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A Meta-analytic Study to Compare Whether Endoscopic Submucosal Dissection Is Therapeutically More Feasible Than Endoscopic Mucosal Resection in Treating both Primary and Recurrent Early Gastric Cancer

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Abstract:
Aim:*To analyze therapeutic efficacy and safety dimension of Endoscopic Submucosal Dissection (ESD) in treating primary and recurrent Early Gastric Cancer (EGC)in comparison with Endoscopic Mucosal Resection (EMR).*
Methods: *Computerized literaturesearch was made on databases which included the Cochrane Library, Google Scholar, PubMed, EMBASE and Science Citation Index. Primary outcome measures were en bloc resection rate and histologically curative resection rate, and secondary outcome measures were total procedural time, procedure related bleeding, post-procedure perforation, and local recurrence. While comparing the involved studies, sub group analysis was done and the bias was removed by performing fixed-effectand random-effect model.*
Results: *Thirteen retrospective studies which include 11full-text and 2 abstract-based research studies were taken into account while compiling this meta-analysis. Also, among these thirteen studies, three studies were related to recurrent EGCs. The total data consists of 4531 lesions, of which 2038 are from ESD and 2493 from EMR group.The en bloc resection rate [OR= 10.27, (95% CI: 8.27-12.76), P=0.08], and histologically curative resection rate [OR= 4.77, (95% CI: 4.06-5.62), P<0.00001] were higher in ESD group. The recurrence rate was lower [OR= 0.09, (95% CI: 0.05-0.15), P=0.26] in ESD group. The mean procedural time was longer for ESD as compared to EMR [standardized mean difference of 27.66, (95% CI: 24.53-30.79), P<0.00001]. The procedure related complications like perforation rate were higher in ESD group [OR=4.62, (95% CI: 2.78-7.69), P=0.28], the bleeding incidence rate was little higher in ESD group [OR=1.87, (95% CI: 1.38-2.53), P=0.007] than in the EMR group.*
Conclusion: *Therapeutic efficacy of ESD outperforms EMR in treating both primary and recurrent early gastric cancer.*
Keywords:*meta-analysis, early gastric cancer, recurrent early gastric cancer, ESD, EMR.*

I. Introduction

Murakami, in 1971, was the first to give the definition of early gastric cancer (EGC). Since then many authors and researchers have debated over the definition and have recognized various other subtypes of EGCs with varying clinical behavior and morphological features [1]. Yet, in widely accepted terminology, the term EGC is any adeno-carcinomatous gastric lesion which is either limited to mucosa or submucosa with or without lymph node metastasis [2]. Treatment strategy is widely dependent on status of EGC at the time of diagnosis. Lymphatic involvementis being considered as one of the key factors to determine the prognosis and survival rate of an EGC patient [3]. The overall 5-year survival rate of EGC is above 90% and it drastically declines once lymphatic involvement is detected[4]. In clinical practice, vast majority of EGC patients are presented without lymphatic involvement and only 10 to 20% show lymphatic metastasis[5].

The endoscopic technique of EMR was first employed in 1984 [6], and it subsequently got developed and paved a way for EGC treatment because of being minimally invasive. Remarkable patient tolerance, overall cost effectiveness, and lesser procedural complications are also notable features of EMR. This procedure, however had potential risk of recurrence and low resection rates for lesions even smaller than 10mm, because of which it had limitations [7].To deal with the limitations of EMR, ESD was developed in late 1990s for en bloc resection and histologically curative resection of lesionslarger than 2cm [8]. Despite these plus points, according to Cao et al, perforation are more frequent in ESD [9]. Meanwhile, in past studies, complications like bleeding, delayed wound healing, infection, and compromised patient compliance have been reported[10,11]. So, in this

study, our main aim is to further explore the effectiveness of ESD by throwing a light in previously published studies of the same field and to update the state of art such that EGC can be more promptly handled by endoscopic therapy.

