META-ANALYSIS

Endoscopic submucosal dissection *vs* endoscopic mucosal resection for early gastric cancer: A meta-analysis

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Received: May 2, 2014   Revised: June 30, 2014
Accepted: October 1, 2014
Published online: November 16, 2014

Abstract

AIM: To compare endoscopic submucosal dissection (ESD) and endoscopic mucosal resection (EMR) for early gastric cancer (EGC).

METHODS: Computerized bibliographic search was performed on PubMed/Medline, Embase, Google Scholar and Cochrane library databases. Quality of each included study was assessed according to current Cochrane guidelines. Primary endpoints were *en bloc* resection rate and histologically complete resection rate. Secondary endpoints were length of procedure, post-treatment bleeding, post-procedural perforation and recurrence rate. Comparisons between the two treatment groups across all the included studies were performed by using Mantel-Haenszel test for fixed-effects models (in case of low heterogeneity) or DerSimonian and Laird test for random-effects models (in case of high heterogeneity).

RESULTS: Ten retrospective studies (8 full text and 2 abstracts) were included in the meta-analysis. Overall data on 4328 lesions, 1916 in the ESD and 2412 in the EMR group were pooled and analyzed. The mean operation time was longer for ESD than for EMR (standardized mean difference 1.73, 95%CI: 0.52-2.95, *P* = 0.005) and the "*en bloc*" and histological complete resection rates were significantly higher in the ESD group [OR = 9.69 (95%CI: 7.74-12.13), *P* < 0.001 and OR = 5.66, (95%CI: 2.92-10.96), *P* < 0.001, respectively]. As a consequence of its greater radicality, ESD provided lower recurrence rate [OR = 0.09, (95%CI: 0.05-0.17), *P* < 0.001]. Among complications, perforation rate was significantly higher after ESD [OR = 4.67, (95%CI, 2.77-7.87), *P* < 0.001] whereas the bleeding incidences did not differ between the two techniques [OR = 1.49 (0.6-3.71), *P* = 0.39].

CONCLUSION: In the endoscopic therapy of EGC, ESD showed a superior efficacy but higher complication rate with respect to EMR.

Key words: Endoscopic submucosal dissection; Endoscopic mucosal resection; Early gastric cancer; Meta-analysis

Core tip: Endoscopic submucosal dissection (ESD) represents a promising approach to the therapy of Early Gastric Cancer. Preliminar studies showed better outcomes in terms of complete *en bloc* and histologic resection rate with respect to classical Endoscopic Mucosal Resection (EMR). Some concerns raise due to higher complication rate (particularly perforation) and longer operation times related to the complexity of the procedure. The current meta-analysis outline the superiority of ESD in obtaining higher radical resection rate and lower recurrence rates compared to EMR but confirms the aforementioned concerns on higher incidences of perforation and bleeding (in this case non significantly) after ESD.

Facciorusso A, Antonino M, Di Maso M, Muscatiello N. Endoscopic submucosal dissection *vs* endoscopic mucosal resection for early gastric cancer: A meta-analysis. *World J Gastrointest*

INTRODUCTION

Early gastric cancer (EGC) is a malignant tumor confined to the mucosa or the submucosa regardless of lymph node metastases[1].

As the diagnostic rate of EGC increases, endoscopy has become the treatment of choice for the radical cure of EGC. Since the 1980s endoscopic mucosal resection (EMR) has been proposed as a replacement for invasive surgery because of favorable long-term outcomes and improved quality of life for patients[2,3]. EMR is routinely performed due to its safety profile, low cost, patient tolerance and rapid post-procedural recovery.

Endoscopic submucosal dissection (ESD) was developed in the late 1990s to enable the *en bloc* removal of lesions larger than 2 cm[4]. In fact, only a complete pathological specimen may allow clinicians to achieve a reliable diagnosis and hence to plan the correct therapeutic strategy.

ESD uses the technique of improved needle-knife under endoscopy to exfoliate the diseased submucosa with coagulation corrent.

Previous systematic reviews and meta-analyses have reported higher resection rates but also a relatively higher rate of complications such as bleeding and perforation after ESD because of its large wound incidence and difficulties[5,6]. Since these reviews date early 2010s, systematic analyses including pooled data of recent studies on this topic are lacking.

Aim of the current meta-analysis is to update the state of the art of endoscopic therapies of EGC in light of the last studies published in this field.

MATERIALS AND METHODS

Search strategy and selection criteria

Computerized bibliographic search was performed on PubMed/Medline, Embase, Google Scholar, Cochrane library databases using the following key words: "EMR", "ESD", "endoscopic mucosal resection", "endoscopic submucosal dissection" and "early gastric cancer". Complementary manual search was performed by checking the references of all the main review articles on this topic, in order to identify possible additional studies. Moreover, the abstracts of main oncological and endoscopic congresses were retrieved.

Eligible studies were randomized controlled trials, prospective or retrospective cohort and case-control studies and international congress abstracts comparing EMR and ESD for the treatment of EGC in human patients published until April 2014. The search was restricted to English-language articles. Studies were excluded if they had not compared data between the two treatments.

Case reports or studies with insufficient data were also excluded. Included studies were selected independently by two investigators (AF and MA). Disagreements were solved by discussion and following a third opinion (MdM).

The quality of the included studies was assessed according to the guidelines of the Cochrane Reviewer's Handbook recommended by the Cochrane Collaboration[7].

