REVIEW

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Novel colorectal endoscopic in vivo imaging and resection practice: a short practice guide for interventional endoscopists

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Abstract Colorectal cancer remains a leading cause of cancer death in the UK. With the advent of screening programmes and developing techniques designed to treat and stage colorectal neoplasia, there is increasing pressure on the colonoscopist to keep up to date with the latest practices in this area. This review looks at the basic principles behind endoscopic mucosal resection and forward to the potential endoscopic tools, including high-magnification chromoscopic colonoscopy, high-frequency miniprobe ultrasound and confocal laser scanning endomicroscopic colonoscopy, that may soon become part of routine colorectal cancer management.

Key words Colonoscopy · Endoscopic mucosal resection · Colorectal cancer

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Introduction

Colorectal cancer (CRC) remains one of the leading causes of cancer death in the West and in 2002 is estimated to have affected 148 000 and 22 000 people in the USA and UK, respectively [1, 2]. CRC develops in 5%–6% of the adult population, and almost 50% die as a consequence of the disease [3, 4]. Colonoscopy is now widely accepted as the gold standard for the early detection of colorectal cancer with evidence to support a direct mortality reduction in cohorts undergoing screening sigmoidoscopy [5, 6]. Furthermore, total colonoscopy has been shown to reduce the incidence of colorectal cancer in patients with adenomatous polyps [7]. These data support the effectiveness of colonoscopy for the detection of CRC and polypectomy in the secondary prevention of CRC. Furthermore, the prognosis of patients with CRC is dependent on the early detection of disease, with 95% and <50% 5-year survivals observed in patients with stage T1 and T3/4 disease, respectively [8]. Data from Japan [9] and our group in the UK [10–12] now suggest that stage Tim/1 disease can be curatively treated using novel endoluminal resection techniques such as endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). However, despite these data, evidence to suggest failure in secondary prevention of CRC by total colonoscopy and polypectomy is emerging [13–15]. Many reasons may account for these data [16–19]. Importantly, new endoscopic techniques such as chromoscopic colonoscopy and high-magnification chromoscopic colonoscopy (HMCC) have highlighted the clinical importance of flat and depressed non-polypoid colorectal lesions which until recently were believed to be a purely Japanese phenomena know as 'phantom carcinoma' or Akita's disease [19]. Such lesions are difficult to detect using conventional white light colonoscopic techniques and barium studies, but have significant clinicopathological characteristics [20]. Clinically, such lesions have now been shown to have a significant prevalence within Western cohorts [21–25]. Data

from centres outside Japan now suggest that novel endoscopic resection techniques such as EMR and ESD are applicable to Western endoscopic practice.

Endoscopic mucosal resection

Following the initial description of EMR or the 'strip biopsy technique' by Dehyle et al. [26], EMR has been developed by Japanese endoscopists for the resection of sessile and flat lesions of the stomach, oesophagus and colorectum [27]. For pedunculated lesions this technique is not required, as simple snare resection is adequate. EMR permits the resection of flat and sessile lesions by longitudinal section through the submucosal layer [28]. In the colorectum, EMR may provide curative resection for flat and sessile adenomas in addition to early colorectal cancer [28]. For lesions less than 20 mm diameter, en-bloc EMR facilitates complete histological analysis of the resected lesion and makes it possible to determine precisely the completeness of excision in both the horizontal and vertical resection planes [29]. Complete excision may be possible in the majority of cases, with R0 resection rates as high as 96% being described [30]. For lesions greater than 20 mm diameter, historically piecemeal dissection has been required. The principle limitation to piecemeal dissection is the inability to assess the vertical and horizontal resection margins with lesions defaulting at histopathological analysis to Rx (margins not discernable). However, rates for en bloc resection and en bloc plus histopathologically confirmed R0 status of 88.6% and 62.9%, respectively, by ESD have now been described in Western practice and are comparable to the preliminary data from Japan [29]. Such endoscopic resection techniques are preferable to primary tissue ablation such as argon plasma coagulation [31] and electrocoagulation [32] as a definitive histopathological specimen guides subsequent endoscopic and clinical management in the majority of cases. Numerous EMR techniques have now been described which include the lift and cut technique, traction-assisted resection, and that using a transparent cap fitted to the proximal aspect of the endoscope [33] in conjunction with an insulation-tipped cutting knife [34]. While these techniques are primarily reserved for resection of oesophageal, gastric and submucosal posterior rectal tumours [27, 34], ESD has now been shown to be both safe and feasible for the resection of tumours up to and beyond the splenic flexure [35] although this remains a developmental technique not in routine practice at many centres in Europe.

