Original research

Treatment of adenoma recurrence after endoscopic mucosal resection

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ABSTRACT

Objective Residual or recurrent adenoma (RRA) after endoscopic mucosal resection (EMR) of large non-pedunculated colorectal polyps (LNPCPs) of ≥20 mm is a major limitation. Data on outcomes of the endoscopic treatment of recurrence are scarce, and no evidence-based standard exists. We investigated the efficacy of endoscopic retreatment over time in a large prospective cohort.

Design Over 139 months, detailed morphological and histological data on consecutive RRA detected after EMR for single LNPCPs at one tertiary endoscopy centre were prospectively recorded during structured surveillance colonoscopy. Endoscopic retreatment was performed on cases with evidence of RRA and was performed predominantly using hot snare resection, cold avulsion forceps with adjuvant snare tip soft coagulation or a combination of the two.

Results 213 (14.6%) patients had RRA (168 (78.9%) at first surveillance and 45 (21.1%) thereafter). RRA was successfully treated in 149 (92.5%) of 161 in the per-protocol analysis, and 149 (78.8%) of 194 (96.0%) underwent successful endoscopic therapy and 161 (83.4%) had a subsequent follow-up colonoscopy. Of the latter, endoscopic therapy of recurrence was successful in 149 (92.5%) of 161 in the per-protocol analysis, and 149 (73.8%) of 202 in the intention-to-treat analysis, with a mean of 1.15 (SD 0.36) retreatment sessions. No adverse events were directly attributable to endoscopic therapy. Further RRA after endoscopic therapy was endoscopically treatable in most cases. Overall, only 9 (4.2%, 95% CI 2.2% to 7.8%) of 213 patients with RRA required surgery. Thus 159 (98.8%, 95% CI 95.1% to 99.8%) of 161 cases with initially successful endoscopic treatment of RRA and follow-up remained surgery-free for a median of 13 months (IQR 25.0) of follow-up.

Conclusions RRA after EMR of LNPCPs can be effectively treated using simple endoscopic techniques with long-term remission of >90%; only 16% required retreatment. Therefore, more technically complex, morbid and resource-intensive endoscopic or surgical techniques are required only in selected cases.

Trial registration numbers NCT01368289 and NCT02000141

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Residual or recurrent adenoma (RRA) after endoscopic mucosal resection (EMR) of large non-pedunculated colorectal polyps (LNPCPs) of ≥20 mm is a major limitation occurring in approximately 15% of cases.

WHAT THIS STUDY ADDS

⇒ RRA is typically small (2.5–5.0 mm (48.0%)) and unifocal (78.7%).
⇒ Endoscopic treatment of recurrence can be performed successfully using simple endoscopic techniques with 92.5% (95% CI 87.0%–95.9%) of patients achieving long-term remission of RRA.
⇒ Only a single session of endoscopic RRA treatment (85.2%) is commonly required to achieve long-term remission of RRA (mean 1.15 treatment sessions, SD 0.36).
⇒ Requiring surgery for RRA is extremely uncommon after successful EMR for benign LNPCPs (0.5%, 95% CI 0.2% to 1.0%).

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Simple, cost-effective techniques are safe and efficacious to treat RRA with rates of long-term remission of ≥90%. Resource-intensive techniques such as endoscopic submucosal dissection, full-thickness resection or surgery are therefore necessary only in selected cases to treat RRA after EMR of LNPCPs if it occurs during surveillance.

INTRODUCTION

Endoscopic mucosal resection (EMR) is a safe,1,2 effective3 and surgery-sparing technique for the removal of large non-pedunculated colorectal polyps (LNPCPs) of ≥20 mm. The high rate of residual or recurrent adenoma (RRA) after piecemeal EMR is one of the main limitations of the technique and is often used as a justification for the adoption of more expensive and resource-intensive techniques with greater rates of adverse events such as endoscopic submucosal dissection (ESD)4 and surgery.5,6

Significant differences in rates of RRA have been reported,1,7–14 likely due to variations in technique, experience, expertise and the inconsistent application of adjuvant techniques to reduce recurrence. The pooled rate of RRA after EMR is reported at
13.5% (95% CI 12.9% to 14.7%) in a recent meta-analysis of 50 studies including 6779 lesions.\(^1\)

Despite high rates of RRA, the frequency of patients requiring surgery after piecemeal EMR during surveillance in the same meta-analysis was significantly lower (4.2%, 95% CI 2.8% to 5.7%), implying that RRA can be effectively treated endoscopically once detected in the majority of cases. Multiple techniques have been described which could be applied for the endoscopic treatment of RRA including ESD,\(^{15–19}\) full-thickness endoscopic resection\(^{20}\) and a number of avulsion techniques.\(^{21–24}\) None of these techniques have been subjected to large-scale, systematic, prospective study in the treatment of RRA, and the long-term outcomes of the endoscopic treatment of recurrence are unknown.

In this study, we report the long-term outcomes of the endoscopic treatment of recurrence for 213 episodes of RRA, derived from a cohort of 1800 LNPCPs.

**METHODS**

**Recruitment to the study and inclusion criteria**

Patients were eligible for inclusion in the study if they were referred to the study centre (Westmead Hospital, Sydney, Australia) from September 2008 to April 2020 (139 months) for endoscopic resection of LNPCPs. Successive patients who consented and met the inclusion criteria were included in the study. Detailed patient, procedural and lesion characteristics were collected. Multiple lesions in the same patient were excluded with the largest LNPCP retained for analysis. Lesions which were not attempted (due to suspicion for submucosal invasive cancer (SMIC) or technical reasons) or those which were attempted but not completely resected were excluded. Patients who underwent two-stage EMR\(^{25}\) were excluded. Patients with SMIC in the final specimen who were referred for surgery were excluded. The study was registered at Clinicaltrials.gov. The study was reported in accordance with Strengthening the Reporting of Observational Studies in Epidemiology\(^26\) reporting guidelines.

