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Advanced endoscopic resection for colorectal dysplasia in inflammatory bowel disease: a meta-analysis

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ABSTRACT

Background and study aims Little is known about outcomes of advanced endoscopic resection (ER) for patients with inflammatory bowel disease (IBD) with dysplasia. The aim of our meta-analysis was to estimate the safety and efficacy of endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) for dysplastic lesions in patients with IBD.

Methods We performed a systematic review through Jan 2021 to identify studies of IBD with dysplasia that was treated by EMR or ESD. We estimated the pooled rates of complete ER, adverse events, post-ER surgery, and recurrence. Proportions were pooled by random effect models.

Results Eleven studies including 506 patients and 610 lesions were included. Mean lesion size was 23 mm. The pooled rate of complete ER was 97.9 % (95 % confidence interval [CI]: 95.3 % to 99.7 %). The pooled rate of endoscopic perforation was 0.8 % (95 % CI:0.1 % to 2.2 %) while bleeding occurred in 1.6 % of patients (95 %CI:0.4 % to 3.3 %). Overall, 6.6 % of patients (95 %CI:3.6 % to 10.2 %) underwent surgery after an ER. Among 471 patients who underwent surveillance, local recurrence occurred in 4.9 % patients (95 % CI:1.0 % to 10.7 %) and metachronous lesions occurred in 7.4 % patients (95 %CI:1.5 % to 16 %) over a median follow-up of 33 months. Metachronous colorectal cancer (CRC) was detected in 0.2 % of patients (95 %CI:0 % to 2.2 %) during the surveillance period.

Conclusions Advanced ER is safe and effective in the management of large dysplastic lesions in IBD and warrants consideration as first-line therapy. Although the risk of developing CRC after ER is low, meticulous endoscopic surveillance is crucial to monitor for local or metachronous recurrence of dysplasia.

Introduction

Colitis-associated dysplastic lesions are commonly associated with submucosal fibrosis because of submucosal scarring from chronic inflammation. Thus, advanced resection techniques are often required for complete endoscopic resection (ER) of these lesions. The International Consensus Recommendations (SCENIC) suggest complete ER for endoscopically visible non-polypoid dysplastic lesions [1]. However, there is a concern that these lesions can confer a higher risk of CRC, as complete endoscopic removal of such flat and large lesions can be technically difficult. At present, there are limited data on outcomes of advanced ER for the management of large dysplastic lesions, driving uncertainty in clinical decision making.

A meta-analysis by Mohan et al. reported the outcomes of ER of dysplasia in patients with inflammatory bowel disease (IBD), highlighting the safety and effectiveness of ER for these lesions. [2] However, nearly half of the included series in that meta-analysis included patients who had conventional polypectomy where the possibility of achieving a complete ER was low. Moreover, that meta-analysis also included studies that used hot or cold biopsy forceps as resection methods, which are not applicable to large dysplastic lesions in the setting of IBD [3, 4].

Therefore, we conducted a systematic review and meta-analysis of the literature to assess the lesion characteristics and evaluate the efficacy of advanced ER techniques (endoscopic mucosal resection [EMR] and endoscopic submucosal dissection [ESD]) for dysplasia in IBD. We also assessed the risk of local recurrences and metachronous lesions after successful ER of colorectal lesions in these patients.

Methods

Search strategy

All searches were run on October 16, 2019 and updated on January 14, 2021 in Medline (PubMed), Embase, The Cochrane Library, and Web of Science databases. For the search strategies, controlled vocabulary terms for each concept were identified and combined with keyword synonyms (**see Appendix A for exact search strategies)**. Pertinent searches of the references of review papers and gray literature were also conducted for additional studies on this subject.

Study selection

We combined search results from the different databases, removed duplicates electronically, and checked results manually for accuracy. Two reviewers (SM, CL) independently reviewed the abstracts and full texts for inclusion. Any disagreements about inclusion or exclusion of these studies were resolved by consensus, and a third senior reviewer (SN) was consulted to resolve any remaining disagreements.

Eligibility criteria

We considered all original articles on IBD-associated dysplasia that were suitable for ER (distinct margins with no endoscopic features of submucosal invasion) and treated with EMR and ESD. Because the hybrid ESD techniques (ESD with snaring) are substantially different from the standard ESD techniques, they are considered separately in the analysis. Studies were included if they met the following criteria: (1) Original articles that assessed the use of EMR, ESD, and hybrid ESD and provided outcomes of interest; (2) studies performed in humans; (3) studies that included more than five patients; and (4) studies that were published in English. Exclusion criteria were: (1) studies not reporting complete ER rates; (2) studies reporting outcomes of conventional polypectomy only; (3) animal studies; (4) review papers; (5) studies written in languages other than English; (6) case reports with less than five patients; and (7) abstracts.

