Colorectal endoscopic submucosal dissection: a systematic review and meta-analysis

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Background and study aims: Endoscopic submucosal dissection (ESD) is an advanced endoscopic technique that allows en-bloc resection of gastrointestinal tumor. We systematically review the medical literature in order to evaluate the safety and efficacy of colorectal ESD.

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

Results: Included in this study were 13833 tumors in 13603 patients (42 % female) who underwent colorectal ESD between 1998 and 2014. The R0 resection rate was 83 % (95 % CI, 80 – 86 %) with significant between-study heterogeneity ($P<0.001$) which was partly explained by difference in continent ($P=0.004$), study design ($P=0.04$), duration of the procedure ($P=0.009$), and, marginally, by average tumor size ($P=0.09$). Endoscopic en bloc and curative resection rates were 92 % (95 % CI, 90 – 94 %) and 86 % (95 % CI, 80 – 90 %), respectively. The rates of immediate and delayed perforation were 4.2 % (95 % CI, 3.5 – 5.0 %) and 0.22 % (95 % CI, 0.11 – 0.46 %), respectively, while rates of immediate and delayed major bleeding were 0.75 % (95 % CI, 0.31 – 1.8 %) and 2.1 % (95 % CI, 1.6 – 2.6 %). After an average postoperative follow up of 19 months, the rate of tumor recurrence was 0.04 % (95 % CI, 0.01 – 0.31) among those with R0 resection and 3.6 % (95 % CI, 1.4 – 8.8 %) among those without R0 resection. Overall, irrespective of the resection status, recurrence rate was 1.0 % (95 % CI, 0.42 – 2.1 %).

Conclusions: Our meta-analysis, the largest and most comprehensive assessment of colorectal ESD to date, showed that colorectal ESD is safe and effective for colorectal tumors and warrants consideration as first-line therapy when an expert operator is available.

Introduction

Endoscopic submucosal dissection (ESD) is an advanced endoscopic technique that allows complete resection of early-state lesions in the gastrointestinal tract with the aim to achieve accurate histological diagnosis and prevent tumor recurrence [1]. Initially developed for gastric tumors, the procedure has become widely used as standard of care for resection of colorectal tumors in Asian countries (notably in Japan). The main steps involved in the procedure include injecting fluid into the submucosa to elevate the tumor; cutting through surrounding mucosa to gain access into the submucosa layer; and dissecting the submucosa beneath the tumor to enhance complete resection [2]. Given the relatively burdensome maneuverability of the colon in addition to its thin wall, colorectal ESD is associated with greater technical difficulty, increase procedure time and potential high risk of perforation [3]. These concerns have led to the procedure being adopted more slowly in western countries than foregut ESD. Endoscopic mucosal resection (EMR) is the most widely used minimally invasive technique for noninvasive colorectal tumors in the western world. However, accumulating evidence suggests that with adequate training, ESD could be equally as safe as the other minimally invasive alternative in addition to offering superior efficacy and lower rate of tumor recurrence [2,4]. Nevertheless, these reports from several clinical trials and observational studies have yielded mixed results. In order to summarize the literature and assess for potential sources of heterogeneity, we conducted a systematic review and meta-analysis of available literature on the safety and efficacy of colorectal ESD.

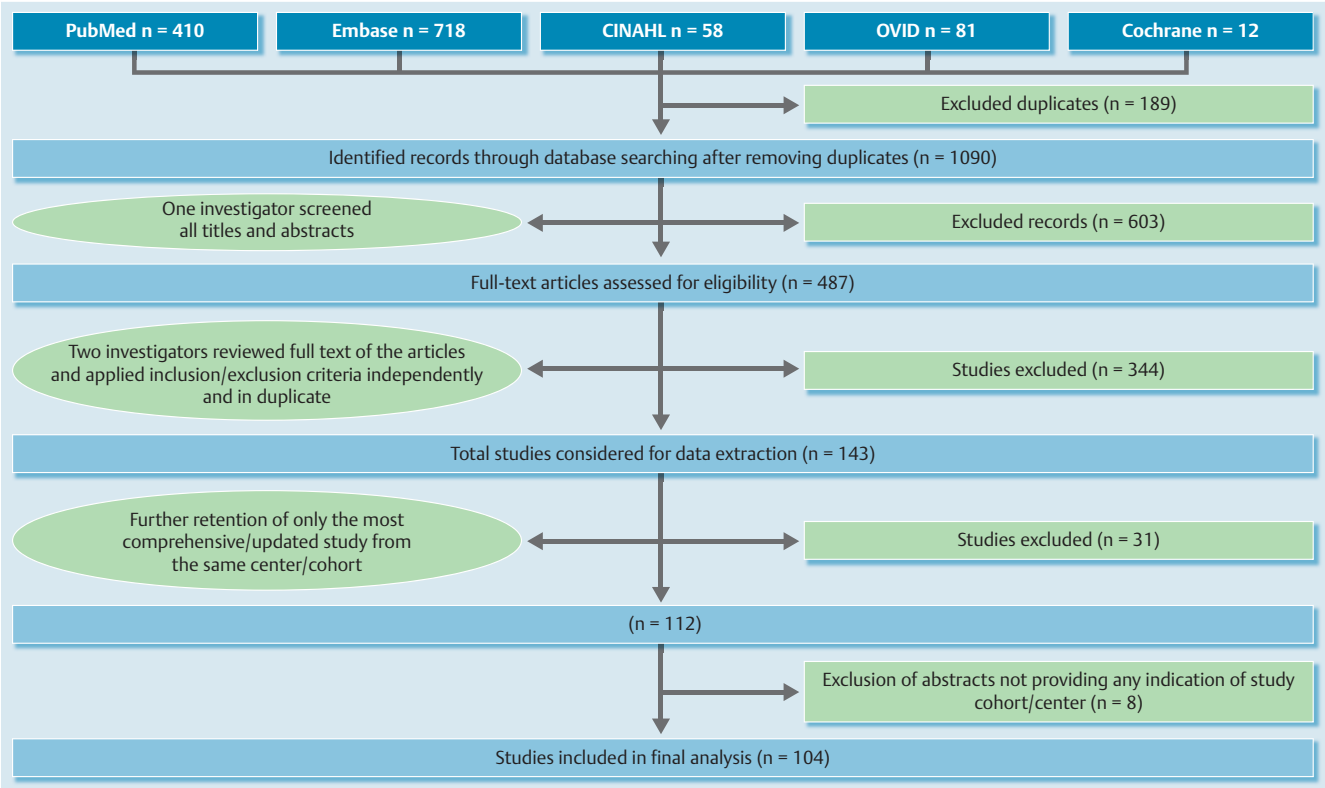

Fig. 1 Screening and selection process.

