

# We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

185,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index  
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?  
Contact [book.department@intechopen.com](mailto:book.department@intechopen.com)

Numbers displayed above are based on latest data collected.  
For more information visit [www.intechopen.com](http://www.intechopen.com)



---

# **Innovative Uses and Emerging Technologies in Endoscopy**

---

J. Van Den Bogaerde and D. Sorrentino

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/52552>

---

## **1. Introduction**

Endoscopy is a fast moving field, and new techniques are constantly emerging. In recent decades, gastrointestinal endoscopy has evolved and branched out from a visual diagnostic modality, using fiberoptic bundles, to enhanced video and computer assisted imaging, with impressive interventional capabilities. Some new endoscopic techniques will be too complex or expensive to make the leap into general gastroenterology practice, others already show major progress in the management of digestive diseases. In this chapter we will discuss some of the emerging techniques and technologies used to increase the diagnostic yield in the colon and small intestine including third eye retrosopes, colon capsule endoscopy, balloon and spiral enteroscopy and confocal laser endomicroscopy. We will also discuss over the scope clip (OTSC) devices, a relatively simple and inexpensive tool potentially capable of closing noninvasively intestinal perforations and allowing the removal of infiltrating tumors. Experimental modalities such as natural orifice transluminal endoscopic surgery (NOTES) will also be discussed, with emphasis on their future clinical use. We will also focus on endoscopic ultrasonography (EUS), which has moved from an experimental technique to a valuable established diagnostic modality which not only competes with modern imaging modalities such as MRI, but is also particularly useful in the interventional setting especially in pancreatic and hepatobiliary pathology. We will also discuss the importance of training endoscopists in the use of these new techniques and we will offer some speculation on which of them may become really useful in routine patient care or remain restricted to large teaching hospitals.

## 2. Improving adenoma detection rate during colonoscopy

The most important task of endoscopists is the early detection and timely removal of colonic polyps. After completing a colonoscopy, the endoscopist should be confident that all polyps have been removed, including proximal flat lesions. Polyps are however missed in up to 35% of colonoscopies, and proximal adenomas are more frequently missed [1]. Proximal sessile serrated adenomas are particularly difficult to diagnose, but are present in up to 13% of screening colonoscopies, and result in colorectal malignancies [2]. Variation in detection rates is related to endoscopic skill and training. Real life data show that colonoscopy reduced mortality from colorectal cancer by 65% [3]. Cancers developing 3 years after a colonoscopy almost certainly represent missed lesions, and as many as 14.4% of right sided neoplasms are not detected during conventional colonoscopy [4]. The data show that endoscopists should focus on improving detection of right sided colonic lesions, where missed lesions and reduction in mortality is not optimal [5,6].

### 2.1. Retroflexion in cecum

The folds of the colon hide neoplastic lesions, and the majority (93.3%) of undiagnosed polyps hide behind folds [7]. Endoscopists know that rectal lesions close to the anal verge are difficult to see, and experienced operators do a thorough rectal examination and retroflex in the rectum to avoid missing these lesions. According to these principles cecalretroflexion with withdrawal and evaluation of the folds of the ascending colon should also be useful. A recent report has documented that cecalretroflexion was safe, achievable in 94.4%, and increased adenoma detection rate by 9.8% [8]. The advantage of this technique is that conventional equipment is used, all competent endoscopists can perform this, and no perforations were documented in this study. The study is however uncontrolled and the authors report that similar results may be achievable by a careful antegrade second look of the ascending colon. The obvious difficulty of examining the proximal colon has resulted in the development of third eye retrosopes.

### 2.2. Third eye devices

Third eye retrosopes are thin fiberoptic probes that fit into the working channel of a colonoscope and can examine folds in the ascending colon, which are not easily visible with forward viewing instruments. In controlled studies adenoma detection rates were improved, with better detection of larger rather than smaller lesions [9-11]. Adenomas larger than 6 mm in size were detected at a 25% higher rate, and 10mm or larger lesions at 33.3% [9]. The reason for this preferential visualization of larger and therefore more important lesions with the retroscope was documented by other authors [10], and no clear explanation for this somewhat surprising finding has been advanced.

In expert hands, use of retrosopes increases withdrawal time from 7.58 to 9.52 minutes [11], but increased adenoma detection of approximately 20% seems worthwhile. A potential

problem is that once a polyp has been detected the retroscope needs to be withdrawn, to make way for the polyp snare, thus losing sight of the polyp. Cost issues are crucial, and adding an expensive piece of equipment to every colonoscopy will increase costs. Indeed, cost issues may be the most important limiting factor in the universal acceptance of this promising new technology.

### 2.3. Mucosal enhancement techniques

Changing the appearance of the mucosa is now accepted as a method of increasing adenoma detection. Two methods exist: dye staining and equipment settings such as narrow band imaging. Blue dyes such as indigo carmine and methylene blue are useful in the colon, where mucosal definition and vascular pattern changes are emphasized. Lugol's iodine is useful in the esophagus, but can cause patient discomfort and allergic reactions.

Dye stains increase precision of diagnosis in Barrett's esophagus [12] and ulcerative colitis [13]. Chromoendoscopy using indigo carmine increased adenoma detection rate in a large and well designed study, from 36.3% to 46.2%, with a marginal increase in withdrawal times [14]. It is surprising that dye spray is not used more to increase adenoma detection. Personal experience and reports from working endoscopists suggest that the effort involved with dye spraying reduces enthusiasm for this technique as time goes by. Dye stains have the advantage of being cheap, but also dirty, time inefficient, and produce variable results [15].

