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Two-stage endoscopic mucosal resection is a safe and effective salvage therapy after a failed single-session approach

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submitted 7.11.2016
accepted after revision 3.4.2017

Bibliography
DOI https://doi.org/10.1055/s-0043-110671
Published online: 31.5.2017 | Endoscopy 2017; 49: 888–898

ISSN 0013-726X

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Fig. e5, Table e4, Table e5
Online content viewable at:
https://doi.org/10.1055/s-0043-110671

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ABSTRACT

Background and study aims Endoscopic mucosal resection (EMR) of laterally spreading colonic lesions ≥ 20 mm (LSLs) is ideally performed in a single session (ssEMR) and avoids surgery in > 90 % of patients. We investigated whether a second attempt is safe or useful when ssEMR fails at a tertiary center.

Patients and methods In a multicenter prospective observational study of patients with LSL treated by EMR at four tertiary centers over 8 years, incompletely resected LSLs were referred for surgery or underwent two-stage EMR (tsEMR). At tsEMR, the scar was located and all visible residual tissue removed by snare, with thermal treatment permitted thereafter. Scheduled surveillance was performed at 5 months (SC1) and 18 months (SC2). The primary outcome was avoidance of surgery.

Results A total of 1944 LSLs (median size 35 mm) underwent EMR. ssEMR was unsuccessful in 127 lesions, 43 of which underwent tsEMR, with success in 36 (83.7 %). Compared with ssEMR, tsEMR lesions were larger (median size 50 mm vs. 30 mm; $P < 0.001$), exhibited more submucosal fibrosis ($P < 0.001$), and histology was more often tubular adenoma and less often serrated ($P = 0.005$). Lesions mainly required tsEMR for nonlifting (41.9 %) or poor endoscopic access (37.2 %). Failure of tsEMR was predicted by larger LSL ($P = 0.03$). Safety was comparable to ssEMR. Of the 33 LSLs that underwent tsEMR for benign disease and completed first surveillance, 27 (81.8 %) avoided surgery to long term follow-up.

Conclusions tsEMR shows promise as a salvage therapy for LSLs that cannot be resected in a single session for patients in whom other options such as surgery are not preferred or not possible.

Trial registered at ClinicalTrials.gov (NCT01368289).

Introduction

Wide-field endoscopic mucosal resection (EMR) has become the primary treatment of large laterally spreading lesions ≥ 20 mm (LSLs) in the colon. As a day case procedure, EMR has cost [1] and morbidity benefits over surgery, and modeling indicates that it is safer [2].

EMR is commonly performed in a single session (ssEMR), with complete snare resection of adenoma achieved in the majority of cases at tertiary endoscopy centers [3]. Failure of ssEMR is often due to nonlifting of the target LSL [4], difficult endoscope positioning or challenging colonic location, including the ileocecal valve [5], appendiceal orifice [6] or the anorectal junction [7]. Failure of ssEMR commonly results in referral of the patient for surgical resection.

When ssEMR has failed, there may be benefit in repeating the procedure after an interval to allow the mucosal defect to heal, highlight the residual adenoma, and allow purchase with the snare or more successful use of adjunctive techniques. We aimed to investigate the safety and efficacy of two-stage EMR (tsEMR) in situations where ssEMR previously failed at a tertiary endoscopy center.

Materials and methods

EMR procedure

Data were collected within a multicenter prospective observational study of patients referred for EMR of colonic LSLs performed at four Australian academic tertiary referral centers from 9/2008 until 06/2016 (The Australian Colonic EMR Resection Study [3]; ClinicalTrials.gov NCT01368289). There were no exclusions to enrollment. Institutional review board approval was obtained at each center.

Video 1 Two-stage endoscopic mucosal resection for large colorectal laterally spreading lesions.
Online content viewable at:
https://doi.org/10.1055/s-0043-110671

EMR procedures were performed by senior endoscopists with extensive EMR experience or by a senior endoscopy fellow under their direct supervision. Written informed consent was obtained from all patients. LSLs were described as "previously attempted" if an attempt at resection had been made at the referring institution or "naïve" if no previous attempt had been made at the referring institution. Split-dose bowel preparation was used. Intravenous sedation was with a combination of fentanyl, midazolam, and propofol. Insufflation of the colon was initially with air, but was switched to carbon dioxide from August 2010 [8].

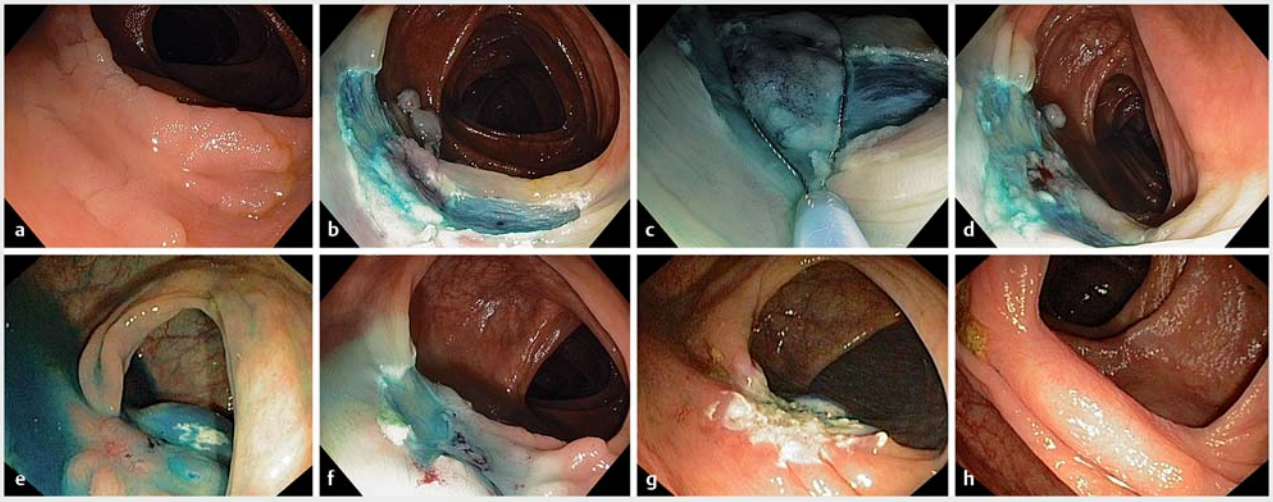
Colonoscopy was performed using Olympus 180 or 190 series high definition variable-stiffness colonoscopes (180/190 PCF/CF; Olympus, Tokyo, Japan). Lesion assessment was performed with high definition white-light and narrow-band imaging. The size of the lesion was determined with reference to an open snare of known diameter. A standardized and previously described inject-and-resect EMR technique [9] was used in an attempt to achieve complete adenoma clearance by snare in a single session (ssEMR) (▶ **Video 1**).

