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Need for adjunctive removal techniques for endoscopic mucosal resection of large non-pedunculated colonic polyps is predictive of recurrence

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ABSTRACT

Background and study aims Endoscopic mucosal resection (EMR) allows for safe and effective removal of large non-pedunculated colon polyps, but recurrence remains a significant concern. Risk factors for recurrence have previously been reported, however, the significance of these factors have varied and has uncertain applicability with recent advances in EMR techniques. We aimed to evaluate rates and risk factors for recurrence in recent years from a major Canadian referral center.

Patients and methods Consecutive patients between April 1, 2017 and March 1, 2019 who underwent piecemeal EMR were retrospectively identified. Patients with non-pedunculated colorectal polyps ≥ 2 cm removed by piecemeal EMR with available follow-up data were included.

Results Five hundred and seventeen patients were reviewed, with 265 patients satisfying inclusion criteria. The median age was 67 years (IQR 14); 48 % were female. 15 % had a recurrence on follow-up endoscopy. Adjunctive removal techniques were utilized in 31 % of patients, 95 % of which was hot avulsion. The use of adjunctive removal techniques (OR 2.87, $P = 0.004$) and male gender (OR 3.31, $P = 0.003$) was significantly predictive of recurrence on multivariate analysis. Receiver operating curve characteristics demonstrated good performance of these factors in predicting recurrence (area under the curve = 0.70).

Conclusions The use of adjunctive removal techniques, particularly hot avulsion and male gender are predictive of recurrence after piecemeal EMR of large non-pedunculated colorectal polyps. Male patients and those who require hot avulsion may be considered high risk for recurrence and warrant closer follow-up.

Introduction

Endoscopic mucosal resection (EMR) is a safe and effective technique for managing large colorectal polyps [1, 2]. Although it has become an established standard of care, concerns remain regarding the potential for local recurrence, particularly after large piecemeal EMR (pEMR) [3]. Historically, recurrence rates have been reported to range as high as 30 % in older series, with recent studies reporting significantly lower rates with the evolution of new techniques [4].

Adjuvant techniques such as the application of snare-tip soft coagulation (STSC) to EMR defect edges and hybrid APC (hAPC) have been shown to reduce recurrence from potential non-visible residual microscopic tissue [4, 5]. Additionally, new adjunc-

tive techniques such as the use of hot avulsion and cold avulsion with snare-tip soft coagulation (CAST) have been shown to be efficacious in recent years to manage macroscopic polyp tissue not amenable to snare resection [6–8].

With the rapid growth and adoption of large polyp EMR, various clinical risk factors for recurrence have been investigated to help stratify recurrence risk and surveillance recommendations [3, 9–12]. The Sydney EMR Recurrence Tool (SERT) and the Size/Morphology/Site/Access (SMSA) Score developed based on these factors has previously been shown to be effective in predicting recurrence in the Australian Colonic EMR (ACE) cohort [9, 10]. However, the performance of these tools has been called into question. Recently, new adjuvant techniques such as STSC have been found to negate the effect of some previously reported risk factors for recurrence, such as polyp size and en bloc versus piecemeal resection [4]. Additionally, the external validity of the SERT score was poor in recent studies from North America [13].

Currently, no risk factors or scoring systems have been well-adopted to stratify and prioritize individualized timing of surveillance colonoscopy after EMR. Guidelines continue to universally recommend that first surveillance colonoscopy (SC1) be done at six months for all patients undergoing pEMR of large polyps [3]. With the advent of newer EMR techniques, variations between reported risk factors, and limited data on polyp recurrence from Canadian centers, we aimed to evaluate rates and risk factors for recurrence in recent years from a major Canadian referral center.

Patients and methods

Study design

Consecutive patients undergoing EMR between April 1, 2017 and March 1, 2019 were retrospectively identified from St. Michaels Hospital endoscopy unit administrative records. The conduct of this study was approved by the Unity Health Toronto research ethics board.

