Colorectal Endoscopic Submucosal Dissection: Past, Present, and Factors Impacting Future Dissemination

Jason Ferreira, MD¹ Paul Akerman, MD¹

¹Division of Gastroenterology, Department of Medicine, Rhode Island Hospital, Providence, Rhode Island

Clin Colon Rectal Surg 2015;28:146–151.

Address for correspondence Jason Ferreira, MD, Division of Gastroenterology, Department of Medicine, Rhode Island Hospital, 593 Eddy Street, Providence, RI 02903 (e-mail: jason.ferreira1@gmail.com).

Abstract

Keywords

- endoscopic submucosal dissection
- colorectal cancer
- endoscopic mucosal resection
- endoscopic en bloc resection

First performed in the stomach for removal of localized gastric tumors, endoscopic submucosal dissection (ESD) has evolved into a technique that is increasingly being employed to resect colorectal lesions. As opposed to endoscopic mucosal resection (EMR), ESD allows the endoscopist to remove large specimens en bloc to provide accurate pathologic evaluation and lower local recurrence rates. ESD is an ideal technique for resection of lesions without lymph node metastases and is becoming the standard of care in Japan as outcomes data has proven it to be equally efficacious, less invasive, and inexpensive as compared with surgery; however, potential risk for complications is high and the procedure is currently not widely available in the Western world. As more interest, endoscopist training, and data supporting the technique's use mount, ESD will also likely become the standard of care in the Western world for resection of localized colorectal lesions.

Endoscopic submucosal dissection (ESD) is an advanced endoscopic technique, originally pioneered in Japan in 1995,¹ whereby resection of gastrointestinal mucosal lesions is performed using special electrosurgical knives that allow direct visualization of the cutting line to carefully dissect an entire lesion en bloc from the mucosa. This technique was developed to overcome the limitations associated with the use of endoscopic mucosal resection (EMR) and it provides a less invasive option to surgery for localized disease.

EMR remains the standard of care in Western countries and it performs well in terms of efficacy and safety for lesions smaller than 2 cm in size.² However, EMR requires piecemeal resection for lesions greater than 2 cm and is, therefore, associated with high local recurrence rates and inability to identify the status of resection margins on pathologic review.³ Surgical treatment for localized disease is more invasive and, therefore, associated with increased morbidity and mortality as compared with endoscopy.⁴

Given the high prevalence of localized gastric cancers in Asian countries, experience with ESD quickly escalated and select skilled endoscopists started to apply this technique for colorectal lesions in the late 1990s.^{5–7} Although associated with high complication rates of perforation and postprocedure bleeding at its inception, colorectal ESD has progressively become safer as experience with the technique has grown and the equipment has become more refined. This review will discuss the history, current indications, and factors limiting future dissemination of colorectal ESD.

Past

Because of the high rate of localized gastric cancers in Asian countries, a handful of skilled endoscopists recognized the need for a minimally invasive endoscopic platform to achieve curative resection of these lesions and were instrumental in developing ESD, which quickly evolved from a procedure designed for gastroesophageal tumors to one for resection

Issue Theme Evolving and Emerging Technologies in Colon and Rectal Surgery; Guest Editors: Thomas E. Cataldo, MD, FACS, FASCRS; Deborah Nagle, MD, FACS, FASCRS

Copyright © 2015 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA.
Tel: +1(212) 584-4662.

DOI <http://dx.doi.org/10.1055/s-0035-1555006>.
ISSN 1531-0043.

of colorectal malignancy as well. Outcomes from initial case series of colorectal ESD procedures performed in the late 1990s to the early 2000s achieved high en bloc resection rates of around 80%, which allowed for accurate pathologic assessment and curative resection, at the expense of high post-procedural complication rates with perforation in some series quoted as more than 10%.^{8,9} Despite this high complication rate, the potential of colorectal ESD as a novel minimally invasive modality to achieve curative resection of gastrointestinal malignancy pushed development of the technique forward. It was clear that modifications to decrease complication rates would need to be instituted before colorectal ESD would be accepted as a viable alternative to surgical intervention. Therefore, further research to refine ESD technique was pursued and resulted in optimization of agents used for submucosal lifting,¹⁰ better electrosurgical knife equipment,^{11–14} realization that CO₂ insufflation was superior,¹⁵ and novel hemostasis¹⁶ and closure techniques.^{17,18}

