Clinical outcomes after endoscopic submucosal dissection for colorectal neoplasia: a systematic review and meta-analysis

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Background and Aims: Endoscopic submucosal dissection (ESD) is an endoscopic resection technique for lesions suspicious of superficial malignancy. It is performed using an ESD knife on its own (standard technique) or by the sequential use of a knife and a snare (hybrid technique). The experience with these techniques is different in Asian and non-Asian countries. We performed a systematic review and meta-analysis of available evidence on colorectal ESD.

Methods: Electronic databases were searched up to August 2016 for studies evaluating R0, en bloc resection, and adverse event rates of both techniques for the treatment of colorectal lesions. Proportions were pooled by a random effects model.

Results: Ninety-seven studies (71 performed in Asia) evaluated the standard technique and 12 studies (7 in Asia) the hybrid technique. The R0 resection rate of the standard technique was 82.9%, and it was significantly lower in non-Asian versus Asian countries: 71.3% versus 85.6%. The en bloc resection rate was 91% and was significantly lower in non-Asian versus Asian countries (81.2% vs 93%, respectively). Surgery was needed in 1.1% of the ESD-related adverse events, with a significant difference between non-Asian and Asian countries (3.1% vs 0.8%). The R0 and en bloc resection rates with the hybrid technique were significantly lower than those achieved with the standard technique: 60.6% and 68.4%, respectively, with similar adverse event rates.

Conclusions: In non-Asian countries the standard ESD technique is still failing to achieve acceptable levels of performance. The hybrid technique showed low R0 resection rates and should not be considered as an adequate alternative to the standard technique. (Gastrointest Endosc 2017;86:74-86.)

Endoscopic submucosal dissection (ESD) is an endoscopic resection technique, first proposed in 1999, with the purpose of achieving en bloc resection of superficial neoplasia in the upper GI tract.[1] Despite being technically more challenging, ESD indications have been extended to colorectal lesions with suspicion of superficially invasive cancer. Unlike the piecemeal snare resection, en bloc resection achieved by ESD allows adequate orientation of the pathology specimen and a reliable staging of the submucosal invasion, preventing unnecessary surgery for lesions at low risk of lymph node metastasis. According to the European Society of Gastrointestinal Endoscopy,[2] ESD in the colorectum is strongly recommended when the likelihood of superficial invasion is high, according to morphologic and endoscopic criteria (ie, depressed morphology, advanced surface pattern, and nongranular lateral spreading tumor), especially for lesions larger than 20 mm. In case of rectal lesions, ESD indications may be further extended to granular type or mixed type ≥20-mm lateral spreading tumor, because of the substantially higher surgery-related morbidity and mortality and the lower risk of major ESD-related adverse events at this site.

The standard technique of ESD is based on the use of an ESD knife to perform the mucosal incision followed by

Abbreviations: CI, confidence interval; ESD, endoscopic submucosal dissection.

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submucosal dissection to achieve an en bloc excision. It can take much longer time and result in higher rates of adverse events as compared with the standard snare-based resection technique. Therefore, a less-challenging technique called hybrid ESD has been proposed. Hybris ESD is based on the sequential use of a knife and a snare, harnessing the technically easy components of ESD (knife-assisted circumferential mucosal incision) and EMR (snare-assisted excision).[3,4] This technique has been proposed as a faster and safer alternative to the standard ESD technique.

Previous systematic reviews on ESD mainly focused on retrospective data and primarily reported data from Asian series.[5,6] In addition, no systematic review on the hybrid technique has been performed. Therefore, the aim of the current review was to capture data on the performance of ESD with the standard technique from Asian and non-Asian countries and to systematically review the available evidence with the hybrid technique to allow greater understanding of the usefulness of ESD in the management of superficial colorectal neoplasia.

METHODS

In accordance with the PRISMA-P Group guidelines,[7] our systematic review protocol was registered with the International Prospective Register of Systematic Reviews, PROSPERO (www.crd.york.ac.uk/prospero/, registration number: CRD42016046056). The following parameters are reported in Appendix 1 (available online at www.giejournal.org): data sources, search strategy, selection process, data extraction, and quality assessment.[8,9]

Inclusion and exclusion criteria

To be included in the meta-analysis, we retrieved studies including patients with a diagnosis of nonpedunculated colorectal tumors treated by ESD and providing the R0 resection rate. Regarding the ESD technique, both standard and hybrid approaches were considered; alternative or additional treatments (eg, EMR) were excluded.

Prospective and retrospective cohort studies, published as full-text or abstract, including at least 10 patients were considered. Only studies published since 1999 were considered for inclusion.

Exclusion criteria were studies with fewer than 10 patients and studies not published in the English language. Because the efficacy of ESD for the management of carcinoid lesions has been well established,[5] all studies in which the study population was exclusively represented by patients with carcinoid lesions were excluded. In cases of mixed population (ie, carcinoid and noncarcinoid lesions), the study was included only when it was possible to selectively extract data for noncarcinoid lesions; when it was not possible to selectively extract data for noncarcinoid lesions, the study was included only when the proportion of carcinoid lesions was less than 5% of the entire sample. Because the hybrid and the standard ESD techniques are substantially different, these techniques were separately considered in the analyses. If it was not possible to separate the primary outcome measure according to the ESD techniques, the study was not included and additional data were directly requested from the corresponding authors.

Outcomes assessment

All of the outcomes were separately assessed for both types of ESD techniques, standard and hybrid techniques. The primary outcome was the R0 (vertical and horizontal margins free of neoplasia) resection rate on a per-lesion basis. The key secondary outcome was the ESD adverse event–related surgery rate on a per-lesion basis. Other secondary outcomes (on a per-lesion basis) included endoscopically complete ESD resection rate (ie, apparently complete en bloc resection at endoscopy, regardless of histology), oncologically curative resection rate (ie, no lymphatic and vascular invasion, proper distance from vertical margin, and malignant invasion limited to sm1 or <1000 μm), delayed bleeding rate, perforation rate, and post-ESD recurrence rate after R0 resection.

Statistical analysis

Proportions and rates were pooled by means of a random effects model where there were indications of heterogeneity across studies; otherwise, a fixed effect model was used.[10] The dependent variables were modeled on the logit (log-odds) scale, converted back to percentages, and then presented as point estimates and 95% confidence intervals (CIs). Statistical heterogeneity was quantified with the I^2 statistic (high heterogeneity level >50%) and tested using the Q^2 test (statistical significance level, $P < .1$). Subgroup meta-analytic models were built considering a priori factors that could affect the outcomes, that is, the country (Asian vs non-Asian), the volume of ESDs performed per year, the proportion of rectal lesions treated, the study design, and the indication for ESD, as stated in the original protocol. To explore the possible sources of heterogeneity, meta-regression was applied. The potential predictors of R0 resection were selected a priori. For each potential predictor we estimated the R^2 statistics that represents the proportion of variance explained by the model.

Main analysis was performed using Comprehensive Meta-Analysis 3.3.070 (Biostat, Englewood, NJ), whereas meta-regression models were fitted with Stata 14.1 SE (Stata Corp, College Station, Tex). All tests were 2-sided, and statistical significance was taken as $P < .05$, except for when investigating heterogeneity across studies in which case it was taken as $P < .10$. It is noted that some data were involved in more than a single statistical comparison; however, because the purpose of this research was to highlight differences, there were no corrections for multiple testing.

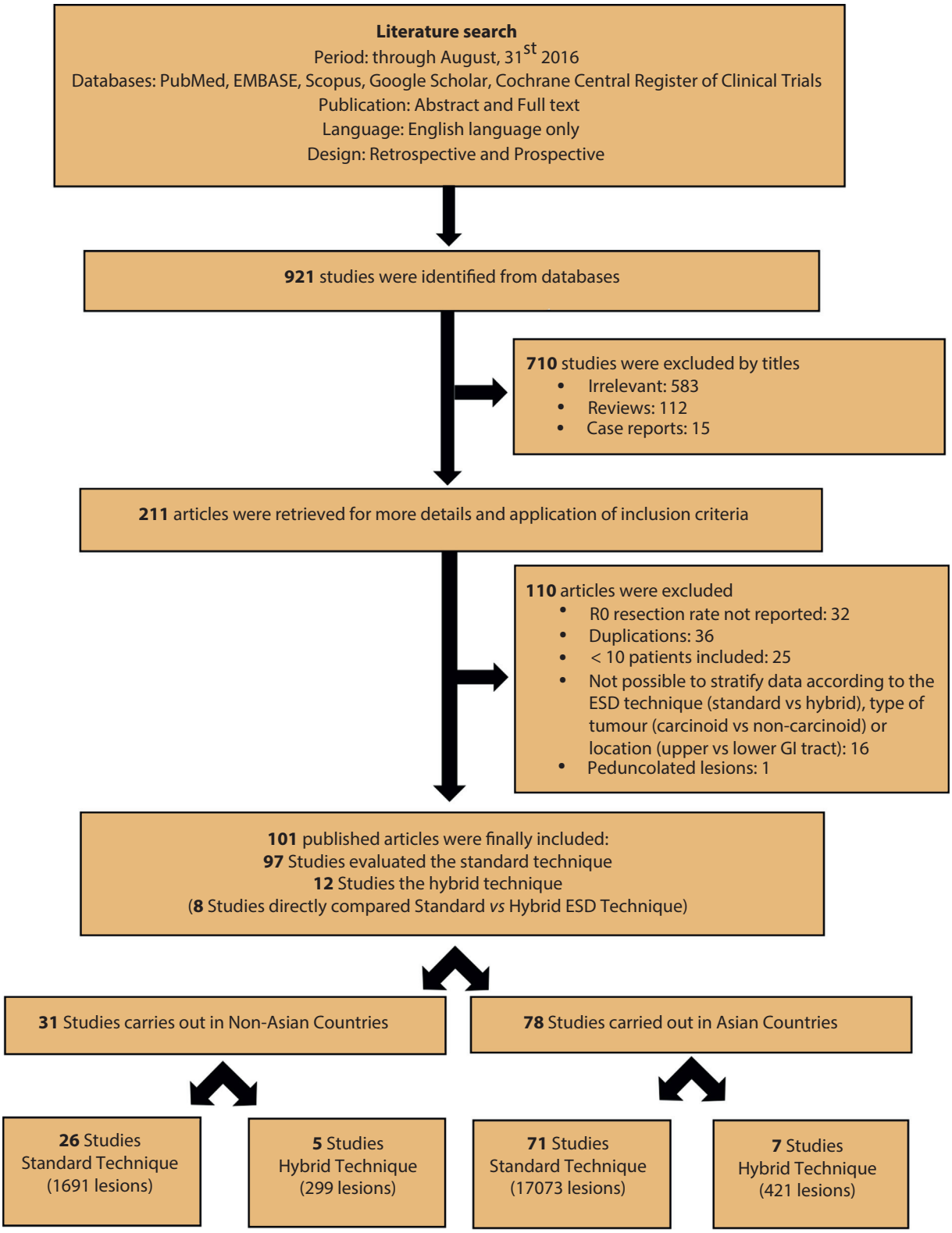

Figure 1. Flow chart of the study selection process.

TABLE 1. Characteristics of the 101 published articles included in the systematic review

	No. of studies
Publication status	
Abstract	29 studies
Full text	72 studies
Study design	
Retrospective	84 studies
Prospective	17 studies
Country	
Asian	72 studies
Non-Asian (Europe and North America)	29 studies
Centers involved	
Monocenter	95 studies
Multicenter	6 studies
Definition of large colorectal tumor	
≥10 mm	2 studies
≥15 mm	1 studies
≥ 20 mm	58 studies
≥30 mm	3 studies
≥40 mm	2 studies
Not reported	35 studies
Modified Newcastle-Ottawa Scale (mean score)	4.1 (range, 3-5)
Indications for standard ESD	
Mixed (tumor dissection, recurrence post-EMR)	34 studies
Asian countries	26 studies (37%)
Non-Asian countries	8 studies (31%)
Tumor dissection	52 studies
Asian countries	39 studies (55%)
Non-Asian countries	13 studies (50%)
Recurrence post-EMR	7 studies
Asian countries	4 studies (6%)
Non-Asian countries	3 studies (12%)
Not reported	4 studies
Indications for hybrid ESD	
Mixed (tumor dissection, recurrence post-EMR)	3 studies
Asian countries	1 studies (14%)
Non-Asian countries	2 studies (40%)
Tumor dissection	6 studies
Asian countries	4 studies (57%)
Non-Asian countries	2 studies (40%)
Recurrence post-EMR	1 study
Asian countries	0
Non-Asian countries	1 study (20%)
Not reported	2 studies

ESD, Endoscopic submucosal dissection.

