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Process of technical stabilization of gastric endoscopic submucosal dissection at the National Cancer Center in Japan

STOMACH

Haruhisa Suzuki, Ichiro Oda, Masau Sekiguchi, Seiichiro Abe, Satoru Nonaka, Shigetaka Yoshinaga
Endoscopy Division, National Cancer Center Hospital, Tokyo, Japan

Original Article

ABSTRACT

Background/Aims: Endoscopic submucosal dissection (ESD) was originally developed in 1995 using an insulation-tipped diathermic knife (Olympus, Tokyo, Japan) to achieve *en-bloc* resection of early gastric cancer (EGC). It has been suggested that advances in endoscopic devices and medical equipment, such as the high-frequency generator (1999) and hemostatic forceps (2000), and procedural improvements including post-ESD preventive coagulation of visible vessels in the resection area (2003) led to further progress of ESD; therefore, we investigated the actual process of technical stabilization of gastric ESD.

Materials and Methods: A total of 1,713 consecutive patients with solitary differentiated-type EGC at initial onset underwent ESD at our hospital from 1995 to 2006. We retrospectively assessed ESD outcomes for all patients by dividing them into three chronological periods: 1995-1998 (1st period; 57 patients), 1999-2002 (2nd period; 563 patients), and 2003-2006 (3rd period; 1,093 patients).

Results: The *en-bloc* resection, intraoperative bleeding, and delayed bleeding in the 1st/2nd/3rd period were 52.6%/94.7%/99.3% (1st vs. 2nd, p<0.01; 2nd vs. 3rd, p<0.01), 8.8%/7.1%/1.6% (1st vs. 2nd, no significant difference; 2nd vs. 3rd, p<0.01), and 15.8%/7.6%/3.3% (1st vs. 2nd, p<0.05; 2nd vs. 3rd, p<0.01), respectively.

Conclusion: Gastric ESD has stabilized technically following advances in endoscopic devices and medical equipment together with procedural improvements.

Keywords: Gastric cancer, endoscopy, treatment outcome, complications

INTRODUCTION

Endoscopic submucosal dissection (ESD) is currently widely used in Japan as an initial treatment for early gastric cancer (EGC) with a negligible risk of lymph node (LN) metastasis, even in cases with large and ulcerative lesions (1-12). ESD was originally developed in 1995 at the National Cancer Center Hospital (NCCH), Tokyo, Japan using an insulation-tipped diathermy (IT) knife (KD-610L, Olympus, Tokyo, Japan) to achieve *en-bloc* resection of EGC lesions (2,3,13-15); at that time, a circumferential incision was first made using the IT knife, followed by snaring of the lesion. Unfortunately, necessary devices, such as hemostatic forceps and the endo-cut mode offered by a high-frequency generator, were not available for adequate control of bleeding. The endo-cut mode in the ICC 200 high-frequency generator (Erbe, Tuebingen, Germany) became available at the NCCH in 1999. The endo-cut mode was equipped with automatically controlled dissection and coagulation functions. Therefore, most cases of intraoperative bleeding, except for bleeding occurring in spurts, could be controlled using the IT knife itself. Bleeding that occurred in spurts, however, continued to pose a challenge. Around the year 2000, hot biopsy forceps (Boston Scientific, MA, USA) using the soft coagulation mode of the ICC 200 high-frequency generator were employed as hemostatic forceps to control such bleeding at the NCCH, enabling complete control of bleeding, even when occurring in spurts. Also around this period, ESD was performed without snaring in the final step of the procedure. Post-ESD preventive coagulation for visible vessels in the resection area was introduced in 2003 (16). Other devices, including a cap attachment and a video endoscope equipped with a water jet function, were also introduced around that time.