**Details of endoscopic resection procedures**

Sequential inject and resect EMR was performed on LNPCP as previously described in detail.\(^{27}\) Snare tip soft coagulation (STSC (ERBE VIO 300D, ERBE Elektromedizin, Tübingen, Germany), effect 4, 80 W) was applied as part of a randomised controlled trial\(^{28}\) over 34 months to May 2016 and universally thereafter.\(^{29}\) All specimens were retrieved and sent for analysis by specialist GI histopathologists. Postprocedural care followed the usual post-EMR plan, including observation for 4 hours and a clear fluid diet overnight.

Adverse events were assessed at a structured telephone interview at 14 days after the index EMR.\(^3\) At this stage, patients with acceptable histopathology were entered into surveillance. **Figure 1** depicts various LNPCPs undergoing EMR and the appearances of the endoscopic resection scar at successive surveillance examinations.

**Residual or recurrent adenoma**

RRA refers to the presence of adenoma at an endoscopic resection scar, whether determined endoscopically or histologically. Surveillance procedures were performed either at the study centre or referring centres (hospitals referring patients with LNPCP to the study centre for EMR). The majority of first surveillance procedures were performed at the study centre. Later surveillance procedures were commonly performed by referring centres. If RRA was detected at a referring centre, the patient was commonly referred back to the study centre for treatment of RRA.

During surveillance colonoscopy (SC), an endoscopic resection scar was defined as a demarcated area of flat, pale mucosa with open Kudo type I pits often associated with effacement, distortion and convergence of adjacent colonic folds. Endoscopic
assess for the presence of RRA was performed during all SCs following a standardised scar assessment protocol. Briefly, the edges of the scar were initially interrogated using high-definition white light and narrow band imaging (Olympus, Tokyo, Japan). The centre of the scar was analysed in the same way. RRA was defined by the detection of a transition point where a non-neoplastic pit/vascular pattern changed to a neoplastic pattern (Kudo III/IV). If this was detected, RRA was recorded as present (figure 2).

Once detected, RRA was described systematically. The position within the scar was noted (as within the scar or at the edge). The size of the RRA was described relative to a closed biopsy forceps (2.2 mm closed diameter, Radial Jaw 4 Standard Capacity Biopsy Forceps; Boston Scientific, Massachusetts, USA). RRA was described as unifocal if a single area was described within the scar and multifocal if more than one area of RRA was detected.

In all cases, if RRA was detected, treatment was attempted, and the resultant specimen was sent for histological analysis. If no RRA was detected, scar biopsy was regularly but not universally performed due to the high negative predictive performance of the endoscopic discrimination of RRA at an endoscopic resection scar.

Endoscopic treatment of recurrence
Early in the study, treatment of RRA was performed in the same way as the initial resection; a submucosal injectate containing succinylated gelatin (Gelofusine; Braun, Bella Vista, Australia), indigo carmine blue and epinephrine diluted to a final concentration of 1/100 000 was injected tangential to the mucosa. For elevated recurrence, snare resection (‘hot snare’) (Olympus SnareMaster 10–15 mm, Olympus) or more recently a stiffer snare (Captivator II 10–15 mm, Boston Scientific) was attempted using either forced coagulation (forced coagulation, effect 2, 30 W) or fractioned current (effect 3) (ERBE VIO 300D).

Since RRA is often tethered and completely flat, snare resection can be difficult. In addition, submucosal injection of the fibrotic tissue at the site of a resection scar may lead to a canyoning effect where the surrounding non-scarred mucosa lifts excessively compared with the scar, further impeding snare capture of the target tissue. For this reason, submucosal injection was minimised later in the study.

Cold forceps avulsion with adjuvant snare tip soft coagulation (CAST22) (figure 3) was used commonly later in the study as a solution to the problem of flat recurrence. Systematic cold forceps (Radial Jaw 4) avulsion was performed to remove all visible RRA. The exposed submucosa of the avulsion site and its margins were then treated with controlled thermal ablation using STSC (ERBE effect 4, 80 W, VIO 300D generator). Thermal ablation was finally extended onto the normal scarred mucosa surrounding the avulsion bed for 1–2 mm. CAST was commonly combined with prior hot snare resection of any elevated recurrence as described previously. Figure 4 displays multiple examples of the endoscopic treatment of recurrence, online supplemental figure 1 displays appearances of scars after endoscopic treatment of recurrence and online supplemental figure 2 is a graphical representation of the techniques used.

Other techniques were infrequently used for treatment of RRA at the discretion of the treating endoscopist. These included cold snare resection combined with any/all of the other modalities. Complex techniques such as ESD and endoscopic full-thickness resection (EFTR) were not used for the treatment of RRA in this study.

Endoscopic treatment of RRA often led to Sydney type II deep mural injury (an uninterpretable submucosal plane due to the application of thermal energy over scarred tissue such that the depth of injury cannot be accurately judged). In such cases, the resection bed was closed with endoscopic clips.

