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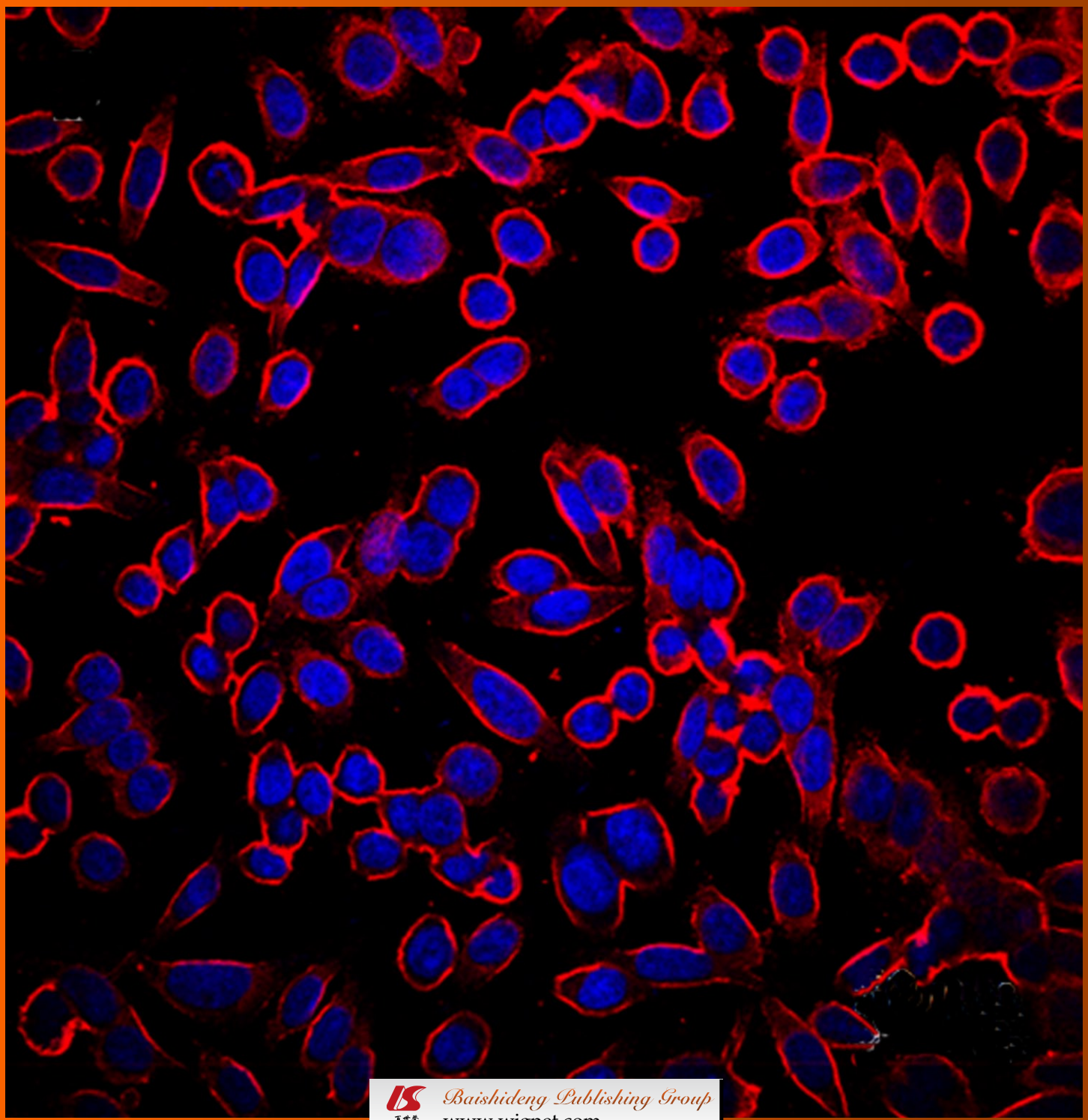

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EDITORIAL

Endoscopic and radiographic features of gastrointestinal involvement in vasculitis

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Abstract

Vasculitis is an inflammation of vessel walls, followed by alteration of the blood flow and damage to the dependent organ. Vasculitis can cause local or diffuse pathologic changes in the gastrointestinal (GI) tract. The variety of GI lesions includes ulcer, submucosal edema, hemorrhage, paralytic ileus, mesenteric ischemia, bowel obstruction, and life-threatening perforation.The endoscopic and radiographic features of GI involvement in vasculitisare reviewed with the emphasis on small-vessel vasculitis by presenting our typical cases, including Churg-Strauss syndrome, Henoch-Schönlein purpura, systemic lupus erythematosus, and Behçet's disease. Important endoscopic features are ischemic enterocolitis and ulcer. Characteristic computed tomographic findings include bowel wall thickening with the target sign and engorgement of mesenteric vessels with comb sign. Knowledge of endoscopic and radiographic GI manifestations can help make an early diagnosis and establish treatment strategy.

Key words: Behçet's disease; Churg-Strauss syndrome; Computed tomography; Endoscopy; Gastrointestinal tract; Henoch-Schönlein purpura; Histopathology; Lupus mesenteric vasculitis; Systemic lupus erythematosus; Vasculitis

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INTRODUCTION

Vasculitis is an inflammation of vessel walls, followed by alteration of the blood flow and damage to the dependent organ. It can affect vessels of all sizes. The clinical course and pathological features are quite variable and

dependon the size and location of the affected vessels[1,2]. Vasculitis can cause local or diffuse pathologic changes in the gastrointestinal (GI) tract. The variety of GI lesions includes ulcer, submucosal edema, hemorrhage, paralytic ileus, mesenteric ischemia, bowel obstruction, and perforation[3]. Of note, bowel ischemia and perforations are significantly associated with increased mortality[4]. Knowledge of endoscopic and radiographic GI manifestations can suggest the possibility of systemic vasculitis and help establish the specific diagnosis[5-7]. Although radiographic features of vasculitis involving the GI tract have been well studied especially in computed tomography (CT), the combination of endoscopic and radiographic features has not been fully evaluated. We herein review the endoscopic and radiographic features of GI involvement in vasculitiswith the presentation of our typical cases.

CLASSIFICATION OF VASCULITIS

Vasculitis is classified as primary or secondary (Table 1). Primary vasculitis was defined by the Chapel Hill International Consensus on the Nomenclature of Systemic Vasculitis[1]. The conference classified ten vasculitides into large-vessel vasculitis, medium-sized-vessel vasculitis, and small-vessel vasculitis, depending on the types of predominantly affected vessels. Large-vessel vasculitis affects the aorta and the largest arterial branches,and includesgiant-cell (temporal) arteritis and Takayasu's arteritis. Medium-sized-vessel vasculitis affects the main visceral arteries and their branches, and includespolyarteritisnodosa and Kawasaki's disease. Small-vessel vasculitis affects arterioles, venules, and capillaries, and includes Wegener's granulomatosis, Churg-Strauss syndrome, microscopic polyangiitis, Henoch-Schönlein purpura, essential cryoglobulinemic vasculitis, and cutaneous leukocytoclastic vasculitis[1].Secondary vasculitis is caused by connective tissue diseases (e.g., systemic lupus erythematosus, Behçet's disease, and rheumatoid arthritis), bacterial and viral infection, malignancy, and drugs. Most cases of secondary vasculitis present with small-vessel vasculitis[2,5].

Table 1 Classification of vasculitis

Primary vasculitis
Large-vessel vasculitis
Giant-cell (temporal) arteritis
Takayasu's arteritis
Medium-sized-vessel vasculitis
Polyarteritis nodosa
Kawasaki's disease
Small-vessel vasculitis
Wegener's granulomatosis
Churg-strauss syndrome
Microscopic polyangitis
Henoch-Schönlein purpura
Essential cryoglobulinemic vasculitis
Cutaneous leukocytoclastic vasculitis
Secondary vasculitis
Connective tissue diseases
Systemic lupus erythematosus
Behçet's disease
Rheumatoid arthritis
Infectious diseases
Bacteria
Virus
Drugs
Non-steroidal anti-inflammatory drugs
Anti-cancer drugs
Antibiotics
Paraneoplastic vasculitis
Carcinoma
Lymphoproliferative neoplasm
Myeloproliferative neoplasm

GASTROINTESTINAL INVOLVEMENT IN VASCULITIS

Large-vessel vasculitis

Giant cell (temporal) arteritis: Giant cell (temporal) arteritis is a form of granulomatous arteritis of the aorta and its major branches, with a predilection for the extracranial branches of the carotid artery[1]. It is often associated with polymyalgia rheumatica. The frequency of its GI involvement is rare[5,8].

Takayasu's arteritis: Takayasu's arteritis (TA) is a form of granulomatous inflammation of the aorta and its major branches[1].It is characterized by ocular disturbances and decreased brachial artery pulse (pulseless disease). The descending aortic syndrome may cause mesenteric vasculitis, but the frequency of mesenteric or celiac involvement is rare[3,5,6,8]. Although the precise etiology is unknown, the coexistence of TA and ulcerative colitis or Crohn's disease has been increasingly reported[9,10].

Large-vessel vasculitis

Polyarteritis nodosa: Polyarteritis nodosa (PN) is a form of necrotizing inflammation of medium-sized or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules[1]. Approximately two-thirds of the patientshave abdominal pain, nausea, vomiting, or other manifestations associated with GI ischemia and infarction[3,5-7]. The clinical course is often dramatic. The typical radiographic feature is an angiographic finding of aneurysms up to 1 cm in diameter within the renal, mesenteric, and hepatic vasculature[3].

Kawasaki's disease: Kawasaki's disease is a form of arteritis involving large, medium-sized, and small arteries and is associated with mucocutaneous lymph node syndrome[1]. It usually occurs in children and coronary arteries are often involved. GI involvement is relatively uncommon but acute abdomen with paralytic ileus, ischemic enteritis, and vasculitic appendicitis may occur[6].

Small-vessel vasculitis

Wegener's granulomatosis: Wegener's granulomatosis (WG) is a form of granulomatous inflammation involv-

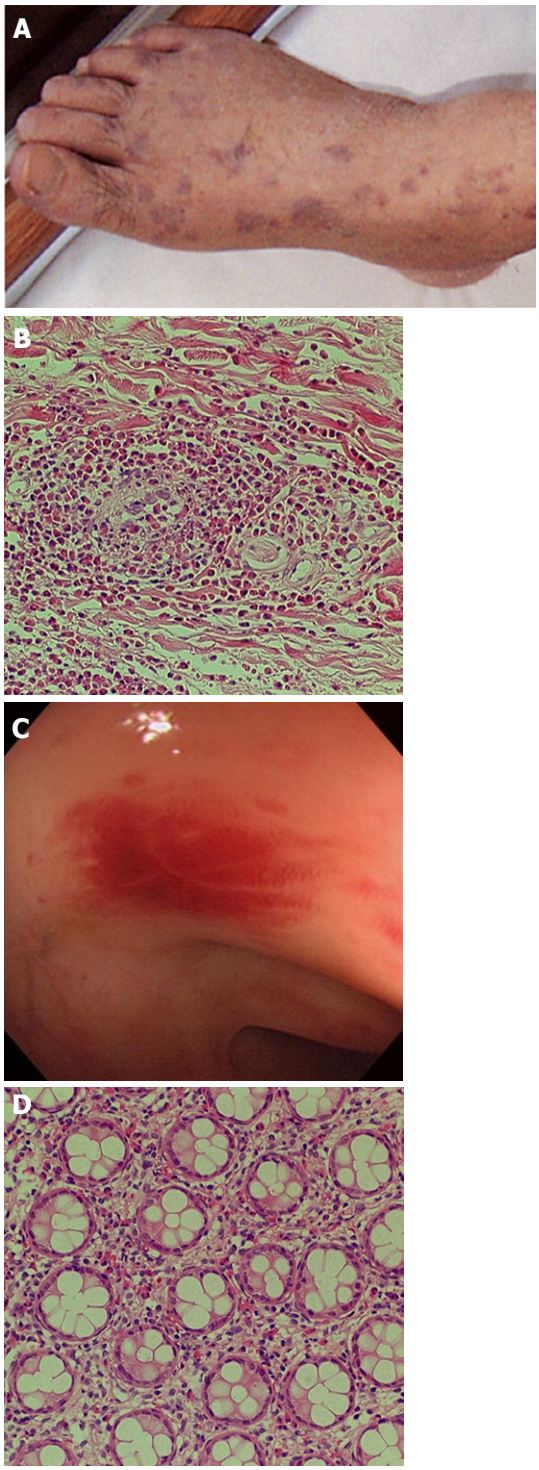

Figure 1 Churg-Strauss syndrome in a 60-year-old man with fever, abdominal pain, diarrhea, facial swelling, and purpura of the lower extremities. A: Purpura of the right foot; B: Biopsy of the purpura revealed small vessel vasculitis with marked inflammatory infiltrate of eosinophils; C: Colonoscopy disclosed numerous areas of patchy mucosal erythema from the sigmoid colon to the splenic flexure; D: Biopsy of erythema showed mild infiltration of eosinophils around crypts. All figures and legends are reproduced from Hokama *et al*[11] with permission from Elsevier.

ing the respiratory tract and necrotizing vasculitis affecting small-to-medium-sized vessels[1]. GI involvement is relatively rare and granulomatous colitis or gastritis may occur[5].

Churg-Strauss syndrome: Churg-Strauss syndrome(CSS) is a form of eosinophil-rich and granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small-to-medium-sized vessels and is associated with asthma and eosinophilia[1]. GI symptoms of CSS are abdominal pain and diarrhea caused by eosinophilic gastroenteritis (Figure 1)[11].Mesenteric vasculitis may occur, leading to GI ulceration, ischemia, and perforation. Among antineutrophil cytoplasmic antibodies-associated vasculitiswhich include WG, CSS, and microscopic polyangiitis (MPA), GI involvement increases the risk of relapse in CSS[12].

Microscopic polyangiitis: MPA is a form of necrotizing vasculitis with few or no immune deposits affecting small vessels[1]. Although necrotizing glomerulonephritis and pulmonary capillaritis are very common, GI involvement is rare[6].

Henoch-Schönlein purpura: Henoch-Schönlein purpura (HSP) is a form of vasculitis with IgA-dominant immune deposits affecting small vessels[1]. Although HSP is typically a disease of children, adult cases present more severe disease compared to children. It involves the skin, joints, GI tract and kidneys. GI symptoms include colicky abdominal pain and bleeding caused by bowel ischemia and edema. Serious complications include intussusception, infarction, and perforation[6,13]. The descending duodenum and the terminal ileum are frequently involved, with endoscopic characteristics of diffuse mucosal redness, petechiae, hemorrhagic erosions and ulcers[14].Longitudinal ulcers may be clear evidence of mesenteric vascular involvement (Figure 2)[15]. The CT features are bowel wall thickening with the target sign and engorgement of mesenteric vessels with comb sign (Figure 2)[15].

Systemic lupus erythematosus: Systemic lupus erythematosus (SLE) is an autoimmune connective tissue disease with local deposition of antigen-antibody complexes or antibodies inducing necrotizing vasculitis[3]. It involves the skin, joints, GI tract, kidneys, central nervous system, and blood cells. Itfrequently involves any part of the GI tract, liver, and pancreas[16,17]. Acute abdominal pain caused by bowel ischemia secondary to lupus mesenteric vasculitis (LMV) is common[18]. The ischemic change can differ according to the sensitivity of the vessels in four different bowel layers; mucosal ulceration and hemorrhage, submucosal edema and intestinal pseudo-obstructiondue to muscular damage, and ascites and perforation due toserosal damage[18]. The endoscopic features areischemic enterocolitis and 'punched out' ulcers (Figure 3). Although histopathological diagnosis of LMV can be obtained[19], most endoscopic superficial biopsies might not yield a definitive diagnosis because the affected vessels are usually located in an inaccessible area[18]. The CT features include focal or diffuse bowel

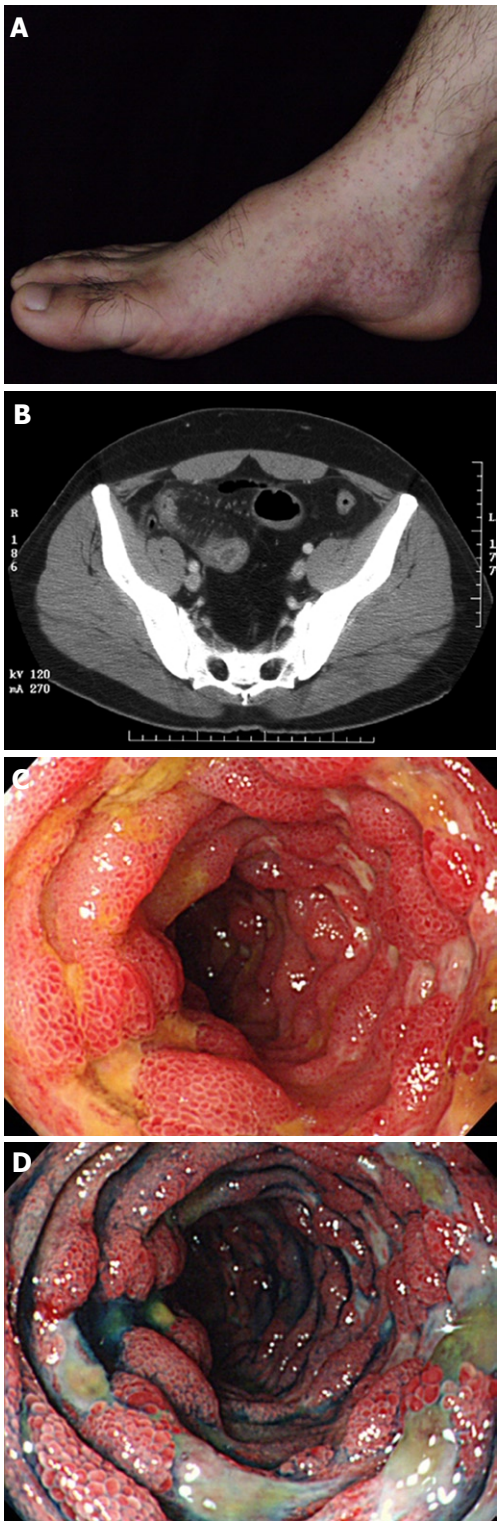

Figure 2 Henoch-Schönlein purpura in a 38-year-old man with hematochezia. A: Palpable purpura of the right foot; B: Contrast-enhanced computed tomography scan of the abdomen showed diffuse thickening of the ileum (target sign) with mesenteric hypervascularity in a palisading pattern (comb sign), suggesting ischemic ileitis; C, D: Single balloon enteroscopy showed edematous petechiae with linear ulcers in the affected ileum. All figures and legends are reproduced from Hokama *et al*[15] with permission from BMJ Publishing Group Ltd.

wall thickening with the target sign, bowel dilatation, ascites, and engorgement of mesenteric vessels with comb

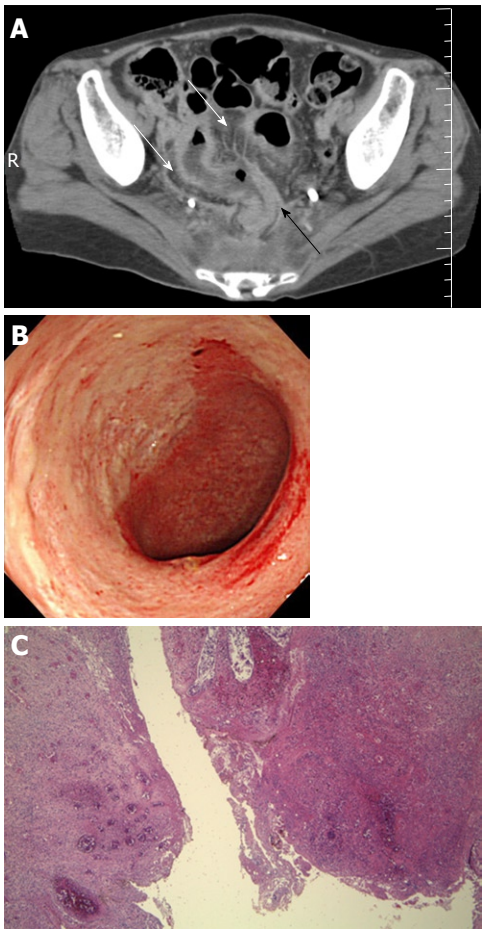

Figure 3 Systemic lupus erythematosus in a 40-year-old woman with lower abdominal pain and fever. A: Contrast-enhanced computed tomography scan of the abdomen showed diffuse thickening of the rectosigmoid colon (black arrow) with engorgement of mesenteric vessels (comb sign, white arrows); B: Colonoscopy disclosed a large punched-out ulcer of the sigmoid colon; C: Perforation of the sigmoid colon occurred despite aggressive immunosuppressive therapy, requiring resection of the affected colon. The resected specimen disclosed bowel perforation with severe transmural inflammation, edema, hemorrhage and vasculitis (hematoxylin-eosin staining, ×40).

sign (Figure 3)[3,17]. LMV rarely causes pneumatosis intestinalis (PI)[20], which is gas collection in the bowel wall (Figure 4). PI may result in hepatic portal venous gas with a high mortality rate. Another important GI manifestation in SLE is protein losing gastroenteropathy[16]. Edematous villi and lymphangiectasia, which may be caused by immunological vascular or mucosal damage, have been the postulated pathology[20].

Behçet's disease: Behçet's disease (BD) is a nonspecific necrotizing vasculitis characterized by recurrent orogenital ulcers, uveitis, arthritis, and skinlesions[21,22]. It frequently involves nerves and the GI tract. The frequently involved sites are the ileocecal region and esophagus. The hallmark of BD is the presence of ulceration. Two types of ulceration occur: localized and diffuse[22]. In the ileocecal region, a localized large deeply penetrating ulcer may present with a high frequency of hemorrhage and perforation. The CT features are mass-like lesions and

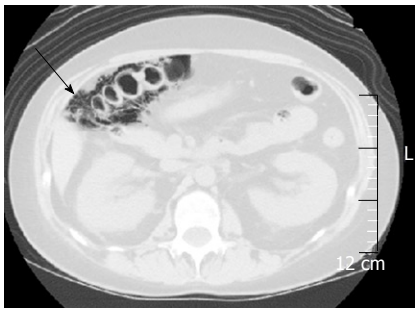

Figure 4 Systemic lupus erythematosus in a 23-year-old woman with abdominal pain and fever. Plain computed tomography scan of the abdomen showed intramural gas of the ascending colon, suggesting pneumatosis intestinalis (arrow). Hyperbaric oxygen therapy was effective for improvement of the pneumatosis.

