Endoscopic resection for colorectal laterally spreading tumors in East Asian countries: a systematic review

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Background: To assess the efficacy and safety of different endoscopic resection methods for colorectal laterally spreading tumors (LSTs) in East Asian countries.

Methods: A literature search was performed in PubMed, Embase, Cochrane Library and Web of Science databases. Colorectal LSTs of the included studies were resected with endoscopic mucosal resection (EMR) and/or endoscopic submucosal dissection (ESD). The main outcomes involved rates of en bloc resection, R0 resection, adverse events and recurrence.

Results: A total of 20 studies were finally included in the present study. The total number of lesions were 3,903 (EMR: 1,230, ESD: 2,673). EMR-en bloc resection was obtained in 395/591 (66.8%), with ESD-en bloc resection reported in 2,020/2,265 (89.2%) [odds ratio (OR) 0.244, $P<0.0001$, 95% confidence interval (CI): 0.197–0.304]. EMR-R0 resection was achieved in 409/547 (74.8%), which was lower than that of ESD (1,895/2,241, 84.6%) (OR 0.541, $P<0.0001$, 95% CI: 0.432–0.677). Bleedings occurred more frequently in EMR than in ESD group (10.4% *vs.* 3.1%, OR 3.559, $P<0.0001$, 95% CI: 2.618–4.836). Rates of perforations in EMR and ESD were 0.4% and 4.1% (OR 0.099, $P<0.0001$, 95% CI: 0.036–0.27). Recurrence of EMR was higher than ESD group (6.3% *vs.* 1.0%, OR 6.732, $P<0.0001$, 95% CI: 3.751–12.082).

Discussion: Endoscopic resections of colorectal LSTs are safe and effective. ESD leads to higher rates of en bloc and R0 resection, as well as lower rates of bleeding and recurrence, but it has a high risk of perforation, compared with EMR.

Keywords: Endoscopic mucosal resection (EMR); endoscopic submucosal dissection (ESD); colorectal laterally spreading tumors (colorectal LSTs)

Introduction

Colorectal cancer (CRC) remains a major health burden with high incidence and mortality worldwide. CRC ranked third in incidence and second in mortality in 2018 among all cancers (1). In East Asian countries, the incidence and mortality of CRC in Japan ranked 4/2 and 3/1 in male/female, respectively (2), which ranked both third in Korea (3) and both fifth in China (4). The early identification and removal of lesions had been shown to reduce the mortality of CRC (5).

Laterally spreading tumors (LSTs) were defined as flat, broad-based lesions with a lateral diameter at least 10 mm (6) that were disposed to locate in colorectum. Based on the endoscopic morphology, LSTs were classified into two categories, either granular type (LST-G), with homogenous and nodular mixed subtypes, or non-granular type (LST-NG), with flat elevated and pseudodepressed subtypes (6,7). LSTs might evolve into high-grade intraepithelial neoplasms with an incidence from 20.9% to 33.8% (8,9). Hence, early detection and resection of colorectal LSTs is vital for the prevention and treatment of carcinogenesis.

Endoscopic treatments were widely accepted because of its minimally invasive methods, rapid recovery and low cost compared with surgery. Endoscopic mucosal resection (EMR) was first described in Japan in the early 1990s, and it was suitable for the majority of gastrointestinal superficial neoplasms (10). If lesions were larger than 15–20 mm or non-lifting, the lesions were resected by piecemeal EMR (EPMR) without en bloc resection, which possibly resulted in a high rate of local recurrence (11). Endoscopic submucosal dissection (ESD) was developed years later to provide R0 resection regardless of the size of tumor and a more precise histopathological assessment, but it was considered technically more difficult to perform and associated with a higher rate of adverse events, such as bleeding and perforation (11,12). The ideal endoscopic method is cost effective with a high rate of curative resection and a low risk of adverse events, minimizing the need for recurrent interventions (13). EMR is widely used in the world, but ESD is always limited to East Asian countries. A previous systematic review showed that western endoscopists had a lower level of experience in ESD with an increasing heterogeneity (14). Our study is aimed to evaluate the efficacy and safety of EMR and ESD for colorectal LSTs in East Asian countries. We present the following article in accordance with the PRISMA reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-21-2074/rc).

