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Cold-forceps avulsion with adjuvant snare-tip soft coagulation (CAST) is an effective and safe strategy for the management of non-lifting large laterally spreading colonic lesions

Authors
David J. Tate[1,2], Farzan F. Bahin[1,2], Lobke Desomer[2], Mayenaaz Sidhu[2], Vikas Gupta[2], Michael J. Bourke[1,2]

Institutions
1 Westmead Clinical School, The University of Sydney, Sydney, New South Wales, Australia
2 Department of Gastroenterology and Hepatology, Westmead Hospital, Sydney, New South Wales, Australia

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Corresponding author
Michael J. Bourke, MB BS, Suite 106a 151-155 Hawkesbury Road, Westmead , NSW 2145, Australia
Fax: +2-9633-3958
Michael@citywestgastro.com.au

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ABSTRACT

Background and aims Non-lifting large laterally spreading colorectal lesions (LSLs) are challenging to resect endoscopically and often necessitate surgery. A safe, simple technique to treat non-lifting LSLs endoscopically with robust long-term outcomes has not been described.

Methods In this single-center prospective observational study of consecutive patients referred for endoscopic mucosal resection (EMR) of LSLs ≥ 20 mm, LSLs not completely resectable by snare because of non-lifting underwent standardized completion of resection with cold-forceps avulsion and adjuvant snare-tip soft coagulation (CAST). Scheduled surveillance colonoscopies were performed at 4 – 6 months (SC1) and 18 months (SC2). Primary outcomes were endoscopic evidence of adenoma clearance and avoidance of surgery. The secondary outcome was safety.

Results From January 2012 to October 2016, 540 lifting LSLs (82.2 %) underwent complete snare excision at EMR. CAST was required for complete removal in 101 non-lifting LSLs (17.8 %): 63 naïve non-lifting lesions (NNLs; 62.7 %) and 38 previously attempted non-lifting lesions (PANLs; 37.3 %). PANLs were smaller ($P < 0.001$) and more likely to be non-granular ($P = 0.001$) than the lifting LSLs. NNLs were of similar size ($P = 0.77$) and morphology ($P = 0.10$) to the lifting LSLs. CAST was successful in all cases and adverse events were comparable to lifting LSLs resected by complete snare excision. Recurrence at SC1 was comparable for PANLs (15.2 %) and lifting LSLs (15.3 %; $P = 0.99$), whereas NNLs recurred more frequently (27.5 %; $P = 0.049$); however, surgery was no more common for either type of non-lifting LSL than for lifting LSLs.

Conclusion CAST is a safe, effective, and surgery-sparing therapy for the majority of non-lifting LSLs. It is easy to use, inexpensive, and does not require additional equipment.

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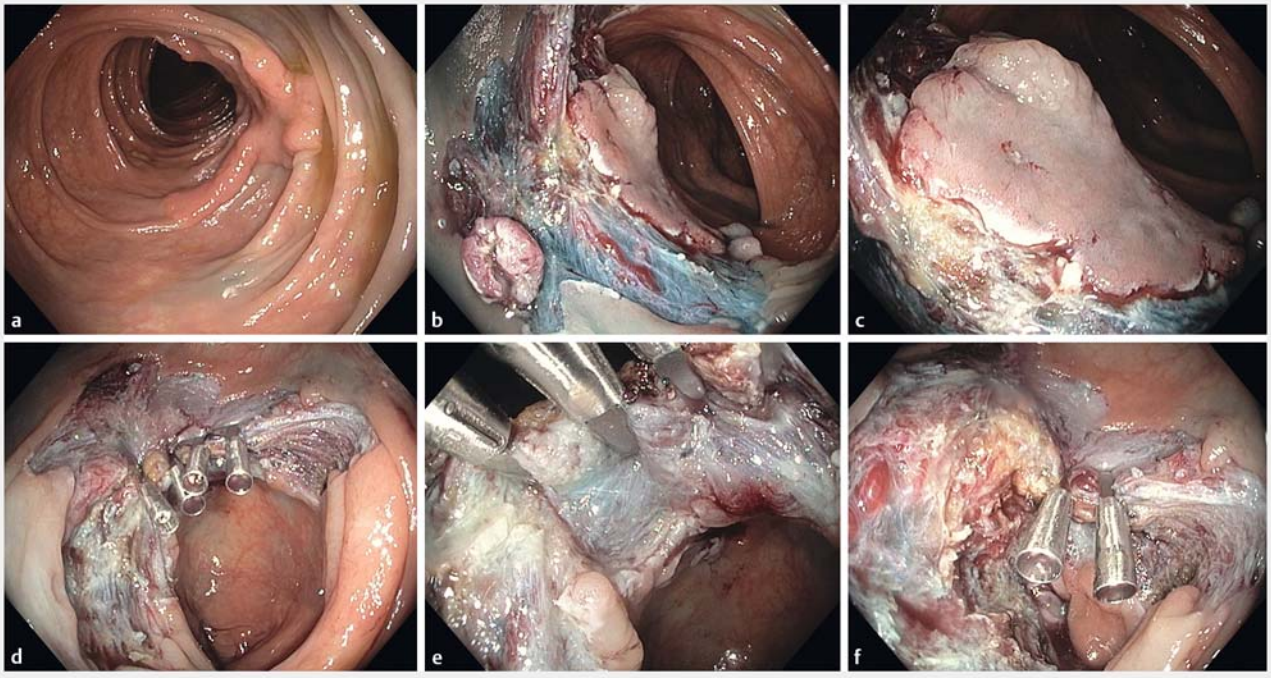
NCT2000141
TRIAL REGISTRATION: Single-Center Prospective Observational Study with Consecutive Patients NCT2000141 at clinicaltrials.gov.