As these refined techniques were implemented and endoscopists became more experienced, further outcomes research of larger case series accumulated and illustrated significantly improved complication rates. One of the largest case series by Saito et al¹⁹ tracked short-term outcomes on 1,111 colorectal tumors treated with ESD at 10 specialized institutions from June 1998 to February 2008 and showed en bloc and curative resection rates of 88 and 89%, respectively. Average procedure time in this series was 116 minutes with mean tumor size of 3.5 cm. Perforations occurred in 54 cases (4.9%) and there were 17 cases of postoperative bleeding (1.5%) with only 5 cases requiring emergency surgery. Similar results were demonstrated in a subsequent single center study by Lee et al²⁰ of 1,000 consecutive colorectal ESD cases performed between October 2006 and August 2011. Overall en bloc resection rate in this study was 97.5% with a mean tumor size of 2.41 cm and a perforation rate of 5.3%. Of the 53 perforations, 50 cases were treated with conservative management with or without endoscopic clipping and only 3 patients required laparoscopic surgery. These findings were also echoed in a systematic review by Repici et al²¹ which reviewed 2,841 colorectal ESD cases performed from January 1999 to December 2010 and showed an 88% rate of curative resection with only a 1% rate of surgery to correct ESD complications.

More recent case series using the most current techniques have shown even better results with shorter procedure times despite resection of larger specimens. Hotta et al²² reported an en bloc resection rate of 92.5% with an average procedural time of 48.5 minutes to resect an average-sized specimen of 4.05 cm in a case series reporting on 146 ESD cases performed between January 2009 and July 2011. Perforation and delayed bleeding occurred only in 2.1 and 1.4% of the cases, respectively. Even more impressive results were recorded in one of the most recent case series by Nawata et al²³ which reviewed 150 colorectal ESD cases from April 2010 to July 2013, including 16 tumors greater than 5 cm with no complications observed.

While there are many case series highlighting the efficacy and safety of colorectal ESD by skilled endoscopists, long-

term outcomes have only recently started to be published. The largest series detailing long-term outcomes was published by Niimi et al²⁴ who reviewed 310 consecutive colorectal ESD cases performed between July 2000 and December 2008. The rate of en bloc resection was 90.3% with a 4.5% intra-endoscopy perforation rate which were all treated successfully during the case by endoscopic clipping. There was one instance of delayed perforation requiring surgical intervention and a 1.3% rate of post-ESD bleeding which was managed endoscopically without blood transfusion. This cohort was followed for a median of 38.7 months at which point 4 of the 20 patients for which en bloc resection via ESD was not possible were found to have local recurrence of disease, whereas no local recurrence was seen in 90.3% of the cases with successful en bloc resection. Three- and 5-year disease specific survival was 100% and overall survival at 3 and 5 years was 97.1 and 95.3%, respectively.

In addition to general outcomes of colorectal ESD, research has also been directed toward outcomes in special populations. Elderly patients would potentially derive the most benefit from a minimally invasive curative procedure for colorectal malignancy and three studies have demonstrated equal outcomes for colorectal ESD in the elderly (defined as > 75 in two studies^{25,26} and > 80 in another study²⁷) when compared with younger populations. Further studies have also reviewed outcomes on patients who have perforated as a result of colorectal ESD and have shown that most perforations can be treated with endoscopic clipping if noted at the time of the procedure, and delayed microperforations can also be treated conservatively by making patients NPO (nil per os or nothing by mouth) and prescribing empiric antibiotics.²⁸ Criteria for nonsurgical treatment of perforation during colorectal ESD have also been established and include absence of diffuse peritonitis and successful closure of the mucosal defect.²⁹

Efforts are now being directed to predict which patients are destined to have incomplete resection as well as preemptively determining those who will develop complications from colorectal ESD. Ozawa et al³⁰ determined that submucosal fibrosis and poor differentiation at the deepest invasive portion of the lesion are risk factors for positive margins in colorectal ESD for tumors with deep submucosal invasion. This group also suggested that the use of magnifying endoscopy and endoscopic ultrasonography (EUS) before ESD can help determine whether or not the lesion is amenable to en bloc resection.