Methods

Study selection

The public databases (PubMed, Embase, Cochrane library, and Web of Science) were retrieved by two investigators using the terms: (endoscopic submucosal dissection) And (colorectal laterally spreading tumor) And (China) or (Korea) or (Japan), (endoscopic mucosal resection) And

(colorectal laterally spreading tumor) And (China) or (Korea) or (Japan). The initial search results were verified between two investigators with the contents, and duplicate literatures were excluded. Disagreements were judged by a third investigator. If there was no difference, the two investigators then screened potential studies by reviewing titles and abstracts (*Figure 1*). The study was registered with PROSPERO (CRD42021226966).

Inclusion criteria

The inclusion criteria were: endoscopic changes based on the characteristics of LST; lesions resected by EMR and/or ESD; randomized control trials (RCTs) or observational studies (both prospective and retrospective) published in English up to June 2021; the clinical outcomes including at least one of en bloc resection rate, R0 resection rate, follow-up periods, recurrence rate and adverse events.

Exclusion criteria

The exclusion criteria were: insufficient or unreliable data about outcome variables (e.g., letters, case reports, comments); duplicated studies or multiple reports on the same study; data not available to be extracted; anus-associated lesions; the clinical outcomes of studies with EMR + ESD or multiple lesions (including LSTs) were not described separately.

Data extraction

The data were extracted by one investigator and confirmed by another investigator, which included first author, publication year, country, design, EMR/ESD, lesion number, en bloc resection rate, R0 resection rate, adverse events, follow-up periods and recurrence rate (*Table 1*). Disagreements were judged by a third investigator.

Quality of study

The Newcastle-Ottawa Scale for Cohort Studies, consisted of selection, comparability and outcome, was used to assess the quality of the included studies. Each study had a total score with a maximum of 13 points (*Table 2*). The specific criteria (14) were representativeness of the exposed cohort (yes+: retrospective studies; yes++: prospective studies; yes+++: RCTs), comparability (studies comparing EMR with
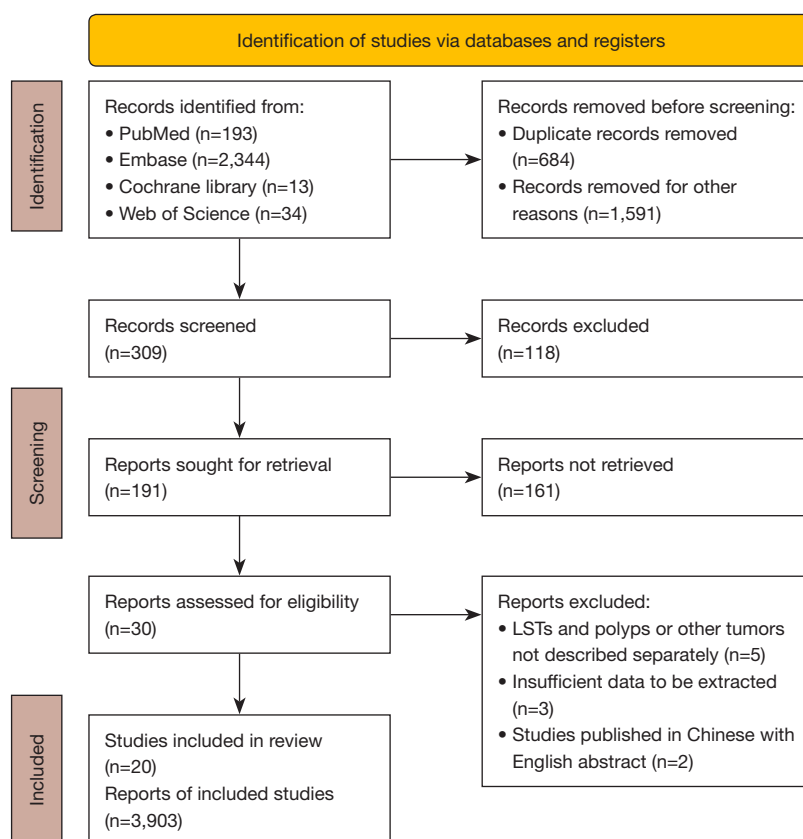
Figure 1 Study flow diagram.

