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Risk factors associated with adenoma recurrence following cold snare endoscopic mucosal resection of polyps ≥ 20 mm: a retrospective chart review



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submitted 23.11.2020

accepted after revision 15.2.2021

Bibliography

Endosc Int Open 2021; 09: E867–E873

DOI 10.1055/a-1399-8398

ISSN 2364-3722

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ABSTRACT

Background and study aims Cold snare endoscopic mucosal resection (EMR) is being increasingly utilized for non-pedunculated polyps ≥ 20 mm due to adverse events associated with use of cautery. Larger studies evaluating adenoma recurrence rate (ARR) and risk factors for recurrence following cold snare EMR of large polyps are lacking. The aim of this study was to define ARR for polyps ≥ 20 mm removed by cold snare EMR and to identify risk factors for recurrence.

Patients and methods A retrospective chart review of colon cold snare EMR procedures performed between January 2015 and July 2019 at a tertiary care medical center was performed. During this period, 310 non-pedunculated polyps ≥ 20 mm were excised using cold snare EMR with follow-up surveillance colonoscopy. Patient demographic data as well as polyp characteristics at the time of index and surveillance colonoscopy were collected and analyzed.

Results A total of 108 of 310 polyps (34.8%) demonstrated adenoma recurrence at follow-up colonoscopy. Patients with a higher ARR were older ($P=0.008$), had endoscopic clips placed at index procedure ($P=0.017$), and were more likely to be Asian and African American ($P=0.02$). ARR was higher in larger polyps ($P<0.001$), tubulovillous adenomas ($P<0.001$), and polyps with high-grade dysplasia ($P=0.003$).

Conclusions Although cold snare EMR remains a feasible alternative to hot snare polypectomy for resection of non-pedunculated polyps ≥ 20 mm, endoscopists must also carefully consider factors associated with increased ARR when utilizing this technique.

Introduction

Endoscopic mucosal resection (EMR) is a technique to remove larger lesions in the digestive tract that have not invaded into the submucosal space. EMR generally involves submucosal injection with en bloc or piecemeal snare resection of a polyp, although the non-injection lift technique of underwater EMR has

more recently been described [1]. Traditionally hot snare polypectomy has been recommended for removal of larger polyps [2]; however, in 2017, the European Society of Gastrointestinal Endoscopy updated guidelines recommending that there may be a role for piecemeal cold snare polypectomy in polyps between 10 to 19 mm to decrease risk of deep mural injury [3].

► **Table 1** Recent studies evaluating adenoma recurrence rate after hot and cold snare EMR.

Study reference	Study design	Hot/cold EMR	Polyps (#)	Polyp size	Polyp recurrence rate	Comments
Buckner et al (2012) [10]	Retrospective	Hot	286	8–100 mm (mean 23 mm)	36/133 (27.1%)	
Choksi et al (2015) [12]	Retrospective	Cold	15	10–60 mm (mean 24 mm)	N/A	Duodenal and colonic polyps
Fujiya et al (2015) [5]	Meta-analysis	Hot/Cold	866	N/A	106/866 (12.2%)	
Piraka et al (2017) [11]	Retrospective	Cold	73	12–60 mm (median 20 mm)	7/72 (9.7%)	ARR was 18.4% in polyps > 20 mm
Thoguluva Chandrasekar et al (2019) [9]	Meta-analysis	Cold	522	10–60 mm (mean 17.5 mm)	All – 4.1% Adenoma – 11.1% SSPs – 1.0%	ARR was 22.6% in polyps > 20 mm
Mangira et al (2020) [15]	Retrospective	Cold	204	21–91 mm (mean 25.5 mm)	9/164 (5.5%)	Majority of polyps were SSA/Ps

N/A, not available; EMR, endoscopic mucosal resection; ARR, adenoma recurrence rate; SSA/P, sessile serrated adenoma/polyp.

