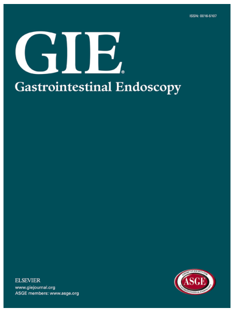
Accepted Manuscript



Endoscopic mucosal resection of laterally spreading lesions around or involving the appendiceal orifice: technique, risk factors for failure, and outcomes of a tertiary referral cohort (with video)

David J. Tate, Lobke Desomer, Halim Awadie, Kathleen Goodrick, Luke Hourigan, Rajvinder Singh, Stephen J. Williams, Michael J. Bourke

PII: S0016-5107(18)30003-8

DOI: 10.1016/j.gie.2017.12.018

Reference: YMGE 10876

To appear in: *Gastrointestinal Endoscopy*

Received Date: 13 July 2017

Accepted Date: 3 December 2017

Please cite this article as: Tate DJ, Desomer L, Awadie H, Goodrick K, Hourigan L, Singh R, Williams SJ, Bourke MJ, Endoscopic mucosal resection of laterally spreading lesions around or involving the appendiceal orifice: technique, risk factors for failure, and outcomes of a tertiary referral cohort (with video), *Gastrointestinal Endoscopy* (2018), doi: 10.1016/j.gie.2017.12.018.

ENDOSCOPIC MUCOSAL RESECTION OF LATERALLY SPREADING LESIONS AROUND OR INVOLVING THE APPENDICEAL ORIFICE: TECHNIQUE, RISK FACTORS FOR FAILURE, AND OUTCOMES OF A TERTIARY REFERRAL COHORT (WITH VIDEO)

DAVID J TATE[1,2], LOBKE DESOMER[1], HALIM AWADIE[1], KATHLEEN GOODRICK[1], LUKE HOURIGAN[3,4], RAJVINDER SINGH[5], STEPHEN J WILLIAMS[1], MICHAEL J BOURKE[1,2*]

[1] Westmead Hospital, Sydney, Australia; [2] Westmead Clinical School, The University of Sydney, Sydney, Australia; [3] Department of Gastroenterology and Hepatology, Princess Alexandra Hospital, Brisbane QLD; Australia; [4]Gallipoli Medical Research Institute, School of Medicine, The University of Queensland, Greenslopes Private Hospital, Brisbane QLD; Australia; [5]Lyell-McEwan Hospital, Adelaide

Contribution statement:

David J Tate	Proceduralist, collected data, analyzed data, wrote manuscript, revised manuscript after co-authors remarks
Lobke Desomer	Proceduralist, collected data, analyzed data, reviewed manuscript
Halim Awadie	Proceduralist, collected data, analyzed data, reviewed manuscript
Kathleen Goodrick	Collected data, collated data prior to final analysis
Luke Hourigan	Proceduralist, collected data, reviewed manuscript
Rajvinder Singh	Proceduralist, collected data, reviewed manuscript
Stephen J Williams	Proceduralist, collected data, analyzed data, reviewed manuscript
Michael J Bourke	Chief investigator, study conception and design, proceduralist, collected data, reviewed manuscript

WORD COUNT

Abstract, 247 words

Body, 3301 words

ABBREVIATIONS

LSL – laterally spreading lesion

PA-LSL – peri-appendiceal laterally spreading lesion

AO – appendiceal orifice

HDWL – high definition white light

NBI – narrow band imaging

EMR – endoscopic mucosal resection

SMIC – submucosal invasive cancer

IQR – interquartile range

STD – standard deviation

CORRESPONDING AUTHOR:

Professor Michael J Bourke

Suite 106a 151-155 Hawkesbury Road

Westmead NSW 2145

Phone: (02)-9633 5953

Fax: (02)-9633 3958

CONFLICT OF INTEREST STATEMENT:

David J Tate	Dr David Tate received a scholarship from the "Westmead Medical Research Foundation". These funds were not used for this study. No other relevant disclosures exist.
Lobke Desomer	No financial disclosures exist
Halim Awadie	No financial disclosures exist
Kathleen Goodrick	No financial disclosures exist
Luke Hourigan	
Rajvinder Singh	No financial disclosures exist
Stephen J Williams	No financial disclosures exist
Michael J Bourke	No financial disclosures exist

FUNDING STATEMENT:

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.

ABSTRACT

BACKGROUND AND AIMS

Endoscopic mucosal resection (EMR) of peri-appendiceal sessile laterally spreading lesions (PA-LSLs) is technically demanding due to poor endoscopic access to the appendiceal lumen and the thin colonic wall at the base of the cecum. We aimed to assess the feasibility and safety of EMR for PA-LSLs.

METHODS

Consecutive LSLs ≥20 mm and PA-LSLs ≥10 mm detected at 3 academic endoscopy centers from September 2008 until January 2017 were eligible. Prospective patient, procedural, and lesion data were collected. PA-LSLs were compared with LSLs in other colonic locations.

RESULTS

Thirty-eight PA-LSLs were compared with 1721 LSLs. Referral for surgery without an attempt at EMR was more likely with PA-LSLs (28.9% vs 5.1%, $P < .001$) and those that involved a greater percentage of the appendiceal orifice (AO) were less likely to be attempted ($P = .038$). The majority (10/11) of PA-LSLs were not attempted due to deep extension into the appendiceal lumen; 2 of 11 of these surgical specimens contained invasive cancer. Once attempted, complete clearance of visible adenoma (92.6%[PA-LSL] versus 97.6%[LSL], $p=.14$), adverse events, and rates of adenoma recurrence did not vary significantly between PA-LSLs and LSLs. Seven of 7 patients with prior appendicectomy achieved complete adenoma clearance. There were no cases of post-EMR appendicitis. Twenty of 22 (91%) PA-LSLs eligible for surveillance avoided surgery to longest follow-up.

CONCLUSIONS

EMR is a safe, effective and durable treatment for PA-LSLs when specific criteria are fulfilled. If the distal margin of the PA-LSL within the appendiceal orifice cannot be visualized or more than 50% of the circumference of the orifice is involved, surgery should be considered. Clinicaltrials.gov (NTC01368289).

BACKGROUND AND STUDY AIMS

Endoscopic mucosal resection (EMR) of laterally spreading colonic lesions (LSLs) has gained widespread acceptance due to cost[1] and morbidity[2] advantages in comparison with surgery. Most procedures are performed on an outpatient basis and in long-term follow-up >95% are cured[3]. However, endoscopic resection of lesions involving the appendiceal orifice (peri-appendiceal LSLs, PA-LSLs) is technically more challenging and such lesions are often managed surgically. Reasons for this complexity are mainly anatomical; the appendix is a narrow blind-ended tube, which cannot be accessed endoscopically and the colonic wall in the cecum is the thinnest of the entire colon. In addition, serrated and tubulovillous adenomas involving the appendix may be more aggressive than their counterparts throughout the rest of the colon[4].

PA-LSLs are relatively uncommon, and technical data regarding how to safely and effectively perform endoscopic resection of such lesions are sparse. Recently an expert multicenter study from Japan[5] described the successful endoscopic submucosal dissection of 76 PA-LSL. Only 40% of these lesions actually involved the appendiceal orifice (AO); however, and such experience with this technique is seldom available in Western centers.

