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**Comparing outcomes for endoscopic submucosal dissection between Eastern and Western countries: A systematic review and meta-analysis**

Daoud DC *et al*. Comparing Eastern to Western ESD

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**Abstract**

***Aim***

To compare endoscopic submucosal dissection (ESD) outcomes between Eastern and Western countries.

***Methods***

A systematic review and meta-analysis was performed using PubMed, MEDLINE, Web of Science, CINAHL and EBM reviews to identify studies published between 1990 and February 2016. The primary outcome was the efficacy of ESD based on information about either curative resection, *en bloc,* or R0 resection rates. Secondary outcomes were complication rates, local recurrence rates and procedure times.

***Results***

Overall, 238 publications including 84318 patients and 89512 gastrointestinal lesions resected using ESD were identified. 90% of the identified studies reporting ESD on 87296 lesions were conducted in Eastern countries and 10%of the identified studies reporting ESD outcomes in 2 216 lesions were from Western countries. Meta-analyses showed higher pooled percentage of curative, *en bloc*, and R0 resection in the Eastern studies; 82% (CI: 81%-84%), 95% (CI: 94%-96%) and 89% (CI: 88%-91%) compared to Western Studies; 71% (CI: 61%-80%), 85% (CI: 81%-89%) and 74% (CI: 67%-81%) respectively. The percentage of perforation requiring surgery was significantly greater in the Western countries (0.53%; CI: 0.10-1.16) compared to Eastern countries (0.01%; CI: 0%-0.05%). ESD procedure times were longer in Western countries (110 min *vs* 77 min).

***Conclusion***

Eastern countries show better ESD outcomes compared to Western countries. Availability of local ESD expertise and regional outcomes should be considered for decision making to treat gastrointestinal lesions with ESD.

**Key words:** curative resection; *en bloc* resection; R0 resection; perforation

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**Core tip:** endoscopic submucosal dissection (ESD) has become the preferred approach to remove larger or advanced gastrointestinal lesions in Asian countries. However, there might be regional differences in outcomes since the majority of ESD publications come from the Eastern world. To provide such information we conducted a systematic review and meta-analysis comparing ESD outcomes for different regions of the world. This study found that there are indeed regional differences for ESD outcomes. Eastern countries had better curative, *en bloc* and R0 resection rate than Western countries as well as less perforation requiring surgery.

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**INTRODUCTION**

Digestive cancers account for 20% of cancers diagnosed worldwide. The global age-standardized incidence rate (ASR) of esophageal, stomach and colorectal cancer is 5.9, 12.1 and 17.2 per 100000, respectively. Some geographic differences in the incidence of gastrointestinal cancers exist. Colorectal cancer rates are considerably higher in Western countries, while gastric cancer is the most prevalent gastrointestinal cancer in Asian countries.Esophageal squamous cell cancer is predominant in Eastern countries, but the incidence of esophageal adenocarcinoma has been increasing significantly in several Western countries[1]. Curative endoscopic therapy is possible for such gastrointestinal cancers or precancerous lesions if they are detected at a stage where the risk of lymph node metastasis is low[2].

Endoscopic submucosal dissection (ESD) has been developed in Japan to allow for endoscopic *en bloc* and curative removal of larger superficial gastrointestinal lesions and early gastrointestinal cancers according to oncologic standards (R0 and *en bloc* resection)[3,4]. It is assumed *en bloc* resection translates into lower recurrence rate compared to other endoscopic treatment options such as endoscopic mucosal resection (EMR). EMR requires to remove gastrointestinal lesions > 20 mm usually in several pieces, thus making it impossible to confirm a complete resection in histopathology and margins free of dysplastic or cancer tissue[5,6]. Consequently, ESD has become the preferred approach to remove larger or advanced gastrointestinal lesions in many Asian countries. Furthermore, previous systematic reviews comparing ESD to EMR have come up with the conclusion that ESD yields better results for complete and *en bloc* removal compared to EMR[7-11].

