

## Comparison of endoscopic submucosal dissection with surgical gastrectomy for early gastric cancer: An updated meta-analysis

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### Abstract

#### BACKGROUND

There are several surgical options for treating early gastric cancers (EGCs), such as endoscopic resection, laparoscopic or open gastrectomy with D1 or D2 lymphadenectomy. Endoscopic resection for EGC with low risk of lymph node metastasis has been widely accepted as a therapeutic alternative. The role of endoscopic submucosal dissection (ESD) in treating EGC is not well established, especially when compared with resection surgery cases in a long-term follow-up scope.

#### AIM

To compare the safety and efficacy of the short- and long-term outcomes between ESD and resection surgery.

#### METHODS

We searched the databases of PubMed, EMBASE, Web of Science, and the Cochrane Library from January 1990 to June 2018, enrolling studies reporting short- or long-term outcomes of ESD in comparison with resection surgery for EGC. The quality of the studies was assessed by the Newcastle-Ottawa Quality Assessment Scale. Stata software (version 12.0) was used for the analysis. Pooling analysis was conducted using either fixed- or random-effects models depending on heterogeneity across studies.

#### RESULTS

Fourteen studies comprising 5112 patients were eligible for analysis (2402 for EGC and 2710 for radical surgery). Our meta-analysis demonstrated that the ESD approach showed advantages through decreased operation time [weighted mean difference (WMD): -140.02 min, 95% CI: -254.23 to -34.82 min,  $P = 0.009$ ], shorter hospital stay (WMD: -5.41 d, 95% CI: -5.93 to -4.89 d,  $P < 0.001$ ), and lower

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postoperative complication rate [Odds ratio (OR) = 0.39, 95% CI: 0.28-0.55,  $P < 0.001$ ]. Meanwhile, EGC patients who underwent ESD had higher recurrence rate (OR = 9.24, 95% CI: 5.94-14.36,  $P < 0.001$ ) than resection surgery patients.

However, the long-term survival including overall survival [Hazard ratio (HR) = 0.51, 95% CI: 0.26-1.00,  $P = 0.05$ ] and event-free survival (HR = 1.59, 95% CI: 0.66-9.81,  $P = 0.300$ ) showed no significant differences between these two groups.

### CONCLUSION

In the treatment of EGC, ESD was safe and feasible in comparison with resection surgery, with advantages in several surgical and post-operative recovery parameters. Although the recurrence rate was higher in ESD group, the long-term survival was still comparable in these two groups, suggesting ESD could be recommended as standard treatment for EGC with indications.

**Key words:** Early gastric cancer; Endoscopic submucosal dissection; Gastrectomy; Clinical outcome; Meta-analysis

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**Core tip:** The role of endoscopic submucosal dissection (ESD) in treating early gastric cancer (EGC) is not well established, especially when compared with resection surgery cases in a long-term follow-up scope. This study collected and analyzed up-to-date clinical data of comparison between ESD and surgical gastrectomy in EGC patients. The results turned out a comparable short- and long-term result between these two groups with more favorable short-term recovery in ESD patients.

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## INTRODUCTION

Gastric cancer remains the fifth common malignancy and the third leading cause of cancer mortality worldwide<sup>[1]</sup>. The prevalence of gastric cancer (GC) is relatively high in East Asia, especially in China, Korea, and Japan, accounting for nearly half of all new cases across the world annually<sup>[2]</sup>. Early GC (EGC) patients constitute a considerable proportion of all GC patients in these countries, therefore, Japan and Korea have implemented a national screening program for GC to detect EGC<sup>[3]</sup>.

Early gastric cancer is defined as a gastric cancer with tumor invasion that is confined to the mucosa or submucosa, irrespective of the presence of lymph node metastasis<sup>[3]</sup>. There are several surgical options for treating EGCs, such as endoscopic resection, laparoscopic or open gastrectomy with D1 or D2 lymphadenectomy. Endoscopic resection for EGC with low risk of lymph node metastasis has been widely accepted as a therapeutic alternative<sup>[4,5]</sup>. Endoscopic resection instead of surgery is currently recommended in certain selected EGC patients who have met these following criteria: (1) differentiated-type mucosal cancer without ulceration, regardless of tumor size; (2) differentiated-type mucosal cancer with ulceration no more than 3 cm in diameter; (3) superficial submucosal cancer no more than 3 cm in diameter; or (4) undifferentiated-type mucosal cancer no more than 2 cm in diameter without ulceration<sup>[6,7]</sup>.

The common endoscopic approaches include endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). The ESD technique is now a more acceptable endoscopic approach for the treatment of EGC without lymph node metastasis compared to EMR. ESD involves the resection of both benign neoplastic (pre-malignant) and malignant noninvasive lesions, and enjoys the advantages of higher curative resection and histologically complete resection rate, and lower local recurrence rate for EGCs, which have been confirmed by several large-scale clinical studies and meta-analyses<sup>[8,9]</sup>.

