



# Comparison of Long-Term Outcomes of Endoscopic Submucosal Dissection and Surgery for Early Gastric Cancer: a Systematic Review and Meta-analysis

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## Abstract

**Background** Endoscopic submucosal dissection (ESD) is an endoscopic alternative to surgical resection of early gastric cancer (EGC). Besides offering both diagnostic and therapeutic capability, it has the benefits of reducing post-operative complications and provides fast recovery and better quality of life compared to surgical resection of neoplastic lesions. However, due to limitations of the procedure, its long-term outcomes are rather controversial.

**Methods** This study has been carried out to investigate the long-term outcomes of ESD which includes the overall survival (OS), disease-free survival (DFS), and recurrence rate. The following databases were used to search for articles published until February 2018: Medline, Cochrane Library, PubMed, Web of Science, and EBSCO.

**Results** A total of 13 eligible studies covering 4986 patients were selected for a meta-analysis based on specified inclusion and exclusion criteria. The difference of OS and disease-specific survival (DSS) between ESD and surgical treatment was not statistically significant (RR = 0.90, 95% CI = 0.68–1.19,  $p = 0.46$ ; RR = 0.40, 95% CI = 0.15–1.03,  $p = 0.06$ , respectively). However, DFS in the ESD group was much lower than that in the surgery group (RR = 3.40, 95% CI = 2.39–4.84,  $p < 0.001$ ). In terms of the treatment after recurrence, the proportion of patients who could receive radical treatment was significantly higher in the ESD than that in the gastrectomy (OR = 5.27, 95% CI = 2.35–11.79,  $p < 0.001$ ).

**Conclusions** This meta-analysis showed that ESD might be an alternative treatment option to surgery for patients with EGC in Asian countries. But a close surveillance program after ESD is of necessity, considering the higher possibility of tumor recurrence after ESD.

**Keywords** Early gastric cancer · Endoscopic submucosal dissection · Surgery · Prognosis · Meta-analysis

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## Introduction

Gastric cancer (GC) is currently the fourth most common malignancy and the second most common malignancy that causes death worldwide.<sup>1</sup> Early detection and treatment are critical for better prognosis and reducing mortality. The use of endoscopy as part of regular health examination is playing an essential role in diagnosis of gastric carcinoma, thus increasing the diagnosis of early gastric cancer (EGC) worldwide. EGC is defined as adenocarcinoma of the stomach in which the neoplastic lesion is confined to the mucosa or submucosa, irrespective of regional lymph node metastasis (LNM). There are several treatment modalities available for EGC, in which radical gastrectomy with lymph node dissection being the most effective as it enables adequate oncological clearance with low recurrence rate. However, patients'

post-operative quality of life is greatly impacted by late-phase complications such as dumping syndrome and decrease in BMI from oral intake disturbance.<sup>2</sup> Study also found that there was only approximately 15% of patients diagnosed with EGC has LNM; thus, standard gastrectomy might consider an over-treatment in patients with no LNM.<sup>3</sup>

Recently, with the development of endoscopic technology, endoscopic resection (ER) has replaced gastrectomy as the main choice for EGC. In Japan and Korea, where the incidence of EGC is more than 50%, the population of EGC patients receiving ER, especially endoscopic submucosal dissection (ESD), is on the rise.<sup>4–6</sup> Japanese Gastric Cancer Association has also recommended ESD as primary treatment of differentiated EGC without ulcerative findings, in which the depth of invasion is confined to mucosa and the diameter is  $\leq 2$  cm. Subsequently, the guidelines were modified to include the expanded indications and thereby causing an increase in the number of patients treated with ESD.<sup>7</sup> However, the outcomes of ER are rather controversial with respect to its high recurrence rate which will eventually affect long-term survival.<sup>8,9</sup> Recent studies have contrasted the long-term outcomes of ESD following the absolute or expanded indications with the outcomes of gastrectomy but the results seem contradictory.<sup>10,11</sup> Thus, we performed a systemic review and meta-analysis to compare the safety and efficacy of ESD with gastrectomy in order to find the best therapeutic option for EGC.