Despite these results, widespread adoption of ESD has remained limited in Western countries and EMR continues to be the mainstay of endoscopic therapy. ESD is known to have high complication rates, demands long procedure times and requires substantial training and expertise development[7-11]. Differences in incidence (*e.g.,* for gastric cancer) provide different local exposure to develop adequate ESD skills. Furthermore, differences in remuneration system (*e.g.,* fee per service systems without specific procedure codes) are other factors that might influence regional uptake of ESD. Such regional differences of case load and/or lesions suitable to develop ESD skills might translate into different regional outcomes for ESD. Consequently, Western centers might have different results and such differences are important to consider for clinical decision-making. Previous studies have focused on comparing ESD to EMR and did not considered that there might be differences for regional ESD outcomes[7-11]. To provide such information we conducted a systematic review comparing ESD outcomes for different regions of the world.

**MATERIALS AND METHODS**

We conducted a systematic review of the literature and meta-analysis, and report our results in accordance to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) recommendations.

***Search strategy***

A computerized, systematic bibliographic search was performed on PubMed, Medline (OVID), EMBASE (OVID), Web of science (Clarivate Analytics), CINAHL (EBSCO) and EBM reviews (OVID) databases to identify relevant publications. The search keywords were “endoscopic submucosal dissection” and “ESD.” The search was limited by the non-restrictive filters “Human”, “Clinical Trial” and publication language “English”. For each database, terms and expressions from controlled vocabulary (MeSH, EMTREE, etc.) were used. Free-text searching was also used for each database. Full paper publications and abstracts from January 1990 through February 2016 were considered for review.

***Trial selection and patient population***

Selection criteria included randomized controlled trials (RCT), prospective and retrospective studies. Non-human trials, case-control studies and publications in a language other than English were excluded. To reduce bias from learning curves of ESD and from possible patient selection, case series and studies with less than 50 patients were excluded. Studies reporting on ESD for non-gastrointestinal lesion (e.g. pharyngeal lesions), studies using hybrid ESD technique or studies targeting subepithelial lesions were excluded. We excluded studies with missing or unclear information on success rates of either *en bloc*, R0 or curative resections. Full-text articles of potentially relevant studies were obtained. Abstract publications containing our primary endpoint were included in the quantitative analysis.

***Data extraction***

Data were extracted by two authors independently (DCD, NS) and were then compared for accuracy. When data did not match, both reviewers reviewed the study a third time and divergences were resolved by consensus. In case of disagreement, a third reviewer (DvR) was available to arbitrate. The following information was collected: first author, journal, year of publication, number of patients, age and sex of patients, number of lesions, location and mean size of lesions, achievement of *en bloc*, R0 and curative resection, procedure time, type of knives used, procedure related bleeding and perforation as well as local recurrences.

***Technical and oncologic outcomes of ESD***

The primary outcome was efficacy of ESD based on information on either *en bloc*, R0 and curative resection rates. *En bloc* resection refers to a one-piece resection without fragmentation, R0 corresponds to a complete resection, which means no residual tumor. A resection was defined as curative when the histological findings showed no neoplasia in both lateral and vertical margins, as well as no lymphatic or venous invasion. The secondary outcomes included perforation, bleeding during or after the procedure, operation time and local recurrence rates. Perforation was either identified endoscopically post resection or by the presence of free air on imaging studies. We planned using the Clavien-Dindo scale for the analysis of procedural complications. In cases where data for number of males, lesion location, *en bloc*, R0, curative resection, or complications were expressed as a percentage, they were mathematically converted and rounded to the closest whole number. Eastern countries included studies reported from China, Japan, Korea and Taiwan. Western countries included studies reported from Europe, North and South America, as well as Australia. Each study’s region was identified in the article or through the affiliation of the corresponding author.

***Quality* *assessment and publication bias***

Quality assessment of the included studies was done by identifying study designs as well as stratifying by study design according to their retrospective or prospective characteristic. We did not rely on GRADE or other tool because the data extracted for this review did not represent the primary outcome of all the included studies[12]. For the same reason, we did not formally assess publication bias by means of funnel plots.

