

Endoscopic submucosal dissection of gastric tumors: A systematic review and meta-analysis

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Abstract

AIM: To systematically review the medical literature in order to evaluate the safety and efficacy of gastric endoscopic submucosal dissection (ESD).

METHODS: We performed a comprehensive literature search of MEDLINE, Ovid, CINAHL, and Cochrane for studies reporting on the clinical efficacy and safety profile of gastric ESD.

RESULTS: Twenty-nine thousand five hundred and six tumors in 27155 patients (31% female) who underwent gastric ESD between 1999 and 2014 were included in this study. R0 resection rate was 90% (95%CI: 87%-92%) with significant between-study heterogeneity ($P < 0.001$) which was partly explained by difference in region ($P = 0.02$) and sample size ($P = 0.04$). Endoscopic *en bloc* and curative resection rates were 94% (95%CI: 93%-96%) and 86% (95%CI: 83%-89%) respectively. The rate of immediate and delayed perforation rates were 2.7% (95%CI: 2.1%-3.3%) and 0.39% (95%CI: 0.06%-2.4%) respectively while rates of immediate and delayed major bleeding were 2.9% (95%CI: 1.3-6.6) and 3.6% (95%CI: 3.1%-4.3%). After an average follow-up of about 30 mo post-operative, the rate of tumor recurrence was 0.02% (95%CI: 0.001-1.4) among those with R0 resection and 7.7% (95%CI: 3.6%-16%) among those without R0 resection. Overall, irrespective of the resection status, recurrence rate was 0.75% (95%CI: 0.42%-1.3%).

CONCLUSION: Our meta-analysis, the largest and most comprehensive assessment of gastric ESD till date, showed that gastric ESD is safe and effective for gastric

tumors and warrants consideration as first line therapy when an expert operator is available.

Key words: Endoscopic submucosal dissection; Gastric neoplasms; Meta-analysis

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Core tip: Our meta-analysis, the largest and most comprehensive assessment of gastric endoscopic submucosal dissection (ESD) to date, showed that gastric ESD is safe and effective for gastric tumors when an expert operator is available. The most compelling evidence is from Asian countries and we recommend the consideration of the procedure as first line therapy in Western countries.

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INTRODUCTION

Advances in diagnostic techniques and an improved understanding of gastric tumors has led to a deepening interest in new management techniques aimed to improve outcomes with minimal complications. In the past, open gastrectomy was the standard of care for gastric tumor but open surgery is typically associated with increased morbidity and mortality rates. Laparoscopy-assisted gastrectomy has also been explored as another option but despite being less invasive, there are known issues with accurately locating the lesion and resection of unnecessary quantities of normal tissue. Endoscopic submucosal dissection (ESD) is an alternative and advance way of managing early-stage lesions in the gastrointestinal tract. It allows for complete resection of early-stage lesions with the aim of providing tissue for accurate histological diagnosis as well as preventing the reoccurrence of tumors. While somewhat similar to endoscopic mucosal resection (EMR), ESD is as feasible but more effective^[1]. As a minimally invasive management technique developed in Japan in the mid-1990s, ESD has gradually become very widely used in Asia and some part of Europe and America. There is an increasing need to synthesize all the literature currently available to evaluate ESD thoroughly for efficacy and safety profile. We therefore conducted a systematic review and meta-analysis of studies reporting on safety and efficacy of gastric ESD, and evaluated for potential sources of heterogeneity with the aim of elucidating factors affecting these outcomes while utilizing this technique.

MATERIALS AND METHODS

We performed meta-analysis of proportion similar to what has been done in prior studies^[2-9]. We followed the recommendations of the meta-analysis of observational studies in epidemiology during all stages of the design, implementation, and reporting of this meta-analysis^[10].

Search strategy

We performed a comprehensive literature search of MEDLINE, Ovid, CINAHL, and Cochrane for studies published up to October 2014. Our search query for MEDLINE was ("endoscopic submucosal dissection"[tiab] OR "endoscopic submucosal resection"[tiab] OR "submucosal dissection"[tiab] OR "ESD"[tiab]) AND ("stomach"[Mesh] OR gastr*[tiab] OR "foregut"[tiab]). Similar search terms were adapted for the other databases (Table 1).

Study selection

One investigator screened all titles and abstracts for relevance to our study. Two investigators reviewed full text of these articles and applied our pre-defined inclusion/exclusion criteria independently and in duplicate (Figure 1). Hand searching of reference list of the articles was also done in order to retrieve other articles that might have been missed by our search strategy. We included all full-text publications reporting clinical outcome(s) after gastric ESD. Our exclusion criteria were: Animal studies; case reports; commentaries or general reviews; or overlapping publications from the same center. However, review papers and overlapping publications from the same center were included in the initial screening for further assessment of the full-text and reference list after which, for the overlapping publications, only the most updated and comprehensive publication was retained. For the multicenter studies, we excluded all individual studies from the contributing centers if their sample size is comparable or less than that contributed to the multicenter study. Otherwise, we excluded the multicenter study if there are more updated studies from individual centers that provided more information. Articles in foreign language were translated *via* Google translator.

Data extraction

Data from each study were extracted using a standardized data extraction sheet. These included publication information such as author name, year of publication; characteristics of study cohort such as country, name of medical center, study design, number of patients, year of data collection, demographics, setting (single or multi center); characteristics of tumor such as anatomical location, number of tumors, average tumor size, macroscopic or microscopic detail; ESD procedural details such as duration of the procedure and number of failed procedure; and number of patients with clinical success and adverse outcomes.

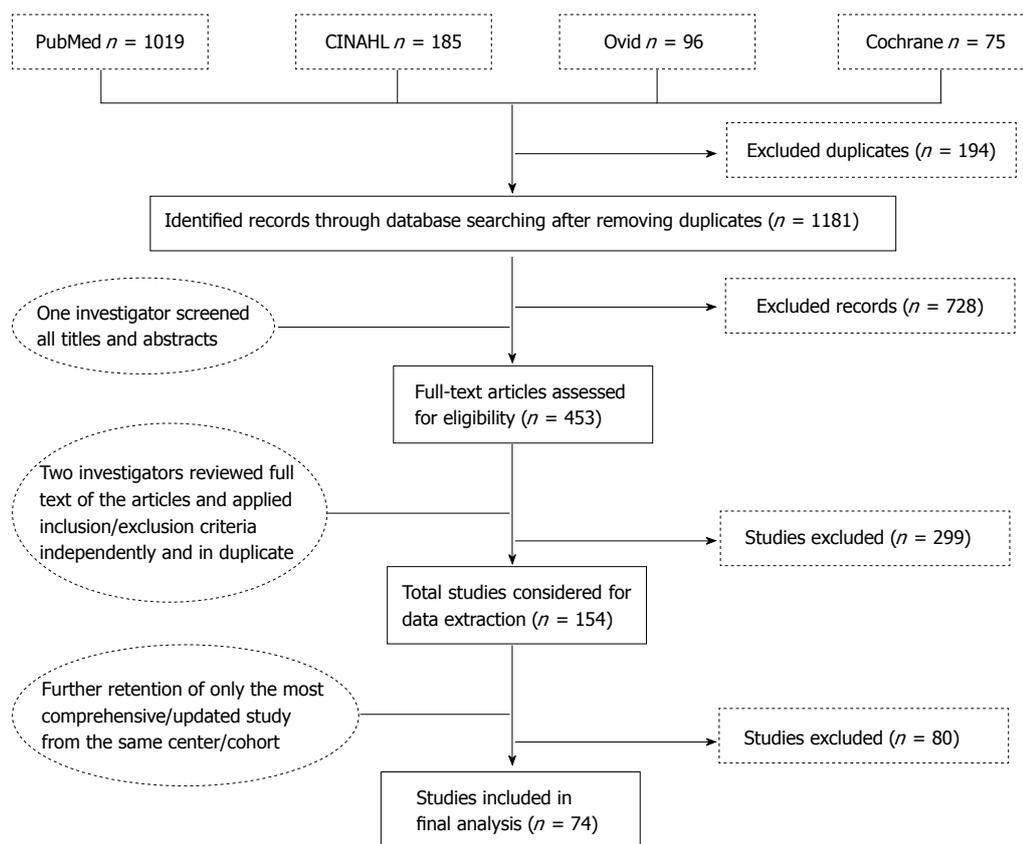


Figure 1 Screening and selection process.

