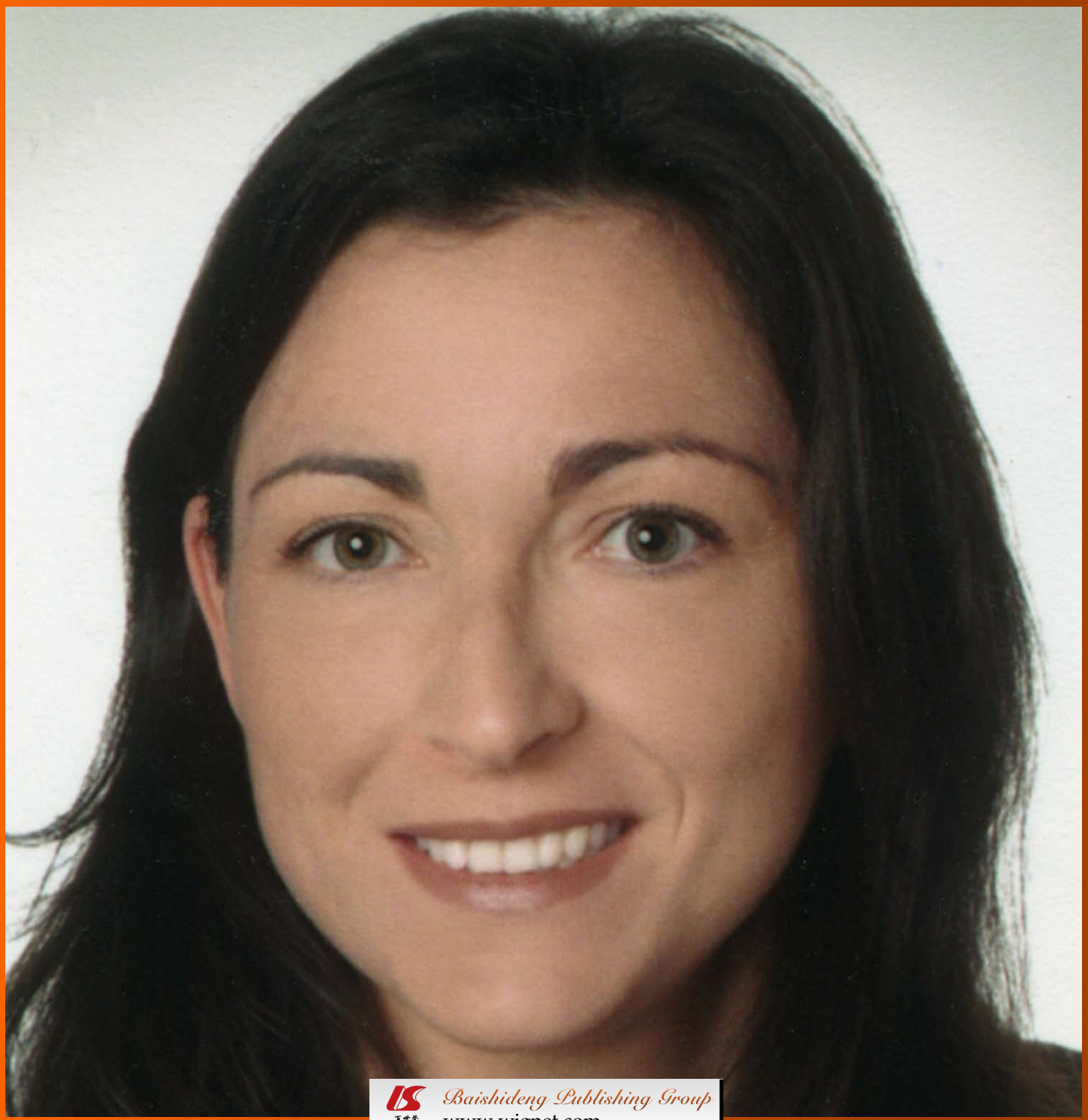
**ISSN** 1948-5190 (online)

# World Journal of *Gastrointestinal Endoscopy*

*World J Gastrointest Endosc* 2012 October 16; 4(10): 438-478



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WJGE World Journal of Gastrointestinal Endoscopy

A peer-reviewed, online, open-access journal of gastrointestinal endoscopy

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WJGE World Journal of Gastrointestinal Endoscopy

## Contents

Monthly Volume 4 Number 10 October 16, 2012

*World Journal of Gastrointestinal Endoscopy*
Volume 4 Number 10 October 16, 2012

## Contents





NAME OF JOURNAL
*World Journal of Gastrointestinal Endoscopy*

ISSN
ISSN 1948-5190 (online)

LAUNCH DATE
October 15, 2009

FREQUENCY
Monthly

EDITING
Editorial Board of *World Journal of Gastrointestinal Endoscopy*,
Room 903, Building D, Ocean International Center,
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PUBLISHER
Baishideng Publishing Group Co., Limited
Room 1701, 17/F, Henan Building,
No.90 Jaffe Road, Wanchai,
Hong Kong, China
Fax: +852-31158812
Telephone: +852-58042046
E-mail: bpgoffice@wjgnet.com
http://www.wjgnet.com

PUBLICATION DATE
October 16, 2012



INSTRUCTIONS TO AUTHORS
Full instructions are available online at http://www.wjgnet.com/1948-5190/g_info_20100316080002.htm

ONLINE SUBMISSION
http://www.wjgnet.com/esps/

World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/esps/
wjge@wjgnet.com
doi:10.4253/wjge.v4.i10.438

*World J Gastrointest Endosc* 2012 October 16; 4(10): 438-447
ISSN 1948-5190 (online)


TOPIC HIGHLIGHT

**Hiroto Kita, MD, PhD, Professor,** *Series Editor*

# Endoscopic submucosal dissection and surgical treatment for gastrointestinal cancer

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Received: October 13, 2011 Revised: September 3, 2012
Accepted: October 13, 2012
Published online: October 16, 2012

## Abstract

Endoscopic submucosal dissection (ESD) is widely used in Japan as a minimally invasive treatment for early gastric cancer. The application of ESD has expanded to the esophagus and colorectum. The indication criteria for endoscopic resection (ER) are established for each organ in Japan. Additional treatment, including surgery with lymph node dissection, is recommended when pathological examinations of resected specimens do not meet the criteria. Repeat ER for locally recurrent gastrointestinal tumors may be difficult because of submucosal fibrosis, and surgical resection is required in these cases. However, ESD enables complete resection in 82%-100% of locally recurrent tumors. Transanal endoscopic microsurgery (TEM) is a well-developed surgical procedure for the local excision of rectal tumors. ESD may be superior to TEM alone for superficial rectal tumors. Perforation is a major complication of ESD, and it is traditionally treated using salvage laparotomy. However, immediate endoscopic closure followed by adequate intensive treatment may avoid the need for surgical treatment for perforations that occur during ESD. A second primary tumor in the remnant stomach after gastrectomy or a tumor in the reconstructed organ after esophageal resection has traditionally required surgical treatment because of the technical difficulty of ER. However, ESD enables complete resection in 74%-92% of these lesions. Trials of a combination of ESD and laparoscopic surgery for the resection of gastric submucosal tumors or the performance of sentinel lymph node biopsy after ESD have been reported, but the latter procedure requires a careful evaluation of its clinical feasibility.



**Key words:** Endoscopic submucosal dissection; Esophageal cancer; Gastric cancer; Colorectal cancer; Laparoscopic surgery; Lymph node metastasis; Perforation; Gastrectomy; Complications

**Peer reviewers:** Jaekyu Sung, MD, PhD, Assistant Professor, Division of Gastroenterology, Department of Internal Medicine, Chungnam National University Hospital, 33 Munhwa-ro, Junggu, Daejeon 301-721, South Korea; Shotaro Enomoto, MD, PhD, Second Department of Internal Medicine, Wakayama Medical University, 811-1, Kimiidera, Wakayama 641-0012, Japan; Taro Osada, MD, PhD, Associate Professor, Department of Gastroenterology, Juntendo University, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421, Japan; Satoru Kakizaki, MD, PhD, Assistant Professor, Department of Medicine and Molecular Science, Gunma University, Graduate School of Medicine, 3-39-15 Showa-machi, Maebashi, Gunma 371-8511, Japan

Asano M. Endoscopic submucosal dissection and surgical treatment for gastrointestinal cancer. *World J Gastrointest Endosc* 2012; 4(10): 438-447 Available from: URL: http://www.wjgnet.com/1948-5190/full/v4/i10/438.htm DOI: http://dx.doi.org/10.4253/wjge.v4.i10.438

## INTRODUCTION

Gastroendoscopic treatments, such as endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), are standard treatments for early gastrointestinal cancer in Japan. Medical endoscopists often perform

these procedures in Japan; however, Masanori Hirao, who first reported endoscopic resection (ER) (a forerunner of ESD) using a local injection of hypertonic saline-epinephrine for the treatment of early gastric cancer[1], was a surgeon with experience in the performance of gastrectomies.

ER was developed to reduce the number of excessive surgeries for early gastric cancer without lymph node metastasis (LNM), but the indications for ER have been expanded to other conditions and organs.

Endoscopic treatment was principally developed for the examination of conditions with no LNM[2-5] and to improve the resectability of tumors[6,7]. ESD has expanded as a new and less invasive treatment that enables complete tumor removal without surgery (Figure 1).

ESD has three main advantages over surgery; specifically, it is less invasive, is less expensive, and better preserves physiological function. However, complete resection is impossible in some difficult cases, and the rate of complete resection is not 100% in high-volume institutes. Subsequent surgery may be required for curative treatment in some cases (Figure 2).

ESD may be applied for secondary lesions after some surgeries, such as esophagectomy and gastrectomy. A new technique in this field is joint laparoscopic surgery and ESD, which has been attempted for the treatment of submucosal tumors, including gastrointestinal stromal tumors (GISTs). The ESD technique is used as a novel, less invasive, natural orifice transluminal endoscopic surgery (NOTES).

This article discusses the relationship between ESD and surgical treatment from several viewpoints.

## ADDITIONAL SURGERY AFTER ESD

Additional surgery with lymph node dissection is recommended when ER is histologically non-curative. Non-curative ESD is defined as the presence of cancer cells in the lateral or deep margins, invasion to the deep layer, the presence of lymphatic vessel invasion, the presence of an undifferentiated cell type, or a combination of these conditions. The definitions vary according to the affected organ.

### *Esophagus*

Mortality after esophagectomy is 14%[8], which is much higher than that after ESD. Therefore, the decision to perform an esophagectomy for esophageal cancer should be carefully considered. The 2007 guidelines of the Japanese Esophageal Society for the diagnosis and treatment of esophageal squamous cell carcinoma (SCC) state that intraepithelial tumors (M1) and tumors invading the lamina propria (M2) that spread to less than two-thirds of their circumference are absolute indications for esophageal ER, and tumors that are in contact with or invading the muscularis mucosa (M3) without clinical lymph node involvement are a relative indication for ER.

Intensive pathological investigations of a large number of surgical resection cases have demonstrated that less than 5% of M1 and M2 cases exhibit LNM, and the 5-year survival rate is greater than 90%; most deaths result from other causes. However, M3 and submucosa (SM1) cases (i.e., tumors that invade the most superficial third of the submucosa) exhibit a 10%-32% risk of LNM[3,6,9]. Therefore, additional treatment is not necessary for M1 and M2 cases, but additional treatment, such as esophagectomy or chemoradiation, must be considered for M3 and SM1 cases. The indication for additional surgery is controversial in M3 cases. Eguchi *et al*[9] investigated 464 consecutive patients who had undergone radical esophagectomy with lymphadenectomy and found that 42% of patients with M3 lesions and lymphatic invasion (LY) exhibited LNM, but only 10% of patients with M3 lesions without LY exhibited LNM. The authors concluded that M3 lesions with LY should be treated similarly to SM lesions, and patients with M3 lesions without LY can be followed up without any additional treatment. Shimizu *et al*[10] found that 16 patients with esophageal carcinoma that invaded the muscularis mucosa or upper submucosa who underwent EMR followed by chemoradiotherapy but refused esophagectomy exhibited no local recurrence or metastasis. The overall survival rate of these 16 patients at 5 years was 100%, but 39 patients with similarly staged cancer who underwent esophagectomy after EMR exhibited a survival rate of 87.5%[10]. A phase Ⅱ study to evaluate the efficacy and safety of combined EMR and chemoradiotherapy treatment for clinical stage I esophageal cancer (T1b: SM1-3) is ongoing[11]. The necessity of additional surgical treatment and alternative treatments should be considered based on the pathological findings, age, comorbidities, and the patient's wishes, and the clinical protocol should be strictly followed.

### *Stomach*

ESD was first applied in the stomach, and most of the clinical and pathological data for this technique can be pooled. The *en bloc* resection and complete resection rates are 83%-95% and 73%-92%, respectively[12-18], which suggests that complete resection is not obtained in 8%-27% of cases. Additional treatments are required in these cases. The 2004 guidelines for the diagnosis and treatment of stomach carcinoma from the Japanese Gastric Cancer Society[19] recommend ER for the lesion, which meets the following criteria: macroscopic mucosal cancer, less than 2 cm, differentiated type (pap, tub1, tub2), and the absence of ulceration and scarring in the case of the depressed type. Expanded criteria include differentiated mucosal cancer without ulceration irrespective of the tumor size, differentiated mucosal cancer with ulceration if the size is less than 3 cm, and differentiated lesions less than 3 cm in size that invade less than 500 μm into the submucosa and without evidence of lymphovascular invasion on computed tomography or endoscopic ultrasound[4,20].

Patients who undergo treatment according to these expanded criteria exhibit similar long-term survival and

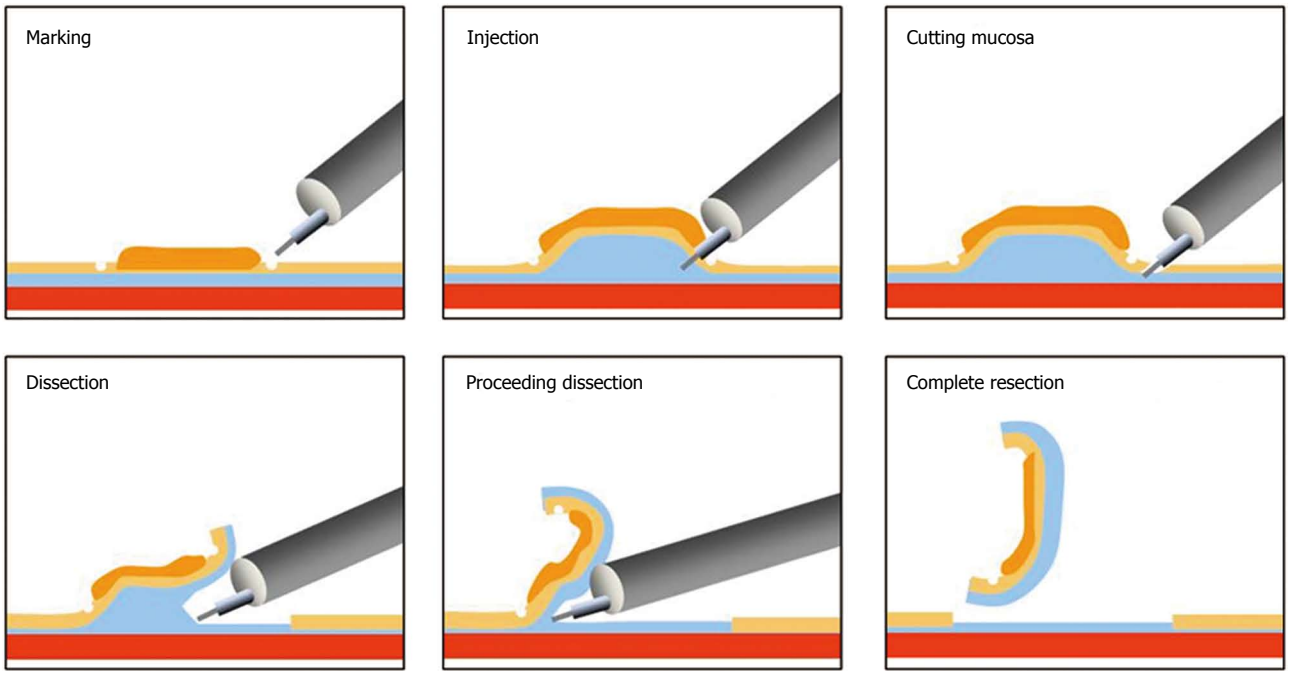


**Figure 1 Image of Endoscopic submucosal dissection: Marking is not necessary in a colorectal case because the lesion margins are clear.**

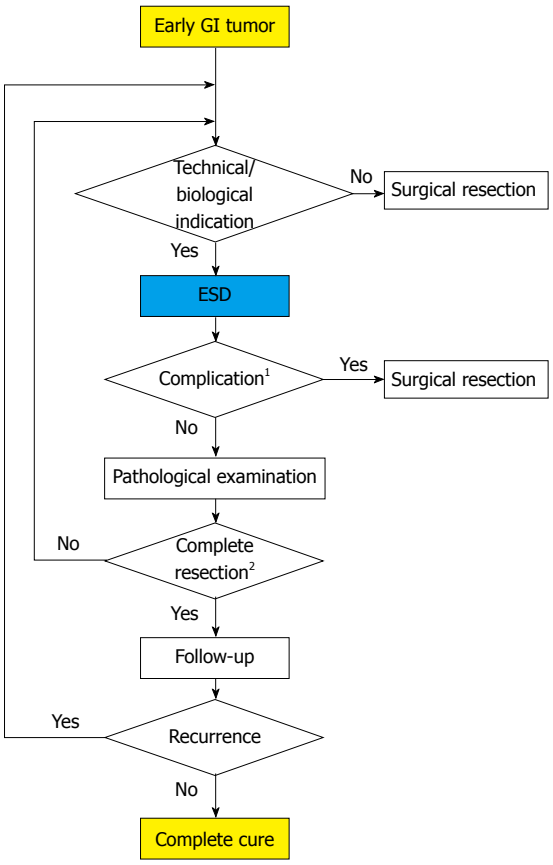


**Figure 2 Algorithm for the treatment of early gastrointestinal tumors.** [1]Perforation or bleeding during endoscopic submucosal dissection which can not be treated endoscopically or delayed perforation; [2]See Table 2.

outcomes as patients who are treated according to the basic criteria[21]. Patients are considered to have undergone non-curative ER when histological examinations reveal that the resected specimen does not meet the criteria for curative ER (Table 1) according to the Japanese Classification of Gastric Carcinoma[22]. Surgery remains the standard treatment after non-curative ER in patients with a possible risk of LNM[23]. The incidence of residual tumors in surgical specimens of gastric cancer was 24.6% (out of 118 cases) after incomplete ESD, and radical gastrectomy should be performed if pathological examination reveals a positive lateral resection margin after ESD[24]. However, gastrectomy with lymph node dissection should be considered for patients with submucosal invasion regardless of margin status because of possible residual tumor or LNM[25]. A suspicious margin status should be managed similarly to a positive margin status after endoscopic treatment because of the high rate of residual cancer. These authors emphasized that gastrectomy is sometimes unnecessary because recurrence may involve only the mucosa, and more minimally invasive treatment modalities, such as re-ESD and other endoscopic interventions, are recommended in these cases. Incomplete resection by gastric ESD significantly increases

**Table 1 Histological criteria for curative endoscopic resection for gastric cancer**

| |
|---|
| Factors associated with no risk of lymph node metastasis |
| Intestinal-type histology |
| No lymphatic or vascular infiltration |
| Intramucosal cancer, regardless of tumor size, without ulcer findings or intramucosal cancer less than 30 mm in size with ulcer findings or minute submucosal invasive cancer (SM1) less than 30 mm in size |
| Factors associated with the resection margin |
| Tumor-free horizontal margin |
| Tumor-free vertical margin |

**Table 2 Factors for which additional treatment after endoscopic submucosal dissection should be recommended**

| |
|---|
| Esophagus (squamous cell carcinoma) |
| Tumors in contact with or invading the muscularis mucosa |
| Tumors invading the submucosal layer |
| Stomach |
| Positive lateral margins |
| Deep submucosal invasion, regardless of positive vertical margins (> 500 μm) |
| Vascular or lymphatic invasion |
| Diffuse-type histology |
| Colon and rectum |
| Positive vertical margins at the site of submucosal invasion |
| Depth of submucosal invasion greater than 1000 μm |
| Vascular or lymphatic invasion |
| Poorly differentiated adenocarcinoma, signet ring cell carcinoma, or mucinous carcinoma |
| High-grade tumor budding[1] |

[1]Tumor budding: An isolated single cell or a cluster composed of fewer than five cancer cells in the stroma of the actively invasive region.

the local recurrence risk, and most initial recurrence lesions that are treated with additional argon plasma coagulation recur[26].

