

BMJ Open Endoscopic submucosal dissection versus endoscopic mucosal resection for patients with early gastric cancer: a meta-analysis

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ABSTRACT

Objectives To investigate the treatment effects of endoscopic submucosal dissection (ESD) versus endoscopic mucosal resection (EMR) for early gastric cancer (EGC).

Design Meta-analysis.

Methods We systematically searched three electronic databases, including PubMed, EmBase and the Cochrane library for studies published with inception to January 2018. The eligible studies should be evaluated for the efficacy and safety of ESD versus EMR for patients with EGC. The summary ORs and standard mean differences (SMDs) with 95% CIs were employed as effect estimates. Sensitivity analyses were conducted to evaluate the impact of single study on overall analysis. Subgroup analyses were performed for investigated outcomes to evaluate the treatment effects of ESD versus EMR for patients with EGC with specific subsets.

Results Eighteen studies, with a total of 6723 patients with EGC, were included in final analysis. The summary ORs indicated that patients with EGC who received ESD were associated with an increased incidence of en bloc resection (OR: 9.00; 95% CI: 6.66 to 12.17; $p < 0.001$), complete resection (OR: 8.43; 95% CI: 5.04 to 14.09; $p < 0.001$) and curative resection (OR: 2.92; 95% CI: 1.85 to 4.61; $p < 0.001$) when compared with EMR. Furthermore, ESD was associated with lower risk of local recurrence (OR: 0.18; 95% CI: 0.09 to 0.34; $p < 0.001$). In addition, there was no significant difference between ESD and EMR for the risk of bleeding (OR: 1.26; 95% CI: 0.88 to 1.80; $p = 0.203$). Though, ESD was correlated with greater risk of perforation (OR: 2.55; 95% CI: 1.48 to 4.39; $p = 0.001$), and longer operation time (SMD: 1.12; 95% CI: 0.13 to 2.10; $p = 0.026$) as compared with EMR. Additionally, several different features observed in included studies and patients could bias the effectiveness of ESD versus EMR in patients with EGC.

Conclusions ESD is superior than EMR for en bloc resection, complete resection, curative resection and local recurrence, while it increased perforation risk and longer operation time.

INTRODUCTION

Gastric cancer (GC) is the second most common cancer worldwide, which accounts for approximately 0.93 million new cases per

Strengths and limitations of this study

- We did a meta-analysis to investigate the treatment effects of endoscopic submucosal dissection (ESD) versus endoscopic mucosal resection (EMR) for early gastric cancer (EGC).
- Several different features observed in included studies and patients could bias the effectiveness of ESD versus EMR in patients with EGC.
- This quantitative analysis was based on published studies and thus publication bias was inevitable.
- The summary analysis was based on pooled data and individual data were not available, which restricted us from conducting more detailing analysis.

year, among which two-thirds come from Asian countries, such as China, Japan and Korea.¹⁻³ Early diagnostic of GC is extremely important for the endoscopic treatment; early gastric cancer (EGC) is defined as malignant lesion that does not go beyond the submucosal layer of the stomach wall irrespective of the presence of lymph node metastasis.⁴ Nevertheless, in China the detection rate of patients with EGC is still low (10%) compared with some other countries.^{5 6} Therapeutic endoscopic resection has been used for EGC since the mid-1980s and is still regarded as standard treatment strategy for patients with EGC without lymph node metastasis.^{7 8} Yet, the effectiveness of endoscopic submucosal dissection (ESD) and endoscopic mucosal resection (EMR) for patients with EGC still remains controversial.

The techniques for ESD were developed since the 1990s, which was associated with expanded indication range for endoscopic resection.⁹ Moreover, EMR was initially carried out through strip biopsy, which are developed combined with a cap-fitted panendoscope and aspiration mucosectomy.⁸ Previous studies have demonstrated that EMR is useful for endoscopically resectable lesions,

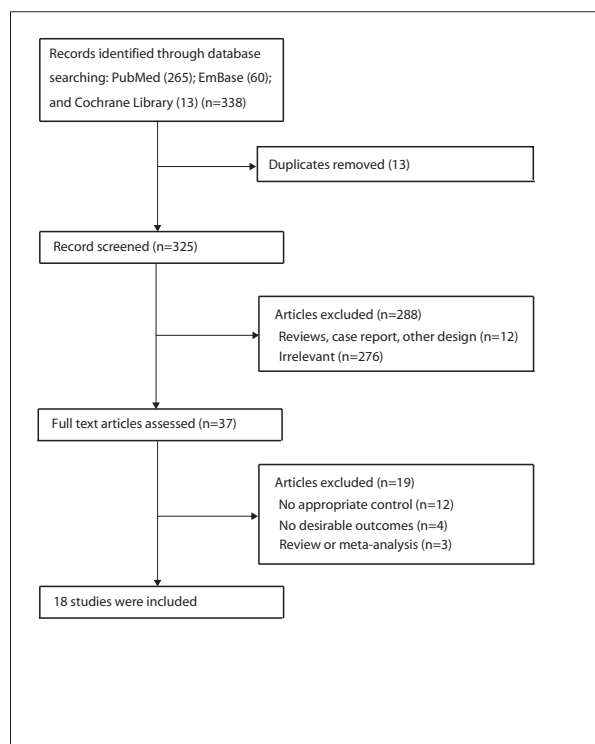


Figure 1 Flow diagram of the literature search and selection process of trials.

but not for histological assessment and cases with high risk of local recurrence.^{10–12} Contrary, ESD has shown to be beneficial for one-piece resection in patients with large and ulcerative lesions regardless of tumour location.^{13–15} Compared with EMR, many studies have shown that patients with EGC who received ESD could achieve higher en bloc resection rate and accurate histological assessment, which in turn could reduce the risk of local recurrence.^{16 17} However, numerous other outcome variables did not provide data suitable for direct comparisons, thus the effectiveness of ESD versus EMR for needs of patients with EGC to be further clarified. The following study thoroughly investigates the efficacy and safety of ESD versus EMR in treating patients with EGC by conducting a comprehensive quantitative meta-analysis.

MATERIALS AND METHODS

Data sources, search strategy and selection criteria

This meta-analysis was performed according to the Meta-Analysis of Observational Studies in Epidemiology guidelines.¹⁸ We performed a systematical search of PubMed (<http://www.ncbi.nlm.nih.gov/pubmed/>), Embase (<http://www.embase.com/>) and Cochrane Library (<http://www.thecochranelibrary.com/>) databases looking for the studies published through January 2018 which evaluated the effectiveness of ESD versus EMR for patients with EGC. We used the following texts and keywords in combination with both MeSH terms and text words: (“stomach” or “gastric”) AND (“neoplasms” or “carcinoma” or “cancer” or “adenocarcinoma”) AND

“endoscopic submucosal dissection” AND “endoscopic mucosal resection”. The details of search strategy are shown in online supplementary file 1. Manual searches of reference lists from potential studies were conducted to select additional eligible studies.