Patients and methods

We followed the recommendations of the Meta-analysis of Observational Studies in Epidemiology (MOOSE) during all stages of the design, implementation, and reporting of this meta-analysis (Stroup 2000) [5].

Search strategy

We performed a comprehensive literature search of MEDLINE, EMBASE, 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 ("colon"[Mesh] OR "colorectal neoplasms"[Mesh] OR "colorectal"[tiab] OR colo*[tiab] OR "large bowel"[tiab] OR hindgut[tiab]). Similar search terms were adapted for the other databases (**Table S1**).

Study selection

One investigator (EA) screened all titles and abstracts for relevance to our study. Two investigators (EA, NK) reviewed full text of these articles and applied our predefined inclusion/exclusion criteria independently and in duplicate (**Fig. 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 studies reporting clinical outcome(s) after colorectal ESD. Our exclusion criteria were: animal studies; case reports; commentaries or general reviews; or overlapping publications (based on study period) from the same center. However, review paper 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 overlapping 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. In the few cases where an abstract provided a more updated and comprehensive reporting of outcomes than the full-text journal article(s) from the same center, the abstract was selected for our main analysis. Articles in foreign language were translated via Google translator and, when possible, a native speaker of the foreign language was solicited to double-check the data.

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, type of publication (e.g. abstract, journal); characteristics of study cohort such as country, name of medical center, study design, number of patients, year of data collection, demographics, setting (single/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 procedure and number of failed procedure; and number of patients with clinical success and adverse outcomes.

Endpoints

We assessed both measures of efficacy and adverse outcomes associated with colorectal 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 verti-

cal margins. In addition, we evaluated endoscopic en bloc (i.e. 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 (< 1000 µm), and with no lymphovascular invasion or poorly differentiated component. Adverse outcomes included viscus perforation, major bleeding requiring intervention, and tumor recurrence. Immediate adverse outcomes refers to those occurring within 24 hours of the procedure while delayed refers to those occurring after 24 hours 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 chi-square statistic of the likelihood ratio test comparing the random effect model with its corresponding fixed effect model; and, for the efficacy measures, evaluation for potential sources of heterogeneity such as type of article , study design, setting, year of data collection (categorized based on start year into <2005, 2005 – 2009, ≥2010), continent, average age, sex distribution, number of tumors, average tumor size, histology (carcinoid vs non-carcinoid), 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. Since traditional method of funnel plot (log of estimate vs 1/standard error [1/SE]) has been shown to be an inaccurate method for assessing publication bias in meta-analysis of proportion, funnel plot was constructed using study size rather than 1/SE has proposed in the literature [6,7]. Due to huge difference in the outcome of ESD between Asian and Western countries, we performed a supplementary analysis of Asian and non-Asian studies separately.

In a sensitivity analysis, we limited our studies to full-text journal publications. The result from the sensitivity analysis was compared to that of the main analysis.

Analyses were performed using STATA (Version 13; StataCorp, College Station, TX), all tests were two-sided and significance level was set at 0.05.

Results

Of the 1090 citations retrieved through database searching, 603 were excluded because they reported no clinical outcome after ESD procedure in human (**Fig. 1**). Full text review was performed on 487 studies using our predefined inclusion and exclusion criteria, after which 112 studies were retained. In order to avoid potential study overlap, we additionally excluded 8 abstracts that provided no indication of the source of data such as country, state, city, or medical center. Overall, 104 articles including 58 full-text journal article and 46 abstracts published between 2007 and 2014 were retained for data synthesis. Seventy-five of these studies were from Asia while 29 were from the Western world.

A total of 13 833 tumors in 13 603 patients (42 % female) with average age 66 years (range: 25 – 92 years) underwent colorectal ESD between 1998 and 2014 (**Table S2**). The majority of these procedures were performed in Asian countries of Japan and South Korea with only a few experiences in the western world (**Fig. 2**). Average tumor size was 31 mm (range: 2 mm – 158 mm), and the procedure was completed in an average time of 75 min (range: 5 min – 600 min).

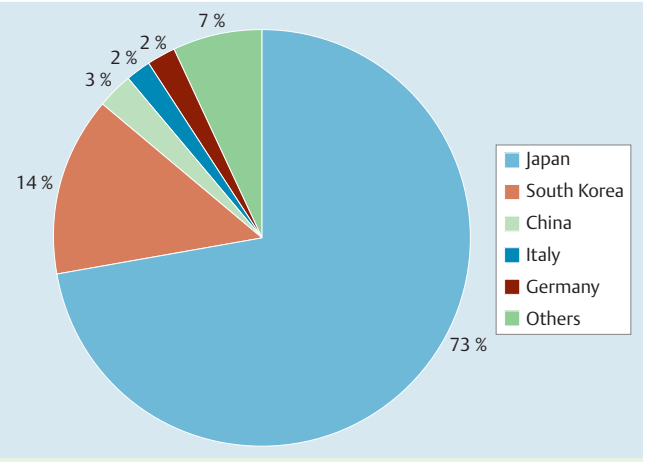

Fig. 2 Percentage distribution of 13 603 patients who underwent colorectal endoscopic submucosal dissection between 1998 and 2014 in 15 countries. Others include Taiwan, Australia, France, Poland, Sweden, Turkey, UK, Brazil, Colombia, and USA that contributed ≤ 1 % each.

Efficacy

R0 resection rate was reported in 60 studies across which meta-analysis yielded a pooled estimate of 83 % (95 % CI, 80 – 86 %) (**Fig. 3**). There was significant between-study heterogeneity (P < 0.001) which was partly explained by difference in continent (P = 0.004), study design (P = 0.04), and duration of the procedure (P = 0.009). In addition, there was a trend toward decreasing R0 with increasing tumor size but this did not reach statistical significance (P = 0.09) (**Table 1**). Subgroup analysis based on sources of heterogeneity showed that R0 resection rate was highest in Asia (87 % [95 % CI, 84 – 90 %] in Asia vs 71 % [95 % CI, 64 – 77 %] in the West) (**Table 3**), among retrospective studies, and decreases with increasing duration of the procedure. Assessment of funnel plot asymmetry based on egger's test also showed no significant publication bias (P = 0.57).

Endoscopic en bloc and curative resection rates were reported in 86 and 14 studies, respectively. Across studies, meta-analysis yielded a pooled estimate of 92 % (95 % CI, 90 – 94 %) (**Fig. S2**) for endoscopic en bloc resection rate and 86 % (95 % CI, 80 % – 90 %) (**Fig. S3**) for curative resection rate, although all but one of the studies reporting curative resection were from Asia. When we performed separate analysis for Asia vs Western countries, endoscopic en bloc resection rate was 94 % (95 % CI, 92 % – 95 %) and 82 % (95 % CI, 76 % – 87 %) for Asian and Western countries, respectively.

