ORIGINAL RESEARCH

Piecemeal cold snare polypectomy versus conventional endoscopic mucosal resection for large sessile serrated lesions: a retrospective comparison across two successive periods

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► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/gutjnl-2020-321753).

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Received 8 May 2020
Revised 20 October 2020
Accepted 21 October 2020

To cite: van Hattem WA, Shahidi N, Vosko S, *et al*. *Gut* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/gutjnl-2020-321753

ABSTRACT

Objective Large (≥20 mm) sessile serrated lesions (L-SSL) are premalignant lesions that require endoscopic removal. Endoscopic mucosal resection (EMR) is the existing standard of care but carries some risk of adverse events including clinically significant post-EMR bleeding and deep mural injury (DMI). The respective risk-effectiveness ratio of piecemeal cold snare polypectomy (p-CSP) in L-SSL management is not fully known.

Design Consecutive patients referred for L-SSL management were treated by p-CSP from April 2016 to January 2020 or by conventional EMR in the preceding period between July 2008 and March 2016 at four Australian tertiary centres. Surveillance colonoscopies were conducted at 6 months (SC1) and 18 months (SC2). Outcomes on technical success, adverse events and recurrence were documented prospectively and then compared retrospectively between the subsequent time periods.

Results A total of 562 L-SSL in 474 patients were evaluated of which 156 L-SSL in 121 patients were treated by p-CSP and 406 L-SSL in 353 patients by EMR. Technical success was equal in both periods (100.0% (n=156) vs 99.0% (n=402)). No adverse events occurred in p-CSP, whereas delayed bleeding and DMI were encountered in 5.1% (n=18) and 3.4% (n=12) of L-SSL treated by EMR, respectively. Recurrence rates following p-CSP were similar to EMR at 4.3% (n=4) versus 4.6% (n=14) and 2.0% (n=1) versus 1.2% (n=3) for surveillance colonoscopy (SC)1 and SC2, respectively.

Conclusions In a historical comparison on the endoscopic management of L-SSL, p-CSP is technically equally efficacious to EMR but virtually eliminates the risk of delayed bleeding and perforation. p-CSP should therefore be considered as the new standard of care for L-SSL treatment.

Significance of this study

What is already known on this subject?

- Large sessile serrated lesions (L-SSL) represent a significant portion of large non-pedunculated colorectal polyps. L-SSL are premalignant and require removal.
- Endoscopic mucosal resection (EMR) is the existing standard of care but carries a substantial risk of adverse events including post-EMR bleeding and deep mural injury (DMI).

What are the new findings?

- In comparison to EMR, piecemeal cold snare polypectomy (p-CSP) is extremely safe essentially eliminating the risk of post-EMR bleeding and DMI.
- Meanwhile, piecemeal p-CSP is technically equally efficacious to EMR with negligible recurrence in long-term follow-up.

How might it impact on clinical practice in the foreseeable future?

- Implementation of p-CSP as new standard of care in L-SSL management would dramatically improve safety outcomes minimising unscheduled hospital admissions.
- Ease of p-CSP combined with improved safety allows for multiple L-SSL to be removed in one setting, potentially reducing the number of colonoscopies required to clear the colon of lesions in patients with serrated polyposis syndrome.

INTRODUCTION

Colorectal cancer (CRC) is the third leading cause of cancer related death worldwide.[1] The vast majority of CRC develop through a stepwise malignant degeneration of precursor lesions.[2] Disruption of this process by means of endoscopic resection of precursor lesions has been shown to be effective in reducing CRC mortality.[3] Sessile serrated lesions (SSL) are recognised as an important precursor of the serrated pathway, which may give rise to as many as 30% of all cases.[4 5]

SSL are typically encountered as indistinct flat elevated lesions of the proximal colon and occur sporadically or as part of the serrated

polyposis syndrome (SPS).[6–8] Although not dysplastic at onset, focal dysplasia within SSL may evolve over time through the accumulation of epigenetic alterations.[9] In a tertiary referral cohort of lateral spreading lesions (LSL) 13.3% were L-SSL (≥20 mm) of which approximately one-third were found to have cytological dysplasia.[10] Once the barrier to dysplasia is breached, progression to cancer may be imminent.[11] Timely and complete resection of L-SSL is therefore paramount, and failure thereof has been shown to contribute to the rapid development of interval cancers.[12 13]