Table 1 Search query

Medline	("endoscopic submucosal dissection"[tiab] OR "endoscopic submucosal resection"[tiab] OR "submucosal dissection"[tiab] OR "ESD"[tiab]) AND ("stomach"[Mesh] OR gastr*[tiab] OR "foregut"[tiab])
Ovid	(endoscopic submucosal dissection OR endoscopic submucosal resection OR submucosal dissection OR endoscopic dissection OR ESD) AND (stomach OR gastr* OR foregut)
CINAHL	(endoscopic submucosal dissection OR endoscopic submucosal resection OR submucosal dissection OR endoscopic dissection OR ESD) AND (stomach OR gastr* OR foregut)
Cochrane	(endoscopic submucosal dissection OR endoscopic submucosal resection OR submucosal dissection OR endoscopic dissection OR ESD) AND (stomach OR gastr* OR foregut)

Endpoints

We assessed both measures of efficacy and adverse outcomes associated with gastric ESD. Our primary measure of efficacy was complete (R0) resection defined as *en bloc* (i.e., one-piece) resection with histologically confirmed tumor-free lateral and vertical margins. In addition, we evaluated endoscopic *en bloc* (i.e., one-piece resection without histological confirmation) and curative resection rate as secondary endpoints. Curative resection was defined as resections with both tumor-free lateral and vertical resection margins, minimal submucosal invasion (< 500 μ m from the muscularis mucosa), and with no lymphovascular invasion or poorly differentiated component. Adverse outcomes include viscus perforation, major bleeding requiring intervention, and tumor recurrence. Immediate adverse events refers to those occurring within 24 h of the procedure

while delayed refers to those occurring after 24 of the procedure. For all endpoints, the rates were evaluated as percentage of number of tumors operated.

Statistical analysis

Proportions from each study were pooled together using logistic-normal random effect model. Study-specific confidence intervals were based on the exact method while confidence intervals for the pooled estimates were based on the Wald method with logit transformation and back transformation. Heterogeneity between studies were assessed *via* visual inspection of the forest plot and χ^2 statistic of the likelihood ratio test comparing the random effect model with its corresponding fixed effect model; Evaluation for potential sources of heterogeneity such as study design, setting, year of data collection (evaluated based on the last year of data collection),

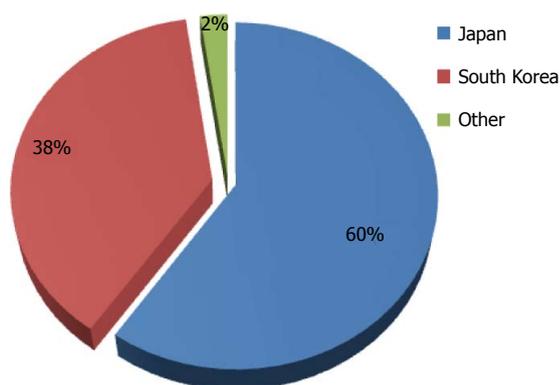


Figure 2 Percentage distribution of 27155 patients who underwent gastric endoscopic submucosal dissection between 1999 and 2014 in 11 countries. Others include China, Taiwan, Australia, Germany, Italy, Poland, Portugal, Brazil and Uruguay that contributed $\leq 1\%$ each.

region (Asia vs Western world), average age, sex distribution, number of tumors, epithelial vs subepithelial tumor, average tumor size, and duration of the procedure were assessed *via* meta-regression. Evaluation for publication bias was assessed *via* visual inspection of the funnel plot and Egger's test. Potential impact of the bias was evaluated with a cumulative meta-analysis after sorting studies in decreasing order of precision (roughly corresponding to largest to smallest study)^[11].

In a subgroup analysis, we evaluated same endpoints in studies reporting outcomes exclusively among patients with cancers, *i.e.*, we excluded studies reporting benign tumors or mixed population of benign and malignant tumors.

Analyses were performed using STATA (Version 13; StataCorp, College Station, TX), 2-tailed $\alpha = 0.05$.

RESULTS

Of the 1181 citations retrieved through database searching, 728 were excluded because they reported no clinical outcome after ESD procedure in human (Figure 1). Four hundred and fifty-three studies underwent full text review using our pre-defined inclusion and exclusion criteria, after which 74 studies published between 2003 and 2014 were retained for data synthesis.

A total of 29506 tumors in 27155 patients (31% female) with average age 67 years (range: 18-95 years) underwent gastric ESD between 1999 and 2014 (Table 2). The majority of these procedures were performed in the Asian countries of Japan and South Korea with very few experiences in the Western world (Figure 2). Average tumor size was 18 mm (range: 1-150 mm), and the procedures were completed in an average time of 73 min (range: 4-750 min).

Efficacy

R0 resection rate was reported in 53 studies across which meta-analysis yielded a pooled estimate of 90% (95%CI: 87%-92%) (Figure 3). There was significant between-study heterogeneity ($P < 0.001$) which was partly

explained by difference in region ($P = 0.02$) and sample size ($P = 0.04$), but not by any of the other pre-specified variables. Specifically, R0 resection rate was higher in Asia compared to the western world, and an increase in number of tumors operated by 100 is associated with 0.7% higher rate. Although significant asymmetry in the funnel plot was apparent ($P = 0.001$) (Figure 4), further exploration with a cumulative meta-analysis suggests that this asymmetry is not likely due to publication bias (Figure 5): The result from high-precision studies (*e.g.*, first 25 studies in Figure 5) did not substantially differ from the overall estimate. In addition, lower estimates were reported in the low-precision studies which is the reverse of what we would expect for a publication bias. Rather, our analysis suggests that the asymmetry is due to true heterogeneity based on sample size. This notion is further supported by finding of sample size as a source of heterogeneity, and lack of asymmetry across quartile of sample size (Figure 6)^[12].

Endoscopic *en bloc* and curative resection rates were reported in 60 and 20 studies respectively. Across studies, meta-analysis yielded a pooled estimate of 94% (95%CI: 93%-96%) (Figure 7) for endoscopic *en bloc* resection rate and 86% (95%CI: 83%-89%) (Figure 8) for curative resection rate. Evaluation for heterogeneity, publication bias, and the result of a cumulative meta-analysis for the secondary endpoints were generally similar to those of R0 resection.

Adverse outcomes

Perforation and major bleeding requiring intervention were the most common peri-operative complications reported (Table 3). Immediate and delayed perforation rates were 2.7% (95%CI: 2.1%-3.3%) and 0.39% (95%CI: 0.06%-2.4%) respectively while rates of immediate and delayed major bleeding were 2.9% (95%CI: 1.3-6.6) and 3.6% (95%CI: 3.1%-4.3%). Evaluation for potential sources of heterogeneity showed that the rate (95%CI) of immediate perforation was significantly lower with epithelial [2.7% (2.2%-3.6%)] compared with subepithelial tumors [8.9% (2.7-15%)] ($P = 0.02$) and has declined by 0.29% (0.05%-0.54%) per year over the duration of study ($P = 0.02$). Similarly, the rate (95%CI) of immediate bleeding has declined by 2.3% (0.72%-3.9%) per year over the duration of study ($P = 0.007$). Lastly, we found that the rate (95%CI) of delayed bleeding increases by 1.3% (0.07%-2.5%) for every 10 years increase in age.