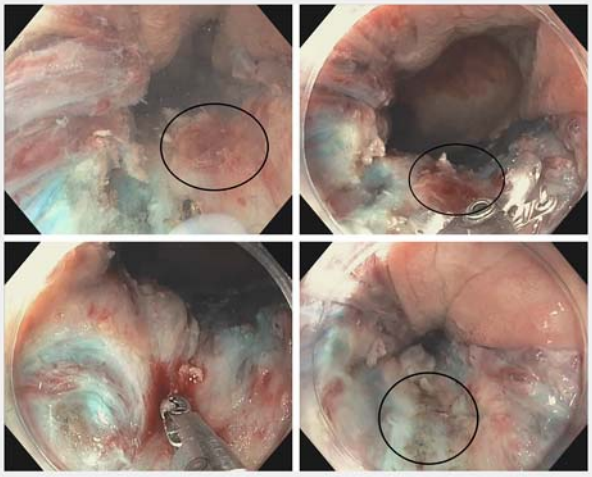
All cases were reviewed against inclusion and exclusion criteria detailed in Supplementary Table 1. All flat non-pedunculated colorectal polyps larger than 20 mm were included in our study. Patients were excluded if they did not undergo their first surveillance colonoscopy (SC1) at St. Michaels Hospital, had index EMR histology demonstrating invasive adenocarcinoma, or EMR was not attempted/incomplete at index procedure.

Definitions

Large non-pedunculated polyps were defined as polyps measuring ≥ 20 mm in size that were not morphologically Ip or Isp on the Paris classification schema.

Polyp recurrence was defined as a positive histology specimen from the EMR scar.

Adjunctive techniques were defined as any non-snare resection technique used to remove macroscopically visible adenoma.



▶ **Fig. 1** Recurrent fibrotic rectal polyp undergoing piecemeal EMR removal with need for adjunctive removal technique. Top two images demonstrate fibrotic non-lifting island of polyp tissue (black oval) unable to be captured by the snare. Bottom left image demonstrates grasping of polyp tissue island with hot-biopsy forceps and removal via hot avulsion technique. Bottom right image demonstrates EMR defect (black oval) after hot avulsion of the polyp island.

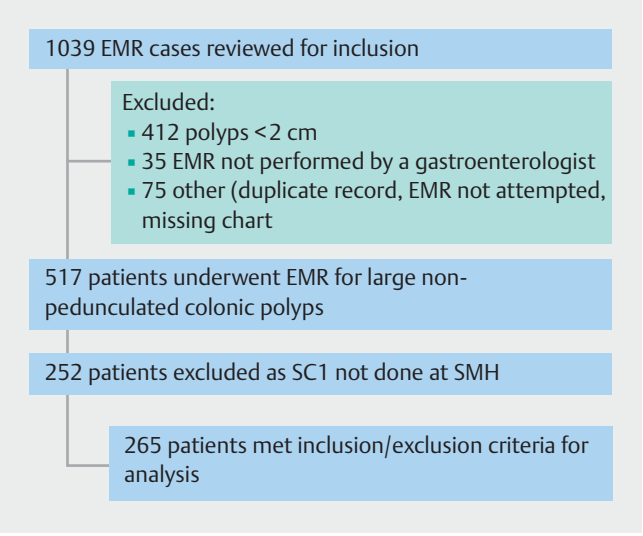
EMR procedure

All procedures were conducted by a senior endoscopist with a minimum of 5 years' experience or a therapeutic endoscopy fellow under the direct supervision of a senior endoscopist. All lesions were removed via traditional injection and hot snare resection technique. Injection solution and the addition of epinephrine were used at the discretion of the endoscopist. As per our center's standard clinical practice and guideline recommendations, adjunctive techniques were indicated in cases where polyp tissue was unable to be captured with a snare via standard snare EMR techniques (▶ **Fig. 1**) [3]. The primary adjunctive techniques utilized at our center included hot avulsion and CAST for which the methods have been well described in prior studies [3, 6, 7].

The timing of SC1 was targeted for six months post EMR based on current guideline recommendations [3]. EMR scar site was examined at SC1 with the decision to biopsy the scar left at endoscopist's discretion. Systematic biopsy of all EMR scar sites was not required if the clinical suspicion for endoscopic recurrence based on thorough high-definition white light (HD-WLE) and narrow-band imaging (NBI) examination was low, a practice that results from the ESCAPE trial have supported [14].