Data extraction

The reviewers independently abstracted the following information from each paper: year of publication, country, setting (single center/multicenter), study design (prospective/retrospective), ER techniques (EMR and/or ESD), number of patients, number of lesions, mean/median size of the polyp, complete ER rates (defined as macroscopic evidence of complete resection), rates of R0 resection (defined as complete ER with free lateral and vertical margins), number of invasive cancer at histology, adverse events (AEs) such as intra-procedural or post-procedural bleeding, rate of perforation, rate of surgery for AEs, mean/median duration of post endoscopic follow-up, rate of local recurrence and metachronous lesions, rate of invasive cancer at follow-up, rate of repeat ER, and surgery.

Risk of bias in individual studies

We assessed the quality of the included studies using the Newcastle Ottawa scale [5]. We evaluated representativeness of the study cohort, ascertainment of exposure, a demonstration that outcome of interest was not available at the start of the study, assessment of outcome, and adequate duration of endoscopic follow-up for each study. Two variables of the Newcastle Ottawa scale, i. e., selecting the non-exposed cohort and comparability of cohorts based on study design or analysis, were not evaluated since cohorts not exposed to endoscopic therapy were not represented in the included studies.

Outcomes

The primary outcomes of this meta-analysis were to determine the rates of: complete ER, adverse events, and post-ER surgery of patients with IBD-associated dysplasia. Secondary outcomes were to determine the rates of: 1) en bloc resection; 2) R0 resection (for patients who underwent ESD); 3) local recurrence at follow-up; 4) metachronous lesions at follow-up; 5) advanced dysplasia and CRC at follow-up; 6) successful ER of any recurrence; and 7) surgery for the recurrent disease after an advanced ER of IBD-associated dysplasia.

Statistical analysis

Pooled analysis was performed using the random effect model using the DerSimonian and Laird method. I^2 statistics was used to describe heterogeneity across studies: low level <25 %), moderate level (25 % to 50 %) and high level of heterogeneity (>75 %). The risk of publication bias was assessed for the pooled rate of complete ER for all lesions. Egger's regression was used

to test for funnel plot asymmetry. Forest plots were drawn, showing the variation of the event rates among all studies together with the pooled measure. A cumulative meta-analysis was performed to assess for the small study effect. The main analysis was performed using Stata, version 16.0 (Stata Corp., College Station, Texas, United States).

Results

Study selection

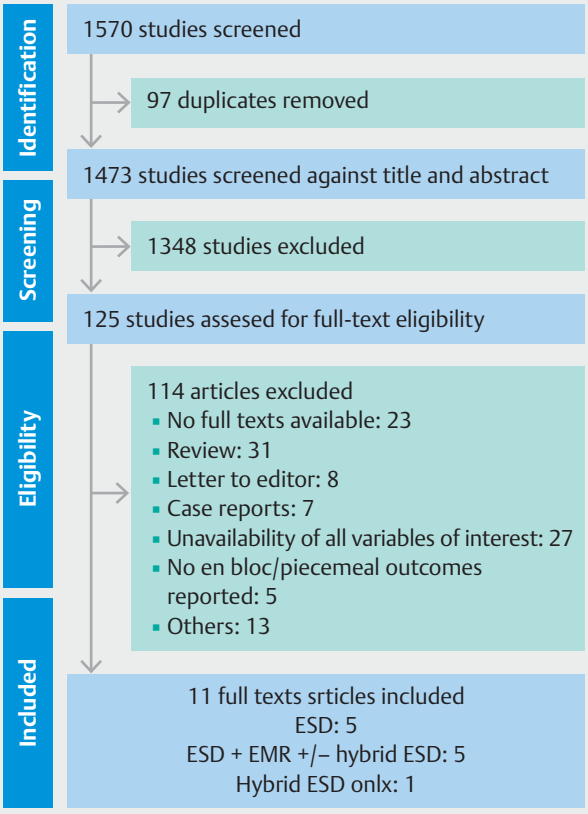
The initial literature search resulted in 1570 citations. After screening titles and removing duplicates, 125 abstracts were identified and screened to assess for eligibility (▶ **Fig. 1**). Of these, 11 studies met the final inclusion criteria for the meta-analysis. Among these, five studies adopted the standard ESD technique [6–10], one study used hybrid ESD technique only [11], and others used a combination of EMR, ESD, and hybrid ESD techniques [12–16]. Median duration of enrollment per study was 7 years (range 2–19 years). Eight of the studies were single-center [8–13, 15, 16], two studies were done in two centers [6, 7], and one was multicenter [14]. Overall, four studies were performed in Europe [11–14], four were from Asia [8–10, 16], two from Europe and Asia [6, 7], and one was from the United States [15].

