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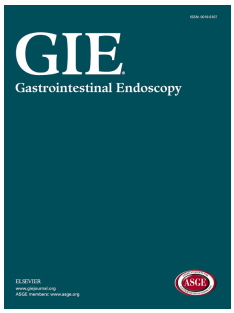

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Prasanna Ponugoti, Jingmei Lin, Robert Odze, Dale Snover, Charles Kahi, Douglas K. Rex

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Prevalence of sessile serrated adenoma/polyp in hyperplastic appearing diminutive rectosigmoid polyps

Authors:
Prasanna Ponugoti[1]
Jingmei Lin[2]
Robert Odze[3]
Dale Snover[4]
Charles Kahi[1]
Douglas K. Rex[1]

1. Division of Gastroenterology/Hepatology; Indiana University School of Medicine, Indianapolis, IN
2. Department of Pathology, Indiana University School of Medicine, Indianapolis, IN
3. Department of Pathology, Harvard Medical School, Boston, MA
4. Department of Pathology, University of Minnesota, Minneapolis, MN

Address correspondence and requests to:
Douglas K. Rex, M.D.
Indiana University Hospital, 100
550 North University Blvd.
Indianapolis, IN 46202
E-mail: drex@iu.edu
Phone 317-948-8741
Fax 317-944-5449

Abstract

Background: The American Society for Gastrointestinal Endoscopy recommends that distal colon hyperplastic lesions can be left in place without resection if adenomatous histology can be excluded with > 90% negative predictive value. However, some of the lesions could be sessile serrated adenoma/polyp (SSA/P), which is also precancerous.

Aim: Describe the prevalence of SSA/P in hyperplastic appearing diminutive rectosigmoid polyps.

Methods: We prospectively placed 513 consecutive diminutive rectosigmoid polyps that appeared hyperplastic to an expert endoscopist in individual bottles for pathologic examination. Each polyp was examined by 3 expert gastrointestinal pathologists.

Results: The prevalence of SSA/P in the study polyps ranged from 0.6% to 2.1%. The endoscopists lowest negative predictive value for the combination of adenomas plus SSA/P was 96.7%

Conclusions: The prevalence of SSA/P in diminutive rectosigmoid hyperplastic appearing polyps is very low. These results support the safety and feasibility of a “do not resect” policy for diminutive hyperplastic appearing rectosigmoid polyps.

Introduction

Approximately 20% to 30% of colorectal cancers arise through the serrated pathway [1]. Subcategories of serrated lesions include hyperplastic polyps (HP), sessile serrated adenoma/polyps (SSA/P; sessile serrated polyp and sessile adenoma are synonymous terms) and traditional serrated adenoma (TSA) [1]. SSA/P and TSA are considered precancerous lesions, whereas HP is generally considered not to be precancerous. Whether HPs are precursors of SSA/P remains uncertain. Because the prevalence of SSA/P is much higher than TSA, SSA/P is the principal serrated precancerous lesion [2].

Endoscopic differentiation of SSA/P from HP is challenging [2]. For example, the NICE classification differentiates serrated lesions from conventional adenomas, but makes no attempt to differentiate SSA/P from HP endoscopically [2]. Recently, the WASP criteria have been validated for endoscopic differentiation of SSA/P from HP, but the success of these criteria in distinguishing HP from SSA/P among diminutive serrated lesions is uncertain [3]. In general, the chance that a given serrated lesion is an SSA/P rather than an HP increases with lesion size and proximal colon location [1, 4, 5]

The issue of defining the prevalence of SSA/P within diminutive rectosigmoid polyps is assuming increasing importance. Anecdotally, we have observed a progressive rise in the frequency with which our pathologists diagnose serrated lesions SSA/P rather than HP over the past decade, which likely reflects ever increasing awareness of SSA/P among practicing pathologists, and this is well documented [6]. Also anecdotally, we have observed interpretations of SSA/P in rectosigmoid serrated lesions. The precise prevalence of SSA/P in diminutive rectosigmoid