Data extraction

Lesion and case details were obtained by reviewing the patient's local electronic health record (EHR). In instances where details were unavailable through the EHR, a physical chart review of the case, including post hoc review of endoscopic images was conducted.



▶ **Fig. 2** Patient study inclusion.

Statistical Analysis

Descriptive variables were summarized as frequencies (%) and medians as appropriate. Mann-Witney U test and Chi-square were used to compare variables between groups with and without recurrence. Binomial univariate and multivariate regression were used to analyze potential variables predictive of polyp recurrence. Variables meeting a threshold $P<0.2$ on univariate analysis were included in multivariate models [15]. Receiver operating curves were constructed, and the area under the curve (AUC) was calculated to assess the performance of selected predictive factors.

Results

A total of 1039 EMR cases were identified and reviewed against inclusion/exclusion criteria. Five hundred seventeen patients underwent EMR of a large non-pedunculated colonic polyp during our study period. Two hundred sixty-five patients met full criteria for analysis in our study (▶ **Fig. 2**). Two hundred fifty-two patients were excluded as SC1 was performed at the initial referring center rather than at our institution.

Demographics and polyp features

The median age at the time of EMR was 67 years (IQR 14). 48 % (n = 127/265) of participants were female. Eighty-four percent of patients with polyps (222 of 265) were referred from other centers.

Of the polyps, 83 % (219 of 265) were located proximal to the splenic flexure (▶ **Table 1**). Fourteen percent of polyps (38 of 265) had prior failed resection attempts. Seventy-three percent of polyps (194 of 265) were between 2 and 4 cm in size and 27 % of polyps were larger than 4 cm (71 of 265). Fifty-three percent (139 of 265), 28 % (73 of 265), 19 % of polyps (49 of 265) were tubulovillous/villous, tubular adenoma, or SSA on histology respectively. Twenty-two percent of polyps (57 of 265) had high-grade dysplasia. Median time to follow-up endoscopy was 224 days (IQR 144).

▶ **Table 1** Baseline patient demographics and polyp/procedure details.

Median age at EMR (yr)	67 (IQR 14)
Male gender	52 % (n = 138)
Polyp details	
Location proximal to splenic flexure	83 % (n = 219/265)
Prior resection attempt	14 % (n = 38/265)
Estimated polyp size	
2–2.9 cm	24 % (n = 64/265)
3–3.9 cm	49 % (n = 130/265)
≥ 4 cm	27 % (n = 71/265)
High-risk SERT score[1]	53 % (n = 137/258)
Median SMSA score	13 (IQR 2)
SMSA grade	
1 or 2	0 %
3	31 % (n = 82/265)
4	69 % (n = 183/265)
Median time to follow-up endoscopy (days)	224 (IQR 144)
Histological classification	
Tubular adenoma	28 % (n = 73/265)
Tubulovillous/villous	53 % (n = 139/265)
SSA	19 % (n = 49/265)
Other	1.5 % (n = 4/265)
Presence of high-grade dysplasia	22 % (n = 57/265)
Endoscopic mucosal resection procedure details	
Piecemeal excision	97 % (n = 258/265)
Use of adjunctive technique	31 % (n = 83/265)
Type of adjunctive technique	
Hot avulsion	95 % (n = 79/83)
Cold avulsion + STSC (CAST)	5 % (n = 4/83)
Intraprocedural bleeding	32 % (n = 84/265)
Deep muscle injury	0.4 % (n = 1/265)
Sedation complications	1 % (n = 3/265)
Defect clip closure	11 % (n = 28/265)
Snare tip soft coagulation to defect edges	94 % (n = 250/265)

EMR, endoscopic mucosal resection; IQR, interquartile range; SERT, Sydney EMR Recurrence Tool; SMSA, Size/Morphology/Site/Access; SSA, sessile serrated adenoma; STSC, snare-tip soft coagulation; CAST, cold avulsion with snare-tip soft coagulation.
[1] Defined as SERT Score ≥ 1.

53 % of polyps (137 of 258) were classified as high risk (score ≥ 1) on SERT score. Thirty-one percent (82 of 265) and 69 % of polyps (183 of 265) were grade 3 or 4 respectively on SMSA grading.

