IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 14, Issue 5 Ver. V (May. 2015), PP 22-30
www.iosrjournals.org

Endoscopic Submucosal Dissection Is Highly Effective Than Endoscopic Mucosal Resection for the Treatment of Superficial Esophageal Cancer: A Meta-Analysis

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Abstract

BACKGROUND: Esophageal carcinoma is an aggressive cancer affecting worldwide population with very high incidence and mortality. The 5-year survival rate is still low even after years of development in the diagnostic and treatment regimens. The aim of this study is to evaluate the efficacy and safety of endoscopic submucosal dissection (ESD) and endoscopic mucosal resection (EMR) in the treatment of superficial esophageal cancer (SEC).

METHODS: Databases including the Cochrane Library, PubMed, EMBASE and Science Citation Index were searched throughout to find the relevant trials. Outcome measures were primarily en bloc resection rates, histologically curative resection rates, complications and local recurrence rates. In order to reduce the bias, subgroup analyses were performed.

RESULTS: The results revealed that en bloc resection rates (OR=35.96, 95% CI 11.87-108.96, P<0.00001), histologically curative resection rates (OR=12.48, 95 %CI 3.85-40.43, P<0.0001) and post-operative perforation rates (OR=2.23, 95% CI 1.10-4.55, P=0.03) were significantly higher in the ESD group than that of the EMR group. Results also showed that ESD can reduce the incidences of local recurrence (OR=0.19, 95% CI 0.05-0.75, P=0.02). However, operation-related bleeding (OR=0.79, 95% CI=0.24-2.61, P=0.70) and stenosis (OR=1.06, 95% CI 0.67-1.68, P=0.80) showed no significant differences between the two methods. The results were further confirmed by subgroup analyses.

CONCLUSION: Comparing the results of these two methods, ESD is more effective than EMR in the treatment of superficial esophageal cancer.

Key words: Meta-analysis; Endoscopic submucosal dissection; Endoscopic mucosal resection; Superficial esophageal cancer.

INTRODUCTION

Esophageal carcinoma is an aggressive cancer affecting the worldwide population with incidences and mortality being more than 20 times in China and other Asian countries [1,2]. The 5-year survival rates have been around 15-25% even after years of development in the diagnostic and treatment regimens [3,4]. It is more than four times common and lethal in males than in females, with a mean age of diagnosis at 67 years[4]. According to the Paris Consensus for endoscopic classification, superficial neoplasia is classified as an injury involving mucosa and submucosa, without affecting the muscularis propria [5]. Also, in general, superficial esophageal cancer (SEC) is defined as a tumor invasion confined to the mucosa and submucosa regardless of metastasis to the lymph nodes. The standard line of treatment for superficial esophageal cancer has been esophagectomy [6,7], such as Trans-hiatal esophagectomy, Ivor Lewis esophagectomy or Lewis-Tanner esophagectomy, the modified three-incision McKeown esophagectomy. However, recently, the viable approach has been the endoscopic therapy, in which the patients are able to retain the esophagus.

Much different from the surgical resection, endoscopic resection (ER) consists of endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), both of which have been extensively used in the clinical practice. Due to its coherent nature, ER has lot of advantages and is often less invasive and presented with fewer complications than the conventional surgical procedures [8]. The core difference between EMR and ESD specimens on a pathological scale is that, the latter is performed as a complete en bloc excision of the lesion, with the need for analyzing the extent of lesion and also analyzing the excised margins [9]. Although several studies have suggested the use of ER being safe and efficient for the detection of early and pre-malignant stage gastrointestinal lesions, but it is often accompanied with complications such as bleeding, stenosis and perforation after ESD or EMR [10]. Among the ER options, studies have shown that ESD has higher en bloc resection rate and histologically curative resection rate than EMR in the cases of early gastrointestinal tumors, but related complications are also higher as compared to EMR [11]. Several scholars have compared the merits and demerits of ESD and EMR in gastric and intestinal cancers. But the literature is still lacking a general consensus when it comes to more difficult esophageal cancer. Several factors may have influenced the dearth of knowledge, some of which include lack of skilled expertise and the difficulty in accessing the much constricted esophageal area. In this regard, the current study is aimed to evaluate the efficacy and safety of ESD and EMR procedures for the detection and treatment of early esophageal cancer.

MATERIALS AND METHODS

Identification and selection of studies

Relevant articles were identified and selected by searching the Cochrane Library, PubMed, EMBASE, and Science Citation Index, which were current through March 2015. All the studies were included if they met the following criteria: 1) Patients were diagnosed with superficial esophageal cancer by histology; 2) Tumor invasion depth of m1 (invasion within the mucosal epithelium) to sm1 (invasion within the upper third stratum of the submucosal layer); 3) Aim of the study was to compare ESD with EMR for SEC. Some studies were excluded if it had only contents related to comments, reviews, and guideline articles or if in case that particular study was previously reported, only the latest version was enrolled.