Address for Correspondence: Haruhisa Suzuki, Endoscopy Division, National Cancer Center Hospital, Tokyo, Japan
E-mail: harusuzu@ncc.go.jp
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Endoscopic submucosal dissection has recently been used increasingly in endoscopic resection (ER) treatment for EGCs, and the total number of patients undergoing ER has increased rapidly not only in our hospital, but also throughout Japan. Under these circumstances, gastric ESD was brought under the cover of the National Health Insurance in 2006. Since it was expected that such advances in endoscopic devices and related medical equipment together with procedural improvements might lead to further technical progress of ESD, we performed this investigation to clarify the technical stabilization of gastric ESD based on our extensive clinical experience.

MATERIALS AND METHODS

Patients

A total of 1,940 patients with 2,198 EGC lesions were diagnosed clinically with differentiated-type EGC with a negligible risk of LN metastasis at initial onset at our hospital. These patients, except those with EGC lesions in the remnant stomach or gastric tube, underwent ESD with curative intent from November 1995 to December 2006 (1,2). We excluded the ESDs performed on 227 patients with 485 synchronous EGCs and retrospectively assessed the clinical outcomes of ESD in the remaining 1,713 patients with solitary EGC lesions by dividing the cases into three chronological groups: 57 patients from the 1st period between 1995 and 1998; 563 patients from the 2nd period between 1999 and 2002; and 1,093 patients from the 3rd period between 2003 and 2006 (Figure 1). During the 1st period, we first made a circumferential incision using the IT knife followed by snaring of the lesion. By the 2nd period, the ICC 200 high-frequency generator and hot biopsy forceps had become available for ESD at the NCCH, and finally, during the 3rd period, post-ESD preventive coagulation for visible vessels in the resection area was performed in most cases of ESD. A step-by-step training system was adopted at our hospital for the ESD procedure (17,18). Trainees at our hospital begin their training by performing surgeries on 10 cases of ESD for lesions in the lower third of the stomach; these lesions are relatively small in size and not associated with ulcer fibrosis, and the surgeries are performed in the presence of hands-on support from experts. Thereafter, they perform ESDs by themselves, primarily with verbal guidance from experts. They are then gradually assigned to perform ESDs in the middle and upper thirds of the stomach for lesions of larger sizes. The learning curve for our trainees to acquire adequate skill in performing ESD in the lower third of the stomach covers about 30 cases. The number of experienced endoscopists who performed at least 30 gastric ESDs among all the endoscopists performing gastric ESD, including trainees, during each of the three chronological periods were as follows: 1 (17%) among 6 in the 1st period, 4 (17%) among 24 in the 2nd period, and 14 (29%) among 48 in the 3rd period.

We assessed the clinical characteristics of the patients with EGC, including age, gender, tumor size, tumor location, the existence of ulceration, and the following ESD outcomes: procedure time, *en-bloc* resection, R0 resection, and complications including bleeding and perforation in each of the three chronological periods. The definitions of the characteristics of the EGC lesions such as the tumor size, tumor location, and the existence of ulceration were based on the Japanese classification of gastric carcinoma and the Japanese gastric cancer treatment guidelines (1,19).

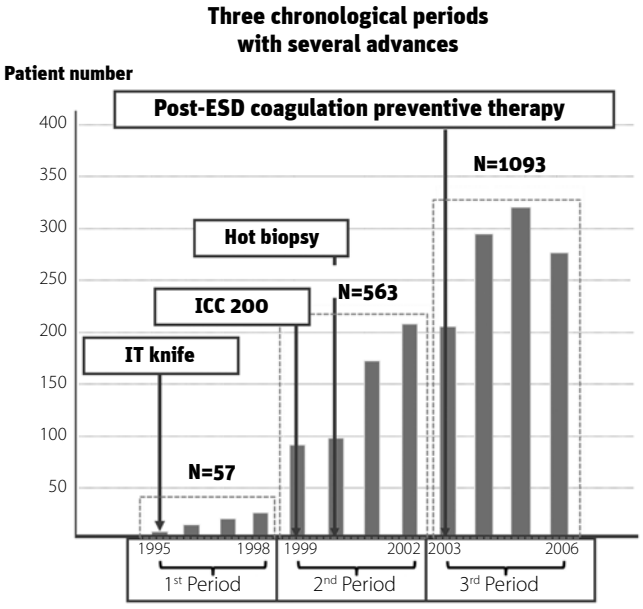

Figure 1. Three chronological periods with multiple advances.