Endpoints evaluated

Primary endpoints were: *en bloc* resection rate (*i.e.*, no piecemeal removal of the lesion)[8] and histologically complete resection rate (no neoplastic cells in lesion edges).

Secondary endpoints were: length of procedure (from marking to removal of the tumor); post-treatment bleeding; post-procedural perforation; and recurrence rate (diagnosed by histology within the treated area during follow-up).

Statistical analysis

Pooled data of continuous variables were expressed as standardized mean difference while data of categorical ones as odds ratio (OR) and 95%CI.

Comparisons between the two treatment groups across all the included studies were performed by using Mantel-Haenszel test for fixed-effects models[9] (in case of low heterogeneity) or DerSimonian and Laird test for random-effects models[10] (in case of high heterogeneity). The level of heterogeneity between the included studies was assessed following the guidelines of the Cochrane Collaboration[7]. Once heterogeneity was noted, between-study sources of heterogeneity were investigated using subgroup analyses by stratifying original estimates according to the study characteristics.

Since the use of scales for evaluating quality or risk of bias is explicitly discouraged in Cochrane reviews[7], in assessing study quality a domain-based evaluation was performed, in which critical assessments were made separately for different domains[7].

Publication biases were assessed using funnel plots visually and performing Begg and Mazumdar's test based on the rank correlation between the observed effect sizes and observed standard errors[11]. Whenever publication biases were found, "trim and fill" method was performed aiming at obviating to these biases.

Significance threshold was assessed at a *P*-value < 0.05.

All calculations were performed using Review Manager (version 5.0 for Windows; the Cochrane Collaboration, Oxford, United Kingdom) and R 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Literature search

Figure 1 shows the flow chart of the search strategy conducted in this meta-analysis.
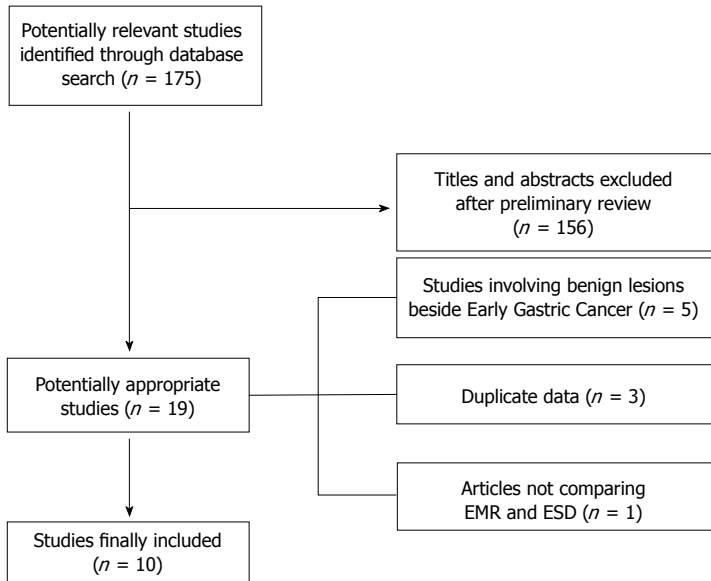
Figure 1 Flow chart of the search strategy. EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection.

Initially, we identified 175 potentially relevant studies. After a preliminary review, 156 papers were excluded, because they were animal studies, case reports, comment letters or descriptive reviews.

Among 19 potentially appropriate articles, we excluded 5 studies[12-16] because did not examine EGC, 3 studies[17-19] because based on the same data and another one due to the lack of comparative results between the two treatments[20]. Finally, 10 studies[8,21-29] were included in the meta-analysis.

Characteristics of included studies

Main characteristics of included studies are shown in Table 1. The current meta-analysis analyzed reports of a total of 4328 lesions, 1916 in the ESD and 2412 in the EMR group. The included papers were all retrospective case-control studies, whereof 8 were full text articles[8,21-23,26-29] and 2 were abstracts[24,25].

In two studies data on the number of patients were not available[25,26], while in three articles[24-26] median follow-up times were not recorded. The studies in which demographic and tumoral baseline parameters were reported did not show significant differences between treatment groups thus obviating to selection biases that could have affect final outcomes. Quality assessment of each study can be seen in Figure 2.

Operation time

Mean length of the procedures was described in four studies[21,22,26,27]. As an high grade of heterogeneity was found ($P < 0.001$; $I^2 = 99\%$), a random effect model was applied. Mean operation time was significantly longer in the ESD group [overall standardized mean difference 1.73 (95%CI: 0.52-2.95), $P = 0.005$, Figure 3]. In order to explore the source of heterogeneity, we performed a sensitivity analysis both by eliminating the study with the

smaller sample size[26] and by removing from the analysis the low-quality study[22]. However, in both cases the results were in favor of a significantly shorter duration of the procedure in the EMR patients [standardized mean difference: 1.58 (0.12-3.03), $P = 0.03$ and 1.33 (0.52-2.14), $P = 0.001$, respectively] without obviating to the aforementioned heterogeneity ($P < 0.001$, $I^2 = 99\%$ and $P \leq 0.001$, $I^2 = 94\%$, respectively).

Eventual sources of publication bias were explored by means of visual examination of funnel plot (Figure 4) and of Begg and Mazumdar's test ($P = 0.03$). After editing funnel plot by trim and fill method, the standardized mean difference in operation time was smaller with the missing studies filled in, but the results still remained significant ($P = 0.04$).