RESULTS

Study characteristics and quality

The literature search resulted in 921 articles (Fig. 1). After applying the selection criteria, 101 published articles for a total of 109 studies were finally included in the systematic review. In particular, 97 studies, with a total of 17,483 patients and 18,764 colorectal lesions, adopted the standard ESD technique,[11-108] and 12 studies, with a total of 694 patients and 720 lesions, adopted the hybrid ESD technique.[3,4,18-20,45,71,95,97,108-110] Notably, 8 studies directly compared the 2 techniques.[18-20,45,71,95,97,108] In these comparative studies, where updated series of one of the treatment arms were subsequently published by the same authors, we included only the most recent one. The definition of R0 and en bloc resection was consistent across studies and reported in all.

An overview of the included studies is reported in Table 1. Supplementary Tables 1 to 4 (available online at www.giejournal.org) summarized the characteristics of the studies, the lesions treated, and the main outcomes and are reported in Appendix 2 (available online at www.giejournal.org).

Standard ESD technique

Baseline characteristics of the study population and the main findings with the standard ESD technique, stratified according to country (ie, Asian and non-Asian countries), are detailed in Tables 2 and 3, respectively.

R0 and en bloc resection rates. Overall, based on the 97 studies included, the pooled R0 resection rate of standard ESD technique in 18,764 colorectal lesions was 82.9% (95% CI, 80.4%-85.1%), with high heterogeneity between studies (Q^2 test: $P < .0001$; $I^2 = 92.8\%$). The en bloc resection rate was 91% (95% CI, 89.2%-92.5%), with high heterogeneity again (Q^2 test: $P < .0001$; $I^2 = 91.2\%$).

Need for surgery for ESD-related adverse events. Based on the data reported by 88 studies, 68 of 14,584 treated lesions resulted in adverse events requiring surgery, yielding a pooled rate of 1.1% (95% CI, .9%-1.3%), with low level of heterogeneity ($Q^2 = .024$). In non-Asian countries 18 of 1182 treated lesions resulted in adverse events requiring surgery, with a pooled rate of 3.1% (95% CI, 2.1%-4.7%; $Q^2 = .23$). In Asian countries a significantly lower rate was reported, with 50 of 13,402 treated lesions resulted in adverse events requiring surgery, yielding a rate of .8% (95% CI, .6%-1.0%; $Q^2 = .82$). The subgroup analyses performed according to the volume of ESD carried out per year revealed that low-volume centers (arbitrarily defined those performing ≤24 ESD per year, see below for explanation), had a significantly higher rate of adverse events requiring surgical management when compared with high-volume centers: 1.9% (95% CI, 1.4%-2.7%) versus .7% (95% CI, .6%-.9%), respectively.

Other main findings. The following outcomes are briefly reported in Table 3 and detailed in Appendix 3

TABLE 2. Baseline characteristics stratified according to the countries

Baseline characteristics	Standard ESD technique			Hybrid ESD technique		
	Overall	Non-Asian countries	Asian countries	Overall	Non-Asian countries	Asian countries
Mean age, y	66 (58-74)	67 (58-74)	66 (58-72)	66 (61-73)	68 (63-73)	64 (61-70)
Male gender, %	57 (32-72)	54 (34-74)	58 (32-70)	57 (42-64)	59 (56-64)	55 (42-62)
Mean lesion size, mm	33 (10.5-80)	38 (23-66)	32 (10.5-80)	31 (17-46)	41 (37-46)	24 (17-31)
Location, % rectum	46 (0-100)	55 (16-100)	42 (0-100)	32 (0-65)	28 (0-65)	34 (17-51)
Histopathology, % benign lesions*	72 (0-100)	80 (24-100)	70 (0-100)	85 (61-100)	89 (84-94)	84 (61-100)

Values in parentheses are ranges.
ESD, Endoscopic submucosal dissection.
*Benign lesions, meaning low- and high-grade (also referred to as in situ carcinoma) adenomas, as opposed to invasive carcinoma.

(available online at www.giejournal.org): oncologically curative resection rate, delayed bleeding rate, perforation rate, and recurrence rate after R0 resection.

Investigation of the heterogeneity. In non-Asian countries, the R0 resection rate was significantly lower than that observed in Asian countries. Indeed, in non-Asian countries the R0 resection, evaluated in 26 studies, was achieved in 1178 of 1691 cases, yielding a pooled rate of 71.3% (95% CI, 66.2%-75.9%; Q^2 test: $P < .0001$; $I^2 = 74.6\%$) (Fig. 2). In Asian countries, pooling the results reported in 71 studies, the R0 resection was achieved in 14,666 of 17,073 colorectal lesions, with a pooled rate of 85.6% (95% CI, 83.3%-87.7%) and high heterogeneity (Q^2 test: $P < .0001$; $I^2 = 92.7\%$) (Fig. 3).

The mean number of ESDs performed per year was also investigated in more detail; we considered the median of the means of the number of ESDs performed per year in each center, that is, 24 lesions treated, and compared the pooled R0 resection rate of centers performing ≤24 ESD per year (43 studies for a total of 3397 ESD performed) with that obtained in centers performing more than 24 ESD per year (49 studies; 15,067 lesions treated). Notably, in 5 studies it was not possible to calculate the mean number of ESD performed per year because the enrollment period was not reported. R0 resection rates of high-volume centers (85.5%; 95% CI, 82.9%-87.7%) was not significantly different from that of low-volume centers (79.6%; 95% CI, 75.4%-83.3%). When stratified according to the country (Asian vs non-Asian), high-volume centers in non-Asian countries presented significantly lower R0 resection rates than those reported in high-volume Asian centers (Supplementary Table 5 in Appendix 4, available online at www.giejournal.org).

The study design did not significantly influence the main outcomes. Indeed, the pooled R0 resection rate was 83.2% (95% CI, 80.5%-85.6%) in the retrospective studies and 81.3% (95% CI, 74.5%-86.6%) in the prospective studies.

Because almost all studies did not provide the results stratified according to the location of the lesion, we arbitrarily compared studies including ≤50% of rectal lesions with those including >50%. The pooled R0 resection rate of the 57 studies (13,130 lesions) including ≤50% of rectal lesions was significantly higher, yielding a rate of 84.9% (95% CI, 82.4%-87.2%), whereas the pooled rate of studies with >50% of rectal lesions (30 studies, 1753 lesions) was 74.7% (95% CI, 69.5%-79.3%). In 10 studies the location of the lesions was not reported. Almost all studies did not stratify the results according to the indications (ie, large colorectal tumor or recurrences after EMR); therefore, this subgroup analysis was not feasible.

Supplementary Table 6 (Appendix 4, available online at www.giejournal.org) shows the covariates considered and their influence on the R0 resection rate evaluated by the multivariate meta-regression. The data demonstrate an inverse association, suggesting that an increase in the number of lesions in rectal location will result in reduction in R0 resection rates. The assessment of publication bias is reported in Appendix 4 (available online at www.giejournal.org).

Hybrid ESD technique

Baseline characteristics of the study population and main findings with the hybrid technique, stratified according to the countries (ie, Asian and non-Asian countries), are detailed in Tables 2 and 4.

R0 and en bloc resection rates. Overall, based on the 12 studies included, the pooled R0 resection rate of hybrid ESD technique in 720 colorectal lesions was 60.6% (95% CI, 40.6%-77.5%), with high heterogeneity between studies (Q^2 test: $P < .0001$; $I^2 = 95.3\%$). The en bloc resection rate was 68.4% (95% CI, 51.7-81.3%), with again high heterogeneity (Q^2 test: $P < .0001$; $I^2 = 93.4\%$).

Need for surgery for hybrid ESD-related adverse event. Based on the data reported by 10 studies, only 1 adverse event was surgically treated out of 655 lesions, yielding a pooled rate of 1% (95% CI, .4%-2.3%), without evidence of heterogeneity ($Q^2 = .9$; $I^2 = 0\%$).

Other main findings. The following outcomes are briefly reported in Table 4 and detailed in Appendix 5 (available online at www.giejournal.org): oncologically curative resection rate, delayed bleeding rate, perforation rate, and recurrence rate after R0 resection.

Investigation of the heterogeneity. Again, the presence of high level of heterogeneity was explored by both

TABLE 3. Main findings with the standard ESD technique stratified according to non-Asian and Asian countries

Outcome (rate)	Overall	Non-Asian countries	Asian countries
En-bloc resection	91.0% (95% CI, 89.2%-92.5%)	81.2% (95% CI, 77.1%-84.7%)	93.0% (95% CI, 91.4%-94.3%)
R0 resection	82.9% (95% CI, 80.4%-85.1%)	71.3% (95% CI, 66.2%-75.9%)	85.6% (95% CI, 83.3%-87.7%)
Need for surgery post-ESD adverse event	1.1% (95% CI, .8%-1.3%)	3.1% (95% CI, 2.1%-4.7%)	.8% (95% CI, .6%-1.0%)
Delayed bleeding	2.7% (95% CI, 2.2%-3.2%)	4.2% (95% CI, 1.9%-5.9%)	2.4% (95% CI, 1.9%-3.0%)
Perforation	5.2% (95% CI, 4.4%-6.1%)	8.6% (95% CI, 5.9%-12.2%)	4.5% (95% CI, 3.9%-5.3%)
Oncologically curative resection	80.9% (95% CI, 76.0%-85.0%)	67.2% (95% CI, 57.5%-75.6%)	84.1% (95% CI, 79.3%-87.9%)
Recurrence post-R0 resection (12 mo)	2.0% (95% CI, 1.3%-3.0%)	5.2% (95% CI, 3.3%-8.1%)	1.1% (95% CI, .7%-1.8%)

ESD, Endoscopic submucosal dissection; *CI*, confidence interval.

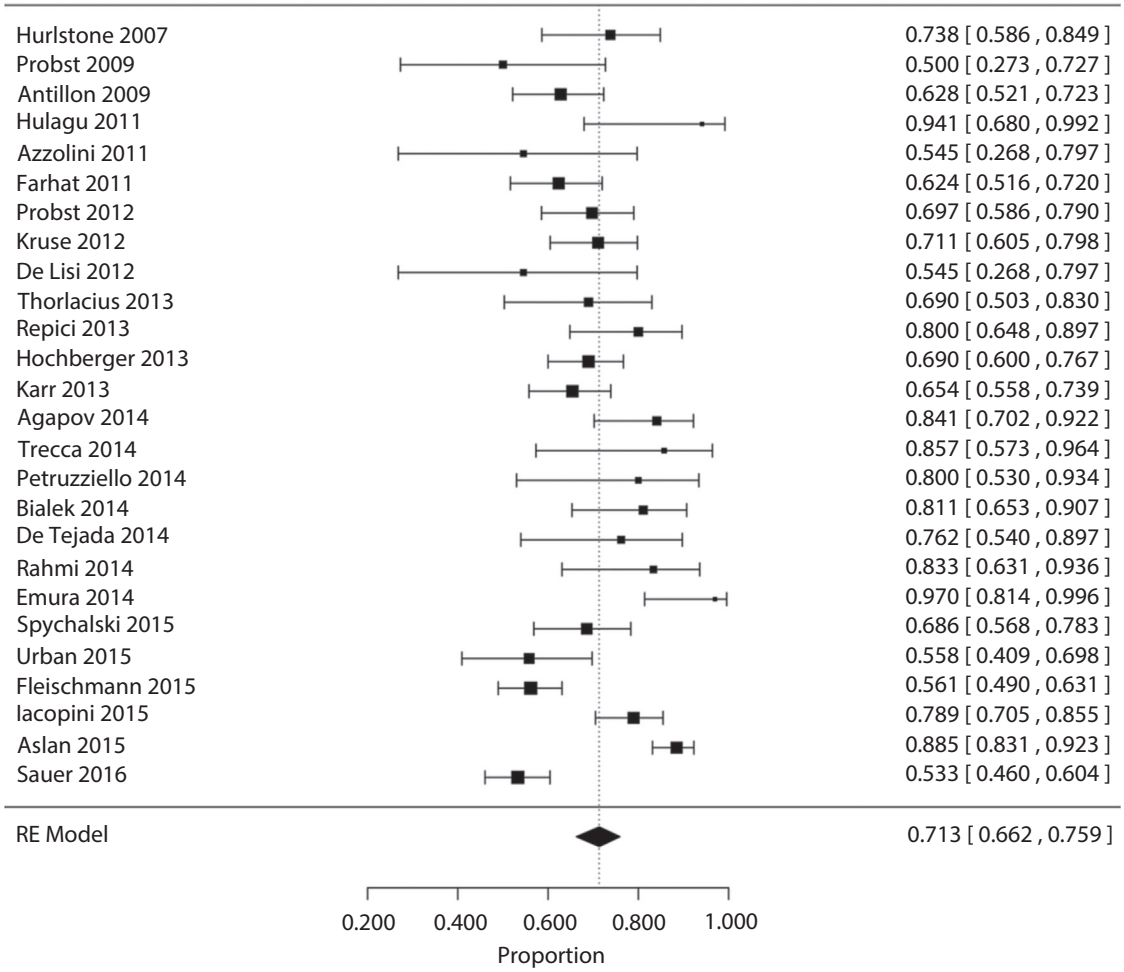

Figure 2. Forest plot of the R0 resection rates of endoscopic submucosal dissection performed with the standard technique in non-Asian countries.