Basic EMR technique

The technique of EMR (Fig. 1) comprises 4 stages:
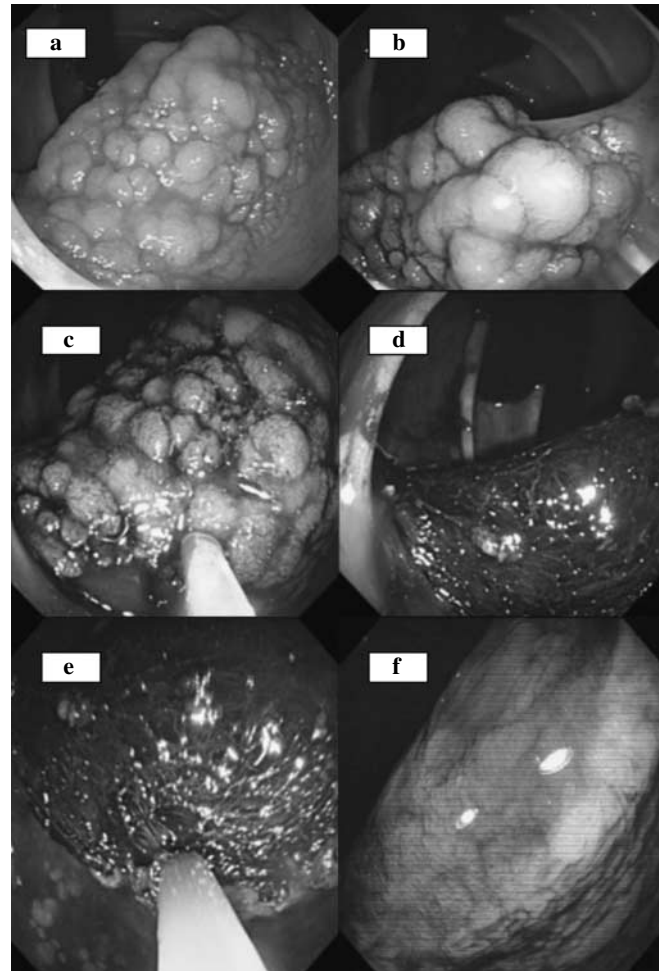1. Diagnosis and localisation of the lesion.

Fig. 1a-f *Endoscopic mucosal resection (EMR).* **a** A G-type lateral spreading tumour of the ascending caecal junction viewed in full retroflexion. **b** Indigo carmine (0.5%) chromoscopy clearly delineates the tumour margins and nodularity. **c** Submucosal cannulation provides a symmetrical and sustained 'lift' prior to submucosal dissection. **d** The exposed post-dissection 'stranding' of the muscularis can be clearly identified following assessment of the post-resection margins using indigo carmine chromoscopy. **e** Argon plasma ablation is applied to the circumferential margins of the resection. **f** Endoscopic appearances of the lesion 12 weeks after resection. There is complete epithelial restoration with a mucosal type I crypt pattern. Curative resection has been achieved

2. Evaluation of invasive depth to exclude lesions invading the deep submucosal layer 3 or beyond (i.e. T2 disease) using HMCC or ultrasonography (US).
3. Excision procedure.
4. Post-resection evaluation.

Initial diagnosis and location of flat and sessile lesions of the colorectum are facilitated by the use of indigo carmine (IC) chromoscopy, which allows observation of detailed morphology [9]. Lesions should then be described according to Paris Workshop guidelines (Table 1). Narrow band imaging (NBI) is an alternative technique in which modified optical filters are used in the light source of the

Table 1 Paris Workshop guidelines [56] for the gross morphological classification of colorectal lesions

Endoscopic appearance	Paris class	Form	Description
Protruded lesions	Ip		Pedunculated polyps
	Ips		Subpedunculated polyps
	Is		Sessile polyps
Flat elevated lesions	0-IIa		Flat elevation of mucosa
	0-IIa /c		Flat elevation with central depression
Flat lesions	0-IIb		Flat mucosal change
	0-IIc		Mucosal depression
	0-IIc / IIa		Mucosal depression with raised edge

Table 2 The modified Kudo criteria for the classification of colorectal crypt architecture in vivo using high-magnification chromoscopic colonoscopy (HMCC)