II. Materials And Methods

A bibliographic and computerized literature search was made on databases which included the Cochrane Library, Google Scholar, PubMed, EMBASE, and Science Citation Index. All these databases were searched systematically. English language was chosen as the language of preference. During the search operation, subject headings were Endoscopic Mucosal Resection, Endoscopic Submucosal Dissection, recurrent Early Gastric Cancer, Gastric cancer. The abstracts and conclusions of important GI meetings and congresses were also taken into cognizance while compiling this study.

Studies eligible for this study were randomized controlled trials, cohort and case-control studies. All the included studies were current up to March 2015 and the studies were included only if they met the following criteria: 1) Patients were diagnosed with early gastric cancer or recurrent EGC histopathologically. 2) The invasion was restricted to gastric mucosal and (or) submucosal layer, irrespective of lymph node involvement. 3) The study was a comparison between ESD and EMR in EGC. Some studies were discarded for enrollment because they didn't compare ESD and EMR in EGCs, some were excluded off because they included previously published data, and some were rejected because they had elaborated only the guidelines and reviews related to ESD and EMR.

Principal outcome measures:

Primary end points were:en bloc resection rate without anypiecemeal removal of the lesion [12]and histologically curative resection rate (diagnosed by histopathological examination of the sample of resected margin during follow up).

Secondary end points were:local procedural bleeding, procedure related perforation (diagnosed immediately by endoscopy or by the presence of free air in abdominal X-ray or CT image), and total procedural time.

Data extraction and study of quality assessment:

Details obtained from each involved study included first author, publication year, number of study subjects in each group, primary and secondary end points of the each study, sex and age of the patients. In order to avoid bias during the data extraction process, two independent investigators assessed the study quality and compared the results. The disagreement between the authors was solved by a third investigator by making a consensus decision.

The methodical quality study was weighed in accordance with the criteria set for non-randomized controlled study [13,14]. This assessment was made up of 6 items: grouping method, blinding, intention to treat analysis, baseline, diagnostic criteria, and control of mixed factors. A quality score for each study was assigned with 12 points being the highest score.

Data analysis:

Cochrane Collaboration's RevMan 5.0 software was used in this meta-analytic study. For continuous data, calculated mean difference was recommended. For dichotomous data, Odds ratio (OR) with 95% confidence interval was recommended. Chi-square test was used to assess the heterogeneity among the studies. The values of P and I were used to infer heterogeneity. $P \geq 0.05$ or $I^2 < 50\%$ indicated that there was not any heterogeneity among the studies and hence fixed-effect model was used. Conversely, $P < 0.05$ or $I^2 > 50\%$ indicated heterogeneity of statistical significance for which random-effects model was used. Publication bias for important outcome measures were assessed by Funnel plot and by performing Begg's and Egger's test with a P value of 0.05.

Literature search:

In the beginning, 602 studies, which were tentativelyrelated to the subject were identified. After an initial review, 578 papers were dropped out because of being case reports, comments, animal studies, reviews, and description letters. Among 24 potentially relevant articles, 6 studies [9,15-19] were excluded because of not examining EGC, 3 studies had same data[20-22]and 2 studies did not have the comparative results between ESD and EMR[23,24]. Finally 13 studies were included in the meta-analysis[7,25-36]. (**Figure 1**)

Salient features of included studies:

The salient features of included studies are shown in **Table 1**.The meta-analysisincludes a total of 13 studies, 11 available as full text and 2 available in abstract form. Furthermore, 3 studies are related to recurrent EGC and the remaining 10 have the reports of primary EGC. In all, we have evaluated the reports of 4531

lesions, of which 2038 belong to ESD and 2493 belong to EMR group. The respective number of patients of each study are mentioned in table alongwith the qualitative criterion of each study.