Risk of bias assessment

No significant selection bias was identified across the studies (**Supplementary Table 1**). All study cohorts included patients who were felt to have lesions amenable to ER. All patients were included based on an endoscopic and/or pathologic report. All studies consistently reported rates of complete ER, post-ER histologic findings, AEs, and surgery for non-curative ER. Post endoscopic surveillance and recurrence were reported as well in all studies. The majority of the studies had a median follow-up of more than 12 months after ER.

Patient characteristics

There were 506 patients with a total of 610 lesions among the 11 studies. The baseline study characteristics are shown in ▶ **Table 1**. The mean age was 56.1 years, with a mean disease duration of 16.5 years. Of the patients, 90.9 % had been diagnosed with ulcerative colitis (UC), 7.3 % with CD, and 1.7 % were indeterminate. Information regarding the severity of the disease was available in seven series: 45.0 % were in clinical remission, 50.3 % had mild to moderate colitis, and 4.6 % had severe colitis [6–9, 12, 13, 15]. The extent of disease was reported in eight studies: 76.1 % of the patients were reported to have pancolitis, followed by 17.1 % with left-sided colitis, 1.6 % proctitis, and 5.2 % were unclassified [6, 8–10, 12–14, 16]. Distribution sites of the lesions was available in eight series: 32 % in the rectum, 1.2 % in the rectosigmoid, 18.7 % in the sigmoid, 7.7 % in the descending, 0.6 % at the splenic flexure, 11.9 % in the transverse, 0.3 % at the hepatic flexure, 21.6 % in the ascending, and 5.1 % in the cecum [6–11, 13, 15] Chromoendoscopy was performed in all series except one series [15], where it was used in 26.6 % of patients.



▶ **Fig. 1** Study design of identification of eligible studies. ESD, endoscopic submucosal dissection; EMR, Endoscopic mucosal resection.

Lesion characteristics

The mean lesion size across all studies was 23 mm. The mean lesion size was 14.6 mm for those resected with EMR, 25.1 mm for the lesions that were resected by ESD and 26 mm for those resected by hybrid ESD (▶ **Table 2**). Among all lesions, 67.7 % were non-polypoid, and 32.3 % polypoid (**Supplementary Table 2**). Eight studies reported the rate of submucosal fibrosis and the pooled rate was 191 /292 lesions (83 %, 95 % confidence interval (CI) 61 % to 98 %, I^2 = 93.3 %) [6–11, 13,17]. Submucosal fibrosis was present in 2.3 %, 88.1 %, and 75.3 % for the lesions resected by EMR, ESD, and hybrid ESD respectively.

Primary outcomes

Rate of complete endoscopic resection

Among 610 lesions, 347 (56.8 %) underwent EMR, 190 (31.1 %) ESD, and 73 (11.9 %) hybrid ESD (▶ **Table 2**). Overall, complete ER was successful in 592 of 610 endoscopic resections (97.9 %, 95 % CI: 95.3 % to 99.7 %, I^2 48.7 %) (▶ **Fig. 2**). Based on the data reported by 10 studies, the rate of incomplete resection following EMR was six of 269 (0.6 %, 95 % CI: 0 % to 2.7 %, I^2 6.3 %), ESD was 10 of 149 (3.8 %,95 % CI: 0.2 % to 10 %, I^2 = 25.6 %), and hybrid ESD was 0 %. Of the 18 lesions with incomplete resection, eight were due to severe fibrosis, two due to non-lifting, two

▶ **Table 1** Baseline study characteristics.