Most cases used a microprocessor-controlled electrosurgical generator (ERBE VIO300D; ERBE Elektromedizin, Tübingen, Germany) [10] with fractionated current. The submucosal injectate comprised normal saline until 2010 when succinylated gelatin was adopted (Gelofusine; B. Braun Australia Pty. Ltd., Bella Vista, Australia) [11]. The fluid was dyed with indigo carmine blue (80 mg/500 mL solution), and adrenaline was added to achieve a solution of 1:100 000. Methylene blue was occasionally used when indigo carmine blue was not available.

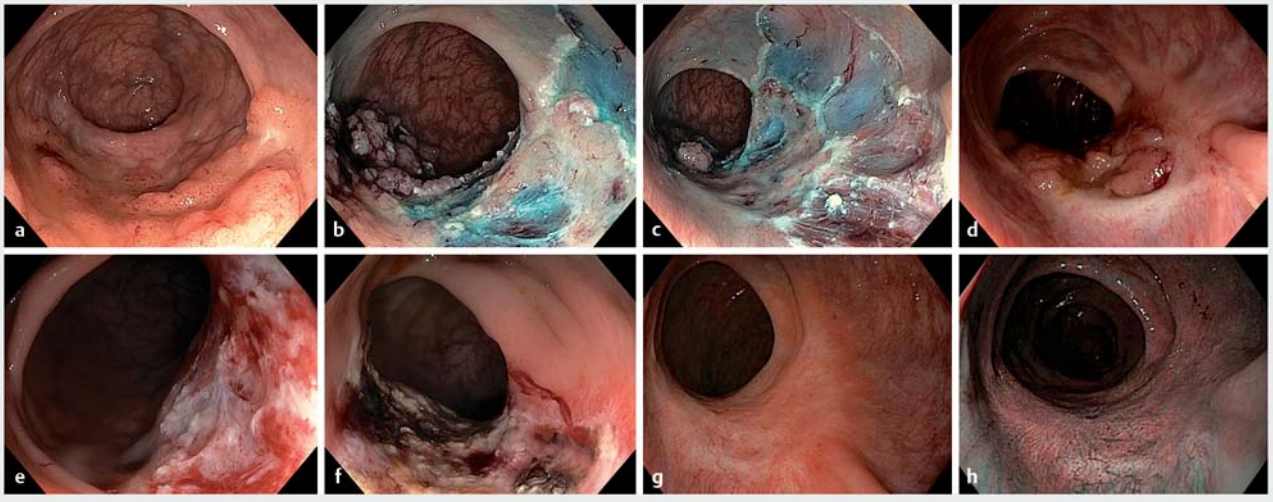
Intraprocedural bleeding was treated with snare tip soft coagulation (ERBE Effect 4, 80 W), and was recorded as present if endoscopic control was required. Intraprocedural perforation was described as the presence of a target sign [12] or actual hole in the colonic wall.

If complete snare excision could not be achieved in a single session at the tertiary center, the patient was either referred for surgery or scheduled for a repeat resection attempt (tsEMR). This decision was completely at the discretion of the individual operator based on the reason for ssEMR failure and the predicted complexity of a future resection. tsEMR always referred to a second procedure at the tertiary center, whether or not the lesion had been previously attempted by the referrer.

If the patient was scheduled for tsEMR, this was arranged for 1 – 2 months after the index procedure. At tsEMR, the EMR scar was located and the residual lesion was then resected by snare using standard EMR technique if possible (▶ **Video 1**). If there was extensive residual adenoma, injection was performed away from the scarred area using resection of normal tissue to isolate the nonlifting area and create a step to allow purchase with the snare. Tangential snare positioning over the residual lesion with firm downward pressure aided tissue capture. Adjuvant thermal therapy with argon plasma coagulation (APC) or snare tip soft coagulation (after 2012) was used to ablate remaining residual adenoma if complete snare excision was not possible. ▶ **Fig. 1** and ▶ **Fig. 2** demonstrate two examples of the tsEMR technique. Technical success was recorded where



▶ **Fig. 1** Two-stage endoscopic mucosal resection (EMR). **a** A large 35 mm resection-naïve nongranular laterally spreading lesion is shown in the ascending colon. **b** Standard inject-and-resect EMR is used to isolate a nonlifting central component. **c** A stiff thin-wire snare is used to attempt resection of the central nonlifting component. **d** Ultimately, the nonlifting component cannot be fully resected by snare and the patient is scheduled for a second-stage procedure. **e** Appearance of the EMR scar at 1.5 months after the initial EMR; scarring can be seen to highlight the residual adenoma. **f** After injection, a thin wire snare is used to resect the residual adenoma. **g** Argon plasma coagulation is applied to the resection bed and surrounding scar tissue. **h** Appearance of the EMR scar at the first surveillance colonoscopy, with no evidence of recurrence.

