Management of colorectal laterally spreading tumors: a systematic review and meta-analysis

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ABSTRACT

Objective and study aims To evaluate the efficacy and safety of different endoscopic resection techniques for laterally spreading colorectal tumors (LST).

Methods Relevant studies were identified in three electronic databases (PubMed, ISI and Cochrane Central Register). We considered all clinical studies in which colorectal LST were treated with endoscopic resection (endoscopic mucosal resection [EMR] and/or endoscopic submucosal dissection [ESD]) and/or transanal minimally invasive surgery (TEMS). Rates of en-bloc/piecemeal resection, complete endoscopic resection, R0 resection, curative resection, adverse events (AEs) or recurrence, were extracted. Study quality was assessed with the Newcastle-Ottawa Scale and a meta-analysis was performed using a random-effects model.

Results Forty-nine studies were included. Complete resection was similar between techniques (EMR 99.5% [95% CI 98.6%-100%] vs. ESD 97.9% [95% CI 96.1–99.2%]), being curative in 1685/1895 (13 studies, pooled curative resection 90%, 95% CI 86.6–92.9%, $I^2=79$%) with non-significantly higher curative resection rates with ESD (93.6%, 95% CI 91.3–95.5%, vs. 84% 95% CI 78.1–89.3% with EMR). ESD was also associated with a significantly higher perforation risk (pooled incidence 5.9%, 95% CI 4.3–7.9%, vs. EMR 1.2%, 95% CI 0.5–2.3%) while bleeding was significantly more frequent with EMR (9.6%, 95% CI 6.5–13.2%; vs. ESD 2.8%, 95% CI 1.9–4.0%). Procedure-related mortality was 0.1%. Recurrence occurred in 5.5%, more often with EMR (12.6%, 95% CI 9.1–16.6% vs. ESD 1.1%, 95% CI 0.3–2.5%), with most amenable to successful endoscopic treatment (87.7%, 95% CI 81.1–93.1%). Surgery was limited to 2.7% of the lesions, 0.5% due to AEs. No data of TEMS were available for LST.

Conclusions EMR and ESD are both effective and safe and are associated with a very low risk of procedure related mortality.

Introduction

Lateral spreading tumors (LST) are considered important precursors of colorectal cancer [1]. LST were first described by Kudo as tumors with predominant spread within the mucosa while still relatively flat [2]. In the Paris consensus of 2002, LST were defined as nonpolypoid lesions larger than 10 mm in width that typically extend laterally and circumferentially along the colonic wall, rather than vertically and were classified as type 0-IIa [3]. LST are distinguished based on their granular or nongranular, homogenous or nonhomogenous appearance [1]. These lesions have been described in several studies with a wide range of definitions, not always concordant. Therefore, it

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Russo Pedro et al. Management of colorectal… Endoscopy International Open 2019; 07: E239–E259

E239

is of paramount importance to establish an unambiguous and consensual definition for these lesions.

LST tend to preferentially spread superficially along the colonic wall rather than invading the submucosal layer and endoscopic resection can be effectively used as a minimally invasive treatment for the majority [4]. The flat morphology and potentially large dimensions of LST may render complete resection challenging [4]. The most common treatment approach for LST is endoscopic mucosal resection (EMR). However, en-bloc resection is usually restricted to lesions of less than 20 mm diameter. Piecemeal EMR of larger lesions is usually safe, but may hinder histologic assessment and lead to an increased risk of local recurrence. Endoscopic submucosal dissection (ESD) may overcome this problem, allowing dissection of larger lesions in one piece, although the procedure is technically more difficult, much more time-consuming, mandates multiday hospital admission and has an increased risk of perforation [5]. The majority of colorectal superficial lesions can be removed in a curative way by polypectomy or EMR; nevertheless, ESD should be considered for the removal of colorectal lesions with high suspicion of limited submucosal invasion, including those with depressed morphology or irregular/nongranular surface pattern, particularly in lesions larger than 20 mm [6].

Some recent meta-analyses have addressed endoscopic treatment outcomes of large non-pedunculated colorectal lesions and large colorectal polyps [7–9]. However, there are no published systematic reviews or meta-analyses focusing exclusively on LST.

In this systematic review and meta-analysis, the authors aimed to evaluate the efficacy and safety outcomes of endoscopic treatment of colorectal LST. Since many authors include purely sessile lesions in the LST group, it was also intended to study the clinical relevance of distinguishing LST from large sessile colorectal lesions.

Methods

A systematic review was conducted according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement [10]. The current systematic review was structured through the following PICO framework, addressing patients with LST, submitted to ESD/EMR/TEMS and evaluating the following outcomes: en-bloc/piecemeal, complete endoscopic resection, R0 and curative resections, adverse events and recurrence.

Eligibility criteria

All clinical studies published before June 15, 2016 in which colorectal LST were treated with endoscopic resection (EMR and ESD) and/or transanal minimally invasive surgery were considered. Only studies that reported at least one of the main treatment outcomes (en-bloc/piecemeal resection; complete endoscopic resection; R0 resection; curative resection; AEs or recurrence), were eligible for inclusion. Prospective and retrospective cohort studies, case-control studies and therapeutic clinical trials were included.

Manuscripts were excluded if they: (1) included sessile lesions (Paris 0-Is) and LST in the same group without a sub-analysis for LST treatment outcome; (2) included fewer than 20 LST (3) were animal or review studies; or (4) were non-English studies.

If there was suspicion of patient overlap between studies, only the study with the largest patient cohort for each of the outcomes was included.

Definitions

En-bloc resection was defined as resection of the lesion in one single piece and piecemeal resection as resection in more than one fragment.

Complete endoscopic resection was defined as the perception of the endoscopist that the lesion had been completely removed during endoscopy.

The resection was considered as R0 when histopathological examination confirmed free vertical and lateral margins, as R1 if the resection margins were involved or as Rx if the lateral or deep margins couldn't be evaluated due to piecemeal resection or coagulation effects.

Local recurrence implies that the patients were followed up for at least one colonoscopy after the index procedure and was defined as the finding of dysplastic tissue with histopathological confirmation detected at the site of previous endoscopic treatment. Resection was considered curative for adenomatous lesions or intramucosal carcinoma if R0 resection was achieved or if there was no recurrence at the end of follow up. For minimally invasive adenocarcinoma (sm1 invasion < 1000 μm) resection was considered curative for well-differentiated tumors if R0 resection was achieved and there was no lymphovascular or perineural invasion.

Bleeding was classified into two subtypes: immediate and delayed. Immediate bleeding was defined as active bleeding that developed during the procedure. Delayed bleeding was defined as melena or bloody stools that occurred after completion of endoscopic resection. Bleeding was further classified as minor (when hemostasis required endoscopic procedures – hemoclip application/injection therapy, without a blood transfusion) or massive (when requiring blood transfusion and/or surgery) [11–15]. Bleeding during the resection procedure that was stopped spontaneously or with hemostatic forceps was not considered to be a complication. [5] In most cases, large visible exposed vessels or bleeding points were coagulated using hemostatic forceps and any remaining vessels visible after completed resection were also coagulated routinely to prevent delayed bleeding.

Perforation was immediate (diagnosed by endoscopic evidence of a definite mural defect with the visualization of an intraperitoneal organ or peritoneal/fat tissue) or delayed (diagnosed after a finished endoscopic resection by presence of free air on abdominal plain radiograph or during a computed tomogram) [11, 12, 14, 15].

Search strategy

Relevant studies were identified in three electronic databases (MEDLINE through PubMed; ISI Web of Knowledge and Cochrane Central Register of Controlled Trials). The search was performed using the following query for PubMed: (polyp OR tumor OR tumour OR tumors OR lesion OR neoplasm OR adenoma) AND (non-pedunculated OR large OR flat OR "lateral spreading"; OR "laterally spreading"; OR LSL OR LST) AND (colon OR rectum OR colorectal OR colorectal OR colonic OR rectal) AND (endoscopic AND (resection OR EMR OR ER OR mucosectomy OR endoscopic submucosal dissection OR ESD OR polypectomy OR transanal endoscopic microsurgery OR TEMS OR TEM OR TAMIS OR "transanal surgery"). The search terms for other databases were adapted from this query. Additional studies were identified by checking the list of references of all included studies and also review articles on this topic. The last search was performed on June 15, 2016.

Study selection

After removal of duplicates, two authors (PR, SB) independently screened all titles and abstracts for relevance. The full text of selected relevant studies was then evaluated by the same two researchers according to the inclusion criteria described above. A third author (MDR) intervened in case of disagreement.

Quality evaluation and data extraction

Data extraction was performed by PR, SB and HA. Another two reviewers (MDR and MJB) independently checked the extracted data and disagreements were solved by consensus.