More recently, there has been a growing interest in cold snare EMR due to its favorable safety profile as compared to hot snare EMR [4–6]. Adverse events appear to occur much more frequently with the use of a cautery based resection technique, including delayed hemorrhage, perforation and post-polypectomy syndrome [4]. By contrast, these adverse events are virtually non-existent with the use of cold EMR, as these appear to be cautery-related phenomena [5, 7, 8].

It is less clear whether there would be a significant trade-off in leaving residual polyp tissue without the use of cautery, either due to microscopic tissue destruction or the ability to resect a lesion with fewer individual pieces. Previously reported risk factors for residual adenoma with hot snare EMR include polyp size >40 mm, piecemeal resection, and the presence of high-grade dysplasia [9, 10]. Several smaller studies have been performed in recent years assessing adenoma recurrence after hot and cold EMR. The results from these studies are summarized in ► **Table 1**. One recent meta-analysis noted a polyp recurrence rate of about 12.2% using hot EMR, although this study did not perform a subgroup analysis between polyps <20 mm or ≥20 mm [5]. Another larger study that looked at procedures done by a single endoscopist noted a recurrence rate of 27% with hot EMR, which was much higher with piecemeal resection versus en bloc [10]. A meta-analysis performed on cold snare polypectomy for lesions ≥10 mm found that the recurrence for adenoma was about 4.7%, and in a subgroup analysis of polyps ≥20 mm, they noted an ARR of 22.6% and 1.0% for sessile serrated polyps [5]. However, only 132 of these polyps were ≥20 mm. More recently, an Australian group retrospectively evaluated 204 polyps ≥20 mm via cold EMR and found a recurrence rate of 5.5% with relatively low adverse outcome profile (less than 4% risk of post-procedure abdominal pain, intra-procedural bleeding, and delayed bleeding) [6]. However, nearly 2/3 of the polyps (65.6%) were SSAs, so this may not be generalizable to other polyp subtypes.

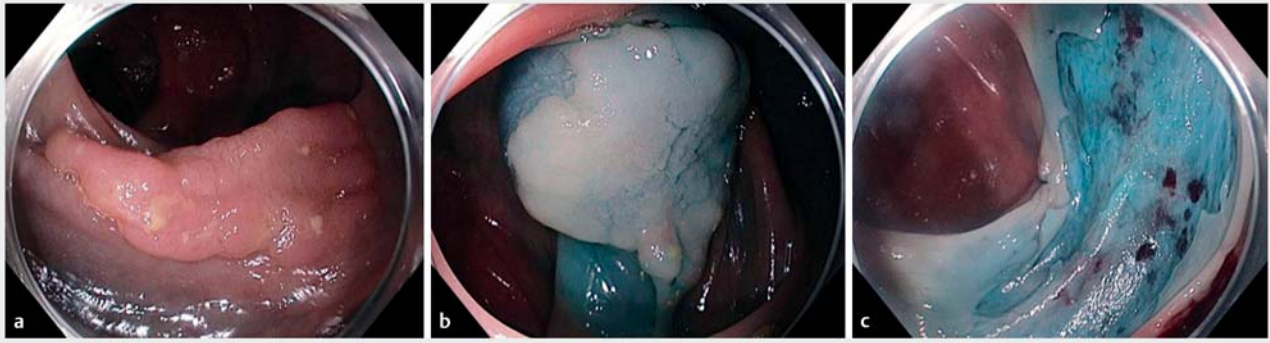
Given the demonstrated safety of cold snare EMR, we were interested in evaluating the recurrence rate and risk factors for

recurrence in large colon polyp cold snare EMR, including more high-risk polyp subtypes.