meta-regression and subgroup analyses. Supplementary Table 7 (Appendix 4, available online at www.giejournal.org) shows the covariates considered and their influence on the R0 resection rate evaluated by the meta-regression. No factor significantly influenced the R0 resection rate.

In non-Asian countries the R0 resection rate was not significantly lower than that observed in Asian countries: 44.4% (95% CI, 24.6%-66.1%, Fig. 4) versus 71.1% (95% CI, 43.3%-88.8%; Fig. 5). Again, high heterogeneity was detected. The median of the means of the number of hybrid ESD performed per year in each center was 16 lesions treated and comparison of the pooled R0 resection rates of centers performing ≤16 hybrid ESD per year (6 studies for a total of 254 ESD performed) with that obtained in centers performing more than 16 hybrid ESD per year (5 studies; 445 lesions treated). In 1 study,[71] it

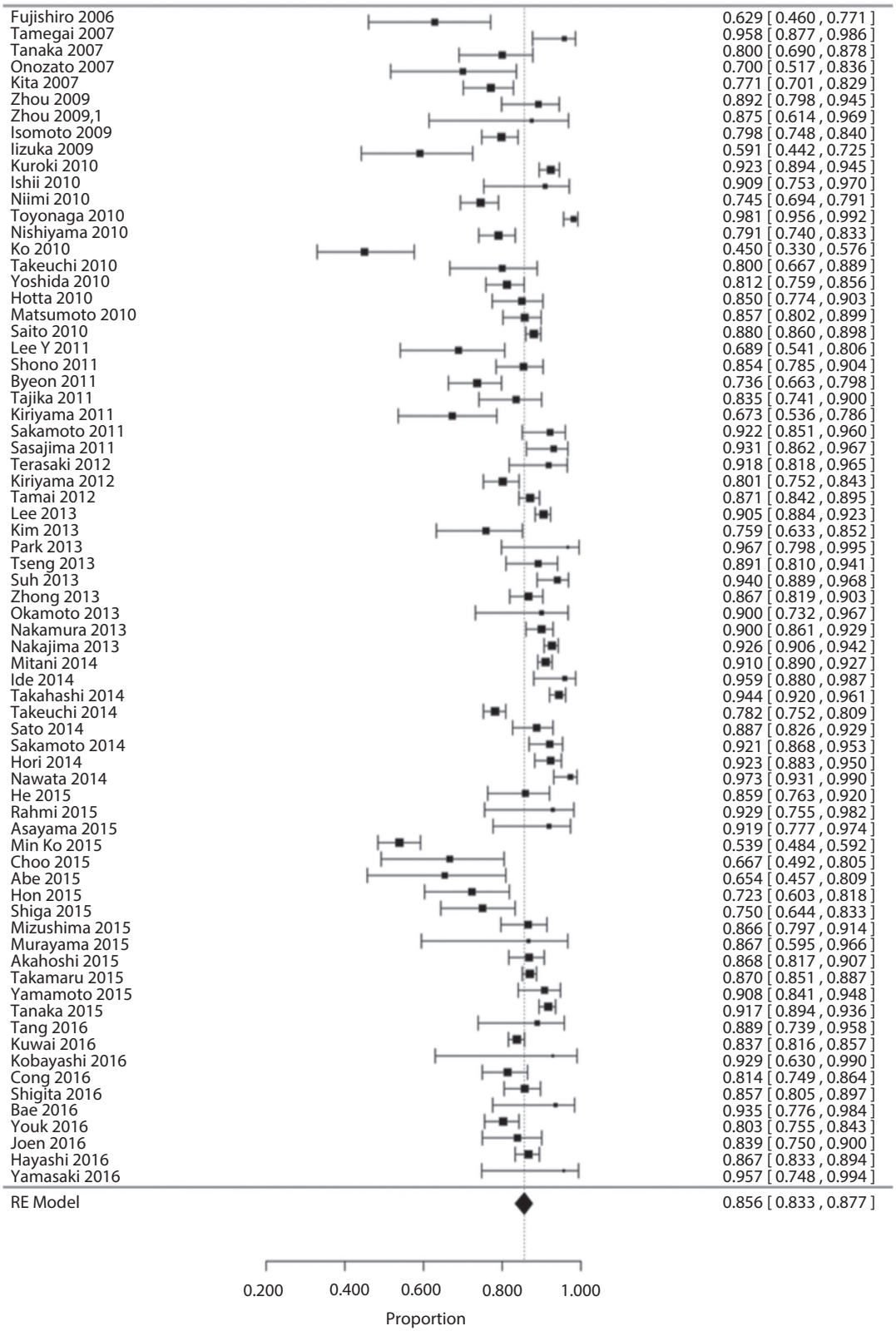

Figure 3. Forest plot of the R0 resection rates of the endoscopic submucosal dissection performed with the standard technique in Asian countries.

TABLE 4. Main findings with the hybrid technique, stratified according to non-Asian and Asian countries

Outcome (rate)	Overall	Non-Asian countries	Asian countries
En-bloc resection	68.4% (95% CI, 51.7%-81.3%)	50.1% (95% CI, 27.4%-72.7%)	78.1% (95% CI, 62.4%-88.4%)
R0 resection	60.6% (95% CI, 40.6%-77.5%)	44.4% (95% CI, 24.6%-66.1%)	71.1% (95% CI, 43.3%-88.8%)
Need for surgery post-ESD adverse event*	1.0% (95% CI, .4%-2.3%)	—	—
Delayed bleeding	4.0% (95% CI, 2.8%-5.8%)	4.7% (95% CI, 2.7%-7.9%)	3.5% (95% CI, 2.1%-5.8%)
Perforation	4.8% (95% CI, 2.4%-9.1%)	3.7% (95% CI, .7%-17.3%)	5.4% (95% CI, 2.9%-9.9%)
Oncologically curative resection†	49.7% (95% CI, 13.0%-86.7%)	—	—
Recurrence post-R0 resection‡ (12 months)	2.0% (95% CI, .7%-5.6%)	—	—

ESD, Endoscopic submucosal dissection; *CI*, confidence interval.
*Only 1 adverse event required a surgical management; therefore, subgroup analysis was not performed.
†Only 4 studies reported the oncologically curative resection rates; therefore, subgroup analysis was not performed.
‡The analysis stratified by location was not performed due to the limited number of studies.

was not possible to extract these data. The pooled R0 resection rates did not significantly differ between low- and high-volume centers: 73.2% (95% CI, 45.2%-90%) versus 53.6% (95% CI, 27.1%-78.6%). The assessment of publication bias is reported in Appendix 4 (available online at www.giejournal.org).

Comparison between standard and hybrid techniques

Eight studies directly compared standard versus hybrid techniques.[18-20,45,71,95,97,108] The standard ESD technique achieved higher R0 resection rates than that observed with the hybrid technique, yielding an odd ratio of 2.44 (95% CI, 1.23-4.85). Details are provided in Appendix 6. (available online at www.giejournal.org).

DISCUSSION

Our meta-analysis of 101 studies shows that ESD performed with the standard technique achieves R0 resection rate of 82.9% with a very low rate of adverse events requiring surgical management. Moreover, almost all the frequently reported adverse events were managed conservatively. This meta-analysis also demonstrates a very low recurrence rate for ESD (2.0%) at 12 months. This is substantially lower than the recurrence rate of 13.8% after colonic EMR as reported by a recent meta-analysis.[111]

The country where the procedure was performed and the experience of the center/operator significantly influenced the main outcomes. Non-Asian countries and centers performing ≤2 ESDs per month had lower R0 and en bloc resection rates and higher incidence of adverse events requiring surgery and recurrence rates. These 2 factors are likely to be linked because it is well known that in non-Asian countries the number of ESD procedures performed and the available expertise are lower than that in Asian countries. This situation is compounded by the lack of well-organized training program for ESD in non-Asian countries.

The other interesting finding of our analysis is the inverse association between R0 resection rate and the rectal location. One possible reason could be that rectal lesions, especially in non-Asian countries, frequently represent the first lesions approached during the training period. In addition, because there is the common belief of the lower risk of major ESD-related adverse events in the rectum, endoscopists may be tempted to carry out ESD for lesions beyond their level of expertise. However, it is important to remind the clinical consequences of potentially complex surgery for low R0 resection rates. Therefore, the resection of rectal lesions by nonexpert endoscopists should be discouraged or only attempted in highly selected cases and, possibly, in the presence of a well-trained ESD expert as compared with chance to guarantee adequate R0 resection rates.

The hybrid ESD technique has been proposed as a faster and safer alternative to standard ESD technique. However, based on the available evidence, the hybrid ESD technique appears to be a good alternative to EMR but is fails to achieve technical outcomes similar to ESD. Therefore, it should be avoided in case of lesions suspicious for superficial malignant invasion or considered as a rescue strategy, when the standard technique fails or is not feasible. The role of the hybrid technique as part of the step-up training process of the standard technique is uncertain and should be investigated.

Strengths and limitations

The search strategy and selection criteria allowed the inclusion of 109 studies with a total of 19,484 lesions, representing the most complete systematic review on this issue. Despite this, only 12 studies investigating the performance of the hybrid technique were included; therefore, further studies are warranted to better understand the role of this technique in the management of colorectal lesions. The evaluation of heterogeneity allowed the exploration of the significant differences between Asian and non-Asian countries as well as the role of the caseload and of the proportion of rectal lesions. All of these issues have not been investigated before. The relation to other meta-analyses is reported in Appendix 7 (available online at www.giejournal.org).