After an average follow up of about 30 mo post-operative, the rate of tumor recurrence was 0.02% (95%CI: 0.001-1.4) among those with R0 resection and 7.7% (95%CI: 3.6%-16%) among those without R0 resection (Table 3). Overall, irrespective of the resection status, recurrence rate was 0.75% (95%CI: 0.42%-1.3%). The rate (95%CI) of recurrence decreases by 0.4% (0.1%-0.7%) for every 10 year increase in age ($P = 0.01$) and there was a trend towards higher rate in Western countries [5.1% (0.5%-11%)] compared with Asia [0.5% (0.3%-0.6%), $P = 0.06$].

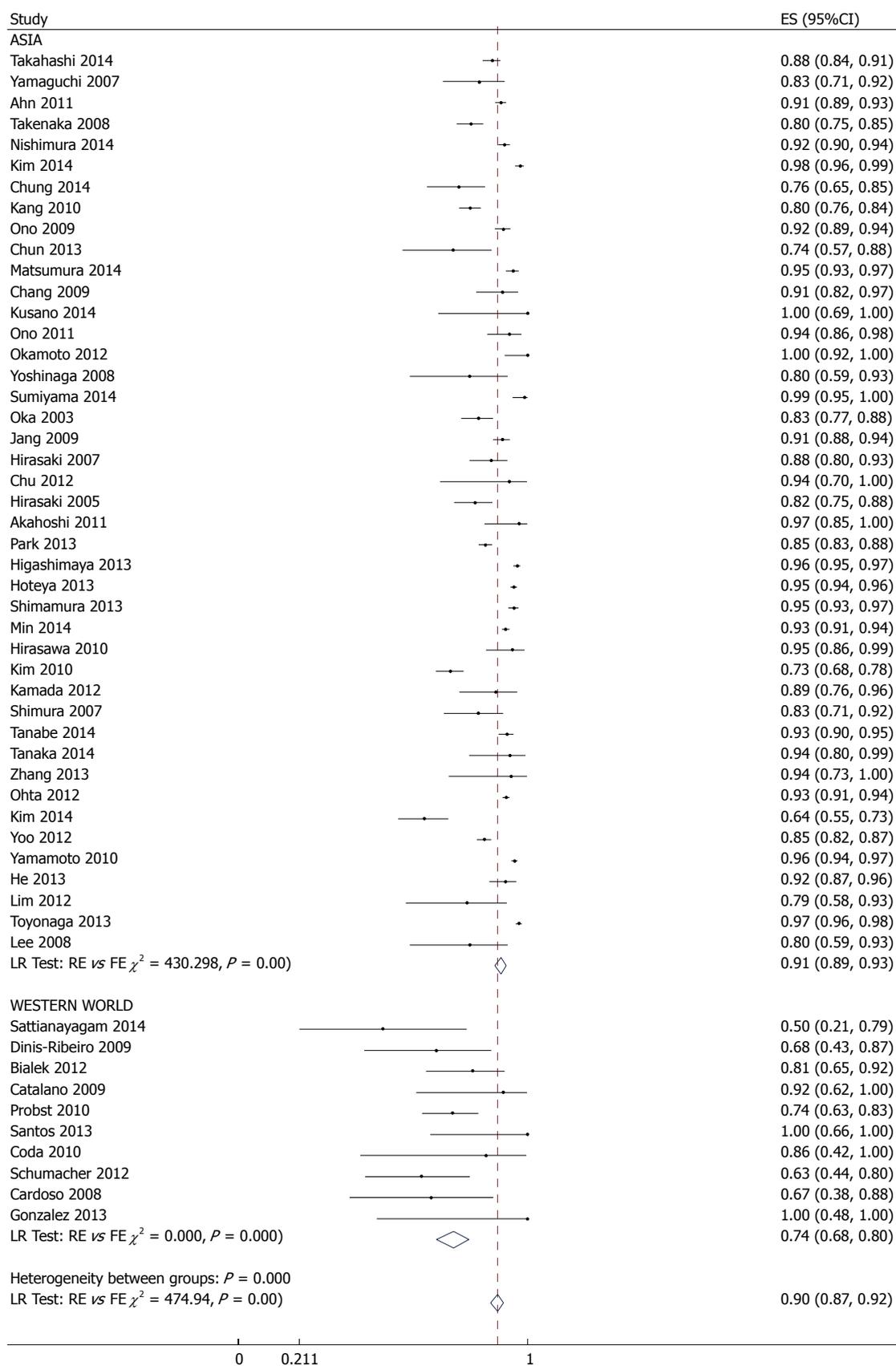


Figure 3 Meta-analysis of histologic *en bloc* resection rate in 53 studies involving 18017 tumors in 16472 patients that underwent gastric endoscopic submucosal dissection, stratified by region. Each dot and the horizontal line through them correspond to the point estimate and confidence interval from each study respectively while the center and width of the diamond corresponds to the pooled estimate and its confidence interval respectively. Even though weighting (not shown) was done, it is not explicit because an iterative procedure was used in parameter estimation. ES: Estimate.

Table 2 Characteristics of studies included in the meta-analysis of gastric endoscopic submucosal dissection