▶ **Table 2** Regression analysis for predictors of need for adjunctive removal technique.

	Univariate Analysis		Multivariate Analysis	
Factor	**Unadjusted OR (95 % CI)**	***P* value**	**Adjusted OR (95 % CI)**	***P* value**
Age	1.02 (1.00–1.05)	0.11	1.02 (0.99–1.05)	0.19
Male gender	1.25 (0.75–2.11)	0.39	–	–
Location in proximal colon	0.83 (0.42–1.62)	0.58	–	–
Prior resection attempt	5.60 (2.69–11.7)	<0.001[1]	5.44 (2.61–11.4)	<0.001[1]
Polyp size				
3–4 cm vs. 2–3 cm	0.85 (0.44–1.61)	0.61	–	–
>4 cm vs. 2–3 cm	1.05 (0.51–2.14)	0.90	–	–
Intraprocedural bleeding	0.83 (0.47–1.46)	0.51	–	–
High-grade dysplasia on histology	1.24 (0.67–2.31)	0.49	–	–

[1] Denotes significance, defined as P<0.05

Procedure characteristics

Ninety-seven percent of polyps (258 of 265) underwent piecemeal excision (▶ **Table 1**). Thirty-one percent of polyps (83 of 265) required adjunctive removal techniques. Ninety-five percent of polyps (79 of 83) requiring adjunctive techniques utilized hot avulsion. Ninety-four percent of polyps (250 of 265) had adjuvant STSC applied to defect edges following completion of the EMR. Eleven percent (28 of 265) had clip closure of the EMR defect.

Prior resection attempt (66 % vs. 26 %, *P*<0.001) and higher SMSA grade (3 vs 4; 20 % vs. 37 %, *P*=0.006) were associated with the need for adjunctive techniques. Prior resection attempt was the only significant variable predictive of the need for adjunctive techniques on multivariate analysis (OR 5.44, *P* <0.001) (▶ **Table 2**).

Adverse events

Thirty-two percent (84 of 265) had intraprocedural bleeding (▶ **Table 1**). Deep muscle injury (DMI) occurred in 0.4 % (1 of 265). The one patient with DMI was successfully managed with endoscopic clip closure. One percent (3 of 265) had sedation-related complications.

Polyp recurrence and risk factors for recurrence

The overall histologic recurrence rate at SC1 was 14.7 % (39 of 265). Risk of recurrence was associated with male gender (74 % of patients with recurrence were male vs. 48 % of patients without recurrence, *P*=0.003) and use of adjunctive techniques (no adjunctive technique [28 %] vs. adjunctive technique used [51 %], *P*=0.004) (▶ **Table 3**). Only male gender (OR 3.31, *P*= 0.003) and use of adjunctive removal techniques (OR 2.87, *P*= 0.004) were predictive of recurrence on multivariate analysis (▶ **Table 4**). These results were similarly seen on sensitivity analysis when excluding previously instrumented polyps (Supplementary Table 1).

SERT score and SMSA grade were not significantly associated with recurrence on regression analysis (OR 1.84, *P*=0.10 and OR 1.89, *P* =0.13, respectively). As seen in ▶ **Fig. 3**, our cohort showed that SERT and SMSA scores performed poorly in predicting recurrence with AUC of 0.56 and 0.53, respectively. Notably, male gender and use of adjunctive resection techniques performed better in predicting recurrence with AUC of 0.64 and 0.62, respectively. Combining the two clinical factors provided the most robust predictive performance of recurrence with an AUC of 0.70 (▶ **Fig. 3**).

Eighty-seven percent of recurrent polyps at SC1 (34 of 39) underwent endoscopic resection with reported technical success. Thirteen percent of recurrent polyps (5 of 39) were unsuccessfully removed endoscopically at SC1. Of these patients, three underwent surgical resection, one returned for a repeat endoscopic resection attempt that was technically successful, and one deferred further intervention due to significant medical comorbidities.

Discussion

Our study has shown that recurrence remains a significant concern after large polyp EMR in current clinical practice despite advances in resection techniques. Our results suggest that male gender and the use of adjunctive removal techniques are independent clinical factors predictive of recurrence and may perform better than previously proposed models. These findings reinforce the importance of close endoscopic follow-up and may help endoscopists stratify and prioritize patients post EMR surveillance.