From each paper the following data were collected: (1) country; (2) publication year; (3) setting (single-center/multi-center); (4) enrollment period; (5) study design (prospective/retrospective); (6) type of resection techniques (EMR/ESD/TEMS); (7) operator (single/multiple; experienced/non-experienced); (8) definition of LST; (9) number of LST; (10) number of patients with LST; (11) mean/median age of the patients with LST; (12) gender distribution; (13) morphology of LST and subtypes (LSTG/LSTNG and LSTGH/LSTGM/LSTNGF/LSTNGPD); (14) mean size of LST; (15) size distribution (number of ≥ 10 mm/≥ 20 mm/≥ 30 mm/≥ 40 mm); (16) site distribution (proximal/distal); (17) type of resection (en-bloc/piecemeal); (18) rate of complete endoscopic resection; (19) histology (R0 and curative resection); (20) rate of AE (bleeding, perforation, death, other); (21) average follow-up period (months); (22) rate of recurrence; (23) treatment of recurrence; and (24) rate of surgery (for unsuccessful complete resection, for non-curative resection, for AE or for recurrence).In some articles, added additional data provided by the authors were added.

Quality evaluation was performed by PR and HA using the Newcastle-Ottawa scale.

Data synthesis and statistical analysis

Raw data for each outcome (number of events and total) were collected allowing calculation of outcome prevalence and standard error. For meta-analysis, as most of the studies report prevalence rates between 0% and 100% (depending on the

► Fig. 1 Flow chart of the selection of studies eligible for data extraction and analysis.
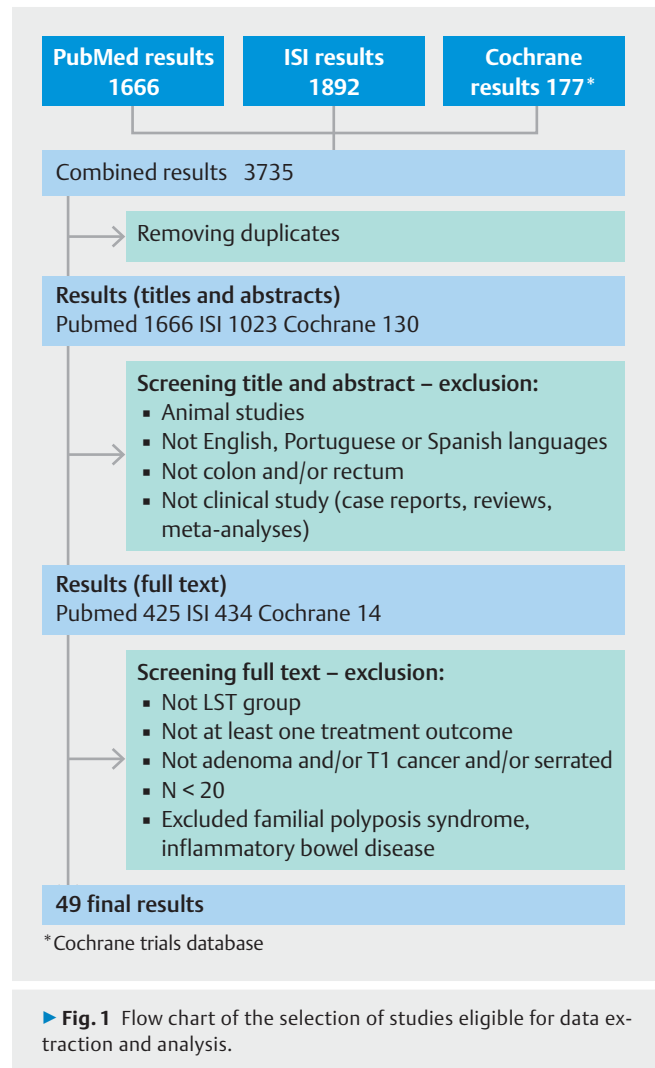
evaluated outcome), the double arcsine transformation (Freeman-Tukey) was used to adjust for variance. Double arcsine transformed proportions were then used for calculation of pooled proportions and were back-transformed for results presentation to allow easier interpretation.

Meta-analysis was performed with MetaXL and Open Meta-analyst using a random-effect model and heterogeneity was evaluated with Cochran's Q test and I^2, a measure of inconsistency. A subgroup analysis was planned according to the resection method used (EMR or ESD). Sensitivity analysis was performed when substantial heterogeneity was detected. Publication bias was assessed visually with funnel plot for the primary outcome.

Results

Study selection

A total of 2819 studies were identified by the searches in PubMed (1666), ISI (1023) and Cochrane Register of Controlled Trials (130). After screening titles and abstracts, 873 studies were found to be eligible. After full-text analysis, 824 studies were excluded (812 did not fill the inclusion criteria; 10 had

Russo Pedro et al. Management of colorectal… Endoscopy International Open 2019; 07: E239–E259

E241

▶ **Table 1** The main characteristics of the included studies.

	Period of enroll-ment, years	Number of LST	Size of LST included, mm	Technical modifications	Quality[1]
EMR					
Prospective, multicenter					
Australia					
Burgess NG, 2014 [69]	2008 – 2013	873	≥ 20		7
Moss A, 2015	2008 – 2012	747	≥ 20		6
Italy					
Conio M, 2010 [16]	2000 – 2007	136	≥ 20	Cap EMR	6
Greece					
Fasoulas K, 2012 [18]	2005 – 2010	49	≥ 30		RCT
Czech					
Urban O, 2008 [4]	2002 – 2006	138	> 10		6
Prospective, single-center					
Germany					
Belle S, 2012 [25]	2006 – 2007	70	> 12	STEP EMR	6
Retrospective, single center					
Japan					
Yoshikane H, 1999 [17]	1996 – 1998	23	NR	Cap EMR	8
Uraoka T, 2005 [14]	1998 – 2003	223	≤ 30		6
Tanaka,2001 [70]	NR	120	≥ 20		6
Tamura S, 2004 [71]	1989 – 2002	67	NR		6
China					
Huang Y, 2009 [38]	2000 – 2007	111	≥ 10		6
Taiwan					
Su MY, 2008 [72]	1999 – 2005	201	> 10		6
UK					
Hurlstone DP, 2004 [73]	1999 – 2003	82	≥ 10		6
Arebi N, 2007 [27]	1997 – 2005	48	≥ 20		6
United States					
Kim HG, 2014 [26]	2009 – 2014	80	LST ≥ 20	Underwater EMR	7
Binmoller KF, 2015 [19]	NR	53	> 20 and < 40	Underwater EMR	5
ESD					
Prospective, single-center					
Japan					
Ritsuno H, 2014 [53]	2010 – 2011	50	> 20	ESD S-O clip traction	RCT
Retrospective, multicenter					
Japan					
Mizushima T, 2015 [54]	2011 – 2013	113	NR		6

	Period of enroll-ment, years	Number of LST	Size of LST included, mm	Technical modifications	Quality[1]
Retrospective, single center					
Japan					
Uraoka T, 2010 [56]	2006 – 2008	37	LSTG ≥ 30 and LSTNG ≥ 20		8
Okamoto K, 2012 [59]	2010 – 2011	30	> 20 LSTNG; > 30 LSTG	Traction vs. no traction	7
Suzuki S, 2014 [13]	2009 – 2013	290	NR		6
Niimi K, 2010 [11]	2000 – 2008	245	NR		6
Nishiyama H, 2010 [12]	2002 – 2008	204	> 20		6
Hotta K, 2012 [58]	2000 – 2010	201	NR		6
Hisabe T, 2012 [57]	2003 – 2011	162	NR		6
Sakamoto T, 2014 [49]	2005 – 2012	139	> 20		6
Nawata Y, 2014 [61]	2010 – 2013	137	18 – 123		6
Toyonaga T, 2010 [55]	2009 – 2010	132	NR		6
Makino T, 2015 [62]	2009 – 2013	58	> 10		5
Okamoto K, 2013 [60]	2010 – 2012	30	28 – 45	M2-SB	5
Korea					
Bae JH, 2015 [15]	2007 – 2014	153	≥ 30	ESD and ESD with snaring	8
EJ Lee 2011 [63]	2006 – 2010	358	≥ 20		7
Hong MJ, 2015 [65]	2010 – 2013	113	> 20		7
Jung DH, 2015 [66]	2009 – 2014	163	NR (subgroup ≥ 100)		6
Yoon JY, 2012 [64]	2008 – 2011	101	≥ 10		6
Kim ES, 2011 [23]	2007 – 2009	81	≥ 10		6
China					
Xu MD, 2013 [41]	2008 – 2011	137	≥ 20		8
Cong ZJ, 2015 [36]	2003 – 2007	177	≥ 30		7
Zhou PH, 2009 [67]	2006 – 2007	74	≥ 20		6
Tang XW, 2016 [30]	2010 – 2014	36	≥ 40		5
Turkey					
Hulagu S, 2013 [20]	2006 – 2011	44	≥ 20		5
Austria					
Berr F, 2014 [24]	2009 – 2012	39	≥ 20		5
UK					
Hurlstone DP, 2007 [22]	2004 – 2006	28	≥ 20		6
Germany					
Probst A, 2012 [5]	2004 – 2011	74	> 15		9
Italy					
Repici A, 2013 [68]	2010 – 2011	40	33 – 80		6
ESD vs. EMR					

Russo Pedro et al. Management of colorectal ... Endoscopy International Open 2019; 07: E239–E259

E243

▶ **Table 1** (Continuation)

	Period of enroll-ment, years	Number of LST	Size of LST included, mm	Technical modifications	Quality[1]
Retrospective, single center					
Japan					
Iizuka H,2009 [21]	2000 – 2004	70	≥ 20		7
Terasaki, 2011 [74]	2006 – 2009	267	> 20	ESD/hybridESD vs. EMR/EMRP	6
India					
Tajika M, 2011 [75]	1995 – 2009	106	> 20		7
UK					
Hurlstone DP, 2006 [52]	1999 – 2004	20	16 – 58	Salvage EMR/ESD	6

[1] Quality evaluation using Newcastle-Ottawa scale. NR-not reported.

risk of patient overlap; two due to conflicting data) while 49 studies were included. A flow chart of the selection process is shown in ▶ **Fig. 1**.

