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Endoscopic Features of Mucous Cap Polyps: A Way to Predict Serrated Polyps

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Background/Aims: The aims of the study were to identify whether a mucous-cap predicts the presence of serrated polyps, and to determine whether additional endoscopic findings predict the presence of a sessile serrated adenomas/polyp (SSA/P).

Methods: We analyzed 147 mucous-capped polyps with corresponding histology, during 2011–2014. Eight endoscopic features (presence of borders, elevation, rim of debris, location in the colon, size ≥ 10 mm, varicose vessels, nodularity, and alteration in mucosal folds) of mucous-capped polyps were examined to see if they can predict SSA/Ps.

Results: A total of 86% ($n=126$) of mucous-capped polyps were from the right sided serrated pathway (right-sided hyperplastic [$n=83$], SSA/Ps [$n=43$], traditional serrated adenoma [$n=1$]), 10% ($n=15$) were left-sided hyperplastic polyps, and 3% ($n=5$) were from the adenoma-carcinoma sequence. The presence of a mucous cap combined with varicose vessels was the only significant predictor for SSA/Ps. The other seven characteristics were not found to be statistically significant for SSA/Ps, although location in the colon and the presence of nodularity trended towards significance.

Conclusions: Our study suggests that mucous-capped polyps have high predictability for being a part of the serrated pathway. Gastroenterologists should be alert for a mucous-capped polyp with varicose veins, as these lesions have a higher risk of SSA/P.

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Key Words: Sessile serrated adenoma; Mucous cap polyp; Serrated pathway; Colorectal neoplasms

INTRODUCTION

The effectiveness of colorectal cancer (CRC) screening is based on the adenoma-carcinoma sequence,¹ in which genetic alterations in the tumor suppressor genes and oncogenes accumulate over time, underscoring the importance of their identification and removal.^{2,3} An alternative theory for the development of colon cancer has been described, known as the serrated adenoma pathway. This pathway involves accumulation of molecular mutations in the serrated adenomas, even-

tually leading to CRC.^{4,5} Torlakovic et al. showed evidence of abnormal proliferation in serrated polyps, which look similar to hyperplastic polyps (HPs), but could be differentiated as sessile serrated adenomas/polyps (SSA/Ps) on histology.⁶

Development of interval colon cancer shares certain features with SSA/Ps including proximal location, high level of microsatellite instability, and the hypothesis that these subtle lesions arise from serrated adenomas missed on routine colonoscopy. There is evidence that a subset of SSA/Ps is characterized by a brown-mucous cap, a distinct endoscopic feature that might be present in up to 60% of these lesions.⁷ It is unknown whether these mucous-capped SSA/Ps share molecular mutations with standard SSA/Ps, or represent a distinct clinical entity.

Screening colonoscopy is effective in reducing the overall rate of colon cancer, but has not been as effective in reducing right-sided colon cancers. In a population-based study, 6% of patients with newly discovered right-sided CRC had undergone colonoscopy 6 months to 3 years before the diag-

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nosis.⁸ Furthermore, Baxter et al. confirmed that screening colonoscopy was effective in reducing CRC-related mortality rates for left-sided disease, but was less effective in preventing death from right-sided CRC.⁹ One explanation for this is that right-sided mucous-capped lesions are often missed during colonoscopy.³ SSA/Ps are subtle polyps that appear similar to HPs and the diagnosis by endoscopists is often varied; thus, they are often not resected or incompletely resected.¹⁰⁻¹⁴ They are difficult to identify with suboptimal bowel preparation and their malignant potential is unknown. Bowel preparation is important for adenoma detection, especially for the identification of flat SSA/Ps on the right side.¹⁵⁻¹⁷

Few retrospective studies have described endoscopic characteristics of SSA/Ps. There is evidence that education and training of endoscopists would increase the diagnosis of these lesions. By identifying the typical the endoscopic features of SSA/Ps during colonoscopy, endoscopists could better manage polyps they encounter and potentially decrease the incidence and mortality of CRC, particularly in the right colon.¹⁸ We hypothesize that mucous-capped SSA/Ps represent an important group of commonly missed right-sided polyps. The goal of the study was to identify whether mucous-capped polyps predict the presence of polyps that were a part of the serrated pathway (right-sided HPs or SSA/Ps). Furthermore, endoscopic features of mucous-capped polyps (presence of borders, elevation, rim of debris, location in colon, size, varicose vessels, nodularity, and alteration in mucosal folds) were examined to determine if they could predict SSA/Ps. These observations could be used by endoscopists to improve endoscopic identification of SSA/Ps, which in turn can improve the detection of CRC.⁷