The risks and benefits of the ESD procedure were thoroughly explained to each patient, and written informed consent was obtained from each patient in accordance with our institutional protocol prior to ESD treatment.

Evaluation of the ESD procedures

An *en-bloc* resection was defined as a one-piece resection, while R0 resection was defined as *en-bloc* resection with tumor-free horizontal margins (HM) and vertical margins (VM) (1).

Definition of complications

Endoscopic submucosal dissection procedure-related bleeding was subdivided into intraoperative and delayed bleeding (13). Intraoperative bleeding was defined as a decrease of at least 2 g/dL between the pre- and post-procedure in the serum hemoglobin (Hb) levels (except for the same condition occurring due to delayed bleeding after the ESD procedure), or uncontrollable bleeding during the ESD procedure necessitating surgical intervention. Even if the Hb level had decreased by 2 g/dL by the day after the procedure, if the Hb value was over the normal minimum limit (males, 13.7 g/dL; females, 11.3 g/dL), we judged the condition as being due to postoperative improvement of hemoconcentration (hemodilution). Delayed bleeding was defined as clinical evidence of bleeding after the ESD procedure, such as hematemesis or melena, occurring within

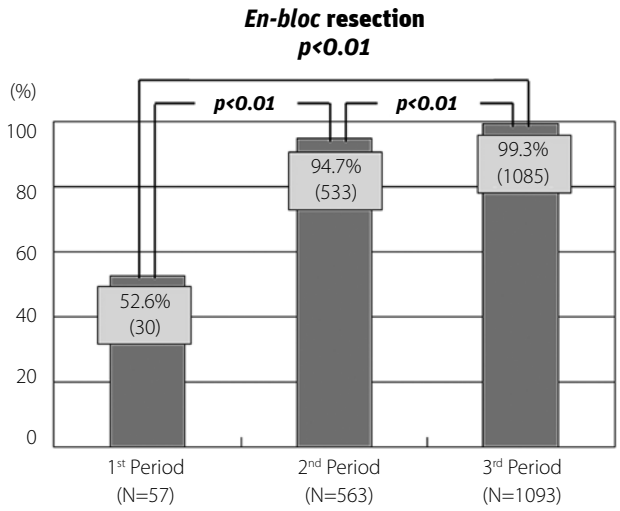

Figure 2. Chronological trends of *en-bloc* resection.

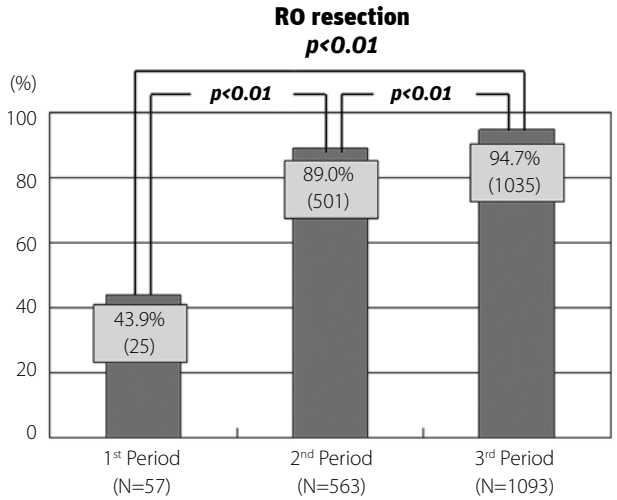

Figure 3. Chronological trends of R0 resection.

30 days after the ESD and necessitating endoscopic treatment. We also evaluated the incidence of bleeding necessitating blood transfusion and the incidence of perforation as observed during ESD procedure or based on clinical evidence after the procedure.

Statistical analysis

Data were analyzed using the Chi-squared test, Fisher's exact test, or Student's t-test, using the statistical analysis software SPSS, version 20 (SPSS Japan Inc, Tokyo, Japan). A probability (p) value of <0.05 was considered statistically significant.

