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Innovative Uses and Emerging Technologies in Endoscopy

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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. CO² insufflation

One technical advance which has improved colonoscopy, both for patients and proceduralists is CO₂ 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 CO₂ 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 an 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 μm , 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 μm^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.

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