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

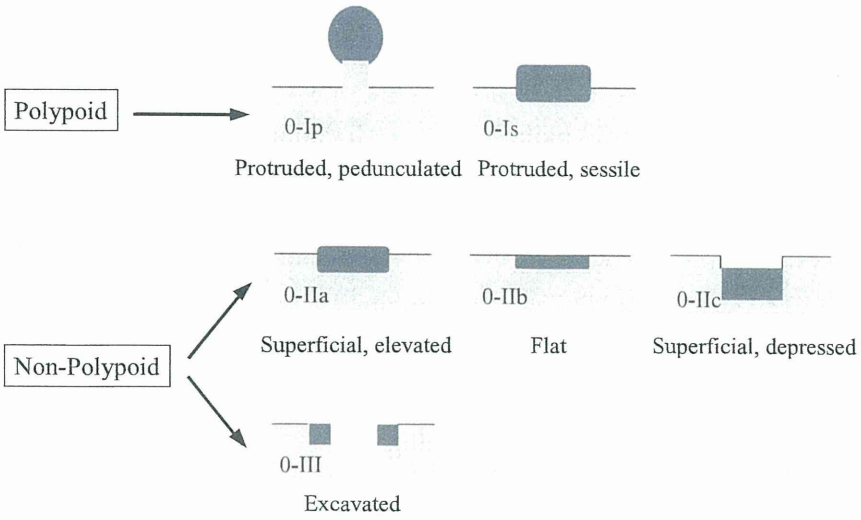

Figure 1 Classification of superficial neoplastic lesions of gastrointestinal tract.

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

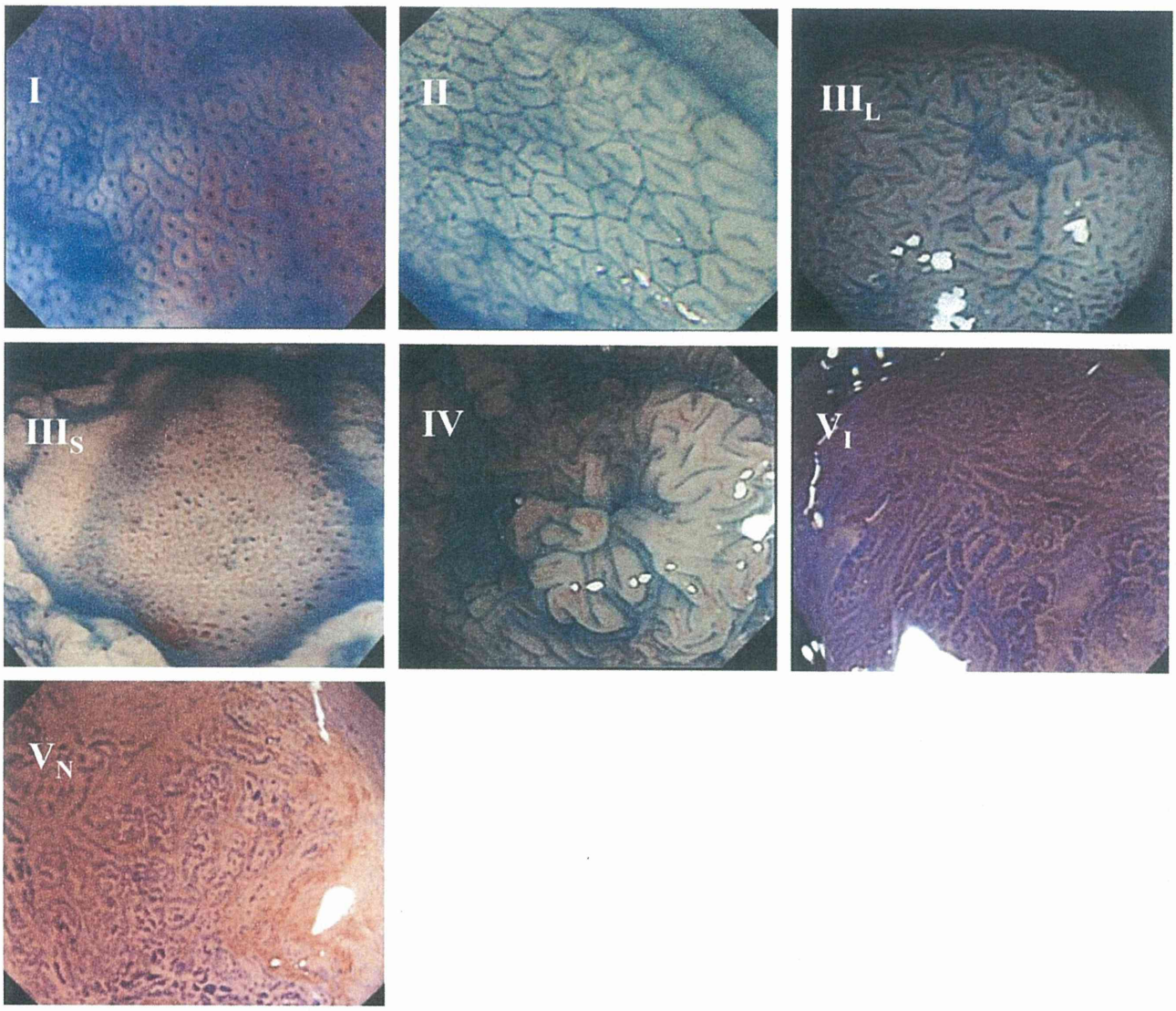

Figure 2 Pit pattern classification of colorectal neoplasia. I, roundish pits; II, stellar or papillary pits; III$_L$, large roundish or tubulart pits (larger than type I pits); III$_S$, small roundish or tubulart pits (smaller than type I pits); IV, branch-like or gyrus-like pits; V$_I$, irregular type;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