Prior data on recurrence risks have been heterogeneous across studies. Initial results from the ACE cohort found polyp size, intraprocedural bleeding, and use of APC to be significantly associated with recurrence [12]. However, other studies have found several different factors including dysplasia, gender, piecemeal resection, bowel preparation, proximal location, and incomplete resection, to be associated with recurrence

▶ **Table 3** Comparison of patient and procedural factors on polyp recurrence.

	No recurrence	With recurrence	*P* value
Median age at EMR (Years)	67 (IQR 15)	70 (IQR 14)	0.14
Male gender	48 % (n = 109/226)	74 % (n = 29/39)	0.003[1]
Location proximal to splenic flexure	83 % (n = 187/226)	82 % (n = 32/39)	0.92
Prior resection attempt	13 % (n = 30/226)	21 % (n = 8/39)	0.23
Polyp size			
2–2.9 cm	23 % (n = 51/226)	33 % (n = 13/39)	0.18
3–3.9 cm	51 % (n = 116/226)	36 % (n = 14/39)	
≥ 4 cm	26 % (n = 59/226)	31 % (n = 12/39)	
Piecemeal excision	97 % (n = 220/226)	97 % (n = 38/39)	0.97
Use of adjunctive technique	28 % (n = 63/226)	51 % (n = 20/39)	0.004[1]
Type of adjunctive technique			
Hot avulsion	94 % (n = 59/63)	100 % (n = 20/20)	0.25
Cold avulsion + STSC	6 % (n = 4/63)	0 % (n = 0/20)	
Intraprocedural bleeding	31 % (n = 71/226)	33 % (n = 13/39)	0.81
Deep muscle injury	0.4 % (n = 1/226)	0 % (n = 0/39)	0.68
Sedation complications	1 % (n = 3/226)	0 % (n = 0/39)	0.47
Polyp histological classification			
Tubular adenoma	27 % (n = 62/226)	28 % (n = 11/39)	0.24
Tubulovillous/villous	50 % (n = 112/226)	69 % (n = 27/39)	
SSA	21 % (n = 48/226)	3 % (n = 1/39)	
Other	1.8 % (n = 4/226)	0 % (n = 0/39)	
Presence of high-grade dysplasia	21 % (n = 48/226)	23 % (n = 9/39)	0.80
Median time to follow-up endoscopy (days)	225 (IQR 130)	189 (IQR 231)	0.30
High risk SERT	51 % (n = 112/220)	66 % (n = 25/38)	0.09
Median SMSA score	13 (IQR 3)	13 (IQR 2)	0.40
SMSA grade			
3	33 % (n = 74/226)	21 % (n = 8/39)	0.13
4	67 % (n = 152/226)	80 % (n = 31/39)	

EMR, endoscopic mucosal resection; IQR, interquartile range; SERT, Sydney EMR Recurrence Tool; SMSA, Size/Morphology/Site/Access.