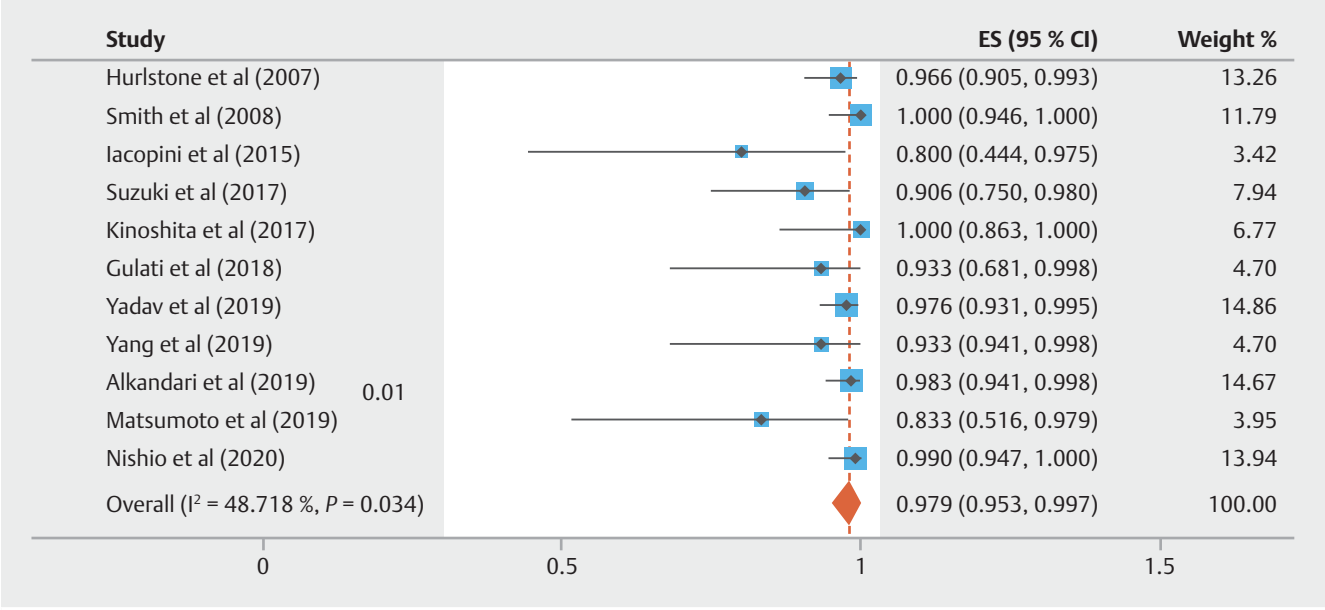
Author (year)	Country	Multicenter/ single center	Study design	Study period	Total patients	Age in years	Male (%)	Type of IBD (n)		
								UC	CD	Indeterminate
Hurlstone et al (2007)[1]	United Kingdom	Single center	Prospective	June 2000–April 2006	74	58.5 (21–74)	–	74	0	0
Smith et al (2008)	United Kingdom	Single center	Prospective	Jan 2006–March 2008	67	54.5 (26–72)	36	67	0	0
Iacopini et al (2015)	Italy and Japan	Two centers	Prospective	Jan 2009–July 2016	09	62 (35–69)	04	9	0	0
Suzuki et al (2017)	UK and Japan	Two centers	Retrospective	Jan 2009–Jan 2016	32	65 (49–86)	18	32	0	0
Kinoshita et al (2017)	Japan	Single center	Retrospective	Feb 2011–Jan 2017	25	61.8 (38–83)	18	25	0	0
Gulati et al (2018)	United Kingdom	Single center	Prospective	Jan 2011–Sept 2017	15	–	11	15	0	0
Yadav et al (2019)	United states	Single center	Retrospective	Jan 2012–June 2016	97	59.1 (49.2–87.7)	59	63	27	7
Yang et al (2019)	Korea	Single center	Retrospective	Aug 2009–July 2017	15	45.3 (18.6–71.5)	10	15	0	0
Alkandari et al (2019)	European	Multicenter	Retrospective	2008–2016	91	62 (26–83)	53	81	10	2
Matsumoto et al (2019)	Japan	Single center	Retrospective	Aug 1999–Jun 2015	07	55 (37–65)	05	7	0	0
Nishio et al (2020)	Japan	Single center	Retrospective	Jan 2000–Oct 2019	74	58 (48–70)	–	74	0	0

[1] 34 % of 112 patients who underwent simple polypectomy were excluded from the final analysis.

▶ **Table 2** Differences in polyp morphology and outcomes between EMR, ESD, and hybrid ESD techniques across all studies.

	Endoscopic mucosal resection (n = 347)	Endoscopic submucosal dissection (n = 190)	Hybrid endoscopic submucosal dissection (n = 73)
Lesion characteristics			
▪ Mean size (mm)	14.6	25.1	26
▪ Proportions of lesions < 20 mm (%)	71.3	36.8	NA
▪ Submucosal fibrosis (%)	2.3	88.1	75.3
Polyp morphology (%)			
▪ Polypoid	43.8	11.1	32.8
▪ Non-polypoid	56.2	88.9	67.1
Rate of incomplete resection (%)	0.6 (95 % CI: 0 %–2.7 %, I^2 6.3 %)	3.8 (95 % CI: 0.2 %–10 %, I^2 25.6 %)	0
Rate of en bloc resection (%)	79.7 (95 % CI: 63 %–90.3 %, I^2 92.6 %)	85.7 (95 % CI: 72.2 %–95.8 %, I^2 73.6 %)	74.6 (95 % CI: 63.1 %–84.8 %, I^2 0 %)
Rate of adverse events (%)	0.7 (95 % CI 0 %–2.7 %, I^2 0 %)	4.4 (95 % CI 0.07 %–10 %, I^2 11.8 %)	11 (95 % CI 4.3 %–19.6 %, I^2 0 %)
Rate of recurrence during follow-up (%)	3.5 (95 % CI 0 %–11.5 %, I^2 83.4 %)	1.7 (95 % CI 0 %–6.5 %, I^2 33.5 %)	4.4 (95 % CI 0.1 %–11.8 %, I^2 0 %)

EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; NA, not available.