Introduction

Endoscopic mucosal resection (EMR) is now the standard of care for large laterally spreading colorectal lesions (LSLs) and a growing body of evidence demonstrates the efficacy and durability of endoscopic resection [1], and its superior cost and safety profile as compared to surgery [2 – 4]. As increasing numbers of LSLs are resected by EMR, tertiary endoscopy centers encounter more LSLs where resection has been previously attempted (previously attempted non-lifting LSLs; PANLs), as well as those which have been biopsied or marked with carbon particle suspension. All these insults are recognized to lead to non-lifting by inducing submucosal fibrosis with consequent obliteration of the submucosal plane, thereby increasing the



▶ **Fig. 1** Endoscopic images showing: **a** a naïve non-lifting laterally spreading lesion (NNL) in the mid-transverse colon; **b,c** a central non-lifting area with significant submucosal fibrosis, which was seen after the commencement of endoscopic mucosal resection; **d – f** endoscopic clips applied to the center of the defect to prevent delayed perforation after the lesion had been completely resected by snare leaving a type II deep mural injury [12]. The histopathology of this lesion showed tubular adenoma with low grade dysplasia.

complexity of endoscopic resection. With the mucosa closely approximated or adherent to the muscularis propria, snare capture is more difficult and there is a higher likelihood of capturing the deep muscle layer within the ensnared tissue, with a risk of subsequent deep mural injury or frank perforation [5].

Traditionally, surgery was required to manage non-lifting LSLs. Endoscopic techniques to treat such lesions have been described but all suffer from either an increase in the complexity of the procedure, limited case experience and follow-up, or lack of availability [6 – 9]. There is a clear need for a safe, reliable, and cost-effective endoscopic treatment for non-lifting LSLs that is easy to use and leads to durable long-term results.

Methods

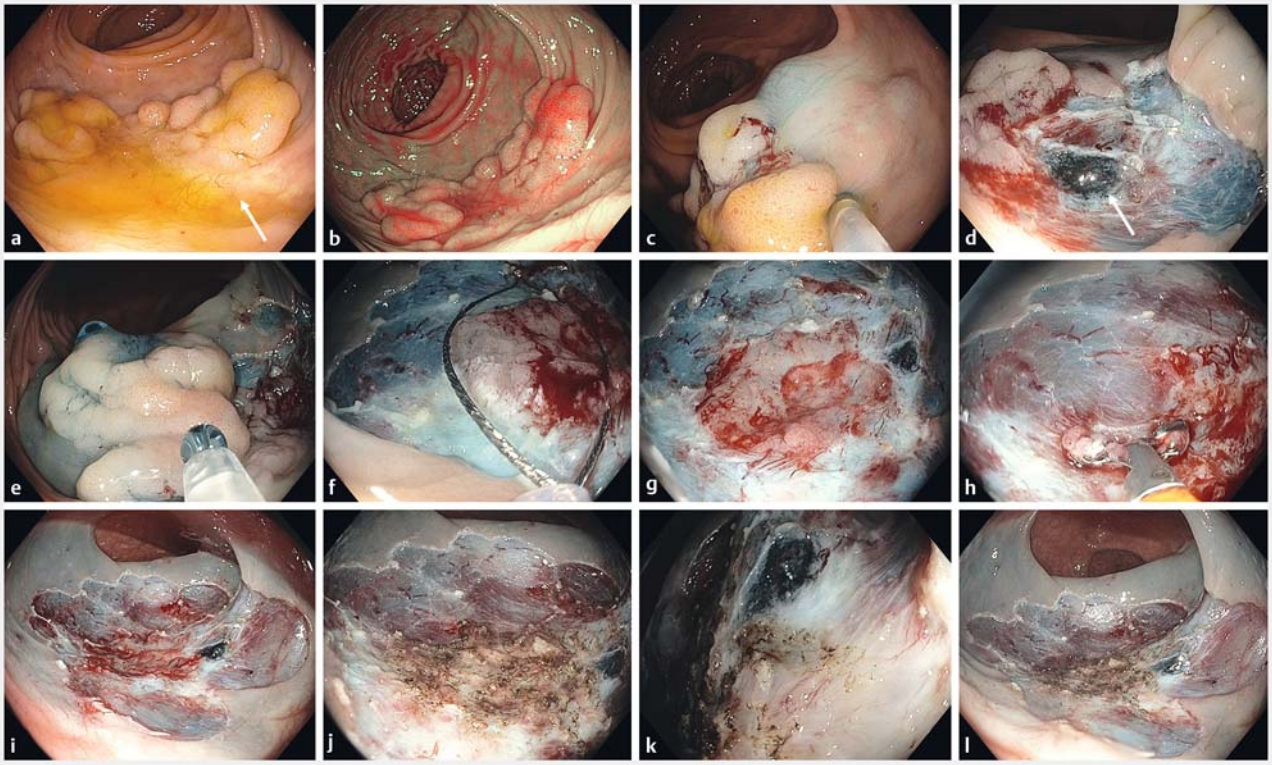
EMR procedure

All 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. Split-dose bowel preparation was used and intravenous sedation was given with a combination of fentanyl, midazolam, and propofol. Consensus stopping rules for antiplatelet and anticoagulant agents in patients undergoing high risk endoscopic procedures were applied [10].

Colonoscopy was performed using Olympus 180 or 190 series high definition variable-stiffness colonoscopes (180/190 PCF/CF; Olympus, Tokyo, Japan). Insufflation of the colon was with carbon dioxide in all patients. A standardized and previously described inject-and-resect EMR technique [11] was used. In all patients a microprocessor-controlled electrosurgical generator (Endocut effect 3, VIO 300D; ERBE Elektromedizin, Tübingen, Germany) with fractionated current was used. The submucosal injectate comprised succinylated gelatin (Gelofusine; B. Braun Australia Pty Ltd, Bella Vista, Australia). The fluid was dyed with indigo carmine blue (80 mg/500 mL solution) and epinephrine was added to achieve a final solution of 1:100 000. Occasionally methylene blue was used as an alternative when indigo carmine blue was not available.

Consecutive EMR procedures during the study period were included. Patients enrolled and randomized to the active arm of the SCAR study (Snare Tip Soft Coagulation to Prevent Adenoma Recurrence Following EMR; NCT NCT01789749) were excluded. There were no other exclusion criteria.