The eligible studies were identified through an initial screen of abstracts and titles, while the second screening included the examination of the full-text of the articles. Two authors evaluated the study selection process independently, and any inconsistencies were resolved by an additional author until a consensus was reached. The studies were eligible for inclusion if they met the following: (1) studies with prospective or retrospective design; (2) patients with EGC; (3) studies which investigated the effectiveness of ESD versus EMR and (4) those reporting at least one of the following outcomes: en bloc resection, complete resection, curative resection, local recurrence, bleeding, perforation and operation time.

Data collection and quality assessment

Two authors independently abstracted and evaluated the following items in each study according to the standard protocols: first author’s surname, publication year, country, study design, number of lesions, mean age, percentage of male, mean size of lesions, disease status and follow-up duration, while any inconsistencies were determined by group discussion and referring to the original article. The methodological quality of included studies was assessed using the Newcastle-Ottawa Scale (NOS), which is comprehensive method for evaluating the quality of observational studies in meta-analysis.¹⁹ The NOS consisted of three subscales including the representative of participants, comparability and outcomes, which ranged from 0 to 9-star system. Studies that were awarded score equal or higher than 6 were regarded of high quality.

Statistical analysis

The summary ORs with corresponding 95% CIs were employed to calculate the dichotomy outcomes including en bloc resection, complete resection, curative resection, local recurrence, bleeding and perforation, while the standard mean difference (SMD) with 95% CI was used to evaluate the difference between ESD and EMR for operation time. The summary results were calculated using the Dersimonian and Laird random-effects models.^{20 21} Heterogeneity among studies was investigated by I^2 , if $I^2 > 50\%$ was regarded as significant heterogeneity.^{22 23} Sensitivity analyses for investigated outcomes were conducted to evaluate the impact of single study on overall analysis.²⁴ Furthermore, subgroup analyses were performed according to publication year, study design, number of lesions, mean age, percentage of male, disease status and follow-up duration. The interaction p value, which was based on Student’s t-test distribution due to small number of included studies, was also calculated to compare the difference between subgroups.²⁵ Publication biases were calculated for investigated outcomes by using Egger

Table 1 Baseline characteristics of included patients and studies in the meta-analysis

Study	Publication year	Country	Study design	No of lesions	Mean age (years)	Percentage of male	Mean size of lesions (ESD/EMR: mm)	Disease status	Follow-up duration (years)
Hirasaki ²⁸	2008	Japan	Retrospective	32	70.9	NA	15.5/12.7	Recurrent EGC	5.8
Hoteya ²⁹	2009	Japan	Retrospective	62	70.3	88.7	18.8/11.8	Recurrent EGC	1.0
Oda ¹⁶	2006	Japan	Retrospective	714	68.0	77.3	NA	EGC	3.2
Min ³⁰	2009	Korea	Retrospective	346	61.6	77.2	NA	EGC	2.4
Catalano ³¹	2009	Italy	Non-concurrent	48	68.8	66.0	NA	EGC	2.6
Yokoi ³²	2006	Japan	Retrospective	64	69.3	81.3	NA	Recurrent EGC	3.6
Hoteya ³³	2009	Japan	Retrospective	900	67.9	78.9	21.3/11.8	EGC	1.0
Oka ¹⁷	2006	Japan	Retrospective	1020	NA	NA	19.4/14.6	EGC	6.9
Watanabe ³⁴	2006	Japan	Retrospective	245	69.5	65.7	NA	EGC	3.2
Shimura ³⁵	2007	Japan	Non-concurrent	107	70.2	80.4	15.5/15.0	EGC	1.0
Nakamoto ³⁶	2009	Japan	Retrospective	202	67.3	75.1	NA	EGC	4.5
Choi ³⁷	2006	Korea	Non-concurrent	66	NA	NA	NA	EGC	NA
Ahn ³⁸	2011	Korea	Retrospective	1370	63.0	76.7	16.0 for all	EGC	2.7
Kim ³⁹	2014	Korea	Retrospective	87	54.0	46.0	NA	EGC	NA
Oka ⁴⁰	2014	Japan	Retrospective	125	62.0	56.0	NA	EGC	7.5
Pimentel-Nunes ⁴¹	2014	Portugal	Retrospective	190	70.0	55.0	NA	EGC	3.2
Tanabe ⁴²	2014	Japan	Retrospective	780	68.1	66.9	24.0/12.0	EGC	5.7
Watanabe ⁴³	2010	Japan	Retrospective	365	NA	NA	≤7.0	EGC	NA

EGC, early gastric cancer; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; NA, not available.

and Begg tests.^{26 27} All reported p values were two sided, and p value <0.05 was considered statistically significant. Statistical analyses were performed using STATA software (V.10.0; Stata Corporation, College Station, Texas, USA).

Patient and public involvement

Not applicable.

RESULTS

Literature search

Figure 1 shows a flow diagram of relevant studies' selection process. The initial electronic search produced 338 articles; 301 studies were excluded based on initial screening of titles and abstracts. Full texts for the remaining 37 studies were retrieved to select relevant studies. Finally, 18 studies including 6723 patients with EGC were finally recruited into this meta-analysis.^{16 17 28–43} Manual search of the reference lists from included studies did not yield new eligible studies.

Study characteristics

We selected a total of 15 retrospective and 3 non-concurrent studies, which included 6723 patients with EGC. Table 1 summarised the general characteristics of the included

studies. The included studies were performed in the Japan (n=12), Korea (n=4), Italy (n=1) and Portugal (n=1). The follow-up period for participants was 1.0–7.5 years, while 32–1370 lesions were included in each study. Fifteen studies included patients with EGC, and the remaining three studies included patients with recurrent EGC. Study quality was assessed by NOS and is shown in online supplementary file 2. Overall, three studies scored 7, nine studies scored 6 and the remaining six studies scored 5.

En bloc resection

Data for the effectiveness of ESD versus EMR for en bloc resection were available in 13 studies (14 cohorts). Briefly, en bloc resection rate resulted significantly higher in ESD patients (OR: 9.00; 95% CI: 6.66 to 12.17; p<0.001; with moderate heterogeneity; figure 2). The result of sensitivity analysis was not altered after sequential exclusion of a single study (online supplementary file 3). Subgroup analyses found these significant differences were persisted in each subgroup, and percentage of male might affect the effectiveness of ESD versus EMR for patients with EGC (table 2). Finally, there was no significant publication bias by Egger and Begg test results (p value for Egger: 0.367; p value for Begg: 0.274; table 3).