Outcome measures

Primary end points were: 1) En bloc resection rate: en bloc removal of tumors without piece-meal separation; 2) Histologically curative resection rate: defined as resection in one piece with no tumor cells in lateral and deep margins, and no lymphovascular tumor emboli.

Secondary end points were: 1) Bleeding: Operation-related incidence of bleeding during or after the operation; 2) Perforation: Diagnosed by endoscopy immediately after resection or by the presence of free air in the plain abdominal radiograph or CT image after the operation; 3) Local recurrence: the same histological type of tumor diagnosed by histology at the resected site during follow-up.

Data extraction

The data included the first author, publication year, number and mean age of participants, number and size of the lesions, the en bloc resection rate, histologically curative resection rate, local recurrence rate and complications of each study. All the data related to the studies was extracted and investigated by two authors independently. Disparities were resolved by mutual discussion between the two authors so that a consensus was reached on all reports. Furthermore, if there was still any disagreement, it was resolved by a third author.

Assessment of quality of study

The quality of each of the selected trials as evaluated by the criteria for non-randomized controlled study [12,13], was made up of 6 items such as method of grouping, blinding, intention-to-treat analysis, baseline, diagnostic criteria, and control of mixed factors. A quality score was determined for each study, with a maximum of 12 points indicating the highest possible score **(Table 1).**

Data analysis

The RevMan 5.0 provided by the Cochrane library was applied in this meta-analysis. The odds ratio (OR), with 95% CI, was recommended for the dichotomous data. Heterogeneity among the studies was assessed by the Chi-square test. When $P \geq 0.05$ or $I^2 < 50\%$, it indicated no heterogeneity among the selected studies so a fixed-effect model was used. Conversely, When $P<0.05$ or $I^2 > 50\%$, the random-effects model was used so as to overcome the heterogeneity among the selected studies. In order to explore the source of the heterogeneity, subgroup and sensitivity analyses were performed. Publication bias for the outcome of en bloc resection rate was detected by a Funnel plot, and then the symmetry of the Funnel plot was confirmed by the Egger's test, with a P value of 0.05.

Subgroup analysis

In order to reduce the bias, subgroup analysis was performed according to the equipment; the size of the lesions; the quality of each enrolled study; and the source of data, whether from a full text or from an abstract.

RESULTS

Studies and Subjects

A total of 547 trials were involved and according to the criteria, 533 studies were excluded for the reason of not comparing ESD with EMR for SEC. Two studies were not included because the data had been published repeatedly [14,15]. Another trial was also excluded because the study compared the healing time of ulcers which were formed after EMR or ESD [16]. Another two studies were excluded because the studies compared the large esophageal squamous cell carcinoma [17,18], **(Fig. 1)**. Finally nine studies, which included 1228 lesions (717 in the ESD group and 511 in the EMR group), were enrolled in the meta-analysis [19-27] (Table 1). All of the enrolled studies were respective case-control studies. Five of the enrolled studies were accessible as full-text and the others were abstract based. The exact number of lesions was not provided in two of the studies [22,26], and hence the number of patients were considered as equal to the number of lesions in these studies. Another one trial provided the number of lesions, which were less than the number of patients, and so number of lesions was used in the meta-analysis [23]. Since one study compared the outcome among ESD, EMRC (EMR using a cap-fitted endoscope) and 2-cEMR (2-channel EMR), so EMRC group and the 2-cEMR group were merged into the EMR group in this study [19]. One other trial studied superficial esophageal cancers, whose diameter was more than 20mm [23].

En bloc resection rate

Eight retrospective studies enrolled 1101 lesions (451 in the ESD group and 650 in the EMR group) which provided the en bloc resection rates for SEC. Because of heterogeneity among these studies (P=0.005, I^2=66%), a random-effects model was applied. The result showed that the ESD group reached a higher en bloc resection rates than the EMR group for SEC (OR=35.96, 95% CI 11.87-108.96, P<0.00001) as seen in the **Fig. 2**. In order to explore the source of the heterogeneity, sensitivity analysis were performed. After excluding a study, there was no more heterogeneity (P=0.16, I^2=35%) [25], and the result also revealed that ESD group reached a higher en bloc resection rate than EMR group for SEC (OR=50.80, 95% CI 18.97-136.08, P<0.00001).

Histologically curative resection rate

Six retrospective studies enrolled 731 lesions (305 in the ESD group vs. 426 in the EMR group), which reported the histologically curative resection rates between the two groups. The heterogeneity test found that there was significant heterogeneity among the studies (P=0.0003, I^2=78%), and therefore the random-effects model was applied. The result confirmed that ESD group has a higher histologically curative resection rate than the EMR group (OR=12.48, 95% CI 3.85-40.43, P<0.0001) as demonstrated in **Fig. 3**. In order to explore the source of heterogeneity, we conducted a sensitivity analysis. In accordance with the sensitivity analysis, two studies were excluded, after this, there was no heterogeneity detected among the studies (P=0.25, I^2=27%) [22,23]. These results further validated the above conclusion (OR=5.68, 95% CI 3.13-10.3, P<0.00001).

