Am J Cancer Res 2023;13(2):669-677
www.ajcr.us /ISSN:2156-6976/ajcr0141187

Original Article

Sporadic hyperplastic polyp associated with above-average risk of developing metachronous colorectal cancer

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Received December 17, 2022; Accepted January 8, 2023; Epub February 15, 2023; Published February 28, 2023

Abstract: Post-colonoscopy surveillance interval for colorectal polyps depends on the size, number, and pathological classification of removed polyps. The risk of sporadic hyperplastic polyps (HPs) for developing colorectal adenocarcinoma remains debatable due to limited data. We aimed to evaluate the risk of metachronous colorectal cancer (CRC) in patients with sporadic HPs. A total of 249 patients with historical HP(s) diagnosed in 2003 were included as the disease group, and 393 patients without any polyp as the control group. All historical HPs were reclassified into SSA or true HP based on the recent 2010 and 2019 World Health Organization (WHO) criteria. Polyp size was measured under light microscope. Patients developed CRC were identified from the Tumor Registry database. Each tumor was tested for DNA mismatch repair proteins (MMR) by immunohistochemistry. Results showed that 21 (8%) and 48 (19%) historical HPs were reclassified as SSAs based on the 2010 and 2019 WHO criteria, respectively. The mean polyp size of SSAs (6.7 mm) was significantly larger than HPs (3.3 mm) (P<0.0001). For polyp size ≥5 mm, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for diagnosing SSA was 90%, 90%, 46%, and 99%, respectively. Left-sided polyps with size <5 mm were 100% of HPs. Five of 249 (2%) patients developed metachronous CRC during the 14-year follow-up from 2003 to 2017, including 2 of 21 (9.5%) patients with SSA diagnosed at intervals of 2.5 and 7 years, and 3 of 228 (1.3%) patients with HP(s) at 7, 10.3, and 11.9 years. Two of 5 cancers showed MMR deficiency with concurrent loss of MLH1/PMS2. Based on the 2019 WHO criteria, the rate of developing metachronous CRC in patients with SSA (P=0.0116) and HP (P=0.0384) was significantly higher than the control group, and no significant difference was observed between patients with SSA and with HP (P=0.241) in this cohort. Patients with either SSA or HP also had higher risk of CRC than average-risk US population (P=0.0002 and 0.0001, respectively). Our data add a new line of evidence that patients with sporadic HP are associated with above-average risk of developing metachronous CRC. Post-polypectomy surveillance for sporadic HP may be adjusted in future practice given the low but increased risk of developing CRC.

Keywords: Hyperplastic polyp, sessile serrated adenoma, colonoscopy, colorectal cancer, surveillance interval

Introduction

Colorectal cancer (CRC) is the third most common type of malignancy and second leading cause of cancer-related death in the United States (US) [1]. Current colorectal cancer screening methods ultimately depend upon colonoscopy, during which the identified polyps will be removed for pathological classification and for reducing the risk of progress to CRC. Post-polypectomy surveillance strategies are determined based on the number, size, and histopathologic classification of the removed polyps. Traditional adenomatous polyps have been accepted as precursors with the potential to progress to colorectal adenocarcinoma through the "tumor suppressor pathway" [2]. In contrast, hyperplastic polyps (HPs) belong to the larger family of heterogenous "serrated polyps" [3], which were historically considered as innocent with no malignant potential [4-7]. Until the 1990s, a subset of large, serrated polyps has

shown frequent genetic mutations, including specifically BRAF mutations as well as reduced expression of DNA mismatch repair (MMR) proteins [8-13]. This subset of serrated polyps was recently recognized as precursor of sporadic colorectal cancer through microsatellite instability (MSI) and the "serrated pathway" [14-16], and was named as sessile serrated adenoma/polyp (SSA) in the 2010 World Health Organization (WHO) classification of digestive system tumors 4th edition. In addition, patients with hyperplastic polyposis syndrome showed increased risk of developing colorectal cancer and shorter surveillance is recommended than non-syndromic patients with sporadic HPs [17]. The 2010 4th edition of WHO diagnostic criteria for SSAs required at least 3 crypts showing crypt architectural distortion at the deep crypt base, while the 2019 5th WHO criteria changed to only one crypt with such distortion that is sufficient for the diagnosis of SSA [18, 19], emphasizing the awareness of the serrated polyp as precursor of CRC. Serrated polyps not meeting these criteria for SSA are considered as simple HPs which are thought to be innocent. Unfortunately, these patients are currently followed up as the average-risk population [20].