serrated lesions is of importance to both proposed and current strategies for management of diminutive rectosigmoid polyps at colonoscopy. For example, the American Society for Gastrointestinal Endoscopy (ASGE) proposed management scheme for diminutive rectosigmoid lesions that are deemed hyperplastic by image enhanced endoscopy, as expressed in the ASGE PIVI (Preservation and Incorporation of Valuable Endoscopic Innovations) document, recommends that such lesions can be left in place without resection if they can be predicted to be non-adenomatous with a greater than 90% negative predictive value (NPV) [7]. However, the PIVI document does not precisely consider the prevalence of SSA/P within diminutive rectosigmoid serrated lesions. Arguably, the negative predictive value of image enhanced endoscopy should exceed 90% for conventional adenomas and SSA/P combined, since both are precancerous and would be expected to shorten surveillance intervals [8]. A number of studies have examined the potential of image enhanced endoscopy to provide adequate NPV for diminutive adenomas in the rectosigmoid colon. [4, 5, 9-14]. In some cases these studies did not include SSPs with conventional adenomas in calculating NPV [5, 12], or did not designate precise numbers of SSPs vs conventional adenomas in the distal colon [9-11], or did not specify findings in the rectosigmoid [13] or excluded SSPs [14]. None of the studies used additional expert assessment of pathology to determine how interobserver variability in SSP interpretation would affect the prevalence of SSP in distal diminutive polyps. Thus, the prevalence of SSPs in diminutive rectosigmoid lesions that appear hyperplastic with image-enhanced endoscopy is low but not precisely defined.

Even in the absence of a formal do not resect paradigm for the management of diminutive rectosigmoid serrated lesions based on image enhanced endoscopy, we considered that precise definition of the prevalence of SSPs in diminutive rectosigmoid hyperplastic was of importance

to current practice. Thus, current endoscopic management of these lesions often involves a strategy of removing only a sample of these lesions. That is, when colonoscopists encounter a number of rectosigmoid diminutive lesions that appear endoscopically uniform and hyperplastic, they commonly remove only one or a few (and perhaps at times none) of these lesions [15]. We suspect that in current practice, many distal hyperplastic appearing lesions are frequently left alone and not even mentioned in colonoscopy reports.

To more precisely define the prevalence of SSA/P within diminutive rectosigmoid serrated lesions, we prospectively removed 513 consecutively encountered lesions that were judged by image enhanced endoscopy to be in the serrated class, and submitted them in individual bottles for pathologic assessment. Further, we had each polyp slide reviewed by an expert GI pathologist at our institution (JL) and 2 outside experts in serrated polyp pathology (DS and RO).

Methods

We prospectively undertook the study as a quality improvement project for our endoscopy unit. The basis for proceeding was collective agreement among our endoscopists that not all rectosigmoid lesions that appeared to be serrated (presumed to be hyperplastic) were being resected. We sought to establish the appropriateness and safety of current practice.

All of the colonoscopic procedures and polyp resections were performed by a single endoscopist (DKR) over a 4-month interval from August 2015 to early December 2015. Patients were excluded if they had a known polyp syndrome (including familial adenomatous polyposis and

serrated polyposis), inflammatory bowel disease, or surgical resection of any portion of the rectosigmoid colon.

All procedures were performed with high definition Olympus (Olympus Corp., Center Valley, Pa) 190 or 180 series colonoscopes. Polyps were usually identified in white light but always assessed in Narrow Band Imaging (NBI) before resection. The NICE criteria were used to establish lesions as belonging to the serrated class (NICE Type 1) [2].

We arbitrarily set the maximum number of diminutive serrated lesions that would be resected from an individual patient as 5 from the rectum and 5 from the sigmoid. Therefore, the total maximum number of endoscopically predicted diminutive serrated lesions that would be resected from a single patient would be 10. Before resection in patients with multiple or numerous diminutive serrated class appearing rectosigmoid lesions, the colonoscopist did an endoscopic overview of the sigmoid and rectum in an effort to select the 5 largest lesions within the diminutive class. No limit was placed on the number of endoscopically predicted serrated lesions6-9 mm in size to be resected. Each lesion was resected either with a cold snare or a cold forceps, as appropriate for the lesion size. In general, most lesions ≤3 mm in size were resected with forceps. All lesions of all sizes were resected using cold techniques. Size was determined by comparison to the known size of the closed forceps or snare sheath, or to the known size of the fully opened forceps or diminutive snare in the case of larger lesions.