Procedure-related bleeding

In all of the enrolled studies, only six studies including 741 lesions (305 in the ESD group vs. 436 in the EMR group) provided the data for procedure-related bleeding. Because of no heterogeneity (P=0.83, I^2=0%) among these studies, fixed-effect model was applied. The results suggested that the operation-related bleeding was not statistically different between ESD and EMR group for SEC (OR=0.79, 95% CI 0.24-2.61, P=0.70) as indicated in **Fig. 4**.

Stenosis

Stenosis was found in seven trials including 1001 lesions (456 in the ESD group vs. 545 in the EMR group). There was no heterogeneity (P=0.25, I^2=24%) in these studies, so a fixed-effect model was applied. The result showed that stenosis in both groups had no statistical significance (OR=1.06, 95% CI 0.67-1.68, P=0.80) as depicted in **Fig. 5.**

Perforation

Eight enrolled studies including 1168 lesions (492 in the ESD group vs. 676 in the EMR group) reported the data for perforation. A fixed-effect model was applied as there was no heterogeneity (P=0.31, I^2=16%) among the study. The results confirmed that post-operative perforation in the EMR group was lesser than that in the ESD group (OR=2.23, 95% CI 1.10-4.55, P=0.03) **Fig. 6**.

Local Recurrence Rates

Seven trials including 992 lesions (372 in the ESD group vs. 620 in the EMR group) provided the local recurrence rates. There was heterogeneity (P=0.03, I^2=56%) among the studies, and so a random-effects model was applied. The result of the analysis confirmed that ESD group can reduce the incidence of local recurrence

(OR=0.19, 95% CI 0.05-0.75, P=0.02) **Fig. 7**. On the basis of results of sensitivity analysis, two studies were excluded [24,26]. The heterogeneity showed no statistical significance (P=0.39, I^2=0%) and the overall results revealed that local recurrence rates in ESD group were lower compared to EMR group for SEC (OR=0.08, 95%CI 0.02-0.30, P=0.0002).

Subgroup analysis

In order to explore the source of the heterogeneity, we performed a subgroup analysis according to the size of lesion, the quality of each enrolled study and the quantitative aspect of each study, whether being a full-text or an abstract. The results of the subgroup analysis showed that ESD group had a higher en bloc resection rate and histologically curative resection rate and lower frequency of local recurrence than EMR group. But, on the whole, the complications were similar between the two groups **(Table 2)**.

Publication bias

When we used the en bloc resection rates as the outcome, no publication bias was detected by the Funnel plot **Fig. 8**, the Begg's Test (P=0.458) and the Egger's Test (P =0.149).

DISCUSSION

There has been considerable interest to develop curative endoscopic therapies for the treatment of superficial esophageal carcinoma. Conventional modes of treatment like surgery, chemotherapy, and radiotherapy are challenged with several disadvantages, such as unforeseen complications, longer recovery time, and more costs. In order to overcome these drawbacks, EMR was introduced and has been popular as 'Strip-biopsy' since 1984 [28], for the resection of early gastric carcinoma, but it was further developed by Hirao and colleagues in 1988 [29]. EMR resects only a limited region, requiring a piece-meal resection and hence increasing the chances of recurrence. While as, ESD is a newly practiced technique which requires advanced skills and uses an electrocautery knife to obtain a single-piece specimen. No doubt ESD is advantageous over EMR, controversies still exist. As there are technical difficulties and risks of complications in the region of esophagus, which have to be accounted for.

The present meta-analysis suggests that using ESD for the treatment of SEC can reach higher en bloc resection rate, histologically curative resection rate, post-operative perforation rate, and reduction in incidences of local recurrence than EMR, but other complications showed no statistical significance by either method. The above data were confirmed by subgroup analyses, enabling us to contemplate that ESD was more effective than EMR. However, this conclusion should be confirmed by further analyses in larger groups of SECs.