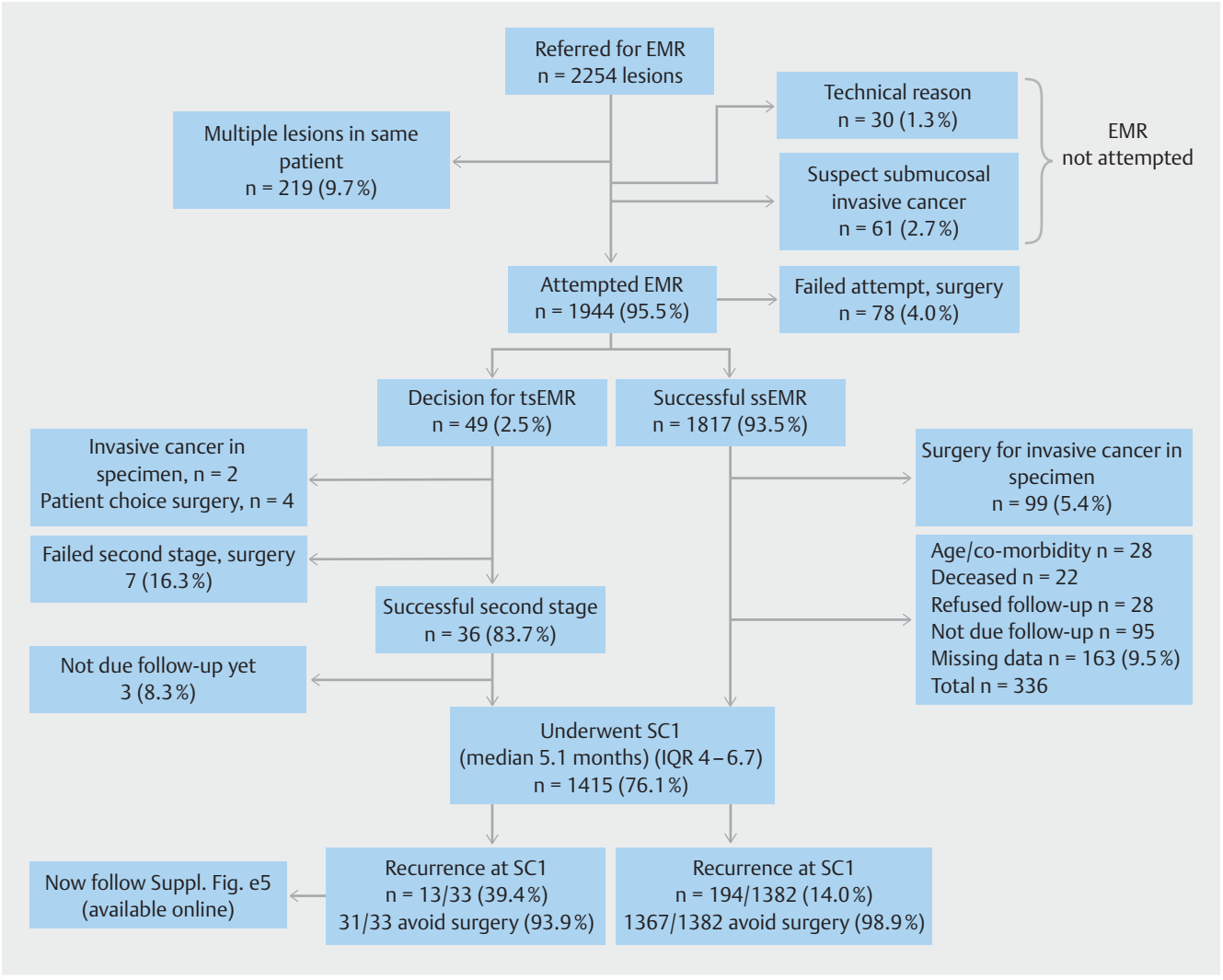


▶ **Fig. 2** Two-stage endoscopic mucosal resection (tsEMR) of a previously attempted laterally spreading lesion (LSL). **a** 50 % circumferential previously attempted granular LSL in the distal rectum extending to the anal verge is shown. **b,c** Standard inject-and-resect EMR is used to isolate a nonlifting central component that cannot be resected by the end of the initial procedure. The patient is scheduled for tsEMR. **d** Appearance of the EMR scar at 1 month after the initial EMR, demonstrating an area of central residual adenoma. **e** Multiple snare excision with coagulation current is used to resect the nonlifting adenoma. **f** Snare tip soft coagulation is applied to the resection bed and surrounding scar tissue. **g,h** Appearance of the EMR scar under high definition white-light and narrow-band imaging at the first surveillance colonoscopy, with no evidence of recurrence.

there was complete removal/destruction of adenomatous tissue.

After EMR, patients were observed for 4 hours and, if well, discharged home. A clear fluid diet was advised until the next morning. Specialist gastrointestinal pathologists at the individual centers reviewed all histological specimens.

Post-procedural data, including delayed adverse events and results of follow-up, were collected by structured telephone interview at 14 days following the index procedure and at the time of each surveillance colonoscopy. Clinically significant post-EMR bleeding was defined as bleeding after EMR that required hospital admission or re-intervention [13]. All authors



▶ **Fig. 3** Recruitment to the study from four academic tertiary referral centers. EMR, endoscopic mucosal resection; ssEMR, single-session EMR; tsEMR, two-stage EMR; SC1, first surveillance colonoscopy; IQR, interquartile range.

had access to the study data and reviewed and approved the final manuscript.

Follow-up

Follow-up data were collected from patients eligible for first surveillance colonoscopy (SC1) at a desired interval of 4–6 months after ssEMR or tsEMR. Time to longest follow-up and any associated endoscopic and histological residual or recurrent adenoma (RRA) after SC1 were recorded if available. Analysis was performed on a per patient basis with only the largest lesion from each patient included.

All EMR scars were evaluated endoscopically at SC1 and at subsequent follow-up. The primary end point of the study was avoidance of surgery. Secondary end points included endoscopically determined recurrence (RRA) and safety. RRA was defined as the presence of tissue suspicious for adenoma under high definition white-light and/or narrow-band imaging. When there was any doubt as to the presence of RRA, biopsies of the EMR scar were taken to document the presence or absence of histological recurrence. Detected RRA, once sampled, was excised by snare or, if this was not possible, removed by cold forceps avulsion followed by snare tip soft coagulation.

