Efficacy and safety of endoscopic submucosal dissection for colorectal neoplasia: a systematic review.

Efficacy and safety of endoscopic submucosal dissection for colorectal neoplasia: a systematic review

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Background and study aims: Endoscopic submucosal dissection (ESD) has been proposed for large colorectal lesions, due to the high risk of recurrence following endoscopic mucosal resection. However, data on the efficacy and safety of colorectal ESD are still controversial. The aim of the current systematic review was to assess the efficacy and safety of colorectal ESD.

Methods: A detailed Medline search of papers published during the period 1999–2010 was performed, using the search terms "Endoscopic submucosal dissection," "Colorectal neoplasia," "Colon," or "Rectum." Published studies that evaluated ESD for colorectal lesions were assessed using well-defined inclusion/exclusion criteria, including histological confirmation and surgery for complications. The process was independently performed by two authors. Forest plots on primary (i.e. histologically verified R0 resection and surgery for ESD complications) and secondary end-points were produced based on random-effect models. Heterogeneity was assessed using the I^2 statistic. Risk for within-study bias was also ascertained.

Results: A total of 22 studies (20 Asian, two European) provided data on 2841 ESD-treated lesions. The per-lesion summary estimate of R0 resection rate was 88% (95%CI 82%–92%; I^2 =91%). At meta-regression, carcinoid vs. non-carcinoid series (R0 93% vs. 87%; P =0.04) and Asian vs. European series (R0 88% vs. 65%; P =0.03) appeared to explain the detected heterogeneity. The per-lesion summary estimate of surgery for ESD complications was 1% (95%CI 0%–1%) with a moderate degree of heterogeneity (I^2 =49%). However, subgrouping of these results according to histological tumor types was not available in the reviewed studies.

Conclusions: ESD appeared to be an extremely effective technique to achieve R0 resection of large colorectal lesions. The very low rate of surgery for complications also shows the potential safety of this approach.

Introduction

Colorectal cancer (CRC) represents a major cause of morbidity and mortality in Western countries [1] [2]. The majority of CRCs arise from premalignant precursors along the long-term adenoma–carcinoma sequence. The identification and removal of such precursors have been associated with CRC incidence and mortality prevention [3].

Large colorectal lesions are usually treated by endoscopic mucosal resection (EMR) or surgery, at least in Western countries. Although EMR is a highly effective and safe procedure for lesions smaller than 20 mm in diameter [4], it is quite ineffective in achieving an en bloc resection of lesions ≥20 mm, resulting into a high rate of local recurrence in these lesions. Piecemeal resection of submucosal cancer lesions also prevents the pathologist from reliably determining the status of the resection margins. Surgical treatment for colorectal lesions is associated with a substantial increase in morbidity and mortality when compared with endoscopy [5], and in patients with benign lesions this additional risk is not clinically warranted.

To overcome these limitations, colorectal endoscopic submucosal dissection (ESD) has been proposed. ESD was initially developed for early gastric cancer, where it has been shown to be a highly effective and safe treatment [6]. The application of ESD to colorectal lesions has been partially limited by the greater technical difficulty involved and the higher risk of perforation. Despite these limitations, an increasing number of series have recently reported the application of ESD to colorectal lesions [7] [8] [9] [10] [11] [12] [13] [14] [15] [16] [17] [18] [19] [20] [21] [22] [23] [24] [25] [26] [27] [28]. However, most of these series were retrospective and single-center studies that included only a relatively small number of cases. When considering the relatively low frequency of post-ESD recurrences or post-ESD surgery for complications, such small sample sizes prevent reliable estimates of the efficacy and safety of colorectal ESD.

The aim of this systematic review and meta-analysis was to assess the efficacy and safety of ESD for colorectal lesions.

Methods

The methods used for the analysis and generation of inclusion criteria were based on PRISMA recommendations [29].

Eligibility criteria

All studies that were published during the period January 1999 (the year ESD was first described) to December 2010, and in which patients underwent ESD for the removal of colorectal lesions were reviewed. Exclusion criteria included case reports (<10 cases), non-human studies, review articles, position papers, editorials, commentaries, and book chapters. If there was any suspicion of cohort overlap between studies, only the most recent study was considered for inclusion.

Information sources

A literature search was performed in December 2010. Relevant publications were identified by Medline for the period 1999−2010. The medical terms “Endoscopic submucosal dissection,” “Colorectal neoplasia,” “Colon,” or “Rectum” were used in the search, adopting “Human studies” as the only limit. The references of review articles were also hand-searched. The full paper of all relevant studies was retrieved, and reference lists from identified papers were hand-searched to identify any additional studies that may have been missed using the above-mentioned process.

Study selection

Potential studies were initially screened by two researchers (A.R., C.H.) based on the title and abstract. The reviewers checked whether inclusion and exclusion criteria were met, and the full text was retrieved and reviewed for all papers that showed even a remote potential for study inclusion.

Data collection process and list of items

Data extraction was independently performed by the two reviewers using pre-defined data extraction forms. A third investigator (R.M.) arbitrated in the event of any lack of agreement. From each report, reviewers independently abstracted the following information: (a) year of publication, (b) country where the study was performed, (c) whether the study was a single- or multicenter study, (d) whether the study was prospective or retrospective, (e) enrollment period, (f) number of patients included, (g) mean age, (h) sex distribution, (i) clinical indication for ESD, (j) number of lesions selected for ESD, (k) lesion localization (colon/rectum), (l) whether endoscopic ultrasound (EUS) was performed, (m) mean tumor size, (n) macroscopic type (lateral spreading tumor [LST] or non-LST), (n) type of ESD devices used, (o) type of solution injected into the submucosa, (p) rate of histologically verified en bloc complete resection (R0), (q) histology (adenoma, carcinoma in situ, submucosal cancer, invasive cancer, carcinoid), (r) whether post-ESD follow-up was available, (s) mean follow-up period (months), (t) rate of post-ESD surgery due to ESD failure, (u) rate of bleeding, (u) rate of perforation, (v) rate of surgery due to complications, (x) mean ESD operation time, and (w) post-ESD mortality.

Risk of bias in individual studies

To assess the methodological quality of the included studies and detect potential bias, the following details were noted: (a) whether the reference standard (histological verification) was available, (b) whether ESD could be replicated based on the information provided in the included studies, and (c) whether data on ESD failure were provided.

Summary measures

The primary end-points of this systematic review were:

1. per-lesion rate of R0 ESD resection (i.e. complete en bloc resection with vertical and lateral margins free of neoplasia at histology)
2. per-lesion rate of surgery for ESD complications.

Secondary end-points were:

1. per-lesion rate of endoscopically complete ESD resection (i.e. apparently complete en bloc resection at endoscopy, regardless of histology)
2. per-lesion rate of bleeding or perforation, regardless of complication-related surgery
3. per-lesion rate of post-ESD surgery for ESD failure (excluding surgery for complications)
4. per-lesion rate of post-ESD recurrence following R0 resection
5. differences between the results of ESD for carcinoid series compared with those of unselected series
6. differences between results of Western series compared with those of Asian series.

Attempts were made to contact authors if data presentation was incomplete or if it was necessary to resolve an apparent conflict or inconsistency in the article. However, additional data were required only when involving the primary end-points.

Planned methods of analysis

Per-lesion R0 ESD resection rate was defined for each study as the ratio between the absolute number of R0 ESD resections and the overall number of lesions in which ESD was attempted (i.e. within an intention-to-treat population). The same methodology was applied to all the other primary and secondary end-points. Both primary and secondary end-points were summarized by a random-effects model, except for cases where fewer than three studies were available; in the latter case a simple pooling with 95% confidence interval (CI) was provided. True positives were defined as the experimental group in which the monitored outcome was present. False negatives were the experimental group in which the outcome was absent. Heterogeneity was assessed using the I^2 statistic. The I^2 statistic provides an estimate of the amount of variance due to heterogeneity rather than chance and is based on the traditional measure of variance, the Cochrane Q statistic [30]. Values of I^2 below 25% and 50%, and above 75% were assumed to represent low, moderate, and high heterogeneity, respectively. When heterogeneity was present, meta-regression analysis was used to determine the study characteristics that influenced the heterogeneity. Egger's test and funnel plots were used to investigate whether publication bias or other small study effects may have adversely affected the results for the primary end-points [31].

Formal investigation of heterogeneity was performed by multiple univariable meta-regression models. Covariates were used as mean-centered continuous or as dichotomous (yes=1, no=0) fixed effects. The effect of each covariate on the true positive rate was estimated. This analysis was performed on logit-transformed proportions by using the meta-regression command of the statistical software. All of the collected variables (see above in the section "Data collection process and list of items") were used in the meta-regression. Pre-specified sensitivity analyses were undertaken to evaluate possible heterogeneity due to the different clinical and technical characteristics of the included studies. Data comparison between Asian and European sub-groups, as well as between carcinoid and non-carcinoid series, was performed using the chi-squared test, as appropriate. A two-sided P value of less than 0.05 was considered statistically significant. All of the calculations were performed with STATA software integration (StataCorp, Houston, Texas, USA).

