

# Serrated colorectal polyps in inflammatory bowel disease

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**Serrated colorectal polyps, which, besides hyperplastic polyps, comprise sessile serrated adenomas/polyps and traditional serrated adenomas, are presumptive precursors of at least 20% of sporadic colorectal carcinomas; however, their significance in patients with inflammatory bowel disease is unclear. We retrospectively evaluated 78 serrated polyps, removed over a 14-year period from 6602 inflammatory bowel disease patients undergoing endoscopic surveillance, with respect to morphologic, clinicopathologic, and molecular features, and compared rates of advanced neoplasia (high-grade dysplasia and carcinoma) development following the index serrated polyp diagnosis to reference inflammatory bowel disease cohorts without serrated polyps. Serrated polyps negative for dysplasia, which morphologically resembled sporadic sessile serrated adenoma/polyps, occurred mainly in females, in the proximal colon, and contained *BRAF* mutations. Serrated polyps with low-grade dysplasia resembled sporadic traditional serrated adenomas and occurred mainly in males, in the distal colon, and contained *KRAS* mutations. Serrated polyps indefinite for dysplasia were morphologically heterogeneous, but similar to serrated polyps positive for low-grade dysplasia with respect to male predominance, left-sided location, and *KRAS* mutation rates. Rates of prevalent neoplasia associated with serrated polyps positive for low-grade dysplasia, indefinite for dysplasia, and negative for dysplasia were 76, 39, and 11%, respectively ( $P < 0.001$ ). Actuarial 10-year rates of incident advanced neoplasia after an initial diagnosis of serrated polyp positive for low-grade dysplasia, indefinite for dysplasia, and negative for dysplasia were 17, 8, and 0%, respectively, the first and last being significantly different ( $P = 0.02$ ) and comparable to those of corresponding reference populations of inflammatory bowel disease patients with and without low-grade dysplasia at baseline, respectively. We conclude that in serrated polyps from inflammatory bowel disease patients, dysplasia grade correlates with morphology, sex, anatomic location, *BRAF* and *KRAS* mutation status, prevalent conventional neoplasia, and rates of advanced neoplasia development.**

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Recognition of the serrated neoplasia pathway to colorectal carcinoma has enhanced our understanding of sporadic carcinogenesis in the general population. Serrated polyps, which encompass, besides hyperplastic polyps, sessile serrated adenomas/polyps and traditional serrated adenomas, have been

implicated in the pathogenesis of at least 20% of sporadic colorectal carcinomas.<sup>1,2</sup> Sessile serrated adenoma/polyps are usually located in the proximal colon, predominate in women, and harbor *BRAF* mutations, whereas traditional serrated adenomas are usually left sided, occur more often in men, and contain *KRAS* mutations.<sup>3–5</sup> The significance of serrated polyps in the general population with respect to carcinoma risk stratification, endoscopic surveillance, and management is becoming increasingly clear and has recently been incorporated into clinical consensus guidelines.<sup>6–8</sup>

Patients with extensive, longstanding colonic inflammatory bowel disease, mainly ulcerative and Crohn's colitis, face an increased risk of developing colorectal cancer compared with the general population.<sup>9,10</sup> Surveillance colonoscopy is advo-

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cated and widely practiced in these patients as a means of reducing cancer mortality by permitting early detection and management of neoplasia in the form of dysplasia or early, curable carcinoma.<sup>9,11</sup> The histologic grading, natural history, clinical implications, and molecular basis of dysplasia in inflammatory bowel disease have been studied extensively and provide essential guidance in this endeavor.<sup>9,11–13</sup>

Nonetheless, recognition of the full range of histologic lesions with malignant potential in the setting of inflammatory bowel disease is incomplete. Although several prior studies have described serrated colorectal lesions in patients with inflammatory bowel disease,<sup>14–17</sup> a systematic characterization of serrated polyps in this population has not been hitherto reported. We hypothesized that serrated polyps in patients with inflammatory bowel disease may have similar biologic characteristics to sporadic serrated polyps and therefore undertook a retrospective review of colorectal serrated polyps diagnosed over a 14-year period among inflammatory bowel disease patients undergoing routine colonoscopic surveillance at our institution. Our aim was to characterize their histologic, clinicopathologic, and molecular features, and determine the associated risk of neoplasia development.

## Materials and methods

### Cases and Patients

Colorectal serrated polyps (index serrated polyps) diagnosed histologically between 2000 and 2013 were identified by query of our comprehensive electronic Gastrointestinal Pathology Division database (maintained prospectively by NH) and by a retrospective, text-based search of our departmental pathology database for the term *serrated* combined with the terms *inflammatory bowel disease*, *Crohn's disease*, or *ulcerative colitis*. Inclusion criteria included patients with medically documented colonic inflammatory bowel disease undergoing surveillance colonoscopy in our institution and a confirmed diagnosis of serrated polyp of the large intestine between 2000 and 2013. Exclusion criteria included unavailability of archived slides for review and serrated polyps with high-grade dysplasia (one case).