## Methods

### Search Strategy

A systematic search of databases which consists of Medline, Cochrane Library, PubMed, Web of Science, and EBSCO was completed in February 2018. The search terms used were as follows: (“early gastric cancer” OR “gastric cancer” OR “stomach cancers”) AND (“ESD” OR “endoscopic submucosal dissection” OR “endoscopic resection”) AND (“surgery” OR “gastrectomy”). Additionally, the reference lists of the selected articles were manually reviewed to obtain potentially relevant articles.

### Selection Criteria

From the potentially relevant original articles obtained above, those reporting the long-term outcomes of ESD and surgery in EGC were selected. Articles selection was determined by the following inclusion and exclusion criteria:

**Inclusion criteria** (1) Articles were limited to primary clinical studies only. (2) All patients with EGC were diagnosed by pathological evidence. (3) All lesions of EGC met the absolute

or expanded indications. (4) All patients were followed up and results were recorded.

**Exclusion criteria** (1) ESD subgroup analysis was not performed as ER included EMR. (2) The end points of the literature did not include the long-term outcomes. (3) The lesions included non-tumor disease, such as severe dysplasia and polyps. (4) Data extraction and quality assessment.

Data from each included study were independently extracted by two authors. A third author would assess it, if the literature has any disagreement. The following baseline information were extracted: year of publication, authors, country where the study was performed, study design, sample size, follow-up time, baseline characteristics of the study population, pathologic data, and long-term outcomes.

This meta-analysis was conducted in accordance with the guidelines of the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement.<sup>12,13</sup> The quality of the included studies was assessed using the Newcastle–Ottawa Quality Assessment Scale (NOS) checklist by two independent authors.<sup>14</sup> This quality assessment tool focuses on eight items categorized in three groups (selection, comparability, and outcome) with a maximum number of nine stars. The articles achieving six or more stars were considered high quality.

### Long-Term Outcomes and Definitions

These research papers reported different long-term outcomes including overall survival (OS), disease-specific survival (DSS), and disease-free survival (DFS). OS was defined as the length of time from the date of ESD or surgery to the date of death from any causes. DSS was defined as the length of time from the date of ESD or surgery to the date of the death related to gastric cancer, whereas DFS was defined as the length of the time from the date of ESD or surgery to the date of the first gastric cancer recurrence, metachronous gastric cancer occurrence, or death for any cause.<sup>15</sup>

Metachronous gastric cancer is a new cancer that was detected over 1 year at a previously uninvolved site after initial treatment. Tumor recurrence was categorized as local, regional, or distant recurrence.

### Statistical Analysis

Risk ratio (RR) including 95% confidence interval (CI) was used to assess the comparison of the long-term outcomes in EGC after either ESD or surgery. An observed  $RR > 1$  implied that ESD was better than surgery at improving the long-term outcomes of EGC. Conversely,  $RR < 1$  implied that ESD was worse than surgery. Revman 5.3 Software (RevMan, The Cochrane Collaboration) was used to perform the meta-analysis and evaluate

heterogeneity between studies by Cochrane *Q* test and *p*-values. Heterogeneity of included studies was assessed and deemed significant if  $p < 0.1$ . The Stata 12.0 Software (Stata, College Station) was used to evaluate the sensitivity and publication bias of the studies. Publication bias was evaluated by Begg’s and Egger’s test;  $p < 0.05$  was considered statistically significant.<sup>16</sup>

## Results

### Study Selection

A total of 2543 relevant clinical studies were derived from the search strategy. Of these, 1406 were eliminated because of repetition, and 1050 were excluded based on evaluation of their title or abstract. The remaining 87 articles were scrutinized by a full-text review. Eventually, 13 studies<sup>10,15,17–27</sup> were included in this meta-analysis, according to the inclusion and exclusion criteria. The detailed search and study selection process is shown in Fig. 1.

