**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)<br>ER for Barrett's esophagus is still being studied |
| Stomach | Standard criteria: Well- or moderately differentiated AC and/or papillary carcinoma;<br>cancer confined to mucosa IIa < 20 mm; cancer confined to the mucosa IIb, IIc < 10 mm, without evidence of lymphatic involvement<br>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<br>High-grade dysplasia<br>The indication for resection of mucosal or AC invading slightly into the SM is still being studied. ESD has been reported for resection of:<br>- well- or moderately differentiated AC; cancer confined to the mucosa: IIa < 20 mm, IIb, IIc < 10 mm, without evidence of venous or lymphatic involvement<br>- 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<br>Well-/moderately differentiated<br>No lymphovascular invasion<br>Irrespective of ulcer findings<br>Tumor less than 3 cm in size | 1230 | 0–0.3% |
| Intramucosal<br>Well-/moderately differentiated<br>No lymphovascular invasion<br>No ulcer<br>Irrespective of tumor size | 929 | 0–0.4% |
| Intramucosal<br>Poorly differentiated<br>No lymphovascular invasion<br>No ulcer<br>Tumor less than 2 cm in size | 141 | 0–2.6% |
| Minute submucosal penetration (SM1)<br>Well-/moderately differentiated<br>No lymphovascular invasion<br>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.

## References

1 Itoh H, Oohata Y, Nakamura K *et al.* Complete ten-year postgastrectomy follow-up of early gastric cancer. *Am. J. Surg.* 1989; **158**: 14–16.
2 Sano T, Sasako M, Kinoshita T, Maruyama K. Recurrence of early gastric cancer. Follow-up of 1475 patients and review of the Japanese literature. *Cancer* 1993; **72**: 3174–8.
3 Soetikno R, Kaltenbach T, Yeh R, Gotoda T. Endoscopic mucosal resection for early cancers of the upper gastrointestinal tract. *J. Clin. Oncol.* 2005; **23**: 4490–8.
4 Gotoda T, Kondo H, Ono H *et al.* A new endoscopic mucosal resection procedure using an insulation-tipped electrosurgical knife for rectal flat lesions: report of two cases. *Gastrointest. Endosc.* 1999; **50**: 560–3.
5 Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma—2nd English edition. *Gastric. Cancer* 1998; **1**: 10–24.

6 Dixon MF. Gastrointestinal epithelial neoplasia: Vienna revisited. *Gut* 2002; **51**: 130–1.
7 Schlemper RJ, Riddell RH, Kato Y *et al.* The Vienna classification of gastrointestinal epithelial neoplasia. *Gut* 2000; **47**: 251–5.
8 The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon: November 30 to December 1, 2002. *Gastrointest. Endosc.* 2003; **58** (Suppl. 6): S3–43.
9 Kiesslich R, Jung M. Magnification endoscopy: does it improve mucosal surface analysis for the diagnosis of gastrointestinal neoplasias? *Endoscopy* 2002; **34**: 819–22.
10 Kida M, Kobayashi K, Saigenji K. Routine chromoendoscopy for gastrointestinal diseases: indications revised. *Endoscopy* 2003; **35**: 590–6.
11 Kudo S, Hirota S, Nakajima T *et al.* Colorectal tumours and pit pattern. *J. Clin. Pathol.* 1994; **47**: 880–5.
12 Kudo S, Rubio CA, Teixeira CR, Kashida H, Kogure E. Pit pattern in colorectal neoplasia: endoscopic magnifying view. *Endoscopy* 2001; **33**: 367–73.
13 Inoue H, Takeshita K, Hori H, Muraoka Y, Yoneshima H, Endo M. Endoscopic mucosal resection with a cap-fitted panendoscope for esophagus, stomach, and colon mucosal lesions. *Gastrointest. Endosc.* 1993; **39**: 58–62.
14 Soetikno RM, Gotoda T, Nakanishi Y, Soehendra N. Endoscopic mucosal resection. *Gastrointest. Endosc.* 2003; **57**: 567–79.
15 Tanabe S, Koizumi W, Kokutou M *et al.* Usefulness of endoscopic aspiration mucosectomy as compared with strip biopsy for the treatment of gastric mucosal cancer. *Gastrointest. Endosc.* 1999; **50**: 819–22.
16 Akiyama M, Ota M, Nakajima H, Yamagata K, Munakata A. Endoscopic mucosal resection of gastric neoplasms using a ligating device. *Gastrointest. Endosc.* 1997; **45**: 182–6.
17 Uno Y, Munakata A. The non-lifting sign of invasive colon cancer. *Gastrointest. Endosc.* 1994; **40**: 485–9.
18 Kobayashi N, Saito Y, Sano Y *et al.* Determining the treatment strategy for colorectal neoplastic lesions: endoscopic assessment or the non-lifting sign for diagnosing invasion depth? *Endoscopy* 2007; **39**: 701–5.
19 Saito Y, Uraoka T, Matsuda T *et al.* Endoscopic treatment of large superficial colorectal tumors: a case series of 200 endoscopic submucosal dissections (with video). *Gastrointest. Endosc.* 2007; **66**: 966–73.
20 Saito Y, Uraoka T, Matsuda T *et al.* A pilot study to assess the safety and efficacy of carbon dioxide insufflation during colorectal endoscopic submucosal dissection with the patient under conscious sedation. *Gastrointest. Endosc.* 2007; **65**: 537–42.
21 Uraoka T, Saito Y, Yamamoto K, Fujii T. Submucosal injection solution for gastrointestinal tract endoscopic mucosal resection and endoscopic submucosal dissection. *Drug Des. Devel. Ther.* 2008; **2**: 131–8.
22 Ishihara R, Iishi H, Takeuchi Y *et al.* Local recurrence of large squamous-cell carcinoma of the esophagus after endoscopic resection. *Gastrointest. Endosc.* 2008; **67**: 799–804.
23 Hotta K, Fujii T, Saito Y, Matsuda T. Local recurrence after endoscopic resection of colorectal tumors. *Int. J. Colorectal. Dis.* 2009; **24**: 225–30.
24 Kaltenbach T, Friedland S, Maheshwari A *et al.* Short- and long-term outcomes of standardized EMR of nonpolypoid (flat and depressed) colorectal lesions > or = 1 cm (with video). *Gastrointest. Endosc.* 2007; **65**: 857–65.
25 Saito Y, Fukuzawa M, Matsuda T *et al.* Clinical outcome of endoscopic submucosal dissection versus endoscopic mucosal resection of large colorectal tumors as determined by curative resection. *Surg. Endosc.* 2009; **24**: 343–52.
26 Oda I, Saito D, Tada M *et al.* A multicenter retrospective study of endoscopic resection for early gastric cancer. *Gastric. Cancer* 2006; **9**: 262–70.
27 Shimura T, Sasaki M, Kataoka H *et al.* Advantages of endoscopic submucosal dissection over conventional endoscopic mucosal resection. *J. Gastroenterol. Hepatol.* 2007; **22**: 821–6.
28 Watanabe K, Ogata S, Kawazoe S *et al.* Clinical outcomes of EMR for gastric tumors: historical pilot evaluation between endoscopic submucosal dissection and conventional mucosal resection. *Gastrointest. Endosc.* 2006; **63**: 776–82.
29 Cao Y, Liao C, Tan A, Gao Y, Mo Z, Gao F. Meta-analysis of endoscopic submucosal dissection versus endoscopic mucosal resection for tumors of the gastrointestinal tract. *Endoscopy* 2009; **41**: 751–7.
30 Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics. *CA Cancer J. Clin.* 2002; **55**: 74–108.
31 Bousamra M Jr, Haasler GB, Parviz M. A decade of experience with transthoracic and transhiatal esophagectomy. *Am. J. Surg.* 2002; **183**: 162–7.
32 Pech O, Gossner L, May A *et al.* Long-term results of photodynamic therapy with 5-aminolevulinic acid for superficial Barrett's cancer and high-grade intraepithelial neoplasia. *Gastrointest. Endosc.* 2005; **62**: 24–30.
33 Ishihara R, Iishi H, Uedo N *et al.* Comparison of EMR and endoscopic submucosal dissection for en bloc resection of early esophageal cancers in Japan. *Gastrointest. Endosc.* 2008; **68**: 1066–72.
34 Jemal A, Murray T, Ward E *et al.* Cancer statistics, 2005. *CA Cancer J. Clin.* 2005; **55**: 10–30.
35 Sharma P, Sidorenko EI. Are screening and surveillance for Barrett's oesophagus really worthwhile? *Gut* 2005; **54** (Suppl. 1): i27–32.
36 Nigro JJ, Hagen JA, DeMeester TR *et al.* Prevalence and location of nodal metastases in distal esophageal adenocarcinoma confined to the wall: implications for therapy. *J. Thorac. Cardiovasc. Surg.* 1999; **117**: 16–23. discussion 23–5.
37 Westerterp M, Koppert LB, Buskens CJ *et al.* Outcome of surgical treatment for early adenocarcinoma of the esophagus or gastro-esophageal junction. *Virchows. Arch.* 2005; **446**: 497–504.
38 Stein HJ, Feith M, Bruecher BL, Naehrig J, Sarbia M, Siewert JR. Early esophageal cancer: pattern of lymphatic spread and prognostic factors for long-term survival after surgical resection. *Ann. Surg.* 2005; **242**: 566–73; discussion 573–5.
39 Ishihara R, Tanaka H, Iishi H *et al.* Long-term outcome of esophageal mucosal squamous cell carcinoma without lymphovascular involvement after endoscopic resection. *Cancer* 2008; **112**: 2166–72.
40 Tajima Y, Nakanishi Y, Ochiai A *et al.* Histopathologic findings predicting lymph node metastasis and prognosis of patients with superficial esophageal carcinoma: analysis of 240 surgically resected tumors. *Cancer* 2000; **88**: 1285–93.
41 Katada C, Muto M, Manabe T, Ohtsu A, Yoshida S. Local recurrence of squamous-cell carcinoma of the esophagus after EMR. *Gastrointest. Endosc.* 2005; **61**: 219–25.
42 Inoue M, Tsugane S. Epidemiology of gastric cancer in Japan. *Postgrad. Med. J.* 2005; **81**: 419–24.
43 Yamao T, Shirao K, Ono H *et al.* Risk factors for lymph node metastasis from intramucosal gastric carcinoma. *Cancer* 1996; **77**: 602–6.
44 Yasuda K, Shiraishi N, Suematsu T, Yamaguchi K, Adachi Y, Kitano S. Rate of detection of lymph node metastasis is correlated with the depth of submucosal invasion in early stage gastric carcinoma. *Cancer* 1999; **85**: 2119–23.
45 Tsujitani S, Oka S, Saito H *et al.* Less invasive surgery for early gastric cancer based on the low probability of lymph node metastasis. *Surgery* 1999; **125**: 148–54.