In terms of predicting post-ESD complications, several studies have described risk factors for adverse outcomes. Risk factors for bleeding after colorectal ESD include lesion location in the cecum and the presence of significant bleeding during the case.³¹ This study also showed a nonsignificant trend toward resection of larger lesions being associated with more delayed bleeding. Inada et al³² found that difficult ESD cases were associated with large tumor size, high rates of severe fibrosis and perforation, low rates of en bloc resection, and endoscopist inexperience. When Matsumoto et al³³ specifically looked at cases with severe fibrosis, it was found that these cases were associated with low en bloc resection

and high perforation rates even in the hands of an experienced endoscopist. Further data suggest that perforation can be decreased by sufficient experience as well as selection of appropriate electrosurgical knives and argue in support of standardization of technique.⁹

As the safety profile of ESD has improved, several studies have sought to compare colorectal ESD to EMR, which is the current standard of care in Western countries.^{34–36} All studies showed superiority of ESD when compared with EMR for large colorectal lesions in terms of en bloc, curative resection rates, and local recurrence at the expense of being more time-consuming and having higher perforation rates. Specific studies looking at ESD versus EMR for rectal carcinoid resection also show superiority of the ESD technique.³⁷

Present

Given the overwhelming data supporting its efficacy and safety in the hands of experienced endoscopists, colorectal ESD has recently become the standard of care in Japan and was first incorporated in the country's 2010 treatment guidelines for localized colorectal malignancies.³⁸ However, determining which lesions are appropriate to be resected by this technique is a topic in itself, as the ideal tumor would be one that is truly localized with no deep invasion or lymph node metastases. Given that it is often difficult for even the experienced endoscopist to predict the presence of invasion or metastases based on appearance alone, several validated classification schemes, such as the Haggitt,³⁹ Kudo,⁴⁰ and Paris,⁴¹ have been proposed over the years to try to predict the risk of malignancy and invasiveness of mucosal lesions often using the help of chromoendoscopy or magnifying endoscopy.

A description of the surface details of colorectal lesions seen using magnifying endoscopy called pit patterns as elucidated by Kudo et al⁴⁰ has been shown to be predictive of the invasiveness of colorectal lesions. A lesion that is suitable for curative resection via ESD is one with only limited invasion into the submucosa of less than 1,000 μ m. The submucosa is typically subdivided into three layers of equivalent thickness called sm1 to sm3 from superficial to deep, and ESD should only be attempted for curative resection if the lesion is thought to invade no deeper than the sm1 layer. A noninvasive pit pattern as described by Kudo et al⁴⁰ is suggestive of an intramucosal lesion or a tumor with superficial invasion to the sm1 layer and an invasive pit pattern suggests deeper submucosal invasion beyond 1,000 μ m into the sm2 or sm3 layers. The correlation between pit pattern and histology has been confirmed in a large series which demonstrated that 98% of the 2,951 lesions with a noninvasive pit pattern were superficial and 86% of the 156 lesions with an invasive pit pattern had deeper submucosal invasion.⁴¹ Furthermore, this same study verified a risk of nodal metastasis of < 1% with sm1, 6% with sm2, and 14% with sm3 lesions in a review of 300 different tumors.⁴¹ Other techniques that have been proposed to help predict depth of submucosal invasion include narrow-band imaging, which was shown in one study to have a negative predictive value of

92% in ruling out deep invasion,⁴² and endoscopic ultrasonography which gauges the depth of invasion on direct imaging.⁴³

Based on these classification schemes, ideal lesions considered amenable to ESD have been deemed as lateral spreading tumors (LST), which can further be subdivided into nongranular (NG) and granular types (G).⁴⁴ These lesions are ideal because they tend to grow in a sprawling fashion and do not invade deeply into the submucosal layers. Approximately 30 to 56% of the LST–NG lesions will have submucosal invasion, but the invasion tends to be limited primarily to the sm1 layer.⁴⁵ LST–G lesions, on the other hand, have lower rates of submucosal invasion that is generally found under the largest depression or nodule.⁴⁴ Given these characteristics, it is recommended to perform ESD on LST–NG lesions greater than 2 cm and LST–G tumors greater than 3 cm, as those less than 3 cm can be treated with EMR given the low rate of submucosal invasion.⁴⁶ In addition, intramucosal tumors which are difficult to lift using submucosal injection techniques and large sessile polyps that are difficult to resect using EMR are also candidate lesions for colorectal ESD. The technique can also be attempted to treat residual or recurrent tumors not completely resected using EMR as well as rectal carcinoid lesions ranging from 1 to 2 cm.⁴⁶