Lesions at and proximal to the hepatic flexure were deemed to be located in the right colon. Prior to resection all lesions were carefully assessed with high definition white-light and narrow-band imaging (NBI). Resection was predominantly with a 15-mm or 20-mm snare (SnareMaster; Olympus, Tokyo, Japan). A stiff, thin wire (0.3-mm diameter) snare (TeleMed 10 mm Hexagonal; TeleMed Systems Inc, Massachusetts, USA) was used in the case of a non-lifting adenoma. Complete snare excision was the goal in all patients. LSLs with adequate lifting after submucosal injection and complete snare excision were labelled lifting LSLs. LSLs that could not be completely excised by snare because of non-lifting were labelled non-lifting LSLs. These were divided into previously attempted non-lifting LSLs



▶ **Fig. 2** Endoscopic images showing: **a,b** a 40-mm Paris 0-IIa granular previously attempted non-lifting laterally spreading lesion (PANL) in the mid rectum, associated with a large scar (white arrow); **c** injection and snare excision of the lifting areas adjacent to the non-lifting adenoma to free the lateral margins; **d** evidence of previous injection of carbon particle suspension within the expanding resection defect (white arrow); **e** further inject-and-resect endoscopic mucosal resection being performed at the opposite lateral margin; **f,g** a large area of non-lifting adenoma remaining despite attempts at complete snare excision using a thin wire snare, which is associated with scarring from the previous attempt; **h,i** cold avulsion being performed on all visible adenoma; **j** soft coagulation of the avulsion bed and surrounding tissue using the snare tip; **k** the extensive submucosal fibrosis associated with the previous resection attempt, which completely obliterates the submucosal plane; **l** the final resection defect.

(PANLs), in which a prior endoscopic resection had been attempted, and naïve non-lifting LSLs (NNLs) (▶ **Fig. 1**).

Non-lifting LSLs underwent completion of resection using a standardized approach with cold-forceps avulsion and adjuvant snare-tip soft coagulation (CAST) (▶ **Fig.2** and ▶ **Fig.3**; ▶ **Video1**). Prior to CAST, the non-lifting area was isolated by snare excision of all adjacent tissue, including adenoma and/or normal mucosa, to free the lateral margins. Systematic cold-forceps avulsion (Radial Jaw Biopsy Forceps; Boston Scientific, Massachusetts, USA) was then performed to remove all visible non-lifting adenoma. The exposed submucosa of the avulsion site and its margins were then treated with controlled thermal ablation using snare-tip soft coagulation (STSC; ERBE effect 4, 80 W; VIO 300 D generator; ERBE Elektromedizin). The endomucosal defect was graded using the Sydney Classification of Deep Mural injury [12]. Areas of endomucosal defect exhibiting type II to V deep mural injury were routinely closed with endoscopic clips (Instinct clip; Cook Medical, Bloomington, Indiana, USA). Intraprocedural perforation was described as a target sign [13] or actual hole in the colonic wall (Sydney deep mural injury classification III, IV, and V).

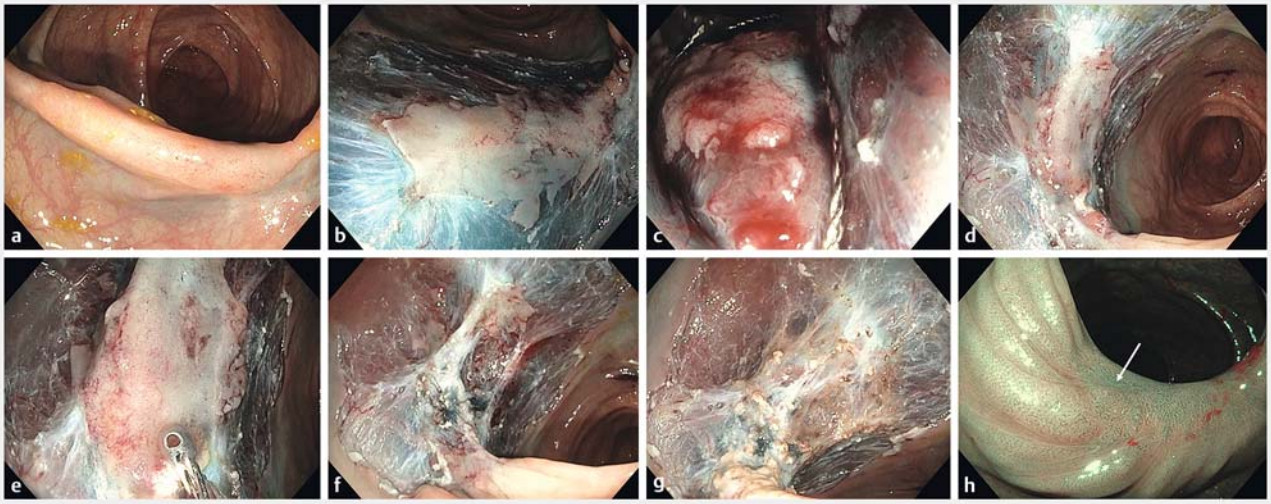
Specialist gastrointestinal pathologists at the study center reviewed all of the histological specimens. After EMR, patients were observed for 4 hours and discharged home if well. A clear fluid diet was advised until the next morning. Patients were contacted by the study coordinator after 2 weeks and a structured telephone interview was performed to assess for adverse events. Delayed bleeding was described as bleeding after the procedure and was recorded if it required readmission or endoscopic intervention.

The study was approved by the Western Sydney Local Health District Human Research Ethics Committee and registered with ClinicalTrials.gov (NCT 2000141).

Follow-up

All lesions were evaluated for endoscopic recurrence at the first surveillance colonoscopy (SC1) and later if further surveillance was undertaken. Patients were excluded if they were referred for surgery at the time of the initial EMR on the basis of lesion morphology or histopathology. Patients with missing data were regarded as lost to follow-up.