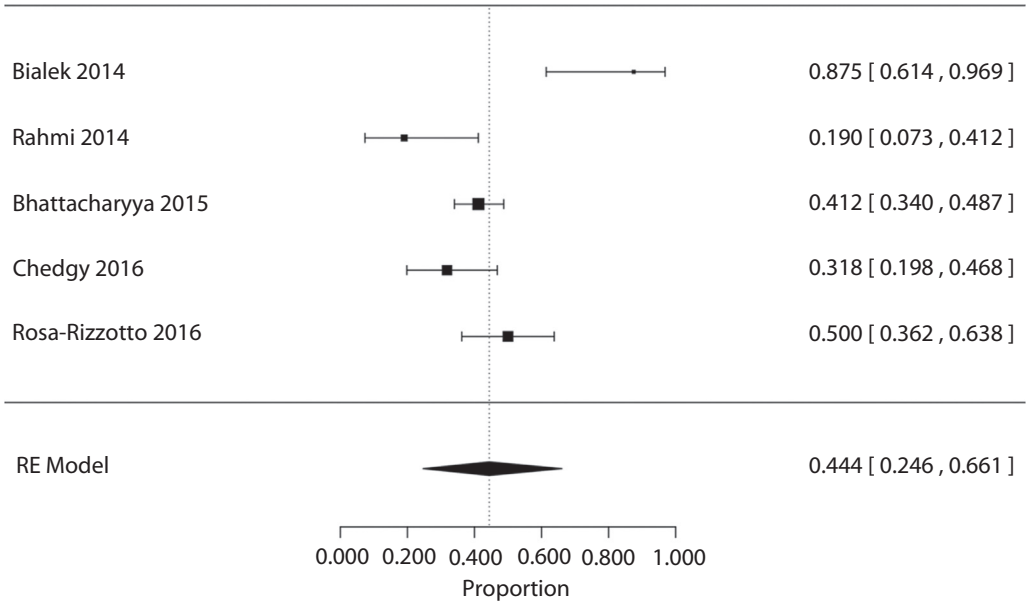

Figure 4. Forest plot of the R0 resection rates of the endoscopic submucosal dissection performed with the hybrid technique in non-Asian countries.

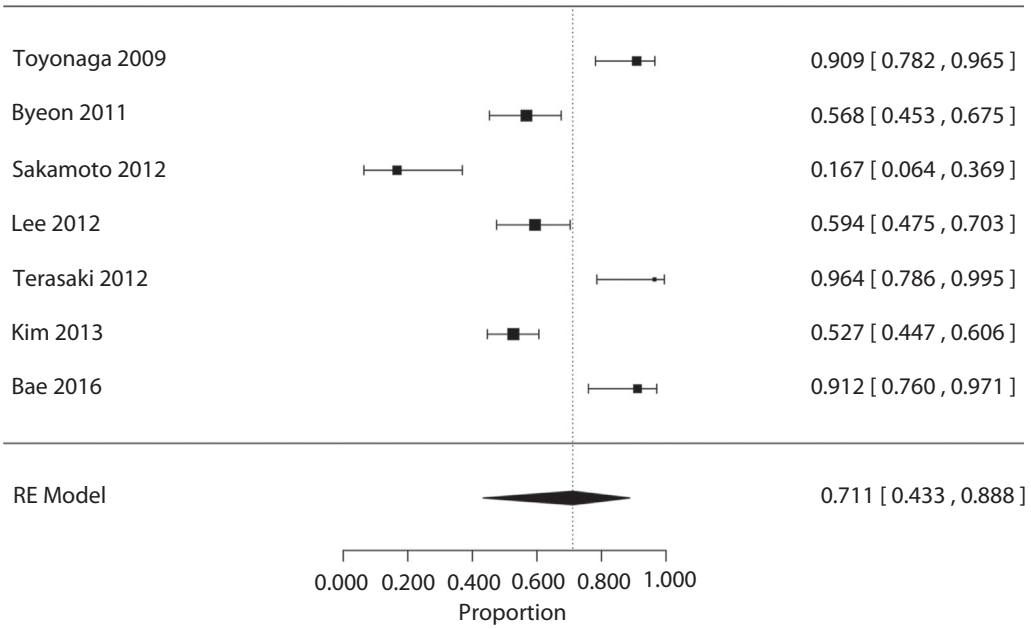

Figure 5. Forest plot of the R0 resection rates of the endoscopic submucosal dissection performed with the hybrid technique in Asian countries.

Our meta-analysis has some limitations. As expected in a meta-analysis with more than 100 studies included, between-study heterogeneity was high, and we made all efforts to explain it. Unfortunately, several possible sources of heterogeneity could not be adequately investigated because of the poor reporting quality of most studies; in particular, very rarely the results were stratified according to the site of the lesions and the indication for the procedure, which could have influenced the main outcomes. Indeed, it is well known that the treatment of recurrences after EMR are more technically challenging and more prone to adverse events than the treatment of naive lesions, mainly because of submucosal fibrosis.[4,17,23,50,59,68,72,107] Because most studies were retrospective, it is likely that the first cases reported were part of the learning curve; however, the results were not stratified accordingly to the experience of the operator, and it was therefore not possible to pool the data by the skill of the endoscopists.

The presence of publication bias did not significantly influence the main outcome measures, as demonstrated by the Duval and Tweedie's trim and fill method, showing that the adjusted R0 resection rate was largely overlapping the observed rate. We restricted our search only to studies published in English, thus potentially introducing the so-called language bias, partly contributing to the publication bias. To minimize the bias to include only positive studies, we performed an extensive search also in the proceedings of international congresses. To avoid duplication bias, 2 investigators independently checked for duplicate studies, excluding 36 duplications.

Most of the included studies were retrospective in design. However, the subgroup analysis performed according to the study design (retrospective vs prospective) did not show significant differences in the main outcomes of interest.

Implications for practice and research

The current review underlined the need for identifying referral centers, especially in non-Asian countries, to guarantee adequate rates of R0 resection and acceptable incidence of adverse events and recurrences. Most importantly, there is an urgent need to implement in non-Asian countries standardized and certified step-up training programs in the ESD procedure to improve the low R0 resection rates reported up to now. The urgency is justified by the fact that most non-Asian studies have been published by referral centers; therefore, an internal and critical appraisal of the outcomes achieved with the ESD procedure for the treatment of colorectal lesions should be promoted in every center and all efforts carried out to improve the main outcome measures. In particular, the approach to rectal lesions should be performed by inexpert endoscopists with caution, only after an accurate case selection. Because ESD is considered an alternative to the surgical approach, it remains unfair and inadequate to choose a procedure for the treatment of cancer when, in many Western centers, the R0 resection is not guaranteed in about one third of the cases.

The recently published European Society of Gastrointestinal Endoscopy guidelines suggested that the learning curve for colonic ESD requires performance of at least 40 procedures to avoid adverse events and of 80 procedures to remove large colorectal tumors.[2] However, several factors influence the minimum number of procedures required to be considered proficient, such as the previous experience with gastric ESD, the presence of an experienced supervisor, and the number of cases performed per year. Therefore, endoscopists working in low-volume centers, without or with just low experience in gastric ESD, might need many more cases to become proficient, thus likely explaining why in Western countries the reported R0 resection rates also in high-volume centers are substantially lower than those reported in low-volume centers in Asian countries, where a step-up training process is routinely and widely adopted.[112]

One of the main limitations of the existing literature is the poor reporting quality. Authors should always clearly report the definition of R0 and en bloc resection and also routinely consider the oncologically curative resection. The results should be stratified at least according to the location of the lesions and the indication for the procedure (eg, large colorectal tumor or recurrence after EMR). In addition, results obtained with both the standard and the hybrid techniques should not be reported cumulatively. Because tumor recurrence is not a negligible issue, it should always represent one of the outcomes and the number of patients effectively screened clearly stated.

Finally, most published evidence is from retrospective studies. Therefore, in the future prospective, multicenter, high-quality studies with adequate follow-up should be carried out.

Conclusion

In non-Asian countries, the standard ESD procedure achieves inadequate levels of performance; thus, efforts to improve the R0 resection and increase the safety are needed. Low R0 resection rates in the rectum are unacceptable because of the important clinical consequences; therefore, endoscopists not yet confident with the procedure should select the cases with attention and possibly perform ESD with the supervision of well-trained colleagues. The role of the hybrid ESD technique in the management of colorectal lesions is still unclear but at the moment should not be considered as an alternative to the standard technique.

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APPENDIX 1

Data sources and search strategy

We performed a comprehensive literature search by using PubMed, EMBASE, SCOPUS, Google Scholar, and the Cochrane Central Register of Clinical Trials (up to August 31, 2016) to identify full articles evaluating outcomes of endoscopic submucosal dissection for the treatment of colorectal lesions. ClinicalTrials.gov was searched for ongoing or recently completed trials, and PROSPERO was searched for ongoing or recently completed systematic reviews. Electronic searches were supplemented by manual searches of references of included studies and review articles.

We identified studies using the following medical subject headings (MeSH) and keywords, including "endoscopic submucosal dissection," "ESD," and "colorectal neoplasms." The search was restricted to English language. The Medline search strategy was ("Colon"[Mesh] OR "Colon"[All fields]) AND ("ESD"[All fields] OR "Endoscopic Submucosal Dissection"[All fields]) AND English[lang].

Selection process

Two review authors (L.F., D.M.) independently screened the titles and abstracts yielded by the search against the inclusion criteria. Full reports were obtained for all titles that appeared to meet the inclusion criteria or where there was any uncertainty. Review author pairs then screened the full text and abstract reports and decided whether these met the inclusion criteria. Disagreements were resolved through discussion of all authors. The reasons for excluding trials were recorded. Neither of the review authors was blinded to the journal titles or to the study authors or institutions. When there were multiple articles for a single study, we used the latest publication and supplemented it, if necessary, with data from the more complete version.

Data extraction

Using standardized forms, 2 reviewers (L.F., D.M.) extracted data independently and in duplicate from each eligible study. Reviewers resolved disagreements by discussion, and the arbitrators (C.H., A.R.) unresolved disagreements. The following data were extracted for each study: publication status, study design and location, number of centers involved, study population and the number of lesions treated, patient characteristics (average age, gender), indication for ESD (eg, large colorectal tumor, recurrence after EMR, fibrosis), ESD technique (standard or hybrid), enrollment period, site of the lesions, mean tumor size, number of lesions resected en bloc, number of lesions with R0 resection, number of lesions in which an oncologically curative resection was achieved, mean operation time, histology of the lesions resected (ie, low-grade and high-grade adenoma, submucosal cancer and deep of infiltration classified in sm1, sm2 or deeper,[8] presence of lymphatic and/or vascular infiltration), number of recurrence after R0 resection, number of patients in follow-up, mean period of follow-up, number of patients developing delayed bleeding after ESD, number of ESD-related perforations, and number of patients who underwent surgery after ESD-related adverse event.

Quality assessment

Quality was assessed by the modified Newcastle-Ottawa Scale for nonrandomized studies, ranging from 0 (low quality) to 5 (high quality).[9] Two reviewers (L.F., D.M.) assessed quality measures for included studies and discrepancies were adjudicated by collegial discussion.