ESD), assessment of outcome (yes: more than one outcomes are not included; yes+: one of the included outcomes was not reported; yes++: all outcomes were reported), and follow-up long enough (yes++: follow up more than 12 months; yes+: follow up 6–12 months; yes: follow up 1–6 months).

Statistical analysis

SPSS software was used for statistical analysis (SPSS version 21, IBM Inc; Armonk, NY, United States). Pooled rates of each outcome were calculated. Differences in en bloc resection and R0 resection rates of EMR and ESD, as well as adverse events and recurrence rates, were evaluated by Chi-square test. Chi-square for trend was used to evaluate heterogeneity. The risk of bias in each study was assessed by the Newcastle-Ottawa Scale for Cohort Studies. All P values were two-sided, and P<0.05 was considered statistically significant.

Results

Numbers and lesions of the included studies

The initial search exhibited a total of 309 studies (EMR: 128, ESD: 181). After removing duplicate records, 191 studies were included (EMR: 71, ESD: 120), which were screened by reading the titles and abstracts. Of these, 30 studies were retrieved by reading the full text carefully and 20 studies (EMR: 4, ESD: 12 and 4 articles including EMR and ESD) were included finally (*Figure 1*): 5 monocentric, 14 multicentric and 1 Cross-sectional; 18 retrospective and 2 prospective; 6 studies in China, 6 in Japan and 8 in Korea. Number of all lesions were 3,903 (EMR: 1,230, ESD: 2,673) (*Table 1*).

En bloc and R0 resection rates

En bloc resection rate was reported in all EMR studies,

Table 1 The characteristics of the included studies

Author, year	Country	Design	EMR/ ESD	Lesions number	En bloc resection rate (n/%)	R0 resection rate (n/%)	Adverse events (n/%)		Follow-up periods (months)	Recurrence rate (n/%)
							Bleedings	Perforations		
Huang et al., 2009 (15)	China	Monocentric retrospective	EMR	111 (EMR 103)	46/44.7 (EPMR 57)	99/96.1 [margin (+) 4]	11/10.7	0	3–26	11/10.7
Son et al., 2019 (16)	Korea	Multicentric retrospective	EMR	275 (EMR 275)	239/86.9 (EPMR 36)	221/80.4	22/8.0	1/0.3	NR	NR
Tanaka et al., 2001 (17)	Japan	Monocentric retrospective	EMR	120 (EMR 81)	41/50.6 (EPMR 40)	18/22.2	16/19.8	1/1.2	1.2–13.5	6/7.4
Kim et al., 2014 (18)	Korea	Cross-sectional retrospective	EMR	80 (EMR 44)	7/15.9	NR	2/4.5	0	NR	17/39.4
Jung et al., 2019 (19)	Korea	Multicentric retrospective	EMR	88	62/70.5	71/81.6	14/15.9	0	NR	NR
			ESD	119	104/87.4	102/90.3	9/7.6	3/2.5	NR	NR
Terasaki et al., 2012 (20)	Japan	Monocentric retrospective	EMR	70	NR	NR	5/7.1	1/1.4	3–35.3	1/1.4
			ESD	61	NR	NR	7/11.5	0	3–35.3	0
Osera et al., 2017 (21)	Japan	Monocentric retrospective	EMR	275	NR	NR	NR	NR	3–12	1/0.4
			ESD	382	323/84.5	303/79.3	12/3.1	18/4.7	3–32	2/0.5
Hong et al., 2018 (22)	Korea	Multicentric retrospective	EMR	294	NDS	NDS	29/9.9	1/0.3	NR	NR
			ESD	209	NDS	NDS	11/5.3	5/2.5	NR	NR
Lian et al., 2018 (23)	China	Monocentric retrospective	ESD	143	125/87.4	119/83.2	2/1.4	5/3.5	6–12	0
Bae et al., 2016 (24)	Korea	Monocentric retrospective	ESD	153	142/92.8	121/79.1	5/3.3	14/9.2	6–89	0
Jeong et al., 2019 (25)	Korea	Multicentric retrospective	ESD	210	187/89.0	180/85.7	11/5.2	4/1.9	NR	NR
Yue et al., 2019 (26)	China	Monocentric prospective	ESD	138	NR	128/92.7	4/2.9	2/1.4	3–12	2/1.4
Youk et al., 2016 (27)	Korea	Multicentric prospective	ESD	195	194/99.5	147/75.4	NDS	NDS	NR	NR
Jung et al., 2015 (28)	Korea	Monocentric retrospective	ESD	163	152/93.3	150/92.0	4/2.5	14/8.6	NR	NR
He et al., 2019 (29)	China	Monocentric retrospective	ESD	162	161/99.3	NR	1/0.6	1/0.6	6–31	0
Tang et al., 2016 (30)	China	Monocentric retrospective	ESD	36	33/91.7	32/88.9	1/2.8	3/8.3	6–43	2/5.6
Nishiyama et al., 2010 (31)	Japan	Monocentric retrospective	ESD	204	177/86.8	158/77.5	2/1.0	20/9.8	12–76	0
Cong et al., 2016 (32)	China	Monocentric retrospective	ESD	177	147/83.1	144/81.4	6/3.4	4/2.3	6–36	11/6.2