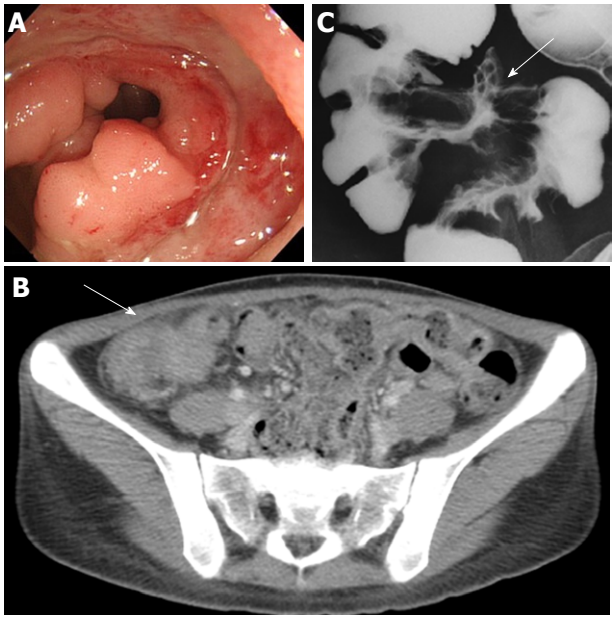

Figure 5 Behçet's disease in a 25-year-old woman with abdominal pain and diarrhea. A: Colonoscopy showed a large punched-out ulcer with elevated margins in the terminal ileum; B: Contrast-enhanced computed tomography scan of the abdomen showed a mass-like lesion with unevenly thickened bowel wall of the ileocecal region (arrow); C: Small bowel barium radiography disclosed the large ulcer (arrow) with convergence of mucosal folds in the terminal ileum.

unevenly thickened bowel wall with marked enhancement[3,22]. Barium examination shows a large irregular ulcer with marked thickening of the surrounding intestinal wall (Figure 5). Diffuse lesions are small, multiple, discrete, "punched-out" ulcers commonly observed in the colon (Figure 6)[23]. A recent large scale study confirmed that patients with intestinal BD younger than 25 years, who had a history of prior laparotomy or volcano-shaped intestinal ulcers (the former type) have an increased risk of free bowel perforation[24].

Other small-vessel vasculitis: Drugs in nearly all pharmacological classes can cause drug-induced vasculitis/drug-induced lupus-like syndrome[25]. As the clinical presentation and pathological features are indistinguishable from primary vasculitis, a high index of suspicion is required for the accurate diagnosis of drug-induced vasculitis. Discontinuation of the suspected drugis often enough to induce prompt improvement, obviating immunosuppressive treatment.

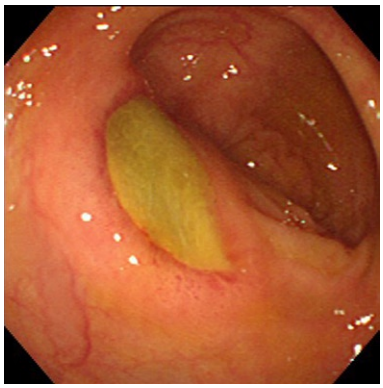

Figure 6 Behçet's disease in a 50-year-old woman with abdominal pain and hematochezia-a large ovoid ulcer in the transverse colon. The figure and legends are reproduced from Hokama *et al*[23] with permission from Elsevier.

Infectious agents often cause vasculitis *via* mechanisms including direct microbial invasion of vascular endothelial cells, immune complex-mediated damage and stimulation of autoreactive lymphocytes through molecular mimicry and superantigens[26]. Causative pathogens include bacteria (e.g., streptococci, mycobacteria, *Treponema pallidum*), viruses (e.g., cytomegalovirus, herpes virus, hepatitis virus B and C, human immunodeficiency virus), fungi, and parasites.

Vasculitis/connective tissue disease and malignancy are related and this association is bidirectional. Malignancy occurs more frequently in the course of vasculitis and vasculitis occurs in the course of malignancy[27,28]. Therefore, the presence of vasculitis/connective tissue disease may justify a workup for hidden malignancy. In addition, as blood hypercoagulability frequently occurs in malignancy, leading to thrombophlebitis and thrombosis[29], we should pay greater attention to vascular diseases in the treatment of cancer patients.

TREATMENT-ASSOCIATED COMPLICATIONS

As immunosuppressive drugs, including prednisolone, cyclophosphamide, azathioprine, cyclosporine A, tacrolimus, and anti-tumor necrosis factor antibodies, have been the key treatment for vasculitis, opportunistic infection can be a life-threatening complication. Cytomegalovirus (CMV) has been increasingly recognized as an important pathogen in such immunocompromised states[30]. GI symptoms of CMV infection are usually nonspecific and include abdominal pain, diarrhea and GI bleeding, which are similar to those of vasculitis. The colon and stomach are the most common sites of

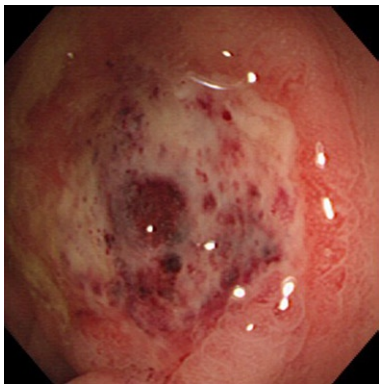

Figure 7 Systemic lupus erythematosus in a 38-year-old woman with diarrhea. Colonoscopy showed cytomegalovirus-associated round ulcer in the transverse colon.

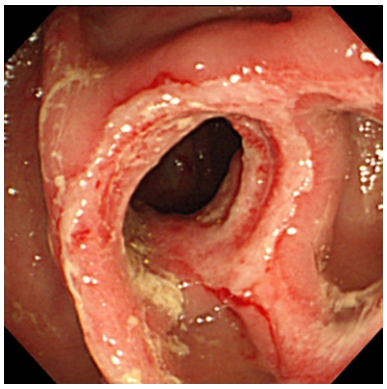

Figure 8 Rheumatoid arthritis in a 75-year-old woman with hematochezia. Colonoscopy showed a diaphragm-like stricture with a circumferential ulcer in the rectum, making the diagnosis of non-steroidal anti-inflammatory drug-induced diaphragm disease. The figure and legends are reproduced from Hokama *et al*[33] with permission from BMJ Publishing Group Ltd.

CMV GI infection. Endoscopic features are quite variable and include macroscopically normal mucosa, diffuse erythema[31], nodules, pseudotumors, erosions and ulcers[32], which are also similar to those of vasculitis. CMV-associated colonic ulcerin SLE is shown in Figure 7. Pathological proof of classical intranuclear inclusions is not always possible because CMV may infect vascular endothelium or connective tissue stromal cells under the ulcers. Therefore, several diagnostic methods should be used including CMV antigenemia assay and polymerase chain reaction of the specimen. Most GI CMV infections respond well to ganciclovir.

Nonsteroidal anti-inflammatory drugs (NSAID) are widely used in long-standing vasculitis/connective tissue diseases. Although gastroduodenal peptic ulceris well-known as a classic NSAID-induced GI damage, diaphragm disease (Figure 8)[33] and various types of enteropathy in the small and large intestine have received greater recognition as adverse effects of NSAIDs. Diagnosis is traditionally made by symptom improvement on discontinuation of the NSAID[34].

CONCLUSION

Any type of vasculitis can involve the GI tract. Bowel ischemia due to mesenteric vasculitis is frequently seen in association with increased mortality. Important endoscopic features areischemic enterocolitis and ulcer. Characteristic CT features include bowel wall thickening with the target sign and engorgement of mesenteric vessels with comb sign. Knowledge of these GI manifestations can help make an early diagnosis and establish a management strategy with prompt immunosuppressive treatment.

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EDITORIAL

Recent advances in targeted endoscopic imaging: Early detection of gastrointestinal neoplasms

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Abstract

Molecular imaging has emerged as a new discipline in gastrointestinal endoscopy. This technology encompasses modalities that can visualize disease-specific morphological or functional tissue changes based on the molecular signature of individual cells. Molecular imaging has several advantages including minimal damage to tissues, repetitive visualization, and utility for conducting quantitative analyses. Advancements in basic science coupled with endoscopy have made early detection of gastrointestinal cancer possible. Molecular imaging during gastrointestinal endoscopy requires the development of safe biomarkers and exogenous probes to detect molecular changes in cells with high specificity anda high signal-to-background ratio. Additionally, a high-resolution endoscope with an accurate wide-field viewing capability must be developed. Targeted endoscopic imaging is expected to improve early diagnosis and individual therapy of gastrointestinal cancer.

Key words: Autofluorescence endoscopy; Confocal endomicroscopy; Endoscopy; Molecular imaging; Molecular probes, Near-infrared fluorescence imaging; Targeted endoscopic imaging

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INTRODUCTION

Molecular imaging is a technique that detects molecular changes in diseased cells within the mucosa. This discipline has great potential to improve medicine *via* detection of diseases in the early stages, identification of the extent of disease, selection of disease- and patient-specific treatments, application of directed or targeted therapy, and measurement of molecularly-specific effects of treatment[1].

Recent developmentsin optics and digital imaging

technology, and new diagnostic methods combined with state-of-the-art technology have been introduced in gastrointestinal endoscopy. Various methods such as narrow-band imaging, autofluorescence imaging (AFI), Raman spectroscopy, confocal endomicroscopy, endoscopic optical spectroscopy, and magnifying endoscopy-have been developed and are under investigation. Some of these methods have already been widely used in clinical practice[2]. These endoscopic detection methods have enabled endoscopists to collect real-time *in vivo* histological images or "virtual biopsies" of the gastrointestinal (GI) mucosa during endoscopy. Although early diagnosis of premalignant GI lesions is very important, many studies have shown thatthe miss rate for GI lesions has not been decreased[3].

The application of molecular imaging to endoscopy for the diagnosis and treatment of GI cancer is aimed at diagnosing cancer by analyzing lesion characteristics based on molecular biological changes rather than lesion morphology, thereby increasing the efficiency of endoscopic screening and surveillance. An important advantage of performing targeted imaging of the GI mucosa is the opportunity to apply exogenous probes. Recently, several different classes of probe technology have been developed to perform targeted imaging. Such probes include antibodies, antibody fragments, peptides, nanoparticles, and activatable probes. Molecular targets for targeted imaging include proteolytic enzymes, extracellular matrix targets, cell-surface receptors, tyrosine kinases, and apoptosis markers[4].

This report aims to evaluate the current data regarding the utility of targeted imaging technology in gastroenterology and its potential future impact, particularly in the early detection of GI neoplasia.

MOLECULAR PROBES (OPTICAL CONTRAST AGENTS)

Optical contrast agents can be classified into endogenous fluorophores and exogenously administered contrast agents. Autofluorescence is the emission of a longer wavelength of light from tissue after it is excited by short-wavelength light. Fluorescence by emission is induced when endogenous tissue fluorophores (collagen, nicotinamide, adenine dinucleotide, flavin, or porphyrins) become excited[5]. Endoscopic AFI produces real-time pseudocolor images by detecting natural tissue fluorescence. Abnormal autofluorescence patterns in neoplastic tissues have been attributed to an increased nuclear-to-cytoplasmic ratio, loss of collagen, and neovascularization[6]. AFI has the advantage of not requiring the use of a contrast agent. However, as many of the autofluorescence alterations are not specific for neoplasia, autofluorescent imaging has disadvantages, such as low specificity and a high false-positive rate. Oh kawa *et al*[7] tested the diagnostic performance of AFI for detecting early gastric cancer. They showed that AFI was highly sensitive (sensitivity, 96.4%) but not very specific (specificity, 49.1%), as 50.9% of lesions identified as abnormal by fluorescence were benign. Although other studies have demonstrated the potential of AFI to target premalignant lesions and early cancer, the important limitation of high false-positive rates should be resolved[8].

Fluorescence imaging using exogenous probes obtains more effective images than AFI. Recent advances in molecular imaging using biomarker-targeted exogenous probes have demonstrated enhanced sensitivity and specificity for *in vivo* tumor imaging[1]. Exogenous probes targeting tumors include smart activatable probes, antibody fragments, peptides, and nanoparticle probes[9]. Weissleder *et al*[10] first introduced a smart activatable probe, which was a synthetic graft copolymer consisting of poly-L-lysine sterically protected by multiple methoxy polyethylene glycol side chains to which multiple fluorochromes were attached. Smart activatable probes have their fluorescent emission effectively inhibited in the native state by fluorescence resonance energy transfer caused by the proximity of the fluorochromes to one another,but they become brightly fluorescent in areas of disease. Due to the high signal-to-background ratio, fluorescence intensity is relatively strong in the target tissue, which allows for a more accurate diagnosis. The specific target is increased protease expressed in neoplastic lesions, which cleaves lysine–lysine bonds resulting in a 15- to 30-fold enhanced signal intensity. In particular, cathepsin B is a major contributor to cleavage and activation *in vivo*. A previous study using a protease activatable probe demonstrated that this probe improved detection of adenomatous polyps in the small bowel of an animal model after resection and flushing[11].

Antibody probes bind to antigenic targets expressed on the cell surface in a specific manner, thereby optimizing the signal-to-background ratio. Antibodies have already been widely used to detect tumors, and the fluorescent probe-labeling method has been well established[12]. Additionally, novel treatment regimens using monoclonal antibodies have been developed to target specific molecules that play pathogenic roles in disease progression. Typical antibodies used for cancer treatment include cetuximab and panitumumab (monoclonal antibodies against epidermal growthfactor receptor) or bevacizumab (monoclonal antibody against vascular endothelial growth factor)[9]. Molecular imaging using antibody probes has a high potential to assist in the selection of patients who are likely to benefit from such tailored therapy and in the monitoring of responses to therapy. Most antibody probes have immunogenic properties and cause anallergic reaction. This type of response is frequently observed after systemic application. As antibody probes have a longer half-life, systemic application may induce the accumulation of antibody probes, causing the generation of a nonspecific background signal. Furthermore, due to the large molecular weight and size of antibody probes, it takes them longer to reach the target structure, which is disadvantageous for systemic application. $F(ab')_2$, Fab', and scFv (single-chain variable)

fragments lack the Fc domain and the complement-activating region, which may reduce immunogenicity[13]. Moreover, compared with an entire monoclonal antibody, antibody fragments are smaller and, therefore, able to more effectively penetrate tumor cells and accumulate. Fab' and scFv fragments have only one binding domain, which reduces their binding ability; however, multivalency is increased by attaching several fragments to the surface of carriers or by engineering bivalent or multivalent fragments[14].

Peptides have several advantages because they consist of only a few amino acids that are highly specific and have high affinity, rapid binding kinetics, and shorter blood-clearance times. Furthermore, they have low immunogenic properties. Peptides with specific amino acid sequences that can preferentially bind to dysplastic or neoplastic tissues can be identified using the phage display technique[15]. This technique uses recombinant DNA technology to generate a library of clones that preferentially bind to the cell surface.

Several types of nanoparticles including magnetic iron oxide (IO), gold, quantum dots, and polymer-based nanoparticles have been developed recently for oncologic applications[16]. The surface of nanoparticles are usually coated with significantly stronger fluorophores for fluorescence imaging[9]. Additionally, nanoparticles can be loaded with targeted ligands, such as small molecules, peptides, antibodies, or aptamers. Nanoparticles must be fully characterized for toxicity, biodistribution, and pharmacokinetics to be highly specific and sensitive for molecular imaging.

Characteristics of exogenous probes that are promising for use in GI endoscopy include biocompatibility, affinity binding, deep tissue penetration, rapid kinetics, and low immunogenicity[12]. With regard to the administration route, the advantages of systemic application include a much more homogenous delivery of the imaging agent and a greater repeatability of agent concentration for serial studies. However, systemic administration produces more side effects than topical application. Topical application results in a much lower systemic concentration of the imaging agent, decreasing safety concerns and producing fewer regulatory hurdles to human translation. When probes are applied topically during or immediately before the endoscopic imaging procedure, specific binding to the targets must occur within several minutes, and a region of interest must be detected quickly.

MOLECULAR IMAGING INSTRUMENTS

Molecular imaging endoscopy requires high resolution to observe the large surface area of the GI mucosa and subsequently localize molecular changes in tumors. Optical spectroscopic and/or imaging techniques offer the potential for detecting the very earliest mucosal changes at the microstructural, biochemical and molecular levels. Several optical techniques currently under investigation for the endoscopic detection of precancerous GI lesions includes fluorescence spectroscopy and imaging, Raman spectroscopy, light-scattering spectroscopy (LSS), optical coherence tomography (OCT), and confocal fluorescence endomicroscopy[17].

AFI visualizes lesions including neoplasms not detectable by conventional white-light endoscopy due to differences in tissue fluorescence intensity. During AFI, normal tissue is pseudocolored green and blood vessels are dark green, whereas the hypertrophic fundic mucosa of the stomach and dysplastic or neoplastic areas appear magenta[8]. New AFI systems have a xenon light source (XCLV-260HP; Olympus, Tokyo, Japan) with a rotary red/green/blue band-pass filter. With this light source, the mucosa is sequentially illuminated with red, green, and blue light at a frequency of 20 cycles/s. The high-resolution videoendoscope (XCF-Q240FAI, Olympus) has two separate monochromatic charge-coupled devices (CCD), one for white-light endoscopy and one for AFI. The white-light mode can be switched to the autofluorescence mode by pressing a small button on the control head, and the switch is completed in 3 s[18]. In the AFI mode, blue-spectrum light (395-475 nm) is delivered to excite AF, together with light in the green (540-560 nm) and red (600-620 nm) spectra. The AFI-CCD has a barrier filter that allows detection of all light with wavelengths from 490 nm to 625 nm, thereby eliminating blue excitation light. The sequentially detected images from AF along with the green reflectance, and red reflectance are integrated by the imaging processor into one AF image. AFI does not require the administration of fluorescence probes. Thus, it can be applied for cancer screening tests. The sensitivity for premalignant GI lesions increases when AFI is combined with high definition white-light imaging and narrow-band imaging to provide endoscopic trimodal imaging[19]. Endoscopic trimodal imaging has been proposed as an alternative to overcome the problems of AFI. Endoscopes with a widefield of view that can detect induced fluorescence during targeted endoscopic imaging have not yet been evaluated in larger clinical trials.

Raman spectroscopy is a form of image enhancement based on the principle that incident light (with wavelengths in the near-infrared region of the spectrum) can induce tissue biomolecules to vibrate and rotate. When light interacts with tissue molecules, it can be absorbed or scattered. Almost all of the scattered light is of the same wavelength as the incident light (elastic scattering)[20]. However, a small fraction of light undergoes so-called Raman (inelastic) scattering, in which slight shifts in energy and wavelength relative to the incident light occur because of energy exchange within a molecular structure. Raman spectroscopy can detect tissue changes at the molecular level, yielding unique "spectral fingerprints" of tissues as they become abnormal. Molckovsky *et al*[21] reported the first *in vivo* study using a fiber-optic probe *via* the accessory channel of the colonoscope. This study resulted in impressive accuracy of diagnosing hyperplastic (n = 9) and adenomatous (n =

10) polyps (100% sensitivity, 89% specificity, 95% overall accuracy).

LSS is based on white-light (400 nm to 700 nm) reflectance, whereby photons incident on tissue are backscattered without a change in their wavelength, providing microstructural information about the tissue. LSS measurements are performed with fiber-optic probes placed on the tissue surface *via* the accessory channel of the endoscope. Analysis of the intensity and wavelength of light reflected from the tissue surface provides an estimate of the size and degree of crowding of epithelial cell nuclei[17]. Recent preliminary work has suggested that LSS can be useful to identify even earlier subcellular changes associated with cancer progression[22]. In this study, a new generation of light scattering technology has detected submicron-size architectural changes in an endoscopically normal rectum. These changes were associated with the presence of neoplasia located elsewhere in the colon.

Confocal microscopy is based on tissue illumination with a low-power laser. The reflected light from the tissue is refocused onto the detector by the same lens, meaning that only returning light refocused through a pinhole is detected[23]. This process provides high-resolution images from a thin section within otherwise optically thick tissue. With technical developments, a miniaturized confocal laser scanner has been integrated into the distal tip of a flexible white-light endoscope for clinical use. Confocal endomicroscopy (Pentax EC-3870 CIFK; Pentax, Tokyo, Japan) enables confocal microscopy in addition to standard videoendoscopy[24]. The diameters of both the distal tip and the insertion tube are 12.8 mm. The distal tip contains an air- and water-jet nozzle, two light guides, a water-jet channel used to apply contrast agent, and a 2.8 mm working channel. The system uses a 488-nm excitation wavelength laser and enables the detection of 205 nm to 585 nm wavelength fluorescence.Confocal images are collected at a scan rate of approximately one frame/s, ata maximum resolution of 1024 × 1024 pixels. The optical slice thickness is 7 μm (axial resolution), and the lateral resolution is 0.7 μm.The range of the z-axis is 0 to 250 μm below the surface layer. Screen images approximate a 1000-fold magnification of the tissue *in vivo*. Confocal images can be generated simultaneously with endoscopic images. A slightly different approach is used for flexible probe-based confocal microscopy. Probe-based confocal laser endomicroscopy (pCLE; Cellvizio-GI; Mauna Kea Technologies, Paris, France) has been developed recently and has the advantage that a miniprobe can be easily passed through the working channel of a standard endoscope[25]. Probes generate dynamic (12 frames/s) images with a scanning field of 30 000 pixels. In addition to faster acquisition, the advantages include greater versatility of pCLE probes, which can be used in conjunction with virtually any endoscope,cholangioscope, bronchoscope, or ureteroscope, and for *ad hoc* usage, such as when a lesion is detected with a normal endoscope[26]. However, pCLE has a slightly lower resolution (approximately 1 μm compared with 0.7 μm for the Pentax confocal endomicroscope) and a smaller field of view (240-600 μm).

In the past few years, newly developed procedures and technologies have improved endoscopic recognition of GI neoplasms. Narrow band imaging (NBI) (with which Olympus scopes are equipped), the contrast enhancement system (i-scan) (associated with Pentax scopes) and multiband imaging (MBI) (with which the Fujinon scope is equipped) are used in combination with magnification and high resolution endoscopy[27]. These imaging techniques can improve visualization of the vascular network and surface texture of the mucosa and can facilitate endoscopic diagnoses. NBI uses rotating filters in front of light sources to narrow the bandwidth of the projected light, and increases the blue spectrum intensity of the light used. This shorter wavelength is more readily absorbed by hemoglobin and has shallow penetration into only the superficial layer, thereby enhancing the visualization of superficial capillaries. The advantages of NBI include enhanced mucosal contrast at the push of a button and ease of neoplastic and non-neoplastic lesion differentiation. However, NBI results in poorer illumination of the background and a learning curve effect is observed, even for experienced endoscopists[28].

To date, AFI, NBI and CLE have been compared separately with conventional endoscopy. Trials should be extended to investigate different patient groups, as the optimal endoscopic modality may vary. AFI or NBI may be the examination of choice for general screening and CLE may be used for ulcerative colitis surveillance. Further large randomized controlled trials are needed to determine which modality would be the most suitable for various patient subpopulations.