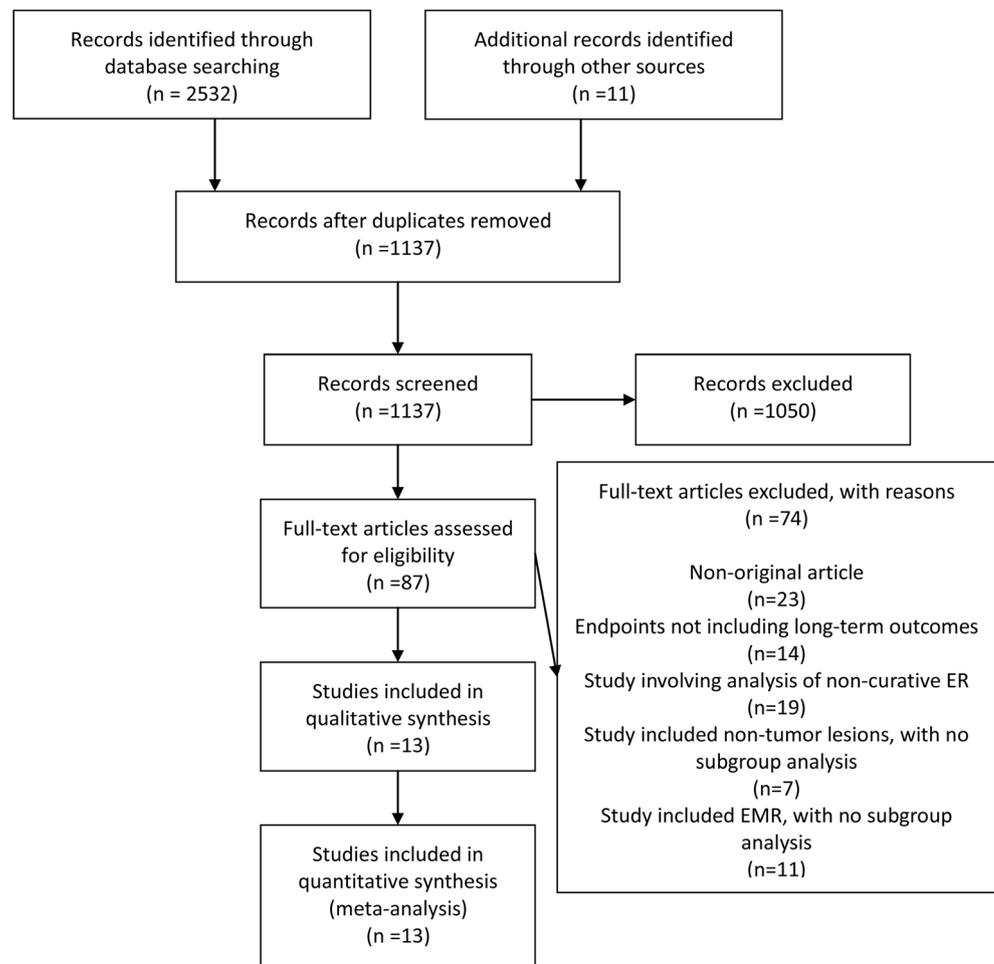
### Study Characteristics

The 13 studies included 4986 patients with EGC at baseline, from year 2014 to 2018, with a maximum sample size of 1988 and a minimum sample size of 64 participants. Among them, 2324 patients received ESD while the other 2662 patients received surgery. Seven studies belonged to propensity score analysis. All the studies were reported in Asia: 12 in South Korea and one in Japan. All the lesions met the absolute or expanded indications. The curative resection rate of ESD group ranged from 82.5 to 100%. The characteristics of the included studies are shown in Table 1.

### Prognosis

A total of 185 patients died in the included studies and the OS was 96.29%. Among them, in the ESD group, 86 patients died and the OS was 96.30%. In the surgery group, 99 patients died and the OS was 96.28%. There was no significant difference between both groups (RR = 0.90, 95% CI = 0.68–1.19,  $p = 0.46$ , fixed-effects model) (Fig. 2). Three literatures (including