En bloc resection rate:

Eleven studies reported the en bloc resection rate [7,25-30,33-36]. As there was no heterogeneity among the studies, a fixed-effect model was applied. The analysis revealed that en bloc resection rates are higher in ESD group (1438/1559) than in the EMR group (1046/2054) [OR=10.27, (95% CI: 8.27-12.76), P=0.08].**(Figure 2)**

Histologically curative resection rate:

Among the enrolled studies, ten studies showed histologically complete resection rate for EGC[7,25,27-35]. A significant heterogeneity was found (P<0.00001, I^2=91%), so a random-effect model was applied. The assessment showed that ESD group (1262/1541) had higher histologically curative resection rate than EMR (873/2071) [OR=4.77, (95% CI:4.06-5.62), P<0.00001]. Sensitivity analysis was also performed on sub group basis and 3 studies were eliminated by considering small EGCs (<10mm) and larger EGCs (≥10mm but<20mm). In both of the cases ESD performed better than EMR [OR=2.68, 95% CI: 2.18-3.29]. **(Figure3)**

Recurrence rate:

Twelve studies reported the data on recurrence rate [7,25-30,32-36]. The analysis showed a lower rate of recurrence in both the procedures, however the recurrence in ESD group (13/1964) was significantly lower than in EMR group (161/2398)[OR=0.09, (95% CI: 0.05-0.15), P=0.26].**(Figure 4)**

Operation time:

Five studies reported the mean operation time for ESD in comparison to EMR [7,26-29]. The calculation showed that there was heterogeneity among the studies (P<0.00001; I^2= 99%), hence a random-effects model was applied. The result demonstrated that ESD needed considerably longer time than EMR group (weighted mean difference 27.66; 95% CI: [24.53, 30.79]). We performed a sensitivity test and eliminated one study with lesser sample size[28]. The results revealed that there was a significant time difference between the two procedures (weighted mean difference 68.91; 95% CI: [63.27, 74.54]) **(Figure 5**). Also we have drawn funnel plot of publication bias for mean operation time.**(Figure 6)**

Procedure related perforation:

From enrolled studies, eleven articles analyzed the procedure related perforation[7,25-30,33-36]. There was no heterogeneity among the studies (P=0.28; I^2=18%) so fixed-effect model was applied. In both the cases ESD had little higher procedural perforation (68/1560) than EMR group (17/2054) [OR=4.62, (95% CI: 2.78-7.69)]. **(Figure 7)**

Bleeding incidences:

Eight studies reported on operation related bleeding incidences. The bleeding rate was higher in ESD group than in the EMR group [OR=1.87, 95% CI: (1.38-2.53)]. Since significant heterogeneity was found, a random-effect model was applied. In particular 1 study was removed [27], after which no heterogeneity resulted [OR=2.34, (95%CI: 1.68-3.27)]. **(Figure 8)**

III. Discussion

ESD has been regarded as a gold standard treatment for the effective removal of primary as well as recurrent early gastric cancers (EGCs)[26].Being less invasive in nature, it is widely preferred over open surgical treatment [37-41]. Ithas good resultsin terms of higher en bloc resection rate and histologically curative resection rate in comparison to conventional EMR. Despite these worthy characteristics, it has certain undesirable outcomes due to procedural complexities, which include perforation and bleeding[10,11]. The main aim of this meta-analysis is to further authenticate the results in light of newly published studies related to the topic and to reinforce the validity of ESD in treating EGCs effectively.

By computerized bibliographic search and manual screening, a total of thirteen studies were included by exclusion and inclusion criteria. A total of 4531 lesions were enrolled for the study, 2038 in the ESD group and 2493 in the EMR group. The pooled data showed significantly higher en bloc resection rate in the ESD group than in the corresponding EMR group. The histologically curative resection rate is also higher in ESD group and local recurrence is undoubtedly lower in ESD group than in the EMR group.

The superiority of ESD in terms of en bloc resection, local recurrence, and histologically curative resection has been also reported in previous meta-analyses[42], which assessed wider variety of malignant

gastrointestinal lesions while as the present study focusses on efficacy of ESD with respect to EMR in primary and recurrent EGCs.

By using the ESD technique, en bloc resection is more easily possible as the lesion is extracted out as a single piece. This in turn leads to acquire the entire pathological specimen, which helps in precise histopathological assessment (such as, the type of malignant cell, extent of invasion, basal and adjacentinvolvement of structures), and henceforthmaking it more possible for resecting the lesion completely. This complete resection capability of ESD paves a way for a low recurrence rate after the ESD procedure than with the conventional EMR technique even for lesions lesser than 20mm, which also agrees with the reports of Cao et al [9].

