REVIEW

Endoscopic submucosal dissection and its potential role in the management of early colorectal neoplasia in UK

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ABSTRACT

In Europe, colorectal cancer is the most common newly diagnosed cancer and the second most common cause of cancer deaths, accounting for approximately 436 000 incident cases and 212 000 deaths in 2008. National screening programmes will increase the number of early (pT1) cancers detected. pT1 cancers are those showing invasion through the muscularis mucosae into the submucosa but not into the muscularis propria. Microstaging of pT1 cancer is crucial in predicting those cases less likely to cause nodal disease and that will be cured with endoscopic resection alone. The submucosal extent and other histological features predict the risk of nodal disease, and for this reason, en bloc resection is highly desirable. Endoscopic submucosal dissection enables en bloc resection of mucosal and submucosal disease and could reduce the need for surgery in some cases by definitive initial resection.

INTRODUCTION

Colorectal cancer (CRC) is a significant health problem, the importance of which will increase substantially in the coming years.¹ Gastrointestinal cancers are often diagnosed at an advanced stage requiring surgery with risk of morbidity and mortality. Cancers involving the submucosa alone are less likely to cause nodal or distant spread and can potentially be cured with endoscopic resection (ER) alone. ER of neoplasms has considerable potential benefits for patients. With increased awareness and the introduction of screening for CRC, the number of early CRCs detected will increase.² Adenocarcinoma has been observed in between 0.5% and 2% of polyps resected

endoscopically.^{3–4} The pT1 cancer incidence in a recent National audit of CRC in the UK was 8.5%.⁵ Concern regarding nodal disease often leads to surgery even if the lesion appears to have been completely resected endoscopically.⁶ Endoscopic mucosal resection (EMR) is a day case procedure with very low level of risk compared with surgery. The EMR technique was developed in Japan for the management of early-stage gastric cancer (EGC). Large lesions can be resected by EMR, but only in a piecemeal fashion (p-EMR). To predict the curative potential of endoscopic treatment, accurate histopathological assessment of completeness of resection is essential. The presence and depth of submucosal extent and other histological features accurately predict the risk for lymph node metastasis.^{7–8} For this reason, en bloc (single fragment resection (SFR)) resection is more desirable than piecemeal resection. Endoscopic submucosal dissection (ESD) enables SFR of GI neoplasms (figure 1).

DEVELOPMENT OF THE ESD TECHNIQUE

The ESD technique has developed from EMR to facilitate en bloc resection of EGC, and it has evolved rapidly.^{9–10} Numerous electrosurgical knives including insulation-tipped diathermic knife (IT-knife), needle knife and hook knife are now available. Flush knives have also recently become available that enable injection of lifting solution through the knife, potentially reducing procedure time. They are used with a transparent cap that fits on the tip of the endoscope.

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Figure 1 A 76-year-old man diagnosed with an 8 cm lateral spreading granular polyp in the rectosigmoid colon. He underwent uncomplicated endoscopic submucosal dissection. The polyp was resected en bloc with no histological evidence of submucosal invasion. Histology revealed high-grade dysplasia.

Development of submucosal injection solutions has helped ESD development.^{11 12} We routinely use a 200 mL glycerol lifting solution with 0.5 mg adrenaline and 0–2.0 mL of indigo-carmin. However, other groups use colloidal solutions that are readily available and seem to function well. As the technique evolves, many solutions are being developed and will become available including biodegradable hydrogels.¹³ ESD involves three key steps: injection of fluid into the submucosa to elevate the lesion from the muscle layer, circumferential cutting of the mucosa surrounding the lesion and dissection of the connective tissue of the submucosa.

The major advantages of ESD compared with pEMR are that high en bloc resection rates are possible, preserving the muscularis mucosae, enabling greater histological confidence of complete resection (R0) and retrieval of the specimen (figures 1 and 2). Lesions with submucosal fibrosis are also potentially resectable. The disadvantages of this technique when compared with EMR are that it requires one or two assistants, it is time-consuming and there is a higher risk of bleeding and perforation.