En bloc resection rate

Eight studies reported the *en bloc* resection rate[8,21-23,25-28]. As no heterogeneity was found ($P = 0.15$, $I^2 = 34\%$), a fix model was performed (Figure 5). Overall *en bloc* resection rate resulted significantly higher in ESD patients [OR 9.69 (7.74-12.13), $P < 0.001$] with 1328 out of 1437 patients in ESD vs 1020/1973 in EMR group who underwent complete resection of the lesion. No publication bias was found ($P = 0.34$).

Histological complete resection rate

Nine studies reported histological resection rates[8,21-28]. A high grade of heterogeneity was found ($P < 0.001$, $I^2 = 92\%$), hence random model with inverse variance analysis was performed (Figure 6). ESD patients obtained a significantly higher histological resection rate [OR = 5.66 (2.92-10.96), $P < 0.001$]. In fact, 1227/1495 ESD patients and 867/2053 EMR patients reached this gold standard of endoscopic intervention.

Sensitivity examination of data was performed by

Table 1 Characteristics of included studies

Ref.	Country	Patients	Lesions	Article	Baseline consistency	Follow-up	End-points
Min *et al*[21] 2009	South Korea	ESD 243 EMR 203	ESD 243 EMR 203	Full text	No	29 (4-44) m	Operation time, *en bloc* resection rate, histologic curative resection rate, bleeding, perforation, recurrence
Oka *et al*[22] 2006	Japan	ESD 185 EMR 711	ESD 195 EMR 825	Full text	No	ESD 19.4 ± 9.2 m EMR 83.2 ± 34.6 m	Operation time, *en bloc* resection rate, histologic curative resection rate, bleeding, perforation, recurrence
Oda *et al*[8] 2006	Japan	655	ESD 303 EMR 411	Full text	No	39 (5-60) m	*En bloc* resection rate, histologic curative resection rate, perforation, recurrence (residual)
Catalano *et al*[23] 2009	Italy	45	ESD 12 EMR 36	Full text	Not Recorded	31 (12-71) m	Operation time, *en bloc* resection rate, histologic curative resection rate, bleeding, perforation, recurrence
Odashima *et al*[24] 2006	Japan	ESD 57 EMR 80	ESD 57 EMR 80	Abstract	Not Recorded	Not Recorded	Histologic curative resection rate
Hoteya *et al*[25] 2007	Japan	Not Recorded	ESD 304 EMR 350	Abstract	Not Recorded	Not Recorded	*En bloc* resection rate, histologic curative resection rate, delayed bleeding rate
Hoteya *et al*[26] 2010	Japan	Not Recorded	ESD 40 EMR 22	Full text	No	Not Recorded	Operation time, *en bloc* resection rate, histologic curative resection rate, perforation, recurrence
Nakamoto *et al*[27] 2009	Japan	ESD 106 EMR 71	ESD 122 EMR 80	Full text	Yes	54 (12-89) m	Operation time, *en bloc* resection rate, histologic curative resection rate, perforation, bleeding
Watanabe *et al*[28] 2010	Japan	ESD 219 EMR 146	ESD 219 EMR 146	Full text	Yes	ESD 14.3 m EMR 17.8 m	*En bloc* resection rate, histologic curative resection rate, perforation, recurrence
Tanabe *et al*[29] 2014	Japan	ESD 421 EMR 359	ESD 421 EMR 359	Full text	No	ESD 65 m EMR 73 m	Recurrence, overall survival

Follow up time (mo) is expressed as median (range) of mean (± SD) when appropriate. ESD: Endoscopic submucosal dissection; EMR: Endoscopic mucosal resection.
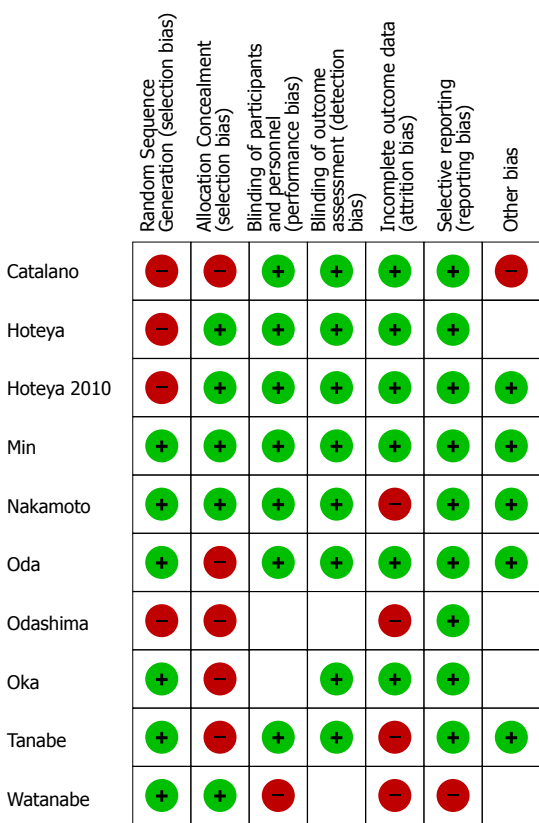
Figure 2 Quality of included studies according to the Cochrane Collaboration guidelines[7].

means of subgroup analysis, considering separately studies including only small EGCs (*i.e.*, < 10 mm)[21,22,27,28] and those based on greater lesions[8,23-26]. In both cases the better performances of ESD with respect to EMR resulted even amplified [OR = 9.28 (4.6-18.72), *P* < 0.001 and OR = 15.21 (11.2-19.98), *P* < 0.001, respectively]. A low grade of heterogeneity in the former studies and no heterogeneity at all in the latter was found (*P* < 0.1, I^2 = 52% and *P* = 0.11, I^2 = 45%, respectively).