Surgical treatment has been performed in a considerable proportion of EGC

patients because of its predictable oncological outcomes. Compared with surgical resection, the endoscopic procedure tends to show advantages in perioperative recovery. And comparisons of clinical parameters or outcomes between ESD and resection surgery for EGC are still lacking and controversial. Several previous meta-analysis either enrolled limited studies nor didn't include the survival comparison<sup>[10,11]</sup>. Moreover, the long-term outcomes in patients with sufficient follow-up who have undergone ESD or surgery remain unclear. Therefore, in this meta-analysis we aimed to compare clinical outcomes in EGC patients who underwent ESD and those who underwent surgery.

## MATERIALS AND METHODS

### Literature search

We searched the databases of PubMed, EMBASE, Web of Science, and the Cochrane Library dating from January 1990 to June 2018. The following search terms were applied: "ESD" or "endoscopic submucosal dissection," "surgery," "resection surgery," "gastrectomy," and "early gastric cancer" or "EGC." Both free terms and MeSH words were included. Citations and references of identified studies were also reviewed for potential literature and trials. There was no restriction of language in the literature search.

### Study selection

The following studies were included: (1) studies involving patients diagnosed with EGC based on histology; (2) studies conducted to compare ESD and surgery for EGC; and (3) studies reporting clinical outcomes after ESD or surgery, long-term outcomes included overall survival (OS) or event-free survival (EFS) (disease-free survival or recurrence-free survival).

Exclusion criteria were: (1) case reports or reviews; (2) ESD or surgery performed in pathological types other than gastric adenocarcinoma; (3) involvement of EMR or other hybrid endoscopic resection techniques; and (4) studies including fewer than 20 patients in each group.

### Data extraction and quality evaluation

Two reviewers independently screened the titles and abstracts of the articles. The following information was extracted from the articles: authors; year of publication; country or region; study design; numbers of patients; and clinical or oncological data consisting of operation time, complete resection rate, estimated blood loss, postoperative complications, total cost, duration of hospital stay, local recurrence rate, and recurrence-free survival.

The quality of the enrolled studies was assessed using the Newcastle-Ottawa Quality Assessment Scale (NOS). The scale measured up to a maximum 9 points, and studies scoring more than 6 points were considered methodologically sound<sup>[12]</sup>.

### Statistical analysis

Weighted mean differences (WMDs) were chosen for continuous variables in this meta-analysis. And odds ratios (ORs) were chosen for measuring dichotomous variables while hazard ratios (HRs) for time-to-event variables. Statistical heterogeneity was assessed by performing  $\chi^2$  tests and calculating the Higgins  $I^2$  statistic, and a value of  $P < 0.10$  or  $I^2 > 50\%$  indicated statistical significance. A random-effect model was generally employed. If the heterogeneity was statistically insignificant, then a fixed-effect model was adopted. Publication bias was evaluated by Begg's test. A  $P$  value of  $< 0.05$  was considered significant. Statistical analyses were performed using Stata software (version 12.0; StataCorp, College Station, TX, USA).

## RESULTS

### Study enrollment and quality assessment

The flow chart of the search strategy is presented in **Figure 1**. A total of 745 studies were retrieved from a search of the aforementioned databases. After checking, 8 duplicate publications were excluded. Through abstract screening, 612 studies were excluded owing to irrelevance to our topics. In the remaining 125 articles with full-text review, 6 case reports and 9 reviews were excluded; 46 were excluded for lack of sufficient data; 24 were excluded because they reported advanced stages other than early stage; 21 were excluded because they reported comparison between EMR and ESD/surgery; and 5 were excluded because they reported pathological types other

than adenocarcinoma. Ultimately, our meta-analysis comprised fourteen studies including a total of 5112 EGC patients.

The main characteristics of the eligible studies and quality assessment results are displayed in [Table 1](#)<sup>[13-26]</sup>. Among these studies, two were performed in China, one in Japan, one in Canada, and the remaining 11 were in Korea. Regarding quality assessment, two studies scored 6 in the NOS and all others achieved 7 or higher ([Table 1](#)).

### Operation time

The length of operation time was significantly lower for EGC patients with ESD than for those who underwent radical operations (WMD: -140.02 min, 95%CI: -254.23 to -34.82 min,  $P = 0.009$ ) ([Figure 2](#)). As significant heterogeneity was observed ( $I^2 = 99.9\%$ ,  $P < 0.001$ ), the analysis was performed using a random-effect model. Further sensitivity analysis showed the study by Song *et al*<sup>[17]</sup> might be the source of heterogeneity, therefore we excluded this study and the results showed a significant decrease in heterogeneity ( $I^2 = 0\%$ ,  $P = 0.607$ ) with still strong correlation ( $P < 0.001$ ).

### Short-term recovery

All fourteen studies reported postoperative complication rate. The pooled analysis showed that the ESD group had a lower postoperative complication rate than that in the surgery group (OR = 0.39, 95%CI: 0.28 to 0.55,  $P < 0.001$ ) ([Figure 3A](#)). Moderate heterogeneity was detected within this comparison ( $I^2 = 46.9\%$ ,  $P = 0.031$ ) and a random-effect model was applied.