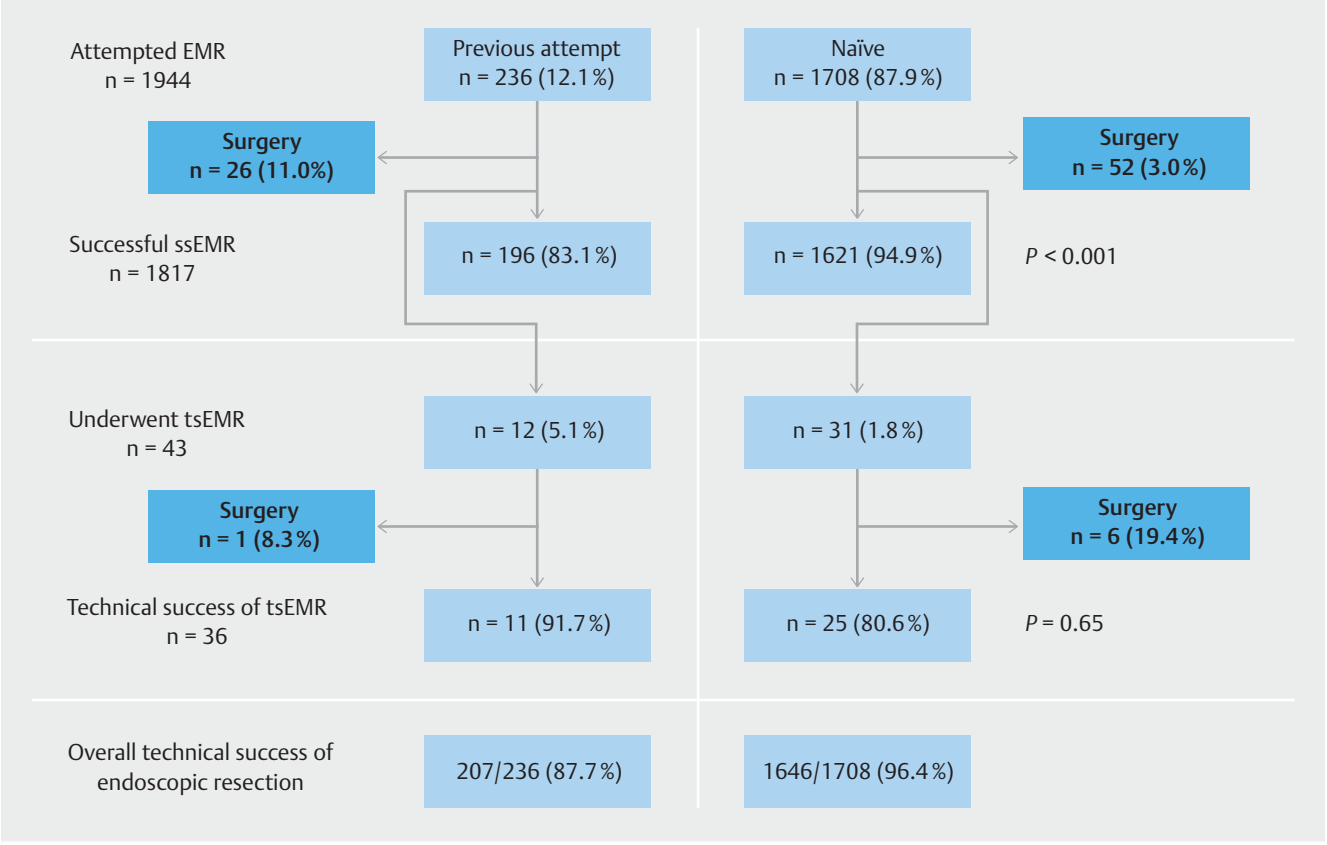
Statistical analysis

Statistical analysis was performed using SPSS version 22 (IBM Corp., Armonk, New York, USA) with two-tailed *t* test used for normally distributed continuous variables, Mann–Whitney *U* test for skewed continuous data, and chi-squared test or Fisher's exact test for categorical variables. Significance of *P* was set at <0.05. Comparisons were made between tsEMR, naïve LSL completed in a single session, and previously attempted LSL completed in a single session.

Results

Patient population

Over 8 years to June 2016, 2254 lesions in 2035 patients were referred for EMR at four academic Australian Tertiary referral centers. A total of 91 lesions (4.0%) were not attempted, either because of concern for submucosal invasive cancer (n = 61) or



▶ **Fig. 4** Description of the outcomes of the 236 previously attempted lesions included in the cohort compared with naïve lesions. EMR, endoscopic mucosal resection; tsEMR, two-stage EMR. Technical success denotes a complete removal/destruction of adenomatous tissue.

owing to technical difficulties (n = 30); these lesions were referred directly for surgery. EMR was attempted in 1944 lesions (95.5 %), of which 222 (11.4 %) had been previously attempted. The median size of LSLs was 35 mm (interquartile range [IQR] 25 – 45 mm).

Successful ssEMR was accomplished in 1817/1944 lesions (93.5 %). Of the 127 lesions that were not completely resected at the initial EMR procedure, 78 (61.4 %) were referred for surgery and 49 (38.6 %) for tsEMR. A total of 26 LSLs (33.3 %) that were referred for surgery were previously attempted, as were 14/49 LSLs (28.6 %) that were referred for tsEMR. Six lesions referred for tsEMR actually underwent surgery, two for submucosal invasive cancer in the initial resection specimen and four because of patient choice. Detailed recruitment and exclusions are shown in ▶ **Fig. 3**.

Characteristics of lesions undergoing tsEMR

A total of 43 lesions underwent tsEMR a median of 2 months (IQR 1 – 2) after the index procedure. Reasons cited by the endoscopist at the initial EMR for the lesion requiring tsEMR were nonlifting of the target lesion in 18/43 lesions (41.9 %); in 9/18 cases (50.0 %) there had been a previous resection attempt and 7 (38.9 %) further cases had undergone previous biopsy. Difficult endoscopic access was cited for 16/43 lesions (37.2 %); these locations included the ileocecal valve (8/16, 50.0 %), the hepatic or splenic flexures (3/16, 18.8 %), and around the base of the cecum or the appendiceal orifice (3/16, 18.8 %). Other reasons given for a lesion requiring tsEMR were concern for submucosal invasive cancer in 4/43 lesions (9.3 %), concern for intraprocedural perforation in 2 (4.7 %), lesion extent in 2 (4.7 %), and problems with patient sedation in 1 (2.3 %).

Baseline lesion characteristics and treatment outcomes are summarized in ▶ **Table 1**. Compared with naïve LSLs completed at ssEMR, LSLs undergoing tsEMR were larger (median 50 mm [IQR 35 – 60] vs. 30 mm [IQR 25 – 45]; $P < 0.001$), exhibited a greater degree of submucosal fibrosis (58.1 % vs. 18.6 %; $P < 0.001$), and were more often tubular adenomas (19 [44.2 %] vs. 385 [24.6 %]), and less often serrated adenomas (2 [4.7 %] vs. 271 [17.3 %]), $P = 0.005$. Surgical referral prior to surveillance colonoscopy was made in seven lesions (16.3 %) and was more common in lesions undergoing tsEMR (7 [16.3 %] vs. 81 [5.0 %]; $P = 0.01$).

Compared with LSLs referred directly for surgery after ssEMR, LSLs referred for tsEMR were found in older patients (mean age 70.4 years [SD 9.5] vs. 66 years [SD 11.7]; $P = 0.049$), were less likely to involve a dominant Is component (7/49 [14.6 %] vs. 21/78 [26.9 %]; $P = 0.01$), and were less likely to contain high grade dysplasia (14/78 [28.6 %] vs. 41/78 [54.7 %]; $P = 0.01$) (▶ **Table 2**).

Technical success at tsEMR was achieved in 36/43 lesions (83.7 %) compared with 1621/1708 (94.9 %) naïve lesions undergoing ssEMR ($P = 0.01$). Primary procedural techniques used to achieve complete clearance of adenoma at tsEMR

▶ **Table 1** Patient and lesion characteristics according to whether or not the procedure was completed in a single endoscopic mucosal resection (EMR) session (further divided by whether a previous attempt was made at the referring institution or not [naïve LSL]) or completion was delayed for a two-stage EMR procedure (tsEMR). For tsEMR, lesion factors relate to the first stage, and procedural and complication characteristics relate to the second-stage procedure.