46 Fujii K. A clinicopathological study on the indications of limited surgery for submucosal gastric cancer. *Jpn. J. Gastroenterol. Surg.* 1998; **31**: 2055–62.

47 Gotoda T, Yanagisawa A, Sasako M *et al.* Incidence of lymph node metastasis from early gastric cancer: estimation with a large number of cases at two large centers. *Gastric. Cancer* 2000; **3**: 219–25.

48 Japanese Gastric Cancer Association. *Gastric Cancer Treatment Guideline*, 2nd edn. Kyoto: Japanese Gastric Cancer Association, 2004 (in Japanese).

49 Hirasawa T, Gotoda T, Miyata S *et al.* Incidence of lymph node metastasis and the feasibility of endoscopic resection for undifferentiated-type early gastric cancer. *Gastric. Cancer* 2009; **12**: 148–52.

50 Li C, Kim S, Lai JF *et al.* Risk factors for lymph node metastasis in undifferentiated early gastric cancer. *Ann. Surg. Oncol.* 2008; **15**: 764–9.

51 Abe N, Watanabe T, Sugiyama M *et al.* Endoscopic treatment or surgery for undifferentiated early gastric cancer? *Am. J. Surg.* 2004; **188**: 181–4.

52 Li H, Lu P, Lu Y *et al.* Predictive factors for lymph node metastasis in poorly differentiated early gastric cancer and their impact on the surgical strategy. *World J. Gastroenterol.* 2008; **14**: 4222–6.

53 Ye BD, Kim SG, Lee JY *et al.* Predictive factors for lymph node metastasis and endoscopic treatment strategies for undifferentiated early gastric cancer. *J. Gastroenterol. Hepatol.* 2008; **23**: 46–50.

54 Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. *Cell* 1990; **61**: 759–67.

55 Shimoda T, Ikegami M, Fujisaki J, Matsui T, Aizawa S, Ishikawa E. Early colorectal carcinoma with special reference to its development de novo. *Cancer* 1989; **64**: 1138–46.

56 Bedenne L, Faivre J, Boutron MC, Piard F, Cauvin JM, Hillon P. Adenoma—carcinoma sequence or 'de novo' carcinogenesis? A study of adenomatous remnants in a population-based series of large bowel cancers. *Cancer* 1992; **69**: 883–8.

57 Soetikno RM, Kaltenbach T, Rouse RV *et al.* Prevalence of nonpolypoid (flat and depressed) colorectal neoplasms in asymptomatic and symptomatic adults. *Jama* 2008; **299**: 1027–35.

58 Rembacken BJ, Fujii T, Cairns A *et al.* Flat and depressed colonic neoplasms: a prospective study of 1000 colonoscopies in the UK. *Lancet* 2000; **355**: 1211–14.

59 Morson BC, Whiteway JE, Jones EA, Macrae FA, Williams CB. Histopathology and prognosis of malignant colorectal polyps treated by endoscopic polypectomy. *Gut* 1984; **25**: 437–44.

60 Kitajima K, Fujimori T, Fujii S *et al.* Correlations between lymph node metastasis and depth of submucosal invasion in submucosal invasive colorectal carcinoma: a Japanese collaborative study. *J. Gastroenterol.* 2004; **39**: 534–43.

61 Egashira Y, Yoshida T, Hirata I *et al.* Analysis of pathological risk factors for lymph node metastasis of submucosal invasive colon cancer. *Mod. Pathol.* 2004; **17**: 503–11.