The pooled analysis of hospital stay showed that patients in the ESD group enjoyed a significant shorter hospital stay than those who underwent surgery (WMD: -5.41 d, 95%CI: -5.93 to -4.89 d,  $P < 0.001$ ) ([Figure 3B](#)). There was significant heterogeneity within studies ( $I^2 = 96.4\%$ ,  $P < 0.001$ ) and therefore a random-effect model was applied.

### Recurrence rate

The postoperative cancer recurrence rate was reported by nine studies, pooled analysis showed a higher recurrence risk in ESD patients (OR = 9.24, 95%CI: 5.94 to 14.36,  $P < 0.001$ ) with no obvious heterogeneity detected ( $I^2 = 0\%$ ,  $P = 0.983$ ) ([Figure 4](#)). Therefore, a fixed-effect model was applied in the pooled analysis.

### Long-term survival

Long-time recurrence-free survival or disease-free survival was regarded as EFS. The results were provided by six studies, the pooled analysis of which showed no significant survival difference between these two groups (HR = 1.59, 95%CI: 0.66 to 9.81,  $P = 0.300$ ) with obvious heterogeneity ( $I^2 = 80.9\%$ ,  $P < 0.001$ ) ([Figure 5A](#)).

The OS also demonstrated no significant difference between ESD and surgery (HR = 0.51, 95%CI: 0.26-1.00,  $P = 0.05$ ) with trivial heterogeneity ( $I^2 = 29.7\%$ ,  $P = 0.212$ ) ([Figure 5B](#)).

### Publication bias

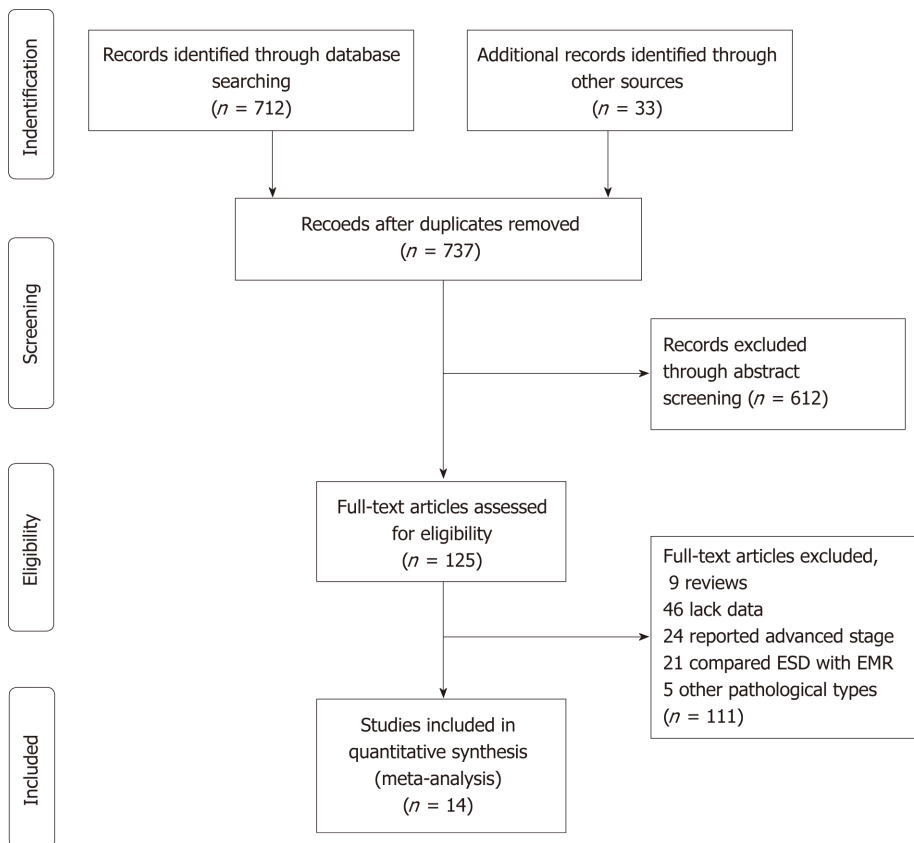
Publication bias was evaluated based on postoperative complication rate and recurrence rate (included in most of the eligible studies) using Begg's test. No publication bias was observed in these analyses ([Figure 6](#), complication rate:  $P = 0.502$ ; Recurrence rate:  $P = 0.754$ ).

## DISCUSSION

Our meta-analysis demonstrated the short- and long-term oncological safety of ESD, as well as the potential superiority of ESD over surgery in treating EGC in regard to some clinical parameters. To the best of our knowledge, our study is the most comprehensive meta-analysis to date comparing clinical outcomes between ESD and surgery in treating EGC, involving more than 5000 patients.

The most important concern about ESD is oncological safety. In both ESD and radical surgery, complete resection should be confirmed by the lateral and vertical margin status<sup>[27]</sup>. The studies enrolled in our meta-analysis also demonstrated that compared with surgery, ESD enjoyed a similar curative resection rate (ranges from 86.7% to 99.4%).