H&E-stained sections of all serrated polyps were reviewed independently by two gastrointestinal pathologists (ADP and NH) who were blinded to original diagnoses and patient outcomes. Serrated polyps were evaluated for the type of serration present (e.g., resembling hyperplastic polyp vs sessile serrated adenoma/polyp) according to WHO criteria and were graded as positive, negative, or indefinite for dysplasia according to established criteria for the diagnosis of dysplasia in inflammatory bowel disease.<sup>18,19</sup> Substantial inter-observer agreement was achieved ( $\kappa=0.63$ , s.e. = 0.08) and discordant

cases were re-reviewed jointly for consensus. A separate control cohort of 28 inflammatory bowel disease patients diagnosed with conventional hyperplastic polyps during routine surveillance colonoscopy was selected randomly from the same patient registry. Clinicians performing surveillance colonoscopy on inflammatory bowel disease patients at our institution generally follow published guidelines, obtaining four-quadrant biopsies every 10 cm.

Clinical information regarding the patients' age, sex, type and duration of inflammatory bowel disease, number of colonoscopic examinations, and the size, location, and endoscopic appearance of the serrated polyps was obtained from electronic medical records, and endoscopy and pathology reports. Polyp size was determined based on histologic measurements in all cases. Right-sided lesions were defined as those located proximal to the splenic flexure. The degree or extent of endoscopic or histologic active inflammation was not included in the analysis.

For each patient, endoscopy and pathology reports from all preceding and subsequent colonoscopic examinations and surgical resections were reviewed and all prior, synchronous, and metachronous diagnoses of dysplasia or carcinoma (prevalent neoplasia) were recorded. Sporadic adenomas, i.e., those occurring outside the documented area of colitis, as well as adenoma-like dysplastic polyps occurring within the area affected by colitis (classified as such based on established endoscopic and histologic criteria<sup>20</sup>), were not included as prevalent neoplasia, but the 11 patients with such sporadic adenomas were included in the analysis of incident advanced neoplasia. For the determination of risk of incident advanced neoplasia (high-grade dysplasia and carcinoma), developing after the diagnosis of each index serrated polyp (Supplementary Table 1), 12 patients in whom dysplasia or carcinoma had occurred before or at the same time as the index serrated polyp diagnosis and 17 patients with no follow-up colonoscopy were excluded. Rates were compared with a cohort of 1465 inflammatory bowel disease patients (from the same source population) with no baseline dysplasia, undergoing colonoscopic surveillance at our institution as previously described,<sup>21,22</sup> after excluding patients with serrated or hyperplastic polyps.

This study was approved by the Institutional Review Board of the Icahn School of Medicine at Mount Sinai.

### Molecular Analysis

Genomic DNA was extracted from formalin-fixed, paraffin-embedded tissue (10 unstained sections, each 5  $\mu\text{m}$  thick). DNA from each index lesion was extracted using the Maxwell Clinical Sample Concentrator instrument and Maxwell FFPE Plus LEV DNA purification kit (Promega, Madison, WI,

USA) according to the manufacturer's recommended protocol. Multiplex PCR was carried out to amplify interested sequences of *KRAS* (exon 2), *BRAF* (exon 15), and *PIK3CA* (exons 9 and 20) genes. The primer sequences used and the expected size of the resulting PCR products were as follows:

*KRAS* E2 Forward (TTATAAGGCCTGCTGAAAA TGACTGAA) and *KRAS* E2 Reverse (TACCTCTATT GTTGGATCATATTCGT) yielding a 132 bp product; *PIK3CA* E9 Forward (GCTAGAGACAATGAATTAA GGG) and *PIK3CA* E9 Reverse (GAGATCAGCCAA ATTCAGTT) yielding a 186 bp product; *PIK3CA* E20 Forward (TGGAATGCCAGAACTACAAT) and *PIK3CA* E20 Reverse (TTTGCCTGCTGAGAGTTA TT) yielding a 255 bp product; and *BRAF* E15 Forward (CTCTTCATAATGCTTGCTCTGATAGG) and *BRAF* E15 Reverse (ATAGCCTCAATTCTTACC ATCCAC) yielding a 203 bp product.

