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Phenotype and Polyp Landscape in Serrated Polyposis Syndrome: A Series of 100 Patients from Genetics Clinics

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Abstract

Serrated polyposis syndrome (SPS), also known as hyperplastic polyposis, is a syndrome of unknown genetic basis defined by the occurrence of multiple serrated polyps in the large intestine and associated with an increased risk of colorectal cancer (CRC). There are a variety of SPS presentations, which may encompass a continuum of phenotypes modified by environmental and genetic factors. To explore the phenotype of SPS, we recorded the histologic and molecular characteristics of multiple colorectal polyps in patients with SPS recruited between 2000 and 2010 from genetics clinics in Australia, New Zealand, Canada and the USA. Three specialist gastrointestinal pathologists reviewed the polyps, which they classified into conventional adenomas or serrated polyps, with various subtypes, according to the current WHO criteria. Mutations in *BRAF* and *KRAS* and mismatch repair protein expression were determined in a subset of polyps. A total of 100 patients were selected for the study, comprising 58 females and 42 males. The total polyp count per patient ranged from 6 to 150 (median: 30). The vast majority of patients (89%) had polyposis affecting the entire large intestine. From this cohort, 406 polyps were reviewed. Most of the polyps (83%) were serrated polyps: microvesicular hyperplastic polyps (HP) (n=156), goblet cell HP (n=25), sessile serrated adenoma/polyps (SSA/P) (n=110), SSA/P with cytological dysplasia (n=28) and traditional serrated adenomas (TSA) (n=18). A

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further 69 polyps were conventional adenomas. *BRAF* mutation was mainly detected in SSA/P with dysplasia (95%), SSA/P (85%), microvesicular HP (76%), and TSA (54%) while *KRAS* mutation was present mainly in goblet cell HP (50%) and in tubulovillous adenoma (45%). Four of 6 SSA/Ps with high grade dysplasia showed loss of MLH1/PMS2 expression. CRC was diagnosed in 39 patients who were more often found to have a conventional adenoma compared to patients without CRC ($P = 0.003$). Patients with SPS referred to genetics clinics had a pancolonic disease with high polyp burden and high rate of *BRAF* mutation. The occurrence of CRC was associated with the presence of conventional adenoma.

Keywords

Serrated polyposis; Colorectal Polyps; Colorectal Cancer

INTRODUCTION

Serrated polyposis syndrome (SPS), also known as hyperplastic polyposis syndrome, is a colonic polyposis condition predisposing affected individuals to a 25–40% risk of developing colorectal cancer (CRC) (3, 5, 6, 17, 24). While the first patients with SPS were documented in the 1970s (8), it has only recently been recognized as a condition with a potential genetic basis, involving serrated polyps as possible precursor lesions to CRC (15, 16, 21, 29). SPS is reported to occur more commonly in individuals with Northern European ancestry, and to demonstrate relationships with current smoking, specifically a positive correlation with the number of serrated polyps but a paradoxically negative correlation with the risk of CRC (5, 6, 33). In addition to multiple serrated polyps, conventional adenomas of the large intestine may be part of the syndrome as they are identified in up to 85% of SPS patients (3, 10, 12).

Serrated polyps represent a group of benign lesions of the large intestine that have in common a serrated, saw-toothed appearance and are further classified into three categories by the World Health Organization (WHO) Classification of Tumours of the Digestive System (26): hyperplastic polyp (HP), sessile serrated adenoma/polyp (SSA/P) with or without cytological dysplasia, and traditional serrated adenoma (TSA). Previously, SPS was called hyperplastic polyposis syndrome when HPs were the only histologically known serrated polyps of the large intestine. Subsequently, studies have described SSA/P as a morphologically distinct and clinically important subset of hyperplastic polyp, as well as a lesion commonly observed in what we now know as SPS. Consequently, the fourth edition of the WHO Classification of Tumours of the Digestive System changed the name of this condition from hyperplastic polyposis to serrated polyposis (26). The current criteria to define SPS are: (1) at least 5 serrated polyps proximal to the sigmoid colon, with two or more of these being >10 mm; or (2) any number of serrated polyps proximal to the sigmoid colon in an individual who has a first-degree relative with serrated polyposis; or (3) > 20 serrated polyps of any size but distributed throughout the colon. However, these criteria remain arbitrary and a meaningful biological classification is more likely to emerge when the genetic basis of the condition is better understood.