RESULTS

The findings in the 1st/2nd/3rd chronological periods were as follows: The mean age of the 1,713 EGC patients was 64.8±7.4/65.2±9.6/67.3±9.2 years [1st vs. 2nd, no significant difference (NS); 2nd vs. 3rd, p<0.05; 1st vs 3rd, p<0.05]; the male/female ratio was 4.2/3.6/3.6 (1st vs. 2nd, NS; 2nd vs. 3rd, NS; 1st vs. 3rd, NS); the

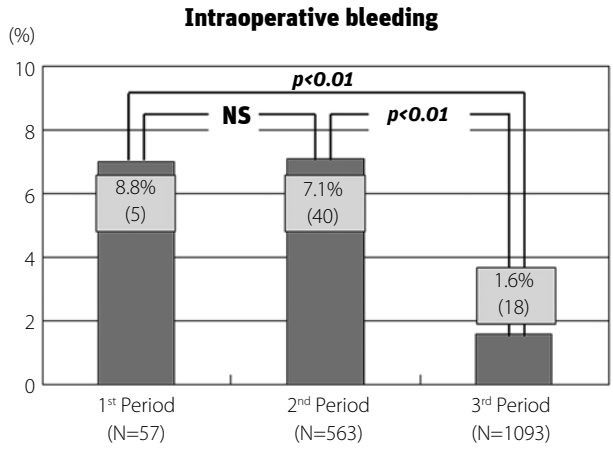

Figure 4. Chronological trends of intraoperative bleeding.

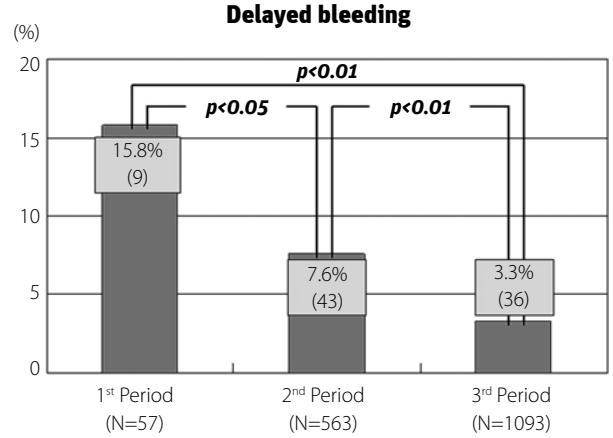

Figure 5. Chronological trends of delayed bleeding.

mean tumor size was 18.8±12.2/20.1±14.0/20.0±13.7 mm (1st vs. 2nd, NS; 2nd vs. 3rd, NS; 1st vs. 3rd, NS); the proportion of lesions in the upper third of the stomach was 7.0% (n=4)/16.7% (n=94)/16.7% (n=182) (1st vs. 2nd, NS; 2nd vs. 3rd, NS; 1st vs. 3rd, NS); the proportion of ulcerative lesions was 3.5% (n=2)/24.2% (n=136)/17.7% (n=194) (1st vs. 2nd, p<0.01; 2nd vs. 3rd, p<0.01; 1st vs. 3rd, p<0.01).

As for the evaluation of the ESD procedures, findings in the 1st/2nd/3rd chronological periods were as follows: the mean procedure time was 85.8±56.7/78.6±65.9/81.7±59.5 min (1st vs. 2nd, NS; 2nd vs. 3rd, NS; 1st vs. 3rd, NS); en-bloc resection was performed in 52.6% (n=30)/94.7% (n=533)/99.3% (n=1.085) of the cases (1st vs. 2nd, p<0.01; 2nd vs. 3rd, p<0.01; 1st vs. 3rd, p<0.01) (Figure 2); R0 resection was performed in 43.9% (n=25)/89.0% (n=501)/94.7% (n=1.035) of the cases (1st vs. 2nd, p<0.01; 2nd vs. 3rd, p<0.01; 1st vs. 3rd, p<0.01) (Figure 3). In addition, regarding ESD-related complications, intraoperative bleeding was observed in 8.8% (n=5)/7.1% (n=40)/1.6% (n=18) of the cases (1st vs. 2nd, NS; 2nd vs. 3rd, p<0.01; 1st vs. 3rd, p<0.01) (Figure 4); delayed bleeding was observed in 15.8% (n=9)/7.6% (n=43)/3.3% (n=36) of the cases (1st vs. 2nd, p<0.05; 2nd vs. 3rd, p<0.01; 1st vs. 3rd, p<0.01) (Figure 5); bleeding that necessitated blood trans-