62 Haggitt RC, Glotzbach RE, Soffer EE, Wruble LD. Prognostic factors in colorectal carcinomas arising in adenomas: implications for lesions removed by endoscopic polypectomy. *Gastroenterology* 1985; **89**: 328–36.

63 Uraoka T, Saito Y, Matsuda T *et al.* Endoscopic indications for endoscopic mucosal resection of laterally spreading tumours in the colorectum. *Gut* 2006; **55**: 1592–7.

64 Matsuda T, Fujii T, Saito Y *et al.* Efficacy of the invasive/non-invasive pattern by magnifying chromoendoscopy to estimate the depth of invasion of early colorectal neoplasms. *Am. J. Gastroenterol.* 2008; **103**: 2700–6.

65 Gotoda T, Friedland S, Hamanaka H, Soetikno R. A learning curve for advanced endoscopic resection. *Gastrointest. Endosc.* 2005; **62**: 866–7.

66 Suzuki N. Endoscopic submucosal dissection (ESD) for large, sessile colorectal polyps: early experience at a UK centre. *CME Gastroenterol. Hepatol. Nutr.* 2008; **9**: 121–6.

67 Dinis-Ribeiro M, Pimentel-Nunes P, Afonso M, Costa N, Lopes C, Moreira-Dias L. A European case series of endoscopic submucosal dissection for gastric superficial lesions. *Gastrointest. Endosc.* 2009; **69**: 350–5.

68 Gastroenterology, BSo. *Guidelines on Safety and Sedation During Endoscopic Procedures*, 2003.

69 Thomson A, Andrew G, Jones DB. Optimal sedation for gastrointestinal endoscopy: review and recommendations. *J. Gastroenterol. Hepatol* 2010; **25**: 469–78.

# Endoscopic Submucosal Dissection of Non-Polypoid Colorectal Neoplasms

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KEYWORDS

- Endoscopic submucosal dissection
- Endoscopic mucosal resection
- Endoscopic piecemeal mucosal resection • Colorectum
- Laterally spreading tumor granular type
- Laterally spreading tumor nongranular type

Traditionally, endoscopic mucosal resection (EMR)[1–5] and surgery were the only available treatments for large colorectal tumors, even for those detected at an early stage. In Japan, EMR is indicated for the treatment of colorectal adenomas, intramucosal and submucosal superficial (invasion <1000 μm from the muscularis mucosae) cancers, because of its negligible risk of lymph node metastasis[6] and excellent clinical outcomes.[2–4]

The endoscopic submucosal dissection (ESD) technique, which enables en-bloc resection of large tumors, is accepted as a standard minimally invasive treatment for early gastric cancer in Japan.[7,8] However, it is not widely used to treat superficial colorectal cancer because of technical difficulty and the higher risk of complications. Conventional EMR, therefore, is used for the resection of non-polypoid colorectal neoplasms (NP-CRNs), including the large flat carpet lesions, called colorectal laterally spreading tumors (LSTs).[4,5] EMR, however, is not designed for en-bloc resection of LSTs larger than 20 mm. Piecemeal EMR is associated with the risks of incomplete removal and local recurrence[9] albeit most recurrences can be successfully treated by additional EMR and only a few cases require surgery.[9] ESD of LSTs larger than 20 mm is therefore an attractive treatment provided that it is safe to use in the colon and rectum.

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Based on the refinement of ESD instruments and progress in the development of ESD skills, the ESD technique has recently been reported to be useful in the treatment of large colorectal LSTs instead of EMR or surgery.[10–15] Herein, the authors describe their experience.

## INDICATIONS FOR COLORECTAL ESD

The indication for colorectal ESD at the National Cancer Center Hospital (NCCH) in Tokyo, Japan, is a nongranular type LST (LST-NG) larger than 20 mm.[12]

Based on clinicopathologic analyses of LSTs,[4,16] LST-NGs, which are large (>1 cm) superficial elevated NP-CRNs with a smooth surface, have a higher rate of submucosal (sm) invasion, which can be difficult to predict endoscopically. About 30% of LST-NGs with sm invasions are multifocal, and such invasions are primarily superficial submucosal cancers (sm1s) and difficult to predict before endoscopic treatment.

Granular type LSTs (LST-Gs) have a lower rate of sm invasion, and most such invasions are found under the largest nodule or depression, which are easier to predict endoscopically.[4,16] LST-Gs larger than 20 mm can be treated by endoscopic piecemeal mucosal resection (EPMR) rather than by ESD, with the area that has the largest nodule resected before resection of the remaining tumor. LST-Gs larger than 30 mm or 40 mm are possible candidates for ESD because they have higher sm invasion rates and are more difficult to treat even by EPMR; so they have been treated by either EPMR or ESD, based on the individual endoscopist's judgment.

## ESTIMATION OF THE DEPTH OF INVASION

A non-invasive pattern[17,18] should be verified in each lesion, indicating suitability for EMR or ESD: the estimated invasion depth should be less than that of superficial submucosal cancers (sm1s). No biopsy is performed before ESD because it can cause fibrosis and may interfere with submucosal lifting.

## CESSATION PERIOD OF ANTICOAGULANT AND ANTIPLATELET BEFORE ESD

ESD is considered to be a high-risk procedure.[19] Most patients receiving aspirin or ticlopidine alone underwent ESD after a cessation period of 5 to 7 days and restarted the drugs after 7 days if possible. Patients receiving warfarin used intravenous heparin or subcutaneous low-molecular-weight heparin in the perioperative period and resumed warfarin after the ESD procedure.

## ESD PROCEDURE AT NCCH

The procedures were primarily performed using a ball-tip bipolar needle knife (B-knife) (XEMEX Co, Tokyo Japan) (**Fig. 1**A)[20] and an insulation-tip (IT) electrosurgical knife (Olympus Optical Co, Tokyo, Japan) (see **Fig. 1**B) with carbon dioxide insufflations instead of air insufflation to reduce patient discomfort (see **Fig. 1**C).[11] After submucosal injection of 10% glycerin and 5% fructose (Glyceol, Chugai Pharmaceutical Co, Tokyo, Japan)[21] and 0.4% hyaluronic acid[14] (MucoUp, Seikakagu Co, Tokyo, Japan) (see **Fig. 1**D) into the sm layer, a circumferential incision was made using the B-knife and an ESD was then performed using the B-knife and IT knife (see **Fig. 1**A, B).

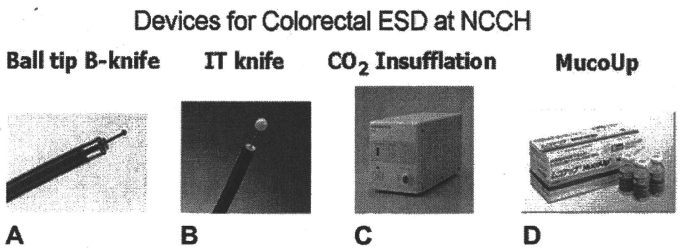


**Fig. 1.** The procedures were primarily performed using a B-knife (*A*) and an IT electrosurgical knife (*B*) with carbon dioxide insufflation (*C*) instead of air insufflation to reduce patient discomfort. After injection of Glyceol (Chugai Pharmaceutical Co, Tokyo, Japan) and MucoUp (Seikakagu Co, Tokyo, Japan) (*D*) into the sm layer, a circumferential incision was made using the B-knife and an ESD was performed using the B-knife and IT knife. (*From* XEMEX Co, Tokyo, Japan; with permission [*A*]; Olympus Optical Co, Tokyo, Japan; with permission [*B*]; and Seikakagu Co, Tokyo, Japan; with permission [*D*].)