Table 1 (*continued*)

Table 1 (*continued*)

Author, year	Country	Design	EMR/ ESD	Lesions number	En bloc resection rate (n/%)	R0 resection rate (n/%)	Adverse events (n/%)		Follow-up periods (months)	Recurrence rate (n/%)
							Bleedings	Perforations		
Sakamoto *et al.*, 2017 (33)	Japan	Monocentric retrospective	ESD	53	49/92.5	48/90.1	2/3.8	2/3.8	NR	NR
Toyonaga *et al.*, 2010 (34)	Japan	Monocentric retrospective	ESD	268	266/99.3	263/98.1	1/0.4	6/2.2	6.5–85.2	0

En bloc resection was defined as the lesion removed as a whole. R0 resection was defined as the pathological specimen with a free margin, both laterally and vertically. Bleeding included early bleeding after EMR/ESD within 24 hours and delayed bleeding beyond the first 24 hours after the procedure. Perforation included intraoperative and postoperative perforation, which was diagnosed by endoscopy or radiograph. EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; EPMR, piecemeal EMR; NR, not reported; NDS, not described separately.

Table 2 Risk of bias in the included studies according to the Newcastle-Ottawa scale

| Author	Selection				Comparability on the basis of design or analysis	Outcome			Score
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration outcome not present at start		Assessment of outcome	Follow-up long enough	Adequacy of follow-up	
Huang	Yes+	No	Yes	Yes	No	Yes++	Yes	Yes	9
Son	Yes+	No	Yes	Yes	No	Yes	No	No	5
Tanaka	Yes+	No	Yes	Yes	No	Yes++	Yes	No	8
Kim	Yes+	No	Yes	Yes	No	Yes	No	No	5
Jung	Yes+	No	Yes	Yes	Yes	Yes	No	No	6
Terasaki	Yes+	No	Yes	Yes	Yes	Yes	Yes	Yes	8
Osera	Yes+	No	Yes	Yes	Yes	Yes	Yes	Yes	7
Hong	Yes+	No	Yes	Yes	Yes	Yes	No	No	6
Lian	Yes+	No	Yes	Yes	No	Yes++	Yes+	Yes	10
Bae	Yes+	No	Yes	Yes	No	Yes++	Yes+	Yes	10
Jeong	Yes+	No	Yes	Yes	No	Yes	No	No	5
Yue	Yes++	No	Yes	Yes	No	Yes+	Yes	Yes	9
Youk	Yes++	No	Yes	Yes	No	Yes	No	No	6
Jung	Yes+	No	Yes	Yes	No	Yes	No	No	5
He	Yes+	No	Yes	Yes	No	Yes+	Yes	Yes	8
Tang	Yes+	No	Yes	Yes	No	Yes++	Yes+	Yes	10
Nishiyama	Yes+	No	Yes	Yes	No	Yes++	Yes++	Yes	11
Cong	Yes+	No	Yes	Yes	No	Yes++	Yes+	Yes	10
Sakamoto	Yes+	No	Yes	Yes	No	Yes	No	No	5
Toyonaga	Yes+	No	Yes	Yes	No	Yes++	Yes+	Yes	10