After identifying a lesion thought to be amenable for curative resection using ESD, careful evaluation of the tumor itself using magnification colonoscopy or EUS should be performed to ensure that the lesion is indeed intramucosal. Biopsies should be avoided before attempted resection, as any manipulation of the tumor tends to cause fibrosis that may interfere with the ability to perform a submucosal lift of the lesion which is required before attempted ESD. Once the lesion is confirmed to be appropriate for intervention, several pieces of equipment are required to carry out an ESD. CO₂ insufflation is necessary to reduce patient abdominal discomfort during these lengthy procedures.¹⁵ Proper submucosal injection agents are also required for successful ESD. Japanese endoscopists appear to currently favor submucosal injections of 10% glycerol and 5% fructose in normal saline solution along with a small amount of indigo carmine dye and sodium hyaluronate solution to achieve a prolonged lift of the lesion and provide direct visualization of the cutting line during dissection of the submucosal layer.^{10,47}

Once the lesion is properly staged and lifted, the next step is to carefully resect it using various electrosurgical knives and counter traction methods that help to reveal the plane of dissection through the submucosa. The technology behind these electrosurgical knives continues to be refined over time to try to optimize the depth of cautery and hemostasis to mitigate risks of perforation and bleeding. Current versions of electrosurgical knives include Flex knife, Hook knife, Flush knife, B-Knife, Mucosectom, Dual knife, and IT knife nano.⁴⁶ There are also several counter traction techniques including distal scope attachments, such as the ST hood short-type, sinker-assisted ESD, thin endoscope-assisted ESD (TEA-ESD), traction S-O clip, clip with line method, and cross-counter technique.⁴⁶ Each knife and counter traction technique confers different characteristics in terms of cutting depths, levels

of hemostasis, and means to expose the submucosal cutting plane which are beyond the scope of this review. There tends to be variation in technique based on the center or individual endoscopist performing the procedure, and efforts are being made to try to standardize technique to optimize curative resection and complication rates.⁹

Future

Given all of the data that is accumulating to support the safety and efficacy of ESD in the hands of skilled endoscopists to achieve curative resection of locally advanced colorectal lesions, it is only a matter of time before it becomes more widely available outside of Asia. One of the major hurdles of disseminating this technique is determining how to train endoscopists in Western countries to not only perform ESD but also to understand how to identify appropriate lesions for the technique using magnification colonoscopy, chromoendoscopy, or EUS. Several recent studies have attempted to address this question. Niimi et al⁴⁸ described a protocol at their institution whereby trainee endoscopists had to complete at least 30 gastric ESD procedures to acquire the basic knowledge and technique of the procedure before being allowed to proceed with attempted rectal ESD under the supervision of experts. This protocol was associated with good results when cases were allocated to the trainee in graded fashion starting with smaller lesions in the distal colon to larger lesions in the proximal colon.

Although this training technique appears to be successful in Asian countries, it would probably not be feasible in Western countries given the decreased prevalence of early gastric cancer and resultant lack of gastric lesions to train on. With this limitation in mind, Iacopini et al⁴⁹ proposed an alternative method of training using pig models of gastric ESD as well as observation time at a high volume center in Japan. After learning ESD techniques in an animal model, the endoscopist being trained then proceeded to perform the human rectal ESD followed by proximal colon ESD in a stepwise fashion once competence, which was defined as an 80% en bloc resection rate and statistically significant decrease in operating time, was achieved in the rectal cases. Using this technique for a single endoscopist, the study reported an 80% resection rate in the rectum after five procedures with the operating time decreasing significantly after 20 procedures, while competence in proximal colonic ESD was achieved after 20 procedures for both resection rate and operating time with perforations occurring in three patients during the training period. Furthermore, a recent study by Sakamoto et al,⁵⁰ detailing the experience of 20 trainee endoscopists performing a total of 164 colorectal ESD cases, confirms the safety and efficacy of this procedure with inexperienced operators under supervision. En bloc resection rate was 95% with a median procedure time of 95 minutes and complications were limited to a 4% perforation rate and 3% rate of delayed bleeding.