The ESD procedure also calls for high levels of training and experience for endoscopy physicians or surgeons. However, the operation time will gradually decrease in line with accumulating experience of the endoscopist while maintaining an advantage over radical surgery in terms of surgical duration<sup>[28]</sup>. Another advantage of ESD procedure was fast recovery after operation than surgery, the hospital stays



**Figure 1** Flow chart of study enrollment. ESD: Endoscopic submucosal dissection; EMR: Endoscopic mucosal resection.

and medical costs thus greatly decreased since less trauma and less medical interventions caused by ESD procedure.

Postoperative complications might affect patients' life quality and prolong hospital stay, leading to increased total medical cost. According to the enrolled studies, the most common complications occurred after ESD intervention were bleeding and perforation while bleeding and anastomotic leakage occurred more often in the surgery group. Some previous studies have reported that postoperative adverse events occurred less frequently in the ESD group than in surgery patients, while others found no significant difference<sup>[29,30]</sup>. After pooled analysis, our results supported that ESD might cause less trauma to EGC patients in the perspective of lower postoperative complication rate happened.

Our pooled analysis also found that recurrence rate in the ESD group was higher than in the surgery group. Theoretically, the ESD technique only allows the removal of the primary tumor along with the submucosal layer; therefore, the remnant surrounding mucosa still might carry the risk of developing cancer<sup>[31,32]</sup>. Although the event-free survival was similar between the two groups ( $P = 0.234$ ), the differences in follow-up, surveillance strategy that adapted and sample scale might have led to this contradictory result. To manage this issue, regular (annual or biannual) endoscopic surveillance and abdominal computed tomography might be conducted for at least 5 years according to GC treatment guidelines<sup>[33,34]</sup>.

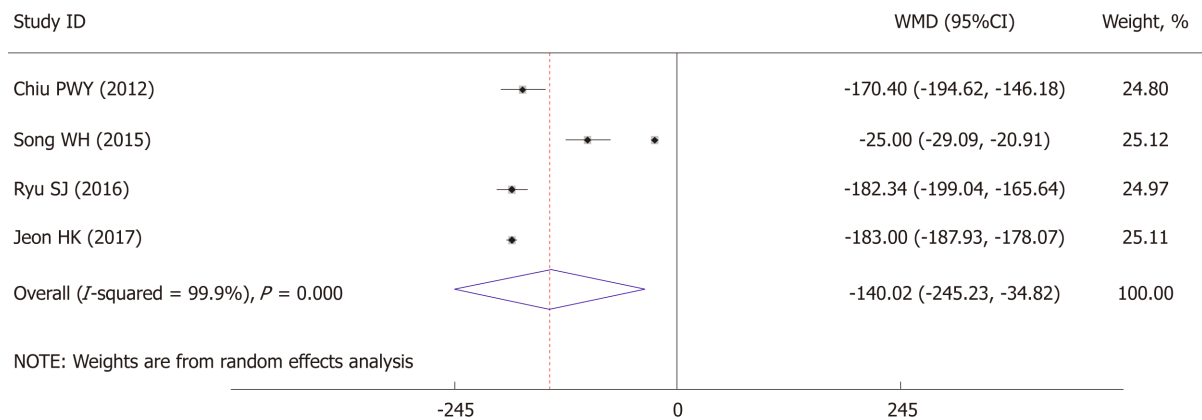
This meta-analysis also has several limitations that should be addressed. First, the clinical heterogeneity of the included studies might affect the reproducibility of our results: the demographic characteristics of enrolled patients, the detailed procedure of ESD, the diagnosis technique of EGC might vary among different institutions. Second, the retrospective nature of enrolled studies limited the application of our results. Third, only one western study from Canada was enrolled and the conclusion might not apply in western countries.

In conclusion, this meta-analysis suggested that ESD is safe and feasible in comparison with resection surgery in treating EGC, with clinical advantages in operation time, hospital stay, postoperative complications. Although with some differences in tumor recurrence rate, the long-term survival also supported the safety of ESD compared with resection surgery. Moreover, further multi-center, prospective randomized controlled trials with longer and standard follow-up strategies are warranted to verify our findings.