***Statistical analysis***

For each outcome of interest, the number of outcomes over the number of lesions with available results for that outcome was expressed as a proportion. Those percentages were amalgamated and analyzed using the *metaprop* command of Stata 11 (StataCorp.2009. Stat Statistical Software: Release 11. College Station, TX: StatCorp LP). Meta-analyses were stratified by Eastern and Western study regions. Random effects meta-analysis was conducted for all outcomes, as heterogeneity was suspected *a priori* between Eastern and Western studies. Heterogeneity was assessed using the I-square statistic, with small p-vales for I-square values indicating high chances of heterogeneity. To compare procedure procedural time among Eastern and Western studies, a weighted average of these as reported in minutes in the different studies was computed.

***Secondary analysis***

We repeated analysis stratifying by organ (oesophagus, stomach, colo-rectum), by study design (retrospective, prospective) and by country.

**RESULTS**

The literature search identified 2532 studies (after duplicates were removed) (Figure 1). Based on title and abstract screening, 2159 studies were excluded. 135 further articles were excluded after full-text review of the publications. Thus, 238 studies were eligible for analysis, including 140 full-text and 98 abstract publications[6,13-249]. One study included ESD data from both a Japanese center and a center from the United States[18]. It was therefore divided into Western and Eastern part for our quantitative analysis, thus counting as two distinct studies. However, it was only considered as a single study when assessed for eligibility. The majority of the studies were retrospective cohort studies (168 / 239 trials). Only 7 studies were randomized controlled trials (although the randomized intervention was not ESD but some other aspect of endoscopy, such as, for example, analgesia type); others were prospective cohort studies. Overall, 90% of the included studies were from Eastern countries (216/239 trials) while only 10% (23 trials) were from Western countries (Belgium, Brazil, Colombia, France, Germany, Italy, Poland, Portugal, Turkey, and the United States).

A total of 84318 patients were enrolled in this analysis, including 82 183 patients in the Eastern group and 2135 patients treated in Western countries. ESD was performed on 89512 lesions, comprising 87296 lesions in the Eastern group and 2 216 in the Western group. Patient age and size of lesions were occasionally missing, and the included studies were heterogeneous in terms of number of patients and lesions. The weighted average of subject’s age was 66.4 and 66 years in the Eastern and Western group, respectively. The weighted average for lesion size was 25.7 mm and 34.1 mm, respectively.Table 1 and supplementary Table 1 show characteristics of the included studies stratified into Eastern versus Western. Data regarding different knives used were not analyzed because most studies used multiple different knifes, and no standardization was available.

***Curative resection rate***

90 studies (81 Eastern, 9 Western) provided the curative resection rate, involving 43 854 lesions in the Eastern group and 922 lesions in the Western group. The overall curative resection percentage was 81.4% (95%CI: 79.6%-83.1%). This analysis showed a significant difference between the two groups, in favor of the Eastern countries, where curative resection reached 82.3% (95%CI: 80.6%-84.1 %) compared to 71.3% (95%CI: 61.1%-80.5%) in Western countries. The results are shown as a forest plot in Figure 2A.

***En bloc* resection rate**

215 studies (192 Eastern, 23 Western) collected the *en bloc* resection rate, including 74 883 lesions in the Eastern group and 2 216 lesions in the Western group. The overall *en bloc* resection percentage was 94.4% (95%CI: 93.7%-95.0%). As for the curative resection, the pooled proportion of *en bloc* resection in the Eastern countries, 95.1% (95%CI: 94.4%-95.7%), was significantly higher than in the Western countries, 85.3% (95%CI: 81.3%-89.0%) (Figure 2B).

***R0 resection rate***

Overall, 154 studies (135 Eastern, 19 Western) reported the R0 resection rate, totaling 50 540 lesions in the Eastern group and 1948 lesions in the Western group. The overall R0 resection percentage was 88.0% (95%CI: 86.7%-89.3%). The R0 resection rate of the Eastern countries was statistically superior. The pooled proportion of the Eastern group was 89.5% (95%CI: 88.3%-90.6%) while that of the Western group is 74.4% (95%CI: 67.3%-80.9%) (Figure 2C).