## SUBMUCOSAL INJECTION SOLUTION

A mixture of 2 solutions was prepared before the procedure to create a longer-lasting sm fluid cushion.

Solution 1: Indigo carmine dye (2 mL of 1% solution) and epinephrine (1 mL of 0.1% solution) were mixed with 200 mL Glyceol[21] in a container, which was then drawn into a 5-mL disposable syringe.

Solution 2: MucoUp was drawn into another 5-mL syringe with a smaller amount of indigo carmine dye and epinephrine. During the actual ESD procedure, a small amount of solution 1 was injected into the sm layer to confirm the appropriate sm layer elevation and then solution 2 was injected into the properly elevated sm layer. Finally, a small amount of solution 1 was injected again to flush out any residual solution 2.

## DETAILED COLORECTAL ESD PROCEDURES

1. The margins of the lesion were delineated before ESD by spraying 0.4% indigo carmine dye (**Fig. 2**A). After creation of the submucosal fluid cushion, an initial incision was made with the B-knife at the oral side of the lesion (see **Fig. 2**B).[20] In colorectal cases, it was not necessary to actually mark around lesions because tumor margins can be visualized clearly with indigo carmine.
2. The B-knife was inserted into the initial incision, and an electrosurgical current was applied in endocut mode (50 W) using a standard electrosurgical generator (ICC 200, ERBE, Tubingen, Germany) to continue the marginal incision around the oral side of the lesion.
3. After partial resection of the margin on the oral side of the lesion to ensure adequate submucosal lifting, submucosal dissection was begun using the same B-knife in retroflex view (see **Fig. 2**B).
4. Additional resection of the margin on the anal side was performed using the B-knife in the straight view (see **Fig. 2**C).
5. After the lesion was partially dissected so that the sm layer could be visualized sufficiently, an IT knife (see **Fig. 2**D) was used to complete the dissection of the sm layer quickly and safely. The previously indicated solutions were injected

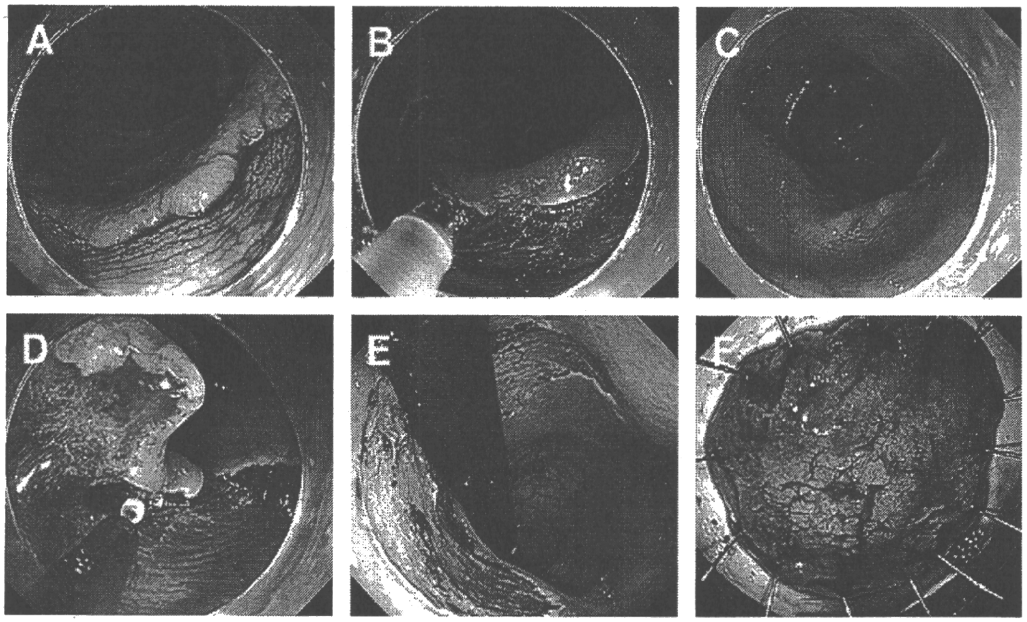


**Fig. 2.** ESD procedures. (*A*) An LST-NG type lesion 40 mm in size located in transverse colon (reverse view). Lesion margins delineated before ESD using 0.4% indigo carmine dye spraying. (*B*) After injection of Glyceol and sodium hyaluronate acid solution into the sm layer, a half-circumferential incision (anal side) was performed using B-knife (retroflex view). After circumferential incision, sm dissection was performed using the same B-knife. (*C*) Straight view of the lesion after half-circumference marginal resection and sm dissection of the oral side. Additional resection of the margin on the anal side was performed using the B-knife in the straight view. (*D*) Dissection of the sm layer from outside to inside of the lesion is easily performed using the IT knife. (*E*) Ulcer bed after successful en-bloc resection in 1.5 hours. (*F*) Resected specimen was 40 × 30 mm in diameter and histologic findings revealed intramucosal cancer with tumor-free margin.

repeatedly into the sm layer to maintain the sm fluid cushion so as to minimize the risk of perforation.

6. Hemostatic forceps were used in soft coagulation mode (70–80 W) to control visible bleeding. The patient's position was sometimes changed to facilitate visualization of the tissue plane, and dissection continued until the lesion was completely excised.
7. After the colorectal ESD was completed, routine colonoscopic review to detect any possible perforation or exposed vessels was conducted and minimum coagulation was performed using hemostatic forceps on nonbleeding visible vessels to prevent postoperative bleeding (see **Fig. 2**E).
8. The resected specimen was stretched and fixed to the board using small pins (see **Fig. 2**F).

## CLINICAL OUTCOME OF ESD AT NCCH

The en-bloc resection rate was 88% and the curative resection rate was 86% among 500 ESDs (**Table 1**). Of these, 127 were tubular adenomas, 315 were intramucosal cancers or minute sm cancers (sm1s), 55 were submucosal deep cancers (sm2s), 2 were carcinoid tumors, and 1 was mucosa-associated lymphoma tissue. The median operation time was 90 minutes, and the mean size of resected specimens was 40 mm (range, 20–150 mm).