**Fig. 1** Flow chart of study selection



**Table 1** Characteristics of studies included in the meta-analysis

Author, year	Country	Follow-up (months)			Patients, <i>n</i>		ESD indications	Long-term outcomes	PSA	CR (%)	NOS*
		ESD	Surgery	At least	ESD	Surgery					
Chang et al., 2017	Korea	2 years	3 years	NA	74	79	Absolute, expanded	OS, DFS	No	92.2	6
Cho et al., 2016	Korea	77	78	NA	88	88	Absolute, expanded	OS	Yes	100	8
Fukunaga et al., 2017	Japan	NA	NA	NA	74	74	Expanded	OS	Yes	100	7
Gong et al., 2017	Korea	NA	NA	12	40	39	Absolute, expanded <sup>^</sup>	OS, DFS	No	82.5	7
Hahn et al., 2017	Korea	38	57	NA	786	1202	Absolute, expanded	OS, DSS,	No	100	8
Jeon et al., 2018	Korea	58	58	12	117	117	Absolute, expanded	OS, DSS, DFS	Yes	100	8
Kim et al., 2014	Korea	77	66	60	142	71	Absolute, expanded	OS, DFS	No	85.6	7
Kim et al., 2018	Korea	50	59	NA	36	28	Absolute, expanded <sup>^</sup>	OS, DFS	No	100	7
Lee et al., 2017	Korea	53	59	12	522	522	Expanded	OS, DSS, DFS	Yes	95.7	7
Park et al., 2014	Korea	18	24	6	108	117	Absolute, expanded	OS, DFS	Yes	100	7
Park et al., 2017	Korea	47	60	NA	81	81	Expanded	OS, DFS	Yes	87.7	7
Ryu et al., 2016	Korea	78	81	60	81	144	Absolute, expanded	OS, DFS	No	92.6	7
Shin et al., 2017	Korea	56	53	36	175	100	Absolute, expanded	OS, DFS	Yes	100	8

ESD endoscopic submucosal dissection, OS overall survival, DSS disease-specific survival, DFS disease-free survival, NA not available, PSA propensity score analysis, CR curative resection

\*NOS Quality Assessment based on Newcastle–Ottawa Scale

<sup>^</sup>The lesions belong to esophagogastric junction adenocarcinoma

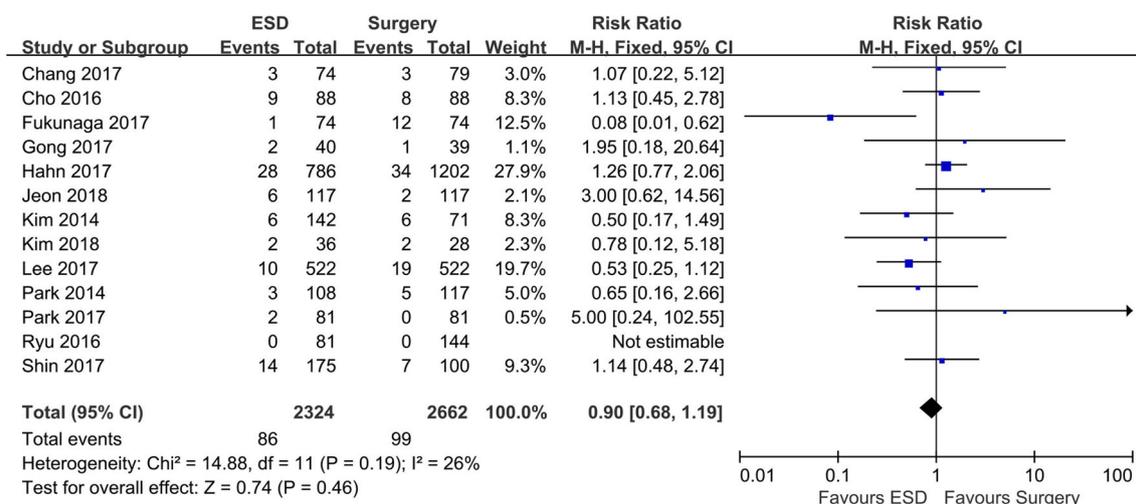
Elderly patients 70 years of age or older

3266 cases) further analyzed DSS, and five patients in the ESD group died of GC recurrence, with DSS of 0.35%. In the surgery group, 17 patients died of gastric cancer recurrence, with DSS of 0.92%. There was no significant difference (RR = 0.40, 95% CI = 0.15–1.03, *p* = 0.06, fixed-effects model) (Fig. 3).