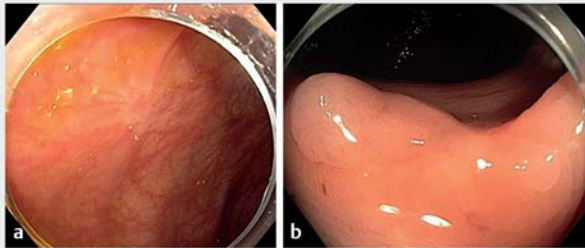
Patients and methods

This study was approved by the Henry Ford Health System Institutional Review Board. A retrospective chart review was conducted looking at colonoscopies with EMR of non-pedunculated polyps ≥20 mm performed between January 2015 and July 2019 at a single tertiary care hospital. Only colonoscopies performed by advanced endoscopists (n = 5), with or without a fellow, were evaluated. All cases were performed under monitored anesthesia care. No differentiation was made between carbon dioxide and room air. Polyps which were incompletely resected on index colonoscopy, used any type of cautery (typically hot snare polypectomy, argon plasma coagulation, or coagulation via tip of the snare), or required band EMR were excluded.

The technique for performing cold-snare EMR is described below and shown in ► **Fig. 1**. Prior to performing polypectomy, polyp characteristics and mucosal pit pattern are assessed using high-definition white light endoscopy with narrow-band imaging and near focus to ensure that there are no features of malignancy. A lifting solution of dilute epinephrine (1:500,000) in normal saline solution with either methylene blue or indigo carmine is used for lifting and submucosal staining agent. A 10 mm thin and stiff snare is then used to resect the polyp. Piecemeal resection typically begins at the lateral margin of the polyp with continually overlapping resection pieces to limit the risk of residual polyp foci. Lateral margins, which include normal appearing mucosa, can safely be extended to ensure a wide resection field. Once the polyp is resected, the base and margins are carefully examined to ensure that no residual polyp remains. All patients who undergo piecemeal cold-snare EMR are scheduled for surveillance colonoscopy within 3 to 6 months per current ASGE guidelines to evaluate for adenoma recurrence. The resection site is assessed at this time using high-definition white light endoscopy with narrow-band ima-



► **Fig. 1** Cold snare EMR endoscopic technique. **a** Large colon polyp prior to resection. **b** Polyp base injected with solution of dilute epinephrine in saline solution with methylene blue to ensure adequate submucosal lift). **c** Polyp base and margins carefully examined following piecemeal resection to ensure that no residual polyp is present.



► **Fig. 2** Post-polypectomy scar and residual polyp. **a** Post-polypectomy scar with no residual or recurrent adenoma. **b** Adenoma recurrence (residual polyp tissue) at polypectomy scar site.

ging and near-focus imaging. If polypoid tissue is found at the EMR site (► **Fig. 2**) during surveillance endoscopy, it is removed with either a snare or forceps. Adenoma recurrence was based on the histologic diagnosis of an adenoma.

A total of 1121 colonoscopy reports from the established timeframe were reviewed; 469 polyps met inclusion criteria. Of these 469 polyps, data from surveillance colonoscopies were only available for 310 polyps. Data including age at index colonoscopy, sex, race, family history of colon cancer, smoking and alcohol history, polyp location, histology, dysplasia at index, and size of the polyp were collected. For continuous variables, univariate two-group comparisons were performed using independent two-sample *t*-tests if the variable was normally distributed and Wilcoxon rank sum tests if the variable was not normally distributed. For categorical variables, univariate two-group comparisons were performed using chi-square tests when expected cell counts were >5 and Fisher's exact tests when expected cell counts were <5. Multivariable logistic regressions were performed to evaluate the combined effects of each variable on the odds of adenoma recurrence. Statistical significance was set at $P < 0.05$. All analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, North Carolina, United States).

Results

A total of 469 non-pedunculated colon polyps ≥ 20 mm were resected with cold snare EMR by 5 endoscopists between January 2015 and July 2019. All were resected in a piecemeal fashion. Of these, 310 had surveillance colonoscopy to evaluate for recurrence and were included for evaluation in our study. ► **Table 2** summarizes the demographic variables and ► **Table 3** summarizes polyp characteristics in the study sample.

Patient characteristics

Of the 310 polyps included, 156 (50.3%) were found in men while 154 (49.7%) were found in women. Patients in the study had a mean age of 66.5 (range 41–90) at the time of the procedure. A majority of polyps were seen in patients who were White (201/310, 64.8%) while 48 polyps (15.5%) were seen in African Americans, four polyps (1.3%) were seen in Asians, two polyps (0.64%) were seen in Hispanic patients, and 55 polyps (17.7%) were seen in patients of other ethnicities or those who declined to report their race. Only three polyps (0.97%) were found in patients who had a personal history of polyposis syndromes and 48 polyps (15.5%) were found patients who had a documented family history of colon cancer.