There are a variety of presentations in SPS, which may encompass a continuum of phenotypes modified by environmental and genetic factors. It has been suggested that there are three phenotypes: large SSA/Ps in the proximal colon with a high risk of CRC; numerous small HPs throughout the colorectum with a lower risk of CRC; and many small left sided serrated polyps (13, 17). Moreover, pathways involved in CRC development appear to be heterogeneous, not only involving the serrated pathway but also others such as the conventional adenoma pathway (2). To better understand the phenotype of SPS and its

relationship to the occurrence of CRC, we report the histologic and molecular characteristics of colorectal polyps in 100 patients with SPS referred to genetics clinics.

MATERIAL AND METHODS

Patient selection

Patients were selected from a cohort of individuals with at least 5 serrated polyps in the colon proximal to the recto-sigmoid region recruited between 2000 and 2010 from genetics clinics in Australia, New Zealand, Canada and the USA. A total of 100 patients for whom definitive serrated polyp counts were available, and who fulfilled at least WHO criterion 1 or 3 for SPS (26), were included in this study. None of the patients was selected based on criterion 2 only. Eighty-three patients were referred to genetics clinics for polyposis (with or without a personal or family history of CRC), and twelve were discovered to have polyposis after family screening. Of these 12 patients, three met WHO criterion-1, and nine met criterion-3. No referring details were available for the remaining 5 patients. Thirty-nine patients were from the Australasian Colorectal Cancer Family Registry, and the remaining patients were enrolled in the Genetics of Serrated Neoplasia study (<http://www.qimr.edu.au/page/GSN/>) to which Ohio State University Medical Center (USA), Cancer Care Ontario (Ontario, Canada), and the Genetics Clinics of Australia and the Familial Gastrointestinal Cancer Registry of New Zealand have contributed (5, 12, 22, 28). Written informed consents were obtained from all patients to take part in research and the study was approved by the Human Research Ethics Committee of Queensland Institute of Medical Research under the Genetics of Serrated Neoplasia Project (QIMR HREC P912).

The age at diagnosis was defined by the age of the first observation of polyposis (regardless of the presence or absence of CRC) in the patient. Information on personal characteristics was obtained at the time of recruitment. Reported cancer diagnoses and age at diagnosis were confirmed, where possible, using pathology reports and/or medical records. Standard white light colonoscopy was used in all patients.

Polyp Review

Three specialist gastrointestinal pathologists (JRJ, NIW and CR) reviewed the polyps, which were classified into conventional adenomas or serrated polyps, with its various subtypes, according to the WHO criteria (26). Information regarding the number, size, distribution, and gross morphology of polyps was derived from the colonoscopy reports. The total numbers for each polyp type were estimated during colonoscopy or from the surgical specimen if a colectomy was performed.

BRAF and KRAS Mutation Analysis

Genomic DNA was extracted from formalin fixed paraffin embedded tissue using QIAamp DNA Micro Kit (QIAGEN, Hilden, Germany) according to the manufacturer's instructions. V600E *BRAF* mutation analysis was performed by a fluorescent allele specific PCR assay, as previously described (5). The mutant allele primer generated a PCR product of 97bp, 3bp larger than the wild-type PCR product after separation on an ABI 3100 genetic analyzer. GeneMarker (SoftGenetics, State College, PA, USA) software was used to score the alleles based on differing size and fluorophore. *KRAS* mutation screening was performed using real-time PCR with high resolution melting (HRM) analysis, with the primer set AGGCCTGCTGAAAATGACTG (forward primer) and TATCGTCAAGGCACTCTTGC (reverse primer), in the presence of the SYTO9 fluorescent intercalating dye. Direct Sanger sequencing was performed for positive cases.

Mismatch Repair Deficiency Testing

Expression of the MMR proteins MLH1, MSH2, MSH6 and PMS2 was assessed by immunohistochemistry on polyp paraffin sections as described previously (30).

Statistical Analysis

Statistical analyses were performed with SPSS statistics software version 17.0 (SPSS Inc., Chicago, IL). Comparisons for categorical variables were performed using Pearson's chi-square test or Fisher's exact test when any expected values were lower than 5. Student's *t*-test was used for continuous variables. A two-tailed *P* value was used for all analyses and a *P* value of less than 0.05 was used to determine statistical significance.

RESULTS

Patients Characteristics

The study comprised 100 patients who fulfilled at least WHO criterion 1 or 3 for SPS (Table 1). Criterion-1 was met for 12 individuals with polyp counts ranging from 6 to 20 (mean: 13.1; median: 12). The remaining patients fulfilled criterion-3 with 21 to 150 polyps identified in the large intestine (mean: 53.4; median: 39). Within criterion-3, a subset of 16 patients also met criterion-1.

