidoscopy or colonoscopy reports with normal pathology or missing pathology report were excluded. In patients with multiple eligible colonoscopies or sigmoidoscopies, the procedure report nearest to the date of MMF prescribing was the one included in the analysis. If a patient had both an eligible colonoscopy and flexible sigmoidoscopy, the colonoscopy report was used.

Demographic information, indication for colonoscopy, indication for MMF, gross and histological findings were recorded. All pathology samples were evaluated by experienced gastrointestinal pathologists. Only pathology reports specifically citing MMF use as the likely etiology were classified as "MMF-colitis". All remaining abnormal findings were broadly classified as "other" abnormal findings, and sub-categorized according to their description in the pathology report. Abnormal histology findings proximal to the splenic flexure were defined as right colonic; findings distal to the splenic flexure were defined as left colonic. Abnormal findings occurring both proximal and distal to the splenic flexure were defined as pancolonic. Location and description of abnormal gross findings on colonoscopy/sigmoidoscopy examination also corresponded to the official procedure report. Our goals

were to describe abnormal histological findings, their location within the colon, and the presence or absence of associated gross endoscopic findings.

RESULTS

A total of 184 colonoscopies and sigmoidoscopies from 170 patients were reviewed during the study period. Overall, screening was the most common indication for a procedure, with organ transplant as the most common indication for MMF use (Table 1). Of these, 34 colonoscopies and 5 sigmoidoscopies from 39 individual patients met inclusion criteria. Fifty-one point three percent were female. Average age at time of procedure was 51.44 years old. For this group with abnormal histology, diarrhea was the most common indication, accounting for 71.8% of the combined sigmoidoscopies and colonoscopies. Two patients had procedures for history of inflammatory bowel disease. Indications for MMF therapy were: Solid organ transplant (71.8%), hematologic disorders (17.9%) and autoimmune disease (10.3%). Of the 28 solid organ transplant patients, 27 were from renal transplants and 1 was from a lung transplant. Demographics of colitis among MMF treated patients (Table 2).

Of the 39 patient reports meeting inclusion criteria, only 11 patient pathology reports (28.2%) indicated a specific histopathology of MMF colitis. Notably, only 9 of 39 (23.1%) specimen request forms sent to pathology provided history of MMF use. Non-specific colitis was identified in 30.8% of the reports. Four reports indicated graft vs host disease (GVHD), and all were from patients who were on MMF for leukemia or lymphoma and underwent stem cell transplant. The remaining twelve cases are included in Table 3.

Overall 23 (59.0%) of abnormal histology corresponded to a reported gross endoscopic abnormality, while 16 (41.0%) demonstrated abnormal histology without a gross abnormality. Of the 28 procedures performed for an indication of diarrhea, 13 (46.4%) of abnormal histology corresponded to a gross endoscopic abnormality, while 15 (53.6%) demonstrated abnormal histology without a gross abnormality. Among the entire 39 cases reviewed only 23.1% of abnormal histology was isolated to the right colon. Among the subgroup of 11 MMF-colitis cases, only one (9.1%) was isolated to the right colon, Figure 1.

DISCUSSION

In our study out of 184 procedures performed on 170 patients using MMF, only 39 colonoscopies/sigmoidoscopies had abnormal pathology. Of these, only 28.2% demonstrated a specific histopathology of MMF colitis. Endoscopic and histological evidence of colitis in patients who developed diarrhea while using MMF have been previously studied^[4]. Those reports, which evaluated the histopathological findings of this MMF-colitis, have shown a variety of features including

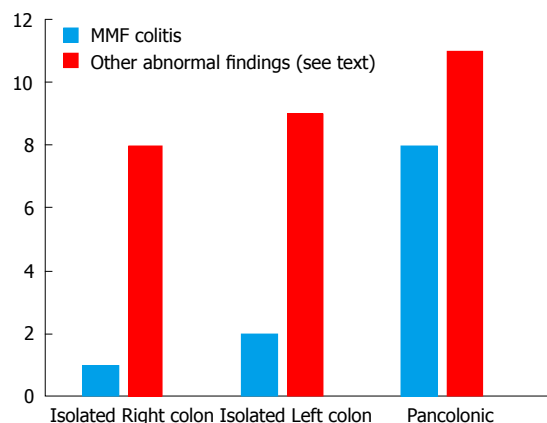
Table 2 Demographic of colitis among mycophenolate mofetil treated patients *n* (%)

Characteristic	
<i>n</i>	39
mean age	51.44
Female	20 (51.3)
Indication for procedure	
Diarrhea	28 (71.8)
Bleeding	2 (5.1)
Anemia	1 (2.6)
Screening	4 (10.3)
Abnormal imaging	2 (5.1)
Other (history of IBD)	2 (5.1)
Indication for MMF	
Organ transplant	28 (71.8)
Autoimmune	4 (10.3)
Blood disorder	7 (17.9)

MMF: Mycophenolate mofetil; IBD: Inflammatory bowel disease.

prominent crypt cell apoptosis and reactive/reparative changes including enterocyte cytologic atypia, lamina propria inflammation, and crypt architectural disarray^[8]. In our study, similar findings were described for MMF-colitis, with the most common feature being cell apoptosis. While the presence of apoptosis is regarded as more typical of a true MMF-related colitis^[8], there is no consensus regarding the spectrum of abnormal histology related to MMF use. Our findings of frequent nonspecific colitis and other histological abnormalities suggests that a broader definition of MMF-colonopathy may be required, with a majority of our abnormal histology falling outside of the more narrowly defined MMF-colitis category.

Prior case series and reports were able to categorize abnormal histological findings in patients on MMF into IBD-like, GVHD-like, ischemic-like, acute colitis, or non-specific colitis^[2,9]. In our study, 30.8% of the reports indicated non-specific colitis. This high frequency of non-specific colitis was also found by de Andrade *et al*^[9]. In addition to non-specific colitis, there were 4 reported cases of GVHD in our study, all in patients with hematologic disease and a history of bone marrow transplant. This suggests that the transplant itself is the cause of the abnormal findings rather than the MMF, although previous studies have described GVHD-like pathology in patients on MMF following solid organ transplant^[1,2,4]. Additionally, it can be difficult to histologically differential between GVHD and MMF colitis. Star *et al*^[10] have found that high eosinophilic count, absence of neuroendocrine cell clusters and apoptotic microabscess are more suggestive of MMF colitis over GVHD. Ischemic-like pathology can also be found in patients on MMF. Johal *et al*^[8] described MMF-induced segmental colitis mimicking ischemic colitis. There was one case of ischemic-like pathology found in our study, however, given lack of multiple biopsies, it is unknown if this patient had segmental colitis. Regardless of the pathology, most of these patients underwent col-

**Figure 1** Distribution of histopathology in confirmed mycophenolate mofetil colitis and other abnormal findings.

onoscopy due to diarrhea.

Gastrointestinal toxicity, usually manifested as diarrhea, is the most common side effect of MMF^[8]. The reported incidence of diarrhea is variable and can range from 13% to 64%^[4]. Diarrhea was the most common indication for colonoscopy in our study population (71.8%). Even though the exact mechanism of MMF induced diarrhea is unknown, different etiologies have been proposed^[4]. In addition to the impact on the quality of life, diarrhea can lead to non-compliance, weight loss, and physician-directed MMF dose reduction^[1].

Data describing the presence of macroscopic abnormalities and distribution of findings associated with MMF-related colitis is limited. Calmet *et al*^[4] found macroscopic findings ranging from erythema to erosions and ulcers. About half of the patients they studied had normal macroscopic findings, similar to our findings of abnormal histology without endoscopic mucosal changes in 41% patients, with others demonstrating erythema, friability, granularity, loss of vascularity, and ulcerations. These findings were found across MMF-related colitis including GVHD, AML, and MMF colitis as shown in Figure 2. Along with Calmet *et al*^[4], our results showing such a high rate of isolated microscopic abnormalities strongly support a diagnostic protocol including random biopsies of normal appearing mucosa in patients on MMF with colitis-like complaints.

Our patients also demonstrated a low frequency of abnormal histology (23.1%) limited to the right colon, proximal to the splenic flexures. This finding was even more pronounced for the subgroup of MMF-colitis, of which only one case was isolated proximal to the splenic flexure. This appears similar to the findings of Calmet *et al*^[4]. In a smaller sample of 20 patients they found that 25% of MMF related colitis was found in the right colon, though "right colon" was not explicitly defined^[4]. Our findings suggest that a viable strategy for evaluation in this patient population could be to initially perform by a sigmoidoscopy, moving on to full colonoscopy only if distal findings are negative. While sigmoidoscopy is

Table 3 Abnormal histological findings by mycophenolate mofetil indication

	Solid organ transplant (<i>n</i>)	Autoimmune (<i>n</i>)	Blood disorder (<i>n</i>)	Total (<i>n</i>)
MMF colitis	10	1	0	11
Graft <i>vs</i> host disease	0	0	4	4
Nonspecific colitis	11	0	1	12
Other	3 (hyperplastic), 1 (lymphoid aggregate), 1 (kayexalate), 1 (ischemic), 1 (amyloid)	1 (IBD), 1 (lymphoid aggregate), 1 (hyperplastic)	1 (AML), 1 (reactive)	12

MMF: Mycophenolate mofetil; IBD: Inflammatory bowel disease.