Surveillance after EMR and endoscopic treatment of RRA
Standard SC after EMR was scheduled at 6 months (first surveillance colonoscopy (SC1), then at subsequent intervals of 1 year (second surveillance colonoscopy (SC2)), 3 years (third surveillance colonoscopy (SC3)) and 5 years (fourth surveillance colonoscopy (SC4)). If the patient underwent treatment of RRA at any surveillance procedure, a further surveillance procedure was
Endoscopy

scheduled 6 months thereafter (at the discretion of the endoscopist). When a negative surveillance procedure (no RRA) was performed after treatment of RRA, the patient returned to the standard surveillance pathway. RRA detected at SC1 was termed early recurrence. RRA detected for the first time after SC1 was termed late recurrence.

If treatment of RRA was unsuccessful, not possible or there was endoscopic or histopathological evidence of submucosal invasive disease at surveillance, a referral for surgical resection was made in discussion with the patient.

Figure 3  Endoscopic treatment of recurrence. An endoscopic resection scar is shown with an extensive flat area of RRA. This is removed using CAST with the rim of coagulation extended onto the normal-appearing scar. CAST, cold avulsion forceps biopsy with adjuvant snare tip soft coagulation; RRA, residual or recurrent adenoma.

Study endpoints
The primary endpoint was the efficacy of endoscopic treatment of RRA. It was a composite endpoint comprising the following outcome measures:

► **Successful endoscopic treatment of RRA** is the complete clearance of RRA without evidence of invasive disease endoscopically or at histopathological assessment.

► **Surgery-free survival** refers to the proportion of patients with an LNPCP treated for RRA using endoscopic treatment

Figure 4  Various techniques of the endoscopic treatment of RRA as described in the Methods section. (A–E,I) Snare resection of recurrence with subsequent application of STSC (B, using cold snare technique). (F,H,J) CAST. (J) Prior injection of chromic dye. (G) Recurrence at the site of a previously placed endoscopic clip, removal of the clip and application of CAST (very high resolution image available separately). CAST, cold avulsion forceps biopsy with adjuvant snare tip soft coagulation; RRA, residual or recurrent adenoma; STSC, snare tip soft coagulation.
methods and not requiring surgery to longest available follow-up.

- **Endoscopic cure** includes patients having undergone successful endoscopic treatment of RRA who subsequently underwent at least one negative SC (EMR scar endoscopically and histologically negative for RRA).

Secondary endpoints were to describe the morphology of RRA detected during surveillance after EMR, to describe techniques used for the endoscopic treatment of recurrence and their safety and to describe patterns of RRA after its endoscopic treatment during long-term surveillance.

**Statistical analysis**

Data on RRA and endoscopic treatment of RRA were analysed at the surveillance time point at which RRA was first detected unless otherwise specified. All percentages throughout the study were calculated from the eligible population of 1800 LNPCPs with successful index EMR unless otherwise stated. Data were presented both in a per-protocol (cases missing follow-up ignored) and intention-to-treat (ITT) (cases missing follow-up included) form. Many of the results can only be described in terms of endoscopically detected RRA, and therefore this is the default denominator presented. The described analysis (per-protocol versus ITT) is always presented in the Results section.

The study data were analysed using SPSS Statistics V.28. Categorical variables were correlated using the \(\chi^2\) test. Continuous variables were analysed using either Student’s t-test (two-tailed) or Mann-Whitney U test. All authors had access to the study data and reviewed the final manuscript.

**RESULTS**

For brevity, the results of the per-protocol analysis for endoscopically detected RRA are presented unless otherwise stated. ITT results for both endoscopically detected RRA and histologically detected RRA are presented in table 1 and online supplemental table 7.

**Demographic data**

Over the study period, 2311 LNPCPs were resected in 2091 patients. Online supplemental figure 3 describes reasons for lesion ineligibility. After exclusions, 1800 patients (mean age 68.2 years (SD 11.6 years), 52.1% male) with 1800 LNPCPs were eligible for the study and their data were analysed (figure 5 and online supplemental figure 3).

**Recurrence during follow-up**

A total of 1458 LNPCPs entered surveillance, of which 213 (14.6%, 95% CI 12.9 to 16.5) had evidence of RRA during a median follow-up of 19 months (IQR 32.6 months). In comparison to LNPCPs that did not recur, recurrent LNPCPs were larger (median 45 mm, IQR 25 mm, \(p<0.001\), less commonly resected en bloc (3.3%, \(p<0.001\) and less commonly underwent thermal ablation of the post-EMR margin (6.1%, \(p<0.001\)). Intraprocedural bleeding was more common during their resection (32.9%, \(p<0.001\), and high-grade dysplasia was more common in the resection specimen (22.5%, \(p=0.020\) of LNPCP with RRA (table 2).