Study characteristics

The main characteristics of the included studies are listed in ▶ **Table 1**. Most of the studies were single-center (43, 87.8 %), and six (12.2 %) were multicenter. The majority (42, 85.7 %) were retrospective. Sixteen studies evaluated EMR, including two studies of cap-assisted EMR and two studies including underwater EMR (one them for recurrent LST); 29 studies reported one or more outcomes for ESD; four studies reported outcomes for both techniques. A total of 27 studies included exclusively laterally spreading tumors, while a sub-analysis for LST was available in the other 22 studies.

Inclusion criteria regarding lesion size varied between the studies: lesions ≥ 10 mm – 7 studies; ≥ 12 mm – 1 study; ≥ 15 mm – 1 study; 20 studies included lesions ≥ 20 mm (one of them ≤ 40 mm); 3 studies included lesions ≥ 30 mm and one ≥ 40 mm; 2 studies included LST-NG ≥ 20 mm and LST-G ≥ 30 mm; one study included lesions ≤ 30 mm; the other studies did not specify inclusion criteria based on size.

En-bloc/piecemeal resection was reported in 12 EMR and 17 ESD studies. Complete endoscopic resection according to our definition was available in 20 studies (8 EMR and 12 ESD). R0 rates were assessed in three EMR and 14 ESD studies, while data on the recurrence was given in 15 EMR and 15 ESD studies. We could extrapolate curative resection according to our criteria in six EMR and eight ESD studies. Twelve studies reported global AE rate for EMR; 13 reported perforation and 14 bleeding. The same information was available for ESD in 21, 25 and 19 studies, respectively.

Information regarding surgical intervention was available in 16 EMR studies (12 for surgery of recurrence; 14 for AE and 12 for incomplete/non-curative resection) and 21 ESD studies (11 for recurrence, 19 for AEs and 10 for incomplete/non-curative resection).

En-bloc resection

Overall, pooled en-bloc resection rate was 75.6 % (95 % CI 60.4 %-88.2 %, I^2 = 99 %), being significantly higher with ESD (93.7 %, 95 % CI 89.3 – 95.6 %) – versus EMR (37.7 %, 95 % CI 23.0 % – 53.5 %) (▶ **Fig. 2a**). Conio M. et al. [16] applied the cap-assisted EMR technique in all of the lesions (≥ 20 mm) which explains the 0 % en-bloc resection in this study. The study by Yoshikane H. et al. [17] also evaluated cap-assisted EMR but included lesions ≥ 10 mm, allowing 65.2 % en-bloc resection. The lower en-bloc rate in Fasoulas K. et al. [18], is explained by the inclusion of larger lesions (≥ 30 mm). In contrast, Binmoller K.F. et al. [19], resected 55 % of the lesions (20 – 40 mm) en-bloc using the underwater EMR technique. The two studies with lower ESD en-bloc rate were Hulagu S. et al. and Iizuka H. et al. [20, 21]. Hulagu S. et al. [20], justified their lower rate of en-bloc resection with the higher rate of partial prior endoscopic resection (polypectomy) and scar tissue formation. The high rate of deep submucosal cancer may have precluded better results in the Lizuka et al. study [21]. En-bloc resection rates were not significantly different for LST-G and LST-NG for both ESD and EMR (ESD: 11 studies, OR 0.837 95 % CI 0.534 – 1.312, I^2 = 0 %; EMR: 4 studies, OR 0.529 95 % CI 0.410 – 0.683, I^2 = 25 %).

The rate of en-bloc resection in EMR studies was not significantly different in studies including lesions > 10 mm and > 20 mm; only two studies using the 30-mm threshold were found and the rate of en-bloc resection was significantly higher in the Study including lesions < 30 mm (53,8 % 95 % CI 47.2 – 60.3 % versus 22.4 % 95 % CI 11.7 – 35.3 %). The rate of ESD en-bloc resection was not influenced by the size of the lesions included, being > 90 % in all subgroups (> 20 mm: 6 studies, 92.8 % 95 % CI 86.8 – 97.5 %; > 30 mm: 4 studies, 91.9 % 95 % CI 83.9 – 98.1 %; > 40 mm: 1 study, > 100 mm: 1 study, 93.3 95 % CI 88 – 96.7 %; not reported: 5 studies, 93.5 % 95 % CI 85.2 – 99.5 %). In a subgroup analysis, according to the size of included lesions, the rate of en-bloc resection was significantly higher in ESD studies whether they included lesions > 20 mm or > 30 mm.

E244

Russo Pedro et al. Management of colorectal… Endoscopy International Open 2019; 07: E239–E259

Study or subgroup	En bloc by technique	Prev (95 % CI)	% Weight
EMR			
Moss A, 2015		0,164 (0,138, 0,191)	3,6
Conio M, 2010		0,000 (0,000, 0,013)	3,6
Fasoulas K, 2012		0,224 (0,117, 0,353)	3,5
Urban O, 2008		0,470 (0,385, 0,555)	3,6
Yoshikane H, 1999		0,652 (0,444, 0,836)	3,4
Uraoka T, 2005		0,538 (0,472, 0,603)	3,6
Tanaka S, 2001		0,506 (0,397, 0,615)	3,6
Huang Y, 2009		0,447 (0,351, 0,544)	3,6
Binmoller KF, 2015		0,547 (0,411, 0,680)	3,6
Iizuka H (EMR), 2009		0,558 (0,407, 0,704)	3,5
Terasaki, 2011		0,393 (0,323, 0,466)	3,6
EMR subgroup		0,376 (0,230, 0,535)	39,3
Q = 372,71, P = 0,00, I^2 = 97 %			
ESD			
Ritsuno H, 2014		0,980 (0,916, 1,000)	3,5
Uraoka T, 2010		1,000 (0,954, 1,000)	3,5
Niimi K, 2010		0,918 (0,880, 0,950)	3,6
Nishiyama H, 2010		0,868 (0,817, 0,911)	3,6
Hotta K, 2012		0,930 (0,890, 0,962)	3,6
Sakamoto T, 2014		0,957 (0,916, 0,985)	3,6
Toyonaga T, 2010		1,000 (0,987, 1,000)	3,6
Okamoto K, 2013		1,000 (0,943, 1,000)	3,5
Bae JH, 2015		0,928 (0,881, 0,964)	3,6
Jung DH, 2015		0,933 (0,888, 0,967)	3,6
Xu MD, 2013		0,985 (0,956, 1,000)	3,6
Cong ZJ, 2015		0,831 (0,771, 0,882)	3,6
Zhou PH, 2009		0,932 (0,862, 0,980)	3,6
Tang XW, 2016		0,917 (0,799, 0,989)	3,5
Hulagu S, 2013		0,773 (0,636, 0,886)	3,5
Repici A, 2013		0,900 (0,784, 0,977)	3,5
Iizuka H (ESD), 2009		0,630 (0,438, 0,804)	3,5
ESD subgroup		0,937 (0,893, 0,956)	60,7
Q = 104,45, P = 0,00, I^2 = 85 %			
Overall		0,756 (0,604, 0,882)	100,0
Q = 2472,25, P = 0,00, I^2 = 99 %			

a 0 — Prevalence — 1

▶ **Fig. 2a** Rate of en-bloc resection by technique.

Complete resection and R0 resection

Complete endoscopic resection by endoscopist opinion was achieved in 98.6 % (95 % CI 97.6 – 99.4 %, I^2 = 58 %), being similar with EMR and ESD (▶ **Fig. 2b**). Pooled R0 resection was 79.2 % (95 % 68.3 – 88.4 %, I^2 = 79.2), being significantly higher with ESD (86.4 % 95 % CI 79.5 – 91.7 % vs. EMR 36.2 % 95 % CI 31.2 – 41.8 %), Once again the study by Lizuka, 2009, showed lower ESD complete endoscopic and R0 resection rates, possibly because of the high incidence of deep submucosal invasion [21]. In the Hurlstone ESD study [22], a low R0 rate (67,9 %) is in correlation with a low en-bloc rate (78,6 % – includes non-LST lesions).