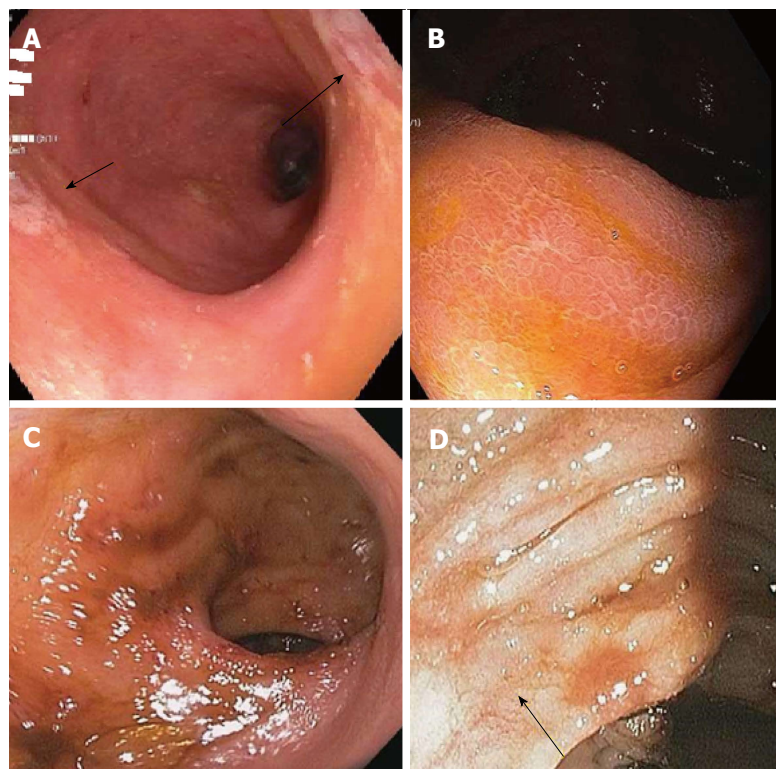


Figure 2 These findings were found across mycophenolate mofetil-related colitis. A: Mycophenolate mofetil (MMF) colitis: erythematous hyperemic mucosa (sigmoid colon); B: MMF colitis: coarse appearing colonic mucosa (ascending colon); C: AML: multiple small ulcers and erosion (rectum); D: GVHD: patchy areas of mucosa (transverse colon).

no longer commonly used for colon cancer screening purposes, it remains a valuable tool for the evaluation of other gastrointestinal conditions. Notably, it may be used for the diagnosis and monitoring of response to therapy in ulcerative colitis due to the near universal involvement of the rectum and left-colon typical of the disorder. Our findings suggest a similar role for sigmoidoscopy for the workup of lower gastrointestinal complaints in patients using MMF. Significant advantages to sigmoidoscopy compared to colonoscopy include avoidance of sedation and lower risk of perforation. Also, since so many of these patients have a history of renal transplantation, the avoidance of a full bowel preparation, required by colonoscopy but unnecessary for sigmoidoscopy, lowers the risk of renal compromise, which has been associated with certain colonoscopy preparations^[11].

In our current series we found a relatively small number of abnormal histology reported with a diagnosis specific for MMF colitis. Notably, a similarly small number of samples that were sent to pathology directly specified usage of MMF. This implies that

some pathologists, if they are not aware of MMF use, or are less familiar with MMF-related colitis, may not consider the diagnosis of MMF-related colitis, leading to decreased specificity of findings and lingering diagnostic uncertainty. It would likely be of value to pathologists to make them aware of MMF usage, so as to improve the rate at which MMF-related colitis is appreciated in pathology samples. Alternatively, as discussed, a more broadly defined MMF-colonopathy may need to be considered when evaluating and managing patients with any abnormal histology using MMF.

Our study had some limitations. The total number of patients we analyzed for abnormal histological findings, while large by comparison to other case series, was still small in absolute numbers due to the rareness of MMF use and occurrence of these findings. Also, though the electronic medical record (EMR) allowed us to track MMF prescribing, we could not confirm patient compliance. In addition, though we did analyze a significant amount of demographic information, there were limits to the EMR, such as our inability to consider patient race/ethnicity as part of our analysis.

In summary, ours is the largest study correlating all abnormal pathology associated with MMF use with both gross endoscopic findings and disease distribution. Our findings reinforce the importance of random biopsies of grossly normal appearing colonic mucosa towards making an accurate diagnosis. Importantly, our findings also support a first line diagnostic approach using a less invasive, lower risk sigmoidoscopy coupled with routine biopsy in selected MMF patients with appropriate complaints. Moving forward, valuable avenues of research would include outcomes analysis of patients diagnosed with MMF-related colonic abnormalities after intervention, whether that be *via* dose modification or discontinuation of MMF or other means of treatment. This would be valuable in further confirming the clinical significance of these findings, as well as the therapeutic benefit of accurately confirming such a diagnosis

COMMENTS

Background

Gastrointestinal complaints are common among patients using mycophenolate mofetil (MMF). Abnormal biopsy findings have been described in this population, but little information exists to guide an effective endoscopic workup of those on MMF such as the presence or absence of gross endoscopic findings and their anatomic distribution.

Research frontiers

Abnormal biopsy findings have been described in patients treated with MMF. The current research focus is to evaluate the endoscopic findings and the proper endoscopic workup in patients with gastrointestinal complaints on MMF.

Innovations and breakthroughs

Prior studies have only described the histology in a limited number of patient on MMF. Most of these studies were limited to renal transplant patients. The authors looked at all patients treated with MMF for a variety of illnesses. Also, there is very limited information describing gross mucosal findings and anatomic distribution of abnormal findings within the MMF population. The authors results demonstrate a high rate of left sided disease and microscopic findings without gross mucosal abnormalities among patients using MMF.

Applications

A broader definition of MMF-colonopathy may be appropriate, with a majority of the authors' abnormal histology falling outside of the more narrowly defined MMF-colitis category. The authors findings support sigmoidoscopy with random biopsies may be an appropriate initial endoscopic evaluation in patients with bowel complaints using MMF.

Terminology

MMF is an immunosuppressive agent that is used mainly for the prevention of organ transplant rejection. This can lead to gastrointestinal toxicity, which typically manifests as diarrhea. Right colonic findings were defined as abnormal

histology findings proximal to the splenic flexure. Left colonic findings were defined as abnormal histology findings distal to the splenic flexure.

Peer-review

This paper study the correlation of abnormal histology with endoscopic findings among Mycophenolate Mofetil treated patients, the sample is large.

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Retrospective Study

Usefulness of the Hook knife in flexible endoscopic myotomy for Zenker's diverticulum

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Abstract**AIM**

To investigate the outcome of flexible endoscopic myotomy performed with the Hook knife in patients with symptomatic Zenker's diverticulum (ZD).

METHODS

All consecutive patients treated for ZD at our institution between 7/2012 and 12/2016 were included. The flexible endoscopic soft diverticuloscope-assisted technique with endoclips placement and Hook knife myotomy were performed in all patients. Here we report a retrospective review of prospectively collected data. Demographics, dysphagia score (Dakkak and Bennett), associated symptoms and adverse events were collected pre-procedure, at 2 and 6 mo post-procedure, and at the end of the follow-up period. Clinical success was defined as at least 1-point improvement in dysphagia score and a residual dysphagia score ≤ 1 , with no need for reintervention. Dysphagia scores were compared before treatment and at end-of-follow-up using the Wilcoxon test.

RESULTS

Twenty-four patients were included. Mean size of ZD was 3.0 cm (range 2-8 cm). Mean number of sessions

was 1.17/patient (range 1-3 sessions). Overall clinical success was 91.7%. Two adverse events (8.3%) occurred, and both were managed conservatively. No bleeding or perforation was reported. Mild pain was reported by 9 patients (37.5%). Median hospital stay was 1 d (range 1-6). Median follow-up was 19.5 mo (range 6-53). Mean \pm SD dysphagia score was 2.25 ± 0.89 before treatment and decreased to 0.41 ± 0.92 at end-of-follow-up ($P < 0.001$). Regurgitation and cough dropped from 91.7% and 50% to 12.5% and 0% at the end of follow-up, respectively. Recurrence was observed in 3 patients, and all 3 were symptom-free after one more session.

CONCLUSION

The Hook knife, used in the soft diverticuloscope-assisted technique setting, is efficient and safe for treatment of ZD.

Key words: Zenker's diverticulum; Flexible endoscopy

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Core tip: Zenker's diverticulum can cause uncomfortable symptoms such as dysphagia, regurgitation and cough, and sometimes weight loss or aspiration pneumonia. Soft diverticuloscope-assisted flexible myotomy is used worldwide and has proven to be safe and efficient. In terms of adverse events, perforation remains the major concern. The most effective tool for performing myotomy in this setting has yet to be determined. Here we treated 24 patients with the Hook knife, resulting in 91.7% overall success, a 13% recurrence rate, and only 2 mild adverse events reported.

Rouquette O, Abergel A, Mulliez A, Poincloux L. Usefulness of the Hook knife in flexible endoscopic myotomy for Zenker's diverticulum. *World J Gastrointest Endosc* 2017; 9(8): 411-416 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v9/i8/411.htm> DOI: <http://dx.doi.org/10.4253/wjge.v9.i8.411>

INTRODUCTION

Zenker's diverticulum (ZD), an acquired rare condition that typically occurs in the elderly^[1], is a pulsion diverticulum developing on the posterior wall of the esophagus through Killian's triangle. ZD development is thought to be caused by dysfunction of the cricopharyngeal muscle resulting in increased intraesophageal pressure^[2]. ZD can cause symptoms such as dysphagia, regurgitations, or chronic cough. Weight loss and aspiration pneumonia are potentially severe complications. Treatment basically consists in myotomy of the cricopharyngeal muscle. Endoscopic myotomy was introduced decades ago, has been widely evaluated since, and is now considered a first-line treatment option^[3]. In Europe, the mini-invasive flexible endoscopic soft diverticuloscope-

Table 1 The Dakkak and Bennett score of dysphagia^[7]

Grade 0	No dysphagia
Grade 1	Solids
Grade 2	Semi-solids
Grade 3	Liquids
Grade 4	Aphagia

assisted technique with endoclip(s) placement, as described by Huberty *et al.*^[4], is common practice and has proven safe and effective. However, various tools are used to perform the myotomy. Submucosal dissection knives have been described in this indication, and appear to be safe and effective^[5]. Myotomy must be continued deep enough to improve clinical symptoms, but dissection must be limited to muscle fibers to avoid perforation. The key issue is where to stop the myotomy^[6]. The Hook knife (Olympus endotherapy, Tokyo, Japan) is designed with a distal tip consisting in a 5 mm-long, rotatable, hook-shaped knife, allowing pulling tissues before cutting. We posit that the Hook knife is the most appropriate tool for this intervention. Here we report short and mid-term outcome and adverse events of soft diverticuloscope-assisted flexible endoscopic myotomy with the Hook knife.

