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Endoscopic submucosal dissection with electrosurgical knives in a patient on aspirin therapy (with video)

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Background: The electrosurgical knives required to perform endoscopic submucosal dissection (ESD) have recently passed the 510(k) premarketing evaluation by the U.S. Food and Drug Administration and are now available for purchase in the United States. Challenges to ESD being more widely performed in the United States include the lack of intensive hands-on training programs and a low incidence of appropriate, highly dysplastic gastric lesions on which an ESD-trained endoscopist can begin performing this procedure in patients. Furthermore, there are no guidelines regarding the safety of continuing antiplatelet therapy in patients undergoing ESD.

Objective: To report on the first gastric ESD performed in the United States by using recently approved electrosurgical knives on a patient who was maintained on aspirin therapy.

Design: Case report.

Setting: Large academic medical center.

Patient: One patient with a 2-cm high-grade dysplasia (HGD) lesion in the posterior antrum who had indwelling coronary stents and was maintained on aspirin therapy throughout the periprocedural period.

Interventions: High-definition white-light and narrow-band imaging endoscopy, endosonography, and ESD by using recently approved electrosurgical knives.

Main Outcome Measurements: Complete resection of the HGD gastric lesion.

Results: En bloc complete resection of the HGD gastric lesion was achieved without any immediate or delayed bleeding or perforation. No residual or recurrent dysplasia was found on 1- or 3-month follow-up endoscopies.

Limitations: Generalizations cannot be made from this single case.

Conclusions: After receiving intensive hands-on training in both ex vivo and in vivo animal models, gastric ESD was successfully performed by 2 U.S. endoscopists by using recently approved electrosurgical knives in a patient maintained on aspirin therapy without any complications.

Endoscopic submucosal dissection (ESD) is an accepted endoscopic therapy for highly dysplastic gastric lesions in Japan and parts of Asia and South America.[1-5] Despite nearly a decade of experience in Asian countries, the expertise to perform ESD in the stomach, or in other parts of the luminal GI tract, is largely lacking in Western countries.[6] This disparity in experience is likely because of the relatively low prevalence of highly dysplastic gastric

Abbreviations: ESD, endoscopic submucosal dissection; HGD, high-grade dysplasia; LGD, low-grade dysplasia; NBI, narrow-band imaging.

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lesions and early gastric carcinomas found in patients living in Western countries.[7] Furthermore, because ESD of esophageal or colorectal lesions is even more challenging than gastric ESD, performing ESD in these locations is considered to be inappropriate for inexperienced operators.[6]

Eastern endoscopists rely on advanced optical imaging techniques (such as chromoendoscopy and narrow-band imaging [NBI]) to identify lesions containing high-grade dysplasia (HGD) or early gastric adenocarcinomas that are suitable for endoscopic resection. Although increasing, experience with these advanced optical imaging technologies is not widespread among Western gastroenterologists.[8] Furthermore, there are no training programs in the United States that offer the intensive hands-on instruction required to learn ESD. A final, yet critically important, issue is that the specialized electrosurgical knives required to perform ESD have only recently passed the 510(k) premarketing evaluation by the U.S. Food and Drug Administration, and as such they have only recently been made available for consumer purchase and use in the United States.

The American Society for Gastrointestinal Endoscopy practice guidelines[9-11] and other sources[12] have recommended, in the absence of a preexisting bleeding disorder, that aspirin or nonsteroidal anti-inflammatory drug therapy may be continued in patients undergoing endoscopic procedures. However, if a procedure with a higher risk of bleeding is planned, an individualized approach has been recommended.[12] For patients undergoing higher-risk endoscopic procedures, it has been recommended that clopidogrel be discontinued 7 to 10 days before their procedures.[10] Finally, American Society for Gastrointestinal Endoscopy guidelines do state that patients on combination antiplatelet therapy (eg, aspirin and clopidogrel) may be at increased risk of bleeding as a result of endoscopic procedures.[10]

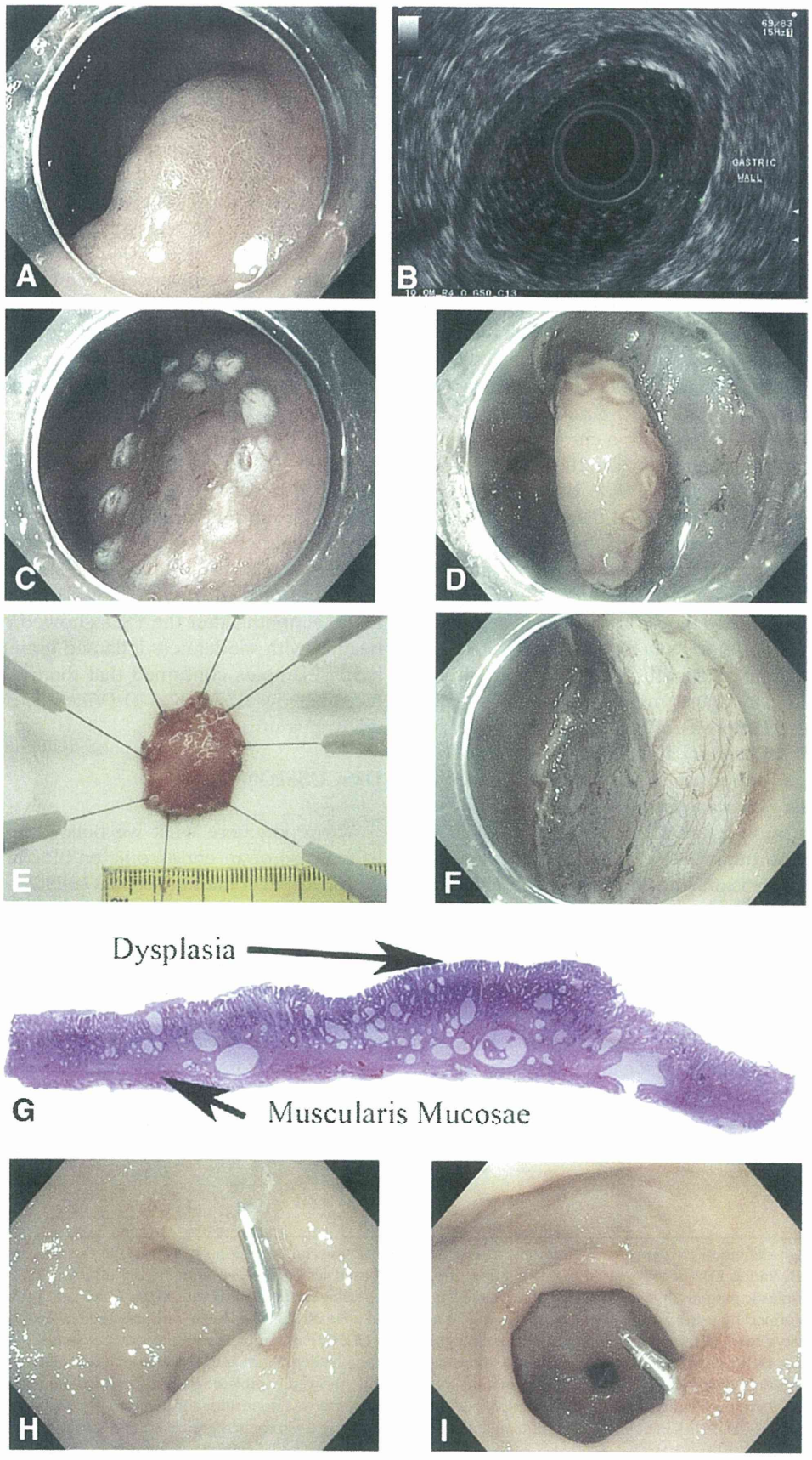
At present, there are no published reports describing the use of the recently approved electrosurgical knives to perform ESD in individuals on antiplatelet therapy in the United States.

CASE REPORT

A 66-year-old Chinese woman with known gastric intestinal metaplasia was referred for dyspepsia and a history of a gastric polyp. She had a history of diabetes mellitus, hypertension, hyperlipidemia, and coronary artery disease with 2 metal stents that had been placed in her right coronary artery 5 years ago in China. One year ago, she underwent cardiac catheterization for chest pain that demonstrated nonobstructive coronary artery disease, and the patient was maintained on aspirin 81 mg/day and clopidogrel 75 mg/day. An initial EGD was performed by using high-definition white light, NBI, and chromoendoscopy by using 0.8% indigo carmine (GIF-H180 gastroscope using the Evis Exera II platform; Olympus America, Center Valley, Pa), which demonstrated a 20-mm raised lesion (Paris 0-IIa),[13] along the posterior wall of the antrum that had dysplastic features. Biopsy samples were taken that confirmed HGD. There were a few other small dysplastic areas identified in other portions of the body and antrum that were found to contain low-grade dysplasia (LGD) on biopsy specimens. The patient's case was presented at a multidisciplinary GI-oncology tumor board at the University of Virginia Hospital. The consensus recommendation was to offer the patient either a subtotal gastrectomy, given the multifocal LGD with focal HGD, or a staging EUS examination followed by ESD of the lesion containing HGD and frequent endoscopic surveillance of the LGD lesions. The patient chose to pursue endoscopic therapy with subsequent close surveillance. Radial EUS demonstrated a lesion in the distal antrum that was confined to the mucosa, and no pathological perigastric lymph nodes were identified, which further confirmed that this lesion was appropriate for ESD.