Pit type	Characteristics	Appearance at HMCC	Pit size, mm
I	Normal round pits		0.07±0.02
II	Stella or papillary		0.09±0.02
IIIs	Tubular, round pits, smaller than pit type I		0.03±0.01
IIIL	Tubular, large		0.22±0.09
IV	Sulcus, gyrus		0.93±0.32
V(a)	Irregular arrangement and sizes of IIIL, IIIs, IV type pits		NA

NA, not applicable

video-endoscope system to provide 'virtual chromoscopy'. Provisional data suggest comparable rates of diagnostic accuracy of NBI [36, 37] to IC chromoscopy. Further randomised controlled trials are now required to clarify this issue prior to implementation of NBI into routine clinical practice.

In vivo staging of lesions can be achieved using HMCC (Table 2) [38], the Olympus Lucera differential of haemaglobin indices function (Hib) (Olympus Lucera, Tokyo, Japan) for vascular ectasia mapping and through-the-scope miniprobe US (12.5–20 MHz), either alone or as a multimodality technique (Table 3) [39]. Flat and sessile lesions up to 20 mm in diameter can be resected by en bloc or 'single pass' resection, but larger lesions usually require a piecemeal approach [29]. A needle catheter is then inserted through the side port of the colonoscope with sterile saline or an alternative submucosal solute (e.g. sodium hyaluronic acid, glycerol, 50% dextrose solution) injected peripherally and centrally into the lesion and surrounding mucosa. A cleavage of the submucosa (having the effect of raising the lesion) then permits simple snare resection. A single cannulation can be used for small lesions (<10 mm diameter) with multiple cannulations usually required for lesions of 20 mm or more [29]. Some authors advocated the use of adrenaline (1:100 000) mixed with saline or twice-normal saline at submucosal injection to maintain a 'dry' dissection field [40]. 50% dextrose solution was shown to provide a longer duration of lift, with smaller injection volumes and higher rates of en-bloc resection, although there were no differences in completeness of resection or complications in the total cohort in Varadarajulu et al.'s study [41]. Other studies have utilised a number of solutes including hyaluronic acid, hydroxypropyl methylcellulose and glycerol, with demonstrably

Table 3 Clinical criteria for submucosal invasive depth estimation using four different diagnostic imaging techniques

Histopathology	HMCC	Hib vascular ectasia mapping	Combined HMCC and vascular ectasia mapping	High-frequency miniprobe endoscopic US
Tis/sm1	Crypt A: crypt fully defined	Normal vascular pattern	Crypt A + normal vascular pattern	Hypoechoic mass within first hypoechoic layer
sm2	Crypt B: crypt partially defined	Vessel tortuosity with dilatation	Crypt B + vessel tortuosity with dilatation	Hypoechoic mass infiltrating second hypoechoic layer
sm3	Crypt C: crypt not defined or absent	Complete disruption of vascular architecture	Crypt C + complete disruption of vascular architecture	Hypoechoic mass infiltrating third layer +/- extension to hyperechoic muscularis

US, ultrasonography

better and longer lasting mucosal lift [42–44]. However, no randomised controlled trial has proved superiority with regard to resection clearance (with specific reference to R0 resection rates), post-EMR haemorrhage or perforation. Whatever injection medium used, it is essential to maintain a sufficient mucosal lift or detachment throughout the dissection, which minimises the risk of the muscularis propria being trapped within the vertical resection plane of the snare and subsequent perforation [27].

After resection, evaluation of the mucosal defect is mandatory, as remnant neoplastic tissue continues to assume an overall risk of progression to invasive neoplasia. Complete resection in the horizontal axis can be determined using IC chromoscopy by the identification of a normal type I pit pattern (as defined by the modified Kudo criteria [38]). Remnant neoplastic tissue (as identified by Kudo crypt types IIIL, IV or V) suggests R1 resection status and should prompt the endoscopist to extend the initial resection or employ an adjunctive ablative technique such as APC to the positive resection margins [45]. The Sheffield group advocate peripheral margin tattoos prior to submucosal injection that delineates the normal mucosal boundaries around the lesion prior to resection [46]. This technique may facilitate R0 resection, as at submucosal lift, the lesion can become distorted and indistinct from the surrounding normal mucosa [46]. If the lesion fails to lift (the non-lifting sign of Uno) or has an asymmetrical appearance, then the resection should be abandoned as this indicates tethering to the underlying muscularis mucosae [47]. Perforation and risk of non-curative resection can occur in this scenario [47, 48]. All lesions should have an adjacent submucosal tattoo applied using India ink or 'Endo Spot' endoscopic marker [Ref: GIS-44, Camp Hill, PA 17011] to facilitate localisation at follow-up colonoscopy or subsequent surgical resection [49].