Narrow band imaging (NBI) uses filters to emphasize blue coloured light, thus accentuating vascular structures. The touch button activation of this makes it user friendly, and NBI can accurately discriminate between hyperplastic and adenomatous polyps, according to pit patterns with a high sensitivity and specificity [16]. Dysplasia in ulcerative colitis [17] and early gastric cancer [18] are amenable to more precise analysis using NBI. In Barrett's mucosa, NBI has been shown to diagnose high grade dysplasia with a very high sensitivity (96%) and specificity (94%) [19].

The problem with NBI, is that the field depth is much reduced when compared to white light. Inevitably white light is used to see an abnormality, and then interrogation with NBI assists in confirming the pathology. It certainly is a "nice to have" technique for endoscopists who use it regularly, and training endoscopists to analyse NBI enhanced mucosal pathology is not daunting [20]. Somewhat disappointingly there is little evidence that NBI increases adenoma detection rate, which is really the point of new equipment [21-24].

The diagnosis of difficult-to-see flat or depressed lesions will remain a challenge. In some studies flat lesions are documented in 9.4% of patients, and 33% of depressed lesions are malignant [25]. Endoscopist skill, training, and continued vigilance, in conjunction with ongoing technical advances will increase adenoma detection rate, and hopefully reduce right sided interval cancers.

## 2.4. CO<sup>2</sup> insufflation

One technical advance which has improved colonoscopy, both for patients and proceduralists is CO<sub>2</sub> insufflation. Although described more than 30 years ago recent data have unequivocally shown superiority to room air insufflation [26-28]. In particular, patient recovery and distention after the procedure are markedly reduced. In our opinion, even the smallest unit should strive to change to CO<sub>2</sub> insufflation.

## 3. Colon capsule endoscopy

Although impressive advances have been made in colonic screening programs, the uptake of colonoscopy, which is the definitive screening tool is still disappointing [29,30]. In a large community based study the uptake of fecal occult blood testing was low (43%, 20.79% men), with obvious limitations of outcome [31].

The perception of what a colonoscopy is, and the perceived danger and invasiveness of the procedure contributes to poor patient uptake [32]. Other less invasive tests such as CT colonography have been suggested, but radiation and inability to detect flat polyps limit the usefulness of this study [33].

The establishment of small bowel capsule endoscopy has resulted in the development of colon capsule endoscopy (CCE), as an alternative to colonoscopy for diagnosis of colonic pathology.

CCE is technically more challenging than small bowel capsule evaluation, since the capsule has to travel through the small bowel, and then into the colon, which requires an increase in battery life. Lesions hidden in folds are difficult to visualize, as they are for conventional colonoscopy, and the bowel has to be even cleaner than for a normal colonoscopy, since mucosal washing is not possible [34].

Technical modifications of the original colon capsule, such as larger batteries, image capturing at both ends of the capsule, and increased image capture rate to accommodate faster colonic transit have improved diagnostic accuracy [35]. Sensitivity for polyp detection with second generation capsules is 89% [35], using colonoscopy as the gold standard.

Bowel preparation has to be rigorous [36], and some issues with capsule battery life remain challenging. Recent evidence-based guidelines for CCE have been produced by the European Society for Gastrointestinal Endoscopy [37].

CCE will probably be used in the same way as CT colonography, as a useful adjunct to colonoscopy. In patients who are at high risk for colonoscopy, or where completion of colonoscopy is not possible, evaluation by CCE may be useful. A small percentage of patients may be put off by colonoscopy and for them, the non invasiveness of CCE would be attractive. Cost comparisons would be essential in determining exactly where the future of CCE lies. Adenoma detection rates in colonoscopy screening populations approximate 50% or more [14,31], which suggests that successful screening procedures would

necessitate colonoscopy in a majority of patients anyway, to remove visualized adenomas. Flat lesions remain a problem, regardless of the screening modality employed.

#### **4. Small bowel evaluation and spiral enteroscopy**

Small bowel evaluation has become precise and relatively easy with small bowel capsule evaluation. MR enterography has added excellent diagnostic capability, particularly in patients with Crohn's disease [38,39].

The different radiological and capsule techniques are complementary, and evaluation of the bowel wall and extraintestinal structures is a particular strength of MR enterography [40].

The challenge of the small bowel is intervention once pathology has been found. A patient with iron deficiency anemia may have small bowel vascular ectasia which are amenable to Argon plasma coagulation, or a polyp which can be removed endoscopically. In the last decade double balloon enteroscopy (DBE) has become an established technique with reported complete small bowel evaluation possible in 40 to 80 % [41]. Subsequently the single balloon enteroscopy (SBE) technique was introduced with lower rates of complete enteroscopy (up to 25% of cases) and a diagnostic yield of 40 - 60% [42,43]. Both DBE and SBE need up to 90 minutes to be completed and are demanding procedures. Complications include perforation (2.3% in SBE) and pancreatitis (0.3% in DBE) [42,43]. Interventions are sometimes difficult due to the unstable endoscope position.

Spiral enterography is a new technique whereby an overtube with a distal thread is placed over a conventional colonoscope and twisted into the small bowel [44]. The insertion time for spiral enterography appears to be shorter than double balloon enterography, but depth of insertion is considerably less [45]. Stent insertion and therapeutic maneuvers may be easier with the spiral technique due to overtube stabilization [46]. DBE uses a Fujinon platform, while the SBE uses an Olympus platform. Spiral enteroscopy has the advantage of using different endoscopic platforms, but its role has not been sufficiently defined to make recommendations yet.

