ORIGINAL ARTICLE

Deep mural injury and perforation after colonic endoscopic mucosal resection: a new classification and analysis of risk factors

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ABSTRACT

Objectives Perforation is the most serious complication associated with endoscopic mucosal resection (EMR). We propose a new classification for the appearance and integrity of the muscularis propria (MP) after EMR including various extents of deep mural injury (DMI). Risk factors for these injuries were analysed.

Design Endoscopic images and histological specimens of consecutive patients undergoing EMR of colonic laterally spreading lesions ≥20 mm at a large Australian tertiary referral endoscopy unit were retrospectively analysed using our new DMI classification system. DMI was graded according to MP injury (I/II intact MP without/with fibrosis, III target sign, IV/V obvious transmural perforation without/with contamination). Histological specimens were examined for included MP and patient outcomes were recorded. All type III–V DMI signs were clipped if possible, types I and II DMI were clipped at the endoscopists' discretion.

Results EMR was performed in 911 lesions (mean size 37 mm) in 802 patients (male sex 51.4%, mean age 67 years). DMI signs were identified in 83 patients (10.3%). Type III–V DMI was identified in 24 patients (3.0%); clipping was successfully performed in all patients. A clinically significant perforation occurred in two patients (0.2%). Only one of the 59 type I/II cases experienced a delayed perforation. 85.5% of patients with DMI were discharged on the same day, all without sequelae. On multivariable analysis, type III–V DMI was associated with transverse colon location (OR 3.55, p=0.028), en bloc resection (OR 3.84, p=0.005) and high-grade dysplasia or submucosal invasive cancer (OR 2.97, p 0.014).

Conclusions In this retrospective analysis, use of the new classification and management with clips appeared to be a safe approach. Advanced DMI types (III–V) occurred in 3.0% of patients and were associated with identifiable risk factors. Further prospective clinical studies should use this new classification.

Trial registration number NCT01368289; results.

Significance of this study

What is already known on this subject?

- Perforation is a major complication associated with endoscopic mucosal resection (EMR). Delayed perforation is associated with poorer outcomes including emergency surgery, morbidity or death.
- The target sign has previously been shown to identify muscularis propria (MP) injury. Prophylactic clipping of MP injury may prevent delayed perforation.

What are the new findings?

- Type III–V deep mural injury (DMI) (target signs or perforation) occurs in 3.0% and is associated with transverse colon location, en bloc resection and high-grade dysplasia or submucosal invasive cancer.
- Attempted en bloc excision of lesions ≥25 mm is strongly associated with major DMI.
- Identification and proactive management of these injuries was associated with low rates of clinically significant sequelae in this large prospective cohort.

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

- Endoscopists should carefully assess the risks and benefits of en bloc resection before attempting endoscopic mucosal resection (EMR) of lesions ≥25 mm in size.
- Transverse colon lesions and those with endoscopic evidence of high grade dysplasia (HGD) or cancer should be resected cautiously due to the risk of deep mural injury (DMI).
- Identification and proactive management of DMI is important in order to minimise clinically significant adverse events related to EMR.

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INTRODUCTION

Endoscopic mucosal resection (EMR) for large colonic laterally spreading lesions is a safe and effective technique that eliminates the need for surgery in the majority of patients and results in substantial reductions in overall healthcare resource utilisation.[1] Perforation remains the most feared complication of EMR and is a potentially life-altering event for both patient and endoscopist. Despite recent advances[2] it remains an inherent limitation of the technique. Delayed perforation is the most serious form as it occurs after the procedure, usually out of hospital and does not afford the endoscopist an opportunity to intervene endoscopically to close the defect non-operatively. It is likely

that endoscopically subtle muscularis propria (MP) injury is responsible for most delayed perforations. Methods of classifying and prophylactically treating MP injury may avert a later complication. Endoscopic clip closure of mucosal and full thickness defects is highly effective;[3] it however relies upon identification of the deep injury at the time of endoscopic resection (ER). Incorporation of a contrast dye into the submucosal lifting solution in combination with careful examination of the postresection defect facilitates assessment of the mucosal defect for evidence of MP injury and is a potential method of stratifying risk for and avoiding delayed perforation. The specimen target sign (STS) and defect target sign (DTS) have been previously proposed as a simple means of identifying injury to the MP[4] however this only represents part of the spectrum of deep mural injury (DMI). In this study we aimed to classify DMI following EMR, identify key predictors of these injuries and correlate DMI types to histological evidence of MP resection and outcomes. We also postulate that DMI can guide postprocedure patient management and propose a management strategy based on the classification system.

METHODS

Consecutive patients referred to a large academic tertiary centre for the management of sessile or laterally spreading colorectal lesions ≥20 mm in size were enrolled in this study. All lesions had been initially identified and referred by a nationally accredited consultant endoscopist. Data were recorded in a comprehensive centralised database from March 2010 to September 2014. The study was approved by the Western Sydney Local Health District Human Research and Ethics Committee. Written informed consent was obtained from each patient on the day of the procedure.

Patients were excluded from analysis if they did not undergo EMR because of suspicion of malignancy or for technical reasons. There were no other exclusion criteria.

All EMR procedures were performed by a study author (MJB or SJW) or a senior therapeutic endoscopy fellow under their direct supervision. Colonoscopy was performed using Olympus 180 or 190 series variable-stiffness colonoscopes (Q180/190 PCF/CF; Olympus, Tokyo, Japan). The EMR technique is standard and has previously been described in detail.[1 5 6] En bloc resection was attempted at the endoscopist's discretion, typically for lesions smaller than 25 mm. For larger lesions, sequential inject-and-resect piecemeal EMR was performed. The injection solution consisted of 1 mL of 0.4% indigo carmine or methylene blue and 1 mL of 1:10 000 adrenaline combined with 8 mL of normal saline solution. After EMR, patients remained in recovery for 4–6 hours until they were medically cleared for discharge by the endoscopist.

A DMI classification system was devised by the study authors based on clinical observations and image analysis. The classification incorporates the established clinical entities of target signs and perforations. It also describes defects where the MP is exposed but not injured (type I) or where assessment is unclear due to fibrosis (type II). These injuries (types I and II) were designated as Potential DMI. The schema is outlined in figure 1. A schematic of DMI is demonstrated in figure 2. Descriptions and examples of DMI type I–V are demonstrated in figures 3–5.

Types I and II DMI was were clipped at the discretion of the treating endoscopist. If a type III or IV DMI (STS/DTS or perforation) was observed then endoscopic clip closure was attempted during the procedure. Closure across the area of MP injury (submucosa to submucosa) was performed. Closure of the entire defect (mucosa to mucosa) was typically not performed. EMR defects without injury were not routinely clipped closed in this study.