MATERIALS AND METHODS

The retrospective study was approved by the Institutional Review Board of the University Of Connecticut Health Center. High-definition (1080i signal wide-angle [170-degree field of view]) Olympus 180 series were used to perform all colonoscopies.¹⁹ The colon was classified into the right and left side, at the splenic flexure.¹⁹ A colonoscopy was considered complete if there was transillumination of the right lower quadrant, or visualization of the ileocecal valve or appendicular orifice.¹⁹ An experienced endoscopist (TJD) identified a mucous-capped polyp from the documentation of a representative group of adenomas. Mucous cap was defined as a focal collection of mucus (clear, bile-stained, or debris-stained) on the mucosal surface that can be removed with irrigation.¹⁴ All polyps were documented next to a snare catheter for *in vivo* measurement.¹⁹ We analyzed 147 mucous-capped pol-

yps identified from 2,069 colonic polyps during 2011–2014. After a review of the literature, predefined criteria for each endoscopic feature were used to identify the mucous-capped polyps from previously taken pictures through retrospective chart review (Table 1).⁷ All images were collected in a database and eight features of the polyp were analyzed including presence of borders, elevation, rim of debris, location in colon, size, varicose vessels, nodularity, and alteration in mucosal folds. One observer (BTM) analyzed each polyp scoring a visual descriptor as absent or present. The observer was blinded to polyp histology during the analysis.

An SSA/P was diagnosed if it demonstrated histologic characteristics confirmed by experienced gastrointestinal (GI) pathologists and an image was available from endoscopy.⁷ 2010 WHO criteria for SSA/Ps were used, which included the following features: deep crypt serration with goblet cells, evidence of crypt base dilation, horizontal crypts at the polyp base with “T” or “boot shapes”, and mild atypia with diffuse proliferative zone.⁷ In our approach, the presence of one crypt with most of the above features was deemed adequate to include the polyp in SSA category. Crypt herniation through the muscularis muscle was another inclusion criterion seen. The slides were interpreted by three pathologists specializing in GI pathology.⁷

Inclusion criteria: Adults above 18 years, who had colorectal lesions during a screening colonoscopy without prior histologic diagnosis. Mucous-capped polyps identified by one endoscopist (TJD) during 2011–2014 were examined.

Exclusion criteria: Medical history or a diagnosis of inflammatory bowel disease, more than two mucous-capped polyps identified in the same patient, serrated polyposis syndrome, familial adenomatous polyposis, Lynch syndrome, patients with inadequate bowel preparation, or incomplete colonos-

Table 1. Individual Endoscopic Descriptors for Sessile Serrated Adenomas

Distinct borders	Demarcation of a subtle or focal border around a lesion
Elevation	Lesions have a rounded apex and is >50% as high as it is wide
Rim of debris	Unique ring of debris/bubble encircling >25% of lesion
Location in colon	Proximal to splenic flexure
Size	Greater than or equal 10 mm
Varicose vessels	Small, curved, or linear vessels seen near the surface of the lesion under the mucous cap
Nodular surface	Irregular or bumpy mucosal surface
Alters fold contour	Lesion lays over a mucosal fold

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copies were excluded from the study. If there was a mix in pathology with adenomatous polyp and SSPs, the polyp was excluded.⁷

Statistical analysis

The study's primary endpoint was identifying endoscopic features of mucous-capped polyps that can predict SSA/Ps. A secondary endpoint looked at the incidence of serrated polyps (right-sided hyperplastic, SSA/Ps, or traditional serrated adenomas [TSAs]) when a mucous cap was present. Each variable was descriptively summarized by mean, standard deviation of a continuous variable, frequency, and percentages of a categorical variable. A generalized linear mixed effects model with logit link was used to model SSA/Ps assuming different random intercepts for each patient. SSA/Ps were associated with each endoscopic predictor with and without adjustment for other predictors: polyp size ≥ 10 mm (Present/Absent), distinct borders (Present/Absent), elevation (Present/Absent), rim of debris (Present/Absent), location in colon (Present/Absent), varicose vessels (Present/Absent), nodularity (Present/Absent), alteration in mucosal folds (Present/Absent). The unadjusted and adjusted odds ratios along with their 95% confidence intervals were reported. A *p*-value smaller than 5% was considered statistically significant.