There were 58 females and 42 males in the study cohort. Age at diagnosis was available for 90 patients and ranged from 17 to 69 years (mean 47.7 SD 14.3). Patients who fulfilled criterion-1 were significantly older than patients who did not (mean age 52.2 SD 14.2 vs. 45.7 SD 14.1; *P* = 0.05). No significant difference in maximum polyp size or gender was found between these two groups.

Polyp distribution

The total polyp count per patient was estimated to be ranged from 6 to 150 (median 30; mean 45.1 SD 32.6). Ten patients had less than 20 polyps and 9 patients had more than 100 polyps. The maximum recorded size of polyps ranged from 3 to 40 mm (mean 14.9 SD 7.5). Details on the distribution of polyps in the large intestine were obtained for 84 patients. The vast majority of them (89%) had polyposis affecting the entire colon. There was proximal colon predominance described for 6 patients (7%) and distal colorectum predominance for 3 patients (4%) (Table 1).

Histologic features of polyps in SPS patients

Of a total of 4462 polyps identified in the 100 patients, 406 were available for pathology review, molecular analysis and immunohistochemistry. Histologic characteristics of the polyps are summarized in Table 2. Most of the polyps (83%) were serrated polyps and further sub-classified into the following categories: microvesicular HP (n=156), goblet cell HP (n=25), SSA/P (n=110), SSA/P with cytological dysplasia (n=28) and TSA (n=18). In 6 SSA/Ps with cytological dysplasia, the dysplasia was of a high-grade appearance. SSA/P with or without cytological dysplasia was more frequently found in the proximal colon compared with microvesicular HPs (63% vs. 36%, *P*<0.001). The average reported size of SSA/P was greater than all HPs (mean 5.0 SD 2.7 mm vs. 3.2 SD 1.8 mm; *P*<0.001). Conventional adenomas represented 17% of all colorectal polyps reviewed in SPS patients, comprising 55 tubular adenomas and 14 tubulovillous adenomas. Tubulovillous adenomas had a significantly larger size than tubular adenomas (mean 9.8 SD 5.3 mm versus 3.9 SD 3.4 mm; *P*<0.001). High grade dysplasia was present in a minority of these polyps (6%, 4/69). The majority of conventional adenomas (63%) were located in the proximal colon.

Molecular and immunohistochemical findings associated with each polyp type

Screening for somatic mutation in *BRAF* was performed for 307 of the 406 polyps (76%) which underwent pathology review. An informative result was obtained for 270 polyps (88%). Overall, V600E *BRAF* mutations were detected for 167 polyps in 42 patients. Table 3 shows that the frequency of *BRAF* mutation, in decreasing order, was 95% in SSA/P with dysplasia, 85% in SSA/P, 76% in microvesicular HP, 54% in TSA, 3% in tubular adenoma, 0% in tubulovillous adenoma and goblet cell HP. The rate of *BRAF* mutation was significantly higher in proximally located SSA/Ps compared to distally located SSA/Ps (91% vs. 67% respectively; $P=0.029$). No other difference in *BRAF* mutation rate was found in other polyp subtypes with regard to their location (Table 3).

KRAS status was determined for 297 of the 406 polyps with pathology review with an informative result in 290 cases (98%). There were *KRAS* mutations detected for 25 polyps in 16 patients, with the following base substitution type, where available: c.34G>A in 1 case, c.34G>T in 5 cases, c.35G>A in 11 cases, and c.35G>T in 3 cases. The frequency of *KRAS* mutation for each polyp type, in decreasing order, was 50% in goblet cell HP, 45% in tubulovillous adenoma, 13% in tubular adenoma, 6% in TSA, 4% in microvesicular HP, 1% in SSA/P, 0% in SSA/P with dysplasia (Table 4). Goblet cell HPs were more likely to harbor *KRAS* mutation when located in proximal colon compared to distal colon (100% vs. 25%; $P=0.009$). No other difference in *KRAS* mutation rate was found in other polyp subtypes with regard to their location.

Mismatch repair protein loss of expression was determined in all SSA/Ps with or without dysplasia. Four SSA/Ps showed loss of MLH1/PMS2 expression; all of them were SSA/Ps with high grade dysplasia.