Results

Study selection

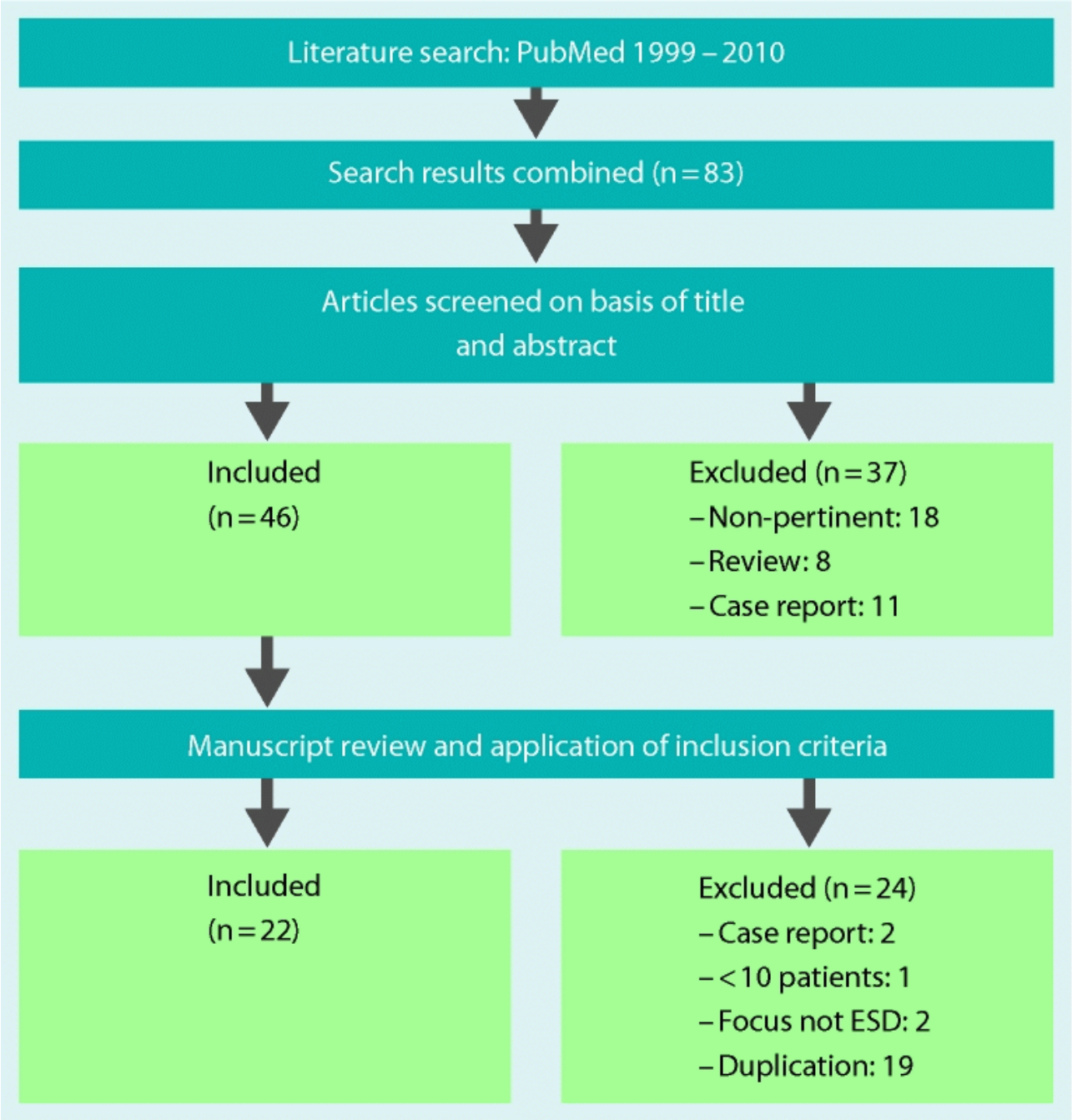
A flow diagram of this systematic review, with the number of papers retrieved, included, and excluded, as well as the reasons for exclusion, is shown in [Fig. 1]. In summary, 83 studies were identified by the Medline search. After removing non-pertinent papers, 46 were considered for inclusion after the search criteria were applied to the electronic abstract. Of these 46 potential papers, 24 were excluded. The reasons for exclusion are given in [Fig. 1] (see [Table e1], online only, for excluded studies). The remaining 22 published papers were included in the systematic review [7] [8] [9] [10] [11] [12] [13] [14] [15] [16] [17] [18] [19] [20] [21] [22] [23] [24] [25] [26] [27] [28].

Table e1

Excluded studies and reasons for exclusion.

First author	Journal	Date	Exclusion
Saito	Surg Endosc	2010	Duplication
Ono	Gut Liver	2008	Case report
Nishiyama	Surg Endosc	2010	Duplication
Saito	Gastrointest Endosc	2007	Duplication
Sakamoto	Gastrointest Endosc	2009	<10 cases
Saito	Gastrointest Endosc Clin N Am	2010	Review
Yoshida	Int J Colorectal Dis	2010	Duplication
Sung	Eur J Gastroenterol Hepatol	2009	Focus not ESD
Fujishiro	Gastrointest Endosc	2006	Duplication
Park	Gastrointest Endosc	2010	Duplication
Kobayashi,	J Gastroenterol Hepatol	2009	Duplication
Morimoto	World J Gastroenterol	2010	Case report
Isomoto	Endoscopy	2009	Duplication
Tamegai	Endoscopy	2007	Duplication
Zhou	Surg Endosc	2009	Duplication
Nimi	Endoscopy	2010	Duplication
Matsumoto	Scand J Gastroenterol	2010	Duplication
Hurlstone	Colorectal Dis	2008	Duplication
Fujishiro	Clin Gastroenterol Hepatol	2007	Duplication
Yoshida	Endoscopy	2009	Duplication
Tanaka	Gastrointest Endosc	2007	Duplication
Matsushita	Scand J Gastroenterol	2008	Focus not ESD
Onozato	Endoscopy	2007	Duplication
Saito	Gastrointest Endosc	2010	Duplication

ESD, endoscopic submucosal dissection.


Literature search: PubMed 1999 – 2010
Search results combined (n = 83)
Articles screened on basis of title and abstract
Included (n = 46)
Excluded (n = 37)
– Non-pertinent: 18
– Review: 8
– Case report: 11
Manuscript review and application of inclusion criteria
Included (n = 22)
Excluded (n = 24)
– Case report: 2
– < 10 patients: 1
– Focus not ESD: 2
– Duplication: 19

Characteristics of the included studies

A total of 20 studies were performed in Asian countries (17 in Japan, two in China, and one in Korea) and two were performed in Europe (one Germany, one United Kingdom) ([Table 2]). All of the included studies were single-center studies, and all but three (two randomized trials, one prospective series) were retrospective. The enrollment period ranged widely, from 1998 to 2010. Five studies reported ESD up to 2006, and the remainder included patients enrolled after 2006 (information not provided for one series).

#

Participants

A total of 2774 patients were enrolled in the selected studies ([Table 2]). The number of patients enrolled in each study ranged from 16 to 400, with a median of 47. The median of the mean ages across the included studies was 66 years (range 48–71 years). The median of the male sex rate was 56% (range 32%–71%). The clinical indication for ESD was ≥20 mm lesions, post-EMR recurrences, post-biopsy fibrosis or otherwise non-specified superficial lesions in 18 studies; the indication was restricted to carcinoids in the remaining four studies ([Table 3]).

Table 2 Characteristics of the included studies.

Table 2

Characteristics of the included studies.

Reference	Study design	Country	Enrollment period	Mono-/multicentric	Patients, n	Age, mean, years	Sex, male, %
Takeuchi et al. 2010 [16]	Randomized trial	Asian	2008/2009	Monocentric	48	68	52
Toyonaga et al. 2010 [23]	Randomized trial	Asian	2008	Monocentric	16	–	–
Hurlstone et al. 2007 [28]	Prospective	Non-Asian	2004–2006	Monocentric	42	68	64
Tamegai et al. 2007 [7]	Retrospective	Asian	2003–2005	Monocentric	70	63	54
Zhou et al. 2009 [8]	Retrospective	Asian	2006–2007	Monocentric	73	64	53
Niimi et al. 2010 [9]	Retrospective	Asian	2000–2008	Monocentric	290	65	32
Matsumoto et al. 2010 [10]	Retrospective	Asian	2002–2009	Monocentric	203	66	65
Ohya et al. 2009 [11]	Retrospective	Asian	2008–2009	Monocentric	45	71	–
Yoshida et al. 2010 [12]	Retrospective	Asian	2005–2010	Monocentric	250	67	–
Yamaguchi et al. 2010 [13]	Retrospective	Asian	2005–2008	Monocentric	20	60	55

Table 2

Characteristics of the included studies.