In order to further investigate OS after ESD or surgery for EGC patients, exploratory subgroup analysis was performed according to indications (absolute or expanded), curative resection (all or majority), and propensity score analysis (yes or no). There was no statistically significant difference (Table 2).

### Recurrence

The DFS in the ESD group was lower than that in the surgery group, with the former being 90.19%, and the latter was 97.15% (RR = 3.40, 95% CI = 2.39–4.84, *p* < 0.001, fixed-effects model). Compared with patients who underwent surgery, patients receiving ESD had a higher incidence of the non-metachronous GC (OR = 4.94, 95% CI = 3.04–8.03, *p* < 0.001, fixed-effects model). Eleven studies reported the incidence of metachronous GC, which was significantly



**Fig. 2** Forest plot describing the association between treatment and OS of patients with EGC



Fig. 3 Forest plot describing the association between treatment and DSS of patients with EGC

higher in the ESD than that in the surgery (OR = 8.64, 95% CI = 5.00–14.95,  $p < 0.001$ , fixed-effects model) (Fig. 4).

### Treatment After Recurrence

A total of nine articles reported treatment after recurrence (including non-metachronous and metachronous). In the ESD group, tumor recurred in 228 patients, and 208 cases underwent the secondary radical therapy including ER or surgery, with the radical cure rate of 91.23%. Of patients, 72.60% received ER while 27.40% received surgery. Of the 228 patients with recurrence, 188 cases of local recurrence, two cases with lymph node metastasis, three cases with distal metastasis, and the others' data were not available. Besides, among the 20 patients who did not undergo the secondary radical therapy, one received argon plasma coagulation treatment, and four refused treatment due to old age; data of other patients were not available.

In the surgery group, there were 29 recurrent cases, of which 18 patients received the secondary radical treatment including ER or surgery, with the radical cure rate of 62.07%, as the ER accounted for 44.44%, the surgical treatment accounted for 55.56%. Comparison between ER and surgery as the treatment after recurrence was performed in seven studies. In subgroup analysis, the proportion of patients receiving the radical treatment (ER or surgery) was significantly higher in the ESD group than in the surgery group (OR = 5.27, 95% CI = 2.35–11.79,  $p < 0.001$ , fixed-effects model) (Fig. 5).

Table 2 Subgroup analysis of comparison between ESD and surgery of OS

	No. of studies	RR	95% CI	p	Heterogeneity		Effect model
					I <sup>2</sup> (%)	p	
AI+EI	10	1.13	0.82–1.56	0.47	0	0.79	Fixed
EI	3	0.47	0.08–2.60	0.39	63	0.07	Random
100% CR	7	1.00	0.72–1.40	1.00	34	0.17	Fixed
Non-100% CR	6	0.69	0.40–1.17	0.17	0	0.48	Fixed
PSA	7	0.85	0.44–1.63	0.63	48	0.07	Random
Non-PSA	6	1.09	0.72–1.64	0.68	0	0.62	Fixed