Amongst the complications in ESD,important one is prolonged bleeding, both during the procedure as well as in post-operative time period. Here we have to focus the dynamics of how to control the bleeding effectively and reduce the rate of procedural bleeding. Since in ESD we aredissecting submucosal layer and the vessels and lesion are under direct endoscopic view. So a skilled endoscopist could coagulate the involved vessels in advance to reduce the bleeding episodes. In previous meta-analyses, bleeding rate is reported more in ESD than in EMR. This fact is not only due to different data extraction methods but also due to procedure-related factors, for example type of devices used in the procedure, endoscopist's experience level, anatomical location of the lesion, etc. Moreover, there is little data available for large-sample studies about the bleeding risk of ESD and EMR, so this needs to be assessed by larger prospective studies.

Another severe complication of ESD is the perforation and several methods are employed to overcome this drawback. The important one is the advent of endo-knife. These instruments reduce the perforation incidence during ESD by having a powerful cutting wave which prevents electric leakage into the muscular wall of stomach[43]. In majority of cases, the perforation could be managed withendoscopic clipping alongwith conservative treatment like fasting, aspiration through nasogastric intubation, broad spectrum antibiotics, etc.[25,28]. Since there is no data regarding life threatening attitude of perforation, hence it is not considered as a very serious complication.

Our meta-analytic study has tried utmost to explore the ever expanding indications of endoscopic technique in treating EGCs. However, there are also certain limitations in our study. First, all the included studies were low quality, significantly heterogeneous, non-randomized retrospective studies. Lack of randomization may have brought together selection bias. Second, the number of included studies is small, which provides insufficient data for a concrete conclusion. Third, the inclusion and selection criteria are ill-defined in most of the trials. Fourth, all the trials are from East Asia and only one study is from Europe (Italy), the quality and case numbers of this study are so low that the conclusions may not apply to the rest of the world. Finally, most of the studiesdid not provide a clear cut definition or criteria for any particular item, especially the definition of bleeding and the criterion for recurrent EGC, which may have a good impact on outcome results.

Despite the above mentioned limitations, our meta-analysis has certain positive aspects. First, it includes the larger number of studies, which is even more than the previously published available meta-analyses. Because of which it has a stronger capability of assessing the therapeutic efficacy, safety dimensions, and procedural complications of ESD versus EMR in EGC. Second, the analysis consists of three retrospective studies related to recurrent EGCs, thus it gives us an idea regarding therapeutic efficacy of ESD in treating recurrent EGCs. Third, the sources of heterogeneity and publication bias that might have influenced the final results was explored by subgroup and sensitivity analysis.

In conclusion, this meta-analysis shows that ESD has higher en bloc resection rate, higher histologically curative resection rate, low post-procedural recurrence rate as compared to EMR in primary as well as recurrent EGCs. Analysis also showed that the mean operation time, bleeding incidences, and procedure related perforation was higher in case of ESD than with conventional EMR. Considering all the plus points of ESD over EMR, ESD should be regarded as first line treatment in dealing with EGC while at the same time it should also be kept in mind that the procedural complications might be eliminated to large extent by better experience and good endoscopic skills. Furthermore, we suggest that the conclusions of our meta-analysis should be accepted with caution. The results should be confirmed by well-designed, randomized, multi-center controlled trials with larger samples from various countries. The multi-sectoral data will help the researchers to validate the efficacy of ESD in treating EGC. This will not only pave a way for better therapeutic results of ESD, but will also help to improve quality of millions of people who are affected with early gastric cancer.