**Table 1** Main characteristics of included studies

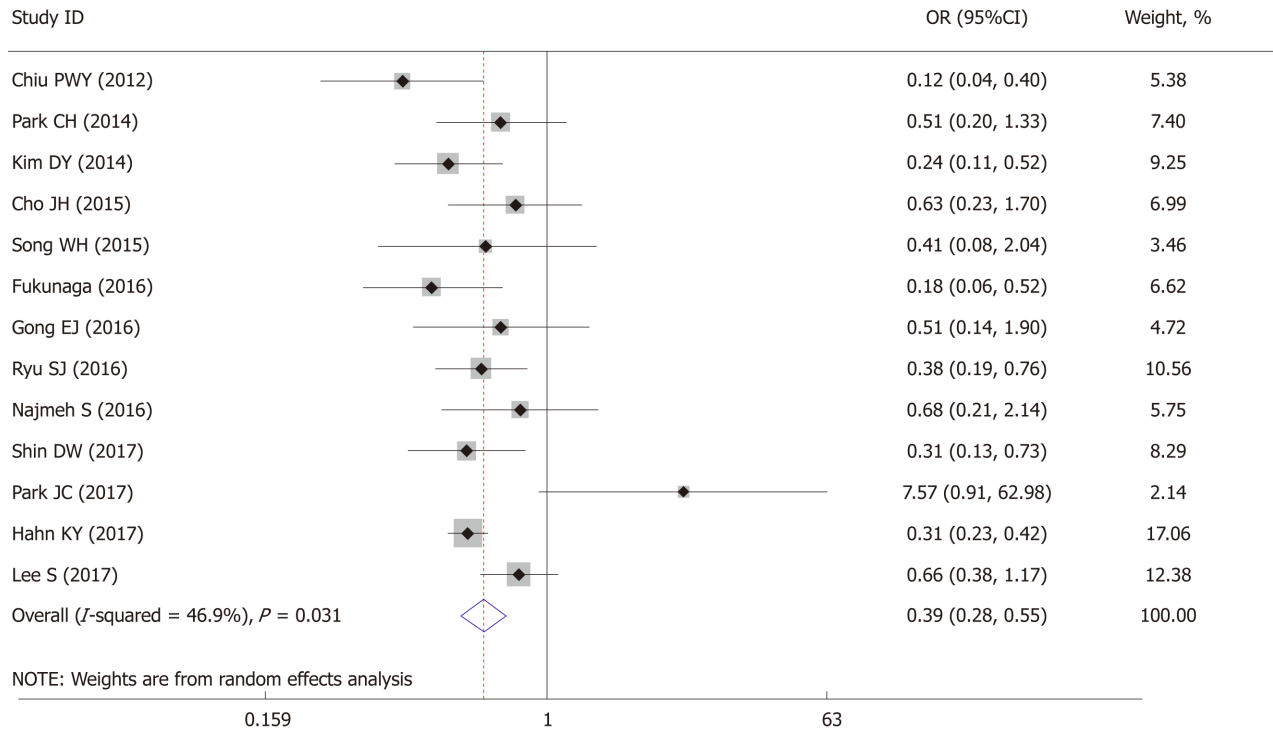
Ref.	Year/regio n	Number		Mean age		Sex (M/F)		Tumor size (mm)		Follow up (mo)		NOS
		ESD	Surgery	ESD	Surgery	ESD	Surgery	ESD	Surgery	ESD	Surgery	
Chiu <i>et al</i> <sup>[13]</sup>	2012/China	74	40	66.3	67.0	49/25	23/17	18.5 (8-40)	24.7 (10-40)	/		6
Park <i>et al</i> <sup>[14]</sup>	2014/Korea	132	132	73.9	74.4	97/35	88/44					7
Kim <i>et al</i> <sup>[15]</sup>	2014/Korea	142	71	62.0	56.7	94/48	58/13	/	/	76.7 ± 16.5	65.5 ± 16.5	6
Cho <i>et al</i> <sup>[16]</sup>	2015/Korea	88	88	61.8	61.3	63/25	62/26	21.8 ± 12.1	21.4 ± 10.1	77 (18-107)	78 (11-113)	7
Song <i>et al</i> <sup>[17]</sup>	2015/China	29	59	65.3	45.8	15/14	38/21			26.9 ± 8.5	22.3 ± 9.4	7
Fukunaga <i>et al</i> <sup>[18]</sup>	2016/Japan	74	74	67.3	67.1	57/17	58/16	23.1 ± 10.1	24.7 ± 11.4	43.5 (26.3-76)	62.9 (36.5-91.7)	8
Gong <i>et al</i> <sup>[19]</sup>	2016/Korea	40	39	65	60	35/5	35/4	17.5 (13.0-24.8)	24 (16-35)	63.2 (53.6-83.5)	60.3 (58.4-68.7)	7
Ryu <i>et al</i> <sup>[20]</sup>	2016/Korea	81	144	63.65	61.37	59/22	118/26	19.32 ± 11.31	20.55 ± 10.68	78.12 ± 9.72	80.56 ± 8.92	7
Najmeh <i>et al</i> <sup>[21]</sup>	2016/Canada	30	37	74	75	23/7	24/13	/	/	20 (5-56)	26.5 (11-94)	7
Shin <i>et al</i> <sup>[22]</sup>	2017/Korea	175	100	61.7	60.5	129/46	73/27	/	/	56 (45-58)	53 (44-60)	8
Jeon <i>et al</i> <sup>[23]</sup>	2017/Korea	117	117	59.9	59.5	82/35	81/36	18 ± 11.0	18 ± 10	57.0 (35.5-65.5)	58 (49.0-61.0)	8
Park <i>et al</i> <sup>[24]</sup>	2017/Korea	81	81	55.0	54.2	33/48	42/39	10.6 ± 5.2	10.3 ± 5.2	48.1 (33.6-71.4)	60 (34.0-70.1)	8
Hahn <i>et al</i> <sup>[25]</sup>	2017/Korea	817	1206	61.9	57.0	605/212	752/454	13.0 ± 9.7	16.8 ± 11.0	37.5 (26.2-59.4)	57.34 (37.63-60.47)	8
Lee <i>et al</i> <sup>[26]</sup>	2017/Korea	522	522	61	61	366/156	370/152	25 (20-35)	25 (21-35)	52.7 (37.7-67.9)	59.2 (47.9-63.4)	8

ESD: Endoscopic submucosal dissection; NOS: Newcastle-Ottawa Scale.