Ref.	Data period, yr	Country	Patients, n	Age, mean (range), yr	Female, %	Tumor, n	Tumor size, mean (range), mm	Procedure length, mean (range), min
Sattianayagam <i>et al</i> ^[21]	2008-2012	Australia	10	75 (43-86)	NA	12	35 (15-65)	NA
Cardoso <i>et al</i> ^[22]	2005-2007	Brazil	12	71.2 (27-91)	50	15	16.8 (8-20)	140
Chaves <i>et al</i> ^[23]	2007-2009	Brazil	15	67.1 (32-81)	20	16	16.2 (6-35)	85 (20-150)
Santos <i>et al</i> ^[24]	2010-2011	Brazil	9	65 (58-73)	0	9	28.6 (20-45)	103 (60-240)
Xu <i>et al</i> ^[25]	2006-2009	China	120	51.5 (26-75)	40	120	18.8 (8-30)	64.6 (30-120)
He <i>et al</i> ^[26]	2008-2012	China	144	55.8 (18-78)	72	145	15.14	63.4 (20-180)
Zhang <i>et al</i> ^[27]	2008-2011	China	18	65.3 (30-71)	61	18	26 (10-35)	90 (50-120)
Probst <i>et al</i> ^[28]	2003-2010	Germany	83	68.6 (41-87)	40	91	NA	142 (60-420)
Schumacher <i>et al</i> ^[29]	2008-2010	Germany	30	61 (35-93)	43	30	25 (20-70)	74 (15-402)
Catalano <i>et al</i> ^[30]	2005-2007	Italy	12	68 (38-83)	100	12	NA	111 (62-150)
Coda <i>et al</i> ^[31]	2007-2009	Italy	7	72 (61-83)	43	7	26 (15-50)	123 (50-360)
Hirasaki <i>et al</i> ^[32]	2000-2004	Japan	144	70 (45-91)	NA	144	13	73
Yokoi <i>et al</i> ^[33]	1999-2003	Japan	46	67 (45-89)	9	46	NA	NA
Ono <i>et al</i> ^[34]	2000-2007	Japan	408	67	NA	444	NA	NA
Hirasawa <i>et al</i> ^[35]	2000-2009	Japan	58	69.3	21	58	20.3 (3-50)	82 (22-275)
Yoshinaga <i>et al</i> ^[36]	2001-2006	Japan	24	61.7 (37-85)	8	25	16.5 (3-60)	NA
Takenaka <i>et al</i> ^[37]	2001-2005	Japan	275	NA	NA	306	NA	NA
Miyahara <i>et al</i> ^[38]	2001-2010	Japan	1082	71.7 (36-92)	29	1190	NA	99.8 (10-675)
Ohnita <i>et al</i> ^[39]	2001-2010	Japan	1209	72 (33-95)	27	1322	NA	NA
Oka <i>et al</i> ^[40]	2002-2004	Japan	185	NA	NA	195	19.4 (5-100)	84.4
Shimura <i>et al</i> ^[41]	2002-2005	Japan	55	71.4 (46-91)	22	59	15.5	58 (7-640)
Hirasaki <i>et al</i> ^[42]	2002-2006	Japan	112	70 (45-89)	NA	112	19	69
Ohta <i>et al</i> ^[43]	2002-2010	Japan	1500	NA	NA	1795	NA	NA
Kamada <i>et al</i> ^[44]	2002-2010	Japan	46	65.5 (29-90)	48	46	NA	NA
Toyonaga <i>et al</i> ^[45]	2002-2007	Japan	821	71 (31-93)	34	1136	13 (1-105)	NA
Kosaka <i>et al</i> ^[46]	2002-2007	Japan	438	69.4	26	438	14.6	47 (8-345)
Yamaguchi <i>et al</i> ^[47]	2003-2005	Japan	54	NA	NA	54	19.1 (30-70)	129 (29-440)
¹ Akasaka <i>et al</i> ^[48]	2003-2008	Japan	1188	71	27	1188	20 (2-105)	90 (6-750)
Ono <i>et al</i> ^[49]	2003-2011	Japan	80	69.6	20	80	NA	83.7
¹ Toyokawa <i>et al</i> ^[50]	2003-2010	Japan	967	NA	32	1123	18	98
Tanabe <i>et al</i> ^[51]	2003-2007	Japan	421	69 (41-91)	23	421	NA	67 (7-360)
Shimamura <i>et al</i> ^[52]	2004-2012	Japan	521	NA	NA	616	NA	NA
Takahashi <i>et al</i> ^[53]	2004-2013	Japan	459	71.4	25	459	17.2	NA
Yamamoto <i>et al</i> ^[54]	2005-2011	Japan	1430	69.6	28	1520	15.3	101
Higashimaya <i>et al</i> ^[55]	2005-2011	Japan	891	69.1	27	1027	18.3	NA
Hoteya <i>et al</i> ^[56]	2005-2010	Japan	1224	68	24	1463	21	89
Matsumura <i>et al</i> ^[57]	2005-2014	Japan	413	72.1	30	425	18.4	NA
Sohara <i>et al</i> ^[58]	2006-2011	Japan	681	70.9 (45-91)	40	850	20.8 (2-150)	42 (4-360)
¹ Nishimura <i>et al</i> ^[59]	2006-2012	Japan	669	71	27	750	NA	NA
Tsuji <i>et al</i> ^[60]	2007-2009	Japan	328	68	29	398	43	69
Akahoshi <i>et al</i> ^[61]	2007-2009	Japan	35	72 (52-85)	34	35	15.6	104 (33-264)
Mukai <i>et al</i> ^[62]	2007-2010	Japan	142	72.4	32	161	NA	81
Tanaka <i>et al</i> ^[63]	2008-2011	Japan	32	71 (56-84)	63	33	17 (4-67)	111 (23-399)
Okamoto <i>et al</i> ^[64]	2009-2010	Japan	45	69 (49-83)	29	45	14 (10-35)	80
Watari <i>et al</i> ^[65]	2010-2012	Japan	94	70.9 (48-87)	24	98	NA	NA
Sumiyama <i>et al</i> ^[66]	2010-2012	Japan	100	NA	18	105	18 (3-53)	34 (4-151)
Kusano <i>et al</i> ^[67]	2011-2012	Japan	10	69.2	20	10	16.3	130.5
Kawamura <i>et al</i> ^[68]	NA	Japan	4	NA	25	4	24 (14-36)	50.5 (28-72)
Lee <i>et al</i> ^[69]	2003-2008	South Korea	461	62	30	487	NA	NA
Kim <i>et al</i> ^[70]	2003-2006	South Korea	337	NA	23	337	16	49
¹ Shin <i>et al</i> ^[71]	2003-2010	South Korea	1105	65 (27-87)	32	1105	NA	NA
Jang <i>et al</i> ^[72]	2004-2007	South Korea	402	60 (34-84)	37	402	NA	NA
Kim <i>et al</i> ^[73]	2004-2007	South Korea	142	62	34	142	NA	NA
Kang <i>et al</i> ^[74]	2005-2008	South Korea	456	62.4	23	456	20.6	NA
Goh <i>et al</i> ^[75]	2005-2009	South Korea	210	NA	NA	210	NA	NA
Ahn <i>et al</i> ^[76]	2005-2008	South Korea	889	62.8	23	916	21.5	37.5
Yoo <i>et al</i> ^[77]	2005-2010	South Korea	729	64 (55-70)	26	823	18 (12-25)	52 (33-84)
Lim <i>et al</i> ^[78]	2005-2011	South Korea	24	63 (56-75)	21	24	16 (4-52)	42 (16-103)
Park <i>et al</i> ^[79]	2005-2011	South Korea	916	62	73	931	NA	NA
Chung <i>et al</i> ^[80]	2005-2010	South Korea	76	61.1	42	76	NA	NA
Kim <i>et al</i> ^[81]	2007-2012	South Korea	126	55 (28-85)	44	126	12 (1-50)	NA
Min <i>et al</i> ^[82]	2007-2011	South Korea	1527	63 (27-87)	21	1577	16 (1-110)	NA
Kim <i>et al</i> ^[83]	2008-2010	South Korea	440	64	29	450	19	48
Yoon <i>et al</i> ^[84]	2008-2010	South Korea	1319	63	34	1443	15.7	61.8
Choi <i>et al</i> ^[85]	2008-2012	South Korea	616	NA	26	616	12.9	27.7
Chun <i>et al</i> ^[86]	2009-2012	South Korea	35	54.15	NA	35	18	32.3 (7-84)

¹ Chung <i>et al</i> ^[87]	2010-2012	South Korea	76	64	36	76	NA	44
Kim <i>et al</i> ^[88]	2012-2013	South Korea	446	NA	34	446	NA	NA
Bialek <i>et al</i> ^[89]	2007-2010	Poland	37	63 (24-86)	62	37	25 (10-60)	NA
Dinis-Ribeiro <i>et al</i> ^[90]	2005-2008	Portugal	19	74	NA	19	NA	90 (40-300)
Lee <i>et al</i> ^[91]	2004-2006	Taiwan	25	69 (36-82)	44	25	19	NA
¹ Chang <i>et al</i> ^[92]	2004-2007	Taiwan	70	66.5 (35-84)	36	70	18.5 (8-40)	92.4 (25-210)
Chu <i>et al</i> ^[93]	2009-2011	Taiwan	16	51.9 (35-65)	63	16	26.1 (20-42)	52 (30-120)
González <i>et al</i> ^[94]	NA	Uruguay	5	NA	NA	5	25.2	85 (30-180)

¹Multicenter studies. NA: Not available.