Amplified DNAs were mixed with 14 short specific DNA sequences (TAG primers) for each of the wild type or mutated sequences (Supplementary Table 2). When the target sequence is present, the primer binds and extends through allele-specific primer extension (ASPE). During ASPE, a reporter label (biotin-labeled dCTP) is incorporated. Extended TAG primers are then detected by specific anti-TAG sequences, each conjugated to differentially color-coded beads. Owing to the proximity of the DNA sequences involved, the *PIK3CA*-E9-Codon 542 WT and *PIK3CA*-E9-Codon 545 WT TAG primers used were identical. The reporter is streptavidin conjugated with R-phycoerythrin which is detected using the Luminex xMAP system (Luminex, Austin, TX, USA), according to the manufacturer's protocol. Mutations detected included *KRAS* codon 12 (GGT>AGT, TGT, CGT, GAT, GTT, or GCT), *KRAS* E2 codon 13 (GGC>TGC, AGC, CGC, GAC, GTC, or GCC), *PIK3CA* codon 542 (GAA>AAA), *PIK3CA* codon 545 (GAG>AAG), *PIK3CA* codon 1047 (CAT>CGT), and *BRAF* codon 600 (GTG>GAG, or AAG).

### Statistical Analysis

Clinicopathologic characteristics were coded as either categorical (inflammatory bowel disease type, anatomic location) or dichotomous (sex, presence of dysplasia/carcinoma) variables, and frequencies were examined by type of serrated polyp (positive for low-grade dysplasia, indefinite for dysplasia, negative for dysplasia, hyperplastic polyp) with a chi square using the Fisher exact test for statistical significance. Continuous measures (age at diagnosis, size of polyp, number of colonoscopies, and length of colonoscopic surveillance period in months) were evaluated in relation to polyp type using an unbalanced two-way ANOVA design. We generated Kaplan–Meier curves to test for differences in the time to development of advanced neoplasia (high-grade dysplasia or adenocarcinoma) among patients

with different types of index serrated polyps. Patients in whom neoplasia occurred prior to the diagnosis of the index serrated polyp were excluded from this part of the analysis. The Wilcoxon test was used to test for equality across strata. *P*-values less than 0.05 were considered statistically significant. All analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA).

### Results

Serrated polyps were identified in 78 of 6602 inflammatory bowel disease patients (3453 women and 3149 men) undergoing surveillance colonoscopy in our institution during a 14-year period (2000–2013) for an overall prevalence rate of 1.2% (Table 1). Study patients had undergone a mean 8.2 colonoscopic examinations (range: 1–26) over a mean surveillance period of 101.5 months (range: 0–228 months). At least 65 (83%) of the identified serrated polyps had been described by the endoscopist as a polyp, nodule, lesion, or fold (5 of these polyps were identified using chromoendoscopy), and all but 2 (97%) occurred in areas with clinicopathologically documented involvement by inflammatory bowel disease.

Thirty-five (45%) serrated polyps were negative for dysplasia and contained elongated crypts with hyperserrated mucinous epithelium along their entire length and basal dilatation or horizontal growth, features characteristic of sporadic sessile serrated adenoma/polyps<sup>19</sup> (Figures 1a and b). Twenty-five (32%) serrated polyps were positive for low-grade dysplasia and all contained complex, hyperserrated dysplastic epithelium with ectopic crypt formation, pencillate hyperchromatic nuclei and hypereosinophilic cytoplasm, fulfilling WHO criteria for sporadic traditional serrated adenomas<sup>19</sup> (Figures 1c and d). Occasional serrated polyps positive for low-grade dysplasia contained admixed non-dysplastic serrated elements, as commonly occurs in sporadic traditional serrated adenomas. Eighteen (23%) serrated polyps, classified as indefinite for dysplasia, comprised a mixed group with varied architectural features, some more closely resembling sessile serrated adenoma/polyps, others more closely resembling hyperplastic polyps, and others resisting classification, the common feature being serrated epithelium combined with foci of epithelial atypia deemed to fall short of a diagnosis of dysplasia. (Figures 1e and f). Examples of the endoscopic appearances of serrated polyps in the study are shown in Figure 2.

There were no statistically significant differences among patients with serrated polyps with respect to mean age, inflammatory bowel disease type, percentage with disease duration greater than 10 years, mean surveillance period, or mean number of colonoscopies per patient (Table 1). However, serrated polyps negative for dysplasia were more

**Table 1** Clinicopathologic features of study patients with serrated polyps

	SP-LGD (N = 25)	SP-IND (N = 18)	SP-NEG (N = 35)	HP (N = 28)	Reference (N = 1465)
Mean age ± s.d. (years)	56.4 ± 14.4	55.9 ± 13.0	54.3 ± 14.2	55.6 ± 13.7	37.5 ± 16.9
Sex					
M (%)	16 (64%)	15 (83%)	16 (46%)	17 (61%)	737 (50%)
F (%)	9 (36%)	3 (17%)	19 (54%)*	11 (39%)	728 (50%)
Polyp site					
R (%)	5 (20%)	4 (22%)	20 (57%)#	9 (32%)	
L (%)	20 (80%)	14 (78%)	15 (43%)	19 (68%)	
Mean size ± s.d. (cm)	1.23 ± 0.80	0.66 ± 0.55	0.87 ± 0.45	0.52 ± 0.25 <sup>+</sup>	
IBD type (UC:CD:IC)	18:6:1	16:2:0	22:11:2	19:9:0	1416:49:0
Disease > 10 years (%)	84%	89%	86%	89%	60%
Mean surveillance (mo)	101.1	98.7	103.2	113.4	88.0
Mean colonoscopies	9.6	8.8	7.0	7.4	5.8