## COMPLICATIONS OF ESD AT NCCH

The postoperative bleeding rate for ESD was 1.0% (5 of 500), which is almost the same as that for conventional EMR (see **Table 1**). In contrast, the perforation rate for ESD

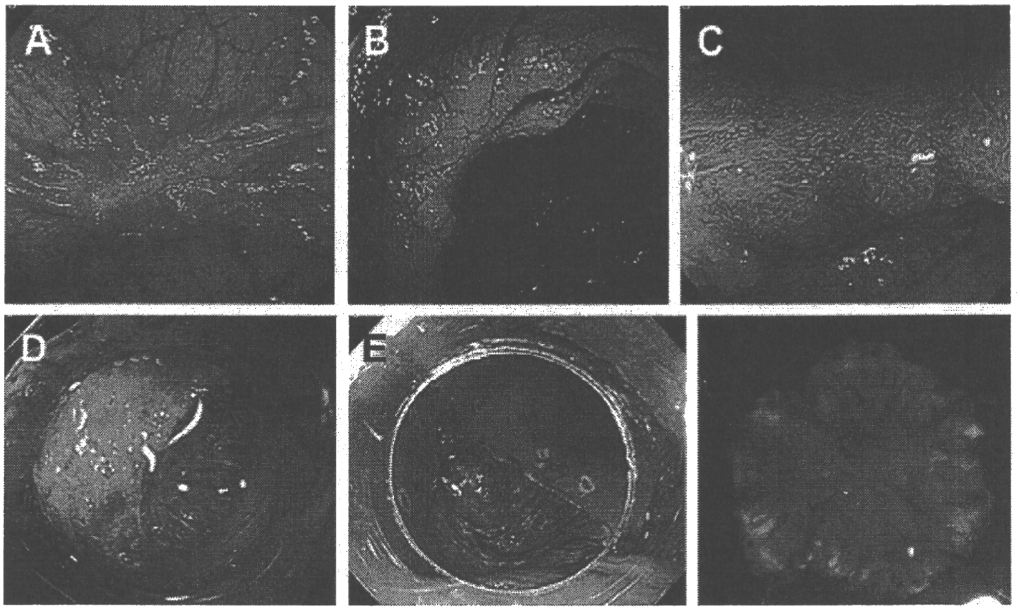


**Fig. 3.** ESD procedures for recurrent tumor. (*A*) A 20-mm flat-type lesion with ulcer scar was located in the transverse colon, and prominent fold convergences were noticed. (*B*) Lesion margins were delineated before ESD using 0.4% indigo carmine dye spraying. (*C*) Crystal violet (0.05%) staining clearly revealed IIIL and IIIs (non-invasive) pit pattern and indicated that this lesion was a good candidate for endoscopic treatment despite severe fibrosis and nonlifting sign. (*D*) After injection of Glyceol and sodium hyaluronate acid solution into the sm layer, circumferential incision was performed using B-knife. After circumferential incision, sm dissection was performed using B-knife and IT knife. Severe sm layer fibrosis was visualized clearly due to the distal attachment, and the sm layer was carefully dissected just below this fibrosis. (*E*) Ulcer bed after successful en-bloc resection in 1 hour. (*F*) Resected specimen was 20 mm in diameter, and histologic findings revealed intramucosal cancer with tumor-free margin.

**Table 1**
**Clinical outcomes of 500 colorectal ESDs at NCCH**

| | |
|---|---|
| Macroscopic Types | |
| LST-G/LST-NG | 220/200 |
| Depressed/Protruded | 18/30 |
| Recurrence | 28 |
| SMT | 4 |
| Location | C:35, Rt: 195, Lt: 130, R:140 |
| Size of Resected Specimens [Mean±SD (range)] | 40 ± 20 (20–150) mm |
| Pathology | Adenoma, 127; m-sm1, 315; sm2, approximately 55; Others, 3 |
| Procedure Time | 90 ± 73 (15–390) min |
| En-bloc Resection | 88% |
| Curative Resection | 86% |
| Complications | |
| Perforation | 13[a] (2.6%) |
| Delayed Bleeding | 5 (1%) |

*Abbreviations:* C, cecum; Lt, left; m-sm1, intramucosal-submucosal superficial (invasive <1000 mm from the muscularis mucosae) cancer; R, rectum; Rt, right; sm2, submucosal deep; SD, standard deviation; SMT, submucosal tumor.

[a] All cases except 1 treated without surgery.

was 2.6% (13 of 500), which is considerably higher than that for conventional EMR (1.3%); only 1 perforation case needed emergency surgery because of ineffective endoscopic clipping. There have been no delayed perforations observed.

## TECHNICAL PROGRESS OF COLORECTAL ESD

Until recently, colorectal ESDs have been performed mainly in Japan[10–15,22,23] because of the technical difficulty involved in the procedure. Also, the most frequent indication for ESD, early gastric cancer, is more common in Japan than in Western countries.[24] Some trained endoscopists, however, have started to do colorectal ESDs in Europe[25] and the United States.[26]

Given the thinness of the colonic wall, the use of specialized knives,[7,20] distal attachments,[14] and hypertonic solutions (Glycerol[21] and MucoUp[14]) that produce a longer-lasting and higher sm elevation cushion are necessary for safe ESD and to reduce the perforation rate. The B-knife[20] is safer because the electric current is limited to the needle and the bipolar system prevents electric current from passing to the muscle layer.

A noninvasive and simple tool that facilitates the direct visualization of the sm layer was needed to reduce the risk of perforations in colorectal ESD. As a result, the authors developed a sinker system for traction-assisted ESD[10] and more recently a thin-endoscope–assisted ESD.[27] In addition, Sakamoto and colleagues[28] reported the usefulness of a new traction device (S-O clip) for ESD of superficial colorectal neoplasms.

ESD enables us to treat recurrent lesions after incomplete endoscopic resections (see **Fig. 3; Fig. 4**) and large colorectal LSTs greater than 10 cm in diameter (**Fig. 5**). It is important, therefore, to diagnose the lesion carefully using chromomagnification colonoscopy[17,18] before treatment to reduce unnecessary noncurative resection for sm deep invasive cancers.[6]

## COMPARISON BETWEEN ESD AND EMR

The primary advantage of ESD compared with EPMR is a higher en-bloc resection rate for large colonic tumors that had been treated by surgery previously. Consequently, ESD has a lower recurrence rate compared with EPMR (2% vs 14%) and also results

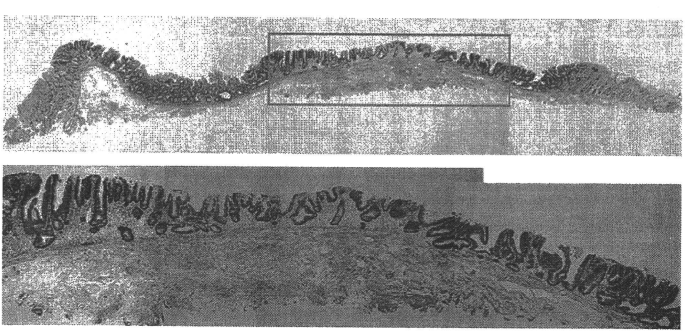

**Fig. 4.** Histologic findings revealed an intramucosal cancer with tumor-free margin. Severe fibrosis caused by previous EMR was observed at the center of this lesion.