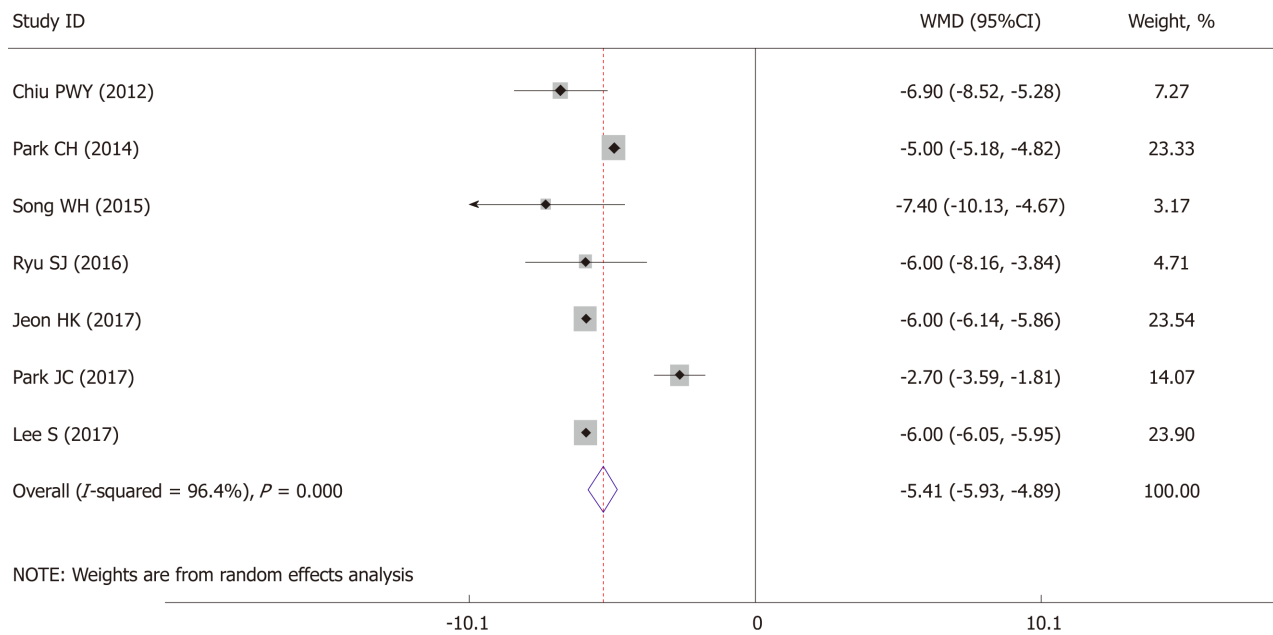


**Figure 2** Comparison of operation time for endoscopic submucosal dissection vs surgical resection in early gastric cancer.

**A**



**B**



**Figure 3 Comparison of post-operation complication rate and hospital stay for endoscopic submucosal dissection vs surgical resection in early gastric cancer. A: Post-operation complication rate; B: Hospital stay.**