MATERIALS AND METHODS

Population

All consecutive patients treated at our institution by flexible endoscopy for symptomatic ZD between July 2012 and December 2016, and with at least 6 mo of follow-up at December 2016, were included in the study. We performed a retrospective review of prospectively collected data. Demographics, dysphagia score, symptoms, outcome, and adverse events were recorded. The Dakkak and Bennett dysphagia score was used (Table 1)^[7]. All patients were seen as outpatients before and at 2 and 6 mo after the procedure, and were asked to phone anytime in case of recurrence. At the end of the follow-up period, all patients were interviewed by phonecall.

This study was conducted according to the ethical principles of the Declaration of Helsinki and in compliance with good clinical practice. Informed consent was obtained from all patients. This study was reviewed and approved by our center's Institutional Review Board, reference 2016/CE 91.

Endoscopic treatment

All patients were treated by a single endoscopist (Olivier Rouquette). All procedures were performed under general anesthesia, with orotracheal intubation, in supine position. All patients were administered amoxicillin-clavulanic acid prophylaxis beforehand. Anticoagulant therapy was discontinued 5 d before procedure and bridged with low molecular-weight heparin. Low-dose aspirin was continued. Other antiplatelet agents were

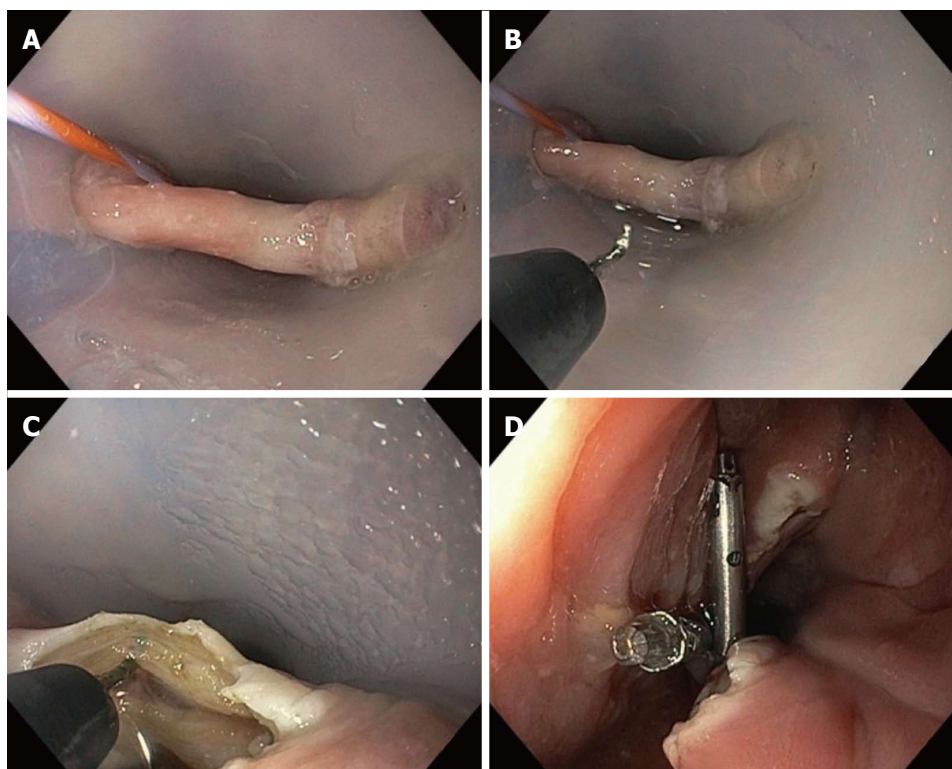


Figure 1 Endoscopic procedure. A: Soft diverticuloscope in place, affording optimal exposure. Esophageal lumen is identified by the guidewire; B: The Hook knife is locked in 12 o'clock position; C: After initial incision, myotomy is performed, pulling the muscle fibers up before cutting; D: End of procedure, with 2 endoclips in place.

discontinued 5 d before procedure and replaced with low-dose aspirin. Anticoagulant and antiplatelet therapies were resumed on the day after the procedure.

Figure 1 describes the endoscopic procedure. First, a complete upper endoscopy, using a standard gastroscope (GIF H180, GIF H190; Olympus, Tokyo, Japan), is performed to rule out any other esophageal or gastric disorder that could explain dysphagia. A 0.035-inch guidewire is advanced in the gastric lumen and left in place for later identification of the esophageal lumen. Then, the soft diverticuloscope (ZDO-22-30, Cook Endoscopy, Winston-Salem, NC) is fitted over the gastroscope and advanced gently, after lubrication, as far as the black mark is located roughly near the incisor line. The endoscope is then slowly withdrawn to allow visualization of the diverticulum and adjust diverticuloscope position across the septum, which is then seen as a bridge, and optimal exposure of the operative site. Once septum exposure is good, myotomy of the cricopharyngeal muscle is performed with the Hook knife (Endocut Q mode, effect 3, 120 W cutting, 40 W soft coagulation; VIO 300; ERBE, Tübingen, Germany). The hook is locked in 12 o'clock position. The initial incision is performed at the top of the bridge. Then, the cricopharyngeal myotomy is continued progressively downward, using the hook to gently pull the muscle fibers before cutting, allowing precise dissection. Myotomy is stopped when the muscle fibers are completely cut. Finally, anterior ZD and posterior esophageal walls are cut up to 5 mm above the bottom of the diverticulum, and one or more

endoclips are placed to prevent delayed perforation or bleeding. If no complication is suspected, oral semi-liquid diet is resumed and patients are discharged from hospital on day one post-surgery.

Primary endpoint was clinical success. Recurrence and adverse event rates were also investigated. Clinical success was defined as at least a 1-point improvement in dysphagia score and a residual dysphagia score ≤ 1 , with no need for reintervention. Recurrence was defined as dysphagia score > 1 after initial clinical success. Any event resulting in readmission or unexpected length of hospital stay post-surgery (> 1 d) was regarded as an adverse event. Bleeding was considered an adverse event if any medical or endoscopic reintervention was needed. Perforation was defined as presence of cervical subcutaneous crepitus, cervical abscess, or free air on computed tomography.

Statistical analysis

The statistical review of the study was performed by a biomedical statistician. Characteristics of the study population are expressed as proportion and means \pm SD. The Wilcoxon matched-pairs signed-rank test was used to compare pre- vs post-treatment dysphagia scores comparison. Statistical significance was set at $P < 0.05$ (two-sided). Statistics were computed using Stata12 (Stata Corp, College Station, TX).

RESULTS

The study included 24 consecutive patients [18 men

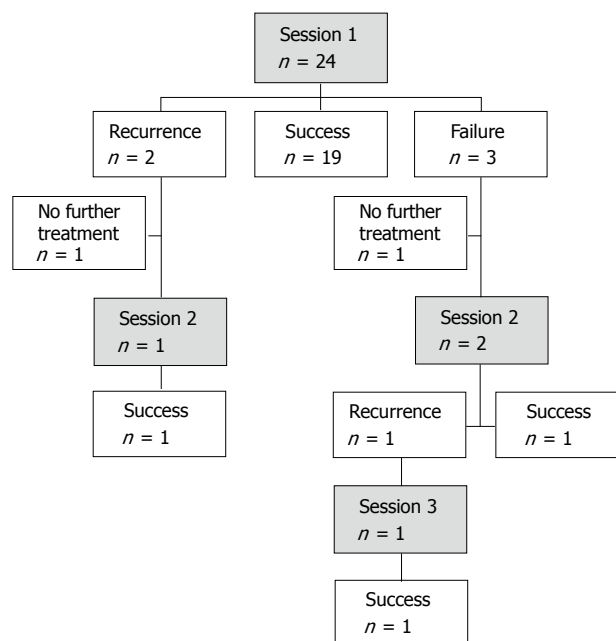
Table 2 Patient characteristics *n* (%)

Characteristics	
Variable	<i>n</i> = 24
Male	18 (75)
Median age (yr)	77
Mean time from onset of symptoms (mo)	18.5
Dysphagia score before treatment	
Grade 1	6 (25)
Grade 2	7 (29)
Grade 3	10 (42)
Grade 4	1 (4)
Weight loss	11 (46)
Mean size of diverticula (cm \pm SD)	3.0 \pm 1.63

(75%), median age 77 years (range 44-90 years)]. Before procedure, seven patients were treated with anticoagulant therapy and 6 with antiplatelet agents. ZD diagnosis was based on esophagogastrosocopy in 12 (50%) patients, and/or barium swallow in 18 (75%) patients or computed tomography in 3 patients. Mean size of ZD was 3.0 cm (2-8 cm). Mean time from onset of symptoms was 18.5 mo. Four patients had a previous rigid endoscopic treatment (CO₂ laser). All patients presented with dysphagia. Other symptoms included regurgitation (*n* = 22, 91.7%), chronic cough (*n* = 12, 50%) and aspiration pneumonia (*n* = 2, 8.3%). Patient characteristics are reported in Table 2.

A total of 28 endoscopic procedures were performed in our 24 patients (mean 1.17 procedures per patient): One procedure in 21 patients, two procedures in two patients and three procedures in one patient. Diverticuloscope insertion and good septum exposition were achieved in all patients. One or two endoclips were placed in all patients. Median follow-up was 19.5 mo (6-53).

