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**Impact of formal training in endoscopic submucosal dissection for early gastrointestinal cancer: A systematic review and a meta-analysis**

Tanimoto MA *et al.* ESD training impact meta-analysis

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**Abstract**

**AIM:** To summarize the clinical impact of a formal training for the effectiveness and safety of endoscopic submucosal dissection for gastrointestinal cancer.

**METHODS:** We searched databases including PubMed, EMBASE and the Cochrane Library and Science citation Index updated to August 2014 to include eligible articles. In the Meta-analysis, the main outcome measurements were *en blo*c resection rate, local recurrence rate (R0) and the incidence of procedure-related complications (perforation, bleeding).

**RESULTS:** *En bloc* resection was high for both, dissecting stomach tumors with an overall percentage of 93.2% (95%CI: 90.5, 95.8) and dissecting colorectal tumors with an overall percentage of 89.4% (95%CI: 85.1, 93.7). Although the number of studies reporting R0 resection (the dissected specimen was revealed free of tumor in both vertical and lateral margins) was small, the overall estimates for R0 resection were 81.4% (95%CI: 72, 90.8) for stomach and 85.9% (95%CI: 77.5, 95.5) for colorectal tumors, respectively. The analysis showed that the percentage of immediate perforation and bleeding were very low; 4.96 (95% 3.6, 6.3) and 1.4% (95%CI: 0.8, 1.9) for colorectal tumors and 3.1% (95%CI: 2.0, 4.1) and 4.8% (95%CI: 2.8, 6.7) for stomach tumors, respectively.

**CONCLUSION:** In order to obtain the same rate of success of the analyzed studies it is a necessity to create training centers in the western countries during the “several years” of gastroenterology residence first only to teach EGC diagnose and second only to train endoscopic submucosal dissection.

**Key words**: Endoscopic submucosal dissection; Training

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**Core tip:** Endoscopic submucosal dissection (ESD) has gained widespread use in Asia because of a well-documented higher en bloc and curative resection rates for early neoplastic gastrointestinal lesions. Unfortunately, ESD has not been yet widespread in the West due to remain the very flat learning curve and lack of training resources. In Asia, ESD skills are acquired in the time-honored mentor/apprentice model over a period of few years. Although, there is a great heterogeneity in the medical literature reports about training and learning curve of ESD. In this meta analysis we had analyzed the results from these training centers reports. Because technical maturation often requires measurable standard to achieve.

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**INTRODUCTION**

There are few training centers around the world in which an endoscopy fellow can be trained in the ESD technique. There is probably only a formal ESD training program in Asian countries (Japan, South Korea and China). As ESD is a highly technical and demanding minimal invasive procedure, endoscopists require training before performing the procedure. The operator must possess a good understanding of all aspects of ESD: full knowledge of early GI lesions, the endoscopes, EUS, ESD knives, electro surgical unit parameters, injection agents, sedation, complications and other aspects.

In Asian countries like Japan, South Korea and China, gastrointestinal intraepithelial neoplasm is more prevalent than in Western countries. Accordingly, most medical institutions in Japan provide training (in a stepwise manner): initially, endoscopists participate as an assistant, starting with ESD in the gastric antrum or the rectum with a supervisor, then in the proximal stomach, the colon or the esophagus. In contrast, in Western countries, cases of early gastrointestinal lesions are less diagnosed, resulting in a slow introduction of the ESD technique. Efforts are currently underway to change this situation. Possible solutions to improve training and experience are the use of animal models and the establishment of training centers. Further, deficiencies in training and experience can now be more rapidly overcome as a result of new technologies. As described above, new advances have led to devices that are easy to handle, making it simpler for beginners to perform ESD. Devices with scissors and forceps, like the Clutch Cutter or other covered devices, are easier to use, leading to fewer complications (*e.g*., perforation), although the procedure time is longer than those with non-covered devices. The other new approach in ESD, the use of mesna (2-mercaptoethanesulfonate sodium), may also make submucosal dissection safer and faster.