Elderly patients should not undergo radical surgery if they have comorbid diseases or a limited life expectancy. However, additional surgery following non-curative ER improves overall and disease-free survival compared with nonsurgical observation in stomach cancer patients > 75 years of age[27], and surgery should be considered following non-curative ER in elderly patients.

### Colon and rectum

The 2010 Guidelines for the Treatment of Colorectal Cancer from the Japanese Society for Cancer of the Colon and Rectum recommends colorectal ER for intramucosal cancer (M) and cancers with slight invasion into the submucosal layer of less than 2 cm in diameter, irrespective of the shape, based on a large number of studies on resected specimens[5,28,29]. The guideline-recommended indications for additional surgical treatment are presented in Table 2. The budding grade and histological type exhibit a greater association with LNM than the depth of submucosal invasion[30,31], and well-differentiated adenocarcinoma without budding may be observed after complete ER even if the cancer invades the submucosal layer.

## ESD FOR RESIDUAL/RECURRENT CANCER

Repeat EMR as a cure for locally recurrent gastrointestinal tumors is difficult to perform because the initial ER or chemoradiotherapy produces submucosal fibrosis. Surgical resection is necessary in these cases. However, ESD allows for a submucosal dissection through the fibrosis to achieve an *en bloc* resection.

### Esophagus

EMR was evaluated as a salvage treatment after chemoradiotherapy for esophageal cancer prior to the introduction of ESD, but the rate of *en bloc* resection was not high enough to warrant its use. Saito *et al*[32] reported that 100% of cases of locally recurrent or residual superficial esophageal SCCs after chemoradiotherapy were successfully resected *en bloc* using ESD, and these results were superior to the *en bloc* resection rate of 47% for EMR.

### Stomach

The rates of *en bloc* resection, complete resection, and curative resection for EMR for locally recurrent gastric cancer are 0%, 41%, and 33%-41%, respectively[17,33]. Surgical resection after EMR should be considered for non-curative cases. The rates of *en bloc* resection, complete resection, and curative resection for ESD are 89%, 95%, and 76%-80%, respectively, even in locally recurrent cases[17,18,33]. Furthermore, the rate of perforation is 3%-9%[17,33], which is comparable to the 3%-10%[12-16,18,34] perforation rate for ESD in new cases. Conservative treatment was performed after closure with an endoscopic clip in all of the perforation cases[17,33]. ESD is a useful treatment that can prevent the need for surgical resection for locally recurrent gastric cancer.

### Colon and rectum

Kuroki *et al*[35] used ESD in 34 consecutive cases of residual or locally recurrent colorectal tumors. The perforation rate was 14.7% (five cases), emergency surgery was required in one case, and the rates of *en bloc* resection and complete resection were 93% and 82%, respectively. These authors concluded that the use of ESD for residual/locally recurrent lesions was curative and efficacious, and this technique reduces surgical resection requirements. The *en bloc*[36] resection rate of ESD in 30 cases of residual or locally recurrent colorectal tumors was 93%, and the complete resection rate was 83%. However, these favorable results were reported at high-volume institutions, and this procedure is not easily performed because of submucosal fibrosis, spastic bowel movements, and the low controllability of the scope in the right colon[37]. The use of ESD for a recurrent lesion requires a highly advanced technique, and the laparoscopic resection of colonic cancer may be performed within almost the same time frame as ESD at some institutions[38]. Therefore, the treatment modality for a residual/recurrent tumor in the colon should be chosen according to the technical abilities of the physician.

## TRANSANAL RESECTION, TRANSANAL ENDOSCOPIC MICROSURGERY, AND ESD

Transanal resection (TAR) (Figure 3A) and TEM (Figure 3B) are well-developed surgical procedures for the local

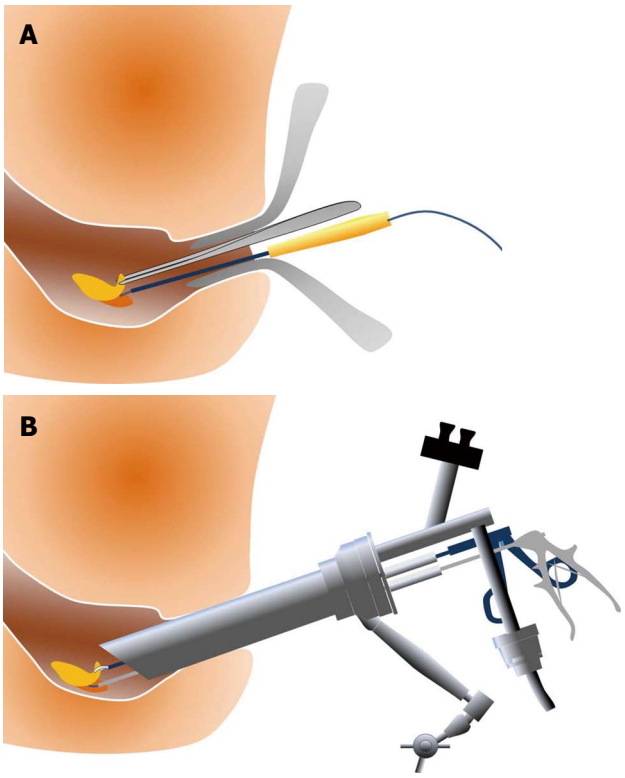


**Figure 3 Resection of a rectal tumor.** A: Transanal resection; B: Transanal endoscopic microsurgery.

excision of rectal adenomas, intramucosal cancers, and superficial submucosal cancers of the rectum. ESD is associated with a longer procedure time than TAR (131 min *vs* 63 min), but ESD is more effective than TAR for the treatment of non-invasive rectal tumors, with a lower recurrence rate (0% *vs* 15.5%) and shorter hospital stays (4.9 d *vs* 7 d)[39]. TEM provides better visualization than TAR, and the clinical results with TEM are superior. However, the recurrence rate is as high as 4%-8%[40-43]. TEM exhibits a technical advantage because it enables the removal of the full thickness of the rectal wall, but the recurrence rates are 0% for SM1, 17% for SM2, and 30% for SM3. Therefore, TEM alone is not a feasible treatment for massive SM rectal cancers, and its indication is not broader than ESD. TEM suffers from poor visualization of the operative field near the dentate line, relatively high recurrence rates, and high instrumentation costs. Therefore, ESD may be a better technique for adenoma, intramucosal cancer, and slightly invasive submucosal cancer in the rectum. Figure 4 presents an example case of ESD for a rectal tumor larger than 10 cm.

## SURGERY FOR ESD COMPLICATIONS

Perforation and bleeding are the major complications during the ESD procedure, and perforation, bleeding, and stenosis may occur after the operation. Most of the bleeding may be treated using an endoscopic approach, but all perforations are traditionally treated using salvage laparotomy with closure of the perforation and intensive intra-abdominal lavage with a large volume of physiological saline. However, perforation during the ESD procedure may be nonsurgically treated using endoscopic closure followed by adequate intensive conservative treatment[44].

### Esophagus

The perforation rate in esophageal ESD is 0%-20%[6,45-51]. Perforation may cause severe emphysema or mediastinal inflammation, which may require surgical or interventional mediastinal drainage[52]. However, immediate endoscopic closure of the perforation followed by intensive conservative treatment can avoid the need for surgery in most perforations during the ESD procedure[44]. Pneumomediastinum, which does not cause clinically significant complications, is frequently detected after esophageal ESD by chest computed tomography (31%)[53]. Esophageal ESD is associated with esophageal stenosis, particularly when ESD involves the entire circumference of the esophageal lumen. Various techniques, including intralesional steroid injection[54], oral prednisolone administration[55,56], balloon dilatation[55-58], and the placement of a self-expanding metal stent, are used[59,60], and surgical treatment is not generally necessary. However, a small risk of perforation has been observed during balloon dilatation[61] and steroid injection[54]; therefore, these procedures should be performed carefully.

### Stomach

Perforation during ESD for stomach tumors occurs in 2%-10% of cases, and most perforations are treated using endoscopic and conservative treatments without a surgical approach[12-18]. However, delayed perforation after gastric ESD generally requires emergency surgery. Hanaoka *et al*[62] demonstrated that delayed perforation after gastric ESD occurred in six of 1159 patients (0.45%), and five of these six patients required emergency surgery. Three of these patients were treated using omentoplasty. However, two patients required gastrectomy because the perforation hole was too large to be closed with an omental patch in one patient, and the omentum had been removed in a previous colectomy in the other patient.

### Colon and rectum

The perforation rate in colorectal ESD is 4%-10%, and most cases are treated nonsurgically[35,62-69]. However, delayed perforation after colorectal ESD generally requires emergency surgery. Saito *et al*[64] observed perforations after colorectal ESD in 54 of 1111 cases (4.9%) and delayed perforation in 4 cases (0.4%). Two immediate perforations with ineffective endoscopic clipping and three delayed perforations required emergency surgery. Fujishiro *et al*[70] reported 11 (5.5%) immediate perforations in 200 cases of colorectal ESD that were successfully managed conservatively, but one delayed perforation (0.5%) required laparotomy.

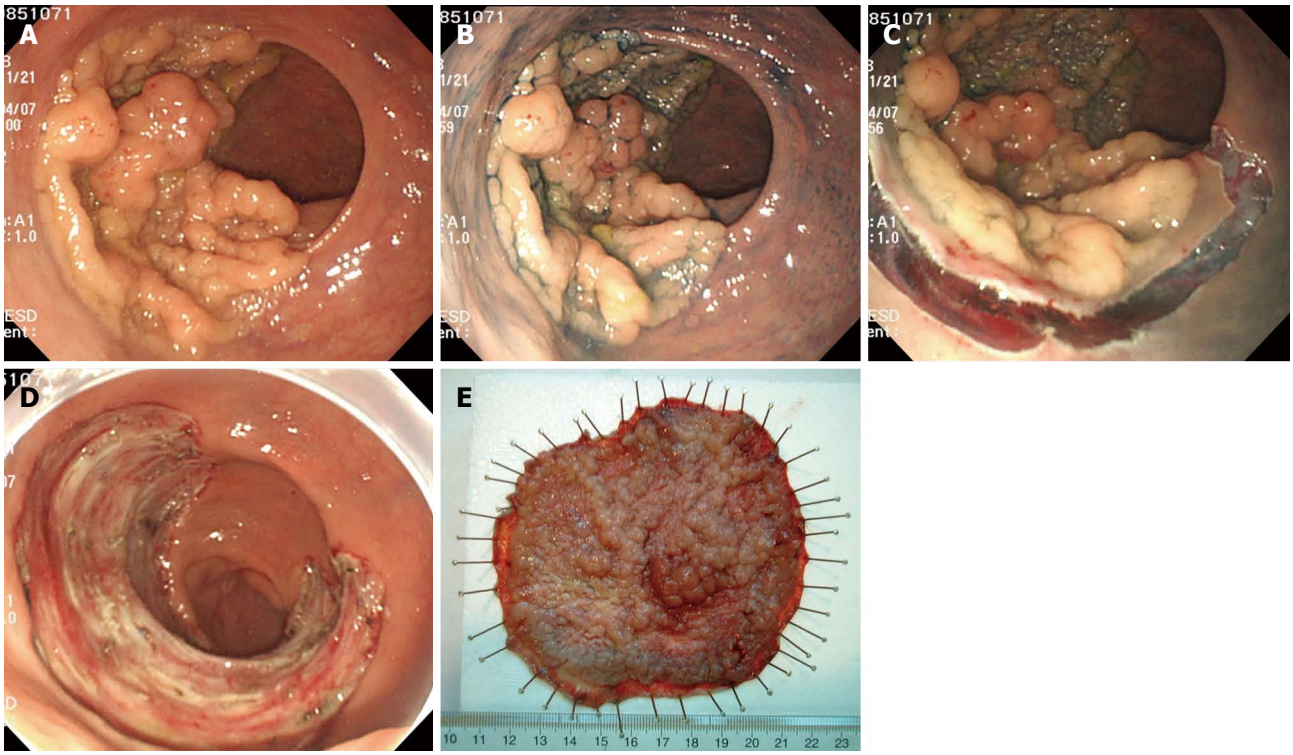


**Figure 4 A case of a rectal tumor resected by endoscopic submucosal dissection in which laparotomy was required.** A: A broad-based tumor spreading to over half of the circumference is observed in the rectum; B: Chromoendoscopy with indigo carmine; C: Mucosal incision with the Flush knife; D: Appearance of the mucosa after complete resection by endoscopic submucosal dissection; E: The fixed resected specimen was 115 mm in diameter.

## ESD AFTER GASTROENTEROLOGICAL SURGERY

The remnant stomach after gastrectomy remains at high risk for a second primary gastric cancer. Traditionally, the outcome for patients with gastric cancer in the remnant stomach has been poor, and the standard treatment for remnant gastric cancer was total gastrectomy with extended lymph node dissection[71]. However, Takeda *et al*[72] observed that none of the 15 patients with early remnant gastric cancer in his consecutive series presented LNM, and the prognosis of these patients was good. The quality of life after total gastrectomy is markedly reduced. Therefore, ER is a highly desirable method for the preservation of the stomach. ER of the lesion in the remnant stomach is technically difficult using the conventional method of EMR because of the narrow inner space and the massive fibrosis around the staples in the suture line. The rates of *en bloc* resection and complete resection in the ESD of remnant gastric tumors are 97%-100% and 74%-92%, respectively[73-75]. The 0%-13% perforation rate is higher than the perforation rate in the normal stomach, but all perforations have been successfully treated[73-75]. ESD improves the avoidance of surgical resection in early lesions in the remnant stomach after gastrectomy.

ESD is also highly indicated for tumors in the gastric tube after esophagectomy. The *en bloc* resection rate of ESD for gastric tube tumors is 88%-90%[76,77], which is higher than the rate associated with EMR[76]. One case of successful ESD for a tumor in a colonic interposition after esophagectomy has been reported[78].

A retrospective analysis of 639 cases of esophageal cancer in patients who underwent gastric tube reconstruction and survived more than 10 years revealed that gastric cancer developed at a constant rate, even many years after esophagectomy, with a 10-year cumulative incidence rate of 8.1%[76]. The duration of survival has improved due to progress in the diagnosis and treatment of esophageal cancer. A lesion in a reconstructed organ, such as a gastric tube or colonic interposition, will likely appear more often, and ESD will play a more important role in the treatment of these lesions.

## COMBINATION OF ESD AND LAPAROSCOPIC SURGERY

### *Sentinel lymph node biopsy after ESD*

ESD is applied to benign or early malignant lesions without LNM, and the indication criteria for its use in each organ are discussed above. Local excision may be permitted if no LNM is specifically proven in cases that do not meet the criteria, such as intramucosal undifferentiated carcinoma or massively invaded submucosal cancer. The use of laparoscopic sentinel lymph node biopsy (SLNB) for the examination of LNM after ESD for early gastric cancer that does not meet the standard or expanded indication criteria has been reported[79]. Additional curative surgical resection was performed when LNM was

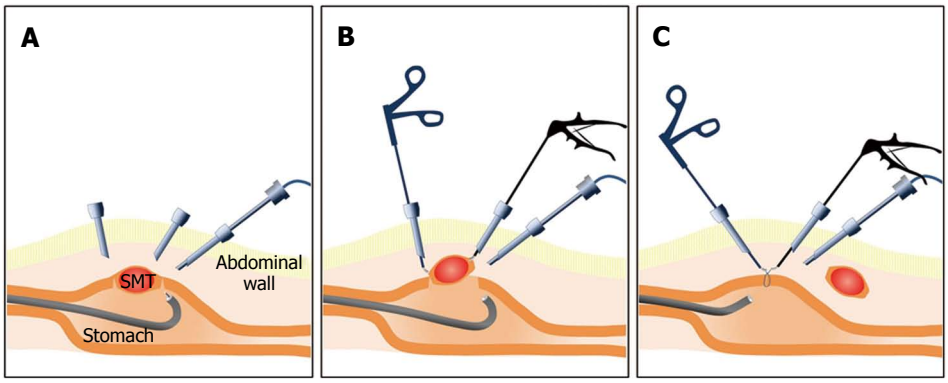


**Figure 5 Combination of endoscopic submucosal dissection and laparoscopic surgery.** A: Confirmation of tumor location and mucosal cutting around the tumor using endoscopic submucosal dissection; B: The full thickness of the stomach wall was cut using a laparoscopic instrument, such as Ligasure®; C: The gastric wall was closed using a laparoscopic hand-sewn technique or laparoscopic suturing device, such as End-GIA.