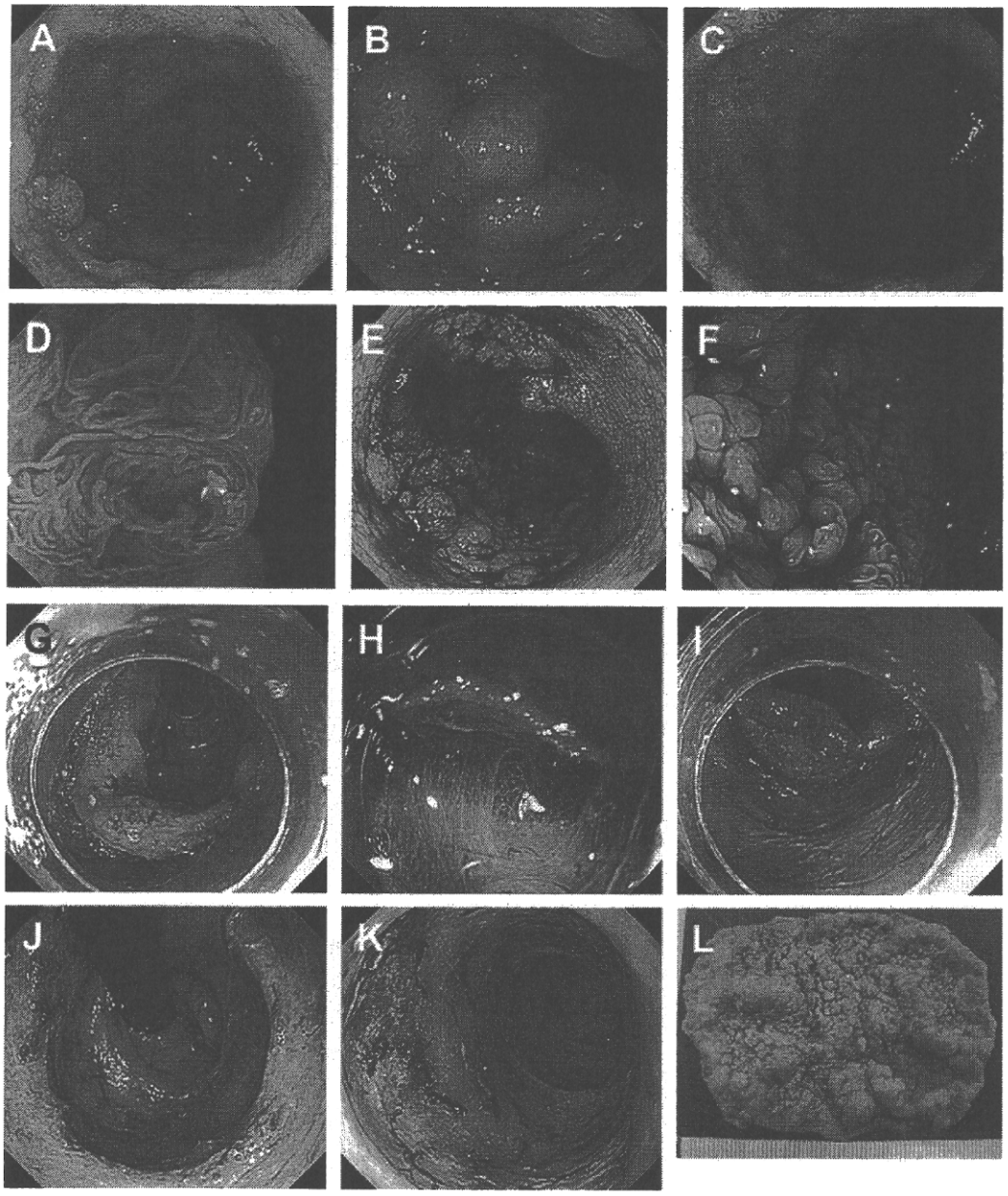


**Fig. 5.** ESD procedures for large LST-Gs. (*A*) An LST-G type lesion 100 mm in size located in the sigmoid colon. (*B*) A large nodule was identified in this LST-G. (*C*) Narrow-band imaging (NBI) revealed this LST-G lesion as brownish and the margin of this lesion became apparent. (*D*) NBI with magnification revealed a type II or IIIA Sano capillary pattern, suggesting intramucosal neoplastic lesion. (*E*) Lesion margins were delineated before ESD using 0.4% indigo carmine dye spraying. (*F*) Magnification colonoscopy with indigo carmine dye revealed non-invasive (IV) pit pattern at the elevated area of this lesion. (*G*) After injection of Glyceol and sodium hyaluronate acid solution into the sm layer, half-circumferential incision was performed using B-knife. (*H*) and (*I*) After circumferential incision, sm dissection was performed using B-knife and IT knife. Thickened sm layer was visualized as blue because of the distal attachment and indigo carmine. Sm dissection was performed carefully at this thickened sm layer above the muscle layer. (*J*) and (*K*) Ulcer bed after successful en-bloc resection in 2 hours. (*L*) Resected specimen was 100 mm in diameter, and histologic findings revealed intramucosal cancer with tumor-free margin.

in a better quality of life for patients compared with surgery. Future studies should be designed to compare the clinical outcomes of ESD and surgery but not of ESD and EMR because the indications for ESD and EMR are different as are the tumor characteristics.

Until now, EPMR had been considered a feasible treatment for colorectal LSTs. Low rates of local recurrence for such tumors and of repeat endoscopic resection were considered sufficient for most local recurrent tumors.[9]

In the authors' case series,[29] EPMR was also effective in treating many LST-Gs 20 mm or larger, but 3 cases (1.3%) required surgery after such piecemeal resections, including 2 cases of invasive recurrence.

Based on these results, cases for EPMRs in which accurate histologic evaluation would be difficult to make should be considered for ESD or laparoscopic surgery.

LST-Gs larger than 30 mm are good candidates for ESD. The sm invasion rate for such lesions was 16%, and multifocal invasion rate outside the large nodule or depression was 25%, which was more difficult to diagnose even using magnification colonoscopy.

## INSTRUCTIONS ON POST-ESD CARE

From data analysis between ESD and EMR, follow-up endoscopy is recommended after 1 year for curative en-bloc ESD cases and after 6 months for piecemeal ESD cases considering local recurrence rates.[28] Even for pathologic curative resection cases, computed tomographic examination or endoscopic ultrasound imaging is recommended to examine lymph node metastasis or distant metastasis for sm1 cases and piecemeal resection cases.

Surgery is recommended for sm2s or cancers of deeper invasion or when lymphovascular invasion is diagnosed histologically.[6]

## SUMMARY

ESD is a safe and effective procedure for treating colorectal LST-NGs larger than 20 mm and LST-Gs larger than 30 mm because it has a higher en-bloc resection rate and is less invasive than surgery. Establishment of a training system for technically more difficult colorectal ESD and further refinement of ESD instruments are encouraged for the increased use of colorectal ESD not only in Japan but also throughout the world.

## REFERENCES

1. Ahmad NA, Kochman ML, Long WB, et al. Efficacy, safety, and clinical outcomes of endoscopic mucosal resection: a study of 101 cases. Gastrointest Endosc 2002;55:390–6.
2. Yokota T, Sugihara K, Yoshida S. Endoscopic mucosal resection for colorectal neoplastic lesions. Dis Colon Rectum 1994;37:1108–11.
3. Soetikno RM, Gotoda T, Nakanishi Y, et al. Endoscopic mucosal resection. Gastrointest Endosc 2003;57(4):567–79.
4. Saito Y, Fujii T, Kondo H, et al. Endoscopic treatment for laterally spreading tumors in the colon. Endoscopy 2001;33:682–6.
5. Kudo S, Kashida H, Tamura T, et al. Colonoscopic diagnosis and management of nonpolypoid early colorectal cancer. World J Surg 2000;24:1081–90.
6. Kitajima K, Fujimori T, Fujii S, et al. Correlations between lymph node metastasis and depth of submucosal invasion in submucosal invasive colorectal carcinoma: a Japanese collaborative study. J Gastroenterol 2004;39(6):534–43.
7. Hosokawa K, Yoshida S. [Recent advances in endoscopic mucosal resection for early gastric cancer]. Gan To Kagaku Ryoho 1998;25:476–83 [in Japanese].