Clinical success was obtained in 21 (87.5%) patients after the first procedure. Two patients developed recurrence, at 4 and 8 mo post-procedure, respectively: One was successfully treated with a second session, the other declined any reintervention. Initial failure was observed in 3 (12.5%) patients: One patient with an 8-cm ZD was contraindicated for general anesthesia for a second session, and two patients with ≤ 3 cm ZD underwent a second procedure. Symptoms resolved in both patients, but one experienced recurrence 6 mo later, which was successfully treated by a third session. Overall clinical success was obtained in 22/24 patients (91.7%). Overall recurrence rate was 13% (3/23). Mean \pm SD dysphagia score was 2.25 \pm 0.89 before treatment and decreased to 0.25 \pm 0.74 at end-of-follow-up (*P* < 0.001). At end-of-follow-up, 19/22 (86.4%) and 12/12 patients were free from regurgitation and cough, respectively. Among 11 patients with preoperative weight loss, 10 (90.9%) regained weight (mean +4.2 kg) at two months post-treatment. Median time to recurrence was 6 mo. Figure 2 and Table 3 summarize treatment outcome. Overall adverse effect rate was 8.3%: Two patients developed

**Figure 2 Clinical outcome of endoscopic myotomy.**

fever with elevated CRP, without evidence of perforation on CT scan with contrast agent ingestion. Conservative management with antibiotics was successful in both patients, who were discharged from hospital on day 4 and day 6 post-procedure, respectively. No perforation or post-procedural bleeding was recorded. Nine patients (37.5%) reported mild pain, lasting a median 3 d. All of them were treated with acetaminophen as outpatients. Mild bleeding during myotomy occurred in two (8.3%) patients and was treated by soft coagulation applied with a Coagrasper (Olympus endotherapy, Tokyo, Japan). These two patients were not treated with anticoagulant or antiplatelet agents, and both were discharged from hospital on day 1 post-procedure. One asymptomatic patient died of unrelated cause during follow-up, at 29 mo after myotomy. Median hospital stay was 1 d (1-6).

DISCUSSION

Open surgery is mainly considered after endotherapy failure or for large diverticula^[2,8]. Along with endoscopic stapling, flexible endoscopic myotomy is a first-line treatment option for symptomatic ZD. The use of a soft diverticuloscope stabilizes the endoscope and provides better exposure of the septum, resulting in a lower adverse events rate^[9]. We perform diverticulotomy in supine position in order to increase the stability of the gastroscope, which may slip out of the diverticuloscope if the patient is lying in left lateral position. Most authors agree with placing endoclips at the end of the procedure to prevent delayed complications^[4]. Nevertheless, various tools are used to perform the myotomy: Argon plasma coagulation has been practically abandoned as it needs multiple procedures and carries a high complication rate^[10], whereas favorable outcome is

Table 3 Dysphagia score before treatment and at end-of-follow-up

Before treatment	End of the follow-up period			
	0	1	2	3
1	n = 6	n = 0	n = 0	n = 0
2	n = 7	n = 0	n = 0	n = 0
3	n = 7	n = 1	n = 1	n = 1
4	n = 1	n = 0	n = 0	n = 0
Total	21	1	1	1

reported with the use of needle-knife^[11], submucosal dissection knives^[5], a Zimmon needle (Cook endoscopy, Winston-Salem, NC)^[4], or endoscopic scissors^[12,13]. The SB-knife® (Sumimoto Bakelite Ltd, Tokyo, Japan), an endoscopic scissor, seems to be safe, fast and effective^[13]. Myotomy with the SB-knife consists in cutting the full thickness of the septum without individualization of muscle fibers, anterior and posterior walls of the diverticulum. It remains unclear where dissection should be stopped in this setting. The most reliable device for diverticulotomy has yet to be determined^[14]. A major concern is perforation risk if dissection extends too deeply. The Hook knife provides advantages for this purpose, as its design allows pulling the muscle fibers upward before cutting. Extensive myotomy can be achieved with complete visual control, and the risk of coagulation-induced injury risk may be reduced by pulling tissues upward instead of pushing downward with most other tools. Unlike previous series on submucosal dissection knives^[5], we believe that these devices-but not the Hook knife-do not confer an optimal visualization, especially in the final steps of the myotomy, before cutting the posterior ZD and anterior esophageal walls, whereas pulling with the hook is helpful to assess the nature and amount of tissue before cutting.

Our 91.7% overall clinical success rate is in line with previous papers. A 95% overall success rate was reported in a series of 46 patients treated with the Hook knife^[15]. However, in this series, initial clinical success was 100%, but recurrence rate was high at 30%, leading to frequent retreatment (mean 1.39 sessions/patient). This might be explained by the interruption of the myotomy 5 to 10 mm above the bottom of the diverticulum, regardless of complete cut of muscle fibers and diverticulum size. Indeed, post-treatment size ≥ 10 mm is suspected to be a risk factor for recurrence at 48 mo^[8]. Moreover, diverticula were larger (median size 42 mm) than in our series. Although diverticulum size was not significantly associated with recurrence rate, pre-treatment size ≥ 50 mm may be an independent factor for clinical failure at 6 mo^[8], and this could also explain such a high recurrence rate. Lower (from 50%) or higher (to 100%) success rates have been reported before^[8,16,17]. With the Zimmon needle, overall success, recurrence and complication rates were respectively 84%, 23.1% and 2.2%^[4]. With a needle knife, overall

success rates ranged from 69%^[8] to 84%^[17] at 6 mo, recurrence rates from 15%^[8] to 30%^[17], and adverse event rates from 3%^[8] to 23%^[17]. Laquière *et al.*^[5] described the use of the Dual-knife® (Olympus endotherapy, Tokyo, Japan) and the HybridKnife® (Erbe elektromedizin GmbH, Tuebingen, Germany), with an overall success rate, recurrence rate and complication rate of respectively 91.7%, 14% and 7.1%. Endoscopic myotomy with the SB-knife® resulted in a 87.1% overall success rate, a 6.5% recurrence rate, and a 3.2% complication rate, with a limited median follow-up of 7 mo^[13]. These variations might be related to how tightly clinical success was defined: Dysphagia score ≤ 1 ^[4], or < 1 ^[8] have been proposed. Moreover, composite scores investigating respiratory symptoms or hoarseness and their weekly frequency have been included in clinical success definition by some authors^[9], resulting in lower success rates. Here however, in our definition of clinical success, no further intervention was needed, which means patients were satisfied with the functional result on the ZD-related symptoms. The initial failure rate of 12.5% and the recurrence rate of 13% are consistent with previous studies given the small mean size of ZD in our series; septotomy length ≤ 25 mm is suspected to be an independent prognostic factor for clinical failure and recurrence (HR = 6.34 at 6 mo and 2.20 at 48 mo)^[8].

Only two patients experienced mild adverse events. No bleeding was reported, when anticoagulant or antiplatelet therapy was resumed the day post-procedure in more than half of patients. No perforation occurred. Moreover, after all but two procedures, patients were discharged from hospital on day 1, demonstrating the safety of this technique.

Retrospective analysis, single-center design, and lack of comparison with other devices are limitations to this study. Even with a minimal follow-up of 6 mo, our median follow-up of 19.5 mo might still be too short to investigate long-term recurrences: Even though another study reported a mean time to recurrence after diverticulotomy with the Hook knife of 4.4 mo^[15], recurrence rate may be underestimated, as success rate for dysphagia decreased between 6 and 48 mo in a large study including 89 patients with a 24-mo minimum follow-up^[8].

Conclusion

The Hook knife is a reliable tool for flexible endoscopic soft diverticuloscope-assisted myotomy in patients with symptomatic Zenker's diverticula. It is safe and efficient and could therefore be considered a device of choice in this indication. Larger comparative studies, with extended follow-up, are needed to determine which tool is the best.

COMMENTS

Background

Zenker's diverticulum can cause dysphagia, regurgitations, and sometimes life-

threatening complications. Endoscopic treatment is a first line option.

Research frontier

Flexible endoscopic myotomy can be performed with various tools. Safety (perforation risk) and efficacy are major concerns. The ideal tool has yet to be determined.

Innovations and breakthroughs

The Hook knife allows precise dissection of muscle fibers and complete myotomy in a safe way, by pulling up tissues before cutting. It results in high clinical success rate and low complication and recurrence rates.

Applications

The Hook knife may be a device of choice for flexible endoscopic diverticulotomy.

Peer-review

The manuscript was well written and helpful.

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Russell body gastritis with Dutcher bodies evaluated using magnification endoscopy

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Author contributions: Yorita K performed pathological diagnosis, collected and analyzed the data, and wrote the paper; Iwasaki T, Uchita K, Kojima K and Iwamura S performed the clinical diagnosis, endoscopic submucosal resection of the lesion, and clinical follow-up; Kuroda N, Tsutsumi Y, Ohno A and Kataoka H performed the pathological diagnosis.

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Abstract

Russell body gastritis (RBG) is an unusual type of chronic gastritis characterized by marked infiltration of Mott cells, which are plasma cells filled with spherical eosinophilic bodies referred to as Russell bodies. It was initially thought that *Helicobacter pylori* (*H. pylori*) infection was a major cause of RBG and that the infiltrating Mott cells were polyphenotypic; however, a number of cases of RBG without *H. pylori* infection or with monoclonal Mott cells have been reported. Thus, diagnostic difficulty exists in distinguishing RBG with monoclonal Mott cells from malignant lymphoma. Here, we report an unusual case of an 86-year-old-Japanese man with *H. pylori*-positive RBG. During the examination of melena, endoscopic evaluation confirmed a 13-mm whitish, flat lesion in the gastric antrum. Magnification endoscopy with narrow-band imaging suggested that the lesion was most likely a poorly differentiated adenocarcinoma. Biopsy findings were consistent with chronic gastritis with many Mott cells with intranuclear inclusions referred to as Dutcher bodies. Endoscopic submucosal dissection confirmed the diagnosis of RBG with kappa-restricted monoclonal

Mott cells. Malignant lymphoma was unlikely given the paucity of cytological atypia and Ki-67 immunoreactivity of monoclonal Mott cells. This is the first reported case of RBG with endoscopic diagnosis of malignant tumor and the presence of Dutcher bodies.

Key words: Russell body gastritis; Mott cell; Dutcher body; Mucosa-associated lymphoid tissue lymphoma; Plasmacytoma; Magnification endoscopy with narrow-band imaging

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Core tip: We report Russell body gastritis (RBG) evaluated by magnification endoscopy with narrow band imaging and pathological evaluation by endoscopic submucosal dissection. The endoscopic features of RBG are exclusively inflammatory; however, our detailed endoscopic evaluation led to misdiagnosis of the lesion as poorly differentiated adenocarcinoma. The histological features of RBG were also unique because the presence of Mott cells with light chain restriction and Dutcher bodies suggested malignant lymphoma. Pathologists should be aware of the existence of this pathological entity, and clinicians should consider RBG as a differential diagnosis in cases where detailed endoscopic examination reveals poorly differentiated early gastric cancer.