In order to prevent over-charging patients for pathology specimens, the pathology department agreed to the following scheme. Patients were charged for one bottle for all diminutive rectal lesions regardless of the number of bottles (which varied from 1 through 5) of diminutive rectal

lesions submitted. Similarly, the patient received one pathology charge for any and all sigmoid diminutive lesions removed, regardless of whether the number of sigmoid bottles reflecting diminutive polyps was 1 through 5. Similarly, for rectal lesions 6 to 9mm in size, patients received one pathology fee regardless of the number of lesions 6-9mm in size submitted (up to 5) and similarly for sigmoid lesions 6 to 9 mm in size. This billing arrangement was selected to ensure that no patient received billing that would exceed that which would occur for the colonoscopist's usual practice of resecting and grouping rectosigmoid lesions that endoscopically appear serrated for submission to pathology.

No special handling of the tissue was performed beyond placement of the tissue into its individual formalin bottle. That is, we did not unroll or flatten the specimens before placement in formalin.

To derive a sample size estimate, we used pilot data as well as estimates based on our previous work. We estimated that the prevalence of SSA/P histology in 1 to 5 mm rectal and sigmoid serrated polyps could range from 2% to 12%, and set the precision of the measurement of prevalence at 3%. These parameters require a sample size of 451 1 to 5 mm polyps. Assuming a prevalence of SSA/P of 2% to 20%, a sample size of 683 6 to 9 mm serrated polyps would be needed to estimate the prevalence of SSA/P in this size class of rectosigmoid polyp with a precision of 3%. Only 53 lesions 6 to 9 mm in size were included, so the study had insufficient power to determine the prevalence of SSA/P in 6 to 9 mm rectosigmoid lesions that appear serrated by endoscopy. We include the data on 6 to 9 mm polyps to inform future sample size estimates and illustrate pathology interpretation issues.

In order to obtain improved confidence regarding the study results and the appropriateness of our current endoscopic practice of not resecting all diminutive rectosigmoid lesions that appear endoscopically to be serrated, we took the following measures. First, we had all slides reviewed at our center by one of our expert gastrointestinal pathologists (JL-Expert 1). In addition, we brought in 2 outside expert pathologists (DS-Expert 2 and RO-Expert 3) to review each slide, each of whom is internationally recognized as an expert in serrated polyp pathology. All 3 experts were blinded to the readings of the original clinical pathologist and to each other's readings. The pathologists were aware that the lesions had been removed from the rectosigmoid and had been judged hyperplastic by the endoscopist.

The pathology interpretations between pathologists were compared using kappa statistics [16].

Results

The total number of eligible colonoscopies performed during the study interval by the study colonoscopist was 524, of which 173 had at least one rectosigmoid lesion predicted to be serrated and was < 10 mm in size. The mean number of rectal and sigmoid lesions included in the study for those patients who had at least one lesion included is shown in Table 1. Again, the maximum number of diminutive lesions in the rectum included from an individual patient was 5, and similarly it was 5 for the sigmoid, so that the maximum number of diminutive rectosigmoid lesions appearing endoscopically to be serrated to be removed was 10. The number of patients with 10 lesions included in the study was 9. No patient had 10 lesions 6 to 9 mm in size included. Overall, 90.6% of included lesions were ≤ 5 mm in size, and 513 lesions ≤ 5 mm in size were included, and 53 6 to 9 mm in size.

Table 2 shows the interpretations of the lesions by size and according to the interpretation of the 3 expert gastrointestinal pathologists. Considering all 3 sets of interpretations for the diminutive lesions, the study colonoscopist's endoscopic predictions had a lowest negative predictive value for conventional adenomas of 98.2% (95% CI, 96.7% - 99.2%)(see pathologist Expert 3; Table 2), a lowest negative predictive value for sessile serrated polyp of 97.9% (95% CI, 96.2% - 98.9%)(see pathologist Expert 1; Table 2) and a lowest negative predictive value for conventional adenoma plus SSA/Ps of 96.7% (95% CI, 94.8% - 98.1%)(see pathologist Expert 1; Table 2).

Table 3 shows pairwise kappa values for the interpretation of lesions between the 3 expert pathologists, and according to lesion size. Agreement between the 2 outside experts was substantial, while agreement between the IU expert and the 2 outside experts was fair to moderate. Table 2 shows that these differences manifest largely in a greater tendency to interpret SSA/P by the IU pathologist compared to the 2 outside experts. A clinical impact of this difference seems minimal for diminutive rectosigmoid lesions, since the absolute level of predicting SSA/P in this size group was very low for all 3 pathologists. A clinical impact is potentially larger for 6 to 9 mm lesions. Although the total number of lesions in that size range is small, and the prevalence of SSA/P estimated by the 3 pathologists lacks precision, the absolute frequency of SSA/P in 6 to 9 mm polyps was 11.3% for the IU expert pathologist, which exceeded the absolute prevalence of SSA/P in 6 to 9 mm lesions interpreted by the 2 outside experts.