Given the patient's coronary artery disease and indwelling coronary stents, it was decided that she should continue her aspirin therapy throughout the periprocedural period and stop her clopidogrel at least 4 days before her procedure. ESD was performed at the University of Virginia Hospital by 2 interventional endoscopists (A.Y.W., P.Y.), who each perform more than 500 interventional endoscopies yearly. Both U.S.-based endoscopists first received hands-on instruction by using an ex vivo and an in vivo porcine model from a visiting professor (H.K.) from Korea who had performed more than 150 gastric ESDs. Further didactic and hands-on training by using an in vivo animal model was obtained by attending an intensive 3-day course in gastric ESD held in Bogotá, Colombia (taught by F.E. and I.O., who are both Japanese-trained endoscopists, who together have performed well over 1000 gastric ESDs).[14] This course culminated with a hands-on practical examination and a written examination followed by observing a live gastric ESD procedure in a human patient, after which university certification in ESD was awarded. Subsequently, both U.S. endoscopists performed at least 5 additional successful ESDs using an in vivo or an ex vivo porcine model before performing this procedure. Institutional credentialing in ESD and informed consent was obtained before performing the procedure.

A span of 4 months elapsed before the ESD could be performed because we were awaiting 510(k) approval of the necessary electrosurgical knives. The procedure was performed with the patient under general endotracheal anesthesia, and preprocedural intravenous ampicillin (2 g) and gentamicin (60 mg) were administered given the patient's diabetes and the potential risks of bleeding and perforation. Intravenous esomeprazole (40 mg) was also administered preprocedurally. A diagnostic gastroscope (GIF-H180; Olympus America) and a processor capable of high-definition white-light imaging and NBI (Evis Exera II; Olympus America) were used during ESD. An ESD cap (D201-11804; Olympus America) was attached to the distal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end of the gastroscope and secured with clear plastic tape. Electrocautery was provided by using an electrosurgical generator (ESG-100, Olympus America). Submucosal injections were performed by using a 1:100,000 solution of epinephrine in normal saline solution tinted with a few drops of 0.8% indigo carmine (a total of 100 mL of this solution was used in divided doses during ESD).

Under high-definition white light and NBI, a 20-mm, raised lesion (Paris 0-IIa),[13] without ulceration or mucosal tenting, was seen in the distal, posterior antrum. NBI without optical magnification allowed clear delineation of the highly dysplastic borders of the lesion. The stomach was lavaged by using simethicone washes, and all the fluid was evacuated. Under high-definition NBI visualization, a HookKnife (KD-620LR; Olympus America) was used to mark a circular border approximately 5 mm outside of the area of HGD by using soft coagulation current set at 20 W. A double marking was placed in the distal/anterior border (at the 12 o'clock position) to provide directionality for subsequent histopathology. The final diameter of the circumscribed lesion was 30 mm. After the circumferential marking was completed, the lesion was lifted by using the dilute epinephrine/indigo carmine/saline solution. The circumferential incision into the submucosa was begun by using a straight needle-knife (KD-10Q-1; Olympus America), and it was completed with a combination of the IT-knife2 (KD-611L; Olympus America) and the FlexKnife (KD-630L; Olympus America) by using a pulse cut slow mode set at 60 W. In sequential fashion, the submucosal dissection was performed with the IT-knife2 and the FlexKnife, by using either a forced coagulation current set at 20 to 50 W or a pulse cut slow current set at 40 to 60 W to carefully dissect through the submucosal plane. During the circumferential incision and the submucosal dissection, any mild oozing encountered was controlled with the short blades of the IT-knife2, by using a forced coagulation current set at 50 W, and when a visible vessel was exposed, it was coagulated by using coagulation forceps (Coagrasper, FD-410LR; Olympus America) with the soft coagulation current set at 50 W. There was no significant bleeding or perforation encountered during this procedure, which was performed in 1 hour and 45 minutes. After ESD was completed, there remained a 30-mm submucosal antral ulcer. Two endoclips (long upper QuickClip2, HX-201LR-135L.B; Olympus America) were used to mechanically obliterate 2 nonbleeding visible vessels seen in the ulcer base to reduce the risk of delayed bleeding.

The resected specimen measured approximately 30 mm when stretched and pinned to a Styrofoam board covered with gauze wetted with saline solution. This specimen was fixed while attached to the Styrofoam and then serially sectioned to evaluate for oncologic resection. Histopathology showed HGD in a background of intestinal metaplasia without evidence of invasive carcinoma. The deep and circumferential margins were free of dysplasia.

The patient was admitted for observation for 3 days after her ESD. She was kept on nothing by mouth for the first night, and then clear liquids were initiated uneventfully the following day. She experienced no new abdominal pain, had no signs of melena or hematemesis, and serial hemoglobin values remained stable. A planned follow-up EGD performed 2 days after her ESD showed early granulation tissue in the ulcer. The patient maintained her aspirin therapy throughout her procedure, and she resumed clopidogrel 7 days after the ESD procedure. A follow-up EGD 1 month later showed a 5-mm clean-based, residual ulcer with an adherent endoclip. Another EGD, 3 months after the ESD, showed complete mucosal healing with moderately inflamed granulation tissue, and biopsy samples confirmed that there was no residual or recurrent dysplasia (Fig. 1) (Video 1, available online at www.giejournal.org).

DISCUSSION

We report here what we believe to be the first published case of an endoscopic en bloc resection of a large gastric lesion containing HGD via ESD in the United States, which was performed by using newly approved electrosurgical knives in a patient maintained on aspirin therapy. Given the differences in histopathological interpretation between Japanese and Western pathologists, this lesion would have likely been called a well-differentiated, mucosally-based early gastric cancer in Japan.[15,16] Given our complete endoscopic resection of this lesion, and because the anticipated risk of lymph node metastasis for this lesion is nearly 0% (according to large published Japanese series on early gastric cancer),[1,17] it would be

Figure 1. A, High-definition NBI endoscopy demonstrated a dysplastic 20-mm raised lesion (Paris 0-IIa) in the distal antrum along the posterior wall. **B,** Radial EUS demonstrated that this was a mucosally-based lesion with no submucosal invasion. **C,** NBI was used to delineate the dysplastic margins and circumferential marking was made by using a HookKnife (with a double mark to provide orientation). **D,** ESD was performed by using a straight needle-knife, an IT-knife2, and a FlexKnife. The lesion was resected en bloc and affixed to wet gauze on top of Styrofoam **(E)**, leaving behind a 30-mm submucosal ulcer **(F)**. **G,** Final surgical pathology demonstrated complete resection of the HGD lesion. **H,** A follow-up EGD 1 month later demonstrated a nearly healed 5-mm antral ulcer with a retained endoclip; there was no recurrent or residual dysplasia. **I,** Another EGD, 3 months after the ESD, showed complete mucosal healing with moderately inflamed granulation tissue and a retained endoclip. Biopsy samples confirmed that there was no residual or recurrent dysplasia. (Special thanks to Edward B. Stelow, MD, and Dirk P. Stanley, MD, for their assistance in obtaining a photomicrograph of the relevant histopathology for this case.)

reasonable to perform surveillance endoscopy on an annual basis primarily to detect metachronous HGD and early gastric cancer.[18] Use of NBI was important in initially identifying the highly dysplastic lesion, subsequently in delineating the dysplastic margins for ESD, and finally in surveying for recurrent or metachronous dysplasia on follow-up endoscopy.