Evidence of publication bias was found (*P* = 0.01), hence trim and fill method was applied without losing the statistical significance of the rates previously reported (*P* < 0.001).

Recurrence rate
Data on local recurrence rate were reported in nine studies[8,21-23,25-29]. Recurrence rate resulted significantly lower after ESD [OR = 0.09 (0.05-0.17), *P* < 0.001] and low grade of heterogeneity was found (*P* = 0.21, I^2 = 29%) (Figure 7). No evidence of publication bias was found (*P* = 0.11).

Perforation rate
Eight articles examined treatment-related perforation rate[8,21-23,25-28]. Perforations were significantly more common after ESD [OR = 4.67 (2.77-7.87), *P* < 0.001] (Figure 8). Further sensitivity analyses were not needed due to the low grade of heterogeneity (*P* = 0.14, I^2 = 36%). Overall, 62/1438 cases of perforation after ESD and 17/1973 af-

| Study or subgroup | ESD | | | EMR | | | | Std. mean difference | | Std. mean difference |
	Mean	SD	Total	Mean	SD	Total	Weight	IV, random, 95%CI	Year	IV, random, 95%CI
Oka	84.4	55.3	195	12.6	9.3	825	25.50%	2.81 [2.61, 3.01]	2006	
Nakamoto	84.4	61.9	122	17.2	18.5	80	25.20%	1.35 [1.04, 1.66]	2009	
Min	33.6	16.6	243	24.3	16.2	103	25.40%	0.56 [0.33, 0.80]	2009	
Hoteya 2010	115.8	48.8	40	25.3	11.6	22	23.90%	2.24 [1.58, 2.90]	2010	
Total (95%CI)			600			1030	100.00%	1.73 [0.52, 2.95]		

Heterogeneity: Tau² = 1.51; χ^2 = 216.15, df = 3 (*P* < 0.00001); *I²* = 99%
Test for overall effect: *Z* = 2.79 (*P* = 0.005)

Figure 3 Forest plot of mean operation time. ESD: Endoscopic submucosal dissection; EMR: Endoscopic mucosal resection; df: Degrees of freedom.

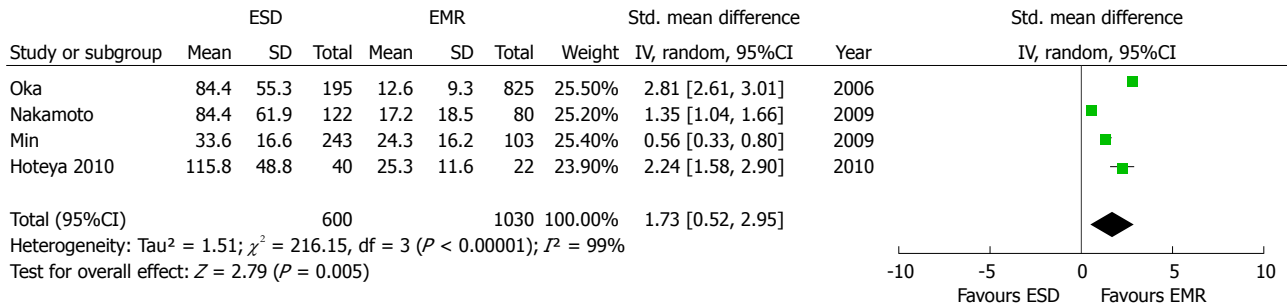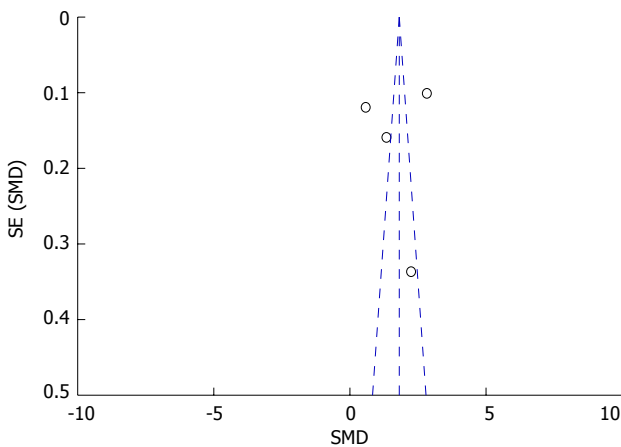**Figure 4 Funnel plot of publication bias for mean operation time.**

ter EMR were reported. There was no evidence of publication bias (*P* = 0.14).

Bleeding rate

Five studies reported post-treatment bleeding rate[21-23,25,27]. As shown in Figure 9, bleeding rate was higher, although not significantly, after ESD [OR = 1.49 (0.6-3.71), *P* = 0.39]. Since high grade of heterogeneity was found (*P* = 0.007, *I²* = 72%), a random effect model was built and sensitivity analyses were performed. In particular, restricting the analysis to the two studies reporting delayed bleeding rate after procedure[21,25], OR slightly decreased (1.04, 95%CI: 0.62-1.75) and no heterogeneity resulted. No evidence of publication bias was found (*P* = 0.09).