fusion occurred in 1.8% (n=1)/1.2% (n=7)/0.2% (n=2) of the cases (1st vs. 2nd, NS; 2nd vs. 3rd, p<0.01; 1st vs. 3rd, NS); and perforation was seen in 5.3% (n=3)/5.2% (n=29)/1.9% (n=21) of the cases (1st vs. 2nd, NS; 2nd vs. 3rd, p<0.01; 1st vs. 3rd, NS). None of the patients developed delayed perforation after the ESD procedure. One patient underwent emergency surgery due to intraoperative bleeding in the 1st period, but the remaining patients with complications were successfully managed endoscopically without any need for surgical intervention. The chronological trends of the ESD procedures and related complications are shown in Figures 2-5.

DISCUSSION

The present study is the first report to clarify the detailed process of the technical stabilization of ESD performed for EGC, from the aspects of resectability and the incidence of complications. The methods of ER vary from conventional endoscopic mucosal resection (EMR) to ESD (6,14,15). During the 1980s, several EMR methods, such as strip biopsy and EMR using a cap-fitted endoscope, were developed as ER techniques to remove EGC lesions. These were technically simple, however, the rate of *en-bloc* resections was low, and resection of large and ulcerative lesions was difficult (6). Under these circumstances, during the second half of the 1990s, ESD was developed to achieve *en-bloc* resections even for large and ulcerative lesions (1-5). As the results of the present study indicate, in the early period of gastric ESD, resectability of gastric ESD had been low, in addition to the higher rates of complications because of the lack of necessary equipment and devices and procedural techniques required for successful gastric ESD. After a lapse of 10 years, endoscopic devices and related medical equipment have been developed with further refinements in the procedural techniques, which have led to a higher rate of resectability and lower rate of complications, as well as technical stabilization of gastric ESD. In particular, control of intraoperative bleeding is critical to a successful outcome of ESD; therefore, it has been estimated that improving the management of intraoperative bleeding by various advances in endoscopic devices and medical equipment, together with procedural refinements has enabled complete and safe resection (20,21). Furthermore, post-ESD preventive coagulation of visible vessels in the resection area of ESD, which was introduced in 2003, may have resulted in the lower rate of delayed bleeding observed in the last period (16). Thus, gastric ESD has been performed safely and efficiently in the recent times, in addition to the excellent postoperative course of the patients; in general, the incidence of ESD-related complications has been minimized as a result of the advances.

In the present study, one patient underwent emergency surgery due to intraoperative bleeding in the early period of gastric ESD, but the remaining patients with complications were successfully managed endoscopically without any need for surgical intervention, consistent with previous reports (20,21). However, in cases with bleeding occurring in spurts, there is a risk of the development of cardiopulmonary instability. In addition, if the perforated area is large or if a large amount of time is taken to close the perforation, pneumoperitonium can cause serious secondary problems such as respiratory failure, decreased blood pressure, or increased abdominal pain. Thus, endoscopists must be aware of not only the risk factors for and the incidence of complications but also of the effective and prompt management of such complications.