Adverse outcomes

Perforation and major bleeding requiring intervention were the most common perioperative complications reported (**Table 2**). Overall, immediate and delayed perforation rates were 4.2 % (95 % CI, 3.5 % – 5.0 %) and 0.22 % (95 % CI, 0.11 % – 0.46 %), respectively, while rates of immediate and delayed major bleeding were 0.75 % (95 % CI, 0.31 % – 1.8 %) and 2.1 % (95 % CI, 1.6 % – 2.6 %). When we performed separate analysis for Asia vs Western countries, immediate and delayed perforation rates were 3.8 % (95 % CI, 3.1 % – 4.6 %) and 0.18 % (95 % CI, 0.08 % – 0.42 %) for Asia and 6.6 % (95 %

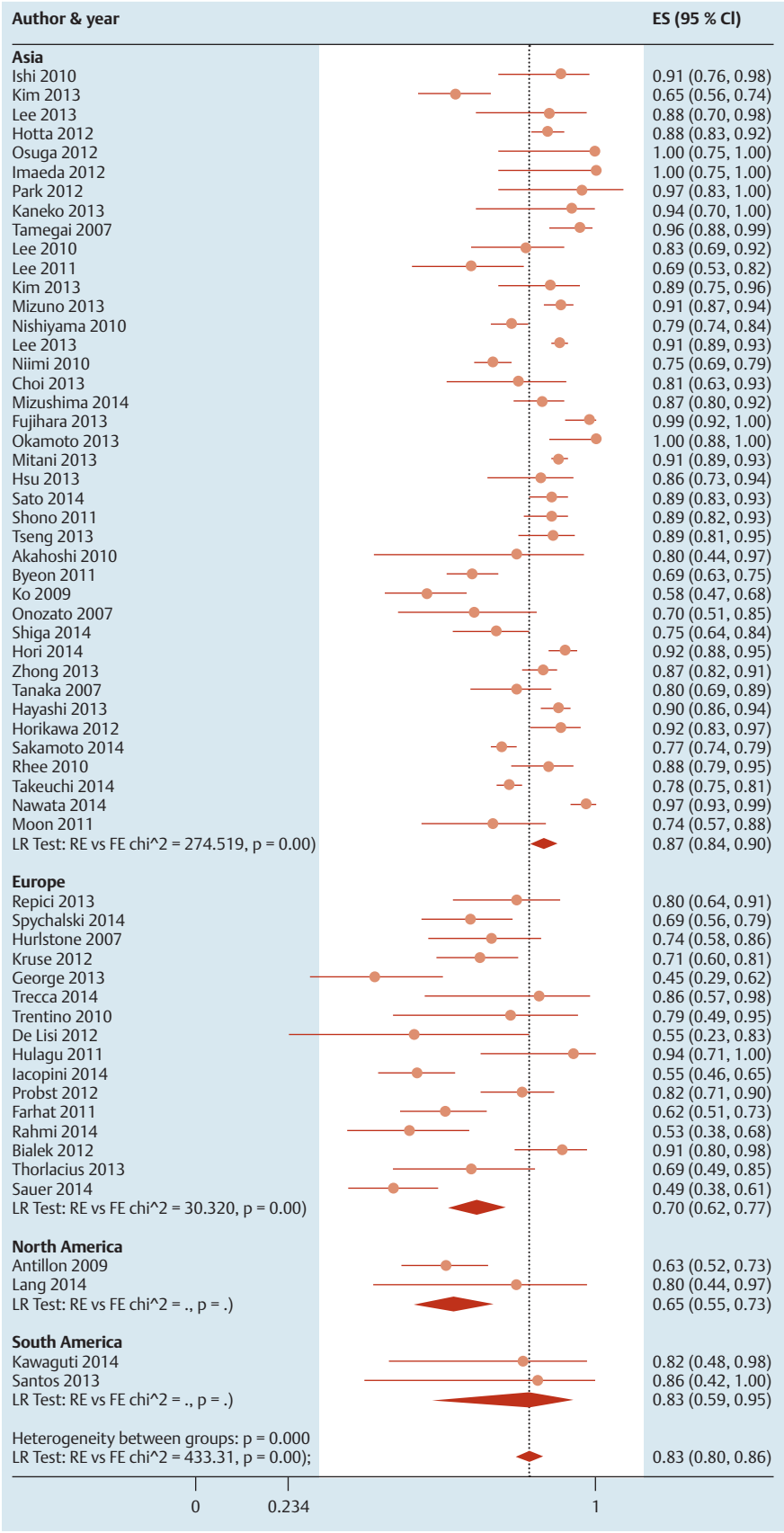

Fig. 3 Meta-analysis of histologic en bloc (R0) resection rate in 60 studies involving 8312 tumors in 8111 patients that underwent colorectal endoscopic submucosal dissection. Each dot and the horizontal line through them correspond to the point estimate and confidence interval from each study respectively while the center and width of the diamond corresponds to the pooled estimate and its confidence interval respectively. Both within continent and overall pooled estimates are presented. Even though weighting (not shown) was done, it is not explicit because an iterative procedure was used in parameter estimation. ES indicates estimate.

Variable	Studies, *n*	Tumors, *n*	R0 resection rate (95% CI), %	*P* value[1]
Type of article				0.23
Full-text journal	41	6006	84 (80, 87)	
Abstract	19	2306	81 (72, 87)	
Study design				0.04
Retrospective	36	6738	85 (81, 88)	
Prospective	7	531	75 (62, 85)	
Setting				0.11
Single center	49	6876	84 (80, 87)	
Multicenter	4	1079	73 (58, 83)	
Start year of data collection				0.31
<2005	14	1586	77 (70, 83)	
2005 – 2009	30	4835	85 (81, 88)	
≥2010	11	826	86 (71, 93)	
Continent				0.004
Asia	40	7392	87 (84, 90)	
Europe	16	806	70 (62, 77)	
South America (Brazil)	2	18	83 (59, 95)	
North America (USA)	2	96	65 (55, 73)	
Average age, years[2]				0.47
≤64	14	1798	84 (77, 88)	
65 – 67	14	3563	82 (77, 87)	
>67	14	1444	87 (78, 93)	
Female, %[2]				0.33
≤36	15	1613	84 (79, 88)	
37 – 43	14	2172	88 (81, 93)	
≥44	14	2066	80 (72, 86)	
Number of tumors[2]				0.71
<40	20	418	86 (78, 91)	
40 – 90	20	1291	80 (73, 86)	
>90	20	6603	84 (79, 88)	
Average tumor size, mm[2]				0.09
≤27	16	1844	85 (81, 89)	
28 – 34	16	2409	85 (78, 90)	
≥34	16	2061	80 (70, 88)	
Histology				
Carcinoid	7	221	85 (79, 89)	0.19
Non-carcinoid	48	5051	82 (78, 86)	
Length of the procedure, min§				0.009
≤61	15	2141	89 (84, 93)	
62 – 101	15	2954	84 (79, 88)	
>101	15	1564	78 (68, 85)	

Table 1 Potential sources of heterogeneity of histologic en bloc (R0) resection rate among 60 studies of patients that underwent colorectal endoscopic submucosal dissection.