EMR is the current standard of care for the management of LSLs; however, the medical literature regarding EMR for PA-LSLs is limited to a report using "underwater" EMR [6]. It is currently unknown whether standard inject and resect EMR for PA-LSL is safe or effective or which lesion features predict success or failure. The present study is a description of the technical aspects, outcomes, and safety for PA-LSL referred for EMR to 3 tertiary referral centers in Australia over an 8-year period.

PATIENTS, MATERIAL AND METHODS

Data were collected and analyzed within a multicenter, prospective observational cohort study of patients referred for EMR of LSLs performed at 3 academic, tertiary referral centers in Australia from September 2008 until January 2017. Consecutive LSLs ≥20 mm and PA-LSLs ≥10 mm were eligible for inclusion.

Demographic, lesion and procedural data was collected on all patients prospectively. Adverse events were assessed at 2 weeks after the procedure by structured telephone interview with the patient. Surveillance examinations were scheduled at desired intervals of 4 to 6 months (first surveillance, SC1) and 18 months (second surveillance, SC2) after the index procedure.

<u>Definitions</u>

LSLs were defined as PA-LSLs when they involved, or were located within 5 mm of the appendiceal orifice (AO). Circumference of involvement of the AO was recorded to the nearest 25%. Deep extension into the AO was recorded if the distal margin of the lesion within the AO could not be visualized.

An attempt at EMR was defined by first snare placement and resection of tissue. Size of LSL was described relative to an open snare of known diameter. Complete snare excision described resection of LSL with no additional modality other than snare. Technical success was defined as complete clearance of visible adenoma. Duration of procedure described time from first submucosal injection to completed EMR. Intraprocedural bleeding (IPB) was described if bleeding during the procedure required endoscopic control. Deep injury to the colonic wall was recorded relative to the Sydney Classification of Deep Mural Injury[7]. Delayed bleeding was recorded if the patient required admission to hospital or repeat intervention after they had left the endoscopy room. Recurrence was described if there was endoscopic evidence of residual or recurrent adenoma at the EMR scar during surveillance colonoscopy. Histologic recurrence described histologic evidence of recurrence at the EMR scar. Late recurrence described recurrence after a previously negative surveillance examination.

Exclusions

Multiple lesions in the same patient were excluded due to the possibility of correlated observations for a single patient. Patients in the active arm of the Soft Coagulation for the prevention of Adenoma Recurrence, "SCAR" randomized trial (NCT01789749) were excluded because there is potential that their outcomes differ significantly from standard inject and resect endoscopic mucosal resection. Similarly patients who underwent snare tip soft coagulation to the lesion margin outside the SCAR study and patients undergoing 2-stage EMR were excluded.

EMR Procedures

Senior endoscopists with extensive EMR experience or senior endoscopy fellows under their direct supervision performed all procedures. A microprocessor-controlled electrosurgical generator (VIO 300D; ERBE Elektromedizin, Tübingen, Germany)[8] was used. The submucosal injectate comprised of succinylated gelatin (Gelofusine; B. Braun Australia Pty Ltd, Bella Vista, Australia)[9] with indigo carmine blue (80 mg/ 500 mL solution) and 1:10,000 epinephrine (1 mL/10-mL injection). Methylene blue was substituted occasionally when indigo carmine blue was unavailable. Sedation was with a combination of midazolam, fentanyl and propofol.

A standardized, previously described inject-and-resect technique[10] was used for EMR of LSLs. Each lesion was carefully assessed using high-definition white light and narrow-band imaging (NBI) [Olympus, Tokyo, Japan] to evaluate morphology and pit pattern. For PA-LSL, an attempt was made to assess deep extension into the AO before endoscopic resection; if this was detected the patient was referred for surgery.

Once a decision had been made to attempt the lesion, careful, small-volume injection of chromogelofusine was made so as not to occlude the appendiceal orifice and obscure visualization of the distal aspect of the lesion. For resections around the AO, a 10-mm snare thin-wire snare was used (eg, Captivator II [Boston Scientific, Mass, USA] or TeleMed Hexagonal Snare [Telemed Systems, Mass, USA]) to maximize tissue capture. Care was taken throughout the resection to ensure deep extension into the AO had not been revealed after removal of surrounding adenoma. Small areas of residual adenomatous tissue that eluded snare capture were treated with argon plasma coagulation (before 2012) or forceps avulsion with adjuvant snare tip soft coagulation [ERBE Soft Coagulation, Effect 4, 80W] thereafter. Examples of the EMR of PA-LSLs are shown in **Figures 1, 2, and 3** and **Video 1.**

After EMR patients were observed for 4 hours and discharged home if well; a clear fluid diet was recommended until the next morning.

At SC1 and SC2, the EMR scar was located and it was assessed under high-definition white light and NBI according to our standardized scar assessment protocol[11]. If there was suspicion for recurrent adenoma, this was removed with a snare or forceps avulsion with adjuvant snare tip soft coagulation and the margins of the resection site over the scar treated with snare tip soft coagulation. If patients were referred for surgery, details of the surgical outcomes and the resection specimen were obtained from the relevant institution.

Statistical Analysis

PA-LSL were compared with LSL. Statistical analysis was performed using SPSS version 22 (IBM, Chicago, Ill) with 2-tailed t-test used for normally distributed continuous variables, Mann Whitney U test for skewed continuous variables and chi-squared test or the Fisher exact test for categorical variables. Significance of *P* was regarded at $p < .05$.

RESULTS

A total of 2119 patients (2376 LSL) were recruited over the study period (**Figure 4**). After exclusions, 38 PA-LSLs and 1721 LSLs were included in the study. The mean age of patients with PA-LSL was 68.1 years (standard deviation [SD] 11.8) versus 67.7 years (SD 11.8, P=.82). Thirteen of 38 (34.2%) in the PA-LSL group were male versus 905 of 1721 (52.6%, P=.025). Eight of 38 (21%) patients with PA-LSLs had undergone prior appendicectomy.

LESION ASSESSMENT

Median size of PA-LSLs was 13 mm (interquartile range [IQR] 20-30) and was smaller than LSLs , median size 35 mm (IQR 25-50, P < .001) **[Table 1]**. Lesion morphology and Kudo classification were broadly similar between PA-LSLs and LSLs. PA-LSLs were more commonly Paris classification 0-IIa (71.1%) than LSLs (48.4%), P =.06.

Six of 38 (22%) PA-LSL did not involve the AO but were located within 5 mm thereof. A further 8 (21%) involved 25% of the AO circumference, 13 (34%) involved 50%, 2 (5%) involved 75% and 9 (24%) involved 100% [**Supplementary table 1**]. Ten (32%) PA-LSLs extended deeply into the appendiceal lumen; in 2 of these cases this was not revealed until midway through the EMR procedure.

EMR PROCEDURES

EMR was attempted in 27 of 38 (71.1%) PA-LSLs versus 1634 of 1721 LSL (94.9%; p <.001). Reasons for not attempting PA-LSLs were deep extension into the AO in 10 of 11 (91%) and concern for submucosal invasive cancer (SMIC) in 2 of 11 (18%). Reasons for not attempting LSLs were concern for SMIC in 65 of 87 (75%) and technical reasons in the remainder.