***Complications***

two hundred and nine studies reported complications related to the procedure, involving 65 956 patients in the Eastern group and 1893 in the Western group. There was no statistical difference for the overall bleeding and perforation rate between the Eastern and Western world. The proportions of bleeding (early and late) were 2.85% (95%CI: 2.44%-3.28%) and 4.03% (95%CI: 2.61%-5.70%) in the Eastern and Western groups, respectively (Figure 3A). Similarly, the perforation rates were 3.11% (95%CI: 2.79%-3.46%) and 3.38% (95%CI: 1.83%-5.29%) respectively (Figure 3B).As for the perforations requiring surgery, the Eastern countries percentage was significantly lower than the Western countries; 0.01% (95%CI: 0%-0.05%) and 0.53% (95%CI: 0.10%-1.16%) respectively (Figure 3C). With regard to complication rates, we initially planned using the Clavien-Dindo scale for the analysis of procedural complications, but because reporting of complication consequences was lacking in many studies we could not analyze this outcome.

***Local recurrence and procedure time***

Local recurrence was reported in 149 studies (12 Eastern, 137 Western), including 40936 patients in the Eastern group and 1188 patients in the Western group. The overall local recurrence percentage was 0.74% (95%CI: 0.48%-1.05%). There was no statistical difference between both groups and the proportion of local recurrence were 0.69% (95%CI: 0.42%-1.00%) and 1.82% (95%CI: 0.84%-3.07%) in the Eastern and Western group respectively (Figure 4).

The Western’s group weighted average of procedure time (110 minutes) was longer than the Eastern countries (77 min) (Table 1).

***Stratification by organ***

Because ESD outcomes may vary according to the organ, studies were stratified by lesion location (oesophagus, stomach, colo-rectum). For the oesophagus, only the pooled proportion of *en bloc* resection showed a significant difference in favor of the Eastern countries. As for gastric lesions, all outcomes were similar except for local recurrence which was superior in Western countries. Finally, for colorectal lesions, Eastern countries had better curative, *en bloc* and R0 resection rate (Supplementary Figures 1-9).

***Stratification by country***

Meta-analyses for primary outcomes were stratified by countries. Secondary outcomes were not stratified because of the limited data available. Pooled proportions for curative, *en bloc* and R0 resections were similar among all Eastern countries and Western countries (Supplementary Figures 10-15).

***Quality assessment***

Stratification by study design was not different form the pooled proportion. The same trend was seen when stratifying by retrospective *vs* prospective results (Supplementary Figures 16-22).

***Heterogeneity assessment***

There was evidence of statistical heterogeneity for curative, *en bloc* and R0 resection as well as for bleeding, perforation, perforation requiring surgery and local recurrences (Figures 2-4).

**DISCUSSION**

To the best of our knowledge, this meta-analysis is the first to compare ESD results between different regions of the world. Our results showed that Eastern countries have better rates of curative, *en bloc* and R0 resection compared to ESD results reported in North and South America, Europe and Australia. Moreover, ESD performed in Western countries was associated with a higher proportion of perforations requiring surgery. There was no significant difference found between regions with regard to other minor complication (e.g. bleeding) or local recurrence rates. Our meta-analysis also supports the fact that ESD efficacy varies according to the location of the lesion. Indeed, both Eastern and Western countries have similar outcomes for gastric lesions. As for colorectal ESD, which is a more difficult technique, the Eastern world shows better results. This difference could be due to the fact that Western countries still favor EMR for colic lesions and are less experienced. Furthermore, procedure times for ESD were longer in Western countries but the lesions removed by ESD in Western countries also tended to be larger.