In Japan, ESD is the standard ER technique for EGC. More recently, ESD has been applied to colorectal neoplasms in some institutions, based on guidelines published by the Japanese Society for Cancer of Colon and Rectum (JSCCR).¹⁴ However, ESD is still controversial considering the technical difficulty, associated risks and favourable outcomes with EMR. However, local excision for colorectal pT1 disease,

particularly in the rectum, is gaining wide acceptance because of the mortality associated with surgery and high rates of functional disturbance, including compromised anorectal, bladder and sexual function.

ENDOSCOPIC ASSESSMENT OF LESIONS AND SUITABILITY FOR ER

Chromoendoscopy is essential to define the suitability of a lesion for ER. Based on their experience with EGC, Japanese endoscopists have developed methods for characterising mucosal crypt and vascular patterns that provide a detailed endoscopic mucosal assessment of lesions.^{15–17} Consequently, endoscopic assessment with or without magnification, white light assessment with dyes such as indigo-carmin coupled with narrow band imaging are very accurate methods for predicting histology and depth of submucosal invasion.^{15 17} This endoscopic assessment dictates whether it is reasonable to resect pT1 lesions. Only lesions felt to be slightly invasive are resected, whereas those felt to be deeply invasive are referred for surgery.

RATIONALE FOR ESD IN THE COLORECTUM

Lateral spreading tumours are lesions greater than 10 mm in diameter with low vertical axis that extend laterally along the luminal wall (LST).¹⁵ LST and some pT1 CRC (SM-CRC) are good candidates for at least initial ER as they carry relatively low risk (LR) of nodal disease. Currently, the management of pT1 cancers is one of the most controversial areas with little evidence base.¹⁸ In pT1 sessile tumours

Figure 2 A 63-year-old man presented via the Bowel Cancer Screening Programme and underwent pEMR of a 5 cm lateral spreading granular polyp located at the hepatic flexure. He underwent uncomplicated piecemeal resection of the polyp following discussion at an multidisciplinary team. Only a small part of the resection was retrieved due to the proximal nature of the polyp. Histology from this section demonstrated low-grade dysplasia.

involving the superficial, middle and deep thirds of the submucosa (so-called Kikuchi levels; sm1, sm2 and sm3, respectively), the frequency of lymph node metastasis has been reported to be 2%, 8% and 23%, respectively.¹⁹ However, the Kikuchi system is not particularly easy to use in practice, especially if there is fragmentation or suboptimal orientation of the tissue, and can only be applied to surgical specimens, as it requires reference to the muscularis propria.²⁰ More recently, Ueno *et al* proposed use of the depth (>2000 µm) and width (>4000 µm) of invasion beyond the muscularis mucosae provides a more objective assessment of lymph node metastatic potential 2.5% vs 18.2% when submucosal invasion width is < or ≥4000 µm, respectively, and 3.9% vs 17.1% when submucosal invasion depth is < or ≥2000 µm, respectively. This approach has been adopted in Japan but is difficult to apply with pEMR due to disruption of the muscularis mucosae.²¹

Japanese consensus guidelines developed recently have suggested that ER alone is adequate for LR SM-CRC, and subsequent surgical resection for high risk (HR) SM-CRC maybe appropriate in view of risk of nodal disease. One of the key features for predicting LR lesions is submucosal invasion depth of less than 1000 µm.^{14 22}

We believe ESD, with or without subsequent surgery, should become the initial procedure of choice for many pT1 lesions, following extremely careful endoscopic assessment of the crypt and vascular pattern, to predict the degree of submucosal invasion. ESD is not generally available in the UK, where the majority of patients go straight to surgery from initial biopsy to ensure clearance of local and distant nodal disease. Evidence from the UK Bowel Cancer Screening Programme (BCSP) suggests that a high proportion of large LSTs and most ECC are referred for surgical resection rather than even initial ER.

Development of ESD in the UK would mean that LSTs and some ECC could be resected as SFRs enabling much more confidence with regard to horizontal clearance and depth of submucosal invasion related to the muscularis mucosae. Individuals with lesions, which exhibit >1000 µm submucosal invasion, lymphovascular invasion, poor or moderate differentiation, or extensive tumour budding (HR SM-CRC), could then be offered surgical resection. However, patient-related factors including age and comorbidities are of primary importance when considering whether or not to perform radical resection for HR SM-CRC. Some patients with HR SM-CRC, after initial ESD and discussion with regard to relative risk of nodal disease, may choose not to undergo surgery. Decision making would be based on individualised surgical risk versus risk of nodal disease. Published 30-day surgical mortality rates vary between 1% and 8%.^{5 23 24} Long-term outcome data from HR SM-CRC are crucial in guiding patients in decision making.