Association with colorectal cancer

In our cohort of 100 SPS patients, information for CRC was available for 93 patients, of whom 39 were diagnosed with CRC (42%), most of them at time of diagnosis. Table 5 shows there was no significant difference between patients with and without CRC with regard to gender, age at diagnosis, polyp distribution pattern, and largest polyp size. There was a direct but non-significant relationship between polyp count and CRC ($P = 0.06$). The presence of at least one conventional adenoma was associated with the occurrence of CRC ($P = 0.003$). No significant association was found between a villous component in conventional adenoma and the occurrence of CRC ($P = 0.54$), or between the presence of SSA/P and CRC ($P = 0.23$).

DISCUSSION

SPS is a polyposis syndrome of unknown genetic basis defined by the occurrence of multiple serrated polyps in the large bowel and associated with an increased risk of CRC (3, 5, 6, 24). This study represents one of the largest published cohorts of SPS patients rigorously selected according to the WHO criteria. We characterized the phenotype of these patients with an emphasis on histologic features and molecular alterations of 406 polyps, with a view to identifying features which predict the occurrence of CRC.

Consistent with other previously reported series (3, 17), our results showed that SPS occurs both in males and females at a wide range of ages at diagnosis from 17 to 69 years (mean 47.7). Interestingly, most patients (89%) presented with a pancolonic distribution of serrated polyps, with a total polyp number ranging from 6 to 150. This is in contrast with previous studies that reported two clinical variants (7, 13): Type 1 SPS corresponding to criterion-1 of the disease with proximal colonic location of large polyps, *BRAF* mutation and high risk of CRC; and type 2 SPS corresponding to criterion-3, with small polyps located throughout the

large intestine, *KRAS* mutation and lower risk of CRC. In our cohort, 12 patients fulfilled criterion-1 only while the remaining patients fulfilled criterion-3. There was no increased prevalence of CRC in patients with criterion-1 compared to patients with criterion-3. *KRAS* mutation was a rare event with only 25 instances observed compared with *BRAF* mutations detected in 167 polyps. Except for goblet cell HP, *KRAS* mutations were mainly identified in conventional adenomas, which were more commonly located in the proximal colon and associated with higher risk of CRC. Our data indicated that SPS as seen in a tertiary referral setting was mainly a pancolonic disease showing a continuous spectrum of polyp count and location with a median polyp count of 30. Standard white-light colonoscopy was used in the majority of the patients. The recent introduction of narrow band imaging colonoscopes have shown to improve polyp detection rate, in particular in patient with SPS (4). It is likely that the median polyp count in our series may actually be greater than 30. Moreover, the recorded size of the polyps was extracted from colonoscopy reports which may underestimate the true polyp size, especially for sessile polyps. Most large polyps were piecemeal resected and a histologic size assessment was not possible.

A more recent study has used a non-traditional classification system and suggested that there are 3 SPS phenotypes: proximal, pancolonic, and distal (17). In that study, patients were derived from clinical databases from a single institution. The age at diagnosis of the patients was considerably greater (mean 62 vs. 47 years) and the serrated polyp burden considerably less (mean 13 vs. 42) than in our study, which recruited patients from clinical genetics services. Most patients in our study had pancolonic polyposis. Since SPS patients seen in genetic services are largely referred for polyp burden, this is not unexpected. The number of criterion-1 cases in our study was, therefore, quite low in comparison, and they had a significantly increased age of onset compared to criterion-3 patients. However, when using either traditional or non-traditional classifications, no relationship was found between criteria and the presence of CRC, which is one of two significant clinical risks for SPS patients; the other being risk of CRC in first-degree relatives. This finding continues to highlight the need to develop criteria with a biological and clinical basis.

Our *BRAF* and *KRAS* mutation rates in different polyp subtypes were in agreement with most previously published series (9, 11, 14, 18, 23, 27, 32). In a recent review reporting collated data gathered from several comparable studies, *BRAF* mutation frequency was 66.3% in microvesicular HP and 83.9% in SSA/P, compared to 76% and 85% in our study, respectively (24). We identified 20 SSA/Ps with cytological dysplasia which showed the highest rate of *BRAF* mutation (95%). Moreover, loss of *MLH1*/*PMS2* expression was identified in 67% of SSA/P with high grade dysplasia while this feature was not observed in SSA/P without dysplasia or with low grade dysplasia. These results are consistent with the hypothesized progression model of serrated neoplasia in which *MLH1* methylation is a late event occurring in high grade lesions with a previously acquired *BRAF* mutation (23, 25). With regard to location in the colon, *BRAF*-mutated SSA/Ps were significantly more common in the proximal colon than in the distal colon. Spring et al previously reported similar findings in a large series of sporadic SSA/Ps (27), in which *BRAF* mutation was found in 85% of proximal SSA/P and 55% of distal SSA/P. Interestingly, goblet cell HPs harbored mutation in *KRAS* more frequently if proximally located compared to distally located (100% vs. 25%, $P=0.009$). Little is known about the significance of goblet HP and their potential for progression to advanced adenoma. In SPS patients, it possible that proximal goblet cell HPs may represent precursors of more advanced lesions with *KRAS* mutation while the majority of distal goblet cell HPs may be innocuous lesions with no potential for progression.