In a previous prospective cohort we demonstrated that L-SSL are effectively managed by endoscopic mucosal resection (EMR)[14] and current guidelines have EMR as the preferred treatment.[15 16] However, even in experienced hands EMR is associated with a risk of serious adverse events such as clinically significant post-EMR bleeding (CSPEB) and deep mural injury (DMI).[14 17 18] CSPEB requires unscheduled hospital admission posing an added burden to patients whom in the setting of SPS are often faced with consecutive colonoscopies and multiple EMR procedures to clear the entire colon of lesions.

EMR bleeding (CSPEB) and DMI.[14 17 18] CSPEB requires unscheduled hospital admission posing an added burden to patients whom in the setting of SPS are often faced with consecutive colonoscopies and multiple EMR procedures to clear the entire colon of lesions.

Cold snare polypectomy (CSP) may provide a safe alternative by omitting electrocautery-induced injury.[19] But in the piecemeal approach required for CSP treatment of L-SSL what is gained in safety[20] may be hard paid for by loss of efficaciousness. As of yet, reliable evidence on success, safety and long-term outcomes of piecemeal CSP (p-CSP) for L-SSL is lacking. In this prospective cohort we examine the utility of p-CSP in L-SSL management by comparing technical success, adverse events and recurrence to conventional EMR outcomes.

METHODS

This manuscript was created in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[21]

Study design and patients

Consecutive L-SSL (≥20 mm) enrolled at four tertiary referral sites in the Australian Colonic Endoscopic Resection (ACE) study between July 2008 and January 2020 were evaluated. The ACE study (clinicaltrials.gov identifiers: NCT01368289; NCT02000141) is a prospective, multi-centre, observational cohort of consecutive patients referred for managing colorectal LSLs ≥20 mm (July 2008–present). Two subsequent groups were defined according to the applied resection technique (p-CSP (April 2016 to January 2020) vs EMR (July 2008 to April 2016)) and compared for technical success, adverse events and long-term outcomes. Conventional EMR outcomes to September 2014 were previously published in this journal.[14] Written informed consent was obtained from each patient prior to study participation.

Lesions

L-SSL (≥20 mm) detected during index colonoscopy were treated as specified previously. All lesions attempted for resection were included for analysis. L-SSL detected during follow-up procedures were not eligible for inclusion so as to allow per patient analysis of outcomes.

In the presence of endoscopic surface features consistent with either focal dysplasia (Kudo III or IV pit-pattern) or submucosal invasive cancer (SMIC, Kudo V pit-pattern), resection by conventional EMR was favoured.[10 22]

Procedure

All endoscopic procedures were performed by a study investigator or by an interventional endoscopy fellow under direct supervision of a study investigator. Antiplatelet and anticoagulation medications were held preprocedure, in accordance with consensus recommendations.[23]

High-definition Olympus 180 or 190 series variable-stiffness colonoscopes (Olympus Tokyo, Japan) were used. Carbon dioxide was routinely used for insufflation.[24] Lesion assessment with high-definition (HD) white light endoscopy (WLE) and narrow-band imaging (NBI) confirmed Kudo II(O) pit-pattern consistent with a serrated morphology.[22] Lesions were routinely lifted using succinylated gelatin (Gelofusine; B. Braun, Bella Vista, Australia) with 0.4% indigo carmine and 1:100 000 epinephrine.[25] Piecemeal excision was performed using a variety of dedicated stiff, thin-wired cold snares (Captivator COLD (Boston Scientific, Marlborough, Massachusetts, USA), TeleMed 10 mm hexagonal (TeleMed Systems, Hudson, Massachusetts, USA), Exacto (US Endoscopy, Mentor, Ohio, USA), AcuSnare mini hexagonal (Cook Medical, Bloomington, Indiana, USA)). A wide rim (≥3 mm) of normal mucosa at the peripheral margin was included in the resection. Where residual polyp was suspected targeted re-resection was performed by snare excision until complete resection was achieved (figure 1).