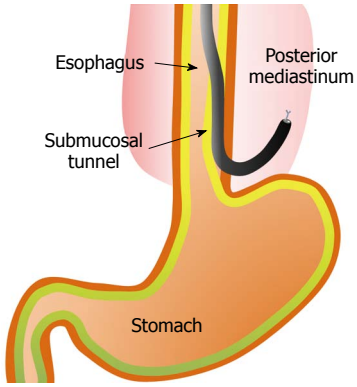


**Figure 6 Natural orifice transluminal endoscopic surgery using the endoscopic submucosal dissection technique (in a porcine model).**

observed. Cahill *et al*[80] applied NOTES after ESD of the stomach and sigmoid colon in a porcine model based on the same criteria. However, a systemic review of 21 articles on SLNB in gastric cancer patients revealed that the overall sensitivity of SLNB was 85.4%[81]. The authors concluded that there was insufficient evidence to introduce SLNB into the treatment protocol for gastric cancer[81]. A meta-analysis of 53 studies on SLNB in colon and rectal cancer revealed a pooled sensitivity of only 76%[82]. The accuracy of SLNB varies according to the biopsy procedure, experience, and method of staining. Therefore, technical improvements in SLNB may lead to the clinical application of the combination therapy of ESD and SLNB using laparoscopic surgery or NOTES.

### *Gastric submucosal tumors*

The combination of ESD and laparoscopic surgery as a novel treatment method for gastric submucosal tumors, such as GISTs, has been reported at some institutions. Laparoscopic excision has been applied to gastric submucosal tumors, but the precise location of the lesion could not be detected in the laparoscopic view. Therefore, excessive resection is inevitable for complete resection. The ESD technique is used for mucosal cutting and full-thickness wall cutting around the lesion prior to laparoscopy to minimize excessive resection. Complete resection is then performed using a laparoscopic approach[79,83-86] (Figure 5).

### *Application of the ESD technique to NOTES*

NOTES has attracted considerable attention as a minimally invasive surgery. Endoscopic transesophageal mediastinal lymph node dissection and epicardial coagulation using mediastinal and thoracic approaches in a porcine model have been reported previously[87] (Figure 6). An element of the ESD technique has been applied to these novel surgeries.

## CONCLUSION

Additional treatments, including surgery with lymph node dissection, should be recommended to patients with non-curative resection following ESD. ESD may be successfully applied for a residual/recurrent gastrointestinal tumor after ER, a second primary tumor in the remnant stomach after gastrectomy, or a tumor in the gastric tube or colon that was reconstructed after gastroenterological surgery. ESD is superior to TAR and TEM for the treatment of an early rectal tumor. Most of the perforations that occur during the ESD procedure can be treated non-surgically using endoscopic closure, but delayed perforations require emergency surgery. This review summarized novel trials of the combination of ESD and laparoscopic surgery, and the application of an element of the ESD technique to NOTES was reported.

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**S- Editor** Song XX **L- Editor** A **E- Editor** Zhang DN

World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/esps/
wjge@wjgnet.com
doi:10.4253/wjge.v4.i10.448

*World J Gastrointest Endosc* 2012 October 16; 4(10): 448-452
ISSN 1948-5190 (online)


TOPIC HIGHLIGHT

**Toru Hiyama, MD, PhD,** *Series Editor*

# What we have learned and what to expect from capsule endoscopy

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Received: April 29, 2012 Revised: August 26, 2012
Accepted: October 10, 2012
Published online: October 16, 2012

## Abstract

Capsule endoscopy was conceived by Gabriel Iddan and Paul Swain independently two decades ago. These applications include but are not limited to Crohn's disease of the small bowel, occult gastrointestinal bleeding, non steroidal anti inflammatory drug induced small bowel disease, carcinoid tumors of the small bowel, gastro intestinal stromal tumors of the small bowel and other disease affecting the small bowel. Capsule endoscopy has been compared to traditional small bowel series, computerized tomography studies and push enteroscopy. The diagnostic yield of capsule endoscopy has consistently been superior in the diagnosis of small bowel disease compared to the competing methods (small bowel series, computerized tomography, push enteroscopy) of diagnosis. For this reason capsule endoscopy has enjoyed a meteoric success. Image quality has been improved with increased number of pixels, automatic light exposure adaptation and wider angle of view. Further applications of capsule endoscopy of other areas of the digestive tract are being explored. The increased transmission rate of images per second has made capsule endoscopy of the esophagus a realistic possibility. Technological advances that include a double imager capsule with a nearly panoramic view of the colon and a variable frame rate adjusted to the movement of the capsule in the colon have made capsule endoscopy of the colon feasible. The diagnostic rate for the identification of patients with polyps equal to or larger than 6 mm is high. Future advances in technology and biotechnology will lead to further progress. Capsule endoscopy is following the successful modern trend in medicine that replaces invasive tests with less invasive methodology.



**Key words:** Capsule endoscopy; Cancer screening; Colon cancer; Artificial intelligence; Technology

**Peer reviewers:** Federico Carpi, PhD, Assistant Professor, Interdepartment Research Centre "E. Piaggio", School of Engineering, University of Pisa, Via Diotisalvi 2, Pisa 56100, Italy; Shinji Tanaka, MD, PhD, Professor, Department of Endoscopy, Hiroshima University Hospital, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan

Adler SN, Bjarnason I. What we have learned and what to expect from capsule endoscopy. *World J Gastrointest Endosc* 2012; 4(10): 448-452 Available from: URL: http://www.wjgnet.com/1948-5190/full/v4/i10/448.htm DOI: http://dx.doi.org/10.4253/wjge.v4.i10.448

## BACKGROUND AND HISTORY

Two researchers, Gabriel Iddan and Paul Swain, independently and extensively investigated the possibility of transmitting images from the digestive tract to an extracorporeal receiver by swallowing a wireless capsule camera. Technological advancements lead to miniaturization of the electronic image processing unit (charged couple device, 1969) and the development of a more energy efficient processor and transmitter of digital information (CMOS 1994). The imagination of these two research-

ers began to reach the fringes of reality. In 1996, Paul Swain-a gastroenterologist-demonstrated that a wireless ingested capsule could transmit on line images from a pig stomach to an outside receiver. At this point this finding remained in the realm of a curiosity. Gabriel Iddan-an electro optic engineer, PhD-contacted Paul Swain and offered him to join forces to conquer new territory in the field of gastroenterology. The next great successful step forward in the research of these scientists was to cooperate and not to compete with each other. And so it came that in 1999 the internal review board permitted the ingestion of a prototype capsule endoscope in a human. Paul Swain executed this honor in Israel. Iddan and Swain had obtained proof of principle.

The concept of wireless capsule endoscopy became more intriguing. Yet the pivotal question remained. Did this device carry any medical relevance? A clinical trial was designed to address this question. A gastrointestinal medical condition, occult gastrointestinal bleeding, was chosen which was known to challenge treating physicians. These are patients with bleeding from the digestive tract who have undergone a work up which includes an esophagogastroduodenoscopy, colonoscopy and some kind of small bowel imaging such as a small bowel series or computerised tomography enterography with negative results. The plan was to take 20 such patients and have the capsule compete with the best available technology at that time, namely fiberoptic enteroscopy. Capsule endoscopy outdid fiberoptic enteroscopy by a ratio of 2:1. Lewis and Swain presented their results at DDW in 2001. The United States Food and Drug Administration immediately recognized the benefit of this concept in summer of 2001. Lewis and Swain's findings were since confirmed by more than a dozen studies. In the meanwhile capsule endoscopy of the small bowel has proven its clinical relevance in diagnosing non-steroidal anti-inflammatory drug (NSAID) induced small bowel disease, Crohn's disease, neoplastic disease and others.

In January 2002, I gave a lecture on capsule endoscopy and pointed out that 3000 capsule ingestions had already taken place. The importance of capsule endoscopy to the field of gastroenterology is reflected in the fact that in the following 10 years over one and half million capsule examinations have been performed. The plethora of information and publications that has accumulated from capsule endoscopy can be seen in Figure 1. That same year I experienced a very moving experience when I presented a review on small bowel pathology induced by NSAIDs. The previous speaker at the conference was Professor Bjarnason. When I asked him if he was the Professor Bjarnason who based on intestinal permeability studies nearly two decades earlier had predicted that NSAIDs caused small bowel mucosal damage he modestly responded with yes. Then I continued to inform him that it was for me a true honor to present to him the images of capsule endoscopy that proved he had been right all along.

## FURTHER DEVELOPMENTS

### *Small bowel*

Capsule endoscopy has undergone many further developments. Picture quality has been improved by the introduction of devices with wider angle of view, better lenses and automatic control of light exposure to improve performance of small bowel survey by the capsule. Capsule endoscopy of the small bowel has made traditional small bowel series obsolete. What has been proven to be correct for the upper gastrointestinal tract and the colon has been proven to be true for the small bowel, too. Direct optical inspection is superior to barium studies, for this reason the gastroscope replaced the upper gastrointestinal series, the colonoscope the barium enema and now capsule endoscopy has replaced the small bowel series examination. Triantafyllou has made the interesting observation that use of a capsule camera with two imagers, an imager at each end of the capsule, for the evaluation of small bowel pathology will increase the diagnostic yield by 5 percent[1]. His observation is in good keeping with our own. Severity of Crohn's disease is influenced by the fact whether the standard capsule, one imager at one end and the antenna at the other end of the capsule, enters the small bowel with the camera leading or the antenna leading[2].

A further step forward is the image modifier software added to the reading package of Given Imaging. I find it very helpful to modify basic colors. For instance partially oxidized blood appears black with standard review software. The FICE option of the new software turns this dark blood into bright red. Pathological mucosa appears different from the background healthy mucosa in blue mode. Whenever I encounter a finding that may be a small superficial ulceration versus overlying debris, I activate the blue mode. If it is a true ulceration or mucosal break then the margin of the ulcer next to healthy mucosa is reflected as a thin hemorrhagic border. The development of this technology may open the doors to optical biopsy.

The advent of double balloon (push pull endoscopy) did not replace the need for capsule endoscopy of the small bowel. Controlled studies have demonstrated that these two procedures are complementary. The diagnostic yield of capsule endoscopy and the ability to screen the entire small bowel are superior with capsule endoscopy. Furthermore capsule endoscopy can indicate if double balloon endoscopy should be performed *via* the oral or anal route[3]. These studies conclude that in case of suspected small bowel disease a capsule study is to be performed. The results of the capsule study may indicate the need for therapeutic or diagnostic intervention. That is when double balloon endoscopy should be performed.

## ESOPHAGUS

Capsule endoscopy has been extended to examine the

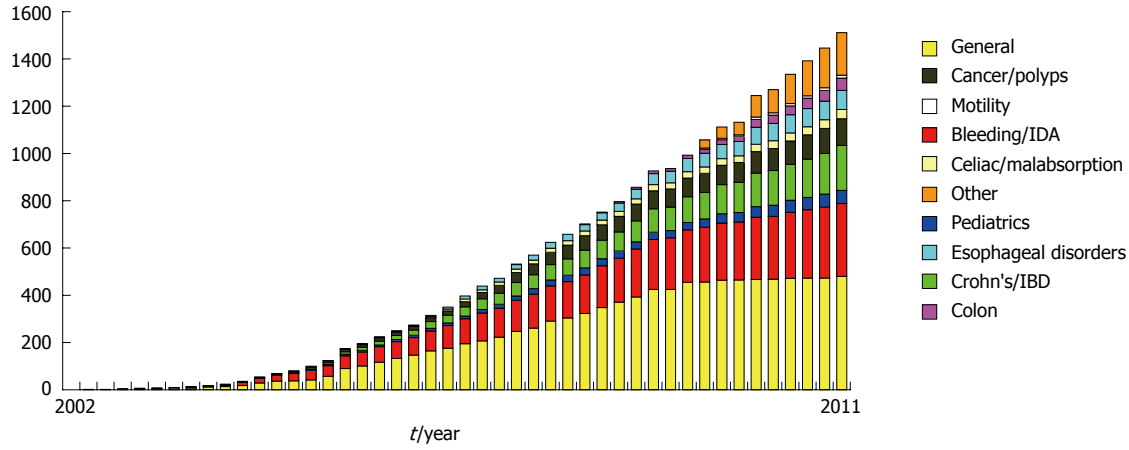


**Figure 1 Number of peer reviewed publications per year.**


**Figure 2 Colon capsule with two video cameras at each end of the capsule.**

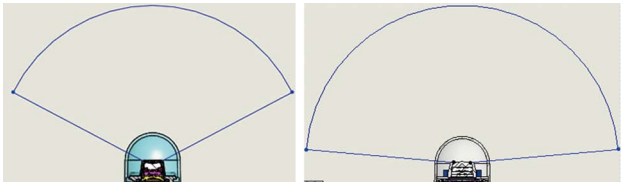


**Figure 3 Extension of angle of view in second generation colon capsule (C2) *versus* first generation colon capsule (C1).**

esophagus. Capsule transit time *via* the esophagus is significantly faster than transit time in the small bowel. For this reason two cameras transmitting images at a high rate (14 frames per second) have been placed at each end of the esophageal capsule camera. These cameras with high transmission screen the esophagus well. The esophageal capsule has a very high diagnostic sensitivity for diseases such as reflux esophagitis, Barrett's esophagus or esophageal varices[4]. The advantages for using capsule endoscopy are the lack of need for sedation, non invasiveness and the possibility of performing the procedure at the first office visit. The disadvantage is that the esophageal capsule is competing with a very good, albeit invasive device, the gastroscope, which is in most places cheaper.

## COLON

The fact that a noninvasive method could provide direct visual inspection of the intestinal lining made the concept of capsule inspection of the colon very attractive. The procedure to obtain direct inspection by standard colonoscopy requires the use of an invasive test with sedation. Although the risks for severe complications with standard colonoscopy are small there is an underrated amount of significant post procedural complaints leading to increased emergency room visits after colonoscopy[5]. Compliance of healthy individuals to undergo colonoscopy for primary colon cancer prevention is suboptimal.

Yet the obstacles to produce a capsule camera that could screen the colon were challenging for the following reasons: (1) The small bowel is narrow compared to the large bowel. As the capsule camera enters the small bowel the lumen of the small bowel is by and large too small to permit the capsule to turn along its own axis. Therefore the capsule will enter either with the camera leading or the part of the capsule containing the antenna leading. The capsule will remain oriented in the given position as it entered the small bowel along its journey through the small bowel. For this reason the single camera of the small bowel capsule will screen the entire small bowel mucosa. This is not true for the colon. There the capsule can tumble backwards and forwards in the wide lumen of the colon. If this were to happen then there would be areas of the colon that the capsule would capture twice and areas that the capsule would not capture at all. The engineers at Given Imaging designed a colon capsule that has two cameras, one camera at each end (Figure 2). The colonic mucosa is visualized from both directions simultaneously and thus complete visual coverage of the entire colon is guaranteed; (2) The transit time to reach the end of the colon is much longer than the time required for the capsule to reach the cecum. Furthermore the colon capsule consumes more energy than the small bowel capsule since it transmits images from two cameras. While the energy needs of the colon capsule are that much greater than the small bowel capsule, the amount of energy available to the capsule for transmitting images to

the external recorder is limited to two watch batteries. To guarantee adequate energy supplies for the transmission of images from the colon, the colon capsule was put to sleep for an hour and a half five minutes after ingestion; and (3) Whereas in standard colonoscopy some minimal amount of liquid debris can be aspirated via the colonoscope, minimal amount of debris may compromise the capsule's ability to identify pathological changes. A more vigorous bowel preparation had to be offered to patients to assure proper cleansing for colon capsule examinations. A clear liquid diet prior to the day of examination and split dose Polyethyleneglycol ingestion achieved adequate cleansing in 80% of patients[6].

The first colon capsule was put to the test in the year 2005 and 2006. The results of three studies were encouraging. Firstly the bowels could be adequately cleansed in 80% of patients. Secondly the capsule could traverse through the entire gastrointestinal tract and transmit images from the entire colon. Finally the capsule did indentify pathologies such as polyps, tumors, colitis, diverticulosis and internal hemorrhoids. The suboptimal identification of patients with colonic polyps as compared to standard colonoscopy fell short of expectations.

What I find impressive is that the engineers at Given Imaging did not accept defeat. Instead of surrendering they analyzed in detail the shortcomings of the colon capsule. With the results of their analysis they created the second generation colon capsule. Here are some of the changes that they made. The angle of view of the first generation colon capsule camera is 154 degrees. The angle of view has been widened to 172 degrees for each camera of the second generation colon capsule. This change provides a near full panorama view (Figure 3). The Data Recorder 3 is a true revolution in capsule endoscopy. This device has been endowed with artificial intelligence. It communicates with the capsule and the capsule is programmed to carry out the instructions received by the data recorder. Not only does this new data recorder speak to the capsule camera, it also communicates with the patient undergoing the colon capsule examination. Let me walk you, the reader, through the process.

The colon capsule is ingested by the patient. After three minutes the rate of transmission is reduced to 16 images per minute to conserve energy. The received images are constantly analyzed and recognized by data recorder 3. If after one hour data recorder 3 notices that the colon capsule is still in the stomach it will talk to the subject by activating an alarm ring tone, a vibrating device attached to the antenna and display number 0 on the liquid crystal display screen. The patient will consult his instruction sheet and learn that the number 0 indicates that he/she has to ingest a prokinetic agent such domperidone or metoclopramide. However if the capsule has left the stomach and entered the small bowel, the artificial intelligence of data recorder 3 will recognize that the capsule is now in the small bowel. Data recorder 3 will order the capsule to raise the transmission rate from 16 images per minute to 4 images per second. At the same time data recorder 3 will communicate with the patient and tell him to ingest his booster. The purpose of this booster is to shorten small bowel transit time and to maintain adequate cleanliness of the bowel. The artificial intelligence of the data recorder will recognize if the capsule is stationary or in motion. Once data recorder 3 recognizes that the capsule is in motion it orders the capsule to raise its transmission rate to 35 images per second. The process of recognition to execution literally takes place in a split second. This rapid transmission rate (35 images per second) provides adequate number of colonic images while the capsule is in motion especially while flying through the transverse colon.

The software program for colon capsule 2 has been equipped with a polyp size assessor. The cursor is drawn from one side of the polyp to the other and the algorithm spits out the size of the polyp in mm. The system is reliable. The same polyp seen from distance or from close up will have the same size.

While these technological achievements are very impressive (a data recorder talking to capsule and patient, analyzing images, determining location, position-stationary versus motion, altering transmission rate) the same question has to be asked as we had asked ourselves at the outset of capsule endoscopy in the year 2000. Is this a high tech toy or a medically relevant tool?

We engaged in a five center prospective double blind feasibility study in Israel in which this second generation colon capsule was compared to standard colonoscopy for the identification of patient with colonic polyps. 104 patients were enrolled. Whereas in the European multicenter trial published in 2009 the sensitivity to identify patients with polyps was only 60% the sensitivity in the multicenter Israel trial with the second generation colon capsule rose to 90%[7]. This marked improved diagnostic sensitivity was reproduced by a recent European study with the second generation colon capsule[8]. This improvement (raise in diagnostic sensitivity from 60% to 90%) has to be attributed to the revolutionary new capsule platform of this second generation colon capsule. The three previous studies with the first generation colon capsule had a very similar design as our present study. Good bowel cleansing was obtained at similar rates as in this new study. The only factor which set this second generation colon capsule study apart from the previous studies is the new technological platform. Protocol restraints contributed to a relatively low specificity. Colonoscopy was defined as the gold standard. Even in good hands standard colonoscopy is known to miss colonic polyps[9,10]. If the capsule identified a polyp and the first colonoscopy missed the polyp yet the polyp was found on repeat colonoscopy this was counted as a false positive capsule finding. The same is true for polyp miss match between colon capsule and colonoscopy. If colon capsule identified the polyp to be 12 mm large and the colonoscopy defined the polyp to be 9 mm then this too was counted as a false positive capsule result.