▶ **Fig. 2** Forest plot, pooled rate of complete endoscopic resection in patients with dysplasia in inflammatory bowel disease. CI, confidence interval.

due to patient intolerance, one due to technical difficulties, and the reason was not provided for five lesions who had incomplete ER.

Histopathology was available in 606 out of 610 lesions. Of 606 lesions, high-grade dysplasia (HGD) was found in in 92 lesions (14.8 %, 95 % CI: 8.7 % to 21.9 %, I^2 84 %), low-grade dysplasia (LGD) in 415 lesions (67 %, 95 % CI: 59.3 % to 74.4 %, I^2 79.4 %), sessile serrated adenoma/polyp in 59 lesions (4.6 %, 95 % CI: 0.1 % to 10.1 %, I^2 87.2 %), hyperplastic and regenerative atypia in nine lesions (0.2 %, 95 % CI: 0 % to 1.2 %, I^2 43.7 %), intramucosal cancer in 12 lesions (0.6 %, 95 % CI: 0 % to 2.8 %, I^2 71.1 %) and invasive cancer in 19 lesions (2 %, 95 % CI 0.2 % to 5.1 %, I^2 74 %).

Adverse events

Endoscopic perforation occurred in 12 of 506 patients (0.8 %, 95 % CI 0.1 % to 2.2 %, I^2 23.9 %) while bleeding occurred in 16 of 506 patients (1.6 %, 95 % CI 0.4 % to 3.3 %, I^2 29.7 %) (Supplementary Fig.1). Nine studies separately reported the bleeding and perforation risks for each resection techniques [6–8, 10–13, 15, 16]. Bleeding occurred in 1.4 % of patients (3/206) after EMR, 2.3 % of patients (3/129) after ESD, and 9.5 % of patients (7/73) after hybrid ESD, whereas perforation occurred in 0 % of patients after EMR, 3.8 % of patients (5/129) after ESD and 4.1 % of patients (3/73) after hybrid ESD. All AEs were managed endoscopically, except for one patient who had a delayed perforation after 24 hours and required surgery. No mortality related to ER was reported.

Rate of surgical resection

After an ER, 42 of 506 patients underwent surgery for a variety of reasons, with a pooled rate of 6.6 % (95 % CI 3.6 % to 10.2 %, I^2 56.8 %) (▶ **Fig. 3**). Of these, 18 patients (3.5 %) underwent surgery due to invasive cancer, 13 patients (2.5 %) underwent surgery due to incomplete or non-R0 resection, one patient (0.2 %) underwent surgery due to perforation, five patients (1 %) underwent surgery due to HGD, and five patients (1 %) referred for surgery for the management of IBD progression with concomitant LGD (**Supplementary Table 3**).