EMR procedures were performed in a standardised fashion as previously described.[26 27] Thermal ablation of the resection margin using snare-tip soft coagulation (STSC) (ERBE VIO SOFT COAG: 80W, Effect 4) was performed in a randomised controlled setting over 34 months to May 2016 and then continued as standard of care (figure 2).[28]

After the procedure was completed patients were observed in recovery for 4 hours and if well, discharged on a clear fluid diet overnight.

Adverse events

Intra-procedural adverse events were documented by the proceduralist on the day of the procedure. These included clinically significant intra-procedural bleeding (CSIPB) and DMI.

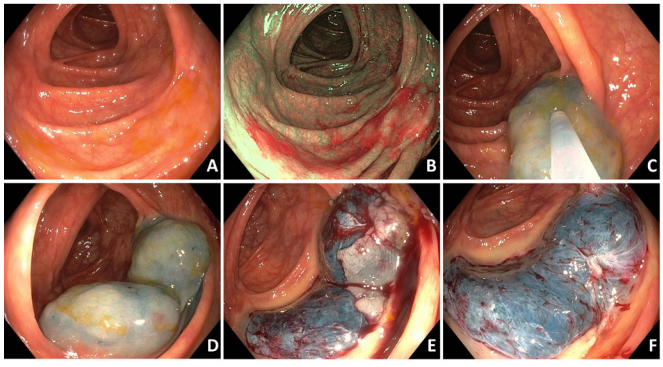

Figure 1 Example of two large sessile serrated lesions resected by piecemeal cold snare polypectomy. Lesion assessment using high-definition white light endoscopy and narrow-band imaging (A–B). Submucosal injection aids in lesion delineation (C–D). Piecemeal cold snare excision including a wide margin of normal colonic mucosa (E–F).

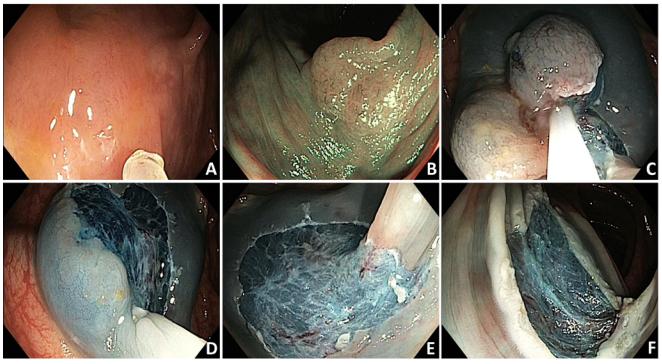

Figure 2 Example of a large sessile serrated lesions resected by endoscopic mucosal resection. Lesion assessment using high-definition white light endoscopy and narrow-band imaging (A–B). Piecemeal excision following submucosal injection (C–D). Defect inspection and snare-tip soft coagulation of the margins (E–F).

CSIPB was defined as any bleeding not responding to water jet irrigation or STSC and therefore requiring either coagulation forceps or mechanical clips to achieve hemostasis.[29] DMI was defined according to the Sydney classification as grade III (muscularis propria injury or 'target sign') or grade IV/V (transmural perforation without or with contamination, respectively).[18] Areas of DMI III-V were treated by mechanical clip closure.

Postprocedural adverse events were identified and recorded by means of a structured telephone interview at 2 weeks by an ACE study coordinator. This included CSPEB and delayed perforation. CSPEB was defined as any bleeding after completion of the procedure requiring emergency room presentation, hospitalisation or re-intervention (endoscopy, angiography, surgery).[17] When suspected, delayed perforation was confirmed by extra luminal pooling of oral contrast on abdominal CT imaging.

Follow-up

Surveillance colonoscopy (SC) was scheduled at 6 and 18 months after the index procedure (SC1 and SC2, respectively). All patients who had undergone a successful resection and were due for SC according to the intervals mentioned were considered eligible. Exceptions were recorded if they were referred for multidisciplinary team meeting or surgery based on procedural or histological outcomes or if age and/or comorbidities did not allow for follow-up. Patients who had missed a previous SC for any reason or those who declined follow-up were not deemed eligible.