Small bowel pathology is an important part of the work up in a substantial proportion of patients with an undefined iron deficiency anemia. The chosen diagnostic modality depends on availability and expertise, but small bowel capsule is probably the choice examination for the time being. Once pathology has been identified, the depth of the lesion in the small bowel determines which of the three interventional modalities is optimal. DBE is the established technology, but in more proximal small bowel lesions, particularly if stenting is required, spiral enterography may be the procedure of choice. The role of this technology outside teaching hospitals awaits good comparative studies.



## 5. ERCP and endoscopic ultrasound

Ironically the greatest advance in ERCP in the last 10 years is the development of MRCP, which has almost completely dispensed with the need for diagnostic ERCP. Techniques have not really changed in 10 years, although some useful stent modifications have occurred. Novel stenting devices include stents impregnated with radioactive seeds, which not only can palliatively drain obstructed common bile ducts, but also irradiate the contiguous pancreatic malignancy [47].

The interplay between endoscopic ultrasound (EUS) and ERCP in challenging patients is an interesting new development. ERCP drainage of malignant biliary strictures often fails, and EUS drainage bypassing the papilla is feasible, and in expert hands has a high success rate [48,49].

Patients with altered anatomy after surgery present a special challenge, and ERCP may be impossible. In expert hands EUS can assist in placing stents, but the authors of an authoritative review point out that the technical difficulties and the specialized nature of these interventions are best left to experts in referral centres [50]. Certainly these technologies are not going to enter community based departments soon.

Exciting applications of EUS based interventions include the now standard celiac plexus blocks and drainage of pseudocysts, as well as implantation of radioactive seeds and even viral vectors in tumours, ablation of cysts, variceal cyanoacrylate injection, and vascular coil placement [47,51-53]. Obviously these techniques are at the moment very far from mainstream gastroenterology.

## 6. Confocal laser endomicroscopy

Confocal laser endomicroscopy (CLE) is a technology which allows real time histology of the mucosa during upper and lower endoscopy. Laser illumination of the mucosa combined with fluorescent dye illumination enables immediate and precise "microscopic" evaluation of mucosal lesions [54]. Fluorescent dye injection is essential for this technique, and tissue uptake occurs within seconds of injection. There is a very extensive literature of fluorescent dye injection in ophthalmology, confirming its excellent safety profile. The limitation of fluorescein is that it highlights cells, connective tissue and vessels but not nuclear material. Topical application of acroflavine stains cell nuclei, and can be used separately or in addition to fluorescein.

Depth of view of the endoscopic CLE system is up to 250  $\mu\text{m}$ , while the probe system which is inserted down the working channel of any endoscope has a more limited depth of view [55]. The area which can be examined is limited - no more than 700  $\mu\text{m}^2$  in the endoscopy based system and even less in the smaller probe based system so precise targeting is important. New generation probes can be placed through needles allowing novel approaches to

endoultrasonographic tissue sampling, hepatobiliary assessment, and even laparoscopically assisted real time hepatic tissue histology [56].

CLE has been used extensively in evaluating Barrett's mucosa. It has also been used in patients with colonic neoplasia, gastric metaplasia, and celiac disease.

When used in combination with conventional endoscopy, CLE allows excellent prediction of high grade dysplasia and malignancy in Barrett's mucosa [57]. In addition to targeting biopsies, assessment of submucosal tissue, which may be particularly important in patients who have undergone ablation of Barrett's dysplasia can be performed. CLE predicted malignancy in Barrett's lesions with a specificity of 96%, and sensitivity of 88% [58]. CLE combined with four quadrant biopsies was twice as effective in detecting neoplasia, and the majority of patients in the CLE arm did not need biopsies at all [59].

Gastric metaplasia or malignancy are amenable to CLE evaluation, with high accuracy and reproducibility, and significantly better accuracy than conventional endoscopy [60-62].

During colonoscopy CLE polyp evaluation, when compared with standard histology produces sensitivity for adenoma of 97.3%, while high and low grade dysplasia was analyzed accurately in 96.7% [63]. CLE evaluation in patients with UC resulted in far higher detection of intra-epithelial neoplasia (4.75 fold), as well as reducing the number of biopsies by half [64].

The future focus of CLE is the use of specific labeled markers in a method similar to immunohistochemistry, to light up pre malignant or malignant mucosa [65,66] The application of this methodology beyond the research setting is however still unclear.

The concept of optical biopsies [67] has been well established for colonic and gastric neoplastic lesions, particularly by Japanese endoscopists assessing flat colonic lesions, but microscopic *in vivo* biopsies using CLE technology advances this concept to a new level. What has not been addressed is the medico legal issue related to this technique. How confident can an endoscopist be when making a diagnosis by CLE of high grade dysplasia in a patient with Barrett's esophagus, and use only this information to guide subsequent therapy? In these cases the gold standard will remain conventional histopathology, with its established and extensive guidelines.

Finally, this technology does not improve detection rate of suspicious lesions, but relies on conventional endoscopic evaluation to target the optical biopsy. As discussed at the beginning of this chapter, the greatest problem with endoscopy is the missed lesion. Although the reduced number of biopsies is mentioned as an advantage this is a tenuous advantage at most. The time taken to analyze tissue by CLE, would be easily spent taking more biopsies if clinically indicated. In a recent study the advantage of optical biopsy in patients on anticoagulation is brought forward as a reason to pursue *in vivo* histology [68] but current guidelines do not exclude patients on anticoagulation from undergoing biopsy [69].

Although CLE appears glamorous and exciting as a technology, it has been around for almost a decade, and has not really expanded its reach beyond the research setting. The time constraints, expense and technical difficulties probably will keep this as a "nice to have" technology in selected tertiary hospitals where enthusiasts will use it.