The negative predictive value of 97% is very high and is clinically very meaningful. The physician offering his patient a colon capsule study can tell his patient that a negative study has 97% accuracy that he harbors no polyps.

The fact that the intelligent data recorder 3 not only talks to the capsule but to the patient too has opened the door to offer colon capsule studies as an outpatient procedure. Increasing compliance to participate in colon screening programs is essential to reduce colon cancer mortality in our society. Hassan *et al*[11] have calculated relying on figures from first generation colon capsule studies with a relative low sensitivity to detect patients with colonic polyps that increasing compliance to participate in capsule colon cancer screening by 4% would save the same amount of lives as colonoscopy does today. With the second generation colon capsule only a 2% increase in compliance will lead to an equal number of patients saved by colon cancer.

## THE FUTURE

The future will be brighter and better than the past and present. Our good technologies will be replaced and retired by better technologies. My immediate expectations are that we will enjoy capsule endoscopes that will give us a realistic assessment of the entire gastrointestinal tract. Invasive diagnostic tests will be a thing of the past. Invasive tests will be reserved for therapeutic interventions. My further expectations are that we will not only look and the mucosal surface of the gastrointestinal tract but that we will focus on the host of molecular signals present in the lumen of the digestive tract. Molecular markers will include tumor markers, oncogenes or oncogene derived proteins, tissue transglutaminase, inflammatory parameters such as calprotectin and others. For us to get there we need the dreams of a Gabriel Iddan and a Paul Swain with the commitment and tenacity that these young and bright people at the Research and Development department of Given Imaging have. It is first and foremost to these bright and dedicated young engineers and scientists that I owe the thrill of the past ten years that permitted me to be part of the team that moved the border of knowledge another mile forward.

So my message to all of you, let's keep our dreams alive.

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World Journal of Gastrointestinal Endoscopy

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wjge@wjgnet.com
doi:10.4253/wjge.v4.i10.453

*World J Gastrointest Endosc* 2012 October 16; 4(10): 453-461
ISSN 1948-5190 (online)


REVIEW

# Current status of device-assisted enteroscopy: Technical matters, indication, limits and complications

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Received: November 28, 2011 Revised: August 24, 2012
Accepted: October 13, 2012
Published online: October 16, 2012

## Abstract

Enteroscopy, defined as direct visualization of the small bowel with the use of a fiberoptic or capsule endoscopy, has progressed considerably over the past several years. The need for endoscopic access to improve diagnosis and treatment of small bowel disease has led to the development of novel technologies one of which is non-invasive, the video capsule, and a type of invasive technique, the device-assisted enteroscopy. In particular, the device-assisted enteroscopy consists then of three different types of instruments all able to allow, in skilled hands, to display partially or throughout its extension (if necessary) the small intestine. Newer devices, double balloon, single balloon and spiral endoscopy, are just entering clinical use. The aim of this article is to review recent advances in small bowel enteroscopy, focusing on indications, modifications to improve imaging and techniques, pitfalls, and clinical applications of the new instruments. With new technologies, the trials and tribulations of learning new endoscopic skills and determining their role in the diagnosis and treatment of small bowel disease come. Identification of small bowel lesions has dramatically improved. Studies are underway to determine the best strategy to apply new enteroscopy technologies for the diagnosis and management of small bowel disease, particularly obscure bleeding. Vascular malformations such as angiectasis and small bowel neoplasms as adenocarcinoma or gastrointestinal stromal tumors. Complete enteroscopy of the small bowel is now possible. However, because of the length of the small bowel, endoscopic examination and therapeutic maneuvers require significant skill, radiological assistance, the use of deep sedation with the assistance of the anesthetist. Prospective randomized studies are needed to guide diagnostic testing and therapy with these new endoscopic techniques.



**Key words:** Device-assisted enteroscopy; Double balloon; Single balloon; Spiral endoscopy

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Riccioni ME, Urgesi R, Cianci R, Bizzotto A, Galasso D, Costamagna G. Current status of device-assisted enteroscopy: Technical matters, indication, limits and complications. *World J Gastrointest Endosc* 2012; 4(10): 453-461 Available from: URL: http://www.wjgnet.com/1948-5190/full/v4/i10/453.htm DOI: http://dx.doi.org/10.4253/wjge.v4.i10.453

## INTRODUCTION

The diagnosis of small-bowel disorders has long been a challenge to gastroenterologists because of the length of the small intestine, its anatomy, and the lack of adequate

diagnostic tools. The advent of capsule endoscopy and push-and-pull enteroscopy during the last decade revolutionized the management of small-bowel disorders.

Although capsule endoscopy can visualize the entire small intestine, a main disadvantage is the inability to obtain biopsy specimens or perform therapeutic manoeuvres *via* this procedure. In contrast, device-assisted enteroscopy techniques, including double-balloon enteroscopy (DBE), single-balloon enteroscopy (SBE), and spiral enteroscopy (SE), have both diagnostic and therapeutic capabilities.

DBE was first introduced by Sugano *et al*[1] in 2001 and has gained widespread acceptance since then. It is the most studied and established deep enteroscopy technique to date. Multiple studies have assessed the utility of DBE for the diagnosis and management of various small-bowel disorders, particularly obscure gastrointestinal bleeding (OGIB) and inflammatory bowel disease.

SBE and SE are the latest breakthrough techniques in endoscopic evaluation of the small bowel. Initial studies of deep enteroscopy focused on presenting narrative experiences with the individual techniques. Since then, comparative trials have been conducted to compare the utility of these various techniques in terms of their diagnostic yield, depth of maximal insertion, efficacy, and complications.

This review presents a detailed analysis of the current status of different types of device-assisted enteroscopy (DAE), with particular focus on indications, contraindications, sedation, choice of insertion route, complications, and relevant technical points.

## DAE

There are currently 3 options available for the performance of deep enteroscopy, DBE, SBE, and spiral enteroscopy.

## DBE

DAE allows deeper intubation of the small bowel compared with push enteroscopy (PE) and ileocolonoscopy. There are two DAEs currently available: the DBE (Fujinon, Wayne, NJ), and the SBE (Olympus America). The concept of DBE was introduced in 1997[1] and was subsequently introduced into the United States in 2004 (Fujinon Inc, Saitama, Japan). The development of DBE was based on the concept that "stretching" of the small intestinal wall prevents further endoscopic advancement, and that the usage of a balloon would grip the intestinal wall and prevent subsequent loop formation[2]. The diagnostic enteroscope (EN450P5) has a 200-cm working length, an endoscope diameter of 8.5 mm, and an accessory channel of 2.2 mm. The therapeutic enteroscope (EN450T5) has a diameter of 9.4 mm and an accessory channel of 2.8 mm. The DBE is composed by both an enteroscope and an overtube, both of which have balloons at the distal end. The two balloons on the DBE are latex made. Both enteroscopies have an overtube length of 140 cm. This type of examinations is generally performed under x-rays control (Figure 1).

Using the DBE entails a series of steps that use a push-and-pull technique[3]. This process facilitates pleating of the small bowel over the enteroscope, allowing for deep enteroscopy. Balloon Assisted Enteroscopy (BAE) can be performed with the antegrade (oral) or retrograde (aboral) approach. DBE allows intubation (240-360 cm antegrade and 102-140 cm retrograde) deeper than possible with PE (90-150 cm) or ileoscopy (50-80 cm).

Its additional diagnostic and therapeutic advantages over capsule endoscopy include its facilitation of biopsies, tattoos, hemostasis, polypectomy, and foreign body removal, dilation and/or stent placement[4-7]. The diagnostic yield of DBE ranges from 60% to 80% in patients with OGIB and other small bowel pathologies. Total enteroscopy with DBE is defined as complete evaluation of the small bowel, with either a single approach or a combined antegrade-retrograde approach. However, it may not be feasible in all patients; the reported success rate is 16%-86%[2,8]. It is likely that the wide range of enteroscopy completion rate among the different Western and Asian study is attributable in part to the different types of patients subject to investigation and partly to the diversity of different chronological studies examined.

The main limitations of DBE include its invasive nature and prolonged duration. The reported complication rate for diagnostic procedures is 0.8% but can be as much as 4% with therapeutics such as electrocoagulation, polypectomy, or dilation. The main complications are pancreatitis, ileus and perforation[5,9,10]. Patients who are not medically stable should not undergo BAE. Those who have had extensive abdominal surgeries may be poor candidates because of adhesions or altered anatomy which may prevent the scope from advancing.

## SBE

The SBE system includes the SIF-Q160 endoscope (Olympus Optical Company, Ltd, Tokyo, Japan) with a working length of 200 cm and 9.8 mm in diameter and contains a 2.8 mm diameter working channel (Figure 2A), the Balloon Control Unit OBCU (Figure 2B) and the ST-SB1 single-use splinting tube (overtube) with a length of 132 cm and an outer diameter of 13.2 mm (Figure 2B).

The splinting tube's smooth glide, hydrophilic coating is activated with the simple addition of 30 mL of water. The SBE is controlled by repeatedly inflating and deflating a single balloon, attached to the distal end of the splinting tube, *via* the remote balloon controller.

Radiopaque material is used in the distal end of the ST-SB1 to allow confirmation of the splinting tube's tip under fluoroscopy, further enhancing insertion performance into the deep small intestine. To improve manoeuvrability of insertion, the SIF-Q160 features a distal-end diameter of just 9.2 mm while maintaining a high-resolution image quality. By optimizing both the distal end length and bending section radius, the SIF-Q160

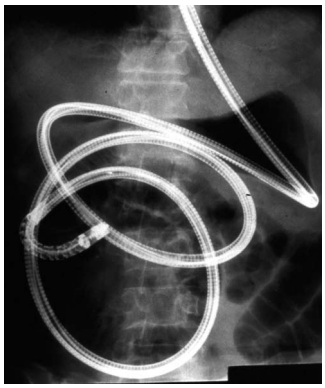

**Figure 1 X-rays control.**

**Table 1 Comparison between the three enteroscopic techniques (single balloon, double balloon, spirus)**

| | Single balloon | Double balloon | Spirus enteroscopy |
|---|---|---|---|
| The depth of insertion | Similar | Similar | Similar |
| Diagnostic yield | Similar | Similar | Slightly lower |
| Therapeutic interventions | Similar | Similar | Similar |
| Complications rate | Similar | Similar | Slightly lower |
| Duration of the enteroscopy | Similar | Similar | Slightly lower |
| Duration of the sedoanalgesia | Similar | Similar | Slightly lower |
| Learning curve | Similar | Similar | Similar |

extensive angulation capability allows acute turns in the small intestine, which allows a smoother insertion. So the ST-SB1 single use splinting tubes used as over-tubes are made from silicone rubber to eliminate the risk of latex allergy[11,12].

### *Spiral enteroscopy*

Spiral enteroscopy is the newest enteroscope system available for clinical use (Figure 2B). The Endo-Ease Discovery SB (Spirus Medical, Stoughton, MA) is a spiral-shaped overtube 118 cm long; its hollow spiral is 5.5 mm high and 22 cm long, with a locking device on the proximal end. It is used for enteroscopy *via* the oral route and can be used only with enteroscopies < 9.4 mm in diameter. Spiral enteroscopy allows for advancement and withdrawal of the enteroscope through the small bowel with rotatory clockwise and counter clockwise movements. The distal end of the overtube is positioned 25 cm from the tip of the enteroscope and locked into place. The system is then advanced to the ligament of Treitz with gentle rotation. Once there, the collar is unlocked and the enteroscope is advanced past the ligament of Treitz[13]. There is also an overtube for a rectal approach called the Endo-Ease Vista Retrograde (Spirus Medical), which can be used for limited ileoscopy, as well as for difficult colonoscopy using a pediatric colonoscope.

Preliminary reports with spiral enteroscopy demonstrate insertion depths less than reported with DBE/SBE but carries the associated advantage of accelerated procedural times. A preliminary study of the Discovery SB suggested a diagnostic yield of 33% and an average depth of insertion of 176 cm from the ligament of Treitz[13]. Another study reported a mean ± SD depth of insertion of 262 ± 5 cm and a mean total procedure time of 33.6 ± 8 min[14]. This modality also allows performance of therapeutics, including biopsy, hemostasis, and polypectomy. The rate of severe complications is reported to be 0.3%, with a perforation rate of 0.27%[15]. No esophageal or gastric perforations have occurred. The device is easy to use and may be effectively operated in as few as five training cases[16,17]. The main characteristics of the three enteroscopic techniques are shown in Table 1.

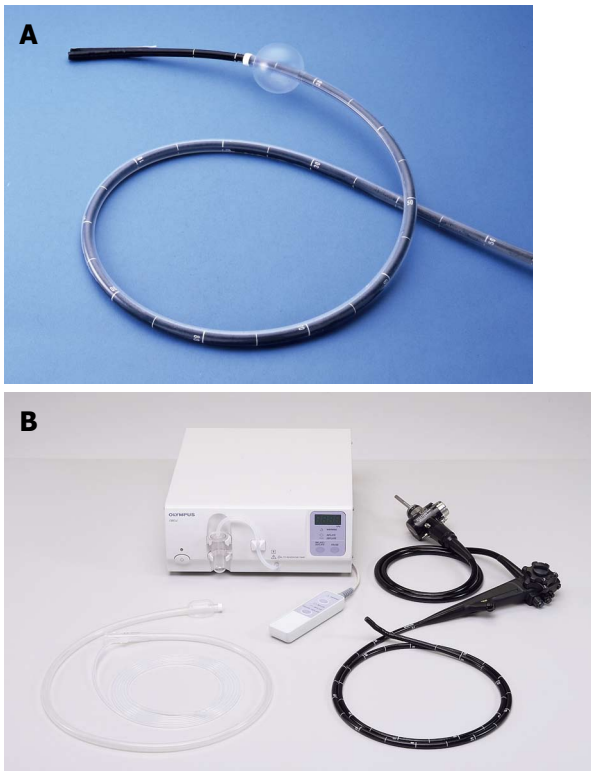


**Figure 2 Single-balloon enteroscopy system.** A: The Single-balloon enteroscopy system system includes the SIF-Q160 endoscope; B: The Balloon Control Unit OBCU and the Splinting Tube-SB1 single-use splinting tube (overtube).

## PATIENTS' PREPARATION FOR DAE

Preparation for DAE examination includes a 12 h overnight fast. Patients, who underwent anterograde and retrograde procedures, received 2 L and 4 L of polyethylene glycol electrolyte lavage solution the day before examination, respectively.

The starting insertion oral or anal route was chosen as per clinical judgement according to the probable location of the suspected lesions on the basis of clinical presentation and of previous investigations. Many of the procedures were performed under deep sedation or general anaesthesia.

## MAIN INDICATIONS FOR DEVICE-ASSISTED ENTEROSCOPY

The main therapeutical indications for BAE include the need for treatment of small intestinal lesions found on other gastrointestinal investigations, such as capsule endoscopy or radiological examinations. However, an initial capsule endoscopy study remained a preferred initial strategy owing to the higher complication rate associated with DAE. The procedure is not used in Western Countries as a first line therapy and is performed only after careful evaluation by a specially trained gastroenterologist[17]. The main indications are: bleeding lesions seen on capsule endoscopy, worrisome lesions or masses seen by other modalities, polyps in patients with hereditary syndromes, retained foreign objects (especially small-bowel capsules), and small bowel strictures[18]. Therapies include treatment of bleeding lesions such as angioectasias, dilation of strictures using a hydrostatic balloon dilator, removal by snare or biopsy of polyps or small bowel masses, retrieval and removal of foreign objects or retained capsules, and biopsy of abnormal tissue. Balloon assisted enteroscopy has also been used in gaining access to parts of the gastrointestinal tract in patients with surgically altered anatomy.

## OBSCURE GASTROINTESTINAL BLEEDING

OGIB has been defined as bleeding from the gastrointestinal tract that persists or recurs after a negative initial evaluation of digestive system by upper and lower endoscopy[19].

BAE (including possible total enteroscopy) should be pursued after a negative CE but high clinical suspicion for a small bowel lesion[20].

In multiple large studies of patients with OGIB who underwent BAE, the diagnostic yield ranged from 43% to 81%[6,21-26]. Treatment success rates of between 43% and 84% have been reported[6,22-25]. Few studies have evaluated a combined antegrade and retrograde approach[6,23-25]. Multiple studies have been conducted to compare BAE with PE and CE. In one controlled, prospective trial of 52 patients with OGIB, BAE was superior to PE in length of small bowel visualized (230 cm *vs* 80 cm, $P < 0.0001$) and diagnostic yield (63% *vs* 44%, $P < 0.0001$)[27].

A meta-analysis of 11 studies comparing the yield of CE and BAE, including 375 patients with small-bowel disease, reported comparable diagnostic yields (60% *vs* 57%, respectively). The pooled yield for angiectasis in the 350 patients with OGIB was similar, with 24% for both CE and BAE[28]. A more recent retrospective study of 162 patients with OGIB also suggested no significant difference in overall diagnostic yield between CE (54%) and BAE (64%)[26]. Similar results were found in another meta analysis. In this study, a sub analysis of 191 patients undergoing only antegrade or retrograde BAE indicated a significantly higher yield of CE *vs* BAE (62% *vs* 50%, $P < 0.05$). However, when both antegrade and retrograde BAEs were performed in 24 patients, the yield of BAE was higher than that of CE (88% *vs* 46%, $P < 0.01$)[29]. Finally, in a retrospective study investigating the role of BAE prior to intraoperative endoscopy for those in whom BAE identified a source (53/56 patients), subsequent intraoperative endoscopy was negative in only one patient[30].

A modeled cost-minimization analysis of the management of occult OGIB proposed BAE as the most cost-effective initial test after standard endoscopy if the goal is treatment or definitive diagnosis[31]. Another model suggested that initial BAE was a cost-effective approach for patients with OGIB who likely have angiectasis in the small bowel accessible with a single antegrade approach[32]. However, comparative studies regarding existing deep enteroscopy techniques are controversial[30].