All patients undergoing EMR were routinely observed for 4 hours following the procedure. Any patient with evidence of type I–IV DMI was closely observed and had urgent CT scan if they had ongoing pain. If they were well and the endoscopist was confident that any clip closure performed was secure, they were discharged with oral antibiotics on a clear fluid diet overnight, resuming a normal diet the following day. If they had ongoing pain, CT evidence of free intraperitoneal air, or abnormal vital signs they were observed in hospital, fasted and started on intravenous antibiotics. Patients with type V DMI were routinely admitted and observed. Surgical consultation was obtained on all patients requiring admission after DMI.

After an uncomplicated procedure patients were eligible for same day discharge. Dietary instructions were for clear fluids overnight and to resume a normal diet the following day. Written postprocedural instructions were provided including information on potential problems and contact details for advice.

Data

Information was prospectively collected at the time of patient admission, during, and then immediately after the procedure. Analysis of outcomes was performed retrospectively. Data included patient demographics and comorbidities, American Society of Anesthesiologists (ASA) grade, and medications, including time of antiplatelet or anticoagulation cessation. Lesion features including surface morphology, size and location were recorded. Paris classification was used to define the overall

Sydney Classification of Deep Mural Injury (DMI) following EMR

Type 0	Normal defect. Blue mat appearance of obliquely oriented intersecting submucosal connective tissue fibres.
Type I	MP visible, but no mechanical injury.
Type II	Focal loss of the submucosal plane raising concern for MP injury or rendering the MP defect uninterpretable.
Type III	MP injured, specimen target or defect target identified
Type IV	Actual hole within a white cautery ring, no observed contamination
Type V	Actual hole within a white cautery ring, observed contamination

Figure 1 Sydney classification of deep mural injury following endoscopic mucosal resection. EMR, endoscopic mucosal resection; MP, muscularis propria.

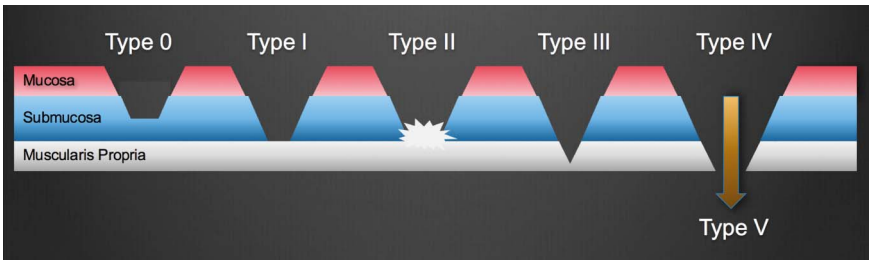

Figure 2 Schematic of the Sydney classification of deep mural injury following endoscopic mucosal resection.

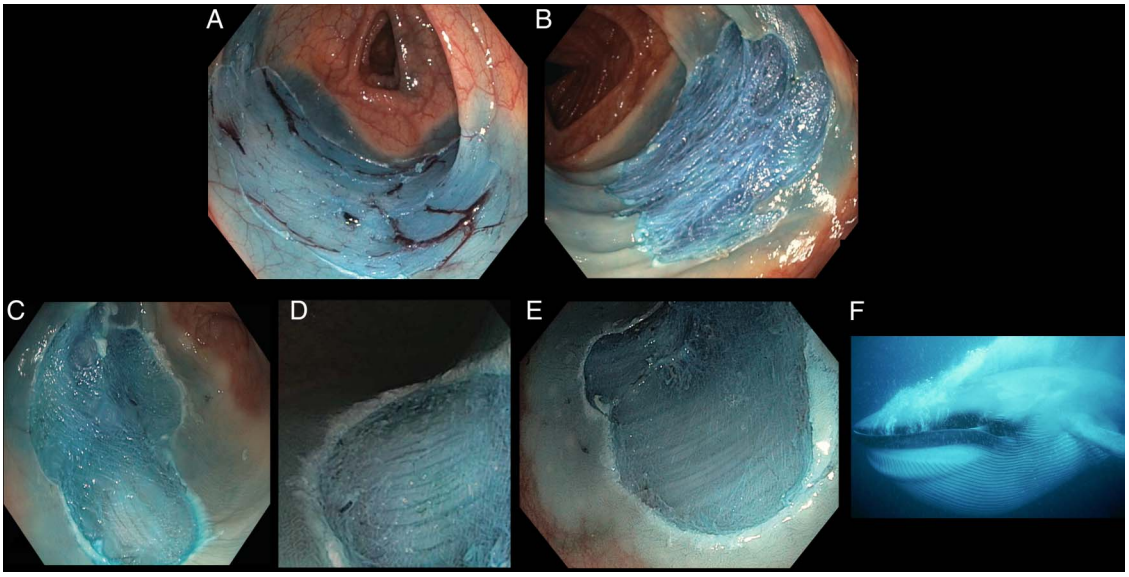

Figure 3 (A, B) A 'type 0' defect is a normal postresection finding. The mucosa has been completely resected revealing the underlying partially resected submucosa. The submucosa is homogeneously stained by the chromogelofusine dye. Submucosal vessels may be exposed but are uninjured. (C, D, E, F) A 'type I' defect occurs when the submucosa has been completely resected and the underlying muscularis propria (MP) is revealed. The MP does not avidly stain with the chromic dye so has a white appearance, and the circumferential striations of the muscle layer are seen. This appearance resembles the ventral pleats of a blue whale seen from underwater so is referred to as the 'whale' sign (F). © Doc White / naturepl.com.