The abovementioned new understandings on serrated polyps raised several practical issues. Firstly, currently there are no consensus on whether the surveillance interval should be adjusted for the patients with historical HPs before the recognition of SSA. Secondly, the interobserver concordance among pathologists for differentiating SSAs from HPs was persistently poor to moderate in previous studies [15, 16, 18, 21, 22]. Thirdly, the risk of CRC in patients with sporadic HPs is still controversial due to limited supportive data. Therefore, in this study, we reclassified the historical HPs based on the new WHO criteria and reassessed their risk in developing metachronous CRC compared with patients without any HP.

Materials and methods

Patient selection

A total of 508 patients who had initial colonoscopy performed in 2003 for the indication of colon cancer screening were retrospectively identified from our electronic medical record using a natural language search for "hyperplastic polyp" or "hyperplastic polyps". A total of 249 patients diagnosed with only HP(s) were assigned as the disease group, while 393 patients in the same period without any polyps or record of colonic polyps were assigned as the control group. This study was approved by the Institutional Review Board. Patients with concurrent and/or previous traditional adenomas, or HPs meeting the WHO criteria of hyperplastic polyposis syndrome were excluded from this study. Patient's demographics and the endoscopic features of each polyp, including the size and anatomic site, were extracted from the electronic medical record, the endoscopy reporting system, and the pathology reporting system.

Reassessment of polyp histology

The archived hematoxylin and eosin (H&E) stained slides were reviewed by a gastrointestinal subspecialty pathologist blinded to the clinical information. All polyps were evaluated and reclassified based on either the 2010 4th WHO criteria with three distorted crypts or less stringent 2019 5th WHO criteria with one distorted crypt that showed: 1) sharp demarcation of the flat polyp from background normal mucosa, 2) saw-tooth/serrated lumen to the bottom of the crypts, and 3) variable dilatation and orientation at the crypt base forming "L, boot, inverted T, or flask" shapes. Polyps that did not meet the 2010 or 2019 WHO criteria were classified as simple true HP in each classification. The size of each polyp was measured under the light microscope from the largest fragment if more than one fragment was present on the slides.

Metachronous colorectal cancer

Patients who developed interval CRC were identified through the Tumor Registry electronic records available from 2003 through 2017. Date of cancer diagnosis was determined based on the first pathology report documenting colorectal adenocarcinoma.

Immunohistochemistry (IHC)

For all five cancer cases, one representative tumor block was selected for IHC to detect MMR protein status, using antibodies against MLH1 (clone M1, Ventana, Benchmark Ultra, Tucson, AZ), MSH2 (clone G219-1129, Ventana), MSH6 (clone 44, Ventana) and PMS2 (clone EPR3947, Sigma, St. Louis, MO). Each

Table 1. Characteristics of patients with historical HPs and reclassification of HPs

Characteristic	Historical HP n (%)	Control group n (%)	*P* value
No. of patients	249	393	
Median age (years)	56	55	0.1
Sex, n (%)			0.26
Male	108 (43)	132 (51)	
Female	141 (57)	127 (49)	
Patients with a single polyp	234 (94)	0	n/a
Patients with 2-3 polyps	15 (6)	0	n/a

n/a: not applicable.

tumor block was sectioned into 5-μm thick sections for IHC. Clinically validated antigen retrieval and IHC assays were performed as follows: MLH1 antigen retrieval in pH 8.0 for 24 minutes, antibody for 28 minutes, amplification for 4 minutes; MSH2 antigen retrieval in pH 8.0 for 21 minutes, antibody for 20 minutes; MSH6 antigen retrieval in pH 8.0 for 24 minutes, antibody for 16 minutes; PMS2 antigen retrieval in pH 8.0 for 64 minutes, antibody for 32 minutes, amplification for 8 minutes, using an autostainer (Ventana).

Statistical analysis

Python with SciPy library was used for all statistical analyses, including Fisher's exact test for comparison of categorical data and two-tailed unpaired T-test for continuous data and for comparison of polyp size. The incidence of CRC was compared between the disease and control group, and between the disease and the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) data for general average-risk US population of 2014 [23]. The difference was considered statistically significant at $P<0.05$.