During SC standardised evaluation and photo documentation of the resection site was performed using HD-WLE and NBI.[30] Suspected endoscopic recurrence was treated using snare excision or cold avulsion with adjuvant snare-tip soft coagulation (CAST) or a combination thereof.[31] Histology was relied on as the reference standard for polyp recurrence where available. Thus, recurrence would be considered negative if histology did not confirm suspected endoscopic recurrence, whereas if histology of a suspected endoscopic recurrence was not available (due to inadequate specimen retrieval) this would be considered positive. Absence of endoscopic recurrence was recorded as such unless routine scar biopsies showed polyp recurrence in which case they were considered positive for recurrence and treated accordingly.

Data extraction and statistical analysis

Prospectively collected data included patient characteristics (sex, age, American Society of Anesthesiologists (ASA) classification), lesion characteristics (size, location, Kudo pit pattern, histopathology), procedure outcomes (technical success, procedure time, adverse events) and long-term outcomes (recurrence). Technical success was defined as complete removal of all polypoid tissue during index procedure. Definitions used to document adverse events and recurrence are described in the previous sections.

The primary outcome was technical success. Secondary outcomes were adverse events and recurrence. All L-SSL attempted for resection during index colonoscopy were included for analysis. If conventional EMR was performed for reasons previously described the outcomes were pooled with the existing comparator group. Technical success was evaluated on a per-lesion basis. Evaluation of adverse events and recurrence was on a per-patient basis. If more than one L-SSL was resected during index colonoscopy, then only the largest lesion was included in the per-patient analysis.

SPSS V.25.0 (IBM Corp) was used for data analysis. Continuous variables were summarised using median (IQR). Categorical variables were summarised as frequencies (%). To test for association between continuous variables a Mann-Whitney U test was used. For categorical variables, the Pearson χ^2 or the Fisher exact tests were used, where appropriate. A probability (p) value <0.05 was considered statistically significant.

Patient and public involvement

Patients and the public were not involved in the design and execution of this study.

RESULTS

Between July 2008 and January 2020, 569 L-SSL were identified in 481 patients. Resection was not attempted in seven L-SSL (1.2%) due to suspected SMIC (n=2) or technical difficulty (n=5). These patients were referred directly to surgery and were not included for analysis. In total, 562 L-SSL in 474 patients were evaluated. Of 168 L-SSL in 133 patients intended for p-CSP management, 12 L-SSL (7.1%) in an equal number of patients were instead removed by conventional EMR due to

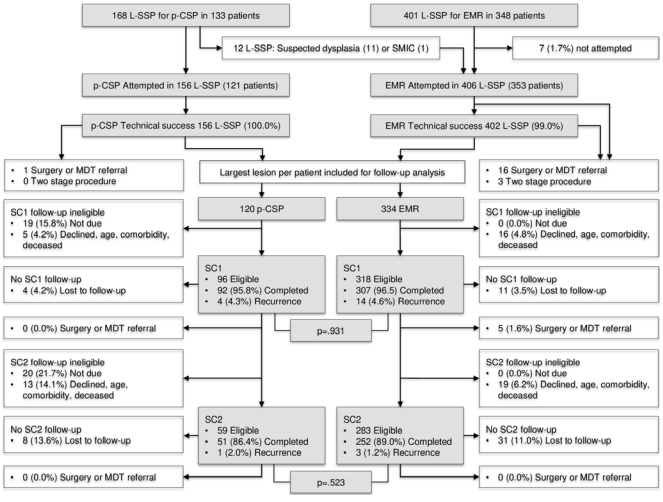

Figure 3 Technical success and long-term outcomes. EMR, endoscopic mucosal resection; L-SSP, large sessile serrated lesions; MDT, multidisciplinary team; p-CSP, piecemeal cold snare polypectomy; SC, surveillance colonoscopy.