The types of current and wattage used to perform ESD will vary depending on the electrosurgical generator and may at times need to be optimized according to the patient and the lesion. At the National Cancer Center in Tokyo, Japan, when using the ESG-100 generator, the recommended standard setting for circumferential dissection is a pulse cut slow current set at 40 W, and for submucosal dissection either a forced coagulation current set at 50 W or a pulse cut slow current set at 40 W is used. Although techniques are emerging that may enable reliable endoscopic apposition of the post-ESD defect,[19] at present, the standard approach at most high-volume ESD centers is to coagulate or clip exposed visible vessels and not to attempt to close the submucosal defect.[20]

Because the electrosurgical knives needed to perform ESD have received 510(k) approval, these tools can now be purchased in the United States. However, despite having the proper tools to perform this advanced procedure, challenges to performing ESD in the United States include the lack of training programs based in the United States and the relatively low prevalence of early gastric cancers or highly dysplastic gastric lesions on which a trained endoscopist can begin to perform this procedure in patients. Although there is the potential to perform ESD in the esophagus and colorectum, procedures in these locations are more challenging because of the thinner walls of these organs, and as such, these locations are considered to be inappropriate areas in which to begin performing ESD.[6]

In addition to training programs in Japan and other East Asian countries (South Korea and Taiwan), there are specialized centers to obtain exposure to and training in ESD in South America (eg, Colombia), where the incidence of gastric cancer is very high.[4,21] A training model similar to the one used by the U.S. endoscopists in this report has been shown to be effective in teaching this procedure.[22] Yamamoto et al[23] studied ESD training by observing 3 Japanese residents, trained in routine endoscopy, perform 30 consecutive, supervised ESDs of small mucosally-based lesions. These authors found that the self-completion rate and operation time were significantly worse for the submucosal dissection part of the procedure than for the circumferential mucosal incision portion. Two of the 3 trainee operators studied showed a flat learning curve for submucosal dissection, and complications were related mainly to uncontrollable hemorrhage.[23] This steep learning curve was further highlighted by Teoh et al,[24] who reported a prospective study of 24 endoscopists participating in a Chinese ESD training program by using a porcine model to teach esophageal and gastric ESD. These investigators found that during gastric ESD, 15 participants (65%) encountered perforations, and bleeding occurred during 57% of ESDs. A significantly higher proportion of perforations occurred with the use of noninsulated knives.[24]

We advise that endoscopists interested in performing gastric ESD should first pursue intensive hands-on training in both ex vivo and in vivo models supervised by an expert in ESD, followed by observing live gastric ESD procedures in patients. This basic training should be followed up by self-study and by successfully performing ESD procedures in both ex vivo and in vivo animal models before performing ESD on a patient. Although in vivo training is more costly and requires animal protocols and special handling, we believe that the experience of performing this procedure in a living animal is invaluable because it offers the opportunity to encounter and treat ESD-associated bleeding, which is paramount to acquiring proficiency in this procedure. Furthermore, skill in coagulating or clipping exposed visible vessels is mandatory, because routine coagulation of visible vessels may prevent delayed bleeding after ESD.[20] Despite advanced hemostasis techniques, the common practice in most high-volume ESD centers is to stop antiplatelet and antithrombotic therapy before performing ESD.[25] In this article, we report on what we believe to be the first ESD performed in the United States in a patient on continuous aspirin therapy. Although generalizations cannot be drawn from a single case, by ceasing clopidogrel but continuing aspirin therapy, ESD was not complicated by immediate or delayed bleeding, and the patient did not experience any cardiovascular complications.

As with all new procedures, specialized institutional credentialing must be obtained before performing this procedure, and careful informed consent is necessary. As more endoscopists become trained in ESD in the United States, a national training program may be feasible, and investigation into the utility of ESD in the esophagus and colorectum for HGD and early carcinomas will be necessary. Last, specialized Current Procedural Terminology codes will be required because this procedure is much more than an upper endoscopy but not quite a subtotal gastrectomy.

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Original article

Endoscopic resection of early gastric cancer treated by guideline and expanded National Cancer Centre criteria

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Background: Criteria for endoscopic resection in patients with early gastric cancer (EGC) have been expanded recently by the National Cancer Centre (NCC). This study compared long-term outcomes in patients with EGC who underwent endoscopic treatment according to guideline criteria with those treated according to expanded criteria.

Methods: Baseline and outcome data from patients undergoing curative endoscopic resection for EGC between January 1999 and December 2005 were collected from electronic medical records. Survival time hazard ratios and 95 per cent confidence intervals were calculated using the Cox proportional hazards model.

Results: Of 1485 patients who had a curative resection, 635 (42·8 per cent) underwent resection according to traditional criteria and 625 (42·1 per cent) according to expanded criteria. There was no significant difference in overall survival between the groups.

Conclusion: Patients who have treatment following the expanded criteria have similar long-term survival and outcomes to those treated according to guideline criteria.

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Introduction

In Japan, endoscopic mucosal resection (EMR) has been the treatment of choice for small early gastric cancer (EGC) for the past two decades[1,2]. Owing to the technical limitations of EMR, traditional indications for endoscopic resection of EGC according to the Gastric Cancer Treatment Guidelines of the Japanese Gastric Cancer Association (JGCA) were restricted to resection of small intramucosal EGCs (smaller than 20 mm) with intestinal-type histology and no ulceration.

The low risk of lymph node involvement in EGC confined to the superficial layers of the submucosa indicated that cure can be achieved by local resection, even of lesions larger than 20 mm, as long as the lesion is removed *en bloc*[3]. Endoscopic submucosal dissection (ESD) has become established as a technique that allows *en bloc* resection regardless of size. Revised criteria were proposed by the National Cancer Centre (NCC) in Tokyo (from January 1999) to expand the indications for endoscopic treatment and avoid unnecessary radical surgery, which until recently was the 'gold standard' for larger lesions[4,5].

This study compared the long-term outcome of patients with EGC who underwent endoscopic treatment based on either guideline of JGCA criteria or expanded NCC criteria.

Methods

Consecutive patients who had endoscopic resection for EGC between January 1999 and December 2005 were studied. Informed consent was obtained from all patients in accordance with the institutional protocol. The procedure was carried out under conscious sedation using a combination of midazolam and pentazocine. Patients who were assessed histologically as having had a non-curative resection owing to positive lateral margins and/or deep submucosal invasion, regardless of positive vertical margins and/or lymphatic–vascular infiltration and/or diffuse-type histology, and those who had undergone endoscopic

resection as a palliative treatment for advanced cancer were excluded.

Curability was based on the histological criteria for curative endoscopic resection (*Table 1*) according to the Japanese Classification of Gastric Carcinoma[6]. Pathological assessment of the resected specimen included: size, location, macroscopic appearance, presence of ulceration, histological type, depth of invasion, lymphatic and vascular involvement, and resection margin status. Tumours smaller than 20 mm without ulceration were included in the JGCA criteria group and those larger than 20 mm in the NCC expanded criteria group. Patients with multiple EGCs were analysed as a separate group.

Baseline and outcome data were collected from electronic medical records. Incomplete and missing data were retrieved from different sources such as telephone contact with patients, family and referring physicians, and checked with statistical data kept by the local government registry.

All patients with curative resection who met JGCA criteria were followed up by annual upper gastrointestinal surveillance endoscopy to identify local recurrence and/or metachronous gastric cancer. Patients who met NCC criteria were additionally followed by thoracic and abdominal computed tomography and/or endoscopic ultrasonography every 6 months. Patients were followed from the date of first treatment until 31 July 2007.

Statistical analysis

Survival time was calculated as the interval between the date of the first treatment and the date of death or the last date confirmed as alive for survivors. Survival curves were calculated using the Kaplan–Meier method. To compare overall survival by treatment method, a Cox proportional hazards model was used to estimate hazard ratios and 95 per cent confidence intervals (c.i.). Age, sex and past history of cancer were included as co-variables in the multivariable analyses. All P values reported are two sided and $P < 0{\cdot}050$ was considered statistically significant.

Table 1 Histological criteria for curative endoscopic resection

Factors for no risk of lymph node metastasis
Intestinal-type histology
No lymphatic or vascular infiltration
Intramucosal cancer regardless of tumour size without ulcer finding or intramucosal cancer less than 30 mm in size with ulcer finding or minute submucosal invasive cancer (sm1) less than 30 mm in size
Factors for resection margin
Tumour-free horizontal margin
Tumour-free vertical margin

Statistical analyses were performed with SAS® software version 9.1 (SAS Institute, Cary, North Carolina, USA).

Results

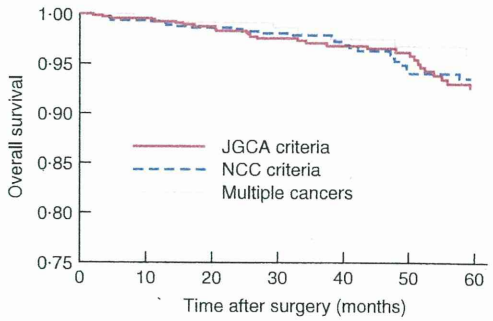
Some 1786 lesions were resected curatively among 1485 patients; 635 patients (42·8 per cent) were treated according to the guideline of JGCA criteria and 625 (42·1 per cent) in accordance with the expanded NCC criteria; 225 patients (15·2 per cent) had multiple EGCs with both criteria. Baseline characteristics by treatment allocation are shown in *Table 2*.