N, number; R0, histologic en bloc resection rate

[1] Potential sources of heterogeneity was assessed with metaregression. $P<0.05$ indicates that the variable significantly explains part of the between study heterogeneity (i.e. an effect mofier). Differences in continent, lenth of the procedure, study design and average tumor size explains 18%, 15%, 8%, and 4% of the heterogeneity respectively.

[2] Indicates variables that were cut at tertiles in order to ensure comparability of number of studies between groups.

CI, 4.6% – 9.4%) and 1.2% (95%, 0.29% – 4.6%) for Western countries, respectively, while rates of immediate and delayed major bleeding were 0.39% (95% CI, 0.11% – 1.3%) and 1.8% (95% CI, 1.4% – 2.4%) for Asia and 3.3% (95% CI, 1.4% – 7.6%) and 3.9% (95%, 2.5% – 5.8%) for Western countries, respectively (**Table 3**). After an average postoperative follow up of 19 months, the rate of tumor recurrence was 0.04% (95% CI, 0.01% – 0.31%) among those with R0 resection and 3.6% (95% CI, 1.4% – 8.8%) among those without R0 resection (**Table 2**). Overall, irrespective of the resection status, recurrence rate was 1.0% (95% CI, 0.42% – 2.1%). For Asian studies, rates of tumor recurrence were 0.05% (95%, 0.01% – 0.33%), 2.3% (95% CI, 1.1% – 4.4%), and 0.37% (95% CI, 0.13 – 0.10) among tumors with R0 resection, without R0 resection, and irrespective of R0 status respectively. On the other hand, tumor recurrence rates for Western countries were 21% (95% CI, 11% – 36%) and 6.5% (95% CI, 3.7% – 11%) among tumors without R0 resection and irrespective of resection status respectively. All four Western studies that assessed recurrence among tumors with R0 resection reported no recurrence among such tumors after an average follow up of 7 months (**Table 3**).

All our estimates were comparable to those of sensitivity analysis as pre-specified (**Table S3**).

Discussion

Our meta-analysis showed that, across multiple studies in 15 countries, ESD demonstrated an excellent treatment success in patients with colorectal tumors. Perioperatively, perforation and major bleeding were the most commonly reported serious ad-

Adverse outcomes	Studies, *n*	Patients, *n*	Tumor, *n*	Rate (95 % CI), %[1]
Immediate[2]				
Perforation	98	13291	13498	4.2 (3.5, 5.0)
Major bleeding	24	2274	2319	0.75 (0.31, 1.8)
Delayed[3]				
Perforation	30	3887	3948	0.22 (0.11, 0.46)
Major bleeding	80	11079	11260	2.1 (1.6, 2.6)
Recurrence[4]				
Among tumors with R0	20	–	2273	0.04 (0.01, 0.31)
Among tumors without R0	18	–	398	3.6 (1.4, 8.8)
Irrespective of R0 status	32	4143	4315	1.0 (0.42, 2.1)

Table 2 Rates of adverse outcomes in patients undergoing colorectal endoscopic submucosal dissection between 1998 and 2014.

N, number; R0, histologically-confirmed en bloc resection
[1] The rates are calculated as a percentage of the total number of tumors operated.
[2] Immediate refers to adverse outcomes occurring within 24 hours of the procedure.
[3] Delayed refers to adverse outcome occurring 24 hours after the procedure.
[4] Average follow-up was ~19 months for assessment of recurrence among tumors with and without R0; and ~23 months for the assessment of recurrence irrespective of R0 status.

	Asia		Western world	
	Studies, n	Rate (95 % CI), %[1]	Studies, n	Rate (95 % CI), %[1]
Efficacy measures				
Histologic en bloc resection	40	87 (84, 90)	20	71 (64, 77)
Endoscopic en bloc resection	63	94 (92, 95)	23	82 (76, 87)
Safety measures				
Immediate perforation[2]	71	3.8 (3.1, 4.6)	27	6.6 (4.6, 9.4)
Immediate major bleeding[2]	17	0.39 (0.11, 1.3)	7	3.3 (1.4, 7.6)
Delayed perforation[3]	25	0.18 (0.08, 0.42)	5	1.2 (0.29, 4.6)
Delayed major bleeding[3]	59	1.8 (1.4, 2.4)	21	3.9 (2.5, 5.8)
Recurrence (if R0)[4]	16	0.05 (0.01, 0.33)	4	0
Recurrence (if not R0)[4]	14	2.3 (1.1, 4.4)	4	21 (11, 36)
Recurrence (irrespective of R0 status)[4]	21	0.37 (0.13, 0.10)	11	6.5 (3.7, 11)

Table 3 Clinical outcomes of colorectal endoscopic submucosal dissection in Asia as compared to the western world.

N, number; R0, histologically-confirmed en bloc resection
[1] The rates are calculated as a percentage of the total number of tumors operated.
[2] Immediate refers to adverse outcomes occurring within 24 hours of the procedure.
[3] Delayed refers to adverse outcome occurring 24 hours after the procedure.
[4] Average follow-up was ~20, 19, and 25 months for assessment of recurrence among tumors with R0, without R0, and irrespective of R0 status respectively (for Asian studies); and ~7, 7, and 10 months for assessment of recurrence among tumors with R0, without R0, and irrespective of R0 status respectively (for western studies).

verse outcomes but their risk is somewhat comparable to EMR [4,8]. 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 3 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 which were partly explained by four main factors: first, the estimates vary by continent. Difference in continent accounted for most of the heterogeneity with highest rates of clinical success being reported by studies from Asia. This, in a way, was expected because 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 as well as development of better techniques. On the other hand, the acceptance rate of the procedure had been low in other parts of the world. Second, lower rates of treatment success were reported in the prospective studies as compared to retrospective studies. However, only a few of the studies were prospective and most of these were from Europe, which further underscores the lower rates of treatment success in countries outside Asia. Third, rates of treatment success increase with decreasing length of the procedure. Because length of the procedure is expected to correlate with level of expertise and size of tumor, we presume this is an indicator of higher rates with better expertise/years of experience and smaller tumor size. This notion is further supported by difference in estimates by tumor size, the fourth sources of heterogeneity in our analysis, although this was only marginally significant.