DISCUSSION

ESD represents a promising alternative to classical EMR for the treatment of EGCs. Two previous meta-analyses clearly demonstrated the superiority of ESD in terms of resection (both *en bloc* and histological) rate and recurrence rate with higher percentages of complications due to the complexity of the procedure[5,6]. Aim of this meta-analysis is to validate such results in light of the recently published studies on this topic.

A total of 10 studies analyzing the endoscopic treatment of 4328 lesions (1916 in the ESD and 2412 in the EMR group) were included in the current review. ESD

was found to provide better outcomes in terms of lower recurrence rate and higher *en bloc* resection rate. As a consequence, ESD reached more frequently the complete histological removal of the treated lesions, which is the gold standard of each endoscopic interventional procedure. In this setting, the high OR [5.66 (2.92-10.96), *P* < 0.001] in favor of ESD stands for a clear superiority of such procedure for the treatment of non metastatic mucosal cancerous lesions of the stomach. The robustness of this finding was not affected from the high grade of heterogeneity because stratifying the analysis by the diameter of the lesions, no changes in the final outcomes were found. In fact, ESD resulted superior with respect to EMR in all the reviewed studies, regardless of the size of the treated lesions.

Unfortunately, broad and robust data on overall survival after endoscopic treatment of EGC are still too few for being included in a meta-analysis, hence this outcome could not be explored. However, the low aggressiveness and scarce attitude to extragastric spread of EGC should result in slight differences of survival outcomes between the two treatments. In fact, a recent study did not show significant differences in terms of overall survival between ESD and EMR despite lower recurrence rate after submucosal dissection[29].

Indubitably, ESD is a more complex procedure that should be performed in high-volume centers. Our meta-analysis confirms the results of previous systematic reviews finding higher procedure-related complication (both perforation and bleeding) rates and longer operation times in ESD patients. Among complications, particular concerns raise on regard to perforations. In fact our meta-analysis shows a significant association between ESD and perforation rate [OR = 4.67 (2.77-7.87), *P* < 0.001], thus meaning higher morbidity with respect to classical mucosal resection. Interestingly, bleeding rate showed only a non-significant trend in favor of EMR and restricting the analysis to delayed bleeding (the more insidious and difficult to treat), the two procedures resulted in similar rates (OR = 1.04, 95%CI: 0.62-1.75).

There are some limitations in our study. First, only retrospective non randomized studies are currently available in the literature, hence the absence of randomization may introduce patient selection biases. Second, the number of included studies is small. Third, estimation
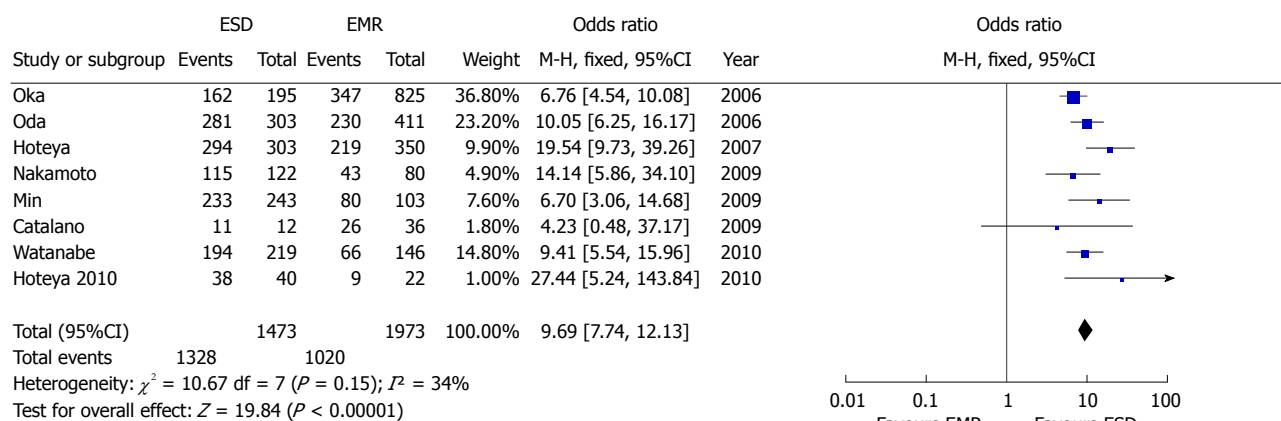
Study or subgroup	ESD Events	Total	EMR Events	Total	Weight	Odds ratio M-H, fixed, 95%CI	Year	Odds ratio M-H, fixed, 95%CI
Oka	162	195	347	825	36.80%	6.76 [4.54, 10.08]	2006	
Oda	281	303	230	411	23.20%	10.05 [6.25, 16.17]	2006	
Hoteya	294	303	219	350	9.90%	19.54 [9.73, 39.26]	2007	
Nakamoto	115	122	43	80	4.90%	14.14 [5.86, 34.10]	2009	
Min	233	243	80	103	7.60%	6.70 [3.06, 14.68]	2009	
Catalano	11	12	26	36	1.80%	4.23 [0.48, 37.17]	2009	
Watanabe	194	219	66	146	14.80%	9.41 [5.54, 15.96]	2010	
Hoteya 2010	38	40	9	22	1.00%	27.44 [5.24, 143.84]	2010	
Total (95%CI)		1473		1973	100.00%	9.69 [7.74, 12.13]		
Total events	1328		1020					

Heterogeneity: $\chi^2 = 10.67$ df = 7 ($P = 0.15$); $I^2 = 34\%$
Test for overall effect: $Z = 19.84$ ($P < 0.00001$)

0.01 0.1 1 10 100
Favours EMR   Favours ESD

Figure 5 Forest plot of *en bloc* resection rate. ESD: Endoscopic submucosal dissection; EMR: Endoscopic mucosal resection; M-H: Mantel-Haenszel; df: Degrees of freedom.