Other than training, remaining barriers for widespread dissemination of colorectal ESD include the fear of procedural

complications and resulting litigation as well as the lack of a dedicated reimbursement scheme to incentivize the performance of this high-risk, time-consuming procedure. Questions also remain as to the prevalence of amenable lesions for ESD in Western countries and whether or not tumor lateral spreading lesions are more prevalent in Asia.⁵¹ On the other hand, mounting evidence suggests that colorectal ESD for localized colorectal tumors may be more cost effective than traditional surgical resection, which is appealing in our increasingly cost-conscious society.⁵² Furthermore, the patient demands for more minimally invasive procedures with shorter recovery times may also increase adoption of this technique over time.

Conclusion

Colorectal ESD is an endoscopic technique developed in Asia in the late 1990s whereby large locally advanced lesions can be resected en bloc with curative intent as an alternative to more invasive surgical procedures. At first, the technique was limited to a small group of pioneering endoscopists and was associated with a high complication rate, however, with increased experience and better equipment, curative resection rates have increased and complication rates have dramatically decreased. Colorectal ESD has now become the standard of care for appropriate lesions in Asian countries and growing evidence suggests its long-term efficacy and cost reduction when compared with other surgical techniques. Given its advantages, colorectal ESD will probably also become the standard of care in Western countries; however, factors currently limiting its dissemination include adequate endoscopist training, higher than usual procedural complication risk and resulting fear of litigation, as well as establishing a reimbursement scheme that fairly compensates for the higher procedural risk and prolonged time required to complete the procedure. Ongoing efforts need to be directed toward setting protocols whereby Western endoscopists can be trained in the technique and better infrastructure must be organized to establish referral centers of excellence to bring this innovative minimally invasive platform to patients outside of Asia.

References

- 1 Hosokawa K, Yoshida S. Recent advances in endoscopic mucosal resection for early gastric cancer [in Japanese]. *Gan To Kagaku Ryoho* 1998;25(4):476-483
- 2 Repici A, Pellicano R, Strangio G, Danese S, Fagoonee S, Malesci A. Endoscopic mucosal resection for early colorectal neoplasia: pathologic basis, procedures, and outcomes. *Dis Colon Rectum* 2009;52(8):1502-1515
- 3 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(6):1066-1072
- 4 Alves A, Panis Y, Manton G, Slim K, Kwiatkowski F, Vicaute E. The AFC score: validation of a 4-item predicting score of postoperative mortality after colorectal resection for cancer or diverticulitis: results of a prospective multicenter study in 1049 patients. *Ann Surg* 2007;246(1):91-96