There were no statistically significant differences between R0 resection for LST-G and LST-NG (OR 1.082 CI 0.770 – 1.519, I^2 0 %). R0 resection was achieved in 673 /763 (83.5 %) of LST-G and 347 /417 (83.2 %) of LST-NG (▶ **Fig. 2c**).

Curative resection

Overall, endoscopic resection of LST was curative in 1685/1895 (13 studies, pooled curative resection 90 %, 95 % CI 86.6 – 92.9 %, I^2 = 79 %). Subgroup analysis according to the technique used showed significantly higher curative resection rates with ESD (93.6 % 95 % CI 91.3 – 95.5 %, versus 84 % 95 % CI 78.1 – 89.3 % with EMR) (▶ **Fig. 2d**). It is worth highlighting the study

Study or subgroup	Complete endoscopic resection by technique	Prev (95 % CI)	% Weight

EMR
Conio M, 2010 — 1,000 (0,987, 1,000) 6,5
Fasoulas K, 2012 — 0,959 (0,881, 0,999) 4,2
Urban O, 2008 — 1,000 (0,987, 1,000) 6,4
Belle S, 2012 — 0,970 (0,911, 0,999) 4,9
Huang Y, 2009 — 1,000 (0,983, 1,000) 5,9
Binmoller KF, 2015 — 1,000 (0,968, 1,000) 4,4
Iizuka H (EMR), 2009 — 1,000 (0,960, 1,000) 3,9
Terasaki, 2011 — 1,000 (0,990, 1,000) 7,0

EMR subgroup — 0,995 (0,986, 1,000) 43,2
Q = 10,50, P = 0,16, I² = 33 %

ESD
Ritsuno H, 2014 — 1,000 (0,966, 1,000) 4,3
Okamoto K, 2012 — 0,900 (0,762, 0,986) 3,1
Hotta K, 2012 — 0,970 (0,941, 0,990) 7,2
Toyonaga T, 2010 — 1,000 (0,987, 1,000) 6,4
Makino T, 2015 — 0,983 (0,927, 1,000) 4,6
Okamoto K, 2013 — 1,000 (0,943, 1,000) 3,1
Bae JH, 2015 — 0,987 (0,961, 1,000) 6,7
Zhou PH, 2009 — 1,000 (0,977, 1,000) 5,2
Hulagu S, 2013 — 0,977 (0,905, 1,000) 4,0
Repici A, 2013 — 1,000 (0,957, 1,000) 3,8
Iizuka H (ESD), 2009 — 0,815 (0,643, 0,942) 2,9
Terasaki (ESD), 2011 — 0,978 (0,935, 1,000) 5,6

ESD subgroup — 0,979 (0,961, 0,992) 56,8
Q = 27,03, P = 0,00, I² = 59 %

Overall — 0,986 (0,976, 0,994) 100,0
Q = 45,48, P = 0,00, I² = 58 %

Prevalence scale: 0,64 0,66 0,68 0,7 0,72 0,74 0,76 0,78 0,8 0,82 0,84 0,86 0,88 0,9 0,92 0,94 0,96 0,98 1

b

▶ **Fig. 2b** Rate of complete endoscopic resection by technique.

by Fasoulas et al. [18], with the lowest curative resection rates among the EMR studies that included larger lesions (≥30 mm).

Submucosal invasion

Prevalence of cancer was similar between the EMR and the ESD series, despite the trend towards more submucosal invasion in the ESD series (EMR 5.6 % 95 % CI 2.0 – 10.2 % versus ESD 11 % 95 % CI 5.9 – 17.0 %) (▶ **Fig. 2e**). If we exclude the outliers (studies with a prevalence of submucosal invasion > 20 %), (Terasaki EMR; Uraoka T; Terasaki ESD, Yoon JY) the difference is still not significant (EMR 4.1 % 95 % CI 2.3 – 6.2 % versus ESD 5.8 % 95 % CI 4.4 – 9.6 %). LST-G presented less submucosal invasion (39/503) when compared to LST-NG (OR 0.47 95 % CI 0.29 – 0.74).

Adverse events

Resection of LSTs was associated with a pooled incidence of overall AEs of 9.2 % (7.2 – 11.5 %). No significant differences between EMR and ESD were found (▶ **Fig. 3a**).

Overall, pooled perforation rate was 4.1 % (95 % CI 2.7 – 5.6 %, I² = 84 %). However, ESD was associated with a significantly higher perforation risk (pooled incidence 5.9 % 95 % CI 4.3 – 7.9 %, versus EMR 1.2 % 95 % CI 0.5 – 2.3 %) (▶ **Fig. 3b**). The studies by Kim [23] and Berr [24] registered the larger number of perforations. The latter study evaluated the untutored learning of ESD in a series of 50 lesions including 33 colorectal LST and 15.2 % of the colorectal procedures were complicated with perforation. If this study is excluded the perforation rate is 5.7 %.

On the other hand, pooled bleeding rate was 5.3 % (95 % CI 3.6 – 7.2 %) and was significantly more frequent with EMR (9.6 % 95 % CI 6.5 – 13.2 %; versus ESD 2.8 % 95 % CI 1.9 – 4.0 %)

Study	Complete histological resection (LST-g vs LST-ng)	OR (95 % CI)	% Weight
Toyonaga T, 2010		1,533 (0,030, 78,474)	0,7
Niimi K, 2010		1,324 (0,741, 2,365)	34,3
Nishiyama H, 2010		0,814 (0,380, 1,744)	19,9
Iizuka H, 2009		3,333 (0,263, 42,212)	1,8
Okamoto K, 2013		1,696 (0,031, 91,392)	0,7
Hotta K, 2012		0,746 (0,332, 1,674)	17,7
Cong ZJ, 2015		0,852 (0,366, 1,982)	16,2
Xu MD, 2013		2,447 (0,473, 12,670)	4,3
Hurlstone Dp, 2007		2,143 (0,428, 10,738)	4,4
Overall		1,082 (0,770, 1,519)	100,0
Q = 4,59, P = 0,80, I^2 = 0 %			

▶ **Fig. 2c** Rate of complete endoscopic resection by type of lesion.

(▶ **Fig. 3c**). Bleeding rate was particularly high in the study by Belle et al. [25], in which 25/66 patients required hemostasis with clips. If this atypical study is excluded, the bleeding rate is 4.8 % (95 % CI 3.4 %-6.5 %) and remains significantly higher with EMR.

If we only consider major bleeding there were no statistically significant differences between both techniques (EMR 0.2 % 95 % CI 0 – 0.04 % versus ESD 0.4 % 95 % CI 0.1 – 0.7 %). Immediate minor bleeding was significantly less frequent for ESD (0.5 % 95 % CI 0.1 – 1.0 % versus EMR: 7.7 % 95 % CI 1.5 – 15.9 %). No differences were found between EMR and ESD for delayed major or minor bleeding.

Coagulation syndrome was evaluated in five studies including 718 patients (3 EMR, 1 EMR&ESD and 1 ESD studies) and pooled rate was 3.1 % (95 % CI 0.3 – 8.0 %, I^2 = 86 %).

One patient died following EMR due to complications of acute myocardial infarction [4]. Pooled procedure-related mortality was 0.1 % (95 % CI 0.0 – 0.3 %, I^2 = 0 %).

Between both subtypes of LST there were no differences in perforation or bleeding rates. In LST-G, perforation occurred in 52/906 (5.74 %) while in LST-NG it occurred in 20/446 (4.48 %) (OR 1.072, 95 % CI 0.497 – 2.310, I^2 = 36.94 %). Bleeding was more frequent with LST-G (26/585 – 4.44 %) compared with LST-NG (11/424 – 2.59 %) (OR 2.460, 95 % CI 0.476 – 12.729, I^2 = 75.05 %).

Recurrence

Overall, recurrence occurred in 5.5 % (95 % CI 3.0 – 8.6 %) being significantly more frequent with EMR (12.6 % 95 % CI 9.1 – 16.6 %) vs. ESD (1.1 % 95 % CI 0.3 – 2.5 %). However, the majority of the recurrences were amenable to successful endoscopic treatment (87.7 %, 95 % CI 81.1 – 93.1 %). The timing of endoscopic surveillance was heterogeneous between the studies which may have affected the rate of early recurrence. Mean follow-up ranged from 9.2 to 60.8 months.

The retrospective study from Kim et al. evaluated the efficacy of underwater versus conventional EMR for the treatment of recurrence after piecemeal resection of LST [26]. Underwater EMR was successful in 18/20 patients and conventional EMR was successful in only 20/33 [26]. Two EMR studies demonstrated the highest recurrence rates, Arebi N. et al. [27] (40.9 %, 95 % CI 26.7 – 55.9 %) and Fasoulas et al. [18] (27.3 %, 95 % CI 15.0 – 41.5 %). The latter, probably because larger lesions (≥30 mm) were included with only 22.4 % removed enbloc [18].

Surgery rates

Overall, LSTs submitted to endoscopic resection led to surgery in 2.7 % (95 % CI 1.8 – 3.8 %), without significant differences in surgery rates according to the endoscopic resection technique despite a trend to higher surgery rates with EMR (▶ **Fig. 4a**). Concerning the reasons for surgery:
- 33 studies involving 3857 patients reported 12 surgeries due to AEs (pooled rate was 0.5 %, 95 % CI 0.3 – 0.7 %, I^2 = 0 %); there was no difference in surgery due to AEs between the ESD and the EMR group.