Score: no =0; yes =1; yes+ =2; yes++ =3.
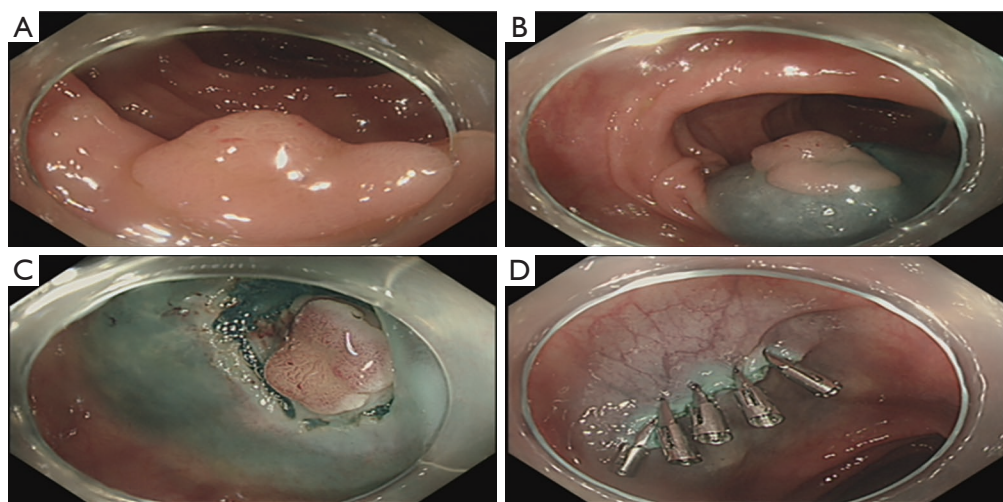
Figure 2 Endoscopic mucosal resection (EMR) procedure. (A) 2.0 cm × 2.5 cm, rectum, laterally spreading tumor-non-granular type (LST-NG) with flat elevated subtype; (B) LST-NG after submucosal injection of sodium hyaluronate, methylene blue and glycerol fructose solution (1:1:4); (C) endoscopic snare resection; (D) closure with titanium clips.

in 1/4 of EMR + ESD (1 not described separately, 1 not reported about EMR and 1 not reported both EMR and ESD), and in 11/12 of ESD. En bloc resection rate of EMR (*Figure 2*) was reached in 395/591 (66.8%, exclusive of lesions not described separately and not reported), with en bloc resection rate of ESD (*Figure 3*) reported in 2,020/2,265 (89.2%) [odds ratio (OR) 0.244, P<0.0001, 95% confidence interval (CI): 0.197–0.304].

R0 resection rate was obtained in 3/4 studies about EMR, in 1/4 about EMR+ESD, and in 11/12 about ESD. R0 resection rate was achieved in 409/547 (74.8%) with EMR and in 1,895/2,241 (84.6%) with ESD (OR 0.541, P<0.0001, 95% CI: 0.432–0.677).

Adverse events and follow-up periods

Adverse events occurred in 18/20 studies, including bleeding and perforation. Bleedings occurred in 99/955 (10.4%) with EMR and in 78/2,478 (3.1%) with ESD (OR 3.559, P<0.0001, 95% CI: 2.618–4.836). Perforations in EMR and ESD were in 4/955 (0.4%) and in 101/2,478 (4.1%), respectively (OR 0.099, P<0.0001, 95% CI: 0.036–0.27).

Follow-up periods were described in 2/4 EMR studies (ranging from 1.2 to 26 months), in 2/4 EMR + ESD (3 to 35.3 months), and in 8/12 ESD (3 to 89 months), respectively.

Recurrence rate

Recurrence rate was described in 3/4 EMR studies, in 2/4 EMR + ESD, and in 8/12 ESD, which was associated with follow-up periods. Recurrence rate of EMR occurred in 36/573 (6.3%), while the rate of ESD appeared in 17/1,724 (1.0%) (OR 6.732, P<0.0001, 95% CI: 3.751–12.082).

The risk of bias

The risk of bias was small in 6/20 studies with a score ≥10, moderate in 14/20 studies with a score ranging from 5 to 9. The average score was 7.65 (*Table 2*). On account of the stringency of the inclusion criteria, the studies were expected to be homogeneous. Chi-square for trend exhibited P>0.05 suggesting little heterogeneity among the included studies.