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Table 1: Salient features of the included studies

Reference detail	Country	No. of patients	Lesions: ESD/EMR	Article availability	Nature of study	Quality score	Major outcomes
Min et al, 2009	South Korea	346	243/103	Full text	EGC	8	OT, EBR, HCR, BR, PR, RR
Yokoi et al, 2006	japan	64	46/18	Full text	Recurrent EGC	5	EBR, BR, PR, RR
Catalano et al, 2009	Italy	45	12/36	Full text	EGC	5	OT, EBR, HCR, PR, RR
Oda et al, 2006	Japan	655	303/411	Full text	EGC	7	EBR, HCR, BR, PR, RR
Nakamoto et al, 2009	Japan	202	122/80	Full text	EGC	6	OT, EBR, HCR, BR, PR
Oka et al, 2006	Japan	896	195/825	Full text	EGC	4	OT, EBR, HCR, BR, PR, RR
Hoteya et al, 2010	Japan	Not recorded	40/22	Full text	Recurrent EGC	4	OT, EBR, HCR, PR, RR
Odashima et al, 2006	Japan	137	57/80	Abstract	EGC	5	HCR
Hoteya et al, 2007	Japan	Not recorded	304/350	Abstract	EGC	5	EBR, HCR, BR
Tanabe et al, 2014	Japan	780	421/359	Full text	EGC	6	RR, Overall survival
Shimura et al, 2007	Japan	107	59/48	Full text	EGC	5	OT,EBR, BR, PR, RR
Watanabe et al, 2010	Japan	365	219/146	Full text	EGC	5	EBR, HCR, PR, RR
Hirasaki et al, 2008	Japan	32	17/15	Full text	Recurrent EGC	5	OT,EBR, BR, RR, PR

*OT= operation time; EBR= en bloc resection; HCR= histologically curative rate; BR= bleeding rate; PR= perforation rate; RR= recurrence rate