Reference	Study design	Country	Enrollment period	Mono-/multicentric	Patients, n	Age, mean, years	Sex, male, %
Nishiyama et al. 2010 [14]	Retrospective	Asian	2001–2008	Monocentric	286	69	57
Uraoka et al. 2010 [15]	Retrospective	Asian	2006–2008	Monocentric	21	67	71
Zhou et al. 2010 [17]	Retrospective	Asian	2005/2006	Monocentric	20	48	60
Saito et al. 2009 [18]	Retrospective	Asian	–	Monocentric	400	–	–
Kita et al. 2007 [20]	Retrospective	Asian	1998–2005	Monocentric	166	–	–
Toyonaga et al. 2010 [21]	Retrospective	Asian	2002–2007	Monocentric	268	68	53
Lee et al. 2010 [22]	Retrospective	Asian	2003–2009	Monocentric	46	49	46
Iizuka et al. 2009 [24]	Retrospective	Asian	2000–2004	Monocentric	44	69	55
Kuroki et al. 2010 [25]	Retrospective	Asian	2005–2009	Monocentric	395	66	66
Ishii et al. 2010 [26]	Retrospective	Asian	2004–2008	Monocentric	21	55	67
Ishii et al. 2010 [27]	Retrospective	Asian	2005–2009	Monocentric	33	66	61
Probst et al. 2009 [19]	Retrospective	Non-Asian	2003–2007	Monocentric	17	–	–

Table 3 Clinical characteristics of the lesions in which endoscopic submucosal dissection (ESD) was applied.

Table 3

Clinical characteristics of the lesions in which endoscopic submucosal dissection (ESD) was applied.

Reference	ESD indication[1]	EUS staging reported	Rate of rectum localization, %[2]	Tumor size, mean, mm	Rate of LSTs, %[3]	Device for ESD, knife type[4]	Solution for submucosal injection	ESD duration, minutes
Zhou et al. [8]	≥20mm	Yes	57	32.6	72	Needle / hook / insulated-tip	–	110
Yoshid	≥20mm							

Table 3

Clinical characteristics of the lesions in which endoscopic submucosal dissection (ESD) was applied.

Reference	ESD indication[1]	EUS staging reported	Rate of rectum localization, %[2]	Tumor size, mean, mm	Rate of LSTs, %[3]	Device for ESD, knife type[4]	Solution for submucosal injection	ESD duration, minutes
a et al. [12]								
Takeuchi et al. [16]	≥20mm	Yes	30	28	–	Flush / flex	Hyaluronate	74
Kita et al. [20]	≥20mm	No	–	33	93	Needle	Hyaluronate/epinephrine	102
Ishii et al. [27]	≥20mm	No	27	35	0	Flex	Hyaluronate/epinephrine/indigo carmine	121
Tamegai et al. [7]	≥20mm/submucosal fibrosis	No	24	32.7	70	Hook	Hyaluronate/glycerol	61.1
Niimi et al. [9]	Neoplasia	Yes	26	28.9	79	Flex / hook	Hyaluronate/indigo carmine	–
Uraoka et al. [15]	≥20mm LST	No	67	43.6	100	Needle / insulated-tip/Mucosectom	Hyaluronate/indigo carmine/glycerol	96
Saito et al. [18]	≥20mm LST	No	27	40	84	Needle / insulated-tip	Hyaluronate/glycerol	90
Toyonaga et al. [21]	≥20mm LST	No	26	33	100	Flush / flex / hook/needle	Hyaluronate	63
Matsumoto et al. [10]	≥20mm/submucosal fibrosis	No	–	32.4	81	Flex / dual / hook	Hyaluronate/indigo carmine/epinephrine	–
Ohya et al. [11]	≥20mm/submucosal fibrosis/post-EMR	No	–	35	–	Flex / dual / hook	Hyaluronate / indigo carmine / epinephrine	60
Nishiyama et al. [14]	≥20mm/submucosal fibrosis/post-EMR	Yes	27	26.9	80	Flush / flex / hook	Glycerol / fructose	–
Yamag	Carcinoid	Yes	100	7.6	0[	Flush	Glycerol / fructose	45

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Clinical characteristics of the lesions in which endoscopic submucosal dissection (ESD) was applied.

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uchi et al. [13]					5]			
Zhou et al. [17]	Carcinoid	Yes	100	7.2	0[5]	Needle	Indigo carmine/epinephrine	28
Lee et al. [22]	Carcinoid	Yes	100	6.2	0[5]	Hook	Saline	18.9
Ishii et al. [26]	Carcinoid	Yes	100	6.4	0[5]	Flex	Hyaluronate/epinephrine/indigo carmine	37
Kuroki et al. [25]	Post-EMR	No	21	30.4	78	Flex / dual	Glycerol/hyaluronate/fructose/indigo carmine/epinephrine	73.88
Iizuka et al. [24]	–	No	59	36	–	Flex	Hyaluronate/glycerol/indigo carmine/epinephrine	110
Toyonaga et al. [23]	Neoplasia	No	–	–	100	Flush	Hyaluronate	–
Hurlstone et al. [28]	Neoplasia	Yes	67	30.5	67	Flex / insulated-tip	Hyaluronate/epinephrine/indigo carmine	48
Probst et al. [19]	Rectal lesions	Yes	100	39.4	–	Needle / insulated-tip/triangle / flex / hook	Epinephrine/glycerol/indigo carmine/hyaluronate	–

ESD, endoscopic submucosal dissection; EUS, endoscopic ultrasound; LST, lateral spreading tumor.

Only carcinoids were included.

[1] ≥20 mm, ≥20 mm neoplasia; post-EMR, recurrence/residual after endoscopic mucosal resection.

[2] Remaining lesions were located in the colon.

[3] Remaining lesions were non-LST (either polypoid or non-LST non-polypoid).

[4] Hook knife, needle knife, flex knife, flush knife, dual knife, insulated-tip knife, triangle knife, Mucosectom (Pentax Co., Tokyo, Japan).

[5] Only carcinoids were included.

Interventions

EUS was systematically performed in all or selected cases in 10 studies; the other 12 studies did not report its use ([Table 3]). Multiple cutting devices were used in the majority of the studies, with flush/flex knives being consistently adopted in the most recent publications. Similarly, a mixed solution containing either glycerol or hyaluronate was used to inject the submucosal layer in most of the studies. The median of the mean operation time of the included studies was 74 minutes (range 18.9−121 minutes); operation time was statistically significantly shorter in the four carcinoid series than in the other studies (86 vs. 32 minutes; $P<0.001$).

Outcomes

Overall, 2841 colorectal lesions were selected for ESD in the included studies. Nearly half of all lesions were located in the rectum, with a median occurrence of 44% (range 21%−100%); the remaining lesions were located in the colon ([Table 4]). In particular, all of the lesions included in the four carcinoid series were located in the rectum. The median of mean tumor size was 32.4 mm (range 6.2−43.6 mm). Tumor size was statistically significantly smaller in the four carcinoid studies than in the other studies (7 vs. 34 mm; $P<0.001$).

Table 4 Endoscopic submucosal dissection (ESD) success and complications rates. Post-ESD histology is also reported.

Table 4

Endoscopic submucosal dissection (ESD) success and complications rates. Post-ESD histology is also reported.

Reference	Number of lesions, n	R0 ESD resection, %	Post-ESD surgery for complications, %	Endoscopic en bloc ESD resection, %	Post-ESD surgery, %[1]	Bleeding, %	Perforation, %	Adenoma, %	Cancer in situ, %	Submucosal cancer, %
Kuroki et al. [25]	418	92	1	98	0	2	5	43	39	13
Saito et al. [18]	405	86	0	87	–	1	3	25	63	11
Niimi et al. [9]	310	69	0	90	3	2	5	47	35	17
Nishiyama et al. [14]	300	78	1	88	3	1	8	41	48	10
Toyonaga et al. [21]	268	98	0	99	10	0	2	21	63	16
Yoshida et al. [12]	250	81	0	87	4	2	6	45	48	7
Matsumoto et al. [10]	203	86	1	86	–	0	7	48	27	23
Kita et al. [20]	166	77	1	100	0	2	4	–	–	–
Zhou et al. [8]	74	89	1	93	1	1	8	57	32	4
Tamegai et al. [7]	71	96	0	99	10	0	1	17	66	15
Takeuchi et al. [16]	50	80	0	94	6	6	2	60	28	12
Lee et al. [22]	46	83	0	100	2	4	2	0[2]	0[2]	0[2]
Ohya et al. [11]	45	93	0	96	2	2	0	44	47	9
Iizuka et al. [24]	44	59	5	64	16	0	7	0	0	0
Ishii et al. [27]	33	91	0	91	0	3	3	36	55	9
Ishii et al. [26]	22	95	0	100	0	9	0	0[2]	0[2]	0[2]
Uraoka et al. [15]	21	100	0	100	0	0	0	38	52	10

Table 4

Endoscopic submucosal dissection (ESD) success and complications rates. Post-ESD histology is also reported.