Table 1 Patient and lesion characteristics

	p-CSP	EMR	
Patients (n, %)	**121 (25.5)**	**353 (74.5)**	**P value**
Age (median, IQR)	60 (50–72)	66 (57–73)	0.007
Female (n, %)	85 (70.2)	230 (65.2)	0.306
ASA score (n, %)			0.396
≤2	100 (82.6)	303 (85.8)	
3	21 (17.4)	50 (14.2)	
Lesions (n, %)	**156 (27.8)**	**406 (72.2)**	
Size, mm (median, IQR)	25 (20–30)	25 (20–30)	0.004
Size group (n, %)			0.016
<25 mm	65 (41.7)	131 (32.2)	
25–34 mm	64 (41.0)	174 (42.9)	
≥35 mm	27 (17.3)	101 (24.9)	
Location (n, %)			0.309
Rectum	0 (0.0)	5 (1.2)	
Sigmoid, desc colon, splen flexure	10 (6.4)	35 (8.6)	
Transverse colon, hepatic flexure	55 (35.3)	135 (33.3)	
Ascending colon	59 (37.8)	158 (38.9)	
Caecum	32 (20.5)	73 (18.0)	
Previously attempted (n, %)	5 (3.2)	29 (7.1)	0.112

ASA, American Society of Anesthesiologists; EMR, endoscopic mucosal resection; p-CSP, piecemeal cold snare polypectomy.

surface features consistent with dysplasia (n=11) or suspicion of superficial SMIC (n=1) (figure 3).

Patient and lesion characteristics

156 L-SSL among 121 patients were treated by p-CSP (table 1). Median age was 60 years (IQR 50–72 years) with 70.2% being women. The majority were ASA II (79, 65.2%). Median lesion size was 25 mm (IQR 20 mm–30 mm), ranging up to 70 mm. Lesions were predominantly located in the transverse colon and hepatic flexure (n=55, 35.3%), the ascending colon (n=59, 37.8%) and the caecum (n=32, 20.5%). Five lesions (3.2%) had been previously attempted. Dysplasia was found in 15 (9.6%) L-SSL (online supplemental table 1).

Technical success: per lesion analysis

Technical success was achieved in all 156 (100.0%) lesions (table 2). All were resected in piecemeal. Median resection time was 10 min (IQR 10 min–15 min).

Adverse events: per patient analysis

No CSIPB or DMI was encountered during p-CSP of 156 L-SSL. In the 14-day period following the procedure no CSPEB or delayed perforation occurred (table 3).

Long-term outcomes: per patient analysis

Of 121 patients treated by p-CSP, 96 and 59 were eligible for SC1 and SC2, respectively. Of these, 92 (95.8%) and 51 (86.4%) underwent endoscopic follow-up (figure 3). From index procedure, median time to follow-up for SC1 and SC2 was 6 months (IQR 4–8 months), and 15 months (IQR 12–20 months), respectively. Recurrence was identified in 4 (4.3%) at SC1 and 1 (2.0%) at SC2. One patient who had undergone a successful resection of a caecal L-SSL was sent directly for surgery after the index procedure for a synchronous cancer in the sigmoid. No patients required surgery during the follow-up period.

Table 2 Resection outcomes per lesion

	p-CSP	EMR	
Per lesion resection outcomes (n, %)	**156 (27.8)**	**406 (72.2)**	**P value**
Technical success (n, %)	156 (100.0)	402 (99.0)	1.000
En-bloc resection (n, %)	0 (0.0)	77 (19.0)	<0.001
Resection time, min (median, IQR)	10 (10–15)	10 (5–20)	0.584

EMR, endoscopic mucosal resection; p-CSP, piecemeal cold snare polypectomy.

Table 3 Adverse events per patient

	p-CSP	EMR	
Per patient resection outcomes (n, %)	**121 (25.5)**	**353 (74.5)**	**P value**
CSPEB (n, %)	0 (0.0)	18 (5.1)	0.010
CSIPB (n, %)	0 (0.0)	5 (1.4)	0.336
DMI total (n, %)	0 (0.0)	10 (2.8)	0.071
Type 3 ('target sign')		9 (2.5)	
Type 4/5 (transmural perforation)		1 (0.3)	
Delayed perforation (n, %)	0 (0.0)	2 (0.6)	1.000