Submucosal fibrosis within the EMR defect was more common in PA-LSLs undergoing EMR (14/27, 51.9%) versus LSL (405/1634, 24.8%, P < .001), and complete snare excision was lower in the PA-LSL group (18, 66.7%) versus the LSL group (1287, 78.8%, p=.13). Adjuvant modalities used to assist resection in the PA-LSL group were APC in 6 of 27 (22.2%) cases and forceps biopsy with adjuvant snare tip soft coagulation in 3 (11.1%). Procedures were of similar median duration (23 vs 20 min, p=.319). Technical success of EMR was not different between the PA-LSL group (25/27, 92.6%) and the LSL group (1595/1634, 97.6% P=.14). Lesions achieving technical success in the PA-LSL group involved a smaller percentage of the AO (P=.038) and did not deeply involve the AO (P<.001). Seven of 7 patients with a prior appendicectomy attempted for EMR achieved technical success **[Table 2]**.

The rates of intraprocedural bleeding (7, 25.9% [PA-LSL] vs 254, 15.5% [LSL], P=.18) and occurrence of deep injury to the colonic wall (P=.61) did not differ between the cohorts. Histological type and dysplasia grade did not vary between the cohorts. There was no SMIC in histological specimens after EMR of PA-LSL versus 116 of 1634 (7.1%) after EMR of LSL, P=.25.

Post Procedural Adverse Events

Three patients in the PA-LSL cohort were admitted overnight after the procedure. One patient was admitted directly for significant pain with a normal CT scan, required supportive measures only and was discharged the next day. The other 2 patients were admitted due to delayed bleeding; this occurred at a similar rate in the PA-LSL cohort (2/27, 7.4%) as the LSL cohort (93/1634, 7.1%, P=.67). There were no delayed perforations in the PA-LSL cohort versus 4 (0.2%) in the LSL cohort (p=1.000).

Follow-Up

The outcomes of PA-LSL are summarized in **Figure 4**. Twenty-two PA-LSL (22/22 (100%) due surveillance) underwent first follow-up (SC1) at median 5.7 months. Recurrence was detected in 5 of 22 (22.7%) and was treated endoscopically in 3 of 5 (60%) cases. Two of 5 recurrences measured between 2 mm and 5 mm, 2 of 5 were between 5.1 and 10mm, and 1 of 5 was >10 mm. Histologic confirmation of recurrence was available in 2 of 5 cases. 2 patients were referred for surgery due to inability to resect recurrence. One of these patients, having undergone a successful EMR of a 30 mm peri-appendiceal lesion, had attempted hot snare excision of a 5 mm recurrence at the edge of the EMR scar; this led to a full-thickness perforation that could not be closed endoscopically. The patient was referred for surgery and underwent emergency right hemicolectomy with no long-term adverse event. In comparison LSL recurred with similar frequency (186/1263, 14.7%, P=.36). One hundred sixty-nine (91%) were treated endoscopically and 17 (1.3%) required surgery due to inability to resect recurrence.

Fourteen (/15 (93%) due surveillance) PA-LSL (underwent second follow-up (SC2) at median 18 months after index EMR. Recurrence was detected in 1 of 14 (7.1%) cases. The previous surveillance procedure had been clear. This recurrence was successfully treated endoscopically. Of those PA-LSL undergoing surveillance colonoscopy 20 of 22 (91%) avoided surgery to longest follow-up. In comparison 52 of 751 (6.9%) patients with LSL experienced recurrence (P=1.0), of which 29 (3.9%) were late recurrences (P=1.0). Forty-nine of 52 (94%) were treated endoscopically, and 3 of 52 required surgery. A total of 1243 of 1263 (98%) LSL and 20 of 22 (91%) PA-LSLs undergoing surveillance colonoscopy avoided surgery to longest follow-up.

Details of PA-LSL Referred For Surgery

Thirteen of 38 (34%) patients with PA-LSLs were referred for surgery within 2 weeks of the index procedure, 11 without an attempt at EMR and 2 after technical failure of EMR **[Supplementary Table 2]**. Although this was higher than LSL (237/1721, 13.8%), after EMR was attempted rates of surgery were similar between the cohorts (2/27, 7.4% [PA-LSL] versus 111/1634, 6.8% [LSL], P=.71). **Figure 5** demonstrates examples of PA-LSL referred directly for surgery.

Ten patients with a PA-LSL underwent laparoscopic right hemicolectomy and 3 patients laparoscopic caecectomy. Two of 11 (18.2%) patients with endoscopic evidence of deep extension into the AO had evidence of invasive carcinoma in the surgical specimen. No malignant histology was found in patients who achieved technical success at EMR. One patient experienced significant wound haematoma and malunion of their abdominal wound after laparascopic caecectomy with a protracted inpatient stay. Other surgical outcomes were successful and uneventful in terms of adverse events.

Discussion

Endoscopic mucosal resection is the standard of care for colorectal LSLs without evidence of submucosal invasive cancer. We present a prospective cohort study of EMR of PA-LSLs in comparison to those in other colonic locations. The results demonstrate that EMR is a safe and effective technique for the management of PA-LSLs. Meticulous case selection is required. If there is no endoscopic imaging evidence of SMIC and provided the distal margin of the lesion can be visualized within the appendiceal orifice, 91% of patients who underwent surveillance colonoscopy avoided surgery to a median of 18 months.

Although there are few reports of standard EMR to remove PA-LSLs other techniques have been explored. Binmoeller et al[6] described the use of 'Underwater EMR' to remove 27 PA-LSLs involving the AO. The distance from the AO was not defined although 22 of 27 were described as extending into the AO. Median lesion size was 15 mm, significantly smaller than this study. Technical success was 89% although the cohort from which these patients originate was not described, and therefore no comparator arm was provided. In addition, although 91% of PA-LSLs underwent follow-up with residual adenoma in 10%, median follow-up was only 29 weeks. One of the resected specimens contained invasive cancer and 2 of 27 patients experienced post-polypectomy syndrome, perhaps highlighting the difficulties of lesion and defect assessment underwater and without a chromic dye.

Recently an expert multicenter study from Japan[5] described the endoscopic submucosal dissection (ESD) of 76 PA-LSLs. Although over 60% of the lesions (median size 49 mm) did not involve the AO (definition included up to 12 mm from AO), impressive rates of en bloc resection (94.7%) and R0 resection (89.5%) were achieved. Zero of 63 patients undergoing follow-up experienced recurrence. Such expertise, although admirable, is not available in the vast majority of Western centers. In addition, the opportunity cost for this procedure (mean duration 91 minutes versus 20 minutes in this study) is high for benign disease (2/76 lesions had SMIC at histology, both had SM2 disease and underwent surgery). Of note appendicitis was experienced in 2 of 76 patients in this study.

A similarly contemporary study, while examining the feasibility of endoscopic full-thickness resection (EFTR) for colorectal LSLs[12], included 5 cases of PA-LSL. Two of 5 could not be successfully resected en bloc. One-third that were resected had a positive peripheral margin of the specimen for adenoma. Appendicitis was not observed in the 3 successful cases. A further study described the use of EFTR to resect 4 PA-LSL [13]. Relationship to the AO was not discussed neither was PA-LSL specific rates of complete/R0 resection. Appendicitis requiring laparascopic appendicectomy of the residual appendix was noted in 1 of the 4 cases. Despite these mediocre initial results and despite technical drawbacks of the device, the technique is conceptually appealing for this indication and further results are awaited.