The relatively high risk of adverse outcome associated with the procedure had been one of the factors against the acceptability of the procedure in western countries [3]. Intraoperatively, perforation was the most common serious adverse outcome. However, most of the perforations were successfully sealed with endoscopic clips with only large ones requiring surgical intervention. More than 24 hours after the procedure, major bleeding becomes the most common serious adverse event. These cases of delayed bleeding often require endoscopic re-exploration. Although the incidence of delayed perforation is very low, it is a more serious adverse event because these usually require surgery for peritonitis [9]. The relatively low risk of recurrence has been the attractive feature of ESD. After a moderate follow up, tumor recurrence was present in only 1 in 100 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 very negligible: 4 in 10 000 tumors. Overall, rates of adverse events were generally better in Asia compared to the Western world.

Before the invention of ESD in the late 1990s in Japan, EMR was the most widely used minimally invasive option for noninvasive colorectal tumors in the world and it is still the most widely used in many western countries. Over the years, numerous comparative studies and reviews had shown the superior benefit of ESD in terms of complete resection and tumor recurrence as compared to EMR [4,8,10]. In addition, its risk of complication is comparable to other minimally invasive alternative including EMR and laparoscopic assisted colectomy (LAC) [11]. However, given the low risk of malignancy among small tumors (<20 mm in diameter) in addition to comparable rate of recurrence between EMR and ESD for small tumors, EMR remains a suitable option in this subgroup especially when ESD cannot be performed due to lack of expertise or patient-related factors e.g. weak intestinal wall [10]. Furthermore, ESD is not recommended for invasive cancers with risk of lymph node metastasis. LAC remains the only minimally invasive option in such cases [11].

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 including all comprehensive abstracts and placing no restriction on language of publication. Our moderately large number of studies enabled us to shed more light on potential sources of heterogeneity in treatment success after ESD, and the comparability of the main findings to those in sensitivity analysis further ensures the robustness of our result. Although similar studies exist in the literature [12–14], our study is the largest and most updated. In addition, we provided the most comprehensive reporting of all clinically relevant outcomes while also identifying potential sources of heterogeneity.

Limitations of this study should also be considered. First, due to rapidly evolving techniques in ESD procedure, 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. There was also a suggestion of increasing rate of treatment success over time, indicating that newer techniques may be associated with higher success rate, although this was not statistically significant. 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, we could not evaluate for potential heterogeneity of clinical outcomes between mucosal and submucosal tumors as most of the studies involved a mixed population of mucosal and submucosal tumors. Further studies are needed to evaluate these 2 classes of tumors in a head-to-head comparison.

Conclusion

In conclusion, colorectal ESD appears safe and effective based on the large and broad body of current medical literature. It compares favorably with other minimally invasive options and warrants consideration as first-line therapy when an expert operator is available. However, the result is not optimal yet given that R0 resection rate is still only 86% and there is enough room for improvement to achieve rates close to 100%.

Competing interests: Dr. Christopher Thompson serves as consultant to the following organizations: Boston scientific; covidien; USGI Medical; Olympus; and Apollo Endosurgery

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Table S1 Search query.

Medline	**("endoscopic submucosal dissection"[tiab] OR "endoscopic submucosal resection"[tiab] OR "submucosal dissection"[tiab] OR "ESD"[tiab]) AND ("colon"[Mesh] OR "colorectal neoplasms"[Mesh] OR "colorectal"[tiab] OR colo*[tiab] OR "large bowel"[tiab] OR hindgut[tiab])**
Embase	('endoscopic submucosal dissection'/exp OR 'endoscopic submucosal resection':ab,ti OR 'submucosal dissection':ab,ti OR submuco* NEAR/2 dissection OR 'ESD':ab,ti) AND ('colon'/exp OR 'large intestine tumor'/exp OR colorectal:ab,ti OR colo*:ab,ti OR 'large bowel':ab,ti OR hindgut:ab,ti) AND [embase]/lim NOT [medline]/lim
Ovid	(endoscopic submucosal dissection OR endoscopic submucosal resection OR submucosal dissection OR endoscopic dissectionOR ESD) AND (colon OR colorectal OR colo* OR large bowel OR hindgut)
CINAHL	(endoscopic submucosal dissection OR endoscopic submucosal resection OR submucosal dissection OR endoscopic dissectionOR ESD) AND (colon OR colorectal OR colo* OR large bowel OR hindgut)
Cochrane	(endoscopic submucosal dissection OR endoscopic submucosal resection OR submucosal dissection OR endoscopic dissectionOR ESD) AND (colon OR colorectal OR colo* OR large bowel OR hindgut)

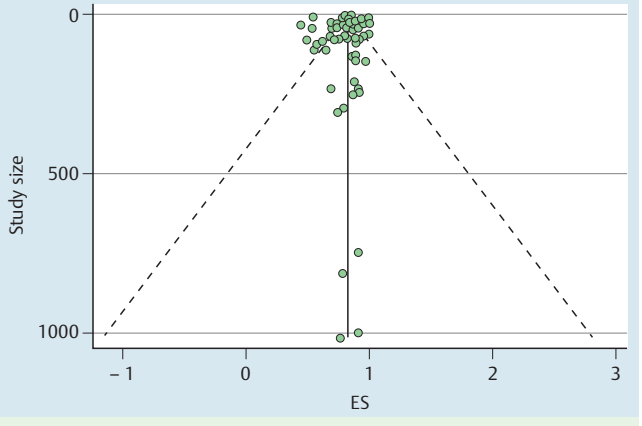

Fig. S1 Funnel plot of histologically confirmed en bloc (R_0) resection rate in 60 studies involving 8312 tumors in 8111 patients that underwent colorectal endoscopic submucosal dissection. Each dot represents the R_0 resection rate. Lack of asymmetry in the distribution of study estimates around the center of the funnel suggests no publication bias. *P* value for egger's test = 0.57. ES, estimate; se(ES), standard error of estimate.