Although many meta-analyses suggested ESD to be more effective and safer in early gastric and rectal cancer treatment, it is still controversial in the case of SEC. The conclusion of our meta-analysis should be accepted enthusiastically but with little caution: Firstly, nine studies including 1228 lesions (717 in the ESD group and 511 in the EMR group) were enrolled in this meta-analysis. Secondly, in order to reduce the bias, subgroup analyses according to the differences between enrolled trials were performed. Thirdly, in order to make the results more credible, we performed sensitivity analyses in the outcome measures which had heterogeneity. Finally, there were some positive differences in the outcome of the local recurrence rates and the results of subgroup analyses, which made us to comprehend that ESD was more suitable for the treatment of SEC. The result of this meta-analysis, which demonstrated that en bloc resection rate and histologically curative resection rates in ESD could be significantly higher compared to EMR, is in correspondence with Lian et al and Cao et al [30,31]. But there are also some differences from Lian et al. Firstly, Lian et al only evaluated the efficacy and safety of ESD and EMR in early gastric cancer, but there were no cases of SECs included in that meta-analysis. Secondly, the differences in structural organization and physiological functioning between gastric and esophageal regions may cause different levels of difficulty in the operation, so the result from Cao et al may not suit for SEC. The results of Cao et al showed high procedure-related bleeding and perforation rates in the ESD group. The explanation for this kind of discrepancy may have been due to following factors. Firstly, Cao et al included studies of premalignant and malignant lesions of the gastrointestinal tract, and there was no subgroup analysis conducted between premalignant and malignant lesions. Secondly, although Cao et al performed a subgroup analysis for the esophageal cancer, it only included 3 studies with 175 lesions, which is suggestive of an indefinite conclusion. Thirdly, only the en bloc resection rates and histologically curative resection rates were involved in the subgroup analysis for esophageal lesions, without further elaborating the differences in complications and incidences of local recurrence. Finally, that study included gastrointestinal carcinomas as a whole and hence, the bias was inevitable. Our results are almost in line with Guo et al [32], but there is also an important deviation from Guo et al. In his meta-analysis, he had observed that the advantage of less local recurrence in ESD is found only in SECs with diameters larger than 20mm and according to him, ESD had no advantage over EMR if the SEC size was smaller than 20mm. But according to our analysis, ESD is equally advantageous in smaller SECs. The fact is verified by our meta-analytic study in which most of studies included the trials with smaller SECs. Hence the findings of Guo et al regarding less local recurrences after ESD in SECs greater than 20mm do not have a proper validation.

As a matter of fact, the present meta-analysis also has some limitations. First, all of the enrolled studies were respective case-control studies and four studies provided only abstracts. So, in order to overcome this limitation, randomized control trials (RCTs) are necessary for further analysis. Second, although the Egger's test was applied for the publication bias, still there existed biasing because of the limited literature. Third, although the sensitivity analysis was applied only when the heterogeneity was significant, the 95% CI was broader in en bloc resection rates and histologic curative resection rates, which may have slightly different perspective on the results. Fourth, among the nine enrolled trials, eight studies were from Asia, so the conclusions may not accurately represent the worldwide population; comparison of data across continents may be warranted to derive a universal prospect. Finally, although we performed a subgroup analysis, still there exists bias because of the difference in techniques as EMR group were only evident in three trials among the enrolled studies.

In summary, comparing endoscopic mucosal resection (EMR) with endoscopic submucosal dissection (ESD) for superficial esophageal cancer (SEC), ESD, without any doubt, outperforms EMR with distinct advantages in terms of en bloc resection rate, histologically curative resection rate and local recurrence rate. Of note, it is relevant to stipulate that there are no significant differences in terms of complications like stenosis or post-operative bleeding. Future analysis should be confirmed by large-scale, impactful, placebo-controlled and double-blind trials from different countries for a more robust data interpretation.

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Table 1: Details of enrolled studies

Author	Year	Country	Method	Patients (n)	Mean age	Lesions (n)	Size of Lesion (mm)	Full text/Abstract	Quality score
Ryu ishihare[19]	2008	Japan	ESD	29	64	31	16±4	Full text	8
			EMRC	58	65	68	13±4		
			2-cEMR	61	64	72	12±4		
Jung H-Y[20]	2010	Korea	ESD	34	64	37	Not on record	Abstract	6
			EMR	28		32			
Anthony Yuen Bun Teoh[21]	2010	China	ESD	18	67.5	22	Not on record	Full text	4
			EMRC	10	61	13			
Hiroaki Takahashi[22]	2010	Japan	ESD	116	67.1	Not on record	30±16	Full text	7
			EMR	184	66.4		20±11		
Kubota Y[23]	2010	Japan	ESD	38	Not on record	36	31	Abstract	6
			EMR	129		131	30		
Tatsuya yamashita[24]	2011	Japan	ESD	112	Not on record	71	21.3±11.1	Full text	8
			EMRC			56	19.4±11.2		
Kim DH[25]	2011	Korea	ESD	91	66	100	Not on record	Abstract	4
			EMR	31		37			
Depre Z[26]	2011	Belgium	ESD	30	59	Not on record	Not on record	Abstract	3
			EMR	30	59				
Urabe [27]	2011	Japan	ESD	59	63.8±10.1	79	Not on record	Full text	6
			EMR	63	65.3±9.2	83			