The majority of RRA was detectable endoscopically (202 of 213 (94.8%)) (table 3). Of the 202 endoscopically detectable RRAs, 194 (96.0%) were confirmed at histopathology. The majority of RRA (168 (78.9%)) was detected at SC1 (early recurrence). RRA first detected after SC2 (14 (6.6%)) was rare.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Important outcomes after the endoscopic resection of LNCP focussed on the treatment of recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Per-protocol, n (%) (95% CI)</strong></td>
<td><strong>ITT, n (%) (95% CI)</strong></td>
</tr>
<tr>
<td><strong>n=202</strong></td>
<td><strong>n=202</strong></td>
</tr>
<tr>
<td><strong>Underwent treatment of RRA</strong></td>
<td>202/202 (100) (97.7 to 100) Same</td>
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<tr>
<td><strong>Successful treatment of RRA</strong></td>
<td>194/202 (96.0) (92.1 to 98.2) Same</td>
</tr>
<tr>
<td><strong>Underwent surgery for any reason</strong></td>
<td>8/202 (4.0) (1.9 to 7.9) Same</td>
</tr>
<tr>
<td><strong>Underwent surveillance after treatment of RRA</strong></td>
<td>161/194 (83.0) (76.8 to 87.9) Same</td>
</tr>
<tr>
<td><strong>Failed treatment of RRA requiring surgery</strong></td>
<td>8/161 (5.0) (2.3 to 9.9) Same</td>
</tr>
<tr>
<td><strong>RRA after successful treatment</strong></td>
<td>26/161 (16.1) (11.0 to 23.0) Same</td>
</tr>
<tr>
<td><strong>Successful repeat treatment of RRA</strong></td>
<td>24/26 (92.3) (73.4 Same</td>
</tr>
<tr>
<td><strong>Survival (no surgery) after successful treatment of RRA</strong></td>
<td>159/161 (98.8) (95.1 to 99.8) Same</td>
</tr>
<tr>
<td><strong>Endoscopic cure</strong></td>
<td>149/161 (92.5) (87.0 to 95.9) Same</td>
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<tr>
<td><strong>Multiple recurrence after successful treatment</strong></td>
<td>11/26 (42.3) (24.0 to 62.8) Same</td>
</tr>
<tr>
<td><strong>Survivor for multiple recurrence after successful treatment</strong></td>
<td>2/11 (18.2) (3.2 to 52.2) Same</td>
</tr>
</tbody>
</table>

See online supplemental table 7 for more detailed results. Same indicates columns to the left containing the same result; horizontal shading indicates component of composite primary outcome.

Per protocol analysis versus ITT analysis. Endoscopically detected recurrence separated from all RRAs which includes histologically detected.

*All surgeries including for reasons other than recurrence. 95% CI, 95 percent confidence interval; ITT, intention-to-treat; LNCP, large non-pedunculated colorectal polyp; RRA, residual or recurrent adenoma.

**Primary endpoint: efficacy of the endoscopic treatment of RRA**

Of 202 scars with endoscopically detectable RRA, 194 (96.0%, 95% CI 92.1% to 98.2%) underwent successful endoscopic treatment. For a median of 13 months (IQR 25.0) of follow-up, 159 (98.8%, 95% CI 95.1% to 99.8%) of 161 patients avoided surgery in the per-protocol analysis versus 159 (82.0%, 95% CI 75.7% to 87.0%) of 194 in the ITT analysis after successful endoscopic treatment for RRA (table 1).

Endoscopic cure was achieved in 149 (92.5%, 95% CI 87.0% to 95.9%) of 161 patients in the per-protocol analysis and in 149 (73.8%, 95% CI 67.0% to 79.6%) of 202 in the ITT analysis.
who underwent surveillance after successful treatment of recurrence. The majority of endoscopic cure was achieved after one session of recurrence treatment (127 of 149, 85.2%). Eight of 213 (3.8%) patients required surgery throughout the study due to failed endoscopic treatment for RRA, and a further patient (1 of 213, 0.5%) due to persistent positive scar histology without endoscopic correlate at a distant referring centre (figure 6). One further surgery occurred during surveillance due to an endoscopically unresectable lesion in a distant colonic segment (original resection site demonstrated no RRA). The overall rate of surgery after successful EMR for LNPCP was therefore 10 out of 1800 (0.6%, 95% CI 0.3% to 1.0%) (table 1).

Secondary endpoints
Description of the endoscopic appearance of RRA
A total of 202 RRAs were described at their first occurrence during surveillance (online supplementary table 1). RRA was commonly 2.5–5.0 mm in size (48.0%), unifocal (78.7%) and located within the endoscopic scar (55.4%) rather than at the edge. Figure 2 and online supplemental video 1 present examples of the endoscopic appearance of RRA taken from LNPCPs in the study population.

Techniques used for the endoscopic treatment of recurrence and safety
Submucosal injection for lifting prior to treatment of RRA was performed in a minority of cases (10.9%). The most common techniques used for RRA treatment were hot snare plus STSC (28.2%) and CAST (28.2%). Hot snare alone was used in 18.3% of treatments of RRA and CAST combined with hot snare in 6.9%. Other techniques for treatment of RRA were used in 15.8% including cold snare resection. The use of CAST for treatment of RRA increased significantly between the first half (21.1%) and the second half (58.1%, p<0.001) of the study. Figure 3 and online supplemental figure 1 display the appearances of scars after the application of endoscopic treatment methods.

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Figure 5 Recruitment to the study (Strengthening the Reporting of Observational Studies in Epidemiology diagram). All recurrences after EMR are displayed, including those detected only at histopathological analysis. Throughout eligibility for surveillance was determined by those eligible for the prior surveillance subtracting surgical referrals, deceased patients or those too comorbid and those not yet due follow-up. RRA post prior treatment denotes RRA detected after a previous session of endoscopic treatment of RRA. Numbers within brackets indicate IQRs of median value. *New RRA and RRA after endoscopic treatment detected at this surveillance time point. A more detailed version of this figure is available in online supplemental figure 3. **Endoscopically detected recurrences only, described from entire cohort not just RRA. EDR, endoscopically detectable recurrence; EMR, endoscopic mucosal resection; FU, follow-up; HDR, histologically detected residual or recurrent adenoma with no endoscopic correlate; LNPCP, large non-pedunculated colorectal polyp; RRA, residual or recurrent adenoma; SC1–4, surveillance colonoscopy 1–4.
Eight (4.0%) scars with suspected RRA could not be treated using endoscopic treatment methods at the initial detection. There were no significant adverse events directly attributable to the endoscopic treatment of recurrence.