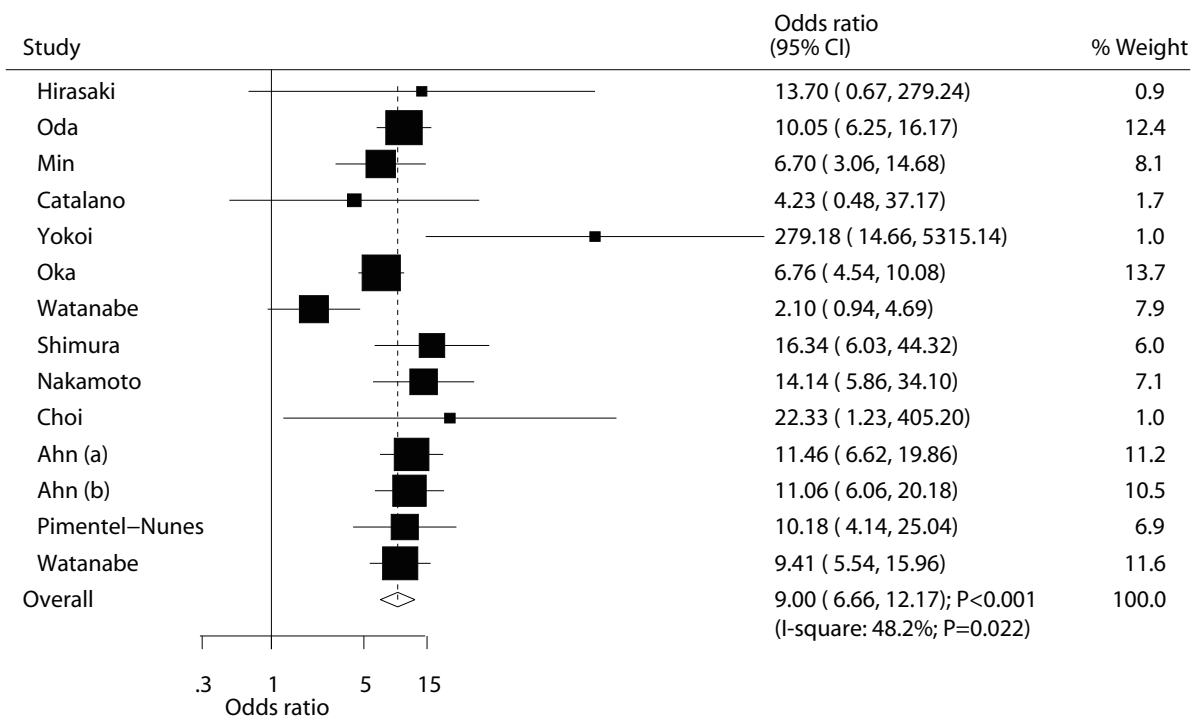


Figure 2 Effect of endoscopic submucosal dissection on the incidence of en bloc resection in patients with early gastric cancer.

Complete resection

Data for the effectiveness of ESD versus EMR for complete resection were available in 11 studies (12 cohorts). Overall, complete resection rate was significantly higher in ESD patients (OR: 8.43; 95% CI: 5.04 to 14.09; $p < 0.001$; with substantial heterogeneity; [figure 3](#)). After sequential exclusion, we noted that summary result was not changed (online supplementary file 3). The findings from subgroup analyses were consistent with overall analysis, while publication year, mean age, percentage of male and follow-up duration have been associated with the treatment effects of ESD versus EMR for patients with EGC ([table 2](#)). Furthermore, no publication bias was observed for complete resection (p value for Egger: 0.668; p value for Begg: 0.373; [table 3](#)).

Curative resection

Data for the effectiveness of ESD versus EMR for curative resection were available in six studies. Overall, curative resection rate was significantly higher in ESD patients (OR: 2.92; 95% CI: 1.85 to 4.61; $p < 0.001$; with substantial heterogeneity; [figure 4](#)). Sensitivity analysis was conducted, and the conclusion was not changed (online supplementary file 3). Although the results in most subgroups were statistically significant, we found no significant difference between ESD and EMR for curative resection if: the study was published in 2010 or after, the mean age of patients was ≥ 70 years and the percentage of male was $< 70\%$. Interaction p value suggested that sample size, disease status and follow-up duration could affect the effectiveness of ESD versus EMR for curative resection ([table 2](#)). In addition, there was no significant

publication bias for curative resection (p value for Egger: 0.352; p value for Begg: 1.000).

Local recurrence

Data for the effectiveness of ESD versus EMR for local recurrence were available in 12 studies (13 cohorts). The summary OR suggested that ESD was associated with a reduced risk of local recurrence (OR: 0.18; 95% CI: 0.09 to 0.34; $p < 0.001$; with moderate heterogeneity; [figure 5](#)). The conclusions of sensitivity analyses were not altered by sequential excluding single studies (online supplementary file 3). Furthermore, the results of subgroup analyses were consistent with overall analysis ([table 2](#)). Finally, no significant publication bias for local recurrence was observed (p value for Egger: 0.099; p value for Begg: 0.360; [table 3](#)).

Post-treatment bleeding

Risks of bleeding after ESD and EMR were available in 15 studies (16 cohorts). The summary OR indicated no significant difference between ESD and EMR for the risk of bleeding (OR: 1.26; 95% CI: 0.88 to 1.80; $p = 0.203$; with moderate heterogeneity; [figure 6](#)). After sequential exclusion of individual study, the summary results were not altered (online supplementary file 3). Subgroup analyses indicated no significant differences between ESD and EMR for bleeding risk in all of subsets, while mean age, percentage of male and follow-up duration might affect the effectiveness of ESD versus EMR for patients with EGC ([table 2](#)). The Egger and Begg test results suggested no publication bias for bleeding (p value for Egger: 0.096; p value for Begg: 0.392; [table 3](#)).