APPENDIX 2

SUPPLEMENTARY TABLE 1. Characteristics of the included studies

Study, publication year [reference]	Type of publication	Country	Design	Mono/ Multicenter	Enrollment period	Technique	No. of patients	Mean age (y)	Sex (% male)
Fujishiro, 2006 [28]	Full text	Asia	Retrospective	Mono	2001-2005	Standard	35	NA	NA
Agapov, 2014 [12]	Full text	Europe	Retrospective	Mono	2009-2013	Standard	44	64	52
Spychalski, 2015 [83]	Full text	Europe	Retrospective	Mono	2013-2014	Standard	70	67	42.9
Probst, 2012 [70]	Full text	Europe	Retrospective	Mono	2004-2011	Standard	76	64	64.5
Thorlacius, 2013 [96]	Full text	Europe	Retrospective	Mono	2012-2013	Standard	29	74	48
Trecca, 2014 [98]	Full text	Europe	Retrospective	Mono	2012-2013	Standard	14	66	43
Hurlstone, 2007 [36]	Full text	Europe	Prospective	Mono	2004-2006	Standard	42	68	60.6
Lee Y, 2011 [43]	Abstract	Asia	Retrospective	Mono	2004-2010	Standard	45	64	62
He, 2015 [30]	Full text	Asia	Retrospective	Mono	2012-2013	Standard	78	62	49
Sakamoto, 2011 [74]	Full text	Asia	Retrospective	Mono	2008-2009	Hybrid	24	69	42
Petruzziello, 2014 [68]	Abstract	Europe	Retrospective	Mono	2011-2013	Standard	15	NA	NA
Bialek, 2014 [19]	Full text	Europe	Retrospective	Mono	2007-2013	Standard	37	64	NA
Shono, 2011 [82]	Full text	Asia	Retrospective	Mono	2007-2010	Standard	137	67	57.7
Mitani, 2014 [57]	Abstract	Asia	Retrospective	Mono	2005-2013	Standard	846	65.4	61
Tamegai, 2007 [91]	Full text	Asia	Retrospective	Mono	2003-2005	Standard	70	63	54,3
Kuroki, 2010 [52]	Full text	Asia	Retrospective	Mono	2005-2009	Standard	418	66	62
Bialek, 2014 [19]	Full text	Europe	Retrospective	Mono	2007-2013	Hybrid	16	64	NA
Repici, 2013 [73]	Full text	Europe	Prospective	Mono	2010-2011	Standard	40	65	67.5
Lee, 2013 [54]	Full text	Asia	Retrospective	Mono	2006-2011	Standard	874	62	59.2
Byeon, 2011 [20]	Full text	Asia	Retrospective	Mono	2004-2010	Standard	162	61	63
Zhou, 2009 [106]	Full text	Asia	Retrospective	Mono	2006-2007	Standard	73	64,2	53
Tajika, 2011 [85]	Full text	Asia	Retrospective	Mono	2005-2009	Standard	85	64	57.6
Zhou, 2009 [107]	Full text	Asia	Retrospective	Mono	2006-2007	Standard	16	64.6	56.3
Probst, 2009 [69]	Full text	Europe	Retrospective	Mono	2003-2007	Standard	16	67	NA
Lee, 2012 [108]	Full text	Asia	Retrospective	Mono	2006-2009	Hybrid	67	62	58
Hulagu, 2011 [35]	Abstract	Europe	Retrospective	Mono	2007-2010	Standard	17	NA	71
Rahmi, 2015 [72]	Full text	Asia	Retrospective	Mono	2008-2013	Standard	28	66.5	54
Hochberger, 2013 [31]	Abstract	Europe	Retrospective	Mono	2006-2012	Standard	113	68	64
Tang, 2016 [94]	Full text	Asia	Retrospective	Mono	2010-2014	Standard	35	63	54.3
Azzolini, 2011 [17]	Full text	Europe	Prospective	Mono	2007-2010	Standard	11	58	54.5
Kim, 2013 [45]	Full text	Asia	Retrospective	Mono	2007-2011	Standard	58	64	62.1
Kim, 2013 [45]	Full text	Asia	Retrospective	Mono	2007-2011	Hybrid	148	61	51
Tanaka, 2007 [92]	Full text	Asia	Retrospective	Mono	2003-2005	Standard	70	66	67
Ishii, 2010 [40]	Full text	Asia	Retrospective	Mono	2005-2009	Standard	33	66	60.6
Park, 2013 [67]	Full text	Asia	Retrospective	Mono	2007-2011	Standard	30	59	46.7
Byeon, 2011 [20]	Full text	Asia	Retrospective	Mono	2004-2010	Hybrid	71	61	62
Terasaki, 2012 [95]	Full text	Asia	Retrospective	Mono	2006-2009	Standard	61	65	62.3
Terasaki, 2012 [95]	Full text	Asia	Retrospective	Mono	2006-2009	Hybrid	28	70	61
Onozato, 2007 [66]	Full text	Asia	Retrospective	Mono	2002-2006	Standard	30	70,3	53
Tseng, 2013 [99]	Full text	Asia	Retrospective	Mono	2006-2011	Standard	92	66	64
Ide, 2014 [38]	Abstract	Asia	Retrospective	Mono	2009-2013	Standard	73	NA	NA
Kuwai, 2016 [53]	Abstract	Asia	Retrospective	Mono	2008-2014	Standard	1227	69	61

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SUPPLEMENTARY TABLE 1. Continued

Study, publication year [reference]	Type of publication	Country	Design	Mono/ Multicenter	Enrollment period	Technique	No. of patients	Mean age (y)	Sex (% male)
Asayama, 2015 [15]	Full text	Asia	Retrospective	Mono	2003-2013	Standard	37	68	70
Kobayashi, 2016 [50]	Abstract	Asia	Retrospective	Mono	2005-2015	Standard	14	NA	NA
Niimi, 2010 [63]	Full text	Asia	Retrospective	Mono	2000-2008	Standard	290	65	32.4
Toyonaga, 2010 [97]	Full text	Asia	Retrospective	Mono	2002-2007	Standard	268	69	53
Bhattacharyya, 2015 [3]	Full text	Europe	Prospective	Mono	2007-2013	Hybrid	170	71	56
Isomoto, 2009 [41]	Full text	Asia	Retrospective	Mono	2001-2008	Standard	278	69	57.6
Nishiyama, 2010 [64]	Full text	Asia	Retrospective	Mono	2001-2008	Standard	282	70	57.4
Suh, 2013 [84]	Full text	Asia	Retrospective	Mono	2007-2012	Standard	150	62	60
Chedgy, 2016 [4]	Full text	Europe	Prospective	Mono	2007-2014	Hybrid	44	73	64
Min Ko, 2015 [56]	Abstract	Asia	Retrospective	Mono	2003-2013	Standard	256	61	67.6
Kiriyama, 2012 [47]	Full text	Asia	Retrospective	Mono	1998-2008	Standard	297	65	59
Cong, 2016 [22]	Full text	Asia	Retrospective	Mono	2003-2007	Standard	156	63	59
Kiriyama, 2011 [47]	Full text	Asia	Retrospective	Mono	2003-2006	Standard	52	61	NA
Takahashi, 2014 [86]	Abstract	Asia	Retrospective	Mono	2005-2013	Standard	482	68.9	NA
Kruse, 2012 [51]	Abstract	Europe	Retrospective	Mono	2006-2011	Standard	83	69	67
Shigita, 2016 [81]	Full text	Asia	Retrospective	Mono	2003-2010	Standard	222	66	65.3
Bae, 2016 [18]	Full text	Asia	Prospective	Mono	2014-2014	Hybrid	34	63	59
Bae, 2016 [18]	Full text	Asia	Prospective	Mono	2014-2014	Standard	31	66	58
Karr, 2013 [44]	Abstract	America	Retrospective	Mono	NA	Standard	103	66	NA
Choo, 2015 [21]	Full text	Asia	Retrospective	Mono	2009-2013	Standard	33	63	45
Zhong, 2013 [105]	Abstract	Asia	Retrospective	Mono	2006-2011	Standard	NA	NA	NA
Rahmi, 2014 [71]	Full text	Europe	Prospective	Mono	NA	Hybrid	NA	NA	NA
Ko, 2010 [49]	Abstract	Asia	Retrospective	Mono	NA	Standard	60	NA	NA
Sauer, 2016 [79]	Full text	Europe	Retrospective	Mono	2012-2015	Standard	178	70	59
Rosa-Rizzotto, 2016 [109]	Abstract	Europe	Retrospective	Mono	2012-2015	Hybrid	48	63	56
De Lisi, 2012 [23]	Abstract	Europe	Retrospective	Mono	NA	Standard	11	70.6	36
Urban, 2015 [104]	Abstract	Europe	Retrospective	Mono	2011-2014	Standard	43	69.6	74.4
Fleischmann, 2015 [27]	Abstract	Europe	Prospective	Mono	2004-2014	Standard	187	NA	NA
Iizuka, 2009 [39]	Full text	Asia	Retrospective	Mono	2000-2004	Standard	44	69	64,3
Farhat, 2011 [26]	Full text	Europe	Prospective	Multi	2008-2010	Standard	85	NA	NA
Antillon, 2009 [14]	Abstract	America	Retrospective	Mono	2006-2008	Standard	86	NA	NA
Abe, 2015 [11]	Abstract	Asia	Retrospective	Mono	1998-2014	Standard	26	65.5	42
Hon, 2015 [32]	Full text	Asia	Retrospective	Mono	2009-2013	Standard	65	69	54,5
Shiga, 2015 [80]	Full text	Asia	Retrospective	Mono	2009-2013	Standard	80	68.1	68
De Tejada, 2014 [24]	Abstract	Europe	Prospective	Mono	2012-2014	Standard	21	63.8	38
Kita, 2007 [48]	Full text	Asia	Retrospective	Mono	1998-2005	Standard	NA	NA	NA
Takeuchi, 2014 [89]	Full text	Asia	Retrospective	Multi	2007-2010	Standard	816	67	57.4
Iacopini, 2015 [37]	Abstract	Europe	Prospective	Mono	2010-2014	Standard	106	66	57
Takeuchi, 2010 [89]	Full text	Asia	Prospective	Mono	2008-2009	Standard	49	67	51
Youk, 2016 [103]	Full text	Asia	Prospective	Mono	2012-2014	Standard	319	58	57
Yoshida, 2010 [102]	Full text	Asia	Retrospective	Multi	2005-2010	Standard	250	67	NA
Rahmi, 2014 [71]	Full text	Europe	Prospective	Mono	NA	Standard	NA	NA	NA
Jeon, 2015 [42]	Full text	Asia	Retrospective	Mono	2009-2012	Standard	93	65	51
Hotta, 2010 [34]	Full text	Asia	Retrospective	Mono	2003-2008	Standard	115	70	66.7

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SUPPLEMENTARY TABLE 1. Continued

Study, publication year [reference]	Type of publication	Country	Design	Mono/ Multicenter	Enrollment period	Technique	No. of patients	Mean age (y)	Sex (% male)
Matsumoto, 2010 [55]	Full text	Asia	Retrospective	Mono	2002-2009	Standard	203	66	64.5
Mizushima, 2015 [58]	Full text	Asia	Retrospective	Multi	2009-2013	Standard	122	68	59
Murayama, 2015 [59]	Abstract	Asia	Retrospective	Mono	2013-2015	Standard	15	NA	NA
Akahoshi, 2015 [13]	Abstract	Asia	Prospective	Mono	2007-2015	Standard	220	69	55
Hayashi, 2016 [29]	Full text	Asia	Retrospective	Mono	2010-2014	Standard	472	68	57
Takamaru, 2015 [87]	Abstract	Asia	Retrospective	Mono	1998-2015	Standard	1268	NA	NA
Tamai, 2012 [90]	Full text	Asia	Retrospective	Mono	1998-2010	Standard	614	65.1	58.3
Aslan, 2015 [16]	Abstract	Europe	Retrospective	Mono	2012-2015	Standard	185	103	34
Sato, 2014 [78]	Full text	Asia	Retrospective	Mono	2009-2013	Standard	147	72	57.8
Okamoto, 2013 [65]	Full text	Asia	Retrospective	Mono	2010-2011	Standard	30	69	53.3
Nakamura, 2013 [61]	Abstract	Asia	Prospective	Mono	2009-2012	Standard	NA	NA	NA
Yamamoto, 2015 [100]	Full text	Asia	Retrospective	Mono	2011-2013	Standard	107	69	58
Sakamoto, 2011 [74]	Full text	Asia	Retrospective	Mono	2008-2010	Standard	101	NA	NA
Tanaka, 2015 [92]	Full text	Asia	Retrospective	Mono	2008-2013	Standard	629	70	55
Sakamoto, 2014 [75]	Full text	Asia	Retrospective	Mono	2005-2012	Standard	164	NA	NA
Hori, 2014 [33]	Full text	Asia	Prospective	Mono	2006-2010	Standard	232	70	65.6
Nakajima, 2013 [60]	Full text	Asia	Prospective	Multi	2007-2010	Standard	816	67	57.4
Sasajima, 2011 [77]	Abstract	Asia	Retrospective	Mono	NA	Standard	100	NA	NA
Yamasaki, 2016 [101]	Full text	Asia	Retrospective	Mono	2014-2015	Standard	23	72	58
Emura, 2014 [25]	Abstract	America	Retrospective	Mono	2008-2013	Standard	32	NA	NA
Nawata, 2014 [62]	Full text	Asia	Retrospective	Mono	2010-2013	Standard	145	70	63.4
Toyonaga, 2009 [97]	Full text	Asia	Retrospective	Mono	2002-2008	Hybrid	44	NA	NA
Saito, 2010 [76]	Full text	Asia	Retrospective	Multi	1998-2008	Standard	1090	66	62.1

NA, Not available.