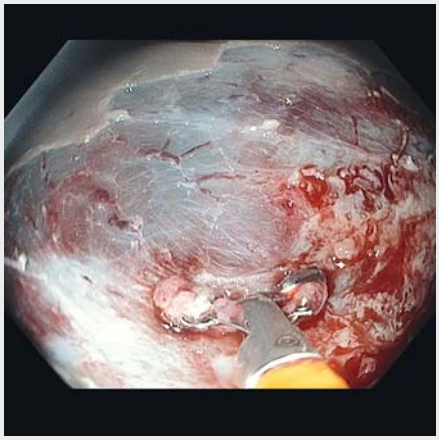
The primary endpoints of the study were endoscopic recurrence (unless otherwise stated “recurrence” throughout this



▶ **Fig. 3** Endoscopic images showing: **a** a 45-mm previously attempted non-lifting laterally spreading lesion (PANL) in the mid-transverse colon associated with a large scar; **b** snare excision of the area adjacent to the non-lifting adenoma to free the lateral margins and create a "step" for snare capture; **c,d** a central non-lifting area that remains despite attempts at complete snare excision; **e,f** cold-forceps avulsion of all visible non-lifting adenoma; **g** snare-tip soft coagulation applied to the avulsion bed; **h** appearance of the endoscopic mucosal resection scar at first follow-up colonoscopy; a small area of residual adenoma (white arrow) was easily treated at this examination. Procedure also shown in ▶ **Video 1**.

manuscript refers to endoscopic recurrence), defined as the presence of tissue suspicious for adenoma under high definition white-light and/or NBI, and avoidance of surgery. When there was doubt as to the presence of recurrence endoscopically, biopsies of the EMR scar were taken to document the absence of histological recurrence. Late endoscopic recurrence was defined as recurrence occurring after a previous negative surveillance procedure. ▶ **Fig.3** shows an example of a PANL treated by CAST with the appearances of the endoscopic resection scar at SC1. Detected recurrence, once sampled, was excised by snare or, if this was not possible, removed by CAST.

The secondary endpoints of the study were the rates of adverse events, including intraprocedural bleeding requiring endoscopic control, delayed bleeding, and delayed perforation.



Video 1 The endoscopic resection procedure for the 45-mm previously attempted non-lifting laterally spreading lesion in the transverse colon shown in ▶ **Fig. 3**. The techniques of isolation of the non-lifting area, use of cold-forceps avulsion with adjuvant snare-tip soft coagulation (CAST) to remove the non-lifting central portion, and meticulous scar assessment at first surveillance colonoscopy are demonstrated.
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Statistical analysis

Statistical analysis was performed using SPSS version 23 (Armonk, New York, USA) with a two-tailed *t* test used for parametric continuous variables, Mann–Whitney *U* test for non-parametric continuous data, and chi-squared test for categorical variables. A P value of <0.05 was regarded as significant. Multiple lesions within the same patient were excluded to avoid the bias associated with correlated findings for a single patient; in this case the largest LSL or the non-lifting LSL (if smaller) was retained.

Results

From January 2012 to October 2016, 829 patients (51.0 % men) with 929 lesions (52.7 % located in the right colon) were referred for EMR (▶ **Fig .4**). After exclusions, EMR was attempted on 787 patients with 787 LSLs (94.9 %); 130 LSLs that were enrolled and randomized to the active arm of the SCAR study were excluded. Of the 657 remaining eligible LSLs, 540 (82.2 %) underwent complete resection by snare and were labelled lifting LSLs, while 117 LSLs (17.8 %) were not able to undergo com-

▶ **Table 1** Laterally spreading lesions (LSLs) where cold-forceps avulsion and snare-tip soft coagulation (CAST) was used in the resection of previously attempted non-lifting LSLs (PANLs) or naïve non-lifting LSLs (NNLs) in comparison to complete snare excision of lifting lesions.

	PANL (n = 38)	*P* value[1]	NNL (n = 63)	*P* value[1]	Lifting LSL (n = 540)
Patient					
Age, mean (SD), years	69.9 (9.1)	0.14	71.7 (10.4)	0.003	66.8 (12.1)
Sex, male, n (%)	19 (50.0)	0.91	33 (52.4)	0.83	275 (50.9)
Lesion					
Size, median (IQR), mm	27.5 (20 – 40)	< 0.001	40 (30 – 50)	0.77	35 (30 – 50)
Highest Kudo pit pattern, n (%)[2]					
▪ II	3 (7.9)	0.36	4 (6.3)	0.19	72 (13.5)
▪ III	16 (42.1)		19 (30.2)		155 (29.0)
▪ IV	19 (50.0)		40 (63.5)		301 (56.3)
▪ V	0 (0)		0 (0)		7 (1.3)
Paris classification, n (%)					
▪ 0-IIa	31 (81.6)	< 0.001	47 (74.6)	0.04	294 (54.4)
▪ 0-Is	1 (2.6)		1 (1.6)		33 (6.1)
▪ 0-IIa + Is	1 (2.6)		12 (19.0)		170 (31.5)
▪ 0-IIb	5 (13.2)		3 (4.8)		29 (5.4)
▪ Other	0 (0)		0 (0)		14 (2.6)
Morphology, n (%)					
▪ Granular	10 (26.3)	0.001	29 (46.0)	0.10	283 (52.4)
▪ Non-granular	23 (60.5)		28 (44.4)		172 (31.9)
▪ Unable to classify	5 (13.2)		6 (9.5)		85 (15.7)
Location proximal to transverse colon, n (%)	15 (39.5)	0.09	34 (54.0)	0.95	289 (53.5)
Complex location[3], n (%)	7 (18.4)	0.32	13 (20.6)	0.09	69 (12.8)
Submucosal fibrosis, n (%)	38 (100)	< 0.001	64 (100)	< 0.001	143 (26.5)
Previous resection attempt, n (%)	38 (100)	< 0.001	0 (0)	0.02	44 (8.1)
Previous biopsy, n (%)	17 (44.7)	< 0.001	19 (30.2)	< 0.001	72 (13.3)
Marked with carbon particle suspension within 10 mm of LSL, n (%)	9 (23.7)	< 0.001	14 (22.2)	< 0.001	24 (4.4)
Histopathology, n (%)					
▪ Tubular adenoma	14 (36.8)	0.24	24 (38.1)	0.008	130 (24.1)
▪ Tubulovillous adenoma	21 (55.3)		35 (55.6)		304 (56.3)
▪ Sessile serrated adenoma	3 (7.9)		3 (4.8)		101 (18.7)
Submucosal invasive cancer, n (%)	1 (2.6)	0.72	4 (6.3)	0.78	32 (5.9)
Dysplasia, n (%)					
▪ None	1 (2.6)	0.16	3 (4.8)	0.17	63 (11.7)
▪ Low grade	31 (81.6)		44 (69.8)		374 (69.3)
▪ High grade	6 (15.8)		16 (25.4)		103 (19.1)