PRECLINICAL AND CLINICAL STUDIES IN GI ENDOSCOPY

In vivo molecular imaging has been applied to GI endoscopy in various preclinical and clinical trials. Keller *et al*[29] performed fluorescence endoscopy with a fluorescent dye-labeled monoclonal antibody against carcinoembryonic antigen in patients with colonic polypoid lesions. Fluorescence probes were topically applied during a colonoscopy. A conventional endoscope was used, and its optical range was improved *via* two narrow-band filters. Specific fluorescence signals were present in most carcinomas and some adenomas. This study provided important information for further trials. Further advances were achieved in subsequent animal studies. Wang's group[12] performed *in vivo* molecular imaging using topically applied fluorescence-labeled peptides to target the detection of high-grade dysplasia in Barrett's esophagus. An affinity peptide with the ASYNYDA sequence was selected using phage display techniques. Fluorescent images using a wide-field endoscope sensitive to fluorescence revealed a region of high-grade dysplasia that was confirmed by histology. In a more recent study by the same group, peptides, which preferentially bind to

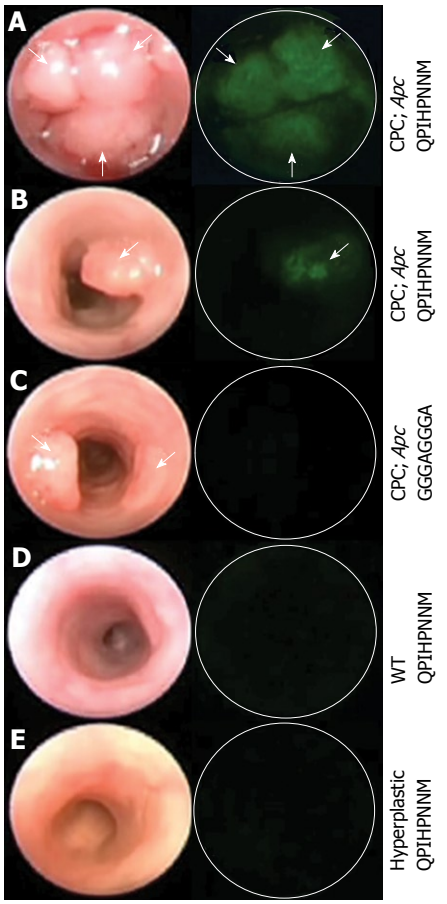

Figure 1 Images from wide-field endoscopy videos after topical application of fluorescence-labeled peptides. The left and right columns represent frames from white light and fluorescence endoscopy, respectively. A: Multiple adenomas; B: Single adenoma in a *CPC; Apc* mouse. The fluorescently labeled target peptide shows positive binding to multiple adenomas and a single adenoma; C: The control peptide shows minimal binding to a single adenoma; D:Control mouse lacking Cre recombinase transgene; E:The hyperplastic epithelium in a mutant *K-ras* mouse model. The target peptide also shows minimal binding to control mouse and hyperplastic epithelium. White arrows identify adenomas. Reproduced from Miller *et al*[30].

adenomas in the *CPC; Apc* mouse model, a genetically engineered mouse that produces adenomatous polyps, were selected using an *in vivo* phage display[30]. *In vivo* binding was demonstrated using a fluorescein label with a wide-field endoscope (Figure 1).

Recently, near-infrared (NIR) fluorescence probes suitable for *in vivo* imaging have been developed. Several proteases are overexpressed in a number of cancers[31,32]. NIR imaging techniques combined with an NIR optical molecular probe activated by protease shows high specificity and sensitivity for tumor detection. In an animal study, an NIR probe specific for the enzyme cathepsin B, a protease upregulated in colorectal neoplasia, was administered intravenously[11]. The cathepsin B-activated molecular beacon demonstrated a high specificity for detecting small adenomatous polyps in $Apc^{Min/+}$ mice. Recently, a minimally invasive imaging catheter has been developed to simultaneously and independently emit white light and NIR fluorescence[33]. When a protease-activatable probe was administered to an orthotopic colon cancer mouse model, microcatheter imaging demonstrated tumors with a higher target-to-background ratio[34]. Another study demonstrated that capsule endoscopy can be combined with molecular imaging[35]. NIR fluorescent signals of different intensities were detected after mouse models with adenomas were injected intravenously with a cathepsin B-activated probe, and the dissected intestine was imaged with capsule endoscopy under white or NIR fluorescent light.

Currently, targeted imaging techniques using Raman spectroscopy for clinical applications are being developed. This methodology includes the use of an accessory Raman endoscope in conjunction with topically applied tumor targeting Raman nanoparticles. Zavaleta *et al*[36] utilized surface-enhanced Raman scattering (SERS) nanoparticles as tumor targeting contrast agents. SERS is a plasmonic effect in which small molecules absorbed onto a nanoroughened noble metal surface, like gold, experience a dramatic increase in the incident electromagnetic field, resulting in a 2- to 4-fold higher Raman effect. In this study, intrarectally injected mice had localized uptake in the colon with minimal uptake in other organs. The benefit of SERS Raman nanoparticles as molecular imaging agents is the ability to conjugate them with specific tumor-targeting ligands, such as tumor-specific peptides, and then topically apply them to the tissue of interest to increase targeting efficiency while decreasing systemic toxicity.

Since confocal laser endomicroscopy was introduced, several studies have reported molecular imaging with CLE. In the first study, Hsiung *et al*[15] developed a specific heptapeptide sequence (VRPMPLQ), which was screened using a phage display, that preferentially bound to human colorectal neoplasms. This peptide was conjugated with fluorescein and topically applied to the colonic mucosa of patients undergoing colonoscopy. Then an image was obtained using probe-based confocal laser endomicroscopy delivered through the working channel of a standard colonoscope. The fluorescein-conjugated peptide bound more strongly to dysplastic colonocytes than to adjacent normal cell sand had a sensitivity of 81% and a specificity of 82%. In a second trial, differentiation of tumor cells based on their epidermal growth factor receptor (EGFR)-expression patterns was achieved in a mouse model of human colorectal cancer xenografts[37]. After injecting a fluorescently-labeled whole antibody targeting EGFR, confocal laser endomicroscopy accurately identified EGFR expression. Further more, a CLE analysis of EGFR expression in *ex vivo* human tissue specimens allowed neoplastic tissue to be distinguished from non-neoplastic tissues after topical administration of labeled antibodies. We have developed a silica-coated IO nanoparticle that includes fluorescent materials. For whole-body molecular imaging, these nanoparticles were conjugated with cetuximab, a humanized chimeric anti-EGFR monoclonal antibody, that can specifically target colon cancer cells expressing EGFR on their cell membranes (Figure 2)[38]. After intravenously injecting a mouse model with human colorectal cancer

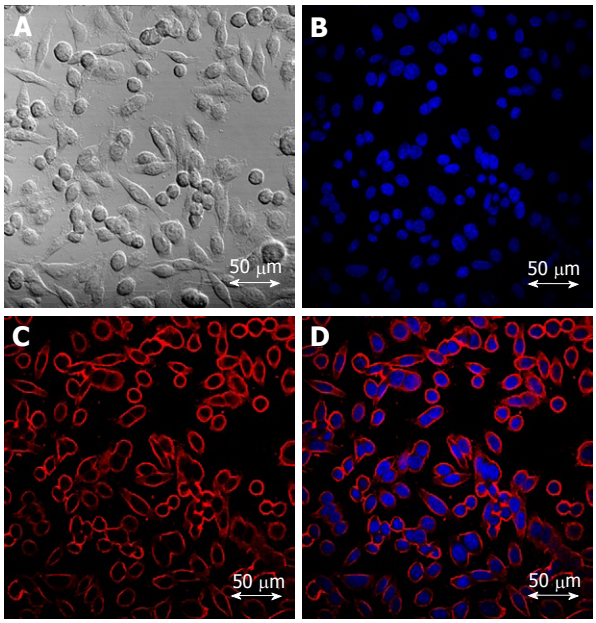

Figure 2 Confocal laser scanning microscopy images of colon cancer cells treated with cetuximab-conjugated magnetofluorescent nanoparticles. A: A bright field image; B: Nuclear staining with DAPI; C: RITC (Rhodamine B isothiocyanate) fluorescent image; D: Overlay of B and C. Cellular uptake was so significant that the outer cell membranes of HCT116 cells can be clearly delineated by the images of the particles.

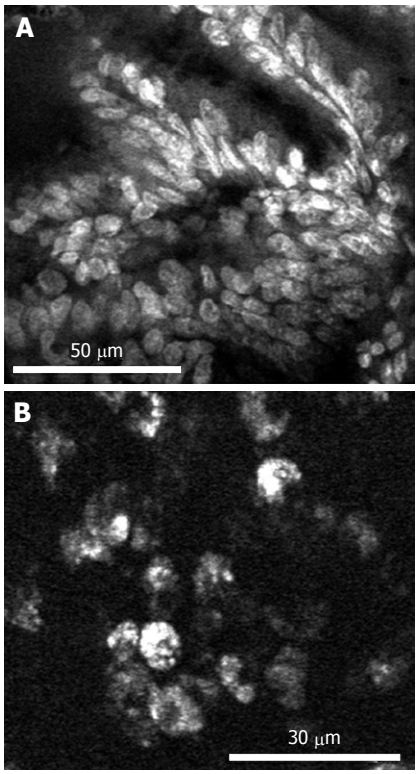

Figure 3 Imaging of vascular endothelial growth factor in the biopsy specimen of human colorectal adenocarcinoma. A: Nonspecific nuclear and cellular staining using acriflavine; B: VEGF-specific staining using AF488-labeled antibodies. The antibody accumulates in the cytoplasm of the tumor cells, but not the nuclei. Reproduced with permission from Foersch *et al*[39].

xenografts, magnetic resonance imaging demonstrated significant changes in T2-weighted signals. Further studies are needed to apply our targeted nanoparticles to confocal endomicroscopy. In another trial, molecular imaging in surgical specimens from patients and in the APC min mouse model, a colorectal cancer xenograft model, was achieved after applying a fluorescein-labeled antibody against vascular endothelial growth factor (VEGF)[39]. CLE enabled the cytoplasmic distribution of VEGF to be displayed in most APC min ouse and xenograft tumors. Additionally, the VEGF-specific signal was significantly higher in malignant specimens than in samples from healthy mucosa (Figure 3). This study showed that CLE can contribute to the early detection of at-risk lesions and potentially predict responses to anti-VEGF-targeted treatment.

FUTURE DIRECTION AND OPPORTUNITIES

The current screening method for premalignant GI lesions and cancers uses standard white-light endoscopy to detect morphological changes and lesions in the mucosa. Subsequent histopathological analysis of biopsy specimens is the gold standard for final diagnosis and treatment. Random biopsy sampling is commonly used for cancer screening and surveillance of diseases such as Barrett's esophagus, gastric intestinal metaplasia, and inflammatory bowel diseases. However, a large mucosal area is at risk for developing cancer, and a nonrepresentative biopsy may miss lesions. Recent advances in molecular imaging have substantially influenced the endoscopic diagnosis of various GI diseases and our understanding of disease pathogenesis.

The essential elements to successfully apply molecular imaging to GI endoscopy are the identification of biomarkers for molecular targets and the development of appropriate molecular probes, application routes, adequate ligand targeting, and a high-resolution endoscope with wide-field view capable of visualizing the fluorescent signal. In the future, multimodality devices incorporating a wide field and high-resolution microscopic morphological imaging could further enhance the imaging-plane depth. For example, two-photon fluorescence endomicroscopy could show higher resolution and deeper penetration compared to single photon devices. The approach of first detecting suspicious lesions using whole-body molecular imaging and then characterizing the lesions by targeted endoscopic imaging might improve early disease diagnosis and evaluate response to therapy. In addition to these requirements, the safety and pharmacokinetics of the molecular probes must be investigated.

Recently, a variety of methods have been developed for computer-aided detection of GI neoplasms to overcome the limitations of conventional structural imaging tools, which include magnetic resonance imaging (MRI) and computed tomography (CT). Computed tomographic colonography (CTC) is an emerging technique for the detection of colorectal neoplasms, which has the potential to become an effective screening procedure for examining the entire colon[40]. However, problems

such as a long interpretation time and the high variability of diagnostic accuracy among reviewers need to be addressed. Computer-aided detection (CAD) for CTC is attractive because it has the potential to circumvent these obstacles. Several approaches have been developed for the detection of polyps in CTC, including the use of the surface curvature with a rule-based filter, a volumetric shape index, and the extent of curvature[41]. Additionally, several methods have been proposed for computer-aided evaluation of GI images or video. Iakovidis *et al*[42] have developed a novel intelligent system for automatic detection of colonic and gastric adenomas in endoscopic videos, which uses color–texture image features and incorporates non-linear Support Vector Machines (SVMs) to achieve improved detection accuracy. Computer-aided evaluation is useful in automatically classifying NBI magnifying colonoscopicimages[43]. These approaches could be used in combination with molecular imaging tools. Advances in molecular imaging techniques will provide better patient-management strategies and make treatment more personalized.

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TOPIC HIGHLIGHT

Toru Hiyama, PhD, Professor, *Series Editor*

Natural orifice translumenal endoscopic surgery applications in clinical practice

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Abstract

To review natural orifice translumenal endoscopic surgery (NOTES) applications in clinical practice and assess the evidence base for each application as reported in the literature. An electronic literature search was performed. Inclusion criteria were publications relating to NOTES applications in humans. For each type of operation the highest level of evidence available for clinical NOTES publications was evaluated. Morbidity and short-term operative outcomes were compared with gold standard published evidence where available. Finally, registered trials recruiting patients for NOTES applications were identified. Human NOTES publications with the highest level of evidence in each application are identified. There were no RCTs in the literature to date. The strongest evidence came in the form of large, multi-centre trials with 300-500 patients. The results are encouraging, comparable with gold standard techniques on morbidity and mortality. While short-term operative outcomes were also similar when compared to the gold standard techniques, other than improved cosmesis little else can definitely be concluded as a clear benefit of a NOTES procedure. The most common procedures are cholecystectomy, appendicectomy and peritoneoscopy mainly performed *via* transvaginal access. It is evident that morbidity appears to be higher when the transgastric route is used. The safety profile of hybrid NOTES transvaginal procedures is beginning to be confirmed as is evident from the large number of procedures presented in this review. A number of authors have presented work on pure NOTES procedures but the results are inconsistent and thus the vast majority of NOTES procedures worldwide are performed in a hybrid fashion with a variable amount of laparoscopy. This review of the clinical applications of NOTES summarises the growing evidence behind this surgical discipline and highlights NOTES procedures with an acceptable safety profile.

Key words: Natural orifice translumenal endoscopic surgery; Humans; Clinical practice

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INTRODUCTION

Natural orifice translumenal endoscopic surgery (NOTES) in general surgery has been performed clinically for the

past 4 years now and there has been an exponential increase in reports of NOTES procedures as the concept moves from experimental to the clinical arena. Given the established safety profile of the colpotomy[1] transvaginal applications have been the first to be adopted clinically, with the proposed benefits of reduced surgical trauma and improved cosmesis compared with standard laparoscopic approaches.

There is a cautious movement in the NOTES community as we move towards pure NOTES procedures without any trans-abdominal assistance and as evidence gathers on the safety of the transgastric approach. This is in the context of numerous multi-centre, international, randomized controlled trials comparing NOTES with standard laparoscopic approaches due to report their results in the near future.

There have however been some significant issues highlighted by the introduction of NOTES into clinical practice. The flexible endoscope has proven inadequate as an operating platform to independently perform intermediate intra-abdominal surgical procedures and industry has not provided us with a viable alternative. There appears to be a hesitation from industry to enter into this market, perhaps due to the significant investment required in the context of estimated initial low volume sales, but sceptics may comment that many companies have large investments in the single-incision laparoscopy market and have chosen to focus on this in the short term.

Nevertheless the initial clinical data on morbidity and outcome appear promising and clinical trials and feasibility studies are on the whole being conducted appropriately under the scrutiny of IRB protocols at centres with suitable experience. It is important to reflect on progress frequently, particularly during the early years of the introduction of NOTES into clinical practice.

The aim of the present study is to review NOTES applications in clinical practice and assess the evidence base for each application as well as define the morbidity and peri-operative outcomes of as reported in the literature.

LITERATURE SEARCH

An electronic keyword literature search using PubMed of the US National Library of Medicine and The Cochrane Library (CENTRAL) of the Cochrane Collaboration as well as Science Direct databases was performed. Inclusion criteria were publications relating to NOTES applications in humans. For each type of operation the highest level of evidence available for clinical NOTES publications was evaluated using the Oxford Level of Evidence guide[2]. Reference lists of all identified publications were manually searched to ensure completeness. Trials were excluded from detailed examination when they were not one of the highest levels of evidence for that category of NOTES procedure.

Morbidity and short-term operative outcomes were compared with gold standard published evidence where available. Finally, registered trials recruiting patients for NOTES applications were identified through EU clinical trials, US clinical trials, UK trials and the medical research council.

The results of this review are summarised in Table 1: NOTES clinical papers.

CHOLECYSTECTOMY

Transvaginal cholecystectomy

This is the most reported organ resected *via* a NOTES procedure. There are now in excess of 26 different authors publishing their results on NOTES cholecystectomies. There is a huge range in patient number with the majority of reports either single cases or less than ten cases in a series. The majority of these cases, especially within the large, multi-centre studies were performed in a hybrid fashion with a variable amount of laparoscopic assistance.

There are 961 cases of transvaginal cholecystectomy reported in the literature with the highest level of evidence being the studies by Zorron *et al* and Lehmann *et al*[3,4] which represents level 3. In these case-controlled, international/national, multicentre studies short term morbidity was 6.67% in the smaller of the trials[3] and in the trial reported by Lehmann *et al*[4] morbidity was reported as 3.3%. This is at the very least equivalent to the 6%-12% morbidity quoted in large series in the literature for the gold standard laparoscopic cholecystectomy[5,6].

The Lehmann group consisted of an analysis of the German NOTES registry. The authors invited all surgeons performing NOTES procedures in Germany to take part on a voluntary basis to allow the monitoring and safe introduction of the technique. Although 64 different institutions registered, only 28 treatment centres entered data, perhaps introducing a degree of publication bias. Over 14 mo 551 patients were operated on using a NOTES technique, the majority were cholecystectomy, all were female and the transvaginal route was invariably used. They report an overall complication rate of 3.1% and a conversion rate of 4.9%. In this study most procedures were performed in a hybrid fashion, however they report that much of their dissection for their Hybrid-NOTES Cholecystectomies was performed through the umbilical laparoscopic port and they used a rigid endoscope in the majority of cases. An average of 1.2 abdominal trocars was used in this series.

A multitude of surgical techniques have been described in the literature. The most common surgical technique described is a hybrid approach, with umbilical laparoscopic assistance. Additionally, both rigid and dual channel flexible endoscopes have been used and between 1 and 3 abdominal trocars for laparoscopic assistance.

Numerous other authors report the use of laparoscopic assistance to dissect calots triangle and the gall bladder bed[3,7,8]. Laparoscopic clips are considered "absolutely necessary" for patient safety as the endoscopic clips are not fully occlusive[7].

Table 1 Natural orifice translumenal endoscopic surgery clinical papers

Author	Yr	Operation	No. of patients	Operative time (min)	Route of access	Hybrid/pure	Morbidity	Level of evidence
Cholecystectomy								
Marescaux[11]	2007	Cholecystectomy	1	180	Transvaginal	Pure	Nil	4
Bessler[51]	2007	Cholecystectomy	1	NA	Transvaginal	Hybrid	NA	4
Dolz[52]	2007	Cholecystectomy	1	95	Transvaginal	Hybrid	Nil	4
Zornig[53]	2007	Cholecystectomy	20	63	Transvaginal	Hybrid	Nil	3b
Forgione[7]	2007	Cholecystectomy	3	136	Transvaginal	Hybrid	Nil	3b
Zorron[54]	2007	Cholecystectomy	1	81	Transvaginal	Hybrid	Nil	4
Ramos[55]	2008	Cholecystectomy	32	38	Transvaginal	Hybrid	Nil	3b
Zornig[56]	2009	Cholecystectomy	68	51	Transvaginal	Hybrid	Douglas pouch abscess, conserv. Mx	3b
Dallemagne[15]	2009	Cholecystectomy	5	150	Transgastric	Hybrid	Nil	3b
Decarli[57]	2008	Cholecystectomy	1	85	Transvaginal	Hybrid	Nil	4
Decarli[58]	2009	Cholecystectomy	12	125.8	Transvaginal	Hybrid	Vulval lac, Nil post-op	3b
Gumbs[12]	2009	Cholecystectomy	4	209 (hybrid) 185 (pure)	Transvaginal	3 hybrid/ 1 pure	Nil	3b
Auyang[59]	2009	Cholecystectomy	1		Transgastric	Hybrid	Nil	4
Horgan[60]	2009	Cholecystectomy	1	96	Transvaginal	Hybrid	Nil	4
Seven[61]	2009	Cholecystectomy	2	130	Transvaginal	Hybrid	Nil	4
Castro-Perez[62]	2009	Cholecystectomy	7	72.4	Transvaginal	Hybrid	Nil	3b
Horgan[8]	2009	Cholecystectomy	9	114	Transvaginal	Hybrid	Nil	3b
De Sousa[13]	2009	Cholecystectomy	4	45-115	Transvaginal	Pure	Nil	3b
Navarra[63]	2009	Cholecystectomy	6	NA	Transvaginal	Hybrid	Nil	3b
Noguera[10]	2009	Cholecystectomy	15	NA	Transvaginal	Hybrid	Haematuria no intervention	3b
Noguera[64]	2009	Cholecystectomy	20	66.5	Transvaginal	Hybrid	UTI	3b
Palanivelu[65]	2009	Cholecystectomy	6	148.5	Transvaginal	Hybrid	Subhepatic collection USS drainage	3b
Pugliese[66]	2010	Cholecystectomy	18	75	Transvaginal	Hybrid	1 biliary leak, healed 7 d	3b
Zorron[3]	2010	Cholecystectomy	240	96	Transvaginal	Hybrid/pure	6.67%	3a
Zorron[3]	2010	Cholecystectomy	29	111	Transgastric	Hybrid	24.14%	3a
Lehmann[4]	2010	Cholecystectomy	488	61.9	Transvaginal	Hybrid	17 bladder/bowel injuries/ vaginal bleeding/UTI/ wound infection	3a
Appendicectomy								
Palanivelu[19]	2008	Appendicectomy	3	103.5	Transvaginal	2 hybrid/ 1 pure	Nil	4
Bernhart[20]	2008	Appendicectomy	1	NA	Transvaginal	Pure	Nil	4
Rao[22]	2008	Appendicectomy	8	NA	Transgastric	Pure	2 converted out of 10 attempted	3b
Horgan[60]	2009	Appendicectomy	1	78	Transvaginal	Hybrid	Nil	4
Horgan[60]	2009	Appendicectomy	1	150	Transgastric	Hybrid	Nil	4
Tabutsadze[21]	2009	Appendicectomy	2	82	Transvaginal	Hybrid	Nil	4
Shin[67]	2010	Appendicectomy	1	60	Transvaginal	Hybrid	Nil	4
Park[23]	2010	Appendicectomy	3	NA	Transgastric	Pure	1 converted to lap / 1 converted to open + pneumonthorax	4
Zorron[3]	2010	Appendicectomy	37	60.5	Transvaginal	Hybrid	8.10%	3a
Zorron[3]	2010	Appendicectomy	14	135.5	Transgastric	Hybrid	21.42%	3a
Lehmann[4]	2010	Appendicectomy	42	47.1	Transvaginal	41 hybrid / 1 Pure	Nil	3a
Peritonoscopy								
Gettman[36]	2007	Peritonoscopy	1	40	Transvesical	Hybrid	Nil	4
Pearl[68]	2007	Peritonoscopy	4	NA	Transgastric	Hybrid	NA	4
Hazey[33]	2008	Peritonoscopy	10	24.8	Transgastric	Hybrid	Nil	3b
Zorron[34]	2008	Peritonoscopy	1	105	Transvaginal	Pure	Nil	4
Nikfarjam[32]	2010	Peritonoscopy	9	NA	Transgastric	Hybrid	1	4
Nau[30]	2011	Peritonoscopy	130	NA	Transgastric	Hybrid	NA	3b
Memark[31]	2010	Peritonoscopy	40	19.5	Transgastric	Hybrid	Nil	3b
Zorron[3]	2010	Peritonoscopy	8	35	Transvaginal	Hybrid	Nil	3a
Zheng[35]	2011	Peritonoscopy	5	NA	Transgastric	Pure	Nil	3b
Sleeve Gastrectomy								

Ramos[28]	2008	Sleeve Gastrectomy	1	95	Transvaginal	Hybrid	Nil	4
Fischer[69]	2009	Sleeve Gastrectomy	1	NA	Transvaginal	Hybrid	NA	4
Lacy[70]	2009	Sleeve Gastrectomy	1	150	Transvaginal	Hybrid	Nil	4
Chouillard[27]	2010	Sleeve Gastrectomy	20	116	Transvaginal	Hybrid	1 pneumonia	3b
Buesing[71]	2010	Sleeve Gastrectomy	14	NA	Transvaginal	Hybrid	Nil	3a
Zorron[3]	2010	Sleeve Gastrectomy	5	NA	Transvaginal	Hybrid	NA	3a
Lehmann[4]	2010	Sleeve Gastrectomy	6	103.9	Transvaginal	Hybrid	Nil	3a
Nephrectomy								
Kaouk[45]	2009	Nephrectomy	1	420	Transvaginal	Pure	Nil	4
Zorron[3]	2010	Nephrectomy	4	NA	Transvaginal	Hybrid	NA	3a
Sigmoidectomy / Colectomy								
Lacy[38]	2008	Sigmoidectomy	1	150	Transvaginal	Hybrid	Nil	4
Zorron[3]	2010	Sigmoidectomy	12	192	Transvaginal	Hybrid	1 UTI	3a
Lehmann[4]	2010	Sigmoidectomy	14	122.6	Transvaginal	Hybrid	Nil	3a
Leroy[39]	2011	Sigmoidectomy	1	105	Transanal	Hybrid	Nil	4

NA: Not available.