	tsEMR		ssEMR		
		P[1]	Naïve LSL	Previously attempted LSL	*P*[1]
Total number of LSLs, N	43		1621	196	
Patients					
Age, mean (SD), years	70.0 (9.75)	0.12	67.2 (11.9)	69.2 (10.2)	**0.02**
Sex, male, n (%)	23 (53.5)	0.77	833 (51.4)	109 (55.6)	0.26
Procedure in first half of study, n (%)	30 (69.8)	**0.001**	714 (44.0)	97 (49.5)	0.15
Lesions					
Size, median (IQR), mm	50 (35 – 60)	**<0.001**	30 (25 – 45)	30 (25 – 40)	0.08
Paris (%)	N = 42		N = 1615	N = 195	
▪ 0-Is	5 (11.9)	0.75	278 (17.2)	37 (19.0)	0.32
▪ 0-IIa	21 (50.0)		818 (50.7)	106 (54.4)	
▪ 0-IIa/Is	12 (28.6)		396 (24.5)	36 (18.5)	
▪ Others (IIb, IIa + c, etc)	4 (9.5)		123 (7.6)	16 (8.2)	
Morphology (%)					
▪ Granular	28 (65.1)	0.69	949 (58.5)	100 (51.0)	**0.02**
▪ Nongranular	9 (20.9)		399 (24.6)	66 (33.7)	
▪ Unable to classify	6 (14.0)		273 (16.8)	30 (15.3)	
Location, n (%)					
▪ Left colon	19 (44.2)	0.69	766 (47.3)	104 (53.1)	0.12
▪ Right colon	24 (55.8)		855 (52.7)	92 (46.9)	
En bloc, n (%)	0 (0)	**0.002**	288 (17.8)	18 (9.2)	**0.002**
Resection attempt prior to EMR, n (%)	12 (27.9)	**<0.001**	0 (0)	196 (100)	**<0.001**
Procedures					
Submucosal fibrosis, n (%)	25 (58.1)	**<0.001**	301 (18.6)	124 (63.3)	**<0.001**
Intraprocedural bleeding, n (%)	10 (23.3)	0.29	276 (17.0)	26 (13.3)	0.18
Intraprocedural perforation, n (%)	2 (4.7)	0.71	69 (4.3)	14 (7.1)	0.07
Histopathology, n (%)	N = 43		N = 1563	N = 190	
▪ Tubular adenoma	19 (44.2)	**0.005**	385 (24.6)	59 (31.1)	**0.03**
▪ Tubulovillous adenoma	22 (51.2)		907 (58.0)	110 (57.9)	
▪ Serrated adenoma	2 (4.7)		271 (17.3)	21 (11.1)	
Technical success, n (%)[2]	36/43 (83.7)	**0.01**	1621/1708 (94.9)	196/236 (83.1)	**<0.001**
Complications					
Clinically significant post endoscopic bleeding. n (%)	0 (0)	0.26	74 (4.6)	8 (4.1)	0.76
Delayed perforation, n (%)	0 (0)	>0.99	3 (0.2)	1 (0.5)	0.37
Surgical referral prior to first surveillance, n (%)	7 (16.3)	**0.01**	81 (5.0)	18 (9.2)	**0.02**

tsEMR, two-stage endoscopic mucosal resection; ssEMR, single-session endoscopic mucosal resection; LSL, laterally spreading lesions; IQR, interquartile range.
Note, not all data points were available for all lesions; denominator indicated where different to column heading.
[1] P values indicate comparison with naïve LSL.
[2] Note the different denominator for technical success, which includes all attempted lesions.

▶ **Table 2** Patient and lesion characteristics after failed single-session endoscopic mucosal resection (EMR), according to whether or not the lesion was referred for surgery or scheduled for two-stage EMR.

Failed ssEMR	Surgery	tsEMR planned	*P*
Total number of lesions, n	78	49	
Patient			
▪ Age, mean (SD), years	66.0 (11.7)	70.4 (9.5)	0.049
▪ Sex, male, n (%)	43 (55.1)	24 (49.0)	0.50
Lesion			
Size, median (IQR), mm	40 (30 – 60)	50 (35 – 60)	0.30
Paris, n (%)	N = 78	N = 48	
▪ 0-Is	21 (26.9)	7 (14.6)	0.01
▪ 0-IIa	18 (23.1)	22 (45.8)	
▪ 0-IIa/Is	17 (21.8)	14 (29.2)	
▪ Others (IIb, IIa + c, etc)	22 (28.2)	5 (10.4)	
Morphology, n (%)			
▪ Granular	38 (48.7)	30 (61.2)	0.32
▪ Nongranular	25 (32.1)	10 (20.4)	
▪ Unable to classify	15 (19.2)	9 (18.4)	
Location, n (%)			
▪ Left colon	35 (44.9)	22 (44.9)	0.99
▪ Right colon	43 (55.1)	27 (55.1)	
Submucosal fibrosis, n (%)	33 (42.3)	26 (53.1)	0.24
Intraprocedural bleeding, n (%)	9 (11.5)	11 (22.4)	0.33
Intraprocedural perforation, n (%)	5 (6.4)	2 (4.1)	0.71
Histopathology, n (%)	N = 70	N = 49	
▪ Tubular adenoma	21 (30.0)	20 (40.8)	0.12
▪ Tubulovillous adenoma	48 (68.6)	26 (53.1)	
▪ Serrated adenoma	1 (1.4)	3 (6.1)	
Dysplasia	N = 75	N = 49	
▪ None	3 (4.0)	2 (4.1)	0.01
▪ Low grade	31 (41.3)	33 (67.3)	
▪ High grade	41 (54.7)	14 (28.6)	

ssEMR, single-session endoscopic mucosal resection; tsEMR, two-stage endoscopic mucosal resection; IQR, interquartile range.

were repeat snare excision in 33/43 (76.7 %), cold forceps avulsion with adjunctive thermal therapy in 8 (18.6 %), and APC to visible adenoma in 2 (4.7 %). Additional thermal therapy was applied to the margin of the EMR defect or over the scarred mucosa in 12/33 (36.4 %) lesions where repeat snare excision was used. Additional techniques used to clear adenoma at tsEMR included use of a short transparent endoscope cap for LSLs located at the ileocecal valve (4/43, 9.3 %), scarred retraction of adenoma at the ileocecal valve allowing snare resection (3/43, 7.0 %), and use of a gastroscope allowing retroflexion and improved visualization at the splenic flexure in one case (2.3 %). Complete clearance of residual adenoma was achieved in 14/16 (87.5 %) lesions where poor access required tsEMR, and in 16/18 (88.9 %) cases where nonlifting adenoma was the primary reason for tsEMR.

Complications at tsEMR were intraprocedural bleeding in 10/43 (23.3 %) and 2 cases (4.7 %) of intraprocedural perforation. The two perforations were treated with endoscopic clips with no clinical sequelae. These rates were not significantly different from those of ssEMR (▶ **Table 1**). A single patient had un-

▶ **Table 4** Follow-up data from the cohort with rates of residual or recurrent adenoma to specific follow-up intervals. The number of patients undergoing each stage of follow-up is included as the denominator in each case.