▶ **Table 1** (Continuation)

	PANL (n = 38)	*P* value[1]	NNL (n = 63)	*P* value[1]	Lifting LSL (n = 540)
Procedure					
Duration, median (IQR), minutes	35 (21.3 – 47.5)	0.003	30 (20 – 41.3)	0.002	20 (15 – 35)
Intraprocedural bleeding, n (%)	5 (13.2)	0.08	18 (28.6)	0.68	141 (26.1)
Sydney classification type II deep injury, n (%)	7 (18.4)	0.001	5 (7.9)	0.17	20 (3.7)
Intraprocedural perforation[4], n (%)	2 (5.3)	0.64	1 (1.6)	0.71	19 (3.5)
Clip closure of endoscopic resection defect, n (%)	9 (23.7)	0.14	10 (15.9)	0.82	80 (14.8)
Delayed bleeding, n (%)	1 (2.6)	0.50	5 (7.9)	0.80	38 (7.0)
Delayed perforation, n (%)	0 (0)	> 0.99	0 (0)	> 0.99	1 (0.2)
Overnight hospital admission on day of EMR, n (%)	2 (5.3)	> 0.99	6 (6.3)	> 0.99	37 (6.9)

SD, standard deviation; IQR, interquartile range; EMR, endoscopic mucosal resection.
[1] Compared with lifting LSLs with complete snare excision.
[2] Data on Kudo pit pattern available for all non-lifting LSLs and 535/540 lifting LSLs.
[3] Includes the appendiceal orifice, ileocecal valve, and hepatic and splenic flexures.
[4] Corresponds to Sydney classification III – IV deep mural injury. In all cases the area of perforation was successfully closed with endoscopic clips.

plete excision by snare because of non-lifting and were labelled non-lifting LSLs. Of these patients, 16/117 (13.7 %) were referred for a second-stage procedure because there was extensive residual adenoma. The remainder (101/117 [86.3 %]) were treated by CAST.

Amongst the non-lifting LSLs treated by CAST, there were 38 PANLs and 63 NNLs. Key comparisons between non-lifting and lifting LSLs are presented in ▶ **Table 1**.

PANLs were smaller than lifting LSLs with a median size of 27.5 mm (interquartile range [IQR] 20 – 40 mm) vs. 35 mm (IQR 30 – 50; $P < 0.001$) and were more often non-granular in morphology (23/38 [60.5 %] vs. 172/540 [31.9 %]; $P = 0.001$). They invariably demonstrated submucosal fibrosis within the resection site (38/38; 100 %) and took longer to resect than lifting LSLs (median time 35 minutes [IQR 21.3 – 47.5] versus 20 minutes [IQR 15 – 35]; $P = 0.003$).

NNLs were similarly sized to lifting LSLs (median size 40 mm (IQR 30 – 50), $P = 0.77$) and were not more likely to be non-granular (28/63 [44.4 %]; $P = 0.10$). Similarly to PANLs, they took longer to resect than lifting LSLs (median time 30 minutes [IQR 20 – 41.3]; $P = 0.002$).

Both PANLs (31/38 [81.6 %]; $P < 0.001$) and NNLs (47/63 [74.6 %]; $P = 0.04$) were more commonly of Paris 0-IIa morphology than lifting LSLs (294/540 [54.4 %]). Neither type of non-lifting LSL was distributed differently through the colon when compared with lifting LSLs (PANLs 15/38 [39.5 %] located in the right colon [$P = 0.09$] and NNLs 34/63 [54.0 %] located in the right colon [$P = 0.95$] vs. 289/540 [53.5 %] for lifting LSLs).

Both PANLs and NNLs had been biopsied more commonly than lifting LSLs (PANL 17/38 [44.7 %; $P < 0.001$] and NNL 19/63 [30.2 %; $P < 0.001$] vs. lifting LSL 72/540 [13.3 %]) and marked with carbon particle suspension (PANL 9/38 [23.7 %; $P < 0.001$] and NNL 14/63 [22.2 %; $P < 0.001$] vs. lifting LSL 24/540 [4.4 %]). The histopathology of non-lifting LSLs was more often tubular adenoma than lifting LSLs, but this was significant only for NNLs (24/63 [38.1 %]) vs. lifting LSLs (130/540 [24.1 %]; $P = 0.008$).

Safety

CAST was successful at complete removal of visible non-lifting adenomas in all 101/101 cases (100 %) where it was performed. One patient with a severely scarred lesion, on which multiple previous resection attempts had been made, experienced a full-thickness perforation secondary to the avulsion phase for this non-lifting adenoma; this was closed successfully with endoscopic clips without clinical sequelae. Pathology subsequently showed a tubulovillous adenoma with high grade dysplasia.

Type II deep mural injury was observed more commonly in PANLs treated by CAST (7/38 [18.4 %]) vs. lifting LSLs (5/63 [7.9 %]; $P = 0.001$). This difference was not observed for NNLs. There was no difference in the rates of intraprocedural bleeding or perforation, hospital admission on the night of the procedure, delayed bleeding, or delayed perforation between non-lifting LSLs treated by CAST and lifting LSLs that were completely resected by snare (▶ **Table 1**).

Follow-up

The key features during follow-up of all LSLs in the cohort are presented in ▶ **Table 2**. At 2 weeks after the initial procedure, 1/38 PANLs (2.6 %; $P = 0.72$) and 3/63 s NNLs (4.8 %; $P > 0.99$) vs. 32/540 lifting LSLs (5.9 %) had been referred for surgery be-

▶ **Table 2** Outcomes of previously attempted non-lifting LSLs (PANLs) and naïve non-lifting LSLs (NNLs) treated by CAST to complete their resection compared with lifting lesions.