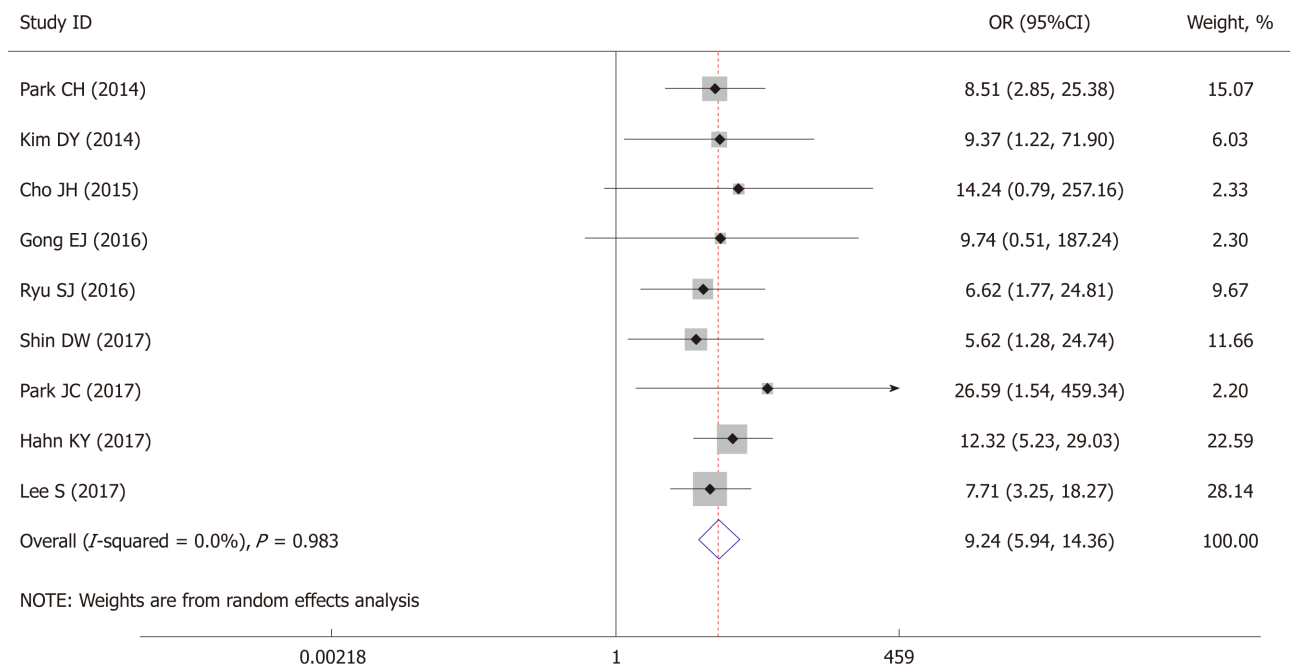
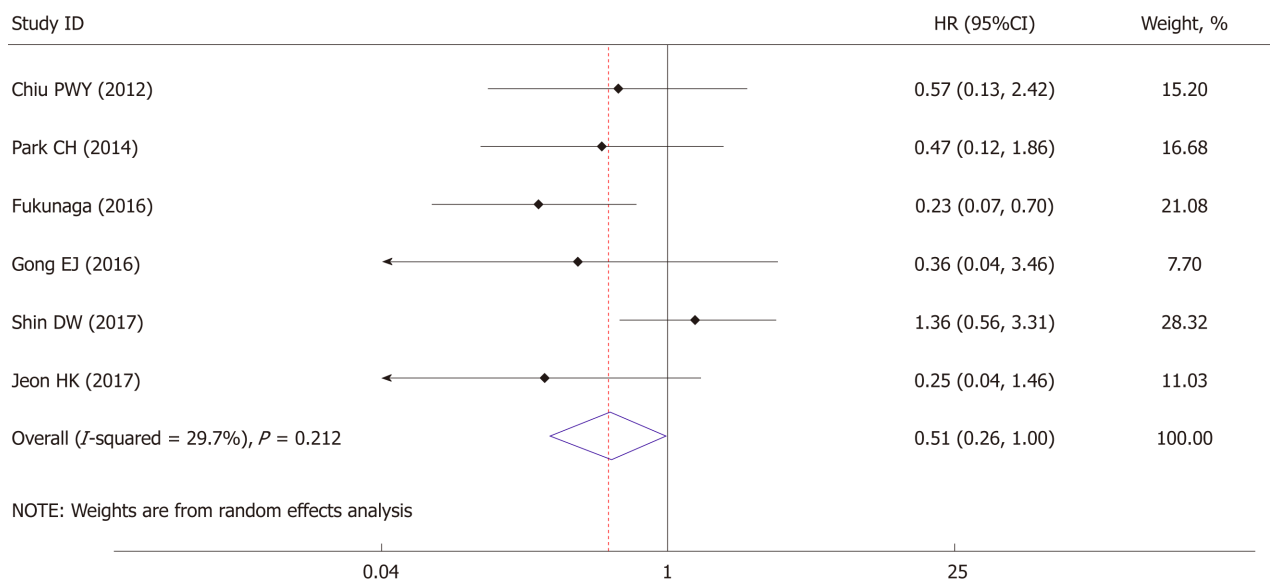


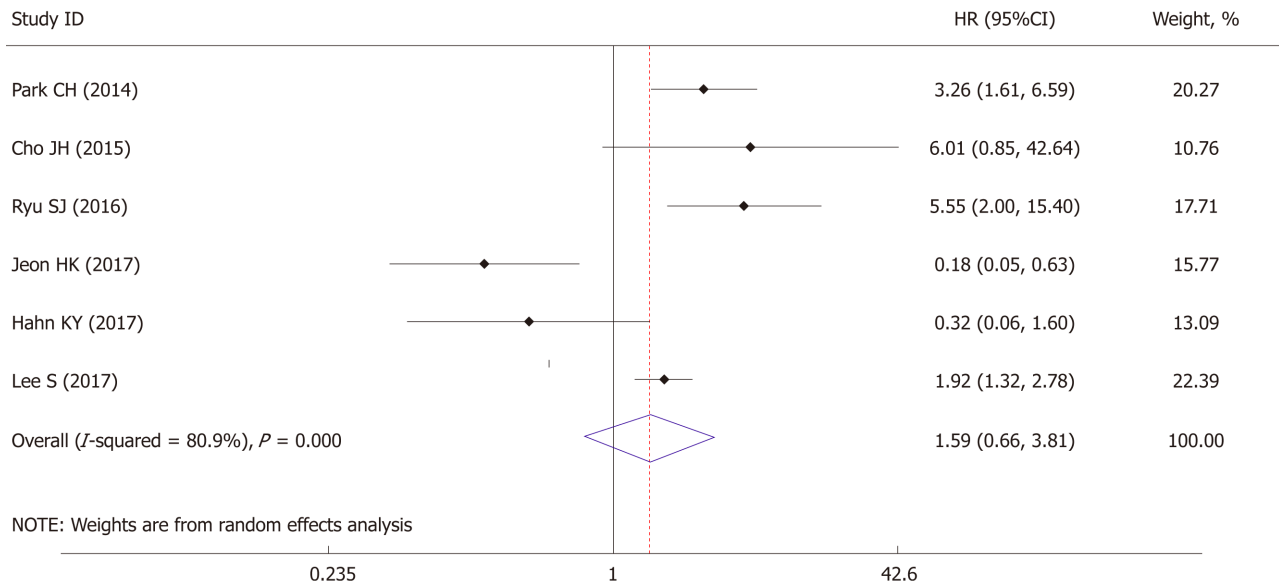
Figure 4 Comparison of recurrence rate for endoscopic submucosal dissection vs surgical resection in early gastric cancer.