Zornig *et al*[9] compared 200 case matched cholecystectomies undergoing conventional laparoscopy and hybrid NOTES. They used a 5 mm, deep umbilical port for laparoscopic dissection and clipping of the artery and duct. The operative time for the NOTES cholecystectomies was longer (52 min *vs* 35 min; $P < 0.001$) than the conventional laparoscopic operation. However, there was no difference between the groups in relation to intra/post operative complications, length of stay, consumption of analgesia or sick leave. The authors conclude, the only difference other than operative time, was that the NOTES procedure produced no visible scar. Noguera *et al*[10] 2009 performed a much smaller comparative analysis between laparoscopy and NOTES for cholecystectomies and report similar results to Zornig.

Pure NOTES procedures have been described in at least 6 cases[3,11-13]. Prof Marescaux performed a pure (other than using a 2 mm insuflator, no laparoscopic assistance was required) NOTES tranvaginal cholecystectomy, operative time was 3 h and there were no intra/post-operative complications[11]. Gumbs *et al*[12] performed a pure NOTES cholecystectomy using a 15 mm port placed transvaginally to maintain pneumoperitoneum, with an additional 5 mm port to allow for the placement of a retractor. Calot's triangle was dissected using a dual-channel endoscope, the duct and artery were clipped endoscopically with extraction transvaginally and the colpotomy was closed with absorbable sutures. Interestingly, they had to surgically modify the endoscopic clips by manually straightening the tips to ensure they were fully occlusive. De Sousa *et al*[13] report 4 pure NOTES cholecystectomies, performing the procedure with 2 endoscopes, one for insufflation and retraction and one for dissection, clipping and resection of the gall bladder. Operative time was wide ranging from 45-115 min. Similarly to Gumbs et al they report no post-operative complications, with patients discharged on day 1 or 2 of surgery. Totally NOTES cholecystectomies were found to have a significantly longer operative time compared to hybrid NOTES > 120 *vs* < 60 min respectively[3]. Although Zorron *et al*[3] in 2010 describe two techniques for pure NOTES cholecystectomies they do not report how many of their large number of operations were performed in this pure fashion. The first technique they describe employs a dual scope technique with a single channel gastroscope which is used for insufflation and retraction and a double-channel colonoscope used for dissection, endoscopic clipping and resection of the specimen, removing the need for laparoscopic assistance. The second approach to pure NOTES Zorron *et al*[3] describe, utilises a transvaginal multi-port with an insufflation device attached negating the need for a second endoscope. Dissection was once again performed with hot biopsy forceps and polypectomy snares along with transvaginal laparoscopic clips. In both cases pneumoperitoneum was aspirated transvaginally before withdrawal of the scope.

There are 15 registered trials for cholecystectomy. One of these trials represents a prospective, multi-centre randomized controlled trial comparing conventional laparoscopic cholecystectomy to NOTES cholecystectomy. This trial is supported by NOSCAR with the American Society of gastrointestinal endoscopy. The authors are recruiting from multiple centres across the United States, aiming to recruit 200 patients to randomise[14]. There are also comparative analysis between NOTES and conventional laparoscopy to add strength to the trials by Zornig and Noguera, including a cost effectiveness analysis[9,10]. Notably, there is a large multi-centre international study of NOTES cholecystectomy registered[14].

Transgastric cholecystectomy

There are 35 cases of transgastric cholecystecomy reported in the literature with the highest level of evidence being the study by Zorron *et al*[3] which represents level 3. In this case-controlled, international, multicentre study short term morbidity was 24.14%; significantly higher than the same procedure using the transvaginal route. This is greater than the 6%-12% quoted in large series in the literature for the gold standard laparoscopic cholecystectomy[5,6].

The most common surgical technique described is a

hybrid approach, using umbilical laparoscopic assistance. The 29 transgastric cholecystectomies performed by Zorron *et al*[3] used a laparoscopic port for the safe formation and closure of the gastrotomy. If the specimen was too large for the oesophagus the umbilical incision was extended to allow extraction of the gallbladder. This group performed a variable amount of the operation using laparoscopic assistance. To close the gastrotomy safely required the addition of between 1 and 3 abdominal ports. While this group reported a significantly shorter hospital stay in their transgastric cholecystectomies compared to their transvaginal cholecystectomies (38 h *vs* 46 h respectively), there was a vast difference in complications with 24.14% in the transgastric group compared to 6.67% in the transvaginal group[3].

Dallemagne *et al*[15] performed 5 transgastric cholecystectomies using laparoscopic assistance in all cases to enable safe gastrotomy and closure, exposure of the gallbladder and to clip the cystic pedicle. They report that a variable amount of laparoscopic assistance was required, with an average operative time of 150 min and no intra or post-operative complications.

APPENDICECTOMY

Transvaginal appendicectomy

This is the second most reported of the human NOTES operations performed, with over 11 different centres reporting clinical results on 113 patients. To date there are no randomised controlled trials or systematic reviews comparing NOTES appendicectomies to either open or laparoscopic appendicectomies (D'Souza clinical evidence[16] and Sodergren *et al*[17]).

There are 87 cases of transvaginal appendicectomy reported in the literature with the highest level of evidence being the studies by Zorron *et al* and Lehmann *et al*[3,4] which represents level 3. In these case-controlled, international/national, multicentre studies short term morbidity was 0%-8% compared to 4.13% quoted in large series in the literature for the gold standard laparoscopic appendicectomy or 6.39% for open appendicectomy in the same series[18].

The publication by Zorron *et al*[3] included 16 centres in 9 different countries whose NOTES protocols were approved to participate in their international, multi-centred study. They report NOTES procedures on 362 patients with an overall complication rate of 8.84%. They additionally report a wide range of procedures including right hemicolectomy, nephrectomy, hepatic cyst excision, sleeve gastrectomy, gynaecological surgery and rectosigmoidectomy. There were 51 appendicectomies in the Zorron group in total, 37 were performed transvaginally, with a reported complication rate of 8%, resulting from intra-operative bleeding from the appendiceal artery.

The most common surgical technique described is a hybrid approach, using umbilical laparoscopic assistance with a left iliac fossa port for retraction. The appendix was dissected in most cases in the large trials with endoscopic dissection using hot-biopsy forceps and a polypectomy snare. Coagulation forceps and a needleknife have also commonly been used in the dissection of the mesoappendix, with endoloops to secure the base of the appendix. The use of a dual channel endoscope is utilised, which allows the left channel to be used for traction and the right for dissection.

There are only 3 cases of pure NOTES transvaginal appendicectomies, reported by three different authors[4,19,20]. NOTES appendicectomies were found to have a significantly longer operative time compared to hybrid NOTES > 90 *vs* < 60 min respectively[3].

Palanivelu *et al*[19] performed 2 hybrid and 1 pure NOTES appendicectomies. A laparoscope was used for the first two cases to aid colpotomy and a double channel endoscope was used to retract and dissect the appendix. In one case the appendicectomy was complicated by a bleed from the appendicular artery but this was controlled endoscopically. Post-operatively 2 out of 3 patients complained of vaginal discomfort, nevertheless, all patients were discharged after 48 h. The operative time was 103.5 min. Other small studies have noted that operative time can average 78 min[21].

Interestingly Palanivelu *et al*[19] attempted to perform 6 pure NOTES appendicectomies but were only able to perform one due to technical difficulties resulting in the other 5 cases being converted to hybrid NOTES or pure laparoscopy.

There are 5 registered trials for appendicectomy, one of these is a single centre study assessing the transrectal route, from Northwestern University in the United States, aiming to recruit 10 patients. None of these are randomized controlled trials or large, multi-centre international studies[14].

Transgastric appendicectomy

There are 26 cases of transgastric appendicectomy reported in the literature with the highest level of evidence being the study by Zorron *et al*[3] which represents level 3. In this case-controlled, international, multicentre study short-term morbidity was 21.42%, compared to 4%-6% quoted in large series in the literature for the gold standard laparoscopic appendicectomy[18].

The most common surgical technique described employs a hybrid approach, with umbilical laparoscopic assistance with a 3 mm or 5 mm port. This port allows direct vision of the endoscope's entry into the abdominal cavity, to enable retraction of the appendix and to assist with closure of the gastrotomy.

Pure NOTES procedures have been described in 11 cases. Rao et al attempted 10 transgastric appendicectomies. A double-channel endoscope was employed using rat toothed forceps to retract the appendix. Dissection, as with the majority of NOTES appendicectomies, was with hot biopsy forceps, an endoloop and polypectomy snare. They used multiple endoscopic staples to close the gastrotomy. They report no infectious complications, but do report a needle-knife injury to the anterior abdominal

wall, 2 conversions to laparoscopy due to a retrocaecal appendix and one post-operative ileus[22]. Park *et al*[23] reported 3 attempts at pure NOTES with one conversion to laparoscopy and one conversion to open with a pneumothorax complicating the open case.

SLEEVE GASTRECTOMY

Transvaginal sleeve gastrectomy

Laparoscopic sleeve gastrectomy has been widely reported as a safe and improved treatment for morbid obesity [24]. More recently NOTES sleeve gastrectomy has been reported in 48 patients, invariably using a hybrid technique although the number of laparoscopic ports and assistance does vary between the studies.

The majority are single case reports performed using the transvaginal approach. Once again the Zorron and Lehmann papers represent the highest level of evidence[3,4]. However, other than using a transvaginal, hybrid approach with a rigid endoscope in the Lehmann cases there is very little additional operative detail described in either paper. In these case-controlled, national/international, multicentre studies short term morbidity was 0% compared with 12.1% quoted in the large series in the literature for the gold standard laparoscopic sleeve gastrectomy[25,26].

Chouillard *et al*[27] in 2010 reports the highest number of NOTES sleeve gastrectomies in the literature. They describe 20 cases using one or two abdominal ports. The mean operative time was 116 min. The only morbidity was one patient with pneumonia and there were no reported leaks. However, 30% were converted to more formal laparoscopic sleeve gastrectomy, most of these were in the first batch of patients suggesting a learning curve to the procedure, although no cases were converted to open.

Ramos *et al*[28] also describe 4 cases of hybrid transvaginal NOTES sleeve gastrectomy by using 3 abdominal trocars (umbilical/right upper quadrant/left upper quadrant). They report no post-operative complications and an operative time of 95 min.

At the time of writing there were no further registered trials, specifically assessing NOTES sleeve gastrectomy. Pure NOTES sleeve gastrectomy has not been described in the literature.

PERITONEOSCOPY

This has been attempted through a more varied route with transvaginal, transvesical and transgastric routes in a total of 208 cases. The indication for peritoneoscopy is wide-ranging from diagnostic in cancer patients to gastric bypass to visceral biopsy.

Transgastric peritoneoscopy

There are 198 cases of NOTES transgastric peritoneoscopy reported in the literature. Once again the Zorron and Lehmann papers represent the highest level of evidence, with no reported complications[3,4]. In comparison, Camacho *et al*[29] assessed 115 patients for pancreatic cancer staging *via* laparoscopy and then laparotomy to confirm stage/findings, reporting no complications in any of the laparoscopies.

The largest is the study by Nau *et al*[30] which included 130 patients assessed through 3 different arms. They retrospectively evaluated the bacterial load in the peritoneal cavity before and after open gastrotomy, open endoscopic gastrotomy and pure NOTES gastrotomy. They found there was no significant increase in clinical manifestations of peritoneal infection.

Other than Memark *et al*[31] who reported 40 cases of hybrid transgastric peritneoscopy, with no abscesses or anastomotic leaks but one port-site infection, the other trials involving NOTES peritoneoscopy are small ranging from 1-10 patients. Interestingly, Nikfarjam *et al*[32] report that in only one of their prospective series of 9 patients was NOTES peritoneoscopy satisfactory, with difficulty viewing the left upper quadrant. The single case where peritoneoscopy was satisfactory was achieved with entry through the greater curve.

Hazey *et al*[33] in 2008 compared transgastric NOTES peritoneoscopy to laparoscopic peritoneoscopy for pancreatic masses. They assessed differences in operative findings, operative times and clinical course in 10 patients. Laparoscopy was faster (12.3 min *vs* 24.8 min) than NOTES and in 9 out of 10 patients the decision to proceed with laparotomy was confirmed by NOTES as with laparoscopy.

Transvaginal peritoneoscopy

There are 9 reported cases of transvaginal peritoneoscopy, including one case report and a small series of 8 by Zorron *et al*[3,34]. The series does not describe operative details, other than an operative time of 35 min and report no complications.

Pure NOTES peritoneoscopy has been described by Zorron *et al*[34] who report 1 transvaginal case and Zheng *et al*[35] who report 5 transgastric cases. Neither author report any complication from their method of peritoneoscopy and operative time was reported at 105 min[34].

Transvesical peritoneoscopy

There is one reported case in the literature by Gettman and Blute in 2007[36]. They present a case report of a 56 year old gentleman who underwent robotic prostatectomy for cancer. The case proceeded in the usual fashion with the abdominal laparoscopic ports inserted. Under laparoscopic guidance a portal was created in the bladder and a flexible ureteroscope was used to view all intraperitoneal structures. The patient went on to have a successful prostatectomy, the cystotomy was closed with vicryl and the patient suffered no complications.

At the time of writing there were two small registered trials, specifically assessing NOTES peritoneoscopy. One is a 10 participant trial by ethicon and the second is from Ohio State University comparing laparoscopy to

NOTES peritoneoscopy in 40 patients[14].

SIGMOIDECTOMY/RECTAL EXCISION/ HEMICOLECTOMY

Transvaginal sigmoidectomy

There are 27 cases of transvaginal sigmoidectomy reported in the literature with the highest level of evidence being the studies by Zorron *et al* and Lehmann *et al*[3,4] which represents level 3. In these studies short term morbidity was 0%-10% compared to the 11.5% quoted in large series in the literature for the gold standard sigmoidectomy[37].

There are two papers to highlight here, one case report of a single patient undergoing a sigmoidectomy and the large Lehmann trial. The single case report is by Lacy *et al*[38] who report a hybrid NOTES sigmoidectomy in a 78 year old female for sigmoid adenocarcinoma. While performing the dissection and stapling of the inferior mesenteric vessels and upper rectum endoscopically the colonic resection was performed extracorporeally with an intra-abdominal endoscopically assisted stapled anastomosis. The outcome was a successful resection, no complications and discharge on the fourth post-operative day.

The German Registry paper reports 3 cases of hybrid NOTES sigmoidectomy for diverticulitis and 11 cases of colonic resection for which there is no indication and we have very little published detail on the operative technique. They do however, report no complications in any of their cases[4]. Moreover, Zorron *et al*[3] present 12 cases of rectosigmoidectomy, once again with no operative details and just one case complicated by a urinary tract infection.

More recently Leroy *et al*[39] in 2011 has reported a hybrid sigmoidectomy with transanal extraction of the specimen. They took 105 min to perform the procedure and report no complications. There are other reports of similar work, where the majority of the procedure is performed laparoscopically and the natural orifice is used simply for extraction of the specimen. This may be classed as natural orifice specimen extraction rather than NOTES[40].

Rectal excision

The first reported human case of a hybrid NOTES rectal cancer (CA) transanal excision was by Sylla *et al*[41]. They used TEM and laparoscopic assistance to resect a rectal CA. Operative time was under five hours, the tumour was resected with negative margins and an intact mesorectum. The patient was discharged on the fifth post-operative day with no complications recorded.

Tarantino *et al*[42] present 40 patients who underwent a transvaginal hybrid NOTES anterior resection for diverticulitis. They report 4 conversions to minilaparotomy and 2 conversions to laparotomy, with 5% major morbidity and 25% minor morbidity. However the operative procedure was performed almost entirely laparoscopically, with the transvaginal access to allow extraction and resection of the distal segment.

Zorron[43] in 2011 report 5 cases of transcolonic endoscopic NOTES TME with laparoscopic assistance. They performed the mesorectal dissection in a down to up fashion, the opposite to the laparoscopic technique. Their operative time was 350-360 min, one conversion and one complication of bilateral foot parasthesia which resolved spontaneously after 10 d.

Other NOTES colorectal resections include a right hemicolectomy by Burghardt who performed a laparoscopic procedure with transvaginal extraction of the specimen with no intra/post-operative complications[44]. There are no reported cases of pure NOTES colonic resections. There is 1 registered trial for NOTES rectosigmoidectomy from the University of Leuven, Belgium[14]. This trial represents a randomized controlled trial comparing laparoscopic rectosigmoid resection with a hybrid NOTES procedure with laparoscopic assistance but specimen removal through the colon rather than extending the umbilical incision for retrieval.

NEPHRECTOMY

Transvaginal nephrectomy

Zorron *et al*[3] report 4 transvaginal NOTES nephrectomies in their group but fail to give any further operative details, other than an operative time of 170 min. However, they did report a complication in one of their nephrectomies, of subcutaneous and mediastinal surgical emphysema which was managed conservatively.

Kaouk *et al*[45] 2009 present the first NOTES transvaginal nephrectomy. This was performed in a 57 year old woman for an atrophic right kidney. Although all of the dissection and resection of the procedure was performed in a pure NOTES fashion the authors used an umbilical port for direct vision when placing the vaginal port, necessitated by dense adhesions from a previous hysterectomy and for retraction of the colon. The procedure took 307 min, there were no complications and the patient was discharged within 24 h. Of note the visual analogue pain score during the admission was 5.6 and on day two post-operatively was 1 out of 10.

To date there are no reported pure NOTES or transgastric NOTES nephrectomies. In addition there are no registered trials specifically assessing NOTES nephrectomy.

LIVER BIOPSY/RESECTION

Transvaginal/gastric liver biopsy or resection

Lehmann *et al*[4] report 5 cases of liver resection with minimal detail but no reported complications. Noguera *et al*[46] in 2008 report a NOTES transvaginal liver resection including cholecystectomy. They used two abdominal ports for retraction and laparoscopic assistance. They removed the specimen transvaginally, operative time was 110 minutes and they reported no complications, with a short hospital stay (48 h).

Steele *et al*[47] performed a hybrid transgastric peri-

toneoscopy and liver biopsy at the time of performing laparoscopic gastric bypass surgery. They achieved an adequate biopsy and good visualisation.

There are 3 reported cases of pure NOTES liver biopsies by Rao *et al*[22]. They performed pure NOTES transgastric peritoneoscopy and liver biopsy. The peritoneoscopy was performed using retro-flexion of the endoscope, aided by patient positioning on the table to move the bowel out of sight as necessary. The biopsy was performed using jumbo biopsy forceps and haemostasis was achieved using hot biopsy forceps. Endoscopic clips were used to close the gastrotomy. The authors report that the gastrotomy spontaneously closes once the balloon is removed and it becomes difficult to locate the defect.

To date there are no new registered trials which are specifically assessing NOTES liver biopsies or liver resections.

SPLENECTOMY

Transvaginal Splenectomy

Targarona *et al*[48] in 2009 is the only author to date to publish NOTES splenectomies. They report two transvaginal, hybrid NOTES splenectomies, using three laparoscopic ports. Mobilisation of the spleen was performed transabdominally, the pedicle was stapled transvaginally with laparoscopic guidance and the specimen extracted through the vagina. Operative time was 180 min and there were no reported intra or post-operative complications.

To date there are no pure NOTES splenectomies reported and no new registered trials which are specifically assessing NOTES splenectomies.

DISCUSSION

This review represents an up to date summary of human NOTES procedures reported in the literature. It is not inclusive of all human NOTES procedures, but does include those trials demonstrating the highest level of evidence for each application. Evidence of surgical outcome and morbidity for all organs targeted by NOTES has been evaluated.

Overall, considering the volume of procedures performed, the multitude of techniques used, the variety of centres/countries performing NOTES and even different specialties performing the procedures the morbidity and mortality appears acceptable, often comparing favourably to the gold standard techniques. The most commonly performed application is transvaginal cholecystectomy with acceptable reported outcomes and complications reported through trials producing level 3 evidence.

There are however some reports of high morbidity for certain applications, almost exclusively related to the transgastric approach. The large number of cases performed in the multicentre studies has enabled us to broadly compare the transvaginal and transgastric techniques[3,4]. The main issue relating to transgastric (and transcolonic) NOTES is closure of the enterotomy. Although several methods have been proposed, to date there is no robust evidence for a reliable method of closure of the gastrotomy[49].

As a product of the concern over the associated morbidity and safety of transgastric NOTES the majority of human NOTES cases have been performed in females via the transvaginal route which has a proven safety profile[1]. This raises the issue of acceptability to the general public, which is an area which has not been extensively explored. Strickland *et al*[50] surveyed 300 women asking their views on NOTES. Interestingly, they report that three quarters of the women they questioned were either neutral or unhappy about the prospect of NOTES. Most of the concern was in relation to sexual function post transvaginal surgery and only a minority were concerned about the cosmetic effect of conventional laparoscopic surgery. Although the sample size was small in this study and just one un-validated questionnaire was used, it does raise some important questions. If the procedures are deemed unacceptable to the general public then should we pursue the advancement of this technique with such vigour?