Follow-up was complete for all 1485 patients, with a median observation period of 44·1 months. During follow-up, 77 patients died (5·2 per cent). Only one patient treated according to JGCA criteria died from metachronous invasive gastric cancer, which was detected 5 years later. Locally recurrent gastric cancer was found in another patient who underwent piecemeal endoscopic resection. This patient underwent ESD for local recurrence 18 months after the first endoscopic resection and was alive with no evidence of recurrence after 57 months. There was

Table 2 Baseline patient characteristics by treatment group

	JGCA criteria ($n = 635$)	NCC criteria ($n = 625$)	Multiple cancers ($n = 225$)
Mean age (years)	66·4	66·5	68·6
Men	479 (75·4)	505 (80·8)	180 (80·0)
Past history of cancer	154 (24·3)	87 (13·9)	95 (42·2)
Mean tumour size (mm)	10·8	23·8	12·4

JGCA, Japanese Gastric Cancer Association; NCC, National Cancer Centre.



No. at risk							
JGCA criteria	635	631	584	455	346	264	186
NCC criteria	625	621	559	433	314	242	156
Multiple cancers	225	223	210	180	156	126	89

Fig. 1 Survival by treatment group. JGCA, Japanese Gastric Cancer Association; NCC, National Cancer Centre

Table 3 Hazard ratio for all-cause mortality according to treatment group

	No. of deaths	5-year survival rate (%)	Hazard ratio	
			Crude	Adjusted*
JGCA criteria	36	92·4	1·00	1·00
NCC expanded criteria	31	93·4	0·93 (0·57, 1·50)	1·10 (0·67, 1·81)
Multiple cancers	10	95·6	0·63 (0·31, 1·26)	0·46 (0·23, 0·94)

Values in parentheses are 95 per cent confidence intervals. JGCA, Japanese Gastric Cancer Association; NCC, National Cancer Centre. *Multivariable Cox proportional hazards model, adjusted for age, sex and past history of cancer.

no significant difference in the rate of local and/or systemic recurrence between the JGCA and the NCCH groups.

Survival curves are shown in *Fig. 1*. The 5-year survival rate was 92·4 per cent in the JGCA group, 93·4 per cent in the NCCH group and 95·6 per cent among those with multiple cancers. There was no significant difference in overall survival (*Table 3*). In multivariable analysis, the hazard ratio for survival of patients in the NCC group compared with those in the JGCA group was 1·10 (95 per cent c.i. 0·67 to 1·81).

Discussion

Radical surgery with complete removal of first- and second-tier lymph nodes is accepted as a standard treatment for patients with EGC. A 5-year survival rate of around 90 per cent has been achieved in oriental and Western patients[7–9]. In patients with cancer limited to the mucosa, the incidence of lymph node metastasis is less than 3 per cent. This risk increases to 20 per cent when the cancer invades the submucosa[10].

Radical surgery may not be not the optimal treatment approach in all patients with EGC because it carries a significant risk of morbidity and mortality, and is associated with a significant reduction in quality of life[11–13]. Patients with no risk of lymph node metastasis can be treated safely by endoscopic resection[14].

Accepted indications for EMR of ECG have been (1) well differentiated elevated cancers less than 2 cm in diameter and (2) small (maximum 1 cm) depressed lesions without ulceration. These indications were established because of the technical limitations of EMR. In larger lesions, EMR has a high risk of recurrence as a result of incomplete resection when piecemeal EMR is used for larger lesions[15]. Specimens obtained by piecemeal EMR are difficult to analyse and there is a high risk of inadequate histological staging[16]. From a histological point of view, *en bloc* removal should be considered essential for endoscopic resection of larger lesions to ensure accurate histological staging. The treatment strategy for EGC has been revolutionized recently by the ESD procedure. This method is superior to other endoscopic techniques used for EGC as it makes *en bloc* resection possible, allowing precise histological staging and minimizing recurrence risk compared with standard EMR techniques[17].

Kojima and colleagues[18] have reviewed the outcomes of EMR from 12 major institutions in Japan. Long-term outcomes after EMR for small differentiated mucosal EGC less than 2 cm in diameter have been reported to be comparable to those following gastrectomy[19], but the long-term outcome of endoscopic resection of large EGCs has not been reported.

The present study has demonstrated that there is no difference in 5-year survival and local and/or systemic recurrence rates between patients treated according to JGCA or NCC criteria. The hazard ratio for overall survival showed no significant difference between the two groups.

Final staging can be carried out accurately only by formal histological analysis, especially with regard to potential lymphovascular infiltration. Therefore, *en bloc* resection is a prerequisite for accurate staging and prediction of a patient's risk of lymph node metastasis.

Expanded NCC criteria for patients with EGC are safe and practicable. As a result of the ability to achieve *en bloc* resection by ESD, more patients may benefit from endoscopic resection, further reducing the need for radical surgery.

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ENDOSCOPY MINISERIES

Endoscopic resection of gastrointestinal lesions: Advancement in the application of endoscopic submucosal dissection

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Abbreviations
GIT, gastrointestinal tract; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; LST, laterally spreading tumor; LST-G, laterally spreading tumor granular type; LST-NG, laterally spreading tumor non-granular type.

Abstract

Curative endoscopic resection is now a viable option for a range of neoplastic lesions of the gastrointestinal tract (GIT) with low invasive potential. Risk of lymph node metastasis is the most important prognostic factor in selecting appropriate lesions for endoscopic therapy, and assessment of invasion depth is vital in this respect. To determine appropriate treatment, detailed endoscopic diagnosis and estimation of depth using magnifying chromoendoscopy is the gold standard in Japan. En bloc resection is the most desirable endoscopic therapy as risk of local recurrence is low and accurate histological diagnosis of invasion depth is possible. Endoscopic mucosal resection is established worldwide for the ablation of early neoplasms, but en bloc removal using this technique is limited to small lesions. Evidence suggests that a piecemeal resection technique has a higher local recurrence risk, therefore necessitating repeated surveillance endoscopy and further therapy. More advanced endoscopic techniques developed in Japan allow effective en bloc removal of early GIT neoplasms, regardless of size. This review discusses assessment of GIT lesions and options for endoscopic therapy with special reference to the introduction of endoscopic submucosal dissection into Western countries.

Introduction

The presence of lymph node metastasis is an important prognostic factor in gastrointestinal malignancy.[1,2] Lesions known to have a low risk of lymph node metastasis can be considered for curative endoscopic resection, thus avoiding radical surgery. Endoscopic mucosal resection (EMR) is now a well-established technique worldwide for the treatment of benign and small malignant lesions in the gastrointestinal tract (GIT).[3] Endoscopic submucosal dissection (ESD) is a more advanced technique and was pioneered by Japanese endoscopists.[4] It has become standard treatment in Japan for superficial esophageal and early gastric cancers and has recently been implemented in major centers to achieve en bloc resection of colorectal lesions that would otherwise necessitate piecemeal or surgical resection. Few centers offer ESD in the West, and there are currently no publications of significant patient cohorts. In the following article we give an overview of endoscopic resection of GIT lesions and consider the application of ESD in Western countries.

Assessment of GIT lesions

Histological assessment

Early or superficial gastrointestinal cancer is confined to the mucosa and submucosa, irrespective of the presence of lymph node metastasis.[5] Comparison between Eastern and Western publications has been difficult in the past due to a divergence in the histological definition of gastrointestinal neoplasia. One of the main differences was that lesions with high-grade intraepithelial neoplasia and no invasion of the lamina propria were defined as high-grade dysplasia in the West, but as intramucosal carcinoma in Japan. In an attempt to overcome these discrepancies, the Vienna Workshop produced a consensus classification, revised in 2002,

Table 1 The revised Vienna classification of gastrointestinal epithelial neoplasia

Category	Diagnosis
1	Negative for neoplasia
2	Indefinite for neoplasia
3	Mucosal low-grade neoplasia
	Low-grade adenoma
	Low-grade dysplasia
4	Mucosal high-grade neoplasia
	4.1 High-grade adenoma/dysplasia
	4.2 Non-invasive carcinoma (carcinoma *in situ*)
	4.3 Suspicious for invasive carcinoma
	4.4 Intramucosal carcinoma
5	Submucosal invasion by carcinoma

and now used worldwide.[6,7] High-grade dysplasia and intramucosal carcinoma are now considered subdivisions of the same group (Table 1).