Abbreviations: CD, Crohn's disease; F, female; HP, hyperplastic polyps; IBD, inflammatory bowel disease; IC, indeterminate colitis; L, left colon; M, male; mo, months; R, right colon (proximal to splenic flexure); s.d., standard deviation; SP-IND, serrated polyps indefinite for dysplasia; SP-LGD, serrated polyps positive for low-grade dysplasia; SP-NEG, serrated polyps negative for dysplasia; UC, ulcerative colitis. *P*-values were calculated for the indicated polyp type vs all other polyps in this study combined; all other *P*-values (not shown) were not significant.

\**P* = 0.03 vs other SPs and HPs in this study; #*P* = 0.001 vs other SPs and HPs in this study; <sup>+</sup>*P* = 0.009 vs other SPs in this study.

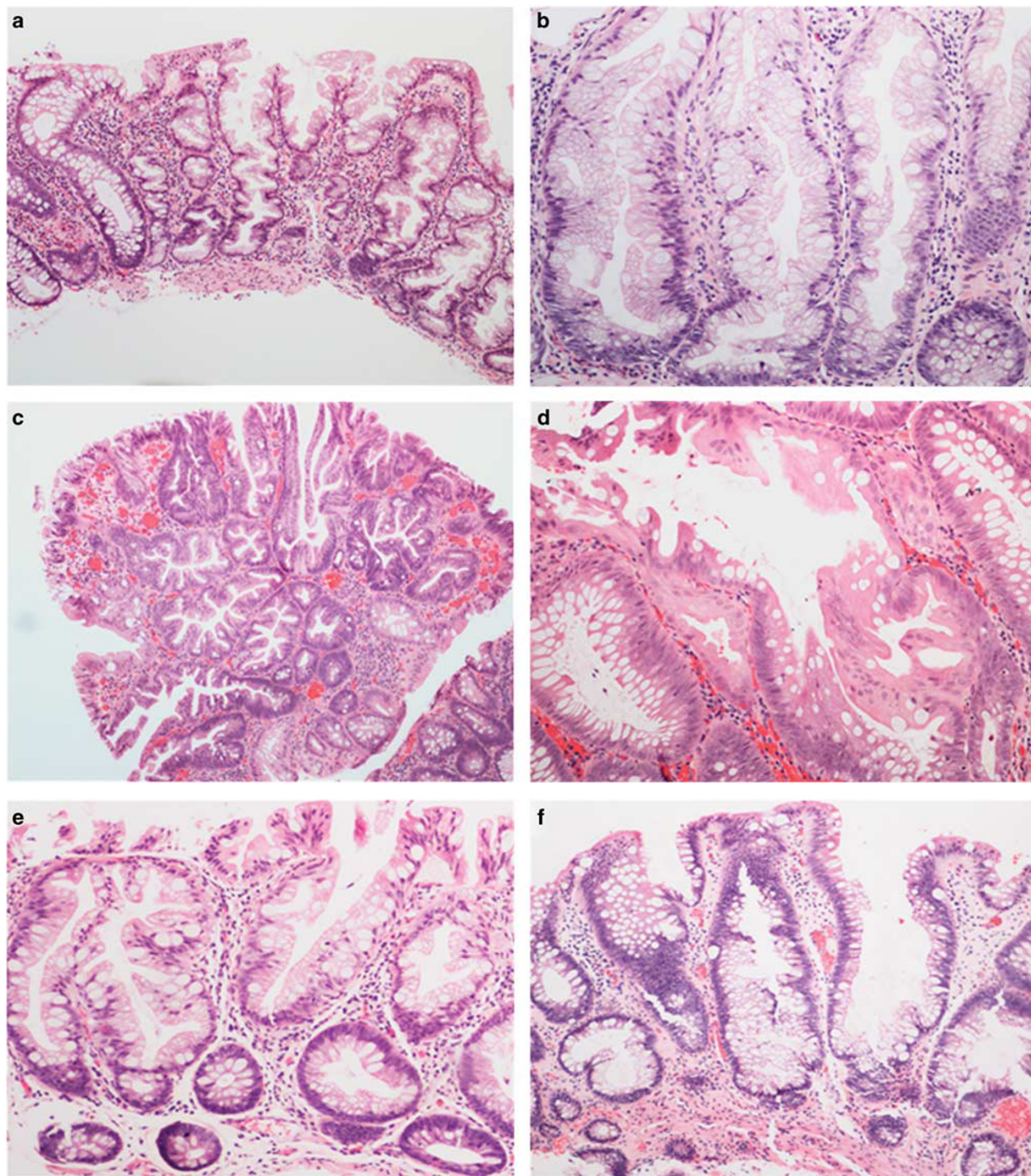
common in women (*P* = 0.03) and were mostly right sided (*P* = 0.001), whereas serrated polyps positive for low-grade dysplasia and serrated polyps indefinite for dysplasia predominated in males and were more commonly left sided. The control cohort of inflammatory bowel disease patients with conventional hyperplastic polyps was statistically similar to the entire cohort with serrated polyps with respect to mean age, sex distribution, anatomic location, inflammatory bowel disease type, disease duration, mean surveillance period, and number of examinations. Hyperplastic polyps were smaller on average than other serrated polyps (*P* = 0.009).