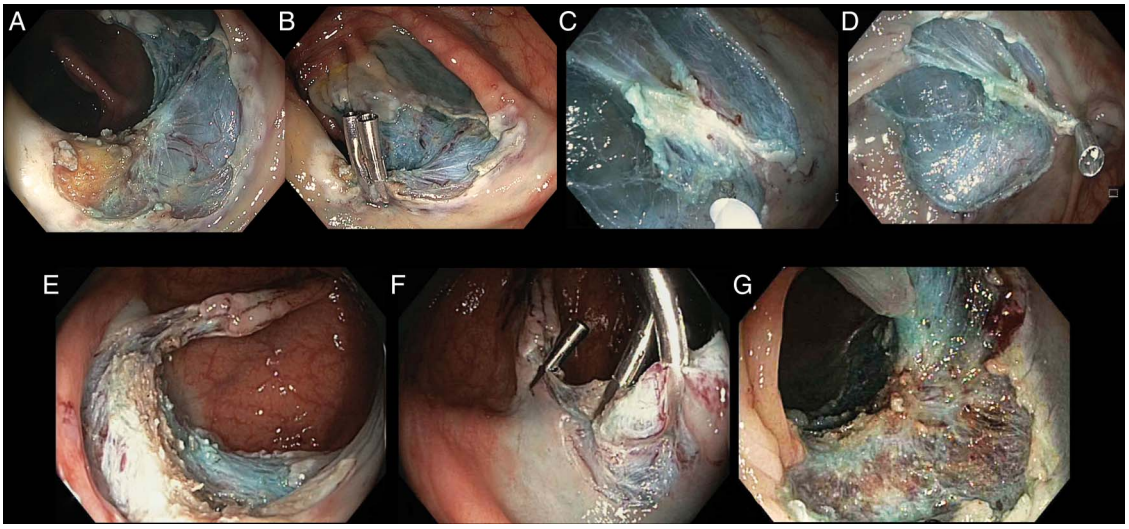

Figure 4 In a 'type II' defect, the distinction between submucosa and muscularis propria is unclear often due to poorly staining submucosal fibrosis. (A) In this image, an area of poorly staining defect and submucosal fat is noted following snare resection. (B) Two clips are placed over the area of concern. (C) A focal area of fibrosis is noted following resection of a 30 mm caecal lesion. The area is interrogated by topical application of dye staining via an injection catheter with the needle retracted, however, it remains unstained. Clips are then placed across the area of concern. The first clip is shown in-situ, further clips were subsequently placed to close the entire fibrotic area. (E, F) An area of poor staining overlying a fold is treated with three clips. (G) This defect has a central area of fibrosis and cautery effect impairing the assessment of deep injury.

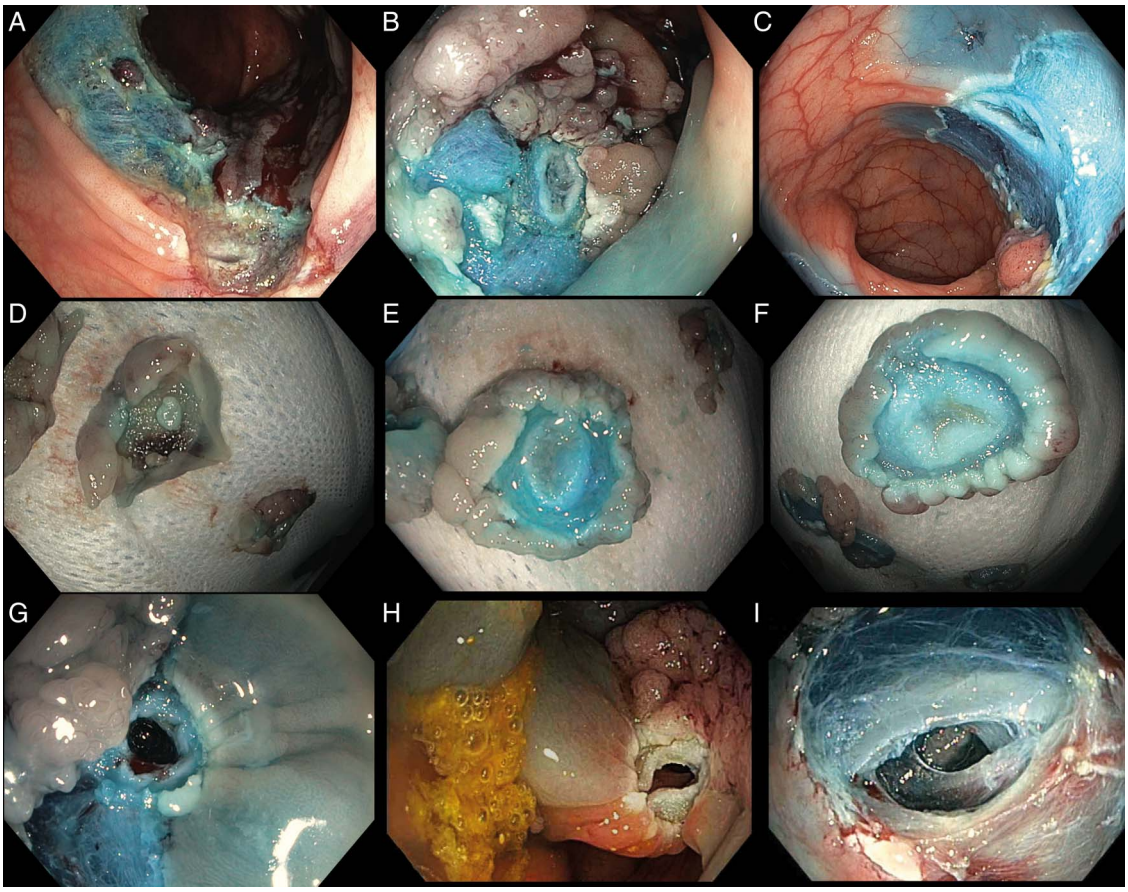

Figure 5 A 'type III' defect refers to partial resection of the muscularis propria resulting in a defect target sign (DTS) (A, B, C) or a specimen target sign (D, E, F). These defects require clip closure of the DTS to prevent delayed perforation. A type IV defect is a complete hole, or full-thickness resection of the muscularis propria which is clean and not contaminated by faecal effluent. (G, H, I) A concentric ring of cautery artefact to the muscularis is observed. These defects should be closed immediately, although resection of the surrounding adenoma prior to clip placement should be performed where possible. If the closure site is not clear of adenoma, follow-up attempts at resection may be hampered by submucosal fibrosis, clip artefact and buried adenoma. A type V defect occurs where the full thickness perforation is contaminated by faecal effluent. These defects should also be closed and a surgical consultation obtained. Acute surgical intervention is required if there is clinical deterioration, features of peritonitis, evidence of significant free intraperitoneal fluid or failed endoscopic resection.

polyp morphology.[7] Technical aspects were noted, including the subjective level of difficulty in accessing and positioning for resection of the lesion, adrenaline use in the submucosal injectate, en bloc or piecemeal resection and whether complete snare excision was achieved. Lifting was assessed in three categories: 'Lifts freely' for lesions that lift well without tethering; 'Partial lifting' for lesions where lifting is impaired but the resection is proceeded with; and 'Non-lifting' where the procedure is abandoned and snare resection is not attempted. Snare resection was not attempted on non-lifting lesions so these were excluded from analysis. Where patients had two or more lesions resected in one procedure, one lesion was selected at random for analysis.

Clinical follow-up for the index procedure was obtained at 14 days by structured telephone interview in accordance with American Society for Gastrointestinal Endoscopy (ASGE) guidelines[8] and at 4–5 months scheduled endoscopic review.

Data on DMI type III–V and clip placement were collected prospectively from March 2010 onwards after the target sign had been described.[4] In addition to this, all endoscopy reports were reviewed systematically for the keywords deep, muscularis, muscle, clip, clips, clipping, closed, closure, perforation and injury. Types I and II DMIs were collected prospectively and assessed in real time from August 2013 and reviewed retrospectively from procedure reports and a comprehensive photo record prior to that. In the total cohort, photographs were not available or inadequate in 67/911 lesions (7.4%) or 55/802 patients (6.9%). In all of the cases without images there was no description of deep injury in the procedure report. Clinically significant perforation was defined as perforation with associated peritoneal contamination or clinical signs of peritonitis, and any perforation requiring surgical management. Perforation without peritoneal contamination, managed with endoscopic clipping and observation in an asymptomatic patient was not deemed clinically significant as management was identical to that of a type III DMI. Delayed perforation was defined as readmission occurring after procedural discharge with clinical and imaging findings consistent with perforation at the EMR site. Delayed perforation is an infrequent outcome, so it is important to stress that the study was not designed to predict delayed perforation, but to characterise or clarify the appearance of the EMR defect at the completion of EMR and classify DMI.