Macroscopic assessment

Careful endoscopic diagnosis is essential in the selection of suitable lesions for endoscopic removal. The Paris classification of superficial neoplasia of the GIT allows for straightforward endoscopic diagnosis of early lesions, whilst simultaneously allowing estimation of depth, and therefore likely risk of lymph node metastasis (Fig. 1).[8] Lesions that are of mixed morphology, for example a superficial elevated lesion (IIa) with a centrally depressed area (IIc), can also be described logically using this system. Laterally spreading tumors (LST) of the colorectum are not described by the Paris classification and are defined as lesions $\geq$ 10 mm in diameter with a low vertical axis extending laterally along the interior luminal wall. LST are further subdivided into granular type (LST-G) and non-granular type (LST-NG), depending on surface appearance.

Magnifying chromoendoscopy

Detailed endoscopic diagnosis and estimation of depth using magnifying chromoendoscopy is the gold standard in Japan for determination of appropriate treatment. Standard endoscopic images can be enlarged up to 150×, enabling easier recognition of lesion margins and superior visualisation of surface architecture.[9] Lesion visualisation can be enhanced further when magnification is used in combination with dye spraying using stains such as Lugol's solution, indigo carmine and cresyl violet. Normal esophageal non-keratinized squamous epithelium is stained dark brown by Lugol's solution due to the presence of glycogen-rich granules, whereas dysplasia and carcinoma are left unstained. This method has proven to be successful in the detection of early esophageal lesions that might otherwise be missed. Indigo carmine is the most commonly used dye in Japan for early cancer screening of the stomach and colon and for differentiation between benign and malignant lesions in the colon. Pooling of the blue dye in grooves and depressed areas highlights mucosal irregularities. Crystal violet is an alternative dye that is absorbed across epithelial cell membranes accentuating mucosal patterns of gastric and colonic neoplasia.[10]

Colonic pit pattern classification

Whilst gastric mucosal changes can prove more difficult to assess due to gastric acid damage and presence of other pathologies, such as gastritis, clear magnified images can usually be obtained in the colon. Kudo *et al.* used magnifying endoscopy to observe the shape of colorectal crypt openings (pits) on the surface of normal bowel and colorectal tumors *in vivo*. They observed a distinct correlation between lesion type and pit pattern and devised a classification system that is now considered standard in Japan and specialist centers worldwide for the diagnosis of colorectal lesions (Fig. 2). Pit patterns I and II are found in the majority of non-neoplastic lesions; III_L and III_S are present predominantly in adenomas; while the type IV pit pattern is seen in 75% of adenomas, but also found in some carcinomas. The distribution of type V irregular-type (V_I) was found to be 61% in carcinomas, and the non-structural pit pattern (V_N) was present in over 93% of intramucosal and submucosal carcinomas.[11,12]

Once the characteristics of a lesion have been fully defined, the appropriate mode of treatment can be determined. The choice between surgery, EMR or ESD can be made using the methods described above; it will depend on several factors including lesion size, pathological differentiation and estimation of depth.

Endoscopic mucosal resection

EMR is a minimally invasive technique for effective curative treatment of early-stage GIT lesions with no invasive potential. It involves complete mucosal removal by excision though the submucosal layer of the gastrointestinal wall. Several EMR techniques have been described. Cap-assisted EMR is frequently used to excise early esophageal lesions; it involves fitting a transparent plastic cap to the tip of a standard endoscope. After submucosal injection to separate the lesion from the muscle layer, a crescent-shaped snare is deployed into a groove at the tip of the cap. After suction of the lesion into the cap, the snare is closed around the base and electrocautery is used to complete the excision.[13]

The 'inject and cut' method is safe and straightforward and is used extensively for colonic EMR. The submucosa is injected to create a fluid cushion before a snare is closed around the base of the lesion and current applied.[14] Less commonly employed techniques include the use of a double channel endoscope to lift the lesion with a grasper while a snare is deployed through the second channel, or use of a variceal ligation device to release a band around the lesion base before snare resection.[15,16] The 'non-lifting' sign has been reported in the past as a viable assessment tool for invasion depth of colonic lesions prior to resection.[17] Kobayashi *et al.*, however, were unable to reliably predict deep cancer invasion with the 'non-lifting' sign when compared with magnifying endoscopic diagnosis.[18]

Endoscopic submucosal dissection

ESD was developed in Japan to enable larger lesions of the GIT to be removed en bloc.[4] Figure 3 illustrates important steps in this procedure using gastric ESD as an example. The borders of the

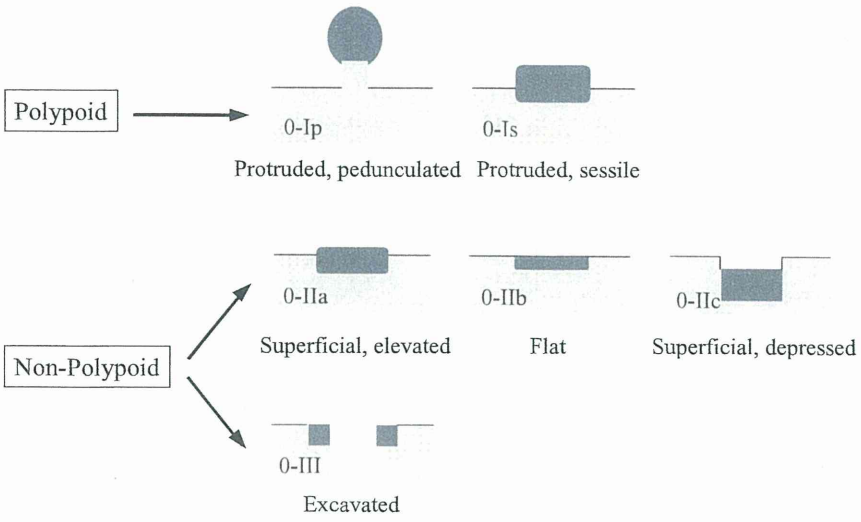

Figure 1 Classification of superficial neoplastic lesions of gastrointestinal tract.

lesion are initially highlighted using indigo carmine and marks placed 5 mm from the lateral edge using a needle knife (KD-1L-1; Olympus, Tokyo, Japan/Center Valley, PA, USA/Hamberg, Germany). Submucosal injection is used to lift the lesion from the muscularis propria, and is followed by one or more needle knife pre-cuts into the submucosa. Circumferential incision into the submucosa around the lesion using a specialized electrocautery knife is performed 5 mm outside the initial markings. Further submucosal injection takes place before submucosal dissection begins. A plastic cap can be attached to the endoscope at any time during the procedure to lift the lesion and to define tissue planes if required. Any procedural bleeding is controlled by careful hemostasis with coagulation current using the electrocautery knife, hot biopsy forceps or electrosurgical hemostatic forceps. The resected specimen is flattened and mounted on a cork or polystyrene block and oriented to facilitate histological examination.

The choice of electrocautery knife for ESD is dependent on position of the lesion and operator choice. At the National Cancer Center Hospital in Tokyo, the IT-2 knife (Olympus) with a three-pointed star-shaped blade, is used most commonly for gastric ESD, whereas the bipolar B knife (Xemex, Tokyo, Japan) is preferred for colonic ESD. The colonic mucosa is very thin and the narrow lumen makes endoscope manipulation more difficult, thereby increasing the risk of perforation.

The B knife was developed specifically to reduce perforation rate during colonic ESD by minimizing the application of high-frequency current to the muscle layer through current direction back from the knife towards the sheath tip.[19] This knife is currently only available in Japan. Colonic ESD can be slow, and once the submucosal plane has been established, the IT knife (KD-610L; Olympus) is frequently used to speed up the procedure. Carbon dioxide insufflation has proved safe and effective during lengthy colonic ESD, resulting in less abdominal pain and requirement of lower sedation doses compared to air insufflation.[20] Submucosal injection plays a vital role in endoscopic resection, enabling safe exclusion of the muscularis propria from the cutting zone. Glycerol and hyaluronic acid are used commonly in Japan to achieve a long-lasting submucosal cushion, thereby facilitating safe resection. They are often combined with epinephrine and indigo carmine to reduce bleeding and clearly define tissue planes.[21]

EMR or ESD?