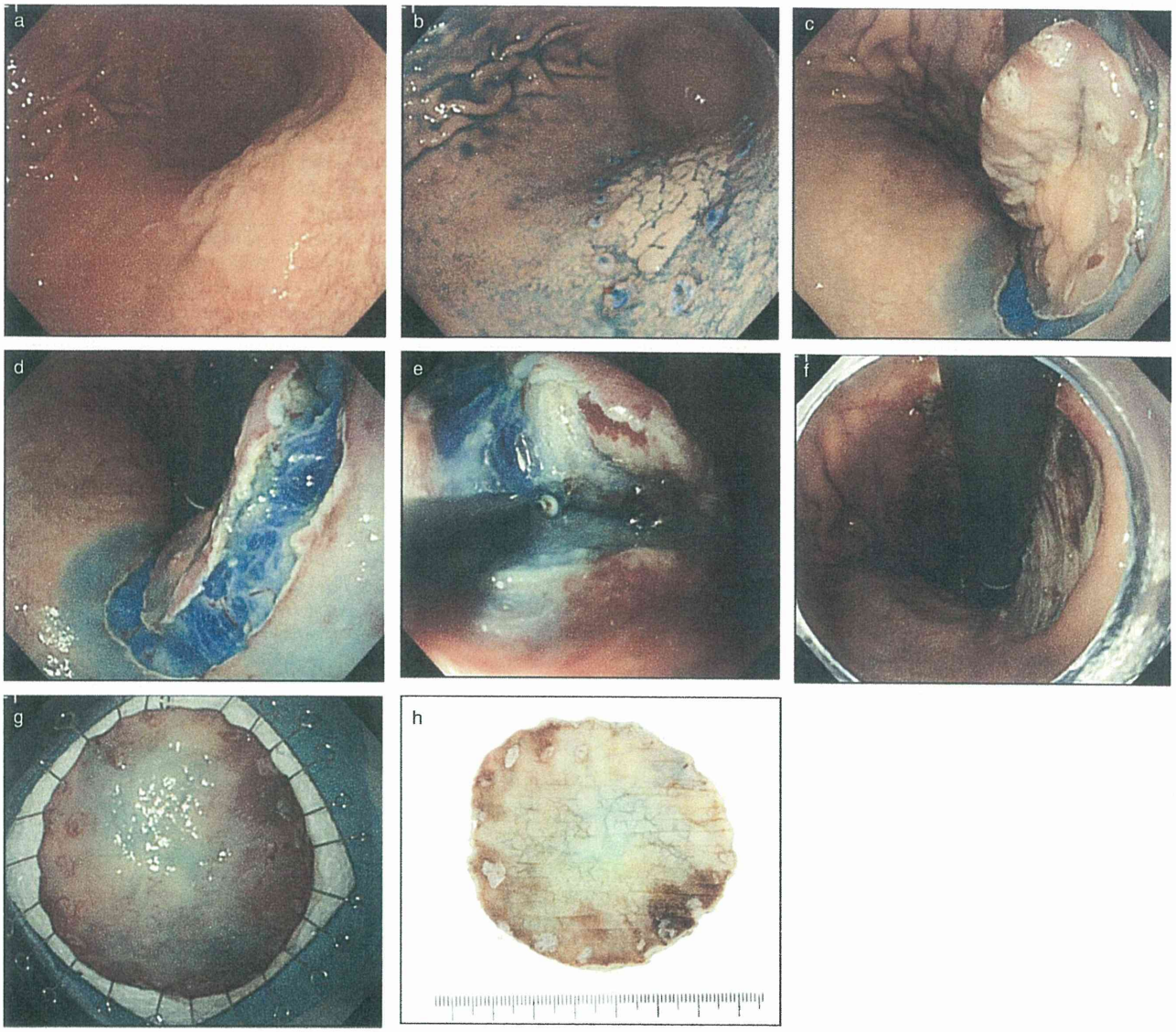

Figure 3 Gastric endoscopic submucosal dissection technique. a, conventional view; b, chromoendoscopy and marking of lesion margins; c, circumferential incision; d, submucosal injection; e, submucosal dissection; f, gastric wall defect after resection; g, mounted lesion; h, pathological specimen.

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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ORIGINAL ARTICLE—ALIMENTARY TRACT

Safe and effective sedation in endoscopic submucosal dissection for early gastric cancer: a randomized comparison between propofol continuous infusion and intermittent midazolam injection

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Abstract
Purpose Endoscopic submucosal dissection (ESD) for early gastric cancer (EGC) generally takes longer to perform than conventional endoscopy and usually requires moderate/deep sedation with close surveillance for patient safety. The aim of this study was to compare the safety profiles and recovery scores propofol continuous infusion and intermittent midazolam (MDZ) injection as sedation for ESD.
Methods Sixty EGC patients scheduled for ESDs between August and November 2008 were included in this prospective study and randomly divided into a propofol (P-group, 28 patients) and an MDZ (M-group, 32 patients) group using an odd–even system. The P-group received a 0.8 mg/kg induction dose and a 3 mg/kg/h maintenance dose of 1% propofol using an infusion pump. All patients received 15 mg pentazocine at the start of the ESD and at 60-min intervals thereafter. We recorded and analyzed blood pressure, oxygen saturation and heart rate during and following the procedure and evaluated post-anesthetic recovery scores (PARS) and subsequent alertness scores.
Results The propofol maintenance and total dose amounts were (mean ± standard deviation) 3.7 ± 0.6 mg/kg/h and 395 ± 202 mg, respectively. The mean total dose of MDZ was 10.3 ± 4.5 mg. There were no cases of de-saturation <90% or hypotension <80 mmHg in either group. Alertness scores 15 and 60 min after the procedures were significantly higher in the P-group (4.9/4.9) than in the M-group (4.6/4.5; $p < 0.05$). The mean PARS 15 and 30 min after the ESDs were significantly higher in the P-group (9.6/9.9) than in the M-group (8.6/9.2; $p < 0.01$).
Conclusion Based on our results, the ESDs for EGC performed under sedation using propofol continuous infusion were as safe as those performed using intermittent MDZ injection. Propofol-treated patients had a quicker recovery profile than those treated with MDZ. We therefore recommend the use of continuous propofol sedation for ESD, but sedation guidelines for the use of propofol are necessary.