**MATERIALS AND METHODS**

***Data sources and searches***

We searched databases including PubMed, EMBASE and the Cochrane Library and Science citation Index updated to August 2014 to identify related articles in English language that review Endoscopic submucosal dissection training[1-121]. All bibliographies were indentified in the reference lists and were analyzed separately by two experts in ESD during the selection process. The initial searching Medical Subject Headings *(*MeSH*)* used were “Endoscopic submucosal dissection”, afterwards “Endoscopic submucosal dissection training” and finally the articles that does not analyze the operation time, en bloc resection rate, local recurrence rate and the incidence of procedure-related complications were excluded (Figure 1A).

***Study selection***

The inclusion and exclusion criteria are shown in Table 1.

***Data extraction and quality assessment***

Data were extracted with a predefined MeSH criteria by one investigator and confirmed by the others according to a data extraction form. The following data were collected: year of publication, first author, country, number of participants, site of the lesions and lesions in each group, tumor size and endpoints (*en bloc* resection rate, local recurrence rate, and complications). The definitions of the endpoints were: (1) site of resection; (2) *en bloc* -removal in one piece without fragmentation; (3) local recurrencte rate - during the follow-up an histological diagnosis of tumor at the resected site; (4) operation time - from marking to complete resection; and (5) rate of complications - related bleeding or perforation incidence.

***Statistical analysis***

**Meta-analysis:** The statistical review of the study was performed by a biomedical statician of the Infectology department from the National Institute of Medical Sciences and Nutrition S.Z. (Mexico). The Dersimonian/Laird random effects model was used due to expected heterogeneity among studies. Statistical heterogeneity was assessed using the Higgins *I2* test. For the Higgins test, *I2* < 25% indicates low heterogeneity, 25%-50% moderate and > 50% severe heterogeneity. Preplanned analyses included analyses limited to studies including resection of stomach tumors and colorectal tumors using endoscopic submucosal dissection. Data quality assurance and data analysis were conducted using StataTM 12.0 (Statistics/Data analysis Special Edition; Statacorp, College Station, Texas, U.nited States). All statistical test in the analysis were two-sided and were conducted with α = 0.05 [95% Confidence intervals (CI)].

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**RESULTS**

***Study selection***

A total of 1853 were retrieved with the MeSH “endoscopic submucosal dissection” to estimate the potential studies for the meta-analysis. Afterwards, we refine the search including the word training with the MeSH “endoscopic submucosal dissection training” and 1740 were excluded. In the remaining 113 potential studies 68 were excluded because of the exclusion criteria in Table 1[1-12,14-16,18-28,30-33,35-40,42-50,52-62,64-82,95,96-114].

From the 45 remaining studies 28 were included in the meta-analysis. All of these 28 studies were in human patients respective case/control studies, not randomized controlled trials.

***En bloc resection rate (Figures 1B and C)***

The present analysis shows that the percentage of *en bloc* resection was high for both, dissecting stomach tumors with an overall percentage of 93.2% (95%CI: 90.5, 95.8) and dissecting colorectal tumors with an overall percentage of 89.4% (95%CI: 85.1, 93.7).

***Local recurrence rate (Figures 1D and E)***

Although the number of studies reporting R0 resection (the dissected specimen was revealed free of tumor in both vertical and lateral margins) was small, the overall estimates for R0 resection were 81.4% (95%CI: 72, 90.8) and 85.9% (95%CI: 77.5, 95.5) for stomach and colorectal tumors, respectively.

***Procedure-related complications***

Data for procedure-related complications were reported in all of the studies included in the meta-analysis. The analysis showed that the percentage of immediate perforation and bleeding were very low.

***Perforation rate (Figures 1F and G)***

The perforation rate was 3.1% (95%CI: 2.0, 4.1) for stomach tumors and 4.96 (95% 3.6, 6.3) for colorectal tumors. In most studies, late perforation and bleeding was not reported and thus not included in the current analysis.

***Bleeding rate (Figures 1H and I)***

The bleeding rate was 4.8% (95%CI: 2.8, 6.7) for stomach tumors and 1.4% (95%CI: 0.8, 1.9) for colorectal tumors.