Results

Demographics and reassessment of historical hyperplastic polyps

The demographic data of the disease and control group were shown in **Table 1**. In disease group, a total of 234 (94%) patients had a single polyp, the remaining 15 patients had up to three polyps, and therefore all met the definition of non-syndromic or sporadic HPs. The reclassification found that 48 (19%) patients with historical HPs were SSAs based on the 2019 5th edition WHO criteria (1-crypt distortion), and 21 (8%) of the polyps were SSAs based on the 2010 4th edition WHO criteria (3-crypt distortion), respectively (**Table 2**). Most of the historical HPs (81%) was true HPs based on the 2019 WHO classification criteria. There was no significant difference in the age and gender between patients with SSAs or HPs in each WHO classification. The distinctive morphological features of serrated polyps were crypt lumen serration with "saw-tooth" configuration starting at the superficial layer with or without deep crypt serration (**Figure 1**).

Only 43 cases had a recorded polyp size in the electronic endoscopic reports. The polyp size was then measured under the light microscopy, with the largest fragment measured when more than one fragment was present in some cases. Overall, the microscopically measured polyp size ranged from 1.5 to 10 mm. As expected, the mean polyp size was significantly larger for the SSAs based on both the 2010 WHO criteria (6.7 mm) and 2019 WHO criteria (5.5 mm) than the HPs (3.3 and 3.1 mm, respectively) ($P<0.0001$) (**Table 2**). With a polyp size cutoff of ≥5 mm, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for a diagnosis of SSA (using 2010 WHO criteria) was 90%, 90%, 46%, and 99%, respectively. In other words, the chance for a polyp smaller than 5 mm being an HP was 99%. For a polyp larger than 5 mm, only 46% chance was an SSA, and 54% chance was HP.

The location of the polyps was defined as "right-sided" if they were from the cecum, ascending colon or transverse, and as "left-sided" if they were from the descending, sigmoid or rectum. In this cohort, when a poly was left-sided and smaller than 5 mm, it had a 100% chance of being simple HP.

Incidence of metachronous colorectal cancer

Five of 249 (2%) patients in the disease group developed single-site CRC during the 14-year follow-up from 2003 to 2017, whereas none of the 393 patients in the control group developed CRC. In the disease group, two of 48 (4.2%) patients with SSAs based on the 2019 WHO criteria were diagnosed with CRC at inter-

Table 2. Reclassification of polyps initially diagnosed as HPs based on 2010 and 2019 WHO criteria

Reclassification criteria	SSA		HP	
	n (%)	Size (mm, mean ± SD)	n (%)	Size (mm, mean ± SD)
WHO criteria 2010	21 (8)	6.7±0.2*	228 (92)	3.3±0.1
WHO criteria 2019	48 (19)	5.5±0.1*	201 (81)	3.1±0.1

*The poly size of SSA comparing to that of HP was significantly different (P<0.0001).