The choice of endoscopic resection technique depends on a number of factors. One of the main limitations of EMR is the inability to remove lesions larger than 2 cm en bloc. Piecemeal removal is possible, but studies have shown that the risk of local recurrence is higher than one-piece resection.[22,23] It has, however, been shown that safe and complete resection can be achieved after piecemeal EMR in the colon if vigilant surveillance and careful removal of recurrent lesions is carried out.[24] The rate of perforation is higher after ESD compared to EMR, but ESD facilitates removal of much larger lesions en bloc, whilst being less invasive than major surgery. Most perforations can be treated endoscopically using clips without the need for surgical intervention. Hemorrhage is generally higher for ESD, although some studies do not include data on minor bleeding, so comparisons are difficult. Data from studies comparing complication rates of EMR and ESD are shown in Table 2,[22,25–29] and indications for endoscopic resection of GIT lesions are displayed in Table 3.[31–33]

Early esophageal neoplasms

Esophageal cancer is only the eighth most common malignancy worldwide, but survival is very poor with a 16% 5-year survival rate in the USA and 10% in the UK. High-risk areas include China, South and East Africa, South Central Asia and Japan (only in men) and squamous cell carcinoma is the most prevalent type.[26] In the Western world, adenocarcinoma arising from Barrett's mucosa has replaced squamous cell cancer as the predominant tumor type. Detection and cure of esophageal neoplasms at an early stage is therefore essential in high-risk groups. Esophagectomy used to be the only available management strategy for esophageal cancer, but significant complication rates make other treatment modalities

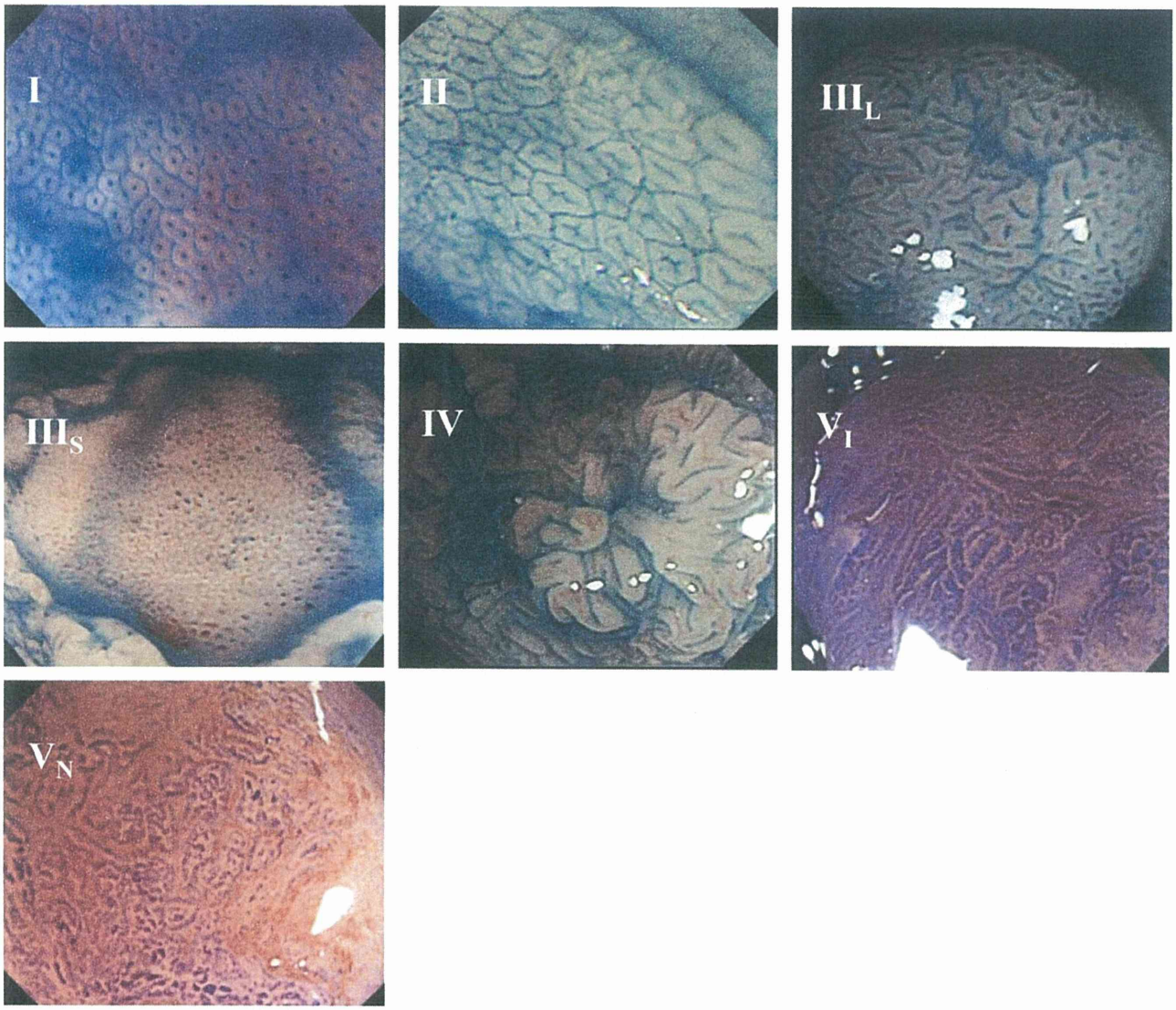

Figure 2 Pit pattern classification of colorectal neoplasia. I, roundish pits; II, stellar or papillary pits; III$_L$, large roundish or tubulart pits (larger than type I pits); III$_S$, small roundish or tubulart pits (smaller than type I pits); IV, branch-like or gyrus-like pits; V$_I$, irregular type; V$_N$, non structural type.

more attractive, especially for early-stage disease.[27] Photodynamic therapy for high-grade intraepithelial neoplasia and early adenocarcinoma arising from Barrett's mucosa has proven to be safe and effective and is the treatment of choice for non-localized lesions.[28] Endoscopic therapy is used increasingly to cure early esophageal lesions worldwide; ESD is now standard treatment in Japan.[30] The incidence of adenocarcinoma of the esophagus has risen in recent years in the West as a consequence of increased gastro-esophageal reflux disease and subsequent Barrett's mucosa.[34] This has led to the adoption of endoscopic surveillance programs in many centers, but the actual benefit of surveillance in terms of cost and survival is still uncertain; it remains a controversial issue.[35]

The prognosis of established early esophageal adenocarcinoma is dependent on depth of invasion, which in turn determines the risk of lymph node metastasis. Nigro *et al.* showed that lesions confined to the mucosa had a 7% risk of lymphatic metastasis, whereas 80% of those invading into muscularis propria had spread to lymph nodes.[36] This study, as with other early studies of esophageal adenocarcinoma, was small and involved only 37 patients. Since then, larger studies have shown that tumors of the mucosa and the superficial 500 μm (SM1) of the submucosa provide negligible risk of lymph node metastasis. Westerterp and colleagues demonstrated lymph node metastasis in only 1/79 mucosal and SM1 adenocarcinomas, while Stein *et al.* reported no lymphatic spread in 53 similar cases.[37,38]

Early squamous cell carcinoma of the esophagus has been much more extensively studied, in part, due to the routine use of endoscopic ablation in Japan. Patients with early squamous cell carcinoma, no lymph node metastasis on computed tomography scan and no evidence of a second primary cancer have been shown to