As well as considerable benefits to the individual of avoiding surgery, there are significant socioeconomic benefits. The socioeconomic costs of CRC are considerable, and surgical treatment for CRC accounts for more hospital in-patient expenditure than cancer at any other site.²⁵

EVIDENCE FOR ESD SAFETY AND EFFICACY FOR COLONIC SM-CRC LESIONS: JAPANESE EXPERIENCE

Some caution needs to be employed when comparing Japanese data with US and European literature. In Japan, a diagnosis of carcinoma can be made on cases of neoplasia without submucosal invasion. In Europe, the term mucosal cancer in the colorectum is not used and should be substituted by mucosal high-grade dysplasia according to the WHO classification.

Shono *et al*²⁶ published their experience of colorectal ESD in 2011. Over 5 years they resected 137 consecutive colorectal tumours in 137 patients. The rate of SFR was 89.1% (122/137). Seven other clinical studies describing the efficiency and safety of ESD in the colon and rectum were reported between 2007 and 2010,^{27–34} all from Japan. In these studies, the en bloc resection rate for colorectal ESD was reported to be 80–98.6%, and the complete resection rate was 70–98.6%. The rate of perforation in these reports ranged from 1.4 to 10.4%, while the rate of perforation in the Shono paper was 3.6%. Different electrosurgical knives were used in each of these reports, and this may be in part responsible for the different rate of perforation.

Saito *et al* recently published their retrospective single-centre experience of ESD compared with laparoscopic-assisted colorectal surgery (LAC) for CRC. The study included 589 patients; 297 patients with intramucosal cancer or pT1 cancers undergoing ESD with 292 patients with pT1 cancer undergoing LAC. All patients were treated at the National Cancer Centre, Tokyo, Japan, between January 1998 and September 2008. In the ESD group, the mean procedure time was 106 min, and en bloc and curative resection rates were 87% and 80%. There were 14 perforations (4.7%) and five postprocedural bleeding episodes (1.7%). Only one of the perforations required emergency surgery. In the LAC group, mean operation time was 206 min. There were 31 wound infections, 3 anastomotic leaks and 1 anastomotic bleed. Stomas were necessary in 93% of patients with rectal T1 cancer below the peritoneal reflection.³⁵

In terms of outcome, a large-scale multicentre study of long-term outcomes of ESD for submucosal invasive CRC has been recently published. This study retrospectively analysed all patients with pT1 cancer treated by ESD. pT1 cancer with negative vertical margins, well or moderately differentiated histology, absence of lymphovascular invasion and SM invasion depth of <1 mm, was classified as LR SM-CRC. All other patients with SM-CRC with any of these findings were regarded as

HR. Among the 120 LR SM-CRC cases treated with ESD alone, the 5-year recurrence-free survival rate (RFS) was 98%. In the HR SM-CRC, the RFS for ESD alone and ESD+surgery were 87% and 97%, respectively. The 5-year survival rates were 94% in the ESD group and 98% and 99% for the HR groups. In the high-risk patients, 196 underwent additional surgical resection after ER. One hundred and six patients did not undergo additional surgery because they refused or had significant comorbidities. Lymph node metastases were identified in 12% of these patients. This study has confirmed that ER alone is adequate treatment for LR SM-CRC.³⁶ However, there was one case of recurrence in this group, and when the histology was reviewed, lymphovascular invasion was seen on one additional slice. This highlights the importance of taking adequate levels through the specimen and the potential challenges and workload for pathologists.

As colorectal ESD is adopted in the UK, there will be a learning curve for UK pathologists. Conventional measurements of submucosal invasion were originally devised for surgical specimens, so full thickness colonic wall was available and it was easy to orientate specimens. ESD does make it easier for pathologists to orientate specimens compared with pEMR. Japanese endoscopists take great care to pin SFR specimens on board to enable this.