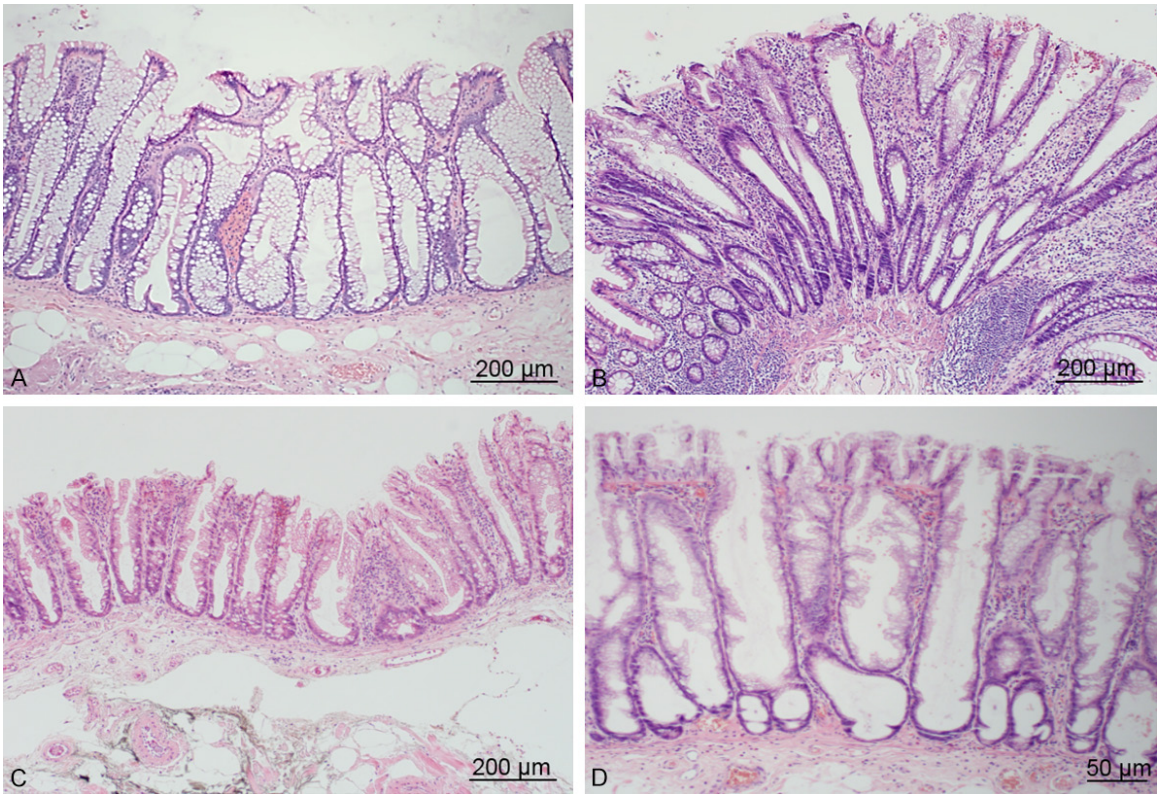

Figure 1. Spectrum of histomorphology of serrated polyps. HP with abundant goblet cells and less crypt luminal serration (A). HP with gastric foveolar type mucinous cytoplasm and more crypt serration (B). SSAs with at least 1 deep crypt architectural distortion forming "L, inverted T, flask, and boot" shapes (C, D). Original magnifications: 40× (A-C) and 100× (D).

vals of 2.5 and 7 years, and 3 of 201 (1.5%) among patients with true HP were diagnosed with CRC at intervals of 7, 10.3, and 11.9 years (**Table 3**). Only one CRC was from the same location as the initial serrated polyp. No intervening colonoscopy procedures were performed per our electronic medical record for all 5 patients who developed metachronous CRC. Two of 5 (40%) CRC showed microsatellite high (MSI-H) phenotype supported by concurrent loss of DNA mismatch protein of MLH1 and PMS2 in the cancer cells by IHC (**Figure 2**).

Compared with the control group, the disease group of patients with historical HPs carried a significantly higher risk of developing metachronous CRC (P=0.0087) (**Table 4**). After reclassification of the historical HPs based on the 2019 WHO criteria, patients with either SSA or true HP had a significantly higher risk of developing CRC (P=0.0116 and 0.0384, respectively) than the control group (**Table 4**), and no significant difference was observed between the SSA and HP (P=0.241).

We further compared the incidence of CRC in the disease group to the general population with average-risk from The Surveillance, Epidemiology, and End Results (SEER). Based on the SEER data, the age-adjusted incidence rate of CRC in all age groups was 39 per 100,000 (0.039%) in the United States in 2014 [23]. When compared with the incidence of the 2014 SEER data, the incidence of CRC in all 249

Table 3. Five patients with initial diagnosis of HPs developed CRC with a high frequency of MMR deficiency

Reclassified polyp type*	Polyp fragment size (mm)	Interval to CRC (years)	Location of CRC	MMR loss
SSA	9	7	Transverse	No
SSA	3.5	2.5	Ascending	Yes (MLH1-/PMS2-)
HP	3	7	Sigmoid	No
HP	4	11.9	Transverse	Yes (MLH1-/PMS2-)
HP	3	10.3	Sigmoid	No

*Reclassification based on WHO 2019 criteria.