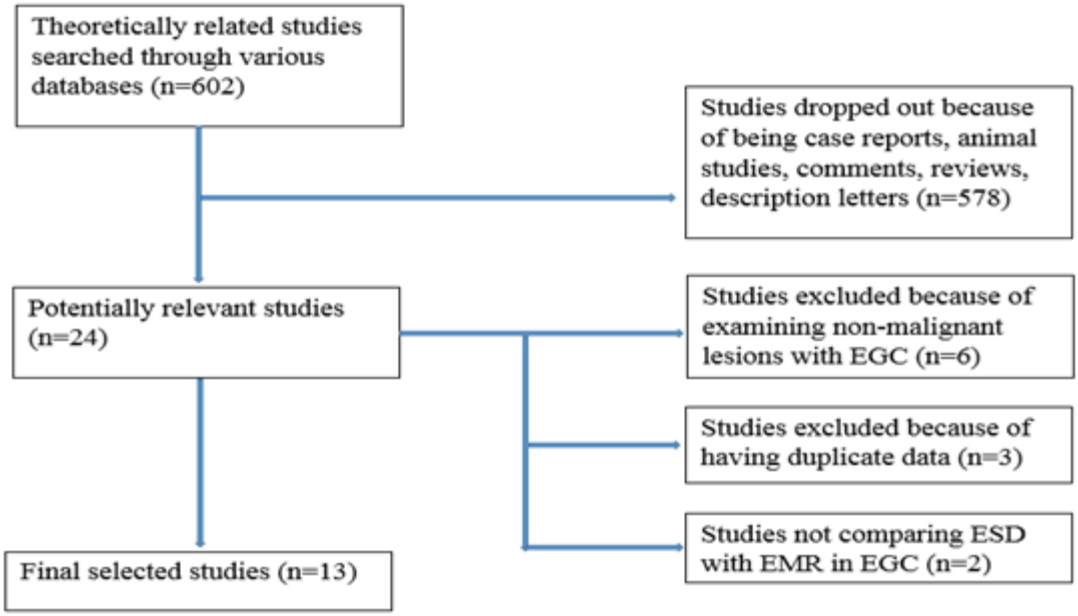

Figure 1: Flow diagram of trial selection

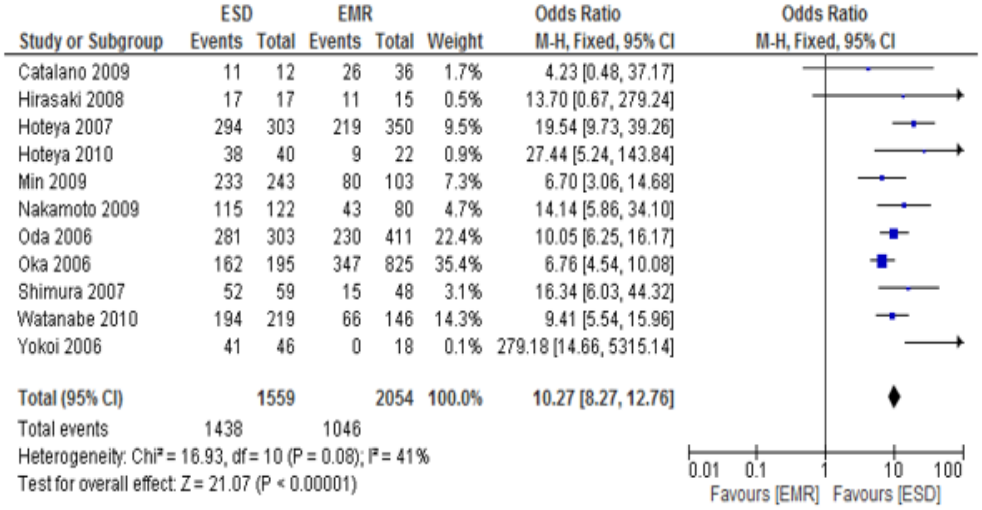

Figure 2: En bloc resection rate for endoscopic submucosal dissection (ESD) versus endoscopic submucosal resection (EMR) in primary and recurrent early gastric cancer (EGC).

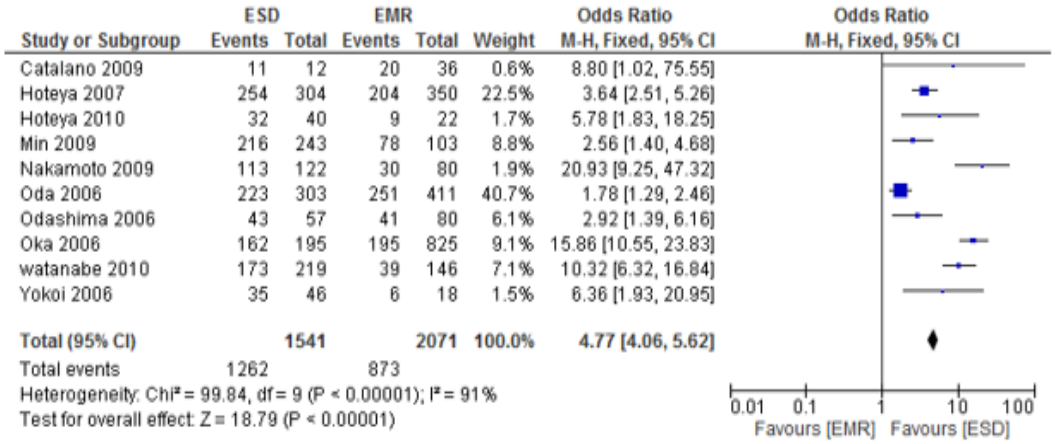

Figure 3: Histologically curative resection rate for endoscopic submucosal dissection (ESD) versus endoscopic submucosal resection (EMR) in primary and recurrent early gastric cancer (EGC).