Table 3 Rates of adverse outcomes in patients undergoing gastric endoscopic submucosal dissection between 1998 and 2014

Adverse outcomes	Studies, <i>n</i>	Patients, <i>n</i>	Tumor, <i>n</i>	Rate (95%CI), % ¹
Immediate ²				
Perforation ³	66	24855	27118	2.7 (2.1, 3.3)
Major bleeding ⁴	19	3815	3943	2.9 (1.3, 6.6)
Delayed ⁵				
Perforation	13	2570	2852	0.39 (0.06, 2.4)
Major bleeding ⁶	63	21612	23338	3.6 (3.1, 4.3)
Recurrence ⁷				
Among tumors with R0	17	-	2027	0.02 (0.001, 1.4)
Among tumors without R0	13	-	203	7.7 (3.6, 16)
Irrespective of R0 status ⁸	33	11256	12398	0.75 (0.42, 1.3)

¹The rates are calculated as a percentage of the total number of tumors operated; ²Immediate refers to adverse outcomes occurring within 24 h of the procedure; ³The rate (95%CI) of immediate perforation was significantly lower with epithelial [2.7% (2.2%-3.6%)] compared with subepithelial tumors [8.9% (2.7%-15%)] ($P = 0.02$) and declined by 0.29% (0.05%-0.54%) per year over the duration of study ($P = 0.02$); ⁴The rate (95%CI) of major immediate bleeding declined by 2.3% (0.72%-3.9%) per year over the duration of study ($P = 0.007$); ⁵Delayed refers to adverse outcome occurring 24 h after the procedure; ⁶The rate (95%CI) of delayed bleeding increases by 1.3% (0.07%-2.5%) for every 10 year increase in age; ⁷Average follow-up was 26, 28 and 32 mo for assessment of recurrence among tumors with R0, without R0, and irrespective of R0 status respectively; ⁸The rate (95%CI) of recurrence decreases by 0.4% (0.1%-0.7%) for every 10 year increase in age ($P = 0.01$) and there was a trend towards higher rate in Western countries [5.1% (0.5%-11%)] compared with Asia [0.5% (0.3%-0.6%)] ($P = 0.06$). R0: Histologically-confirmed *en bloc* resection.

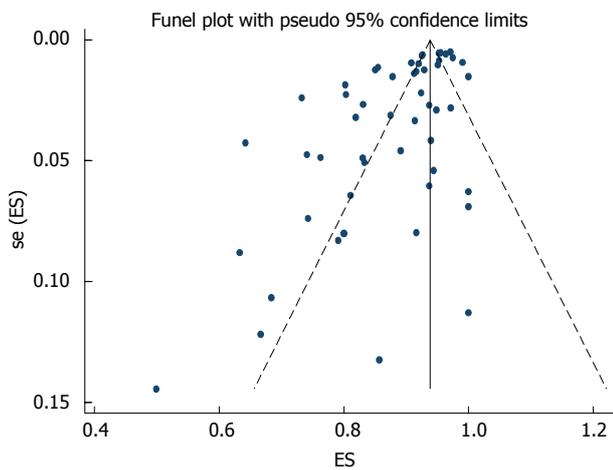


Figure 4 Funnel plot of histologically confirmed *en bloc* (R0) resection rate in 53 studies involving 18017 tumors in 16472 patients that underwent gastric endoscopic submucosal dissection. Each dot represents the R0 resection rate. Asymmetry in the distribution of study estimates around the center of the funnel suggests a potential publication bias. P value for egger's test < 0.001. ES: Estimate; se (ES): Standard error of estimate.

Our estimates were generally comparable to those of subgroup analysis restricting to studies reporting outcomes exclusively among patients with cancer although with slightly higher risk of recurrence (Table 4).

DISCUSSION

Our meta-analysis showed that, across multiple studies in 11 countries, ESD demonstrated an excellent treatment success in patients with gastric tumors. Perioperatively, perforation and major bleeding were the most commonly reported serious adverse outcomes but their risk is modest. In addition, the risk of tumor recurrence in patients with treatment success after a moderate duration of follow-up is very low. These findings provide evidence that ESD is effective and offers a reasonable safety profile across a wide range of patients.

Treatment success was assessed in three ways: R0, endoscopic *en bloc* and curative resection rates. In this study, we considered R0 resection as primary endpoint. Across studies, there were excellent results based on this endpoint. However, there was significant heterogeneity in study estimates that was partly explained by two main factors: First, the estimates vary by region, with higher rates of clinical success being reported by studies from Asia compared to the western world. This, in a way, was expected since the procedure was developed in Asia and has been used for a long time in this part of the world allowing for the development of expert skill needed for the procedure