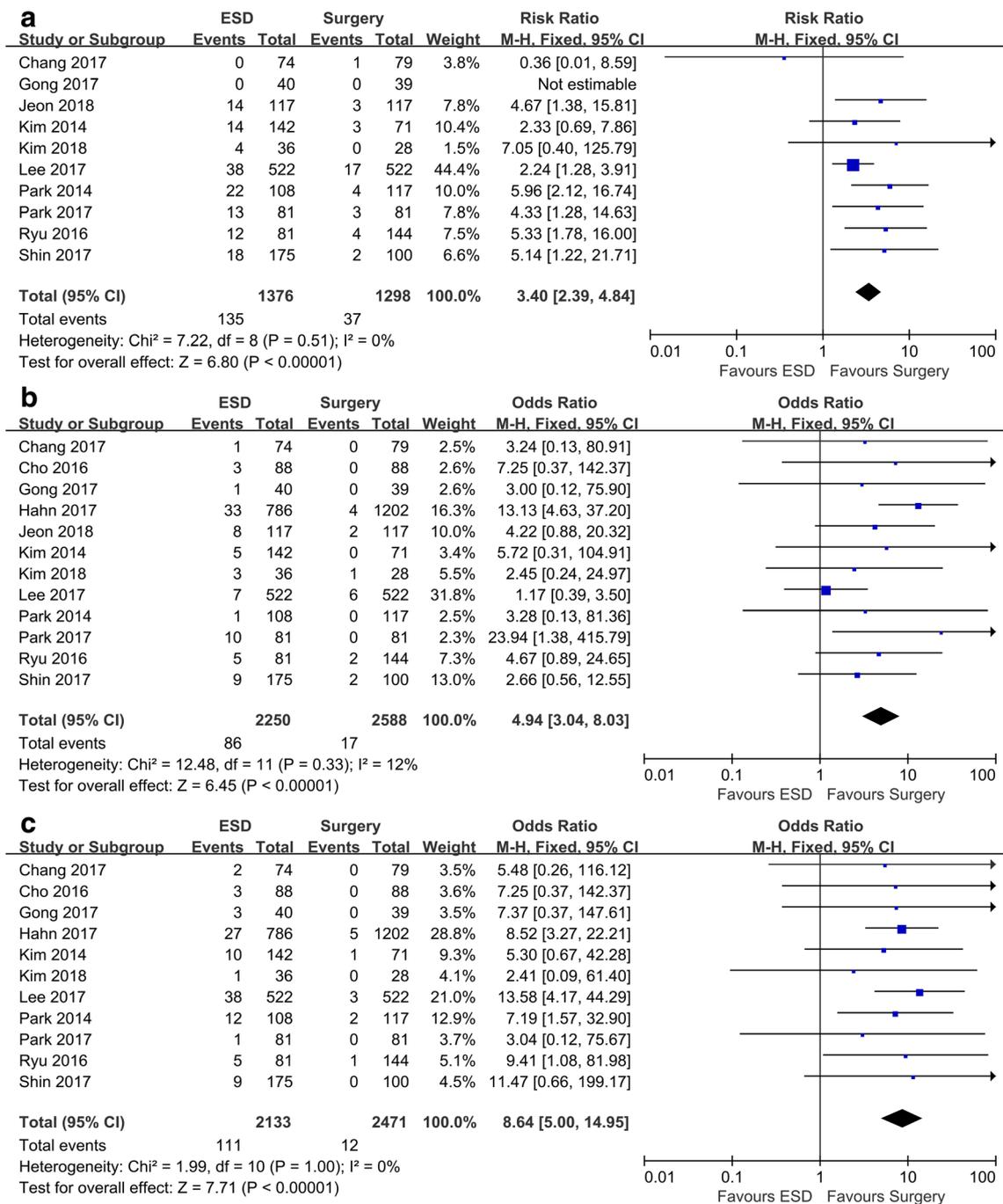
RR risk ratio, 95% CI 95% confidence interval, ESD endoscopic submucosal dissection, OS overall survival, AI absolute indication, EI expanded indication, PSA propensity score analysis, 100% CR the rate of curative resection was 100% in ESD, Non-100% CR the rate of curative resection was not 100% in ESD, Non-PSA the studies were not the propensity score analysis

### Publication Bias and Sensitivity Analysis

Publication bias was evaluated by the Begg's and Egger's test. In this meta-analysis, Begg's and Egger's test indicated no publication bias among included articles regarding the RR of OS (Begg's test  $p = 0.451$  and Egger's test  $p = 0.408$ ) (Supplementary Fig. 1). Sensitivity analysis was used to assess whether the individual studies affected the overall results or not. The results indicated that individual study had little influence on the final results, and the analysis was relatively stable and credible (Supplementary Fig. 2).