SUPPLEMENTARY TABLE 2. Characteristics of the lesions treated

Study, publication year [reference]	ESD indication	No. of lesions (total)	No. of rectal lesions (%)	Mean operation time (min)	Mean tumor size (mm)
Fujishiro, 2006 [28]	Large rectal neoplasia >20 cm or recurrence after EMR	35	100	NA	33
Agapov, 2014 [12]	Large CR tumor >20 mm or recurrence after EMR	44	43	120	35
Spychalski, 2015 [83]	Large CR tumor >20 mm, fibrosis	70	56	106	34
Probst, 2012 [70]	Large CR tumor or recurrence after EMR	76	93	176	46
Thorlacius, 2013 [96]	LST >20 mm/fibrosis/post-EMR	29	59	142	28
Trecca, 2014 [98]	Large CR tumor >20 mm	14	36	123	30
Hurlstone, 2007 [36]	Large CR tumor >20 mm	42	33	48	31
Lee Y, 2011 [43]	CR cancer	45	44	NA	35
He, 2015 [30]	Large CR tumor >20 mm	78	53	64	32
Sakamoto, 2011 [74]	Large CR tumor >20 mm	24	21	40	25
Petruzziello, 2014 [68]	Recurrences	15	73	70	23
Bialek, 2014* [19]	Large CR tumor >20 mm	37	68	70	37
Shono, 2011 [82]	Large CR tumor >20 mm, fibrosis	137	26	79	29
Mitani, 2014 [57]	Large CR tumor	958	NA	68	30.7
Tamegai, 2007 [91]	LST >20 mm/fibrosis	71	24	61	33
Kuroki, 2010 [52]†	Large CR tumor or recurrence after EMR	418	21	74	32
Bialek, 2014† [19]	Large CR tumor >20 mm	16	6	39	37
Repici, 2013 [73]	LST >30 mm	40	100	86	47
Lee, 2013 [54]	Large CR tumor >20 mm or recurrence after EMR	874	21	54	27
Byeon, 2011* [20]	Large CR tumor >15 mm	163	53	49	33
Zhou, 2009 [106]	Large CR tumor >20 mm	74	57	110	32.6
Tajika, 2011 [85]	Large CR tumor >20 mm	85	36	87	32
Zhou, 2009 [107]	Recurrences	16	62.50	87	19
Probst, 2009 [69]	Rectal lesion	16	100	21	39
Lee, 2012 [108]	Large CR tumor >20 mm	69	17	NA	24
Hulagu, 2011 [35]	Large CR tumor >20 mm	17	18	NA	NA
Rahmi, 2015 [72]	Recurrences	28	25	63	17.5
Hochberger, 2013 [31]	Large CR tumor and recurrences	116	53	NA	NA
Tang, 2016 [94]	LST >40 mm	36	100	126	59
Azzolini, 2011 [17]	Recurrences	11	100.0	132	60
Kim, 2013* [45]	NA	58	84	66	31
Kim, 2013† [45]	NA	148	50	43	23
Tanaka, 2007 [92]	Large CR tumor >20 mm, fibrosis or recurrence after EMR	70	48	71	28
Ishii, 2010 [40]	Large CR tumor >20 mm	33	27	121	35
Park, 2013 [67]	Large CR tumor	30	100	84	25
Byeon 2011† [20]	Large CR tumor >15 mm	74	51	35	24
Terasaki, 2012* [95]	LST >20 mm/fibrosis	61	51	85	42
Terasaki, 2012† [95]	LST >20 mm/fibrosis	28	29	58	31
Onozato, 2007 [66]	Rectal tumors	30	100	81	26.2
Tseng, 2013 [99]	Large CR tumor >20 mm, fibrosis and submucosal tumor	92	25	59	37

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SUPPLEMENTARY TABLE 2. Continued

Study, publication year [reference]	ESD indication	No. of lesions (total)	No. of rectal lesions (%)	Mean operation time (min)	Mean tumor size (mm)
Ide, 2014 [38]	Rectal tumors	73	100	NA	37
Kuwai, 2016 [53]	Large CR tumor	1259	40	92	33
Asayama, 2015 [15]	T1 CRC tumor	37	NA	60	25
Kobayashi, 2016 [50]	Recurrences	14	57	78	10.5
Niimi, 2010 [63]	LST >20 mm/fibrosis/post-EMR	310	26	NA	29
Toyonaga, 2010 [97]	LST >20 mm	268	26	63	33
Bhattacharyya, 2015 [3]	Large CR tumor >20 mm or recurrence after EMR	170	0	150	46
Isomoto, 2009 [41]	Large CR tumor >20 mm, fibrosis and submucosal tumor	292	27	NA	26.8
Nishiyama, 2010 [64]	LST >20 mm/fibrosis/post-EMR	296	27	NA	27
Suh, 2013 [84]	Submucosal invasive colorectal cancer	150	39	62	25
Chedgy, 2016 [4]	Fibrosis post-EMR, biopsy specimen, tattoo	44	39	NA	40
Min Ko, 2015 [56]	Large CR tumor	323	46	NA	31.6
Kiriyama, 2012 [47]	Large CR tumor >20 mm and recurrences	297	38	106	37
Cong, 2016 [22]	LST >30 mm	177	55	64	52
Kiriyama, 2011 [47]	Noninvasive rectal tumor	52	100	131	40
Takahashi, 2014 [86]	Large CR tumor	501	NA	NA	NA
Kruse, 2012 [51]	Large CR tumor >20 mm or recurrence after EMR	83	15.70	NA	66
Shigita, 2016 [81]	Large CR tumor; fibrosis, recurrences after EMR	224	50	77	31
Bae, 2016† [18]	Large CR tumor >20 mm	34	38	27	27
Bae, 2016* [18]	Large CR tumor >20 mm	31	35	40	30
Karr, 2013 [44]	Large CR tumor >20 mm and recurrences	104	NA	96	NA
Choo, 2015 [21]	Large CR tumor >20 mm and recurrences	33	30	NA	30
Zhong, 2013 [105]	CR submucosal tumor	255	NA	NA	NA
Rahmi, 2014† [71]	Rectal tumors >10 mm	21	NA	NA	NA
Ko, 2010 [49]	Large CR tumor >30 mm	60	60	NA	40
Sauer, 2016 [79]	Large CR tumor	182	35%	128	41
Rosa-Rizzotto, 2016 [109]	Large CR tumor >20 mm and recurrences	48	65	99	NA
De Lisi, 2012 [23]	Recurrences	11	64	137	24
Urban, 2015 [104]	Large CR tumor	43	18.60	NA	24
Fleischmann, 2015 [27]	Large CR tumor	187	84	NA	NA
Iizuka, 2009 [39]	Large CR tumor >20 mm	44	59	48	15
Farhat, 2011 [26]	Large CR tumor	85	85	130	NA
Antillon, 2009 [14]	NA	86	27	NA	42
Abe, 2015 [11]	Rectal tumors	26	100	220	80
Hon, 2015 [32]	Large CR tumor >20 mm	65	9	113	30
Shiga, 2015 [80]	Large CR tumor >20 mm and recurrences	80	30	109	34,9
De Tejada, 2014 [24]	Large CR tumor	21	33	108	NA
Kita, 2007 [48]	Large CR tumor >20 mm	166	NA	102	33
Takeuchi, 2014 [89]	Large CR tumor > 20 mm	816	36	78	35
Iacopini, 2015 [37]	Large CR tumor >20 mm and recurrences	114	25	NA	NA
Takeuchi, 2010 [89]	Large CR tumor >20 mm	50	30	40	36
Youk, 2016 [103]	Biopsy-proven cancer, LST >20, submucosal tumor	319	47	46	24

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SUPPLEMENTARY TABLE 2. Continued

Study, publication year [reference]	ESD indication	No. of lesions (total)	No. of rectal lesions (%)	Mean operation time (min)	Mean tumor size (mm)
Yoshida, 2010 [102]	Large CR tumor >20 mm	250	32	106	29
Rahmi, 2014* [71]	Rectal tumors >10 mm	24	NA	NA	NA
Jeon, 2015 [42]	Large CR tumor >20 mm or recurrence after EMR	93	33	45	30
Hotta, 2010 [34]	Large CR tumor >20 mm	120	28	141	35
Matsumoto, 2010 [55]	LST >20 mm/fibrosis/post-EMR	203	NA	NA	32
Mizushima, 2015 [58]	Large CR tumor or recurrence after EMR	134	38	64	27
Murayama, 2015 [59]	Recurrences	15	40	65	24.8
Akahoshi, 2015 [13]	NA	220	21	89	26.7
Hayashi, 2016 [29]	Large CR tumor >20 mm	472	29	64	35
Takamaru, 2015 [87]	Large CR tumor	1333	NA	101	NA
Tamai, 2012 [90]	Large CR tumor >20 mm and recurrences	635	26.50	NA	31
Aslan, 2015 [16]	NA	191	45	78.5	37.9
Sato, 2014 [78]	Large CR tumor >20 mm or recurrence after EMR	151	20	72	32
Okamoto, 2013 [65]	Large CR tumor >20 mm or LST >30	30	0	146	37
Nakamura, 2013 [61]	Large CR tumor	300	NA	90	30
Yamamoto, 2015 [100]	LST >20 mm	119	26	82	33
Sakamoto, 2011 [74]	Large CR tumor >20 mm, fibrosis or recurrence after EMR	102	28	74	30
Tanaka, 2015 [92]	Large CR tumor >20 mm, fibrosis or recurrence after EMR	674	24	65	35
Sakamoto, 2014 [75]	Large CR tumor >20 mm, fibrosis or recurrence after EMR	164	38	95	30
Hori, 2014 [33]	Large CR tumor >20 mm or recurrence after EMR	247	5	60	35
Nakajima, 2013 [60]	LST >20 mm/fibrosis/post-EMR	816	36	96	39
Sasajima, 2011 [77]	Large CR tumor	101	34	91	NA
Yamasaki, 2016 [101]	LST >20 mm	23	0	61	27
Emura, 2014 [25]	Large CR tumor >20 mm	33	64	109	33
Nawata, 2014 [62]	Large tumor	150	21	43	30
Toyonaga, 2009† [97]	NA	44	NA	27	17
Saito, 2010 [76]	LST >20 mm/fibrosis/post-EMR	1111	30	116	35

ESD, Endoscopic submucosal dissection; *NA*, not available; *LST*, lateral spreading tumor; *CR*, colorectal; *CRC*, colorectal cancer.
*Standard technique arm.
†Hybrid technique arm.