Patterns of RRA after the endoscopic treatment of RRA
A total of 161 scars underwent further surveillance after endoscopic treatment for RRA (figure 5). Ninety-two scars (57.1%) underwent one, 40 (24.8%) two and 17 (10.6%) three negative surveillance examinations after successful treatment of RRA (table 3). RRA at subsequent surveillance after endoscopic treatment was uncommon (26 of 161; 16.1%, 95% CI 11.3% to 22.6%) and could be endoscopically retreated in all but two (7.7%) cases, with further follow-up of these patients (n=16 of 26, 61.5%) showing two (12.5%) further cases of RRA, both amenable to further endoscopic treatment (table 1).
Table 3  Details of RRA detected endoscopically and histologically during surveillance with characteristics of the treatment of RRA

<table>
<thead>
<tr>
<th></th>
<th>Early recurrence n=168</th>
<th>Late recurrence n=45</th>
<th>SC1</th>
<th>SC2</th>
<th>SC3</th>
<th>SC4</th>
<th>All</th>
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</thead>
<tbody>
<tr>
<td>Total recurrences at follow-up interval (/all recurrences %)</td>
<td>168 (78.9)</td>
<td>n=31 (14.6)</td>
<td>n=11 (5.2)</td>
<td>n=3 (1.4)</td>
<td>N=213</td>
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<td>Characteristics of RRA</td>
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<td>EDR, n (%)</td>
<td>162 (96.4)</td>
<td>29 (93.5)</td>
<td>8 (72.7)</td>
<td>3 (100)</td>
<td>202 (94.8)</td>
<td></td>
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<tr>
<td>Histologically detected RRA, n (%)</td>
<td>6 (3.6)</td>
<td>2 (6.5)</td>
<td>3 (27.3)</td>
<td>0 (0)</td>
<td>11 (5.2)</td>
<td></td>
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</tr>
<tr>
<td>Median time to detection (months, IQR)</td>
<td>5.0 (2)</td>
<td>18.0 (13)</td>
<td>36.0 (30)</td>
<td>48.0 (x)</td>
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<tr>
<td>Previous negative surveillance procedure, n (%)</td>
<td>x</td>
<td>31 (100)</td>
<td>11 (100)</td>
<td>3 (100)</td>
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<tr>
<td>EDR, n (%)</td>
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<td>29 (93.5)</td>
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<td>3 (100)</td>
<td>202 (94.8)</td>
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<td>18.0 (13)</td>
<td>36.0 (30)</td>
<td>48.0 (x)</td>
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<td>Previous negative surveillance procedure, n (%)</td>
<td>x</td>
<td>31 (100)</td>
<td>11 (100)</td>
<td>3 (100)</td>
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<td>Dysplasia grade (% histological correlate)</td>
<td>160 (98.7)</td>
<td>26 (89.7)</td>
<td>6 (75.0)</td>
<td>2 (66.7)</td>
<td>194 (96.0)</td>
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<tr>
<td>None (but adenoma)</td>
<td>29 (18.1)</td>
<td>7 (26.9)</td>
<td>0 (0)</td>
<td>36 (18.6)</td>
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<td>LGD</td>
<td>125 (78.1)</td>
<td>19 (61.2)</td>
<td>6 (100)</td>
<td>152 (78.4)</td>
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<td>HGD</td>
<td>6 (3.6)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>6 (3.1)</td>
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<td>Endoscopic treatment of recurrence (/all endoscopically detected RRA)</td>
<td>n=162</td>
<td>n=29</td>
<td>n=8</td>
<td>n=3</td>
<td>/202</td>
<td></td>
<td></td>
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<tr>
<td>Attempt at lifting prior to Rx (%)</td>
<td>22 (13.1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>22 (10.9)</td>
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<td>Treatment modality (%)</td>
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<td>Hot snare alone</td>
<td>25 (15.4)</td>
<td>9 (31.0)</td>
<td>3 (37.5)</td>
<td>0 (0)</td>
<td>37 (18.3)</td>
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<tr>
<td>Hot snare and STSC</td>
<td>52 (32.1)</td>
<td>4 (13.8)</td>
<td>0 (0)</td>
<td>1 (33.3)</td>
<td>57 (28.2)</td>
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<td>CAST</td>
<td>41 (25.3)</td>
<td>10 (34.5)</td>
<td>4 (50.0)</td>
<td>2 (66.7)</td>
<td>57 (28.2)</td>
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<tr>
<td>Hot snare and CAST</td>
<td>14 (8.6)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>14 (6.9)</td>
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<tr>
<td>Other</td>
<td>26 (16.0)</td>
<td>6 (20.7)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>32 (15.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not treated</td>
<td>4 (2.4)</td>
<td>0 (0)</td>
<td>1 (12.5)</td>
<td>0 (0)</td>
<td>5 (2.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Successful treatment of RRA</td>
<td>157 (97.0)</td>
<td>28 (96.6)</td>
<td>7 (87.5)</td>
<td>3 (100)</td>
<td>194 (96.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Failed treatment of RRA (ever, requiring surgery)</td>
<td>6 (3.7)</td>
<td>1 (3.4)</td>
<td>1 (12.5)</td>
<td>0 (0)</td>
<td>8 (4.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surveillance after treatment of RRA</td>
<td>137 (87.3)</td>
<td>20 (74.1)</td>
<td>4 (66.7)</td>
<td>0 (0)</td>
<td>161 (83.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underwent further surveillance after treatment of RRA, n (%)</td>
<td>129 (94.2)</td>
<td>16 (80.0)</td>
<td>4 (100)</td>
<td>na</td>
<td>149 (92.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Longest follow-up post treatment of RRA (months), median, (IQR)</td>
<td>20 (27)</td>
<td>12 (23)</td>
<td>18 (38)</td>
<td>na</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery-free survival after treatment of RRA (to longest follow-up)</td>
<td>136 (99.3)</td>
<td>19 (95.0)</td>
<td>4 (100)</td>
<td>x</td>
<td>159 (98.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative surveillance procedures after treatment of RRA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>8 (5.8)</td>
<td>4 (20.0)</td>
<td>0 (0)</td>
<td>x</td>
<td>12 (7.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>75 (54.7)</td>
<td>13 (65.0)</td>
<td>4 (100)</td>
<td>x</td>
<td>92 (57.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>37 (27.0)</td>
<td>3 (15.0)</td>
<td>0 (0)</td>
<td>x</td>
<td>40 (24.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>17 (12.4)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>x</td>
<td>17 (10.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Repeat treatment of RRA after endoscopic treatment</td>
<td>/161</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RRA after endoscopic treatment</td>
<td>18 (13.1)</td>
<td>8 (40.0)</td>
<td>0 (0)</td>
<td>x</td>
<td>26 (16.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Successful repeat treatment</td>
<td>16 (88.9)</td>
<td>8 (100)</td>
<td>x</td>
<td>x</td>
<td>24/26 (92.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underwent surveillance after repeat treatment of RRA</td>
<td>12 (66.7)</td>
<td>4 (50.0)</td>
<td>x</td>
<td>x</td>
<td>16/26 (61.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RRA after repeat treatment of RRA</td>
<td>2 (16.7)</td>
<td>0 (0)</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative surveillance procedures after repeat treatment of RRA</td>
<td>/16</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>2 (16.7)</td>
<td>0 (0)</td>
<td>x</td>
<td>x</td>
<td>2 (12.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>5 (41.7)</td>
<td>4 (100)</td>
<td>x</td>
<td>x</td>
<td>9 (56.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>5 (41.7)</td>
<td>0 (0)</td>
<td>x</td>
<td>x</td>
<td>5 (31.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of treatment sessions required for endoscopic cure outcome</td>
<td>/149</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>120 (93.0)</td>
<td>3 (18.8)</td>
<td>4 (100)</td>
<td>x</td>
<td>127 (85.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>9 (7.0)</td>
<td>13 (81.3)</td>
<td>x</td>
<td>x</td>
<td>22 (14.8)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Histologically detected recurrence describes scars with no endoscopic finding where adenoma was detected at routine scar biopsy. Endoscopic cure describes one or more surveillance procedures with scar assessment and biopsy negative for adenoma after treatment of RRA. Successful treatment of RRA describes success in the complete clearance of recurrent adenoma, endoscopically assessed, at the specified surveillance time point and is described in relation to endoscopically detected recurrence. RRA after EMR is recorded and described at the stage where it was first detected, regardless of further treatment.