Outcome	PANL (n = 38)	*P* value[1]	NNL (n = 63)	*P* value[1]	Lifting LSL (n = 540)
Surgery at week 2, n (%)	1 (2.6)	0.72	3 (4.8)	> 0.99	32 (5.9)
Due SC1, n	33		46		416
Underwent SC1, n (% due)	33 (100)		40 (87.0)		340 (81.7)
Months to SC1, median (IQR)	5 (4.1 – 6.0)	0.25	5.1 (4.4 – 5.7)	0.07	5.4 (4.8 – 6.7)
Recurrence at SC1, n (%)	5 (15.2)	0.99	11 (27.5)	0.049	53 (15.3)
Histologic recurrence at SC1, n (%)	4/26 (15.4)	> 0.99	7/37 (18.9)	0.74	38/228 (16.7)
Surgery at SC1, n (%)	0 (0)	> 0.99	0 (0)	> 0.99	3 (0.9)
Due SC2, n	21		34		310
Underwent SC2, n (% due)	16 (76.2)		24 (70.5)		109 (35.2)
Months to SC2, median (IQR)	17.5 (11.8 – 21.6)	0.85	14.7 (9 – 16.7)	0.04	17.2 (13.1 – 19.3)
Recurrence at SC2, n (%)	1 (6.3)	0.57	5 (20.8)	0.02	5 (4.6)
Late recurrence at SC2[2], n (%)	1 (6.3)	0.50	1 (4.2)	> 0.99	4 (3.7)
Histologic recurrence at SC2, n (%)	1/7 (14.3)	0.44	2/16 (12.5)	0.60	4/59 (6.8)
Surgery at SC2, n (%)	0 (0)	> 0.99	1 (4.2)	0.18	0 (0)

LSL, laterally spreading LSL; CAST, cold avulsion and adjuvant snare-tip soft coagulation; SC1, first surveillance colonoscopy; SC2, second surveillance colonoscopy; IQR, interquartile range;
[1] Compared with lifting LSLs.
[2] Late recurrence was defined as recurrence occurring after a previously negative surveillance examination. Recurrence denotes endoscopic determination of adenoma recurrence at an endoscopic resection scar unless otherwise stated.

cause of submucosal invasive cancer in the EMR specimen. One of these patients with a lifting LSL had surgery as an inpatient because of a delayed perforation. One NNL containing submucosal invasive cancer was managed with endoscopic follow-up owing to the age and wishes of the patient.

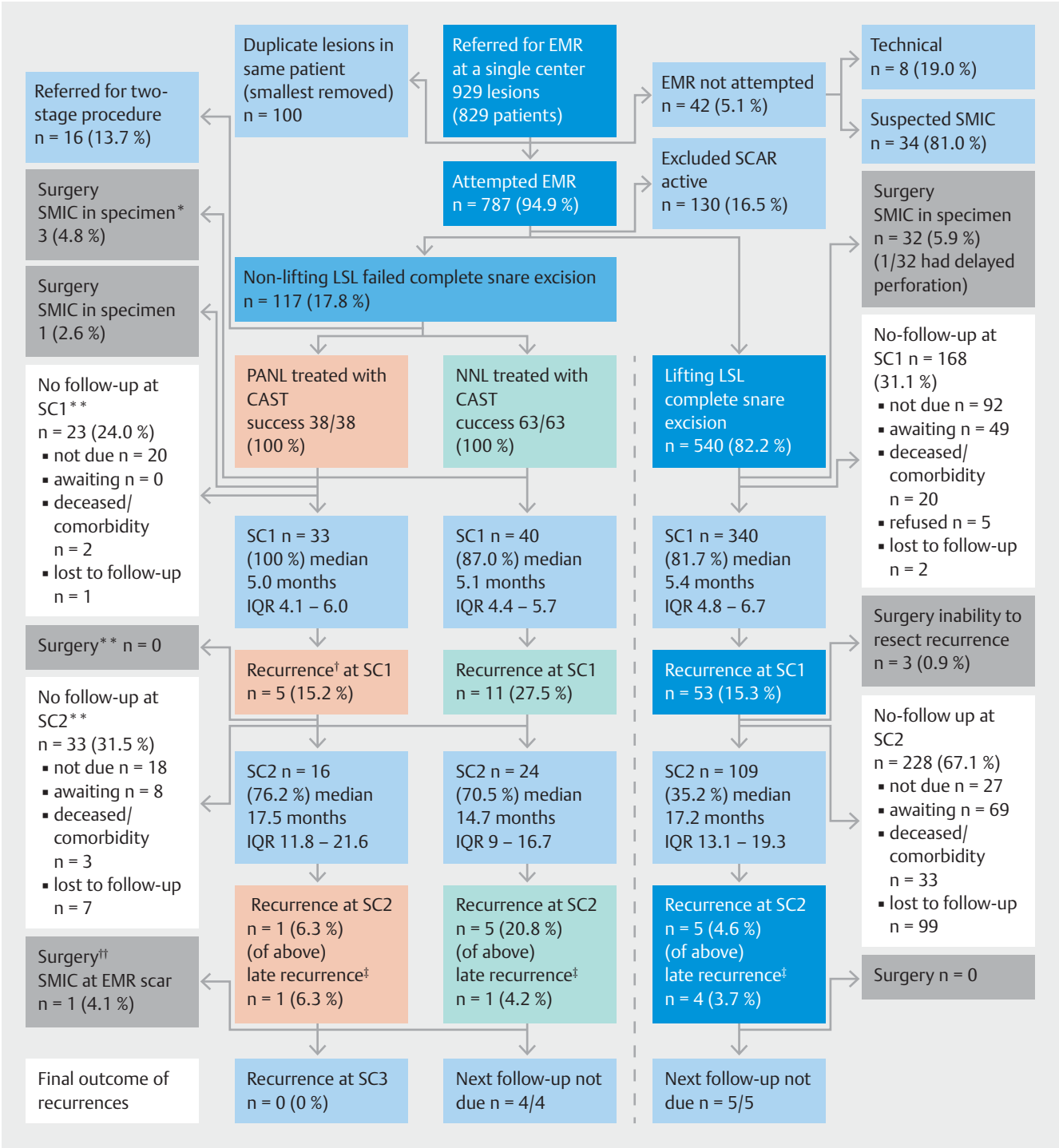
The first follow-up examination (SC1) was performed in 33 PANLs, 40 NNLs, and 340 lifting LSLs (100 %, 87.0 %, and 81.7 % of eligible patients, respectively) at a median of 5.4 months (IQR 4.6 – 6.5 months). Reasons for missing follow-up data are presented in ▶ **Fig. 4**. Recurrence at SC1 was detected in the EMR scar of 5/33 PANLs (15.2 %; *P* = 0.99) and 11/40 NNLs (27.5 %; *P* = 0.049) compared with 53/347 lifting LSLs (15.3 %). Histologically determined recurrence was no different between the groups. Amongst all of the non-lifting LSLs, there was no significant difference vs. lifting LSLs in recurrence at SC1 (16/73 [21.9 %] vs. 53/347 (15.3 %); *P* = 0.16). Of these 69 cases of recurrence, 66 (95.7 %) were treated endoscopically at SC1. No surgery was performed in the PANL and NNL groups at SC1. Three patients (0.9 %) in the lifting LSL group underwent surgery because of inability to resect the recurrence.