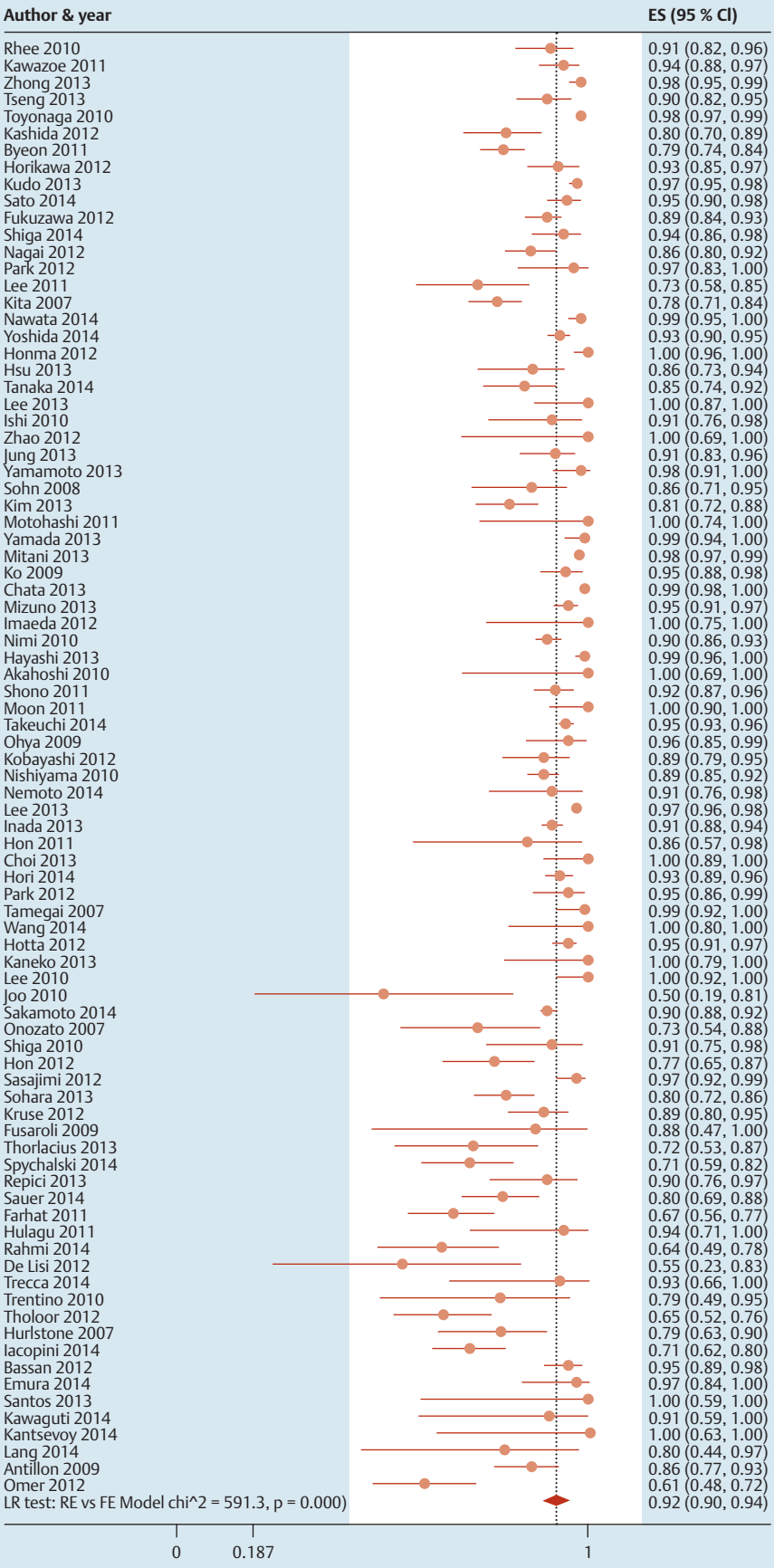

Fig. S2 Meta-analysis of endoscopic en bloc resection rate in 86 studies involving 12 346 tumors in 12 151 patients that underwent colorectal endoscopic submucosal dissection. Each dot and the horizontal line through them correspond to the point estimate and confidence interval from each study respectively 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. ES, estimate.

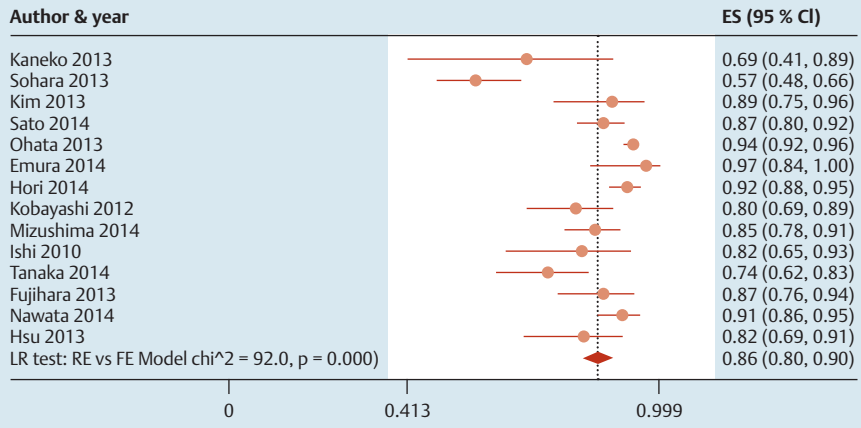

Fig. S3 Meta-analysis of curative resection rate in 14 studies involving 1805 tumors in 1784 patients that underwent colorectal endoscopic submucosal dissection. Each dot and the horizontal line through them correspond to the point estimate and confidence interval from each study respectively while the 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.

Table S2 Characteristics of studies included in the meta-analysis of colorectal endoscopic submucosal dissection.