All the statistical analyses were performed in R 3.3.1 (ref). R Core Team (2016). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. <https://www.R-project.org/>.

RESULTS

Polyp characteristics

A total of 147 mucous-capped polyps were identified from 2,069 colonic polyps, during 2011–2014. During the 4-year study period, 7.1% of all examined polyps contained a mucous cap. Twenty-one patients had 2-mucous capped polyps identified. Thus, all polyp characteristics were considered from 126 patients who underwent colonoscopies at a single tertiary referral center. Overall, the average polyp size was 8.23 mm. The average size of an SSA/P was 8.84 \pm 4.23 mm while size of a non-SSA/P was 7.62 \pm 3.00 mm. Majority of the polyps (*n*=100) were in the range of 6–10 mm (Table 2). One hundred and thirty-two mucous-capped polyps were right sided (Table 2).

Mucous cap and association with the serrated pathway

In the primary analysis, presence of a mucous cap and its association with being a serrated polyp were studied. 86%

(*n*=126) of mucous-capped polyps were from the right sided serrated pathway (right-sided hyperplastic [*n*=83], SSA/Ps [*n*=43], TSA [*n*=1]), 10% (*n*=15) were left-sided HPs, and 3% (*n*=5) were from the adenoma–carcinoma sequence (Figs. 1–4, Table 3). None of the SSA/Ps had cancer or high-grade dysplasia.

Mucous cap with endoscopic features predicting SSA/P histology

Endoscopic predictors of SSA/Ps are described in Table 3. SSA/Ps with a mucous cap were over 10 mm in 35% of samples, the presence of distinct borders was observed in 81%, elevation in 70%, a rim of debris in 98%, were right sided in 95%, had varicose vessels in 91%, nodularity in 35%, and alteration in mucosal folds in 60% of all samples confirmed SSA/Ps by histology. The unadjusted and adjusted results were consistent (Table 3). The presence of a mucous cap combined with varicose vessels was the only statistically significant predictor for SSA/Ps. The adjusted odds ratio was 10.75 with 95% confidence interval (3.34, 34.61). Polyp size ≥ 10 mm, nodular-

Table 2. Size, Location, and Histology of Mucous-Capped Polyps

Size of mucous-capped polyps (mm)	No. of mucous capped polyps (<i>n</i> =147)
0–5	28
6–10	100
11–15	15
16–20	2
21–25	2
>26	0
Location of mucous-capped polyps	No. of mucous capped polyps (<i>n</i> =147)
Cecum	18
Ascending colon	104
Transverse colon	10
Descending colon	9
Sigmoid colon	6
Rectum	0
Histology of mucous-capped polyps	147 Mucous Capped Polyps (%)
SSA/P	43 (29%)
Right sided HP	83 (56%)
Right sided serrated polyp (right sided HP or SSA)	126 (86%)
Left sided HP	15 (10%)
Tubular adenoma	5 (3%)
Traditional serrated adenoma	1 (0.7%)

SSA/P, sessile serrated adenomas/polyp; HP, hyperplastic polyp.

ity, elevation, distinct borders, location in the colon, alteration in mucosal folds, and rim of debris were negatively associated with the polyp being an SSA/P, although they did not reach statistical significance ($p \leq 0.05$). Location in the colon and the presence of nodularity trended towards significance and predicted an increase the risk of SSA/P by 4.43 and 2.39 times, respectively. The wide confidence intervals suggest heterogeneity among patients, which might be explained by different patient characteristics. Patient characteristics such as demographic variables were not collected in our study.