Finally, the last 17 studies were in animal models and even though they were not included in the meta-analysis, we resume them in a table that contains: author, year, type of animal model, number of patients, organ and main conclusion. (Table 2)[13,17,29,34,41,51,63,83,94,96,115-121].

**DISCUSSION**

To our knowledge, this systematic review and meta-analysis is the first to analyze the impact of a formal training in ESD for early gastrointestinal cancer. Probably there are ESD formal training centers only in the Asian countries (Japan, China and South Korea). For the above reason almost 100% of the analyzed studies were from Asia. All the studies included in our analysis were done in a formal ESD training setting although most of them does not include the number of trainees and/or a comparison between preceptees *vs* experts and thus not included in the current analysis. The present study shows that the percentage of *en bloc* resection was high for both, dissecting stomach and colorectal tumors. Even with a small number of studies reporting R0 resection (the dissected specimen was revealed free of tumor in both vertical and lateral margins), the overall estimates for R0 resection were 81.4% (95%CI: 72, 90.8) and 85.9% (95%CI: 77.5, 95.5) for stomach and colorectal tumors respectively. The analysis also showed that the percentage of immediate perforation and bleeding were very low. ESD was developed in Japan in the year 1999 to preserve intact gastrointestinal function and for *en bloc* resection of lesions larger than 2 cm. ESD also has made it possible to resects early gastrointestinal tumors even with large submucosal fibrosis or ulcerative scars in an *en bloc* fashion and it has gradually gained acceptance as a standard treatment for these tumors. The ESD era began with pioneers trained in Japan on South Korea (2003-now) and in China (2006-now) rapidly gaining expertise and acceptance. Hotta *et al*[77] reported that 80 procedures must be carried out to acquire skill at ESD. In order to acquire this skill all the procedures even in animal models must be carried out under supervision of ESD experts and with availability of all the equipment and high trained team. Because this is not just a fact of endoscopic skills but of knowledge, technology and team work. This procedure should never be trained in an experimental (“not supervised by an ESD expert”) fashion with animal models just focusing on the dissection technique without firstly make a good analysis of the borders and deepness of the early gastrointestinal cancer (EGC) lesion invasion under an expert supervision. Probably the lack of research, diagnose and case series of early gastrointestinal cancer lesions in the western countries are due to a lack of formal training centers firstly with certified EGC experts and afterwards ESD experts. In order to obtain the same rate of success of the analyzed studies it is a necessity to create training centers in the western countries during the “several years” of gastroenterology residence first only to teach EGC diagnose and second only to train ESD. In the same manner that the medical techniques should never anticipate the clinic, nor the endoscopic skills, nor the technology or both could substitute tutorial training by an expert.

Although, there is a great heterogeneity in the medical literature reports about training and learning curve of ESD. In this meta analysis we had analyzed the results only from the formal training centers reports. The results presented in the literature that can be included in our meta analysis to clarify the training efficacy concerning the procedure length, completeness and complications such as En bloc resection rate, Local recurrence rate, Procedure-related complications, Perforation and Bleeding rate were included. But unfortunately, we can only assume that the procedure was done in a formal training center, such as the one in which some of the authors had been trained. Even when there are very detailed description of the learning curve specially in the Japanese and European reports there is a great heterogeneity of the numeric information presented and thus cannot be included in a meta analysis. There is not uniform information if the procedure was done by a trainee with/without supervision. Also, the analyzed issues in each report has great heterogeneity (animal model, human, periods of time, *etc.*) and the results are presented for example in ranges but not in mean ± SD. Because technical maturation often requires measurable standard to achieve. As this procedure become more standardized in the Western countries we can also be able to make more precise comparisons between training centers and learning curve. There are no shortcuts and probably we have to find out the way to establish training centers with the same training scheme as the Asian countries if we are expecting to have similar rates of success, but as always time will say.

**COMMENTS**

***Background***

Endoscopic submucosal dissection (ESD) was originally developed to preserve intact gastrointestinal function after *en bloc* resection of early GI cancer lesions larger than 2 cm.

***Research frontiers***

This systematic review and meta-analysis is the first to analyze the impact of a formal training in ESD for early gastrointestinal cancer.