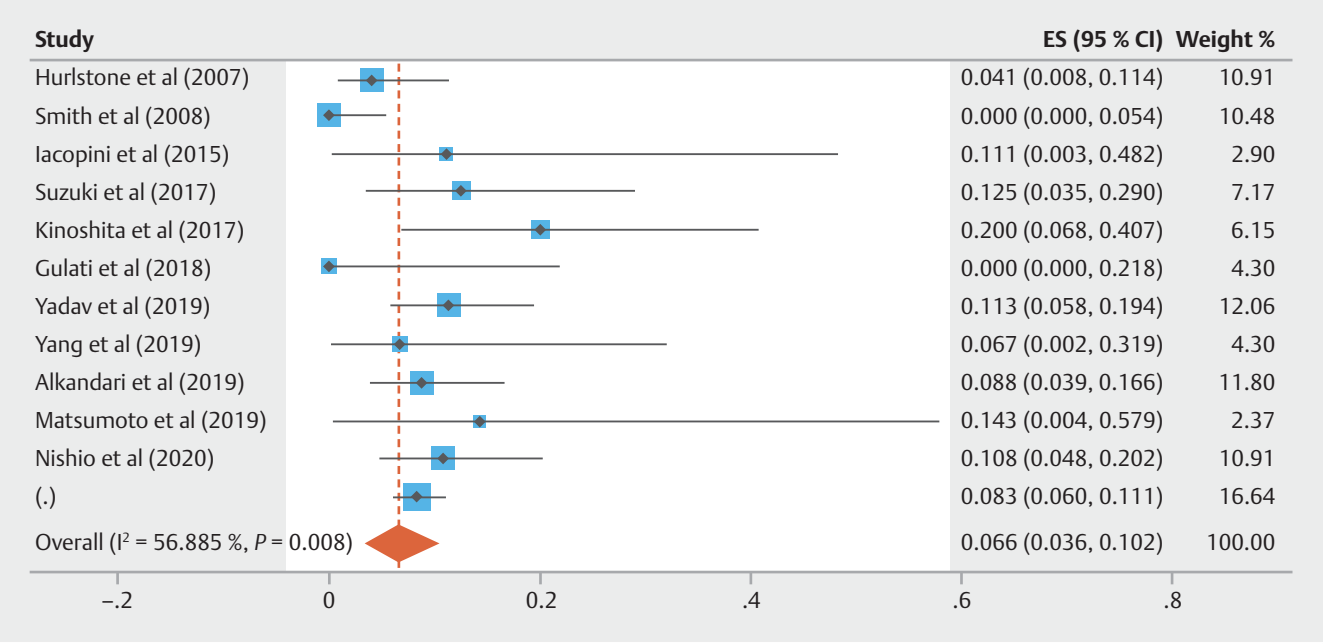
Secondary outcomes

En bloc and R0 resection rates

The overall rate of en bloc resection was 485 of 610 lesions (83.4 %, 95 % CI 73 % to 91.8 %, I^2 87 %). The pooled rate of en bloc resection for ESD technique was 160/190 lesions (85.7 %, 95 % CI: 72.2 % to 95.8 %, I^2 73.6 %), for hybrid ESD was 53/73 lesions (74.6 %, 95 % CI: 63.1 % to 84.8 %, I^2 0 %) and for EMR was 272/347 colorectal lesions (79.7 %, 95 % CI: 63 % to 92.6 %, I^2 89.8 %) (Supplementary Fig.2). R0 resection rate was reported in eight series with per-lesion pooled R0 resection rate of 74.3 % (95 % CI: 64.6 % to 83.1 %, I^2 57.5 %) [6–11, 13, 16].

Follow-up outcomes

Of 506 patients, a total of 471 patients (93.1 %) underwent surveillance endoscopy with a combined 1514 years of patient follow-up. Thirty-five of 506 patients (6.9 %) were lost to follow-up. The median follow-up period was 33 months (range 18 to 180 months). The pooled incidence of any dysplasia after ER was 56 cases per 1000 years of patient follow-up (95 % CI:33 to –97/1000, I^2 = 79.3 %). The pooled incidence of any advanced lesion (HGD or CRC) was 15 cases per 1000 years of patient follow-up (95 % CI:7 to 32/1000, I^2 = 53.3 %).



▶ **Fig. 3** Forest plot, pooled rate of surgery after an endoscopic resection in patients with IBD-associated dysplasia. CI, confidence interval.

Rate of local recurrence

Local recurrence was detected at surveillance in 39 of 471 patients (4.9 %, 95 % CI 1.0 % to 10.7 %, I^2 73.7 %) (**Supplementary Fig. 3**). Of the 39 lesions with local recurrence, 38 patients were found to have LGD and one patient had HGD. No CRC at the site of prior ER was detected during the follow-up period. The local recurrence was found to be higher when the lesions were resected in piecemeal fashion compared to those series who used only en bloc (20/125, 16 % vs. 17 /485, 3.5 %, $P<0.001$) resection.

The pooled rate of local recurrences after EMR was 26/347 lesions (3.5 %, 95 % CI 0 % to 11.5 %, $I^2=83.4$ %), after ESD 8/190 lesions (1.7 %, 95 % CI 0 % to 6.5 %, $I^2=33.5$ %) and after hybrid ESD five of 73 lesions (4.4 %, 95 % CI 0.1 % to 11.8 %, $I^2=0$ %), respectively.

Of the 39 patients with local recurrence, repeat ER was successful in 37 patients (94.8 %) whereas two patients (5.1 %) required surgery. One patient with a recurrent lesion underwent surgery because of an unsuccessful second stage EMR. Another patient with a local recurrence who also had a synchronous locally recurred dysplasia at the previous polypectomy site required colectomy as neither of the recurrent lesion was amenable to repeat ER.

Rate of metachronous lesions

Metachronous lesions were detected in 26 of 471 patients (7.4%, 95 % CI 1.5 % to 16 %, I^2 84.7 %) (**Supplementary Fig. 3**). Of 471 patients, 13 patients (1.7 %, 95 %CI 0 % to 5.7 %, I^2 69 %) developed HGD or CRC, and seven patients (0.2 %, 95 %CI:0 % to 2.2 %, I^2 56 %) developed CRC during the surveillance period.