Table 2 Subgroup analyses for investigated outcomes

Factors	Group	No of included cohorts	OR or SMR and 95% CI	P value	Heterogeneity (%)	P value between subgroups	
En bloc resection rates	Publication year						
	Before 2010	10	8.43 (5.20 to 13.67)	<0.001	60.1	0.135	
	2010 or after	4	10.50 (7.76 to 14.22)	<0.001	0.0		
	Study design						
	Non-concurrent	2	13.56 (5.71 to 32.22)	<0.001	0.0	0.311	
	Retrospective	12	8.71 (6.29 to 12.06)	<0.001	56.0		
	Sample size						
	≥100	10	8.69 (6.48 to 11.65)	<0.001	52.1	0.287	
	<100	4	21.01 (3.52 to 125.45)	0.001	41.8		
	Mean age (years)						
	≥70	3	12.64 (6.58 to 24.27)	<0.001	0.0	0.405	
	<70	8	8.69 (5.26 to 14.36)	<0.001	67.2		
	Percentage of male						
	≥70	7	11.17 (8.27 to 15.10)	<0.001	17.6	0.008	
	<70	3	4.48 (1.36 to 14.69)	0.013	69.7		
	Disease status						
	EGC	12	8.66 (6.55 to 11.45)	<0.001	44.0	0.062	
Recurrent EGC	2	62.93 (3.28 to 1208.40)	0.006	49.1			
Follow-up duration (years)							
≥3.0	7	8.38 (4.72 to 14.90)	<0.001	69.7	0.343		
<3.0	5	10.45 (7.47 to 14.60)	<0.001	0.0			
Complete resection rates	Publication year						
	Before 2010	7	14.11 (10.85 to 18.35)	<0.001	0.0	<0.001	
	2010 or after	5	4.35 (1.76 to 10.78)	0.001	86.5		
	Study design						
	Non-concurrent	2	14.69 (5.69 to 37.93)	<0.001	0.0	0.318	
	Retrospective	10	8.00 (4.57 to 13.99)	<0.001	83.9		
	Sample size						
	≥100	8	8.42 (4.71 to 15.07)	<0.001	87.1	1.000	
	<100	4	9.07 (3.33 to 24.73)	<0.001	3.5		
	Mean age (years)						
	≥70	3	15.13 (7.11 to 32.23)	<0.001	0.0	0.003	
	<70	7	6.44 (3.24 to 12.80)	<0.001	86.2		
	Percentage of male						
	≥70	6	8.29 (3.48 to 19.78)	<0.001	88.1	0.003	
	<70	3	9.43 (5.33 to 16.69)	<0.001	23.8		
	Disease status						
	EGC	10	7.92 (4.55 to 13.79)	<0.001	83.8	0.490	
Recurrent EGC	2	13.70 (3.59 to 52.29)	<0.001	25.2			
Follow-up duration (years)							
≥3.0	5	13.37 (9.94 to 18.00)	<0.001	12.6	<0.001		
<3.0	5	6.84 (2.66 to 17.54)	<0.001	88.0			

Continued



Table 2 Continued

Factors	Group	No of included cohorts	OR or SMR and 95% CI	P value	Heterogeneity (%)	P value between subgroups
Curative resection rates	Publication year					
	Before 2010	5	3.28 (1.95 to 5.54)	<0.001	68.3	0.340
	2010 or after	1	1.70 (0.72 to 4.04)	0.225	–	
	Study design					
	Non-concurrent	1	8.80 (1.02 to 75.55)	0.047	–	0.259
	Retrospective	5	2.79 (1.75 to 4.44)	<0.001	67.4	
	Sample size					
	≥100	3	2.26 (1.39 to 3.66)	0.001	74.0	0.017
	<100	3	6.35 (2.93 to 13.75)	<0.001	0.0	
	Mean age (years)					
	≥70	2	2.95 (0.90 to 9.70)	0.075	63.9	0.929
	<70	4	3.00 (1.72 to 5.24)	<0.001	72.1	
	Percentage of male					
	≥70	4	3.11 (1.82 to 5.32)	<0.001	73.7	0.741
	<70	2	2.89 (0.62 to 13.44)	0.176	50.5	
	Disease status					
	EGC	4	2.40 (1.48 to 3.87)	<0.001	67.0	0.035
Recurrent EGC	2	6.05 (2.65 to 13.85)	<0.001	0.0		
Follow-up duration (years)						
≥3.0	3	2.23 (1.20 to 4.14)	0.011	52.1	0.005	
<3.0	3	3.45 (2.57 to 4.63)	<0.001	0.0		
Local recurrence rates	Publication year					
	Before 2010	9	0.12 (0.04 to 0.39)	<0.001	51.4	0.100
	2010 or after	4	0.27 (0.17 to 0.44)	<0.001	0.0	
	Study design					
	Non-concurrent	1	0.03 (0.00 to 0.25)	0.001	–	0.047
	Retrospective	12	0.21 (0.11 to 0.39)	<0.001	39.4	
	Sample size					
	≥100	10	0.18 (0.09 to 0.38)	<0.001	56.7	0.422
	<100	3	0.11 (0.02 to 0.66)	0.016	0.0	
	Mean age (years)					
	≥70	4	0.14 (0.05 to 0.45)	0.001	20.9	0.442
	<70	8	0.20 (0.08 to 0.47)	<0.001	58.0	
	Percentage of male					
	≥70	9	0.18 (0.08 to 0.42)	<0.001	57.3	0.729
	<70	2	0.15 (0.03 to 0.75)	0.021	52.5	
	Disease status					
	EGC	10	0.18 (0.09 to 0.38)	<0.001	56.7	0.422
Recurrent EGC	3	0.11 (0.02 to 0.66)	0.016	0.0		
Follow-up duration (years)						
≥3.0	7	0.15 (0.07 to 0.34)	<0.001	19.1	0.350	
<3.0	6	0.21 (0.07 to 0.61)	0.004	63.8		

Continued

Table 2 Continued

Factors	Group	No of included cohorts	OR or SMR and 95% CI	P value	Heterogeneity (%)	P value between subgroups
Bleeding	Publication year					
	Before 2010	10	1.26 (0.72 to 2.21)	0.413	51.0	0.032
	2010 or after	6	1.16 (0.82 to 1.64)	0.416	5.7	
	Study design					
	Non-concurrent	3	0.88 (0.38 to 2.06)	0.767	0.0	0.191
	Retrospective	13	1.32 (0.89 to 1.97)	0.168	53.9	
	Sample size					
	≥100	11	1.31 (0.86 to 1.99)	0.215	59.6	0.335
	<100	5	1.07 (0.51 to 2.26)	0.853	0.0	
	Mean age (years)					
	≥70	4	0.78 (0.40 to 1.54)	0.481	0.0	<0.001
	<70	10	1.17 (0.87 to 1.56)	0.294	0.0	
	Percentage of male					
	≥70	8	1.01 (0.73 to 1.39)	0.975	0.0	<0.001
	<70	5	1.44 (0.87 to 2.38)	0.155	0.0	
	Disease status					
EGC	14	1.30 (0.89 to 1.89)	0.175	51.8	0.288	
Recurrent EGC	2	0.72 (0.18 to 2.91)	0.646	0.0		
Follow-up duration (years)						
≥3.0	7	1.54 (0.81 to 2.92)	0.190	51.7	0.001	
<3.0	7	1.00 (0.73 to 1.38)	0.999	0.0		
Perforation rates	Publication year					
	Before 2010	11	3.73 (1.99 to 6.99)	<0.001	30.9	0.003
	2010 or after	6	1.19 (0.65 to 2.19)	0.578	0.0	
	Study design					
	Non-concurrent	3	4.50 (0.90 to 22.46)	0.067	0.0	0.456
	Retrospective	14	2.39 (1.30 to 4.39)	0.005	49.5	
	Sample size					
	≥100	12	2.38 (1.23 to 4.59)	0.010	57.1	0.537
	<100	5	3.68 (0.99 to 13.61)	0.051	0.0	
	Mean age (years)					
	≥70	3	1.53 (0.30 to 7.88)	0.611	0.0	<0.001
	<70	12	1.82 (1.20 to 2.77)	0.005	0.0	
	Percentage of male					
	≥70	9	2.54 (1.49 to 4.32)	0.001	0.0	<0.001
	<70	6	1.12 (0.60 to 2.10)	0.719	0.0	
	Disease status					
EGC	15	2.54 (1.42 to 4.57)	0.002	47.0	0.935	
Recurrent EGC	2	2.68 (0.30 to 23.99)	0.377	0.0		
Follow-up duration (years)						
≥3.0	8	2.31 (0.82 to 6.56)	0.114	71.8	0.955	
<3.0	7	2.38 (1.27 to 4.47)	0.007	0.0		