Russo Pedro et al. Management of colorectal … Endoscopy International Open 2019; 07: E239–E259

E247

Study or subgroup	Submucosal invasion by technique	Prev (95 % CI)	% Weight
EMR			
Moss A, 2015		0,053 (0,038, 0,070)	4,0
Urban O, 2008		0,037 (0,010, 0,076)	3,8
Belle S, 2012		0,029 (0,000, 0,084)	3,6
Yoshikane H, 1999		0,000 (0,000, 0,074)	2,9
Tanaka, 2001		0,086 (0,033, 0,159)	3,6
Tamura S, 2004		0,090 (0,031, 0,172)	3,6
Su MY, 2008		0,080 (0,046, 0,123)	3,9
Hurlstone DP, 2004		0,000 (0,000, 0,029)	3,5
Binmoller KF, 2015		0,000 (0,000, 0,032)	3,4
Terasaki, 2011 (EMR)		0,281 (0,217, 0,349)	3,9
EMR subgroup		0,056 (0,020, 0,102)	36,1
Q = 90,90, P = 0,00, I² = 90 %			
ESD			
Ritsuno H, 2014		0,080 (0,018, 0,174)	3,4
Uraoka T, 2010		0,676 (0,515, 0,818)	3,2
Niimi K, 2010		0,143 (0,102, 0,190)	3,9
Nishiyama H, 2010		0,069 (0,037, 0,108)	3,9
Sakamoto T, 2014		0,158 (0,102, 0,224)	3,8
Makino T, 2010		0,155 (0,072, 0,261)	3,5
Bae JH, 2016		0,072 (0,036, 0,119)	3,8
Yoon JY, 2012		0,277 (0,194, 0,369)	3,7
Xu MD, 2013		0,080 (0,040, 0,132)	3,8
Cong ZJ, 2015		0,073 (0,039, 0,117)	3,9
Zhou PH, 2009		0,043 (0,006, 0,107)	3,6
Tang XW, 2016		0,000 (0,000, 0,047)	3,2
Hulagu S, 2013		0,000 (0,000, 0,039)	3,3
Berr F, 2014		0,000 (0,000, 0,044)	3,3
Hurlstone DP, 2007		0,000 (0,000, 0,061)	3,0
Probst A, 2012		0,081 (0,028, 0,156)	3,6
Repici A, 2013		0,050 (0,001, 0,145)	3,3
Terasaki, 2011 (ESD)		0,539 (0,435, 0,642)	3,7
ESD subgroup		0,110 (0,059, 0,170)	63,9
Q = 222,71, P = 0,00, I² = 92 %			
Overall		0,088 (0,055, 0,128)	100,0
Q = 337,78, P = 0,00, I² = 92 %			

Prevalence: 0   0,2   0,4   0,6   0,8

d

▶ **Fig. 2d** Rate of curative resection according to technique.

Study or subgroup	Recurrence by technique	Prev (95 % CI)	% Weight
EMR			
Moss A, 2015		0,139 (0,112, 0,168)	3,9
Conio M, 2010		0,024 (0,003, 0,060)	3,7
Fasoulas K, 2012		0,273 (0,150, 0,415)	3,2
Urban O, 2008		0,136 (0,083, 0,201)	3,7
Yoshikane H, 1999		0,045 (0,000, 0,185)	2,7
Uraoka T, 2005		0,104 (0,063, 0,153)	3,8
Tanaka, 2001		0,077 (0,026, 0,148)	3,5
Tamura S, 2004		0,104 (0,041, 0,191)	3,5
Huang Y, 2009		0,139 (0,071, 0,225)	3,5
Hurlstone DP, 2004		0,172 (0,085, 0,282)	3,4
Arebi N, 2007		0,409 (0,267, 0,559)	6,2
Binmoller K, 2015		0,047 (0,001, 0,135)	3,2
Terasaki, (EMR), 2011		0,080 (0,044, 0,125)	3,8
Tajika M (EMR), 2011		0,171 (0,062, 0,317)	3,1
EMR subgroup Q = 58,39, *P* = 0,00, I² = 78 %		0,126 (0,091, 0,166)	48,3
ESD			
Ritsuno H, 2014		0,000 (0,000, 0,038)	3,2
Nishiyama H, 2010		0,000 (0,000, 0,008)	3,8
Makino T, 2015		0,000 (0,000, 0,030)	3,4
Bae JH, 2015		0,000 (0,000, 0,011)	3,7
Jung DH, 2015		0,000 (0,000, 0,011)	3,8
Xu MD, 2013		0,008 (0,000, 0,036)	3,7
Cong ZJ, 2015		0,077 (0,038, 0,128)	3,7
Zhou PH, 2009		0,000 (0,000, 0,023)	3,5
Tang XW, 2016		0,065 (0,001, 0,185)	3,0
Hulagu S, 2013		0,047 (0,001, 0,135)	3,2
Berr F, 2014		0,061 (0,001, 0,174)	3,0
Probst A, 2012		0,000 (0,000, 0,025)	3,5
Repici A, 2013		0,026 (0,000, 0,110)	3,1
Terasaki M (ESD), 2011		0,000 (0,000, 0,019)	3,6
Tajika M (ESD), 2011		0,000 (0,000, 0,024)	3,5
ESD subgroup Q = 43,73, *P* = 0,00, I² = 68 %		0,011 (0,003, 0,025)	51,7
Overall Q = 296,82, *P* = 0,00, I² = 91 %		0,055 (0,030, 0,086)	100,0

e   Prevalence

▶ **Fig. 2e** Submucosal invasion by technique.

▶ Fig. 2f Recurrence rate by technique.

- 23 studies involving 2257 patients reported eight surgeries due to recurrences detected during follow up (pooled rate was 0.5 %, 95 % CI 0.2 – 0.8 %, I² = 0%) (▶ Fig. 4b). There was no significant difference between the two techniques.
- 21 studies involving 2799 lesions reported 125 surgeries due to incomplete/non-curative resection (pooled rate was 4.3 %, 95 % CI 3.3 – 5.5 %, I² = 44 %). No significant difference between EMR and ESD was found (pooled rate EMR was 3.9 %, 95 % CI 2.5 – 5.5 %, I² = 55 % vs. pooled rate ESD was 4.6 %, 95 % CI 3.0 – 6.3 %, I² = 30 %) (▶ Fig. 4c).

Publication bias

Visual inspection of the funnel plot and doi plot analysis (LFK index 0.14 – absence of asymmetry) suggests the absence of publication bias for the primary endpoint (curative resection).

Discussion

According to our analysis, both EMR and ESD were effective and safe with a low risk of procedure-related morbidity and rare mortality. Cure from the primary intervention was more fre-

quently achieved with ESD (93.6 % vs. 84 % for EMR) with higher recurrence among patients submitted to EMR (12.6 % vs. 1.1 % for ESD) but the endoscopic treatment of recurrence was highly effective (87.7 %). We found no difference in surgery between both techniques due to incomplete endoscopic/histologic resection or recurrence.

The rate of AEs was low and most complications could be managed endoscopically, as shown by a surgery rate for AEs of 0.3 %. Clearly both techniques are very safe. Risk of perforation was significantly higher for ESD (5.9 % vs. 1.2 % for EMR) and risk of bleeding was statistically greater with EMR (9.6 % vs. 2.8 % for ESD), but major bleeding and delayed bleeding rates were similar for both techniques.

In this meta-analysis, we exclusively included LSTs according to the accepted definition of flat laterally spreading lesions > than 10 mm. These lesions often cannot be reliably excised en-bloc by conventional snare polypectomy, especially if larger than 20 mm. In this study, we have examined the interface between the two available therapeutic techniques of EMR and ESD. This study evaluates outcomes in a defined, discrete and