Of 26 patients with metachronous lesions, repeat ER was successful in 10 patients (38.4 %) whereas surgery was needed for 15 patients (57.6 %). Reasons for surgery included metachronous CRC in six patients, metachronous dysplasia in four patients, metachronous HGD in four patients, and failed ER in one patient. One of the 26 patients with metachronous lesions (indistinct LGD) refused a colectomy, and no progression to advanced histology was identified at 28.6 months after detection of the metachronous lesion.

Publication bias

The possibility of publication bias was examined by funnel plot for the main outcome (**Supplementary Fig. 4**). No evidence of publication bias was found for the rate of complete ER. Egger's regression ($P=0.48$) was negative for any small study effects. An additional analysis was performed for large studies (studies ≥ 25) to assess for sample size bias. Seven studies were included in this additional analysis with a pooled complete ER rate of 98.4 % (95 % CI: 96.7 % to 99.6 %, $I^2=25.4$ %), statistically similar to the original effect. The sensitivity analysis demonstrated no drift in the cumulative effect estimate as studies with small sample sizes were added.

Discussion

Our meta-analysis of 11 studies of large colorectal lesions in IBD patients shows that, despite a high prevalence of submucosal fibrosis, advanced ER appears to be effective in preventing surgery in 93.4 % of patients with IBD-associated dysplasia. The need for surgery immediately after an ER was mostly because of invasive cancer on the resected specimen. Advanced ER also seemed to be safe, with surgery for AEs limited to 0.2 % of patients. Furthermore, local recurrence occurred in approximately 4.9 % of patients, which was amenable to further endoscopic treatment in most cases. Metachronous dysplasia oc-

▶ **Table 3** Incidence of colorectal cancer and dysplasia during follow-up in patients with IBD-associated dysplasia.

	Present study	Mohan et al (2020) [2]	Wanders et al (2014) [21]	Thomas et al (2007) [20]
No. of included studies	11	18	10	20
No. of patients (n)	506	1037	376	508
Inclusion criteria				
▪ Study population	UC or CD with any dysplasia size > 10 mm	UC + CD with any dysplasia	UC with any dysplasia	UC with only LGD
▪ Intervention	EMR, ESD, hybrid ESD	Simple polypectomy, EMR, ESD or hybrid	Simple polypectomy	Surveillance colonoscopy or colectomy
Lesion characteristics (%)	▪ Non-polypoid (67.7) ▪ polypoid (32.3)	▪ Non-polypoid (25) ▪ Polypoid (9.4) ▪ Non-polypoid + Polypoid (65.4)	▪ Polypoid (100)	▪ Non-polypoid (93.8) ▪ Polypoid (6.1)
Follow-up period (person-years)	1514	NA	1704	1520
Polyp size (cm)	2.3 (mean)	NA	0.5–1.2	NA
Incidence of any dysplastic lesion (per 1000 person-years)	56 (95 % CI, 33–97)	43 (95 % CI, 30–57)	65 (95 % CI, 54–78)	NA
Incidence of HGD/CRC (per 1000 person-years)	15 (95 % CI: 7–32)	NA	7.0 (95 % CI, 4.0–12.4)	30 (95 % CI, 12–76)
Incidence of CRC[1] (per 1000 person-years)	NA	2 (95 % CI: 0–3)	5.3 (95 % CI, 2.7–10.1)	14 (95 % CI, 5–34)

IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; LGD, low-grade dysplasia; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; HGD, high-grade dysplasia; CRC, colorectal cancer; CI, confidence interval.

[1] Unable to report incidence of CRC per 1000 person years in the present study because of a very low event rate; overall 0.2 % CRC was detected during the surveillance period. IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; LGD, low-grade dysplasia; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; HGD, high-grade dysplasia; CRC, colorectal cancer; CI, confidence interval.

curred in 7.4 % of cases, with a 0.2 % rate of CRC during follow-up.

In this study, we found that mean lesion size across all studies was 23 mm. The mean lesion size resected by EMR technique was smaller (14.6 mm) than those resected by ESD (25.1 mm). In addition, prevalence of submucosal fibrosis in the EMR group was lower than the ESD group or hybrid technique (2.3 % vs 88.1 %/75.3 %). This finding is likely explained by selection of ESD or hybrid technique for the larger lesions or lesions with submucosal fibrosis which were not well lifted with submucosal injection. The use of needle knife dissection allows resection of fibrotic mucosal and submucosal tissue, which permit subsequent removal of the lesion with ESD or snaring.