Data are available on 16 patients with PANL, 24 with NNL, and 109 with lifting LSL who have undergone a second follow-up colonoscopy (SC2). Recurrence was more common in the NNL group (5/24 [20.8 %]) than in the lifting LSL group (5/109 [4.6 %]; *P* = 0.02), whereas PANL recurred at a similar rate to lifting LSL (1/16 [6.3 %]; *P* = 0.57). Surgery was required at SC2 owing to malignancy within the EMR scar in one patient who had undergone CAST 11.7 months previously for a 40-mm NNL with focal high grade dysplasia. No surgery was required in the other two groups at SC2. After two follow-up procedures, 94/95 patients (98.9 %) that underwent CAST and were eligible for follow-up had avoided surgery.

Discussion

Non-lifting adenomas are difficult to resect endoscopically and have traditionally necessitated surgery. A simple, safe, and effective technique to manage non-lifting LSLs has not been described. In this study, CAST was technically successful in the complete removal of all 101 cases of non-lifting adenoma within a complex population of LSLs referred for tertiary endoscopic resection. The adverse event profile was similar to that of standard EMR for lifting lesions during the same time period. In addition, adenoma recurrence was not significantly more common overall than it was following the standard EMR technique at SC1. Amongst a group of LSLs that would otherwise have required surgery, 94/95 patients (99 %) eligible for follow-up avoided surgery.

Other endoscopic techniques to treat non-lifting LSLs have been described, but all suffer from increased complexity of the procedure, limited experience and/or follow up, or lack of availability. Hot avulsion [8, 9] is the most promising technique; first described by Haber et al., it is effective and, similarly to CAST, can precisely target non-lifting adenomas. Histology of the non-lifting area may not be reliably obtained because of electrocautery artefact. In the largest (retrospective) descrip-



▶ **Fig. 4** Design of the study and recruitment. The fate of all lesions referred for EMR during the study period is displayed. CAST, cold-forceps avulsion with adjuvant snare-tip soft coagulation; EMR, endoscopic mucosal resection; IQR, interquartile range; LSL, laterally spreading lesion; NNL, naïve non-lifting LSL; PANL, previously attempted non-lifting LSL; SC1/2, surveillance colonoscopy 1/2; SCAR, randomized study assessing the effect of snare-tip soft coagulation of the margin of the EMR defect on adenoma recurrence; SMIC, submucosal invasive cancer. * One patient declined surgery but had submucosal invasive cancer in the specimen. ** Denotes losses from both non-lifting LSL cohorts. † Denotes endoscopic determination of recurrence. †† Surgery was performed on a patient in the NNL cohort. ‡ Late recurrence was that which occurred after a previously negative surveillance examination.

tion of hot avulsion to date [14], 46 LSLs with non-lifting were treated with complete snare excision and subsequent hot avulsion, within a parent cohort where 49 % of the LSLs required methods other than complete snare excision for complete removal (17.8 % in our study). The recurrence rate was 10.3 % in 29 patients who underwent first follow-up. No description of later follow-up was given. There is also concern regarding the unpredictability of the depth of thermal injury when using hot biopsy forceps for diminutive polypectomy [15]; this may be an issue for the hot-avulsion technique, although it is argued that the risk is mitigated by using cutting current.

Circumferential mucosal incision prior to EMR [6] allows resection of non-lifting adenomas by creating a mucosal step and enhancing snare capture. The technique is limited by the lesion size for en bloc resection and the requirement for skill in endoscopic submucosal dissection (ESD) techniques to create the mucosal incision. In our experience, snare purchase on non-lifting adenomas can be improved by using the standard EMR technique to resect surrounding lifting tissue (both normal and adenomatous) in a similar fashion, without the need for the ESD techniques.

ESD has been described in the context of non-lifting LSLs in multiple small case series that have all found lower rates of en bloc resection with increased rates of complications as compared to ESD for lifting LSLs [16 – 19]. In a recent (retrospective) analysis by Lee et al. [20], 173 patients with F1 (mild) or F2 (severe) submucosal fibrosis underwent ESD in a Korean center; en bloc resection rates were 93.6 % and 77.4 % for F1 and F2 fibrosis, respectively. In the F2 group, 19.4 % patients experienced a perforation, 27.4 % required surgery, and 40.3 % of procedures lasted longer than 90 minutes. While we did not prospectively grade the degree of fibrosis in this study, all non-lifting LSLs had submucosal fibrosis comparable to F1 or F2. Given the median procedure time for EMR with CAST of 30 – 35 minutes for our group of similarly sized lesions, the significantly higher rate of complications and surgery associated with ESD, and the higher opportunity cost of ESD, the CAST technique is appealing.

Forced argon plasma coagulation (APC) following injection of a saline cushion showed promise in a small single-center series [7], but does not allow for histopathological analysis, so there is concern regarding missed high grade histology within non-lifting adenomas. In addition, if the submucosa is able to be expanded with a saline cushion then snare resection is likely to be possible.