## 7. Over the scope clip devices

Colonic perforation remains an important complication of colonoscopy, with a large recent series reporting an alarming 0.33% rate [70].

Both diagnostic and therapeutic interventions can cause perforation, and even argon plasma coagulation (APC) can result in perforations. Even in the best hands, perforation occurs when complex polyps are removed, and indeed increased polyp detection and removal of increasingly large polyps will result in more rather than less colonic endoscopic complications [71].

Over the scope clip devices (OTSC) are pre armed on a transparent silicone cap, and are released by winding up a pre loaded thread similar to band ligators. A large pair of forceps is passed through the working channel to approximate the defect and pull the tissue into the cap, followed by release of the bear trap-like device. Even deep lesions penetrating into the serosa can be closed. OTSC devices have been successfully used in animal models to close full thickness perforations [72]. Perforation closure strength has been shown to approximate conventional surgical techniques [73].

In a small clinical case report study perforation closure was achieved in 6 of 7 cases, and avoidance of any surgery achieved in 4 of 7 [74]. Perforations of up to 20 mm were managed using these clips in a clinical setting [75], and surgery was performed in only one of 10 patients.

These clips have been shown to close colonic fistulae, without surgical intervention [76]. In another report, 11 of 12 patients were treated successfully for chronic fistulae and colonic perforations with no reported complications [77]. Placing clips is technically challenging, but a mean procedure time of 54 minutes for fistula closure is not dauntingly long when compared to other difficult endoscopic techniques [78].

Even refractory chronic duodenal fistula and esophageal anastomotic perforation after gastrectomy have been managed by OTSC devices [78,79].

The bear trap structure of these clips does however demands caution when placing, and very careful consideration of clip removal if placement is incorrect.

Large defects greater than 2.5 cm are not amenable to treatment with these clips, but application of more than one clip may be helpful. Severe fibrosis over a large area is also not amenable to clip application in patients with long standing ulcers or fistulae. Reports of complications are scarce. One paper reports no complications [77] but post clip pain may be due to grasping of visceral fat or peritoneum [75]. Strictures can also develop, particularly when large portions of mucosa are grasped and clipped.

In addition, when drawing back the mucosa with forceps, the clip must not grasp the forceps during deployment, since loosening of the clip is impossible. This then results in the clip and forceps being stuck in the channel of the endoscope, and stuck to the mucosa. Surgical removal is the only option: a true endoscopic nightmare.

OTSC devices can control bleeding in animal models [80]. A recent study of upper gastrointestinal bleeding documented a 13% re-bleed rate after initial endoscopy, and a mortality of 10% [81]. Although the study does not precisely detail the endoscopic appearance of peptic ulcers in re-bleeding patients, a substantial percentage of these patients probably had chronic fibrotic ulceration, with endoscopically difficult to control visible vessels in the ulcer base. It is well recognized that these patients often re-bleed and need surgical intervention. Placing conventionally available clipping devices on these vessels is challenging, dangerous and often unsuccessful. In theory, the OTSC device offers a far better approach to these patients, and this indication may actually become the most important of these devices.

### 7.1. OTSC and endoscopic submucosal dissection

Endoscopic submucosal dissection (ESD) allows *en block* removal of gastric and colonic neoplasia. Perforation rates of 4.1% in gastric [82] and as high as 20.4% in colon lesions have been reported [83]. OTSC devices may assist in closing some of the larger perforations in these patients. Full thickness endoscopic resection of tumours or polyps is possible with a combination of OTSC and snare devices [84]. In those patients where endoultrasonography has shown invasion of the muscular wall, and endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) is not feasible, the OTSC device may offer a non surgical approach for removal of these neoplastic and invasive lesions in selected patients. In particular, this technique could be potentially useful in treating gastrointestinal stroma tumors, granulosa cell tumours, carcinoids, or any other slowly growing neoplasms which invade the muscular wall and are therefore not amenable to other endoscopic techniques.

### 7.2. NOTES

One of the problems of natural orifice transluminal endoscopic surgery (NOTES) procedures is the gastrotomy, which may be amenable to OTSC closure [85]. However, NOTES remains a modality that has yet to find its place outside the experimental sphere. The technical challenges of these procedures, with the relatively minimal gain of avoiding minor entrance wounds in laparoscopic surgery, would suggest that these techniques may not be going to become routine.

## 8. Endoscopic control of bleeding

Techniques for controlling bleeding have not substantially changed in the last decade, but a new method of nanopowder spray seems to be both effective and easy to apply [86,87]. This powder could be of potential benefit in difficult to control arterial bleeds, where visibility is an issue, or as a bridge to surgery. The major advantage of this would possibly be that less experienced endoscopists could obtain control of bleeding, without performing technically difficult procedures. In our opinion, most senior endoscopy consultants would appreciate this modality if it would mean that more junior consultants could safely handle emergency bleeds.