Data analysis

SPSS statistical software (IBM, 2012, IBM SPSS Statistics, V.22.0. Armonk, New York, USA) was used to analyse the data. All analyses were exploratory and two-tailed tests with a

significance level of 5% were used throughout. No attempt was made to correct for multiple comparisons. Mann-Whitney U tests were used to test for differences in the distribution of age, lesion size and ASA grade by bleeding status. Pearson's χ^2 test or Fisher's exact test was used to test for association between categorical variables and outcome. Multiple logistic regressions with backward stepwise variable selection were used to identify the independent predictors of outcomes of interest. Candidate variables with p values for association that were ≤0.1 on univariable analysis were considered as potential risk factors in multiple logistic regression analysis. Backward stepwise variable selection was used to identify the best fitting model for independent predictors of DMI type I–II or DMI type III–V (target signs or perforation). ORs with 95% CIs from the model were used to quantify the extent of this association.

RESULTS

Between March 2010 and September 2014, 983 lesions were assessed for endoscopic resection (figure 6).

EMR was attempted in 911 lesions (mean size 37 mm, hepatic flexure and proximal 53.3%) in 802 patients (male sex 51.4%, mean age 67 years). DMI signs were identified in 83 patients (10.3%). Study patient characteristics are listed in table 1.

Complete excision was achieved in 874/911 lesions (95.9%). One hundred and nineteen of 911 lesions (13.0%) were resected en bloc with a mean size 23.3 mm (SD 4.6). Thirty-seven patients had incomplete excision. Sixteen patients were referred for elective surgical resection. Eighteen patients returned for successful endoscopic treatment of the residual polyp, one patient required two sessions for complete resection. Three patients had incomplete follow-up data at 5 months.

Deep mural injury

Of the 83 patients with DMI, 19 patients (22.9%) had DMI type I, 40 (48.2%) had DMI type II. Nineteen patients had DMI type III, of which 12 patients (14.5%) had both a DTS and STS and 7 (8.3%) had a DTS alone. Five patients had an intraprocedural perforation; four patients (4.8%) had perforation without contamination (type IV) and one patient (1.2%) had contamination (type V). A clinically significant intraprocedural perforation occurred in one patient (1.2%). Twenty-four patients (28.9%) had DMI type III–V, representing 3.0% of the total cohort.

Of the cases 74.7% were managed with clip placement (mean no. of clips 3.1, SD 1.6) (table 2). Of the type I defects 31.6% were clipped at the endoscopists' discretion. All but one of the major DMI signs were clipped. One type III defect was not clipped, contrary to the established protocol to clip all type III–V injuries. Of the patients 71/83 (85.5%) were discharged on the same day. One patient had surgery following complete clip closure of an intraprocedural perforation where the lesion was in a difficult position with significant submucosal fibrosis (SMF) meaning that subsequent attempts at removing the residual adenoma would be difficult. There were no deaths in the cohort.

Rates of postprocedure pain did not differ between those who had DMI compared with those without injury (any DMI 2.4% vs 2.1%, p 1.0; DMI type III–V 0% vs 2.2%, p=0.68).

Type II injuries were rated according to focal or generalised fibrosis. We defined focal as involving ≤10% of the completed defect. After review only one defect had generalised fibrosis, and this was largely because it was a smaller (20 mm) lesion.

Histology

MP was not present in any type 1 DMI histology specimens, but was found in increasing frequency in DMI types II–V (table 2). MP was present in 83% of type III DMIs where both an STS and DTS were present. MP was less often seen in type III DMI (40%) where only a DTS was present as although the MP may have been disrupted and resected in the defect, this was either superficial or not evident in the resected specimen presented to

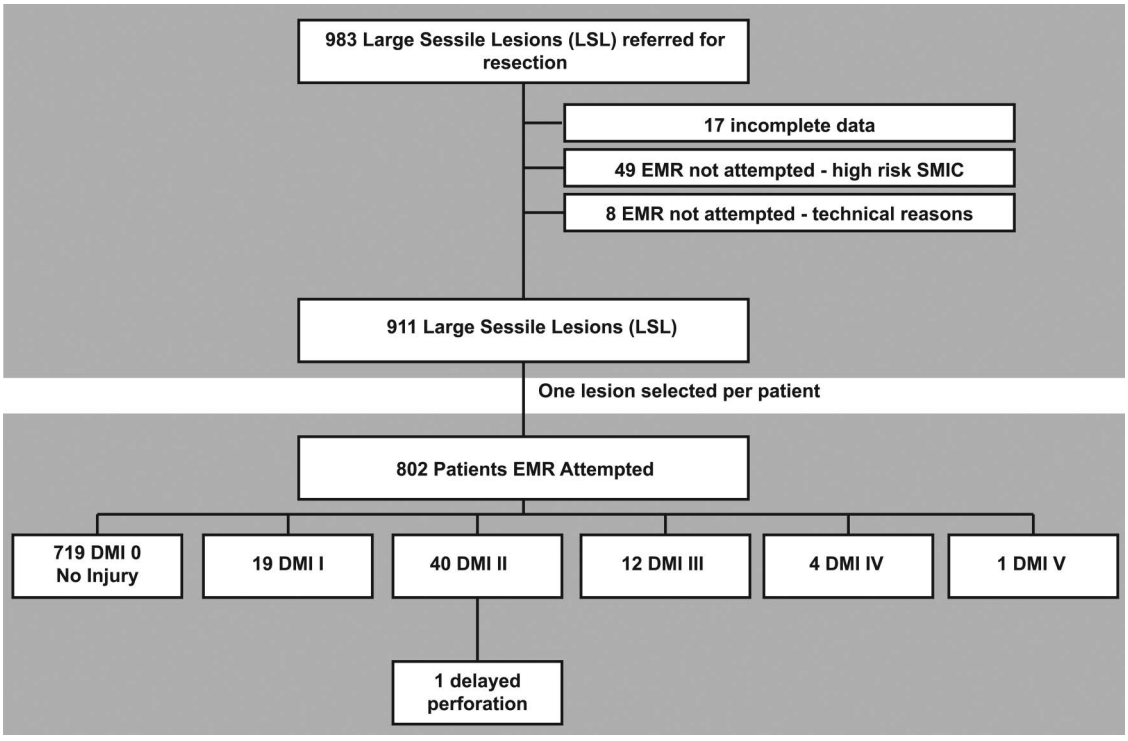

Figure 6 Study flow diagram. DMI, deep mural injury; EMR, endoscopic mucosal resection; SMIC, submucosal invasive cancer.