It seems reasonable to conclude from our study that several advances in endoscopic devices and related medical equipment along with refinements in procedural techniques might have contributed to the stabilization of gastric ESD from the technical aspects. However, it should be noted that the present study was conducted at the National Cancer Center Hospital in Tokyo, which is a major referral cancer center in Japan with vast experience in performing gastric ESD. Therefore, not only advances in ESD procedures, but also greater opportunities to learn and master gastric ESD on the basis of our extensive clinical experience may have led to the satisfactory ESD outcomes in the last period at our hospital. Other countries in East Asia (e.g., Korea) that have the highest incidence rates of gastric cancer have also obtained almost similarly favorable ESD outcomes (22-24). In contrast, some investigators from Western countries have reported poor feasibility and a relatively high postoperative complication rate for ESD, probably because these countries have lesser opportunities for acquiring technical skills for performing ESD due to the lower incidence rates of gastric cancer (25-27). Thus, in order to introduce and standardize ESD in regions where ESD is still in the developmental stage (e.g., European countries), it is necessary to establish an effective training system for ESD in addition to introducing the several advances of ESD (17,18,28,29). Further advances in ESD, including establishment of an effective training system, is expected to facilitate global expansion of the use of ESD in the future.

In conclusion, ESD for EGC has stabilized technically due to advances in endoscopic devices and related medical equipment along with refinements in procedural techniques.

Ethics Committee Approval: N/A.

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author contributions: Concept - H.S., I.O.; Design - H.S., I.O.; Supervision - I.O.; Resource - H.S., I.O.; Materials - H.S., I.O.; Data Collection and/or Processing - H.S.; Analysis and/or Interpretation - H.S., I.O.; Literature Search - H.S., I.O.; Writing - H.S.; Critical Reviews - H.S., I.O., M.S., S.A., S.N., S.Y.

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Conflict of Interest: No conflict of interest was declared by any of the authors.