Follow-up	tsEMR	*P*[1]	ssEMR		*P*[1]
			Naïve LSL	Previously attempted LSL	
SC1					
▪ Time to SC1, median (IQR), months	6.7 (5.9 – 9.9)	< 0.001	5.1 (4.0 – 6.7)	4.8 (3.8 – 6.4)	0.12
▪ RRA, n/N (%)	13/33 (39.4)	< 0.001	166/1224 (13.6)	28/158 (17.7)	0.16
▪ Surgery, n/N (%)	2/33 (6.1)	0.06	14/1224 (1.1)	1/158 (0.6)	> 0.99
SC2					
▪ Time to SC2, median (IQR), months	14 (11.4 – 22.5)	0.10	17.7 (14.7 – 22.0)	17.8 (14.0 – 21.3)	0.73
▪ RRA, n/N (%)	6/23 (26.1)	0.001	31/592 (5.2)	8/99 (8.1)	0.26
▪ Surgery, n/N (%)	2/23 (8.7)	0.01	2/592 (0.3)	2/99 (2.0)	0.10
SC3					
▪ Time to SC3, median (IQR), months	40.1 (33.7 – 48.0)	0.10	33.3 (25.4 – 42.9)	29.6 (24.3 – 42.8)	0.39
▪ RRA, n/N (%)	2/12 (16.7)	0.09	5/142 (3.5)	5/22 (22.7)	0.004
▪ Surgery, n/N (%)	2/12 (16.7)	0.02	1/142 (0.7)	1/22 (4.5)	0.25

tsEMR, two-stage endoscopic mucosal resection; ssEMR, single-session endoscopic mucosal resection; LSL, laterally spreading lesion; RRA, residual or recurrent adenoma; SC1, 2, 3, surveillance colonoscopy 1, 2, 3; IQR, interquartile range.
[1] *P* values indicate comparison with naïve LSL.

controllable bleeding from a tsEMR site; thermal therapy with snare tip soft coagulation and coagulation forceps failed to control the bleeding, and endoscopic clip placement was not possible owing to extensive fibrosis from the previous resection. After blood transfusion, emergency angioembolization resolved the bleeding with no negative consequences for the patient.

Failure of tsEMR requiring surgery occurred in seven lesions. It was not more common with previously attempted lesions ($P = 0.65$) (▶ **Fig. 4**). LSLs where tsEMR failed were larger (median 50 mm [IQR 50 – 120] vs. 40 mm [IQR 35 – 60]; $P = 0.03$) lesions than those in which tsEMR was successful, with sizes in the failed group ranging from 40 mm to 120 mm. No other procedural or lesion factor was significantly different. Reasons given by the endoscopist as to why tsEMR was abandoned were persistent nonlifting in three lesions (42.9 %), difficult endoscopic access in two (28.6 %), deep ileal infiltration in one (14.3 %), and suspicion of submucosal invasive cancer in one (14.3 %). ▶ **Table e3** (available online) presents all lesions that were directly referred for surgery after failed tsEMR. All surgical specimens contained residual adenoma, and none contained invasive malignancy.

Follow-up

Median time to SC1 for lesions successfully resected by tsEMR was 6.7 months (IQR 5.9 – 9.9) and was undertaken in 33 patients (▶ **Table 4**, ▶ **Fig. e5** [available online]). Three patients were not due SC1 at the time of writing. RRA at SC1 was detected in 13/33 patients (39.4 %). Histological data were available in eight cases where endoscopic recurrence was present and was positive in 8/8 cases (100 %). Other histology was not retrieved or did not survive processing. After ssEMR of naïve LSLs, RRA was detected in 166/1224 (13.6 %; $P < 0.001$) cases. Histological data were available in 573 cases and was positive in 114 (19.9 %). RRA was detected in 28/158 cases (17.7 %; $P = 0.16$) after ssEMR of previously attempted LSL. Two patients (6.1 %) undergoing SC1 after tsEMR were referred for surgery ($P = 0.06$), one because of inability to resect RRA (attributed to extensive fibrosis and nonlifting) and another because of a proximal metachronous malignancy detected at the surveillance procedure; in the latter case, while technically possible, no attempt was made to resect the residual adenoma at the EMR scar as it was to be included in the surgical specimen.

Four patients did not undergo second surveillance colonoscopy (SC2) because of age and/or co-morbidity, two were deceased, one was missing follow-up data (moved abroad), and one was not due. SC2 was performed on 23 lesions at a median of 14 months (IQR 11.4 – 22.5), and 6/23 (26.1 %) lesions demonstrated RRA, of which 2/23 (8.7 %) were referred for surgery. In comparison, SC2 was performed on 691 lesions that underwent ssEMR of naïve LSLs with RRA in 31/592 (5.2 %; $P = 0.001$), and 2 (0.3 %) of which were referred for surgery ($P = 0.01$).

SC3 or later was performed on 12 of the 21 eligible tsEMR patients at a median of 40.1 months (IQR 33.7 – 48). Three patients did not undergo surveillance because of co-morbidities, two were deceased, one refused, and three were not due. RRA was detected in 2/12 (16.7 %), with both patients referred for surgery because of nonlifting adenoma. At ssEMR of naïve LSLs, 5/142 patients (3.5 %; $P = 0.09$) had RRA and one patient (0.7 %; $P = 0.02$) was referred for surgery. ▶ **Table e5** (available online) presents all lesions that were referred for surgery during follow-up.

Overall, if a patient underwent successful tsEMR and completed their first follow-up procedure, 27/33 (81.8 %) avoided surgery to longest follow-up.

Comparison between naïve LSL and previously attempted LSL

A total of 236 LSLs (12.1 %) that underwent EMR had been previously attempted. Previously attempted LSLs were significantly less likely to be resected successfully in a single session compared with naïve LSLs (83.1 % vs. 94.9 %; $P<0.001$). Those that were successfully resected were more likely to be nongranular than naïve LSLs (33.7 % vs. 24.6 %; $P=0.02$) and were less commonly resected en bloc (9.2 % vs. 17.8 %). They often exhibited submucosal fibrosis (63.3 % of cases vs. 18.6 %) and were more commonly tubular adenoma ($P=0.03$) (▶ **Table 1**). During long term follow-up previously attempted LSLs did not recur or undergo surgery more frequently than naïve LSL (▶ **Table 4**).

Comparison between first and second half of the cohort

The cohort was divided temporally directly in half between 9/2008 and 6/2016. ssEMR was a more likely outcome of an attempt at EMR in the second half of the cohort (1006/1047 [96.1 %]) than in the first half of the cohort (811/897 [90.4 %]; $P=0.001$), and consequently both tsEMR and surgery were less frequently required. When comparing the fate of lesions that failed ssEMR, tsEMR and surgery were of equal likelihood in the first (tsEMR 35/86 [40.7 %]) and second (tsEMR 14/41 [34.1 %]; $P=0.48$) half of the cohort (▶ **Table 6**).

Discussion

ssEMR is the gold standard and preferred approach for the treatment of large LSLs [14]. It is inexpensive, safe, effective, and avoids surgery in > 90 % of patients referred in a tertiary setting. However, for a variety of reasons it does not always succeed and at the present time the general default position is to refer the patient to surgery. In this study, we demonstrated that among 43 LSLs that could not be resected in a single session by EMR at a tertiary referral center, 36 (83.7 %) could be resected at a second EMR procedure (tsEMR) at an interval of 1 – 2 months, thereby avoiding surgery. We compared the outcomes of tsEMR with ssEMR of naïve LSLs to inform discussion; however, tsEMR should be seen as a salvage therapy where ssEMR has failed.