TSA was the least common serrated polyp in our series with 18 polyps identified. The prevalence of TSA in polyposis patients and in the general population is not well known.

This is likely due to a lack of standardized histologic criteria to diagnose TSA which can be complicated when conventional dysplasia is superimposed. The rate of mutations in *BRAF* and *KRAS* was 54% and 6% in TSA, respectively. Most previous studies reported higher rates of *KRAS* mutations and lower rates of *BRAF* mutations in TSA (19, 20, 23). This discrepancy may be partially due to diagnostic criteria heterogeneity. It may also be possible that TSAs arising in SPS patients are different from TSAs arising in the general population. In our series, the majority of TSAs (71%) was located in the proximal colon while it is more commonly found in the distal large bowel sporadically. This difference in location may also account for the higher rate of *BRAF* mutation in SPS-associated TSA compared to sporadic TSA. It was previously reported that the *BRAF* mutation occurs at higher frequency in serrated polyps from SPS patients compared to in the general population (1, 2, 18). Interestingly, Boparai et al. reported a *BRAF* mutation in all three analyzed TSAs from patients with SPS, while no *KRAS* mutation was found in this polyp subtype (2).

Another important aspect of our study was the presence of at least one conventional adenoma in 80% of individuals with SPS, which conferred an increased risk to these patients of being diagnosed with a CRC. Previous studies reported the occurrence of conventional adenoma in 69% to 85% of SPS patients (3, 10, 12). The increased risk of CRC in these patients, up to 4-times compared to SPS patients without conventional adenoma (5), supports the hypothesis that some CRC in SPS patients may develop from conventional adenoma through the *APC*-driven pathway rather than from serrated polyps through the methylation/*BRAF*-driven pathway. A *BRAF* mutation has been reported in 33% to 53% of CRC in SPS patients (2, 31), leaving the balance of CRC developing through a non-serrated pathway and potentially from a conventional adenoma.

Limitations of our study include recruitment of patients from genetics clinics rather than from the general population, with most of them referred for a suspected polyposis condition. This may account for an increased polyp count, a higher proportion of WHO criterion-3 patients and frequent presentation as a pancolonic disease. It is also possible that a large proportion of asymptomatic SPS patients may carry an average lower count of serrated polyps and may also have a decreased risk of CRC.

In summary, we report the phenotype and polyp features in one of the largest published cohorts of SPS patients. Patients with SPS referred to genetics clinics present with a pancolonic polyp distribution, a high polyp burden, and CRC in over 40%. The majority of polyps are of the serrated type with a high frequency of *BRAF* mutation, including in TSA. The high prevalence of conventional adenoma and the correlation with CRC risk have implications for colonoscopic surveillance and management of patients with SPS, particularly if endoscopic polyp control is proving difficult.

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Figure 1.

Sessile serrated adenoma/polyp with high grade cytological dysplasia from the ascending colon in a male patient diagnosed with serrated polyposis at age 36 years (A, magnification $\times 40$; B magnification $\times 100$). Traditional serrated adenoma with *BRAF* mutation (C, magnification $\times 40$). Colorectal cancer arising from a sessile serrated adenoma/polyp (D, magnification $\times 20$).

Table 1

Characteristics of 100 patients with serrated polyposis.

Characteristics	N
Recruitment sites	
Australia	40/100
New Zealand	28/100
USA	26/100
Canada	6/100
Gender	58% females
Age of diagnosis (years)	Mean 47.7; SD 14.3; median 50; range 17–69
WHO criteria 2010	
Criterion-1	12/100
Criterion-3	72/100
Criteria-1 and 3	16/100
Total polyp count	Mean 45.1; SD 32.6; median 30; range 6 – 150
Polyp distribution	
Pancolonic	75/84 (89%)
Mostly proximal	6/84 (7%)
Mostly distal	3/84 (4%)
Colorectal cancer present	39/93 (42%)
Conventional adenoma present	64/80 (80%)

Table 2

Histologic types of 406 polyps reviewed in patients with serrated polyposis.