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REFERENCES

1. Japanese gastric cancer treatment guidelines 2010 (ver. 3). Japanese Gastric Cancer Association. Gastric Cancer 2011; 14: 113-23. **[CrossRef]**
2. 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. **[CrossRef]**
3. Ono H, Kondo H, Gotoda T, et al. Endoscopic mucosal resection for treatment of early gastric cancer. Gut 2001; 48: 225-9. **[CrossRef]**
4. Oyama T, Kikuchi Y. Aggressive endoscopic mucosal resection in the upper GI tract - Hook knife EMR method. Minim Invasive Ther Allied Technol 2002; 11: 291-5.
5. Yamamoto H, Kawata H, Sunada K, et al. Successful one-piece resection of large superficial tumors in the stomach and colon using sodium hyaluronate and small-caliber-tip transparent hood. Endoscopy 2003; 35: 690-4. **[CrossRef]**
6. Gotoda T, Yamamoto H, Soetikno RM. Endoscopic submucosal dissection of early gastric cancer. J Gastroenterol 2006; 41: 929-42. **[CrossRef]**
7. Isomoto H, Shikuwa S, Yamaguchi N, et al. Endoscopic submucosal dissection for early gastric cancer: a large-scale feasibility study. Gut 2009; 58: 331-6. **[CrossRef]**
8. Goto O, Fujishiro M, Kodashima S, Ono S, Omata M. Outcomes of endoscopic submucosaldissection for early gastric cancer with special reference to validation for curabilitycriteria. Endoscopy 2009; 41: 118-22. **[CrossRef]**
9. Gotoda T, Iwasaki M, Kusano C, Seewald S, Oda I. Endoscopic resection of early gastric cancer treated by guideline and expanded National Cancer Centre criteria. Br J Surg 2010; 97: 868-71. **[CrossRef]**
10. Kosaka T, Endo M, Toya Y, et al. Long-term outcomes of endoscopic submucosal dissection for early gastric cancer: A single-center retrospective study. Dig Endosc 2014; 26: 183-91. **[CrossRef]**
11. Tanabe S, Ishido K, Higuchi K, et al. Long-term outcomes of endoscopic submucosal dissection for early gastric cancer: a retrospective comparison with conventional endoscopic resection in a single center. Gastric Cancer 2014; 17: 130-6. **[CrossRef]**
12. Oda I, Oyama T, Abe S, et al. Preliminary results of multicenter questionnaire study on long-term outcomes of curative endoscopic submucosal dissection for early gastric cancer. Dig Endosc 2014; 26: 214-9. **[CrossRef]**
13. Oda I, Gotoda T, Hamanaka H, et al. Endoscopic submucosal dissection for early gastric cancer: technical feasibility, operation time and complications from a large consecutive series. Dig Endosc 2005; 17: 54-8. **[CrossRef]**
14. Gotoda T. Endoscopic resection of early gastric cancer. Gastric Cancer 2007; 10: 1-11. **[CrossRef]**
15. Gotoda T, Jung HY. Endoscopic resection (endoscopic mucosal resection/ endoscopic submucosal dissection) for early gastric cancer. Dig. Endosc 2013; 25 (Suppl 1): 55-63. **[CrossRef]**
16. Takizawa K, Oda I, Gotoda T, et al. Routine coagulation of visible vessels may prevent delayed bleeding after endoscopic submucosal dissection-an analysis of risk factors. Endoscopy 2008; 40: 179-83. **[CrossRef]**
17. Gotoda T, Friedland S, Hamanaka H, Soetikno R. A learning curve for advanced endoscopic resection. Gstrointest Endosc 2005; 62: 866-7. **[CrossRef]**
18. Oda I, Odagaki T, Suzuki H, Nonaka S, Yoshinaga S. Learning curve for endoscopic submucosal dissection of early gastric cancer based on trainee experience. Dig Endosc 2012; 24: 129-32. **[CrossRef]**
19. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma: 3rd English edition. Gastric Cancer 2011; 14: 101-12. **[CrossRef]**
20. Oda I, Suzuki H, Nonaka S and Yoshinaga S. Complications of Gastric Endoscopic Submucosal Dissection. Dig Endosc 2013; 25 (Suppl 1): 71-8. **[CrossRef]**
21. Kim YJ, Park DK. Management of complications following endoscopic submucosal dissection for gastric cancer. World J Gastrointest Endosc 2011; 3: 67-70. **[CrossRef]**
22. Uedo N, Jung HY, Fujishiro M, et al. Current situation of endoscopic submucosal dissection for superficial neoplasms in the upper digestive tract in East Asian countries: a questionnaire survey. Dig Endosc 2012; 24 (Suppl 1): 124-8. **[CrossRef]**
23. Chung IK, Lee JH, Lee SH, et al. Therapeutic outcomes in 1000 cases of endoscopic submucosal dissection for early gastric neoplasms: Korean ESD Study Group multicenter study. Gastrointest Endosc 2009; 69: 1228-35. **[CrossRef]**
24. Ahn JY, Jung HY, Choi KD, et al. Endoscopic and oncologic outcomes after endoscopic resection for early gastric cancer: 1370 cases of absolute and extended indications. Gastrointest Endosc 2011; 74: 485-93. **[CrossRef]**
25. Farhat S, Chaussade S, Ponchon T, et al.; SFED ESD study group. Endoscopic submucosal dissection in a European setting. A multi-institutional report of a technique in development. Endoscopy 2011; 43: 664-70. **[CrossRef]**
26. Neuhaus H. Endoscopic submucosal dissection in the upper gastrointestinal tract: present and future view of Europe. Dig Endosc 2009; 21 (Suppl 1): S4-6. **[CrossRef]**
27. Othman MO, Wallace MB. Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) in 2011, a Western perspective. Clin Res Hepatol Gastroenterol 2011; 35: 288-94. **[CrossRef]**
28. Kakushima N, Fujishiro M, Kodashima S, Muraki Y, Tateishi A, Omata M. A learning curve for endoscopic submucosal dissection of gastric epithelial neoplasms. Endoscopy 2006; 38: 991-5. **[CrossRef]**
29. Yamamoto Y, Fujisaki J, Ishiyama A, Hirasawa T, Igarashi M. Current status of training for endoscopic submucosal dissection for gastric epithelial neoplasm at Cancer Institute Hospital, Japanese Foundation for Cancer Research, a famous Japanese hospital. Dig Endosc 2012; 24: 148-53. **[CrossRef]**