Table 2: Subgroup analysis of the ESD vs EMR

	En bloc resection rate		histologic curative resection rate		Operation relate bleeding		stenosis		perforation		Local recurrence	
	Heterogeneity test	OR(95%CI),P	Heterogeneity test	OR(95%CI),P	Heterogeneity test	OR(95%CI),P	Heterogeneity test	OR(95%CI),P	Heterogeneity test	OR(95%CI),P	Heterogeneity test	OR(95%CI),P
abstract	P=0.0001, I^2=82%	52.93 (8.05-348.01) P<0.0001	P=0.0008, I^2=82%	8.50 (2.06-35.11) P=0.003	P=0.83, I^2=0%	1.51 (0.21-10.67) P=0.68	P=0.61, I^2=0%	0.63 (0.20-1.97) P=0.43	P=0.84, I^2=0%	6.46 (1.21-34.558) P=0.03	P=0.0005, I^2=88%	0.23 (0.00-16.12) P=0.49
Full-text	P=0.26, I^2=26%	37.19(13.19-104.85) P<0.00001	P=0.59, I^2=0%	31.35 (8.91-110.33) P<0.00001	P=0.67, I^2=0%	0.50 (0.09-2.62) P=0.41	P=0.16, I^2=39%	1.17 (0.71-1.93) P=0.54	P=0.19, I^2=35%	1.51 (0.66-3.45) P=0.32	P=0.72, I^2=0%	0.13 (0.04-0.43) P=0.0009
ESD/EMRC	P=0.97, I^2=0%	9.72 (1.48-63.92) P=0.02	P=0.34, I^2=0%	26.07 (7.52-90.40) P<0.00001	P=0.57, I^2=0%	0.36 (0.04-3.62) P=0.39	P=0.50, I^2=0%	0.64 (0.25-1.64) P=0.35	P=0.17, I^2=44%	0.75 (0.20-2.74) P=0.66	P=0.71, I^2=0%	0.11 (0.01-0.96) P=0.05
Low quality	P=0.12, I^2=52%	15.78 (3.15-79.14) P=0.0008	P=0.34, I^2=0%	3.45 (1.60-7.42) P=0.002	P=0.44, I^2=0%	0.45 (0.06-3.49) P=0.45	P=0.27, I^2=19%	0.80 (0.21-3.00) P=0.74	P=0.48, I^2=0%	5.49 (0.68-44.46) P=0.11	P=0.66, I^2=0%	0.09 (0.02-0.52) P=0.007
High quality	P=0.17, I^2=37%	56.50 (22.38-142.61) P<0.00001	P=0.02, I^2=71%	26.57 (6.47-109.06) P<0.00001	P=0.76, I^2=0%	1.03 (0.24-4.50) P=0.96	P=0.18, I^2=36%	1.10 (0.68-1.79) P=0.70	P=0.18, I^2=34%	1.81 (0.84-3.93) P=0.13	P=0.58, I^2=0%	0.08 (0.02-0..24) P<0.0001
Lesion Size <20mm	P=0.76, I^2=0%	14.02 (1.78-110.26) P=0.01	P=0.85, I^2=0%	19.76 (4.49-87.06) P<0.00001			P=0.92, I^2=0%	0.56 (0.08-3.72) P=0.54	P=0.36, I^2=0%	3.96 (0.59-36.93) P=0.16	P=0.60, I^2=0%	0.49 (0.05-4.60) P=0.53
Lesion Size >20mm	P=0.001, I^2=91%	23.18 (0.37-1463.20) P=0.14	P=0.31, I^2=3%	168.52 (43.94-646.29) P<0.00001					P=0.04, I^2=70%	1.75 (0.15-19.92) P=0.65	P=0.58, I^2=0%	0.04 (0.01-0.34) P=0.003