*Histologically determined recurrence without endoscopically detected recurrence (all low-grade dysplasia) was treated at a follow-up exam. Further details can be found in online supplemental table 3.

CAST, cold forceps avulsion with adjuvant snare tip soft coagulation; EDR, endoscopically detectable recurrence; EMR, endoscopic mucosal resection; HGD, high-grade dysplasia; LGD, low-grade dysplasia; na, not applicable; RRA, residual or recurrent adenoma; Rx, treatment; SC1–4, surveillance colonoscopy 1–4; STSC, snare tip soft coagulation.
majority of endoscopic cure was achieved after a single session of endoscopic treatment (127 of 149, 85.2%), with a mean of 1.15 (SD 0.36) retreatment sessions and confirmed by negative high-resolution endoscopic imaging in all cases and negative biopsies in 66 of 149 (44.3%) (tables 1, 3 and 4).

Eleven instances of RRA after endoscopic treatment of RRA with multiple recurrence and three instances that occurred for the first time at long-term follow-up (SC4) are described in detail in online supplemental table 2. Potential reasons for multiple episodes of RRA after endoscopic treatment were LNPCP resected early in the centre’s experience, complex LNPCP location such as ileocaecal valve (ICV) and multiple surveillance procedures outside of the study centre.

RRA detected histologically where a scar appeared normal endoscopically

Eleven of 213 (5.2%) EMR scars which were negative for RRA at endoscopic assessment contained evidence of RRA at histopathology online supplemental table 3. All of these specimens were reported as low-grade dysplasia at histopathology. Nine of 11 (81.8%) of these surveillance procedures occurred outside of the study centre. Successful endoscopic treatment of recurrence was performed at a further scheduled surveillance examination in 4 of 11; 3 were ineligible for further follow-up due to age/ comorbidity; 1 was lost to follow-up; and 1 was pending further follow-up. One patient underwent surgery at SC2 for the lesion that underwnt EMR, and one patient underwent surgery at SC3 for a high-grade lesion in a different colonic segment.