The true benefits of NOTES, such as improved cosmesis, reduced hospital stay as a proxy marker of recovery, reduced incidence of hernia and post-operative pain may not be well demonstrated until it is practised in a pure fashion. Even then, due to the low morbidity and complications associated with the laparoscopic approach for many procedures, randomized controlled trials of very large numbers may be required to prove any difference between the techniques.

What is certain is that available technology is limiting the current applicability of NOTES and whilst we wait for a better toolbox hybrid procedures will be necessary to ensure patient safety. It may be that hybrid NOTES procedures are the optimal for certain applications and patient groups. Ultimately NOTES is likely to complement laparoscopy for specific patient groups and procedures and as technology evolves specific NOTES procedures will enter mainstream clinical practice. As a result of this we have not yet identified a "target" procedure from which maximum patient benefit can be demonstrated using the NOTES technique. Bariatric surgery seems promising for NOTES approaches and the next few years are not only crucial in the development of NOTES as a concept but have the potential to revolutionise minimally invasive surgery with the rapid potential for technological innovation and further fusion of the boundaries between laparoscopy and endoscopy.

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TOPIC HIGHLIGHT

Eduardo Redondo-Cerezo, PhD, Professor, *Series Editor*

Diagnosis of boundary in early gastric cancer

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Abstract

Endoscopic submucosal dissection (ESD) is an advanced therapeutic endoscopic technique, which allowsresection of larger superficial tumors in the esophagus, stomach, and colon. Precise diagnosis of the boundary between tumor and the non-tumorous surrounding portion is especially important before starting ESD, because too much resection can potentially take more time and can induce a higher complication rate, while too little resection can result in a non-curative resection. The boundary diagnosis is often difficult for early gastric cancer, mainly because of the underlying condition of chronic gastritis. Due to recent developments in endoscopy, including magnified endoscopy and narrow band endoscopy, the boundary diagnosis is becoming easy and more accurate.We have also applied magnified endoscopy combined with narrow band imaging to fresh specimens immediately after resection using thetiling method and XY stage.

Key words: Boundary diagnosis; Early gastric cancer; Endoscopic submucosal dissection; Magnified endoscopy; Narrow band imaging; Tiling method

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INTRODUCTION

Duringendoscopic mucosal resection (EMR) of early gastric cancer, large lesions were previously segmentally resected due to limitation of size, which led to insufficient pathological evaluation. With the recent development of endoscopic submucosal dissection (ESD), this limitation has been overcome and en bloc resection is now possible, and the importance of diagnosing the range of lateral advancement has increased. In this report, diagnosis of the boundary in the era of ESD is assessed.

BOUNDARY DIAGNOSIS BY CONVENTIONAL ENDOSCOPY (WHITE LIGHT ENDOSCOPY)

The advent of new techniques makes boundary diagnosis much easier (discussed below). Nevertheless, the conventional endoscopic method using white light is still important and requires adequate steps in order to reach a more accurate diagnosis. The procedure begins with identifying lesions by removing mucus. Since gastric mucus is viscous, pretreatment with pronase is used to degrade the mucus, and molecules are cleaved into short fragments and are easily washed out by flushing with water. It is also important to perform this procedure atraumaticallyas lesions are hemorrhagic in many cases. To determine the boundary, the mucosa is carefully

observed, paying attention to the following points: (1) surface morphology, such as protrusion and concavity; (2) changes in color, such as reddening and paleness; and (3) differences from the background mucosa. For observation of the surface morphology, small differences in the height can be observed by slightly deaerating, and it is useful to adjust the air volume and observe the region from several directions (Figures 1A-B and 2A).

BOUNDARY DIAGNOSIS BY IMAGE-ENHANCED ENDOSCOPY

Chromoendoscopy

Chromoendoscopy is the collective name for the test methods in which the digestive tract mucosa is closely observed following the spraying of a dye. There are various methods depending of the mechanismand include a contrast method in which unevenness is emphasized using indigo carmine, a staining method in which biological tissue is stained with toluidine blue, a dye reaction method utilizing specific reactions of dyes, such as Congo red, and a fluorescence method in which a fluorescence-sensitive dye, such as acridine orange, is injected into the mucosa and fluorescence is observed. Here, the frequently used indigo carmine and acetic acid methods are outlined.

Indigo carmine is a blue/dark blue liquid. It is retained around concave and protruding regions and emphasizes unevenness, facilitating clear observation of the surface morphology of lesions. Observation from several directions and adjustment of the air volume are useful, but these should be performed after sufficient observation because differences in color become unclear after spraying the dye (Figure 1C).

In the acetic acid method, superficial mucus shows a reversible reaction, whitish turbidity, when sprayed with 1.5% acetic acid. When the mucus volume in tumor regions is smaller than that in non-tumorous regions, the boundary may be clearly visualized based on the color change. In addition, whitish turbidity emphasizes the mucosal surface, in which the boundary may be clarified by combining magnifying narrow band imaging (NBI) described below or indigo carmine spraying because the mucus is fixed[1-4] (Figure 2C-D).

Optical digital endoscopy

NBI. The central wavelength is optimized to 415 and 540 nm as light is strongly absorbed by blood and strongly reflected/scattered at the mucosa, respectively, and the spectrum width is narrowed to enhance micro blood vessels and micro patterns on the mucosal surface. Compared to other image-enhancing techniques, this is superior for obtaining specifically clear images in the short-wavelength spectrum. The usefulness of NBI and FICE described below for diagnosing the boundary of lesions is increased by combining with magnifying endoscopic observation[5-9] (Figure 2B).

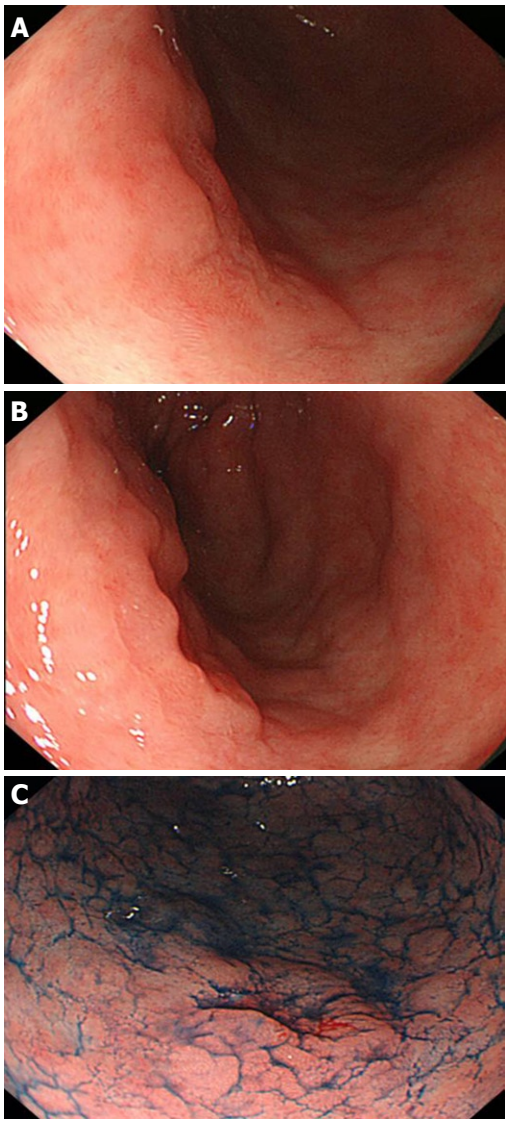

Figure 1 Endoscopic image of superficial gastric cancer. A: White light (WL) endoscopy; B: WL endoscopy at deaeration; C: WL endoscopy after indigocarmine spraying.

Digital endoscopy

Flexible spectral imaging color enhancement (FICE). In this technique, a specific observation wavelength is set based on conventional endoscopic images to enhance and process images for visualization. FICE has flexibility: information collected under white light can be analyzed in various spectral combinations, and relatively bright images can be observed depending on the wavelength setting, showing differentcharacteristics tothose of NBI[10-12].

BOUNDARY DIAGNOSIS BY MAGNIFIED ENDOSCOPY

Using a magnifying electronic endoscope, up to about 100-times-magnified images are optically displayed on a 14-inch monitor, and micro mucosal patterns and micro blood vessels can be observed in detail. The diameter

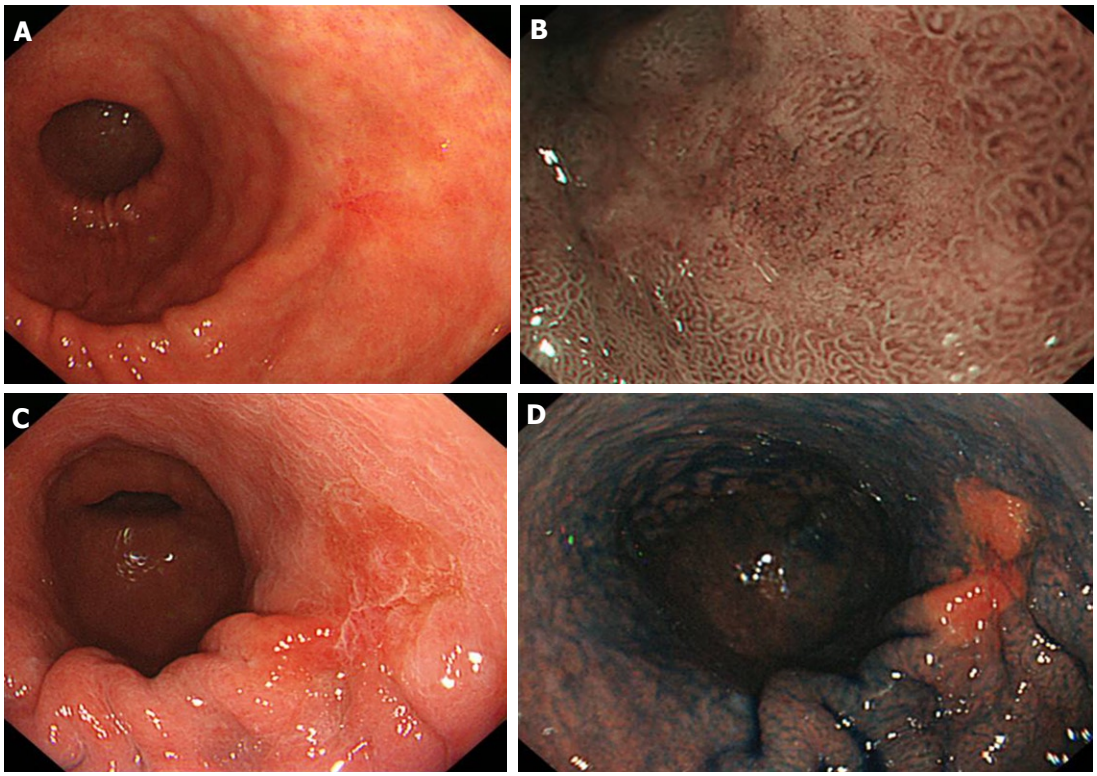

Figure 2 Endoscopic image of superficial gastric cancer. A: White light (WL) endoscopy; B: Magnifying endoscopy combined with narrow band imaging; C: WL endoscopy after acetic acidspraying; D: WL endoscopy after the acetic acid plus indigocarminemethod.

was initially large because the endoscope is equipped with a zoom lens at the tip, but recent technical progress has reduced the diameter close to that of a conventional scope. Combining other techniques with magnifying endoscopy enables theidentification of the boundary of lesions with an unclear margin of advancement undetectable using a single method.

BIOPSY OF THE SURROUNDING REGION

Although determination of the boundary by biopsy alone should be avoided, the boundary is still unclear even after sufficient observation in some lesions, and biopsy of the surrounding region may be useful in such cases.

PREPARATION OF A COMPOSITE OF MAGNIFIED IMAGES BY TILING

It is important to confirm whether the preoperative diagnosis of the range is correct by analyzing endoscopically resected specimens. When the diagnosis is incorrect, the correct range can be identified by investigating the reason for the failure. In addition, clarification of the conditions leading to an incorrect diagnosis of the range facilitates careful investigation in combination with other methods. We developed a method to prepare a composite of magnified images by tiling in which the mucosal surface of the excised specimen can be closely observed. In this unique method, a magnifying endoscope was fixed, the entire specimen was magnified, and images were segmentally acquired and arranged in a tile pattern to prepare a composite. Unlike the current observation under a stereoscopic microscope, resected lesions can be observed and imaged in a condition very close to that of endoscopic observation in the body, and magnified images of the entire lesion can be acquired under conventional light as well as NBI. We investigated whether an accurate range could be identified using this method (Table 1).

SUBJECTS AND METHODS

Seventeen lesions of differentiated gastric adenocarcinoma were imaged employing this method following ESD at our department in April-September 2010. GIF-H260Z (Olympus) was attached to a device with a modified electric XY stage, and the whole excised lesion which was immersed in water was segmentally imaged at the highest magnification employing NBI (Figure 3A). The acquired images were pasted together into a composite by tiling using a computer program (Figure 3B). After the range of the lesion was assumed by drawing a demarcation line based on the mucosal surface structure and vascular atypia, the range was compared with mapping in the pathological preparation referring to the marking to confirm the accuracy of the assumed range. The accuracy was evaluated by 3-step grading as follows: the demarcation line was perceived, O; perceived, although partially unclear, Δ; completely unclear, ×.

Table 1 Endoscopic imaging-object-oriented classification[13]

Conventional (white light)	Image-enhancing	Magnifying	Microscopic	Tomographic
	Digital Contrast method Delineation-enhanced method	Optical	Optical	Endoscopic ultrasonography
	Optical-digital Autofluorescence Narrow band light Infrared light	Digital	Confocal	Optical coherence tomography
	Chromoendoscopy Absorbed dye Contrast dye			

Table 2 The range of the perceived lesion

	Tumor size (mm)	Histological type	Macroscopic type
Case 1	8 × 4	tub1> tub2	0-Ⅱc
Case 2	16 × 12	tub1	0-Ⅱc
Case 3	15 × 7	tub1	0-Ⅱc

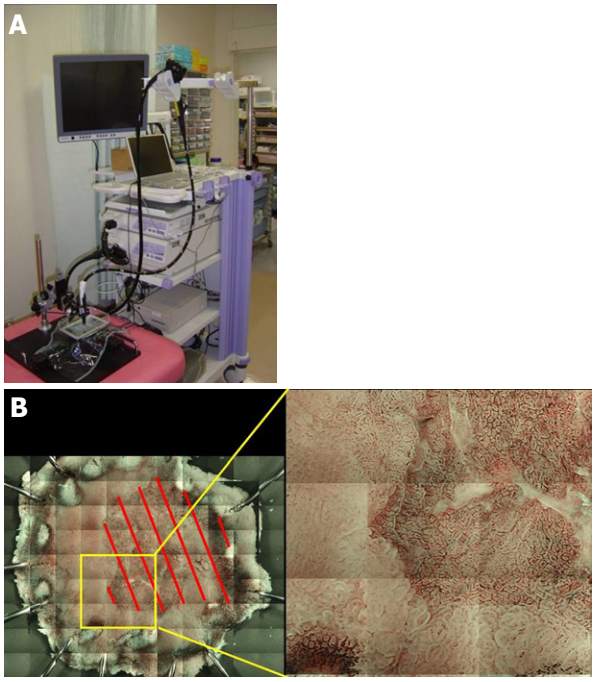

Figure 3 Tiling method. A: Electric XY stage attached to the endoscopy; B: Composite image of magnified images by tiling.

CONCLUSION

The lesions were tumors with a diameter of 8-43 mm (mean 19 mm). The histologic type was Tub1 in 11 lesions, Tub1+Tub2 in 3, Pap > Tub1 in 1, and Tub2 > por2 in 1. The macroscopic type was 0-Ⅱc in 9 lesions, 0-Ⅲa+LLc in 2, 0-Iia in 2, 0-Ⅱb in 2, 0-I in 1, and 0-I+Ⅱa+Ⅱc in 1. The accuracy of the assumed range was ○ in 14, Δ in 3, and × in 0.

An example of the range perceived is shown in Figure 4. Indigo carmine emphasized an approximately 15-mm

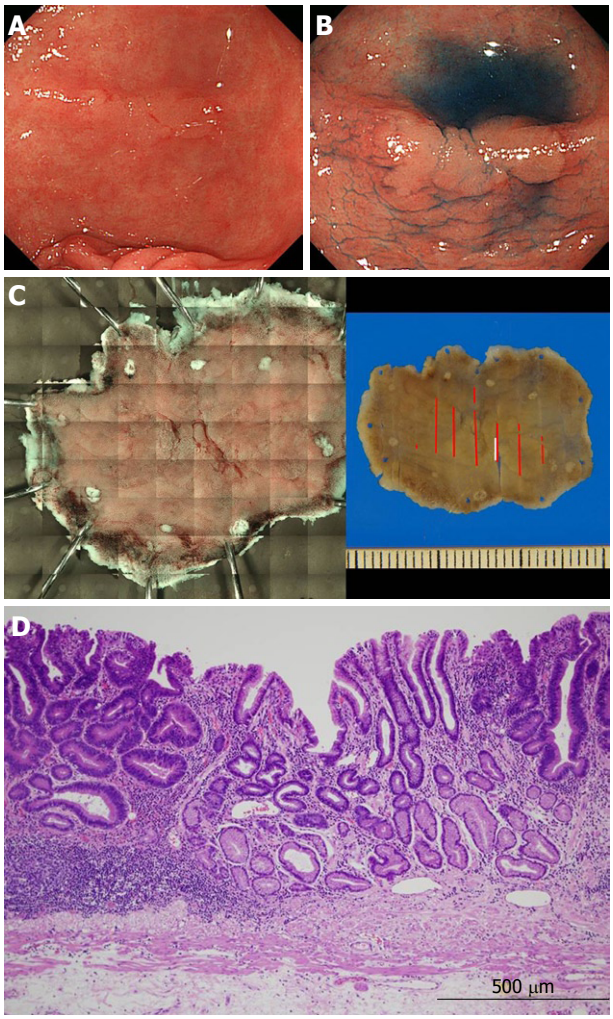

Figure 4 A case with clear boundaries. A: White light (WL) endoscopy; B: WL endoscopy after indigocarmine spraying; C: Comparison of tiling and specimen; D:Histopathological findings showed adenocarcinoma, consistent with gastric cancer (hematoxylin and eosin).

protruding lesion on the lesser curvature side of the stomach antrum. When the specimen excised by ESD was compared with the photograph prepared by the tiling method, the range of the perceived lesion was consistent with the histopathological range. The range was partially unclear in 3 cases. The details of these are presented in Table 2. All were concave lesions with a relatively small tumor diameter. One of these lesions is shown in Figure 5. This was a 10-mm concave lesion in the anterior wall of the stomachantrum, and the concave surface was perceived using indigo carmine.

When the photograph of the specimen resected by ESD was prepared employing the tiling method, the assumed range was mostly consistent with the histopathol ogicalrange,however, a partially unclear region was present. When the region difficult to perceive endoscopicallywas investigated in the pathological preparation, the cancerous gland duct was present only in the deep layer of the lamina propria mucosae, and the superficial layer was covered with non-tumorous epithelium, suggesting that the lesion was difficult to perceive because of poor

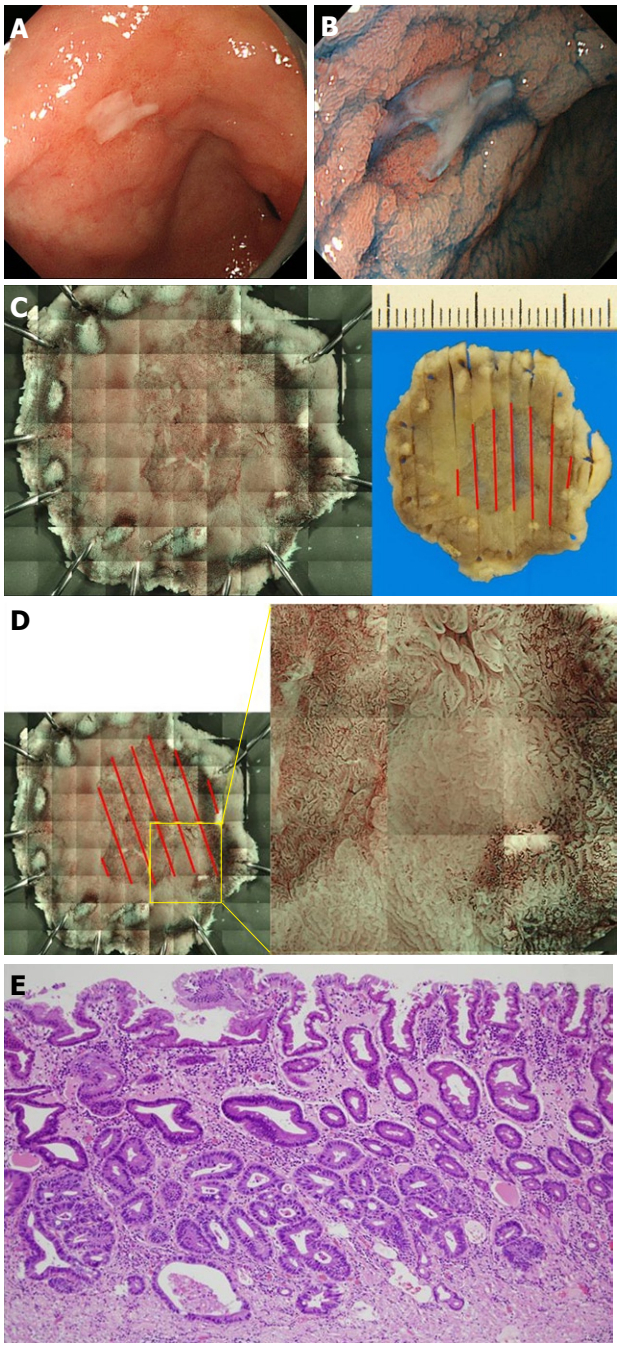

Figure 5 A case with partially unclear boundaries. A: White light (WL) endoscopy; B: WL endoscopy after indigocarmine spraying; C: Comparison of tiling and specimen; D: Preparation of composite of magnified images by tiling; E: Cancerous gland ducts are observed only in the deep layer of the lamina propria mucosae and the superficial layer is covered with non-tumorous epithelium.

atypia. The lesions were divided into those with a tumor diameter smaller and greater than the median (17 mm) and compared using Fisher's exact test. The *P*-value was 0.08, showing no significant difference, but there may have been a tendency for significance.

In conclusion, the tiling method was capable of stably preparing clear, magnified NBI images of entire resected lesions with a small to relatively large size, and enabled sufficient evaluation of the demarcation lines, leading to accurate identification of the range in most cases. The identification of the range may be difficult in cases with cancerous gland ducts unexposed to the superficial layer. With the spread of ESD, its indication has expanded, but stump-positive cases have also increased, although the number of these cases was small. It is necessary to acquire conventional observation skills and combine various methods to make accurate diagnoses of the boundary.

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ORIGINAL ARTICLE

Diazepam during endoscopic submucosal dissection of gastric epithelial neoplasias

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Abstract

AIM: To investigate risk factors and adverse events related to high-dose diazepam administration during endoscopic submucosal dissection for gastric neoplasias.