Yorita K, Iwasaki T, Uchita K, Kuroda N, Kojima K, Iwamura S, Tsutsumi Y, Ohno A, Kataoka H. Russell body gastritis with Dutcher bodies evaluated using magnification endoscopy. *World J Gastrointest Endosc* 2017; 9(8): 417-424 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v9/i8/417.htm> DOI: <http://dx.doi.org/10.4253/wjge.v9.i8.417>

INTRODUCTION

Russell body gastritis (RBG) was first described by Tazawa *et al.*^[1] in 1998 and is considered as a unique form of chronic gastritis characterized by infiltration of plasma cells filled with spherical eosinophilic cytoplasmic globules, referred to as Russell bodies. The endoscopic features of RBG are most in keeping with an inflammatory condition, and biopsy is required to confirm the pathological diagnosis. RBG is considered a reactive condition; however, monoclonal Mott cells have been shown in a number of cases of RBG, and therefore whether or not RBG with monoclonal Mott cells is benign remains debatable. This uncertainty is due to the fact that monoclonal Mott cells can show regional lymph node metastasis^[2] and have been identified in mucosa-associated lymphoid tissue (MALT) lymphoma with extreme plasmacytoid differentiation^[3]. Here, we report a unique case of RBG with endoscopic features of a malignant tumor, which consisted of monoclonal Mott cells with Dutcher bodies identified histologically following endoscopic submucosal resection.

CASE REPORT

An 86-year-old Japanese man with a history of rheumatoid arthritis, type 2 diabetes mellitus, and hypertension was referred to our medical center with melena. He took non-steroidal anti-inflammatory drugs for arthralgia but did not take immunosuppressive drugs. Physiological examination was unremarkable. Laboratory findings revealed anemia (Hb 6.5 g/dL) and no other abnormal results. Endoscopic evaluation of the upper and lower digestive tracts did not reveal any active bleeding. *Helicobacter pylori* (*H. pylori*) infection was confirmed on a positive serum anti-*H. pylori* antibody test. The patient was initially diagnosed with atrophic and erosive gastritis secondary to *H. pylori* infection, and eradication therapy was initiated. The first esophagogastroduodenoscopy revealed a 13-mm flat lesion (Figure 1A and B) of white and slightly brown discoloration in the lesser curvature of the antrum. A magnification endoscope (Gastrointestinal fiber-H260Z, Olympus, Tokyo, Japan) with a narrow-band imaging (NBI) system (EVIS LUCERA SPECTRUM ELITE system, Olympus) was used, and magnification endoscopy with NBI (M-NBI) of the lesion showed loss or irregularity of microsurface pattern, irregular microvascular proliferation, and a demarcation line (Figure 1C and D). Poorly differentiated adenocarcinoma was suspected, and a biopsy was performed. The duodenum appeared to be intact. The biopsy specimen (Figure 2A-D) showed chronic gastritis with infiltration of lymphocytes, plasma cells, eosinophils, and small-to large-sized granulated cells (Figure 2B-D). Spiral-shaped bacilli were focally located in the mucin on the foveolar epithelium, confirming the diagnosis of *H. pylori*. Substantial amounts of granulated cells with eosinophilic cytoplasmic granules and eccentric nuclei were seen (Figure 2B), which were of a similar size to the eosinophilic granules (Figure 2C). The small-sized granulated cells showed plasmacytoid morphology with eccentric and cartwheel-like nuclei, while ballooning large granulated cells showed histiocytoid morphology (Figure 2C). Intranuclear eosinophilic granules were also observed in some granulated cells (Figure 2D) but were not apparent in infiltrating plasma cells without cytoplasmic granules. Lymphoid follicles were not observed. Neither lymphoepithelial lesions nor monotonous proliferation of centrocyte-like cells or monocytoid-B cells were observed. The cytoplasmic granules were stained by phosphotungstic acid-hematoxylin (PTAH) and periodic acid Schiff with or without diastase treatment. Immunohistochemically, the granulated cells including histiocytoid cells were positive for CD79a (Clone HM57, DAKO, Glostrup, Denmark) and multiple myeloma oncogene 1 (Clone MUM1p, DAKO, Glostrup, Denmark) and negative for pancytokeratin (Clone CAM5.2, Becton Dickinson, CA), CD20 (Clone L26, DAKO, Glostrup, Denmark), CD138 (Clone MI15, DAKO, Glostrup, Denmark), CD68 (Clone KP-1, DAKO, Glostrup, Denmark), CD163

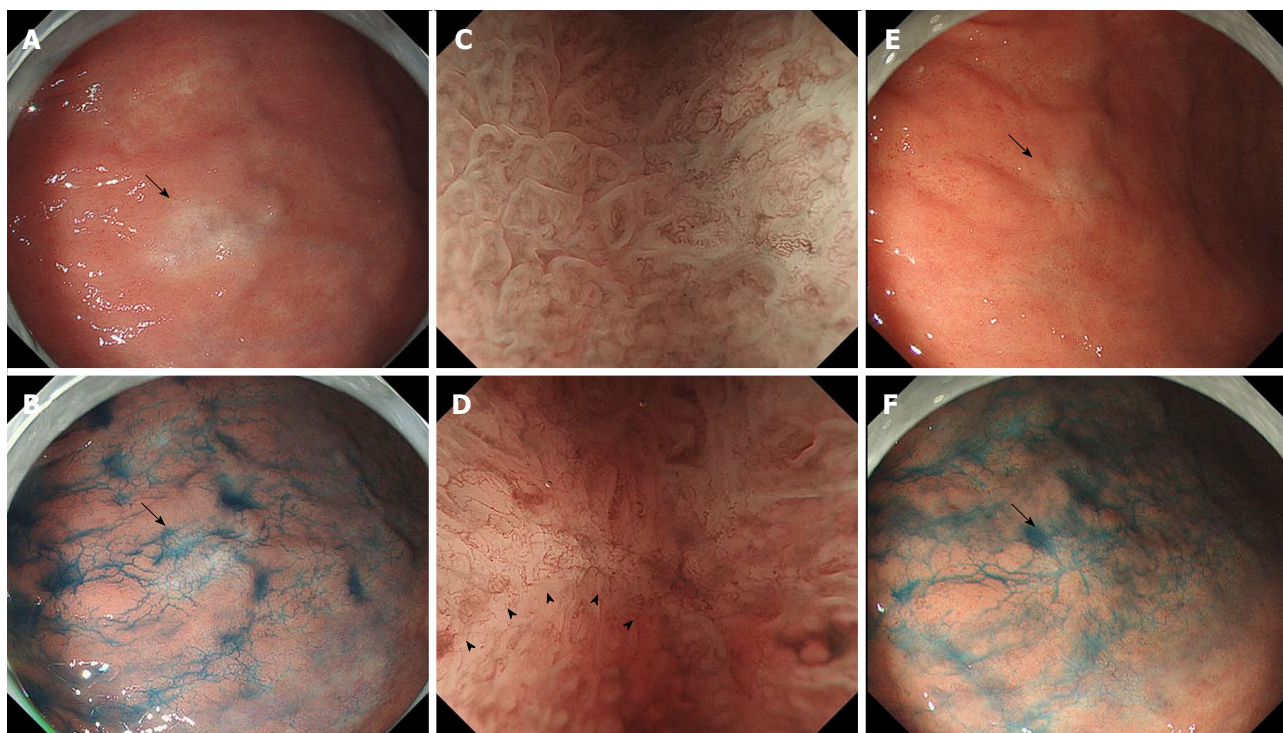


Figure 1 Endoscopic imaging of the antral lesion before and after the eradication. A: An endoscopic image before the eradication shows a 13-mm whitish/slightly brownish lesion (arrow) on the lesser curvature of the antrum; B: Indigo carmine dye spray reveals that the antral lesion (arrow) is almost flat; C: Magnification endoscopy with narrow-band imaging shows the lesion (C, right side) exhibits loss or irregularity of the microsurface pattern and irregular microvascular proliferation compared to the background mucosa (C, left side). A demarcation line (D, arrowheads) is seen at the periphery of the lesion. E-F: Endoscopic images after the eradication therapy exhibit that the mucosal lesion (arrow) decreases in size to 7 mm in diameter (E) and preserves the gross appearance with indigo carmine dye spray (F).

(10D6, Thermo scientific), CD1a (Clone 10, DAKO, CA), S100 (polyclonal, DAKO, Glostrup, Denmark), c-KIT (polyclonal, DAKO, Glostrup, Denmark), mast cell tryptase (Clone AA1, DAKO, Glostrup, Denmark), and Ki-67 (Clone MIB-1, DAKO, Glostrup, Denmark). Thus, the granulated cells were considered to be plasma cells and identified as Mott cells with cytoplasmic eosinophilic globules (Russell bodies). Intranuclear eosinophilic granules in some Mott cells were considered to be Dutcher bodies. Immunohistochemically, the Mott cells appeared to be negative for light chains and immunoglobulin G (IgG, polyclonal, Novocastra Laboratories Ltd., Newcastle, United Kingdom), IgA (polyclonal, Novocastra Laboratories Ltd., Newcastle, United Kingdom), and IgM (polyclonal, Novocastra Laboratories Ltd., Newcastle, United Kingdom), while plasma cells without Russell bodies showed polytypic light chain staining pattern and were reactive for IgG, IgA, or IgM in varying proportions. Taken together, these findings were most in keeping with a diagnosis of RBG, but malignant lymphoma, particularly MALT lymphoma, was a differential diagnosis. However, chest-abdomen-pelvis computed tomography showed no abnormal mass, no swollen lymph nodes, and no lytic bone lesion. Two months after completion of eradication therapy, the patient consented to undergo endoscopic submucosal dissection (ESD), which was performed with the aim of histologically evaluating the entire lesion.

After eradication therapy, the mucosal lesion decreased in size to 7 mm in diameter (Figure 1E-F) and loss or irregularity of the microsurface pattern, irregular microvascular proliferation, and a demarcation line with M-NBI were seen. ESD was successfully performed. The patient was discharged without any complications and there was no endoscopic evidence of recurrence 14 mo after the ESD treatment.