No other case series has addressed EMR of PA-LSLs using standard inject and resect EMR techniques. This is surprising because EMR is the standard of care for LSLs among Western endoscopists for predicted benign disease. The present study records 38 PA-LSLs, which were assessed for EMR over an 8-year time period. These lesions are uncommon (1% of our overall cohort). Once an LSL involves the AO it is paramount to assess the degree of extension into the appendiceal lumen. This can often be performed with a biopsy forceps, manipulating the LSL in an attempt to visualize the distal extent. In this series we did not perform EMR if the lesion extended beyond visualization within the AO. This approach is borne out by the surgical specimens from patients who had deep extension into the AO in which 2 of 12 (17%) specimens contained invasive cancer. In 2 cases of deep extension, it was not possible to assess the degree of extension before resection, this only becoming clear midway through the resection. These resections were terminated when the degree of extension became clear. Neither of these specimens contained invasive cancer.

PA-LSLs present the endoscopist with particular technical challenges. Access to the base of the cecum is often difficult. The colonic wall at the base of the cecum is thin; this necessitates precise direction of submucosal injection (tangential to the lesion) to prevent transmural injection and its attendant risks. Submucosal fibrosis is common in this location (observed in over 50% of PA-LSLs in this study) and may hamper tissue capture. For this reason we prefer a stiff, thin-wire snare in this location. Adjuvant techniques such as cold avulsion with adjuvant snare tip soft coagulation were necessary in over 30% of cases.

If the distal margin of the lesion within the AO can be visualized, PA-LSL EMR outcomes are very good. Technical success of PA-LSLs (93%) was similar to LSLs (98%). There was no difference in either intraprocedural or postprocedural adverse events. No resection specimens contained malignant histology. Recurrence and surgery were not more common during surveillance than LSLs. The lack of appendicitis is perhaps surprising given that 14 of 20 (70%) of attempted PA-LSLs in this study without prior appendicectomy involved the AO. We suggest that this reflects small-volume injection and careful snare placement during the procedures. We also note that we have completed resections of LSL in patients with previous appendicectomy where the LSL completely encircles the prior AO. Intense submucosal fibrosis is experienced in this situation but is technically possible **[Figure 3]**. Of two patients we have performed this procedure, both had recurrence successfully treated at surveillance.

Given the advances in laparascopic surgery with techniques to remove part of the cecum and spare the ICV[14], the data from this study will inform a careful discussion with the patient about which approach to take to the initial lesion. In particular, the patient must understand that surveillance colonoscopy and treatment of recurrence is a necessary part of the endoscopic treatment of their lesion. A suggested scheme for the management of PA-LSLs is given in **Figure 5.** If the lesion does not fulfill the stated criteria for endoscopic resection, there is high likelihood that the lesion will eventually require surgery. In this context it is hardly ethical or cost effective to attempt a resection that will commit the patient to endoscopic surveillance procedures if the risk of recurrence at those procedures or initial incomplete resection is so high that surgery will eventually be required.

Limitations of this study include the small sample size of PA-LSLs. This is due to the rarity of these lesions. PA-LSLs are often small, and we included lesions ≥10 mm whereas LSLs included were ≥20 mm; this may have provided an over stringent comparator arm and failed to highlight differences between PA-LSL and LSL. There was high compliance to follow-up for PA-LSLs and LSLs at SC1, but this was lower at SC2. If anything this likely biases toward worse reported outcomes at SC2 because we routinely followed-up patients with recurrence at the study center. Despite these drawbacks the data were prospectively collected from three tertiary endoscopy centers, and the LSL cohort derives from the same centers allowing valid comparison. The lack of males in the PA-LSL cohort is of interest and deserves further attention; this was also the case in the study of Jacob et al. [5]

In conclusion, EMR of PA-LSLs is a safe, effective and durable treatment but is technically challenging. PA-LSLs are less likely to be suitable for EMR than LSLs throughout the rest of the colon and careful assessment of the lesion at the index colonoscopy is essential. If the distal margin of the LSL within the appendiceal lumen cannot be visualized surgery is the treatment modality of choice. If the distal margin is visualized, EMR offers excellent outcomes that avoid the risks of surgery and in the vast majority of cases offers a cure for the patient.

References

1. Jayanna M, Burgess NG, Singh R, Hourigan LF, Brown GJ, Zanati SA, et al. Cost Analysis of Endoscopic Mucosal Resection vs Surgery for Large Laterally Spreading Colorectal Lesions. Clinical Gastroenterology and Hepatology. 2016 Feb;14(2):271–2.

2. Ahlenstiel G, Hourigan LF, Brown G, Zanati S, Williams SJ, Singh R, et al. Actual endoscopic versus predicted surgical mortality for treatment of advanced mucosal neoplasia of the colon. Gastrointest Endosc. 2014 Oct;80(4):668–76.

3. Moss A, Williams SJ, Hourigan LF, Brown G, Tam W, Singh R, 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. 2015;64:57–65.

4. Rubio CA. Serrated adenomas of the appendix. Journal of Clinical Pathology. 2004 Sep 1;57(9):946–9.

5. Jacob H, Toyonaga T, Ohara Y, Tsubouchi E, Takihara H, Baba S, et al. Endoscopic submucosal dissection of cecal lesions in proximity to the appendiceal orifice. Endoscopy. 2016 Aug 29;48(09):829–36.

6. Binmoeller KF, Hamerski CM, Shah JN, Bhat YM, Kane SD. Underwater EMR of adenomas of the appendiceal orifice (with video). Gastrointest Endosc. 2015 Sep;83(3):638–42.

7. Burgess NG, Bassan MS, McLeod D, Williams SJ, Byth K, Bourke MJ. Deep mural injury and perforation after colonic endoscopic mucosal resection: a new classification and analysis of risk factors. Gut. 2016 Jul 27;:gutjnl–2015–309848.

8. ERBE VIO 300 D, Product Information Guide. httpswww.erbe-med.comdemedical-technologypublicProductsElectrosurgeryUnits-and-modulesVIO----D.

9. Moss A, Field A, Bourke MJ, Metz AJ. A Randomized, Double-Blind Trial of Succinylated Gelatin Submucosal Injection for Endoscopic Resection of Large Sessile Polyps of the Colon. The American Journal of Gastroenterology. Nature Publishing Group; 2010 Nov 1;105(11):2375–82.

10. Bourke M. Endoscopic mucosal resection in the colon: A practical guide. Techniques in Gastrointestinal Endoscopy. 2011 Jan;13(1):35–49.

11. Desomer L, Tutticci N, Tate DJ, Williams SJ, McLeod D, Bourke MJ. A standardized imaging protocol is accurate in detecting recurrence after EMR. Gastrointest Endosc. 2017

Mar;85(3):518–26.

12. Schmidt A, Bauerfeind P, Gubler C, Damm M, Bauder M, Caca K. Endoscopic full-thickness resection in the colorectum with a novel over-the-scope device: first experience. Endoscopy. 2015 Jul 30;47(08):719–25.

13. Valli PV, Mertens J, Bauerfeind P. Safe and successful resection of difficult GI lesions using a novel single-step full-thickness resection device (FTRD®). Surg Endosc. 2017 Jun 29;28(1):2641.