Following successful submucosal lift, a spiked or 'barbed' snare is applied over the lesion and slowly closed under gentle suction [27]. This permits the lesion to be retained within the snare boundaries before final resection [27]. Prior to final cutting (usually using a 25 W or 10 W coagulation current for lesions distal or proximal to the splenic flexure, respectively), the snare should be relaxed slightly to allow any entrapped muscularis mucosa to retract [27]. Following resection, the lesion should be retrieved using pronged grasping forceps or preferably a Roth net which limits tissue trauma to the specimen, prior to 'pinning out' and immediate fixation in 10% formalin solution. Japanese endoscopists 'pin out' the lesion onto a solid cork or polystyrene plate prior to fixation, which limits shrinkage of the resection specimen and permits easier and more accurate histopathological sectioning [34].

Complications of EMR

The main complications of EMR are haemorrhage, perforation and stenosis [49, 50]. The immediate and early complications (10% of cases) described in the first 12 hours after resection are principally haemorrhage and rarely perforation [50]. The Sheffield group reported bleeding complications in only 2% of patients undergoing EMR in their cohort of 599 lesions [10], which was significantly lower than that reported in Ahmed et al.'s retrospective analysis (22%) [51]. However, other Japanese authors have reported haemorrhage rates after colonic EMR of 1.16% (10 of 863) [52], comparable to those observed in the Sheffield series [10]. Okamoto et al.'s review of interventional colonoscopic resections also reported a perforation rate secondary to EMR of only 0.35% [50], and Kaneko et al.'s multicentre analysis of endoscopic mortality showed rates

of less than 0.0001% for this procedure [53]. In Hurlstone et al.'s evaluation of 599 EMR procedures, no patient required emergency laparotomy for bleeding or perforation, whilst 15 (2.5%) had incomplete vertical excision margins with 9 requiring surgical excision (<1%) at a median of 3.5 years follow-up [10]. EMR may therefore be a safe and effective endoscopic therapy that may enhance our current strategies aimed at the secondary prevention of colorectal cancer.

Endoscopic submucosal dissection

ESD allows en bloc knife dissection of lesions usually in excess of 20 mm diameter to the vertical depth of the muscularis mucosa [54, 55]. Determination of the morphological class by chromoscopic colonoscopy as per the Paris consensus criteria [56] and on-table staging of the lesion by high-frequency ultrasound (HFUS) with differentiation of tumour stage and nodal disease status as per the Cho criteria [57] enables accurate assessment as to the feasibility of ESD. Lesions with a fixed Paris type IIc component (defined as a fixed depression whether air is insufflated or deflated) or Cho criteria for T2/N1 disease are not amenable to ESD (Fig. 2). Following submucosal catheterisation and lifting with either sodium hyaluronic acid or glycerol submucosal infiltration, circumferential mucosal incisions are made at 5- to 6-mm intervals around the pan-circumference of the lesion. Submucosal dissection can then be initiated from the most proximal aspect of the lesion using the insulation-tipped knife. Maintenance of the dissection plane, by patient manoeuvring, in addition to direct tissue traction from the distally attached endoscopic dissection assistance cap, enables visualisation of the exposed muscularis layer and reduces the risk of per-

foration. The resected specimen can be retrieved by Roth net and then pinned out (to reduce shrinkage) before undergoing histological assessment for resection completeness (i.e. R stage).

Complications of ESD

As with EMR, the main complications include haemorrhage and perforation [54, 55, 58, 59] with Fujishiro et al. [59] reporting a bleeding rate of 12% and an overall perforation rate of 5.7% (2 of 35). However, in this series, both perforations were treated conservatively without need for surgical intervention [59]. The learning curve and optimal teaching modality for ESD have not yet been described in the literature, but this is now required should this novel yet technically demanding endoscopic technique become adopted outside of tertiary referral practice.