METHODS: Between February 2002 and December 2009, a total of 286 patients with gastric epithelial neoplasia underwent endoscopic submucosal dissection in our hospital. To achieve moderate sedation, 5-7.5 mg of diazepam was administered intravenously by non-anesthesiologists. Intermittent additional administration of 2.5-5 mg diazepam was performed if uncontrollable body movement of the patient was observed. All patients were classified into groups based on the required diazepam dose: low-dose ($\leqslant$ 17.5 mg, n = 252) and high-dose (> 17.5 mg, n = 79).

RESULTS: Differences between the low- and high-dose diazepam groups were observed in lifetime alcohol consumption (0.30 ± 0.48 *vs* 0.44 ± 0.52 tons, P = 0.032), body weight (58.4 ± 10.3 *vs* 62.0 ± 9.9 kg, P = 0.006), tumor size (15 ± 10 *vs* 23 ± 18 mm, P < 0.001), lesion location (P < 0.001) and the presence of ulcerative findings (14/238 *vs* 18/61, P < 0.001). Multivariate analysis identified all five variables as independently related to required diazepam dosage. In terms of adverse reactions to diazepam administration, paradoxical excitement was significantly more frequent in the high-dose diazepam group (P < 0.001).

CONCLUSION: Intermittent administration of diazepam enabled safe completion of gastric endoscopic submucosal dissection except in patients who were alcohol abusers or obese, or who showed complicated lesions.

Key words: Diazepam; Endoscopic submucosal dissection; Gastric epithelial neoplasias; Moderate sedation; Non-anesthesiologists

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Moribata K, Shingaki N, Deguchi H, Ueda K, Inoue I, Tamai H, Kato J, Fujishiro M, Ichinose M. Diazepam during endoscopic submucosal dissection of gastric epithelial neoplasias. *World J Gastrointest Endosc* 2012; 4(3): 80-86 Available from: URL: http://www.wjgnet.com/1948-5190/full/v4/i3/80.htm DOI: http://dx.doi.org/10.4253/wjge.v4.i3.80

INTRODUCTION

Endoscopic submucosal dissection (ESD) is a novel and minimally invasive procedure for the treatment of gastric epithelial neoplasia. As this technique permits en bloc resection of lesions, ESD has the advantages of enabling accurate pathological assessment and reducing the risk of local recurrence[1]. However, in comparison to conventional endoscopic mucosal resection (EMR), ESD requires a high level of endoscopic competence and a longer resection time[2-4]. In addition, many cases of early gastric cancer occur in elderly patients, who also display increased sensitivity to sedatives and a higher risk of adverse reactions, including respiratory and cardiovascular depression[5]. Suitable sedatives that do not cause complications and permit safe completion of ESD thus need to be identified.

The American Society of Anesthesiologists (ASA) classifies the degree of sedation into four levels: minimal sedation; moderate or conscious sedation; deep sedation; and general anesthesia[6]. Given that deep sedation or even general anesthesia can be achieved with propofol, the ASA suggests that care must be taken even if aiming for moderate sedation[6]. In addition, due to the narrow therapeutic window[7-9], the American Society for Gastrointestinal Endoscopy has recommended the presence of trained personnel dedicated to the administration of propofol[10]. To date, the safety and efficacy of sedation using propofol have been reported in esophagogastroduodenoscopy, colonoscopy, endoscopic ultrasonography and endoscopic retrograde cholangiopancreatography[11-15]. In contrast, due to the risk of cardiorespiratory complications, particularly in the elderly, the Japan Gastroenterological Endoscopy Society does not recommend sedation using propofol for endoscopic procedures. Thus, there is an in-principle requirement in Japan that propofol be administered by an anesthesiologist. As a result, not many institutions use propofol for sedation during ESD[16,17].

Of the available sedatives, benzodiazepines are generally considered to have a broad safety margin as they do not activate the gamma-aminobutyric acid $(GABA)_A$ receptor in the absence of endogenous GABA[18]. Diazepam is the least potent injectable benzodiazepine sedative, with a long history of clinical use, even by non-anesthesiologists. Moreover, unlike in the case of propofol administration, if a patient falls into deep sedation while being treated with diazepam, a pharmacological antagonist (flumazenil) can be administered to counter this effect[19,20]. Fujishiro *et al*[21] reported that, in principle, ESD for esophageal squamous cell neoplasms could be performed with the patient under conscious sedation induced by intermittent administration of diazepam and pentazocine. However, administration methods have yet to be clearly established for safe and effective sedative use during the gastric ESD procedure.

The objectives in this retrospective study were to evaluate variables relating to the diazepam dosage during ESD for gastric epithelial neoplasia and to investigate the characteristics and adverse events of patients administered high-dose diazepam.

MATERIALS AND METHODS

Patients

Between February 2002 and December 2009, we performed ESD for 446 gastric epithelial neoplastic lesions in 342 consecutive patients treated at Wakayama Medical University Hospital. ESD was indicated for patients with adenomas suspected of being malignant on the basis of endoscopic findings or biopsy. In addition, ESD was indicated for patients with early gastric cancers that were considered to have a nominal risk of lymph node metastasis according to the criteria of Gotoda *et al*[22], excluding undifferentiated cancers. For this study, we retrospectively analyzed ESDs that had been performed for 331 lesions in 286 patients (mean age, 69.5 years; range, 42-90 years). Excluded lesions comprised 77 cases for which multiple lesions had been simultaneously dissected by ESD, 26 cases for which diazepam had not been administered, 7 lesions in which other investigations had been carried out, and 7 lesions for which the intraoperative records were unclear (with an overlap of 2 lesions). All patients underwent blood tests, chest X-rays and electrocardiographic testing before treatment. ESD was indicated for patients with an ASA classification of 1-3[23]. This study was approved by the ethics committee of Wakayama Medical University, and all patients provided written informed consent prior to undergoing ESD.

ESD procedures

ESD was performed by one of four experienced therapeutic endoscopists, each of whom had performed ESD for more than 50 cases of early gastric cancer or gastric adenoma. We predominantly used a flex electrosurgical knife (KD-630L; Olympus, Tokyo, Japan)[2,24], along with a hook knife (KD-620LR; Olympus) when necessary[25]. Hemostatic forceps (HDB2422W; Pentax, Tokyo, Japan)[26-28] were used to reduce bleeding during ESD.

Diazepam administration

We aimed to achieve moderate sedation during ESD. For introduction, we intravenously administered diazepam (Cercine®; Takeda Pharmaceutical, Osaka, Japan) at 5-7.5 mg/body (5 mg/body for patients $\geqslant$ 75 years old or weighing $\leqslant$ 50 kg) prior to insertion of the endoscope; in principle, administration of diazepam was continued

up to 10 mg during ESD. When the sedative effect of 10 mg diazepam was judged sufficient, administration of the drug was continued without any change, and additional administration was performed in intermittent doses of 2.5-5 mg/body each, only when uncontrollable body movement was observed (maximal dose: 40 mg). When the sedative effect of 10 mg diazepam was judged to be insufficient and patient distress was considered great, diazepam was switched to midazolam (Dormicum®; Astellas Pharmaceutical, Tokyo, Japan) for rescue, administered intermittently at 1-2 mg/body. Intermittent sedative administration was performed by non-anesthesiologists (i.e., gastroenterologists) at the direction of the operator. For the purposes of pain relief, 15 mg of pentazocine (Sosegon®; Astellas Pharmaceutical) was administered intramuscularly to all patients at the start of ESD. When the level of anesthesia reached deep sedation, flumazenil (Anexate®; Astellas Pharmaceutical) was administered as deemed necessary.

Patient monitoring

Blood pressure, heart rate, electrocardiography (ECG), and peripheral oxygen saturation (SpO_2) were monitored during the procedure. Blood pressure was measured at 5-min intervals, while heart rate, ECG tracing and SpO_2 were measured continuously. Supplementary oxygen was administered to patients with SpO_2 below 90%. Administered dosages of sedatives and analgesics, all adverse events (such as decreases in SpO_2 below 90% and blood pressure below 90 mmHg), and uncontrollable body movements were recorded by trained nurses.

Patients were instructed to rest in bed for 3 h following ESD, and to remain under strict observation until the next morning. All ESD procedures were performed on an inpatient basis, and patients were discharged within 10 days after ESD if no problems were encountered.

Parameters assessed

Since several reports have indicated that it is advisable that ESD requiring around 1.5 h or more should be carried out under general anesthesia[21], patients were stratified into two groups according to procedure time (≤ 1.5 h or > 1.5 h) and then compared in terms of the following variables: age; sex; lifetime alcohol consumption; smoking habit; body weight (BW); tumor size (maximal diameter of the lesion); location (upper-third, middle-third, or lower-third of the stomach); gross morphological type (0-Ⅰ/Ⅱa, 0-Ⅱb/Ⅱc or combined type); tumor depth (mucosal or submucosal tumor); histological type (cancer or adenoma); ulcerative findings in the submucosal layer; and diazepam dosage.

Patients were also stratified into two groups according to diazepam dose: low-dose diazepam (≤ 17.5 mg, n = 252) and high-dose diazepam (> 17.5 mg, n = 79). These two groups were then compared in terms of age, sex, lifetime alcohol consumption, smoking habit, BW, use of anxiolytic agents, ASA classification, comorbidities (hypertension, diabetes mellitus, heart disease, respiratory disease, chronic renal failure, or liver cirrhosis), tumor size, tumor location, gross morphological type, tumor depth, histological type, ulcerative findings, type of resection (en bloc or piecemeal), postoperative bleeding, perforation, use of midazolam, and sedative-related adverse events such as oxygen desaturation (SpO_2 below 90%), hypotension (blood pressure below 90 mmHg), delayed awakening and paradoxical excitement.

Statistical analysis

Univariate analysis was performed using an unpaired t-test for numerical data and Fisher's exact test or the chi-squared test for categorical data. Variables that differed significantly between groups in univariate analysis were then subjected to multivariate analysis using a logistic regression model. All tests were two-sided, with values of $P < 0.05$ being considered statistically significant. All analyses were performed using SPSS software (SPSS, Chicago, IL, United States).

RESULTS

Comparison of clinicopathological features according to procedure time

The outcome of univariate analyses comparing variables according to the ESD procedure time (i.e., ≤ 1.5 h *vs* > 1.5 h) is outlined in Table 1. Significant differences were found between the two groups in relation to tumor size, location, ulcerative findings and diazepam dosage ($P < 0.001$, respectively). Specifically, mean diazepam dosage among patients with an ESD procedure time of > 1.5 h was 17.5 mg.

Comparison of clinicopathological features according to diazepam dose

Based on the above results, patients were divided into a low-dose (≤ 17.5 mg) diazepam group and a high-dose (> 17.5 mg) diazepam group. Results of univariate analyses of patient variables in relation to diazepam dosage are shown in Table 2. Significant differences in lifetime alcohol consumption and BW ($P = 0.032$ and $P = 0.006$, respectively) were found between the dosage groups. The results of univariate analyses for clinicopathological features of the lesion and clinical outcomes in relation to diazepam dosage are shown in Table 3. Significant differences in tumor size, location, ulcerative findings and resection style ($P = 0.001$ for each) were found between the two dosage groups.

Multivariate logistic analysis was performed including lifetime alcohol consumption, BW, tumor size, location and ulcerative findings in the prediction of the diazepam dosage. Each variable included in the model was shown to be independently associated with a need for high diazepam dosage (Table 4).

Patients were stratified into two groups on the basis of lifetime alcohol consumption (alcohol), using > 0.4 and ≤ 0.4 t as the strata. Finally, a second stratification was performed on the basis of BWs of > 60 kg and ≤

Table 1 Clinicopathological features of study subjects with a low (≤ 1.5 h) or high (> 1.5 h) procedure time

Variables	Procedure time ≤ 1.5 h (*n* = 180)	Procedure time > 1.5 h (*n* = 151)	*P* value
Age (yr) (mean ± SD)	69.9 ± 9.1	69.0 ± 9.6	NS
Sex (male/female)	136/44	125/26	NS
Lifetime alcohol consumption (t) (mean ± SD)	0.30 ± 0.50	0.37 ± 0.48	NS
Smoking habit (Brinkman index) (mean ± SD)	655.1 ± 777.7	563.0 ± 666.9	NS
Body weight (kg) (mean ± SD)	58.5 ± 10.9	60.1 ± 9.6	NS
Tumor size (mm) (mean ± SD)	13.3 ± 7.7	22.3 ± 16.0	< 0.001
Tumor location in stomach (U + M/L)	54/126	94/57	< 0.001
Gross morphological type (0-I / IIa *vs* 0-IIb / IIc *vs* combined)	92/68/20	76/66/9	NS
Tumor depth (mucosa/submucosa)	168/12	134/17	NS
Histological type (cancer /adenoma)	124/56	108/43	NS
Ulcerative findings, *n* (%)	2 (1.1)	30 (19.9)	< 0.001
Diazepam (mg) (mean ± SD)	9.9 ± 3.3	17.5 ± 7.8	< 0.001

SD: Standard deviation; NS: Not significant; U: Upper-third of the stomach; M: Middle-third of the stomach; L: Lower-third of the stomach.

Table 2 Clinical features of study subjects administered low- or high-dose of diazepam

Variables	Low-dose group (*n* = 252)	High-dose group (*n* = 79)	*P* value
Age (yr) (mean ± SD)	69.8 ± 9.1	68.3 ± 10.1	NS
Sex (male / female)	194/58	67/12	NS
Lifetime alcohol consumption (t) (mean ± SD)	0.30 ± 0.48	0.44 ± 0.52	0.032
Smoking habit (Brinkman index) (mean ± SD)	649.5 ± 767.7	497.8 ± 582.5	NS
Body weight (kg) (mean ± SD)	58.4 ± 10.3	62.0 ± 9.9	0.006
Anxiolytic agents (used/not used)	46/206	7/72	NS
ASA classification (ASA 1/ ASA 2 / ASA 3)	48/151/53	20/47/12	NS
Comorbidities			
Hypertension, *n* (%)	127 (50.3)	39 (49.4)	NS
Diabetes mellitus, *n* (%)	44 (17.5)	11 (13.9)	NS
Heart disease, *n* (%)	58 (23.0)	18 (22.8)	NS
Respiratory disease, *n* (%)	30 (11.9)	4 (5.1)	NS
Chronic renal failure, *n* (%)	4 (1.6)	0 (0)	NS
Liver cirrhosis, *n* (%)	21 (8.3)	5 (6.3)	NS

SD: Standard deviation; NS: Not significant; ASA: American Society of Anesthesiologists.

60 kg. Thus, four subgroups were created and analyzed in relation to the diazepam dosage. The odds ratios of this logistic regression analysis are shown in Table 5. The combination of alcohol ≤ 0.4 t and BW ≤ 60 kg was defined as the standard subgroup. Odds ratios for the other three subgroups were found to increase in a stepwise fashion, with the greatest risk of high diazepam dose among patients with both alcohol > 0.4 t and BW > 60 kg (odds ratio = 4.52, 95% CI: 2.07 to 9.86).

Table 3 Clinicopathological features and clinical outcomes of subjects administered low- or high-dose of diazepam

Variables	Low-dose group (*n* = 252)	High-dose group (*n* = 79)	*P* value
Tumor size (mm) (mean ± SD)	15.4 ± 10.1	23.9 ± 18.2	< 0.001
Tumor location in stomach (U and M/L)	96/156	52/27	< 0.001
Gross morphological type (0-I / IIa *vs* 0-IIb / IIc *vs* combined)	129/100/23	39/34/6	NS
Tumor depth (mucosa/submucosa)	233/19	69/10	NS
Histological type (cancer/ adenoma)	176/76	56/23	NS
Ulcerative findings, *n* (%)	14 (5.6)	18 (22.8)	< 0.001
Resection style (en bloc/ piecemeal)	246/6	63/16	< 0.001
Postoperative bleeding, *n* (%)	1 (0.4)	1 (1.3)	NS
Perforation, *n* (%)	8 (3.2)	6 (7.6)	NS
Midazolam (added / not added)	43/209	20/59	NS

SD: Standard deviation; NS: Not significant; U: Upper-third of the stomach; M: Middle-third of the stomach; L: Lower-third of the stomach.

Table 4 Factors associated with the need for high doses of diazepam: Results of multivariate logistic analysis

Variable	*P* value	Odds ratio	95% CI
Lifetime alcohol consumption	0.041	1.74	1.02-2.97
Body weight	0.034	1.03	1.00-1.06
Tumor size	0	1.05	1.03-1.08
Location in stomach	0	2.87	1.61-5.12
Ulcerative findings	0.001	4.45	1.92-10.34

CI: Confidence interval.

Adverse events

Comparisons of adverse events according to diazepam dosage are included in Table 6. The incidence of paradoxical excitement was significantly higher in the high-dose diazepam group ($P < 0.001$). However, no other significant differences in adverse events were found.

DISCUSSION

This retrospective study revealed that gastric ESD can be performed in nearly 80% of patients under sedation achieved using a low dosage of diazepam. Patients with a long ESD procedure time were characterized by large-diameter tumors, lesions located in the upper- or middle-third of the stomach, and those accompanied by ulcerative findings. Outcomes found to be predictive of

Table 5 Comparison of need for high diazepam dose between subgroups stratified for lifetime alcohol consumption and body weight

Subgroup	Low-dose group (*n* = 252)	High-dose group (*n* = 79)	Odds ratio	95% CI
Alcohol > 0.4 t, BW > 60 kg	31	20	4.52	2.07-9.86
Alcohol > 0.4 t, BW ≤ 60 kg	38	17	3.13	1.43-6.88
Alcohol ≤ 0.4 t, BW > 60 kg	72	27	2.63	1.31-5.28
Alcohol ≤ 0.4 t, BW ≤ 60 kg	105	15	1	Referent

CI: Confidence interval. Alcohol: Lifetime alcohol consumption; BW: Body weight.

Table 6 Adverse events in patients administered a low *vs* high dose of diazepam

Variables	Low-dose group (*n* = 252)	High-dose group (*n* = 79)	*P* value
SpO2 < 90%, *n* (%)	70 (27.8)	18 (22.8)	NS
Blood pressure < 90 mmHg, *n* (%)	8 (3.2)	2 (2.5)	NS
Delayed awakening (flumazenil used/not used)	4/248	0/79	NS
Paradoxical excitement, *n* (%)	6 (2.4)	13 (16.5)	< 0.001

NS: Not significant.

a long ESD procedure time in the current study agreed with those previously reported by Goto *et al*[29]. To the best of our knowledge, no previous reports have confirmed that the sedative dose used during gastric ESD is increased in special patient groups (e.g., alcoholics or patients with higher BW). However, we found that a number of lesion-specific findings, as well as lifetime alcohol consumption and BW, were also associated with high-dose diazepam administration. In particular, lifetime alcohol consumption > 0.4 t and BW > 60 kg were additive risk factors for increased diazepam dosage. Specifically, patients with both a lifetime alcohol consumption > 0.4 t and a BW > 60 kg showed the greatest risk of needing a high diazepam dosage during ESD. While habitual alcohol consumption may increase the clearance of diazepam, the high lipid-solubility of diazepam may also result in rapid removal from the plasma and uptake by adipose tissue[30,31]. Therefore, when predicting diazepam dosages prior to starting gastric ESD, it is important to take into account not only the difficulty of the ESD procedure, but also the alcohol history and BW of the patient.

Although both respiratory and cardiovascular depression are common adverse events of diazepam administration, we encountered no serious events in the current study. For example, while oxygen saturation < 90% was observed in approximately 26% of patients, all recovered quickly in response to intraoperative supplemental oxygen administration and none required endotracheal intubation.

Debate is continuing regarding the proper depth of anesthesia required to perform lengthy endoscopic procedures such as ESD. We consider moderate sedation, which does not appear to cause respiratory depression, as the appropriate level of sedation. If the aim is to maintain the patient under moderate sedation with intermittent administration of a benzodiazepine, long-acting drugs such as diazepam are thought to be suitable in treatments requiring a relatively long time. Indeed, ESD procedures in almost all Japanese institutions are performed by an endoscopist who not only performs the ESD, but is also responsible for sedation during the operation. Due to a long half-life, diazepam is more suitable for intermittent than for continuous administration. Furthermore, intermittent administration in response to uncontrollable body movement is easy for a single operator to manage. The current analysis did not find any significant differences in the incidence of oxygen desaturation (SpO_2 below 90%) or hypotension (blood pressure below 90 mmHg) as a function of the administered diazepam dosage. These findings not only indicate the safety of diazepam, but also the suitability of its administration method.

Due to deep sedation in response to diazepam in the low-dosage diazepam group, flumazenil had to be administered to 4 patients (1.2%). Three of those patients had been coadministered 10 mg of midazolam, while another was an 85-year-old patient with a BW of only 42 kg. Kiriyama *et al*[17] reported that post-ESD recovery from sedation was faster with propofol than with midazolam. The present study did not perform scoring to investigate the recovery from sedation, but almost all patients were awake after returning to their hospital room following completion of the ESD procedure. Also, no cases showed carry-over of the sedative effect to the following morning. All patients who were administered flumazenil also showed rapid awakening, and no problems due to re-sedation were noted. Nevertheless, since ESD in Japan is currently performed as an inpatient treatment, as long as sufficient postoperative management is carried out, there may be no need for quick recovery of wakefulness.

Paradoxical excitement represents restless motion that occurs during diazepam administration. This reaction is reportedly caused, at least in part, by the toxicity of propylene glycol, an included diazepam solvent[32]. Propylene glycol is also a solvent that causes local irritation of veins. Some patients in the present study complained of transient vascular pain, but phlebitis was not seen in any patients. However, a notable increase in restlessness was observed with increasing diazepam dosages. Such reactions made the operation difficult to continue. Accordingly, in cases where preoperative prediction shows a strong possibility that a large dose of diazepam will be required, a different approach to sedation may be advisable. Examples include continuously administering propofol or dexmedetomidine from the start of the

operation, a technique that has recently been reported as useful during ESD[17,33].

The present study has several limitations. First, data generated from only a single hospital were reviewed retrospectively. Second, the decision to administer additional diazepam was left up to the operator, and the timing of such administration was not consistent across patients. However, the most important aspect of this study was the evaluation of the suitability of intermittent administration of diazepam prior to ESD. Further studies at multiple institutions should be conducted using different benzodiazepines and concomitant drugs, with different methods of administration.

In conclusion, among patients who are predicted to require only a low dosage of diazepam during ESD, intermittent administration of diazepam for sedation during gastric ESD will enable safe completion of the surgery. The need for high-dose diazepam can be expected in patients with lifetime alcohol consumption > 0.4 t, BW > 60 kg, or requiring a technically difficult ESD procedure. Given the present results, further randomized trials performed in a prospective manner with clear inclusion criteria and a clear injection protocol should be conducted for such patients.

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COMMENTS

Background

Endoscopic submucosal dissection (ESD) is a curative treatment for gastric epithelial neoplasia. Many cases of gastric epithelial neoplasia occur in elderly patients, who show increased sensitivity to sedatives and a higher risk of adverse reactions. Suitable methods for the administration of sedatives during ESD thus need to be established.

