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Piecemeal mucosectomy, submucosal dissection or transanal microsurgery for large colorectal neoplasm

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Introduction

Although smaller colonic polyps are removed by snare polypectomy or Endoscopic Mucosal Resection (EMR), there is evidence from the British Bowel Cancer Screening Programme that many larger lesions are referred for surgical resection. There is, however, a significant morbidity and mortality attached to surgery, with 30 day mortality rates varying between 1% and 8% [1]. In addition, surgery is expensive. In the UK, the surgical treatment of colonic lesions accounts for more hospital in-patient expenditure than for cancer at any other site.

In contrast to surgical resection, endoscopic resection allows colonic lesions to be removed with a minimum of cost, morbidity and mortality [2-4]. The recognition and removal of precancerous lesions are important to reduce the risk of subsequent colorectal cancer [5]. Furthermore, many likely early colonic cancers are considered for removal by endoscopic resection such as EMR or Endoscopic Submucosal Dissection (ESD) [6]. EMR is now a well-established technique for the treatment of colorectal neoplasms with minimal invasiveness [7, 8, 2]. However, it entails a high frequency of local recurrence after piecemeal EMR for large lesions [9, 10]. ESD was conceived in Japan with the aim to avoid this problem, allowing *en bloc* resection of larger colorectal lesions. Despite its longer procedure time and higher complication rate, ESD results in a higher *en bloc* resection rate compared with conventional or piecemeal EMR [11-13]. ESD for colorectal lesions is not yet fully established as a standard therapeutic method for colorectal lesions worldwide.

In this review we discuss the therapeutic strategies available to manage non-polypoid early cancer of the colon and rectum, with particular regard to differences in Eastern and Western practice.

EMR or ESD? The western position

Several methods of EMR have been described. The most common is the 'strip biopsy method'. With this technique a liquid is injected into the submucosa below the lesion to

create a 'cushion' to carry out the snare polypectomy. Different EMR solutions have been described. In general, more viscous solutions such as succinylated gelatine, hydroxy-propyl-methyl-cellulose [14], hyaluronic acid [15] or dextrose [16] are preferred as they last longer. In most cases, a small amount of adrenaline is added making a 0.5% solution together with indigo carmine to achieve a light bluish colour. The adrenaline reduces immediate oozing from small vessles during the procedure but does not reduce the risk of delayed bleeding [17]. The dye added to the solution allows the extent of lift to be ascertained.

The 'pull within the snare' ('grasp and snare') technique, less commonly used requires a double channel endoscope as it uses a grasping forceps to pull the lesion into the snare. The technique allows otherwise unresectable or poorly lifting lesions to be removed, but the 'pull within the snare' technique is associated with a higher risk of perforation [18].

Whereas ESD has the clear advantage of achieving a single specimen, allowing for more accurate histological assessment and lower risk of recurrence, the general perception in the western scientific community is that it is a more complex technique, requiring greater experience, longer procedure time, higher risk of complications, the need for admission and the availability of specialised equipment including carbon dioxide insufflation and, usually in the West, general anaesthesia with all that this entails.

A recent comparative study [19] demonstrated that there was a higher *en bloc* resection rate of 83.5% with colorectal ESD compared with 48.1% for lesions removed by EMR, but in this study, ESD was associated with greater risk of perforation than when lesions were removed by EMR (5.9% *vs* 0%). This was confirmed in an analysis of 17 case series ($n = 1858$) in which the overall risk of perforation complicating an EMR was found to be 0.2% [20]. The largest ESD experience published in Europe [21] reports perforation rates up to 18%. Furthermore, the equipment used for ESD is expensive, an important consideration for National Health Care Systems. The pros and cons of ESC and EMR are shown in Table 1.