Study or subgroup	ESD Events	Total	EMR Events	Total	Weight	Odds ratio IV, random, 95%CI	Year	Odds ratio IV, random, 95%CI
Oka	162	195	195	825	12.60%	15.86 [10.55, 23.83]	2006	
Odashima	43	57	41	80	11.40%	2.92 [1.39, 6.16]	2006	
Oda	223	303	251	411	12.90%	1.78 [1.29, 2.46]	2006	
Hoteya	254	304	204	350	12.80%	3.64 [2.51, 5.26]	2007	
Catalano	11	12	20	36	5.50%	8.80 [1.02, 75.55]	2009	
Nakamoto	113	122	30	80	11.00%	20.93 [9.25, 47.32]	2009	
Min	216	243	78	103	12.00%	2.56 [1.40, 4.68]	2009	
Hoteya 2010	32	40	9	22	9.50%	5.78 [1.83, 18.25]	2010	
Watanabe	173	219	39	146	12.40%	10.32 [6.32, 16.84]	2010	
Total (95%CI)		1495		2053	100.00%	5.66 [2.92, 10.96]		
Total events	1227		867					

Heterogeneity: Tau^2 = 0.85; $\chi^2 = 99.48$ df = 8 ($P < 0.00001$); $I^2 = 92\%$
Test for overall effect: $Z = 5.14$ ($P < 0.00001$)

0.01 0.1 1 10 100
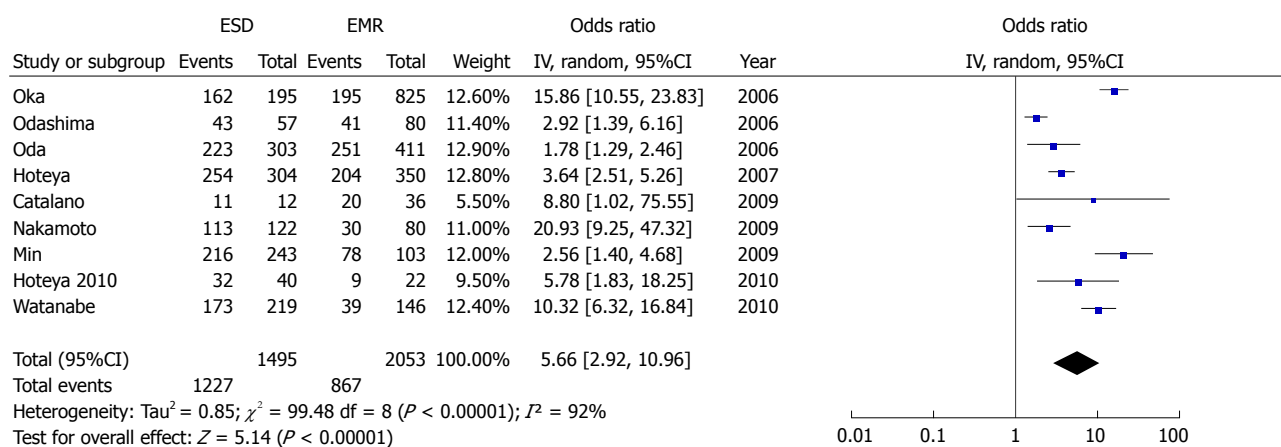Favours EMR   Favours ESD

Figure 6 Forest plot of complete histologic resection rate. ESD: Endoscopic submucosal dissection; EMR: Endoscopic mucosal resection; IV: Inverse variance; df: Degrees of freedom.

Study or subgroup	ESD Events	Total	EMR Events	Total	Weight	Odds ratio M-H, fixed, 95%CI	Year	Odds ratio M-H, fixed, 95%CI
Oka	0	195	31	825	9.30%	0.06 [0.00, 1.06]	2006	
Oda	6	303	27	411	17.30%	0.29 [0.12, 0.70]	2006	
Hoteya	0	304	13	350	9.70%	0.04 [0.00, 0.69]	2007	
Nakamoto	0	122	14	80	13.40%	0.02 [0.00, 0.32]	2009	
Min	0	243	0	103		Not estimable	2009	
Catalano	0	12	0	36		Not estimable	2009	
Watanabe	5	219	39	146	35.30%	0.06 [0.02, 0.17]	2010	
Hoteya 2010	0	40	2	22	2.40%	0.10 [0.00, 2.21]	2010	
Tanabe	1	421	15	359	12.50%	0.05 [0.01, 0.42]	2014	
Total (95%CI)		1859		2332	100.00%	0.09 [0.05, 0.17]		
Total events	12		141					

Heterogeneity: $\chi^2 = 8.48$ df = 6 ($P = 0.21$); $I^2 = 29\%$
Test for overall effect: $Z = 8.18$ ($P < 0.00001$)