Other authors have recognized the skill of the endoscopist as a risk factor for incomplete polypectomy [15], and it is likely that this effect is more pronounced for complex endoscopic resection. In the current study, EMR procedures that had previously been attempted but failed at the referring center could be completed in 83.1 % of cases in a single session, although this was lower than the rate for naïve LSLs (94.9 %). In addition, once fully resected, previously attempted LSLs did not recur more frequently than naïve LSLs resected in a single session, whereas lesions requiring tsEMR did. Taken together these observations indicate that a second-stage procedure at a tertiary endoscopy center is not equivalent to complete resection of a previously attempted LSL in a single session, and validates the study description of tsEMR as a specific situation within the referral pathway of LSL.

The majority of failures of ssEMR and consequent need for tsEMR were due to nonlifting adenoma, a sign commonly associated with previously attempted LSL resection or lesion biopsy

▶ **Table 6** Fate of lesions according to temporal location within the lesion cohort (9/2008 until 6/2016) and details of their resection.

	First half of cohort	Second half of cohort	*P* value
Lesion outcomes, n (%)	N = 897	N = 1047	
▪ ssEMR	811 (90.4)	1006 (96.1)	0.001
▪ tsEMR	35 (3.9)	14 (1.3)	
▪ Surgery	51 (5.7)	27 (2.6)	
After failed ssEMR, n (%)	N = 86	N = 41	
▪ tsEMR	35 (40.7)	14 (34.1)	0.48
▪ Surgery	51 (59.3)	27 (65.9)	
Reason for tsEMR, n (%)	N = 30	N = 13	
▪ Nonlifting	12 (40.0)	6 (46.2)	0.83
▪ Access	12 (40.0)	4 (30.8)	
▪ Other	6 (20.0)	3 (23.1)	
Failure of tsEMR, n (%)	N = 30	N = 13	
▪ Need for surgery	5 (16.7)	2 (15.4)	> 0.99

ssEMR, single-session endoscopic mucosal resection; tsEMR, two-stage endoscopic mucosal resection.

but also associated with submucosal invasive cancer or increasingly recognized to be part of the biology of certain LSL subtypes such as nongranular lesions. Nonlifting may be overcome by other published techniques including hot avulsion [16, 17], forced APC using a saline cushion [18], and needle-knife incision of the LSL margin [19] prior to snare resection. However, these techniques are limited to case series and tertiary institutions, and in our experience patients with nonlifting LSLs are often referred for surgery. tsEMR may offer an alternative to treating nonlifting adenoma, as 16/18 such lesions were resected successfully.

Other reasons for failure of ssEMR and need for tsEMR are without a clear single-session solution. Access to the lesion was the second most common reason for cases requiring tsEMR. In 14/16 of these cases, complete excision of residual adenoma was achieved. This highlights a potential benefit of tsEMR – retraction of the mucosal defect via scarring and exposure of residual adenoma. In addition, with the knowledge of particular complexities of the previous procedure, one can of course employ an alternative approach to optimize access: different endoscope, a short transparent cap, patient position, etc.

Younger patients, lesions with high grade dysplasia, and lesions with large Is components were more likely to be referred for surgery rather than tsEMR when ssEMR failed. These factors highlight the benefits of tsEMR and the situations in which it is most useful. The disadvantages of surgery compared with EMR [2] are magnified with advancing age and co-morbidity. If the patient, their family, and the physician agree that resection of the LSL is appropriate, tsEMR may offer an attractive solution. Large Is components may be a marker for particularly difficult EMR procedures and the endoscopist must consider the patient and their future trajectory; for example, if a lesion is complex to resect and these difficulties will likely be encountered again at the tsEMR procedure in a surgically fit patient, then surgery is likely the better option. High grade dysplasia in the histology of the first EMR may be a marker for more serious unresected pathology or propagation of adenoma in between procedures, and these lesions should not wait for definitive treatment.

The commonest techniques employed to resect residual adenoma at tsEMR were further snare resection with or without additional thermal therapy in almost 80 %, and cold forceps avulsion with adjuvant snare tip soft coagulation after its introduction in mid-2012. The ability to ensnare adenoma that was previously inaccessible was mainly due to the retraction effect of scarring discussed above. Failure of tsEMR was predicted only by increasing lesion size and this group contained some very large lesions (maximum diameter 120 mm).

There is a large body of evidence for the safety and efficacy of ssEMR [20 – 22]; owing to its superior safety profile compared with surgery, and simplicity compared with endoscopic submucosal dissection, it has become the primary technique for the treatment of LSLs. As the tsEMR technique is analogous to ssEMR, one would expect a similar complication profile. In this series, a single adverse event involving uncontrolled bleeding was resolved with angioembolization, and was attributed to the scarred area from the initial EMR being fibrotic and therefore difficult to close with endoscopic clips. There were no episodes of delayed perforation or delayed bleeding at tsEMR.

Rates of RRA after tsEMR were significantly higher than those seen after ssEMR of naïve and previously attempted LSLs. In addition, rates of surgery at SC2 and SC3 were significantly higher than lesions that underwent ssEMR of naïve LSL, and need for surgery was related to an inability to resect the RRA endoscopically in all but one case. Overall, however, LSLs that underwent first follow-up examination after successful tsEMR for benign disease avoided surgery in > 80 % of cases to longest follow-up, and there was no evidence that propagation of residual adenoma between procedures led to invasive malignancy.

Several important considerations flow from the high rates of RRA and surgery after tsEMR. First, meticulous follow-up is required with careful attention to the EMR scar [23]. This should be performed at the tertiary center that undertook the resection, particularly for SC1, and if there is any doubt, biopsies should be taken from the EMR scar. RRA should be treated using standard techniques [24]. Second, comprehensive information must be communicated to the patient, with agreement from both parties, prior to embarking upon a tsEMR strategy. In particular, patients must understand that more procedures will be required to achieve adenoma clearance with tsEMR than ssEMR, and that this may translate into lost work days or morbidity related to the procedure or bowel preparation. They must also understand that compliance with follow-up examinations is mandatory. The metachronous cancer detected in a patient at SC1 serves as a reminder to practitioners of the need to inspect the whole colonic mucosal surface when undertaking surveillance procedures after EMR of LSLs [25].

tsEMR may be viewed by some authorities as a means to complete procedures that the endoscopist should not have initially attempted as they were too complex for their skillset. Indeed, splitting our cohort into two time periods showed that the rate of ssEMR in lesions attempted increased over the second 4-year period. This is almost certainly due to the technical skill and increased understanding of the study endoscopists. However, while the need for tsEMR decreased, the proportion of lesions referred for tsEMR vs. surgery did not change and this suggests a role for the procedure independent of the skill of the endoscopist. In support of this, the proportion of patients requiring tsEMR for nonlifting adenoma and access to the lesion did not change between the two periods.