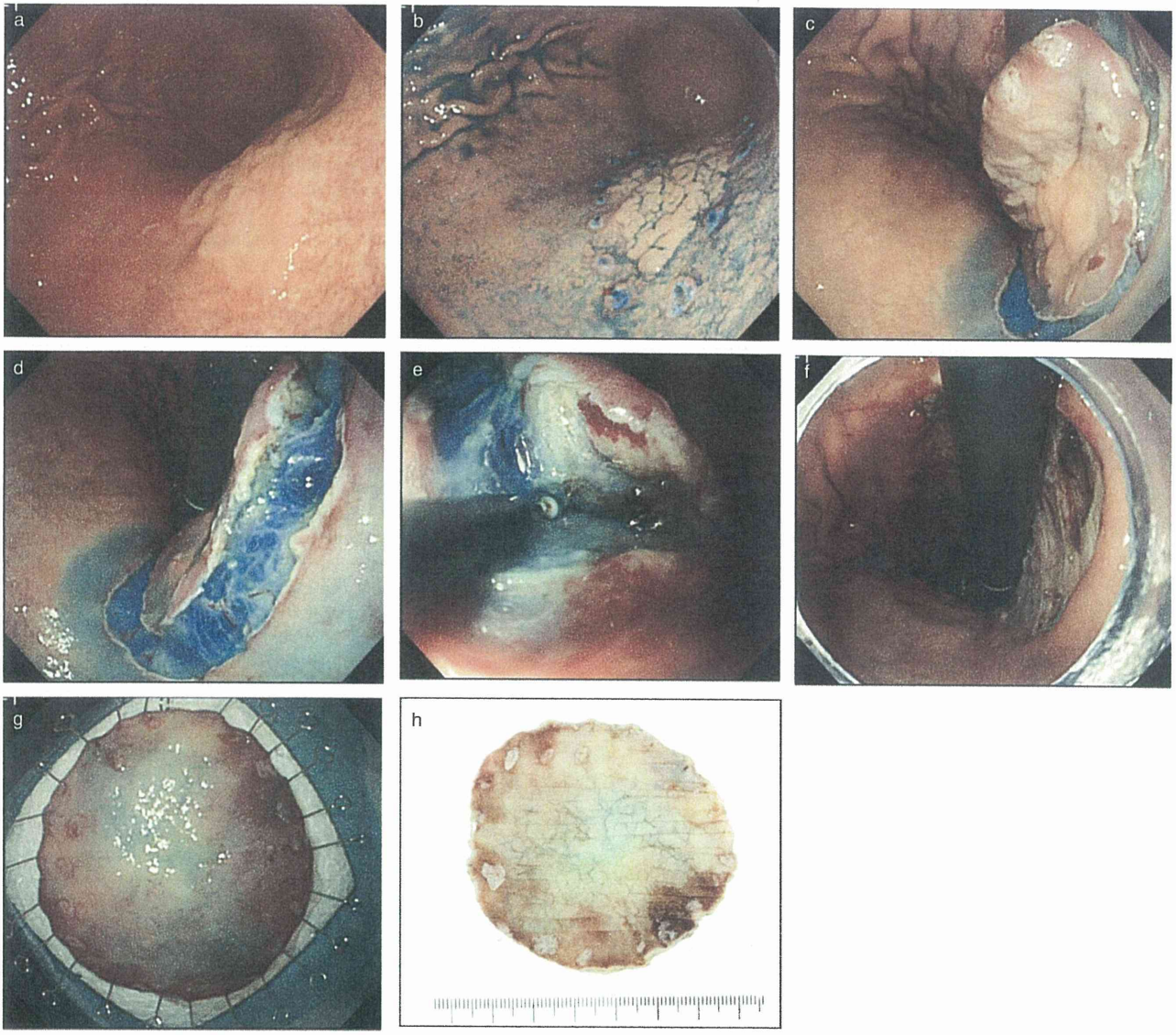

Figure 3 Gastric endoscopic submucosal dissection technique. a, conventional view; b, chromoendoscopy and marking of lesion margins; c, circumferential incision; d, submucosal injection; e, submucosal dissection; f, gastric wall defect after resection; g, mounted lesion; h, pathological specimen.

have a similar survival rate as the general population following endoscopic therapy.[39] Mucosal and superficial submucosal squamous cell cancers have an excellent prognosis due to low risk of lymph node metastasis. Tajima *et al.* reported on 240 patients after surgical resection of squamous cell cancer and showed that none of the mucosal or SM1 tumors had metastasized to lymph nodes.[40] Stein and colleagues found a higher rate of lymphatic spread of 7.7%, but this was based on just 26 mucosal/SM1 patients.[38]

Minimally invasive squamous cell esophageal cancer can be cured endoscopically; early detection is therefore crucial. In this context, the use of high-resolution video-endoscopy with adjuncts, such as chromoendoscopy and narrow-band imaging, are useful technologies. Although the cure rate is high, surveillance after endoscopic therapy is necessary due a significant risk of local recurrence.[41] Data on endoscopic treatment of early esophageal adenocarcinoma are limited; therefore, evidence-based treatment recommendations are not yet available.

Early gastric cancer

Although the worldwide incidence of gastric cancer is slowly declining, it is still the fourth most common malignancy and the second most frequent cause of cancer death. Five-year survival is relatively good in Japan at 40–60%, compared to about 20% in Western countries. Over 50% of gastric cancers diagnosed in Japan are early lesions, and this may explain the overall better survival.[30,42]

Table 2 Published reports comparing complication rates of EMR and ESD

Author	Site	EMR					ESD			
		Number of lesions	Removed en bloc %	Bleeding %	Perforation %	Recurrence %	Number of lesions	Removed en bloc %	Bleeding %	Perforation %	Recurrence %
Saito[25]	Colon	228	84.0	3.1 (minor)	1.3	14.5	145	33.0	1.4 (minor)	6.2	2.1
Oda[26]	Gastric	411	56.0	0.2 (transfused)	1.2	6.6	303	92.7	0.0 (major)	3.6	2.0
Shimura[27]	Gastric	48	31.3	12.5	0.0	35.4	59	88.1	13.6	3.4	1.7
Watanabe[28]	Gastric	125	63.6 (> 10 mm)	1.8	3.2	5.6	120	91.3 (> 10 mm)	0.0 (major)	4.2	2.5
Ishihara[22]	Oesophagus	52	10.9 (out of 46 lesions)	0.0	0.0	22.0	33	90.6 (out of 32 lesions)	0.0	0.0	3.1
Cao*[29]	All	2987	57.7	5.8	1.0	5.2	1804	94.6	9.2	4.5	0.3

*Meta-analysis of 15 studies of EMR and ESD.
EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection.

Table 3 Indications for endoscopic resection of early gastrointestinal neoplasm

Lesion Position	Indication
Esophagus	Well- or moderately differentiated m1 or m2 SCC or AC < 20 mm, without venous or lymphatic involvement; less than a third of the circumference involved (to avoid risk of post-resection stricture formation) ER for Barrett's esophagus is still being studied
Stomach	Standard criteria: Well- or moderately differentiated AC and/or papillary carcinoma; cancer confined to mucosa IIa < 20 mm; cancer confined to the mucosa IIb, IIc < 10 mm, without evidence of lymphatic involvement Expanded criteria: Mucosal well-/moderately differentiated AC, irrespective of size, without ulceration; ≤ 30 mm with ulceration; if minute submucosal invasion is found then the size of the lesion is ≤ 30 mm, without venous or lymphatic involvement; mucosal undifferentiated AC ≤ 20 mm, without lymphovascular involvement or ulceration
Colorectum	Laterally spreading tumors High-grade dysplasia The indication for resection of mucosal or AC invading slightly into the SM is still being studied. ESD has been reported for resection of: - well- or moderately differentiated AC; cancer confined to the mucosa: IIa < 20 mm, IIb, IIc < 10 mm, without evidence of venous or lymphatic involvement - superficially invading the SM (< 500 μm from the muscularis mucosa); without venous or lymphatic involvement

AC, adenocarcinoma; ER, endoscopic resection; IIa, slightly elevated superficial tumor; IIb, flat superficial tumor; IIc, slightly depressed superficial tumor; m, mucosal; SCC, squamous cell carcinoma; SM, submucosa.

Gastrectomy with regional lymph node dissection was formerly the only available curative treatment for early gastric cancer. In 1996, the National Cancer Center Hospital (Tokyo) published their data describing over 1000 patients with intramucosal early gastric cancer who underwent surgical resection. This study provided some of the first evidence to suggest that radical surgery with lymphadenectomy was unnecessary for certain gastric cancers due to the extremely low incidence of spread to lymph nodes.[43] Curative endoscopic resection of early intramucosal gastric cancers has since become a valid therapeutic option, but until recently was restricted to small lesions less than 2 cm in size with no evidence of surface ulceration. Although other publications suggested that certain lesions invading into the submucosa also carried a low risk of progression, these studies were limited by small patient cohorts.[44–46]

Gotoda and colleagues published extensive data in 2000 that provided a more robust evidence base for the expansion of endoscopic resection criteria. They examined the presence of lymph node metastasis in 5265 patients who underwent gastrectomy with

Table 4 Early gastric cancer with no risk of lymph node metastasis

Tumor characteristics	Number of cases	95% confidence interval
Intramucosal Well-/moderately differentiated No lymphovascular invasion Irrespective of ulcer findings Tumor less than 3 cm in size	1230	0–0.3%
Intramucosal Well-/moderately differentiated No lymphovascular invasion No ulcer Irrespective of tumor size	929	0–0.4%
Intramucosal Poorly differentiated No lymphovascular invasion No ulcer Tumor less than 2 cm in size	141	0–2.6%
Minute submucosal penetration (SM1) Well-/moderately differentiated No lymphovascular invasion Tumor less than 3 cm in size	145	0–2.5%

lymph node dissection for early gastric cancer from two centers. Only 2.2% (65/3016) of intramucosal cancers were associated with regional lymph node metastasis. Of these lesions, lymph node metastasis was associated with poor differentiation, signet ring histology, lymphovascular invasion and lesions greater than 3 cm with surface ulceration. Specifically, intramucosal lesions without ulceration did not demonstrate lymph node metastasis irrespective of size. Gotoda *et al.* also showed that 18% of cancers with deeper invasion into the submucosal layer were associated with lymph node metastasis. However, lesions less than 3 cm in size with submucosal invasion less than 500 μm, well- or moderately differentiated histology and no evidence of lymphovascular involvement demonstrated no lymph node metastasis. Table 4 summarizes data from this study, showing the lesion types that displayed no evidence of lymph node metastasis.[47]