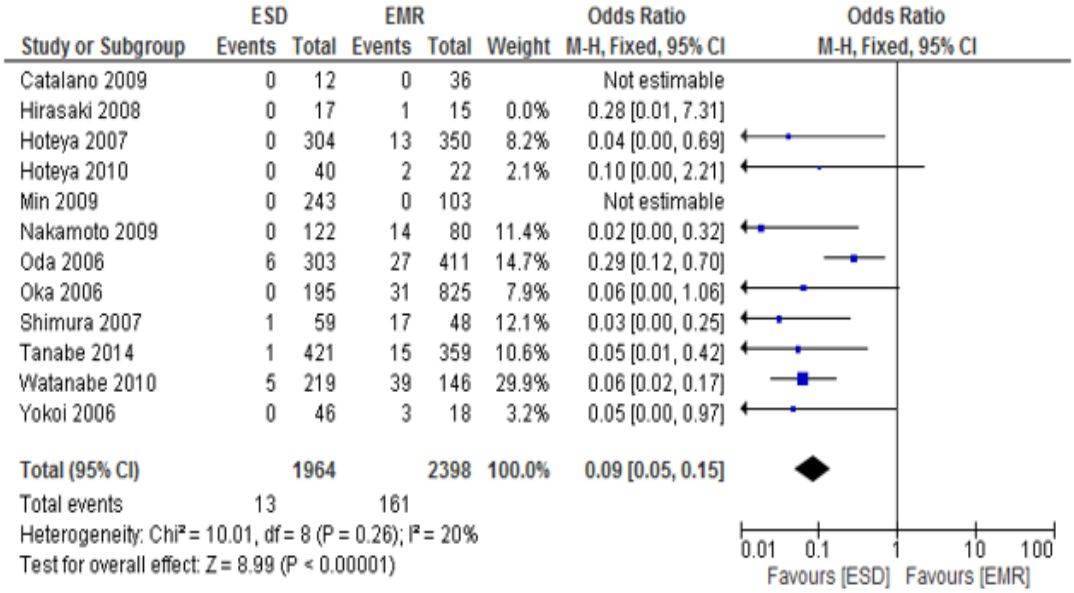

Figure 4: Post-procedural recurrence rate for endoscopic submucosal dissection (ESD) versus endoscopic submucosal resection (EMR) in primary and recurrent early gastric cancer (EGC).

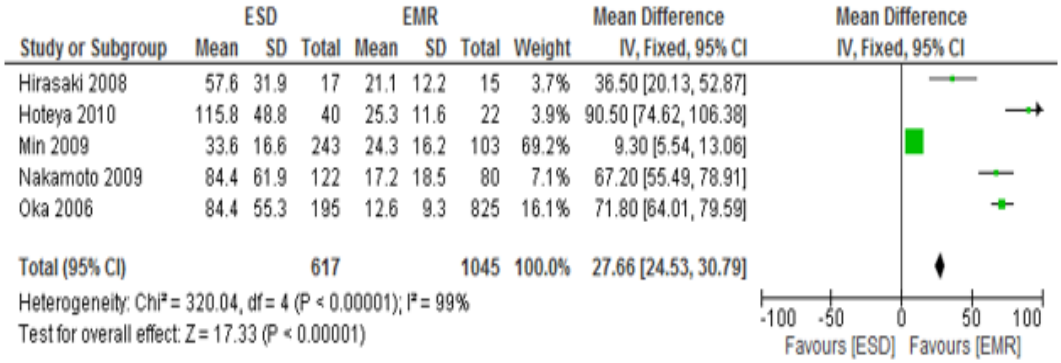

Figure 5: Operation time for endoscopic submucosal dissection (ESD) versus endoscopic submucosal resection (EMR) in primary and recurrent early gastric cancer (EGC).

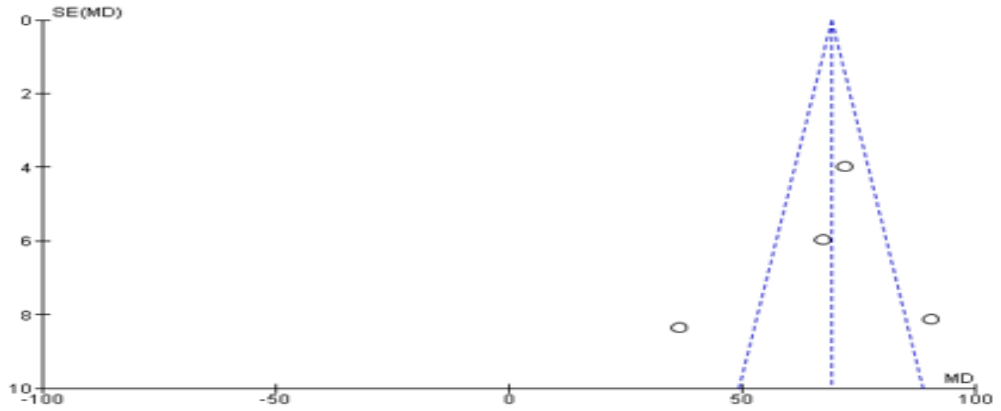

Figure 6: Funnel plot of publication for the mean operation time.