Table 1 Characteristics of study patients

	Patient characteristics
Patient factors	
Age (years); mean (SD)	66.8 (11.8) Range (18–88 years)
Sex	
Male	412 (51.4%)
Female	390 (48.6%)
ASA (n, %)	
ASA 1	433 (53.9%)
ASA 2	321 (40.0%)
ASA 3	45 (5.6%)
Lesion and procedure factors	
Lesion size (mm); mean (SD)	29.2 (9.9) Range (20–80 mm)
Lesion location (n, %)	
Rectum <5 cm	39 (4.9%)
Rectum >5 cm	122 (15.2%)
Sigmoid	86 (10.7%)
Descending colon	24 (3.0%)
Splenic flexure	11 (1.4%)
Distal transverse	24 (3.0%)
Mid transverse	38 (4.7%)
Proximal transverse	34 (4.2%)
Hepatic flexure	57 (7.1%)
Ascending colon	185 (23.1%)
Caecum	140 (17.5%)
Caecum ICV involved	37 (4.6%)
Caecum appendiceal orifice involved	5 (0.6%)
Lesion location (n, %)	
Rectum to proximal transverse colon (distal colon)	378 (47.1%)
Hepatic flexure to cecum (proximal colon)	424 (52.9%)
Paris classification (n, %)	
0–IIa or 0–IIb	453 (56.5%)
0–IIa+Is	240 (29.9%)
0–Is	75 (9.4%)
Any 0–IIc component (0–IIa+c, 0–IIc)	33 (4.1%)
Histology	
Majority polyp histology (n, %)	
Tubular adenoma	213 (26.6%)
Tubulovillous adenoma	458 (57.1%)
Villous adenoma	3 (0.4%)
Sessile serrated adenoma/polyp (SSA/P)	116 (14.4%)
Traditional serrated adenoma (TSA)	7 (0.9%)
Other	5 (0.6%)
Submucosal invasive cancer (SMIC)	53 (6.6%)

ASA, American Society of Anesthesiologists; ICV, ileo-caecal valve.

the pathologist. The mean area and depth of MP in the specimen did not differ between type III, IV and V DMIs. DMI types I and II differed from DMI types III, IV and V by mean area (3.6 mm^2 vs 21.1 mm^2, p 0.007) and mean depth (0.65 mm vs 1.38 mm, p 0.004) (figure 7).

On multivariable analysis, DMI type I–II was predicted by increasing size >40 mm (OR 1.78 (95% CI 1.02 to 3.11), p 0.043), SMF (OR 2.66 (95% CI 1.55 to 4.57), p<0.001) and transverse colon location (OR 2.43 (95% CI 1.11 to 5.34), p 0.027) compared with distal colon location (see online supplementary table S1). DMI type III–V (target signs or perforation) was associated with transverse colon location (OR 3.55 (95% CI 1.15 to 11.0), p=0.028), en bloc resection (OR 3.84 (95% CI 1.51 to 9.77), p=0.005) and high-grade dysplasia or submucosal invasive cancer (SMIC) (OR 2.97 (95% CI 1.25 to 7.06), p=0.014) (table 3).

En bloc resection

In 88 patients 119 lesions were resected en bloc. DMI type I–II was noted in two lesions and DMI type III–V in seven lesions. On univariable analysis, DMI type III–V was associated with larger lesion size (no injury 23.0 mm SD 4.6; DMI type III–V 27.1 mm SD 2.7, p=0.003) and SMIC (no SMIC 5/114, (4.4%) versus SMIC 2/5, (40%), p=0.027). Rates of DMI type III–V in those with no/low grade dysplasia (LGD) versus high grade dysplasia (HGD)/SMIC did not differ. Study power was inadequate to demonstrate a significant difference in the location of DMI for en bloc resected lesions, although a similar pattern to that seen in the larger study group was noted: rectum to splenic flexure 2/30 (6.7%), transverse colon 3/24 (12.6%), hepatic flexure to caecum 2/65 (3.1%) (p 0.26). No association was found when comparing sex, Paris or Kudo classification, SMF or lesion histology (sessile serrated adenoma/polyp (SSA/P) vs adenoma). All major DMIs occurred in lesions >25 mm in size. (<25 mm (0/69) 0% vs ≥25 mm (7/50) 14.0%, p=0.002).

Follow-up outcomes

Follow-up data for clinical events were available for 802 patients (100%) at 2 weeks and 683 patients (85.2%) at surveillance colonoscopy 1 (5 months). A delayed perforation occurred in one patient (0.1%). This 66-year-old patient had a DMI type II injury at the completion of resection of a 40 mm Paris 0–IIa tubulovillous adenoma with a focus of SMIC in the distal transverse colon. The defect was not closed with clips. Eight days following discharge, the patient developed low-grade abdominal pains and fevers. She presented to hospital 12 days following the procedure and was found to have small collections adjacent to the transverse colon with locules of gas suggesting perforation. An extended right hemicolectomy was performed. There was no residual polyp and no involvement of 14 resected lymph nodes. She was discharged well after 9 days in hospital.

DISCUSSION

Perforation is the most concerning complication associated with colonoscopic polypectomy and fortunately remains an infrequent event. In general endoscopic practice outside of academic referral centres, the perforation rate associated with polypectomy is 0.2–1.1%.[9 10] The largest prospective study, the Munich Polypectomy Study, reported a perforation rate of 1.1% from 3976 snare polypectomies. Major complications (combined perforation and major bleeding) were more common where polyps were sessile, over 20 mm in size or located in the right colon. The majority of perforation events were delayed. The perforation rate associated with EMR is less clear as the majority of studies are retrospective, have enrolled less than 200 patients and have considerable variation in follow-up practices. Prospective multicentre contemporary analyses of EMR[11 12] report perforation rates of 1.0–1.9% and a recent large meta-analysis reported rates of 1.5%, (95% CI 1.2% to 1.7%).[13] The perforation rate in this study of 0.5% and clinically significant perforation rate of 0.2%, fall below these figures and are less than the lower CI of the meta-analysis. Recent British Society of Gastroenterologists/Association of Coloproctology of Great Britain and Ireland guidelines for the management of large colon polyps suggest an 'aspirational standard' for EMR perforation of <0.5%.[14] This is unlikely to be achieved without a proactive and defined approach to the management of DMI (figure 8).