0.01 0.1 1 10 100
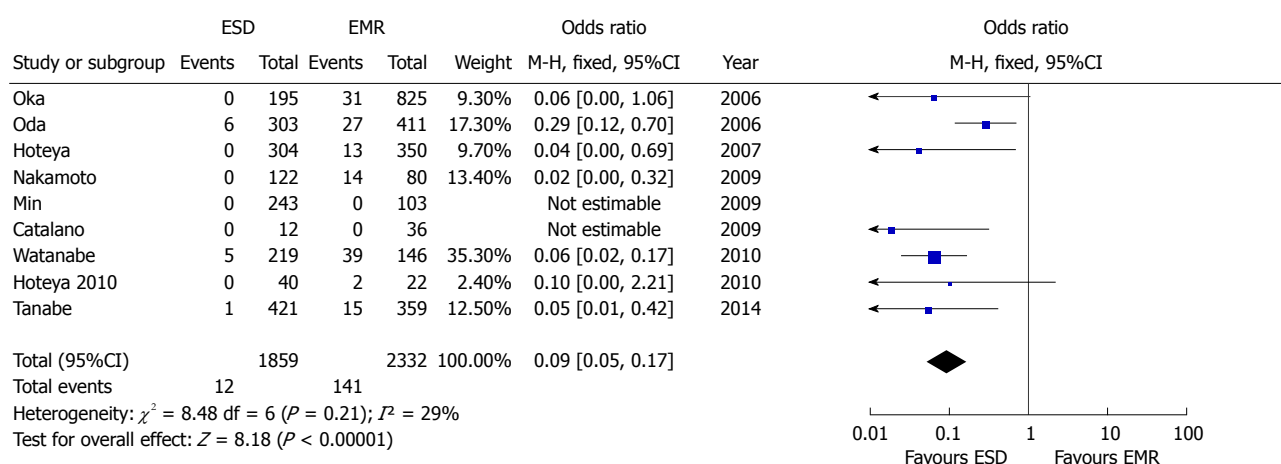Favours ESD   Favours EMR

Figure 7 Forest plot of recurrence rate. ESD: Endoscopic submucosal dissection; EMR: Endoscopic mucosal resection; M-H: Mantel-Haenszel; df: Degrees of freedom.
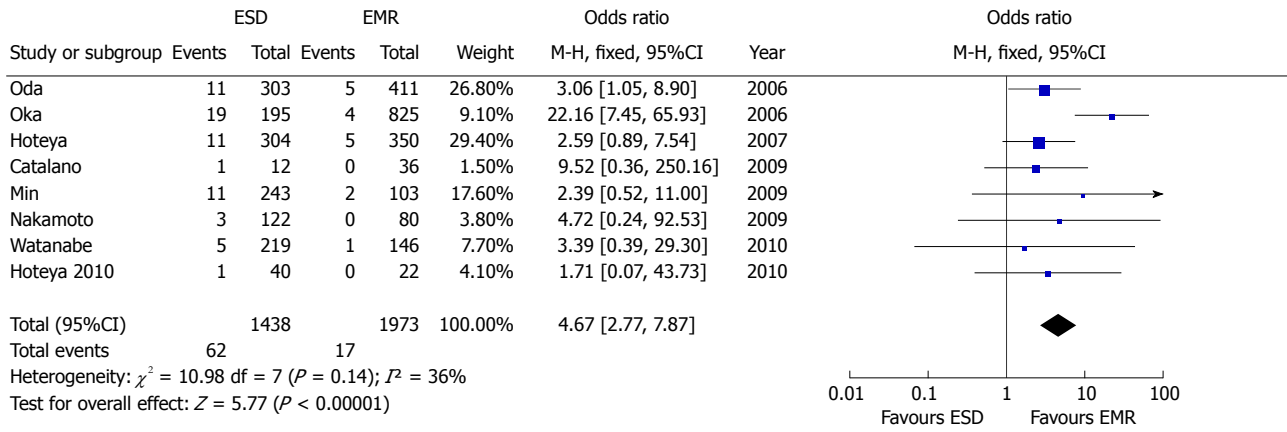
Study or subgroup	ESD Events	Total	EMR Events	Total	Weight	Odds ratio M-H, fixed, 95%CI	Year	Odds ratio M-H, fixed, 95%CI
Oda	11	303	5	411	26.80%	3.06 [1.05, 8.90]	2006	
Oka	19	195	4	825	9.10%	22.16 [7.45, 65.93]	2006	
Hoteya	11	304	5	350	29.40%	2.59 [0.89, 7.54]	2007	
Catalano	1	12	0	36	1.50%	9.52 [0.36, 250.16]	2009	
Min	11	243	2	103	17.60%	2.39 [0.52, 11.00]	2009	
Nakamoto	3	122	0	80	3.80%	4.72 [0.24, 92.53]	2009	
Watanabe	5	219	1	146	7.70%	3.39 [0.39, 29.30]	2010	
Hoteya 2010	1	40	0	22	4.10%	1.71 [0.07, 43.73]	2010	
Total (95%CI)		1438		1973	100.00%	4.67 [2.77, 7.87]		
Total events	62		17					

Heterogeneity: $\chi^2 = 10.98$ df = 7 ($P = 0.14$); $I^2 = 36\%$
Test for overall effect: $Z = 5.77$ ($P < 0.00001$)

Figure 8 Forest plot of perforation rate. ESD: Endoscopic submucosal dissection; EMR: Endoscopic mucosal resection; M-H: Mantel-Haenszel; df: Degrees of freedom.