Evolving technology for the future

Magnification chromoscopy

Accurate in vivo staging is essential at colonoscopy prior to consideration of local endoluminal resection. Flat focal submucosal invasive CRCs which are limited to the submucosal layer 1 can be managed by EMR as the risk of lymphovenous invasion and nodal metastasis is low (<5%) [60–62]. For lesions with deeper vertical invasion into the submucosal layer 3 or beyond (stage T2), the risk of nodal disease increases to 10%–15% [63]. EMR in this group is therefore undesirable due to a higher risk of perforation, non-curative excision and untreated nodal disease [28].
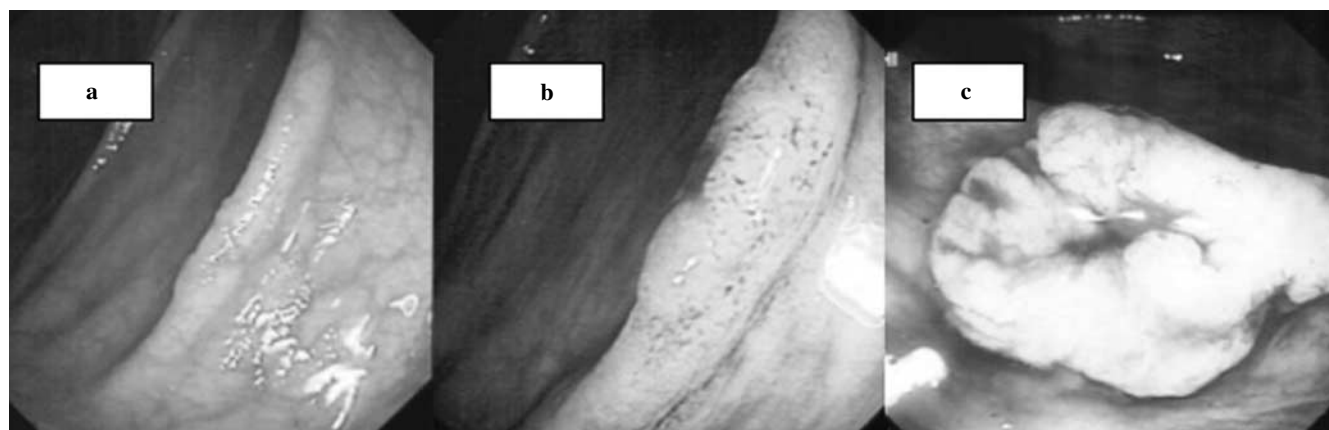
Fig. 2a-c *Lesion with a fixed Paris type IIC component not amenable to endoscopic submucosal dissection (ESD).* **a** Nodularity of fold noted using conventional colonoscopy in the mid-ascending colon. **b** Indigo carmine (0.5%) chromoscopy shows a diminutive Paris type 0-II lesion. **c** Zoom view at 30x magnification shows a clear type 0-IIc depressed component to the lesion. An invasive adenocarcinoma (stage T2/N0) was evident at post-surgical resection histopathology
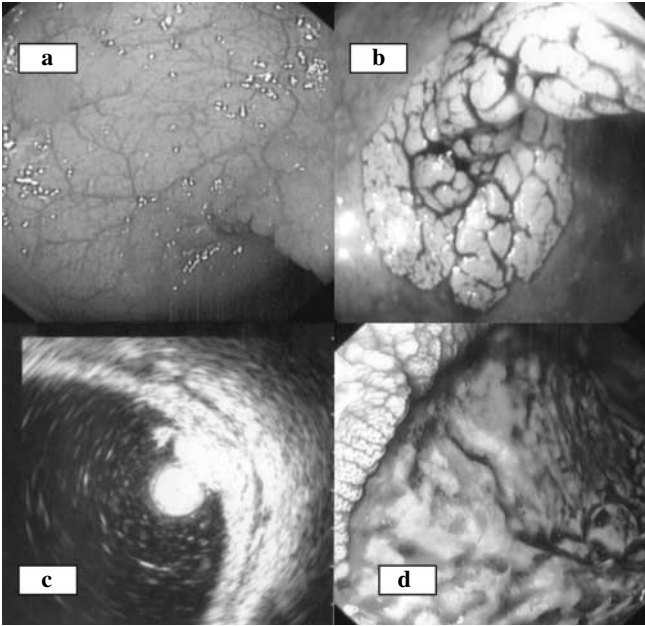
Fig. 3a-d *High-frequency miniprobe ultrasonography*. **a** Focal erythema and nodularity present in the distal sigmoid colon at conventional endoscopy. **b** Indigo carmine (0.5%) chromoscopy delineates a flat Paris type 0-IIa lateral spreading tumour. **c** High-frequency 'through the scope' miniprobe 12.5 MHz endoscopic ultrasound shows bluring of the submucosal layer 1/2 but a preserved muscularis (thick adjacent hyperechoic band). There is no associated per-colic lymphadenopathy. Endoscopic submucosal dissection is indicated given the 'on-table stage' of Tim/N0. **d** Endoscopic view of the lesion 1 month after resection. Note the granulation tissue present at the resection base with a surrounding normal type I crypt architecture. Curative resection was achieved