Article	Data period, *yr*	Country	Patients, *n*	Age, mean (range), *yr*	Female, %	Tumor, *n*	Tumor size, mean (range), *mm*	Procedure length, mean (range), *min*
Kawaguti 2014 [15]	2008 – 2011	Brazil	11	62	NA	11	65	133
Santos 2013 [16]	2010 – 2011	Brazil	7	54 (45 – 60)	43	7	26 (20 – 50)	163 (80 – 242)
Wang 2014 [17]	NA	China	17	NA	NA	17	9.4 (7 – 25)	NA
Zhao 2012 [18]	2002 – 2008	China	10	NA	NA	10	NA	(16 – 35)
Hon 2011 [19]	2000 – 2010	China	14	65	64	14	29	78 (25 – 180)
Rahmi 2014[1] [20]	2010 – 2012	France	45	67	47	45	35 (10 – 100)	110 (30 – 280)
Farhat 2011[1][21]	2008 – 2010	France	85	NA	NA	85	NA	NA
Probst 2012 [22]	2004 – 2011	Germany	76	64 (38 – 85)	43	82	45.5	176
Repici 2013 [23]	2010 – 2011	Italy	40	65 (43 – 83)	33	40	47 (33 – 80)	86 (40 – 190)
Fusaroli 2009 [24]	NA	Italy	8	64	63	8	42	110
Trecca 2014 [25]	2012 – 2013	Italy	14	(50 – 82)	57	14	3 (1.5 – 5.5)	123 (60 – 240)
Niimi 2010 [26]	2000 – 2008	Japan	290	65 (29 – 88)	68	310	29 (6 – 100)	NA
Nishiyama 2010 [27]	2001 – 2008	Japan	282	69 (30 – 91)	48	296	27 (4 – 75)	NA
Tamegai 2007 [28]	2003 – 2005	Japan	70	63	46	71	33 (13 – 80)	61 (7 – 164)
Hotta 2012 [29]	2000 – 2010	Japan	215	69	37	219	30 (6 – 100)	101 (20 – 595)
Ishi 2010 [30]	2005 – 2009	Japan	33	66 (42 – 89)	39	33	35 (20 – 80)	121 (22 – 240)
Imaeda 2012 [31]	2008 – 2010	Japan	13	69 (42 – 90)	31	13	33 (20 – 80)	60 (20 – 150)
Tanaka 2007 [32]	2003 – 2005	Japan	70	66 (36 – 85)	33	70	28	71 (15 – 180)
Onozato 2007 [33]	2002 – 2006	Japan	30	70 (51 – 89)	47	30	26 (8 – 60)	70 (8 – 360)
Sohara 2013 [34]	2006 – 2011	Japan	129	66 (44 – 80)	33	129	32 (2 – 92)	60 (7 – 300)
Hori 2014 [35]	2006 – 2010	Japan	242	70 (62 – 75)	32	247	35 (23 – 46)	60 (40 – 120)
Ohya 2009 [36]	2008 – 2009	Japan	45	71 (58 – 83)	NA	45	35 (13 – 98)	60 (12 – 200)
Fujihara 2013 [37]	2010 – 2012	Japan	68	71 (37 – 88)	43	68	35	105 (45 – 250)
Okamoto 2013 [38]	2010 – 2012	Japan	30	69 (63 – 76)	43	30	36 (28 – 45)	61 (58 – 72)
Akahoshi 2010 [39]	NA	Japan	10	66 (55 – 74)	40	10	NA	155
Shono 2011 [40]	2007 – 2010	Japan	137	67 (40 – 90)	42	137	29 (20 – 150)	79 (20 – 100)
Izumi 2014 [41]	2006 – 2011	Japan	199	66 (35 – 90)	40	199	35 (20 – 110)	
Motohashi 2011 [42]	NA	Japan	12	NA	NA	12	(22 – 42)	45 (30 – 110)
Mizushima 2014[1] [43]	2009 – 2013	Japan	122	68 (38 – 91)	41	134	27 (5 – 65)	64 (8 – 189)
Takeuchi 2014[1] [44]	2007 – 2010	Japan	808	67	43	816	NA	78 (50 – 120)
Kita 2007 [45]	1998 – 2005	Japan	166	NA	NA	166	33	102
Homma 2012[1] [46]	2009 – 2010	Japan	100	71 (30 – 88)	48	102	32 (12 – 120)	54 (15 – 270)
Sato 2014 [47]	2009 – 2013	Japan	147	72 (37 – 89)	42	151	32 (20 – 85)	72 (15 – 340)
Shiga 2014 [48]	2009 – 2013	Japan	80	68.1	33	80	35	109
Sakamoto 2014 [49]	NA	Japan	1017	66	43	1017	38	103
Nagai 2012 [50]	2007 – 2011	Japan	139	(39 – 89)	35	140	NA	70 (15 – 350)
Ohata 2013 [51]	2007 – 2012	Japan	608	67	NA	608	36	69.5
Nawata 2014 [52]	2010 – 2013	Japan	150	69 (36 – 91)	39	150	30 (18 – 123)	43 (6 – 235)
Yoshida 2014 [53]	2010 – 2013	Japan	371	70 (35 – 92)	NA	371	30 (6 – 100)	59 (6 – 385)
Toyonaga 2010[1] [54]	2002 – 2008	Japan	512	NA	NA	512	29 (4 – 158)	57 (11 – 335)
Kim 2013 [55]	2005 – 2011	S.Korea	44	47	27	44	6	9.4
Lee 2010 [56]	2003 – 2009	S.Korea	46	49	54	46	6.2 (2 – 15)	18.9
Park 2012 [57]	2007 – 2011	S.Korea	30	59	53	30	25	84
Lee 2013 [58]	2005 – 2011	S.Korea	26	NA	15	26	6.2	22
Kim 2013 [59]	2007 – 2011	S.Korea	115	63 (31 – 87)	38	115	29 (10 – 64)	65 (6 – 220)
Lee 2013 [60]	2006 – 2011	S.Korea	974	61 (25 – 86)	NA	1000	24 (3 – 145)	49 (3 – 321)
Sohn 2008 [61]	2003 – 2006	S.Korea	41	53 (32 – 78)	46	42	4.4 (2 – 10)	7.8 (2 – 22)
Moon 2011 [62]	2007 – 2009	S.Korea	35	49 (32 – 74)	29	35	4.7 (1 – 9)	36 (7 – 82)
Jung 2013 [63]	2009 – 2011	S.Korea	82	59	46	82	27	52
Choi 2013 [64]	2008 – 2011	S.Korea	31	48	35	31	5.2	15
Byeon 2011 [65]	2004 – 2010	S.Korea	233	61	37	237	30	44.6
Spychalski 2014 [66]	2013 – 2014	Poland	70	67 (38 – 84)	57	70	34 (15 – 75)	106 (30 – 225)
Thorlacius 2013 [67]	2012 – 2013	Sweden	29	74 (46 – 85)	52	29	28 (11 – 89)	142 (57 – 291)
Hsu 2013 [68]	2010 – 2013	Taiwan	50	64 (46 – 82)	50	50	33 (12 – 70)	71 (16 – 240)
Tseng 2013 [69]	2006 – 2011	Taiwan	92	66	36	92	37	59
Hurlstone 2007 [70]	2004 – 2006	UK	42	68 (52 – 79)	36	42	NA	48 (18 – 240)
Lang 2014 [71]	2006 – 2013	USA	11	NA	NA	11	34 (10 – 50)	106 (16 – 166)
Kantsevoy 2014 [72]	2012 – 2013	USA	8	NA	63	8	NA	NA
Bassan 2012[2] [73]	2010 – 2011	Australia	104	NA	NA	104	38	95
Zhong 2013[2] [74]	2006 – 2011	China	255	NA	NA	255	NA	NA