8. Ono H, Kondo H, Gotoda T, et al. Endoscopic mucosal resection for treatment of early gastric cancer. Gut 2001;48:225–9.
9. Hotta K, Fujii T, Saito Y, et al. Local recurrence after endoscopic resection of colorectal tumors. Int J Colorectal Dis 2009;24(2):225–30.
10. Saito Y, Emura F, Matsuda T, et al. A new sinker-assisted endoscopic submucosal dissection for colorectal tumors. Gastrointest Endosc 2005;62:297–301.
11. Saito Y, Uraoka T, Matsuda T, et al. A pilot study to assess safety and efficacy of carbon dioxide insufflation during colorectal endoscopic submucosal dissection under conscious sedation. Gastrointest Endosc 2007;65(3):537–42.
12. Saito Y, Uraoka T, Matsuda T, et al. Endoscopic treatment of large superficial colorectal tumors: a cases series of 200 endoscopic submucosal dissections (with video). Gastrointest Endosc 2007;66(5):966–73.
13. Yamazaki K, Saito Y, Fukuzawa M. Endoscopic submucosal dissection of a large laterally spreading tumor in the rectum is a minimally invasive treatment. Clin Gastroenterol Hepatol 2008;6(1):e5–6.
14. Yamamoto H, Kawata H, Sunada K, et al. Successful en-bloc resection of large superficial tumors in the stomach and colon using sodium hyaluronate and small-caliber-tip transparent hood. Endoscopy 2003;35:690–4.
15. Fujishiro M, Yahagi N, Kakushima N, et al. Outcomes of endoscopic submucosal dissection for colorectal epithelial neoplasms in 200 consecutive cases. Clin Gastroenterol Hepatol 2007;5(6):674–7.
16. Uraoka T, Saito Y, Matsuda T, et al. Endoscopic indications for endoscopic mucosal resection of laterally spreading tumours in the colorectum. Gut 2006; 55(11):1592–7.
17. Fujii T, Hasegawa RT, Saitoh Y, et al. Chromoscopy during colonoscopy. Endoscopy 2001;33:1036–41.
18. Matsuda T, Fujii T, Saito Y, et al. Efficacy of the invasive/non-invasive pattern by magnifying estimate the depth of invasion of early colorectal neoplasms. Am J Gastroenterol 2008;103(11):2700–6.
19. Friedland S, Sedehi D, Soetikno R. Colonoscopic polypectomy in anticoagulated patients. World J Gastroenterol 2009;15(16):1973–6.
20. Sano Y, Fu KI, Saito Y, et al. A newly developed bipolar-current needle-knife for endoscopic submucosal dissection of large colorectal tumors. Endoscopy 2006;38(Suppl 5):E95.
21. Uraoka T, Fujii T, Saito Y, et al. Effectiveness of glycerol as a submucosal injection for EMR. Gastrointest Endosc 2005;61(6):736–40.
22. Tamegai Y, Saito Y, Masaki N, et al. Endoscopic submucosal dissection: a safe technique for colorectal tumors. Endoscopy 2007;39:418–22.
23. Tanaka S, Oka S, Kaneko I, et al. Endoscopic submucosal dissection for colorectal neoplasia: possibility of standardization. Gastrointest Endosc 2007;66(1): 100–7.
24. Soetikno R, Kaltenbach T, Yeh R, et al. Endoscopic mucosal resection for early cancers of the upper gastrointestinal tract [review]. J Clin Oncol 2005;23(20): 4490–8.
25. Hurlstone DP, Atkinson R, Sanders DS, et al. Achieving R0 resection in the colorectum using endoscopic submucosal dissection. Br J Surg 2007;94(12): 1536–42.
26. Antillon MR, Bartalos CR, Miller ML, et al. En bloc endoscopic submucosal dissection of a 14-cm laterally spreading adenoma of the rectum with involvement to the anal canal: expanding the frontiers of endoscopic surgery (with video). Gastrointest Endosc 2008;67(2):332–7.

27. Uraoka T, Kato J, Ishikawa S, et al. Thin endoscope-assisted endoscopic submucosal dissection for large colorectal tumors (with videos). Gastrointest Endosc 2007;66:836–9.
28. Sakamoto N, Osada T, Shibuya T, et al. The facilitation of a new traction device (S-O clip) assisting endoscopic submucosal dissection for superficial colorectal neoplasms. Endoscopy 2008;40(S 02):E94–5.
29. Saito Y, Fukuzawa M, Matsuda T, et al. Clinical outcome of endoscopic submucosal dissection versus endoscopic mucosal resection of large colorectal tumors as determined by curative resection. Surg Endosc 2010;24(2):343–52.

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ENDOSCOPY MINISERIES

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

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**Key words**
chromoendoscopy, colonic, endoscopic, esophageal, gastric, gastrointestinal, IT-2, resection.

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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