Polyp characteristics

The mean size of resected polyps was 29.4 mm (range 20–80 mm) of which 221 polyps (71.3%) were 20 to 30 mm, 65 polyps (21.0%) were 31 to 40 mm, 11 polyps (3.5%) were 41 to 50 mm, and 13 polyps (4.2%) were >50 mm. An average of 3.8 polyps of any size (range 1–24) were removed during each colonoscopy. A total of 85 polyps greater than 20 mm were removed from the cecum, two from the terminal ileum, 105 from the ascending colon, 27 from the hepatic flexure, 37 from the transverse colon, five from the splenic flexure, 11 from the descending colon, 18 from the sigmoid colon, and 20 from the rectum. Hemostatic clips were used following polyp resection in 16 of 310 cases (5.2%). In a majority of these cases (13/16), clips were placed as a prophylactic measure as the patient was planned to be restarted on anticoagulation or antiplatelet therapy after the procedure. In the other three cases, clips

► **Table 2** Demographic factors and adenoma recurrence rate after cold snare EMR.

	All cases (N=310)	Recurrence (N=108)	No recurrence (N=202)	P value
Sex (%)				0.877
▪ Male	156 (50.3)	55 (50.9)	101 (50)	
▪ Female	154 (49.7)	53 (49.1)	101 (50)	
Race (%)				0.020
▪ White	201 (64.8)	58 (53.7)	143 (70.8)	
▪ African American	48 (15.5)	24 (22.2)	24 (11.9)	
▪ Asian	4 (1.3)	3 (2.8)	1 (0.50)	
▪ Hispanic	2 (0.64)	1 (0.9)	1 (0.50)	
▪ Other/declined	55 (17.7)	22 (20.3)	33 (16.3)	
▪ Mean age at EMR, years (range)	66.5 (41–90)	68.5 (49–87)	65.5 (41–90)	0.008
▪ Personal history of polyposis syndromes (%)	3 (0.97)	1 (0.93)	2 (0.99)	0.963
▪ Family history of colon cancer (%)	48 (15.5)	15 (13.9)	33 (16.3)	0.570
Smoking History (%)				0.992
▪ Current smoker	62 (20.0)	22 (20.4)	40 (19.8)	
▪ Former smoker	135 (43.5)	47 (43.5)	88 (43.6)	
▪ Never smoker	113 (36.5)	39 (36.1)	74 (36.6)	
Significant alcohol consumption (%)	25 (8.1)	11 (10.2)	14 (6.9)	0.316

EMR, endoscopic mucosal resection.

were used to achieve hemostasis of bleeding after polyp resection.

In terms of polyp histology, 114 polyps (36.8%) were tubulovillous adenomas, 135 (43.5%) were tubular adenomas, 45 (14.5%) were sessile serrated adenomas, 15 (4.8%) were hyperplastic, and one (0.32%) was an adenocarcinoma. Of these, 28 polyps (9.0%) had features of high-grade dysplasia.

Factors impacting adenoma recurrence rate

A total of 310 polyps were followed by surveillance colonoscopy after index cold snare polypectomy with a mean time to follow-up of 6.5 months (range 1–39 months). Of these follow-up colonoscopies, residual or recurrent adenoma were found on biopsy in 108 cases (34.8%).

Polyps with residual or recurrent adenoma on surveillance colonoscopy were significantly larger with an average initial size of 33.5 mm (range 20–80 mm) compared to the average initial size of 27.2 mm (range 20–65 mm) for polyps without recurrence ($P < 0.001$). ARR also rose dramatically as the size of the resected polyps increased. For example, polyps 20 to 30 mm had a recurrence rate of 26.7% while polyps greater than 50 mm had a recurrence rate of 76.9% (► **Table 4**).