Surgical excision is recommended in this group [28, 34].

Chromoscopic colonoscopy used as an in vivo staging tool has been reported by Saitoh et al. [64]. In this retrospective analysis of depressed type early CRCs, combined video-endoscopy and chromoscopy was used to characterise the essential endoscopic features favoured by lesions with submucosal layer 1 and 2 invasion, which at the time of endoscopy may be used as a tool to guide the colonoscopic management (i.e. attempted EMR or biopsy alone with surgical referral) [64]. Using Saitoh et al.'s criteria (expansion appearance, present; surface depression, deep; irregularity of depressed surface, uneven; and converging folds toward the tumour), the sensitivity and specificity for determining submucosal layer 2 disease were both 90% [64]. However, when 21 lesions showing intramucosal carcinoma were excluded from the analysis, specificity fell to 70% [64]. In Hurlstone et al.'s prospective analysis of endoscopic morphological anticipation of submucosal invasion in flat and depressed lesions [65] using the Nagata subtype analysis [66] of the Kudo type V pit pattern [38], the K coefficient of agreement between pit type V and histologically confirmed sm2 invasion was 0.51. Using pit types Vn(B) and Vn(C) as clinical indicators of invasive disease, 97% of lesions was correctly anticipated to have sm2+ invasion; however, specificity was low at 50% (overall accuracy, 78%) [65]. Similar problems have been encountered using the 7.5 MHz ultrasound probe in the staging of rectal carcinoma, with variable accuracy rates reported (from 60% to 79%) according to the T stage system [67, 68]. High-frequency 20 MHz 'miniprobe' ultrasound has now been reported to have a high overall accuracy when used to determine submucosal invasion for flat and depressed lesions (Fig. 3) [69] with 93% accuracy in determining invasive depth staging and 80% sensitivity for predicting lymph node metastasis [70]. However, ultrasound imaging requires further training, has significant expense and may prolong the procedure [70].

In summary, the limitations of HMCC technology are:

- High sensitivity and specificity for the differentiation of non-neoplastic from neoplastic disease, but low overall sensitivity for the anticipation of high-grade dysplasia.
- Effective over-staging of submucosal layer 3 / T1 neoplasia.
- Significant operator-dependent error.

Autofluorescence colonoscopy

Chromoscopic and high-magnification techniques have been introduced in an attempt to improve the sensitivity and specificity of 'white-light' colonoscopy. However, a new endoscopic technology that is fluorescence-based is under evaluation by many groups [71, 72]. This technology exploits either the autofluorescence of naturally occurring molecules, such as collagen, NAD-H, flavins and porphyrins, or the fluorescence of exogenously administered fluorescent drugs.

The detection of neoplastic lesions using autofluorescence depends on subtle changes in the concentration or distribution in depth of endogenous fluorophores, changes in tissue micro-architecture and altered mucosal thickness or blood concentrations [73]. All these factors affect the fluorescence intensity or spectrum due to wavelength-specific light absorption [73]. Using exogenous fluorophores, the detection of lesions is based on selective drug uptake or target tissue retention relative to uptake by normal tissue [73].

Kapadia et al. used ultraviolet (UV) light in the colon to discriminate normal mucosa, adenomas and hyperplastic lesions with accuracies of 100%, 100% and 94%, respectively [72]. In the first in vivo human colonic spectroscopic study by Cothren et al., differentiation between adenoma and non-adenomatous lesions was achieved in 97% of cases [74]. Cothren et al. in the first blinded study also identified colonic dysplasia with 90% sensitivity and 95% specificity [75].

However, the clinical potential of spectroscopy in routine endoscopic practice has not yet been clarified.