Research frontiers

This study can help us to understand the diazepam dosage required during ESD for gastric epithelial neoplasia and the characteristics of and adverse events encountered by patients administered high-dose diazepam.

Innovations and breakthroughs

Diazepam is the least potent injectable benzodiazepine sedative, with a long history of clinical use. However, administration methods have yet to be clearly established for safe and effective sedative use during gastric ESD procedures.

Applications

The results have demonstrated that intermittent administration of diazepam enabled safe completion of gastric ESD except for patients who are alcohol abusers or obese, or those with complicated lesions.

Peer review

This retrospective study investigated risk factors and adverse events related to high-dose diazepam administration during ESD for gastric neoplasias. Based on the present results, further randomized trials performed prospectively with clear inclusion criteria and a clear injection protocol should be conducted.

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BRIEF ARTICLE

Small bowel capsule endoscopy in patients with cardiac pacemakers and implantable cardioverter defibrillators: Outcome analysis using telemetry review

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Abstract

AIM: To determine if there were any interactions between cardiac devices and small bowel capsules secondary to electromagnetic interference (EMI) in patients who have undergone small bowel capsule endoscopy (SBCE).

METHODS: Authors conducted a chart review of 20 patients with a cardiac pacemaker (CP) or implantable cardioverter defibrillator (ICD) who underwent continuous electrocardiographic monitoring during their SBCE from 2003-2008. authors searched for unexplained electrocardiogram (ECG) findings, changes in CP and ICD set parameters, any abnormality in transmitted capsule data, and adverse clinical events.

RESULTS: There were no adverse events or hemodynamically significant arrhythmias reported. CP and ICD set parameters were preserved. The majority of ECG abnormalities were also found in pre- or post- SBCE ECG tracings and the CP behavior during arrhythmias appeared appropriate. Two patients seemed to have episodes of undersensing by the CP. However, similar findings were documented in ECGs taken outside the time frame of the SBCE. One patient was observed to have a low signal encountered from the capsule resulting in lack of localization, but no images were lost.

CONCLUSION: Capsule-induced EMI remains a possibility but is unlikely to be clinically important. CP-induced interference of SBCE is also possible, but is infrequent and does not result in loss of images transmitted by the capsule.

Key words: Small bowel capsule endoscopy; Cardiac pacemakers; Implantable cardioverter defibrillators; Electromagnetic interference; Telemetry review

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INTRODUCTION

Small bowel capsule endoscopy (SBCE) is firmly established as a diagnostic modality in the evaluation of obscure gastrointestinal bleeding and Crohn's disease. Based on concerns that radio signals that transmit images obtained from the capsule to an external sensory array could interfere with cardiac pacemaker functions, the US Food and Drug Administration required the manufacturer to insert language in the package insert that specifically contraindicates the use of capsule endoscopy in patients with these devices. When other diagnostic modalities fail to identify disease, many clinicians still perform capsule endoscopy in patients with pacemakers on the premise that the benefits of obtaining a diagnosis outweigh the proposed risks of the study. In addition, there is some skepticism over whether or not electromagnetic interference (EMI) by the capsule actually occurs and, if so, results in pacemaker malfunction[1]. There have been several preliminary studies suggesting that there are no verifiable clinically relevant malfunctions associated with the use of capsule endoscopy in patients with cardiac pacemakers[2-4]. Knowing the potential danger of EMI from prior studies, manufacturers of pacemakers and implantable cardioverter defibrillators (ICDs) have designed these devices to be shielded from small amounts of radiofrequency energy[5-7]. Transmissions to and from cardiac pacemakers to program the device occur in the 402 – 405 MHz band[8]. The radiofrequency energy from a small bowel capsule device may not be sufficient enough to cause clinically relevant malfunctions of the implanted cardiac pacemaker device as the capsule transmits images to the recorder in the 432-434.09 MHz band range (personal communication with Given Imaging, manufacturer of Pillcam SB™). The potential for adverse interactions between the cardiac device and ingested capsule has led us to perform capsule endoscopy under continuous electrocardiographic (ECG) telemetry monitoring. In this study, we review our experience with patients who had cardiac pacemakers or ICDs that underwent SBCE specifically looking for evidence implicating EMI between devices.

MATERIALS AND METHODS

We reviewed the charts of 20 patients (13 men, 7 women; mean age 71 years, range 57-80 years) with implanted pacing systems seen from September 2003 to June 2008. All of the patients presented with an indication for SBCE (either GI bleed or iron deficiency anemia) and gave written informed consent to the procedure after explaining risks, benefits, and alternatives. All SBCE investigations utilized the Pillcam SB™ capsule (Given Imaging Ltd., Isreal). The patients were advised to eat nothing after midnight, in compliance with an 8 hour fast prior to the procedure, but were allowed to take essential medications two hours before ingesting the capsule and at two hours post capsule ingestion. The sensor array was applied to the abdomen using adhesive pads, and was connected to the data recorder and battery pack. The battery pack was worn on a belt around the patient's waist. Pacemaker nurse specialists performed interrogation of the cardiac device and adjusted settings according to a standardized protocol. All patients with ICDs had their sensing function turned off. Continuous ECG telemetry monitoring was performed during the study. The ECG data was transmitted to a central station which notifies nursing staff of abnormal rhythms. Concerning ECG waveforms such as premature ventricular contractions (PVCs), atrial fibrillation, brady-arrythmias, non-sustained ventricular tachycardia (NSVT) or sustained ventricular tachycardia (VT) were recorded and placed in the patient's chart. Patients were instructed to avoid strenuous activity during the study period, and to call for help if they experienced concerning symptoms. When the patient had either passed the capsule or surpassed the life span of the battery, usually 8-9 h after the start of the examination, the capsule endoscopy data recorder was removed, and the ECG leads disconnected for those without an indication for continued telemetry monitoring. The cardiac device was then re-interrogated by the pacemaker nurse specialist to ensure proper function.

Several different models of pacemaker and ICDs produced by three manufacturers were studied see Table 1. The different types of pacemakers are categorized according to the NASPE/BPEG (North American Society of Pacing and Electrophysiology/ British Pacing and Electrophysiology Group) generic pacemaker code. The first letter identifies the chamber paced, the second letter identifies the chamber sensed (V, ventricular; A, atrial; D, dual ventricular or atrial), the third letter identifies the response to sensing (I, inhibited; T, triggered; D, dual), and the fourth letter identifies the response rate (R). The following parameters were assessed: adverse events occurring during and immediately after the capsule study; abnormal rhythms detected during telemetry monitoring; if available, ECG tracings taken prior to ingestion of the capsule and following the completion of the study for comparison; changes in set parameters that are documented in pacemaker interrogation reports; and findings concerning for oversensing or undersensing were interpreted by a staff electrophysiologist.

Each patient's final capsule endoscopy report was reviewed to evaluate for pacemaker induced interference of images transmitted by the capsule. We considered any alteration in the appearance of the images transmitted by the capsule, inability to localize the capsule, or any change in the strength of the transmitted signal to be positive markers for interference.

RESULTS

Twenty patients with cardiac pacemakers or ICDs implanted subcutaneously over the chest in the infraclavicular region were studied (13 men, seven women; mean age of 71 years, range of 57-80 years old). The indication for SBCE was either anemia or gastrointestinal bleeding of unknown origin. The indications for pace-

Table 1 Pacemakers and implantable cardioverter defibrillators studied

Patient	Manufacturer	Device	Model	Implanted	Mode	Polarity
No. 1	Medtronic	ICD	Virtuoso DR	Oct. 2006	AAI↔DDD	Bipolar
No. 2	St Jude	CP	Integrity AF pacesetter	Aug. 2001	DDDR	Bipolar
No. 3	Medtronic	ICD	Concerto DWK	Apr. 2007	DDD→VOO	Bipolar
No. 4	Medtronic	CP	Enrhythm DR	Feb. 2006	AAI↔DDD →VOO	Bipolar
No. 5	St Jude	CP	Integrity DR	Aug. 2003	DDDR	Bipolar
No. 6	Medtronic	ICD	Concerto DWK	Oct. 2007	DDD→VOO	Bipolar
No. 7	Medtronic	CP	Kappa KDR901	Oct. 2004	DDDR	Bipolar
No. 8	St Jude	CP	Affinity SR pacesetter	Sept.2000	VVIR	Unipolar
No. 9	St Jude	CP	Integrity DR	Mar. 2003	DDDR	Bipolar
No. 10	Medtronic	ICD	Virtuoso VR	Jun. 2007	VVIR→VOO	Bipolar
No. 11	Medtronic	CP	Sigma SSR		VVIR→VOO	Bipolar
No. 12	St Jude	ICD	Atlas HF	Feb. 2004	DDDR→DOO	Bipolar
No. 13	Medtronic	CP	Enrhythm DR	Aug. 1997	DDDR	Bipolar
No. 14	Medtronic	CP	Enpulse E2DR01	Oct. 2004	DDD→DOO	Bipolar
No. 15		CP				
No. 16		CP				
No. 17						
No. 18						
No. 19	ELA	CP	Brio	Sept. 2003	DDD	Bipolar
No. 20	Medtronic	CP	Enrhythm DR	Aug. 2006	DDDR↔ AAIR→DOO	Bipolar

Blank spaces represent information that was unavailable. PPM: Permanent pacemaker; ICD: Implantable cardioverter defibrillator; CP: Permanent pacemaker.

maker or ICD included symptomatic tachy- or bradyarrhythmia, primary prevention for cardiomyopathy, or was not documented. Of these 20, four charts lacked an interrogation report, so baseline characteristics and changes that took place for the capsule study could not be assessed. Telemetry reports were available for all of these patients except two, and hence, 18 patients were included in the analysis of data from telemetry monitoring. Of the 16 patients whose interrogation reports were available to us, 15 devices were programmed to the bipolar output and sensing configuration and one pacemaker was committed to unipolar settings. Eleven of the 16 devices were pacemakers and five were ICDs. There were 10 different models placed between 1997 and 2007 that were manufactured by three brands—10 by Medtronic, Inc. (Minneapolis, MN), five by St Jude Medical, Inc. (St. Paul, MN), and one by ELA Medical (Arvada, CO). The pacing configuration in eight of 16 devices was changed for purposes of the capsule study, while the other eight retained their pre-SBCE set parameters. The devices were programmed to the following pacing modes: three were set to DDD, six to DDDR, one to DOO, four to VOO, one to VVIR, and one to AAI→DDD (Table 1). A pacemaker nurse specialist checked pacemaker function pre- and post procedure for each patient. Following the capsule study, none of the pre-SBCE configurations were found to be altered per review of the chart and interrogation reports.

Runs of PVCs were reported in six of 18 patients. A few patients' alarms went off for what the telemetry system called PVCs, but on further review, these were thought to be artifact or insignificant findings. The clinically relevant PVCs were found in other ECG tracings within these patients' charts before, after, or before and after the capsule endoscopy took place, suggesting that these abnormalities were part of the patient's underlying cardiac rhythm derangement and had not been induced by the capsule. There was uncertainty over the exact number of PVCs in one patient because of the proximity of a PVC with the end of data recording. Similarly, NSVT- defined as three or more consecutive ventricular beats with a duration of less than 30 s, was seen in three patients, and all of these were documented before, after, or before and after the procedure. The number of beats of NSVT varied for each patient, but none of these episodes developed into sustained VT (> 30 consecutive beats or greater than 30 s in length) or ventricular fibrillation. Underlying arrhythmias such as atrial fibrillation, atrial flutter with variable AV block, and bradycardia were seen in several patients. All episodes of atrial fibrillation – five total, and the single incident of atrial flutter were documented in prior EKGs and/or in telemetry readings before or following the completion of the capsule endoscopy. The one patient with bradycardia (heart rate < 60) was found to have this in other ECGs. Six out of 18 patients were free of any irregularities during telemetry monitoring (Table 2). One patient had a shorter time on telemetry monitoring than capsule study duration, presumably from early defecation of the capsule or late application of ECG monitoring; regardless, no significant events were noted per chart review. A hemodynamically significant arrhythmia was not recorded for any patient, nor was there documentation of symptoms during the aforementioned arrhythmias.

Eight of the 16 patients whose pacing interrogation reports were available were placed in an asynchronous mode (VOO or DOO) for the study and had their sensing capability turned off, and the other eight were placed in demand pacing mode (AAI→DDD, DDD, DDDR, or VVIR). Two patients being paced on demand were found to be in an asynchronous rhythm throughout the study. On further review, we noted that they had been receiving 100% of their beats from the pacemaker because of an underlying bradycardia that was found in old ECGs and those from after the completion of the study. Of the 8 patients in sensing mode, two had inappropriate pacer spikes due to undersensing of very subtle atrial fibrillation (Figure 1A and B). These patients had similar

Table 2 Summary of important events observed on telemetry monitoring

Patient	Device	Mode	Polarity	Induction of asynchronous mode	Undersensing	Oversensing	Threshold change	Symtoms	Holter findings
No. 1	ICD	AAI↔DDD	Bipolar	No, occassional v-pacing on demand	No	No	No	No	PVC[2]
No. 2	CP	DDDR	Bipolar	No, occasional a-pacing and v-pacing on demand	Yes[1]	No	No	No	A fib[1], PVC[1], Nonsustained VT[1]
No. 3	ICD	VOO	Bipolar	NA	NA	NA	No	No	Nonsustained VT[1], PVC[1],
No. 4	CP	VOO	Bipolar	NA	NA	NA	No	No	A fib[1], PVC
No. 5	CP	DDDR	Bipolar	No, a-pacing and v-pacing on demand	Yes[1]	No	No	No	A fib[1], PVC[1],
No. 6	ICD	VOO	Bipolar	NA	NA	NA	No	No	PVC[1]
No. 7	CP	DDDR	Bipolar	No. Intrinsic rhythm without paced beats	No	No	No	No	No events
No. 8	CP	VVIR	Unipolar	No, 100% v-paced on demand[1]	No	No	No	No	No events
No. 9	CP	DDDR	Bipolar	No, 100% a-paced on demand[1]	No	No	No	No	No events
No. 10	ICD	VOO	Bipolar	NA	NA	NA	No	No	No events
No. 11	CP	VOO	Bipolar	NA	NA	NA	No	No	A fib[1]
No. 12	ICD	DOO	Bipolar	NA	NA	NA	No	No	No events
No. 13	CP	DDDR	Bipolar	No, occasional v-pacing on demand	No	No	No	No	No events
No. 14	CP	DOO	Bipolar	NA	NA	NA	No	No	No events
No. 15	CP			100% v-pacing				No	No events
No. 16	CP			100% v-pacing				No	No events
No. 17	ICD			On demand pacing				No	Sinus brady[1]
No. 18	CP			On demand pacing				No	A flutter[1], non-sustained VT[1]
No. 19	CP	DDD	Bipolar				No	No	
No. 20	CP	DOO	Bipolar				No	No	

Blank spaces represent information that was unavailable. [1]Findings that were observed either before or after, or before and after the capsule study. [2]Findings that may have occurred before or early into the capsule study. NA: not applicable; CP: Permanent pacemaker; ICD: Implantable cardioverter defibrillator; a-pacing: Atrial pacing; v-pacing: ventricular pacing; A fib: Atrial fibrillation; Sinus brady: sinus bradycardia; VT: Nonsustained ventricular tachycardia; PVC: Premature ventricular contraction.

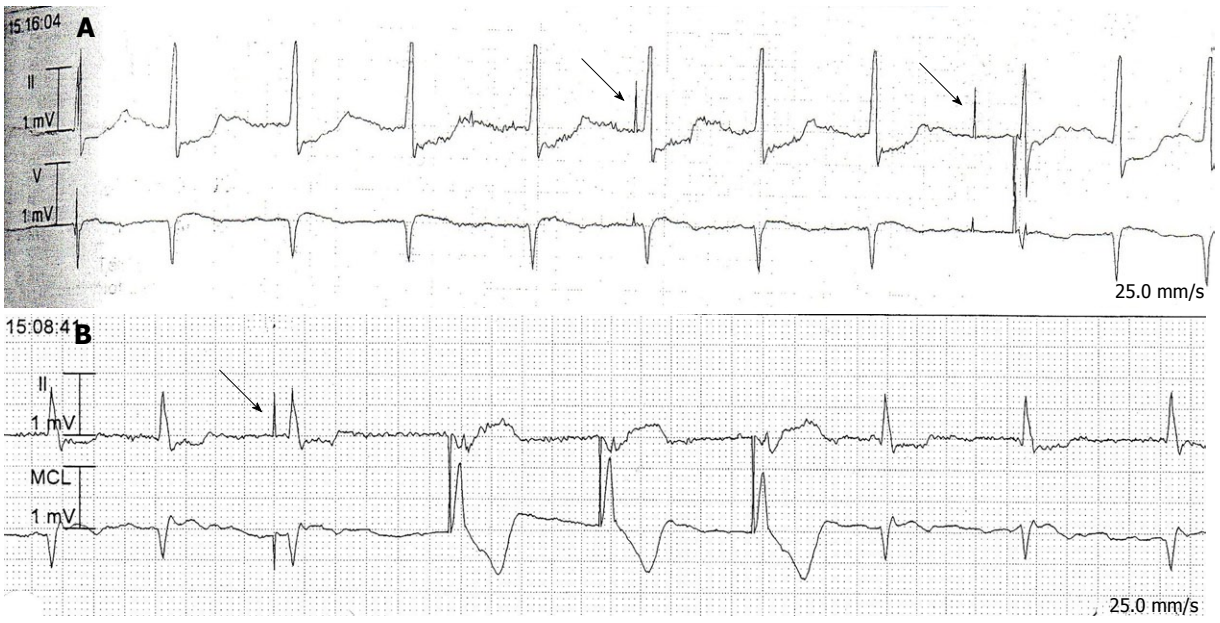

Figure 1 Electrocardiographic telemetry tracings from 2 patients with inappropriate pacer spikes (denoted by arrows). A: Undersensing of atrial fibrillatory waves is evident by the atrial pacer spikes preceding the 6th and 9th R waves; B: The atrial pacer spike preceding the 3rd R wave represents undersensing of a fibrillatory wave.

pacer spikes found in tracings that were recorded before and after the capsule endoscopy, respectively. The pacemaker responses to episodes of NSVT, PVCs, and atrial fibrillation in other tracings appeared appropriate.

For details about the duration of the examination and location of the capsule at various time points, refer

to Table 3. One out of 20 patients was found to have a low signal encountered from the capsule resulting in lack of localization. However, images were still able to be obtained from the exam. This patient had an ICD with sensing detections turned off. PVC's were documented during their SBCE. The other 19 patients were free of image interference or other irregularities in data recording.

Table 3 Data from capsule study

	n	Minimum	Maximum	Mean	SD
Duration of Holter monitoring	20	05:54.4	08:30.0	07:48.0	01:48.0
Time to pass pylorus	20	00:03.1	02:38.6	00:41.1	00:45.0
Time to pass cecum	17	01:25.6	End of recording		

DISCUSSION

Our experience with SBCE in patients with cardiac rhythm devices is consistent with other investigations done on capsule endoscopy in patients with cardiac pacemakers or ICDs, in that no clinically significant arrhythmias have been linked to electromagnetic interference from capsule transmission. However, it is well established that EMI between pacemakers, ICDs, and other medical devices is a real danger with potentially life-threatening consequences. For example, studies have shown that percutaneous catheter ablation of atrial arrhythmias can cause pacemaker malfunction and circuitry failure, necessitating replacement in some patients[9]. Devices which emit electromagnetic waves from a distance, such as digital cell phones, electronic surveillance systems, and electrocautery instruments may also interfere with pacemakers/ICDs[10,11]. Studies conducted on the C-net cellular phone system, which operates at 450 MHz, have shown a rate of interference up to 30%, clinically manifested as pacemaker mediated tachycardia and switch to interference mode, in some cases[12-14]. It is important to note that despite having a similar frequency, the radiated power of the video capsule is very low compared to that of the C-net mobile phone system, 50nW versus 2W, respectively[15]. Alternatively, equipment for electrocautery, defibrillation, catheter ablation, and lithotripsy are known to cause interference with cardiac devices, but operate at frequencies far below the 434.09 MHz used by the Pillcam SB™ capsule[3].

Studies on cell phones have demonstrated that interference is to some extent inversely proportional to the distance between the source of EMI and the cardiac device[13]. However, when the capsule travels past the heart, under most circumstances it will not come closer than fifteen centimeters from the implanted cardiac device, which is how far patients are told to keep mobile phones from their pacemaker[3]. The leads of the cardiac device may come much closer to the capsule as it traverses the esophagus, especially at the left atrium which is within centimeters of the esophagus. If proximity is indeed a factor, this is where a cardiac device is most vulnerable to EMI. However, exposure here is minimal as the capsule generally moves rapidly down the esophagus.

It is widely accepted that EMI is significantly reduced by a bipolar, as opposed to unipolar, configuration, and this is clinically relevant with regards to certain cellular phone and security systems[16,17]. However, Dubner et al performed a study using a SBCE simulation probe (Test Cap™, Given Diagnostic System) that emits electromagnetic waves at the same frequency as a real capsule and noted that EMI occurred in 4% of patients (four out of 100), and this occurred only in bipolar pacemakers[16]. Confounding this data is the fact that 95 of the 100 pacemakers in that study were programmed to bipolar mode. Similarly, all but one pacemaker in our study was configured in bipolar mode, so a direct comparison cannot be made.

Multiple studies have shown that body tissues serve as protection against EMI. Building on this concept, Bandorski *et al* (2008) and Payeras *et al*[3,18] built in vitro models, exposing pacemakers immersed in water or open to air to small bowel capsules. They found no interference in pacemaker function regardless of level of pacemaker sensitivity or bipolar versus unipolar settings. In the present study, we were not able to determine the exact time at which the capsules were swallowed, and thus cannot correlate the ECG abnormalities and episodes of undersensing with the location of the capsule.

In contrast to most observational studies, some prospective research points to the potential for clinically relevant EMI between capsules and cardiac devices. For example, the study utilizing the Test Cap™ by Dubner et al reported EMI when the capsule was hovering above the skin at a distance of less than 10 cm from the pacemaker. This effect was reproducible a week later in all four cases. The interference took the form of forcing the pacemaker into noise mode function, which is a safe-mode design that causes the pacemaker to change to an asynchronous pacing state when it cannot differentiate electromagnetic noise from a true signal. This change was reversible and there was no permanent damage to pacemaker. Pacemaker inhibition, which can have very serious consequences, was not observed and none of their patients developed symptoms[16]. It is thought that the site of entry for the noise signals was the unshielded part of the connector block which could occur as the swallowed capsule passes posterior to the heart while descending through the esophagus, consistent with studies on mobile phones[16,18]. This study very closely replicated a real capsule endoscopy, and involved a large number of patients. However, it was limited by the fact that several components of the capsule endoscopy system were not part of the simulation and the capsule was never actually swallowed. So, their findings may not be reliably translated to a real capsule study.