DISCUSSION

Colonoscopies have been used to detect and resect adenomatous polyps to prevent CRCs.⁷ During the past decade, clinical experience and new insights have drawn attention to the serrated pathway, which can transform serrated non-dysplastic lesions into unstable cancers.⁷ Serrated polyps can be divided into three distinct subtypes, HPs, TSAs, and SSA/Ps, each with different molecular and clinical features.

HPs account for 80%–90% of serrated polyps.²⁰ HPs are defined as elongated crypts with serrated architecture in the top half of the crypts.²¹ Histology reveals epithelial dysplasia with serration of the crypt luminal surface. The luminal portion of

a polyp has a “saw tooth” appearance.²² HPs can be categorized into microvesicular HPs (MVHPs), goblet-cell rich HPs (GC-HPs), and mucin poor HPs. MVHPs are located on the right side of the colon and GCHPs are found on the left side of the colon.²³ Differentiating between MVHPs and SSA/Ps is necessary in preventing interval cancer.^{23–27} These cells typically lack dysplasia and the potential to develop into cancer.²⁰ GCHPs were found to be 3- to 5-mm sessile lesions that are pale, multiple, and located in the left colon at the rectosigmoid area.²⁰ Size >5 mm or right-sided lesions should raise the possibility of an SSA/P or MVHPs.²²

SSA/Ps were first described by Fengolio-Presier.²⁰ SSA/Ps account for 5.8%–7.5% of all colorectal carcinomas and 17.5% of proximal colon cancers.^{22,28} Previous endoscopic features for SSA/Ps described in the literature with a predictive potential for SSA/Ps include indistinct borders with vague demarcation, mucous cap, disruption of a fold, rim of debris, dome-like distribution, dark spots inside the crypts, cloud-like surface featuring a nodular surface resembling a cumulus cloud, and irregular shape with asymmetry.²⁹ The SSA/Ps are found primarily in the cecum or proximal ascending colon, which were the focus of this study. Although, SSA/Ps have a right-sided predominance, they can appear in the rectosigmoid area and are often left in situ because of their benign “hyperplastic” appearance.²⁹ The oversight of SSA/Ps during screening colonos-

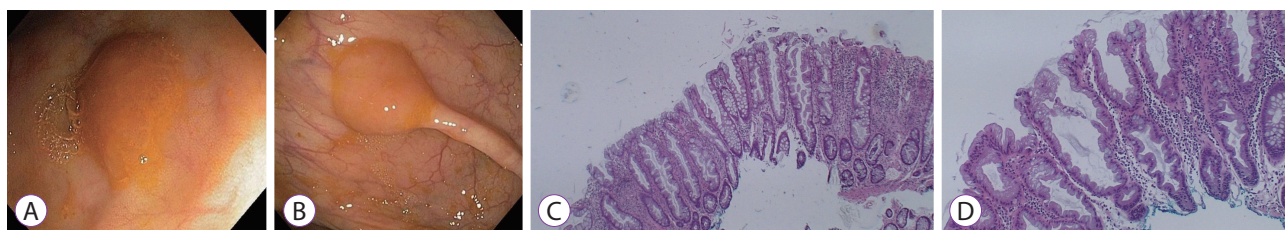


Fig. 1. (A) An 8 mm mucous-capped polyp in the ascending colon with a distinct border, elevation, and rim of debris. The polyp is ≤ 10 mm, without varicose vessels, nodular surface, and altering contour folds. The histology is a hyperplastic polyp. (B) A 15 mm mucous-capped polyp in the ascending colon with size ≥ 10 mm, a distinct border, elevation, rim of debris, and altering contour folds. The polyp is without varicose vessels and a nodular surface. The histology is a hyperplastic polyp. (C) The histology on hematoxylin and eosin (H&E) stain is a hyperplastic polyp. The crypts are elongated but straight, narrow, and hyperchromatic with an ordinary base ($\times 40$). (D) The histology on H&E stain is a hyperplastic polyp ($\times 100$).