Continued



Table 2 Continued

Factors	Group	No of included cohorts	OR or SMR and 95% CI	P value	Heterogeneity (%)	P value between subgroups
Operation time (min)	Publication year					
	Before 2010	7	1.57 (0.75 to 2.38)	<0.001	97.4	<0.001
	2010 or after	1	-2.03 (-2.55 to -1.51)	<0.001	-	
Study design	Non-concurrent	1	1.32 (0.79 to 1.85)	<0.001	-	0.464
	Retrospective	7	1.09 (-0.00 to 2.19)	0.051	98.6	
Sample size	≥100	4	1.48 (0.31 to 2.65)	0.013	98.7	<0.001
	<100	4	0.75 (-1.28 to 2.78)	0.470	97.7	
Mean age (years)	≥70	2	1.90 (1.13 to 2.67)	<0.001	56.0	<0.001
	<70	4	0.29 (-0.85 to 1.42)	0.622	97.7	
Percentage of male	≥70	3	1.34 (0.51 to 2.17)	0.002	93.9	<0.001
	<70	2	-0.41 (-3.58 to 2.76)	0.800	98.9	
Disease status	EGC	6	0.88 (-0.30 to 2.06)	0.144	98.8	0.090
	Recurrent EGC	2	1.90 (1.13 to 2.67)	<0.001	56.0	
Follow-up duration (years)	≥3.0	4	1.73 (0.76 to 2.69)	<0.001	96.6	<0.001
	<3.0	2	1.38 (-0.30 to 3.06)	0.107	95.7	

EGC, early gastric cancer; SMR, standard mean difference.

Perforation

Data for the effectiveness of ESD versus EMR for perforation were available in 16 studies (17 cohorts). The summary OR suggested ESD was associated with an increased risk of perforation compared with EMR (OR: 2.55; 95% CI: 1.48 to 4.39; $p=0.001$; with moderate heterogeneity; figure 7). Sensitivity analyses revealed that results were statistically significant (online supplementary file 3). Additionally, the subgroup analyses suggested that the significant difference in the treatment effect between ESD and EMR for perforation was mainly due to the studies published before 2010, study with retrospective design, sample size ≥ 100 , mean age <70.0 years, percentage of male $\geq 70\%$, patients with

EGC and follow-up duration <3.0 years. Interaction test results indicated that publication year, mean age and percentage of male could affect the treatment effects between ESD and EMR for perforation (table 2). Finally, there was no publication bias between ESD and EMR for perforation (p value for Egger: 0.818; p value for Begg: 0.303; table 3).

Operation time

Data for the effectiveness of ESD versus EMR for operation time were available in eight studies. We found that ESD was correlated with longer operation time as compared with EMR (SMD: 1.12; 95% CI: 0.13 to 2.10; $p=0.026$; with substantial heterogeneity; figure 8). The results of sensitivity analyses indicated that the conclusion was variable by excluding several studies (online supplementary file 3). The findings from subgroup analyses indicated that ESD was associated with longer operation time if: the study was published before 2010, the study had non-concurrent design, sample size was ≥ 100 , mean age was ≥ 70.0 years, percentage of male was $\geq 70\%$, there were patients with recurrent EGC and the follow-up duration was ≥ 3.0 years. Nevertheless, ESD was associated with shorter operation time compared with EMR if the study was published after 2010 (table 2). Finally, no significant publication bias for operation time was observed (p value for Egger: 0.344; p value for Begg: 0.711; table 3).

Table 3 Publication biases for investigated outcomes

Outcomes	P value for Egger	P value for Begg
En bloc resection rates	0.367	0.274
Complete resection rates	0.668	0.373
Curative resection rates	0.352	1.000
Local recurrence rates	0.099	0.360
Bleeding	0.096	0.392
Perforation rates	0.818	0.303
Operation time	0.344	0.711

