



## Reinterpretation of histology of proximal colon polyps called hyperplastic in 2001

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Received: April 7, 2009 Revised: July 16, 2009

Accepted: July 23, 2009

Published online: August 14, 2009

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**Key words:** Colonoscopy; Colorectal polyps; Hyperplastic polyps; Inter-observer variability; Serrated adenomas; Sessile serrated polyps

**Peer reviewers:** Javier San Martín, Chief, Gastroenterology and Endoscopy, Sanatorio Cantegril, Av. Roosevelt y P 13, Punta del Este 20100, Uruguay; Francis Seow-Choen, MBBS, FRCSed, FAMS, Professor, Seow-Choen Colorectal Centre, Mt Elizabeth Medical Centre, Singapore, 3 Mt Elizabeth Medical Centre #09-10, 228510, Singapore

Khalid O, Radaideh S, Cummings OW, O'Brien MJ, Goldblum JR, Rex DK. Reinterpretation of histology of proximal colon polyps called hyperplastic in 2001. *World J Gastroenterol* 2009; 15(30): 3767-3770 Available from: URL: <http://www.wjgnet.com/1007-9327/15/3767.asp> DOI: <http://dx.doi.org/10.3748/wjg.15.3767>

### Abstract

**AIM:** To evaluate how proximal colon polyps interpreted as hyperplastic polyps in 2001 would be interpreted by expert pathologists in 2007.

**METHODS:** Forty consecutive proximal colon polyps  $\geq 5$  mm in size, removed in 2001, and originally interpreted as hyperplastic polyps by general pathologists at Indiana University, were reviewed in 2007 by 3 GI pathologists.

**RESULTS:** The gastrointestinal (GI) pathologists interpreted 85%, 43% and 30% of the polyps as sessile serrated polyps (sessile serrated adenomas). The overall Kappa was 0.16. When diagnoses were compared in pairs, Kappa values were 0.38 and 0.25 (fair agreement) and 0.14 (slight agreement).

**CONCLUSION:** Many polyps interpreted as hyperplastic in 2001 were considered sessile serrated lesions by GI pathologists in 2007, but there is substantial inter-observer variation amongst GI pathologists.

### INTRODUCTION

Serrated colorectal polyps in the proximal colon are now recognized as precancerous lesions that should be removed during colonoscopy<sup>[1-3]</sup>. Previously, hyperplastic polyps have been considered innocuous when identified anywhere in the colon; however, some proximal colon serrated polyps are better classified as sessile serrated polyps (sessile serrated adenomas) and closer endoscopic follow-up may be appropriate<sup>[4-7]</sup>.

Much about hyperplastic polyps remains unknown. The extent to which they are recognized as polyps by endoscopists is uncertain, since miss rates for proximal colon hyperplastic polyps have not been reported<sup>[8]</sup>. Further, the extent to which they have been recognized endoscopically but not removed (their endoscopic appearance might initiate observation or sampling, rather than removal), or ineffectively removed, is uncertain and has not been reported. Finally, the extent to which proximal colon serrated lesions are distinguished as hyperplastic *versus* sessile serrated polyps (or sessile serrated adenomas) *versus* traditional serrated adenomas by pathologists is not known<sup>[9,10]</sup>.

In this report, we describe the results of a quality improvement project in which we sought to estimate the extent to which proximal colon polyps removed in prior years and designated as hyperplastic polyps by

pathologists might now be considered more clinically significant lesions, such as sessile serrated polyps or serrated adenomas<sup>[11-13]</sup>. The issue was deemed pertinent to our colonoscopy callback process, since in prior years we had recommended routine colonoscopic follow up if only hyperplastic polyps were removed from the colon, including from the proximal colon. Recently, we began recommending follow up at shorter intervals if hyperplastic or other serrated polyps were removed from the proximal colon<sup>[14]</sup>. In order to assess whether we had patients who had serrated proximal colon polyps removed earlier and whom we should consider calling back earlier than we previously recommended, we evaluated histologic slides of 40 consecutive proximal colon “hyperplastic polyps”  $\geq 5$  mm in size removed at Indiana University Hospital in 2001 which were reviewed by three expert gastrointestinal (GI) pathologists.