## Author details

J. Van Den Bogaerde<sup>1,2\*</sup> and D. Sorrentino<sup>1,2,3</sup>

\*Address all correspondence to: Johan\_van\_den\_Bogaerde@health.qld.gov.au

1 Department of Gastroenterology, Nambour General Hospital, University of Queensland, Australia

2 Sunshine Coast Clinical School, Australia

3 University of Udine Medical School, Udine, Italy

## References

- [1] Laiyemo AO, Doubeni C, Sanderson AK, Pinsky PF, Badurdeen DS, Doria-Rose VP, et al. Likelihood of missed and recurrent adenomas in the proximal versus the distal colon. *GastrointestEndosc* 2011, Aug;74(2):253-61.
- [2] Kahi CJ, Hewett DG, Norton DL, Eckert GJ, Rex DK. Prevalence and variable detection of proximal colon serrated polyps during screening colonoscopy. *ClinGastroenterolHepatol* 2011, Jan;9(1):42-6.
- [3] Kahi CJ, Imperiale TF, Juliar BE, Rex DK. Effect of screening colonoscopy on colorectal cancer incidence and mortality. *ClinGastroenterolHepatol* 2009, Jul;7(7):770-5; quiz 711.
- [4] Singh H, Nugent Z, Demers AA, Bernstein CN. Rate and predictors of early/missed colorectal cancers after colonoscopy in manitoba: A population-based study. *Am J Gastroenterol* 2010, Dec;105(12):2588-96.
- [5] Singh H, Nugent Z, Demers AA, Kliever EV, Mahmud SM, Bernstein CN. The reduction in colorectal cancer mortality after colonoscopy varies by site of the cancer. *Gastroenterology* 2010, Oct;139(4):1128-37.
- [6] Brenner H, Hoffmeister M, Arndt V, Stegmaier C, Altenhofen L, Haug U. Protection from right- and left-sided colorectal neoplasms after colonoscopy: Population-based study. *J Natl Cancer Inst* 2010, Jan 1;102(2):89-95.
- [7] Pickhardt PJ, Nugent PA, Mysliwiec PA, Choi JR, Schindler WR. Location of adenomas missed by optical colonoscopy. *Ann Intern Med* 2004, Sep 9;141(5):352-9.
- [8] Hewett DG, Rex DK. Miss rate of right-sided colon examination during colonoscopy defined by retroflexion: An observational study. *GastrointestEndosc* 2011, Aug;74(2):246-52.

- [9] Wayne JD, Heigh RI, Fleischer DE, Leighton JA, Gurudu S, Aldrich LB, et al. A retrograde-viewing device improves detection of adenomas in the colon: A prospective efficacy evaluation (with videos). *GastrointestEndosc* 2010, Mar;71(3):551-6.
- [10] DeMarco DC, Odstrcil E, Lara LF, Bass D, Herdman C, Kinney T, et al. Impact of experience with a retrograde-viewing device on adenoma detection rates and withdrawal times during colonoscopy: The third eye retroscope study group. *GastrointestEndosc* 2010, Mar;71(3):542-50.
- [11] Leufkens AM, DeMarco DC, Rastogi A, Akerman PA, Azzouzi K, Rothstein RI, et al. Effect of a retrograde-viewing device on adenoma detection rate during colonoscopy: The TERRACE study. *GastrointestEndosc* 2011, Mar;73(3):480-9.
- [12] Kouklakis GS, Kountouras J, Dokas SM, Molyvas EJ, Vourvoulakis GP, Minopoulos GI. Methylene blue chromoendoscopy for the detection of barrett's esophagus in a greek cohort. *Endoscopy* 2003, May;35(5):383-7.
- [13] Kiesslich R, Fritsch J, Holtmann M, Koehler HH, Stolte M, Kanzler S, et al. Methylene blue-aided chromoendoscopy for the detection of intraepithelial neoplasia and colon cancer in ulcerative colitis. *Gastroenterology* 2003, Apr;124(4):880-8.
- [14] Pohl J, Schneider A, Vogell H, Mayer G, Kaiser G, Ell C. Pancolonichromoendoscopy with indigo carmine versus standard colonoscopy for detection of neoplastic lesions: A randomised two-centre trial. *Gut* 2011, Apr;60(4):485-90.
- [15] Kwan V. Advances in gastrointestinal endoscopy. *Intern Med J* 2012, Feb;42(2):116-26.
- [16] East JE, Suzuki N, Bassett P, Stavrinidis M, Thomas HJ, Guenther T, et al. Narrow band imaging with magnification for the characterization of small and diminutive colonic polyps: Pit pattern and vascular pattern intensity. *Endoscopy* 2008, Oct;40(10):811-7.
- [17] Esaki M, Kubokura N, Kudo T, Matsumoto T. Endoscopic findings under narrow band imaging colonoscopy in ulcerative colitis. *Dig Endosc* 2011, May;23Suppl 1:140-2.
- [18] Zhang J, Guo S-B, Duan Z-J. Application of magnifying narrow-band imaging endoscopy for diagnosis of early gastric cancer and precancerous lesion. *BMC Gastroenterol* 2011;11:135.
- [19] Mannath J, Subramanian V, Hawkey CJ, Ragunath K. Narrow band imaging for characterization of high grade dysplasia and specialized intestinal metaplasia in barrett's esophagus: A meta-analysis. *Endoscopy* 2010, May;42(5):351-9.
- [20] Higashi R, Uraoka T, Kato J, Kuwaki K, Ishikawa S, Saito Y, et al. Diagnostic accuracy of narrow-band imaging and pit pattern analysis significantly improved for less-experienced endoscopists after an expanded training program. *GastrointestEndosc* 2010, Jul;72(1):127-35.