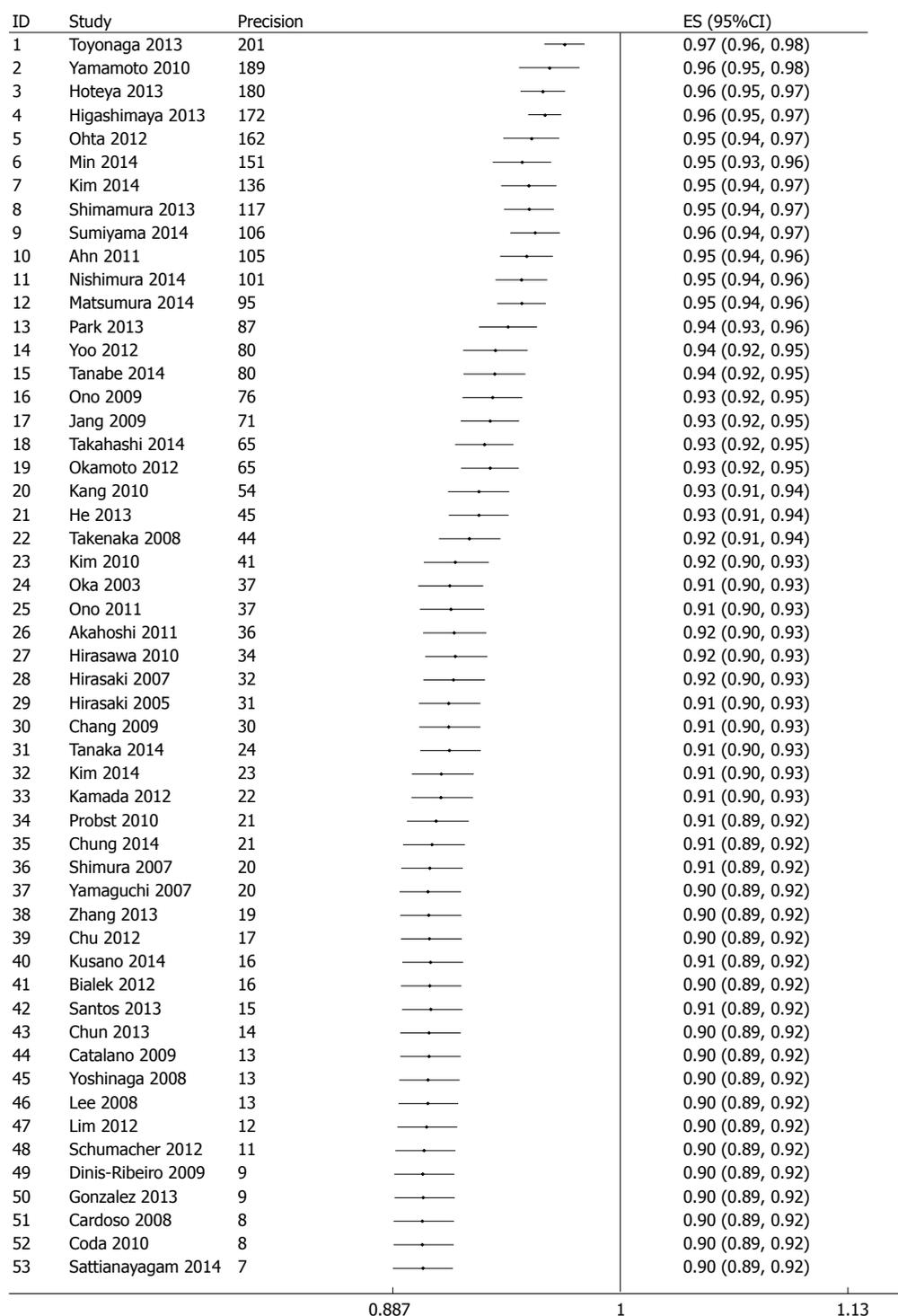


Figure 5 Evaluation of potential publication bias via a cumulative meta-analysis plotted as a function of study precision. The dots and the error bars correspond to the cumulative estimates and associated 95%CI respectively. After sorting by precision (calculated as inverse of standard error) from most precise to least precise study, a variance - weighted method was used to obtain cumulative meta-analysis estimates by adding one study at a time. Analysis begins with the most precise study; thereafter, effect estimate from the next study in order of decreasing precision are added at each step in the analysis and cumulative estimate and 95%CI is recalculated until the least precise study is added.

as well as development of better techniques. On the other hand, experience in the procedure had been low in other parts of the world. Second, lower rates of treatment success were reported in the smaller studies compared to the large ones. Since the number of tumor operated is expected to correlate with level of expertise,

we presume this is an indicator of better outcome with increasing level of expertise or experience.

Perioperatively, major bleeding and perforation were the most common serious adverse events. However, most of these adverse events were successfully managed endoscopically with only very few ones requiring surgical

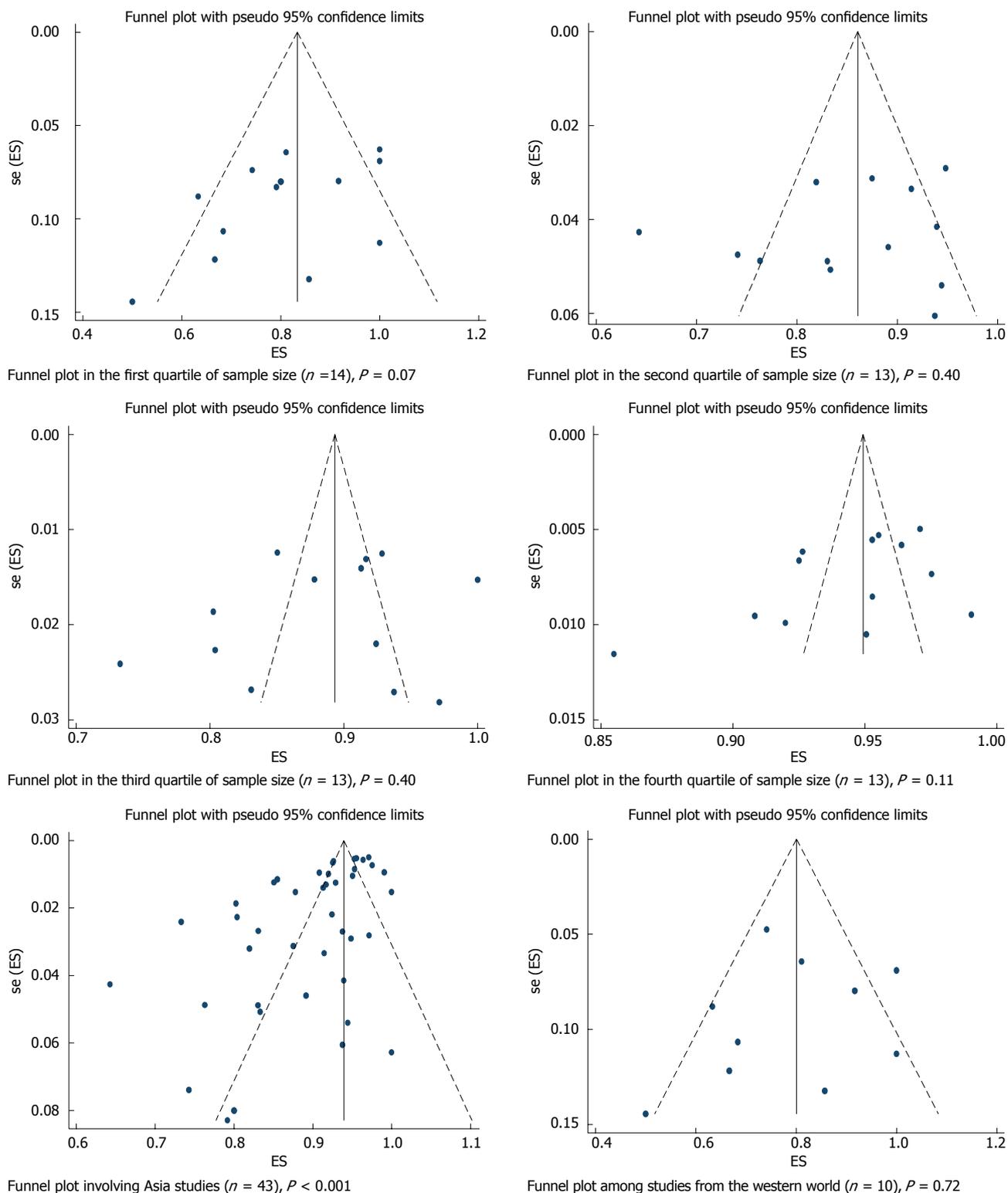


Figure 6 Funnel plot of histologically confirmed *en bloc* (R0) resection rate in 53 studies involving 18017 tumors in 16472 patients that underwent gastric endoscopic submucosal dissection, stratified based on sources of heterogeneity. Each dot represents the R0 resection rate. Lack of asymmetry in the funnel plot within quartile of study precision (calculated as inverse of standard error) indicates that the asymmetry in the overall plot (Figure 4) is most likely due to true heterogeneity by sample size rather than a publication bias. P values were calculated based on Egger's test. ES: Estimate; se (ES): Standard error of estimate.