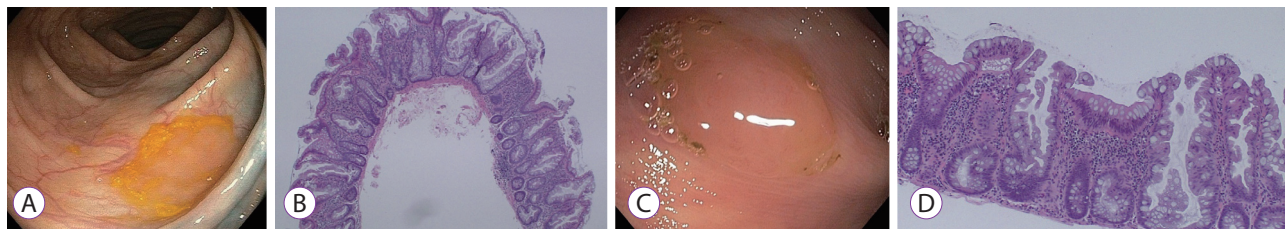


Fig. 2. (A) A 25 mm mucous-capped polyp in the ascending colon with size ≥ 10 mm, a distinct border, varicose vessels, and nodular surface. The polyp is without elevation, altering contour fold, and rim of debris. The histology is an sessile serrated adenomas/polyp (SSA/P). (B) The histology on hematoxylin and eosin (H&E) stain is an SSA/P. Disorganized, markedly dilated crypts showing extension of goblet cells to the base, and sideways growth of the crypt base is shown ($\times 40$). (C) A 6 mm mucous-capped polyp in the ascending colon with distinct borders, rim of debris, and varicose vessels. The size of the polyp is ≤ 10 mm, without a nodular surface, and altering contour fold. The histology is an SSA/P. (D) The histology on H&E stain is an SSA/P. Disorganized, markedly dilated crypts showing extension of goblet cells to the base, and sideways growth of the crypt base is shown ($\times 100$).

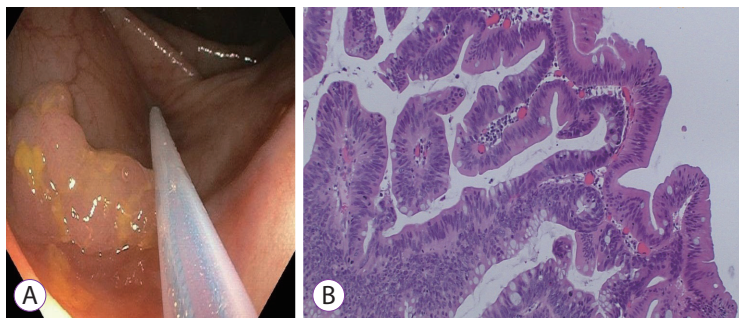


Fig. 3. (A) A 15 mm mucous-capped polyp in ascending colon with size ≥ 10 mm, distinct border, elevation, varicose vessels, and nodular surface. The polyp is without a rim of debris and doesn't alter contour folds. The histology is a traditional serrated adenoma (TSA). (B) Features of a TSA on hematoxylin and eosin stain show low grade dysplasia with serration separating it from an ordinary tubular adenoma. Note the presence of an eosinophilic cytoplasm of the surface epithelial columnar cells ($\times 200$).

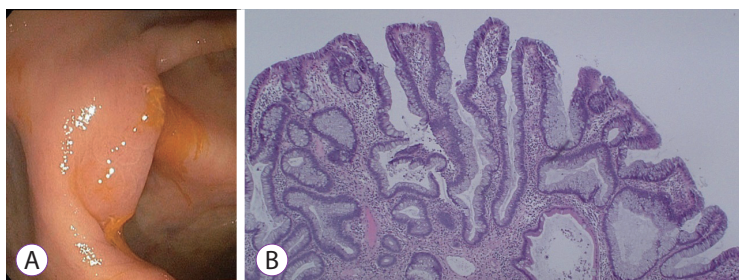


Fig. 4. (A) A 12 mm mucous-capped polyp in cecum with size ≥ 10 mm, distinct border, elevation, varicose vessels, nodular surface, and altering contour folds. The polyp is without a rim of debris. The histology is a tubular adenoma. (B) Tubular Adenoma is shown on hematoxylin and eosin stain ($\times 100$).