The superiority of ESD compared to EMR with regard to curative, *en bloc* and R0 resection has been demonstrated in several meta-analysis[7-11]. However, these previous meta-analyses included studies only from the Eastern world, thereby they do not provide an accurate representation for ESD outcomes in other regions of the world. The results from our meta-analysis showed that ESD outcomes differ globally and ESD results achieved for critical outcomes were different in the Western hemisphere. This might explain why the Western world is more reluctant to adopt widespread ESD use. However, there remains some level of uncertainty to what extend this is influenced by e.g. procedural expertise, case volumes and/or patient or lesion selection. With regard to regional complication rates, our analysis did not show any statistical differences in terms of overall perforation and bleeding rates, but we also found that ESD perforations requiring surgery occurred more often in Western countries. These results point out that the East has been doing these procedures longer than the West and therefore has more expertise with it. Furthermore, the overall numbers of lesions resected using ESD reflects well the steep difference in utilization (and thus likely expertise) with ESD in Eastern versus Western countries. Out of a total of 91 582 ESD resection only 2289 ESDs were reported from the Western countries. It might therefore be important to consider available local expertise for clinical decision making and not assume that local outcomes will necessarily resemble outcomes from high volume Asian ESD centers. However, such expertise can be learned. A recent prospective multicenter French study reported outcomes for 314 patients undergoing ESD between 2010 and 2013 and 188 patients undergoing ESD between 2008 and 2010, an improvement in the rates of *en bloc* resection from 77.1% to 91.7% as well as a decrease in the complication rates (from 29.2% to 14.1% *p* < 0.0001) was demonstrated[250]. These rates are similar to outcomes reported from Japan, suggesting that adequate training, caseload and practice are mandatory to achieve optimal outcomes. However, at present few endoscopists in Western countries are adequately trained for ESD. Consequently, lesion size, lesion location and available expertise for ESD versus EMR need to be considered when choosing the appropriate approach for an individual patient. A recent literature review of the colorectal ESD series showed a low rate of superficially invasive cancer (8%) with a number needed to treat (NNT) for curative resection of 16. The majority of resected lesions were benign adenomas (82.2%) of which 26.8% were low grade dysplasia[251]. This study shows that histological description is a key element in evaluating ESD outcomes. Data regarding the histology of the resected lesions was not analyzed in our meta-analysis because information was often incomplete or not available. We suggest that in future studies the histological features be described and analyzed.

Our meta-analysis has several limitations. First, there is an unequal distribution of studies between both groups. All the included RCTs are from the Eastern world, which also carries far more prospective studies than the Western world. Secondly, there is a lack of high quality studies, given that more than half of the included studies in this meta-analysis are retrospective. But in order to ensure the best snapshot of global ESD outcomes and include Western ESD outcomes, retrospective trial data needed to be included in our review. The large amount of retrospective studies and the differences of methodology in the prospective trials included are a limitation inherent to the current literature available. In order to avoid disadvantaging the Western group, the inclusion of these publications was necessary. We propose that further studies be done in a more rigorous and standardized way. Because few studies reported systematic outcomes for trainee level, we decided to exclude studies with less than 50 patients to reduce bias from learning curves and patient selection. Future studies should report systematic outcomes for trainee level. Thirdly, there was evidence of statistical heterogeneity for most of our endpoints because of differences between study participants and differences of lesions size between the included studies. To reduce this heterogeneity, an exclusion of studies contributing to the high heterogeneity could have been made. However, it was not done because this would have implied the exclusion of several Western studies that are already scarce. Fourthly, analyses were limited by missing data. Data regarding bleeding and use of anti-thrombotic were not analyzed because they were incomplete or unavailable in most studies. Such limitations seem to be an inherent weakness in the currently published ESD literature and a standardized and detailed reporting of ESD outcomes and use of anti-thrombotic seems warranted for future studies. However, our meta-analysis included 238 studies with 84318 patients (89512 ESD procedures) which reduces the above-mentioned risk for bias, thus optimizing generalizability.

In conclusion, this meta-analysis shows that ESD performed in Eastern countries is associated with better outcomes than studies reported from Western countries with regard to R0, *en bloc* and curative resection rates. Moreover, ESD perforations requiring surgery are more common in Western studies. The clinical decision-making for or against ESD versus EMR should consider regional outcomes and locally available expertise as well as the necessity for resection according to oncologic standard based on the risk for cancer versus pre-cancerous lesions. Furthermore, standardized reporting of outcomes should be used for future ESD studies.

**ARTICLE HIGHLIGHTS**

***Research background***

endoscopic submucosal dissection (ESD) has become the preferred approach to remove advanced gastrointestinal lesions in Asian countries while widespread adoption in the Western world remains limited.

***Research motivation***

Many previous meta-analyses suggest that ESD is a superior technique for treatment of precancerous gastrointestinal lesions or early cancers. However, there might be regional differences in outcomes since the majority of ESD publications come from the Eastern world. Studies evaluating differences for ESD outcomes between Eastern and Western countries are lacking.