Study or subgroup	Adverse events by technique	Prev (95 % CI)	% Weight
EMR			
Moss A, 2015		0,072 (0,055, 0,092)	3,9
Conio M, 2010		0,103 (0,057, 0,160)	3,4
Fasoulas K, 2012		0,204 (0,101, 0,330)	2,6
Urban O, 2008		0,121 (0,070, 0,183)	3,4
Belle S, 2012		0,470 (0,350, 0,591)	2,9
Yoshikane H, 1999		0,087 (0,002, 0,245)	1,9
Uraoka T, 2005		0,094 (0,059, 0,136)	3,6
Tanaka, 2001		0,173 (0,097, 0,264)	3,0
Tamura S, 2004		0,015 (0,000, 0,063)	2,9
Huang Y, 2009		0,107 (0,054, 0,175)	3,2
Hurlstone DP, 2004		0,103 (0,036, 0,197)	2,8
Binmoller KF, 2015		0,038 (0,001, 0,110)	2,7
EMR subgroup Q = 77,58, P = 0,00, I² = 86 %		0,122 (0,078, 0,170)	36,2
ESD			
Ritsuno H, 2014		0,020 (0,000, 0,084)	2,6
Mizushima T, 2015		0,053 (0,018, 0,103)	3,3
Uraoka T, 2010		0,027 (0,000, 0,113)	2,3
Okamoto K, 2012		0,033 (0,000, 0,138)	2,1
Suzuki S, 2014		0,045 (0,024, 0,072)	3,7
Niimi K, 2010		0,065 (0,037, 0,100)	3,7
Nishiyama H, 2010		0,108 (0,069, 0,154)	3,6
Hotta K, 2012		0,075 (0,042, 0,116)	3,6
Hisabe T, 2012		0,086 (0,047, 0,135)	3,5
Nawata Y, 2013		0,000 (0,000, 0,013)	3,4
Okamoto K, 2013		0,000 (0,000, 0,057)	2,1
Bae JH, 2015		0,124 (0,076, 0,182)	3,4
Jung DH, 2015		0,110 (0,066, 0,164)	3,5
Kim ES, 2011		0,247 (0,158, 0,347)	3,0
Xu MD, 2013		0,058 (0,024, 0,105)	3,4
Cong ZJ, 2015		0,056 (0,027, 0,096)	3,5
Zhou PH, 2009		0,095 (0,037, 0,173)	3,0
Tang XW, 2016		0,139 (0,042, 0,274)	2,3
Hulagu S, 2013		0,136 (0,048, 0,256)	2,5
Probst A, 2012		0,176 (0,094, 0,277)	2,9
Repici A, 2013		0,075 (0,010, 0,181)	2,4
ESD subgroup Q = 87,12, P = 0,00, I² = 77 %		0,078 (0,056, 0,102)	63,8
Overall Q = 172,32, P = 0,00, I² = 81 %		0,092 (0,072, 0,115)	100,0

0 0,05 0,1 0,15 0,2 0,25 0,3 0,35 0,4 0,45 0,5 0,55 0,6

Prevalence

a

▶ **Fig. 3a** Adverse events. Overall adverse events by technique.

well characterized subgroup of large colorectal neoplasms and is substantially different from previous work [7, 28, 29].

Hassan et al. assessed efficacy and safety of endoscopic resection of large colorectal lesions (>20 mm) [7]. Broadly classified as sessile, pedunculated or non-polypoid, in this study, all types of tissue resection techniques including conventional po-

lypectomy (26 %) were included. Consequently, there is relative data heterogeneity and the results are thus hard to interpret. Detailed morphological features are not described and thus the influence of morphology outcomes was not evaluated. Paris classification and surface morphology (granular/non-granular) were not assessed. Endoscopic tissue resection has continuous-

Russo Pedro et al. Management of colorectal … Endoscopy International Open 2019; 07: E239–E259

E251

Study or subgroup	Perforation by technique	Prev (95 % CI)	% Weight

EMR

Moss A, 2015	0,004 (0,000, 0,010)	3,3
Conio M, 2010	0,000 (0,000, 0,013)	2,9
Fasoulas K, 2012	0,020 (0,000, 0,086)	2,3
Urban O, 2008	0,038 (0,011, 0,078)	2,9
Belle S, 2012	0,076 (0,022, 0,154)	2,5
Yoshikane H, 1999	0,043 (0,000, 0,178)	1,7
Uraoka T, 2005	0,004 (0,000, 0,019)	3,1
Tanaka S, 2001	0,012 (0,000, 0,052)	2,6
Huang Y, 2009	0,000 (0,000, 0,017)	2,8
Hurlstone DP, 2004	0,000 (0,000, 0,029)	2,4
Arebi N, 2007	0,000 (0,000, 0,036)	2,3
Binmoller KF, 2015	0,000 (0,000, 0,032)	2,4
Terasaki (EMR), 2011	0,017 (0,002, 0,042)	3,0

EMR subgroup 0,012 (0,005, 0,023) 34,1
Q = 26,89, P = 0,01, I² = 55 %

ESD

Ritsuno H, 2014	0,020 (0,000, 0,084)	2,3
Mizushima T, 2015	0,053 (0,018, 0,103)	2,8
Uraoka T, 2010	0,027 (0,000, 0,113)	2,1
Okamoto K, 2012	0,033 (0,000, 0,138)	1,9
Niimi K, 2010	0,045 (0,022, 0,075)	3,1
Nishiyama H, 2010	0,098 (0,061, 0,143)	3,1
Hotta K, 2012	0,045 (0,020, 0,079)	3,0
Hisabe T, 2012	0,086 (0,047, 0,135)	3,0
Sakamoto T, 2014	0,036 (0,010, 0,075)	2,9
Nawata Y, 2014	0,000 (0,000, 0,013)	2,9
Makino T, 2015	0,017 (0,000, 0,073)	2,4
Okamoto K, 2013	0,000 (0,000, 0,057)	1,9
Bae JH, 2015	0,092 (0,050, 0,143)	2,9
Lee EJ, 2011	0,095 (0,067, 0,128)	3,2
Jung DH, 2015	0,086 (0,047, 0,134)	3,0
Yoon JY, 2012	0,089 (0,040, 0,154)	2,8
Kim ES, 2011	0,247 (0,158, 0,347)	2,6
Xu MD, 2013	0,022 (0,003, 0,055)	2,9
Cong ZJ, 2015	0,023 (0,005, 0,051)	3,0
Zhou PH, 2009	0,081 (0,028, 0,156)	2,6
Tang XW, 2016	0,083 (0,011, 0,201)	2,1
Hulagu S, 2013	0,045 (0,001, 0,132)	2,2
Berr F, 2014	0,152 (0,046, 0,297)	2,0
Probst A, 2012	0,074 (0,021, 0,150)	2,5
Teraski (ESD), 2011	0,022 (0,000, 0,067)	2,7

ESD subgroup 0,059 (0,043, 0,079) 65,9
Q = 93,96, P = 0,00, I² = 74 %

Overall 0,041 (0,027, 0,056) 100,0
Q = 227,83, P = 0,00, I² = 84 %

0   0,05   0,1   0,15   0,2   0,25   0,3   0,35

b   Prevalence

▶ **Fig. 3b** Adverse events. Perforation by technique.

Study or subgroup	Bleeding by technique	Prev (95 % CI)	% Weight
EMR			
Burgess NG, 2014		0,111 (0,090, 0,134)	3,9
Conio M, 2010		0,096 (0,051, 0,151)	3,5
Fasoulas K, 2012		0,143 (0,057, 0,257)	2,8
Urban O, 2008		0,015 (0,000, 0,045)	3,4
Belle S, 2012		0,379 (0,265, 0,500)	3,0
Yoshikane H, 1999		0,043 (0,000, 0,178)	2,0
Uraoka T, 2005		0,090 (0,055, 0,131)	3,7
Tanaka, 2001		0,160 (0,088, 0,249)	3,2
Tamura S, 2004		0,015 (0,000, 0,063)	3,0
Huang Y, 2009		0,107 (0,054, 0,175)	3,3
Hurlstone DP, 2004		0,103 (0,036, 0,197)	2,9
Binmoller KF, 2015		0,019 (0,000, 0,079)	2,8
Terasaki (EMR), 2011		0,084 (0,047, 0,130)	3,6
EMR subgroup Q = 69,37, P = 0,00, I² = 83 %		0,097 (0,063, 0,134)	41,1
ESD			
Ritsuno H, 2014		0,000 (0,000, 0,034)	2,8
Uraoka T, 2010		0,000 (0,000, 0,046)	2,5
Okamoto K, 2012		0,000 (0,000, 0,057)	2,3
Suzuki S, 2014		0,045 (0,024, 0,072)	3,7
Niimi K, 2010		0,020 (0,006, 0,043)	3,7
Nishiyama H, 2010		0,010 (0,000, 0,029)	3,6
Hotta K, 2012		0,030 (0,010, 0,059)	3,6
Nawata Y, 2014		0,000 (0,000, 0,013)	3,5
Okamoto K, 2013		0,000 (0,000, 0,057)	2,3
Bae JH, 2015		0,033 (0,009, 0,068)	3,5
Jung DH, 2015		0,025 (0,005, 0,055)	3,5
Xu MD, 2013		0,036 (0,010, 0,076)	3,5
Cong ZJ, 2015		0,028 (0,008, 0,059)	3,6
Zhou PH, 2009		0,014 (0,000, 0,057)	3,1
Tang XW, 2016		0,028 (0,000, 0,116)	2,5
Hulagu S, 2013		0,091 (0,021, 0,197)	2,7
Probst A, 2012		0,088 (0,030, 0,169)	3,0
Repici A, 2013		0,050 (0,001, 0,145)	2,6
Teraski (ESD), 2011		0,115 (0,045, 0,209)	2,9
ESD subgroup Q = 39,80, P = 0,00, I² = 55 %		0,029 (0,019, 0,042)	58,9
Overall Q = 199,64, P = 0,00 I² = 84 %		0,053 (0,036, 0,073)	100,0

Prevalence: 0   0,05   0,1   0,15   0,2   0,25   0,3   0,35   0,4   0,45   0,5

c

▶ **Fig. 3c** Adverse events. Bleeding rate by technique.

ly developed and improved over time, particularly in the last 10 years. Hassan et al. included eight studies before 2000 which may have substantially influenced the outcomes of the analysis [7]. The main outcome of this study was the rate of subsequent surgery for all reasons. The surgery rate was 8.3 %, among these 0.5 % due to AEs and 7.8 % due to non-curative resections. In our study, of LSTs excised by EMR or ESD, the rate of post-endo-scopic resection surgery was 2.7 %. In pooled rate analysis of our data, surgery due to non-curative endoscopic resection,

AEs and recurrence were 4.2 %, 0.5 % and 0.5 % respectively. Overall AEs were 9.2 %, perforations accounted for 4.1 % and bleeding was 5.3 %.