Pathological diagnosis on ESD specimens

The endoscopically resected tissue was extended on a board with pins, fixed in 10% formalin for 24 h, cut into 2- to 3-mm thick sections, and embedded in paraffin. Four μ m-thick sections were obtained from the paraffin blocks and stained with hematoxylin and eosin. Pathology showed that the mucosal lesion had regional accumulation of substantial amounts of granulated cells associated with mild lymphocytic and plasma cell infiltration (Figure 2E and F). The immunohistochemical results of ESD were similar to those of the biopsy specimens (Figure 2G and H). In situ hybridization revealed that the Mott cells showed kappa light chain restriction (Figure 2I and J), whereas the plasma cells without Russell bodies were polyphenotypic. Cellular atypia and mitosis were not seen in the plasma cells or Mott cells, and less than 1% of the infiltrating cells were Ki67-positive, whereas no Mott cells were Ki67-positive. At the periphery of the lesion and in the background

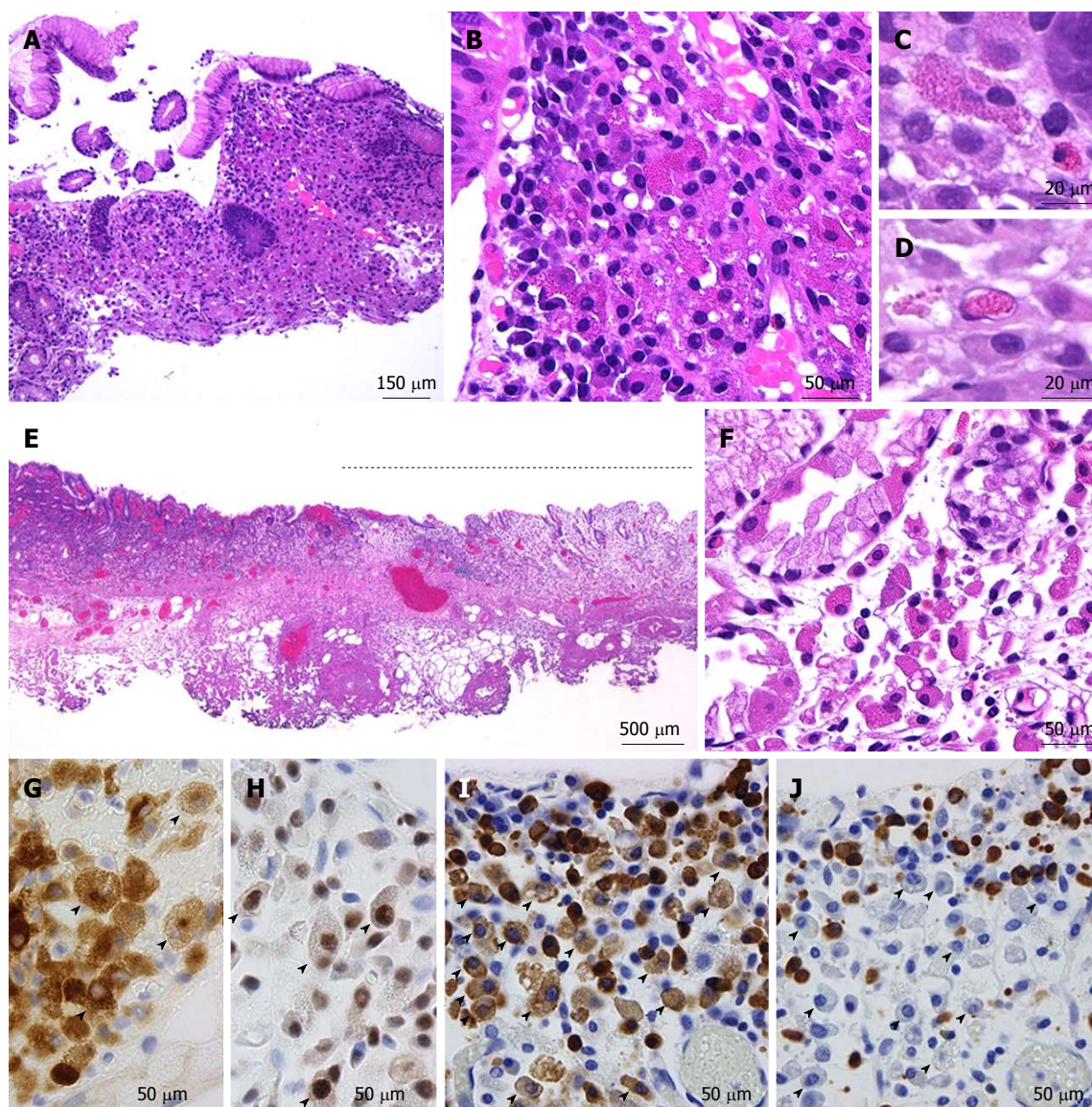


Figure 2 Pathological features of the antral lesion. The biopsy specimen stained by hematoxylin and eosin shows chronic gastritis with crowded granulated cells (A, B). The histiocytoid cells have fine eosinophilic granules similar to those of eosinophils (C). Intranuclear cytoplasmic granules suggesting Dutcher bodies are observed (D). E-F: The ESD specimen stained by hematoxylin and eosin shows that the lesion (E, indicated by a dotted line) is edematous and demarcated and includes many granulated cells (F). G-J: Immunohistochemical (G-H) and in situ hybridization (I-J) findings with ESD specimens show that the granulated cells (arrowheads) are positive for CD79a (G), multiple myeloma oncogene 1 (H), and kappa (I) and negative for lambda (J), while plasma cells without cytoplasmic granules are polyphenotypic.

mucosa and submucosa, Mott cells and Dutcher bodies were absent. Lymphoid follicles were observed in the periphery of the lesion and the background mucosa, but not within the collection of Mott cells. There were no pathological features suggestive of carcinoma or MALT lymphoma. Amyloid deposition was unlikely because no amorphous materials were identified, and there was no characteristic apple green birefringence noted when the Congo Red stained section was viewed under polarized light. Thus, our final diagnosis was Russell body gastritis. However, the diagnostic assessment utilized had several limitations, as we did not assess for the presence of M protein in the serum, Bence-Jones protein in the urine, or genetic alterations in the immunoglobulin locus, and we did not perform

cytopathological examination of the bone marrow.

DISCUSSION

We presented a unique case of RBG with *H. pylori* infection. Russell body gastritis is characterized by a dense accumulation of plasma cells with Russell bodies, referred to as Mott cells^[1]. Russell bodies are eosinophilic spherical or globular cytoplasmic inclusions in plasma cells that were first described by Russell *et al*^[4] in 1890. The globules differ from normal secretory granules in that they are larger and much more electron dense, and they lie in the distended cisternae of the rough endoplasmic reticulum^[5]. These globules mainly consist of condensed immunoglobulin^[6] and are

related to abnormalities in the synthesis, trafficking, or excretion of immunoglobulin^[7]. The Russell bodies seen in the present case were much smaller compared to those in previous reports; however, the granules were stained positive by periodic acid Schiff and PTAH, as described in previous case reports of RBG^[8,9].

Table 1 summarizes the results of 31 previously published cases of RBG, including our own^[1,8-25]. We excluded two cases reported as RBG^[26] and Russell body carditis^[27] because in these cases the inflammation site was at the esophagogastric junction. One case of RBG associated with advanced signet ring cell cancer^[28] was also excluded because the authors did not describe whether or not RBG was present in the background gastric mucosa. The mean age of the patients described in previous case reports of RBG was 60 (range 24 to 86) years old, and our patient was the oldest. The male ($n = 19$) to female ($n = 12$) ratio was approximately 2:1. Twenty-one cases (68%) of RBG accompanied *H. pylori* infection, and the majority of patients in all cases presented with non-specific symptoms. The gastric antrum appears to be the predominant location for RBG, although there is one reported case of an immunocompromised patient with RBG associated with Russell body enterocolitis^[25].

The endoscopic features of RBG are non-specific, and in most cases, the inflammatory phenotype of the condition has been attributed largely to the presence of swollen, erythematous mucosa. The pathological features of RBG can mimic those of gastric xanthoma^[19]. To the best of our knowledge, this is the first case of RBG with a clinical diagnosis highly suggestive of a malignant tumor. In the present case, M-NBI confirmed a flat mucosal lesion in the antrum with a demarcated line, loss of microsurface pattern, and irregular microvascular proliferation. Nishimura *et al.*^[29] also reported that partial loss of microsurface structure and abnormal microvessels were observed in a case of RBG with M-NBI, but the demarcation line of RBG was not reported. Magnification endoscopy permits visualization of mucosal details that cannot be seen with standard endoscopy, and NBI is a novel endoscopic approach to visualize the microvasculature on the tissue surface. M-NBI has been proven to be highly sensitive, specific, and accurate at detecting early gastric neoplasms. Pathological evaluation revealed that the lesion was characterized by regional and intramucosal accumulation of Mott cells. The proliferation of Mott cells might induce expansion of the lamina propria, decrease the density of gastric glands and pits, and influence the microvasculature of the lesion. At present, RBG is considered a rare entity, but its incidence may increase in the future secondary to the increased use of M-NBI. It may be better that clinicians raise RBG as a differential diagnosis of poorly differentiated early gastric cancer upon examination by M-NBI.

Of pathological interest, Mott cells were monoclonal and had Dutcher bodies, which caused difficulty in making a histological diagnosis. Only two cases^[8,12]

of RBG and Dutcher bodies have been described in the literature to date, and both failed to identify a Dutcher body in the lesion. Considering the presence of monoclonal Mott cells and Dutcher bodies, the differential diagnoses that we considered were plasma cell neoplasm, MALT lymphoma, and lymphoplasmacytic lymphoma. In the present case, MALT lymphoma could not be diagnosed on account of the lack of histological features suggestive of MALT lymphoma, such as a lymphoepithelial lesion and proliferation of monocytoid B-cells or centrocyte-like cells. Moreover, Mott cells showed neither cellular atypia nor mitotic activity. Plasma cell neoplasm was excluded due to hypoproteinemia, lack of osteolysis in computed tomography images, and lack of nuclear atypia or mitotic activity of monoclonal Mott cells, although paraproteinemia was not evaluated *via* serum protein electrophoresis. Lymphoplasmacytic lymphoma was ruled out because of an absence of splenomegaly and lymphadenopathy. Monoclonal gammopathy of undetermined significance^[13], which can be associated with *H. pylori*-positive RBG, could not be evaluated in this case.