***Research objectives***

To provide a global comparison of ESD outcomes between Eastern and Western countries.

***Research methods***

A systematic review and meta-analysis were conducted on studies reporting ESD outcomes. Were excluded studies with less than 50 patients, using hybrid ESD technique or targeting subepithelial lesions. Primary and secondary outcomes were efficacy of ESD (curative, *en bloc* and R0 resection), complications (bleeding, perforation) and other related factors as local recurrence and procedural time.

***Research results***

Our meta-analysis showed that Eastern countries have better ESD outcomes compared to Western countries for curative, *en bloc* and R0 resection. ESD performed in Western countries were associated with a higher proportion of perforation requiring surgery. Subgroups analysis by organ showed similar outcomes for gastric lesions while Eastern countries had better curative, *en bloc* and R0 resection rate for colorectal lesions.

***Research conclusions***

This meta-analysis provided evidence that there are regional differences for ESD outcomes. Eastern countries show better ESD outcomes compared to Western countries.

***Research perpective***

Clinical decision-making for or against ESD should consider such outcomes and locally available expertise. Standardized reporting of outcomes should be used for future ESD studies.

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**P-Reviewer:** Kim BW, Nishida T, Sugimoto M **S-Editor:** Gong ZM

**L-Editor:** **E-Editor:**

**Specialty type:** Gastroenterology and hepatology

**Country of origin:** Canada

**Peer-review report classification**

Grade A (Excellent): 0

Grade B (Very good): B

Grade C (Good): C

Grade D (Fair): D

Grade E (Poor): 0

Records after duplicates removed

n = 2532

Records screened

n = 2532

Records identified through database searching

Pubmed, MEDLINE, EMBASE, Web of science, COCHRANE search

n = 4210

Studies assessed for eligibility

n= 3731

Records excluded on basis of title and abstract  
n = 2159

Records excluded (n = 135)

*Exclusion criteria:*

2Incomplete data n = 69

3Non-ESD technique n = 27

N<50 n = 21

4Lesion characteristic n = 8

Article not in english n = 4

Animal studies n = 3

5Study design n = 3

Studies included in quantitative analysis

n= 2391

**Figure 1 Flow diagram.** The flow diagram shows the study selection process. 1One study was divided into Western and Eastern parts for our quantitative analysis (thus counting as two studies). It was however only counted as a single study when assessed for eligibility; 2Missing/incomplete data regarding our primary outcome (curative, *en bloc*, R0 resection); 3Non-ESD study, hybrid ESD technique, ESD with snare; 4Submucosal lesions, pharyngeal lesions; 5Case-control, case report, questionnaire. ESD: endoscopic submucosal dissection.



**A**

**B**

**C**

**Figure 2 Efficacy of endoscopic submucosal dissection.** Forest plot for curative resection (A), *en bloc* resection (B) and R0 resection (C).



**A**

**B**

**C**

**Figure 3 Complications of endoscopic submucosal dissection.** Forest plot for bleeding (A), perforation (B) and perforation requiring surgery (C).

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**Figure 4 Forest plot for local recurrence.**

**Table 1 Characteristics of the included studies and patients**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Total** | **Eastern countries** | **Western countries** |
| Age (yr)1 | 66.4 | 66.4 | 66 |
| Total number of patients (*n*) | 84318 | 82183 | 2135 |
| Total number of lesions (*n*) | 89512 | 87296 | 2216 |
| Esophagus | 5597 | 5 276 | 321 |
| Stomach | 59966 | 59 173 | 793 |
| Duodenum | 15 | 8 | 7 |
| Colo-rectum | 23934 | 22839 | 1095 |
| Lesion diameter (mm)1 | 26 | 25.7 | 34.1 |
| Procedure time (min)1 | 78 | 77 | 110 |
| Total number of studies | 239 | 216 | 23 |
| Randomized controlled trial | 7 | 7 | 0 |
| Prospective studies | 61 | 53 | 11 |
| Retrospective studies | 168 | 156 | 12 |
| Full-text | 140 | 130 | 10 |
| Abstract | 99 | 86 | 13 |

1weighted average, with number of patients in study used as weights.