Table 2 Summary data of injury type, clip closure, histology and admission rates

Type	n	Per cent	Clip closure %	Mean n clips (SD)	MP in histology specimen	MP resection depth (n, %)	MP area mean mm^2 (SD)	Mean MP depth (mm)	Admission
Type 1	19	2.4	6 (31.6%)	2.00 (1.41)	0 (0.0%)	–	–	–	1 (5.3%)*
Type 2	40	5.0	33 (82.5%)	2.77 (1.26)	3 (7.5%)	'Nick' 2 (66.7%) Partial MP 1 (33.3%) Pericolic fat 0 Serosa 0	3.60 (1.73)	0.65 (0.22)	4 (10.0%)
Type 3	19	2.4	18 (94.7%)†	3.53 (1.70)	13 (68.4%)‡	'Nick' 0 Partial MP 4 (30.8%) Pericolic fat 8 (61.5%) Serosa 1 (7.7%)	22.0 (14.0)	1.36 (0.45)	6 (31.6%)
Type 4	4	0.5	4 (100%)	6.50 (0.71)	3 (75.0%)§	'Nick' 0 Partial MP 2 (66.7%) Pericolic fat 1 (33.3%) Serosa 0	16.33 (13.7)	1.57 (0.60)	3 (75.0%)
Type 5	1	0.1	1 (100%)	4	1 (100%)	'Nick' 0 Partial MP 0 Pericolic fat 0 Serosa 1 (100%)	27.0	1.10	1 (100%)

*Admission for bleeding, not MP injury. All other admissions in this table were for postprocedural pain following deep mural injury.
†One type III injury was not clipped. The lesion was identified at the time of the procedure as a type II injury, but on image review was thought to represent a target sign.
‡Presence of MP in the histological specimen split into defect target sign 11/12 (83%) and specimen target sign 2/7 (28.6%).
§MP was not identified in one case of perforation. In this case, a complete resection was performed by snare resection, including cold forceps avulsion over an area of submucosal fibrosis. The fibrotic area subsequently split during this procedure resulting in a full perforation. Due to the fibrotic element no MP was included in the pathological specimen.
MP, muscularis propria.

This study has shown that type III–V DMI (target signs and perforation) occurs proportionally more often in the transverse colon. The 'right colon' is at higher risk for perforation following standard snare polypectomy,[10] however definitions of what constitutes the right colon vary, and although the caecum has been identified as a risk area few studies have definitively shown this. The higher rate of DMI in the transverse colon may reflect the fact that this is a highly mobile, intraperitoneal segment of colon with a long mesentery. Gas aspiration and snare closure during EMR may allow the full thickness of the bowel wall to inadvertently slip inside the snare. A key safety aspect of EMR is demonstration of tissue mobility following closure of the snare. In the usual situation, if the MP is accidentally ensnared, the mobility sign is absent or diminished because of relative fixation by the mesentery or retroperitoneal location indicating that it is unsafe to proceed with tissue transection.[15] In the transverse colon this sign may be less reliable and falsely reassuring resulting in an increased propensity to DMI.

En bloc resection is related to DMI in this study. The mean size of lesions resected en bloc resulting in major DMI was 27.1 mm vs 23.0 mm in those without DMI (p=0.003). Avoiding en bloc resection of lesions larger than 25 mm, particularly in the transverse colon, is advisable for this reason.

SSA/Ps had a similar rate of major DMI to conventional adenoma in this study, (4.3% vs 2.8%, p=0.42). The majority of SSPs are found in the ascending colon and caecum, however SSPs are over-represented in the high DMI risk transverse colon where they form 27% of all transverse colon lesions. In addition the major DMI rate for SSPs in the transverse colon was 11.5% compared with 4.4% for conventional adenoma. A smaller size lesion may tempt endoscopists to excise these en bloc, however this has proven to be a recipe for deep injury and an oligopiecemeal approach to SSPs in this high-risk location may be more prudent.

Increasing levels of dysplasia are associated with DMI in this study, and HGD or cancer is associated with an OR of 2.97 for major DMI. The desmoplastic tissue reaction associated with HGD or cancer may impair the separation of tissue layers following submucosal lifting. Non-lifting is closely related to SMF and SMIC, but is not always present. EMR is not attempted in lesions with clear evidence of non-lifting and therefore these lesions were not included in the analysis. There was no association between partial lifting and DMI type III–V, however this may have been because very high-risk lesions had been excluded. DMI type I–II DMI was associated with partial lifting. This was likely due to exposure of the submucosal fibrosis and it may be that the endoscopist takes greater care when this sign is present. Our usual strategy is to isolate any area of partial lifting prior to resection, then cautiously resect using smaller snares or employ cold avulsion followed by thermal ablation.

The strongest factors associated with potential DMI (type I–II) were increasing lesion size and the presence of SMF. Types I and II DMI represent a situation where there is possible injury to the deeper MP layer and the endoscopist must make a decision about prophylactic closure. Fibrosis interferes with the assessment of the submucosal plane following resection. The reassuring homogeneous blue mat of interwoven submucosal connective tissue fibres is not seen, and is replaced by fibrotic white tissue obscuring the colour contrast between submucosa and MP injury. Incorporation of a contrast dye into the submucosal injectate is critical for the assessment of post-EMR defects. Low concentration indigo carmine or methylene blue in the submucosal injectate avidly binds to the areolar tissue of the submucosal layer but does not stain the MP, allowing exposed muscle to be easily seen as white on a blue background. Topical application of the same dyes applied with an injection catheter with the needle retracted, a technique known as topical submucosal chromoendoscopy,[16] may be useful in enhancing the contrast, but if ineffective, closure is required. We support the use of a contrast dye and careful defect assessment for any form of submucosal lift EMR regardless of size, as the dye is inexpensive, deep injury is simple to identify and targeted prophylactic clipping may prevent delayed perforation.