- 5 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(4):560–563
- 6 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(8):690–694
- 7 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):678–683
- 8 Taku K, Sano Y, Fu KI, et al. Iatrogenic perforation associated with therapeutic colonoscopy: a multicenter study in Japan. *J Gastroenterol Hepatol* 2007;22(9):1409–1414
- 9 Tanaka S, Oka S, Kaneko I, et al. Endoscopic submucosal dissection for colorectal neoplasia: possibility of standardization. *Gastrointest Endosc* 2007;66(1):100–107
- 10 Fujishiro M, Yahagi N, Nakamura M, et al. Successful outcomes of a novel endoscopic treatment for GI tumors: endoscopic submucosal dissection with a mixture of high-molecular-weight hyaluronic acid, glycerin, and sugar. *Gastrointest Endosc* 2006;63(2):243–249
- 11 Takeuchi Y, Uedo N, Ishihara R, et al. Efficacy of an endo-knife with a water-jet function (Flushknife) for endoscopic submucosal dissection of superficial colorectal neoplasms. *Am J Gastroenterol* 2010;105(2):314–322
- 12 Lee BI. Indications, knives, and electric current: what's the best? *Clin Endosc* 2012;45(3):285–287
- 13 Takeuchi Y, Shimokawa T, Ishihara R, et al. An electrosurgical endoknife with a water-jet function (flushknife) proves its merits in colorectal endoscopic submucosal dissection especially for the cases which should be removed en bloc. *Gastroenterol Res Pract* 2013;2013(13):530123
- 14 Harada A, Gotoda T, Fukuzawa M, Moriyasu F. Clinical impact of endoscopic devices for colorectal endoscopic submucosal dissection. *Digestion* 2013;88(2):72–78
- 15 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(3):537–542
- 16 Yoshida N, Naito Y, Kugai M, et al. Efficient hemostatic method for endoscopic submucosal dissection of colorectal tumors. *World J Gastroenterol* 2010;16(33):4180–4186
- 17 Tsuji Y, Ohata K, Gunji T, et al. Endoscopic tissue shielding method with polyglycolic acid sheets and fibrin glue to cover wounds after colorectal endoscopic submucosal dissection (with video). *Gastrointest Endosc* 2014;79(1):151–155
- 18 Fujihara S, Mori H, Kobara H, et al. The efficacy and safety of prophylactic closure for a large mucosal defect after colorectal endoscopic submucosal dissection. *Oncol Rep* 2013;30(1):85–90
- 19 Saito Y, Uraoka T, Yamaguchi Y, et al. A prospective, multicenter study of 1111 colorectal endoscopic submucosal dissections (with video). *Gastrointest Endosc* 2010;72(6):1217–1225
- 20 Lee EJ, Lee JB, Lee SH, et al. Endoscopic submucosal dissection for colorectal tumors—1,000 colorectal ESD cases: one specialized institute's experiences. *Surg Endosc* 2013;27(1):31–39
- 21 Repici A, Hassan C, De Paula Pessoa D, et al. Efficacy and safety of endoscopic submucosal dissection for colorectal neoplasia: a systematic review. *Endoscopy* 2012;44(2):137–150
- 22 Hotta K, Yamaguchi Y, Saito Y, Takao T, Ono H. Current opinions for endoscopic submucosal dissection for colorectal tumors from our experiences: indications, technical aspects and complications. *Dig Endosc* 2012;24(Suppl 1):110–116
- 23 Nawata Y, Homma K, Suzuki Y. Retrospective study of technical aspects and complications of endoscopic submucosal dissection for large superficial colorectal tumors. *Dig Endosc* 2014;26(4):552–555
- 24 Niimi K, Fujishiro M, Kodashima S, et al. Long-term outcomes of endoscopic submucosal dissection for colorectal epithelial neoplasms. *Endoscopy* 2010;42(9):723–729
- 25 Yoshida N, Naito Y, Sakai K, et al. Outcome of endoscopic submucosal dissection for colorectal tumors in elderly people. *Int J Colorectal Dis* 2010;25(4):455–461
- 26 Tamai N, Saito Y, Sakamoto T, Nakajima T, Matsuda T, Tajiri H. Safety and efficacy of colorectal endoscopic submucosal dissection in elders: clinical and follow-up outcomes. *Int J Colorectal Dis* 2012;27(11):1493–1499
- 27 Uraoka T, Higashi R, Kato J, et al. Colorectal endoscopic submucosal dissection for elderly patients at least 80 years of age. *Surg Endosc* 2011;25(9):3000–3007
- 28 Yoon JY, Kim JH, Lee JY, et al. Clinical outcomes for patients with perforations during endoscopic submucosal dissection of laterally spreading tumors of the colorectum. *Surg Endosc* 2013;27(2):487–493
- 29 Hotta K, Shinohara T, Oyama T, et al. Criteria for non-surgical treatment of perforation during colorectal endoscopic submucosal dissection. *Digestion* 2012;85(2):116–120
- 30 Ozawa S, Tanaka S, Hayashi N, et al. Risk factors for vertical incomplete resection in endoscopic submucosal dissection as total excisional biopsy for submucosal invasive colorectal carcinoma. *Int J Colorectal Dis* 2013;28(9):1247–1256
- 31 Suzuki S, Chino A, Kishihara T, et al. Risk factors for bleeding after endoscopic submucosal dissection of colorectal neoplasms. *World J Gastroenterol* 2014;20(7):1839–1845
- 32 Inada Y, Yoshida N, Kugai M, et al. Prediction and treatment of difficult cases in colorectal endoscopic submucosal dissection. *Gastroenterol Res Pract* 2013;2013(13):523084
- 33 Matsumoto A, Tanaka S, Oba S, et al. Outcome of endoscopic submucosal dissection for colorectal tumors accompanied by fibrosis. *Scand J Gastroenterol* 2010;45(11):1329–1337
- 34 Tajika M, Niwa Y, Bhatia V, et al. Comparison of endoscopic submucosal dissection and endoscopic mucosal resection for large colorectal tumors. *Eur J Gastroenterol Hepatol* 2011;23(11):1042–1049
- 35 Kobayashi N, Yoshitake N, Hirahara Y, et al. Matched case-control study comparing endoscopic submucosal dissection and endoscopic mucosal resection for colorectal tumors. *J Gastroenterol Hepatol* 2012;27(4):728–733
- 36 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(9):751–757
- 37 Zhong DD, Shao LM, Cai JT. Endoscopic mucosal resection vs endoscopic submucosal dissection for rectal carcinoid tumours: a systematic review and meta-analysis. *Colorectal Dis* 2013;15(3):283–291
- 38 Watanabe T, Itabashi M, Shimada Y, et al. Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2010 for the treatment of colorectal cancer. *Int J Clin Oncol* 2012;17(1):1–29
- 39 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(2):328–336
- 40 Kudo S, Kashida H, Nakajima T, Tamura S, Nakajo K. Endoscopic diagnosis and treatment of early colorectal cancer. *World J Surg* 1997;21(7):694–701
- 41 The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon: November 30 to December 1, 2002. *Gastrointest Endosc* 2003;58(6, Suppl):S3–S43
- 42 Hayashi N, Tanaka S, Hewett DG, et al. Endoscopic prediction of deep submucosal invasive carcinoma: validation of the narrow-band imaging international colorectal endoscopic (NICE) classification. *Gastrointest Endosc* 2013;78(4):625–632