Despite the technical difficulties, the pooled rate of en bloc resection was numerically higher in patients who underwent ESD (85.7 %) than EMR (79.7 %) and hybrid ESD (74.6 %), which are consistent with outcomes data of ER for colorectal lesions in patients without IBD.[18] For large dysplastic lesions with higher probability of advanced histology (i. e. prior biopsy showing HGD or depressed lesions), en bloc resection by ESD may be a preferred option to maximize chance of curative resection in case there is superficial invasive cancer in the resected specimens. In addition, for lesions with severe submucosal fibrosis that is not amenable to EMR, ESD or hybrid ESD should be considered as an alternative to colectomy.

The rate of AEs in our meta-analysis was low. We observed that endoscopic perforation (0.8 %) and bleeding (1.6 %) rates were similar to those reported from patients without IBD [19]. However, most of the procedures in the included studies were performed by expert endoscopists. Thus, the results may not be generalizable to other settings. In subsequent analysis, we found that the rate of AEs after EMR was lower than ESD and hybrid ESD, which may be related to the differences in the lesion size and underlying fibrosis.

A meta-analysis by Mohan et al. summarized the results of 18 studies with 1037 IBD patients who underwent ER for dysplasia and showed that 9.9 % of the patients in their study were referred for surgery [2]. Our study demonstrated a comparatively lower pooled rate of surgical referral (6.6 %), with the reasons for surgery being invasive cancer in the resected specimen (3.5 %), failed ER (2.7 %), and for surgical management of underlying IBD with or without concomitant dysplasia (1.9 %). The relatively higher surgery rate by Mohan et al. could be because half of their included studies were published at a

time when the advanced resection techniques were still in their infancy and the possibility of a complete endoscopic removal of the lesion was low [2]. This explanation is supported by a slightly decreased rate of surgical referrals between 2017 and 2019 in that study [2].

The incidence of CRC and dysplasia during the surveillance endoscopy is reported in a few other meta-analyses [2, 20,21], and the results are summarized in ▶ **Table 3**. We found a very low risk of CRC (0.2 %) over a mean follow-up of 33 months for the patients who underwent advanced ER for large dysplastic lesions in IBD. Overall, the incidence of CRC after an ER is decreasing over time (as shown in ▶ **Table 3**), which could be because of advances in endoscopic technologies improving the diagnosis and management of non-polypoid dysplasia. Furthermore, local recurrence occurred in 4.9 % of patients in our study, which was amenable to further endoscopic treatment in most cases. Despite a low incidence of CRC after advanced ER, we found a high rate of metachronous lesions, suggesting that close endoscopic surveillance is necessary to diagnose and treat these lesions. At present, surveillance intervals after an ER of IBD-associated dysplasia are not well defined and are mainly based on individual risk profiles. The patients with IBD with large dysplastic lesions removed with EMR or ESD likely should return at 3 to 6 months, with subsequent annual surveillance, if the initial repeat colonoscopy result is negative [1].

Our meta-analysis has several strengths. First, we included only studies using EMR or ESD for removal of large and/or flat colorectal dysplastic lesions in patients with IBD. To our knowledge, no previous meta-analysis was specifically designed to evaluate the role of advanced ER for these difficult lesions. Second, we differentiated the lesion characteristics and separately analyzed clinical outcomes for patients who underwent EMR, ESD, and hybrid ESD, which may provide valuable evidence for guideline formulation to establish a proper therapeutic strategy. Finally, we separately reported the incidence of local recurrences and rate of metachronous lesions after an ER in colitis-associated dysplasia, which was not reported in previous meta-analyses [2, 20, 21].

Our study has some limitations. Most of the included studies were either retrospective or single-center and based on small sample sizes with inherent possibility of selection bias. Some of the information was missing or incomplete from some of the studies. The number of studies describing the outcome of the hybrid resection technique was low; thus, the results of hybrid ESD should be interpreted cautiously. The rates of en bloc and R0 resection according to the macroscopic shape of the lesion (polypoid or non-polypoid) would have been helpful in selecting the appropriate resection technique; however, they were not reported separately in the majority of the included studies, therefore, we were unable to summarize this information in our study. Finally, most of the studies were performed in referral centers by expert endoscopists in Asia and Europe; studies from the United States demonstrating the efficacy and safety of these techniques are lacking.

Conclusions

In conclusion, our study demonstrated the safety and efficacy of EMR or ESD in treating large colorectal dysplastic lesions in patients with IBD. Depending on the availability of expertise, lesion size, and severity of disease, each case should be individualized, and each patient needs to be treated with the most appropriate technique. Although the risk of developing cancer after ER is low, close endoscopic follow-up is crucial to monitor for local recurrence or metachronous lesions. Future large prospective studies with long-term surveillance are warranted to better understand the natural history of IBD-associated dysplastic lesions and outcomes after endoscopic resection.

Competing interests

Dr. Ngamruengphong is a consultant for Boston Scientific.

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