SUPPLEMENTARY TABLE 3. En bloc, R0, and adverse event rates

Study, publication year [reference]	No. of lesions (total)	En bloc resection rate	R0 resection rate	Oncologically curative resection rate	Delayed bleeding rate	Perforation rate	Surgery due to ESD-related adverse event rate
Fujishiro, 2006 [28]	35	89%	63%	97	0%	6%	0%
Agapov, 2014 [12]	44	84%	84%	77%	0%	11%	0%
Spychalski, 2015 [83]	70	71%	69%	NA	4%	6%	6%
Probst, 2012 [70]	76	82%	70%	NA	8%	1%	0%
Thorlacius, 2013 [96]	29	72%	69%	76%	0%	7%	0%
Trecca, 2014 [98]	14	93%	86%	86%	7%	29%	7%
Hurlstone, 2007 [36]	42	79%	74%	NA	2%	2%	0%
Lee Y, 2011 [43]	45	73.3%	68.9%	NA	0%	13%	0%
He, 2015 [30]	78	88%	86%	82%	1%	9%	1%
Sakamoto, 2011 [74]	24	67%	17%	17%	0%	0%	0%
Petruzziello, 2014 [68]	15	93.3%	80%	NA	NA	20%	7%
Bialek, 2014* [19]	37	87%	81%	NA	5%	0%	0%
Shono, 2011 [82]	137	89%	85%	NA	4%	4%	1%
Mitani, 2014 [57]	958	98.5%	91%	NA	3%	3%	1%
Tamegai, 2007 [91]	71	99%	96%	90%	0%	1%	0%
Kuroki, 2010 [52]	418	98%	92%	84%	2%	6%	1%
Bialek, 2014† [19]	16	88%	88%	NA	6%	0%	0%
Repici, 2013 [73]	40	90%	80%	75%	0%	3%	0%
Lee, 2013 [54]	874	97%	91%	NA	0.5%	6%	0%
Byeon, 2011* [20]	163	87%	75%	NA	1%	7%	0%
Zhou, 2009 [106]	74	93%	89%	NA	1%	8%	1%
Tajika, 2011 [85]	85	84%	84%	NA	2%	6%	4%
Zhou, 2009 [107]	16	93.8%	87.5%	88%	0%	6%	0%
Probst, 2009 [69]	16	63%	50%	NA	0%	13%	0%
Lee, 2012 [108]	69	65%	59%	NA	3%	3%	0%
Hulagu, 2011 [35]	17	94.1%	94.1%	NA	17.6%	12%	6%
Rahmi, 2015 [72]	28	96.4%	92.9%	NA	0%	4%	0%
Hochberger, 2013 [31]	116	92.2%	69%	NA	4.3%	3%	1%
Tang, 2016 [94]	36	92%	89%	89%	3%	8%	0%
Azzolini, 2011 [17]	11	54.5%	54.5%	55%	0%	18.2%	0%
Kim, 2013* [45]	58	97%	76%	NA	9%	16%	0%
Kim, 2013† [45]	148	63%	53%	NA	5%	11%	0%
Tanaka, 2007 [92]	70	80%	80%	NA	1%	10%	3%
Ishii, 2010 [40]	33	91%	91%	82%	3%	3%	0%
Park, 2013 [67]	30	97%	97%	97%	0%	3%	0%
Byeon 2011† [20]	74	64%	57%	NA	3%	3%	0%
Terasaki, 2012* [95]	61	100%	92%	92%	11%	3%	0%
Terasaki, 2012† [95]	28	100%	96%	96%	0%	0%	0%
Onozato, 2007 [66]	30	73.3%	70%	NA	0%	3%	0%
Tseng, 2013 [99]	92	95%	89%	89%	0%	12%	0%
Ide, 2014 [38]	73	100%	95.9%	82%	2.7%	0%	0%
Kuwai, 2016 [53]	1259	92.6%	83.7%	NA	3.7%	4%	NA
Asayama, 2015 [15]	37	100%	92%	16%	8%	5%	0%

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SUPPLEMENTARY TABLE 3. Continued

Study, publication year [reference]	No. of lesions (total)	En bloc resection rate	R0 resection rate	Oncologically curative resection rate	Delayed bleeding rate	Perforation rate	Surgery due to ESD-related adverse event rate
Kobayashi, 2016 [50]	14	100	92.9%	NA	0%	0%	0%
Niimi, 2010 [63]	310	90%	75%	NA	2%	5%	0%
Toyonaga, 2010 [97]	268	99%	98%	90%	0%	2%	0%
Bhattacharyya, 2015 [3]	170	41%	41%	41%	5%	2%	.5%
Isomoto, 2009 [41]	292	90%	80%	NA	1%	8%	.7%
Nishiyama, 2010 [64]	296	89%	79%	NA	1%	8%	1%
Suh, 2013 [84]	150	98%	94%	NA	0%	5%	0%
Chedgy, 2016 [4]	44	32%	32%	32%	5%	0%	0%
Min Ko, 2015 [56]	323	82%	53.9%	NA	17%	2.2%	NA
Kiriyama, 2012 [47]	297	87.2%	80.1%	NA	1.7%	5%	0%
Cong, 2016 [22]	177	83%	81%	NA	3%	2%	0%
Kiriyama, 2011 [47]	52	88%	67%	62%	2%	6%	0%
Takahashi, 2014 [86]	501	96.2%	94.4%	NA	NA	NA	NA
Kruse, 2012 [51]	83	89	71	NA	2.4	6%	1.2
Shigita, 2016 [81]	224	89.7%	85.7%	83	6.3%	5%	0
Bae, 2016† [18]	34	94%	91%	NA	3%	9%	0%
Bae, 2016* [18]	31	100%	94%	NA	3%	6%	0%
Karr, 2013 [44]	104	81.7%	65.4%	NA	1%	3%	0%
Choo, 2015 [21]	33	72.7%	66.7%	58%	0%	15%	0%
Zhong, 2013 [105]	255	98%	86.7%	NA	2.7%	6%	NA
Rahmi, 2014† [71]	21	24%	19%	NA	NA	NA	NA
Ko, 2010 [49]	60	96.7%	45%	NA	0%	5%	0%
Sauer, 2016 [79]	182	75.3%	53.3%	NA	2.7%	9%	0%
Rosa-Rizzotto, 2016 [109]	48	68.8%	50.0%	NA	4.2%	19%	0%
De Lisi, 2012 [23]	11	54.5%	54.5%	55%	0%	27%	0%
Urban, 2015 [104]	43	69.8%	55.8%	56%	4.7%	12%	2%
Fleischmann, 2015 [27]	187	77%	56.1%	49%	NA	NA	NA
Iizuka, 2009 [39]	44	64%	59%	NA	0%	7%	5%
Farhat, 2011 [26]	85	67%	62%	NA	9%	27%	NA
Antillon, 2009 [14]	86	86%	62.8%	NA	3.5%	6%	2%
Abe, 2015 [11]	26	88.5%	65.4%	NA	7.7%	0%	0%
Hon, 2015 [32]	65	82%	72%	NA	3%	8%	2%
Shiga, 2015 [80]	80	93.8%	75%	NA	3.8%	8%	0%
De Tejada, 2014 [24]	21	81%	76.2%	NA	0%	29%	14%
Kita, 2007 [48]	166	100%	77%	NA	2%	4%	1%
Takeuchi, 2014 [89]	816	95%	78%	NA	2%	2%	0%
Iacopini, 2015 [37]	114	80.7%	78.9%	75%	NA	4%	NA
Takeuchi, 2010 [89]	50	94%	80%	80%	6%	2%	0%
Youk, 2016 [103]	319	98%	80%	72%	3%	1%	0%
Yoshida, 2010 [102]	250	87%	81%	NA	2%	6%	0%
Rahmi, 2014* [71]	24	100%	83%	NA	NA	NA	NA
Jeon, 2015 [42]	93	90%	84%	NA	0%	6%	0%
Hotta, 2010 [34]	120	93%	85%	NA	NA	8%	1%

(*continued on the next page*)

SUPPLEMENTARY TABLE 3. Continued

Study, publication year [reference]	No. of lesions (total)	En bloc resection rate	R0 resection rate	Oncologically curative resection rate	Delayed bleeding rate	Perforation rate	Surgery due to ESD-related adverse event rate
Matsumoto, 2010 [55]	203	86%	86%	NA	0%	7%	1%
Mizushima, 2015 [58]	134	87%	87%	85%	4%	7%	0%
Murayama, 2015 [59]	15	93.3%	86.7%	NA	13.3%	0%	0%
Akahoshi, 2015 [13]	220	99.1%	86.8%	NA	2.3%	2%	0%
Hayashi, 2016 [29]	472	98%	87%	83%	2%	3%	0%
Takamaru, 2015 [87]	1333	91.5%	87.0%	NA	2%	3%	NA
Tamai, 2012 [90]	635	89.4%	87.1%	NA	1.4%	3%	0%
Aslan, 2015 [16]	191	90.1%	88.5%	NA	1%	3%	1%
Sato, 2014 [78]	151	95%	89%	87%	1%	1%	0%
Okamoto, 2013 [65]	30	90%	90%	NA	0%	3%	0%
Nakamura, 2013 [61]	300	92%	90%	NA	5%	2%	0%
Yamamoto, 2015 [100]	119	97%	91%	NA	2%	1%	0%
Sakamoto, 2011 [74]	102	94%	92%	92%	0%	2%	0%
Tanaka, 2015 [92]	674	94%	92%	NA	1%	3%	0%
Sakamoto, 2014 [75]	164	95%	92%	NA	3%	4%	0%
Hori, 2014 [33]	247	93%	92%	92%	0%	2%	0%
Nakajima, 2013 [60]	816	94%	93%	85%	2%	2%	0%
Sasajima, 2011 [77]	101	95%	93.1%	NA	2%	1%	0%
Yamasaki, 2016 [101]	23	100%	96%	83%	4%	0%	0%
Emura, 2014 [25]	33	97%	97%	NA	3%	9%	6%
Nawata, 2014 [62]	150	99%	97%	91%	0%	0%	0%
Toyonaga, 2009† [97]	44	91%	44	NA	2%	5%	NA
Saito, 2010 [76]	1111	89	88%	87	2%	5%	0%

ESD, Endoscopic submucosal dissection; *NA*, not available.
*Standard technique arm.
†Hybrid technique arm.

SUPPLEMENTARY TABLE 4. Recurrences after R0 resection

Study, publication year [reference]	R0 resection rate	No. of patients in follow-up	Recurrence after R0 rate	Mean follow-up period (mo)
Fujishiro, 2006 [28]	63%	35	3%	2
Agapov, 2014 [12]	84%	44	0%	3
Spychalski, 2015 [83]	69%	41	5%	3
Probst, 2012 [70]	70%	62	9.6%	3
Thorlacius, 2013 [96]	69%	5	0%	6
Trecca, 2014 [98]	86%	5	0%	6
Hurlstone, 2007 [36]	74%	36	11%	6
Lee Y, 2011 [43]	68.9%	26	0%	10
He, 2015 [30]	86%	78	0%	10
Sakamoto, 2012 [74]	17%	24	0%	12
Petruzziello, 2014 [68]	80%	12	0%	12
Bialek, 2014* [19]	81%	37	0%	12
Shono, 2011 [82]	85%	132	0%	12
Mitani, 2014 [57]	91%	509	0%	12
Tamegai, 2007 [91]	96%	64	0%	12
Kuroki, 2010 [52]	92%	307	.3%	12
Bialek, 2014† [19]	88%	16	2%	12
Repici, 2013 [73]	80%	38	2.6%	12
Lee, 2013 [54]	91%	631	.4%	13
Byeon, 2011* [20]	75%	92	1%	13
Zhou, 2009 [106]	89%	NA	0%	14
Tajika, 2011 [85]	84%	85	1%	14
Zhou, 2009 [106]	87.5%	15	0%	16
Probst, 2009 [69]	50%	16	0%	16
Lee, 2012† [108]	59%	64	3%	16
Hulagu, 2011 [35]	94.1%	16	0%	17
Rahmi, 2015 [72]	92.9%	22	0%	18
Hochberger, 2013 [31]	69%	111	0%	18
Tang, 2016 [94]	89%	30	0%	19
Azzolini, 2011 [17]	54.5%	10	0%	19.2
Kim, 2013* [45]	76%	58	2%	20
Kim, 2013† [45]	53%	148	0%	20
Tanaka, 2007 [92]	80%	62	0%	20
Ishii, 2010 [40]	91%	33	0%	20
Park, 2013 [67]	97%	29	0%	20
Byeon, 2011† [20]	57%	56	2%	20
Terasaki, 2012* [95]	92%	56	0%	22
Terasaki, 2012† [95]	96%	27	0%	22
Onozato, 2007 [66]	70%	23	0%	26
Tseng, 2013 [99]	89%	82	0%	27
Ide, 2014 [38]	95.9%	73	0%	27
Kuwai, 2016 [53]	83.7%	894	0%	30
Asayama, 2015 [15]	92%	37	0%	30
Kobayashi, 2016 [50]	92.9%	14	0%	30

(*continued on the next page*)

SUPPLEMENTARY TABLE 4. Continued

Study, publication year [reference]	R0 resection rate	No. of patients in follow-up	Recurrence after R0 rate	Mean follow-up period (mo)
Niimi, 2010 [63]	75%	224	1.7%	31
Toyonaga, 2010 [97]	98%	227	0%	32
Bhattacharyya, 2015 [3]	41%	160	13%	32
Isomoto, 2009 [41]	80%	180	0%	33
Nishiyama, 2010 [64]	79%	213	.4%	34
Suh, 2013 [84]	94%	55	2%	36
Chedgy, 2016 [4]	32%	38	15%	39
Min Ko, 2015 [56]	53.9%	136	0%	40.1
Kiriyama, 2012 [46]	80.1%	21	0%	44
Cong, 2016 [22]	81%	142	8%	44
Kiriyama, 2011 [47]	67%	32	0%	60
Takahashi, 2014 [86]	94.4%	401	0%	60
Kruse, 2012 [51]	71%	82	1.2%	66
Shigita, 2016 [81]	85.7%	201	1.5%	76
Karr, 2013 [44]	65.4%	104	0%	NA
Choo, 2015 [21]	66.7%	33	0%	NA
Zhong, 2013 [105]	86.7%	221	0%	NA

*Standard technique arm.
†Hybrid technique arm.