CSIPB, clinically significant intra-procedural bleeding; CSPEB, clinically significant post-EMR bleeding; DMI, deep mural injury; EMR, endoscopic mucosal resection; p-CSP, piecemeal cold snare polypectomy.

p-CSP versus conventional EMR

Both groups were comparable for gender distribution, ASA, lesion location and previous attempt, but median lesion size was smaller (p=0.004) and median age younger (p=0.007) in the p-CSP group (table 1). Dysplasia was more prevalent in the EMR group (p<0.001) (online supplemental table 1). Technical success rate was high at 100.0% for p-CSP and 99.0% for EMR (table 2). En-bloc resection was not attempted in the p-CSP group whereas en-bloc resection was achieved in 19.0% of L-SSL treated by EMR. No adverse events occurred in the p-CSP group (0.0%) as opposed to 5.1% CSPEB (p=0.010), 1.4% CSIPB (p=0.336), 2.8% DMI (p=0.071) and 0.6% delayed perforation (p=1.000) in the EMR group (table 3). Median SC1 intervals were similar at 6 months (IQR 4–8 months vs IQR 5–9 months) for p-CSP and EMR, respectively (p=0.143), but median SC2 interval was shorter for p-CSP at 15 months (IQR 12–20 months) versus 19 months (IQR 16–24 months) for EMR (p<0.001). Of those eligible, 95.8% versus 96.5% completed SC1 and 86.4% versus 89.0% completed SC2 for p-CSP and EMR, respectively. Recurrence rates for p-CSP were equally low in comparison to EMR at both SC1 (4.3% vs 4.6%, p=0.931) and SC2 (2.0% vs 1.2%, p=0.523) (figure 3).

DISCUSSION

CRC can be effectively prevented by the endoscopic resection of precursor lesions.[3] SSL are a unique subclass of precursor lesions that are increasingly being detected with the advent of HD endoscopy and well-defined endoscopic criteria.[32] EMR has matured as the treatment of choice for L-SSL,[26–28 33] but carries the risk of serious adverse events.[34] CSPEB especially remains a major drawback not uncommonly necessitating unscheduled hospital admission. Colonoscopy for haemostasis is performed in roughly 50% of CSPEB cases.[35]

Alternatively, CSP is extremely safe but has been restricted to small (<10 mm) lesions due to limitations of mechanical (cold) tissue transection.[19] Cold snare resection of LSL demands a piecemeal approach and requires transection of an at times thick tissue attachment with inherent compromise of efficacy. Logically, a decrease in technical success and an increased rate of recurrence may result. Contrary to most adenomatous LSL,

L-SSL have a comparatively thin mucosal profile which is only slightly thickened beyond the normal surrounding mucosa. Indeed, many are flat and barely perceptible. The submucosa is also generally loose with little or no submucosal fibrosis. These properties may render L-SSL uniquely amenable to p-CSP.[36] We are the first to compare p-CSP and EMR outcomes in L-SSL management in a large prospective cohort establishing p-CSP as safer yet equally efficacious.

Importantly, equally high rates of technical success were achieved in p-CSP and EMR at 100.0% and 99.0%, respectively (table 2, figure 3). Of four L-SSL in which the initial EMR procedure was not successful all were due to difficult scope positioning or access. Two were designated as two-stage procedures at index and both achieved technical success at second stage. The remaining two patients were referred for surgery, one of whom denied after the option was discussed. That patient went on to have an endoscopic salvage procedure with successful treatment of the residual polyp.

Twelve L-SSL intended for p-CSP were actually resected by EMR due to the presence of endoscopic features of focal dysplasia (L-SSL-D). All 12 L-SSL-D were successfully resected by EMR and none recurred during follow-up. The option to cross over was initially made available to the endoscopist as a safeguard bearing in mind the novelty of the piecemeal cold snare approach combined with the concern for interval cancers following incomplete resection of L-SSL-D. The endoscopists decision to opt for EMR instead of p-CSP was not considered a failure of p-CSP technique as such. In fact, 15 L-SSL resected by p-CSP were found to have dysplasia on histological evaluation. All 15 had been successfully resected suggesting that presence of dysplasia in L-SSL does not necessarily limit technical success of p-CSP treatment.