- [21] Sabbagh LC, Reveiz L, Aponte D, de Aguiar S. Narrow-band imaging does not improve detection of colorectal polyps when compared to conventional colonoscopy: A randomized controlled trial and meta-analysis of published studies. *BMC Gastroenterol* 2011;11:100.
- [22] Ikematsu H, Saito Y, Tanaka S, Uraoka T, Sano Y, Horimatsu T, et al. The impact of narrow band imaging for colon polyp detection: A multicenter randomized controlled trial by tandem colonoscopy. *J Gastroenterol* 2012, Mar 3.
- [23] Nagorni A, Bjelakovic G, Petrovic B. Narrow band imaging versus conventional white light colonoscopy for the detection of colorectal polyps. *Cochrane Database Syst Rev* 2012;1:CD008361.
- [24] Pasha SF, Leighton JA, Das A, Harrison ME, Gurudu SR, Ramirez FC, et al. Comparison of the yield and miss rate of narrow band imaging and white light endoscopy in patients undergoing screening or surveillance colonoscopy: A meta-analysis. *Am J Gastroenterol* 2012, Mar;107(3):363-70; quiz 371.
- [25] Soetikno RM, Kaltenbach T, Rouse RV, Park W, Maheshwari A, Sato T, et al. Prevalence of nonpolypoid (flat and depressed) colorectal neoplasms in asymptomatic and symptomatic adults. *JAMA* 2008, Mar 3;299(9):1027-35.
- [26] Hsu W-H, Sun M-S, Lo H-W, Tsai C-Y, Tsai Y-J. Carbon dioxide insufflation during withdrawal of the colonoscope improved postprocedure discomfort: A prospective, randomized, controlled trial. *Kaohsiung J Med Sci* 2012, May;28(5):265-9.
- [27] Geyer M, Guller U, Beglinger C. Carbon dioxide insufflation in routine colonoscopy is safe and more comfortable: Results of a randomized controlled double-blinded trial. *DiagnTherEndosc* 2011;2011:378906.
- [28] Wang WL, Wu ZH, Sun Q, Wei JF, Chen XF, Zhou DK, et al. Meta-analysis: The use of carbon dioxide insufflation vs. Room air insufflation for gastrointestinal endoscopy. *Aliment PharmacolTher* 2012, May;35(10):1145-54.
- [29] McGregor SE, Hilsden RJ, Li FX, Bryant HE, Murray A. Low uptake of colorectal cancer screening 3 yr after release of national recommendations for screening. *Am J Gastroenterol* 2007, Aug;102(8):1727-35.
- [30] Hoffman-Goetz L, Thomson MD, Donelle L. Reasons for declining colorectal cancer screening by older Canadians: A pilot study. *J Cancer Educ* 2008;23(1):32-6.
- [31] Gupta S, Saunders BP, Fraser C, Kennedy RH, Ignjatovic A, Sala S, et al. The first 3 years of national bowel cancer screening at a single UK tertiary centre. *Colorectal Dis* 2012, Feb;14(2):166-73.
- [32] Marshall DA, Johnson FR, Kulin NA, Ozdemir S, Walsh JME, Marshall JK, et al. How do physician assessments of patient preferences for colorectal cancer screening tests differ from actual preferences? A comparison in Canada and the United States using a stated-choice survey. *Health Econ* 2009, Dec;18(12):1420-39.



- [33] Hock D, Ouhadi R, Materne R, Mancini I, Nchimi A. Screening for colorectal cancer in asymptomatic average risk patients: Role of imaging. *ActaGastroenterolBelg* 2011, Mar;74(1):70-6.
- [34] Sieg A. Colon capsule endoscopy compared with conventional colonoscopy for the detection of colorectal neoplasms. *Expert Rev Med Devices* 2011, Mar;8(2):257-61.
- [35] Eliakim R, Yassin K, Niv Y, Metzger Y, Lachter J, Gal E, et al. Prospective multicenter performance evaluation of the second-generation colon capsule compared with colonoscopy. *Endoscopy* 2009, Dec;41(12):1026-31.
- [36] Spada C, Hassan C, Ingrosso M, Repici A, Riccioni ME, Pennazio M, et al. A new regimen of bowel preparation for pillcam colon capsule endoscopy: A pilot study. *Dig Liver Dis* 2011, Apr;43(4):300-4.
- [37] Spada C, Hassan C, Galmiche JP, Neuhaus H, Dumonceau JM, Adler S, et al. Colon capsule endoscopy: European society of gastrointestinal endoscopy (ESGE) guideline. *Endoscopy* 2012, May;44(5):527-36.
- [38] Smith EA, Dillman JR, Adler J, Dematos-Maillard VL, Strouse PJ. MR enterography of extraluminal manifestations of inflammatory bowel disease in children and adolescents: Moving beyond the bowel wall. *AJR Am J Roentgenol* 2012, Jan;198(1):W38-45.
- [39] Herraiz Hidalgo L, Alvarez Moreno E, CarrascosoArranz J, Cano Alonso R, Martínez de Vega Fernández V. [Magnetic resonance enterography: Review of the technique for the study of crohn's disease]. *Radiologia* 2011;53(5):421-33.
- [40] Tennyson CA, Semrad CE. Advances in small bowel imaging. *CurrGastroenterol Rep* 2011, Oct;13(5):408-17.
- [41] Yamamoto H, Sekine Y, Sato Y, Higashizawa T, Miyata T, Iino S, et al. Total enteroscopy with a nonsurgical steerable double-balloon method. *GastrointestEndosc* 2001, Feb;53(2):216-20.
- [42] Kawamura T, Yasuda K, Tanaka K, Uno K, Ueda M, Sanada K, Nakajima M. Clinical evaluation of a newly developed single-balloon enteroscope. *GastrointestEndosc* 2008, Dec;68(6):1112-6.
- [43] Tsujikawa T, Saitoh Y, Andoh A, Imaeda H, Hata K, Minematsu H, et al. Novel single-balloon enteroscopy for diagnosis and treatment of the small intestine: Preliminary experiences. *Endoscopy* 2008, Jan;40(1):11-5.
- [44] Akerman PA, Cantero D. Spiral enteroscopy and push enteroscopy. *GastrointestEndoscClin N Am* 2009, Jul;19(3):357-69.
- [45] Frieling T, Heise J, Sassenrath W, Hülsdonk A, Kreysel C. Prospective comparison between double-balloon enteroscopy and spiral enteroscopy. *Endoscopy* 2010, Nov;42(11):885-8.