Sequencing analysis for mutations in the *KRAS* (codons 12 and 13), *BRAF* (V600E/K), and *PIK3CA* (E542K, E545K, and H1047R) genes was undertaken for 42 serrated polyps where material was available and genomic DNA yield was adequate (Table 2). The majority of serrated polyps negative for dysplasia had mutations in *BRAF* (*P* < 0.001) whereas few serrated polyps positive for low-grade dysplasia and no serrated polyps indefinite for dysplasia had *BRAF* mutations. In contrast, *KRAS* mutations were the most common mutations in serrated polyps positive for low-grade dysplasia and serrated polyps indefinite for dysplasia, but were only seen in a minority of serrated polyps negative for dysplasia. No mutations were identified in *PIK3CA* or *BRAF* V600K. *KRAS* and *BRAF* mutations were mutually exclusive in all cases.

The association of serrated polyps with conventional (non-serrated) dysplasia and carcinoma was evaluated in two ways. First, the rate of prior, synchronous or metachronous dysplasia (any grade) or carcinoma (prevalent neoplasia) was determined over the entire duration of surveillance per patient (Table 3). Sporadic adenomas and adenoma-like

dysplastic polyps (as defined in Materials and Methods) occurred in 11 of 106 patients in our study (10.4%) and were not included in this analysis of prevalent neoplasia. Four of 35 (11%) inflammatory bowel disease patients with serrated polyps negative for dysplasia were diagnosed with non-serrated dysplasia or carcinoma during a mean surveillance period of 103.2 months and a mean 7.0 colonoscopies per patient. In contrast, 19 of 25 (76%) patients with serrated polyps positive for low-grade dysplasia and 7 of 18 (39%) patients with serrated polyps indefinite for dysplasia were diagnosed with dysplasia or carcinoma during a similar mean surveillance interval and a similar mean number of colonoscopies (*P* < 0.001). In the majority of these patients (74%), neoplastic lesions were identified in the same colonic segment as the index serrated polyp and in 7 of 19 (37%) patients with serrated polyps positive for low-grade dysplasia, prevalent neoplasia consisted of a persistent serrated lesion with low-grade dysplasia (i.e., an incompletely resected or recurrent lesion). By comparison, 6 of 28 (21%) patients with conventional hyperplastic polyps had dysplasia or carcinoma, but this was not statistically significantly different from patients with serrated polyps negative for dysplasia and likely reflects the underlying neoplasia risk in this patient population.

Second, we examined the risk of incident advanced neoplasia (high-grade dysplasia and adenocarcinoma) developing among 77 patients with index serrated polyps (including hyperplastic polyps) and no prior or synchronous dysplasia or carcinoma (12 patients in whom any grade dysplasia or carcinoma had occurred before or at the same time as the index serrated polyp diagnosis and 17 patients with no follow-up colonoscopy were excluded). These were compared with a reference cohort of



**Figure 1** Photomicrographs of H&E-stained sections from serrated polyps histologically classified as (a and b) negative for dysplasia; (c and d) positive for low-grade dysplasia; and (e and f) indefinite for dysplasia (original magnification:  $\times 200$ ). H&E, hematoxylin and eosin.

1465 inflammatory bowel disease patients with no dysplasia at baseline, undergoing colonoscopic surveillance (Table 1 and Figure 3). Among 27 patients with index serrated polyps negative for dysplasia and no prior diagnosis of dysplasia, only 1 (4%) developed conventional low-grade dysplasia and

none developed advanced neoplasia during the follow-up period. In contrast, among 21 patients with index serrated polyps positive for low-grade dysplasia, 3 (14%) developed metachronous high-grade dysplasia and 1 (5%) developed adenocarcinoma. Of 11 patients with index serrated polyps



**Figure 2** Endoscopic images of serrated colorectal polyps classified as negative for dysplasia: a 2-cm sessile polyp in the transverse colon (a) and a 5-mm flat polyp at 70 cm (b); positive for low-grade dysplasia: a 1–2-cm irregular sessile polyp with central umbilication at 40 cm (c) and a 6–7-mm slightly raised lesion in the ascending colon (d); and indefinite for dysplasia: a diminutive nodule in the ascending colon (e) and an ill-defined irregular raised area in the sigmoid colon (f) (courtesy of: James George, MD, Steven H Itzkowitz, MD, Mejdi Ahmad, MD, and Neville D Bamji, MD).