No CSPEB occurred in 156 L-SSL removed by p-CSP. In contrast, CSPEB in the comparator group was 5.1%, similar to numbers previously reported.[14] Suzuki *et al* demonstrated that in comparison to CSP, use of electrocautery in hot snare polypectomy (HSP) generates a deeper resection plane increasing the risk of encountering and transecting larger vessels buried deep in the submucosal layer.[37] Indeed higher rates of submucosal arterial injury have been shown in HSP compared with CSP.[38]

We previously demonstrated that the event rate of IPB in EMR for L-SSL is lower in comparison to adenomatous LSL.[14] Moreover, IPB management has much improved and can often be swiftly treated by STSC avoiding any interference with the resection as such.[29] Indeed one might argue that IPB in the treatment of L-SSL especially has lost relevance. Be that as it may, when initial management fails the consequences are still clinically significant as lesions may be at higher risk for recurrence.[39] We defined stringent criteria by which CSIPB is an infrequent event occurring in only five L-SSL (1.4%) treated by EMR. No CSIPB was encountered in the p-CSP cohort. Whereas minor oozing after p-CSP was almost invariably present it unequivocally responded to waterjet expansion of the submucosal space and eventually stopped omitting the need for any cautery assisted haemostasis.

Although DMI in CSP has been reported it seems an extremely rare event and we did not encounter any DMI in this large p-CSP cohort.[40] In L-SSL treated by EMR DMI occurred in 2.8% of cases (n=10). In addition, two patients (0.6%) experienced delayed perforation following EMR requiring emergency surgery. Electrocautery allows for larger snares facilitating unintended transmural capture. This holds especially true in the transverse colon as it lies intraperitoneal and is mobile creating a falsely reassuring mobility sign after snare closure.[18] Being relatively over-represented in the transverse colon (33.8% in our combined cohort), L-SSL may be particularly vulnerable.

With CSP resection depth generally being more superficial than in HSP concern may be raised for incomplete mucosal resection increasing the risk of recurrence. Importantly, our data show that recurrence rates following p-CSP were equally low in comparison to EMR as demonstrated in figure 3. To evaluate recurrence, histology was used as the reference standard. Technological advancement of optics used in endoscopy potentially places historical findings at a disadvantage risking bias when addressing endoscopic recurrence. Given the time span over which the study was conducted and the comparator arm being a historical cohort, histological recurrence was deemed more appropriate as it is more consistent over time.

Of four p-CSP recurrences identified at SC1, three were effectively treated and did not recur at SC2, but in one of four the recurrence was found to persist at SC2 despite CAST treatment at initial surveillance. No new cases of late recurrence were identified at SC2 following p-CSP. In the comparator group all three recurrences at SC2 were new, effectively adding to the 14 patients with recurrence identified at SC1. Of 14 patients with recurrence at SC1, 9 patients underwent SC2 none of whom had recurrence at that time. One patient was referred for surgery due to HGD. The remaining four patients that were treated for recurrence at SC1 were deemed ineligible for SC2.

These data convincingly show that adopting a piecemeal approach for the management of L-SSL does not compromise the efficaciousness of CSP. Provided snare placement systematically overlaps previous resected areas and includes a wide peripheral margin of normal mucosa the risk of recurrence following p-CSP is in fact comparable to that of EMR in the management of L-SSL. Crucial herein is that any residual polyp in the defect margin or suspicion thereof is immediately and widely re-excised using the snare (figure 1). This process of 'cleaning the margin' is essentially limitless and can be safely continued until complete resection is assured, as we show that incremental defect size will not increase the risk of delayed bleeding.