APPENDIX 3

Oncologically curative resection rate

Oncologically curative resection was reported only in some studies (36/97 studies). Overall, it was achieved in 4.654 cases of 5.625 lesions dissected, yielding a pooled rate of 80.9% (95% CI, 76%-85%). In non-Asian countries the curative resection rate was significantly lower, 67.2% (95% CI, 57.5%-75.6%), than that observed in Asian countries, 84.1% (95% CI, 79.3%-87.9%). Low-volume centers reported lower but not statistically significant rates of oncologically curative resection in comparison with high-volume centers: 77.6% (95% CI, 66.6%-85.7%) versus 84.6% (95% CI, 81.4%-87.3%).

Delayed bleeding

Overall, a delayed bleeding was reported in 91 studies for a total of 439 cases out of 17,803 lesions, with a pooled rate of 2.7% (95% CI, 2.2%-3.2%), with high level of heterogeneity ($Q^2 < .001$; $I^2 = 66.2\%$). A significant difference was observed between non-Asian versus Asian countries: 4.2% (95% CI, 2.9%-5.9%) versus 2.4% (95% CI, 1.9%-3.0%), respectively. In addition, low-volume centers presented a significantly higher rate of delayed bleeding (3.8%; 95% CI, 2.95%-5.1%) in comparison with high-volume centers (2.2%; 95% CI, 1.7%-2.9%).

Perforation

In 94 studies were reported 775 cases of perforations out of 18,052 treated lesions, yielding a pooled rate of 5.2% (95% CI, 4.4%-6.1%), with high level of heterogeneity ($Q^2 < .001$; $I^2 = 74.9\%$). In non-Asian countries a significantly higher rate was observed when compared with that reported by Asian countries: 8.6% (95% CI, 5.9%-12.2%) versus 4.5% (95% CI, 3.9%-5.3%). A significant difference was also observed in the comparison between low- and high-volume centers: 7.7% (95% CI, 6.2%-9.5%) versus 4.2% (95% CI, 3.4%-5.0%), respectively.

Post-ESD recurrence rate after R0 resection

In following table shows reported estimates from the univariable meta-regression models of the recurrence rates after R0 resection, stratified according to the country. The recurrence rates in non-Asian countries was significantly higher than those observed in Asian countries ($P < .001$):

Recurrence rate after R0 resection achieved by the standard technique: estimates from univariable meta-regression models

	Recurrence rates					
	6 mo		12 mo		24 mo	
	%	(95% CI)	%	(95% CI)	%	(95% CI)
All studies*	2.2	(1.3-3.5)	2.0	(1.3-3.0)	1.7	(1.2-2.5)
Asian studies†	1.0	(.6-1.8)	1.1	(.7-1.8)	1.3	(.9-1.8)
Non-Asian studies‡	6.4	(4.0-10.0)	5.2	(3.3-8.1)	3.4	(1.8-6.4)

*P-value per unitary increase (1 month) in follow-up length: .201.
†P-value per unitary increase (1 month) in follow-up length: .238.
‡P-value per unitary increase (1 month) in follow-up length: .049.

APPENDIX 4

SUPPLEMENTARY TABLE 5. R0 resection rates stratified according to the number of lesions resected per year and per countries

Mean number of ESDs/year	Overall	Non-Asian countries	Asian countries
Low volume (≤24 ESDs/year)	79.6% (95% CI, 75.4%-83.3%)	71.6% (95% CI, 64.2%-78.0%)	82.3% (95% CI, 77.9%-85.9%)
High volume (>24 ESDs/year)	85.5% (95% CI, 82.9%-87.7%)	72.0% (95% CI, 59.5%-81.8%)	87.4% (95% CI, 85.2%-89.4%)

ESD, Endoscopic submucosal dissection.

SUPPLEMENTARY TABLE 6. ESD standard technique: covariates and their influence on R0 resection rate measured by univariate and multivariate meta-regression

	Univariate meta-regression				Multivariate meta-regression		
	Coefficient	Standard error	*P* value	R^2	Coefficient	Standard error	*P* value
Asian (yes)	.839	.170	<.001	26.0%	.689	.166	<.001
Design (retrospective)	.130	.229	.568	.1%	—	—	—
Mean age	.018	.028	.526	.9%	—	—	—
Male rate (%)	.006	.011	.578	.2%	—	—	—
Mean no. lesion/year	.003	.001	.031	8.7%	.001	.001	.407
Mean tumor size	–.017	.009	.055	4.2%	—	—	—
Lesion of the rectum (%)	–.012	.003	.001	19.8%	–.008	.003	.006
Benign lesions* (%)	–.002	.004	.629	.1%	—	—	—

*Benign lesions meaning low- and high-grade (also referred to as in situ carcinoma) adenomas vs invasive carcinoma.

SUPPLEMENTARY TABLE 7. ESD hybrid technique: covariates and their influence on R0 resection rate measured by univariate meta-regression

	Univariate meta-regression			
	Coefficient	Standard error	*P* value	R^2
Asian (yes)	1.049	.719	.144	19.4%
Design (retrospective)	.792	.789	.315	9.4%
Mean age	–.082	.076	.282	22.3%
Male rate %	.088	.053	.101	27.0%
Mean no. lesion/year	–.029	.032	.355	6.9%
Mean tumor size	–.039	.04	.399	11.1%
Lesion of the rectum (%)	–.002	.018	.905	0%
Benign lesions* (%)	–.063	.035	.072	22.5%

*Benign lesions meaning low- and high-grade (also referred to as in situ carcinoma) adenomas vs invasive carcinoma.

Publication bias

ESD standard technique. The funnel plot was examined and revealed asymmetry and the estimated number of missing studies on the left side was 13 (standard error = 6.4). According to the Duval and Tweedie trim and fill, the adjusted valued with the 13 studies trimmed (80.6%; 95% CI, 78.1%-82.9%) was overlapping the observed value (82.9%; 95% CI, 80.4%-85.1%). The funnel plot for R0 resection rates reported a significant Egger test ($P = .006$) and a nonsignificant Begg and Mazumdar rank correlation ($P = .56$). All in all, these statistical analyses suggested the presence of publication bias, but its impact on the results was trivial, as stated by the overlap between the adjusted and the observed values.

ESD hybrid technique. The examination of the funnel plot did not show any asymmetry; indeed, no study was missing. The statistical analysis confirmed the absence of this bias. However, because of the small number of studies, these results should be treated cautiously.

APPENDIX 5

Oncologically curative resection rate

Oncologically curative resection was reported only in 4 studies and achieved in 115 cases out of 266 lesions treated, with a pooled rate of 49.7% (95% CI, 13.0%-86.7%). Because there were too few studies assessing this outcome, subgroup analyses were not carried out.

Delayed bleeding

Overall, a delayed bleeding was reported in 11 studies for a total of 26 cases out of 699 lesions, with a pooled rate of 4.0% (95% CI, 2.8%-5.8%), without evidence of heterogeneity ($Q^2 = .9$; $I^2 = 0\%$). No significant difference was observed between non-Asian and Asian countries: 4.7% (95% CI, 2.7%-7.9%) versus 3.5% (95% CI, 2.1%-5.8%), respectively. Similarly, there was no significant difference between low- and high-volume centers: 3.6% (95% CI, 1.8-6.8%) versus 4.3% (95% CI, 2.7%-6.6%).

Perforation

In 11 studies were reported 36 cases of perforations out of 699 treated lesions, yielding a pooled rate of 4.8% (95% CI, 2.4%-9.1%), with high level of heterogeneity ($Q^2 < .003$; $I^2 = 65\%$). No significant difference was observed between non-Asian countries and Asian countries: 3.7% (95% CI, .7%-17.3%) versus 5.4% (95% CI, 2.9%-9.9%). Similarly, no difference was detected as concerns the volume of the centers: low- versus high-volume centers: 4.7% (95% CI, 1.7%-12.6%) versus 4.5% (95% CI, 1.8%-11.2%).

Post-ESD recurrence rate after R0 resection

The following table reports estimates of the recurrence rates from the univariable meta-regression models:

Recurrence rates after R0 resection achieved with the hybrid technique

	Disease-free survival					
	6 mo		12 mo		24 mo	
Location	%	(95% CI)	%	(95% CI)	%	(95% CI)
All studies*†	1.2	(.3-4.5)	2.0	(.7-5.6)	5.7	(3.4-9.3)

*P value per unitary increase (1 month) in follow-up length: .018.

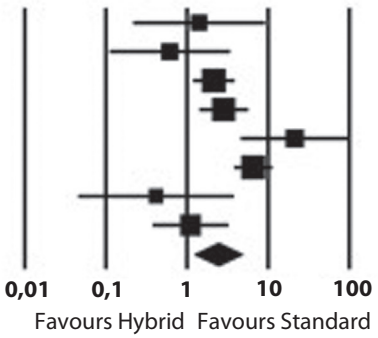
†The analysis stratified by location was not performed due to the limited number of studies.

APPENDIX 6

Comparison between standard and hybrid techniques

Eight studies directly compared the standard versus the hybrid techniques.[18-20,45,71,95,97,108] In 2 studies,[97,108] the standard technique group was updated with the most recent publication from the same authors.[54,94] In the standard technique group, R0 resection was achieved in 1708 of 1922 lesions, whereas in the hybrid group it was achieved in 277 of 434 cases, yielding an odds ratio of 2.44 (95% CI, 1.23-4.85), with high level of heterogeneity ($Q^2 < .001$; $I^2 = 73.4\%$) (see Supplementary Fig. 1, available online at www.giejournal.org). Similarly, en bloc resection rate was significantly higher in the standard technique group (odds ratio, 6.03; 95% CI, 2.18-16.66). No adverse events needing surgery were detected in both groups.

Study name	Odds ratio	Lower limit	Upper limit	R0 / Total Standard	Hybrid
Bae, 2016	1,403	0,219	9,009	29 / 31	31 / 34
Bialek, 2014	0,612	0,112	3,334	30 / 37	14 / 16
Byeon, 2011	2,126	1,194	3,786	120 / 163	42 / 74
Kim, 2013	2,821	1,425	5,581	44 /58	78 / 148
Rahmi, 2014	21,250	4,605	98,068	20 / 24	4 / 21
Lee, 2012	6,508	3,827	11,069	791 / 874	41 / 69
Terasaki, 2012	0,415	0,046	3,727	56 / 61	27 /28
Toyonaga, 2009	1,104	0,381	3,197	618 / 674	40 / 44
	2,442	1,230	4,846	1708 / 1922	277 / 434



Supplementary Figure 1. Forest plot of the studies comparing the standard versus hybrid technique.

APPENDIX 7

Relation to other meta-analyses

The current meta-analysis is an update of the previously published systematic review by Repici et al,[5] which considered studies published up to December 2010. In the current review we included 17 of 22 studies previously considered. Five studies were excluded for the following reasons: in 2 cases the study population consisted of all carcinoids,[A,B] in 1 case we included the most recent series published by the same authors,[C] and, finally, in 2 cases the R0 resection rates were not clearly provided.[D,E] In these latter cases we unsuccessfully contacted the corresponding authors for further information. Differently from the previous systematic review, we also included studies in which the hybrid ESD technique was evaluated.

More recently, another systematic review has been published on this issue.[6] The authors performed a literature search up to May 2014, and after applying the selection criteria, 20 studies were included. In the current review we included 13 of 20 studies considered by Patel et al,[6] 7 studies were excluded because in 5 cases we included the more recent data published by the same authors,[F-J] 1 study was excluded because ESD was used for the treatment of large pedunculated polyps,[K] and, finally, 1 study because it included fewer than 10 cases.[L]

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