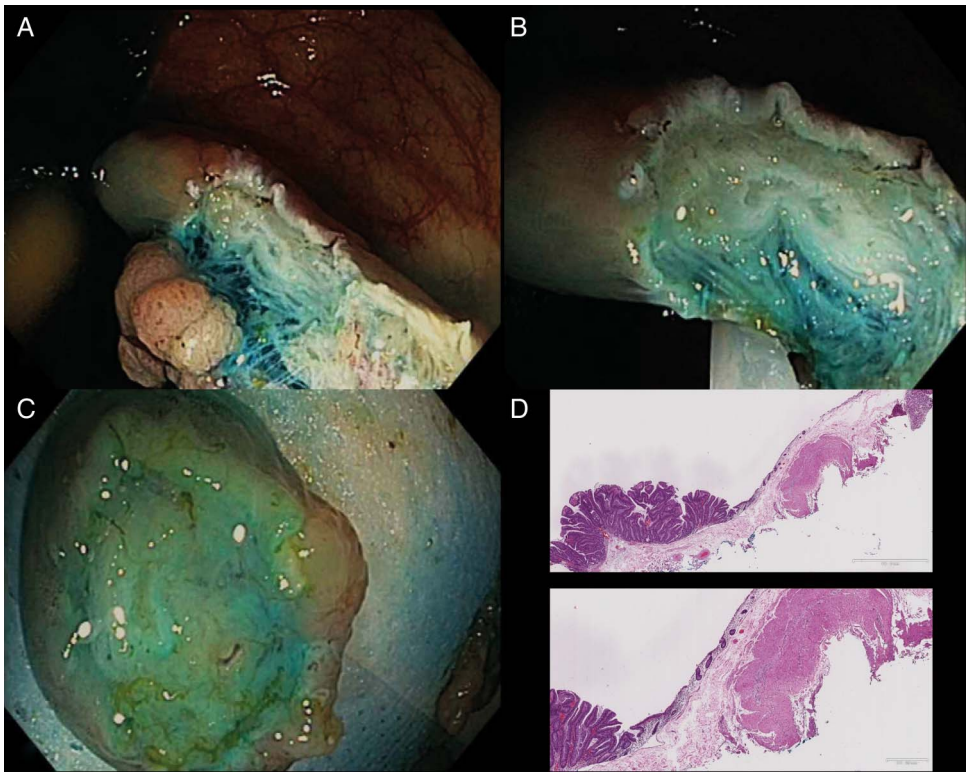

Figure 7 Following initial snare resection a subtle irregularity is noted in the defect base. (A). The area is interrogated by topical application of dye staining via an injection catheter with the needle retracted and a type III deep mural injury is apparent (B). This area was focally treated by clip application. A specimen target sign is noted on the resected specimen (C). The histological specimen reveals a focal area of included muscularis propria (D).

Histological analysis of DMI in the cohort revealed that MP was absent in all type I DMI. Type I defects were clipped in 31.6% of cases in this study. The majority of these were early in the study experience. It is likely that the underlying risk of subsequent perforation is low when the MP is completely uninjured, so more recently these have simply been documented. No patients have had sequelae related to this injury. By contrast, MP was present in 7.5% of type II DMI. The challenge with type II injuries is that one cannot be certain if the MP has been truly injured. Although unproven, it is logical that even small injuries to the MP may result in a focal area of mural weakness with the potential for a delayed perforation. In this study, endoscopists elected to close the majority (82.5%) of type II defects. Importantly, one type II defect that was not closed resulted in the only delayed perforation in the cohort. As a result of this event, we would strongly recommend clip placement in all cases of type II injury. Not all DMI type III were associated with histological evidence of MP. Type III DMI where only a DTS is evident is indicative of partial MP injury. Small areas of MP on the specimen may have been ablated in the resection or missed ('cut out') in histological processing. Type III DMI is an endoscopic sign of MP injury rather than a histological finding, so MP may not always be present.

The management strategy presented is derived from experience at Westmead hospital and aligns with current international expert opinion on postendoscopic perforation management.[3 17] Patients without evidence of clinical signs or symptoms of peritoneal irritation following type I–IV DMI can be safely discharged the same day if well. Extraluminal gas on CT scan in the absence of detectable intraperitoneal fluid following the adequate closure of a non-contaminated intraprocedural perforation is not an indication for surgery. We plan to continue to assess the efficacy of this approach by applying it in a prospective multicentre observational study.

The strengths of this study include the number of included DMI cases and the comprehensive associated data. Routine clip closure of defects without DMI was not performed, supporting the argument that routine closure of defects without injury is unnecessary. Limitations include the retrospective analysis of prospective data, and that type I and II cases prior to August 2013 were retrospectively identified from endoscopy reports and a comprehensive image bank and as a result may be underreported. Despite the size of the cohort, small differences in patient related factors (such as comorbidities) may not be able to be distinguished due to the low number of patients with each variable. It is important to note that the factors derived from the multivariable analysis are not intended to predict delayed perforation, they simply predict DMI as assessed by the appearance of the EMR defect at the completion of resection. The defect assessment provides the endoscopist a framework for the decision to place clips, and guides postprocedural management. The effectiveness of the approach we employ is confirmed by the low rate of delayed perforation that occurred in this cohort and the fact that no patients had surgery for failed endoscopic management of perforation.

In summary, DMI during EMR occurs in 10.2% of patients. Potential DMI (type I and II) is associated with increasing lesion size, SMF and transverse colon location. DMI type III–V: (target signs and perforations) are associated with en bloc resection, transverse colon location and HGD or SMIC. We suggest that patients with type I injuries do not require clip placement, however all patients with DMI type III–V require closure of the

Table 3 Univariable analysis and best fitting multiple logistic regression model for factors associated with deep mural injury (type III–V)

Univariable factors	No major DMI	Major DMI	Totals	p Value
Patient factors				
Age (mean, SD)	67.3 (11.8)	66.1 (13.2)		0.73
Sex				
Male	400 (97.1%)	12 (2.9%)	412	0.89
Female	378 (96.9%)	12 (3.1%)	390	
Lesion and procedure				
Lesion size (mean, SD)	38.3 (16.2)	38.3 (15.3)		0.97
Lesion size* (n,%)				
<40 mm	546 (97.0%)	17 (3.0%)	563	0.95
>40 mm	231 (97.1%)	7 (2.9%)	238	
Lesion location (n,%)				
Rectum <5 cm	39 (100.0%)	0 (0.0%)	27	**0.034**
Rectum >5 cm	120 (98.4%)	2 (1.6%)	96	
Sigmoid	80 (93.0%)	6 (7.0%)	66	
Descending colon	21 (87.5%)	3 (12.5%)	18	
Splenic flexure	11 (100.0%)	0 (0.0%)	9	
Distal transverse	22 (91.7%)	2 (8.3%)	13	
Mid transverse	37 (97.4%)	1 (2.6%)	28	
Proximal transverse	31 (91.2%)	3 (8.8%)	30	
Hepatic flexure	56 (98.2%)	1 (1.8%)	46	
Ascending colon	182 (98.4%)	3 (1.6%)	139	
Caecum	137 (97.9%)	3 (2.1%)	120	
Caecum ICV involved	37 (100.0%)	0 (0.0%)	26	
Caecum appendiceal orifice involved	5 (100.0%)	0 (0.0%)	5	
Location group† (n, %)				
Distal colon (rectum to splenic flexure)	271 (96.1%)	11 (3.9%)	282	**0.033**
Transverse	90 (93.8%)	6 (6.3%)	96	
Proximal colon (hepatic flexure to caecum)	417 (98.3%)	7 (1.7%)	424	
Paris classification* (n, %)				
0–IIa	444 (98.0%)	9 (2.0%)	453	0.21
0–IIa+Is	232 (96.7%)	8 (3.3%)	240	
0–Is	71 (94.7%)	4 (5.3%)	75	
Any depressed 'c' component	31 (93.9%)	2 (6.1%)	33	
Paris classification* (n, %)				
Any Is component	469 (97.9%)	10 (2.1%)	479	0.11
No Is component	309 (96.0%)	13 (4.0%)	322	
Endoscopic access (n,%)				
Easy to reach and position	497 (97.6%)	12 (2.4%)	509	0.51
Easy to reach, difficult to position	225 (96.2%)	9 (3.8%)	234	
Difficult to reach, easy to position	6 (100.0%)	0 (0.0%)	6	
Both difficult	50 (96.2%)	2 (3.8%)	52	
Submucosal injectate lift				
Lifts well	736 (96.8%)	24 (3.2%)	760	0.11
Poor lifting	41 (100.0%)	0 (0.0%)	41	
Resection technique† (n, %)				
Piecemeal excision	697 (97.6%)	17 (2.4%)	714	**0.004**
En bloc excision	81 (92.0%)	7 (8.0%)	88	
Submucosal fibrosis (n,%)				
Yes	535 (97.1%)	16 (2.9%)	551	0.83
No	243 (96.8%)	8 (3.2%)	251	
Procedure duration† (mean, SD)	24.8 (23.2)	34.0 (26.7)		**0.011**
Postprocedure pain* (n, %)				
No	760 (96.9%)	24 (3.1%)	784	0.68
Yes	17 (100.0%)	0 (0.0%)	17	
Majority polyp histology† (n, %)				
Tubular, tubulovillous or villous adenoma	655 (97.2%)	19 (2.8%)	674	0.42
Sessile serrated adenoma/polyp (SSA/P)	89 (95.7%)	4 (4.3%)	116	
Other (ie, invasive cancer and underlying polyp histology not reported, lipoma)	11 (100.0%)	1 (9.0%)	12	