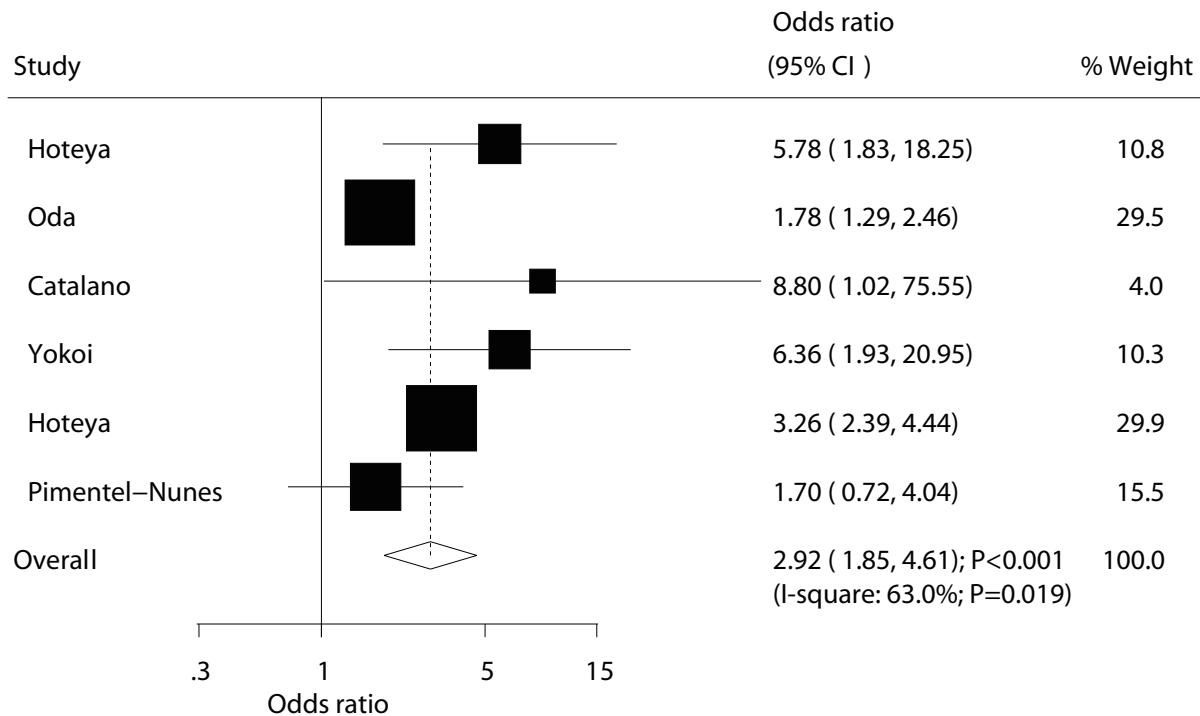


Figure 4 Effect of endoscopic submucosal dissection on the incidence of curative resection in patients with early gastric cancer.

DISCUSSION

Since the effectiveness of ESD versus EMR for patients with EGC has been previously investigated by different researchers, it can be very useful to summarise the results from these same studies via meta-analysis, which in turn could effectively assess the treatment effects.⁴⁴ This

systematic review and meta-analysis included 18 observational studies and 6723 patients with EGC. Briefly, we found that patients with EGC who underwent ESD had higher incidence of en bloc resection, complete resection, curative resection and lower risk of local recurrence compared with patients who received EMR. Yet, ESD

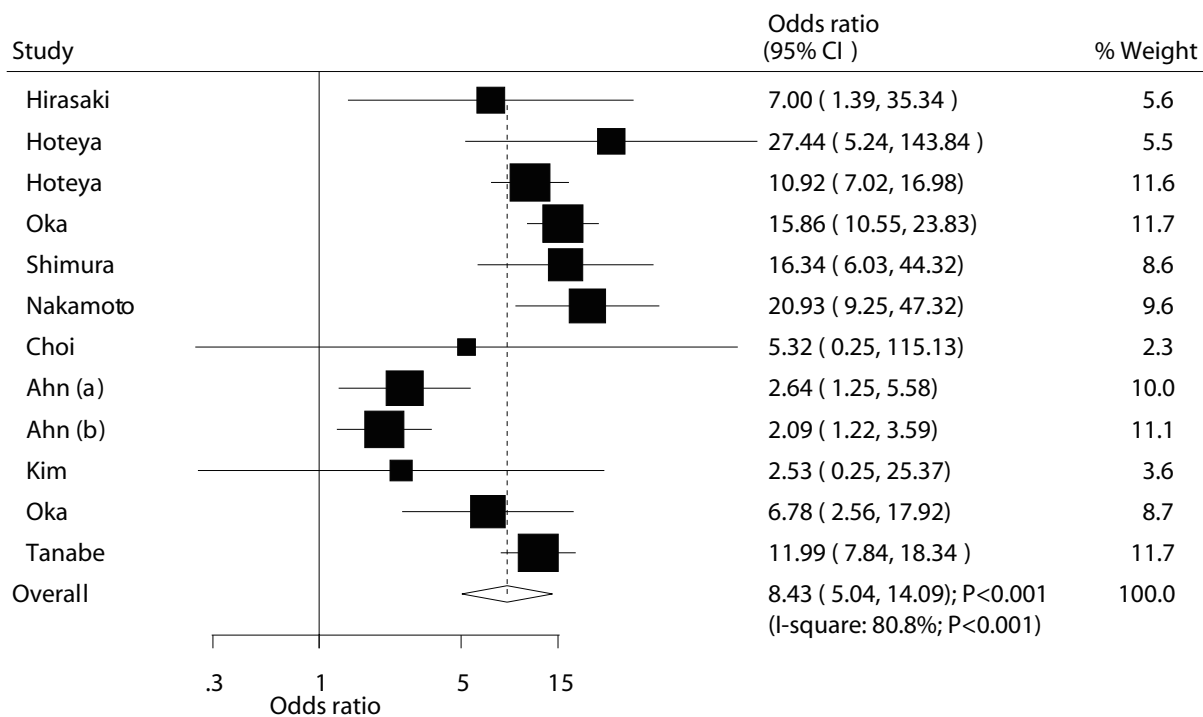


Figure 3 Effect of endoscopic submucosal dissection on the incidence of complete resection in patients with early gastric cancer.

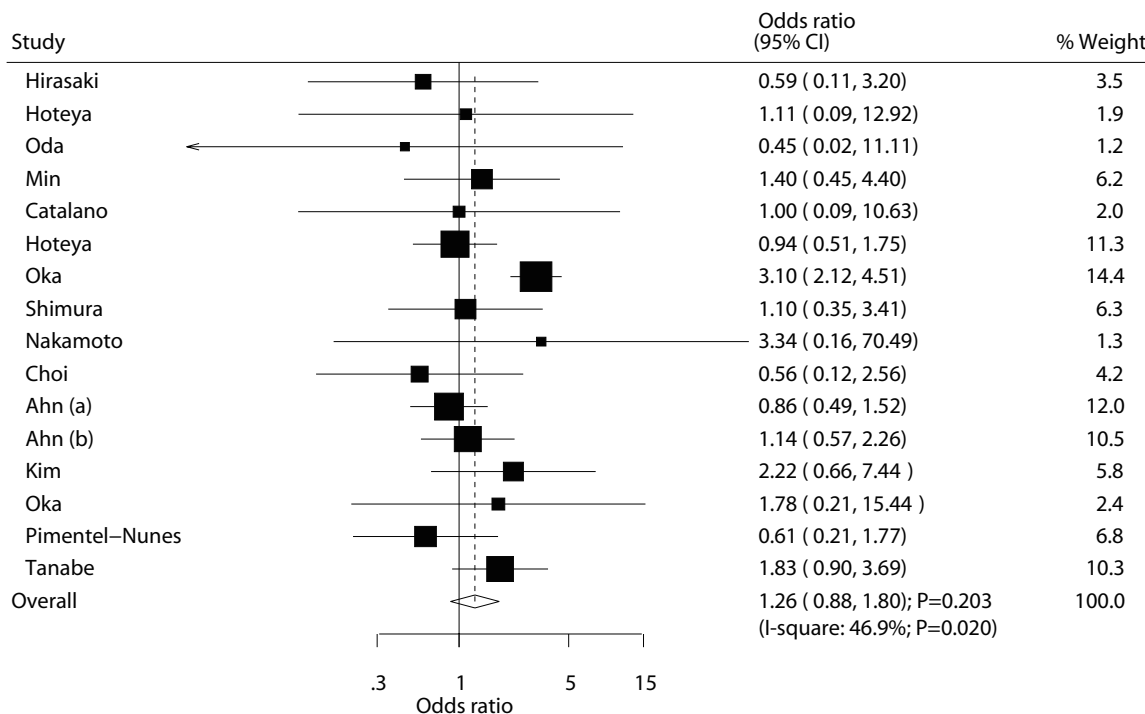


Figure 6 Effect of endoscopic submucosaldissection on the risk of bleeding in patients with early gastric cancer.

was associated with an increased risk of perforation and longer operation time. Furthermore, no significant difference in post-treatment bleeding was found between the two approaches. Although results from subgroup analyses were mostly consistent with overall analysis, the treatment effect of ESD versus EMR in patients with EGC might be biased by certain features observed in different studies.