Surgery performed for RRA during the study

Nine of 213 (0.5%, 95% CI 0.2% to 1.0%) patients underwent surgery during the study for the treatment of RRA. Eight (88.9%) of nine surgeries were for LNPCP with initial EMR within the first half of the study period (<70 months). Of nine RRAs requiring surgery, five were detected at SC1, two at SC2 and two at SC3. Further details can be found in online supplemental appendix 1 and online supplemental table 4.

DISCUSSION

RRA after successful EMR occurs in approximately 15% of cases. Significant progress has been made in mitigating RRA through predicting which LNPCP will recur and dramatically reducing the risk of its occurrence through complete thermal ablation of the post EMR defect margin. However, if RRA does occur, no systematic approach to its treatment or data on the success rate of such treatment exist to guide therapy. In this study of 1800 LNPCPs having undergone successful EMR with strong compliance to surveillance colonoscopy (SC), we demonstrate that the majority of RRA is small, unifocal and that the endoscopic treatment of recurrence using easily learnt endoscopic techniques is successful in >90% of cases and, if successful, leads to long-term remission of RRA.

The literature regarding RRA after EMR is beset by studies which have heterogenous or poorly described inclusion criteria, describe no standardised technique for the endoscopic treatment of RRA and/or are retrospective nature with short (limited to a single surveillance procedure) or poorly described follow-up. Many studies simply describe the treatment of recurrent LNPCP without describing the original lesion (inadequate distinction between complete resection or prior attempt). Furthermore, the majority of such studies lack a systematic scar assessment protocol for the detection of RRA, use endoscopic recurrence as an endpoint without a systematic description of histology, do not discuss scars without endoscopic evidence of RRA where RRA was discovered histologically, do not present results from successive surveillance examinations (describing the endoscopic treatment of RRA at a single point in time rather than throughout the whole breadth of follow-up) and do not describe follow-up into the long term. Furthermore, such studies do not provide a comprehensive description (visual and descriptive) of
In this study, we sought to address these issues by taking a systematic approach to the description of RRA. Only LNPCPs with successful EMR (without invasive cancer outside criteria for endoscopic surveillance) were eligible. Surveillance data were presented over four successive time points. At every SC, the endoscopic resection scar was located and, if RRA occurred, it was described using a standardised protocol. The success rate of treatment of RRA and the endoscopic technique used were recorded. At subsequent SC, the number of treatments required to achieve one or more negative scar assessments was determined (termed endoscopic cure). Scars were routinely biopsied, and any that contained microscopic evidence of RRA without an endoscopic correlate were also included in the description of RRA and described separately. Any surgery that occurred during surveillance was recorded, and the reasons for each individual case were presented separately.

We found that the overwhelming majority of RRA was endoscopically detectable. Reports of RRA that was not endoscopically detectable (unexpected scar biopsy positive for adenoma) often originated from referring centres. Based on this finding, further education of the wider endoscopic community as to the appearance of endoscopic resection scars and RRA after EMR is clearly necessary and required. For now, perhaps routine biopsy of the post-EMR scar in centres without extensive EMR experience should remain the gold standard.

RRA was predominantly detected at first surveillance, commonly <5 mm and located within the scar (figure 2 and online supplemental video S1). When RRA was detectable endoscopically, endoscopic treatment was performed successfully in >95% of cases. A histological correlate for RRA was demonstrated in 96% of cases. We believe this minor overtreatment (of suspected RRA endoscopically which cannot be proven histologically) is justified for two reasons. First, true RRA may be missed by tissue acquisition or sectioning and preparation techniques prior to histopathology. Second, since endoscopic treatment of RRA has been demonstrated to be safe. Conversely if RRA which is suspected is not treated, the patient must return for a further procedure with implicit cost and morbidity implication.

Studies on EMR often discuss endoscopic treatment of RRA without a description of the actual technique used. In this study, particularly where RRA was >5 mm in size, treatment of RRA was commonly performed using hot snare excision (with forced coagulation) and cold avulsion forceps biopsy with adjuvant snare tip soft coagulation (CAST). Submucosal injection was not performed as this often-impeded access to the target tissue. It was common practice during the study to then treat the normal scarred mucosa (halo of 1 mm) surrounding the resection/avulsion site to ablate microscopic residual adenoma. Snare resection is often challenging when RRA is <5 mm in size or completely flat. In such cases, CAST was preferred and allowed reliable clearance of RRA. Again, the surrounding scarred mucosa was treated with a 1 mm halo of soft coagulation (online supplemental figure 2). No specific adverse events were described after the application of endoscopic treatment methods for RRA during surveillance procedures.

Taken together, these findings suggest the use of CAST or snare resection for the treatment of RRA is safe and effective. Furthermore, these techniques are complementary to those used during EMR, are easily learnt and inexpensive. To the authors’ knowledge, no other techniques have been subjected to similar systematic prospective study.

Multiple other techniques have previously been described to treat RRA (online supplemental table 5). Unfortunately, in the majority of case series after EMR, techniques to treat RRA are simply described as endoscopic treatment of recurrence (leaving the reader to assume a combination of standard EMR or ablative techniques). ESD is the most commonly described technique, particularly in Japanese studies. It is certainly effective with an en bloc resection rate of 100%, R0 rate of 88.4% and a single recurrence during follow-up (non-R0) described in one expert Japanese series. However, it is time-consuming, comparatively expensive, mandates hospital admission and is often extremely technically challenging for scarred lesions.