14. Fujino S. Single-incision laparoscopic cecectomy for low-grade appendiceal mucinous neoplasm after laparoscopic rectectomy. WJGS. 2014;6(5):84.

TABLES

	PA-LSL n=38	LSL n=1721	P
Patient			
Age, mean (SD)	68.1 (11.8)	67.6 (11.8)	.82
Sex, Male, n(%)	13 (34.2)	905 (52.6)	**.025**
LSL			
Size, mm, IQR	25 (20-30)	35 (25-50)	**<.001**
Previous Attempt , n(%)	3 (7.9)	215 (12.5)	.62
Morphology, n(%)			
Granular	24 (63.2)	919 (53.4)	.42
Non granular	11 (28.9)	497 (28.9)	
Mixed	2 (5.3)	124 (7.2)	
Unable to classify	1 (2.6)	181 (10.5)	
Paris, n(%)			
0-Is	5 (13.2)	321 (18.7)	.06
0-IIa	27 (71.1)	833 (48.4)	
0-IIa,Is	5 (13.2)	382 (22.2)	
Other (IIb, IIa+c etc)	1 (2.6)	185 (10.7)	
Kudo*, n(%)			
II	2 (5.3)	193 (11.8)	.340
III	10 (26.3)	500 (30.6)	
IV	25 (65.8)	832 (50.9)	
V	1 (2.6)	111 (6.8)	
Attempted EMR, n(%)	27 (71.1)	1634 (94.9)	**<.001**
	n=27	**n=1634**	
Procedure			
Submucosal Fibrosis, n(%)	14 (51.9)	405 (24.8)	**<.001**
Duration, min, IQR	23 (14-68)	20 (10-30)	.319
Complete snare excision , n(%)	18 (66.7)	1287 (78.8)	.13
Adjuvant technique (of remainder , n(%)			
APC	6 (22.2)	48 (2.9)	
Forceps biopsy and STSC	3 (11.1)	299 (18.3)	
Technical success, n(%)	25 (92.6)	1595 (97.6)	.14
IPB, n(%)	7 (25.9)	254 (15.5)	.18
Deep Injury, n(%)			
II	2 (7.4)	55 (3.4)	.61
III	0 (0)	37 (2.3)	
IV	0 (0)	9 (0.6)	
V	0 (0)	2 (0.1)	
Histology, n(%)			

TA	4 (14.8)	414 (25.3)	.14
TVA	17 (63.0)	945 (57.8)	
Serrated	5 (18.5)	267 (16.3)	
Other	1 (3.7)	8 (0.5)	
Dysplasia, n(%)			
None	4 (14.8)	186 (11.4)	.23
LGD	19 (70.4)	1021 (62.5)	
HGD	3 (11.1)	427 (26.1)	
Cancer, n(%)	0 (0)	116 (7.1)	.25
Post procedural AE			
Delayed bleeding, n(%)	2 (7.4)	93 (5.7)	.67
Delayed perforation, n(%)	0 (0)	4 (0.2)	1.000
Follow up			
Surgery by 2 weeks, n(%)	2 (7.4)	111 (6.8)	.71
	n=22	**n=1263**	
Time to SC1	5.7 (4.9-6.8)	5.1 (4.0-6.9)	
Recurrence at SC1, n(%)	5 (22.7)	186 (14.7)	.36
Histologic Recurrence at SC1, n(%)	2/14 (14.3)	129/574 (22.5)	.75
Surgery at SC1, n(%)	2 (9.1)	17 (1.3)	.40
	n=14	**n=751**	
Time to SC2, n(%)	18.0 (16.0-21.5)	18 (14.9-22.5)	
Recurrence at SC2, n(%)	1 (7.1)	52 (6.9)	1.0
Late Recurrence at SC2, n(%)	0 (0)	29 (3.9)	1.0
Surgery at SC2, n(%)	0 (0)	3 (0.4)	1.0

Table 1; Characteristics of PA-LSL versus LSL. PA-LSL – peri-appendiceal LSL, LSL – laterally spreading lesion, SD – standard deviation, IQR – interquartile range, APC – argon plasma coagulation, STSC – snare tip soft coagulation, LGD – low grade dysplasia, HGD – high grade dysplasia, SC1 – surveillance colonoscopy 1, SC2 – surveillance colonoscopy 2. *observations available in 1539 cases. Recurrence denotes the endoscopic detection of recurrence at an EMR scar and histologic recurrence the histologic confirmation of recurrence.

	Not Attempted n=11	**Attempted, failed n=2**	**Successful EMR n=25**	**Overall n=38**	P
Size of LSL median (mm)	20 (15-20)	28 (25-28)	25 (20-30)	25 (20-30)	**.034**
% involvement of AO, n (%)					
Within 5mm	0	0	6 (24)	6 (22)	**.038**
25%	1 (9)	0	7 (28)	8 (21)	
50%	3 (28)	2 (100)	8 (32)	13 (34)	
75%	2 (18)	0	0	2 (5)	
100%	5 (46)	0	4 (16)	9 (24)	
Deep extension into Appendiceal orifice, n (%)	10 (91)	2 (100)	0	12 (32)	**<.001**
Prior Appendicectomy, n (%)	1 (9.1)	0 (0)	7 (28)	8 (21.1)	.498
Appendicitis, n (%)	x	0 (0)	0 (0)	0 (0)	1

Table 2; Specific characteristics of PA-LSL. PA-LSL – periappendiceal LSL, LSL – laterally spreading lesion, AO – appendiceal orifice.

Figure Legends

Figure 1 – a) Half circumferential LSL at the base of the caecum extending to the appendiceal orifice. b) LSL seen to involve 50% of the appendiceal orifice. c-d) Sequential inject and resect endoscopic mucosal resection used to isolate the peri-appencieal component e). f) Thin wire snare and cold forceps avulsion (white arrow) used to remove the portion of the LSL involving the appendiceal orifice. g) Completed resection defect. h) Appearances of the endoscopic resection scar at second surveillance examination (18 months after index) with no evidence of recurrence. LSL – laterally spreading lesion.

Figure 2 – a) Peri-appendiceal LSL involving 50% circumference of the appendiceal orifice. b) Snare resection with margin of normal tissue. c) Snare resection is hampered by submucosal fibrosis. d-e) Standard biopsy forceps used to avulse residual non-lifting adenoma. f) Snare tip soft coagulation is applied to the avulsion bed. g) Completed resection with complete removal of visible adenoma. e) Surveillance colonoscopy with a well-formed scar at the appendiceal orifice 6 months after the index procedure. LSL – laterally spreading lesion.

Figure 3 – EMR in patients with prior appendicectomy. a,b) Fully circumferential PA-LSL at the AO in a patient with a previous appendicectomy. c) Sequential inject and resect has been performed to completely resect the lesion. d) At first surveillance colonoscopy a central focus of recurrent adenoma is seen overlying the EMR scar. e) Complete destruction of residual adenoma is achieved using a thin wire snare and coagulation current with snare tip soft coagulation applied to the surrounding scar. f) 35mm Paris 0-IIa LSL overlying the prior AO in another patient with prior appendicectomy. g+h) Sequential inject and resect EMR used to completely remove the lesion revealing underlying submucosal fibrosis at the site of the prior AO. LSL – laterally spreading lesion, PA-LSL, periappendiceal laterally spreading lesion, EMR – endoscopic mucosal resection, AO – appendiceal orifice.