In terms of patient demographic factors, we saw no association of ARR with sex. However, there was an association between race and recurrence, as African Americans and Asians were more likely to have a recurrent or residual adenoma relative to white patients ($P = 0.020$). We also observed an associa-

tion between age and ARR, with patients who were older being more likely to demonstrate recurrence ($P = 0.008$). No association was found between personal history of polyposis syndromes or family history of colon cancer and ARR. Smoking history and alcohol consumption also were not associated with recurrence.

The location of a polyp within the colon did not correlate with ARR. However, there was a strong association between polyp histology and recurrence ($P < 0.001$). Tubulovillous adenomas were more likely to recur, whereas tubular adenomas, sessile serrated polyps, and hyperplastic polyps had lower rates of recurrence. Polyps with high grade dysplasia also had a higher ARR ($P = 0.003$). Utilization of a hemostatic clip at the time of EMR was also associated with increased ARR ($P = 0.017$). Among all 310 polyps, there was no interval cancer found between index polypectomy and follow-up surveillance colonoscopy. There were also no immediate post-procedural complications necessitating hospitalization among all the patients evaluated.

A multivariable logistic regression model was constructed to assess the combined effects of each variable on the odds of adenoma recurrence. ► **Table 3** displays the overall p-values for each effect in the multivariable logistic regression model. This analysis demonstrated that that age ($P = 0.024$), polyp size ($P < 0.001$), and polyp histology ($P = 0.023$) were significantly associated with adenoma recurrence, while controlling for all other variables (► **Table 5**). Other variables including race, smoking history, alcohol consumption, polyp location, and

► **Table 3** Polyp characteristics and adenoma recurrence rate after cold snare EMR.

	All cases (N= 310)	Recurrence (N= 108)	No Recurrence (N=202)	P value
Mean size of polyp removed by cold snare EMR, mm (range)	29.4 (20–80)	33.5 (20–80)	27.2 (20–65)	<0.001
Mean number of polyps of any size removed at index colonoscopy (range)	3.8 (1–24)	3.2 (1–21)	4.1 (1–24)	0.036
Polyp location (%)				0.072
▪ Terminal ileum	2 (0.65)	2 (1.9)	0	
▪ Cecum	85 (27.4)	37 (34.3)	48 (23.8)	
▪ Ascending colon	105 (33.9)	32 (29.6)	73 (36.1)	
▪ Transverse colon	37 (11.9)	10 (9.3)	27 (13.4)	
▪ Descending colon	11 (3.5)	2 (1.9)	9 (4.5)	
▪ Sigmoid	18 (5.8)	5 (4.6)	13 (6.4)	
▪ Rectum	20 (6.4)	11 (10.2)	9 (4.5)	
▪ Hepatic flexure	27 (8.7)	7 (6.5)	20 (9.9)	
▪ Splenic flexure	5 (1.6)	2 (1.9)	3 (1.5)	
Polyp histology (%)				<0.001
▪ Hyperplastic	15 (4.8)	1 (0.9)	14 (6.9)	
▪ Tubular adenoma	135 (43.5)	40 (37.0)	95 (47.0)	
▪ Tubulovillous adenoma	114 (36.8)	60 (55.5)	54 (26.7)	
▪ Sessile serrated	45 (14.5)	6 (5.6)	39 (19.3)	
▪ Adenocarcinoma	1 (0.3)	1 (0.9)	0	
Polyps with high grade dysplasia (%)	28 (9.0)	17 (15.7)	11 (5.4)	0.003
Mean time to follow-up, months (range)	6.5 (1–39)	5.6 (1–29)	7.2 (1–39)	0.007
Residual polyp seen on follow-up	113 (36.5)	96 (88.9)	17 (8.4)	<0.001
Residual polyp pathology (%)				<0.001
▪ Hyperplastic	5 (4.4)	2 (2.1)	3 (17.6)	
▪ Tubular adenoma	61 (54.0)	57 (58.8)	4 (23.5)	
▪ Tubulovillous adenoma	29 (25.4)	29 (29.9)	0	
▪ Sessile serrated	8 (7.0)	7 (7.2)	1 (0.59)	
▪ Adenocarcinoma	0	0	0	
▪ Normal tissue	11 (9.6)	1 (1.0)	10 (58.8)	
EMR scar biopsied on follow-up (%)	188 (60.6)	52 (48.1)	136 (67.3)	0.001
Scar biopsy pathology (%)				<0.001
▪ Hyperplastic	10 (5.3)	2 (3.8)	8 (5.9)	
▪ Tubular adenoma	24 (12.8)	24 (46.2)	0	
▪ Tubulovillous adenoma	6 (3.2)	6 (11.3)	0	
▪ Sessile serrated	2 (1.1)	1 (1.9)	1 (0.74)	
▪ Adenocarcinoma	0	0	0	
▪ Normal tissue	146 (77.2)	19 (35.8)	127 (93.4)	