A previous meta-analysis evaluated the efficacy and safety of ESD compared with EMR for patients with EGC, concluding that the benefit of ESD could outweigh the risk of perforation. Furthermore, the risk of bleeding events between ESD and EMR was statistically significant.⁴⁵ Moreover, Lian *et al* conducted a meta-analysis of eight retrospective studies and found ESD versus EMR

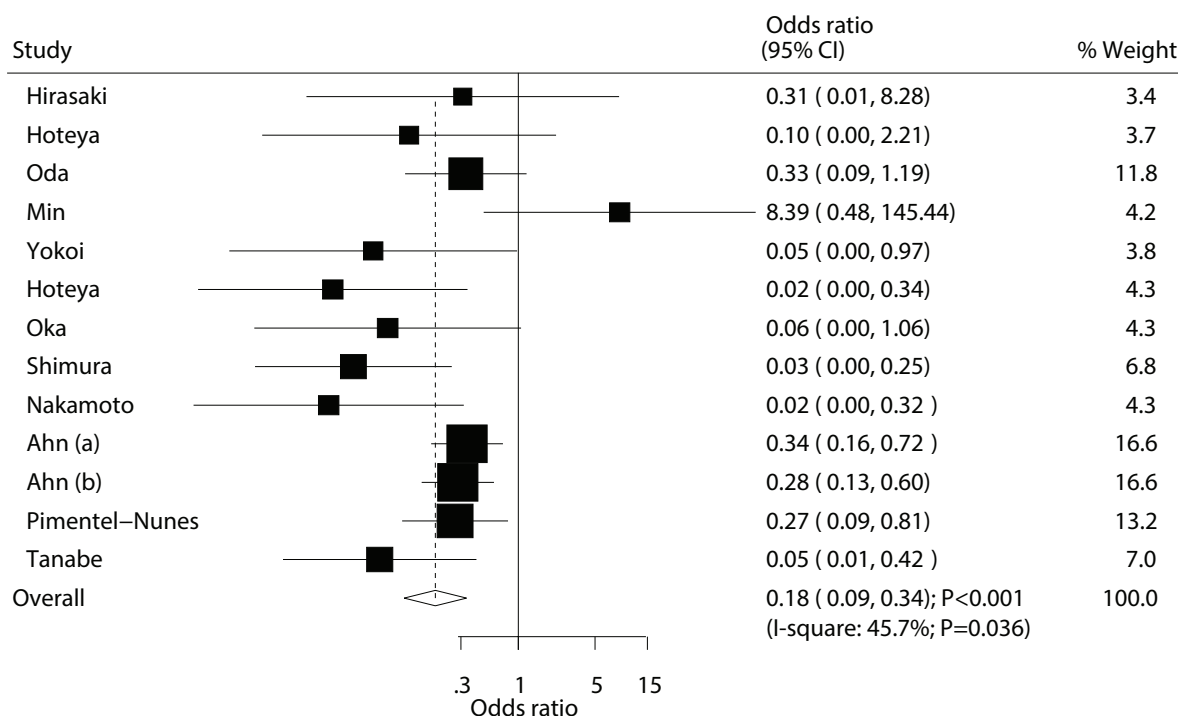


Figure 5 Effect of endoscopic submucosaldissection on the risk of local recurrence in patients with early gastric cancer.

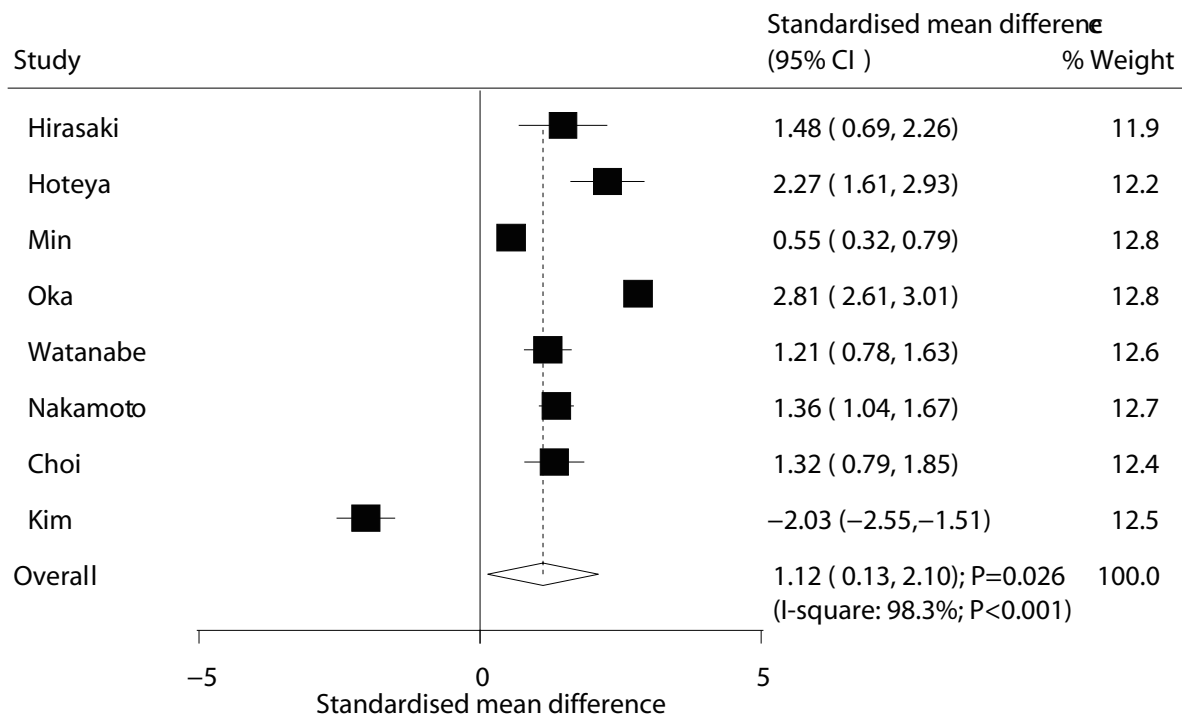


Figure 8 Effect of endoscopic submucosal dissection on operation time in patients with early gastric cancer.