Table 1. Comparison of endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD)

	EMR	ESD
Cost	Cheap	Expensive
Technique	Less complex	More Complex
Duration	Short	Long
Bleeding risk	< 1%	2%
Perforation risk	< 1%	5–18%

Table 1. Comparison of endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD)

	EMR	**ESD**
Need for inpatient care	Not usually needed	Up to 5 days normally
Need for CO_2 insufflation	Not needed	Needed
Sedation	Conscious sedation/rarely general anaesthetic	In Japan conscious sedation/general anaesthetic rare In the West general anaesthetic more common
En bloc resection	Not possible if piecemeal EMR	Usually possible

EMR or ESD ? The eastern position

There is increasing evidence that well differentiated cancers invading up to 1000 µm beyond the muscularis mucosae without lymphovascular invasion have a minimal risk of lymph node metastasis [22] and can be cured by local excision alone. Lymphovascular invasion and poor differentiation are detected following histopathological examination of the resection specimen, but the vertical depth of invasion may be estimated by the appearance of the lesion during endoscopy.

EMR is an effective minimally invasive technique for early stage lesions. The 'inject and cut' method is simple and safe and is used widely. Lesions that do not lift during submucosal injection are generally not candidates for local excision. Due to the size of snares, EMR cannot be used to remove lesions larger than 20 mm in one piece, which prevents precise histopathological assessment and increases the risk of local recurrence. The estimation of the depth of cancer invasion before treatment is not always reliable, although it is crucial to decide the therapeutic strategy. Magnifying chromoendoscopy is a validated method that facilitates detailed analysis of the morphological architecture of colonic mucosal crypt orifices (pit pattern) in a simple and efficient manner. The clinical classification of the colonic pit pattern (invasive and non-invasive) by using magnifying chromoendoscopy was originally described by Fujii with the aim to discriminate between intramucosal-submucosal superficial invasion and submucosal deep invasion [23] (Fig. 1). An invasive pattern is characterized by irregular and distorted pits observed in a demarcated area suggesting submucosal deep invasion ($\geq$ 1000 µm). At the National

Cancer Center Hospital (NCCH) in Japan, the indication for *en bloc* resection is considered as follows: laterally spreading tumour (LST) non-granular type (LST-NG) lesion ≥ 20 mm and LST granular (LST-G) type lesion ≥ 30 mm, which have higher submucosal invasion rates (Table 2) [24]. In particular, the LST-NG type lesion ≥ 20 mm is technically difficult to remove completely even by piecemeal EMR and these lesions are regarded as a 'definite indication for *en-bloc* resection'. In contrast, LST-G type lesions ≥ 30 mm are considered a 'relative indication for en-bloc resection'. Moreover, large villous tumours, recurrent lesions, and residual intramucosal lesions showing non-lifting after EMR may also be considered potential candidates for ESD.

Table 2. Relationship betweens size of laterally spreading tumour (LST) and incidence of submucosal invasion. National Cancer Center Hospital, Tokyo, 1998–2006

	10 mm (%)	20 mm (%)	30 mm (%)	40 mm (%)	Total (%)
IIa (LST-Ga): LST-G, uniform type	0/115 (0)	0/70 (0)	1/31 (3.2)	0/13 (0)	1/229 (0.4)
Is+IIa (LST-G): LST-G, mixed type	4/72 (5.6)	6/70 (8.6)	9/65 (13.8)	25/114 (21.9)	44/321 (13.7)
IIa (LST-NGb)	12/246 (4.9)	24/106 (22.6)	11/33 (33.3)	8/17 (47.0)	55/402 (13.7)

1. [a]

LST-G: laterally spreading tumour, granular type.

2. [b]

LST-NG: laterally spreading tumour, non-granular type.

Figure 1. Colorectal Endoscopic Submucosal Dissection (ESD). (a, b) 30 mm, IIa+IIc lesion located in rectum (Ra). (c) Magnifying chromoendoscopy revealed non-invasive pattern. (d, e) After injection of glycerol and sodium hyaluronic acid into submucosal layer, circumferential incision was made using bipolar needle knife (B-knife) and performed submucosal dissection using both B-knife and insulation-tipped (IT) knife. (f) Ulcer bed after *en bloc* resection. (g) *En bloc* resected specimen. (h) Histopathology revealed superficial submucosal cancer (SM: 800 μm with no lymphovascular invasion, negative cut margin).