EMR, endoscopic mucosal resection.

► **Table 4** Adenoma recurrence rate based on polyp size.

Polyp size (mm)	Total polyps	Recurrence rate (%)
20–30	221	59/221 (26.7)
31–40	65	31/65 (47.7)
41–50	11	7/11 (63.6)
>50	13	10/13 (76.9)

time to follow-up colonoscopy were not found to be independently associated with adenoma recurrence in this model.

Discussion

In this study, we evaluated factors that are associated with adenoma recurrence following cold snare endoscopic mucosal resection of large (≥ 20 mm) non-pedunculated colonic polyps. To our knowledge, our study is the largest to date that has assessed colonic polyps of this size removed by cold snare EMR. It also includes a large fraction of polyps that are larger and have advanced histology, with a relatively low rate of sessile serrated polyps. Cold EMR generally was only considered when there was no suspected invasive component to the polyp.

Our group previously published data on the safety and efficacy of cold snare polypectomy for polyps ≥ 10 mm [11, 12]. The largest of these studies included 73 patients and found that the rate of recurrent or residual adenoma was 9.7%. All instances of recurrence in our prior study occurred in polyps ≥ 20 mm where the recurrence rate was 18.4% [11]. A recently published Australian study examined adenoma recurrence of 204 polyps ≥ 20 mm that were resected by cold snare EMR across 5 hospitals and found an early ARR of 5.5% [6].

In our current study that assessed 310 polyps, we found that the overall ARR was 34.8%. While this is higher than previous studies, it should be noted that one likely contributing factor for this difference is that the average polyp size in our study was relatively large at 29.4 mm, with a large proportion that were greater than 3 cm (28.7%); this study even included polyps as large as 8 cm. As far as we know, this is one of the highest mean size cohorts of polyps studied that were removed with cold snare EMR. When ARR was stratified by polyp size (► **Table 4**), we noted a trend wherein larger polyps were far more likely to demonstrate adenoma recurrence. This was especially evident for polyps >40 mm, which had an ARR of over 50%. In contrast, smaller polyps 20–30 mm demonstrated an ARR of 26.7%, which is more comparable to previously reported data. As in hot EMR, polyp size is a risk factor for recurrence with resection by cold EMR.

Another likely contributor to the high ARR is that our study had a very large proportion of polyps with advanced histology, including 36.8% that were tubulovillous adenomas and 9.0% with high grade dysplasia. This study confirms a correlation between polyp histology and ARR in cold EMR as has previously been demonstrated with hot EMR, with tubulovillous adenomas and polyps with high grade dysplasia having a significantly

► **Table 5** Multivariable logistic regression of variables affecting adenoma recurrence rate.

Variable	P value
Age	0.002
Race	0.101
Sex	0.911
Smoking history	0.791
Significant alcohol consumption	0.927
Polyp size	<0.001
Polyp location	0.102
Polyp histology	0.023
Time to follow-up colonoscopy	0.253

higher recurrence rate as compared to tubular adenomas, sessile serrated polyps, and hyperplastic polyps [5, 9]. Although the ARR in the aforementioned Australian study [6] was very low (5.5%), the majority of polyps were sessile serrated adenomas (65.6%). In contrast, most polyps resected in our study were tubulovillous adenomas and tubular adenomas (80.3%), with only a small fraction being sessile serrated polyps (14.5%). This difference in polyp histology may explain the large discrepancy in rate of recurrence as the large proportion of serrated polyps in that recent study almost certainly skewed the recurrence rate down given how much easier it typically is to cut through a serrated polyp cold.