### Discussion

This study was carried out to compare the long-term outcomes of ESD with gastrectomy. After analyzing the selected studies, we find that patients suffering from EGC have been markedly increased and more patients have been receiving ESD as treatment option due to the fact that the incidence of LNM in EGC is relatively low, especially when the lesion meets the indication of ER. Furthermore, it is evident that the immediate outcomes of ESD are better than that of surgery.<sup>28–30</sup> However, the long-term outcomes of ESD are still debatable. Researchers hold different views with regard to the indication of ESD.<sup>31</sup>

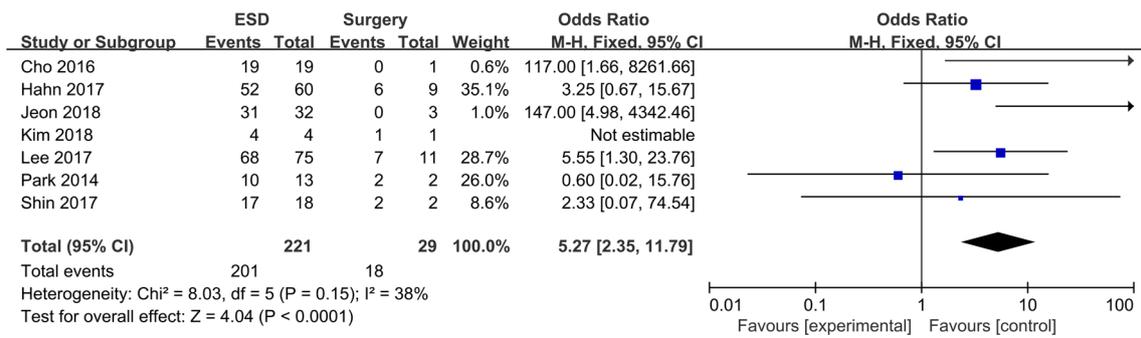


**Fig. 4** Forest plot describing the association between treatment and recurrence of patients with EGC. **a** DFS. **b** Non-metachronous GC rate. **c** Metachronous GC rate

Lee et al.<sup>27</sup> reported that the prognosis of patients who underwent ESD was better as compared to surgery. Conversely, a study by Hahn<sup>10</sup> and his colleagues suggested that both ESD and surgery had similar OS in patients with EGC. Fukunaga et al.<sup>25</sup> showed that there was no significant difference in prognosis between ESD and surgery in patients with American Society of Anesthesiologists Physical Status (ASA-PS) 1, but the OS of ESD was relatively better in the case of patients with ASA-PS 2. Consistent with the results of

Shin et al.,<sup>20</sup> this meta-analysis also shows that there was no significant difference between the OS of ESD and gastrectomy.

In addition to the long-term survival, a lot of papers focused on tumor recurrence. Kim et al.<sup>24</sup> observed the recurrence rates in ESD and surgery groups were similar. By contrast, Ryu et al.<sup>26</sup> and Jeon et al.<sup>15</sup> both suggested that 5-year cancer recurrence rate in the ESD group was significantly higher than that in the surgery group. From this meta-analysis, the DFS of patients in the surgery group was significantly



**Fig. 5** Forest plot describing the association between first treatment and secondary radical therapy of patients with recurrent GC

higher than that in the ESD group. Further analysis showed that, compared with surgical treatment, the incidence of non-metachronous and metachronous cancer was higher in the ESD treatment.

Reasons of this phenomenon are as follows: patients after receiving ESD still had a more or less intact stomach wall, which might be the basement for the new primary tumors. It is likely to contribute to a higher occurrence rate of metachronous cancer. On the other hand, in the ESD treatment, few tumor cells may have been left and remain within the area. These patients consequently receive non-curative ESD, which then leads to tumor recurrence in the original site.<sup>32</sup> Additionally, ESD treatment may leave out atypical lesions in some patients with synchronous multiple primary cancers, increasing the recurrence rate of ESD patients. Besides, a few patients with EGC have had occult lymph node metastasis before the operation.<sup>33</sup>

Although patients in the ESD group have higher recurrence rate compared with the surgery, this meta-analysis shows that there is no difference between the two groups in terms of DSS as well as OS. Subgroup analysis shows that, compared with the surgery, ESD group patients have higher rate (70%) of radical treatment (ER and surgery) after recurrence.

