MINI REVIEW

Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) in 2011, a Western perspective

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Summary  Endoscopic mucosal resection (EMR) has become the standard of care for removal of large flat and sessile neoplastic lesions of the GI tract. Recently, endoscopic submucosal dissection (ESD) was introduced in Japan as an alternative technique, which allows en bloc resection of large lesions. The applications of EMR and ESD are expanding and many Western endoscopists are adopting these techniques. Paris classification and Kudo pit pattern classification allows prediction of the depth of invasion of early neoplastic lesions and thus, avoids resection of lesions invading the deep submucosa which have higher rates of lymphatic spread. ESD of early stomach cancer is the standard of care in Japan. Recent published reports from Western countries showed comparable results for ESD of early gastric cancers to those done in Japan. Recently, EMR combined with ablation has been used frequently in Western countries for treatment of high-grade dysplasia in early adenocarcinoma of the esophagus. Although ESD of early neoplastic lesions of the esophagus is technically difficult, few promising reports were published proving the feasibility of this technique in the West. ESD has been shown to achieve higher en bloc resection and lower rates of tumour recurrence in removal of lateral spreading colonic polyps. A hybrid technique of circumferential submucosal incision followed by en bloc EMR has been used for removal of large colonic lesions in some Western endoscopy centres. In Western countries, training for ESD is challenging given the lack of training in the relatively easier early gastric cancer lesions. Animal model training combined with observing experts in ESD could be an alternative for Western endoscopists. Inspite of obstacles, ESD applications are continuing to grow in Western countries.

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Background of endoscopic mucosal resection/endoscopic submucosal dissection

Endoscopic Mucosal Resection (EMR) has been used for the resection of early gastrointestinal neoplastic lesions for...
Endoscopic Mucosal Resection (EMR) and Endoscopic Submucosal Dissection (ESD)

Endoscopic Mucosal Resection (EMR) and Endoscopic Submucosal Dissection (ESD) more than a decade [1]. EMR allows the complete removal of large sessile or flat neoplasms, which could not be removed otherwise [2,3]. Typically, EMR of large lesions requires piecemeal resection. Endoscopic submucosal dissection (ESD) is an alternative technique which enables en bloc resection of large lesions [4]. En bloc resection allows better histopathological assessment of specimen for lymphovascular invasion and higher curative rate in comparison with EMR [5]. ESD was initially developed in Japan for the resection of early gastric cancer [6]. Recently, many endoscopists in the Western countries have adopted ESD techniques for en bloc resection of large esophageal, gastric or colonic lesions. In this review, we will discuss the applications and recent advances in EMR/ESD techniques with a focus in the Western experience and issues related to EMR/ESD training.

Identifying lesions suitable for endoscopic mucosal resection/endoscopic submucosal dissection

Ruling out lymph node metastasis is a crucial step prior to attempting EMR or ESD. Advanced lesions without lymph node invasion can be managed endoscopically, while lesions with lymph node metastases usually require surgery [7]. Lymph node metastasis are rare in lesions confined to the superficial mucosa and the risk of nodal invasion increases with lesions extending to the muscularis mucosa or submucosa [8]. Endoscopic morphological assessment of the lesion prior to resection is crucial for deciding whether it is suitable for EMR or not [9]. In 2002, a group of Western and Eastern endoscopic experts met in Paris and developed the Paris classification based on the Japanese criteria for classifying superficial neoplastic lesions [10]. Protruded lesions are Paris Class I, flat elevated lesions are Paris Class II and are subdivided into Ila (slightly elevated), Iib (completely flat) and Iic (depressed) (Fig. 1). Paris class III lesions, which are typically found in the esophagus or stomach, have ulceration of the mucosa. This classification provided a simplified and unified system to describe superficial neoplastic lesions of the GI tract [11]. However, the Paris classification did not include lateral spreading tumours (LST) of the colon, which are defined as 10 mm or larger flat lesions spreading in the GI lumen [12,13] (Fig. 2). The main advantage of the Paris classification is its ability to predict depth of invasion, and lymph node metastases, and thus, guide selection of lesions suitable for endoscopic resection.