Chwirot et al. performed multi-spectral autofluorescence imaging in the colon of polyps ex vivo [76], and Wang et al. recently described a prototype fluorescence imaging system applied ex vivo to detect and localise adenomas in colectomy specimens from patients with familial adenomatous polyposis [77]. A second-generation fluorescence imaging system was described by Wang et al. in 1999 for the in vivo detection of colorectal adenomas in which UV light was transmitted through a fibre-optic bundle inserted through the side port of the endoscope [78]. A video-colonoscope was then used to capture the fluorescence light within the wavelength band 400–700 nm [78]. False-colour images were then overlaid onto the conventional white-light images, displaying regions where the fluorescence intensity exceeded threshold values relative to a moving image [78]. In this study of 30 patients, 18 lesions visible with white-light imaging were examined, all 6 hyperplastic lesions were correctly identified, and the sensitivity for dysplasia was 83% [78]. However, despite these encouraging initial data, further studies are required before such technology can be implemented in routine endoscopic clinical practice.

Confocal laser endomicroscopic colonoscopy

Given the limitations of HMCC and autofluorescence, laser scanning confocal microscopy (LCM) has recently been developed as an alternative means of in vivo histopathological diagnosis. LCM is an adaptation of light microscopy whereby focal laser illumination is combined with 'pinhole limited detection' to geometrically reject out of focus light. In single-point scanning confocal microscopes, the point is typically scanned in a raster pattern and measurements of light returning to the detector from successive points are digitized so an image of the scanned
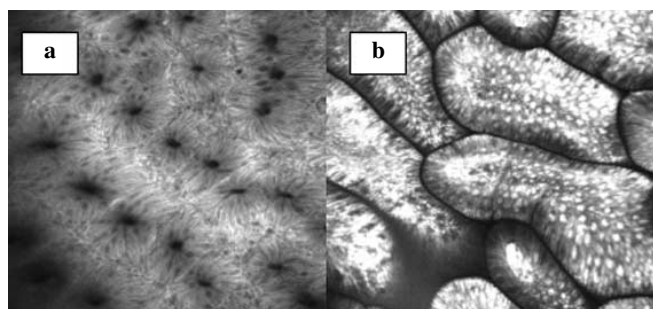
Fig. 4 a, b *Confocal laser endomicroscopic colonoscopy.* **a** Normal rectal mucosa. Note the halo or peri-cryptic goblet cells. **b** Normal terminal-ileum. Note the brush border containing goblet cells interspersed with columnar epithelium. The central crypt has a single capillary with erythrocytes visible within. The surrounding peri-stromal cellular architecture traverses the interface between the brush border and vascular net

region can be constructed. Each resultant image is an 'optical section' representing approximately one focal plane within the specimen (Fig. 4).

The components of the laser confocal colonoscope are based on the integration of a confocal laser microscope mounted in the tip of a conventional colonoscope (EC3870K; Pentax, Tokyo, Japan), which enables confocal microscopy in addition to standard videoendoscopy. During LCM, an argon ion laser delivers light at an excitation wavelength of 488 nm with a maximum laser output of <1 mW at the surface mucosa. Confocal images can then be collected at a scan rate of 0.8 frames per second (1024x1024 pixels) or 1.6 frames per second (1024x512 pixels). The optical slice thickness is 7 μm with a lateral resolution of 0.7 μm and a z-axis range of 0–250 μm below the surface layer.

Conclusions

There is much further potential for evolving practice and research at the present time. The key areas at present we perceive are:
- Early cancer detection and intraepithelial neoplasia detection in sporadic colorectal cancer and chronic ulcerative colitis.
- Targeted "smart" biopsies using confocal laser scanning endomicroscopy. This technique would optimise the yield of high quality biopsies being interpreted by histopathologists and confer significant economic benefits.
- Advanced endoscopic resection practice.

This review shows that emerging concepts in endoscopic detection and therapeutic techniques, initially pioneered by the Japanese, are applicable to Western practice. We hope that chromoscopic colonoscopy and magnification imaging in addition to EMR will now be more widely practiced by both surgical and medical gastroenterologists. However, while differences remain between Japanese and Western classification systems it is difficult to extrapolate endoscopic and pathological data reported in Japanese studies to our practice. Furthermore, additional studies are required to clarify the role of chromoscopic colonoscopy and magnification imaging in routine clinical practice. Confocal endomicroscopy may change the in vivo diagnostic paradigm once again. Finally, all practitioners require further education and training, if new diagnostic techniques and therapeutic procedures are to be adopted.

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