We previously evaluated EMR outcomes for L-SSL in a prospective cohort,[14] which partially overlaps with our current EMR comparator cohort. Herein the overall risk of recurrence was threefold higher in adenoma's than in L-SSL with a multivariable adjusted HR of 1.7. In subgroup analysis this only reached significance in lesions up to 25 mm in size, indicating increasing lesion size may be a driver of recurrence in L-SSL. Our current data do not allow for a reliable multivariate risk analysis given the low number of recurrences in our p-CSP cohort. Of the four recurrences that we identified two were 25 mm, one was 30 mm and one was 40 mm. Of note, three of four (75.0%) L-SSL that recurred following p-CSP did not have submucosal injection prior to resection whereas the vast majority did (144 of 156, 92.3%). Of the 92 L-SSL that were evaluated at SC1 only 9 (9.8%) had not been not lifted and of these 3 (33.3%) developed recurrence. The disproportionate high rate of recurrence in L-SSL that were not lifted prior to resection suggests submucosal lift may be an important factor contributing to complete resection. Blue dye in the submucosal lifting solution aids in the demarcation of these indistinct lesions and allows for careful snare positioning to include a wide margin of normal tissue ensuring complete resection. Also, diluted epinephrine in the submucosal injectate limits intra-procedural oozing improving mucosal views and subsequent systematic and overlapping snare placement preventing formation of mucosal islands within the defect. In addition, both blue dye and the minimal oozing

enhance post resection interrogation of the defect for residual polyp requiring re-resection.

A recently published observational study describing p-CSP of a mixed cohort of large (≥20 mm) sessile serrated and adenomatous LSL, identified epinephrine use and caecal location among others, as potential risk factors for recurrence in univariate analysis. In a multivariate logistic regression limited by the low number of recurrences only caecal location remained significant. This Australian study by Mangira *et al* had a minimal overlap of 10 cases with the cohort described here.[41]

Despite the multicentre prospective design of this study a limitation remains that it was not conducted in a randomised controlled setting. This carries the risk of introducing bias in lesion selection. One such bias was introduced by allowing for suspected L-SSL-D to be treated by EMR as opposed to p-CSP for purposes explained previously. Although this applied only to a small subset of lesions it does interfere with interpreting the role of p-CSP in L-SSL-D treatment. As p-CSP technique matures, future research will need to be conducted to address this important issue. Other limitations include the technical aspects of p-CSP. The use of diluted epinephrine may have influenced delayed bleeding, although it should be noted that epinephrine was used both in the p-CSP cohort as well as the comparator.[17] Also, in p-CSP not al L-SSL were consistently lifted prior to resection. Whereas p-CSP of L-SSL without submucosal lift has been shown to be feasible and safe the effect thereof on recurrence rates requires further investigation.[20] Finally, procedures were performed at expert centres. The numbers as presented in this study may not reflect those in the everyday practice of less experienced endoscopists. The design of the study did not allow for any learning curve of the endoscopists involved to be accurately quantified.

Based on our findings, widespread application of p-CSP in the treatment of L-SSL has the potential to dramatically improve safety outcomes minimising unscheduled hospital admissions. Moreover, improved safety aspects could allow for multiple L-SSL to be treated in a single colonoscopy session whereas in current practice the number of EMR's is often limited to avoid the accumulating risk of adverse events. A shift to p-CSP may as a result have a significant effect on the number of colonoscopies required to clear the colon of lesions in the setting of SPS. Future research will need to focus on these economic ramifications to further establish p-CSP as the new standard of care for L-SSL treatment.

We conclude that p-CSP in the management of L-SSL is essentially safer and equally efficacious in comparison to conventional EMR. We propose p-CSP be incorporated in clinical guidelines as a reliable option for L-SSL treatment. For L-SSP-D the role of p-CSP needs to be further elucidated.

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Funding WAvH and SV were supported by scholarships from the Westmead Medical Research Foundation. NS was supported by the University of British Columbia Clinician Investigator Fellowship. LH received support from the Gallipoli Medical Research Foundation. There was no influence from the institutions regarding study design or conduct, data collection, management, analysis or interpretation or preparation, review, or approval of the manuscript.

Competing interests MJB: Research Support by Olympus Medical, Cook Medical, Boston Scientific.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. All data relevant to the study are included in the article or uploaded as supplementary information. Deidentifed individual participant data that underlie the results reported in this article will be made available upon reasonable request immediately following publication for a period of six months, to investigators who provide a methodologically sound proposal. Proposals should be directed at the corresponding author and should include a signed data access agreement.

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