A second classification system, also developed in Japan, classifies lesions according to the pattern of “pits”, which correspond to the crypt opening at the surface of the GI tract wall. Magnifying endoscopy with the use of narrow band imaging or chromoendoscopy enables identifying the pit pattern of neoplastic lesion, commonly known as Kudo classification [14]. Five pit patterns were identified, Type I and II are usually non-neoplastic, type III is mostly adenomatous lesions, type VI and V are either adenoma or carcinoma with a majority of type V as carcinomas. Lesions with Kudo class V are associated with deep submucosal invasion (SM2, 3) and higher lymph node metastasis (10 to 15%) [15]. In a study by Mastuda et al., 4215 lesions were examined by magnifying chromoendoscopy, among lesions that were labelled as non invasive based on pit pattern appearance, 99.4% were either adenoma, high-grade dysplasia (HGD) or adenocarcinoma with minimal invasion of the submucosa (SM1 lesions). The diagnostic accuracy to differentiate superficial lesions (HGD, mucosal carcinoma, SM1) from lesions invading deeper in the submucosa (SM2, 3) was 98.8% [16].

Applications of endoscopic mucosal resection/endoscopic submucosal dissection in neoplastic lesions of the stomach

Resection of early gastric cancer (EGC) was one of the initial applications of EMR and ESD techniques. Because of the screening program for gastric cancer in Japan, 53% of diagnosed gastric cancers are localized lesions [17]. In the seminal study by Gotoda et al., of 5265 patients who underwent gastrectomy with lymph node dissection for EGC, lymph node invasion was observed in only 2.7% of mucosal tumours and 18.6% of EGC invading the submucosa [18]. This led to the expanding of indications of EMR/ESD in EGC by the Japanese Gastric Cancer Association. This expanded criteria includes differentiated mucosal cancer without ulceration irrespective of the tumour size, differentiated mucosal cancer with ulceration if the tumour size is less than 3 cm, poorly differentiated cancer without ulcer and tumour size
greater than 2 cm, and differentiated lesions invading less than 500 μm in the submucosa, less than 3 cm in size and without evidence of lymphovascular invasion (on CT scan or Endoscopic Ultrasound) [19]. Long-term outcomes of ESD on lesions included in the above-expanded criteria are lacking. However, a short-term outcome study by Goto et al. showed a cancer recurrence rate of 0.9% in a median follow-up period of 36 months [20].

The first reports of ESD for EGC in the West were published in 2009. Catalano et al. reported their experience of 36 EMR procedures and 12 ESD procedures for EGC in Italian patients. The surgical free margin was significantly higher in the ESD group compared to the EMR group (92% vs 56%). There was no recurrence of gastric cancer in patients with surgical free margin in a mean follow-up period of 31 months. One of the 12 patients in the ESD group had perforation but without mortality [21]. In the same year, Dinis-Ribeiro et al. from Portugal reported their experience in managing EGC with ESD in 19 patients. En bloc resection was achieved in 78% of the patients. One patient developed major bleeding but without perforations and one patient has recurrence in a mean follow-up period of 10 months [22].

In an abstract presented in Digestive Disease Week in 2009, Emura et al. reported their experience of nine ESD cases of EGC in Colombia. En bloc resection was successful in all patients, surgical free margin was seen in seven of the nine patients (78%). No complications were reported. However, the mean procedure time for lesions larger than 30 mm was 137 minutes [23]. Recently, a case report from the United States describing a successful ESD of EGC lesion in a patient on aspirin therapy was published [24]. The fact that EGC is not as common worldwide as in Japan is an important factor in the scarcity of publications regarding the utility of ESD for EGC lesions outside of Asia. Other applications for EMR/ESD in the esophagus and the colon may be important alternatives to maintain proficiency in these procedures.