Reference	Number of lesions, n	R0 ESD resection, %	Post-ESD surgery for complications, %	Endoscopic en bloc ESD resection, %	Post-ESD surgery, %[1]	Bleeding, %	Perforation, %	Adenoma, %	Cancer in situ, %	Submucosal cancer, %
Yamaguchi et al. [13]	20	90	0	100	0	0	5	0[2]	0[2]	0[2]
Zhou et al. [17]	20	100	0	100	0	0	5	0[2]	0[2]	0[2]
Toyonaga et al. [23]	16	100	0	100	0	0	0	31	44	25
Hurlstone et al. [28]	42	74	0	79	2	12	2	95	0	2
Probst et al. [19]	17	53	0	65	12	0	12	76	0	18

[1] Only for ESD failure (i.e. excluding surgery for complications).

[2] Only carcinoids were included.

Regarding morphology, the majority of lesions were LSTs, with a median occurrence of 78% (range 0%–100%). At histology, the median of adenoma, carcinoma in situ, and submucosal cancer rates across the studies were 43% (range 0%–95%), 44% (range 0%–66%), and 11% (range 2%–25%), respectively, when excluding the four carcinoid series ([Table 4]).

Risk of bias in individual studies

Potential risk of bias in individual studies is reported in [Table 5] (online only). All but four studies clearly reported the selection criteria. The reference standard (histology) was likely to correctly classify the target condition (i.e. R0 resection) in all of the studies, despite the pathologist being aware of the results from the index test (i.e. ESD resection). The time period between the ESD and post-ESD fixation of the specimen and histological assessment was short enough in all studies to exclude the possibility of disease progression in the interim. As shown in [Table e5] (online only)

the majority of the studies reported data on withdrawals due to technical failures, as well as ample information to enable replication of the procedure by others.

Table e5 Assessment of the risk of bias in individual studies.

Table e5

Assessment of the risk of bias in individual studies.

Potential bias	Included studies																					
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
1. Was the spectrum of patients representative of the patients who will receive the test in practice?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
2. Were selection criteria clearly described?	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	Y	Y	N
3. Is the reference standard likely to correctly classify the target condition?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
4. Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
5. Did the whole sample or a random selection of the sample, receive verification using a reference standard of diagnosis?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
6. Did patients receive the same reference standard regardless of the index test result?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
7. Was the reference standard independent of the index test i.e. the index test did not form part of the reference standard?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
8. Was the execution of the index test described in sufficient detail to permit replication of the test?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
9. Was the execution of the reference standard described in sufficient detail to permit its replication?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
10. Were the index test results interpreted without knowledge of the results of the reference standard?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
11. Were the reference standard results interpreted without knowledge of the results of the index test?	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
12. Were the same clinical data available when test results were	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

Table e5

Assessment of the risk of bias in individual studies.

Potential bias	Included studies																					
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
interpreted as would be available when the test is used in practice?																						
13. Were withdrawals from the study explained?	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y

N, no; Y, yes.

Synthesis of results

The results of the included individual studies are provided in [Table 4].

R0 ESD resection rate

A histologically verified complete R0 resection was achieved in 2395 of 2841 lesions in which ESD was attempted. The per-lesion summary estimate of R0 resection rate was 88% (95%CI 82%–92%), as shown in [Fig. 2a]. Inter-study heterogeneity (I^2) was 91% ([Fig. 2a]). At meta-regression, carcinoid vs. non-carcinoid series (R0 93% vs. 87%; P = 0.04) and Asian vs. European series (R0 88% vs. 65%; P = 0.03) appeared to explain the detected heterogeneity. The Egger's test was not significant (coefficient = 0.09; 95%CI −0.1 to +0.3; P = 0.4); the corresponding funnel plot is shown in [Fig. e3a] (online only).

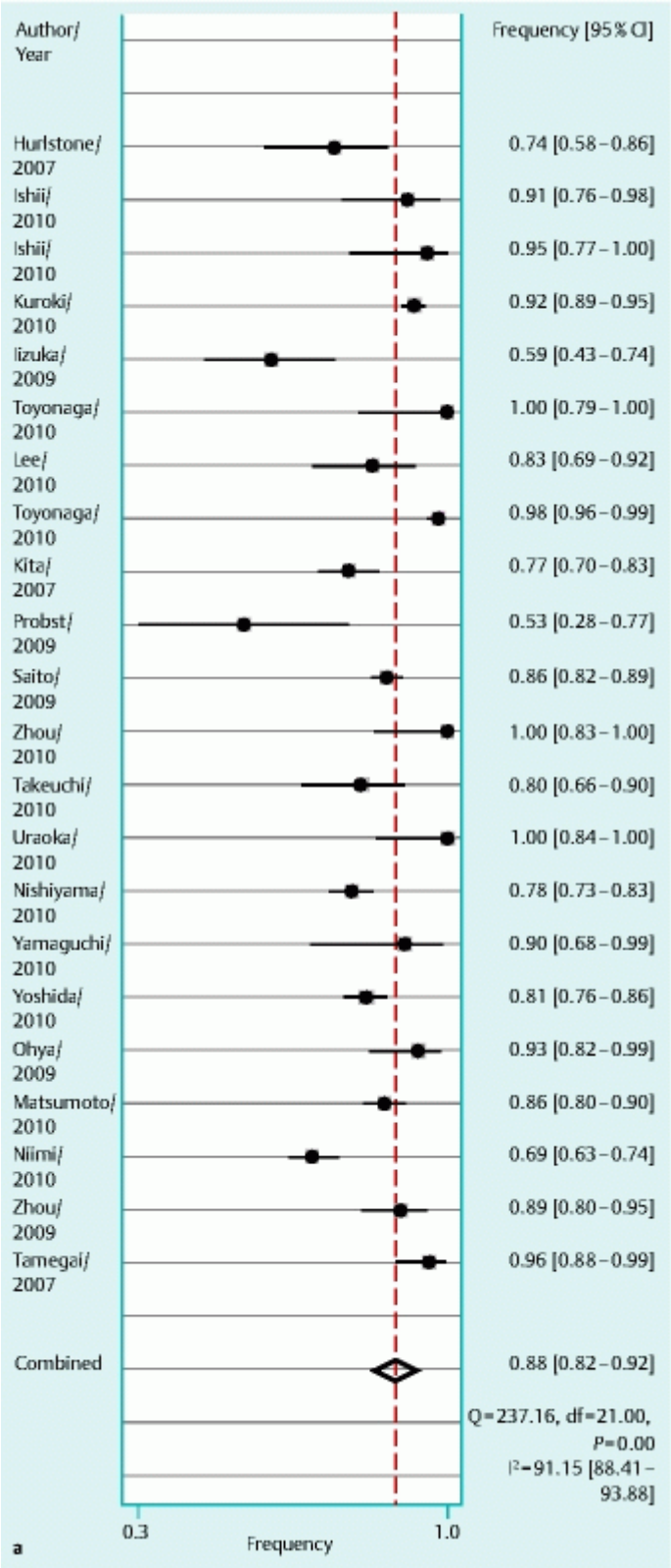
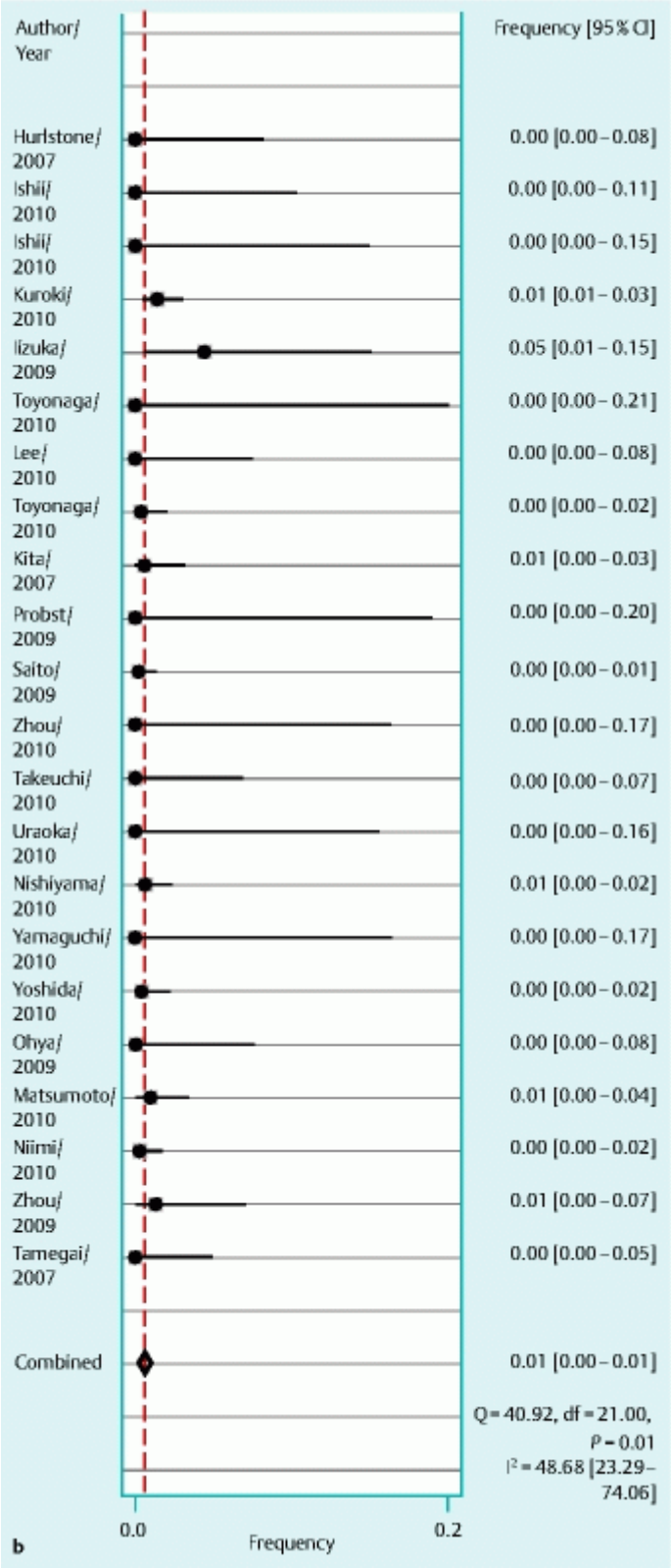