- [46] Lennon AM, Chandrasekhara V, Shin EJ, Okolo PI. Spiral-enteroscopy-assisted enter-al stent placement for palliation of malignant small-bowel obstruction (with video). *GastrointestEndosc* 2010, Feb;71(2):422-5.
- [47] Du Y-Q, Li Z-S, Jin Z-D. Endoscope-assisted brachytherapy for pancreatic cancer: From tumor killing to pain relief and drainage. *J IntervGastroenterol* 2011;1(1):23-7.
- [48] Kim TH, Kim SH, Oh HJ, Sohn YW, Lee SO. Endoscopic ultrasound-guided biliary drainage with placement of a fully covered metal stent for malignant biliary obstruction. *World J Gastroenterol* 2012, May 5;18(20):2526-32.
- [49] Park DH, Koo JE, Oh J, Lee YH, Moon S-H, Lee SS, et al. EUS-guided biliary drainage with one-step placement of a fully covered metal stent for malignant biliary obstruction: A prospective feasibility study. *Am J Gastroenterol* 2009, Sep;104(9):2168-74.
- [50] Will U, Meyer F. [Endoscopic ultrasonography (EUS)-guided transluminalcholangio-drainage (EUCD) - a novel option of interventional endoscopy in the interdisciplinary management of obstructive jaundice]. *ZentralblChir* 2012, Feb;137(1):20-31.
- [51] Cho CM, Dewitt J, Al-Haddad M. Echo-endoscopy: New therapeutic frontiers. *Minerva GastroenterolDietol* 2011, Jun;57(2):139-58.
- [52] Ponnudurai R, Sachithanandan S, George A. Endoscopic ultrasound-guided injection therapy for hepatobiliary disease. *J HepatobiliaryPancreatSci* 2011, May;18(3):311-8.
- [53] Trevino JM, Varadarajulu S. Endoscopic ultrasonography-guided ablation therapy. *J HepatobiliaryPancreatSci* 2011, May;18(3):304-10.
- [54] Kiesslich R, Goetz M, Neurath MF. Confocal laser endomicroscopy for gastrointestinal diseases. *GastrointestEndoscClin N Am* 2008, Jul;18(3):451-66, viii.
- [55] Matloff JL, Abidi W, Richards-Kortum R, Sauk J, Anandasabapathy S. High-resolution and optical molecular imaging for the early detection of colonic neoplasia. *GastrointestEndosc* 2011, Jun;73(6):1263-73.
- [56] Wallace MB, Fockens P. Probe-based confocal laser endomicroscopy. *Gastroenterology* 2009, May;136(5):1509-13.
- [57] Canto MI. Endomicroscopy of barrett's esophagus. *GastroenterolClin North Am* 2010, Dec;39(4):759-69.
- [58] Wallace MB, Sharma P, Lightdale C, Wolfsen H, Coron E, Buchner A, et al. Preliminary accuracy and interobserver agreement for the detection of intraepithelial neoplasia in barrett's esophagus with probe-based confocal laser endomicroscopy. *GastrointestEndosc* 2010, Jul;72(1):19-24.
- [59] Dunbar KB, Okolo P, Montgomery E, Canto MI. Confocal laser endomicroscopy in barrett's esophagus and endoscopicallyinapparentbarrett'sneoplasia: A prospective, randomized, double-blind, controlled, crossover trial. *GastrointestEndosc* 2009, Oct;70(4):645-54.

- [60] Guo Y-T, Li Y-Q, Yu T, Zhang T-G, Zhang J-N, Liu H, et al. Diagnosis of gastric intestinal metaplasia with confocal laser endomicroscopy in vivo: A prospective study. *Endoscopy* 2008, Jul;40(7):547-53.
- [61] Li C-Q, Li Y-Q. Endomicroscopy of intestinal metaplasia and gastric cancer. *GastroenterolClin North Am* 2010, Dec;39(4):785-96.
- [62] Lim LG, Yeoh KG, Salto-Tellez M, Khor CJL, Teh M, Chan YH, et al. Experienced versus inexperienced confocal endoscopists in the diagnosis of gastric adenocarcinoma and intestinal metaplasia on confocal images. *GastrointestEndosc* 2011, Jun;73(6):1141-7.
- [63] Sanduleanu S, Driessen A, Gomez-Garcia E, Hameeteman W, de Bruïne A, Masclee A. In vivo diagnosis and classification of colorectal neoplasia by chromoendoscopy-guided confocal laser endomicroscopy. *ClinGastroenterolHepatol* 2010, Apr;8(4):371-8.
- [64] Kiesslich R, Goetz M, Lammersdorf K, Schneider C, Burg J, Stolte M, et al. Chromoscopy-guided endomicroscopy increases the diagnostic yield of intraepithelial neoplasia in ulcerative colitis. *Gastroenterology* 2007, Mar;132(3):874-82.
- [65] Goetz M, Ziebart A, Foersch S, Vieth M, Waldner MJ, Delaney P, et al. In vivo molecular imaging of colorectal cancer with confocal endomicroscopy by targeting epidermal growth factor receptor. *Gastroenterology* 2010, Feb;138(2):435-46.
- [66] Hsiung P-L, Hsiung P-L, Hardy J, Friedland S, Soetikno R, Du CB, et al. Detection of colonic dysplasia in vivo using a targeted heptapeptide and confocal microendoscopy. *Nat Med* 2008, Apr;14(4):454-8.
- [67] Hurlstone DP, Sanders DS. Recent advances in chromoscopic colonoscopy and endomicroscopy. *CurrGastroenterol Rep* 2006, Oct;8(5):409-15.
- [68] Minami H, Inoue H, Yokoyama A, Ikeda H, Satodate H, Hamatani S, et al. Recent advancement of observing living cells in the esophagus using CM double staining: Endocytoscopycatypia classification. *Dis Esophagus* 2011, Sep 9.
- [69] Anderson MA, Ben-Menachem T, Gan SI, Appalaneni V, Banerjee S, Cash BD, et al. Management of antithrombotic agents for endoscopic procedures. *GastrointestEndosc* 2009, Dec;70(6):1060-70.
- [70] Hagel A, Boxberger F, Dauth W, Kessler H, Neurath M, Raithel M. Colonoscopy-associated perforation: A 7-year survey of in-hospital frequency, treatment and outcome in a german university hospital. *Colorectal Dis* 2011, Nov 11.
- [71] Moss A, Bourke MJ, Williams SJ, Hourigan LF, Brown G, Tam W, et al. Endoscopic mucosal resection outcomes and prediction of submucosal cancer from advanced colonic mucosal neoplasia. *Gastroenterology* 2011, Jun;140(7):1909-18.