It can be seen that EGC could be treated by ESD, and during the follow-up, most recurrent tumors are also diagnosed as EGC, regardless of local recurrence or secondary primary tumors. Thus, these recurrent lesions are analogically appropriate for ESD treatment or surgical treatment. Meanwhile, prognosis can also be good. A few cases with LNM can be treated by radical gastrectomy accompanied with lymph node dissection (D2). In contrast, patients have lower tumor recurrence rate in surgery, but the possibility of second operation or ER seems very low. The cause might be due to the anatomical structure changes occurring after the first operation. Moreover, the quality of life of patients who underwent surgical treatment might decline, which also increases the risk of surgical complications, resulting in a decrease on the proportion of secondary radical treatment. In other words, EGC patients who underwent ESD have higher recurrence rate than that in the surgery group, but their long-term outcomes were similar.

To the best of our knowledge, this is the first meta-analysis to systematically compare the long-term outcomes in EGC between ESD and surgery. According to the similar OS and DSS, ESD could be a reasonable alternative to surgery for EGC meeting the expanded indication. It is worth noting that during the follow-up, patients who underwent ESD might have a higher tumor recurrence rate, which would be suggestive of a closer monitoring via endoscopy. Once detected, these lesions can and should be immediately treated.

In the included studies, some researchers reported that the time of recurrence was mostly 20–30 months (median) after ESD, and the majority of patients with recurrence were local recurrence<sup>23,27</sup>. Therefore, we believed that the value of endoscopic examinations in patients with EGC after ESD may be greater than that of other methods, including contrast-enhanced abdominal CT. Therefore, it is recommended that endoscopy should be scheduled every 3–6 months for the third years after ESD. Endoscopy was performed every 6–12 months in the fourth and fifth years and annually thereafter. Additionally, a recent randomized trial showed that patients with EGC who received *Helicobacter pylori* treatment had lower rates of metachronous gastric cancer and more improvement from baseline in the grade of gastric corpus atrophy<sup>34</sup>. We believed that radical treatment of *Helicobacter pylori* was of great significance for patients with EGC, and *Helicobacter pylori* should be more actively eradicated in patients with EGC received ESD treatment.

**Limitations**

The limitations of this study should be stressed on. Firstly, all included research papers were retrospective studies, thereby having disadvantages including selection bias, information bias, and so on. It inevitably leads to a decline in the level of evidence in this article. Secondly, the patients covered in this study were all from Asian countries (Korea and Japan), where the incidence of GC was relatively high. We were unable to control such factors as environmental conditions, racial differences, socioeconomic situation, and treatment concept. Consequently, the conclusions of this study cannot be applied to western countries directly. Last but not least, publication

bias was another issue that could not be ignored, and this article was limited to English. Therefore, further large-scale and comprehensive researches are needed to support our results and conclusion.

## Conclusions

This study showed that due to the similar OS and DSS, ESD is comparable to surgery for EGC treatment meeting the expanded indication in Asian countries. But a careful and strict monitoring is needed after receiving ESD, considering the higher chances of recurrence after the procedure.

**Authors' Contributions** Lihu Gu and Manman Chen assisted the conception and design. Lihu Gu and Liangliang Chen acquired the necessary data. Xinlong Li and Hepan Zhu assisted with statistical analysis and interpretation of data and provided critical revision of drafts. Parikshit A. Khadaroo and Manman Chen assisted with abstracts selection and also checked meta-data against the included manuscripts. Lihu Gu and Xin Zhong drafted the manuscript. Junhai Pan assisted with conception and design, assisted with statistical analysis and interpretation of data, and provided critical revision of drafts. All authors read and approved the final manuscript.

**Data Availability** The datasets supporting the conclusions of this article are included within the article.

## Compliance with Ethical Standards

**Conflict of Interest** The authors declare that they have no conflict of interest.

**Ethical Standards** This article does not contain any studies with human or animal subjects performed by any of the authors.

**Abbreviations** ESD, endoscopic submucosal dissection; ER, endoscopic resection; EMR, endoscopic mucosal resection; EGC, early gastric cancer; GC, gastric cancer; LNM, lymph node metastasis; OS, overall survival; DSS, disease-specific survival; DFS, disease-free survival; RR, risk ratio; OR, odds ratio; CI, confidence interval

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