In 2004, the Japanese Gastric Cancer Association issued expanded criteria for the treatment of early gastric cancer based on this study.[48] Hirasawa and colleagues have since explored undifferentiated early gastric cancers in a similar population of 3843 Japanese patients. Undifferentiated lesions confined to the mucosa, less than 20 mm in diameter, without lymphovascular involvement or ulcer presence showed no lymph node metastasis. They proposed that endoscopic resection should also be considered for these lesions, thus further expanding the criteria for endoscopic management of gastric cancer.[49] Other studies of the risk of lymph node metastasis in poorly differentiated lesions have produced similar results, although they involved smaller patient numbers.[50–53]

Early lesions of the colorectum

Worldwide, colorectal cancer incidence ranks fourth in frequency in men and third in women. Despite a relatively good prognosis, rates of colorectal cancer are rising rapidly in countries such as Japan where the risk was previously low.[30] Important work done in the 1980s demonstrated that specific genetic alterations occurred in adenomas and carcinomas, suggesting that colorectal cancer development involved mutational activation of an oncogene and loss of tumor suppressor genes. This evidence led to the development of a genetic model for colorectal tumorigenesis, and to the suggestion that most carcinomas arise from benign adenomatous precursors.[54] In contrast, a proportion of colorectal cancers appear to arise from normal mucosa and do not follow the adenoma–carcinoma sequence. These de novo carcinomas tend to be small, depressed-type lesions and may have an increased invasive tendency.[55,56] Originally, depressed-type colorectal neoplasms were thought to exist only in Eastern populations, but their existence and invasive potential in the West have since been proven by groups from the UK and the USA.[57,58]

Intramucosal colorectal lesions have no risk of lymph node metastasis and can be cured by endoscopic resection.[59] Once the submucosa has been breached, the incidence of lymphatic spread rises to around 10%, but this is dependent on depth of invasion. Lesions with submucosal invasion less than 1000 μm have a low risk of lymph node metastasis and are good candidates for endoscopic therapy.[8] Kitajima *et al.* reported an overall incidence of lymph node metastasis in 865 submucosal invasive colorectal cancers of 10%. Poor differentiation, lymphatic invasion and venous invasion were significant risk factors for metastasis. They showed that pedunculated lesions with submucosal invasion less than 3000 μm and no evidence of lymphatic invasion displayed no evidence of lymph node metastasis. All sessile cancers with lymph node metastasis had invaded the submucosal layer by more than 1000 μm.[60]

Egashira and colleagues demonstrated a similar rate of lymph node metastasis of 9%, and identified submucosal invasion greater than 2000 μm as an independent risk factor. Their study was smaller, involving only 140 cancers, and cases were not subdivided into pedunculated and non-pedunculated.[61] With regard to pedunculated lesions, Haggitt identified stalk invasion as an important factor in predicting clinical outcome. Tumors extending beyond the stalk into the submucosa, but not reaching the muscularis propria (Haggitt level 4) were associated with poor outcome. This study was limited by moderate patient numbers ($n = 129$), a factor that should be taken into consideration in practical application.[62]

Special consideration should be given to LST of the colorectum. Uraoka *et al.* studied 511 colorectal LST and reported significant differences in depth of invasion between granular and non-granular lesions. LST-NG had a higher potential for malignancy compared to LST-G with frequency of submucosal invasion of 14% versus 7%. Whilst piecemeal resection was considered acceptable for LST-G type, en bloc resection was suggested as the best therapeutic approach for LST-NG type.[63]

The therapeutic approach to lesions of the colorectum is very much dependent on the accuracy of endoscopic diagnosis. Matsuda *et al.* recently carried out a large prospective study of 4215 lesions in 3029 consecutive patients between 1998 and 2005 at the National Cancer Center Hospital, Tokyo. All lesions were detected via the conventional endoscopic view and assessed using magnifying chromoendoscopy for evidence of invasive features according to pit pattern evaluation. They showed that 99.4% of lesions diagnosed endoscopically as 'non-invasive' were adenoma, high-grade dysplasia or adenocarcinoma with submucosal inva-

sion less than 1000 μm. Among lesions diagnosed with 'invasive' pattern, 87% were cancers with submucosal invasion deeper than 1000 μm. This is the first large-scale prospective study to validate the use of magnifying chromoendoscopy as a highly effective method in the prediction of invasion depth of colorectal neoplasms.[64]

Application of ESD in countries other than Japan

ESD is an appealing prospect for treatment of certain lesions of the GIT in the West, such as superficial carcinomas of the esophagus, high-grade dysplasia in Barrett's mucosa and large flat non-granular tumors of the colorectum. There are, however, a number of limitations to widespread use of ESD outside Japan.

Firstly, selection of appropriate lesions for ESD is crucial, and the diagnostic skills to facilitate this, including determination of lesion characteristics, are of great importance. Whilst optical magnification is used in Japan allowing up to 150× image enlargement, digital magnification is more commonly available in the West, providing views with less resolution. Chromoendoscopy is also a routine modality in GI lesion assessment in Japan, but rarely used outside specialist units in the West. Consequently, the ability to analyze lesion surface vascularity and pit pattern in detail and therefore lesion selection for ESD is limited. These assessment techniques are considered crucial in Japan to enable correct diagnosis of lesion type, depth and amenability to endoscopic treatment. Successful application of ESD in the West will certainly require a change in diagnostic technique and close reference to Japanese literature in selection of lesions for resection.

Secondly, ESD is a technically demanding procedure requiring a high level of endoscopic skill and intensive training. The learning curve is steep and involves animal model work in the first instance. Unlike Western countries, facilities for animal model training are readily available in Japan and materials such as the isolated pig stomach can be supplied at low cost. Initial ESD training in patients entails removal of small gastric lesions in the antrum under close expert supervision, and generally, at least 30 procedures are required to reach basic proficiency.[65] The likelihood of major complications for ESD of lesions in this position is low, even for endoscopists with less experience. The large lumen allows easy maneuvering and the risk of perforation is reduced due to the relative thickness of the gastric wall. Bleeding is common during ESD and safe hemostasis is one of the most important aspects of the procedure. However, acquiring skills for basic ESD maneuvers from the beginning of training is vital and the lower vascularity of the antral wall allows this due to reduced bleeding risk.

The incidence of early gastric cancer in the West is very low compared to Japan, so opportunities to perform training gastric ESD are few. Alternatively, rectal ESD is a comparatively safe procedure and may provide a useful training medium for Western endoscopists. Certain skills can be acquired during animal model training, but collaboration with expert Japanese endoscopists and training periods in their units may be helpful in order to reach the necessary skill level. Suzuki *et al.* recently reported their early experience of ESD as a modality to remove large sessile colorectal polyps at the Wolfson Endoscopy Unit, UK. Although only nine patients were enrolled in the study, en bloc resection was achieved in seven patients, with only one major complication of post-procedural bleeding requiring blood transfusion. Importantly, the ESD technique was acquired under the supervision of an expert.[66] Dinis-Ribeiro *et al.* published a case series of 19 gastric ESD from Portugal reporting only one hemorrhage and no perforations.[67]

Thirdly, ESD is considered more economical and less invasive compared to surgery. Nevertheless, mean hospital inpatient stay for ESD is 5 days and this could prove logistically difficult in the West where bed availability is often limited. In addition, it could be argued that laparoscopic surgery and transanal resection for colorectal lesions in the West are more established techniques, requiring a shorter or similar length inpatient stay; thus, they may be a more viable option.

Finally, management of GIT lesions using ESD in the West will undoubtedly require a multidisciplinary team. During each procedure, several endoscopists are often present in Japan, either to assist or monitor patients, and propofol is frequently given without anesthetists being present. However, although conscious sedation is standard practice in the UK, anesthetists would be required to administer propofol.[68] Practice varies worldwide, with anesthetist- or nurse-administered propofol common in Australia and the USA.[69] Endoscopy nurse training would also need to be addressed in the West, as ESD requires highly trained assistants as well as skilled technicians. Introduction of ESD into Western countries could be of huge benefit to the management of GIT lesions. However, close and supportive working relationships between endoscopists, pathologists and surgeons would be vital for it to succeed as a viable therapeutic option.

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Disclosure statement

The authors report no conflicts of interest in this work.

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