The pathogenesis of RBG remains unknown. Tazawa *et al.*^[1] firstly postulated that RBG might be induced by *H. pylori* infection, and this is in keeping with previously published literature, in which two thirds of RBG cases were *H. pylori*-positive (Table 1). A recent study^[30] showed that *H. pylori* with vacA m1 genotype produces more prominent Russell bodies in the antrum but not in the body. Indeed, the literature review revealed that the incidence of antral RBG was higher in *H. pylori*-positive cases (70%) than in *H. pylori*-negative cases (40%). On the other hand, our case showed endoscopic regression of the lesion from 13 mm to 7 mm at 2 mo after eradication of *H. pylori*, and similar findings were observed in previous studies^[16,18,19,21]. These observations suggest that the successful eradication of *H. pylori* may eliminate the proliferative stimulation of Mott cells. However, case reports of RBG without *H. pylori* infection have also been described, although those cases were complicated by HIV infection^[11], post-transplant status^[25], or monoclonal gammopathy of uncertain significance^[13]. Therefore, it is likely that *H. pylori*-unrelated pathogenesis of RBG is present, and an immunocompromised status may be partly related to the occurrence of RBG. In our case, the patient was elderly and had a history of rheumatoid arthritis; therefore, it is possible that the occurrence of RBG in this patient may have been due, in part, to his immunocompromised status.

RBG is considered to be a benign condition, and clinical follow-up data of 19 cases of RBG to date has failed to reveal any malignant change (Table 1). Among the 19 cases described in the literature, ten cases received *H. pylori* eradication therapy after diagnosis of RBG, and most of these showed endoscopic or histological resolution at three months, whether or not monoclonal Mott cells were present. Thus, follow-

Table 1 Literature review of clinicopathological findings of Russell body gastritis

Ref.	Age/sex	Endoscopic finding or diagnosis (size)	Site of mott cells	HP	Mott cells	ET and follow-up
Tazawa <i>et al</i> ^[1] (1998)	53/M	Multiple ulcer scars with redness and swelling	Antrum	Yes	Poly	Follow-up biopsy after ET showed no RBG Follow-up period was not available
Erbersdobler <i>et al</i> ^[8] (2004)	80/F	Circumscribed irregular swelling (30 mm)	Fundus	No	Poly	NA
Ensari <i>et al</i> ^[10] (2005)	70/M	Pangastritis/flattened, edematous gastric folds	Body and antrum	Yes	Poly	ET was performed, but patient refused to be re-examined endoscopically
Drut <i>et al</i> ^[11] (2006)	34/M	A raised, swollen area (20 mm)	Body	No	Poly	NA
Paik <i>et al</i> ^[12] (2006)	47/F	Focal erythematous swelling	Antrum	Yes	Poly	ET was performed. Follow-up data: NA
	53/F	A geographical yellowish raised lesion (25 mm)	Body	Yes	Poly	ET was performed Follow-up data: NA
Wolkersdorfer <i>et al</i> ^[13] (2006)	54/M	Mild erythema and small erosions with slight edema	Antrum	Yes	Mono (λ chain)	One year after ET, the lesion had not resolved macroscopically, but biopsy found resolution of Mott cells
Pizzolitto <i>et al</i> ^[14] (2007)	60/F	Minute-raised granular areas	Antrum	Yes	Poly	ET was performed, and clinical follow-up was uneventful
Licci <i>et al</i> ^[15] (2008)	59/M	Mild hyperemia	Antrum	Yes	Poly	Mott cells were absent in biopsy specimen taken 3 mo after ET
Tabata <i>et al</i> ^[16] (2010)	72/M	Multiple ulcers	Body and antrum	Yes	Mono (κ chain, IgG)	Mott cells were absent in biopsy specimen taken 3 mo after ET
Habib <i>et al</i> ^[17] (2010)	75/M	Nodular chronic active gastritis	Antrum	No	Poly	NA
Miura <i>et al</i> ^[18] (2012)	63/F	Low elevated lesions in the antrum	Antrum	Yes	Mono (λ chain)	Mott cells were absent in biopsy specimen taken 4 mo after ET
Yoon <i>et al</i> ^[19] (2012)	57/M	A slightly raised whitish lesion with a mild central depression (20 mm)	Body	Yes	Poly	The lesions were cleared 3 mo after ET. A follow-up biopsy was not performed
	43/M	A whitish oval shaped flat lesion with a slight central depression (20 mm)	Antrum	Yes	Poly	The lesions were cleared 2 mo after ET. A follow-up biopsy was not performed
Choi <i>et al</i> ^[20] (2012)	55/M	A mucosal elevation with a central depression (10 mm)	Antrum	Yes	Mono (λ chain)	NA
Karabagli <i>et al</i> ^[21] (2012)	60/M	Erythema (body) and ulcer (incisura angularis)	Body and antrum	Yes	Poly	Three months and 6 mo after ET, Mott cells were decreased and absent in biopsy specimens, respectively
Coyne <i>et al</i> ^[22] (2012)	49/M	Severe, raised, erosive gastritis	NA (Biopsy site; NA)	No	Mono (κ chain, IgM)	NA
Araki <i>et al</i> ^[9] (2013)	74/F	Open ulcer	Gastric angle	Yes	Mono (κ chain, IgM)	NA
Zhang <i>et al</i> ^[23] (2014)	78/F	Uneven mucosa	Body, incisura angularis, antrum	No	Mono (κ chain)	Clinical follow-up evaluations were uneventful
	77/F	Uneven mucosa	Incisura angularis	Yes	Mono (κ chain)	
	77/F	punctiform erosion	Body	Yes	Mono (κ chain)	
	56/M	Raised erosions	Antrum	Yes	Mono (κ chain)	
	76/M	Erythema	Body	Yes	Mono (κ chain)	
	50/M	Flat and raised erosions	Antrum	Yes	Mono (κ chain)	
	28/M	Erythema	Antrum	No	Mono (κ chain)	
	24/F	Erythema	Antrum	No	Mono (κ chain)	
	66/M	Ulcer, stage A2	Incisura angularis	No	NA	
Klair <i>et al</i> ^[24] (2014)	76/F	Cobblestoned, whitish, raised, and irregular mucosa	Fundus	No	Poly	NA
Muthukumarana <i>et al</i> ^[25] (2015)	44/M	Diffuse mild erythematous gastric mucosa	Stomach, duodenum, terminal ileum, colon	No	Poly	NA
Nishimura <i>et al</i> ^[29] (2016)	64/F	A white, granular lesion (2 cm)	Body	Yes	Poly	The lesion had grown larger 15 mo after the diagnosis, and the lesion had disappeared 15 mo after eradication
Present case	86/M	A demarcated whitish flat lesion (13 mm)	Antrum	Yes	Mono (κ chain)	Two months after ET, the lesion decreased in size. There was no evidence of recurrence 14 mo after ESD

HP: *Helicobacter pylori*; ET: Eradication therapy; Poly: Polyclonal; Mono: Monoclonal; RBG: Russell body gastritis; NA: Not available; Ig: Immunoglobulin.

up might be a better approach for the present case. However, whether or not RBG with monoclonal Mott cells is a reactive or neoplastic phenomenon remains debatable. To date, a total of 15 cases (50%, 15/30) of RBG with monoclonal Mott cells, including our case, have been described, and all of these RBG cases had uneventful clinical follow-up. Brink *et al.*^[31] reported a case with a rectal tubulovillous adenoma accompanied by a proliferation of monoclonal Mott cells and concluded that the phenomenon indicated an inflammatory response. As Araki *et al.*^[9] discussed, monoclonal B cell proliferation can be seen in cases of chronic inflammation such as lymphoid follicle-forming gastritis^[32], Sjögren's syndrome^[33], Hashimoto's thyroiditis^[34], and chronic liver disease secondary to hepatitis C virus^[35]. Thus, the above data support the theory that RBG with monoclonal Mott cells is a benign condition. However, Fujiyoshi *et al.*^[2] described a gastric tumor consisting of monoclonal Mott cells which metastasized to the perigastric lymph nodes, and they concluded that the gastric tumor was most likely an extramedullary plasmacytoma or a MALT lymphoma. Joo^[3] and Kai *et al.*^[36] also showed that monoclonal Mott cells can be a neoplastic component of MALT lymphoma with extreme plasmacytoid differentiation. Fujiyoshi *et al.*^[2], Joo^[3], and Kai *et al.*^[36] did not describe cellular atypia or mitotic activity in monoclonal Mott cells in their cases, and therefore the histopathological distinction of monoclonal Mott cells in RBG and in MALT lymphoma and plasmacytoma remains unknown. In the present case, we concluded that the monoclonal Mott cells were non-neoplastic cells mainly because of the absence of cellular atypia and mitotic activity. Nevertheless, future studies are warranted to clarify the distinction between RBG with monoclonal Mott cells and MALT lymphoma or plasmacytoma.

In conclusion, we presented an unusual case of an 86-year-old man with *H. pylori*-positive RBG. This is a valuable case of RBG evaluated by M-NBI and pathological evaluation of the entire lesion. The detailed endoscopic evaluation led to the clinical diagnosis of a poorly differentiated adenocarcinoma, despite the fact that previous endoscopically diagnosed cases of RBG were exclusively inflammatory. Pathological evaluation of ESD-obtained specimens confirmed the presence of regional proliferation of kappa-restricted Mott cells within the mucosal lesion and failed to identify an epithelial malignancy. RBG is a rare condition whose incidence is expected to increase in proportion to the increased use of M-NBI. Therefore, it is of great clinical importance to increase our understanding of the pathological features of RBG in order to effectively diagnose and manage future cases.

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COMMENTS

Case characteristics

An 86-year-old Japanese man with melena and a history of rheumatoid arthritis and type 2 diabetes mellitus.

Clinical diagnosis

The patient was initially diagnosed with atrophic and erosive gastritis secondary to *Helicobacter pylori* (*H. pylori*) infection, and the first esophagogastroduodenoscopy revealed a 13-mm flat lesion of white and slightly brown discoloration in the lesser curvature of the antrum.