Polyp	N	Location in Proximal Colon, n (%)	Size in mm, mean $\pm$ SD
Conventional adenoma–Total	69		
Tubular adenoma, low grade dysplasia	54	27/38 (71%)	3.8 $\pm$ 3.3
Tubular adenoma, high grade dysplasia	1	0/1 (0%)	10
Tubulovillous adenoma, low grade dysplasia	11	1/4 (25%)	9.8 $\pm$ 5.4
Tubulovillous adenoma, high grade dysplasia	3	1/3 (33%)	9.7 $\pm$ 3.9
Serrated polyps–Total	337		
Microvesicular hyperplastic polyp	156	47/132 (36%)	3.2 $\pm$ 1.8
Goblet cell hyperplastic polyp	25	7/22 (32%)	3 $\pm$ 1.6
Sessile serrated adenoma/polyp	110	55/86 (64%)	4.9 $\pm$ 2.6
Sessile serrated adenoma/polyp, low grade dysplasia	22	11/20 (55%)	5.4 $\pm$ 2.6
Sessile serrated adenoma/polyp, high grade dysplasia	6	4/5 (80%)	5.7 $\pm$ 2.9
Traditional serrated adenoma	18	12/17 (70%)	8.1 $\pm$ 5.4

Table 3

BRAF mutation according to polyp subtype and location.

Polyp subtype	<i>BRAF</i> , n (%)			P value, proximal vs. distal
	Proximal	Distal	Overall*	
Tubular adenoma	1/12 (8)	0/10 (0)	1/32 (3)	1
Tubulovillous adenoma	0/0 (0)	0/4 (0)	0/9 (0)	NA
Microvesicular hyperplastic polyp	27/36 (75)	42/53 (79)	80/105 (76)	0.64
Goblet cell hyperplastic polyp	0/5 (0)	0/12 (0)	0/20 (0)	NA
Sessile serrated adenoma/polyp	32/35 (91)	10/15 (67)	60/71 (85)	0.029
Sessile serrated adenoma/polyp with dysplasia	9/10 (90)	8/8 (100)	19/20 (95)	1
Traditional serrated adenoma	5/10 (50)	1/2 (50)	7/13 (54)	1

* The overall number for each polyp subtype also comprises polyps with unknown location;

NA: not assessable.

Table 4

KRAS mutation according to polyp subtype and location.

Polyp subtype	<i>KRAS</i> , n (%)			P value, proximal vs. distal
	Proximal	Distal	Overall*	
Tubular adenoma	1/12 (8)	1/10 (10)	4/31 (13)	1
Tubulovillous adenoma	0/1 (0)	3/5 (60)	5/11 (45)	1
Microvesicular hyperplastic polyp	1/40 (2)	3/57 (5)	4/112 (4)	0.64
Goblet cell hyperplastic polyp	5/5 (100)	3/12 (25)	10/20 (50)	0.009
Sessile serrated adenoma/polyp	0/40 (0)	1/15 (7)	1/77 (1)	0.27
Sessile serrated adenoma/polyp with dysplasia	0/11 (0)	0/8 (0)	0/22 (0)	NA
Traditional serrated adenoma	1/12 (8)	0/4 (0)	1/17 (6)	1

* The overall number for each polyp subtype also comprises polyps with unknown location;

NA: not assessable.

Table 5

Clinical features of serrated polyposis patients with and without colorectal cancer.

	Colorectal Cancer Absent	Colorectal Cancer Present	P value
Gender			
Female	33/54	22/39	0.65
Male	21/54	17/39	
Age at Diagnosis, years mean $\pm$ SD	46.8 $\pm$ 14.3	48.4 $\pm$ 14.8	0.61
Total number of polyps, n mean $\pm$ SD	39.2 $\pm$ 26.7	51.9 $\pm$ 37.8	0.06
Largest polyp size, mm mean $\pm$ SD	14.1 $\pm$ 7.1	15.1 $\pm$ 7.6	0.54
Polyp distribution			0.81
Pancolonic	41/47 (87%)	33/36 (92%)	
Mostly proximal	4/47 (9%)	2/36 (6%)	
Mostly distal	2/47 (4%)	1/36 (2%)	
Conventional adenoma present	33/47	30/31	0.003
WHO criteria 2010			0.61
Criterion-1	14/54	12/39	
Criterion-3	40/54	27/39	