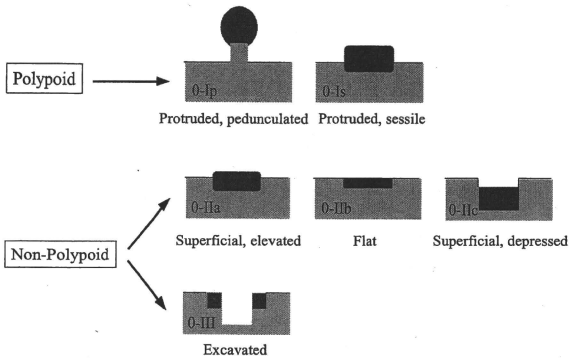


**Figure 1** Classification of superficial neoplastic lesions of gastrointestinal tract.

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

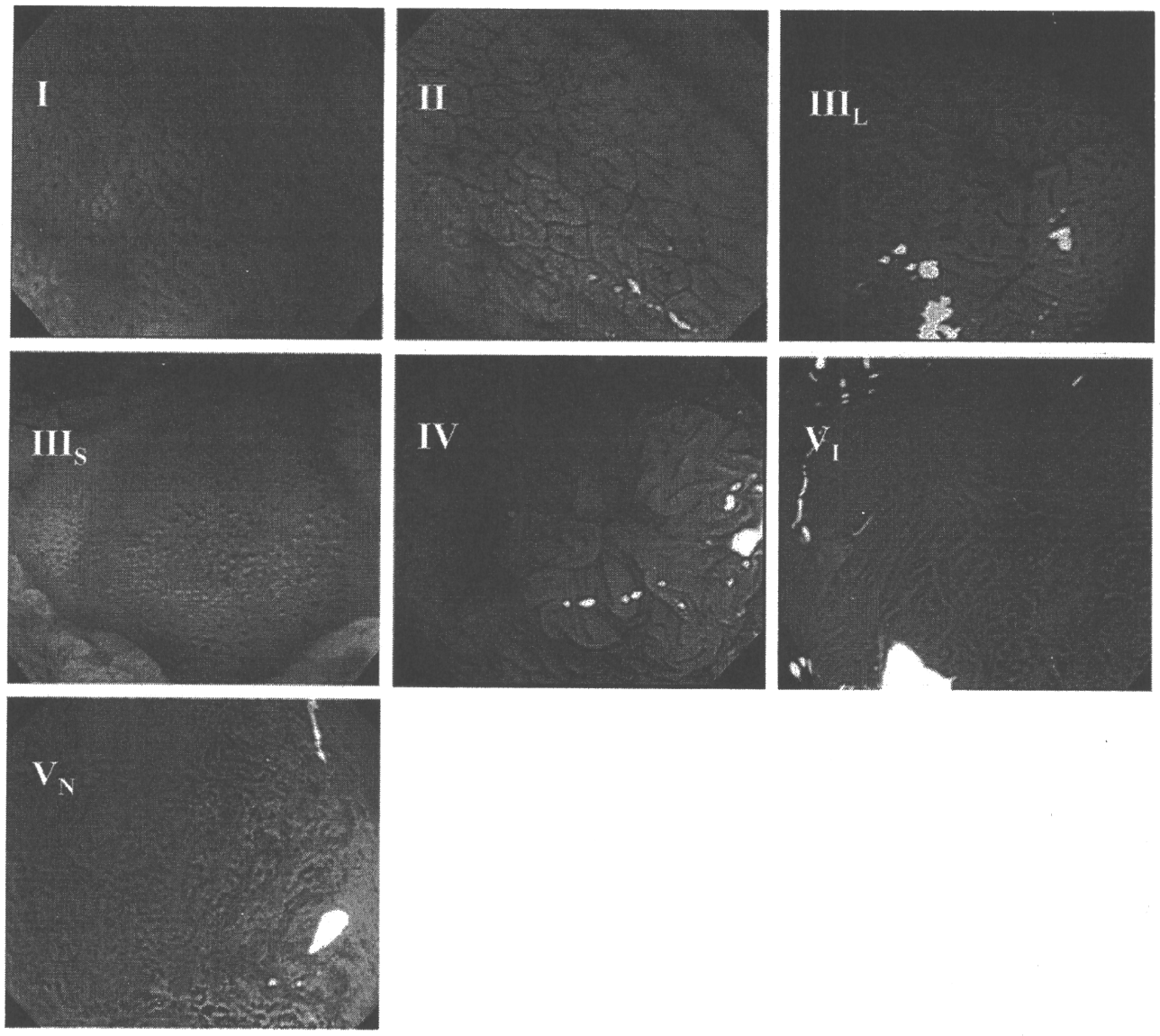


**Figure 2** Pit pattern classification of colorectal neoplasia. I, roundish pits; II, stellar or papillary pits; III$_L$, large roundish or tubulart pits (larger than type I pits); III$_S$, small roundish or tubulart pits (smaller than type I pits); IV, branch-like or gyrus-like pits; V$_I$, irregular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

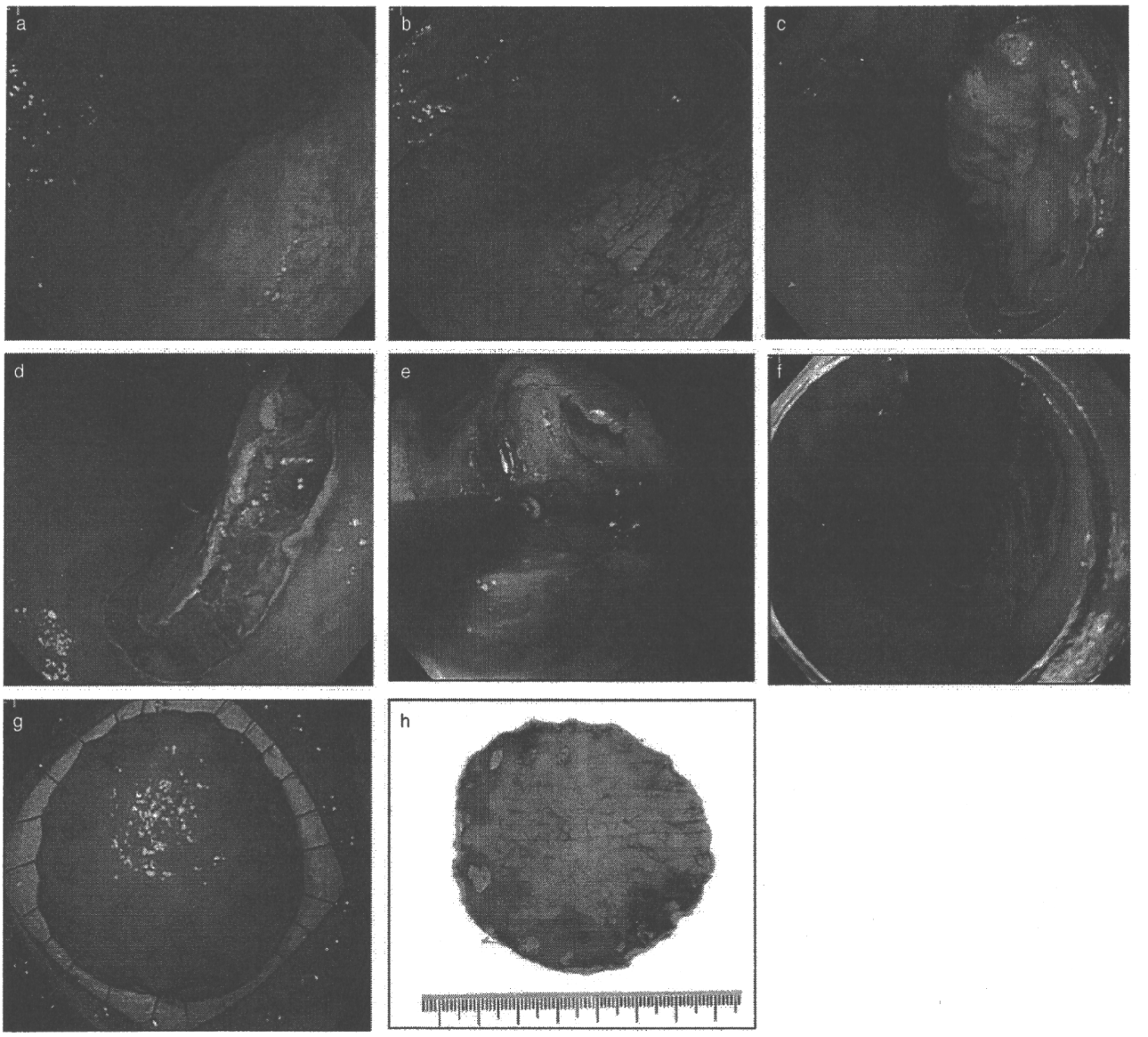


**Figure 3** Gastric endoscopic submucosal dissection technique. a, conventional view; b, chromoendoscopy and marking of lesion margins; c, circumferential incision; d, submucosal injection; e, submucosal dissection; f, gastric wall defect after resection; g, mounted lesion; h, pathological specimen.

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]