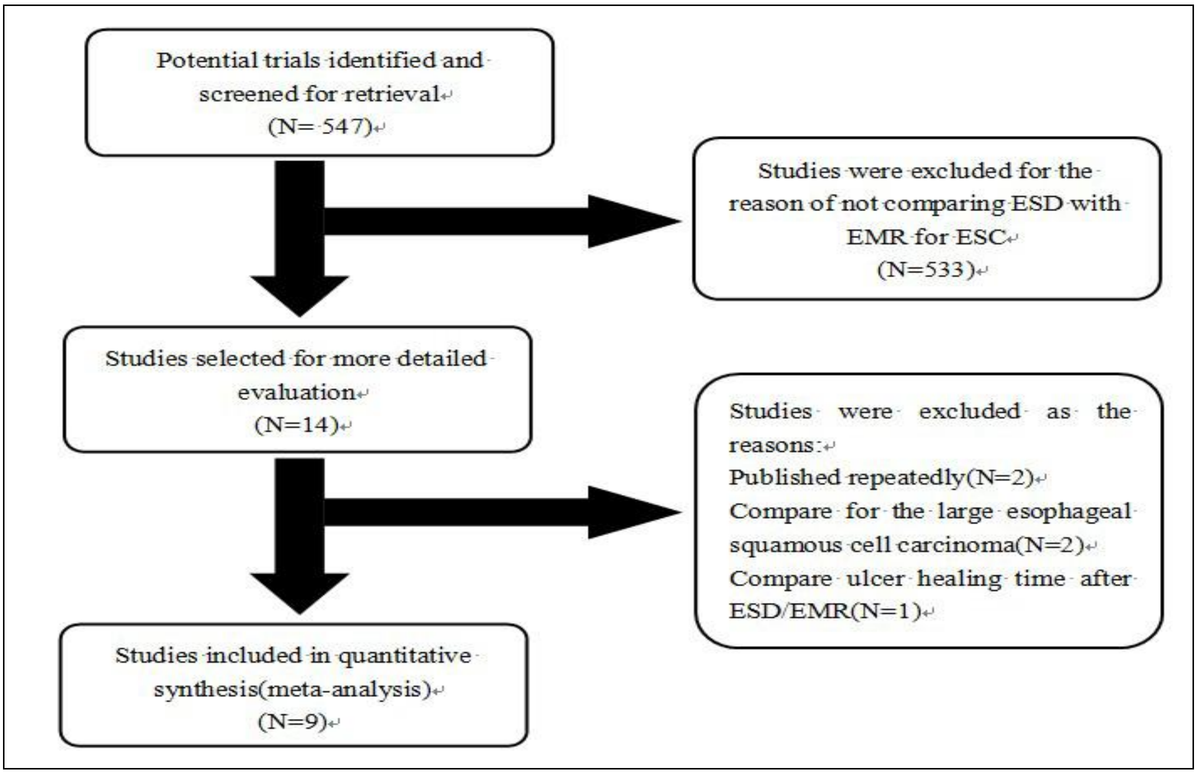

Figure 1: Flow diagram of trial selection.

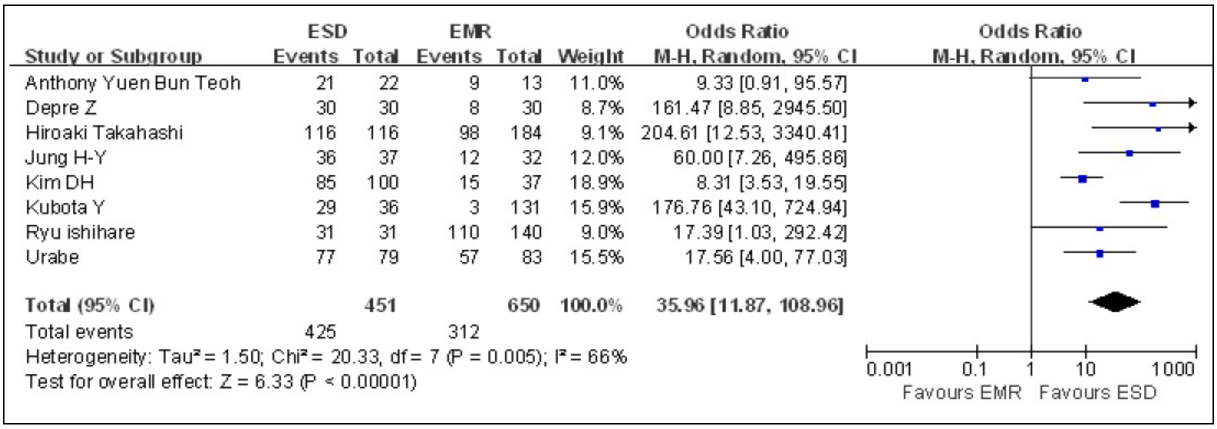

Figure 2: En bloc resection rates of ESD/EMR.

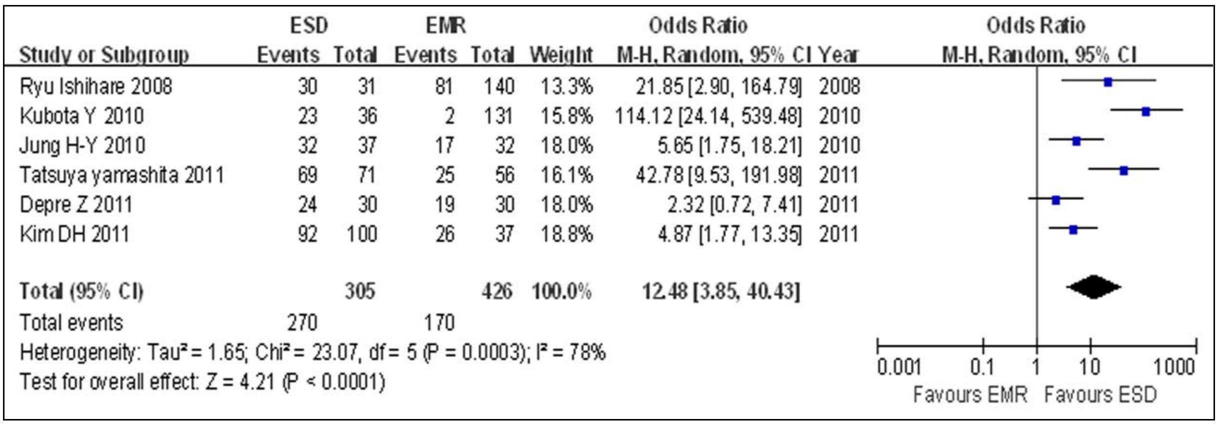

Figure 3: Histologically curative resection rates of ESD/EMR.