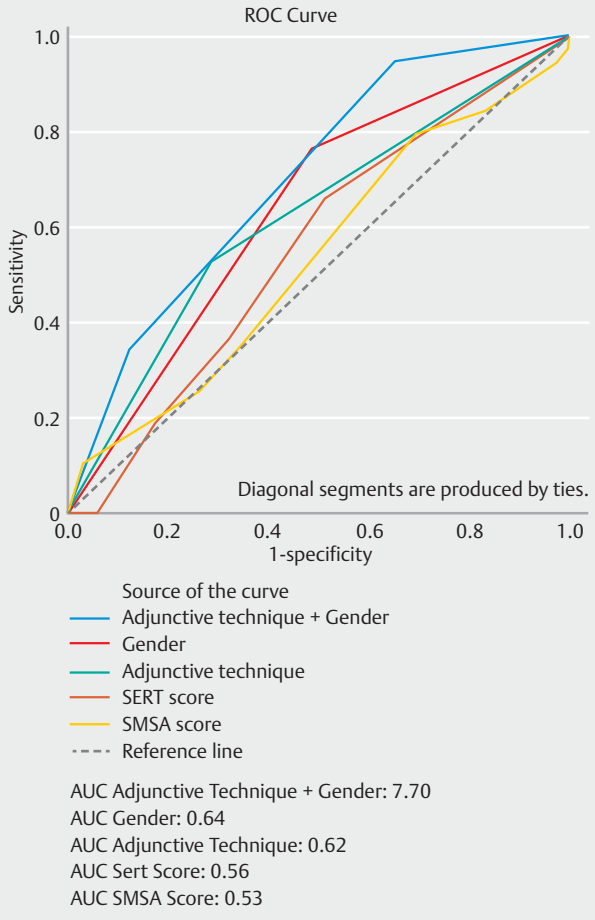
[9, 10, 16–21]. Despite the variation, one of the most consistent risk factors reported across studies appears to be a larger polyp size. Interestingly, the recent study demonstrating the efficacy of adjuvant STSC in preventing recurrence found that the use of STSC seemed to negate the risk of polyp size, with recurrence risks being similar between polyps ≥ 40 mm and < 40 mm in the treatment arm [4]. These findings agree with our results, where polyp size was not found to be significantly associated with recurrence. Although adjuvant STSC to defect edges had recently become widely adopted and recommended by guidelines, most published studies evaluating recurrence risks were conducted when STSC was not consistently utilized. This may explain the discrepancy between our findings and prior studies, as well as the poor performance of the SERT and SMSA scores, which were developed utilizing a cohort that did not consistently receive adjuvant STSC.

The efficacy of adjuvant STSC to EMR defect edges suggests that a significant mechanism of recurrence may be related to microscopic non-visible residual polyp tissue left at the edges of the resection defect. A recent study from Emmanuel *et al.* reinforces this concept, where they detected microscopic residual adenoma in 19 % of macroscopically clear defect margins. However, this study also found a significant proportion of microscopic residual adenoma in the resection bed of EMR defects

▶ **Table 4** Regression analysis for predictors of polyp recurrence.

	Univariate analysis		Multivariate analysis	
Factor	**Unadjusted OR (95 % CI)**	***P* value**	**Adjusted OR (95 % CI)**	***P* value**
Age	1.02 (0.99–1.06)	0.12	1.02 (0.98–1.06)	0.35
Male gender	3.20 (1.49–6.88)	0.003[1]	3.31 (1.50–7.30)	0.003[1]
Location in proximal colon	1.03 (0.43–2.51)	0.94	–	–
Prior resection attempt	1.66 (0.70–3.95)	0.25	–	–
Polyp size				
3–4 cm vs. 2–3 cm	0.47 (0.21–1.07)	0.07	0.49 (0.21–1.16)	0.11
>4 cm vs. 2–3 cm	0.80 (0.33–1.90)	0.61	0.75 (0.30–1.88)	0.54
Intraprocedural bleeding	1.09 (0.53–2.25)	0.81	–	–
Use of adjunctive removal technique	2.67 (1.34–5.34)	0.005[1]	2.87 (1.39–5.93)	0.004[1]
High-grade dysplasia on Histology	1.09 (0.49–2.46)	0.83	–	–
High-risk SERT score	1.84 (0.89–3.78)	0.10	–	–
SMSA grade	1.89 (0.83–4.31)	0.13	–	–

SERT, Sydney EMR Recurrence Tool; SMSA, Size/Morphology/Site/Access.



▶ **Fig. 3** Receiver operating curve analysis of predictors of polyp recurrence

[22]. These findings support our results, as although hot avulsion has been proven to be a safe and effective tool for removing non-lifting visible polyp within the resection bed that cannot be removed by snare, residual microscopic polyp tissue may remain [6]. Recent data evaluating CAST for adjunctive removal of non-lifting visible polyp reported 100 % technical success in removing visible macroscopic adenoma but found a 15 % to 27.5 % recurrence rate at SC1 [7]. Comparative studies between hot avulsion and CAST techniques have yet to be conducted. Given the concerns for potential residual microscopic tissue within the EMR resection bed, novel adjuvant techniques such as hAPC applied to the resection bed are undergoing evaluation. Notably, an early pilot study has shown a significant reduction in recurrence, with a 0 % recurrence rate at SC1 in patients undergoing adjuvant hAPC versus 20.7 % ($P = 0.01$) in the standard EMR arm [5]. However, data from larger comparative studies are needed. In the meantime, our data have prompted us to minimize the use of hot avulsion to treat non-lifting visible polyp fragments that fail to be successfully removed by snare resection due to our high rates of recurrence when using this technique. Instead, we now preferentially use underwater EMR or hybrid EMR/ESD techniques to remove areas of polyp that are embedded in fibrosis.