In addition to polyp size and histology, we identified the demographic risk factors of race and age to be associated with adenoma recurrence. Although it is widely recognized that age plays a significant role in incidence of colon polyps, previous studies have not shown any association between race and polyp recurrence rate [13]. Our data suggest that African Americans and Asians may be more susceptible to having recurrent or residual adenoma on surveillance endoscopy. However, our patient sample size for these groups was relatively small, thus limiting the overall significance of this finding. Furthermore, in our multivariate analysis controlling for other variables, race was no longer independently associated with adenoma recurrence. Other demographic risk factors such as cigarette smoking and alcohol consumption were not found to be associated with adenoma recurrence in our study.

The only intraprocedural risk factor that was associated with ARR in our study was hemostatic clip use. Notably, only 16 of 310 patients (5.2%) in our study required use of hemostatic clips. As discussed previously, clips were primarily used as a prophylactic measure in patients who were planned to be reinitiated on systemic anticoagulation or antiplatelet therapy after their procedure. In a small group of patients, clips were used to achieve hemostasis of bleeding after polyp resection. In our practice, hemostatic clips were initially used by some endoscopists as a prophylactic measure for high-risk patients however, this practice has since been abandoned as our experience has not shown a substantial increase in a risk of bleeding. The

observed increased risk for adenoma recurrence in these patients may reflect added caution on behalf of the endoscopist at the time of procedure and perhaps be related to challenging polyp anatomy leading to a high propensity for bleeding. Prior studies have demonstrated an association between intra-procedural bleeding and risk for adenoma recurrence [14]. Bleeding during the procedure may also negatively affect visualization of polyp margins leading to incomplete resection.

There are several limitations of this study. Primarily, we did not evaluate the frequency of adverse events or post-procedural complications; therefore, we cannot make any direct conclusions about certain safety aspects of cold snare EMR in this patient population. Part of the reason we could not extrapolate this information was that a large majority of these patients were referrals, and should there have been a complication, we may not have been able to find all relevant information in our electronic medical record system. In addition, all procedures were performed by advanced gastroenterologists at a large tertiary referral center, which limits the generalizability of our data in the community setting. However, within the limits of what was available with standard chart review, no adverse events were encountered, including no immediate or known delayed admissions, transfusions, or need for surgery. Furthermore, polyp morphology (such as LST, Paris, Kudo, or NICE classification) was not routinely reported, and so correlation with different polyp subtypes could not be assessed.

Conclusions

In summary, our study demonstrates that cold snare EMR remains a feasible alternative to hot snare EMR even for resection of non-pedunculated polyps larger than 20 mm. Although ARR is somewhat high with larger polyps, there were no immediate post-procedural complications and no detection of interval cancer between index and surveillance colonoscopy. Risk factors associated with polyp recurrence with hot EMR correlate with those in cold EMR, including larger size and advanced histology. We also found some association with older patient age and Asian or African American ethnicity in the univariate analysis, although the significance of this is unclear. Ultimately, an ongoing multicenter randomized controlled trial should further delineate the risk factors and rate of polyp recurrence between cold and hot snare EMR of matched large colonic polyps. This should further inform which techniques are ideal for any given polyp.

Acknowledgements

The authors thank Karla D. Passalacqua, Ph.D., at Henry Ford Hospital for editorial assistance and Stephanie Stebens, MLIS, for her help in manuscript formatting. We would also like to thank Abigail Chatfield at Henry Ford Hospital for statistical support.

Competing interests

Dr. Zuchelli is a consultant for Boston Scientific. Dr. Piraka receives research funding support from US Endoscopy and Aries.

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