Keywords Endoscopic submucosal dissection · Midazolam · Propofol · Sedation

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Introduction

Endoscopic submucosal dissection (ESD) reduces the risk of local recurrence following treatment for early gastric cancer (EGC) even when large and/or ulcerated lesions are involved because ESD has a higher en-bloc resection rate with a more accurate histological assessment. ESD generally takes longer than conventional endoscopic mucosal resection (EMR), and multiple doses of medications are usually required to achieve an adequate level of sedation and analgesia [1]. However, the most effective and safest sedation agent for ESD and the method by which to deliver this to the patient have not yet been clearly established.

A lengthy and potentially uncomfortable endoscopic procedure like ESD usually requires at least moderate (conscious) sedation using a method that maintains a stable sedation level while also avoiding related complications. In addition, the guidelines from the American Society of Anesthesiology (ASA) for sedation by non-anesthesiologists recommends an accurate titration of sedation at a conscious level for patients undergoing upper endoscopy [2]. Sedation through the intermittent intravenous administration of benzodiazepine combined with an opioid often results in variable outcomes due to difficulty in maintaining stable levels of sedation [3]. The titration of such medications requires meticulous attention in adjusting the dose to be appropriate for the patient based on age, gender and medical background. Consequently, over-sedation can frequently occur in such cases [4].

Propofol is a short-acting sedative with a rapid recovery profile, and its use is associated with a number of additional advantages, including the relative ease to safely maintain a proper sedation level and a good amnesic effect. These advantages have resulted in an increased use of propofol worldwide for standard endoscopy procedures [5–7]. A study comparing patient satisfaction in terms of sedation with propofol, benzodiazepine and other agents found that patients were more satisfied with propofol [8]. A number of other studies comparing propofol with conventional sedation for gastroscopy and colonoscopy have demonstrated the benefit of propofol over such conventional sedation [9–15]. A few reports have focused on the administration of propofol for lengthy procedures, such as endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasonography (EUS) [16–18] but, to the best of our knowledge, there have been no studies that have compared propofol with the benzodiazepine midazolam (MDZ) as sedation for gastric ESD. The aim of this study was, therefore, to compare the safety profiles and recovery scores between propofol and midazolam (MDZ) as sedation for gastric ESD.

Methods

Patients

At total of 60 EGC patients scheduled for ESD at the National Cancer Center Hospital (NCCH) in Tokyo from August to November 2008 were included in this prospective study. Patients were excluded if they were <18 years of age and/or pregnant, had a history of sulfite, egg, soybean or propofol allergy or did not provide informed consent. Patients with an ASA physical status class of >2, severe liver disorders (liver transaminase >100 IU/l; liver cirrhosis, due to high alcohol intake), severe renal failure (serum creatinine level >2 mg/dl), severe heart disease (New York Heart Association Class III or IV), mental incompetence, systolic blood pressure (SBP) <80 mmHg and baseline oxygen saturation measured by pulse oximetry to be <90% in room air or <95% with oxygen at 2 l/min administered by nasal cannula due to smoking were also excluded. The participating patients were then divided randomly using an odd–even system based on randomly assigned hospital registration numbers into a propofol group (P-group, n = 28) and an MDZ group (M-group, n = 32). Informed consent was obtained as per institutional protocol from all patients who underwent endoscopic treatment. This study was performed in accordance with the 1989 revised Helsinki Declaration.

Personnel

All medications were administered by physicians from the endoscopy division who did not participate in the actual endoscopic procedures. At least one physician with advanced training in basic and cardiac life support was present during every ESD. An anesthesiologist was also on standby in case of an emergency, and resuscitation equipment was always present in the endoscopic room.

Medication

Local pharyngeal anesthesia was performed using an 8% topical lidocaine spray prior to intravenous administration of the sedation drugs. Patients in the P-group received a slow initial intravenous bolus of 0.8 mg/kg of 1% propofol emulsion (10 mg/ml) (Maruishi Pharmaceutical, Osaka, Japan). Additional intravenous boluses of 0.5 mg/kg of 1% propofol emulsion were administered until the patient fell asleep, as determined by a Ramsay 5–6 sedation score. After each bolus infusion, a waiting period of usually 30–60 s was observed to assess the complete effect of the drug before making a decision on the next bolus. An automatic infusion pump (Terufusion syringe pump TE-332S; Terumo Corp, Tokyo, Japan) was used to maintain a continuous infusion of 3 mg/kg/h in order to maintain the same level of sedation. The objective was to maintain a patient sedation level between moderate (patient responds properly to verbal commands either alone or accompanied by light tactile stimulation) and deep (patient cannot be easily aroused, but may respond properly to repeated or painful stimulation) [19]. When a particular patient's body mass index (BMI) was >25, sedation doses were calculated based on body weight for a BMI of 25. For elderly patients >70 years of age, the initial bolus was reduced to 0.5 mg/kg. When a patient seemed to be in discomfort or exhibited restlessness following verbal stimulation, an

additional 10 mg of propofol was given as a bolus injection and the infusion rate was increased by 1 mg/kg/h. Conversely, if an adverse event occurred, such as hypotension with SBP <80 mmHg or oxygen de-saturation <90%, the maintenance dose was reduced by 1 mg/kg/h. Propofol infusion was continued until removal of the endoscope.