Applications of endoscopic mucosal resection/endoscopic submucosal dissection in neoplastic esophageal lesions

Squamous cell carcinoma (SCC) is the most common esophageal cancer worldwide. Recent studies confirmed that SCC limited to the mucosa (m1-3) or slightly invading the submucosa (vertical invasion depth of less than 50 microm) has negligible lymph node metastasis [25]. SCC invading deeper in the submucosa can have lymph node metastasis in up to 20 to 30% of the surgically resected specimens [26]. Long-term follow-up of patients who underwent ESD for early esophageal SCC is very promising, with a 5-year survival rate in up to 100% of patients with SCC limited to lamina propria mucosa and 85% for lesion invading deeper than the lamina propria mucosa [27]. In 2010, numerous papers discussing the feasibility and the long-term outcomes of ESD in early SCC were published. Takahashi et al. compared EMR and ESD for early esophageal SCC in a retrospective study of 300 patients. The tumour recurrence rate was significantly lower in the ESD group (0.9%) compared to the EMR group (9.8%), pathological free margin was
also significantly higher in the ESD group (97%) compared to the EMR group (78%) with no significant difference in perforation rates between ESD (2.6%) and EMR (1.6%) groups [28]. This data concurs with prior publications recommending ESD for early SCC larger than 15 to 20 mm in diameter [29,30].

While ESD of early esophageal SCC is gaining popularity in Japan, Repici et al. published in April 2010 the first Western experience of ESD in early esophageal SCC. The prospective study included 20 Italian patients with the mean lesion size of 32 mm. En bloc resection with cancer free margin was achieved in 90% of patients; mediastinal emphysema was seen in two cases, but without overt perforation [31]. This impressive result is comparable to the Asian experience and it is expected that more Western studies will be published in coming years.

Although esophageal SCC is common worldwide, esophageal adenocarcinoma (EAC) is steadily increasing in the Western world to rates higher than esophageal SCC [32,33]. Screening programs for Barrett’s esophagus led to an increase in detection of early EAC. Interestingly, the pattern of lymphatic and depth invasion is different in esophageal SCC compared to EAC. Early EAC limited to

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**Figure 4** Endoscopic mucosal resection-endoscopic submucosal dissection hybrid technique. a: narrow band imaging of the colonic polyp; b: submucosal injection of the lesion; c: initial circumferential submucosal incision; d: en bloc endoscopic mucosal resection of the lesion; e: the polypectomy bed after endoscopic mucosal resection-endoscopic submucosal dissection hybrid technique; f: the margin of the polypectomy bed after treatment with argon plasma coagulation.
mucosa has virtually no lymphatic spread and invasion of the superficial submucosa has lower rates of lymphatic spread compared to esophageal SCC \[26,34\]. This phenomenon makes EMR and ESD more appealing in early esophageal AC. In western countries, a combination of EMR with endoscopic ablation has been proven to provide similar survival rates and lower morbidity compared to esophagectomy in early EAC \[35–37\]. However, data on ESD for early EAC is sparse. In a retrospective study of 24 patients, Yoshinaga et al. were able to achieve ESD in all patients with curative resection rate of 72%. Stenosis occurred in two patients which was managed successfully with repeat dilations \[38\]. In another retrospective study by Ishi et al., ESD was done for 34 early esophageal SCC lesions and three AC lesions, en bloc resection was achieved in all patients and curative resection was achieved in 95% of the lesion including the three EAC \[39\]. It is important to note that ESD for early EAC is more technically difficult than early esophageal SCC giving the location of lesions in the distal esophagus and the fibrotic submucosa from recurrent reflux induced esophagitis \[40\]. Although stricture is common after extensive EMR or ESD of the esophagus \[41\], it usually responds well to endoscopic dilation. Preventive endoscopic dilation after extensive EMR was shown to lower the structuring rate (8%), decrease the severity of the stricture and shorten the duration required to manage developed stricture \[42\].