We have some experience of completing complex and non-lifting lesions at a second stage procedure at our center [21]. This represents a safe and effective alternative to single-session EMR when there is extensive residual adenoma. The downside of this approach is the need for a repeat colonoscopy, its morbidity, patient compliance, and loss of workdays. The majority of non-lifting LSLs have small areas of non-lifting that are readily amenable to CAST and therefore two-stage EMR seems applicable to the very complex lesions encountered in tertiary centers.

Recently the use of a device allowing endoscopic full-thickness resection in the colon has been described in cases of non-lifting adenoma [22]. The acquisition of full-thickness histology was described in 21/24 cases (87.5 %), in lesions with a mean diameter of 24 mm. However, the device is large and cumbersome, requires re-insertion of the colonoscope to mount, and is very expensive. Future iterations of the device are awaited and may provide a useful option for the treatment of PANLs.

CAST is a simple technique that can be performed by all interventional endoscopists. It requires no extra equipment in addition to a biopsy forceps, which is ubiquitous in endoscopy departments worldwide. Key to the technique is the removal of normal and/or adenomatous tissue surrounding the non-lifting area with a snare prior to attempting CAST. After this, the non-lifting adenoma tears away from the underlying fibrosis easily once the lateral margins have been freed. Accurate targeting of the non-lifting adenoma is possible by working systematically and controlling the tip with the shaft of the endoscope. Histology of the non-lifting area is reliably obtained, which is important because of the association of non-lifting with high grade dysplasia and submucosal invasion. A systematic approach should be made to ensure complete removal of all visible non-lifting adenoma. STSC is applied to the avulsion bed using the tip of the same snare used to perform the EMR. Standard snares produce the best effect. The technique is a light touch of the snare over the avulsion bed and is extremely precise and very safe owing to the properties of the soft-coagulation current [23].

The recently described Sydney Classification of Deep mural injury [12] describes five levels of potential injury to the colonic wall after EMR that can be identified by features of the post-EMR defect. As may be evident from the figures, CAST can lead to type II deep mural injury within the post-EMR defect; this describes focal loss of the submucosal plane raising concern for muscularis propria injury or rendering the defect uninterpretable. It is our practice to close all defects exhibiting type II deep mural injury with endoscopic clips. There was no incidence of delayed perforation within non-lifting LSLs treated with CAST.

The rates of adenoma recurrence in PANLs after the use of CAST were comparable to those after resection of lifting LSLs with complete snare excision, which is remarkable given the complexity of these lesions. Moreover, late recurrence – that which occurs after a negative surveillance examination – was comparatively rare in all of the groups. While it is therefore possible to treat PANLs successfully, the optimal scenario would be their avoidance by complete snare excision at the first attempt. This is achievable in the vast majority of lesions with good technique and, perhaps, more attention should be paid to teaching programs for advanced endoscopy and lesion selection; for example, a recent scoring system showed the utility of predicting the difficulty of EMR from a well-worded referral letter [24].

The reason for the higher rate of adenoma recurrence in NNLs is not immediately obvious. NNLs are a population of naïve lesions that all exhibit dense submucosal fibrosis (F1 or F2), are biopsied, and marked with carbon particle suspension at a similar rate to PANLs and do not display any evidence of higher rates of submucosal invasive cancer than lifting LSLs. Further study is required to unravel the details, but it is possible that NNLs are a specific subset of LSLs with unique biology that makes them difficult to resect endoscopically because of exten-

sive submucosal fibrosis. An ability to predict whether a specific LSL is an NNL would be helpful in this context, although no such red flag was identified in this study. Overall, despite a higher incidence, all recurrences were endoscopically treatable in the NNL group, except for the single malignancy detected at SC2.

The only surgery performed during follow-up of the NNL group was for a 40-mm tubulovillous adenoma with focal high grade dysplasia in the distal transverse colon of a patient with serrated polyposis syndrome. The EMR scar had been reported clear at the first surveillance procedure (5.7 months after the index procedure) but had not been biopsied and multiple other large lesions were removed during this procedure. At 12 months after the index procedure, when the procedure was repeated, a 10-mm depressed lesion consistent with malignancy was detected in the transverse colon. The patient was referred for surgery and the specimen showed submucosal invasive cancer (SM3), with no lymph nodes involved. On retrospective review of this case, it is possible that the scar was not correctly visualized at SC1 and that the endoscopist was distracted by the many other lesions and scars. This case demonstrates the need for rigorous follow-up examinations after EMR, especially if ablative techniques are used, including localization and meticulous interrogation of the EMR scar with a structured scar assessment [25], using high definition white-light and NBI.

The strengths of this study include the fully characterized, prospectively collected, large population of complex non-lifting LSLs with a large comparator cohort of lifting LSLs, themselves complex, which serve to highlight the difficulty of resecting non-lifting LSLs, even in expert tertiary centers. Excluding 130 lesions that underwent thermal ablation to the margin as part of a randomized trial (the SCAR study) allowed a fair comparison of recurrence rates between non-lifting LSLs and LSLs because non-lifting LSLs were excluded from SCAR.

A limitation of this study is that it comes from a single center. In addition, further long-term follow-up data (particularly for the lifting LSL cohort) are clearly required to validate these initially promising results. Moreover, a large multicenter study would be beneficial to ensure the wider applicability of the technique.

In conclusion, in this prospective series of over 100 patients, drawn from a cohort of 829 referred for EMR, CAST was a safe, effective, and cost-saving method to avoid surgery in patients with non-lifting adenoma. PANLs treated in this way are similar to lifting LSLs resected by complete snare excision as, once they are fully resected, they do not recur more frequently. Methods of matching the complexity of a lesion to the skillset of individual operators/departments are required to avoid the occurrence of PANLs. NNLs are a specific subset of lesions whose biology makes them uniquely more difficult to resect endoscopically because of dense submucosal fibrosis, and they recur more frequently. Further characterization of NNLs to identify and direct them to tertiary endoscopic centers is required.

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Competing interests:

None

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