Fig. 2 Forest plot of the included studies analyzing primary end-points of the systematic review. a Rate of R0 endoscopic submucosal dissection (ESD) resection. b Surgery for ESD complications.


Author/ Year
Frequency [95% CI]
Hurlstone/ 2007
0.00 [0.00 – 0.08]
Ishii/ 2010
0.00 [0.00 – 0.11]
Ishii/ 2010
0.00 [0.00 – 0.15]
Kuroki/ 2010
0.01 [0.01 – 0.03]
Iizuka/ 2009
0.05 [0.01 – 0.15]
Toyonaga/ 2010
0.00 [0.00 – 0.21]
Lee/ 2010
0.00 [0.00 – 0.08]
Toyonaga/ 2010
0.00 [0.00 – 0.02]
Kita/ 2007
0.01 [0.00 – 0.03]
Probst/ 2009
0.00 [0.00 – 0.20]
Saito/ 2009
0.00 [0.00 – 0.01]
Zhou/ 2010
0.00 [0.00 – 0.17]
Takeuchi/ 2010
0.00 [0.00 – 0.07]
Uraoka/ 2010
0.00 [0.00 – 0.16]
Nishiyama/ 2010
0.01 [0.00 – 0.02]
Yamaguchi/ 2010
0.00 [0.00 – 0.17]
Yoshida/ 2010
0.00 [0.00 – 0.02]
Ohya/ 2009
0.00 [0.00 – 0.08]
Matsumoto/ 2010
0.01 [0.00 – 0.04]
Niimi/ 2010
0.00 [0.00 – 0.02]
Zhou/ 2009
0.01 [0.00 – 0.07]
Tamegai/ 2007
0.00 [0.00 – 0.05]
Combined
0.01 [0.00 – 0.01]
Q = 40.92, df = 21.00, P = 0.01
I² = 48.68 [23.29 – 74.06]
0.0
0.2
Frequency
b

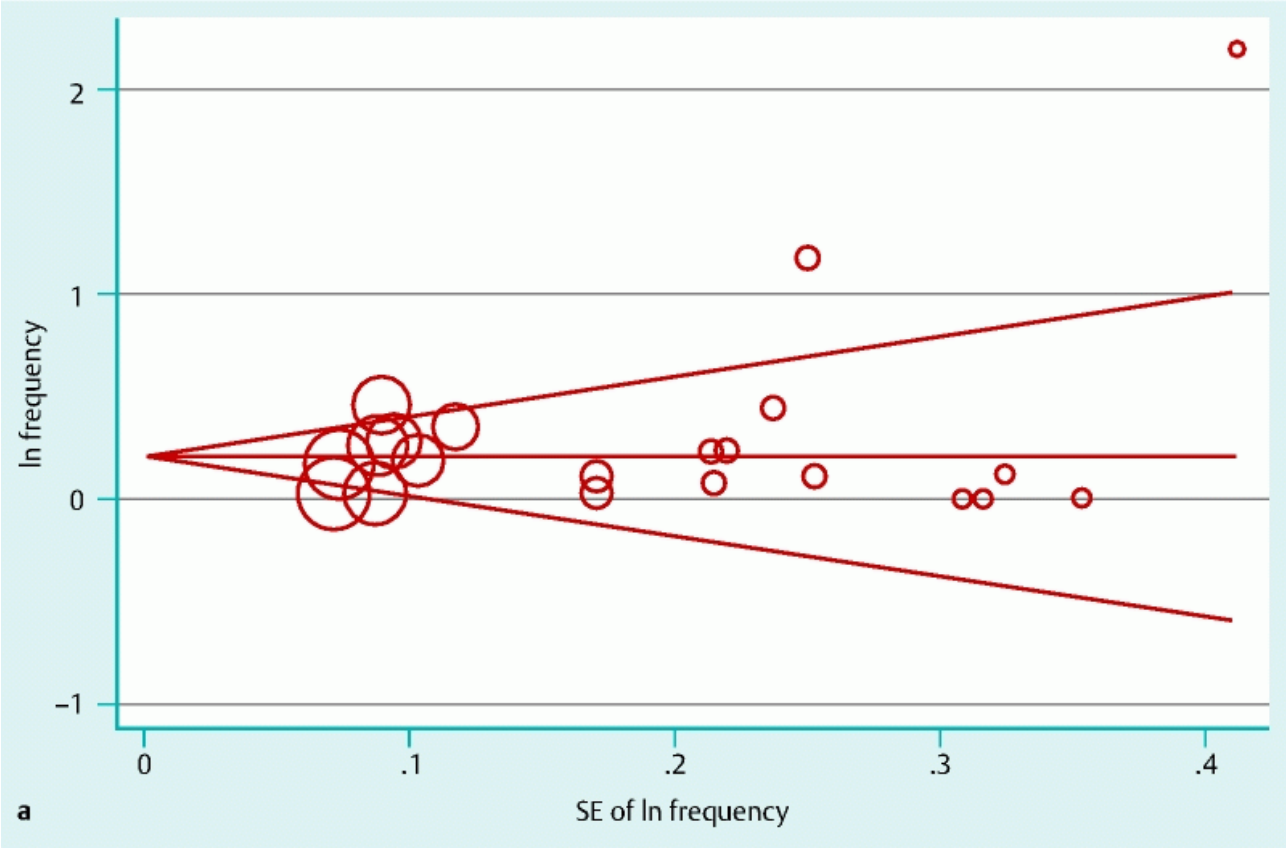
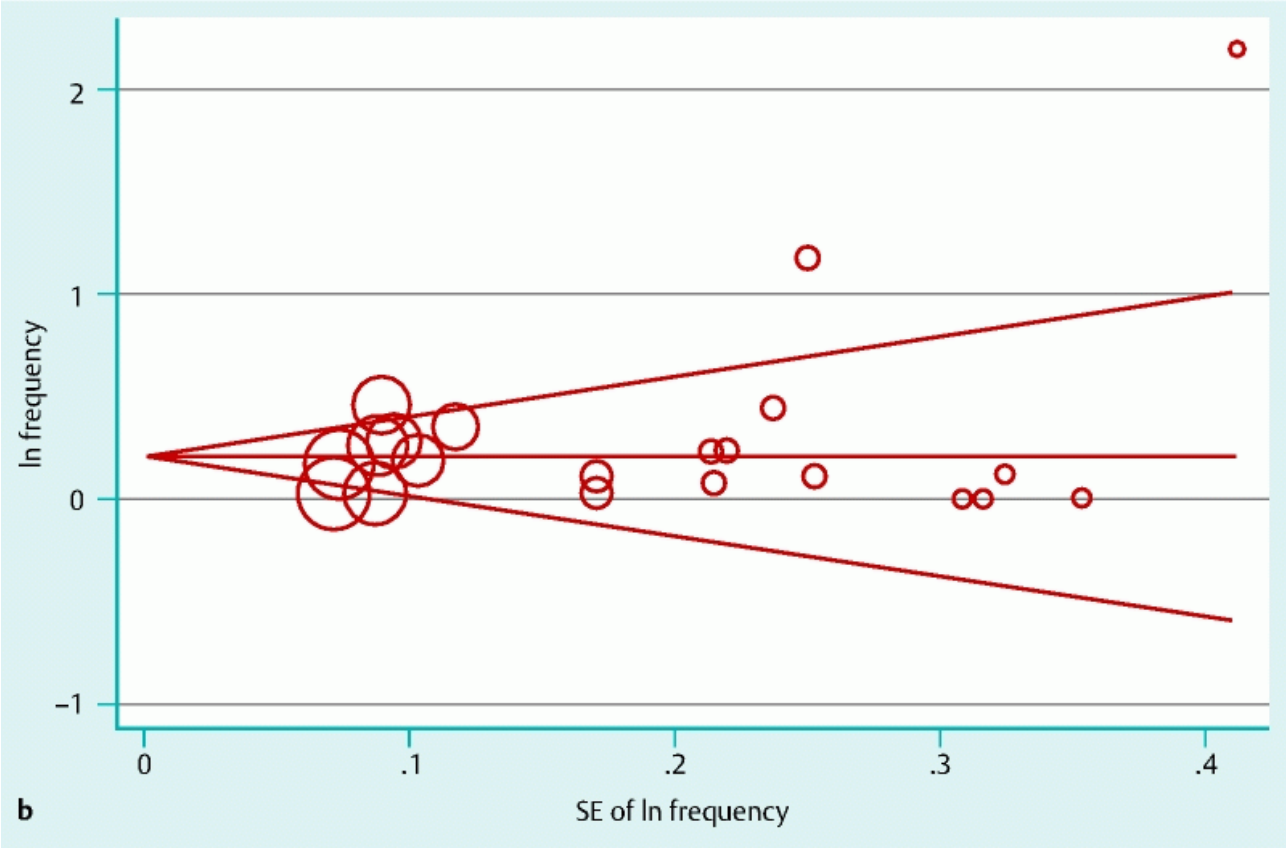