Table 3. Descriptive and Association Analyses of Endoscopic Characteristics of Mucous Cap Polyps

Predictor	Mean \pm SD or frequency (%)			Unadjusted		Adjusted	
	SSA/P+ (n=43)	SSA/P- (n=104)	Total (n=147)	OR (95% CI)	p-value	OR (95% CI)	p-value
Polyp size ≥ 10 mm (Present)	15 (35%)	29 (28%)	44 (30%)	1.39 (0.65, 2.96)	0.4	1.57 (0.65, 3.82)	0.320
Distinct Borders (Present)	35 (81%)	80 (77%)	115 (78%)	1.31 (0.54, 3.21)	0.551	2.54 (0.64, 10.09)	0.184
Elevation (Present)	30 (70%)	73 (70%)	103 (70%)	0.98 (0.45, 2.13)	0.959	0.39 (0.11, 1.43)	0.157
Rim of debris (Present)	42 (98%)	93 (89%)	135 (92%)	4.97 (0.62, 39.73)	0.131	4.76 (0.50, 45.51)	0.176
Location in Colon (Present)	41 (95%)	91 (88%)	132 (90%)	2.93 (0.63, 13.57)	0.170	4.90 (0.94, 25.62)	0.060
Varicose Vessels (Present)	39 (91%)	56 (54%)	95 (65%)	8.36 (2.79, 25.08)	0.000	10.75 (3.34, 34.61)	0.000
Nodular surface (Present)	15 (35%)	23 (22%)	38 (26%)	1.89 (0.87, 4.11)	0.110	2.43 (0.93, 6.31)	0.069
Alters fold contour (Present)	26 (60%)	52 (50%)	78 (53%)	1.53 (0.74, 3.15)	0.249	1.48 (0.60, 3.66)	0.398

SD, standard deviation; SSA/P, sessile serrated adenomas/polyp; OR, odds ratio; CI, confidence interval.

copy due to their morphology (flat or sessile), color (similar to the surrounding mucosa), and the endoscopists' unfamiliarity with these lesions are the factors for the incidence of CRC in the right colon not decreasing.¹⁸ Because of their similarity to HPs, it is reasonable to think that many of these polyps are left in situ when they are misinterpreted by endoscopists.²⁹ Detecting SSA/Ps is at times more difficult to identify than

adenomatous polyps on colonoscopy, because SSA/Ps are often pale, flat, and endoscopists might be less aware of their appearance and relevance.⁷

SSA/Ps are characterized by serration, distorted crypt dilatation ("L, inverted T, hockey stick or boot"), horizontally extended crypt bases, and nuclear changes that are not dysplastic.^{21,22} WHO criteria require one unequivocal crypt with

features characteristic of an SSA/P. The epithelial cells around SSA/Ps have enlarged cytoplasm with microvesicular mucin leading to the formation of a mucous-capped polyp. This epithelium has the potential to undergo dysplastic mutation and lead to invasive adenocarcinoma.

Torlakovic et al. proposed that mucous caps have a higher risk for SSA/Ps, because mucous excretion results in the absorptive epithelium to be pushed towards the stromal area leading to a dilated pit opening.^{6,30} Tadepalli et al. specifically compared SSA/Ps ($n=158$) and adenomatous polyps ($n=40$).⁷ Approximately 65% ($n=103$) of SSA/Ps were found to have a mucous cap.⁷ This is the first study to analyze if mucous-capped polyps in combination with other endoscopic characteristics previously defined in the literature, have better predictability for identifying SSA/Ps under standard white light endoscopy (WLE).

In our study, we identified varicose vessels along with the presence of a mucous cap as being a predictor for SSA/Ps. In prior studies, varicose vessels were defined as a positive visual descriptor for 32.3% ($n=51$) of SSA/Ps analyzed.^{7,31} One theory is that SSA/Ps alter the contour of the mucosal folds and one-third of polyps develop changes in the underlying vascular pattern.⁷ A darker vascular pattern might correlate with neoplasia, while a normal or lighter pattern might suggest a non-neoplastic pattern.^{29,32} Uraoka et al. showed that the presence of varicose vessels had higher specificity at 87.8%, but lower sensitivity at 57.9% for identifying SSA/Ps.³¹ In a study by Yamashina et al., expanded crypt opening or thick-branched vessels were seen in 50/51 SSA/Ps.³³ Expanded crypt openings were seen in 43/51 SSA/Ps and thick-branched vessels were seen in 23/51 of SSA/Ps.³³ Angiogenesis is important for malignant cells to proliferate. It seems plausible to suggest vascular morphology as a predictor for transformation to a malignant phenotype.³¹