There is the potential that capsule-induced EMI of the pacemaker may result in breakthrough arrhythmias secondary to undersensing or oversensing. We saw many arrhythmias, but virtually all of them were documented

outside the timeframe of the SBCE study, and thus were unlikely to be the result of undersensing induced by the capsule. Most importantly, the pacemakers appeared to function appropriately during these arrhythmias, and each episode was brief, isolated, and was not associated with symptoms or changes in pacemaker set parameters. In addition, we cannot conclusively say why there was undersensing in two patients in our population, the most likely possibility is that the thresholds for atrial pacing were set too high, resulting in the pacemaker not sensing underlying low-amplitude fibrillatory atrial electrical activity. However, the possibility of capsule interference cannot be completely excluded. Knowing where in the abdomen the capsule happened to be at the time of interference would help since EMI seems to vary with distance from the source and position relative to the pacemaker.

It is important to determine whether or not ICDs, with their more complex program function and electronic circuitry, are susceptible to EMI. Both Bandorski et al and Leighton et al report no serious complications in respective papers involving SBCE in patients with ICDs[17,19,20]. We also studied patients with ICDs, but all of our patients had their ICD detection capability turned off prior to capsule ingestion, thus preventing the provision of shocks by the ICD in the setting of a dysrhythmia. In this regard, we are not able to say whether or not capsules may cause dysfunction of ICDs when sensing is activated.

Very few studies have reported problems with the capsule system caused by cardiac pacemakers or other sources of EMI. A 2011 retrospective study by Bandorski found gaps the capsule video processing in two of 13 patients on telemetry[20]. There was no capsule interference in 49 patients without telemetry monitoring, leading to their hypothesis that ECG-monitoring devices have the capacity to suppress processing of the capsule signal[20]. The incidence of interference of the capsule in this study was small at 5% (one out of 20 patients). Although interference prevented capsule localization, it was clinically insignificant as images were still obtained. However, because of the small patient population, we cannot reliably comment on the expected incidence of pacemaker or ECG-monitoring device induced EMI. In addition, it should be noted that obscuring or loss of images can occur in patients for many different reasons. In the population of patients at our medical center who have undergone capsule endoscopy that do not have pacemakers or ICDs, we have seen gaps in recording secondary to the sensor array not being plugged in, leads having fallen off or being improperly connected, discharged batteries, and many times, there is no clear explanation. Pacemakers, capsules, and ECG monitoring devices have different electromagnetic and radiofrequency characteristics depending on the type and brand, which may also play a role. To date, there been no large, prospective studies describing the incidence of capsule image loss.

In conclusion, in the largest study known to date with a complete review of continuous ECG-monitoring during capsule endoscopy, we observed no clinically significant interaction between the capsule endoscopy device and pacemakers or ICDs whose sensing capacity had been deactivated. Gaps in the recorded images were noted in one patient possibly due to EMI from the cardiac pacemaker, but EMI secondary to the ECG-monitoring device is another very plausible possibility. However, similar gaps occur in patients who do not have such devices. Undersensing and abnormal electrocardiographic findings were noted in a limited number of patients but were of no clinical importance. These unexpected findings likely represent underlying problems that were picked up incidentally and most likely were not due to EMI from the capsule. Based on our findings and review of previous studies on capsule endoscopy in patients with pacemakers, it appears safe to perform capsule endoscopy in these individuals without the use of telemetry monitoring. However, we cannot assume this with regards to our patients that had ICDs, as their sensing detections were turned off.

COMMENTS

Background

Electromagnetic interference (EMI) can cause pacemaker or implantable cardioverter defibrillator (ICD) malfunction in addition to loss of images or transmitted data from small bowel video capsules during capsule endoscopy. Although there is limited data on the clinical relevance of this interaction between the two devices, the US Food and Drug administration has mandated that manufacturers include language in the package insert contraindicating capsule endoscopy in patients with an implanted cardiac pacing device. Looking for electrocardiogram (ECG) abnormalities in patients with pacemakers during a capsule study could offer insight as to whether or not such an interaction actually takes place.

Research frontiers

The indications for capsule endoscopy are expanding and the technology continues to evolve. Normally an outpatient procedure, the package insert warning has led some providers to monitor their patients in an in-patient setting to mitigate the risks of EMI on pacemaker function. This adds cost to the procedure without a definite benefit and may limit the use of capsule endoscopy in select patients with a pacemaker or ICD.

Innovations and breakthroughs

Although all ICDs and pacemakers have a shield built into the device, it is still possible for high energy electromagnetic radiation to enter and cause sensing abnormalities or alterations in configured settings. Fortunately, small bowel capsules are designed in such a way that the radio energy emitted has a frequency and wattage that should not cause interference with a thoracic cardiac device when traveling through the abdomen under normal circumstances.

Applications

Given that clinically significant EMI with pacemaker function was not noted in this study, it may be safe to perform capsule endoscopy in out-patients without the use of continuous ECG telemetry monitoring as a precautionary measure. However, the incidence of interference with capsule function appears to be higher and we cannot comment on the impact of capsules on ICD function as these devices had their sensitivities turned off during the study. Large, prospective, randomized trials are needed before final recommendations can be made.

Terminology

EMI is a disturbance that affects an electrical circuit due to electromagnetic

radiation emitted from an external source. Authors use this term interchangeably with radiofrequency interference and energy. Pacemaker sensing refers to the detection of heart rate and rhythm patterns by the cardiac device; under- and oversensing are electrocardiographic signs of pacemaker malfunction that may be due to EMI.

Peer review

This outcomes analysis study in which the authors review their experience performing capsule endoscopy on patients with pacemakers or ICDs while under continuous ECG monitoring is the largest experience of its kind reported in the literature. The results reiterate the concept that capsule endoscopy is a safe procedure to perform in patients with a pacemaker or an ICD with its detections turned off. EMI by one device on the other remains a possibility but appears to lack clinical significance.

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CASE REPORT

Acquired double pylorus, due to penetrating gastric ulcer, presenting with melena

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Abstract

Acquired double pylorus (DP) is an uncommon condition consisting of two communicating channels between the gastric antrum and the first part of duodedum. Little is known about the origin of DP. As there is no specific gastrointestinal symptom due to DP, most often it is diagnosed by gastroscopy while performing for other indicationsFew data are also known about the clinical course of DP. In the patients with peptic ulcer symptoms, the pyloroplasty-like drainage effect, improving gastric emptying after the estabilishment of the fistula, could relieve these symptoms. This represents an unresolved issues about the necessity of repeating endoscopy to document in the patients with DP its final outcome, as the risk of ulcer recurrence. We describe a case of a 76-years-old woman admitted to our department for hyposideremic anemia associated to a recent history of melena.

Key words: Double pylorus; Gastric ulcer

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INTRODUCTION

Acquired double pylorus (DP) is an uncommon condition (less than 0.4% of gastroscopies)[1,2] consisting of two communicating channels between the gastric antrum and the first part of duodedum. It represents often an incidental finding at the upper endoscopy, when this is performed for other indications[3], and because of its rarity few data are available about its clinical course and consequently about the way to follow up this endoscopical entity. We describe a case of a 76-years-old woman with hyposideremic anemia, associated to a recent history of melena, in which an upper endoscopy showed an acquired double pylorus, due to penetrating gastric ulcer.

CASE REPORT

We describe a case of a 76-years-old woman admitted to our department for hyposideremic anemia (Hb 5 g%) associated to a recent history of melena. A gastroscopy was performed, showing a fistula, into the antral superior wall, between the prepyloric antrum and the duodenal bulb, with hyperaemic stigmata into the mucosa associated with scarred sign, typical of past penetrating ulcer (Figure 1). Hystology of the antrum showed the features of mild chronic erosive gastritis Helicobacter pylori (HP)

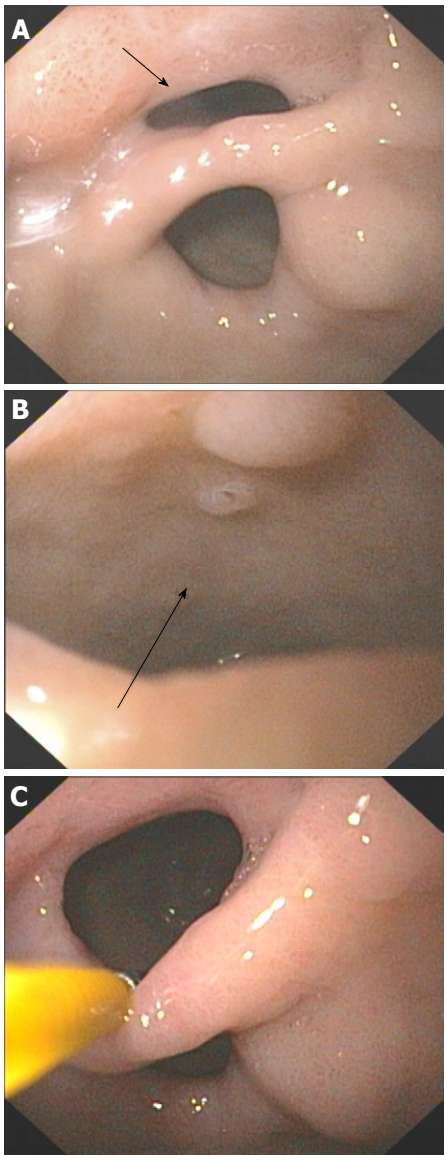

Figure 1 A fistula, into the antral superior wall, between the prepyloric antrum and the duodenal bulb, with hyperaemic stigmata into the mucosa associated with scarred sign, typical of past penetrating ulcer.

positive. Upper gastrointestinal series were performed, but they were not diagnostic because repeated vomiting of the patient during the exam; despite they did not confirm the presence of a DP, the visualization of an eccentric pylorus could be compatible with the gastroduodenal fistula seen at the gastroscopy (Figure 2). A colonoscopy did not show any source of bleeding. After three blood transfusions, the patient was discharged with a triplex HP eradication therapy and a procinetic, with disappearance of melena and improvement of Hemoglobin value (10 g %). Urea breath test was performed one month later, showing the eradication of HP infection. Normal haemoglobin levels and the absence of gastrointestinal symptoms were noted on follow-up.

DISCUSSION

Little is known about the origin of DP. As there is no specific gastrointestinal symptom due to DP, most often it is diagnosed by gastroscopy while performing for other indications[3]. The radiological features are characteristic: there are two channels connecting the gastric antrum to the superior fornix of the duodenal bulb, while the fistula usually arises from the lesser curvature of the antrum. Despite this, it is sometimes difficult to distinguish between double pylorus and marked pyloric deformity[4]. Association with HP has been observed in other case report series[5,6], while other authors reported that double pylorus could be an extremely uncommon presentation of gastric adenocarcinoma[7].

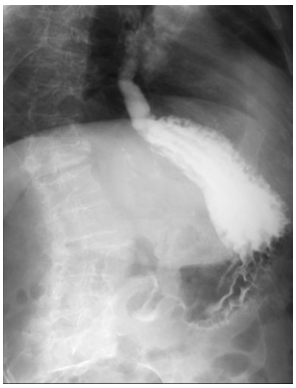

Figure 2 The visualization of an eccentric pylorus.

Few data are also known about the clinical course of DP. In the patients with peptic ulcer symptoms, the pyloroplasty-like drainage effect, improving gastric emptying after the estabilishment of the fistula, could relieve these symptoms[4]. Hu *et al*[2] noted that majority of the cases of DP treated with eradication therapy for HP remained open. This represents an unresolved issues about the necessity of repeating endoscopy to document in the patients with DP its final outcome, as the risk of ulcer recurrence.

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CASE REPORT

Typical gastroduodenal endoscopic findings in a Crohn's disease patient in remission stage

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Abstract

A 39-year-old patient with Crohn's disease (CD) was referred to our hospital for maintenance treatment of CD. He was diagnosed as having CD of the small and large intestines at 32 years old. He underwent partial resection of the ileum at 35 years old because of ileal perforation. He had received enteral nutritional supplement (1200 kcal/d) and metronidazole preparation (500 mg/d), and was in remission Crohn's disease activity index 73. We performed a routine gastroduodenal endoscopic examination, which revealed the representative endoscopic findings of gastroduodenal lesions in CD, namely, bamboo-joint-like appearance of the gastric body and cardia and a notched sign in the duodenum. These findings were clearly observed by using indigo carmine dye spraying. In our patient, typical gastroduodenal findings were observed even in the remission stage, suggesting that these findings would contribute to the early diagnosis of CD not only in the active stage but also during remission.

Key words: Crohn's disease; Gastroduodenal findings; Bamboo-joint-like appearance; Notched sign

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INTRODUCTION

Crohn's disease (CD) is an intractable chronic inflammatory bowel disease with unknown etiology that can affect any part of gastrointestinal tract. Typical endoscopic findings of CD in the small intestine and colon have been shown as follows, longitudinal ulcers, nodular (cobblestone) mucosa, aphthous ulcers, and strictures. With regard to the gastroduodenal findings of CD, previous reports showed that the lesions were usually located in the antrum and mainly nonspecific redness or erosion[1-5]. However, such erosive gastritis lesions of the antrum were also commonly observed in non-CD patients, and thus, these gastric lesions can not be specific for CD[5,6]. Thereafter, recent studies have revealed representative endoscopic findings of gastroduodenal lesions in CD, namely, bamboo-joint-like appearance[6], which is characterized by swollen longitudinal folds transversed by erosive fissures or linear furrows and is most frequently found at cardiac area in the stomach[6,7], and notches in the Kerckring's folds in the duodenum[8,9]. It has been thought that these representative endoscopic findings of gastroduodenal lesions in CD would contribute to the early diagnosis of CD. However, it is unclear

whether these representative gastroduodenal findings are observed in remission stage of CD as well as in active stage. In this case report, we have shown a CD patient having representative gastroduodenal endoscopic findings even in remission stage.

CASE REPORT

A 39-year-old patient with CD was referred to our hospital for maintenance treatment of CD in May 2009. He was diagnosed as having CD of the small and large intestines at 32 years old. He underwent partial resection of the ileum at 35 years old because of ileal perforation. He had received enteral nutritional supplement (1200 kcal/d) and metronidazole preparation (500 mg/d), and was in remission [Crohn's disease activity index (CDAI[10]) 73]. On physical examinations, only a slight tenderness was observed in the upper abdomen. Laboratory data of the patient were as follows, hemoglobin 13.7 g/dL, hematocrit 42.1%, white blood cell count (WBC) 7600 /μL, C-reactive protein 0.72 mg/dL, total protein 7.5 g/dL, albumin 3.3 g/dL, L-aspartate: 2-oxoglutarate aminotransferase 20 IU/l, L-alanine: 2-oxoglutarate aminotransferase (ALT) 16 IU/L, alkaline phosphatase 184 IU/L, blood urea nitrogen 13.5 mg/dL, creatinine 0.97 mg/dL. Although he complained very slight abdominal discomfort, we performed a routine gastroduodenal endoscopic examination to check gastroduodenal lesions of CD. As a result, we found representative endoscopic findings of gastroduodenal lesions in CD, namely, a bamboo-joint-like appearance of the gastric body and cardia (Figure 1A and B), and a notched sign in the duodenum (Figure 1C and D). These findings were clearly observed by using indigo carmine dye spraying (Figure 1B and D). The bamboo-joint-like appearance was localized in the lesser curvature of the upper gastric body and cardia (Figure 1E). Thus, typical endoscopic gastroduodenal findings of CD were clearly found in our patient even in the remission stage. Thereafter, he has continued enteral nutritional supplement and has been in remission approximately for 2 years.

DISCUSSION

A bamboo-joint-like (BJA) appearance is thought be the most representative gastroduodenal endoscopic finding of CD and was first reported by Yokota *et al*[6]. They showed that BJA was found in the gastric body and cardia in 54% of CD patients[6]. They also showed that the occurrence of BJA did not correlate with sex, age, age at onset of CD, the site of CD in the small and/or large bowel, or the medications being taken at the time of gastroscopy. Concerning the specificity of BJA in CD, Kuriyama *et al*[11] showed that BJA was found in 44% of CD patients, 5% in ulcerative colitis patients, and 0% in gastroesophageal reflux disease, and thus, they suggested that BJA could be a unique marker of CD. Hirokawa *et al*[7] also showed that BJA was found in 65.2% of CD patients and in 1.1% of non-CD patients. With regard to the histopathological findings of BJA, Hirokawa *et al*[7] showed sharp, fissure-like erosion or mucosal cleft in 50% of 14 CD patients. They also showed that all cases with fissure-like erosion or mucosal cleft revealed lymphoid aggregates, eosinophilic infiltration and edema in the superficial portion of the surrounding lamina propria. Epitheloid granuloma is known as a specific histopathological finding in CD. Yokota *et al*[6] showed that the detection rate for glanulomas tended to be higher for the lesions with a bamboo joint-like appearance (45%) than in those from longitudinally aligned furrows (0%). On the other hand, Hirokawa *et al*[7] showed that epitheloid granuloma was found at the base of the fissure-like erosion in two cases out of 14 CD patients. In addition, Yokota *et al*[6] showed that *Helicobacter pylori* was histologically detected only 9% of CD patients with BJA. They suggested that *Helicobacter pylori* infection did not correlate with the presence of BJA.

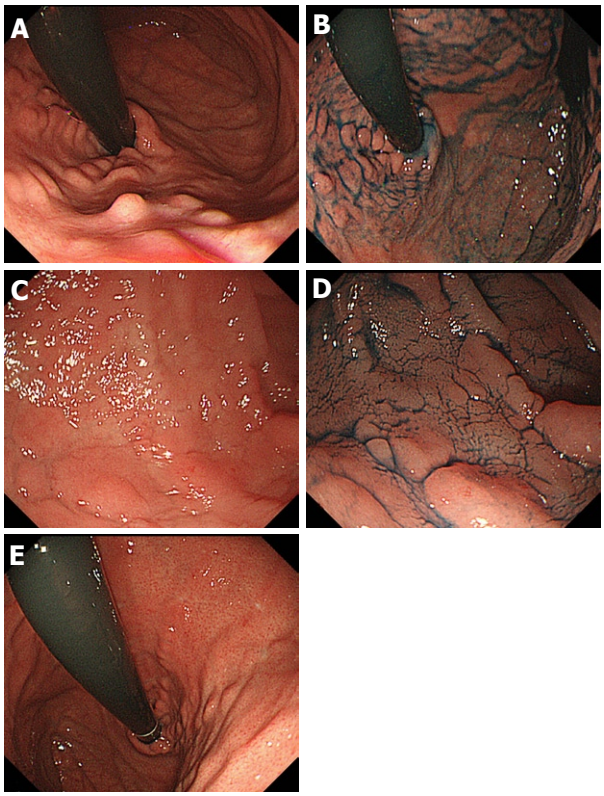

Figure 1 Gastroduodenal endoscopic findings of the patient. A: Endoscopic view of bamboo-joint-like appearance on the lesser curvature of the gastric body and cardia; B: Bamboo-joint-like appearance was more clearly observed by spraying with indigo carmine dye; C: Endoscopic view of notches on the Kerckring's folds of the duodenum; D: Notch sign was more clearly observed by spraying with indigo carmine dye; E: The bamboo-joint-like appearance was localized in the lesser curvature of the upper gastric body and cardia.

The presence of BJA in the stomach and notches in the Kerckring's folds in the duodenum are thought to be a useful tool for early diagnosis of CD. These findings would be more powerful tools for early diagnosis of CD if they are observed in CD patients in remission as well as in active stage. However, in this point detailed analy-

sis has not been done, and only a few case studies have been reported[9,12]. Hokama *et al*[9] showed that notched sign and BJA in the duodenum were found in an asymptomatic CD patient. Kuwaki *et al*[12] showed that BJA in the stomach of a CD patient was not changed in both remission and active stages. In this context, our case report supports these case studies and suggests that the representative gastroduodenal findings are present even in remission stage of CD.

CD is an intractable chronic inflammatory bowel disease, and the numbers of CD patients are increasing in Asian countries as well as in Japan[13]. On the other hand, recent studies have shown that biologic therapy has changed the way to treat CD and that early induction with infliximab was effective for reducing the relapse rate compared to conventional therapies[14,15], suggesting that biologic therapy in early stage of CD might change the natural history of CD. Thus, the typical gastroduodenal findings of CD can contribute to early diagnosis of CD and better prognosis of CD patients.

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Events Calendar 2012

January 19-21, 2012
American Society of Clinical Oncology 2012 Gastrointestinal Cancers Symposium
San Francisco, CA 3000, United States

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San Francisco, CA 94103, United States

January 20-21, 2012
American Gastroenterological Association Clinical Congress of Gastroenterology and Hepatology
Miami Beach, FL 33141, United States

February 2-4, 2012
14th Dusseldorf International Endoscopy Symposium 2012
Dusseldorf, Germany

February 24-27, 2012
Canadian Digestive Diseases Week 2012
Montreal, Canada

March 1-3, 2012
International Conference on Nutrition and Growth 2012
Paris, France

March 7-10, 2012
Society of American Gastrointestinal and Endoscopic Surgeons Annual Meeting
San Diego, CA 92121, United States

March 12-14, 2012
World Congress on Gastroenterology and Urology
Omaha, NE 68197, United States

March 30-April 2, 2012
Mayo Clinic Gastroenterology and Hepatology
San Antonio, TX 78249, United States

March 31-April 1, 2012
5th Annual Endoscopy Directors Meeting Endoscopy Unit Management in the 21st Century: Issues, Solutions, and Plans for the Future
Washington, DC 20057, United States

April 8-10, 2012
9th International Symposium on Functional GI Disorders
Milwaukee, WI 53202, United States

April 15-17, 2012
European Multidisciplinary Colorectal Cancer Congress 2012
Prague, Czech

April 19-21, 2012
Internal Medicine 2012
New Orleans, LA 70166, United States

April 20-22, 2012
Diffuse Small Bowel and Liver Diseases
Melbourne, Australia

April 22-24, 2012
EUROSON 2012 EFSUMB Annual Meeting
Madrid, Spain

April 28, 2012
Issues in Pediatric Oncology
Kiev, Ukraine

May 3-5, 2012
9th Congress of The Jordanian Society of Gastroenterology
Amman, Jordan

May 7-10, 2012
Digestive Diseases Week
Chicago, IL 60601, United States

May 17-21, 2012
2012 ASCRS Annual Meeting-American Society of Colon and Rectal Surgeons
Hollywood, FL 1300, United States

May 18-23, 2012
SGNA: Society of Gastroenterology Nurses and Associates Annual Course
Phoenix, AZ 85001, United States

May 19-22, 2012
2012-Digestive Disease Week
San Diego, CA 92121, United States

June 18-21, 2012
Pancreatic Cancer: Progress and Challenges
Lake Tahoe, NV 89101, United States

September 8-9, 2012
New Advances in Inflammatory Bowel Disease
La Jolla, CA 92093, United States

September 8-9, 2012
Florida Gastroenterologic Society 2012 Annual Meeting
Boca Raton, FL 33498, United States

September 15-16, 2012
Current Problems of Gastroenterology and Abdominal Surgery
Kiev, Ukraine

October 4-6, 2012
EURO-NOTES 2012: NOTES and Advanced Interventional Endoscopy
Prague, Czech Republic

October 19-24, 2012
American College of Gastroenterology 77th Annual Scientific Meeting and Postgraduate Course
Las Vegas, NV 89085, United States

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Modern Technologies in Diagnosis and Treatment of Gastroenterological Patients
Dnepropetrovsk, Ukraine

December 1-4, 2012
Advances in Inflammatory Bowel Diseases
Hollywood, FL 33028, United States

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16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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