Overall the recurrence rate in our study was 5.5 % which is lower than reported in other studies. Hassan et al. reported an overall recurrence rate of 13.8 %, while the recurrence rate post-EMR versus post-ESD in both studies was 12.7 % vs. 1.1 % and 15 % vs. 1 %, respectively [7]. Belderbos et al. evaluated 33 EMR (>10 mm) studies for recurrence rate [28]. The overall re-
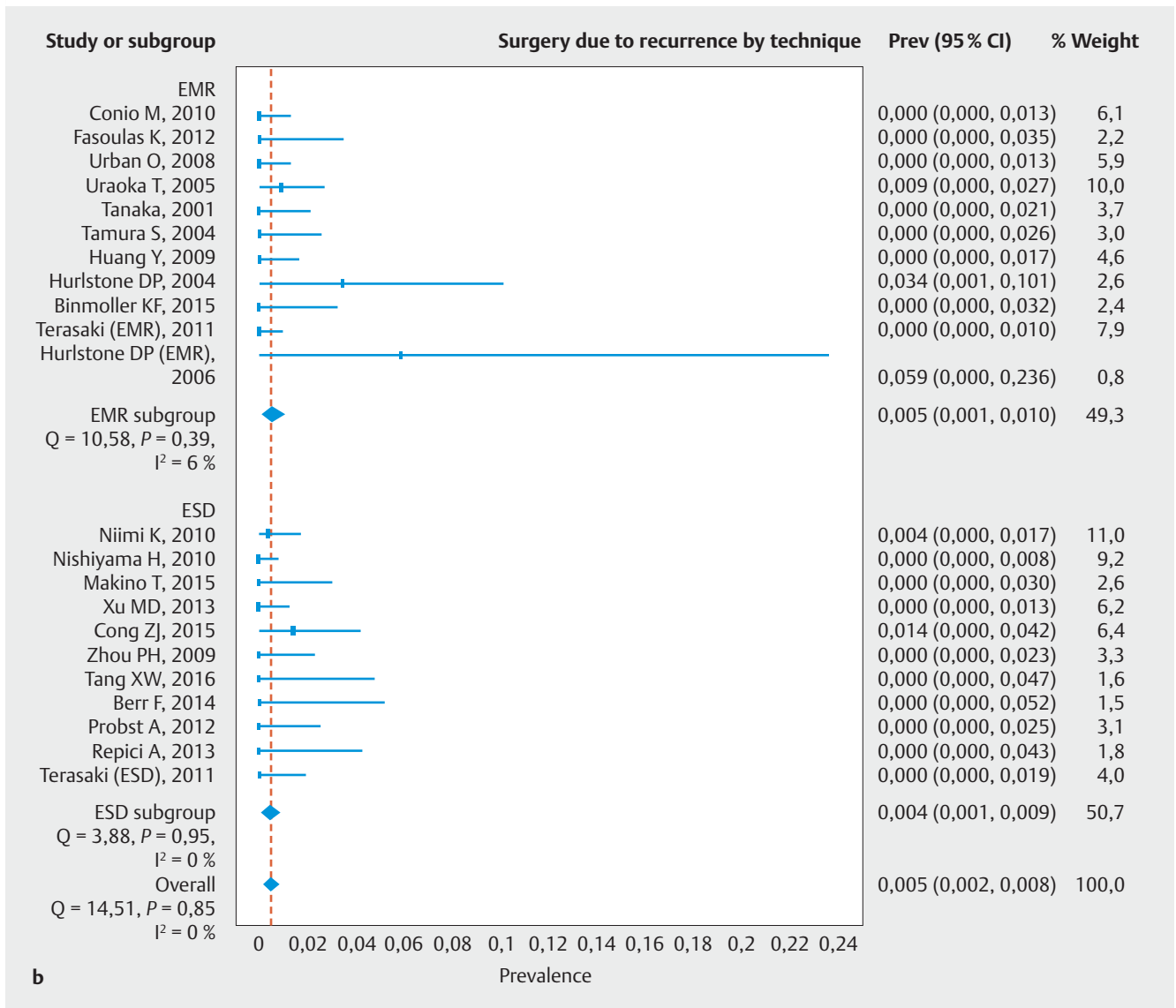
Russo Pedro et al. Management of colorectal … Endoscopy International Open 2019; 07: E239–E259

E253

Study or subgroup	Surgery overall by technique	Prev (95 % CI)	% Weight
EMR			
Moss A, 2015		0,051 (0,036, 0,068)	4,1
Conio M, 2010		0,051 (0,020, 0,096)	3,3
Fasoulas K, 2012		0,102 (0,030, 0,205)	2,3
Urban O, 2008		0,061 (0,025, 0,109)	3,2
Belle S, 2012		0,000 (0,000, 0,026)	2,6
Uraoka T, 2005		0,009 (0,000, 0,027)	3,6
Tanaka, 2001		0,037 (0,005, 0,092)	2,8
Tamura S, 2004		0,060 (0,013, 0,132)	2,6
Su MY, 2008		0,080 (0,046, 0,121)	3,5
Huang Y, 2009		0,039 (0,008, 0,087)	3,0
Hurlstone DP, 2004		0,034 (0,001, 0,101)	2,5
Arebi N, 2007		0,000 (0,000, 0,036)	2,3
Binmoller KF, 2015		0,000 (0,000, 0,032)	2,4
Terasaki (EMR), 2011		0,011 (0,000, 0,034)	3,5
Hurlstone DP (EMR), 2006		0,059 (0,000, 0,236)	1,2
EMR subgroup Q = 41,42, P = 0,00, I² = 66 %		0,037 (0,023, 0,054)	42,9
ESD			
Ritsuno H, 2014		0,000 (0,000, 0,034)	2,3
Uraoka T, 2010		0,000 (0,000, 0,046)	2,0
Suzuki S, 2014		0,000 (0,000, 0,006)	3,7
Niimi K, 2010		0,008 (0,000, 0,024)	3,7
Nishiyama H, 2010		0,025 (0,007, 0,051)	3,5
Hotta K, 2012		0,005 (0,000, 0,021)	3,5
Makino T, 2015		0,000 (0,000, 0,030)	2,5
Okamoto K, 2013		0,000 (0,000, 0,057)	1,8
Jung DH, 2015		0,067 (0,033, 0,112)	3,4
Yoon JY, 2012		0,000 (0,000, 0,017)	3,0
Kim ES, 2011		0,000 (0,000, 0,021)	2,8
Xu MD, 2013		0,073 (0,035, 0,123)	3,3
Cong ZJ, 2015		0,062 (0,031, 0,103)	3,5
Zhou PH, 2009		0,014 (0,000, 0,057)	2,7
Tang XW, 2016		0,028 (0,000, 0,116)	2,0
Hulagu S, 2013		0,023 (0,000, 0,095)	2,2
Berr F, 2014		0,030 (0,000, 0,126)	1,9
Hurlstone DP, 2007		0,000 (0,000, 0,061)	1,7
Probst A, 2012		0,000 (0,000, 0,025)	2,6
Repici A, 2013		0,050 (0,001, 0,145)	2,1
Terasaki (ESD), 2011		0,077 (0,030, 0,142)	2,9
ESD subgroup Q = 71,97, P = 0,00, I² = 72 %		0,020 (0,010, 0,034)	57,1
Overall Q = 130,33, P = 0,00 I² = 73 %		0,027 (0,018, 0,038)	100,0

0 0,02 0,04 0,06 0,08 0,1 0,12 0,14 0,16 0,18 0,2 0,22 0,24
Prevalence
a

▶ **Fig. 4a** Follow-up and surgery. Overall surgery rate by technique.

currence rate was as high as 15 %, with 3 % for en-bloc resections and 22 % for piecemeal resections. Treatment of recurrence was successful in 91.4 % of the lesions, after a median of 1.2 endoscopic retreatments. Piecemeal resection was the only risk factor that was clearly associated with recurrence in multivariable analysis [28].

In ESD treatment, Puli and Hassan both reported en-bloc rates of 85 % and 50 %, respectively [7, 29]. These rates are lower than our data (93.7 % en-bloc). In our analysis, according to our predefined and more stringent criteria most of the ESD studies were from the east.