Discussion

In the present study, ESD was associated with higher rates of en bloc resection (89.2% *vs.* 66.8%) and R0 resection (84.6% *vs.* 74.8%) and a lower risk of bleeding (3.1% *vs.* 10.4%), resulting in a lower risk of recurrence (1.0% *vs.* 6.3%) with adequate follow-up periods (3–89 months), but it was accompanied by a higher risk of perforation (4.1% *vs.* 0.4%) compared with EMR.
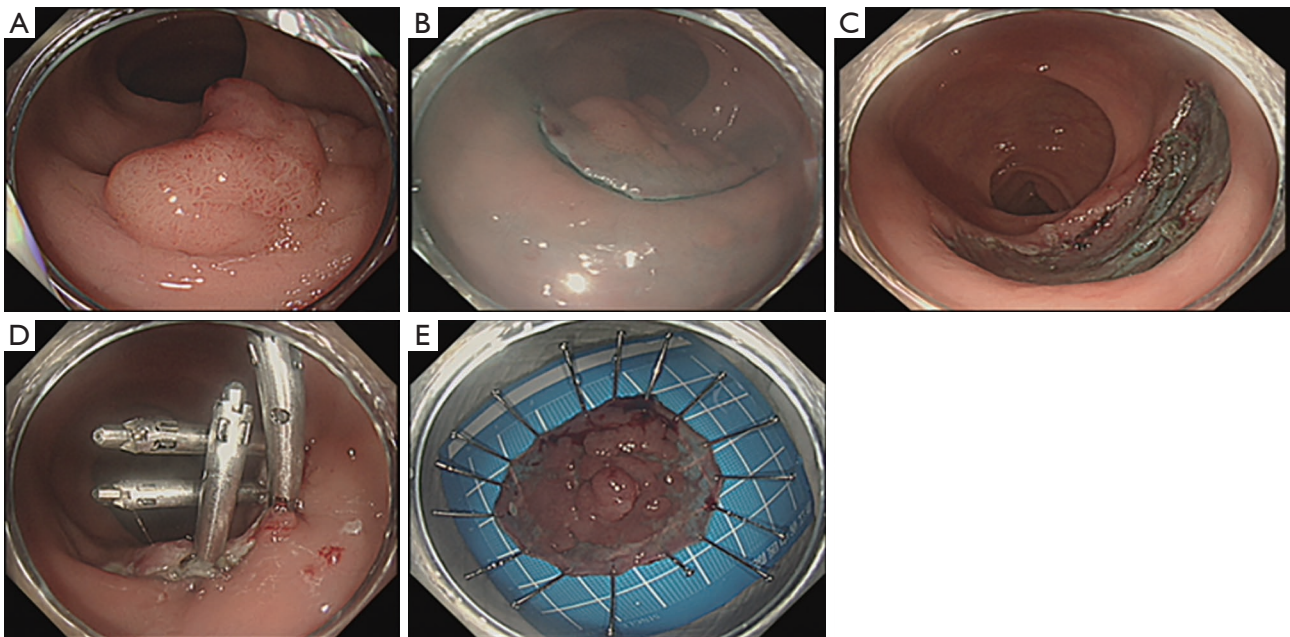
Figure 3 Endoscopic submucosal dissection (ESD) procedure. (A) 3.0 cm × 3.5 cm, rectum, laterally spreading tumor-granular type (LST-G) with nodular mixed subtype; (B) submucosal injection with Sodium hyaluronate, methylene blue and glycerol fructose solution (1:1:4) and a circumferential mucosal incision using a Jet bipolar needle knife (Jet B-knife); (C) submucosal dissection with a Jet B-knife; (D) titanium clips closing wound; (E) en bloc resected specimen.