For pathology expert 1, the 17 SSA/Ps came from 13 different patients. For pathology experts 2 and 3 (Table 2), each SSA/P identified came from a different patient.

Discussion

In this prospective study we demonstrated that the prevalence of SSA/P is very low in diminutive endoscopic lesions predicted endoscopically to be serrated by an expert endoscopist. The absolute level of SSA/P in diminutive rectosigmoid lesions ranged from 0.6% to 2.1% as interpreted by 3 expert gastrointestinal pathologists. The small number of SSA/Ps identified had minimal tendency to cluster within individual patients. We believe these results support the current colonoscopic practice of our endoscopists, which is to not resect all diminutive endoscopically serrated appearing (hyperplastic appearing) rectosigmoid polyps. We believe this conclusion is reinforced by the limited certainty regarding appropriate pathologic definitions of SSA/P versus HP, and the unknown clinical importance of diminutive SSA/Ps anywhere in the colon. We caution, however, that endoscopic criteria for differentiation of SSA/P from HP are emerging, and endoscopists could still be reasonably advised to resect and submit to pathology any lesion with endoscopic features found in the WASP classification that predict SSA/P histology, even when the lesion is diminutive and located in the rectosigmoid. In our experience, this consideration mainly applies to serrated lesions with large open pits because other WASP criteria such as indiscrete edges, a cloud-like appearance, and an irregular surface [3], are seldom observed in diminutive lesions that appear otherwise to be serrated class (NICE type I lesions).

Our data are also reassuring with regard to the PIVI policy that proposes management of diminutive rectosigmoid lesions by a “do not resect” approach. First we confirm that the

negative predictive value of an expert endoscopist for interpretation of conventional adenomas far exceeds the recommended PIVI threshold of 90%[7]. Further, the 90% negative predictive value threshold is exceeded for the combination of conventional adenoma and SSA/P. Our sample size is sufficient to establish that the lower confidence limit for our estimate of the prevalence of TA an SSA/P combined is such that the negative predictive value still substantially exceeds 90%.

Other studies have reported that academic and community endoscopist can meet the PIVI threshold of at least 90% NPV for adenomas in diminutive rectosigmoid lesions [5, 9-14], including when SSPs were counted as adenomas [9-11, 13]. We found that absolute prevalence of SSPs in diminutive rectosigmoid lesions that appear hyperplastic was 0.6% to 2.1% according to pathology interpretations by three expert pathologists. Our results are similar to but numerically slightly higher than 0.5% prevalence of SSP determined by a single expert Japanese pathologist in diminutive rectosigmoid lesions that appeared endoscopically hyperplastic [4].

We observed a very good agreement between 2 outside expert pathologists in the interpretation of diminutive rectosigmoid lesions that were endoscopically predicted to be serrated lesions. This excellent agreement between the 2 outside expert pathologists extended to the small number of lesions 6 to 9 mm in size. Agreement between our expert pathologist and the 2 outside experts was only moderate. In general, our expert tended to call more SSA/Ps than the outside experts, and although our estimates lacked precision for 6-9 mm lesions because of limited sample size, the absolute level of SSA/P interpretation was of potential clinical significance for our pathologist. Our data indicate that to some extent interpretation of SSA/P is occasionally challenging even for expert pathologists.

Some recent work found that some pathologists were never diagnosing SSA/P in serrated lesions as late as a few years ago [17]. Further, substantial data suggest that polyps read as HP a decade or more ago are commonly currently interpreted by experts as SSA/P [18]. We observed this in our own program nearly a decade ago [19]. Individual endoscopists in either community or academic settings are unlikely to have a sense of the frequency with which their own pathologists interpret precancerous serrated lesions (SSA/P without or with cytological dysplasia and TSA) unless they measure these frequencies and compare them to published frequencies by pathology experts. Unfortunately, there is enough variation between expert pathologists in interpretation of SSA/P, that establishing standards for the expected prevalence of SSA/P in serrated lesions of different sizes, and from different portions of the colon, would be hard to establish. Fortunately, our data show that the prevalence of SSA/P in diminutive rectosigmoid serrated lesions is very low across 3 expert pathologists, supporting current practice of not systematically resecting all diminutive serrated appearing lesions in the rectosigmoid during colonoscopy. Our data also support that, while the prevalence of SSA/P in 6 to 9 mm serrated appearing lesions is low, such lesions should likely be resected and submitted to pathology. Such a policy is certainly consistent with the PIVI proposed paradigm, which suggests that "do not resect" be applied only to diminutive rectosigmoid lesions that appear serrated. Finally, our data suggest that more sophisticated or advanced endoscopic quality programs might survey the prevalence of SSA/P in diminutive rectosigmoid serrated appearing lesions in their own institutions, to establish whether the observed prevalence is consistent with the very low prevalences of SSA/P observed in this study. Higher rates of SSA/P in individual programs might warrant review of histologic criteria for SSA/P by individual pathologists or consultation with an outside expert pathologist.