## MATERIALS AND METHODS

We utilized an endoscopic database that includes histology of more than 10000 consecutive colorectal polyps<sup>[15]</sup>. We selected 40 consecutive lesions originally diagnosed as hyperplastic polyps removed from the proximal to the sigmoid-descending junction that were at least 5 mm in size. The sample size was selected for feasibility of review in our quality improvement process and not on the basis of a power calculation. The original interpretation in each case was made by 1 of 8 attending pathologists at Indiana University Hospital, none of whom was a specialist in GI pathology. The review was performed by a specialist in GI pathology currently in GI practice at I.U. (OC) and two outside pathologists (J.G. and M.O.). Each of the reviewers was aware that the original slide had been interpreted as a hyperplastic polyp. Each pathologist performed their review independently without any knowledge of the other’s findings. We did not supply the reviewing pathologists with standard terminologies to utilize in describing their findings. Permission to report the results of the quality study was granted by the Institutional Review Board of Clarian Health Partners. The Kappa statistic was used to determine agreement between the three specialists in interpretation of the polyps. For the purposes of the comparisons, we considered “sessile serrated polyp” and “sessile serrated adenoma” to be equivalent, but distinct from traditional serrated adenoma.

After the reviews, the pathologists were asked to provide the criteria they used to interpret the histology. Pathologist A indicated that he used the World Health Organization criteria<sup>[16]</sup> for serrated adenoma and published criteria from another source for sessile serrated adenoma and hyperplastic polyp<sup>[2]</sup>. Pathologist B utilized the criteria of Torlakovic *et al*<sup>[17]</sup> that described 3 variants of hyperplastic polyp (the microvesicular serrated polyp, the goblet cell serrated polyp, and the sessile serrated adenoma). The term serrated adenoma was used by pathologist B when some component of the polyp has serrated architecture and overt cytological dysplasia was present. Pathologist C provided two references that best described his criteria for diagnosis of serrated polyps<sup>[18,19]</sup>.

**Table 1** Pathologic interpretation of the 40 polyps by the 3 GI specialist pathologists

Polyp <sup>1</sup>	Pathologist A	Pathologist B	Pathologist C
1	SSA	HP	SSP
2	HP	HP	SSP
3	HP	HP	SSP
4	SSA	SSA	SSP
5	HP	SSA	SSP
6	HP	HP	HP
7	HP	HP	SSP
8	SSA	HP	SSP
9	HP	HP	SSP
10	SSA	HP	SSP
11	SSA	SSA	SSP
12	SSA	SSA	SSP
13	HP	HP	SSP
14	SSA	SSA	SSP
15	SSA	HP	SSP
16	HP	HP	SSP
17	SSA	SSA	SSP
18	HP	HP	HP
19	SSA	HP	SSP
20	HP	HP	SSP
21	HP	HP	SSP
22	SSA	HP	SSP
23	HP	HP	SSP
24	HP	HP	SSP
25	SSA	SSA	SSP
26	HP	SSA	SSP
27	SA	HP	SSP
28	HP	HP	HP
29	HP	HP	HP
30	HP	HP	SSP
31	SSA	SSA	SSP
32	SSA	SSA	SSP
33	HP	HP	SSP
34	HP	HP	HP
35	HP	HP	SSP
36	SSA	HP	SSP
37	SSA	HP	SSP
38	HP	HP	HP
39	SSA	SSA	SSP
40	HP	SSA	SSP

<sup>1</sup>Polyp number (there are 40 polyps). HP: Hyperplastic polyp; SSP: Sessile serrated polyp; SSA: Sessile serrated adenoma; SA: Serrated adenoma; GI: Gastrointestinal.

## RESULTS

The three GI pathologists interpreted 43%, 30% and 85% of the (cases) as sessile serrated polyps or sessile serrated adenomas (Table 1). Only one polyp was called a traditional serrated adenoma, and by only one of the pathologists.

Based on diagnoses for all three pathologists, the overall Kappa value was 0.16, indicating only slight agreement. When the pathologists’ diagnoses were compared in pairs, the Kappa values for the comparisons were 0.38 and 0.25 (fair agreement) and 0.14 (slight agreement).

## DISCUSSION

In this report, we describe a quality improvement project in which we explored issues relating to pathologic interpretation of proximal colon polyps with serrated

histology. Our results indicate that polyps interpreted as hyperplastic in 2001 by non-specialist pathologists at a university hospital were frequently called sessile serrated polyps or sessile serrated adenomas by GI pathologists in 2007. To the extent that “sessile serrated polyp” triggers a recommendation for earlier colonoscopic follow-up compared to “hyperplastic polyps,” this could affect clinical outcomes for patients. The extent to which earlier follow-up by clinicians would be undertaken is unknown, as current postpolypectomy surveillance colonoscopy guidelines indicate that shorter intervals are appropriate for these patients but these guidelines do not make distinct interval recommendations for these patients<sup>[14]</sup>.