## CROHN'S DISEASE

The yield of Crohn's disease (CD) in patients who undergo DAE (DBE) for suspected small bowel disorders has been reported as 5%-13%[33], whereas the yield is substantially higher (74%-96%) in patients with known inflammatory bowel disease[34,35]. The diagnosis of CD, reached by BAE, influenced medical management in 63% but the procedure was unsuccessful in 26% of patients who underwent previous abdominal surgery[35]. In a recent study comparing the diagnostic yield of DBE and Small Bowel Follow Through, 60% of patients had small bowel involvement proximal to the distal 20 cm of the ileum that was not accessible to detection by ileocolonoscopy[36]. DBE and CE have an apparently equivalent yield for diagnosis of CD and appear to be complementary[37]. A meta-analysis of 11 studies comparing CE with DBE in 375 patients with suspected mild-gut disease found a comparable yield for detection of mild-gut inflammation (pooled yield, 16% with DBE and 18% with CE[28]). When ileocolonoscopy is negative, CE may be helpful because it is relatively non invasive and has a higher rate of success for achieving total enteroscopy, whereas BAE is useful for tissue diagnosis[28].

BAE can also help with regard to therapeutic interventions in CD. DBE appears useful in facilitating endoscopic dilation of strictures, thereby decreasing the need for surgery[38,39]. DBE has an additional role in retrieval of retained capsules, which also helps avoid surgery[40].

## TUMORS AND POLYPS

Primary tumors of the small bowel are approximately 5% of all primary gastrointestinal neoplasms[41]. Traditionally, they have been difficult to diagnose because of a vague clinical presentation and the limitations of the usual diagnostic techniques in SB visualization[42].

Several studies suggest that DBE is useful in the diagnosis and treatment of small bowel tumors and polyps, in-

cluding neuroendocrine tumors, Peutz-Jeghers syndrome, and familial adenomatous polyposis[43-48]. One small study using DBE and intraoperative enteroscopy to evaluate 41 patients with familial adenomatous polyposis suggested that DBE is of equivalent value for evaluation of SB adenomas[49]. A meta-analysis found DBE and CE to be equal in diagnostic yield[28]. DBE can also identify single-mass lesions missed on capsule endoscopy[50].

In a published series is discussed the role of enteroscopy and endoscopic tattoos to facilitate minimal-invasive surgery[18].

## MINOR INDICATIONS FOR DEVICE-ASSISTED ENTEROSCOPY

### *Celiac disease*

Few published studies address the role of DAE in evaluating celiac disease. One study examined the role of DBE in patients with refractory disease[51]. Twenty-four procedures were performed in 21 patients. Enteropathy-associated T-cell lymphoma was found in 5 patients, and ulcerative jejunitis was found in 2 patients. In another study evaluating DBE in 12 patients with malabsorption, DBE yielded a diagnosis in 8 patients[52].

Overall, DBE had a diagnostic value of 42% in patients with malabsorption of unclear origin. The authors suggested reserving DBE for patients with unexplained malabsorption and normal duodenal biopsies.

### *Paediatric patients*

Papers related to the use and application of DBE in children and adolescents is limited. Small intestinal DAE in the paediatric population remains a relatively unknown and perhaps an undervalued diagnostic and therapeutic procedure when compared with the collective adult DBE experience in which the therapeutic benefits of this technique have been clearly established. This may be because of a different spectrum of digestive pathophysiology in children in whom small intestinal bleeding, the most common indication for DBE in the adult population, is relatively uncommon. As an essentially unknown procedure in paediatrics, the safety and efficacy of DBE in this population remains to be determined. Thus, the main indications in paediatric patients seem to be related to inflammatory bowel disease.

Recently, Lin *et al*[53] reported thirteen DBE procedures performed on eleven 8- to 20-year old patients. Clinically significant lesions were identified in 46% (6/13) of the procedures performed. 6 procedures (6/13, 46%) were diagnostic or therapeutic for the patient and positively influenced their clinical management. A diagnosis of Crohn's disease was confirmed in 2 patients, and an antegrade DBE procedure for another patient with a cavernous hemangioma proved to be both diagnostic and therapeutic. Three procedures were therapeutic in the patients with Peutz-Jeghers syndrome with removal of symptomatic hamartomatous polyps, an intervention that would traditionally have required a surgical approach.

No serious procedure-related complications occurred. Self limited postprocedure abdominal pain and discomfort from gaseous distension was observed in several patients. DBE appears to be a safe endoscopic modality for the diagnosis and treatment of children and adolescents with suspected small bowel disease.

## DAE IN SPECIAL SITUATIONS

### *Balloon-assisted colonoscopy*

In recent studies using double balloon enteroscopy to complete previously failed colonoscopy successful cecal intubation was achieved in 88% to 100% of patients[54-59]. In the largest study[60], successful DBE colonoscopy was achieved in 93% of patients, with a mean time-to-cecum of 19 min. However, other studies of DBE colonoscopy have illustrated procedure times that are no faster than those in this study, with mean time-to-cecum of 28 min in one study[54] and mean total procedure time of 51 min in another[58]. No studies on these arguments are published on SBE.

In conclusion, balloon assisted colonoscopy seems a safe and effective method for completing colonoscopy in patients with a previously failed or difficult colonoscopy.

## ROLE OF BALLOON-ASSISTED ENTEROSCOPY IN ERCP

There have recently been reports on diagnostic and therapeutic ERCP using a DBE for pancreaticobiliary lesions in patients with a history of intestinal bypass surgery[61-65], in cases of surgical reconstruction, such as Roux-en-Y and Billroth Ⅱ, and cases of anastomosis, such as choledochojejunostomy and hepaticojejunostomy.

As recently outlined by several other investigators in small patients series[63-68], our stepwise approach with push-enteroscope (PE) and DBE in 37 non-selected, consecutive post-surgical patients found that DBE-ERCP was clearly more efficient than PE. By the appropriate use of DBE in over two-thirds of cases, enteroanastomoses or papilla could be repeatedly reached, identified and satisfactorily visualized. DBE-ERCP could be successfully conducted in 74.1% of the cases *via* the enteroscope, while PE reached biliary anastomoses or papilla in only 16.2% of the patients, which resulted in successful ERCP in only a minority of patients. Both results are in good agreement with recently published data for the approach by double- or single-balloon enteroscopy[67-69].

The threading of the small intestine onto the DBE and the option to block the balloons at the enteroscope provides the enteroscope tip with a greater possibility of movement for identifying the biliary or pancreatic anastomoses or the papilla. In addition, sliding back of the enteroscope may be prevented by inflated balloons, which, compared with PE, explains the significantly higher effectiveness of interventions during DBE-ERCP.

In a recent study of Raithel *et al*[70] out of the 37 post-surgical patients with significant cholestasis and cholangitis, PE achieved a successful bile duct drainage in six (16.2%), whereas DBE facilitated successful ERCP with biliary interventional procedures leading to significant reduction of cholestasis or cholangitis in 23 of 31 patients (74.1%). Only one case of post-papillotomy bleeding (3.2%), two of post-ERCP pancreatitis (6.4%) and two perforations (6.4%) occurred following DBE-ERCP, but no cholangitis or mortality has been recorded to date.

Thus, this first prospective investigation from a university tertiary referral center confirms that DBE-ERCP has considerable potential to treat successfully benign (postoperative) or malignant biliary and papillary stenosis.

The key benefits of DBE-ERCP in the care of post-surgical patients with cholestasis/cholangitis and patients with installed percutaneous drainage are somewhat limited by the small caliber of bile duct prostheses that are applied *via* the enteroscope. According to the present state of technology, only an implantation of 5-8 Fr prostheses through an operating channel of 2.8 mm is possible. Consequently, several prostheses (1.5 ± 0.7) were implanted in our patients. Considering the enormous benefit of DBE-ERCP with an approximately 74% successful biliary drainage and a significantly smaller complication rate than Percutaneous Transhepatic Cholangio Draimage (PTCD)[71-73], the effort involved in such an examination seems justified.

In conclusion, DBE for direct cholangiography seems to be a possible option, particularly in patients with a past history of abdominal surgery.

### *Complications and limitations of device-assisted enteroscopy*

The most commonly reported complications to date have included pancreatitis, hemorrhage, and intestinal perforation. In a 10-center study describing 2362 DBE procedures performed in Europe and Japan, there were 40 (1.7%) complications, including pancreatitis in 7 (0.3%), bleeding in 19 (0.8%), and perforation in 6 (0.3%)[10]. Perforation occurred after argon plasma coagulation therapy for AVMs in 3 (1.2%) patients and after stricture dilation in 2 (2.9%) cases. In another publication reporting complications in 178 therapeutic DBE procedures, severe treatment-associated complications occurred in 6 (3.4%): bleeding in 2 patients, perforation in 3 patients after polypectomy of large polyps and segmental enteritis after APC in 1 patient[74]. Although there are no published contraindications to date, inflation of the balloons resulting in distention of the small bowel may lead to perforation in patients with pre-existing weakened small intestine from inflammatory conditions or in areas of surgically altered anatomy.

Perforations have been described in patients with small bowel lymphoma undergoing chemotherapy[33], in patients with recently created intestinal anastomoses[24], in the scenario of stricturing ileal Crohn's disease[33], and in patients with altered surgical anatomy, including ileal anal anastomoses[75]. In a retrospective analysis of 2478 DBE examinations performed in 9 United States centers[76,77] (1691 anterograde examinations and 722 retrograde DBEs), there were a total of 22 (0.9%) major complications, including perforation in 11 (0.4%), pancreatitis in 6 (0.2%), and bleeding in 4 (0.2%). Perforations occurred in 3 of 1691 (0.2%) oral examinations and in 8 of 722 (1.2%) rectal DBEs. Eight (73%) perforations occurred during diagnostic DBE examinations.

Four of 8 rectal DBE perforations occurred in patients with prior ileoanal or ileocolonic anastomoses. In the subset of patients with available data regarding altered surgical anatomy, perforations occurred in 7 (3%) patients. On the basis of these data, the presence of altered surgical anatomy and the execution of therapeutic procedures should be considered to be a higher risk conditions in the performance of balloon-assisted enteroscopy.

In the end, in literature have been reported same cases of unrecognized aspiration pneumonitis during enteroscopy resolved with medical therapy[78,79].

## CONCLUSION

The advent of balloon-assisted enteroscopy has allowed the endoscopist access to areas of the small intestine that were not previously accessible. This article was designed to review the history of small-bowel enteroscopy, the technical aspects of balloon-assisted enteroscopy, and common problems encountered by endoscopists performing DAE.

With this rapidly evolving technology, our ability to diagnose and treat patients with mid-gut diseases has improved enormously, resulting in a substantial change in the management paradigm for these previously elusive disorders. This new technology has improved our ability to diagnose and monitor and treat artero-venous-malformations (AVMs), CD and small bowel neoplasms. In many cases, the ability to perform therapeutic interventions has eliminated the need for invasive surgical procedures. However, larger studies are needed to determine the impact on clinical outcomes. None of the available techniques in this moment seems to be superior to another.

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**S- Editor** Song XX **L- Editor** A **E- Editor** Zhang DN

World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/esps/
wjge@wjgnet.com
doi:10.4253/wjge.v4.i10.462

*World J Gastrointest Endosc* 2012 October 16; 4(10): 462-471
ISSN 1948-5190 (online)


MINIREVIEWS

# Ultra high magnification endoscopy: Is seeing really believing?

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Received: August 30, 2011 Revised: May 29, 2012
Accepted: October 10, 2012
Published online: October 16, 2012

## Abstract

Endoscopy is an indispensible diagnostic and therapeutic instrument for gastrointestinal diseases. Endocytoscopy and confocal endomicroscopy are two types of ultra high magnification endoscopy techniques. Standard endoscopy allows for 50 × magnification, whereas endocytoscopy can magnify up to 1400 × and confocal endomicroscopy can magnify up to 1000 ×. These methods open the realm of real time microscopic evaluation of the GI tract, including cellular and subcellular structures. Confocal endomicroscopy has the additional advantage of being able to visualize subsurface structures. The use of high magnification endoscopy in conjunction with standard endoscopy allows for a real-time microscopic assessment of areas with macroscopic abnormalities, providing "virtual biopsies" with valuable information about cellular and subcellular changes. This can minimize the number of biopsies taken at the time of endoscopy. The use of this technology may assist in detecting pre-malignant or malignant changes at an earlier state, allowing for earlier intervention and treatment. High magnification endoscopy has shown promising results in clinical trials for Barrett's esophagus, esophageal adenocarcinoma, esophageal squamous cell cancer, gastric cancer, celiac disease, colorectal cancer, and inflammatory bowel disease. As the use of high magnification endoscopy techniques increases, the clinical applications will increase as well. Of the two systems, only confocal endomicroscopy is currently commercially available. Like all new technologies there will be an initial learning curve before operators become proficient in obtaining high quality images and discerning abnormal from normal pathology. Validated criteria for the diagnosis of the various gastrointestinal diseases will need to be developed for each method. In this review, the basic principles of both modalities are discussed, along with their clinical applicability and limitations.



**Key words:** Endocytoscopy; Confocal endomicroscopy; Confocal laser endomicroscopy; High magnification endoscopy

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Arya AV, Yan BM. Ultra high magnification endoscopy: Is seeing really believing? *World J Gastrointest Endosc* 2012; 4(10): 462-471 Available from: URL: http://www.wjgnet.com/1948-5190/full/v4/i10/462.htm DOI: http://dx.doi.org/10.4253/wjge.v4.i10.462

## INTRODUCTION

Endoscopy is an essential tool for the diagnosis and treatment of upper and lower gastrointestinal diseases. From the humble beginnings of various tubes and catheters of the 1600 s, the technological development in endoscopic imaging has been astounding. The most significant developments in gastrointestinal imaging include

fibre optic endoscopy with the first clinical publication on fibre optic gastroscopy in 1958, followed by the introduction of video endoscopy first showcased in 1983. Technological progress over the last 20 years has significantly improved the imaging capabilities of endoscopy. Ultra high magnification endoscopy is now possible and has allowed gastroenterologist to see the smallest of lesions for *in vivo* microscopic evaluation in real time. Two major modalities have been developed: endocytoscopy and confocal endomicroscopy.

Each modality has its own strengths and weaknesses, nevertheless each enable "virtual biopsies" and significantly reduce biopsy error by providing a direct microscopic target. High magnification endoscopy has shown promising results in trials for Barrett's esophagus and esophageal adenocarcinoma, esophageal squamous cell cancer, gastric cancer, celiac disease and colorectal cancer. These techniques may allow for the earlier detection and treatment of neoplastic conditions as the earliest changes of malignancies take place at the cellular and subcellular levels, including changes in capillary architecture and the characteristics of the nucleus.

In this review, we discuss the basic principles of endocytoscopy and confocal endomicroscopy along with their clinical applications.

## BASIC PRINCIPLES OF HIGH MAGNIFICATION ENDOSCOPY

### *Endocytoscopy*

Endocytoscopy (ECS) is an ultra-high magnification modality that allows visualization of surface epithelial architecture at the cellular and subcellular level. It is a contact microscopy technique where physical contact with the mucosal surface is required to obtain the image[1]. ECS provides real-time *in vivo* images in a parallel section to the mucosal surface. Highly magnified images from a small sampling site (< 0.5 mm diameter) are obtained using a fixed-focus, high power objective lens. These images are then projected on a charged-couplet device[2]. The use of a contrast agent is necessary for the visualization of subcellular entities. The mucosa is pretreated with a mucolytic agent, such as N-acetylcysteine, and then directly stained with 0.5%-1% methylene blue or 0.25% toluidine blue[2]. Endocytoscopy is limited by its ability to only image a superficial layer of the mucosa and is therefore not well suited for analyzing the depth of suspicious lesions.

There are two types of endocytoscopy instruments available: probe-based and endoscope-based. The probe-based devices are used through the working channel of a standard endoscope (Figure 1). There are 2 probe-based models, each 380 cm long with a diameter of 3.2 mm and both produced by Olympus (Tokyo, Japan; models XEC-300 and XEC-120). One model is able to provide magnification of 450 × representing a field of view of 300 μm × 300 μm, and the other model magnifies to

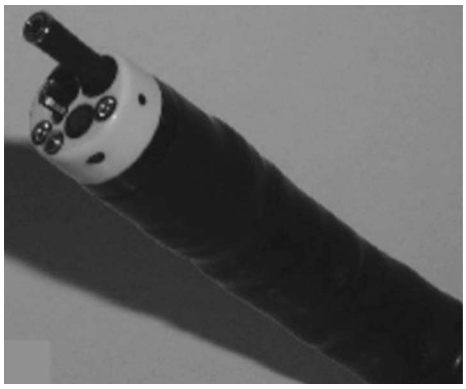

**Figure 1 Probe-based endocytoscope being passed through the working channel of a traditional endoscope.** Image from Sasajima *et al*[4] (used with permission).

1125 ×, representing an area of tissue 120 μm × 120 μm[1,2]. Using a 19-inch monitor, these two models magnify the image to 570 × and 1400 × respectively. The larger the monitor, the greater the magnification, but at the cost of decrease in resolution depending on the resolution capabilities of the probe and monitor. The endoscope-based devices have an integrated endocytoscope and endoscope. There are 2 models by Olympus (models XGIF-Q260EC1 and XCF-Q260EC1) which each provide a magnification of 580 × on a 19 inch monitor[2]. A soft plastic cap at the end of the endoscope allows for stabilization against the mucosal surface.

Diagnosis of gastrointestinal abnormalities is based on the evaluation of a number of cytological and architectural features, including density, size, cellular arrangement, size and shape of nuclei, staining pattern and ratio of nucleus-to-cytoplasm[3,4]. The endocytoscopy system lends itself better to visualization of esophageal structures than gastric or colonic structures as they can easily be stained. Surface mucous must be removed first for effective staining of gastric or colonic mucosa[5]. Table 1 provides a comparison of ECS and Confocal endomicroscopy (CEM).

### *CEM*

CEM is a new imaging technique that allows *in vivo* microscopy and histology of the gastrointestinal tract during endoscopy. Confocal microscopy refers to the use of a fine laser beam that scans over a specimen through an objective lens. Reflected light from contrast-stained tissue is focused through a pinhole (*confocal*) to remove out-of-focus light[6]. By rejecting out of focus light, this technique is effective at producing high-resolution images. Standard endoscopy provides for 50 × optical magnification, whereas confocal endomicroscopy allows for 1000 × magnification[7]. It is able to demonstrate physiological activities such as the release of mucous from crypts and blood flow in capillaries[8]. Unlike endocytoscopy, confocal endomicroscopy is able to obtain images of the lamina propria down to a depth of 250 μm[9].