In the M-group, an initial bolus of 3 mg of MDZ (Astellas Pharma, Tokyo, Japan) for patients with a body weight <50 kg and 4 mg for patients weighing ≥50 kg were administered through an intravenous catheter. Incremental doses (2 mg) were given if the patient showed signs of discomfort, restlessness or agitation or if he/she responded to verbal commands. A reversal agent of MDZ (flumazenil) was administered, if needed, according to NCCH conscious-sedation guidelines.

All patients received 15 mg of pentazocine at the start of the ESD and at 60-min intervals thereafter during the procedures as an analgesic agent. The depth of sedation was monitored by a physician not directly involved in the procedure using a 4-point somnolence score (4, fully alert; 3, awake but lethargic; 2, spontaneous eye closure, but responsive to voice; 1, responds only to shaking or prodding). Endoscopic intubation commenced once the patient reached a sedation level of 2.

Monitoring

Patients received supplemental oxygen (2 l/min) by nasal cannula in the endoscopic room as their vital signs and oxygen saturation were continuously monitored and recorded every 5–10 min using standard three-lead electrocardiogram, pulse oximetry and automatic blood pressure equipment. Chest excursion and respiratory rates were monitored visually, and consciousness levels were assessed initially after the induction of sedation and then at 20-min intervals thereafter during the procedure using the Ramsay sedation score.

Management of adverse events

Adverse events were considered to be a decline in oxygen saturation to <90% and SBP <80 mmHg. If a patient developed oxygen de-saturation <90% for longer than 10 s, supplemental oxygen was used to immediately increase the oxygen flow until the saturation level was >95%. If supplemental oxygen did not improve the patient's oxygenation condition within 3 min, the ESD procedure and sedation were interrupted to secure the airway and administer a reversal agent as necessary. In cases of hypotension, we immediately increased the rate of the intravenous drip (for example, from 100 to 150 ml/h), decreased the propofol infusion rate by 1 mg/kg/h or administered 8 mg of ephedrine by bolus intravenous injection.

Recovery phase

Vital signs (blood pressure, oxygen saturation and heart rate) were recorded immediately upon conclusion of the ESD and then at 15, 30, 60 and 120 min post-ESD. Patients were discharged from the endoscopy room 15 min after the procedure, provided their vital signs were stable. All 15-, 30- and 60-min post-procedure, post-anesthetic recovery scores (PARS; modified Aldrete score [20, 21], where 0 = under anesthesia and 10 = fully awake) were determined by the same physician. All alertness scores (five questions involving name, age, date, day and a simple calculation) were determined at 15, 30 and 60 min after each procedure by the same physician.

Statistical analysis

Category outcomes were analyzed using the Fisher exact test or the chi-square test where appropriate. Continuous outcomes were analyzed with the independent sample *t* test for normally distributed data and the Wilcoxon rank sum test for nonparametric data.

Results

Sixty patients were enrolled in this prospective study, with 28 patients randomly assigned to the P-group and 32 to the M-group. Patient characteristics for both groups are shown in Table 1. An en-bloc resection was achieved in all 60 cases, and there were no statistically significant differences between the two groups in terms of age, gender, BMI, alcohol consumption and tobacco use, tumor size, procedure time and sedation time.

All sedation inductions went smoothly with no complications. The total amount of propofol and MDZ administered to P-group and M-group patients was 395 ± 202 mg (mean ± standard deviation, SD) and 10.3 ± 4.5 mg, respectively (Table 2). The mean maintenance dose of propofol was 3.7 ± 0.6 mg/kg/h. The mean total amount of pentazocine given to the P-group and M-group patients was 25.7 ± 9.9 and 21.8 ± 7.2 mg, respectively. There were no instances of uncontrolled agitation or movement that required a delay during any of the ESD procedures and none of the patients had to be restrained while under sedation.

There were no cases of de-saturation <90% during or after any ESD and no need for intubation or ventilation. Similarly, there were no cases of transient hypotension (SBP < 80 mmHg) in either group. As a result, there were

no statistical differences between the two groups in terms of the above-mentioned parameters.

The recovery phase results are shown in Table 3. The alertness scores recorded at 15 min post-ESD were 4.9 ± 0.4 for the P-group and 4.6 ± 0.8 for the M-group ($p < 0.05$); those recorded 60 min post-ESD were 4.9 ± 0.4 and 4.5 ± 1.2, respectively ($p < 0.05$). The P-group registered higher scores for each measurement. There was a significant difference between the two groups in terms of both the PARS recorded 15 min post-ESD (P-group/M-group 9.6 ± 0.8/8.6 ± 1.5; $p < 0.01$) and 30 min post-ESD (P-group/M-group: 9.9 ± 0.3/9.2 ± 1.2; $p < 0.01$). In addition, the alertness scores recorded 30 min post-ESD and PARS recorded 60 min post-ESD were the highest in the P-group (5.0 ± 0.2 and 10.0 ± 0, respectively), although these scores were not significantly different from those of the M-group (4.8 ± 0.6 and 9.7 ± 1.0, respectively).