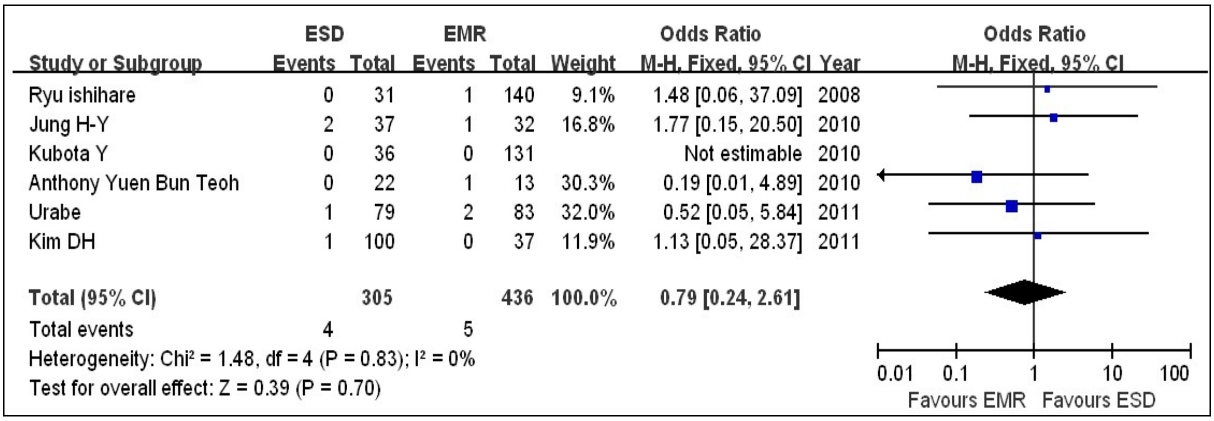

Figure 4: Procedure-related bleeding of ESD/EMR.

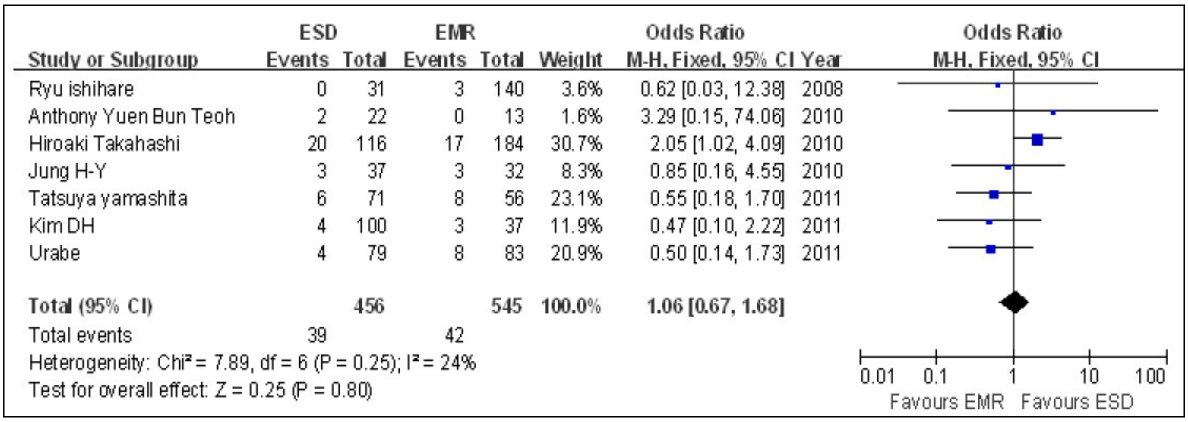

Figure 5: Stenosis after ESD/EMR.