Fig. e3 Begg's funnel plots (with pseudo 95% confidence limits) for the detection of bias within the studies included in the systematic review. a Rate of R0 endoscopic submucosal dissection



(ESD) resection. b Surgery for ESD complications.

Surgery for ESD complications

A surgical intervention following an ESD-related complication (either perforation or bleeding) occured in 18 cases (perforation in all cases). The per-lesion summary estimate of surgery was 1% (95%CI 0%–1%), as shown in [Fig. 2b]. Inter-study heterogeneity (I^2) was 49%. When excluding the only study in which a relatively high rate of surgery was reported [24], only a low degree of heterogeneity remained (I^2 =14%). No variable at meta-regression was able to explain the residual degree of heterogeneity. The Egger's test was significant (coefficient=−3; 95%CI −4.8 to −1.6; P=0.002); the corresponding funnel is shown in [Fig. e3b] (online only).

Secondary end-points

An endoscopically complete ESD-resection (i.e. apparently complete en bloc resection at endoscopy, irrespective of histology) was achieved in 2603 of 2841 lesions in which ESD was attempted. The per-lesion summary estimate of rate of endoscopically complete resection was 96% (95%CI 91%–98%), as shown in [Fig. 4a]. A high degree of heterogeneity was present (I^2 =94%).

Post-ESD surgery due to therapeutic failure (i.e. excluding surgery for complications) occurred in 77 cases. The per-lesion summary estimate was 2% (95%CI 1%–4%), as shown in [Fig.4b]. A high degree of heterogeneity was present (I^2=80%).

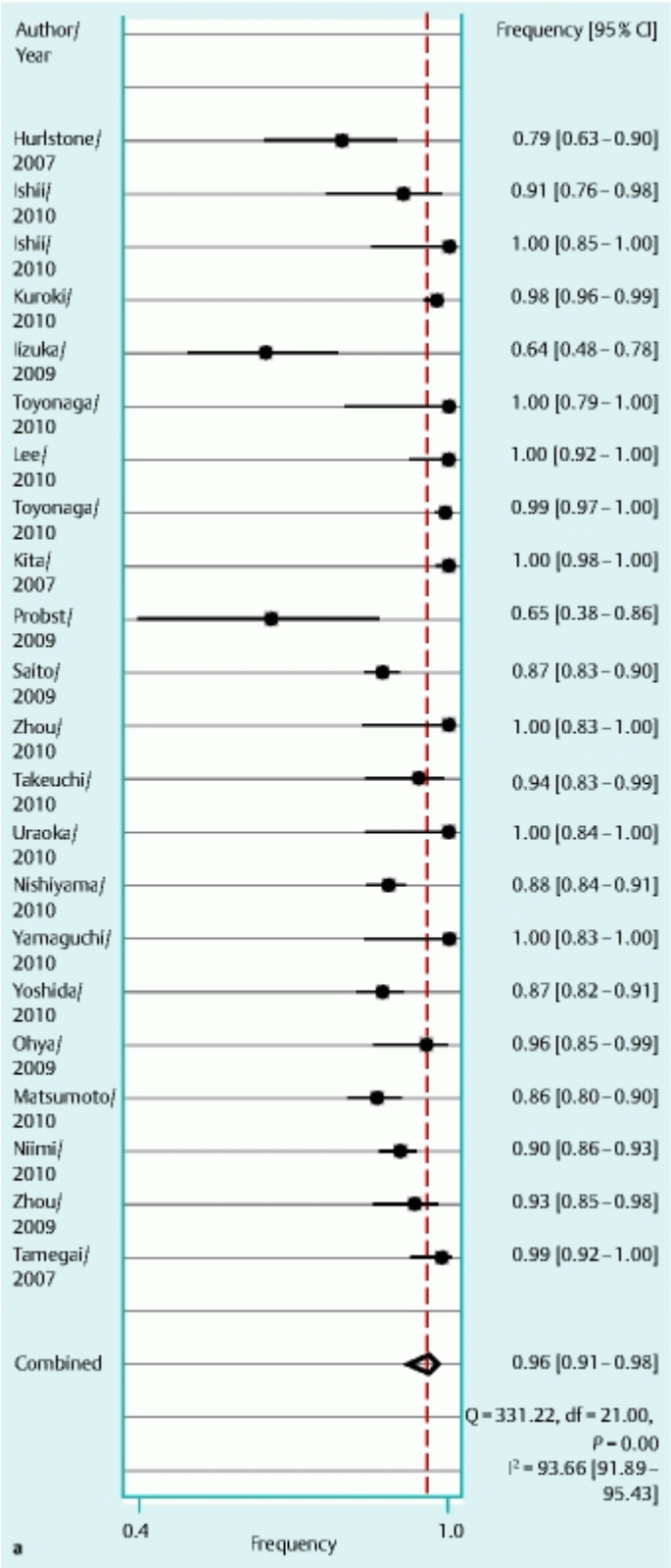
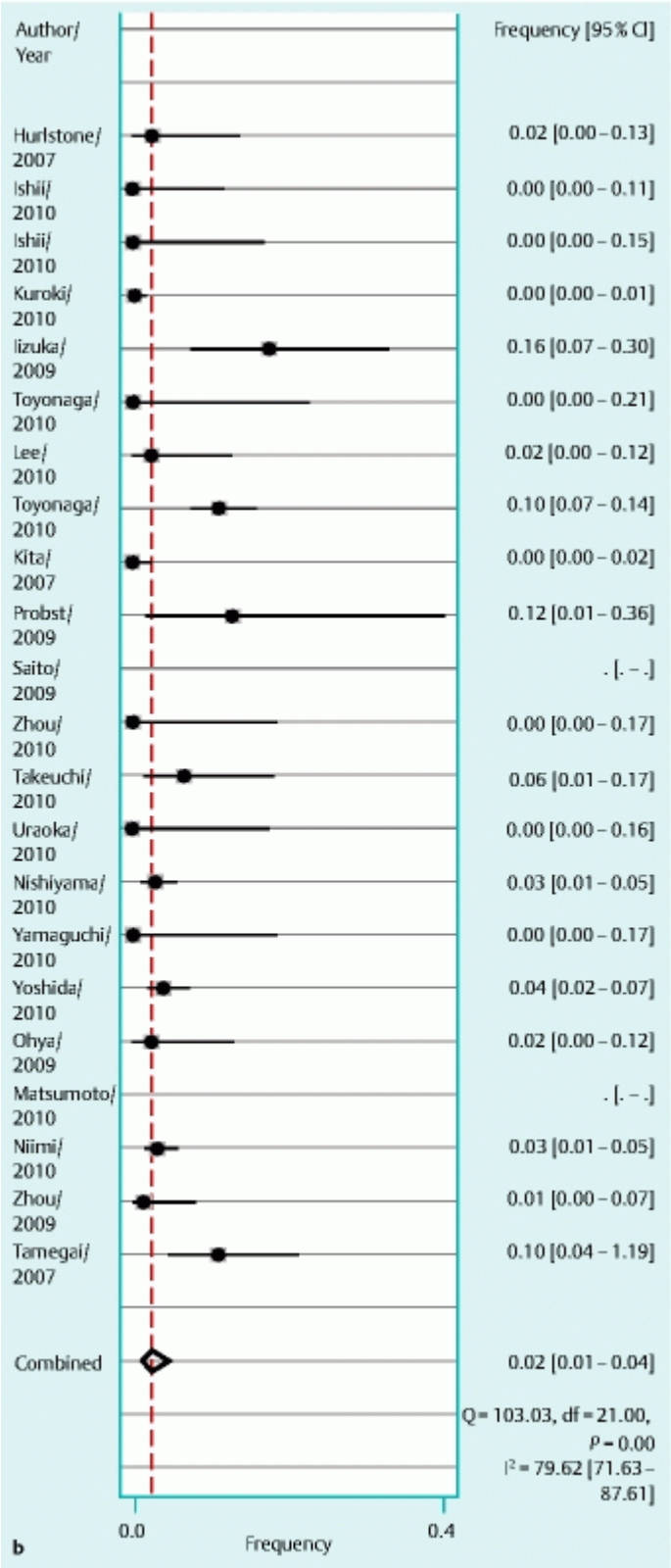


Fig. 4 Forest plot of the included studies analyzing secondary end-points of the systematic review. a Rate of endoscopically complete endoscopic submucosal dissection (ESD) resection. b Post-ESD



surgery for therapeutic failure (i.e. excluding surgery for ESD complication).