Interestingly male gender appeared to be strongly predictive of polyp recurrence in our results. A few prior studies have found that male gender was predictive of recurrence in advanced adenomas; however, the underlying cause is unclear [17, 18]. Male gender is an established and consistent risk factor in developing advanced colonic neoplasia, potentially related to hormonal differences, lifestyle, and genetic differences [23, 24]. Prior studies have suggested that estrogens and progestins may have a protective effect in preventing colon cancer [23]. However, how these findings translate to potential

mechanisms underlying gender differences in recurrence remains unclear. Future studies are necessary to evaluate these findings.

An important finding in our study was that prior resection attempts strongly predict the need for future adjunctive removal techniques if the index resection is not successful. This is not unexpected as previous instrumentation causes significant submucosal fibrosis resulting in poor lifting and thus inability to capture tissue with conventional snares. Although studies have shown the efficacy of adjunctive techniques in managing these polyps, previous instrumentation significantly increases the difficulty and, in certain cases, requires more advanced resource-intensive resection techniques such as hybrid EMR and endoscopic submucosal dissection [3, 6, 7]. Thus, as recommended by recent guidelines, benign colorectal lesions encountered by endoscopists for which they are not confident in removing should be referred to endoscopists experienced in advanced polypectomy [3].

Our study represents the largest Canadian study to date evaluating recurrence following large polyp EMR and in secondarily assessing the external validity of prior recurrence prediction models (SERT and SMSA score) in our population. Nevertheless, our study has several weaknesses. Our study design was retrospective and at a single center, thus limiting its generalizability and our ability to control specific procedural aspects precisely. Although endoscopists are recommended to only utilize adjunctive techniques in cases of polyp tissue that is unable to be captured with a snare, the retrospective nature of our study limits the ability to directly monitor this and thus the threshold before using adjunctive techniques may have varied between practitioners. As our center is a major referral site for advanced endoscopy, a significant proportion of the polyps included in our study are highly complex, which may reflect our relatively high recurrence rate despite the nearly universal use of adjuvant STSC. Additionally, a significant number of patients (n = 252) did not have SC1 surveillance completed at our center as many of our patients are referred to us from other cities and thus were not included in our analysis. This may have introduced selection bias into our sample, as the practice pattern of some of the participating endoscopists during the study period was to preferentially perform surveillance on patients with more concerning lesions at our center, whereas patients with more straightforward lesions were returned to their referring gastroenterologist for follow-up.

Conclusions

Although highly effective, close endoscopic follow-up after large polyp EMR remains crucial due to recurrence risks. Male gender and use of adjunctive resection techniques such as hot avulsion are clinical factors predictive of an increased risk of recurrence. The presence of these factors may identify higher-risk patients and could potentially aid endoscopists in triaging those who need timelier follow-up colonoscopy and identify those most likely to benefit from returning to an expert endoscopy center for surveillance.

Further research is needed to evaluate the reproducibility of our results and to develop accurate models reflecting current techniques for predicting risk of recurrence after EMR to ensure judicious use and access of endoscopy resources.

Competing interests

Dr. Gary May: Pentax (speaker), Medtronic (speaker), Boston Scientific (speaker), Olympus (consultant), Fujifilm (consultant)
Dr. Jeff Mosko: Boston Scientific (speaker), Pendopharm (speaker), Medtronic (speaker), Vantage (speaker), SCOPE (speaker), Pendopharm (advisory board), Janssen (advisory board), KeyOps (advisory board), Pentax/C2 (advisory board), Boston Scientific (advisory board)
Dr. Chris Teshima: Medtronic (speaker), SCOPE (speaker), Vantage (research support), Boston Scientific (consultant)

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