With the miniaturization of confocal devices it is

**Table 1 Comparison of endocytoscopy and confocal endomicroscopy**

| | ECS | CEM |
|---|---|---|
| Available systems | | |
| Probe based | Olympus (Japan) | Optiscan (Australia) endomicroscope integrated into Pentax (Japan) endoscope |
| Integrated | Olympus (Japan) | Cellvizio, Mauna Kea Technologies (France) |
| Max resolution | NA | 1024 × 1024 pixels with integrated system (lower with probe based system) |
| Max magnification | 1400 × (probe)<br>580 × (integrated) | 1000 × |
| Field of view | 300 μm × 300 μm (450 x magnification)<br>120 μm × 120 μm (1125 x magnification) | 475 μm × 475 μm |
| Depth of imaging | Superficial mucosal layer only | Probe based: Different probes allow for different imaging depths<br>Integrated system: Variable, up to 250 μm below surface (lamina propria) |
| Contrast agents | 0.5%-1% methylene blue<br>0.25% toluidine blue | Fluorescein sodium<br>Acriflavine |
| Commercially available? | No | Yes |
| Advantages | Higher magnification than CEM | Can visualize subsurface structures up to 250 μm<br>Commercially available |
| Disadvantages | Cannot visualize subsurface structures<br>Requires mucolytic preparation of tissue<br>Not commercially available | Lower magnification than ECS<br>Two contrast agents required for optimal imaging |

ECS: Endocytoscopy; CEM: Confocal endomicroscopy; NA: Not available.

now possible to use confocal endomicroscopy during routine endoscopy. Two types of confocal endomicroscopy systems are currently available: integrated and probe based systems. The confocal laser endomicroscope is an integrated laser and endoscope that allows for high-resolution images at variable depths below the surface (Figure 2). The integrated system obtains images of a section 475 μm × 475 μm, with variable imaging depth controlled by the user, to a maximum of 250 μm[7]. The maximum depth can be achieved through vertical increments of 7 μm. The lateral resolution is 0.7 μm, which represents the minimum detectable distance between two points. Images in the integrated system are obtained at a rate of 0.8 frames/second (1024 × 1024 pixels) or 1.6 frames/second (1024 × 512 pixels)[9]. The mini-probe system is used through the working channel of a standard endoscope, however only offers a fixed (rather than variable) imaging depth at a lower resolution. Each different probe allows for imaging to a specific fixed depth. The mini-probe system obtains images faster (12 frames/s) than the integrated system, however at the expense of resolution being limited by the number

**Figure 2 A confocal laser endomicroscope with a 5 mm diameter integrated in the distal end of a traditional colonoscope.** Image from Dekker *et al*[1] (used with permission).

of fibers (30 000 single fibers = 30 000 pixels)[7]. The images in both systems are parallel sections to the mucosal surface[10].

CEM requires the use of a fluorescent contrast agent that is excitable and has emission spectra within the blue light range (excitation wavelength 488 nm). Most human studies have used intravenous fluorescein sodium[7,10]. Fluorescein is non-toxic, distributes throughout the tissue within seconds, and is safe for endomicroscopy[7,11]. Fluorescein is effective in demonstrating the structural design of vessels and cellular components but does not have good contrast for nuclei. Acriflavine is another common topical contrast agent, which allows effective visualization of nuclei. In practice, fluorescein and acriflavine may be used together. In animal studies there have been other contrast agents used as well as fluorescently labeled antibodies[2,10].

## CLINICAL APPLICATIONS

The first publications regarding ultra high magnification endoscopy were published in 2004 for both CEM and ECS[12,13]. Since then there have been further studies on a number of upper and lower gastrointestinal tract diseases. Ultra high magnification endoscopy allows for taking fewer targeted biopsies on areas of histological interest visualized by the endomicroscope compared to multiple random biopsy samples[10].

## UPPER GI TRACT

### *Barrett's esophagus and esophageal adenocarcinoma*

Preliminary studies assessed the ability of ECS and CEM for the detection of malignancy in Barrett's esophagus, which was not evident endoscopically. In 2007, Pohl *et al*[14] compared ECS images in 16 patients undergoing Barrett's surveillance with histology. One hundred and sixty-six biopsy sites with no macroscopic evidence of cancer were examined with ECS. Adenocarcinoma was diagnosed in 4.2% of biopsy sites, high-grade dysplasia in 16.9% and low-grade dysplasia in 12.1%. The major

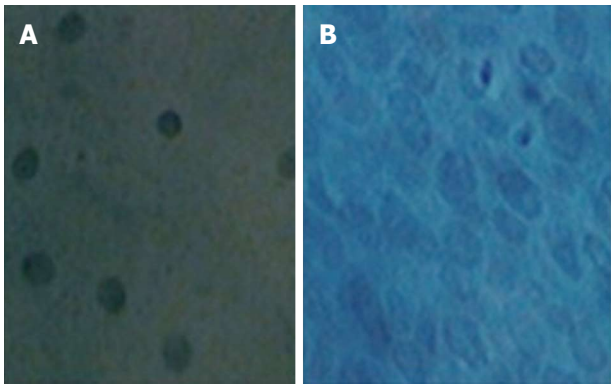


**Figure 3 Endocytoscopic images at 1125 × magnification using XEC120U system.** A: Normal squamous cell epithelium of the esophagus with uniform cells; B: Esophageal squamous cell carcinoma. Heterogeneous cells with increased cell density and abnormal nuclei can be seen. Images adapted from Kumagai *et al*[22] (used with permission).

issue in this early study was image quality: only 23% of images at 450 × magnification, and 41% of images at 1125 × magnification were of sufficient quality to visualize characteristics of neoplastic lesions. Therefore the authors concluded that ECS did not produce images of adequate quality to be useful in the malignancy surveillance for Barrett's esophagus. A 2011 multicentre, randomized controlled trial demonstrated a significant improvement in the ability to detect malignancy in patient's with Barrett's esophagus using probe-based CEM in combination with high-definition white light endoscopy compared to white light endoscopy alone[15].

CEM similarly can target suspicious areas of high-grade dysplasia and may identify abnormal neovascularization in esophageal adenocarcinoma[16]. Dunbar *et al*[17] performed a prospective, double blinded, randomized controlled trial to determine whether confocal endomicroscopy with targeted biopsies improves the diagnostic yield over standard endoscopy and random biopsy alone for unapparent Barrett's associated neoplasms. Of 39 patients, 16 were suspected to have neoplasm, and 23 were for standard surveillance. All patients underwent standard endoscopy with random 4-quadrant biopsies according to Seattle Protocol, as well as confocal endomicroscopy with targeted biopsies. The order in which CEM and standard endoscopy were performed was randomized. The diagnostic yield of high-grade dysplasia or adenocarcinoma with the confocal endomicroscopy protocol was 33.7% *vs* 17.2% in the standard endoscopy arm, resulting in an absolute difference of 16.5% (95%CI: 5.2%-27.8%, $P = 0.01$). Significantly less biopsy samples were required using CEM (9.8 *vs* 23.8, $P = 0.002$).

### *Esophageal squamous cell cancer*

Esophageal squamous cell cancer (SCC) is the most prevalent type of esophageal cancer worldwide, especially in Asia. Patients often have advanced stages at presentation resulting in a very poor prognosis.

Squamous cell esophageal cancers can be easily diagnosed by ECS *via* 2 main criteria: an abnormal nucleus (abnormal staining, size and shape) and an increase in cell density (Figure 3)[5,12,18-23]. When assessed in *ex vivo* resected SCC specimens, cancer cells show an irregular heterogeneous cell distribution compared to normal cells arranged homogeneously with a uniform and low nucleus:cytoplasm ratio[19]. The cellular density is significantly increased with one study demonstrating a mean number of total nuclei per image of 550 ± 66.5 in the cancerous areas versus 129 ± 14.8 in the normal mucosa ($P < 0.0001$)[21]. Kumagai *et al*[22] performed *ex vivo* and *in vivo* studies looking at endocytoscopic observation for esophageal SCC. In 57 *ex vivo* specimens from 28 patients, the sensitivity of ECS for malignant lesions was 94.7%, with a specificity of 84.2%. The *in vivo* component had 71 lesions from 69 patients, each assessed by two endoscopists in consultation with a pathologist regarding nuclear abnormality and density. The 2 endoscopists diagnosed more than 90% of esophageal squamous cell carcinomas as cancers. The pathologist considered nuclear density to be increased in up to 98% of cases and saw nuclear abnormalities in up to 90% of cases. Specificity is very good (and even reported up to 100%[23]) but is reduced if only one criteria is present (either abnormal nucleus or increased cell density).

**Table 2 High magnification endoscopy and esophageal squamous cell cancer**

| Modality | Findings | Test characteristics |
|---|---|---|
| Endocytoscopy | Nuclear atypia<br>Increased nucleus: Cytoplasm ratio<br>Increase in cell density<br>Irregular cellular distribution | Sensitivity 81%-95%[1]<br>Specificity 84%-100%[1]<br>Accuracy 82%-90%[1] |
| Confocal endomicroscopy | Dilated intraepithelial papillary capillary loops<br>Abnormal cellular structures | Accuracy 85%-96% |

[1]Determination of malignant *vs* non-malignant.

ECS may be used in early lesions to diagnose malignancy for consideration of local excision[24]. In an in vivo study of 29 patients assessing for early cellular atypia, the ECS positive predictive value for malignancy was 94%, with a false positive rate of 6.3% and false negative rate of 16.7%. The accuracy of distinguishing malignant (Vienna 4 and 5) versus non-malignant (Vienna 1-3) was 82%[18].

Less data is available for CEM in diagnosing superficial invasion by SCC. Normal squamous epithelium has regular intraepithelial papillary capillary loops that are directed towards the luminal surface. With CEM, SCC demonstrates dilated intraepithelial papillary capillary loops in the upper layer of the squamous mucosa[16]. A 2009 pilot study compared CEM done by 2 endoscopists to histology looking at abnormal cellular and vascular patterns for the diagnosis of SCC. Accuracies of 89% and 96% were obtained for abnormal cellular pattern, and 85% for abnormal vascular pattern[25].

The findings seen by ECS and CEM in esophageal squamous cell cancer are summarized in Table 2.

### Gastric cancer

CEM has been used to compare normal subsurface gastric mucosa with that of malignant lesions[16]. Normal gastric body mucosa shows a honeycomb-like microvascular organization surrounding gastric pits, and a coil-shaped regular microvascular arrangement surrounding the antral gastric pits. In contrast, undifferentiated gastric neoplasms showed decreased vascularity with irregular short branch vessels. Features of gastric neoplasm seen on CEM include cellular atypia with increased nuclear area and increased vascularity with irregularly shaped microvasculature of various diameters[16,26]. Kitabatake *et al*[27] assessed the ability of pathologists to use CEM images as a "virtual biopsy" for the diagnosis of early gastric cancer. Using CEM still images obtained from 27 patients with early gastric cancer compared to standard histology as the gold standard, 2 blinded pathologists obtained accuracies of 94.2% and 96.2% for the diagnosis of malignancy when good quality images are obtained. Unfortunately, only 59% of images were deemed to be of good quality. The accuracy decreased significantly when lower quality images and inaccessible lesions were included, once again highlighting the limitation of being able to acquire high-quality images consistently. Inter observer variability between endoscopists is very good with a mean kappa value of 0.792 for the identification of neoplastic mucosa.

ECS has decreased sensitivity for neoplastic lesions in the stomach compared to esophageal or colonic lesions secondary to gastric mucous secretion. The sensitivity for gastric neoplasms compared to histology was 56%, with a specificity of 89%[23].

### Celiac disease

High magnification endoscopy allows the opportunity for diagnosis of celiac disease *in vivo* as well as targeted biopsies of abnormal lesions, resulting in a higher diagnostic yield compared to random biopsies, in particular for patchy disease.

ECS has demonstrated three distinct patterns of in vivo histolopathology with respect to celiac disease[28]. The first pattern is normal duodenal mucosa showing the presence of normal-appearing, thin, long villi, lined with easily discernible surface epithelial cells. The second pattern of subtotal villous atrophy is demonstrated by thick, shortened villi. The third pattern corresponding to total villous atrophy is shown by the complete absence of villi and the presence of enlarged crypts. In a trial of 40 patients, (32 with known celiac disease, and 8 with suspected disease) 166 ECS recordings were prospectively obtained and compared to histopathology (Marsh classification). Endocytoscopy at 450 × magnification was accurate in predicting moderate to severe celiac disease (Marsh Ⅲ), however was not reliable in detecting early disease pathology (Marsh Ⅰ). The use of 1100 × endocytoscopic magnification provided no additional diagnostic value[29].

The CEM features of celiac disease were initially described in a pediatric trial of 9 patients with suspected celiac disease compared to 10 matched controls[30]. Both endoscopists and pathologists were blinded to the diagnosis. A total of 1384 images were collected from the 19 patients, and 5 images per patient were selected and compared against a biopsy sample of the same site. With subtotal villous atrophy, the duodenal villi are broad and appeared to be folded onto themselves. There is a loss of the normal hexagonal pattern and decrease in goblet cells. With total villous atrophy, duodenal villi are completely absent, and crypts can be visualized with cellular infiltration (increased intraepithelial lymphocytes) in the surrounding stroma. The sensitivity of confocal endomicroscopy compared to histopathology was 100%, specificity was 80% and positive predictive value was 81%[30,31]. In an adult trial of 30 celiac patients, including 6 with disease refractory to a gluten-free diet, sensitivities were good for intraepithelial lymphocytes (81%) but decreased for villous atrophy (74%) and crypt hyperplasia (52%)[32]. Thirty control patients in this study undergoing routine upper endoscopy demonstrated normal duodenal architecture on CEM and histology, resulting in a specificity of 100%. The largest study for CEM in celiac disease assessed 31 patients (17 with celiac disease, 14 controls) and compared over 7000 CEM images with 326 paired biopsy samples[33]. The sensitivity for diagnosis of celiac disease was 94% with a specificity of 92%, with good correlation to the Marsh scoring system. By directing biopsies to microscopically abnormal regions, CEM may be a promising modality to investigate those with a suspected diagnosis of celiac disease but have negative pathology from traditional random biopsies due to patchy disease.

## LOWER GI TRACT

### Colorectal cancer

It is unlikely that virtual biopsies with ultrahigh magnification will replace standard histology for the diagnosis of colorectal cancer. It may however, help in certain situations where biopsies are not conclusive for invasive malignancy or when multiple biopsies pose problems with subsequent management, such as superficial rectal lesions amenable to local excision.

Using ECS, resolution can be so detailed that individual red blood cells can be seen circulating through the microvasculature and normal colonic mucosa can be seen and described[34]. Cellular level and structural abnormalities can be observed and it is possible to differentiate between neoplastic and non-neoplastic lesions, as well as invasive malignancy versus adenoma. Aberrant crypt foci may represent the earliest pre-cancer stage of colorectal cancer. Using ECS, dysplastic aberrant crypt

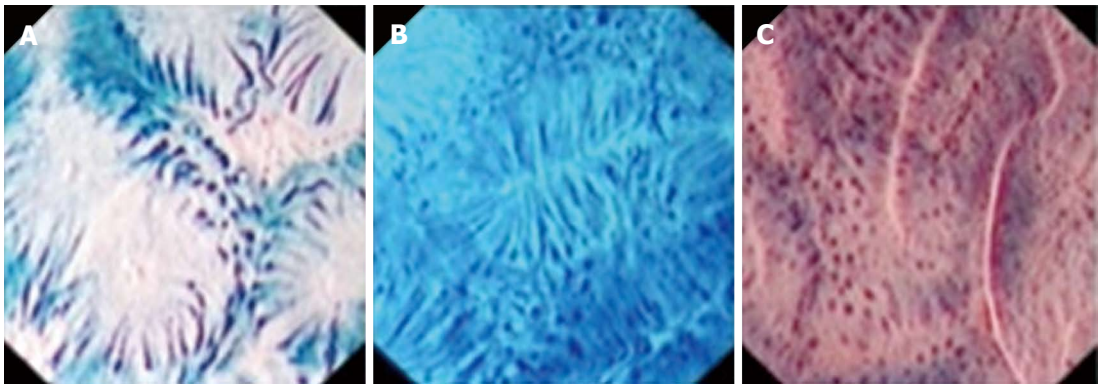


**Figure 4 Endocytoscopic images of colorectal neoplasms at 450 × magnification.** A: Low-grade adenoma with elongated nuclei; B: Low-grade adenoma demonstrating elongated nuclei, polygonal crypts, and heterogeneous arrangement; C: High-grade adenoma demonstrating irregular crypts and nuclei that are larger in size and distorted in shape. Images adapted from Rotondano *et al*[36] (used with permission).

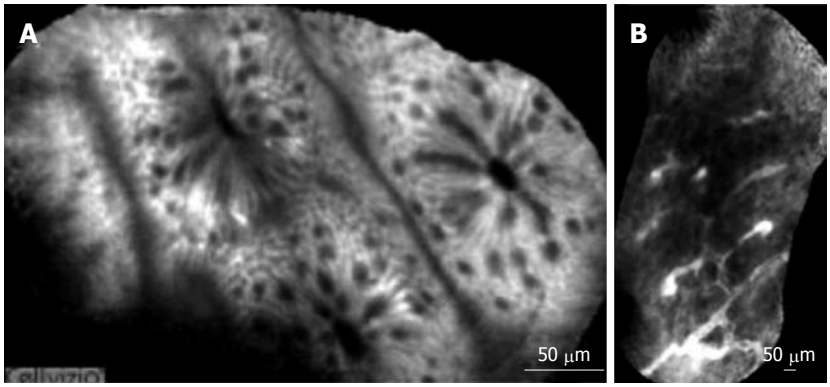


**Figure 5 Probe-based confocal laser endomicroscopy.** A: Normal colon; B: Colon adenocarcinoma demonstrating distorted architecture, dilated and irregular vessels, and loss of crypts. Images adapted from De Palma[38] (used with permission).

foci appear as polygonal instead of round, have elongated cell nuclei, and the crypt lumen is linear instead of circular (Figure 4). ECS provided 91.4% sensitivity for low-grade dysplasia and 100% specificity for absence of dysplasia. The interobserver kappa value between a trained endoscopist and the pathologist was 0.68 (95%CI: 0.59-0.78)[35]. A recent study looking at 52 polypoid and non-polypoid colorectal lesions in 49 patients showed that ECS provided good correlation with final histopathological diagnosis[36]. The positive predictive value (PPV) of endocytoscopy compared to pathology was 100% for normal mucosa, hyperplastic polyp and submucosal invasive cancer. The PPV was 93.1% for low-grade adenoma and 90.1% high-grade adenoma. In one case report, a synchronous microscopic lesion (confirmed with pathology) was found on ECS 7 cm away from a resected cancer of the transverse colon[37]. Overall sensitivity and specificity of ECS for the diagnosis of neoplasm ranges from 79%-91% and 90%-100% respectively[23,35].