The strengths of this study include the large number of mucous capped polyps identified ($n=147$), and the systematic approach to identify endoscopic features of mucous capped polyps that can predict SSA/Ps, which were not looked at in prior studies. The features looked at, are easy to assess with a regular colonoscope, making these details practical during routine colonoscopy.²⁹ The results from this study can be extrapolated to the general population without high-risk conditions like serrated polyposis syndrome.²⁹ Another strength of the study was that the observer who analyzed the characteristics of each polyp was blind to the final histology, to avoid an observer bias. Furthermore, having one endoscopist analyze/resect all mucous-capped polyps helped limit inter-observer variability.

Narrow band imaging (NBI), chromoendoscopy, and magnification are the technologies available in recent years,

which allow for better visualization during endoscopy. Several studies have reported using this technology to help identify predictive endoscopic characteristics of SSA/Ps.^{7,29,31} In a study by Hazewinkel et al., four features were found to be associated with SSA/Ps histology including a cloud-like surface on both high resolution WLE and NBI.²⁹ On NBI, indistinctive borders, dark spots, and an irregular shape were found to be statistically significant for the detection of SSA/Ps.²⁹ Tadepalli et al. showed that NBI increased the visibility of SSA/Ps but there were no statistically specific findings displaying the effectiveness of NBI.^{7,31} They reported that using NBI to detect SSA/Ps has not increased polyp detection.⁷ Hazewinkel et al. showed a cloud surface, indistinct borders, different shapes, and dark spots enhanced by NBI in more than half of SSA/Ps looked at.^{29,31}

The limitations of the study include use of still images as opposed to video clips, which give a more dynamic analysis in characterizing the appearance of SSPs. Appearance of the polyp might change with the angle, illumination, distension of the colon, or with movement of fluid/debris throughout the colon.⁷ The analysis of each polyp is subject to the quality of image taken. Another limitation was that it was a single center study and the histologic analysis was performed by three pathologists. With three pathologists analyzing the histology, there might be interobserver variation among experts in the diagnosis of SSA/Ps. Despite this drawback, this mimics real life practice in many clinical settings. More prospective randomized studies are necessary for further validation.

Accurate differentiation of these endoscopic features can help immediate decisions, rather than wait for pathologic analysis.²⁹ Adequate recognition of SSA/Ps might help endoscopists in selecting a polypectomy technique that will ensure complete removal of the polyp with a lower risk technique.²⁹ Ideally, all detected lesions should be resected, but in practice, endoscopists might not resect benign appearing right-sided polyps in the colon due to time, risks of the procedure, and costs.²⁹ The endoscopic appearance of serrated polyps might not adequately predict the type of histology, thus non-resection of the polyp would preclude the visibility of what cellular transformation might be occurring on the serrated pathway or adenoma-carcinoma sequence. Furthermore, the strategy of “resect and discard” diminutive lesions to control costs has been proposed.³¹ Further studies looking at high risk features of mucous-capped polyps might help an endoscopist decide on complete resection versus removing polyps that appear hyperplastic with lower risk techniques, versus discarding polyps in real time.²⁹

In conclusion, our study suggests that mucous-capped polyps have high predictability in being a part of the serrated pathway. Additionally, brown mucous-capped polyps have

unique characteristics that can be identified during routine standard WLE. Gastroenterologists should be on alert if a mucous-capped polyp has varicose veins as these lesions have a higher risk of being an SSA/Ps. Increased awareness of these findings might improve the detection rates of serrated polyps, promote complete resection of these lesions, and ultimately reduce the rates of interval CRC.¹⁴

Conflicts of Interest

The authors have no financial conflicts of interest.

Author Contributions

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 Data Curation: BTM
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 Supervision: TJD
 Writing-original draft: BTM
 Writing-review&editing: BTM

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