**Table 2** Molecular characteristics of serrated polyps

	SP-LGD (N = 11)	SP-IND (N = 8)	SP-NEG (N = 23)	Total (N = 42)
<i>BRAF</i> mutations (V600E) (%)	2 (18%)	0 (0%)	15 (65%)*	17 (40%)
<i>KRAS</i> mutations (exon E2) (%)	5 (45%)	2 (25%)	4 (17%)	11 (26%)
Wild type for genes tested (%)	4 (36%)	6 (75%)	4 (17%)	14 (33%)

Abbreviations: SP-IND, serrated polyps indefinite for dysplasia; SP-LGD, serrated polyps positive for low-grade dysplasia; SP-NEG, serrated polyps negative for dysplasia. *P*-values were calculated for the indicated polyp type vs all other polyps in this study combined; all other *P*-values (not shown) were not significant.

\**P* < 0.001 vs non-*BRAF* mutated.

**Table 3** Highest grade prevalent neoplasia per patient and serrated polyp type

	SP-LGD (N = 25)	SP-IND (N = 18)	SP-NEG (N = 35)	HP (N = 28)	Total (N = 106)
No neoplastic events	6 (24%)	11 (61%)	31 (89%)	22 (79%)	70 (66%)
Low-grade dysplasia	13 (52%)	4 (22%)	3 (9%)	2 (7%)	22 (21%)
High-grade dysplasia	4 (16%)	2 (11%)	0 (0%)	2 (7%)	8 (8%)
Adenocarcinoma	2 (8%)	1 (6%)	1 (3%)	2 (7%)	6 (6%)

Abbreviations: HP, hyperplastic polyps; SP-IND, serrated polyps indefinite for dysplasia; SP-LGD, serrated polyps positive for low-grade dysplasia; SP-NEG, serrated polyps negative for dysplasia. *P* < 0.001.

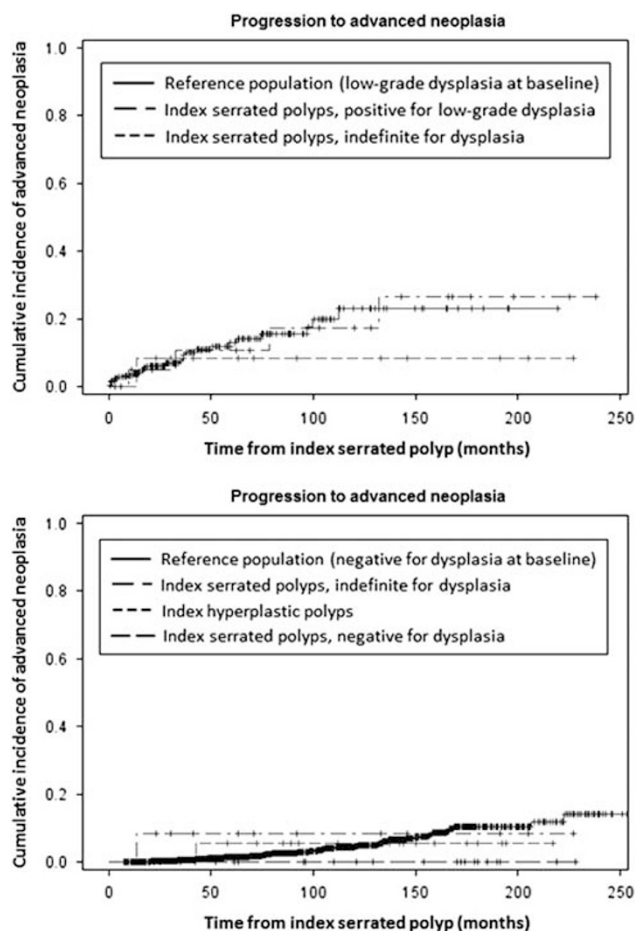
indefinite for dysplasia, 2 (18%) developed conventional low-grade dysplasia and 1 (9%) had a high-grade dysplasia lesion during follow-up. Finally, among 18 patients with hyperplastic polyps, 2 (11%) developed a lesion with conventional low-grade dysplasia and 1 (6%) developed high-grade dysplasia. The 11 patients with sporadic adenomas or adenoma-like dysplastic lesions did not develop advanced neoplasia. As shown in Figure 3 (top panel), there were no statistically significant differences in actuarial 10-year rates of advanced neoplasia development between patients with index serrated polyps positive for low-grade dysplasia (17%), serrated polyps indefinite for dysplasia (8%), and the reference cohort with low-grade dysplasia at baseline (23%). Similarly, Figure 3 (bottom panel) shows that the actuarial 10-year rate of advanced neoplasia for patients with index serrated polyps negative for dysplasia (0%) was not significantly different from that of the reference cohort without dysplasia at baseline (5%) or the group with index hyperplastic polyps (6%). Overall, patients with index serrated polyps positive for low-grade dysplasia had significantly shorter advanced neoplasia-free survival times compared with patients with index serrated polyps negative for dysplasia and index hyperplastic polyps (*P* = 0.02), whereas those with index serrated polyps indefinite for dysplasia fell in-between these groups.