Figure 4 – Flow of patients through the study comparing the outcomes of PA-LSL and LSL. ER – endoscopic resection, LSL – laterally spreading lesion, PA-LSL – peri-appendiceal laterally spreading lesion, SMIC – submucosal invasive cancer, SC1 – first surveillance colonoscopy, SC2 – second surveillance colonoscopy, AO – appendiceal orifice, SCAR RCT – snare tip soft coagulation for the prevention of adenoma recurrence randomized controlled trial, duplicate – smaller lesions in the same patient * indicates percentage of patients undergoing SC1 that avoided surgery to this follow up. Percentages rounded to the nearest whole number.

Figure 5 – Examples of PA-LSL that were referred directly for surgery without an attempt at EMR. a) Circumferential donut shaped LSL fully encircling the AO. b) A biopsy forceps is often useful to expose the orifice if there is doubt about deep extension. c) Large LSL at the base of the caecum seen to completely encircle the AO. d-f) Further views highlight deep extension into the appendiceal lumen beyond the limit of visualization.

Figure 6 – Suggested schema for the management of PA-LSL. High risk features for SMIC include demarcated area of Kudo V pit pattern, NICE III or Sano IIIb morphology and Paris IIa+c morphology. SMIC – submucosal invasive cancer, AO – appendiceal orifice, EMR – endoscopic mucosal resection, LSL – laterally spreading elsion, PA-LSL – periappendiceal laterally spreading lesion.

Video 1 – Video demonstrating the technique of endoscopic mucosal resection of peri-appendiceal laterally spreading lesions.

Supplementary Tables

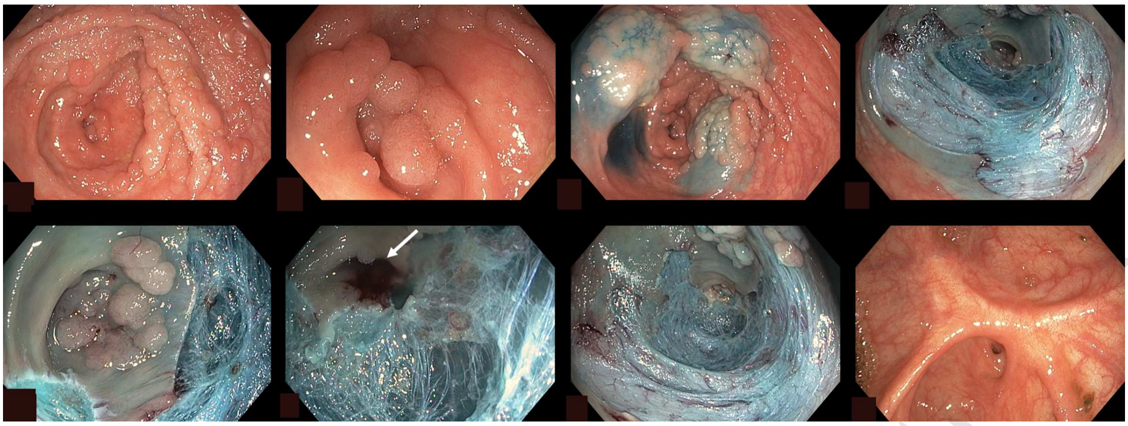
	Not involving AO n=6	<= 50% AO involved n=21	>50% AO involved n=11
Patient			
Age, mean (SD)	73.7 (5.1)	67.9 (12.1)	65.4 (13.4)
Sex, Male, n (%)	3 (50.0)	8 (38.1)	2 (18.2)
LSL			
Size, mm, IQR	27.5 (20-30)	25 (15-32.5)	25 (20-35)
Previous Attempt , n (%)	0 (0)	2 (9.5)	1 (9.1)
Morphology, n (%)			
Granular	3 (50.0)	13 (61.9)	8 (72.7)
Non granular	1 (16.7)	8 (38.1)	2 (18.2)
Mixed	2 (33.3)	0 (0)	0 (0)
Unable to classify	0 (0)	0 (0)	1 (9.1)
Paris, n (%)			
0-Is	3 (50.0)	1 (4.8)	1 (9.1)
0-IIa	3 (50.0)	16 (76.2)	8 (72.7)
0-IIa,Is	0 (0)	4 (19.0)	1 (9.1)
Other (IIb, IIa+c etc)	0 (0)	0 (0)	1 (9.1)
Kudo*, n (%)			
II	0 (0)	1 (4.8)	1 (9.1)
III	2 (33.3)	6 (28.6)	2 (18.2)
IV	4 (66.7)	14 (66.7)	7 (63.6)
V	0 (0)	0 (0)	1 (9.1)
Attempted EMR, n (%)	6 (100)	17 (81.0)	4 (36.4)
	n=6	**n=17**	**n=4**
Procedure			
Submucosal Fibrosis, n(%)	3 (50.0)	9 (52.9)	2 (50.0)

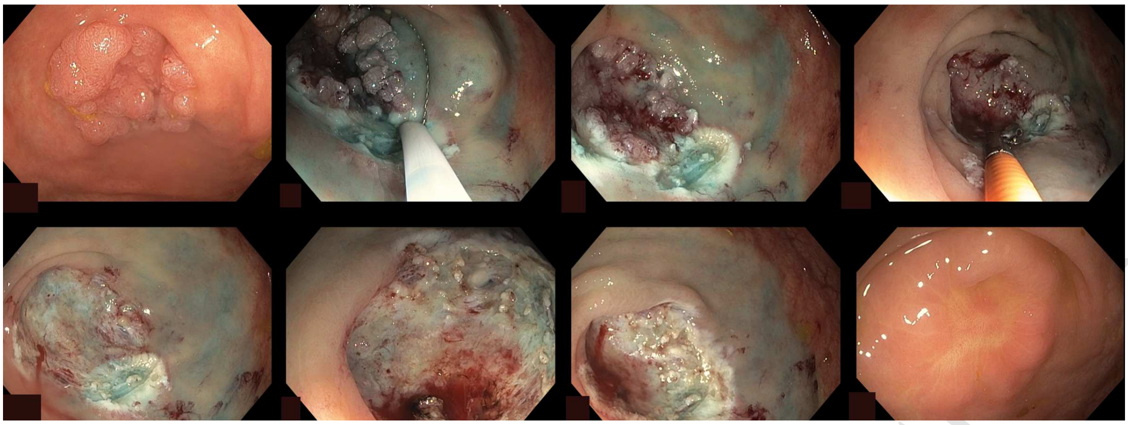
Complete snare excision , n(%)	4 (66.7)	12 (70.6)	2 (50.0)
Technical success, n(%)	6 (100)	15 (88.2)	4 (100)
IPB, n(%)	1 (16.7)	4 (23.5)	2 (50.0)
Histology, n (%)			
TA	1 (16.7)	3 (17.6)	0 (0)
TVA	3 (50.0)	11 (64.7)	3 (75.0)
Serrated	2 (33.3)	2 (11.8)	1 (25.0)
Other	0 (0.0)	1 (5.9)	0 (0)
Dysplasia, n (%)			
None	2 (33.3)	3 (17.6)	0 (0)
LGD	4 (66.7)	11 (64.7)	4 (100)
HGD	0 (0)	3 (17.6)	0 (0)
Cancer, n (%)	0 (0)	0 (0)	0 (0)
Post procedural AE			
Delayed bleeding, n(%)	0 (0)	1 (5.9)	1 (25.0)
Delayed perforation, n(%)	0 (0)	0 (0)	0 (0)
Follow up			
Surgery by 2 weeks, n (%)	0 (0)	2 (11.8)	0 (0)
	n=6	**n=12**	**n=4**
Recurrence at SC1, n (%)	3 (50.0)	1 (8.3)	1 (25.0)
	n=3	**n=9**	**n=2**
Recurrence at SC2, n (%)	0 (0)	1 (11.1)	0 (0)