Study or subgroup	ESD Events	Total	EMR Events	Total	Weight	Odds ratio M-H, random, 95%CI	Year	Odds ratio M-H, random, 95%CI
Oka	56	195	95	825	32.70%	3.10 [2.12, 4.51]	2006	
Hoteya	10	304	18	350	27.50%	0.63 [0.29, 1.38]	2007	
Min	13	243	4	103	22.40%	1.40 [0.45, 4.40]	2009	
Nakamoto	2	122	0	80	7.10%	3.34 [0.16, 70.49]	2009	
Catalano	1	12	3	36	10.40%	1.00 [0.09, 10.63]	2009	
Total (95%CI)		876		1394	100.00%	1.49 [0.60, 3.71]		
Total events	82		120					

Heterogeneity: Tau² = 0.62; $\chi^2 = 14.14$ df = 4 ($P = 0.007$); $I^2 = 72\%$
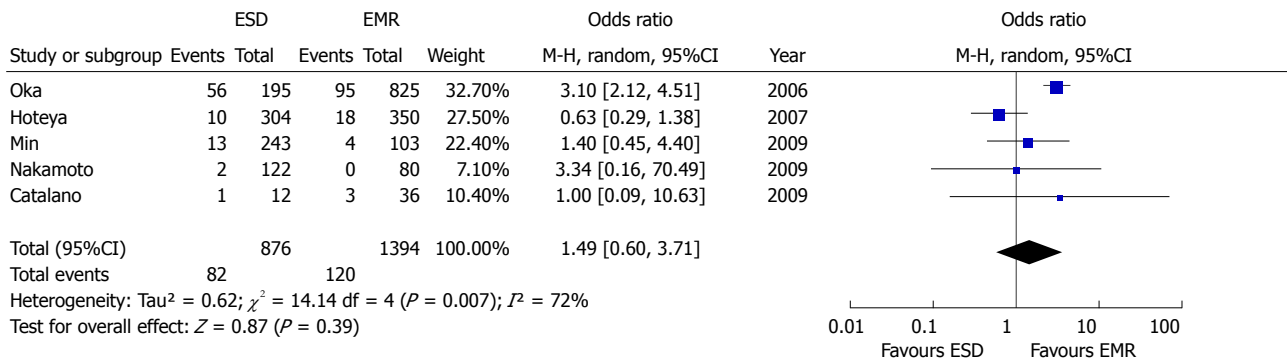Test for overall effect: $Z = 0.87$ ($P = 0.39$)

Figure 9 Forest plot of bleeding rate. ESD: Endoscopic submucosal dissection; EMR: Endoscopic mucosal resection; M-H: Mantel-Haenszel; df: Degrees of freedom.

of overall survival was not feasible because of lack of long-term outcomes data in most of the studies included in the meta-analysis. Finally, only a low-quality, small Western study from Italy was included and most articles were from Eastern Asia, where high-experienced interventional endoscopists in high-volume centers deal with more EGC patients, hence the conclusions of the meta-analysis could be not applicable in Europe and United States.

Despite these limitations, our study has a number of strengths. It provides a comprehensive and simultaneous assessment of therapeutic efficacy, procedural complexity and safety profile of the two treatments. Second, any possible source of heterogeneity and publication bias that could have influenced the final results was explored by means of appropriate statistical tools and all the findings were confirmed performing sensitivity analysis.

In conclusion, ESD is a more effective therapy for EGC with higher *en bloc* and histologically complete resection rate and lower local recurrence in comparison to EMR, regardless of tumor size. On the other hand, its safety profile is affected from higher perforation rate which may limit its application in low-volume centers.

Broad randomized controlled trials from both Eastern and Western countries reporting also overall survival data are warranted in order to validate such findings.

COMMENTS

Background
Early gastric cancer (EGC) is a malignant tumor confined to the mucosa or the submucosa of the stomach regardless of lymph node metastases. Endoscopic submucosal dissection (ESD) was developed to overcome the problem caused by incomplete resection by conventional Endoscopic mucosal resection (EMR) for EGC. Aim of this meta-analysis is to compare the efficacy outcomes, expressed in terms of *en bloc* and histological complete resection rate and recurrence rate, and safety profile of ESD with respect to EMR for early gastric cancer.

Research frontiers
Most of the published literature in the field outlines the superior efficacy as well as the higher complication rate of ESD with respect to EMR.

Innovations and breakthroughs
This study provides an updated comprehensive comparison of therapeutic efficacy, procedural complexity and safety profile of the two treatments. Second, any possible source of heterogeneity and publication bias that could have influenced the final results was explored by means of appropriate statistical tools and all the findings were confirmed performing sensitivity analysis.

Applications
The results could be useful for endoscopists involved in gastric cancer management but they should be confirmed by large randomized controlled trials with long-term follow-up and should be validated both in Eastern and Western countries.

Terminology
EGC is a malignant tumor confined to the mucosa or the submucosa regardless of lymph node metastases. EMR has been proposed as a replacement for invasive surgery because of favorable long-term outcomes and improved quality of life for patients. EMR is widely accepted because of its minimal invasion, low

cost, patient tolerance and better quality of life after the operation. ESD was developed in the late 1990s to enable the *en bloc* removal of lesions larger than 2 cm.

Peer review

This study is a meta-analysis to compare the efficacy outcomes between ESD and EMR for early gastric cancer. The authors describe that ESD shows a superior complete resection rate but higher complication rate with respect to EMR. It has already well known that ESD provide the higher curability but higher complication rate compared to EMR. However, I believe this paper can give gastroenterologists useful information in treatments of early gastric cancer, as a review article of meta-analysis of previously published data.

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