***Innovations and breakthroughs***

Authors designed the meta-analysis to systematically evaluate the ESD formal training impact in the early gastrointestinal cancer regarding *en bloc* resection rate, local recurrence rate and procedure-related complications rate.

***Applications***

The conclusions of this meta-analysis can help the endoscopists to select the right tool to treat early gastrointestinal cancer lesions.

***Terminology***

ESD is a newly developed technique in which submucosal dissection is carried out using an electrocautery knife to acquire a single-piece specimen, it is developed for *en bloc* removal of large (> 2 cm) GI tract lesions.

***Peer-review***

This paper is intereting and valuable because technical maturation often requires measurable standard to achieve.

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**P-Reviewer:** Kita H, Suzuki N **S-Editor:** Ji FF **L-Editor: E-Editor:**

**Table 1 Inclusion and exclusion criteria**

|  |  |
| --- | --- |
| Inclusion criteria | Exclusion criteria |
| ESD in patients Report ESD success en bloc resection rate, local recurrence rate (R0) and the incidence of procedure-related complications (perforation, bleeding)Written in English | Case reportCommentReviewLetters to editorInsufficient dataGuidelines |

ESD: Endoscopic submucosal dissection.

**Table 2 Endoscopic submucosal dissection studies in animal models**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Ref. | Year | Model | N | Organ | Main Conclusion |
| González *et al*[17] | 2013 | Porcine | **30** | Stomach | A sequential ESD training program of a unique endoscopist contributed to learning ESD for its subsequent application in humans, yielding good results in efficacy and safety |
| Takizawa *et al*[13] | 2013 | Porcine | **30** | Colon | Large mucosal target sites in the rectum and distal colon could be safely removed en bloc by means of a hybrid technique, SEMR, with blunt submucosal balloon dissection |
| Moss *et al*[115] | 2012 | Porcine | **10** | Colon | HK-ESD with SG submucosal injection is superior to CSI-EMR for en bloc excision of 50 mm diameter lesions. The technique is rapidly learn |
| Gostout *et al*[41] | 2012 | Porcine | **16** | Rectum and colon | Large mucosal target sites in the rectum and distal colon can be safely removed en bloc by means of a hybrid technique, ie, submucosal endoscopy with mucosal resection, combining elements of ESD with our SEMF method |
| Kumano *et al*[117] | 2012 | Porcine | **24** | Esophagus | PCH permits more reliable ESD of the esophagus without complications than do SH and HS |
| Balogh*et al*[51] | 2012 | Porcine | **15** | Esophagus | Training in live pig models could help endoscopists to overcome the learning curve and minimize the risk of complications before starting the procedure in humans Reduction in the resection time and low risk of complications, especially bleeding, could be achieved by the application of a flush knife |
| Tanaka *et al*[63] | 2012 | Porcine *ex vivo* | **10**  | stomach | Ex vivo training model was helpful to endoscopists with experience in gastric ESD in acquiring the basic skills for performing esophageal ESD |
| Parra-Blanco *et al*[29] | 2011 | Porcine | **18** | Stomach | A Clip-band traction technique is feasible, safe, effective, and relatively inexpensive gastric ESD |
| Von Renteln *et al*[118] | 2011 | Porcine | **12** | Stomach | Submucosal mesna injection did not affect ESD procedure times but was associated with a trend toward a lower incidence of intraprocedural bleeding |
| Tanimoto *et al*[94] | 2011 | Canine | **10** | Esophagus | ECE-ESD training is feasible in canine models for postgraduate endoscopy fellows |
| Hon *et al*[96] | 2010 | Porcine | **10** | Colon | Technical proficiency improved by repetition. This setup may be a promising training model for endoscopists working in areas with a low incidence of early gastric cancer |
| Von Renteln *et al*[119] | 2010 | Porcine | **12** | Stomach | The flexible Maryland dissector was demonstrated to be efficient, safe, and feasible for facilitating gastric ESD  |
| Parra-Blanco *et al*[34] | 2010 | Porcine | **30** | Esophagus Stomach  | Training in animal models could help endoscopists overcome the learning curve before starting ESD in humans |
| Moss*et al*[116] | 2010 | Porcine | **10** | Colon | CSI-EMR with submucosal injection of succinylated gelatin is safe and superior to conventional EMR.With experience, total procedure duration is comparable |
| Von Delius *et al*[120] | 2008 | Porcine | **10**  | Stomach | PMT-ESD is feasible and safe. With the use of PA-ES, mucosal pieces of various sizes can be resected en bloc in gastric locations that are difficult to access by flexible endoscopy alone |
| Yamasaki *et al*[121] | 2006 | Porcine | **2** | Stomach | ESD by submucosal injection of viscous SCMC solution appeared to be an easy, safe, and technically efficient method for dissection of gastric lesions |
| Neuhaus*et al*[83] | 2006 | Porcine | **17** | Stomach | The R-scope (double channel endoscope) facilitated ESD of large gastric areas. Procedure is technically demanding and time-consuming, with a high risk of perforation may be related to an insufficient volume of solution being injected submucosally |