ESD is undoubtedly one of the best methods to achieve *en bloc* resection. At the NCCH, ESD procedures are primarily performed using a bipolar needle-knife (B-knife) (Xeon

Medical Co, Tokyo, Japan) [25] or an insulated-tip (IT) knife (Olympus Co, Tokyo, Japan). Carbon dioxide (CO_2) insufflation is preferred to air insufflation to reduce patient discomfort [12, 26, 27]. Lesion margins are delineated before ESD by using 0.4% indigo-carmine dye spraying. After injection of Glyceol® (10% glycerol and 5% fructose in normal saline solution) [28] and sodium hyaluronate acid into the submucosal layer [15], a circumferential incision is made using the B-knife and ESD is then carried out using both the B-knife, and IT-knife. In some selected colorectal lesions measuring 20–30 mm in diameter, snaring EMR after circumferential mucosal incision (CEMR) technique is possible [29], and has the advantage to reduce significantly the duration of the procedure. Between January 2000 and December 2006 11 488 colorectal neoplasms (excepting advanced cancers) in 6369 patients were treated endoscopically or surgically at the NCCH. To clarify the prevalence of 'definite indication for colorectal ESD', we reviewed and analysed records from our database. There were 9797 adenomas and 1691 early colorectal cancers (intramucosal cancer: 1294, submucosal cancer: 397). Among all neoplastic lesions, the prevalence of LSTs (LST-G and LST-NG) and the proportion for which ESD would have been indicated were 5.9% and 2.6% (Table 3). In contrast, among all early cancers, the prevalence of LSTs was 22.6% and the proportion for which ESD would have been indicated was 15.2% [LST-NG, $\geq$ 20 mm: 5.0% and LST-G (mixed type), $\geq$ 30 mm: 10.2%]. Moreover, the prevalence of 'definite indication for ESD: LST-NG, $\geq$ 20 mm' among all neoplastic lesions and all early cancers was 1.0% (115/11 488) and 5.0% (85/1691).

Table 3. Prevalence of LSTs and indicated lesions for ESD National Cancer Center Hospital, Tokyo, 2000–2006

	All neoplastic lesions % (*n* = 11 488)	Early colorectal cancers % (*n* = 1691)

1. [a]

   LSTs: LST-G and LST-NG.

2. [b]

   Definite indication: LST-NG lesion $\geq$ 20 mm.

3. [c]

   Relative indication: LST-G Mixed type [Is+IIa (LST-G)] $\geq$ 30 mm.

	All neoplastic lesions %	Early colorectal cancers %
LSTsa	5.9 (*n* = 674)	22.6 (*n* = 382)

Table 3. Prevalence of LSTs and indicated lesions for ESD National Cancer Center Hospital, Tokyo, 2000–2006

	All neoplastic lesions % (n = 11 488)	Early colorectal cancers % (n = 1691)
Indication for ESD	2.6 (n = 294)	15.2 (n = 258)
Definite indicationb for ESD	1.0 (n = 115)	5.0 (n = 85)
Relative indicationc for ESD	1.6 (n = 179)	10.2 (n = 173)

We evaluated the clinical outcome of ESD performed by trainees and clarified the learning curve for this procedure [30]. In order to perform colorectal ESD, trainees must show competence in the non-loop insertion colonoscopy technique, in conventional or piecemeal EMR techniques, and experience with over 20 gastric ESD cases and assistance during more than 20 colorectal ESDs conducted by an experienced endoscopist. Since gastric cancer is less common than colorectal cancer in Western countries, trainees should begin clinical training with lower rectal lesions, which have a lower risk of perforation and have a diathermy setting similar to that of gastric lesions. With these expedients, colorectal ESD can be performed without serious complication even by trainee endoscopists under the guidance of experienced specialists, untill they gain experience of over 30 cases.

Post-polypectomy surveillance

Patients with adenomas are at increasing risk of metachronous adenomas or cancers, which may develop within 3–5 years of colonoscopy and polypectomy, so called interval cancers. The recommendations for surveillance do not apply to patients with hereditary colorectal syndromes or inflammatory bowel disease. If no adenoma or polyp is detected at screening endoscopy, the European Society of Gastroenterology (ESGE) recommendation is to repeat examination at 10 years [52]. If small (< 10 mm) hyperplastic polyps, or one to two tubular adenomas < 10 mm with low grade dysplasia are detected, these should be considered low risk and a repeat colonoscopy at 10 years is recommended [53-57]. An adenoma with villous histology or high grade dysplasia or one over 10 mm in diameter or where these are three or more should be considered high risk and a surveillance colonoscopy at 3 years is recommended. Patients with ten or more adenomas should be referred for genetic counseling. Epidemiological studies have indicated that high-risk groups had a 3.6–6.6 fold increase in developing colorectal cancer (CRC) compared with the general population [58, 59], with a high efficacy of endoscopic