The strengths of this study include the involvement of four academic tertiary referral centers, the consecutively described lesions over 8 years collected in a prospective fashion, and the meticulously described outcomes of all lesions described in the study. However, the small number of patients and retrospective description of their outcomes means that this can be at best described as a pilot study. There were also insufficient data available for a meaningful analysis of histological assessment of the EMR scar later than SC1. There was a high rate of dropout between SC1 and later examinations, particularly patients not attending for surveillance because of age and/or co-morbidity. Of course, this has much to do with the cohort that will benefit the most from tsEMR, but also describes the nature of medicine

in rural Australia, where attendance at a tertiary center many miles from the patient's home is often not practical.

In conclusion, this study demonstrates the feasibility of the previously unreported technique of completing an EMR procedure at a separate session. tsEMR is a safe and effective technique which, although cannot be recommended as a first-line therapy, can be a useful salvage therapy when ssEMR fails at a tertiary endoscopy center, particularly when surgery is not preferred or not possible. Such lesions may be expected to be encountered more frequently as EMR becomes the primary technique for resection of LSLs. Compliance with high quality endoscopic surveillance is mandatory as RRA is common.

Acknowledgment

The Cancer Institute New South Wales provided funding for a research nurse and data manager to assist with the administration of the study. There was no influence from the Institution regarding study design or conduct, data collection, management, analysis or interpretation, or preparation, review, or approval of the manuscript.

Competing interests

None

References

[1] Jayanna M, Burgess NG, Singh R et al. Cost analysis of endoscopic mucosal resection vs surgery for large laterally spreading colorectal lesions. Clin Gastroenterol Hepatol 2016; 14: 271 – 272

[2] Ahlenstiel G, Hourigan LF, Brown G et al. Actual endoscopic versus predicted surgical mortality for treatment of advanced mucosal neoplasia of the colon. Gastrointest Endosc 2014; 80: 668 – 676

[3] Moss A, Bourke MJ, Williams SJ et al. Endoscopic mucosal resection outcomes and prediction of submucosal cancer from advanced colonic mucosal neoplasia. Gastroenterology 2011; 140: 1909 – 1918

[4] Buchner AM, Guarner-Argente C, Ginsberg GG. Outcomes of EMR of defiant colorectal lesions directed to an endoscopy referral center. Gastrointest Endosc 2012; 76: 255 – 263

[5] Nanda KS, Tutticci N, Burgess NG et al. Endoscopic mucosal resection of laterally spreading lesions involving the ileocecal valve: technique, risk factors for failure, and outcomes. Endoscopy 2015; 47: 710 – 718

[6] Tate DJ, Desomer L, Hourigan LF et al. Endoscopic mucosal resection of laterally spreading lesions around or involving the appendiceal orifice (PA LSLs): technique, risk factors for failure and outcomes of a tertiary referral cohort. Gastrointest Endosc 2016; 83: AB144

[7] Holt BA, Bassan MS, Sexton A et al. Advanced mucosal neoplasia of the anorectal junction: endoscopic resection technique and outcomes (with videos). Gastrointest Endosc 2014; 79: 119 – 126

[8] Bassan MS, Holt B, Moss A et al. Carbon dioxide insufflation reduces number of postprocedure admissions after endoscopic resection of large colonic lesions: a prospective cohort study. Gastrointest Endosc 2013; 77: 90 – 95

[9] Holt BA, Bourke MJ. Wide field endoscopic resection for advanced colonic mucosal neoplasia: current status and future directions. Clin Gastroenterol Hepatol 2012; 10: 969 – 979

[10] ERBE VIO 300 D. Product Information Guide.https://www.erbe-med.com/erbe/media/Marketingmaterialien/85140-120_ERBE_EN_-VIO_D__D024759.pdf

[11] Moss A, Field A, Bourke MJ et al. A randomized, double-blind trial of succinylated gelatin submucosal injection for endoscopic resection of large sessile polyps of the colon. Am J Gastroenterol 2010; 105: 2375 – 2382

[12] Swan MP, Bourke MJ, Moss A et al. The target sign: an endoscopic marker for the resection of the muscularis propria and potential perforation during colonic endoscopic mucosal resection. Gastrointest Endosc 2011; 73: 79 – 85

[13] Burgess NG, Metz AJ, Williams SJ et al. Risk factors for intraprocedural and clinically significant delayed bleeding after wide-field endoscopic mucosal resection of large colonic lesions. Clin Gastroenterol Hepatol 2014; 12: 651 – 661

[14] Lee EY, Bourke MJ. EMR should be the first-line treatment for large laterally spreading colorectal lesions. Gastrointest Endosc 2016; 84: 326 – 328

[15] Pohl H, Srivastava A, Bensen SP et al. Incomplete polyp resection during colonoscopy – results of the complete adenoma resection (CARE) study. Gastroenterology 2013; 144: 74 – 80.e1

[16] Veerappan SG, Ormonde D, Yusoff IF et al. Hot avulsion: a modification of an existing technique for management of nonlifting areas of a polyp (with video). Gastrointest Endosc 2014; 80: 884 – 888

[17] Andrawes S, Haber G. Avulsion: a novel technique to achieve complete resection of difficult colon polyps. Gastrointest Endosc 2014; 80: 167 – 168

[18] Tsiamoulos ZP, Bourikas LA, Saunders BP. Endoscopic mucosal ablation: a new argon plasma coagulation/injection technique to assist complete resection of recurrent, fibrotic colon polyps (with video). Gastrointest Endosc 2012; 75: 400 – 404

[19] Chedgy F, Bhattacharyya R, Kandiah K et al. Knife-assisted snare resection: a novel technique for resection of scarred polyps in the colon. Endoscopy 2016; 48: 277 – 280

[20] Moss A, Williams SJ, Hourigan LF et al. Long-term adenoma recurrence following wide-field endoscopic mucosal resection (WF-EMR) for advanced colonic mucosal neoplasia is infrequent: results and risk factors in 1000 cases from the Australian Colonic EMR (ACE) study. Gut 2014; 64: 57 – 65

[21] Hassan C, Repici A, Sharma P et al. Efficacy and safety of endoscopic resection of large colorectal polyps: a systematic review and meta-analysis. Gut 2016; 65: 806 – 820

[22] Repici A, Pellicano R, Strangio G et al. Endoscopic mucosal resection for early colorectal neoplasia: pathologic basis, procedures, and outcomes. Dis Colon Rectum 2009; 52: 1502 – 1515

[23] Desomer L, Tutticci N, Tate DJ et al. A standardized imaging protocol is accurate in detecting recurrence after EMR. Gastrointest Endosc 2017; 85: 518 – 526

[24] Klein A, Bourke MJ. Advanced polypectomy and resection techniques. Gastrointest Endosc Clin N Am 2015; 25: 303 – 333

[25] Bick BL, Ponugoti PL, Rex DK. High yield of synchronous lesions in referred patients with large lateral spreading colorectal tumors. Gastrointest Endosc 2017; 85: 228 – 233