- [72] Schurr MO, Hartmann C, Ho C-N, Fleisch C, Kirschniak A. An over-the-scope clip (OTSC) system for closure of iatrogenic colon perforations: Results of an experimental survival study in pigs. *Endoscopy* 2008, Jul;40(7):584-8.
- [73] Voermans RP, Vergouwe F, Breedveld P, Fockens P, van Berge Henegouwen MI. Comparison of endoscopic closure modalities for standardized colonic perforations in a porcine colon model. *Endoscopy* 2011, Mar;43(3):217-22.
- [74] Seebach L, Bauerfeind P, Gubler C. "Sparing the surgeon": Clinical experience with over-the-scope clips for gastrointestinal perforation. *Endoscopy* 2010, Dec;42(12):1108-11.
- [75] Parodi A, Repici A, Pedroni A, Bianchi S, Conio M. Endoscopic management of GI perforations with a new over-the-scope clip device (with videos). *GastrointestEndosc* 2010, Oct;72(4):881-6.
- [76] Grossmann J, Dienes C, Althoff C. [Endoscopic closure of a chronic colonic fistula using the over-the-scope clip (OTSC)]. *Dtsch Med Wochenschr* 2011, Nov;136(44):2245-8.
- [77] Manta R, Manno M, Bertani H, Barbera C, Pigò F, Mirante V, et al. Endoscopic treatment of gastrointestinal fistulas using an over-the-scope clip (OTSC) device: Case series from a tertiary referral center. *Endoscopy* 2011, Jun;43(6):545-8.
- [78] von Renteln D, Denzer UW, Schachschal G, Anders M, Groth S, Rösch T. Endoscopic closure of GI fistulae by using an over-the-scope clip (with videos). *GastrointestEndosc* 2010, Dec;72(6):1289-96.
- [79] Bini R, Coppola F, Recchia S, Fusca M, Gaia S, Leli R. Endoscopic treatment of post-gastrectomy duodenal fistula with an over-the-scope clip. *SurgInnov* 2011, Mar;18(1):102-4.
- [80] Naegel A, Bolz J, Zopf Y, Matthes K, Mueller B, Kraus F, et al. Hemodynamic efficacy of the over-the-scope clip in an established porcine cadaveric model for spurting bleeding. *GastrointestEndosc* 2012, Jan;75(1):152-9.
- [81] Hearnshaw SA, Logan RFA, Lowe D, Travis SPL, Murphy MF, Palmer KR. Acute upper gastrointestinal bleeding in the UK: Patient characteristics, diagnoses and outcomes in the 2007 UK audit. *Gut* 2011, Oct;60(10):1327-35.
- [82] Akasaka T, Nishida T, Tsutsui S, Michida T, Yamada T, Ogiyama H, et al. Short-term outcomes of endoscopic submucosal dissection (ESD) for early gastric neoplasm: Multicenter survey by osaka university ESD study group. *Dig Endosc* 2011, Jan;23(1):73-7.
- [83] Kim ES, Cho KB, Park KS, Lee KI, Jang BK, Chung WJ, Hwang JS. Factors predictive of perforation during endoscopic submucosal dissection for the treatment of colorectal tumors. *Endoscopy* 2011, Jul;43(7):573-8.

- [84] Schurr MO, Baur F, Ho C-N, Anhoeck G, Kratt T, Gottwald T. Endoluminal full-thickness resection of GI lesions: A new device and technique. *Minim Invasive Ther Allied Technol* 2011, May;20(3):189-92.
- [85] Voermans RP, van Berge Henegouwen MI, Bemelman WA, Fockens P. Novel over-the-scope-clip system for gastrotomy closure in natural orifice transluminal endoscopic surgery (NOTES): An ex vivo comparison study. *Endoscopy* 2009, Dec;41(12):1052-5.
- [86] Giday SA, Kim Y, Krishnamurty DM, Ducharme R, Liang DB, Shin EJ, et al. Long-term randomized controlled trial of a novel nanopowder hemostatic agent (TC-325) for control of severe arterial upper gastrointestinal bleeding in a porcine model. *Endoscopy* 2011, Apr;43(4):296-9.
- [87] Sung JJY, Luo D, Wu JCY, Ching JYL, Chan FKL, Lau JYW, et al. Early clinical experience of the safety and effectiveness of hemospray in achieving hemostasis in patients with acute peptic ulcer bleeding. *Endoscopy* 2011, Apr;43(4):291-5.