surveillance in reducing the cancer risk [60-62]. Serrated polyps < 10 mm with no dysplasia polyps should be classified as low risk, while those more than 10 mm or with dysplasia, should be considered high risk. In the case of piecemeal resection of an adenoma over 10 mm, endoscopic follow up within 6 months is recommended. Inadequate polypectomy has been reported in up to 17% of lesions over 10 mm [63]. A normal macroscopic appearance of the polypectomy site and a negative scar biopsy at the first follow-up, have been shown to be predictive of long term eradication [64].

The ESGE found insufficient evidence to provide recommendations on post- polypectomy surveillance based on other potential risk factors such as age or family history of CRC. Age is a strong risk factor for metachronous advanced neoplasia. The risk is almost three times greater among individuals older than 80 years compared with those between 50 and 59, which was no different from those aged 60–69 years [65]. Older people could be more prone to complications of colonoscopy, and the potential benefit of endoscopic surveillance may be limited by reduced life expectancy, especially when the estimated 10–20 years duration of the adenoma-carcinoma sequence is considered. No study has assessed the optimal age for stopping surveillance. Statistical simulations indicate that surveillance should cease at 85 years [66], other recommendations should be individualized, based on general health status and comorbidity [67].

The ESGE recommends an an early repeat of colonoscopy or a shorter surveillance interval in patients in whom inspection of the colonic mucosa was inadequate through poor bowel preparation which is associated with a higher risk of missed lesions. The post polypectomy guidelines of the ESGE and the US Multi Society Task Force (US MSTF) are the same [68]. Further studies especially regarding serrated lesions are mandatory.

In Western countries, many units have concluded that piecemeal resection of rectal lesions is no longer acceptable. This is the reason why many surgeons are favouring transanal single fragment resection over piece-meal EMR. If 'single-fragment resection' is the correct procedure in the rectum, it must also be correct elsewhere in the gastrointestinal tract. In the rectum, truly minimally invasive organ preserving surgery, such as the transanal approach, may offer a better alternative to radical resectional surgery. Supporters of piecemeal resection, even in the rectum, assert that in the case of larger lesions, endoscopic resection is quicker, safer and cheaper than surgical resection. The advantage of ESD is that a single fragment resection potentially allows for a more accurate histological assessment of invasion. As with laparoscopic resection, ESD takes more time than EMR costs more and is more liable to complications. Moving from EMR to

ESD would have far reaching implications, not least in training. As the risk of lymph node metastases is very low with T1 colorectal cancers, a move to ESD means that all small colorectal cancers would first be resected endoscopically. If the histolpathogical examination found lymphovascular invasion, poor differentiation or extensive tumour budding a colectomy would then be advised.

In Eastern countries, supporters of ESD consider it is to be an ideal method to provide '*en bloc* resection' even for large colorectal lesions, but the prevalence of lesions with a 'definite indication for ESD' among all colorectal neoplasms is small. Colorectal ESD should be performed by experienced well-trained endoscopists and trainee endoscopists should focus on mastering the more fundamental techniques of cold or hot snare polypectomy, conventional EMR and single block or piecemeal EMR and have knowledge of the surveillance strategy after endoscopic treatment. Characteristic colonoscopic findings obtained by magnifying chromoendoscopy are useful for determination of the invasion depth of early stage colorectal cancers, which is an essential factor in selecting a treatment modality between endoscopic treatment and surgery. As new therapeutic techniques are developed, preoperative endoscopic diagnosis will become increasingly important.

The rectum offers the further option of transanal endoscopic surgery. TEM entails the true concept of minimally invasiveness and differs from colectomy, which even when performed laparoscopically is still major surgery. In a comparison of techniques, we performed a systematic review of published series and showed an advantage for TEM compared with ESD in achieving an R0 resection.

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