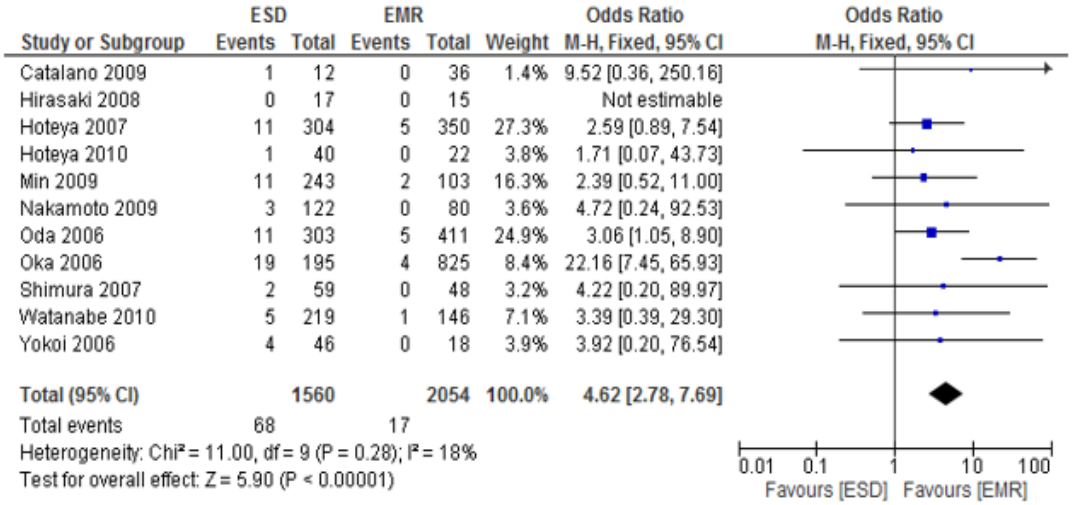

Figure 7: Perforation rate for endoscopic submucosal dissection (ESD) versus endoscopic submucosal resection (EMR) in primary and recurrent early gastric cancer (EGC).

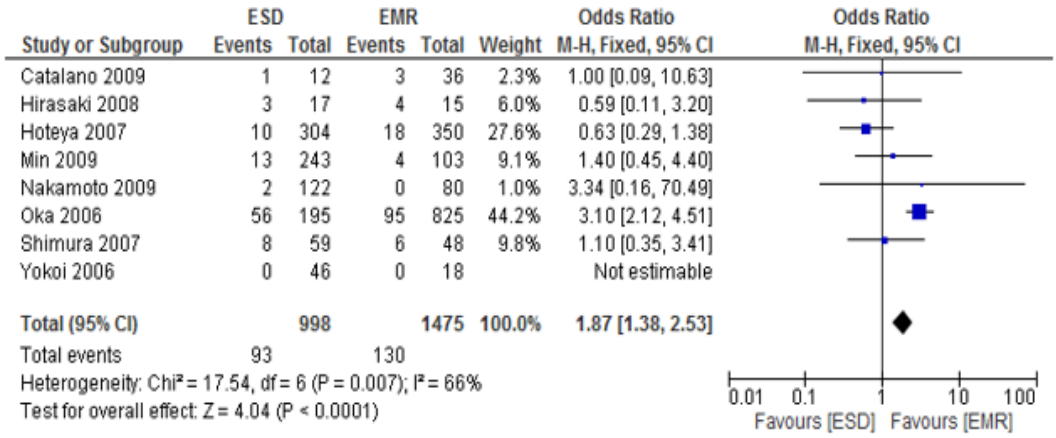

Figure 8: Rate of procedural bleeding for endoscopic submucosal dissection (ESD) versus endoscopic submucosal resection (EMR) in primary and recurrent early gastric cancer (EGC).