- 43 Yanai H, Matsumoto Y, Harada T, et al. Endoscopic ultrasonography and endoscopy for staging depth of invasion in early gastric cancer: a pilot study. *Gastrointest Endosc* 1997;46(3):212–216
- 44 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):1592–1597
- 45 Saito Y, Sakamoto T, Fukunaga S, et al. Significance of macroscopic classification of laterally spreading tumors in determining endoscopic treatment strategy. *Stom Intest* 2010;45(6):1001–1010
- 46 Saito Y, Yamada M, So E, et al. Colorectal endoscopic submucosal dissection: technical advantages compared to endoscopic mucosal resection and minimally invasive surgery. *Dig Endosc* 2014;26 (Suppl 1):52–61
- 47 Uraoka T, Fujii T, Saito Y, et al. Effectiveness of glycerol as a submucosal injection for EMR. *Gastrointest Endosc* 2005;61(6):736–740
- 48 Niimi K, Fujishiro M, Goto O, Kodashima S, Koike K. Safety and efficacy of colorectal endoscopic submucosal dissection by the trainee endoscopists. *Dig Endosc* 2012;24(Suppl 1):154–158
- 49 Iacopini F, Bella A, Costamagna G, et al. Stepwise training in rectal and colonic endoscopic submucosal dissection with differentiated learning curves. *Gastrointest Endosc* 2012;76(6):1188–1196
- 50 Sakamoto T, Sato C, Makazu M, et al. Short-term outcomes of colorectal endoscopic submucosal dissection performed by trainees. *Digestion* 2014;89(1):37–42
- 51 Cohen J. A novel opportunity in minimally invasive colorectal cancer therapy: defining a role for endoscopic submucosal dissection in the United States. *Diagn Ther Endosc* 2013;2013(13):681783
- 52 Kiriya S, Saito Y, Yamamoto S, et al. Comparison of endoscopic submucosal dissection with laparoscopic-assisted colorectal surgery for early-stage colorectal cancer: a retrospective analysis. *Endoscopy* 2012;44(11):1024–1030