Bleeding and perforations were cumulatively reported in 47 and 135 cases, respectively, corresponding to per-lesion summary estimates of 2% (95%CI 1%–2%; I^2=69%; [Fig.5a]) and 4% (95%CI 4%–6%; I^2=45%; [Fig.5b]), respectively. Of note, no case of mortality, either directly or indirectly related to ESD, was reported in any of the included series.

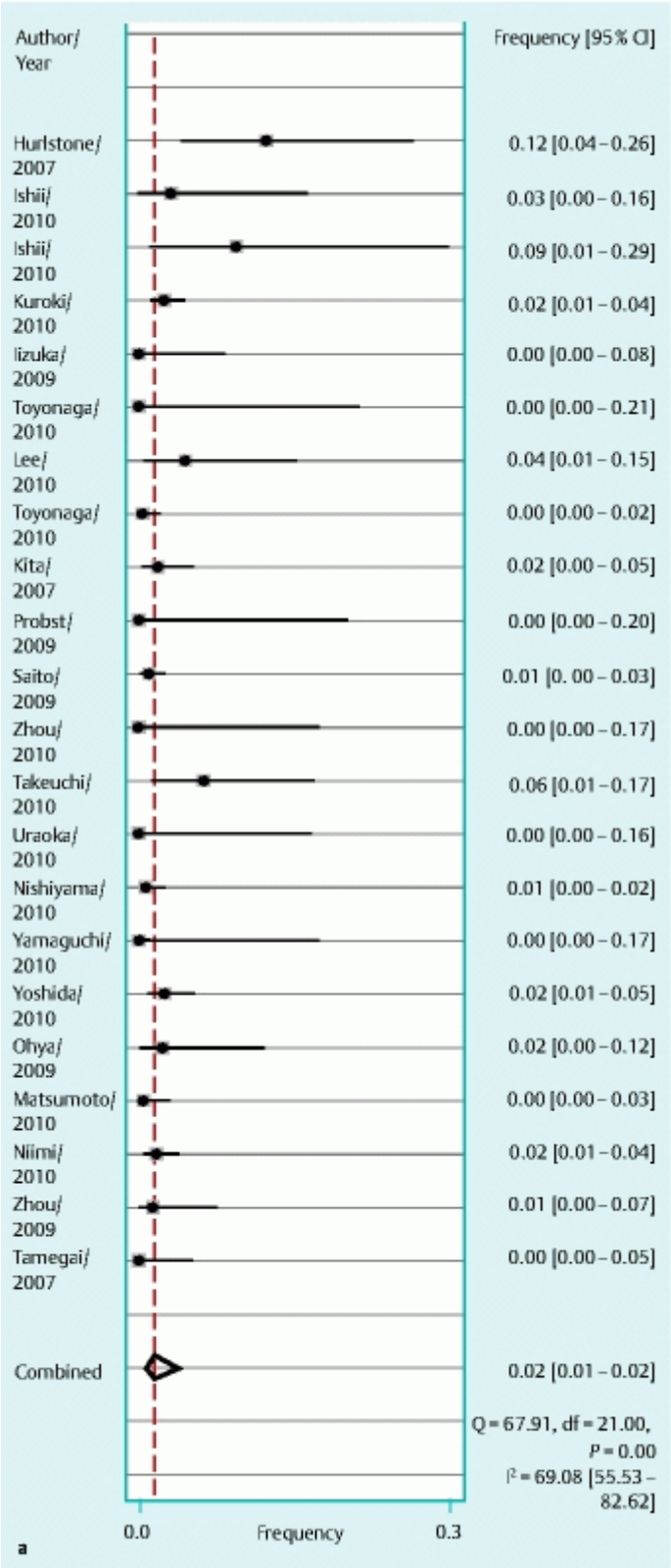
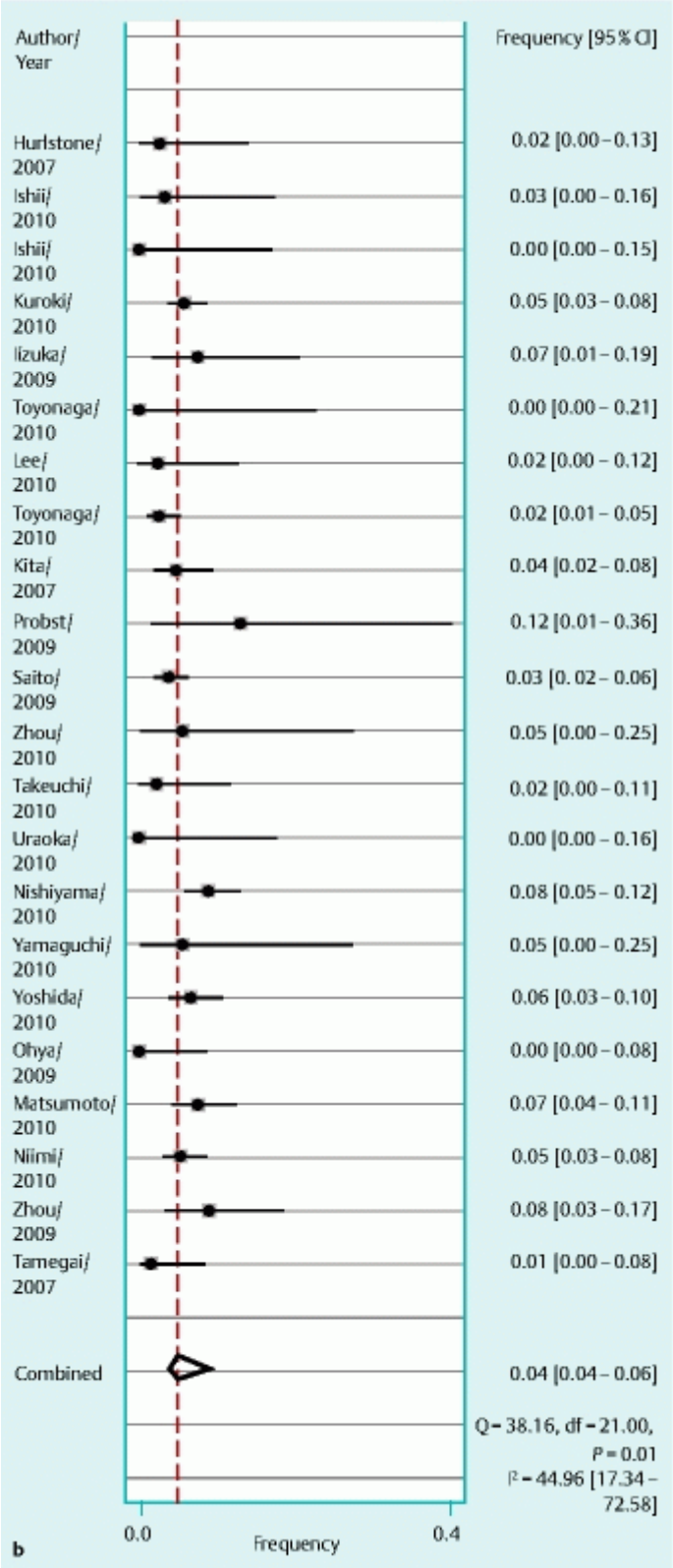

Author/ Year
Frequency [95% CI]
Hurlstone/ 2007
0.12 [0.04 – 0.26]
Ishii/ 2010
0.03 [0.00 – 0.16]
Ishii/ 2010
0.09 [0.01 – 0.29]
Kuroki/ 2010
0.02 [0.01 – 0.04]
Iizuka/ 2009
0.00 [0.00 – 0.08]
Toyonaga/ 2010
0.00 [0.00 – 0.21]
Lee/ 2010
0.04 [0.01 – 0.15]
Toyonaga/ 2010
0.00 [0.00 – 0.02]
Kita/ 2007
0.02 [0.00 – 0.05]
Probst/ 2009
0.00 [0.00 – 0.20]
Saito/ 2009
0.01 [0. 00 – 0.03]
Zhou/ 2010
0.00 [0.00 – 0.17]
Takeuchi/ 2010
0.06 [0.01 – 0.17]
Uraoka/ 2010
0.00 [0.00 – 0.16]
Nishiyama/ 2010
0.01 [0.00 – 0.02]
Yamaguchi/ 2010
0.00 [0.00 – 0.17]
Yoshida/ 2010
0.02 [0.01 – 0.05]
Ohya/ 2009
0.02 [0.00 – 0.12]
Matsumoto/ 2010
0.00 [0.00 – 0.03]
Niimi/ 2010
0.02 [0.01 – 0.04]
Zhou/ 2009
0.01 [0.00 – 0.07]
Tamegai/ 2007
0.00 [0.00 – 0.05]
Combined
0.02 [0.01 – 0.02]
Q = 67.91, df = 21.00, P = 0.00
I² = 69.08 [55.53 – 82.62]
0.0
Frequency
0.3
a

Fig. 5 Forest plot of the secondary end-points of included studies. a Rate of bleeding after endoscopic submucosal dissection. b Perforation, irrespectively of whether the subsequent therapy



was surgical or conservative. **Post-ESD follow-up**

Overall, 13 series including 1397 R0 ESD resections provided information on post-ESD follow-up ([Table6]). Median follow-up across the series was 22 months (range 6–43 months). Only one case of recurrence was reported, corresponding to a pooled risk of 0.07% (95%CI 0%–0.2%).