## Discussion

The morphologic, clinical, and molecular characteristics of sporadic colorectal serrated polyps are

well-recognized,<sup>2–5,8,23</sup> and have resulted in consensus recommendations for short- and long-term patient management.<sup>7,24,25</sup> The present study addresses the dearth of available data regarding such lesions in patients with inflammatory bowel disease by means of a retrospective evaluation of serrated polyps diagnosed during the course of endoscopic surveillance. A low prevalence of serrated polyps in the setting of inflammatory bowel disease, 1.2% in our cohort, might account for the relative lack of attention devoted hitherto to serrated polyps in the inflammatory bowel disease literature. A recent Mayo Clinic study has corroborated this, reporting a combined prevalence of 2.1% for serrated epithelial changes (flat and polypoid serrated lesions) in inflammatory bowel disease patients.<sup>14</sup>

Histologic assessment of the serrated polyps in our cohort resulted in three groups: serrated polyps negative for dysplasia which lacked dysplasia and resembled sporadic sessile serrated adenoma/polyps; serrated polyps positive for low-grade dysplasia which featured low-grade dysplasia and resembled sporadic traditional serrated adenomas; and serrated polyps indefinite for dysplasia, a heterogeneous group with mild cytological atypia that failed to meet criteria for low-grade dysplasia. Of the demographic and clinicopathologic characteristics associated with these polyps, the only ones that correlated with the likelihood of prevalent neoplasia or a future diagnosis of advanced neoplasia were sex and colonic location. Serrated polyps negative for dysplasia, which exhibited 11% rate of prevalent neoplasia and 0% 10-year actuarial rate of incident advanced neoplasia (similar to that of the dysplasia-free at baseline control cohort), predominated in



**Figure 3** Kaplan–Meier curves showing cumulative incidence of advanced neoplasia (high-grade dysplasia or carcinoma) as a function of time (in months) from diagnosis of the indicated type of index serrated polyp compared with a reference cohort from the same overall population with inflammatory bowel disease undergoing surveillance colonoscopy in our institution. The reference cohort in the bottom panel comprised all patients ( $N=1465$ ) negative for dysplasia at baseline, whereas the reference cohort in the top panel comprised of patients ( $N=216$ ) with conventional (i.e., non-serrated), colitis-related low-grade dysplasia at baseline. Cross hatches (+) indicate censoring of patients with no further follow-up; vertical (step) lines indicate advanced neoplasia events.

females and in the right colon. By contrast, serrated polyps positive for low-grade dysplasia, with 76% rate of prevalent neoplasia and 17% 10-year actuarial rate of incident advanced neoplasia (comparable to the 23% rate in our control cohort of inflammatory bowel disease patients with conventional, non-serrated, low-grade dysplasia at baseline), exhibited preponderance in males and in a left-sided colonic location. Other characteristics including mean age, inflammatory bowel disease type, disease duration, mean surveillance period, and mean number of colonoscopies were similar across polyp types, suggesting that our data were not significantly affected by selection or detection bias.

The rates of *BRAF* and *KRAS* mutations in serrated polyps negative for dysplasia and serrated polyps

positive for low-grade dysplasia in our study closely resembles the rates reported in sporadic sessile serrated adenoma/polyps and traditional serrated adenomas, respectively.<sup>4,5,26</sup> This observation, in conjunction with their corresponding sex and anatomical site disparities, suggests that biologic parallels exist with sporadic sessile serrated adenoma/polyps and traditional serrated adenomas, despite the origin of at least 97% of our serrated polyps within chronically diseased inflammatory bowel disease mucosa. Although supervening cytologic dysplasia has been reported in up to 15% of sporadic sessile serrated adenoma/polyps,<sup>27,28</sup> we did not encounter this phenomenon in our study, where serrated polyps with cytologic dysplasia histologically resembled sporadic traditional serrated adenomas. However, the possibility that this might be identified in a larger series cannot be discounted.