These outcomes were similar to the previous meta-analyses (35,36). Zhao *et al.* (35) included 3,062 lesions (EMR: 1,906; ESD: 1,156) compared with EMR, in which ESD had higher rates of en bloc resection and R0 resection, with a lower risk of recurrence and perforation (95.0%, 93.2%, 0.5%, 2.4% *vs.* 42.8%, 71.9%, 15.9%, 1.8% respectively), but with no significant difference of bleeding (3.5% *vs.* 4.2%). Although the included studies of this meta-analysis all came from East Asian countries, it was mainly about single-center retrospective studies, and in our study, 5 monocentric and 14 multicentric studies were included. In addition, in EMR group, we included 3 multicentric studies with high rate of bleeding (8.0%, 15.9%, and 9.9% respectively) resulting in a high bleeding rate (10.4%). Russo *et al.* (36) showed higher rates of R0 resection and perforation in ESD group, a lower risk of bleeding and recurrence (93.6%, 5.9%, 2.8%, 1.1% *vs.* 84.0%, 1.2%, 9.6%, 12.6% respectively) compared with EMR, but with no significant difference of en bloc resection (97.5% *vs.* 99.5%). En bloc resection rate of EMR was primarily associated with the size of lesions, which was difficult to be achieved with the lesions ≥20 mm (11). In the present study, the size of lesions was larger than these from non-East Asian countries extracted by Russo et al, leading to a lower rate of en bloc resection. These findings revealed that ESD had a priority for colorectal LSTs, and EMR was also an option with a lower risk of perforation. The resected lesions with ESD were evidently more than EMR in our study, which revealed that endoscopists in East Asia had a higher tendency to ESD for colorectal LSTs.

Colonoscopy and endoscopic resection of colorectal neoplasia had reduced the incidence and mortality of CRC (37). ESD was an established endoscopic resection method in Asian countries, especially East Asia, which was increasingly practiced in Europe and the United States for removal of early cancers and large lesions. In the United States, accumulating evidence had found that colorectal neoplasms without signs of deep submucosal invasion or advanced cancer could be resected by ESD, and colorectal neoplasms confined to the mucosa (M) was considered as the criterion standard for no risk for lymph node metastasis (38). The indication criteria of ESD in Japan consisted of intramucosal carcinoma or carcinoma with slight submucosal invasion (SM1, invasion ≤1,000 μm or less than one-third of the submucosa), size with no matter and any macroscopic type (39). In addition, EPMR, a segmental

resection method, had some disadvantages in resecting large colorectal tumors owing to incomplete horizontal and vertical margins, and it was difficult to assess invasion depth and lymphovascular invasion. Moreover, EPMR led to significantly higher rates of recurrence compared with en bloc resection (10–20% compared with 1–2% by ESD, OR 8.2) (14,40).

Popularization of ESD in East Asian countries was mainly owing to the high incidence and mortality of CRC. Factors limiting ESD application included equipment requirements, technical difficulties, higher costs, longer hospital stay, higher risk of adverse events, etc. Equipment requirements just demanded a carbon dioxide (CO_2) insufflator and some cutting tools compared with EMR. Zhang *et al.* (41) exhibited a learning curve for ESD in the United States, which revealed operators would be proficient in ESD after ~250 cases. ESD was always accompanied by longer hospital stays and higher costs, but compared with surgery, ESD had the advantage of reducing financial savings (42). Moreover, a lower risk of recurrence after ESD was reached, which also decreased costs in the long run. In our study, we found the perforation rates after ESD were higher than EMR, which could be coped with endoscopic titanium clip with little surgical intervention. However, ESD always had a longer procedure time, increasing the difficulty of patient tolerance and the risk of adverse events.

Our research had some limitations. Our study focused on East Asian countries without adequate representation worldwide. The risk of moderate bias was the majority of the included studies without a RCT study, which declined the evidence level of this study. For colorectal LST-NGs with a higher recurrence rate after ESD (43), the recurrence rate in our study did not distinguish different endoscopic morphological types. Follow-up periods of the eight included articles were not reported, which also influenced the judgment of recurrence rate. The location and size of colorectal LSTs were not conducted in our study, which affected clinical outcomes and needed further research.

Conclusions

EMR is a safe and effective endoscopic resection technique for colorectal LSTs less than 20mm, but the major limitation remains a high risk of recurrence and an inaccurate histologic evaluation of piecemeal specimens.

ESD is a reliable and highly profitable method for larger colorectal LSTs to achieve a higher resection rate, a lower recurrence rate, and an accurate pathological evaluation, but with a higher risk of perforation.

Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-21-2074/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-21-2074/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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