Study or subgroup	Surgery due to recurrence by technique	Prev (95 % CI)	% Weight
EMR			
Conio M, 2010		0,000 (0,000, 0,013)	6,1
Fasoulas K, 2012		0,000 (0,000, 0,035)	2,2
Urban O, 2008		0,000 (0,000, 0,013)	5,9
Uraoka T, 2005		0,009 (0,000, 0,027)	10,0
Tanaka, 2001		0,000 (0,000, 0,021)	3,7
Tamura S, 2004		0,000 (0,000, 0,026)	3,0
Huang Y, 2009		0,000 (0,000, 0,017)	4,6
Hurlstone DP, 2004		0,034 (0,001, 0,101)	2,6
Binmoller KF, 2015		0,000 (0,000, 0,032)	2,4
Terasaki (EMR), 2011		0,000 (0,000, 0,010)	7,9
Hurlstone DP (EMR), 2006		0,059 (0,000, 0,236)	0,8
EMR subgroup		0,005 (0,001, 0,010)	49,3
Q = 10,58, P = 0,39, I² = 6 %			
ESD			
Niimi K, 2010		0,004 (0,000, 0,017)	11,0
Nishiyama H, 2010		0,000 (0,000, 0,008)	9,2
Makino T, 2015		0,000 (0,000, 0,030)	2,6
Xu MD, 2013		0,000 (0,000, 0,013)	6,2
Cong ZJ, 2015		0,014 (0,000, 0,042)	6,4
Zhou PH, 2009		0,000 (0,000, 0,023)	3,3
Tang XW, 2016		0,000 (0,000, 0,047)	1,6
Berr F, 2014		0,000 (0,000, 0,052)	1,5
Probst A, 2012		0,000 (0,000, 0,025)	3,1
Repici A, 2013		0,000 (0,000, 0,043)	1,8
Terasaki (ESD), 2011		0,000 (0,000, 0,019)	4,0
ESD subgroup		0,004 (0,001, 0,009)	50,7
Q = 3,88, P = 0,95, I² = 0 %			
Overall		0,005 (0,002, 0,008)	100,0
Q = 14,51, P = 0,85, I² = 0 %			

0 0,02 0,04 0,06 0,08 0,1 0,12 0,14 0,16 0,18 0,2 0,22 0,24

b   Prevalence

▶ **Fig. 4b** Follow-up and surgery. Rate of surgery due to recurrence by technique.

Mortality related to endoscopic procedures was similar (0.08 % in Hassan C. et al. vs. 0.10 % in our data) [7].

In this meta-analysis, we included mainly observational cohort studies and case-control studies, most of them either single-center or retrospective. However, to mitigate the risk of bias, we used the Newcastle-Ottawa Scale for assessing the quality of nonrandomized studies.

Limitations

Our search did not retrieve any results on minimally invasive transanal surgery (transanal endoscopic microsurgery), mostly because in the studies involving these techniques a morphologic classification was not applied. It would be advisable to apply this classification in future studies evaluating these techniques.

One of the major limitations of our work is the heterogeneous classification of lesions applied in the different papers. Many studies on the endoscopic treatment of large (>10 mm)

Paris 0-IIa lesions (as well as 0-IIa + c or 0-IIa + Is) were excluded because the denomination LST was not present. Most, if not all these lesions probably correspond to LST. Several studies that included LST along with other polypoid and non-polypoid lesions that didn't make a subanalysis of LST subgroup were also excluded. The other major limitation refers to the fact that most of the studies are either single-center or retrospective.

Data are scarce to compare the outcomes for the different LST subtypes (LST-GH, LST-GM, LST-NGF and LST-NGPD). For many non-Japanese studies, chromoendoscopy is not routinely applied, hence this may affect the accuracy of the morphological diagnosis of LST (especially LST-NG-PD) and evaluation of residual neoplasm in resection margin. The histological characteristics were usually not analyzed and they can play a major role in the outcomes, as more advanced histological lesions are related with lower curative resection.

Study or subgroup	Surgery due to incomplete/non-curative resection by technique	Prev (95 % CI)	% Weight
EMR			
Moss A, 2015		0,046 (0,032, 0,062)	10,0
Conio M, 2010		0,051 (0,020, 0,096)	5,7
Fasoulas K, 2012		0,082 (0,018, 0,178)	2,9
Urban O, 2008		0,045 (0,015, 0,089)	5,6
Tanaka, 2001		0,037 (0,005, 0,092)	4,2
Tamura S, 2004		0,060 (0,013, 0,132)	3,7
Su MY, 2008		0,080 (0,046, 0,121)	6,9
Huang Y, 2009		0,039 (0,008, 0,087)	4,9
Hurlstone DP, 2004		0,000 (0,000, 0,029)	3,3
Binmoller KF, 2015		0,000 (0,000, 0,032)	3,1
Terasaki (EMR), 2011		0,011 (0,000, 0,034)	6,5
EMR subgroup Q = 23,40, P = 0,01, I² = 57 %		0,041 (0,026, 0,058)	56,8
ESD			
Nishiyama H, 2010		0,020 (0,004, 0,044)	6,9
Jung DH, 2015		0,067 (0,033, 0,112)	6,2
Xu MD, 2013		0,066 (0,029, 0,114)	5,7
Cong ZJ, 2015		0,051 (0,023, 0,089)	6,5
Zhou PH, 2009		0,014 (0,000, 0,057)	3,9
Tang XW, 2016		0,028 (0,000, 0,116)	2,3
Hulagu S, 2013		0,023 (0,000, 0,095)	2,7
Hurlstone DP, 2007		0,000 (0,000, 0,061)	1,9
Repici A, 2013		0,050 (0,001, 0,145)	2,5
Terasaki (ESD), 2011		0,077 (0,030, 0,142)	4,5
ESD subgroup Q = 12,87, P = 0,17, I² = 30 %		0,046 (0,030, 0,063)	43,2
Overall Q = 36,38, P = 0,01, I² = 45 %		0,043 (0,033, 0,055)	100,0

c Prevalence

▶ **Fig. 4c** Follow-up and surgery. Rate of surgery due to incomplete resection by technique.

The duration from endoscopic treatment to surveillance examination was heterogeneous between the studies and may have affected the rate of early recurrence.

Conclusion

A wide range of definitions was applied to describe LST, not always concordant. Therefore, it is of paramount importance to establish an unambiguous and consensus definition for these lesions.

Definitions are nearly unanimous in describing LST as flat or non-polypoid lesions that extend laterally (or horizontally, or superficially) and circumferentially, rather than vertically along the colonic wall [20, 30–38].

Although some studies consider a minimum of 20 mm of diameter to fit in this classification [39, 40]. Most of the authors include lesions beyond 10 mm in this group [4, 20, 30, 32, 34–38, 41–44]. Another contention appears when establishing the maximum allowed vertical growth. Most commonly lateral-

ly spreading lesions within the fully inflated colon are described as lesions with height of less than half the diameter [45]. Bae JH et al. [15], defined LST as lesions with less than 2.5 mm in height.

Some authors make no distinction between sessile lesions and LST [46], while many other authors, despite making this distinction, analyze them in the same group of large sessile and laterally spreading lesions [47, 48]. The difference between large sessile and laterally spreading tumors can actually be difficult and subjective. The Paris endoscopic classification of superficial neoplastic lesions of 2002 states that slightly elevated lesions are easily misclassified as sessile (polypoid subtype) at endoscopy. This distinction is more reliable on pathologic examination of an operative specimen, in which it is possible to compare the height of the lesion with the full thickness of the normal mucosa, although this also has limitations due to specimen shrinkage with fixation.

When applying the Paris classification into the LST sub-classification, most authors include IIa, IIa + Is and IIa + IIc lesions in this group [5, 24, 49]. Some studies also classify these lesions as IIb [18, 24] and IIa + IIb [19]. Berr F et al. classified LST-GH as IIa, LST-GM as IIa + Is, LST-NGF as IIa or IIb and LST-NGPD as IIa + c [24]. However, some authors have considered LST-NG as IIa and LST-G as IIa + Is lesions [49, 50].

Alternatively, some studies differentiate an LST group from a Paris II group (including IIa lesions), with both groups having large > 10 mm lesions [22, 51, 52].

In the Paris consensus of 2002 "lateral spreading type" lesions were included in type 0-IIa [3].

The authors suggest the following criteria to classify a lesion as LST:

1. Flat or non-polypoid lesions that extend laterally and circumferentially rather than vertically along the colonic wall, with a minimum diameter of 10 mm.
2. Laterally spreading lesions shall be slightly elevated or at least have a real flat component (0-IIa). Pure sessile lesions (Paris 0-Is) shall not be classified as LST. To differentiate LST from sessile lesions the height of these lesions must be less than half of its diameter.
3. LST shall be classified into LST-G, which includes LST-GH (which corresponds to Paris 0-IIa lesions) and LST-GM (Paris 0-IIa + Is lesions) and LST-NG, which includes LST-NGF (Paris 0-IIa) and LST-NGPD (Paris 0-IIa + c).

Competing interests

None

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E259