HK: Hybrid knife; [ESD](http://www.giejournal.org/action/doSearch?searchType=quick&occurrences=all&ltrlSrch=true&searchScope=series&searchText=ESD&seriesISSN=0016-5107): [Endoscopic submucosal dissection](http://www.giejournal.org/action/doSearch?searchType=quick&occurrences=all&ltrlSrch=true&searchScope=series&searchText=endoscopic%20submucosal%20dissection&seriesISSN=0016-5107); CSI-EMR: Circumferential submucosal incision endoscopic mucosal resection; SEMF: Mucosal safety valve flap; [HS](http://www.giejournal.org/action/doSearch?searchType=quick&occurrences=all&ltrlSrch=true&searchScope=series&searchText=HS&seriesISSN=0016-5107): [Hypertonic saline solution](http://www.giejournal.org/action/doSearch?searchType=quick&occurrences=all&ltrlSrch=true&searchScope=series&searchText=hypertonic%20saline%20solution&seriesISSN=0016-5107); [PCH](http://www.giejournal.org/action/doSearch?searchType=quick&occurrences=all&ltrlSrch=true&searchScope=series&searchText=PCH&seriesISSN=0016-5107): [Photocrosslinkable chitosan hydrogel](http://www.giejournal.org/action/doSearch?searchType=quick&occurrences=all&ltrlSrch=true&searchScope=series&searchText=photocrosslinkable%20chitosan%20hydrogel&seriesISSN=0016-5107); [SFC](http://www.giejournal.org/action/doSearch?searchType=quick&occurrences=all&ltrlSrch=true&searchScope=series&searchText=SFC&seriesISSN=0016-5107): [Submucosal fluid cushion](http://www.giejournal.org/action/doSearch?searchType=quick&occurrences=all&ltrlSrch=true&searchScope=series&searchText=submucosal%20fluid%20cushion&seriesISSN=0016-5107); [SH](http://www.giejournal.org/action/doSearch?searchType=quick&occurrences=all&ltrlSrch=true&searchScope=series&searchText=SH&seriesISSN=0016-5107): [Sodium hyaluronate](http://www.giejournal.org/action/doSearch?searchType=quick&occurrences=all&ltrlSrch=true&searchScope=series&searchText=sodium%20hyaluronate&seriesISSN=0016-5107); ECE: En bloc circumferential esophageal; PA-ES: Percutaneously assisted endoscopic surgery; PMT-ESD: PEG-minitrocar ESD; SCMC: Sodium carboxymethylcellulose.

A

B



**C**

**D**



**E** 

**F** 

**G** 

**H**

**I** 

**Figure 1 Flow diagram of trial selection and *en-bloc* resection percentage %.** A: Flow diagram of trial selection; B: Stomach ESD: *En-bloc* resection percentage %; C: Colorectal ESD: *En-bloc* resection percentage %; D: Stomach ESD: Local recurrence (R0) rate %; E: Colorectal ESD: Local recurrence (R0) rate %; F: Stomach ESD: Perforation rate %; G: Colorectal ESD: Perforation rate %; H: Stomach ESD: Bleeding rate %; I: Colorectal ESD: Bleeding rate %. *MeSH*: Medical Subject Heading.