**Applications of endoscopic mucosal resection/endoscopic submucosal dissection in early neoplastic colonic lesions**

EMR has been the standard of care for removal of superficial lateral spreading colonic lesions (Fig. 3). The lower rates of tumour recurrence (7%) and lower rate of perforation (1%) make the EMR an attractive option for treating these lesions \[43,44\]. However, certain lesions such as the non-granular type of lateral spreading tumours should be removed en bloc giving the higher frequency of submucosal invasion and the difficulty in diagnosing the extent of invasion \[45,46\]. ESD was suggested as an alternative to piecemeal EMR for large colonic lesions (> 20 mm). In a study by Saito et al., that involved 373 lesions, ESD was associated with significantly lower tumour recurrence rates compared to EMR (2% vs 14%). However, ESD was associated with higher perforation rates compared to EMR (6.2% vs 1.3%) and longer procedure times. Although it should be emphasized that that greater than 90% of perforations in larger Japanese series are managed endoscopically or with medical (observation and antibiotics) treatment only. \[5\]. Given the lack of experience in ESD by Western endoscopists, Moss et al. from Australia suggested a hybrid technique which involves circumferential submucosal incision followed by en bloc EMR of colonic lesion. The technique was shown to improve en bloc resection rates while decreasing the procedure time in a porcine model \[47\]. A similar technique using submucosal dissection by insulated-tip knife and en bloc EMR was investigated in 29 large colonic lesions by Repici et al. from Italy. En bloc resection was achieved in 95% of the lesion with a complication rate of 13% \[48\]. Fig. 4 illustrates the EMR-ESD hybrid technique, the procedure was done at Mayo Clinic Jacksonville, FL, US.

**Endoscopic submucosal dissection Training in the West**

ESD is a complex procedure that requires familiarity with multiple equipments and various techniques in order to achieve en bloc resection and to manage complications \[49\]. Constant exposure to ESD cases is required in order to decrease the procedure times and complications \[50\]. A learning curve study showed that 30 ESD procedures are required in order to achieve 93% complete resection rates and acceptable rates of complications (4%). In this study, the difficulty for the trainee was mainly related to submucosal dissection and controlling the bleeding \[51\]. In Japan, ESD is currently performed in 195 institutions, 22 of them performed more than 100 cases of ESD \[52\]. Japanese endoscopists start ESD training in stomach lesions and after gaining proficiency in ESD, they move to esophageal and colonic lesions which is technically more difficult given the lesions’ positions and thinner wall of the esophagus and the colon \[53\]. Unfortunately, this large volume of ESD procedures is not available in the West, and Western endoscopists with an interest in ESD usually seek training with a Japanese expert as well as extensive training in animal models \[54\]. Fig. 5 illustrates an example of ESD training in
an animal model. In a feasibility study done by two Italian endoscopists, one of them had 3 months of training in Japan, 25 ESD procedures were performed in various esophageal, stomach and colonic lesions. En bloc resection was achieved in 84% of the specimens, with a 20% perforation rate and 12% bleeding rate. The authors concluded that ESD is feasible in esophageal and stomach lesions but colonic lesions need more expertise [55]. A European panel of experts recommended that Western endoscopists should at least observe 15 live ESD cases by an expert, followed by performing ESD on an isolated stomach and then live animal models prior attempting ESD. They also recommended starting with the distal stomach and rectal lesions before moving to proximal stomach and colonic lesions with esophageal lesions to be attempted only after gaining proficiency in the above sites [56]. Another limitation of training ESD is the lack of standardization in performing the procedure. Multiple knives, solutions for submucosal elevations and various electrocautery coagulation settings are currently being used [57]. More studies are needed to compare the different equipments and techniques in hope of finding the optimal method of performing ESD. In spite of all the above limitations, it is expected that in the next few years, more Western endoscopists will gain familiarity and proficiency in ESD and the procedure will disseminate in the West.

Conclusion

Endoscopists should be familiar with the morphological classification for assessing the lesions depth of invasion prior attempting EMR or ESD. Choices between EMR or ESD is a trade off between the benefit of complete resection of the lesions and risk of perforation and bleeding. Usually early neoplastic lesions larger than 20 mm are best managed with ESD. In the West, EMR is now the standard of care for colonic lateral spreading lesions removal. ESD, although proven feasible and effective in the East, is still in its infancy in Western countries. Cooperation between Eastern and Western endoscopists is necessary in order to transfer the knowledge and the Eastern experience in ESD to the Western endoscopists.

Disclosure of interest

The author declare that he has no conflicts of interest concerning this article.

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References