shows improved incidence of en bloc resection, histologically complete resection and local recurrence, whereas an increased risk of perforation was detected.⁴⁶ The study conducted by Facciorusso *et al* based on 10 retrospective studies and found ESD shows superior effectiveness but higher complication risk as compared with EMR for EGC.⁴⁷ The recently updated study enrolled 18 retrospective studies and found the increased incidences

of complete resection, en bloc resection, and reduced local recurrence but associated with longer operative time and increased risk of gastric perforation.⁴⁸ Nevertheless, previous meta-analyses failed to report the summary analysis based on disease status, as well as whether the effectiveness of ESD versus EMR differed in view to other factors. Moreover, several new studies can be involved in this meta-analysis for re-evaluation. Therefore, we

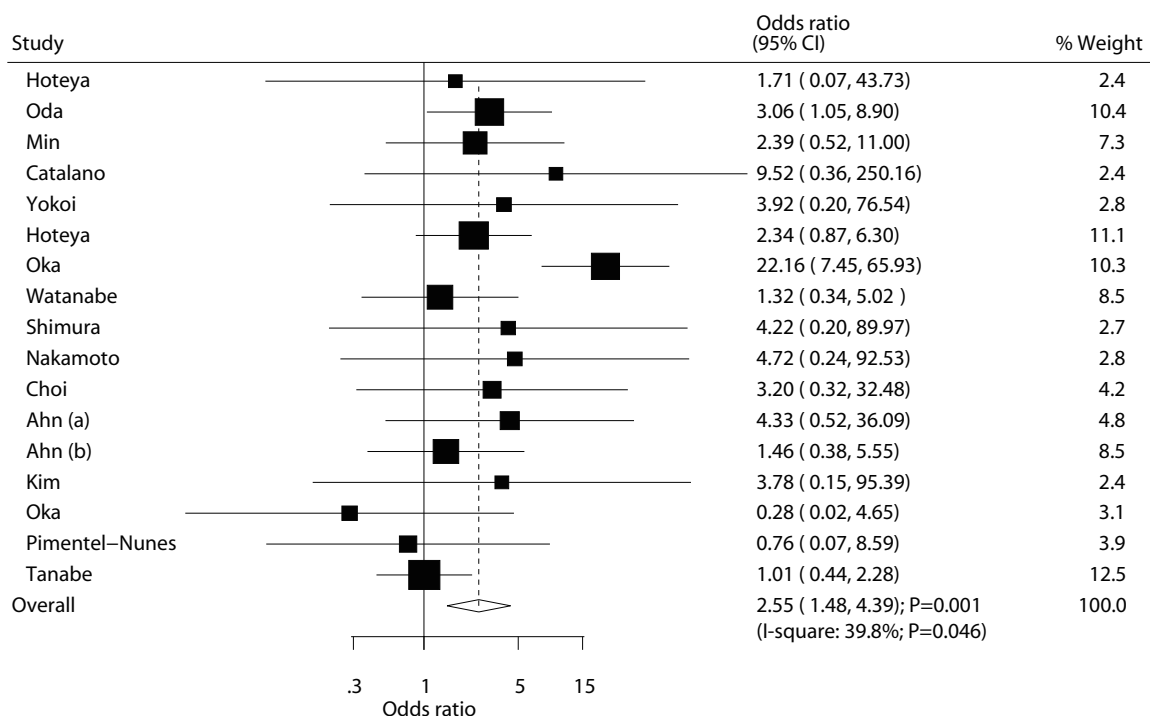


Figure 7 Effect of endoscopic submucosal dissection on the risk of perforation in patients with early gastric cancer.



conducted this comprehensive quantitative meta-analysis to determine the treatment effects of ESD versus EMR in patients with EGC.

Our results indicated that ESD was associated with the increased incidence of en bloc resection, complete resection, curative resection and local recurrence compared with EMR; similar conclusions have been obtained in almost all included studies. Five studies reported no significant difference between ESD and EMR for the risk of local recurrence. We presume that this occurred due to small number of events observed and acquired broad 95% CIs, which was not statistically significant. Additionally, several factors contributed to the treatment effectiveness of ESD versus EMR. First, en bloc resection rate was significantly higher in more than 70% male patients. This could be explained with different disease status. Second, publication year, mean age, percentage of male and follow-up duration could have biased the incidence of complete resection; the reason for this could be that the incidence of complete resection was correlated with statistical power, size of tumour and lifestyle of included patients. Third, the incidence of curative resection could be affected by sample size, disease status and follow-up duration. The reason for this could be the imbalance of number of studies in corresponding subsets. Finally, ESD was associated with lower risk of local recurrence in all subsets, while study design might affect effect size of summary results. This could be due to only one study with non-concurrent cohort design that reported the incidence of local recurrence; nonetheless, this result might vary and thus the effectiveness of ESD versus EMR for the needs of patients with EGC to be further verified.

There was no significant difference between ESD and EMR for the risk of bleeding, while ESD was associated with an increased risk of perforation as compared with EMR. Furthermore, no significant differences for bleeding events were persisted in all of subsets, which could be explained with the mild risk and fewer events than expected. In addition, publication year, mean age and percentage of male could affect the risk of perforation. These factors were correlated with statistical power, tumour size and lifestyle, which could affect the risk of perforation. Moreover, since the perforation was not caused life-threatening complication directly, and could lower with accumulated experience of operators. Therefore, the benefit of ESD could outweigh harms in patients with EGC. Finally, ESD was associated with longer operation time compared with EMR. The reason could be that ESD technique included combined procedure of cutting and coagulation by electrosurgical simultaneously. Thus, EMR was easier for patients to access than ESD.

The limitations of the present meta-analysis should be highlighted. First, moderate or substantial heterogeneity among included studies was observed, which all not fully interpretation. Second, all of the included studies with observational design and uncontrolled confounders might biases the summary results. Third, the subgroup

analyses according to macroscopic type and lymph node metastases were not carried out due to few studies reported these data, which might affect the prognosis of EGC. Fourth, this quantitative analysis was based on published studies and thus publication bias was inevitable. Finally, the summary analysis was based on pooled data and individual data were not available, which restricted us from conducting more detailing analysis.

The findings of this meta-analysis indicated that patients with EGC receiving ESD had higher incidence of en bloc resection, complete resection, and curative resection. Further, ESD could protect against the risk of local recurrence compared with EMR. In addition, ESD could lead to an increased risk of perforation due to complicated technique. Moreover, the risk of bleeding between ESD and EMR was not statistically significant. Further large-scale prospective studies should be conducted to verify the detailed analysis in this quantitative analysis.

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