EFTR has also been described in this specific context (30 cases) with R0 rates of 80% and no follow-up described. A single delayed perforation required emergency surgery. A larger series included 85 recurrent or incompletely resected lesions (not separated); R0 rates were lower (70.5%) than other indications for
EFTR (82.4% overall). Furthermore, 5.7% of lesions could not be reached with the device; serious adverse events occurred in 9.3%; and no long-time follow-up was described. This technique, currently in its first-generation and cumbersome to insert and manoeuvre, should therefore not be considered first-line for the treatment of RRA.

Other techniques described include mechanical avulsion of non-lifting tissue (outside of the specific context of recurrent adenoma after EMR) using a cautery-connected forceps (hot avulsion) or avulsion using argon plasma coagulation. Both techniques suffer from preventing the acquisition of accurate histopathology with the consequent risk of missing invasive disease. The risks of hot biopsy forceps with their unpredictable depth of thermal injury remain a concern. Moreover, both techniques have only been described in small case series without long-term follow-up data.

The majority of surgeries for failed treatment of RRA (5/8) during the study occurred at the SC1 due to an inability to treat RRA endoscopically. Three of five cases involved the ICV (ileocaecal valve) (one appearing malignant) or the appendiceal orifice. Two further cases involved the splenic flexure, one appearing malignant and the other due to difficulty in colonscope positioning. The ICV and appendiceal orifice have previously been described as difficult locations for EMR with outcomes inferior to other locations. Both invasive-appearing RRAs were confirmed by subsequent histology. Neither patient showed evidence of distant or nodal metastases. Taken together, the reasons for failed treatment of RRA at SC1 can be attributed to the complexity and breadth of this tertiary referral EMR series, rather than a significant issue for the failure of the technique when applied to more 'standard' lesions.

After successful treatment of RRA, patients were followed up at successive colonoscopic surveillance examinations. If treatment of RRA was performed, a surveillance examination was usually scheduled 6 months later. The overwhelming majority (92.5%) experienced long-term remission of RRA to long-term follow-up (including at least one negative surveillance examination). Only a minority required two sessions of treatment to achieve endoscopic cure (14.8%) with the rest achieving cure after a single session. Surgery was avoided in >98% of patients. The two cases that required surgery after successful treatment of RRA are described in detail in the Results section (one located at the ICV and one further with intense fibrosis after a perforation at index procedure). These findings add reassurance that the strategy of EMR with structured surveillance including endoscopic treatment of RRA where required is a safe, robust and durable method of treating LNPCP.

The advent of thermal ablation of the post-EMR margin to reduce RRA has additional implications. With its anticipated widespread adoption, significant reduction in rates of RRA and the consequent need for treatment of RRA can be expected in the future. Therefore, this large prospective experience is unlikely to be repeated and may serve as a time capsule in which to view the management of RRA for future practitioners who may only rarely encounter RRA after EMR and may never be exposed to it during their training.

This study is not without limitations. As a single expert centre, the overall rate of RRA in this study (14.6%) is lower than many. All LNPCPs were resected using a 1–2 mm rim of normal tissue. Later in the experience, thermal ablation of the post-EMR margin was performed (see the Methods section), initially within a randomised study and later routinely. Since this was a prospective experience, techniques used for treatment of RRA varied throughout the study. The authors acknowledge that these factors may limit the general applicability of the study; however, routine application of the simple techniques described herein should mitigate this discrepancy. While reflecting the realities of clinical practice, we acknowledge that there is a less than perfect adherence to structured surveillance examination. A significant proportion of patients who undergo EMR are elderly and comorbid, reflecting a selection bias, as they are unfit for surgery, and therefore successive follow-up examination is either declined or not possible. It also reflects the nature of practice in Australia where patients often travel many miles for a procedure at the study centre and cannot repeatedly attend for surveillance due to financial or time constraints. We have attempted to mitigate this as far as possible by routinely performing first follow-up examination at the study centre (compliance to first surveillance >90%) and rigorously following up patient data wherever the examination occurred. Conversely, the need for a structured surveillance programme after EMR is a significant limitation. The possibility to reduce surveillance burden in the era of thermal ablation of the post-EMR margin has yet to be determined.

Another limitation of the study was that scars which were endoscopically negative for RRA were not universally biopsied (online supplemental table 6). This could mean that the true rate of RRA detected histologically without an endoscopic correlate throughout the series is higher than reported here (eg, 7% in one previous study and may be of concern for interval cancer after EMR of LNPCP. Mitigating against this observation are prior expert series reporting very high negative predictive values of scar assessment by experts. Furthermore, in this real-world experience, in the context of a structured surveillance programme with interface between referring and expert centres, no malignant RRA was detected after first surveillance.

CONCLUSIONS

Adenoma recurrence after EMR of LNPCPs is commonly diminutive and can be readily and effectively treated using simple endoscopic techniques in a single session in the vast majority of cases with rates of long-term remission over 90%. Based on these data and given the efficacy of thermal ablation of the post-EMR margin in the prevention of RRA, more technically complex, morbid and resource-intensive endoscopic or surgical techniques are unnecessary to resect the overwhelming majority of LNPCPs or RRA if it occurs in surveillance.

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Contributors DJT designed the data collection, collected and analysed the data, wrote the manuscript and supervised the manuscript. MEA and MA analysed the data, performed the procedures, assisted with writing and revision of the manuscript. MS, SV, NS, SJW and NGB collected and analysed the data, performed the procedures, assisted with writing and revision of the manuscript. MJB designed the study, performed the majority of the procedures and reviewed and supervised the manuscript.

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Patient consent for publication Not applicable.


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