Table 1 Patient characteristics

Patient characteristics	Propofol	Midazolam	*p* value
Number of cases	28	32	
Mean age, years (range)	68 (49–87)	70 (48–86)	NS
Gender, male/female	22/6	27/5	NS
Body mass index	22.9 ± 3.5	22.8 ± 3.4	NS
Habit, cases (*n*)			
Alcohol			
Daily drinker	10	12	NS
Social drinker	5	9	
No drinker	13	11	
Tobacco			
Smoker	6	2	NS
Quit smoking			
40 PY<	8	7	
<40 PY	6	9	
No smoker	8	14	
Mean tumor size (mm)	19.1 ± 11.0	17.3 ± 11.4	NS
Mean procedure time (min)	85.4 ± 50.8	89.6 ± 53.1	NS
Mean sedation time (min)	117.6 ± 58.0	119.7 ± 60.7	NS

Where appropriate, values are given as the mean ± standard deviation (SD)

NS Not significant, *PY* pack-year

Discussion

To the best of our knowledge, this study is the first randomized prospective trial to compare continuous infusion propofol sedation with intermittent MDZ injection sedation administered by a gastroenterologist during an ESD for EGC. The results indicate that propofol was both effective and safe as sedation for ESD, a finding that had previously been established for other lengthy endoscopic procedures, such as ERCP and EUS [22–25]. Our study demonstrates that the induction and maintenance of sedation can be safely performed using propofol, resulting in faster overall patient recovery. The Ramsay score of 6 that we obtained in most cases also indicates the doses of propofol which we calculated were appropriate for achieving moderate to deep patient sedation.

Propofol is a short-acting sedative, with a plasma half-life of only 1–4 min, and the onset of sedation after propofol injection occurs between 30 and 60 s. Consequently, it is difficult to maintain a stable level of sedation using an intermittent propofol injection because of the rapid recovery profile. On the other hand, continuous infusion of a long-acting sedative, such as the benzodiazepines, for longer endoscopic procedures is associated not only with difficulty in maintaining stable levels of sedation but also with an increased risk of complications. Therefore, intermittent benzodiazepine injection or continuous propofol injection has recently been used for lengthy endoscopic procedures, such as ESD, requiring at least moderate sedation. However, many reports have suggested that sedation using intermittent intravenous administration of benzodiazepines often results in variable outcomes due to this known difficulty in maintaining stable levels of sedation. We therefore compared propofol continuous infusion with intermittent MDZ injection as sedation for ESD.

Propofol has been increasingly used in recent years in many gastrointestinal endoscopic procedures [26–28]. Previous studies have demonstrated that, in comparison to conventional sedation, propofol sedation is associated with a lower risk of complications and serious adverse events during standard endoscopy [29]. However, published data on the safety of propofol for prolonged procedures, such as ESD, are limited. The most important finding of such

Table 2 Use of sedation agents during the endoscopic submucosal dissection procedures

Parameters of sedation agents	Propofol ($n = 28$)	Midazolam ($n = 32$)	*p* value
Mean total dose (mg)	395 ± 202	10.3 ± 4.5	
Maintenance rate, mg/kg/h (range)	3.7 ± 0.6 (3.0–5.0)		
Mean pentazocine dose (mg)	25.7 ± 9.9	21.8 ± 7.2	NS
Adverse events (*n*)			NS
Desaturation	0	0	
Hypotension	0	0	

Where appropriate, values are given as the mean ± SD

Table 3 Scores measured during the recovery phase

Scores[a]	Propofol	Midazolam	*p* value
Alertness score			
15	4.9 ± 0.4	4.6 ± 0.8	<0.05
30	5.0 ± 0.2	4.8 ± 0.6	NS
60	4.9 ± 0.4	4.5 ± 1.2	<0.05
Post-anesthetic recovery score (PARS)			
PARS 15	9.6 ± 0.8	8.6 ± 1.5	<0.01
PARS 30	9.9 ± 0.3	9.2 ± 1.2	<0.01
PARS 60	10.0 ± 0	9.7 ± 1.0	NS

Values are given as the mean ± SD

[a] 15, 30, 60 indicate the score measured at 15, 30 and 60 min following the end of the endoscopic submucosal dissection procedure

studies to date has been that recovery from the amnesic stage of propofol sedation is faster than that with standard sedatives, such as the benzodiazepines. As is the case with therapeutic ERCP, ESD generally takes considerably more time than conventional EMR, emphasizing a common need for a sedation agent and a delivery method that better meet the technical difficulty of the procedure.

In ESD, one of risk factors for sedation complications is that the gastroenterologist, as operator, not only performs the ESD but is also responsible for the sedation throughout the procedure. Furthermore, unstable sedation using the intermittent administration of sedative drugs causes interruptions and subsequent lengthening of the procedure. Therefore, the rapid onset and offset of sedation associated with the continuous infusion of propofol decreases the risk of sedation complications and reduces the burden on the gastroenterologist during the procedure.

Our goal was to maintain a moderate to deep sedation level. Quite often, the onset of sedation is deeper at first, with the sedative effect moderating over time. Given the narrow therapeutic window of propofol, fluctuations in the depth of sedation may occur, but none of the ESD procedures in this study had to be delayed or terminated, suggesting that our dose calculations and sedation procedures were effective in addition to being safe.

In our series of patients, the alertness score and PARS 15 were evaluated in the endoscopy room 15 min after the gastric ESD has been completed; the patients were then moved from the endoscopy room to the hospital ward. The PARS were higher in the P-group than in the M-group; this was particularly evident for the initial recovery measurement conducted 15 min post- ESD. In other words, propofol patients recovered from the sedation sooner than MDZ patients, thereby making it easier to evaluate immediate endoscopic- and sedation-related complications. An immediate recovery from sedation is an important feature of safe sedation management in ESD. The higher alertness and PAR scores in the propofol group recorded 15 min post-ESD suggest the possibility of safer management of ESD using propofol. These higher scores in association with no severe adverse events during and after the ESD also suggest that propofol continuous infusion is not only associated with improved safety but also with improved usefulness.