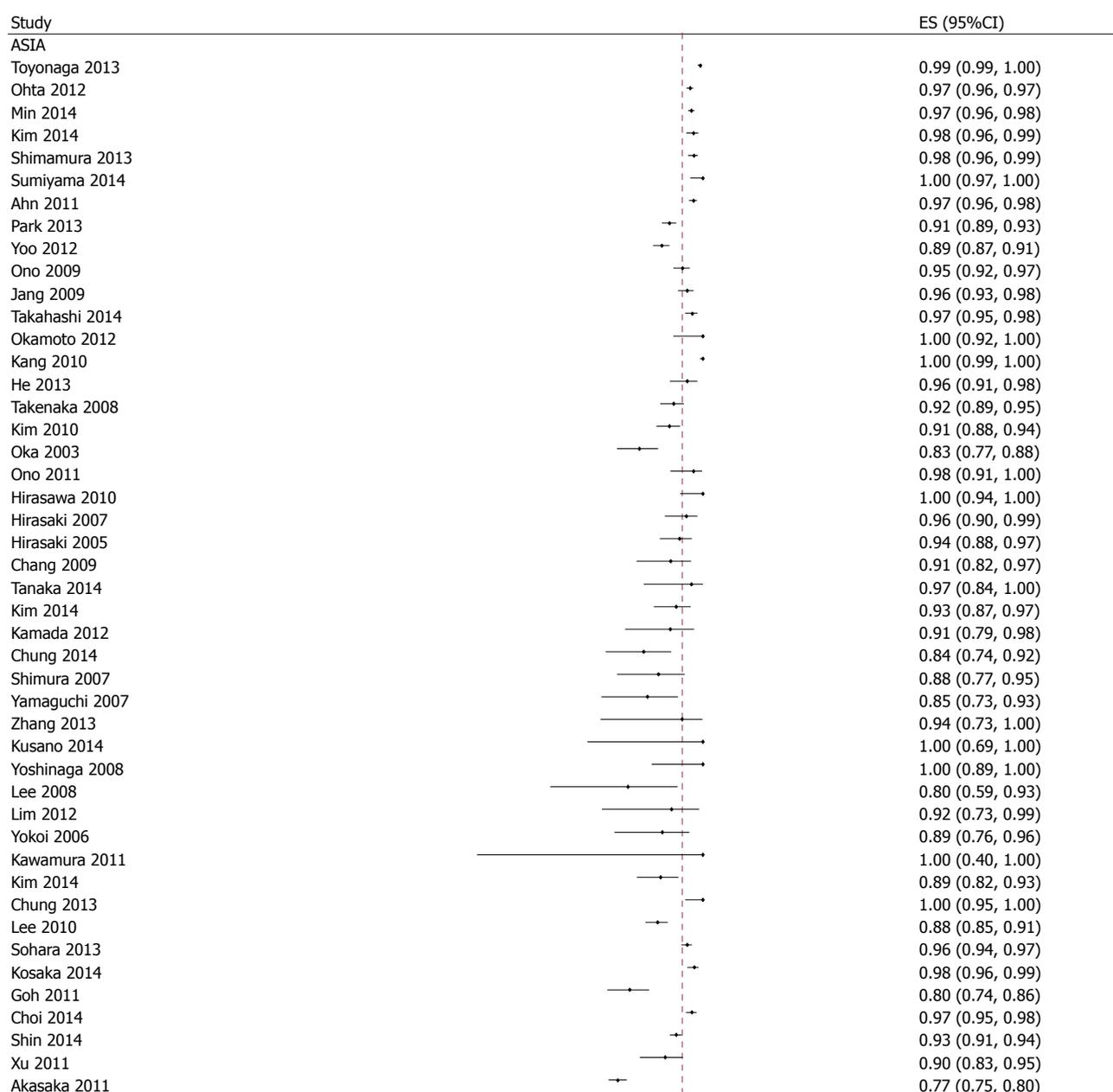
intervention. The relatively low risk of recurrence has been the attractive feature of ESD. After a moderate follow up, tumor recurrence was present in only 8 in 1000 tumors after the procedure, and this rate was

majorly influenced by those without R0 resection, *i.e.*, patients with positive lateral or vertical tumor margins. In patients with R0 resection, the risk of recurrence is negligible: 2 in 10000 tumors. Overall, our estimates

Table 4 Clinical outcomes among patients with gastric cancers who underwent endoscopic submucosal dissection

Outcomes	Studies, <i>n</i>	Tumor, <i>n</i>	Rate (95%CI) ¹
Efficacy measures			
R0 resection	24	8520	87 (84-90)
Endoscopic <i>en bloc</i> resection	29	9652	94 (91-96)
Curative resection	10	5234	83 (80-86)
Safety measures			
Immediate perforation ²	31	12076	3.1 (2.4-3.9)
Immediate major bleeding ²	6	303	2.9 (0.24-27)
Delayed perforation ³	6	1486	0.15 (0.01-3.8)
Delayed bleeding ³	29	11925	3.8 (3.0-4.7)
Recurrence (if R0) ⁴	8	724	0.14 (0.004-4.6)
Recurrence (if not R0) ⁴	7	152	8.5 (3.6-19)
Recurrence (irrespective of R0 status) ⁴	18	7681	0.77 (0.39-1.5)

¹The rates are calculated as a percentage of the total number of tumors operated; ²Immediate refers to adverse outcomes occurring within 24 h of the procedure; ³Delayed refers to adverse outcome occurring 24 h after the procedure; ⁴Average follow-up was about 26, 24 and 37 mo for assessment of recurrence among tumors with R0, without R0, and irrespective of R0 status respectively. R0: Histologically-confirmed *en bloc* resection.



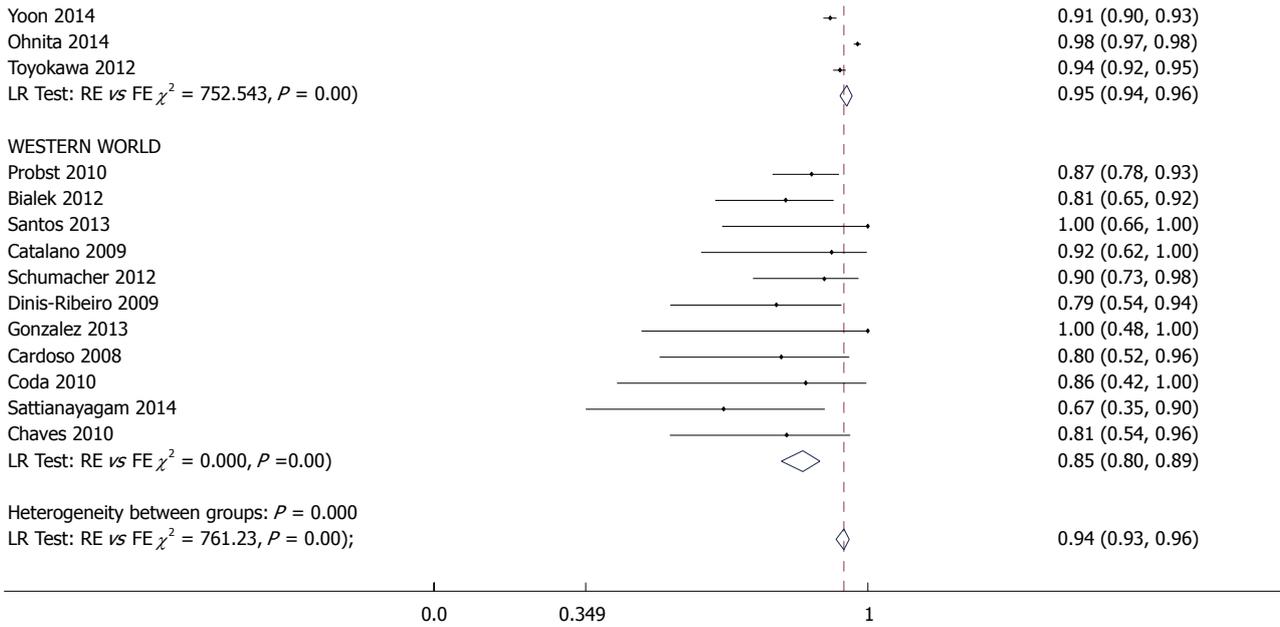


Figure 7 Meta-analysis of endoscopic *en bloc* resection rate in 60 studies involving 21511 tumors in 19935 patients that underwent gastric endoscopic submucosal dissection, stratified by region. Each dot and the horizontal line through them correspond to the point estimate and confidence interval from each study respectively while the center and width of the diamond corresponds to the pooled estimate and its confidence interval respectively. Even though weighting (not shown) was done, it is not explicit because an iterative procedure was used in parameter estimation. ES: Estimate.