In order to capture all patients with serrated polyps, our study did not exclude 11 patients with sporadic adenomas and adenoma-like dysplastic polyps, but we did not include these adenomas in the calculations of prevalent dysplasia (Table 3) on the presumption that they were not relevant to inflammatory bowel disease-associated neoplasia. With respect to neoplastic progression, these 11 patients were not ignored, rather the adenomas themselves did not contain advanced neoplasia and none of the patients with these adenomas developed advanced neoplasia; hence, their inclusion did not influence our conclusions regarding the risk of advanced neoplasia development in inflammatory bowel disease patients with index serrated polyps. Even though the number of cases in our study is small, it seems that sporadic adenomas (occurring outside the area of colitis) and adenoma-like dysplastic polyps (occurring in an area of colitis, but resembling sporadic adenomas endoscopically and histologically) do not appear to impart any additional risk of neoplastic development on top of serrated polyps.

Little attention has been given hitherto to the pathology and possible clinical significance of serrated polyps indefinite for dysplasia in the setting of inflammatory bowel disease. Despite their heterogeneity, the lesions in this group demonstrated similarities to serrated polyps positive for low-grade dysplasia with respect to predominance of male sex, left-sided colonic location, and *KRAS* mutations. These characteristics, combined with a 39% rate of prevalent neoplasia and a rate of incident advanced neoplasia development intermediate between serrated polyps negative for dysplasia and serrated polyps positive for low-grade dysplasia, support a potential role for serrated polyps indefinite for dysplasia in inflammatory bowel disease-related neoplasia which warrants further study.

Previous observations regarding serrated lesions in the colonic mucosa of patients with inflammatory bowel disease adjacent to or in association with adenocarcinoma have led to the conjecture that they might be neoplastic or preneoplastic in nature. Rubio



*et al.*<sup>16</sup> described higher rates of dysplastic serrated lesions near carcinomas in resection specimens from inflammatory bowel disease patients compared with non-inflammatory bowel disease patients. Kilgore *et al.*<sup>15</sup> reported non-dysplastic serrated lesions in 33% of cancer-bearing resection specimens from patients with Crohn's disease compared with 10% of controls without cancer. Srivastava *et al.*<sup>17</sup> described patients with longstanding inflammatory bowel disease and multiple hyperplastic polyps and sessile serrated adenoma/polyps (reminiscent of the serrated polyposis syndrome), nearly half of which contained *KRAS* but not *BRAF* mutations. They reported that cancers developed in two patients with conventional adenomatous dysplasia or traditional serrated adenomas but not in a third patient with non-dysplastic serrated lesions. More recently, a study of serrated epithelial changes in patients with inflammatory bowel disease, evidently comprising both raised and flat lesions, reported a cumulative incidence of subsequent colorectal neoplasia of 30% at 3 years compared with 9% in control patients, but the difference was not significant when history of prior or synchronous dysplasia was taken into account.<sup>14</sup> Bossard *et al.*<sup>29</sup> reported that serrated polyps, including hyperplastic polyps and sessile serrated adenoma/polyps, were present in 7% of patients with inflammatory bowel disease-related neoplasia and that *BRAF* mutations occurred only in some of them, whereas *KRAS* mutations were restricted to non-serrated dysplastic lesions.

The present study is, to our knowledge, the first systematic and comprehensive clinicopathologic, histologic, and molecular characterization of serrated polyps in patients with inflammatory bowel disease and underscores a strong association with neoplasia development in a subset of these lesions. Dysplasia in these polyps was blindly and independently evaluated by two gastrointestinal pathologists with good inter-observer agreement and the rates of prevalent neoplasia and incident advanced neoplasia were compared with control groups and reference population cohorts. However, there are several limitations to our study. First, it is a retrospective analysis of previously identified serrated polyps with no assurance that data collected from patient medical records was entirely reliable or complete. Second, there is a possible referral bias since many patients come to our institution specifically for the management of dysplasia in the setting of inflammatory bowel disease. Third, determination of polyp size by histologic measurement is intrinsically inaccurate. Fourth, we could not determine whether completeness of endoscopic removal of these polyps was uniformly achieved or even attempted. Fifth, we were able to extract *BRAF* and *KRAS* mutation status information in only about half (54%) of the serrated polyps in our study, but we have no indication to suspect that these were not overall representative samples. Finally, comparison of the risks of neoplasia development among patients

with varying surveillance examination intervals is inherently inexact, although we determined that these parameters were statistically similar across all polyp types.

We conclude that the clinical, pathologic, and biologic characteristics of serrated polyps in patients with inflammatory bowel disease resemble those of their sporadic counterparts and are associated with the presence or absence of dysplasia. Additionally, whereas serrated polyps that lack dysplasia seem to pose little additional risk of associated neoplasia, those with low-grade dysplasia, and to a lesser degree those indefinite for dysplasia, are associated with increased rates of synchronous and metachronous neoplasia. Although it is reasonable to conclude that a diagnosis of low-grade dysplasia or indefinite for dysplasia in an inflammatory bowel disease-associated serrated polyp warrants clinical caution and careful follow-up, further studies will be needed to translate these conclusions into specific clinical recommendations.

## Disclosure/conflict of interest

The authors declare no conflict of interest.

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