We found that each of three expert pathologists used different published references to support their criteria for sessile serrated adenoma (polyp) and serrated adenoma. A review of the various references<sup>[2,16-19]</sup> cited by the pathologists indicated that they utilize substantially similar but not identical language to describe these pathologic entities. The extent to which only slight-to-fair interobserver agreement in this report is the result of variations in criteria *vs* interobserver variation with essentially equivalent criteria is uncertain.

After examining these results, we elected not to systematically call back patients for earlier surveillance colonoscopy if they had undergone colonoscopy less than 10 years ago and had proximal colon polyps originally interpreted as hyperplastic and no adenomas anywhere else in the colon. Our rationale for this decision included (1) lack of clear recommendations on appropriate follow up intervals for this population and (2) the marked interobserver variation in the interpretation of these polyps among experts in GI pathology, and (3) no specific observation that patients with these polyps are a source of interval cancers in our endoscopy unit, and (4) no clear evidence that patients would benefit from being called back early for “sessile serrated polyp” or “sessile serrated adenoma.” We were reassured that only one polyp was called a true serrated adenoma, and this by only one pathologist. We acknowledge uncertainty regarding the appropriateness of the decision to not call patients back earlier than originally planned.

Others have also noted interobserver variation in the pathologic interpretation of serrated polyps<sup>[9,10]</sup>, even among specialists in GI pathology<sup>[9]</sup>, as well as variation in the terminology used to describe these lesions<sup>[9]</sup>. Certainly, recent evidence suggesting that colonoscopy is more effective at reducing the risk of distal compared to proximal cancers<sup>[20]</sup> has raised concerns in our unit that these polyps be carefully looked for, removed completely, and interpreted correctly by pathologists.

In summary, our results suggest that as recently as 2001, non-GI pathologists at a university hospital were uniformly interpreting proximal colon polyps with serrated histology as hyperplastic polyps that GI pathologists would now interpret as sessile serrated polyps (sessile serrated adenomas). If this phenomenon has occurred on a widespread basis (which seems likely)

it might have a negative effect on colorectal cancer prevention, but this is very uncertain. We elected not to bring patients with only proximal colon hyperplastic polyps diagnosed in the period around 2001 back for follow-up colonoscopy sooner than originally planned. However, we admit uncertainty regarding the optimal management of these patients, and physicians might reasonably choose to recall these patients for colonoscopy at earlier intervals<sup>[14]</sup>. Clinicians should be aware that substantial percentages of patients with lesions diagnosed as proximal colon hyperplastic polyps may have had lesions which would now be called sessile serrated polyps or sessile serrated adenomas by expert pathologists.

## COMMENTS

### Background

Serrated polyps in the proximal colon share molecular features with a group of proximal colon cancers and maybe precursors of these cancers. Subtypes of serrated polyps include hyperplastic polyps, sessile serrated polyps (also called sessile serrated adenomas) and serrated adenomas.

### Research frontiers

The clinical relevance of the distinction between hyperplastic and sessile serrated polyps is unknown. Possibly the number, size, and location of serrated polyps has as much relevance as the pathologic distinction between hyperplastic polyps and sessile serrated polyps. True serrated adenomas, however, are likely more important than hyperplastic polyps and sessile serrated polyps, and also are much less common. The accuracy of the pathologic distinction of these polyp types in clinical practice is probably quite low.

### Innovations and breakthroughs

Serrated polyps in the proximal colon often have molecular features in common with a subgroup of colon cancers, including *BRAF* mutations, the CpG island methylator phenotype, and microsatellite instability. These common molecular features underlie the hypothesis that some hyperplastic polyps become serrated adenomas and then cancers.

### Applications

The results indicate that clinical decision making regarding serrated polyps is complicated by variations in pathology terms and substantial interobserver variation in pathologic interpretation of serrated polyps, even among experts.

### Terminology

The term “serrated polyps” describes a set of polyps divided into subgroups believed to have variable risk for short term transformation into cancer. Hyperplastic polyps are believed to have the most benign behavior, while true serrated adenomas (which are dysplastic) have the greatest risk. Sessile serrated polyp is a term often used for a set of polyps called sessile serrated adenoma, and these lesions may be intermediate in the transformation of hyperplastic polyp to serrated adenoma.

### Peer review

Original evaluation of histologic features of hyperplastic polyps in different periods, with experienced pathologists applying new concepts. Several problems are highlighted in this paper: Missing polyps during colonoscopy; Absence of unique terminology; Difficulties in interobserver agreement in histologic interpretation.

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S- Editor Tian L L- Editor Webster JR E- Editor Yin DH