Table 6 Follow-up data after endoscopic submucosal dissection (ESD). Post-ESD recurrence rate limited to R0 ESD-resected lesions is reported.

Table6

Follow-up data after endoscopic submucosal dissection (ESD). Post-ESD recurrence rate limited to R0 ESD-resected lesions is reported.

Reference	R0 resection, n	Post-ESD follow-up duration, months	Post-ESD recurrence in R0 ESD resection, %
Tamegai et al. [7]	68	12	0
Zhou et al. [8]	66	14	0
Niimi et al. [9]	213	31	0
Yamaguchi et al. [13]	18	19	0
Nishiyama et al. [14]	234	34	0
Zhou et al. [17]	20	43	0
Probst et al. [19]	9	16	0
Toyonaga et al. [21]	263	30	0
Lee et al. [22]	38	13	0
Kuroki et al. [25]	386	13	0.3
Ishii et al. [26]	21	30	0
Ishii et al. [27]	30	20	0
Hurlstone et al. [28]	31	6	0

Discussion

Our analysis showed that ESD is an extremely effective procedure for removing colorectal neoplastic lesions, with an R0 resection being achieved in 88% of the lesions. Our estimate was based on nearly 3000 colorectal ESD resections, which is more than the previous analysis which included approximately 1000 lesions [32] [33]. Despite the retrospective nature of most of the included series, the strength and independence of the adopted reference standard –a histologically verified R0 resection –may be expected to minimize the potential risk of recall bias. This was indirectly confirmed by the virtually null risk of post-R0-ESD recurrence in the included studies that provided a post-ESD follow-up. The high efficacy of ESD was notable considering the demanding setting in which it was achieved: with the exception of a few series in which only small rectal carcinoids were selected, most of the ESDs were performed for colorectal lesions of size ≥20 mm or post-EMR recurrences, in which no endoscopic alternative for en bloc resection is available. EMR is unlikely to achieve an R0 resection in these cases, and a piecemeal EMR resection results into a high rate of post-EMR recurrence and in some degree of uncertainty in the

histological assessment of the R0 resection [33]. It could be argued that as submucosal cancer occurred in only 11% of the collected cases, ESD was mainly applied to benign lesions that are potentially treatable by piecemeal resection. However, non-invasive cancer was already present in 44% of the ESD-resected lesions, raising concern over the relatively high risk of recurrence following piecemeal removal. It could also be argued that R0-ESD removal of a submucosal cancer does not necessarily represent a radical treatment, with additional surgery being recommended in cases of histological risk factors, such as poor differentiation, lymphovascular infiltration or infiltration deeper than sm1 [4]. According to our analysis, however, additional surgery following ESD occurred in only 2% of the cases, most of them presumably due to failure of R0 resection rather than to further surgery in R0-removed high-risk lesions.

Nearly half of the ESDs were performed for rectal lesions. This is probably justified by the higher feasibility of ESD in the rectum due to rectal anatomy compared with the colon. A potential competitor for ESD in this setting is transanal endoscopic microsurgery (TEM). In fact, the main indication for TEM is sessile adenomas and – to a lesser extent – T1 rectal cancer [34]. Despite the lack of direct comparison between ESD and TEM, a previous systematic review of 1857 TEM procedures showed 10% incomplete excision after TEM for sessile adenomas, resulting into a 4.5% recurrence rate [34]. According to our data, ESD compares favorably with TEM in terms of both complete excision and recurrence rate. Of note, our data would represent a worst-case scenario for rectal ESD, as it was impossible to separate data between rectal and colon ESD, with the latter probably diluting the higher R0 resection rate achievable by rectal ESD. On the other hand, TEM series on T1 rectal cancer provide extensive data on oncological end-points, as well as on pre-operative EUS and post-surgical staging [34], which at the present time are lacking in ESD series. TEM has also been reported as a successful approach for selected cases of T2 rectal lesions following chemoradiotherapy, as this approach allows resection of the whole rectal wall including some peri-rectal fat [34]. In view of these data, ESD and TEM should be considered competitors or alternatives in terms of indications and outcome only in those lesions with malignant infiltration limited to the sm1. For this reason, cohorts of T1 rectal cancer patients treated by ESD under a rigorous surveillance protocol are needed, in order to compare the long-term oncological results of this technique with those of TEM.

Our analysis also showed an adequate safety profile for colorectal ESD. The risk of post-ESD complication-related surgery – occurring in 1% of the cases – was negligible when compared with the high efficacy of this procedure. The outcome “surgery for complications” rather than the overall rate of complications was chosen as a primary end-point in the present analysis for several reasons. In the same way that histological verification is used for efficacy assessment, a robust and independent reference standard was required to minimize the potential risk of publication or recall bias: a surgical intervention is unlikely to have gone unrecorded. Secondly, when passing from an EMR to an ESD procedure, a higher risk of both bleeding and perforation is unavoidable due to the intrinsic aggressiveness of ESD on the bowel wall. However, if such a risk is almost completely compensated for by an improvement in the endoscopic treatment of the ESD-associated complication, the safety profile may still be considered adequate. According to our analysis, a cumulative risk of 6% between bleeding and perforation was reduced to a 1% risk of complication-related surgery due to the endoscopic efficacy in the treatment of ESD-related complications. Thirdly, nearly half of the lesions treated by ESD were located in the rectum. Because of the extra-peritoneal localization of two-thirds of the rectum, most perforations are usually treated conservatively, minimizing the clinical impact of the complication. Fourthly, when considering that, without the option of performing ESD, at least some lesions would have been immediately treated by surgery, the use of ESD would allow surgery to be avoided in the majority of cases even when the low risk of post-complication surgery is taken into account.

There are limitations to the present analysis. A moderate/high degree of heterogeneity was present in the estimates. This may be due to factors related to the study design and the ESD feasibility. Regarding study design, not only were most of the publications retrospective, but they also embraced very long enrollment periods, so that a different mix of learning curve and post-training experience was likely to occur in the different series. Regarding ESD feasibility, there is poor standardization of the colorectal ESD technique, so that we cannot exclude the possibility that the different technical approaches may have prevented more homogeneous study results. Moreover, we included both Japanese and European series, despite the much heavier contribution of Asian endoscopists to the ESD literature (particularly for early gastric cancer treatment), which substantially contributed to the detected heterogeneity, as shown by the meta-regression. Similarly, the inclusion of both carcinoid and non-carcinoid series was shown to reduce the sample homogeneity, because of the higher ESD feasibility for small rectal carcinoids compared with large LST lesions in the remaining colon. Publication bias was also detected in the estimates of post-ESD surgery for complications. This was not surprising given that most of the series were retrospective; this underlines the need for new large prospective ESD series. Most of the included studies reported on the Japanese differentiation between high grade dysplasia and intramucosal cancer, which is no longer accepted by Western pathologists. However, all of the studies also reported the distinction between intra- and submucosal cancer, providing uniformity of interpretation between the two different cultural approaches. The individual studies did not separately report data on efficacy according to the histological subtype (low and high grade adenoma, submucosal cancer). Therefore, we cannot exclude lower rates of R0 resection in more advanced histological lesions that are potentially more difficult to treat. Finally, the ESD technique has not yet been standardized, with a wide variety of different cutting devices, accessories, training periods, and learning curves, so that appropriate technical guidelines may be needed.

In conclusion, this systematic review provided reliable estimates of the efficacy and safety of colorectal ESD in nearly 3000 lesions using robust and independent reference standards. Colorectal ESD appeared to be a very effective and safe procedure, at least in expert hands, for lesions otherwise difficult to be radically treated with snare-based endoscopic resection techniques. Better ESD standardization and a more widespread and systematic implementation in Western countries are required.

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