In both groups, alertness scores recorded 30 min post-ESD were higher than those recorded 60 min post- ESD. A possible explanation for result is that the residual invasive stress of the endoscopic procedure resulted in higher alertness scores 30 min after the procedure and that the relaxation associated with the return to the ward resulted in lower alertness scores at 60 min. In other words, patients may be in a relatively over-sedated state at 15 and 60 min post-ESD. However, the alertness scores of the propofol group were significantly higher than those of the MDZ group at 15 and 60 min post-ESD, suggesting that propofol provides safer sedation management in the post-ESD period, a time when patients are liable to be over-sedated.

Propofol is a short-acting agent, although episodes of prolonged apnea requiring intubations have occurred on rare occasions. With no reversal agent available for propofol, the presence of well-trained personnel in airway rescue is mandatory, although none of the patients in either group in this study required endotracheal intubation. The results of our study confirmed that the recovery profiles for the P-group were better than those of the M-group at every measurement point.

No severe adverse events, such as de-saturation or hypotension, resulted from the administration of propofol by a non-anesthesiologist physician in this study, but the American Society for Gastrointestinal Endoscopy (ASGE) has recommended that additional training be provided for the safe administration of propofol [30]. An ASA/ASGE taskforce further recommended that non-anesthesiologists using propofol for endoscopic procedures should be trained by anesthesiologists. Propofol has a narrow therapeutic window that can result in a rapid depression of consciousness and cardiovascular function, leading to a state of general anesthesia, and there is no reversal agent. Therefore, additional training and the use of a safe infusion protocol are recommended to ensure the safe administration of propofol. The presence of an anesthesiologist and special monitoring equipment, such as an electroencephalogram [31], capnometer and target-controlled infusion system, would entail added costs and an anesthesiologist may simply not be available in some situations. Accordingly, we utilized the services of a properly trained gastroenterologist to administer the sedation agents, with satisfactory results.

The equipment used in this study to monitor the physiological parameters included a pulse oximeter, continuous electrocardiogram and automatic blood pressure monitoring

device. A number of reports have indicated that a capnometer was available during the procedure for deep sedation [32]. Although a capnometer would more readily identify a patient experiencing an apneic episode, the calculated doses of propofol used in our study never caused de-saturation requiring mechanical ventilation; therefore, pulse oximetry may be sufficient for the detection of hypoxia. However, a capnometer is a non-invasive method for measuring respiratory activity, and we are currently investigating whether carbon dioxide monitoring is desirable [33].

In this study, we used pentazocine for both groups as an analgesic agent in smaller doses that is used for general anesthesia. Only a minimum dose of an analgesic agent is needed when deep sedation is used during ESD for EGC. In addition to pentazocine, the use of other analgesic agents, such as remifentanyl, ketamine and pethidine, may be feasible [34], so further research should be conducted to ascertain the optimal combination with propofol.

In conclusion, gastroenterologist-directed and supervised sedation using propofol continuous infusion for ESD in EGC is a safe procedure. Based on our results, propofol sedation is also effective for the evaluation of patients after ESD because it has a significantly better recovery profile than conventional intermittent MDZ injection. It is therefore essential that the most suitable sedation regimen for ESD using propofol be determined as quickly as possible.

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Clinical features and outcomes of delayed perforation after endoscopic submucosal dissection for early gastric cancer

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Perforation is a major complication of endoscopic submucosal dissection (ESD) for early gastric cancer (EGC). However, there have been no reports on delayed perforation after ESD for EGC. We aimed to elucidate the incidence and outcomes of delayed perforation after ESD. Clinical courses in 1159 consecutive patients with 1329 EGCs who underwent ESD were investigated. Delayed perforation occurred in six patients (0.45%). All these patients had complete en bloc resection without intraoperative perforation during ESD. Five of six perforations were located in the upper third of the stomach, while one lesion was found in the middle third. Symptoms of peritoneal irritation with rebound tenderness presented within 24 h after ESD in all cases. One patient did not require surgery because the symptoms were localized, and recovered with conservative antibiotic therapy by nasogastric tube placement. The remaining five patients required emergency surgery. There was no mortality in this case series.

Introduction

Endoscopic submucosal dissection (ESD) was developed in Japan and has been applied in many patients with early gastric cancer (EGC) with little risk of lymph node metastasis [1,2]. The reason why ESD is carried out instead of endoscopic mucosal resection (EMR) is that the en bloc resection rate is higher in ESD and it can remove lesions that are unresectable by conventional EMR [3], such as intramucosal differentiated type EGCs ≥2 cm without scarring or those <3 cm with scarring. Consequently, the indication for endoscopic resection has now been gradually extended to lesions that previously required surgery.

Perforation is a major complication in ESD for EGC. Incidences of perforation during ESD from 3.6% to 8.7% have been reported, while the perforation rate with the conventional EMR method is from 1.2% to 5.3% [4–6]. Minami et al. evaluated 2460 patients with EGC who underwent endoscopic resection, and encountered intraoperative perforations in 121 patients (4.9%). Emergency surgery was required in four of 121 patients (3.3%) with perforation, whereas the remaining 117 patients (96.7%) were treated by immediate endoscopic clipping and recovered without additional surgery. Therefore, perforation during gastric ESD is considered to be mostly manageable by endoscopic closure without surgery [5], However, we have encountered several cases of delayed perforation after ESD where surgery was required. An aim of the present study is to clarify the clinical features and outcomes of delayed perforation after ESD for EGC.