**A**

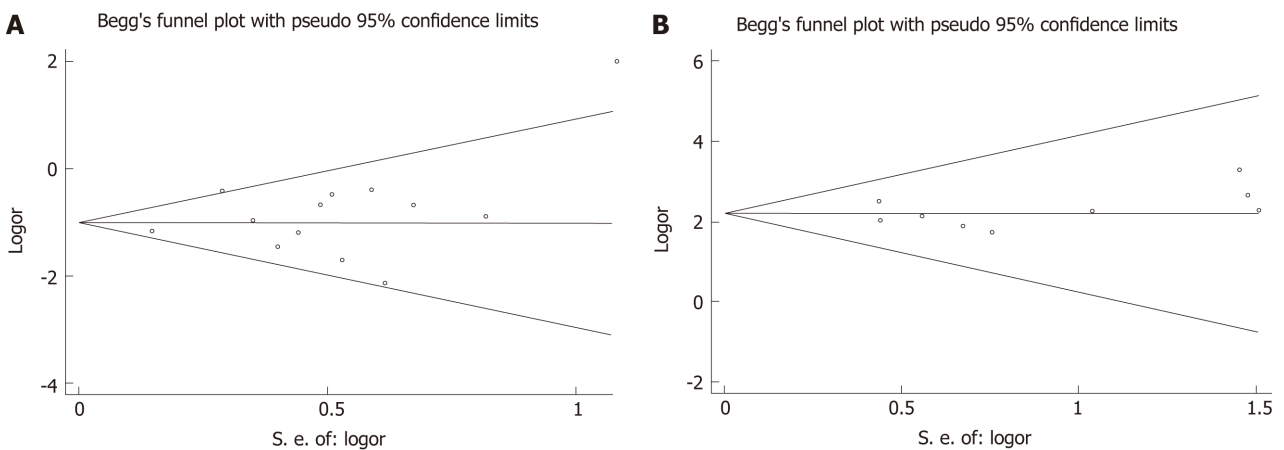




**B**



**Figure 5 Comparison of overall survival and event-free survival for endoscopic submucosal dissection vs surgical resection in early gastric cancer. A: Overall survival; B Event-free survival.**



**Figure 6 Funnel plot for publication bias of post-operation complication and recurrence rate for endoscopic submucosal dissection vs surgical resection in early gastric cancer. A: post-operation complication; B: Recurrence rate.**

**ARTICLE HIGHLIGHTS**

**Research background**

There are several surgical options for treating early gastric cancers (EGCs), such as endoscopic resection, laparoscopic or open gastrectomy. The role of endoscopic submucosal dissection (ESD) in treating EGC is not well established, especially when compared with resection surgery.

**Research objectives**

In this study, the authors aim to compare the safety and efficacy of the short- and long-term outcomes between ESD and resection surgery.

**Research methods**

The databases from January 1990 to June 2018 of PubMed, EMBASE, Web of Science, and the Cochrane Library were searched. The enrolling studies reporting short- or long-term outcomes of ESD in comparison with resection surgery for EGC. The quality of the studies was assessed by the Newcastle-Ottawa Quality Assessment Scale. By using either fixed- or random-effects models depending on heterogeneity across studies, the pooling analysis was conducted.

**Research results**

Fourteen studies comprising 5112 patients were eligible for analysis. This meta-analysis

demonstrated that the ESD approach showed advantages through decreased operation time, shorter hospital stay, and lower postoperative complication rate. And the EGC patients who underwent ESD had higher recurrence rate than resection surgery patients. However, the long-term survival including overall survival and event-free survival showed no significant differences between these two groups.

### Research conclusions

This meta-analysis suggested that ESD is safe and feasible in comparison with resection surgery in treating EGC, with clinical advantages in operation time, hospital stay, and postoperative complications. The long-term survival also supported the safety of ESD compared with resection surgery, although with some differences in tumor recurrence rate.

### Research perspectives

The further multi-center and prospective randomized controlled trials with longer and standard follow-up strategies are warranted to verify the findings of the study.

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