CEM assessment of the colon is similar to ECS. In normal colonic mucosa, the crypts have regular lumens and are covered by a homogenous layer of epithelial and goblet cells (Figure 5). Normal vessel architecture is hexagonal with a honeycomb appearance, which represents capillaries surrounding the stroma of the crypts. Cancerous tissue shows irregular cellular organization and abnormal epithelial cells with a loss of the normal crypts and goblet cells. There is also decreased or complete absence of mucin. In cancer, the capillaries are distorted and dilated with increased leakage. The vessels have a sporadic organization with little or no orientation to the surrounding tissue[38]. A clinical trial of probe-based CEM versus virtual chromoendoscopy for the classification of colon polyps showed a higher sensitivity for CEM (91% *vs* 77%, $P = 0.01$) but no significant difference in specificity, when compared to histology as the gold standard[39]. Virtual chromoendoscopy diagnoses polyps based on the pit pattern seen during chromoendoscopy. CEM may also have a future role for neoplasia surveillance of an ileoanal pouch following proctocolectomy for familial adenomatous polyposis[40]. Table 3 provides a comparison of the colonic architecture in ECS and CEM.

### IBD

Patients with longstanding inflammatory bowel disease involving the colon have a higher risk of developing colon cancer. Routine colonoscopy every 1-2 years with

**Table 3 Confocal endomicroscopy and endocytoscopy findings of colonic architecture[33,34,36]**

| Feature | Normal | Malignant |
|---|---|---|
| Vessel Architecture | Hexagonal, honeycomb appearance of capillaries | Distorted, dilated capillaries with increased leakage |
| | Capillaries surround the stroma, which encircle the crypt openings | Irregular arrangement with no specific relationship to adjacent tissue |
| Crypts | Regular luminal openings and distribution | Heterogeneous distribution with irregular layer epithelial cells |
| | Crypts covered by uniform layer of epithelial cells (including Goblet cells) | Loss of crypts and goblet cells |
| Sensitivity | | ECS: 79%-91%[6,35]<br>CEM: 91%[37] |
| Specificity | | ECS: 90%-100%[6,35]<br>CEM: 76%[37] |

multiple biopsies (> 32 biopsies) is recommended for those with pancolitis after 8 years of disease[41]. Chromoendoscopy further increases the sensitivity of detecting early neoplasm[39]. CEM may help perform targeted biopsies of suspicious areas has been associated with improved detection of intraepithelial neoplasia compared to the current standard of random biopsies with four tissues samples each 10 cm[42-44]. The combination of wide-field chromoendoscopy with narrow-field confocal endomicroscopy can result in a 5 times higher detection rate of neoplastic lesions. This combination technique can be especially helpful for flat lesions that can be otherwise difficult to detect with standard endoscopy[44]. There is still no data suggesting whether this early or increased detection confers any mortality benefit.

CEM can be used with high accuracy for the diagnosis of dysplasia-associated lesion or mass (DALM) or adenoma-like mass (ALM) in the setting of IBD. CEM was used in a study of 36 ulcerative colitis patients who had a DALMs or ALMs diagnosed within the previous 16 wk[45]. The kappa coefficient of agreement between traditional histopathology and confocal endomicroscopy images was 0.91 with 97% accuracy. This *in vivo* technique allowed for the differentiation between the two different types of masses, which provides an opportunity to safely determine which patients require immediate referral for total colectomy versus those patients who are suitable for endoscopic resection.

By providing high definition images, CEM may provide excellent insight into the *in vivo* process of inflammation[46]. A study of 31 patients, 17 with UC (12 active, 5 non-active) and 14 non-UC controls, compared histology of rectal biopsy samples with the images from confocal endomicroscopy[47]. The *in vivo* virtual biopsies from confocal endomicroscopy were congruent with traditional histology. In active inflammation goblet cells were not always visible and the crypts, as well as the lumens, were of various sizes and shapes, with an inconsistent arrangement. The capillaries were more visible in active inflammation and seen in all areas of the lamina propria.

### Other clinical applications

Bojarski *et al*[48] demonstrated the *in vivo* diagnosis of acute intestinal graft-versus-host disease (GvHD) using confocal endomicroscopy. Nineteen out of 35 patients with acute diarrhea after stem cell transplant had histologic evidence of acute GvHD, with 14 of these 19 also showing confocal endomicroscopic evidence. The sensitivity of confocal endomicroscopy was 74% and specificity 100%. Patients with infectious colitis or ulcerative colitis served as controls and none of them showed any endoscopic evidence of GvHD. This modality may be especially helpful in the situation in which biopsies present a high risk, such as increased bleeding risk (from coagulopathy or low platelets) or increased infection risk (in the setting of severe leukopenia).

Venkatesh *et al*[49] looked at the usefulness of confocal endomicroscopy in diagnosing pediatric gastrointestinal diseases. The trial involved 44 patients with a total of 36 upper endoscopies and 31 lower endoscopies using a confocal system. The confocal images were deemed to be comparable to traditional histopathology in both normal tissue and many disease states including esophagitis, H. pylori gastritis, celiac disease, inflammatory bowel disease, colonic heterotopia and graft versus host disease.

A variety of other case reports have been published using ultrahigh magnification endoscopy for the diagnosis of *Helicobacter pylori*[50], collagenous colitis[51], amoebic colitis[52], intraoperative diagnosis of pancreatic cancer in the setting of chronic pancreatitis[53], and intraoperative diagnosis of disseminated malignancy at time of laparoscopy[54]. Confocal endomicroscopy has been used *in vivo* during laparoscopy to analyze healthy and diseased human liver, which offers the possibility for targeted biopsies[55].

## LIMITATIONS OF ENDOCYTOSCOPY AND CONFOCAL ENDOMICROSCOPY

Both confocal ECS and CEM are not effective for wide-field endoscopy, and are better used in conjunction with a wide-field technique. They are both useful for targeted images (optical biopsies) of abnormalities identified by a wide-field technique. As with any new technique, there is an initial learning curve. In this field, the learning curve is not only the technical aspects of attaining high quality images, it also includes learning *in vivo* pathology. While most endoscopists will likely be able to learn the technical aspects, identifying normal and abnormal pathology correctly is more challenging. Both ECS and CEM involve a time-consuming process with multiple steps including washing, staining and imaging[2]. ECS and CEM for diagnostic purposes are also limited by the current lack of validated criteria for diagnosis[10]. Finally, the economics of ultra high magnification endoscopy may

be limiting. The endocytoscopy system is currently not available for commercial use. The current cost effectiveness is uncertain. In the long-term both techniques may be economical if a significant number of biopsies taken per patient is reduced or abandoned altogether[9,56]. However, at least until methods are validated in prospective studies with very high accuracies, histology will remain the gold standard for diagnosis.

## CONCLUSION AND FUTURE DIRECTIONS

Endoscopy is invaluable in gastroenterology for the diagnosis and treatment of upper and lower gastrointestinal disorders. Endocytoscopy and confocal endomicroscopy are emerging endoscopic tools that allow for ultra-high magnification and "virtual biopsies" of tissue deemed atypical by standard endoscopy. Both ECS and CEM can come integrated into the end of an endoscope or as probes that can be used through the working channel of a standard endoscope, however only CEM is currently commercially available.

The benefit of high magnification endoscopy is that it provides for the first time a new opportunity to visualize cellular and subcellular pathology *in vivo*. This allows us to see and understand in real time normal physiologic functions of the GI tract. By knowing this, we can then understand the real time, *in vivo* pathological changes related to disease. Our knowledge of disease can significantly be expanded by this capability. Real time inflammation can be analyzed and explored to better our knowledge of the pathophysiology (and therefore treatment) of inflammatory bowel disease. Cellular and vascular changes related to malignancy can be studied *in vivo* perhaps leading to new therapeutic targets. Early microscopic changes can be visualized without having to wait for larger, later stage macroscopic changes to be evident. As a result, ultra-high magnification endoscopy may conceivably have applications in cancer resections to look for clear resection margins.

Similar to other new technologies developed through the decades, including endoscopic retrograde cholangiopancreatography and endoscopic ultrasound, as the use of high magnification endoscopy increases, clinical applications will expand. Opportunities for research using these techniques are numerous. Further research is required to standardize classification systems for both ECS and CEM in the diagnosis of different malignancies. The current data suggests a promising future for ultra-high magnification endoscopy, and future larger scale research will help clarify the role and indications for endocytoscopy and confocal endomicroscopy.

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**S- Editor** Song XX **L- Editor** A **E- Editor** Zhang DN

World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/esps/
wjge@wjgnet.com
doi:10.4253/wjge.v4.i10.472

*World J Gastrointest Endosc* 2012 October 16; 4(10): 472-478
ISSN 1948-5190 (online)


MINIREVIEWS

# Role of digital chromoendoscopy and confocal laser endomicroscopy for gastric intestinal metaplasia and cancer surveillance

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Received: November 15, 2011 Revised: August 1, 2012
Accepted: October 13, 2012
Published online: October 16, 2012

## Abstract

In Japan and countries such as South Korea and Taiwan, China, the standard technique for detecting early gastric cancer (EGC) is chromoendoscopy. This technique involves a magnified endoscope and the use of an indigo-carmine spray to distinguish between EGC and non-EGC areas. However, this technique is not widely adopted in many parts of the world. One important reason for limited use is that this technique needs an experienced endoscopist to interpret the images during the procedure. In addition, the sensitivity for detecting gastric intestinal metaplasia (GIM), a precancerous lesion of EGC, is graded as suboptimal. Moreover, the requirement of a cumbersome spraying method is inconvenient and needs preparation time. Easier digital chromoendoscopy techniques, such as Narrow-band Imaging and Flexible spectral Imaging Color Enhancement, have been reported to facilitate targeted GIM and EGC biopsy. They provide higher sensitivities over conventional white light endoscopy. Recently, the novel technology of confocal laser endomicroscopy has been introduced as a high-magnification (1000 ×) real-time evaluation for many early gastrointestinal (GI) cancers and precancerous GI lesions, including colonic polyp, Barrett's esophagus, and GIM. The advantage of this technique is that it can be used as an *in vivo* confirmation of the presence of GIM and EGC during endoscopic surveillance. This review aims to explain the current information on the usefulness of digital chromoendoscopy and confocal laser endomicroscopy for evaluating GIM and EGC during endoscopic surveillance and the possible future role of these techniques for GI cancer screening programs.



**Key words:** Confocal laser endomicroscope; Chromoendoscopy; Gastric intestinal metaplasia; Gastric intestinal metaplasia

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Pittayanon R, Rerknimitr R. Role of digital chromoendoscopy and confocal laser endomicroscopy for gastric intestinal metaplasia and cancer surveillance. *World J Gastrointest Endosc* 2012; 4(10): 472-478 Available from: URL: http://www.wjgnet.com/1948-5190/full/v4/i10/472.htm DOI: http://dx.doi.org/10.4253/wjge.v4.i10.472

## INTRODUCTION

Gastric cancer remains the second leading cause of cancer-related deaths in the world. The incidence of gastric cancer is predominant in East Asia[1]. Usually, patients with early gastric cancer (EGC) are asymptomatic, whereas advanced stage patients typically present with bleeding, vomiting, and weight loss and have a dismal prognosis. Although curative surgery is recommended in all patients

with possible resectable lesions, the loss of gastric accommodation is an expected morbidity. There are some patients with EGC who do not require a full-thickness resection by surgery; endoscopic resection, which has less morbidity, is the preferred treatment for these individuals.

The pathogenesis of intestinal type gastric cancer is a sequential multistep pathway, starting with a precancerous lesion such as a gastric intestinal metaplasia (GIM) before developing into EGC and then growing into a full blown carcinoma[2] (Figure 1). Therefore, strategies that can detect precancerous lesions and monitor them before they become more significant cancers are very beneficial. Led by Japanese endoscopists, over the last three decades the tools for EGC detection have progressed from gastro cameras to magnifying chromoendoscopy. Subsequently, a one-button-touch technique called digital chromoendoscopy (DC), including Narrow-band Imaging (NBI) and other optimal band imaging, was promoted as a useful instrument for detecting many GI precancerous lesions, such as colonic adenoma, Barrett's esophagus, and GIM[3-9]. Recently, a confocal laser endoscopy (CLE) technique that provides a higher magnification (× 1000) of the GI tract epithelium has been used by many investigators as a tool for real-time GIM and EGC confirmation[10-13]. Moreover, CLE can be applied at the gastric lesion as a confirmation tool of tumor margin during, before, and after endoscopic treatment[14,15]. In this review, we present the techniques and the possible roles of DC and CLE for GIM and gastric cancer surveillance. Future improvements for technology and a possible protocol are also provided.

## THE HISTORY OF GASTRIC CANCER SURVEILLANCE BY ENDOSCOPY

According to the Correa pathway[2], atrophic gastritis, GIM and dysplasia are premalignant stages of gastric cancer. To date, there have been many technologies developed to detect these precancerous lesions. After the first debut of the gastro-camera in 1962[16,17], Nakayama[18] published a pioneering study of gastric cancer detection with a gastro-camera in 1969. However, the sensitivity and standardization of gastro-cameras for EGC detection were very limited. Subsequently, conventional white light endoscopy (WLE) replaced the use of gastro-cameras in 1984[19]. Unfortunately, the sensitivity of WLE for abnormal gastric epithelial detection was suboptimal (less than fifty percent)[3,6,19]. Later, a more sensitive technique called chromoendoscopy was developed to improve the detection of EGC. This technique was developed by pioneering Japanese endoscopists. It involves the use of a dye spray and a magnified endoscope. The sensitivity for EGC diagnosis was reported to be excellent (98%) with this technique[20,21]. Currently, this technique has been widely adopted as the standard practice in Japan, South Korea, and Taiwan. Among the many premalignant conditions, GIM has been widely targeted because of its unique morphology that has a higher potential for being distinguished from other normal gastric mucosa.

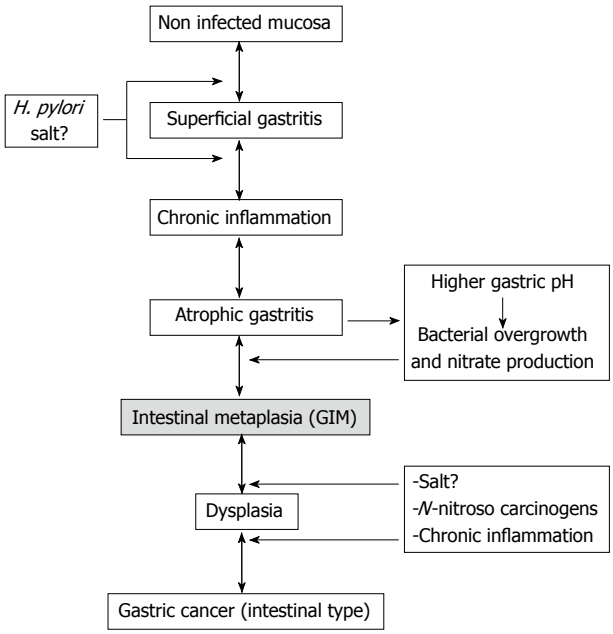


**Figure 1 Multistep pathway in the pathogenesis of intestinal-type gastric cancer (Correa pathway).**

For instance, methylene blue magnified chromoendoscopy provides a fair sensitivity (76%) for confirming a diagnosis of GIM by identifying blue irregular marks, blue round pits, tubular pits, blue villi, and blue small pits[22]. Therefore, the natural dye spraying method is not popular worldwide because it provides suboptimal accuracy for GIM diagnosis. New methods such as NBI and optimal band imaging or the more accurate confocal laser endomicroscopy (CLE) are needed to more easily improve findings. Vascular patterns and image analysis are easier and better detected with these new methods. For instance, Narrow Band Imaging with magnifying endoscopy (NBI/ME) has shown better sensitivity (90%), and CLE has been reported to provide the best sensitivity for confirming a diagnosis of GIM (98%, Table 1).

## DIGITAL CHROMOENDOSCOPES

Currently, there are three commercially available DC systems: Flexible Spectral Imaging Color Enhancement or Fuji Intelligent Color Enhancement (FICE; Fujifilm Corporation, Tokyo, Japan), I-Scan Pentax (Hoya Corporation, Tokyo, Japan), and NBI (Olympus Corporation, Tokyo, Japan). All of these systems provide a real-time image enhanced video stream. FICE and I-Scan rely on post-processing reconstruction of the images captured from white light by selecting only the optimal wavelengths of the three colors (red, green, and blue) in the 400-550 nm range. This in turn enhances the contrast of the captured images[23]. In contrast, NBI relies on a filter that selects only blue and green lights, each delivering a relatively narrow bandwidth that is preferably absorbed by hemoglobin. This in turn enhances areas with hypervascularity such as neoplasms and inflamed mucosa[24].

There have been two published articles on the use of

**Table 1 Sensitivities of different endoscopic technologies for gastric intestinal metaplasia detection**

| Endoscopy in GIM | Ref. | Sensitivity (%) |
|---|---|---|
| White light endoscopy | Sauerbruch *et al*[19] | < 50 |
| Digital chromoendoscopy (NBI) | Capelle *et al*[5] | 71 |
| Methylene blue magnified chromoendoscopy | Dinis-Ribeiro *et al*[22] | 76 |
| Digital magnified chromoendoscopy (Non-sequential-NBI) | Rerknimitr *et al*[7] | 91 |
| Digital magnified chromoendoscopy (sequential-NBI) | Uedo *et al*[4] | 89 |
| Endoscopic-based confocal laser endomicroscopy | Guo *et al*[40] | 98 |

GIM: Gastric intestinal metaplasia; NBI: Narrow-band Imaging.

FICE for EGC detection. Without magnification, Mouri and colleagues showed a 46 % improvement in image quality after applying the FICE system in patients in whom EGC was suspected[25]. However, to characterize the details of the mucosal structure, magnification of the images was required. FICE with a × 20 to × 30 magnification can help to characterize an upper GI tract polypoid lesion by detailing abnormal capillary architecture and pit pattern[23]. For a non-polypoid lesion, FICE can assist in the delineation of abnormal from normal mucosa and can ensure a complete endoscopic resection. A pioneering study of NBI for EGC detection was reported by Yao *et al*[24]. They proposed criteria for EGC diagnosis with NBI/ME and reported their validity in their cohorts with the negative and positive predictive values as 100% and 93%, respectively[26]. Following that study, there have been many reports of the usefulness of NBI for EGC detection. For instance, in 2010, Ezoe *et al*[3] published the diagnostic accuracy of NBI/ME for EGC diagnosis in 57 suspected depressed-EGC lesions. The study concluded that by adding NBI/ME to WLE, NBI/ME significantly increased the accuracy and sensitivity for EGC diagnosis from 44% to 79% and from 33% to 70%, respectively[3]. Later, Kato *et al*[6] used triad-based diagnosis [(1) the disappearance of fine mucosal structure; (2) the presence of microvascular dilation; and (3) the evidence of heterogeneity in the shape of microvessels] to diagnose EGC in 201 suspected EGC lesions in 111 patients at high risk for EGC. They found that the sensitivity and specificity of magnified NBI/ME for EGC diagnosis using these criteria were 92% and 94%, respectively, whereas the sensitivity and specificity of WLE were only 42.9% and 61.0%, respectively[6]. However, the generalization of DC for EGC screening has been challenged by many experts; therefore, the reading accuracy of all of the criteria needs to be validated in larger populations.