Case series

Patients and method

A total of 1159 consecutive patients with 1329 early gastric cancers underwent ESD at the Osaka Medical Center for Cancer and Cardiovascular Diseases between April 2003 and April 2009. The procedural details were recorded prospectively on a database. Patients with delayed perforation were identified from the database and their medical records were thoroughly investigated.

Before endoscopic treatment, written informed consent was obtained from all patients, after explanation of the possible risks and complications of the procedures, anticipated results, and alternative approaches, including surgery and non-treatment. The study protocol was approved by the institutional ethics committee.

ESD procedure

The ESD procedures were performed as previously reported [8,9]. An ICC-200 (Intelligent Cut and Coagulation; Erbe, Tübingen, Germany), PSD-60

(Power Supply Diathermy; Olympus, Tokyo, Japan), and VIO300D (Erbe) were used as the electrosurgical unit. After the tumor outlines had been delineated by chromoendoscopy, marker dots were circumferentially placed outside the tumor margin using a needle knife (KD-1L-1; Olympus). An insulated-tip knife (KD-610L or KD-611L; Olympus) was used for circumferential mucosal incision and submucosal dissection. For submucosal injection, 2% epinephrine (Bosmin; Daiichi Pharmaceuticals, Tokyo, Japan) added to 20% concentrated glycerin-fructose (Glyceol; Chugai Pharmaceuticals, Tokyo, Japan) was used until March 2007, and 0.4% sodium hyaluronic acid (Mucoup; Johnson and Johnson K.K., Tokyo, Japan) was used from April 2007.

Minor bleeding was stopped using the endoscopy knives in a forced coagulation mode. When hemorrhage from larger vessels was observed, the bleeding point was coagulated with a hemostatic forceps (FD-410LR; Olympus), using the soft coagulation mode at 80 W. When large vessels were visible in the submucosa during dissection, they were precoagulated using the hemostatic forceps in soft coagulation mode at 80 W. The patients fasted on the day of ESD and on the day following ESD.

Definition of delayed perforation

Delayed perforation was defined as no perforation during the ESD procedure and no symptom or free air immediately after ESD, followed by sudden appearance of symptoms of peritoneal irritation, with free air seen at computed tomography (CT) scan or roentgenography.

Results

Delayed perforation occurred in six patients (0.45%) after ESD. The clinicopathological features and clinical outcomes of the patients with delayed perforation are shown in **Table 1**.

Multiple tumors were seen in three patients (#1, #3, and #5). Five lesions were located in the upper third of the stomach and one lesion was observed in the middle third. Two lesions were in the lesser curvature, two were in the anterior wall, and two were in the posterior wall; one of the two lesions on the anterior wall and both of the two lesions on the posterior wall were situated on the lesser curvature side. The median (range) tumor size was 16.5 (12–50)mm, and four tumors were confined to the mucosa and two lesions invaded the submucosa. The two lesions including massive submucosal invasion and two lesions with ulcer scarring demanded deep submucosal dissection.

The symptoms of peritoneal irritation with rebound tenderness presented within 24 h after ESD. Time to oral intake ranged from 5 days to 14 days. Among the six patients with delayed perforation, one (#3) did not require emergency surgery because the peritonitis was localized and the symptoms were tolerable and improved with conservative antibiotic therapy. However, the other five patients required emergency surgery because of panperitonitis or an unimproved clinical course (**Fig. 1**). Three of these patients were treated by omentoplasty; however, two patients required gastrectomy because the perforation hole was too large to be closed by an omental patch in one patient and the omentum had been removed at previous colectomy in the other patient.

There was no mortality related to incidents of delayed perforation. In these six cases of delayed perforation, no recurrence such as peritoneal dissemination was observed during a median (range) follow-up period of 52 (13–77) months.

Table 1 Clinicopathological features and clinical outcomes of 6 patients with delayed perforation after endoscopic submucosal dissection (ESD).

Case no.	Age, years	Sex	Multiple tumors	Tumor location	Tumor size, mm	Depth of tumor	Scar in tumor	Histological type	Time required for ESD, hours	Device	Resected specimen size, mm	Time until peritonitis, hours	Emergency surgery	Time to oral intake, days	Hospital stay, days
1	50	Female	Present	U, L	20	Mucosa	Present	Differentiated	3.5	IT2	50	24	Distal gastrectomy	5	16
2	60	Male	Absent	M, A	18	Submucosa	Absent	Differentiated	2	IT	32	19	Omentoplasty,	6	14
3	70	Male	Present	U, A	15	Mucosa	Absent	Differentiated	3	IT	45	21	None	10	15
4	61	Male	Absent	U, P	50	Submucosa	Absent	Differentiated	9	IT	85	15	Total gastrectomy	14	33
5	64	Female	Present	U, L	12	Mucosa	Absent	Differentiated	2.2	IT	50	23	Omentoplasty	7	20
6	64	Male	Absent	U, P	15	Mucosa	Present	Differentiated	1.5	IT2	45	10	Omentoplasty	5	12

M, middle third; U, upper third; L, lesser curvature; A, anterior wall; P, posterior wall; IT, insulated-tip knife KD-610L; IT2, insulated-tip knife KD-611L.