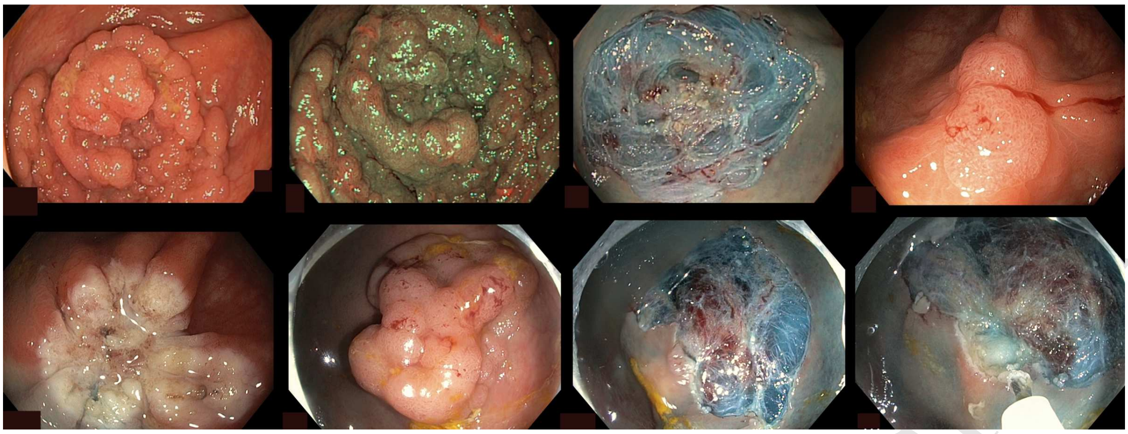
Supplementary table 1 - Characteristics of PA-LSL split by percentage involvement of the appendiceal orifice. PA-LSL – peri-appendiceal LSL, LSL – laterally spreading lesion, SD – standard deviation, IQR – interquartile range, APC – argon plasma coagulation, STSC – snare tip soft coagulation, LGD – low grade dysplasia, HGD – high grade dysplasia, SC1 – surveillance colonoscopy 1, SC2 – surveillance colonoscopy 2.

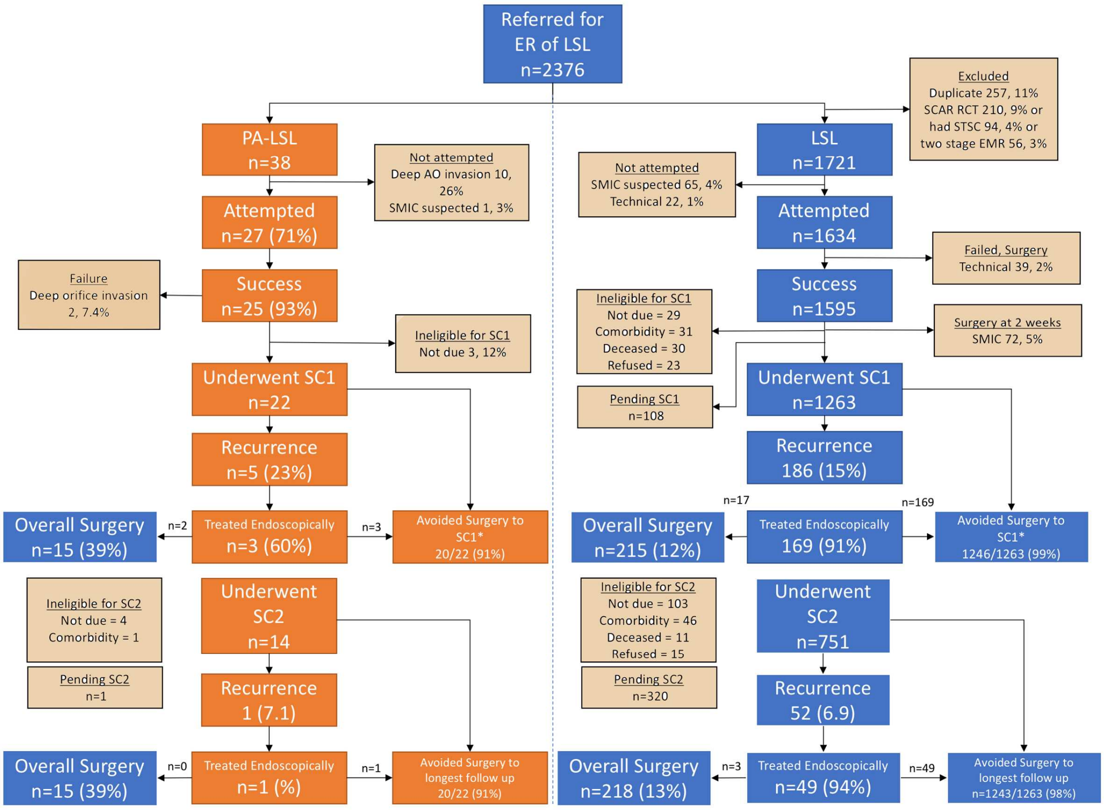
Patient		PA-LSL						Surgery			
Age (years)	**Prior Appendicectomy**	**PA-LSL size (mm)**	**EMR attempted?**	**Reason for surgery**	**%AO involved**	**Paris**	**Morphology**	**Type**	**Histology**	**(Remnant) dysplasia**	**(Remnant) malignancy**
46	No	60	No	SMIC and Deep AO	100	0-Is	G	RH	*	*	*
66	No	15	No	SMIC	50	0-IIa	G	RH	TVA	HGD	Yes
73	No	20	No	Deep AO	100	0-IIa	NG	RH	TVA	LGD	No
50	No	20	No	Deep AO	100	0-IIa	G	C	SSA	None	No
71	No	15	No	Deep AO	75	0-IIa	NG	RH	TVA	HGD	Yes
77	No	10	No	Deep AO	25	0-IIa	NG	C	SSA	None	No
65	No	10	No	Deep AO	50	0-IIa	NG	RH	TVA		Yes
77	No	15	No	Deep AO	50	0-IIa	NG	RH	TVA	LGD	No
60	No	20	No	Deep AO	100	0-IIa	G	RH	SSA	None	No
49	Yes	20	No	Deep AO	100	0-IIb	NG	RH	Tubular	LGD	No
71	No	25	No	Deep AO	75	0-IIa	G	RH	SSA	Focal HGD	No
60	No	25	Yes	Deep AO	50	0-IIa	NG	RH	TVA	LGD	No
56	No	30	Yes	Deep AO	50	0-IIa/Is	G	C	Tubular	LGD	No

Supplementary Table 2; Detailed characteristics of lesions that underwent surgery which were not attempted or failed at the index EMR. Remnant describes the presence of dysplasia or malignancy in the surgical specimen. EMR – endoscopic mucosal resection, PA-LSL – peri appendiceal laterally spreading lesion, C – caecectomy, RH – right hemicolectomy, ICV – ileo-caecal valve, G – granular, NG – non-granular, TVA – tubulovillous adenoma, S – serrated lesion, TA – tubular adenoma, time – timing within the lesion cohort (1 – first half, 2- second half), LGD – low grade dysplasia, HGD – high grade dysplasia, NL – non-lifting, SMIC – submucosal invasive cancer. All described lesions involved the AO. *In one case details of the surgical specimen are not available. Deep AO – describes deep extension into the AO. SMIC – describes suspicion for SMIC.