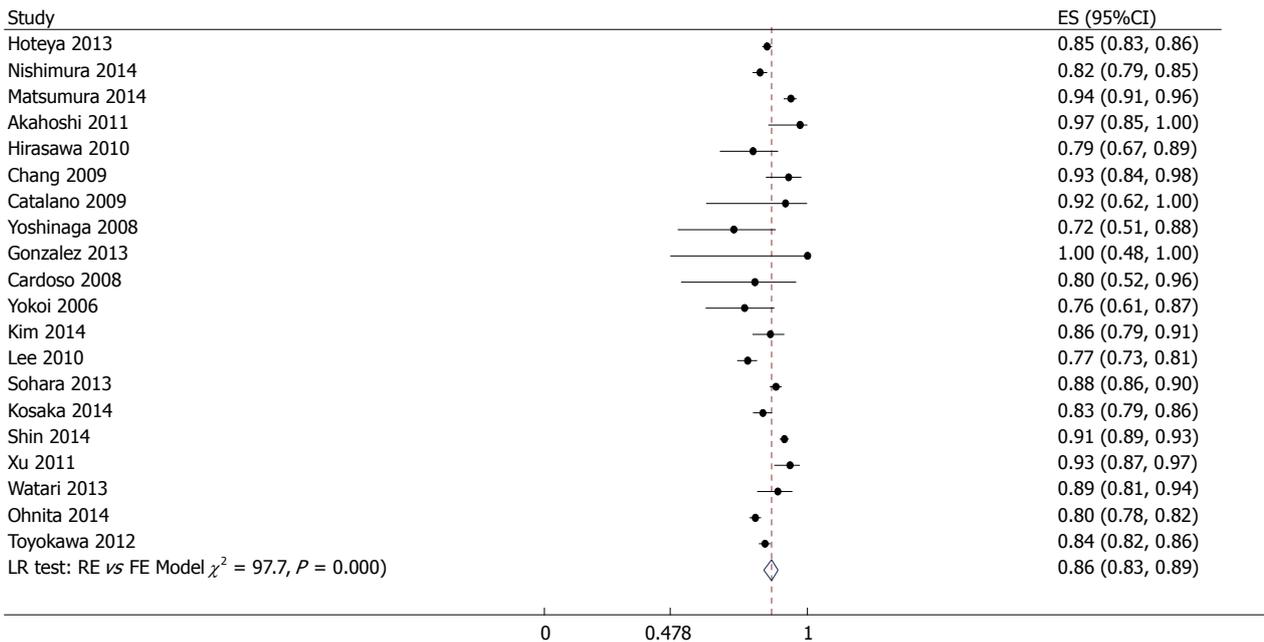


Figure 8 Meta-analysis of curative resection rate in 20 studies involving 8589 tumors in 7785 patients that underwent gastric endoscopic submucosal dissection. Each dot and the horizontal line through them correspond to the point estimate and confidence interval from each study respectively while the center and width of the diamond corresponds to the pooled estimate and its confidence interval respectively. Even though weighting (not shown) was done, it is not explicit because an iterative procedure was used in parameter estimation. All studies except one (Emura 2014, Colombia) were from Asia. ES: Estimate.

were comparable to those of subgroup analysis involving studies exclusively among patients with cancer, although with slightly higher risk of recurrence in this subgroup.

Before the invention of ESD in the late 1990s in Japan, EMR was the most widely used minimally invasive option for non-invasive gastric tumors in the world; and it's still the most widely used in many Western countries.

However, the superior benefit of ESD in terms of complete resection and tumor recurrence as compared to EMR had been demonstrated in a few meta-analysis^[13-15]. Although the risk of bleeding and perforation tends to be higher with ESD, most cases of such adverse event were amenable to endoscopic management; thus, making the benefit to outweigh the risk^[16]. Absolute indications for

endoscopic resection had included moderately or well-differentiated elevated cancers ≤ 20 mm in diameter; and small (≤ 10 mm), flat and depressed lesions without ulceration or scarring. In addition, these lesions must be intra-mucosal and with no lymphovascular involvement. However, the success of ESD has led to the extension of this criteria to include intra-mucosal cancer without ulceration > 20 mm or with ulcerations ≤ 30 mm, and upper submucosal cancer ≤ 30 mm. Overall, ESD remains the best endoscopic option for cancers ≥ 20 mm while EMR is an option for those < 20 mm. Endoscopic resection is however not indicated in tumors with poorly differentiated component or signet ring cell^[17]. Furthermore, the proficiency of the ESD procedure takes some time to acquire as prior studies have suggested that it takes at least 30 procedures for a beginner to overcome the learning curve^[18,19].

Our study has several strengths. Notably, a guideline-driven approach ensures that our analysis was systematic and comprehensive. In addition, we made attempt to gather all available data by placing no restriction on language, date of publication, location, *etc.* Our moderately large number of studies enabled us to shed more light on potential sources of heterogeneity in clinical outcomes after ESD.

Limitations of this study should also be considered. First, due to rapidly evolving techniques in ESD procedures, the rates of each outcome may vary slightly by technique and our rates of adverse outcomes might have been over-estimated compared to new technique. This is particularly apparent with the finding of declining rates of immediate perforation and bleeding over the study period. Second, the recurrence rates were assessed after variable follow-up between and within study, and since the rate of recurrence is time-dependent, cautious interpretation of average follow-up reported is warranted when applied to individual cases. Third, there was significant asymmetry in the funnel plot of histologic *en bloc* resection rate indicating potential selective reporting of outcomes by authors. However, further exploration with cumulative meta-analysis indicates that this asymmetry is not likely due to publication bias since lower estimates were reported in the low precision studies^[20]. Rather, we presume that the asymmetry is probably due to chance or better expertise among the high precision studies since precision is proportional to the number of tumors operated, which in turn is expected to correlate with level of expertise. In addition, we mitigated against publication bias in our methodology by placing no restriction on publication language and excluding all overlapping studies^[20].

In conclusion, gastric ESD is a safe and effective technique based on the large and broad body of current medical literature. It compares favorably with EMR and warrants consideration as first-line therapy when an expert operator is available.

COMMENTS

Background

Advances in endoscopic techniques have led to the development of endoscopic

submucosal dissection (ESD) for *en-bloc* resection of gastrointestinal tumors. The authors systematically reviewed the medical literature to evaluate the safety and efficacy of gastric ESD.

Research frontiers

Accumulating evidence from Asia suggests that ESD is safe and more effective than other minimally invasive alternative such as endoscopic mucosal resection. However, the procedure is still not popular in the West and the available results (even from Asia) are mixed. The authors therefore performed a systematic review and meta-analysis to analyze available evidence and explore for potential sources of heterogeneity.

Innovations and breakthroughs

This meta-analysis represents the largest assessment of gastric ESD to date. The authors were able to show that gastric ESD is safe and effective when an expert operator is available. More importantly, they were also able to explore for sources of heterogeneity among the available results in the literature.

Applications

The authors believe that with proper training in the techniques of gastric ESD, this procedure can become the first line therapy for gastric tumor in Western countries.

Terminology

ESD is an advanced endoscopic technique used to remove gastrointestinal tumors. The procedure involves passage of endoscopic tube through the throat in order to assess the tumor in the stomach. Thereafter, the tumor dissection is performed by injecting fluid below the lesion at the submucosal layer in order to elevate the tumor. The procedure is completed by dissecting through the surrounding mucosa to the submucosal layer beneath the tumor. Meta-analysis is a statistical method used to combine results from multiple similar studies in order to achieve a greater statistical power and evaluate for potential sources of heterogeneity.

Peer-review

The article is very interesting and well written. The number of studies and patients included is also very satisfactory.

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