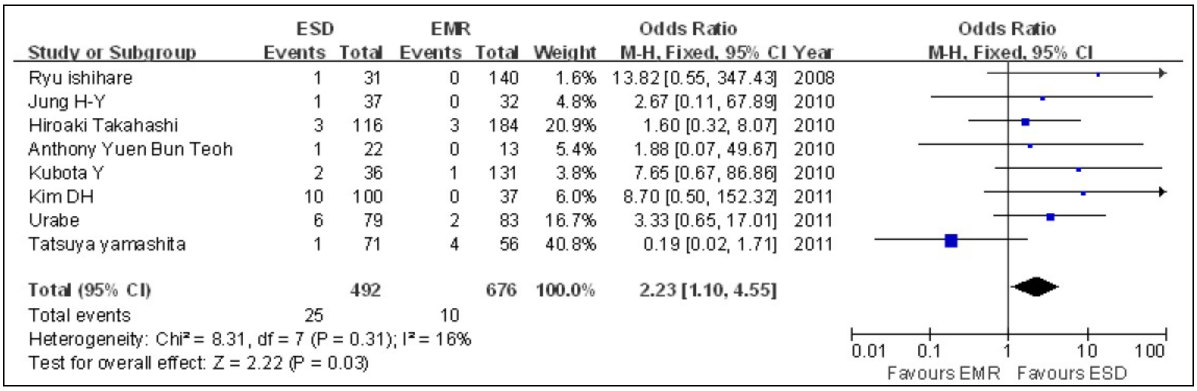

Figure 6: Perforation after ESD/EMR.

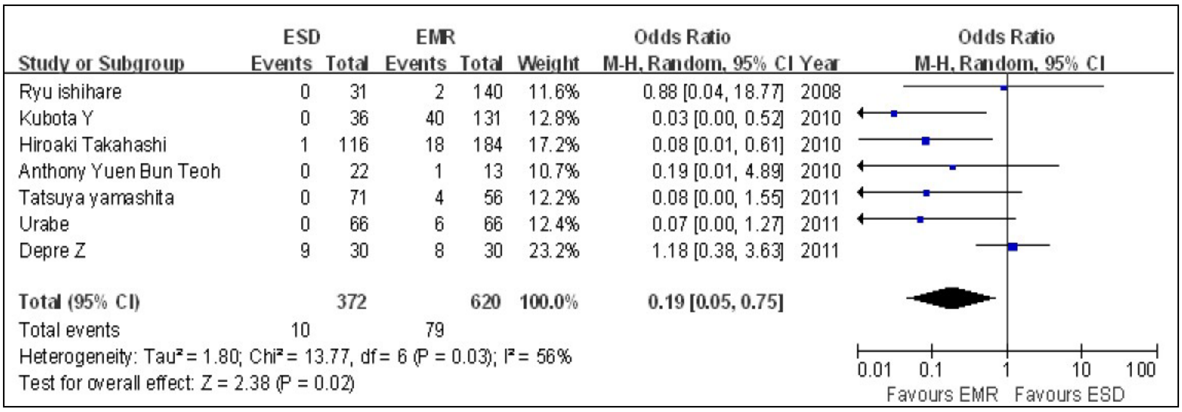

Figure 7: Local recurrence rates after ESD/EMR.

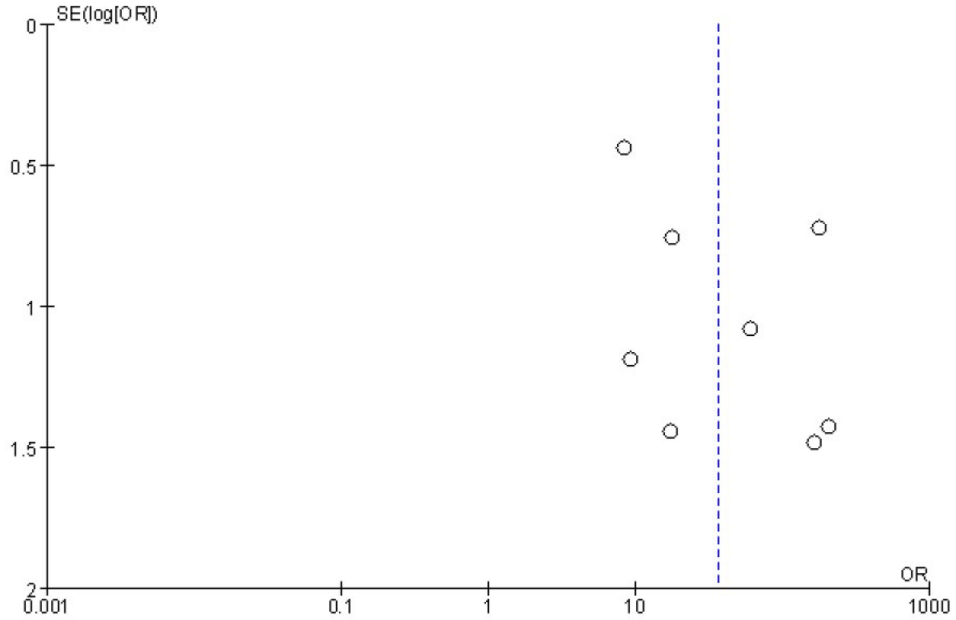

Figure 8: Funnel plot for publication bias.