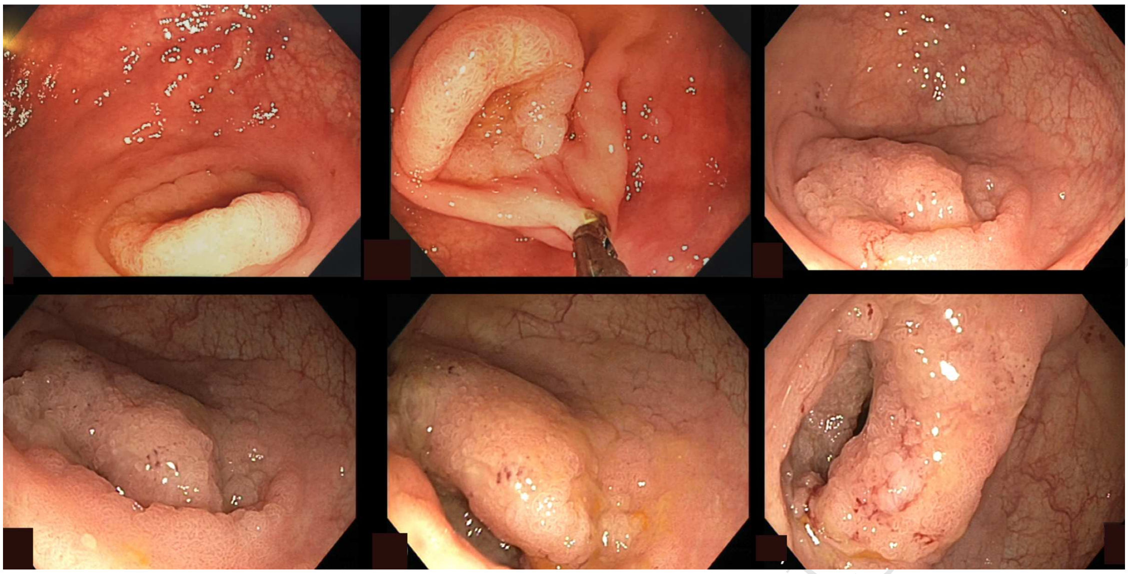


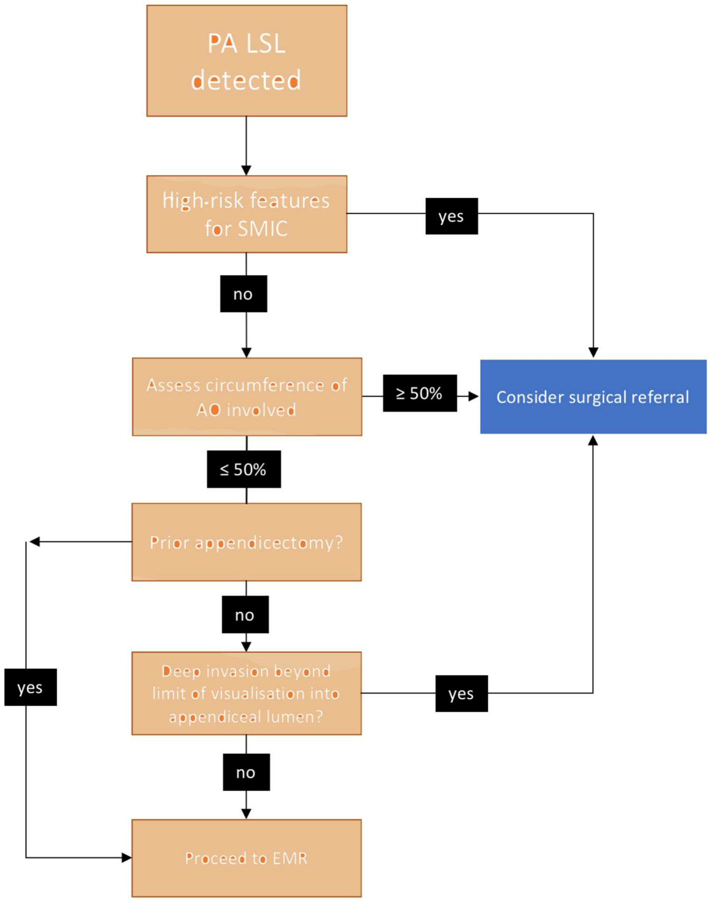






Referred for ER of LSL n=2376
PA-LSL n=38
Not attempted Deep AO invasion 10, 26% SMIC suspected 1, 3%
Attempted n=27 (71%)
Failure Deep orifice invasion 2, 7.4%
Success n=25 (93%)
Ineligible for SC1 Not due 3, 12%
Underwent SC1 n=22
Recurrence n=5 (23%)
Overall Surgery n=15 (39%)
n=2
Treated Endoscopically n=3 (60%)
n=3
Avoided Surgery to SC1* 20/22 (91%)
Ineligible for SC2 Not due = 4 Comorbidity = 1
Pending SC2 n=1
Underwent SC2 n=14
Recurrence 1 (7.1)
Overall Surgery n=15 (39%)
n=0
Treated Endoscopically n=1 (%)
n=1
Avoided Surgery to longest follow up 20/22 (91%)
Excluded Duplicate 257, 11% SCAR RCT 210, 9% or had STSC 94, 4% or two stage EMR 56, 3%
LSL n=1721
Not attempted SMIC suspected 65, 4% Technical 22, 1%
Attempted n=1634
Failed, Surgery Technical 39, 2%
Success n=1595
Ineligible for SC1 Not due = 29 Comorbidity = 31 Deceased = 30 Refused = 23
Surgery at 2 weeks SMIC 72, 5%
Pending SC1 n=108
Underwent SC1 n=1263
Recurrence 186 (15%)
n=17
n=169
Overall Surgery n=215 (12%)
Treated Endoscopically 169 (91%)
Avoided Surgery to SC1* 1246/1263 (99%)
Ineligible for SC2 Not due = 103 Comorbidity = 46 Deceased = 11 Refused = 15
Pending SC2 n=320
Underwent SC2 n=751
Recurrence 52 (6.9)
Overall Surgery n=218 (13%)
n=3
Treated Endoscopically n=49 (94%)
n=49
Avoided Surgery to longest follow up n=1243/1263 (98%)




PA LSL detected
High-risk features for SMIC
yes
no
Assess circumference of AO involved
≥ 50%
Consider surgical referral
≤ 50%
Prior appendicectomy?
no
yes
Deep invasion beyond limit of visualisation into appendiceal lumen?
yes
no
Proceed to EMR