Limitations of the study include the small number of experts who evaluated the slides. Further, the experts were aware that the polyps were removed from the rectosigmoid, and that they were considered serrated lesions by the endoscopist. The latter awareness might have biased the interpretations of the endoscopists. However, in clinical practice pathologists are also generally aware of colon segments from which polyps were removed. Also, the kappa values between the outside expert pathologists showed substantial interobserver agreement, suggesting that any bias had very limited impact in the differentiation of HP from SSA/P.

In summary, we established in a prospective study designed to verify the safety of our current endoscopic practice, that the prevalence of SSA/P in rectosigmoid diminutive lesions judged to be in the serrated class by an expert endoscopist is very low. These results support current colonoscopic practice of not systematically removing all diminutive rectosigmoid lesions that appear serrated (hyperplastic) and support the "do not resect" paradigm proposed by the ASGE PIVI on management of diminutive colorectal polyps [7].

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Table 1: Mean numbers of serrated lesions by location and size in 173 patients with at least one study polyp

Lesion size	Number of patients with ≥ 1 polyp	Number of patients with only 1 lesion	Mean number of study lesions per patient with ≥ 1 lesion	Number of patients with 10 lesions
≤ 5 mm	159	56	3.22	9
6-9 mm	22	10	1.31	0

Table 2: Polyp histology according to size by three expert pathologists in 566 polyps deemed to be serrated endoscopically by a single expert endoscopist.

Polyp Size	Reviewer	Polyp Histology				
		HP	SSA/P	TSA	TA	Mucosa
≤ 5mm	Expert 1	436 (85.0%)	11 (2.1%)	0 (0%)	6 (1.2%)	60 (11.7%)
	Expert 2	449 (87.5%)	3 (0.6%)	0 (0%)	8 (1.6%)	53 (10.3%)
	Expert 3	451 (87.9%)	7 (1.4%)	0 (0%)	9 (1.8%)	46 (9.0%)
6-9 mm	Expert 1	43 (81.1%)	6 (11.3%)	0 (0%)	2 (3.8%)	2 (3.8%)
	Expert 2	48 (90.6%)	1 (1.9%)	1 (1.9%)	2 (3.8%)	1 (1.9%)
	Expert 3	49 (92.5%)	1 (1.9%)	0 (0%)	2 (3.8%)	1 (1.9%)

HP: hyperplastic polyp; SSA/P: sessile serrated adenoma/polyp; TSA: traditional serrated adenoma; TA: tubular adenoma; Mucosa: no histological evidence of polyp

Table 3: Pairwise kappa value comparison between expert pathologists

Comparison	Kappa values (95% CI)	
	≤ 5mm	6-9mm
Expert 1 vs Expert 2	0.58 (0.48-0.69)	0.42 (0.12-0.72)
Expert 1 vs Expert 3	0.59 (0.49-0.69)	0.39 (0.05-0.72)
Expert 2 vs Expert 3	0.74 (0.66-0.83)	0.77 (0.49-1.00)

SSA/P: sessile serrated adenoma/polyp

HP: hyperplastic polyps

TSA: traditional serrated adenoma

NICE: Narrow band imaging International Colorectal Endoscopic Classification

WASP: Workgroup serrated polypS & Polyposis

ASGE: American Society for Gastrointestinal Endoscopy

PIVI: Preservation and Incorporation of Valuable Endoscopic Innovations

GI: gastrointestinal

JL: Jingmei LIn

DS: Dale Snover

RO: Robert Odze

DKR: Douglas Kevin Rex

mm: Millimeters

IU: Indiana University

TA: tubular adenoma