The current Asia-Pacific Consensus on the role of DC for the diagnosis of upper GI tract superficial neoplasia does not recommend the use of DC as the initial test because it is claimed that it is impractical to scan the whole gastric lumen with a magnified endoscope. However, they recommend using DC to distinguish malignant from non-malignant abnormal gastric lesions only after spotting the suspicious lesions with WLE. In addition, they recommend using DC to determine the extent but not the depth of EGC[27].

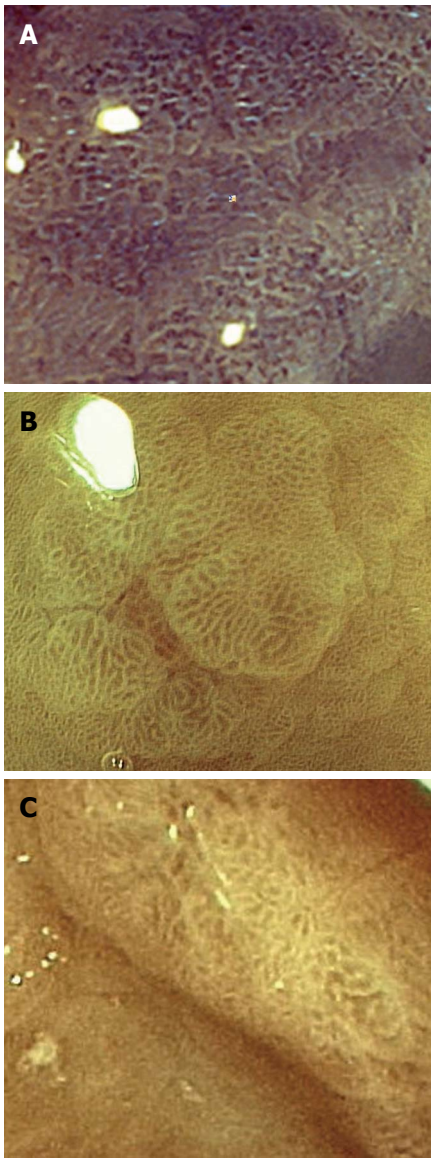


**Figure 2 Pictures under flexible spectral imaging color enhancement.** A: Light blue crest; B: Villous pattern; C: Large long crest.

Technically, GIM can be detected by DC due to a typical characteristic called light blue crest (LBC)[4,5,7] (Figure 2A). LBC is defined as a fine, blue-white line on the crests of the epithelial surface. LBC has the highest sensitivity for GIM detection (89%)[4]. In addition, Bansal *et al*[28] showed that the sensitivity and specificity of the ridge/villous pattern for the diagnosis of GIM were 80% and 100%, respectively; Tahara *et al*[29] reported a high sensitivity of ridge/villous pits for GIM diagnosis at 95%. Moreover, the results of other endoscopic patterns for GIM diagnosis have been studied by Rerknimitr *et al*. They added the villous pattern (VP; Figure 2B) and large long crest (LLC; Figure 2C) to improve the yield for GIM diagnosis. By using all three criteria (LBC, VP and LLC), the sensitivity for GIM diagnosis increased to 91%[7] (Ta-

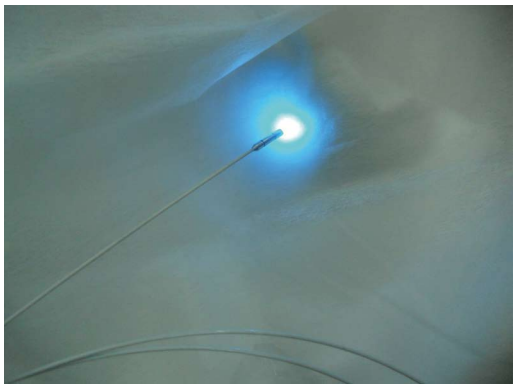

**Figure 3 The probe-based confocal laser endomicroscope probe.**

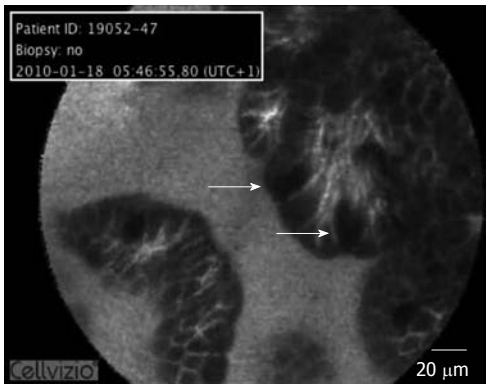


**Figure 4 An image of gastric intestinal metaplasia from a probe-based confocal laser endomicroscope (mucin-containing goblet cells; arrows).**

ble 1). Currently, there are more NBI/ME studies than FICE studies of GIM diagnosis by DC.

In summary, DC (FICE, I-Scan, and NBI) is a non-invasive test that provides higher sensitivities for EGC and GIM detection than WLE. DC is more convenient to use than conventional chromoendoscopy. It helps to distinguish suspicious EGC lesions and can delineate the extent of the cancer. Practically, primary screening should be performed with WLE; DC can be used after spotting suspicious lesions.

## CONFOCAL LASER ENDOMICROSCOPY

CLE is the latest novel endoscopic device[30]. CLE is a refined instrument that provides high-magnification (× 1000) imaging compared to standard microscopic examination. It enables a real-time display of a 12 frames/second video stream during the endoscopic examination. In other words, it is a real-time endoscopic read for histology without the need for a biopsy[10,11,31-34]. Currently, there are two techniques: (1) endoscopic-based confocal laser endomicroscopy (eCLE; Pentax, Tokyo, Japan) and (2) probe-based confocal laser endomicroscopy (pCLE, Mauna Kea Technologies). Both require an intravenous contrast injection (fluorescein) or a topical dye spray (e.g., acriflavine hydrochloride, tetracycline, or cresyl violet) to enhance all of the vascular supplied mucosal

**Table 2 Criteria for mature and immature gastric intestinal metaplasia by endoscopic-based confocal laser endomicroscope[40]**

| | Mature GIM | Immature GIM |
|---|---|---|
| Gland | Regular | Tortuous |
| Capillary | Regular | Irregular |
| Goblet cell | Regular | Regular |

GIM: Gastric intestinal metaplasia.

structures[35]. eCLE is an endoscopic-based CLE that integrates a confocal fluorescence microscope into the distal tip of a conventional 12.8-mm diameter flexible videoendoscope. The other system, known as pCLE, is provided by Mauna Kea Technologies (Paris, France) and is a 2.5-mm catheter probe transported 488-nm laser beam with a scanning field of 30 000 pixels[34,35] (Figure 3). With the current technology, the eCLE imaging system provides a superior quality of confocal image over pCLE. Although eCLE shares the same wavelength (488 nm) as pCLE for detecting the fluorescence effect at 505-585 nm, eCLE also provides a Z-axis, which creates an adjustable focus at different depths. In contrast, the image from pCLE is fixed at only one depth. Therefore, different levels of histological structures can be displayed by eCLE. Another advantage is that eCLE can provide a better (0.7 μm) lateral resolution than pCLE (1 μm)[34,36]. In addition, eCLE has a field of view of 475 × 475 μm with a variable imaging plane depth of up to 250 μm, whereas the pCLE system has a fixed imaging plane at the maximum depth of 200 μm. However, pCLE is more flexible because it can be used with any endoscopes that accept 10 Fr size accessories. Moreover, the frame rate of the pCLE system is much faster (12 images/second) than the current eCLE system (± 1 image/second)[37]. Therefore, the stream of pCLE images is closer to standard video output (Table 2).

Fluorescein, which is a slightly acidic and hydrophilic dye, has been used intravenously as a staining substance. Almost immediately after injection, it can be found distributed throughout the surface of columnar epithelial cells arranged in a cobblestone pattern with round gland openings. Fluorescein enhances a real-time histological reading by staining the connective tissue matrix of lamina propria and blood vessels running in the deeper mucosa[32,38]. A standard structure that contains vessels, such as a normal gastric epithelium, can be observed as a brighter object after fluorescein injection. In contrast, any structure that has no vascular supply, such as mucin, will not be stained by fluorescein. Hence, mucin-containing goblet cells, indicating GIM, will appear dark[32]. Fluorescein is a very safe contrast agent, with less than two percent of patients developing mild side effects such as nausea/vomiting, transient hypotension without shock, injection site erythema, diffuse rash and mild epigastric pain[39].

Another agent, acriflavine hydrochloride, has been most extensively used as a topical dye. However, it only

stains the very superficial layer of the GI tract mucosa[33] and does not penetrate into the deeper mucosa. Hence, it is not currently recommended for EGC screening.

Mucin-containing goblet cells can be readily recognizable by CLE (Figure 4). The sensitivity of eCLE for GIM diagnosis is excellent at 98%[12]. In addition, eCLE can further diagnose gastric dysplasia and early malignant gastric change with a very high sensitivity at 89%-91%[10,11]. Although current CLE technology is still not optimal for distinguishing between mature (regular glands, goblet cells, and columnar mucous cells) and immature (tortuous alveolar and irregular capillaries) GIM (Table 2), eCLE may be able to do so with 68% sensitivity[40]. In addition, Li *et al*[41] revealed that the score included 3 parameters: gland architecture, cell morphology, and vessel architecture, with marks ranging from 0-3 for each parameter. If the summation of the score $\geqslant$ 5, eCLE could differentiate high-grade from low-grade dysplasia with a sensitivity and specificity of 66% and 88%, respectively[41].

Recently, Lim *et al*[42] reported the validity scores from 3 experienced and 3 inexperienced readers who read GIM on the images captured by eCLE. They found that the experienced group had greater specificity in GIM interpretation (93% *vs* 62%, $P < 0.001$). However, the reading results of *ex-vivo* gastric cancer between the two groups were not different (a sensitivity of 93% *vs* 86%, $P = 1.00$, and a specificity of 87% *vs* 80%, $P = 0.34$)[42]. Another pCLE study on the learning curve for GIM diagnosis revealed that it is possible to train beginners to read GIM after a 3-d training session. However, the reading results were not as good as the experts' readings (the sensitivities, specificities and accuracies were 96% *vs* 87%, $P = 0.03$; 95% *vs* 82%, $P = 0.03$; and 95% *vs* 84%, $P = 0.01$; respectively)[43].

Although pilot studies have reported excellent results in EGC reading[10,11], the appearance of EGC under confocal laser microscopy has not been standardized due to the difficulty in reading the non-structural mitotic glands of the stomach. *In vivo* histological diagnosis for gastric cancer was first reported as an observational study in 2006 by a Japanese group[10]. Using conventional histology as the gold standard, in this study the *ex vivo* examination of 27 gastric cancerous tissues under eCLE yielded 89% sensitivity, 100% specificity, and 94% accuracy[10]. Another study by Kitabatake *et al*[11] showed comparable results for EGC reading by eCLE (91% sensitivity, 97% specificity, and 95% accuracy). Of note, the authors excluded 40% of their images due to suboptimal quality. Because undifferentiated adenocarcinoma is not amenable to endoscopic therapy, surgery is the only option. Therefore, it is important to have a tool that accurately distinguishes between differentiated and undifferentiated adenocarcinoma like eCLE (86%-95%)[15,44]. However, because these studies were performed by the experts in CLE reading, there is no guarantee that others will duplicate the results in standard practice. Therefore, further study on the learning curve for EGC reading by CLE is required. In the authors' opinion, employing CLE for GIM diagnosis in standard practice is more promising when using the well-described findings that require only a short learning curve. In contrast, there is a need for standardization for EGC reading by CLE before it can be recommended for use in routine work.

## ENDOSCOPIC TECHNIQUES FOR GIM AND EGC DIAGNOSIS

Because GIM and EGC are usually observed as diminutive lesions, a biopsy targeted by conventional WLE may be difficult. However, many synchronous GIMs or EGC lesions can be found in the stomach, and random biopsy may not be practical because it would be time consuming. Likewise, using CLE as the initial mode for screening is impractical because of its limited field of view per one examination. Therefore, we recommend using WLE (preferably with a high definition model) to identify abnormal gastric epithelium, and then to use magnified DC imaging to further characterize and perhaps identify more lesions if possible. We recommend performing a further study on the suspicious lesion with CLE by applying the scope or probe on the lesion and taking a biopsy if EGC or GIM with high grade dysplasia is suspected. In contrast, taking a biopsy from a lesion confirmed as a complete GIM by CLE may not be necessary because a complete GIM contains a very low risk for developing gastric cancer. By using this protocol, the procedure duration can be shortened. We recommend this combination of techniques because our study showed higher sensitivity (89%) and specificity (94%) for GIM diagnosis by adding pCLE on DC[43]. In addition, NBI/ME needs intensive training for GIM interpretation[45], whereas pCLE requires a shorter training session. Moreover, interobserver agreement among expert endoscopists for GIM detection based on each criterion of NBI/ME is still suboptimal ($\kappa = 0.60$ for LBC and no data for the other criteria)[45], whereas pCLE provided a better score by showing an almost perfect agreement ($\kappa = 0.83$) among experienced readers[46].

To avoid the shaking of the picture during the CLE procedure, adequate sedation is necessary in every patient because the procedure requires a very cooperative subject. A standard conscious sedation with intravenous midazolam and meperidine or propofol is recommended. Moreover, hyoscine or glucagon injection to decrease bowel movement is a requisite to ensure the stability of the examination. In addition, a simethicone solution should be rinsed to reduce mucous and gas bubbles in the stomach. Intravenously administering 10% fluorescein sodium at a dose of 2.5 mL right before the examination is adequate for a 30-min study.

A transparent cap is needed to maintain the focus distance during examination with pCLE. Slight pressure on the endoscope with the cap on is recommended to stabilize the target; once the target is identified, a biopsy can be obtained. For pCLE, a mark should be made by pressing a probe on the targeted gastric mucosa. The biopsy needs to be performed immediately after replacing the probe with a forceps into the endoscope accessory

channel. Of note, a procedure duration of longer than 20-30 min may have an impact on the image quality due to procedure-related mucosal damage and contrast leakage. The most important factor for excellent image interpretation is the experience of the endoscopist.

DC has been proven to delineate the EGC margin from non-malignant gastric mucosa[47,48]. The Asia-Pacific Consensus recommended DC as an adjunctive tool for evaluation of the EGC margin. They recommended using DC both before and after endoscopic mucosal resection or endoscopic submucosal dissection[27]. To date, there has been no study published on employing CLE to evaluate the EGC margin. In the authors' opinion, CLE may be useful for evaluating the residual malignant mucosa after endoscopic treatment. In addition, DC has been proven to be useful for GIM surveillance[49]. A group from South Korea recommended a 2-year surveillance interval in patients with GIM[50]. However, in a patient with extensive GIM, a much shorter annual surveillance with magnified DC is recommended after the resection of EGC[49].

## CONCLUSION

There has been a significant evolution in the endoscopic diagnosis of GIM and EGC. The current standard practice relies on a random biopsy under WLE. Although many expert centers have put magnified chromoendoscopy into their standard protocol for EGC surveillance, this practice has not been accepted worldwide for many reasons. Magnified DC is a promising tool for overcoming this problem, and may be beneficial for targeted biopsy. As an additional asset, CLE has been proposed for real-time confirmation of GIM without the need for a biopsy. However, the use of CLE is practical only in a patient with GIM, whereas the use of CLE for EGC confirmation is limited due to poor standardization of the criteria, for which a long learning curve may be required. In conclusion, histological examination by DC targeted biopsy may be recommended as a new "gold standard" for EGC diagnosis. CLE is a better alternative over a routine randomized biopsy in GIM surveillance because it can reduce unnecessary random biopsies.

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*World J Gastrointest Endosc* 2012 October 16; 4(10): I
ISSN 1948-5190 (online)




# Acknowledgments to reviewers of *World Journal of Gastrointestinal Endoscopy*

We acknowledge our sincere thanks to our reviewers. Many reviewers have contributed their expertise and time to the peer review, a critical process to ensure the quality of our World Series Journals. Both the editors of the journals and authors of the manuscripts submitted to the journals are grateful to the following reviewers for reviewing the articles (either published or rejected) over the past period of time.

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*World J Gastrointest Endosc* 2012 October 16; 4(10): I
ISSN 1948-5190 (online)




## Events Calendar 2012

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

January 19-21, 2012
2012 Gastrointestinal Cancers Symposium
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

November 3-4, 2012
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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*World J Gastrointest Endosc* 2012 October 16; 4(10): I-V
ISSN 1948-5190 (online)




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The major task of *WJGE* is to report rapidly the most recent results in basic and clinical research on gastrointestinal endoscopy including: gastroscopy, intestinal endoscopy, colonoscopy, capsule endoscopy, laparoscopy, interventional diagnosis and therapy, as well as advances in technology. Emphasis is placed on the clinical practice of treating gastrointestinal diseases with or under endoscopy. Papers on advances and application of endoscopy-associated techniques, such as endoscopic ultrasonography, endoscopic retrograde cholangiopancreatography, endoscopic submucosal dissection and endoscopic balloon dilation are also welcome.

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The columns in the issues of *WJGE* will include: (1) Editorial: To introduce and comment on major advances and developments in the field; (2) Frontier: To review representative achievements, comment on the state of current research, and propose directions for future research; (3) Topic Highlight: This column consists of three formats, including (A) 10 invited review articles on a hot topic, (B) a commentary on common issues of this hot topic, and (C) a commentary on the 10 individual articles; (4) Observation: To update the development of old and new questions, highlight unsolved problems, and provide strategies on how to solve the questions; (5) Guidelines for Basic Research: To provide guidelines for basic research; (6) Guidelines for Clinical Practice: To provide guidelines for clinical diagnosis and treatment; (7) Review: To review systemically progress and unresolved problems in the field, comment on the state of current research, and make suggestions for future work; (8) Original Article: To report innovative and original findings in gastrointestinal endoscopy; (9) Brief Article: To briefly report the novel and innovative findings in gastrointestinal endoscopy; (10) Case Report: To report a rare or typical case; (11) Letters to the Editor: To discuss and make reply to the contributions published in *WJGE*, or to introduce and comment on a controversial issue of general interest; (12) Book Reviews: To introduce and comment on quality monographs of gastrointestinal endoscopy; and (13) Guidelines: To introduce consensuses and guidelines reached by international and national academic authorities worldwide on basic research and clinical practice in gastrointestinal endoscopy.

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2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarrhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

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3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

*Organization as author*

4 **Diabetes Prevention Program Research Group**. Hyperten sion, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

*Both personal authors and an organization as author*

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

*No author given*

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

*Volume with supplement*

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

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8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

*No volume or issue*

9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

**Books**

*Personal author(s)*

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

*Chapter in a book (list all authors)*

11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

*Author(s) and editor(s)*

12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

*Conference proceedings*

13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

*Conference paper*

14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

**Electronic journal** (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

**Patent** (list all authors)

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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Write as mean ± SD or mean ± SE.

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