Continued

Table 3 Continued

Univariable factors	No major DMI	Major DMI	Totals	p Value
Dysplasia† (n, %)				
No or LGD	632 (97.8%)	14 (2.2%)	646	**0.009**
HGD or submucosal invasive cancer	146 (93.6%)	10 (6.4%)	156	
Submucosal invasive cancer (n, %)				
No	730 (97.5%)	19 (2.5%)	746	**0.017**
Yes	48 (90.6%)	5 (9.4%)	53	
Best fitting multiple logistic regression model	**Adjusted OR**	**p Value**		
Location group				
Distal colon (rectum to splenic flexure)	2.03 (0.76 to 5.46)	0.160		
Transverse	3.55 (1.15 to 11.0)	**0.028**		
Proximal colon (hepatic flexure to caecum)	1			
Dysplasia				
None or LGD	1			
HGD or submucosal invasive cancer	2.97 (1.25 to 7.06)	**0.014**		
Resection technique				
Piecemeal excision	1			
En bloc excision	3.84 (1.51 to 9.77)	**0.005**		

Bold indicates p values <0.05.
*Data missing where totals do not add up to 802.
†Included in multivariable analysis.
DMI, deep mural injury; HGD, high grade dysplasia; ICV, ileo-caecal valve; LGD, low grade dysplasia.

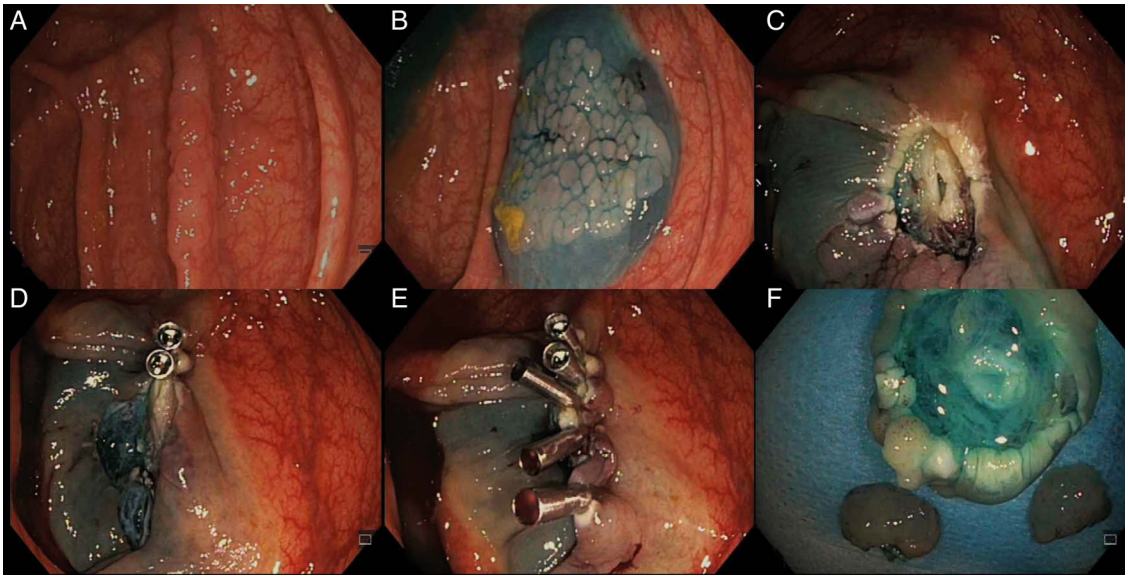

Figure 8 (A) A 25 mm Paris 0–IIa granular lesion in the proximal ascending colon, overlying a fold. (B) The lesion is lifted with a chromogelofusine solution clearly delineating the margins and obliterating the fold. (C) The initial snare resection crosses the fold and following excision, a type III defect target sign (DTS) is noted. (D) The resection is completed, then the defect is closed, commencing at the site of the DMI. (E) Care is taken to place clips so that the lesion's edges are opposed and everted. (F) A specimen target sign is noted on the underside of the retrieved tissue and highlighted with topical application of chromogelofusine solution (topical submucosal chromoendoscopy). Although prospective data were not collected on this aspect, anecdotally, lesions overlying folds may be at higher risk of perforation when the underlying colon topography has been obliterated by submucosal injection.

injured MP. On the basis of our experience, all type II injuries should also ideally be clipped. The majority of patients with target signs (type III DMI) can be managed with same day discharge if they are well and the injury is securely closed. Intraprocedural perforation occurs in 0.5% and clinically significant perforation occurs in 0.2%. As EMR becomes increasingly aggressive the paradigm of DMI management is changing. Potentially serious DMI syndromes are not infrequent, but if recognised they may be managed safely and effectively without serious clinical sequelae, in many cases on an outpatient basis. Recognition is the key.

Contributors NGB: designed the study, collected data, performed procedures, analysed data, wrote the manuscript and revised the manuscript after review by the coauthors. MSB, SJW: identified and recruited patients, performed procedures,

collected data and critically reviewed the manuscript. DM: collected and organised data, examined histological and pathological specimens and critically reviewed the manuscript. KB: assisted with data analysis and critically reviewed the manuscript. MJB: initiated, designed and led the study, identified and recruited patients, performed procedures, collected data, co-wrote the manuscript and critically reviewed the manuscript.

Competing interests None declared.

Ethics approval The study was approved by the Western Sydney Local Health District Human Research and Ethics Committee. The study is part of the Australian Multicentre Colonic Endoscopic Mucosal Resection trial which is registered at ClinicalTrials.gov (NCT01368289). Expanded data collection was approved by local ethical review boards in August 2013, and registered at ClinicalTrials.gov (NCT02000141).

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Deep mural injury and perforation after colonic endoscopic mucosal resection: a new classification and analysis of risk factors

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