Table S2 (Continuation)

Article	Data period, *yr*	Country	Patients, *n*	Age, mean (range), *yr*	Female, %	Tumor, *n*	Tumor size, mean (range), *mm*	Procedure length, mean (range), *min*
Hon 2012[2] [75]	2009 – 2012	China	61	NA	NA	61	25	NA
Emura 2014[2] [76]	2008 – 2013	Colombia	32	NA	NA	32	33	109
Kruse 2012[2] [77]	2006 – 2011	Germany	81	69 (47 – 90)	31	83	NA	NA
Sauer 2014[2] [78]	2012 – 2013	Germany	81	NA	NA	83	35	103 (20 – 600)
Iacopini 2014[2] [79]	2009 – 2013	Italy	112	NA	NA	112	NA	NA
Trentino 2010[2] [80]	NA	Italy	14	NA	NA	14	28	NA
De Lisi 2012[2] [81]	NA	Italy	11	71	64	11	24 (10 – 40)	137 (45 – 270)
Petruzziello 2014[2] [82]	2011 – 2013	Italy	15	65 (40 – 77)	33	15	23	70
Andrisani 2014[2] [83]	2011 – 2013	Italy	30	NA	NA	30	29	71
Kaneko 2013[2] [84]	2001 – 2012	Japan	16	NA	NA	16	6.6	NA
Kudo 2013[2] [85]	2001 – 2012	Japan	485	NA	NA	485	NA	NA
Mizuno 2013[2] [86]	2005 – 2009	Japan	227	NA	NA	236	NA	NA
Osuga 2012[2] [87]	NA	Japan	13	NA	NA	13	NA	NA
Kashida 2012[2] [88]	NA	Japan	74	68	38	76	38	
Kawazoe 2011[2] [89]	2006 – 2011	Japan	114	NA	NA	114	NA	NA
Nemoto 2014[2] [90]	2013	Japan	33	NA	NA	33	28 (15 – 67)	53 (26 – 247)
Hayashi 2013[2] [91]	2010	Japan	214	NA	NA	214	NA	NA
Inada 2013[2] [92]	2006 – 2012	Japan	502	NA	NA	502	31	94.9
Mitani 2013[2] [93]	2005 – 2011	Japan	647	66 (34 – 91)	36	748	32.9	68 (5 – 500)
Shiga 2010[2] [94]	2007 – 2010	Japan	32	70	56	32	27.4	70.9
Nio 2013[2] [95]	2008 – 2012	Japan	92	NA	NA	92	NA	NA
Sasajimi 2012[2] [96]	NA	Japan	150	NA	NA	150	33	86 (15 – 420)
Tanaka 2014[2] [97]	2009 – 2013	Japan	72	NA	NA	72	NA	NA
Yamamoto 2013[2] [98]	NA	Japan	61	NA	NA	61	31	65
Oyama 2010[2] [99]	NA…	Japan	148	NA	NA	148	31	NA
Horikawa 2012[2] [100]	2008 – 2012	Japan	83	NA	NA	83	NA	101
Kojima 2013[2] [101]	2007 – 2012	Japan	233	69 (33 – 87)	41	233	22	NA
Fukuzawa 2012[2] [102]	2007 – 2012	Japan	200	NA	NA	200	NA	100
Yamada 2013[2] [103]	2009 – 2012	Japan	92	NA	NA	92	34	65
Kobayashi 2012[2] [104]	2005 – 2011	Japan	71	NA	NA	71	29	141
Hayashi 2013[2] [105]	2010 – 2013	Japan	247	NA	NA	247	NA	79
Lee 2011[2] [106]	2004 – 2010	S.Korea	45	64 (26 – 85)	36	45	35	NA
Ko 2009[2] [107]	2004 – 2008	S.Korea	95	NA	NA	95	29 (12 – 86)	77
Park 2012[2§] [108]	2009 – 2011	S.Korea	59	NA	NA	61	20 (5 – 50)	74 (11 – 280)
Kim 2010[2] [109]	NA	S.Korea	7	63	43	7	2.7	NA
Rhee 2010[2] [110]	2008 – 2010	S.Korea	78	NA	NA	80	27	50 (11 – 152)
Joo 2010[2] [111]	2007 – 2009	S.Korea	10	62 (50 – 75)	60	10	43	99 (22 – 246)
Bialek 2012[2] [112]	2006 – 2012	Poland	45	64 (49 – 85)	47	47	26 (10 – 60)	NA
Hulagu 2011[2] [113]	2007 – 2010	Turkey	17	NA	29	17	NA	NA
Tholoor 2012[2] [114]	2006 – 2011	UK	66	69	68	66	NA	NA
George 2013[2] [115]	2004 – 2012	UK	38	NA	NA	38	41 (15 – 100)	NA
Gorgun 2013[2] [116]	NA	USA	8	66 (50 – 88)	63	8	NA	126 (62 – 196)
Omer 2012[2] [117]	2009 – 2011	USA	66	NA	NA	66	NA	NA
Antillon 2009[2] [118]	2006 – 2008	USA	86	NA	NA	86	42	NA

yr, year; n, number; mm, millimeter; min, minute; NA, not available
[1] Multicenter studies
[2] Abstracts

Outcomes	Studies, *n*	Tumor, *n*	Rate (95 % CI)[1]
Efficacy measures			
R0 resection	41	6006	84 (80 – 87)
Endoscopic en bloc resection	51	7862	93 (90 – 95)
Curative resection	10	1614	87 (81 – 91)
Safety measures			
Immediate perforation[2]	53	8184	4 (3 – 5)
Immediate major bleeding[2]	20	2154	0.82 (0.32 – 2.1)
Delayed perforation[3]	22	3313	0.24 (0.11 – 0.54)
Delayed bleeding[3]	47	7398	1.7 (1.2 – 2.4)
Recurrence (if R0)[4]	16	1999	0.05 (0.01 – 0.35)
Recurrence (if not R0)[4]	15	367	3.6 (1.3 – 9.9)
Recurrence (irrespective of R0 status)[4]	18	2391	0.58 (0.19 – 1.7)

Table S3 Clinical outcomes among patients who underwent colorectal endoscopic submucosal dissection (analysis restricted to only studies published as full-text journal article).

n, number; R0, histologically-confirmed en bloc resection
[1] The rates are calculated as a percentage of the total number of tumors operated.
[2] Immediate refers to adverse outcomes occurring within 24 hours of the procedure.
[3] Delayed refers to adverse outcome occurring 24 hours after the procedure.
[4] Average follow-up was ~18, 21 and 19 months for assessment of recurrence among tumors with R0, without R0, and irrespective of R0 status, respectively.

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