COLORECTAL ESD EXPERIENCE IN EUROPE

Colorectal ESD experience in Europe is limited at best and confined to very few centres. One of the largest reported experiences is from the group in Augsburg, who reported on 82 colonic ESD cases with 71 cases within the rectum, and described their learning curve for the procedure. Neither of the two endoscopists involved received any formal training in ESD but had made short training visits to Japan, followed by a reciprocal visit by a Japanese expert who assisted in the first few cases. Both endoscopists did have some prior upper gastrointestinal ESD training. Interestingly, despite patients being informed in detail of the experimental nature of ESD and increased level of risk, only one patient opted for surgery rather than ESD in the first instance.

The study described three stages, pending on the overall number of ESDs performed and demonstrated a significant learning curve. The en bloc resection rates in first, second and third stages of the study were 60%, 88% and 96% with mean procedure times of 200, 193 and 136 min. Complication rates were low, with only one perforation, which was managed conservatively. The post-ESD bleeding rate was 8%, with no cases requiring a blood transfusion.³⁷

RECOMMENDATION FOR COLORECTAL-ESD TRAINING IN UK

Prior to contemplating training in ESD, endoscopists should have an extensive experience of traditional

colonoscopy, preferably as part of the BCSP, having performed a minimum number of EMRs.

The National Institute of Health and Care Excellence (NICE) recognised the potential advantages of ESD and published guidance in 2010. NICE highlighted the lack of evidence on long-term survival when used to treat malignant lesions is limited in quantity and that there are some concerns about safety with regard to the risk of perforation and bleeding. The NICE document stressed that the procedure should only be used with special arrangements for clinical governance, consent and audit or research.³⁸

Due to low prevalence of EGC in the West, there is limited opportunity to obtain high-volume preliminary experience of gastric ESD. A panel of Japanese experts recommended specialised training with porcine oesophagogastric and colonic models before attempting CR-ESD. Other recommendations include observing procedures in specialised centres, attending 'hands-on' courses and performing circumferential incision followed by snaring in the first 5–10 cases. Careful selection of cases is also recommended. LST-G type 11a lesions (2–4 cm) in the rectum would be appropriate lesions in the early stage of training, and very large lesions should be avoided during the initial training phase.³⁹

CONCLUSIONS

In the West, there has been a reluctance to adopt ESD due to the small number of suitable lesions, the safety of EMR and the perceived high complexity, cost and risk of the ESD procedure. However, ESD has evolved rapidly and is now widely accepted in Japan for management of early upper and lower GI tract cancer. Specialised training and education have been instrumental in the remarkable improvement in endoscopic outcomes.

Although the incidence of EGC in the West is far less than in Japan, epidemiological data suggest that the incidence of CRC is similar.⁴⁰ LST-non-granular type >2 cm and LST-granular type >4 cm were regarded as absolute indications for ESD in Japan. However, with increasing expertise and experience, the indications have broadened considerably and now include LR ECC. In the multicentre Japanese study reporting long-term outcomes of ER for pT1 CRC, 30% of the cases were LR disease and cured by ER alone.³⁶ The UK BCSP experience has demonstrated a considerable shift in the Duke's stage of CRC and identified a significant number of large benign lesions requiring endoscopic therapy. ESD has the potential to remove the need for a significant number of these patients to undergo surgery, providing an SFR for accurate histological assessment.

Significant variations in endoscopic therapeutic practice documented in the BCSP and in other studies,⁴¹ combined with an increase in ECC and LST cases, we believe, will drive demand for a network of

therapeutic colonoscopic centres, based around screening centres. A system of risk stratification for colonic polyps will enable identification of complex polyps⁴² and ECC that should be discussed at multi-disciplinary team meetings, where optimal management can be decided. We believe that ESD needs to become part of the diagnostic and therapeutic strategy, particularly for rectal lesions. This will require considerable training in endoscopy and should be restricted at least initially to specialist centres. Although perforation and bleeding rates are relatively high, advances in endoscopic techniques mean that complications can often be managed endoscopically without the need for surgery. The lessons learnt in Japan will hopefully shorten the learning curve for ESD training. The UK, with its national endoscopy training strategy, is in a good position to oversee the development of a structured training programme. The development of designated therapeutic colonoscopic lists (pEMR and ESD) will enhance the training opportunities for nurses and registrars in the use of therapeutic equipment, including polypectomy snares, knives and electrosurgical equipment.

We believe the development of ESD will have significant benefit for patients, as the management of early CRC needs to strike a balance between curing the patient and minimising the morbidity and mortality associated with the treatment recommended.

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