Differential diagnosis

Findings of magnification endoscopy with a narrow-band imaging (M-NBI) of the flat gastric lesion suggested poorly differentiated adenocarcinoma.

Laboratory diagnosis

Laboratory findings revealed anemia and a positive serum anti-*H. pylori* antibody test.

Imaging diagnosis

M-NBI of the lesion showed loss or irregularity of microsurface pattern, irregular microvascular proliferation, and a demarcation line, which suggested poorly differentiated early gastric cancer.

Pathological diagnosis

The final diagnosis was Russell body gastritis (RBG) with substantial infiltration of granulated plasma cells. Although the granulated plasma cells showed kappa light chain restriction and the presence of Dutcher bodies, malignant lymphoma was unlikely partly because of the paucity of the cellular atypia and mitotic activity.

Treatment

Endoscopic submucosal dissection (ESD) was selected for therapeutic diagnosis.

Related reports

Thirty-one previously published cases of RBG, including the authors own, has been reported, and this is the first reported case of RBG with the endoscopic diagnosis of malignant tumor with M-NBI, pathological evaluation of the entire lesion with ESD-obtained specimens, and the presence of Dutcher bodies.

Term explanation

RBG is considered as a unique form of chronic gastritis characterized by infiltration of plasma cells filled with spherical eosinophilic cytoplasmic globules, referred to as Russell bodies.

Experiences and lessons

The endoscopic features of RBG are exclusively inflammatory; however, clinicians should consider RBG as a differential diagnosis in cases where detailed endoscopic examination reveals poorly differentiated early gastric cancer. Pathologists should be aware of the existence of this pathological entity, because histological features of RBG can overlap with those of malignant lymphoma.

Peer-review

Excellent case report article.

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Simultaneous Courvoisier's and double duct signs

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Abstract

Presence of Courvoisier's or double duct signs in a jaundiced patient is suggestive of malignant obstruction of the pancreaticobiliary ductal system. The oncologic impact of the simultaneous occurrence of these signs on the survival of patients with periampullary cancer is unknown. We report a case of obstructive jaundice secondary to an ampullary cancer demonstrating the Courvoisier's sign on clinical examination and a double duct sign on imaging. The patient underwent a pancreaticoduodenectomy which confirmed an ampullary adenocarcinoma.

Key words: Ampullary cancer; Obstructive jaundice; Double duct sign; Courvoisier's law; Prognosis

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Core tip: Presence of Courvoisier's or double duct signs in a jaundiced patient is indicative of obstruction of the pancreaticobiliary ductal system most likely of malignant etiology. This study reports classic clinical and radiologic findings in ampullary adenocarcinoma. The oncologic impact of the simultaneous occurrence of these signs on the survival of patients with ampullary cancer is unknown.

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INTRODUCTION

Recent studies validate Courvoisier's observation that gallbladder distension seldom occurs in stone obstruction of the bile duct and is usually seen with other causes of biliary obstruction^[1,2]. The radiographic double duct sign comprising of the simultaneous dilation of the common bile duct (CBD) and main pancreatic duct (MPD) se-

condary to biductal obstruction is highly suggestive but not diagnostic of pancreatic cancer^[3,4]. Despite a common etiology there is little data on the simultaneous occurrence of the two signs.

CASE REPORT

A 52-year-old male presented to the clinic with complaints of yellow discoloration of eyes and generalized pruritis since one month. He denied fever, chills or weight loss and maintained a normal appetite. He denied abdominal pain or backache. He quit smoking 15 years ago and denied consumption of alcohol. His past medical, surgical or family history were noncontributory. On examination he was icteric with no supraclavicular lymphadenopathy. Abdominal examination revealed a palpable liver edge 3 cm below the costal margin and a distended gall bladder consistent with a Courvoisier's sign. Laboratory tests were remarkable for elevated liver function tests- total bilirubin 5.4 mg/dL, direct bilirubin 4.4 mg/dL, glutamic-oxalacetic transaminase (AST) 107 IU/L, alanine aminotransferase (ALT) 189 IU/L, alkaline phosphatase 489 U/L with a normal tumor marker CA 19-9.

Abdominal ultrasound (US) demonstrated hepatomegaly, distended gallbladder with sludge, dilated MPD, CBD and intrahepatic biliary radicles. Pancreatic protocol computed tomography (CT) demonstrated a sessile enhancing mass in the medial wall of the second portion of the duodenum in the region of the ampulla with upstream dilation of the CBD, MPD, IHBR and a distended gallbladder. CBD and MPD measured 16 mm and 7 mm respectively and pancreatic parenchyma was normal (Figure 1). MR cholangiopancreatography confirmed an ampullary mass, a double duct sign with MPD dilated in its entire course and a prominent cystic duct (Figure 2). Upper gastrointestinal endoscopy demonstrated a periampullary tumor with surface ulceration and biopsy confirmed an adenocarcinoma (Figure 2, inset). The patient underwent a classic pancreaticoduodenectomy or Whipple operation. Postoperative course was unremarkable and the patient was discharged home on postoperative day six. Surgical pathology demonstrated a pT₁N₁M₀ ampullary adenocarcinoma with vascular invasion. Adjuvant chemotherapy was administered and the patient remains without evidence of tumor recurrence at 18 mo following surgery.

DISCUSSION

The lack of gallbladder distension in 80.4% patients with calculous obstruction of the CBD was first reported by Courvoisier and is typically explained by fibrotic or atrophic changes in the gallbladder wall secondary to repeated inflammatory episodes however, recent data suggests that gallbladders are equally distensible regardless of the underlying pathology and it is the markedly higher and sustained elevation in ductal pressure in malignant obstruction that results in a

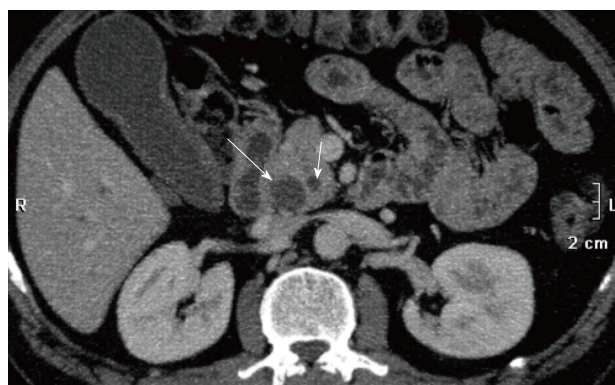


Figure 1 Double duct sign in a 52-year-old male with ampullary adenocarcinoma. Contrast-enhanced CT scan shows dilatation of the main pancreatic duct (short arrow) and common bile duct (long arrow).

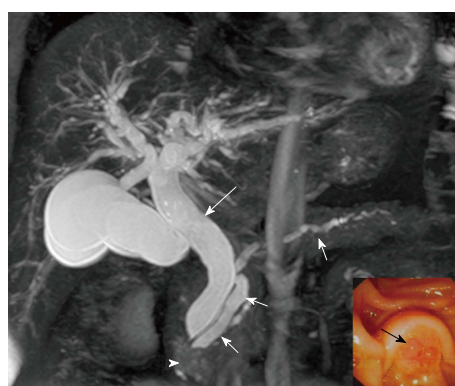


Figure 2 MR cholangiopancreatography shows a distended gallbladder, dilatation of the common bile duct (long arrow) and main pancreatic duct (short arrows) consistent with a double duct sign. A mass is noted in the region of the ampulla of Vater (arrowhead) and a periampullary tumor (black arrow) is confirmed on upper gastrointestinal endoscopy (inset).

distended gallbladder in contrast to the intermittent obstruction produced by gallstones^[1,5,6]. The double duct sign initially described on endoscopic retrograde cholangiopancreatography (ERCP) has also been seen with US, CT or MRCP and is usually caused by cancer of the pancreatic head or ampulla of Vater and less commonly, chronic pancreatitis or ampullary stenosis^[3]. Other malignant causes include cholangiocarcinoma, metastatic lymphadenopathy, lymphoma and rare causes include primary retroperitoneal fibrosis, Kaposi sarcoma or parasitic infestation of the bile ducts^[3]. The prevalence of malignancy in patients with the double duct sign varies from 58%-85% particularly, in association with obstructive jaundice^[4,7,8]. However, the MPD caliber is normal in 20% patients with pancreatic cancer and isolated dilation of the MPD (single duct dilation) is due to chronic pancreatitis in the majority of the patients^[9,10].

Biductal obstruction of the CBD and MPD may result in the Courvoisier's and/or double duct signs and the diagnostic value of these signs in the evaluation of a patient with obstructive jaundice is widely accepted. Despite extensive evaluation of the etiology,

pathogenesis and mechanism of these signs no study has reported the incidence or prognostic significance of the simultaneous occurrence of these signs in a patient with an ampullary cancer. The impact of the simultaneous occurrence of the Courvoisier's and double duct signs on survival outcome is unknown and an area for future investigation.

COMMENTS

Case characteristics

A 52-year-old male presented to the clinic with obstructive jaundice and abdominal examination revealed a palpable liver edge and a distended gall bladder consistent with the Courvoisier's sign. Abdominal imaging revealed an ampullary mass and a double duct sign. Upper endoscopy and biopsy confirmed ampullary adenocarcinoma. A classic pancreaticoduodenectomy was performed. Postoperative recovery was uneventful and adjuvant chemotherapy was administered. The patient remains without evidence of tumor recurrence at 18 mo following surgery.

Clinical diagnosis

Obstructive jaundice with ampullary tumor.

Differential diagnosis

Ampullary adenoma.

Laboratory diagnosis

Blood investigations confirmed obstructive jaundice.

Imaging diagnosis

Triphasic computed tomography and magnetic resonance cholangiopancreatography confirmed an ampullary mass, a double duct sign with the common bile and main pancreatic ducts dilated in their entire course.

Pathological diagnosis

Ampullary adenocarcinoma on esophagogastroduodenoscopy and biopsy.

Treatment

A classic pancreaticoduodenectomy (Whipple Operation).

Experiences and lessons

A double duct sign in a patient with obstructive jaundice is indicative of an

ampullary tumor. A pancreaticoduodenectomy is potentially curative for ampullary adenocarcinoma.

Peer-review

This is a good clinical case report with good quality imaging studies to support the case.

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