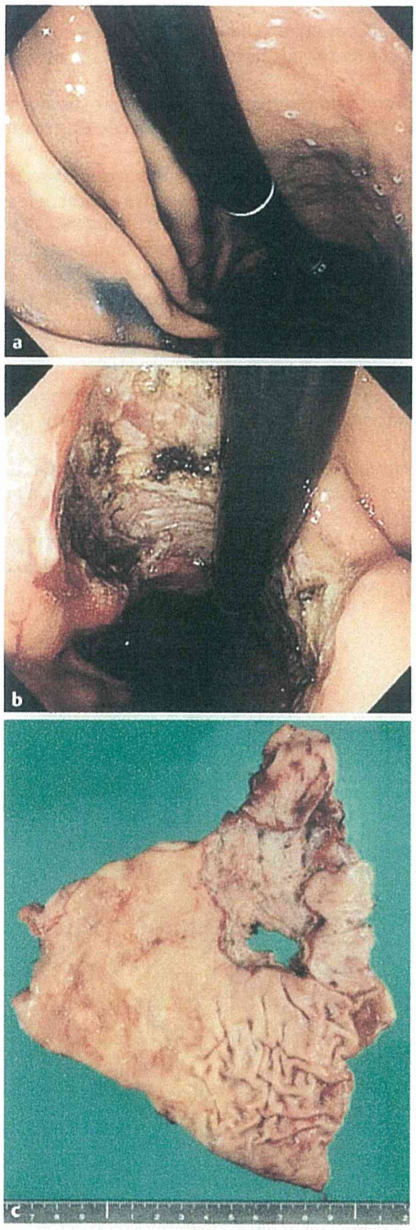

Fig. 1 Dleayed perforation after endoscopic submucosal dissection (ESD) for early gastric cancer (EGC): patient #1 of the case series. **a** ESD was performed for the lesion located on the lesser curvature of the upper gastric body that was 15 mm in size. **b** Hemorrhages from large vessels were observed during submucosal dissection and were repeatedly coagulated with the hemostatic forceps. The tumor had submucosal fibrosis and ESD took 3.5h, but perforation did not occur during the procedure. Peritoneal irritation with high grade fever developed 24 hafter ESD and laboratory examinations showed elevation of the white blood cell count (14 000/mm^3) and C-reactive protein (12.9 mg/dl). Free air and fluid collection in the peritoneal cavity was detected by computed tomography (CT) and delayed perforation was diagnosed. A nasogastric tube was placed in expectation of improvement in the patient's condition. Nevertheless, the symptoms worsened within several hours and an emergency operation was carried out. **c** At laparotomy, a 20-mm perforation was found at the lesser curvature of the upper gastric body. Histological findings showed that necrotic change was more distinct on the inner side of the muscularis propria than on the outer side, suggesting that the inner side was affected by transluminal burn.

Discussion

Although we found the incidence of delayed perforation after ESD to be very low (0.45%), in absolute numbers we have encountered several cases. Because we had not met with such complications in patients treated by conventional EMR (between April 1990 and April 2009, none in 1213 cases; 0%, 95% confidence interval [CI] 0%–0.32%), we suspected that the delayed perforation cases were related to a specific ESD procedure, such as dissection of a larger area of mucosa or frequent hemostasis of submucosal vessels by electrocautery.

Except for one lesion in the anterior wall of the gastric angle (in patient #2), all the post-ESD ulcers involved the lesser curvature of the gastric body even if the lesion itself had been in the anterior or posterior wall side, and therefore we considered that the incidence of delayed perforation might be affected by the location of the tumor. Branches of the right and left gastric artery penetrate the gastric wall at the anterior and posterior walls, and run through the submucosa toward the lesser curvature without forming a submucosal plexus at the center of the lesser curvature [10]. Therefore, the lesser curvature has little blood supply and this area has the potential for developing ischemia. In addition, most patients with differentiated adenocarcinoma have atrophic gastritis that reduces the mucosal height, which might aggravate electrical damage to the gastric wall. Regarding tumor characteristics, two lesions had massive submucosal tumor invasion and two had ulcer scarring that demanded deep submucosal dissection. One tumor was 5 cm in size and required a 9-hour procedure. Therefore, the procedure in these cases might have affected the gastric wall by extensive electrical thermal damage. Taking all this into consideration, we speculate that the essential mechanism of delayed perforation is electrical cautery during submucosal dissection or repeated coagulation that causes ischemic change to the gastric wall resulting in necrosis.

It is difficult to predict delayed perforation after ESD procedures because of its low incidence and unknown risk factors. Increased intragastric pressure has been reported to reduce mucosal blood flow and result in ischemic changes [11, 12]; therefore, one of the solutions to prevent delayed perforation would be insertion of a nasogastric tube for decompression of the gastric lumen. We have now adopted the practice of placing a nasogastric tube after ESD if the post-ESD ulcer was large, involved the lesser curvature of the gastric body, or had scarring, or when frequent hemostasis for intraoperative bleeding had been required. The nasogastric tube has been kept in place at least for 24 h after ESD or, if there was epigastric pain or abdominal tenderness, until the first oral intake; i.e., 2 days after ESD, because all the cases of delayed perforation occurred within 24 h after ESD. In the future, further case accumulation would clarify the risk for delayed perforation after gastric ESD.

In this case series, one patient avoided emergency surgery because the peritonitis was localized and the symptoms improved gradually with conservative therapy, but the other five patients needed emergency surgery because of severe peritonitis or because the clinical course showed no improvement. The duration of symptoms is known to be a factor that influences the prognosis after surgery for peptic ulcer perforation and it is particularly important for elderly patients, contributing significantly to mortality [13]. Conservative therapy would be possible for delayed perforation, but all patients who underwent emergency surgery had a favorable course and were discharged early without any operation-related complications. Based on our result,

once delayed perforation occurs after gastric ESD, it is important not to hesitate to carry out emergency surgery.

Competing interests: None

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