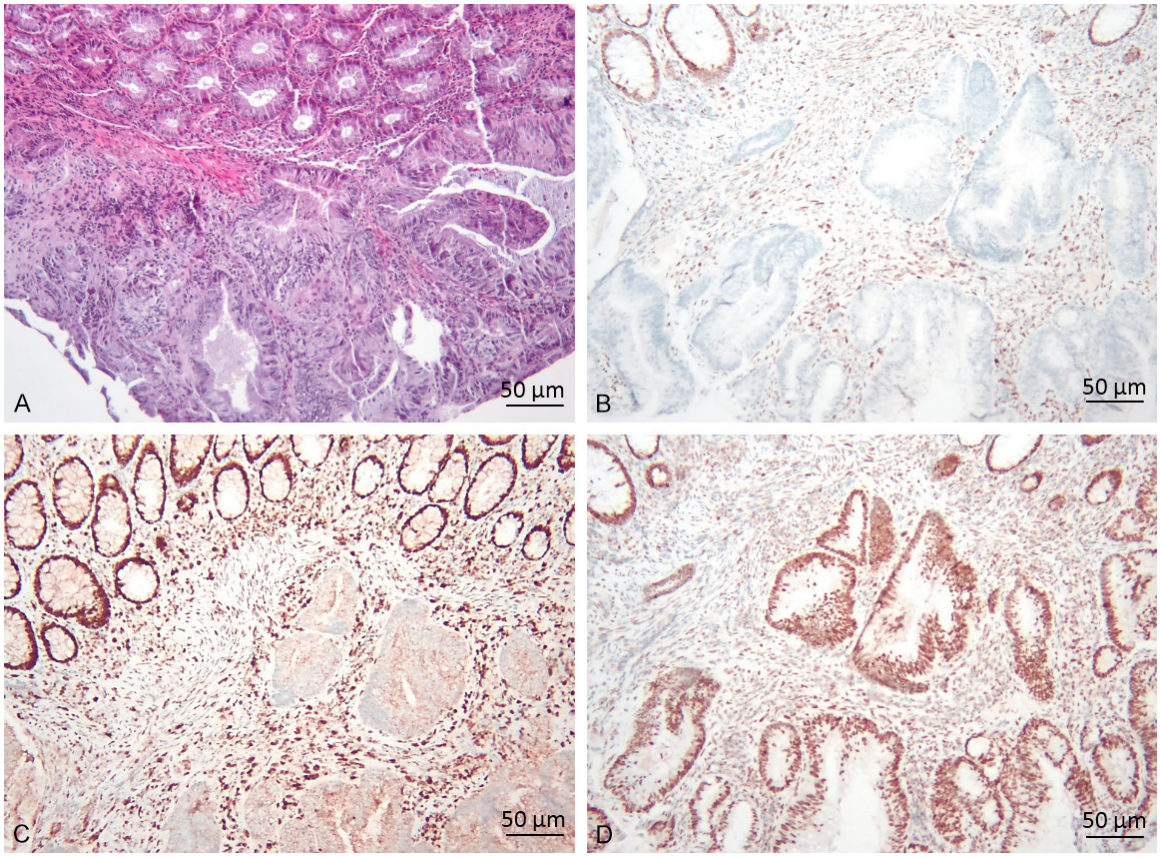

Figure 2. Representative colon cancers with MMR deficiency. (A) Hematoxylin and eosin staining of cancer cells. (B) Loss of nuclear protein of MLH1 in cancer cells in contrast to intact protein expression in the normal epithelium and inflammatory cells. (C) Loss of nuclear protein of PMS2 in cancer cells. (D) Intact nuclear protein of MSH6 in cancer cells. Original magnifications (A-D): 100×.

patients with historical HPs, patients with reclassified SSA based on the 2019 WHO criteria, or patients with true HP was significantly higher than the average-risk US population (P<0.0001, P=0.0002, and P=0.0001, respectively) (**Table 4**).

Discussion

In this cohort, 19% of historical HPs diagnosed in 2003 were reclassified as SSAs based on the 2019 5th edition WHO diagnostic criteria, and 8% were SSAs based on the more stringent 2010 4th edition WHO criteria. This rate of SSA reclassification based on the new WHO criteria was similar to previously reported rates of reclassification of HPs in the literature (rate ranging from 6.9% to 65%) [24-28]. Our data also demonstrated that historical HPs reclassified as SSAs were significantly larger than the true HPs, even though the polyp size was not measured by the gastroenterologists histori-

Table 4. Rate of development of colorectal carcinoma in patients with serrated polyps

Parameter	Historical HP n (%)	SSA, Reclassified per 2010 WHO n (%)	HP, Reclassified per 2010 WHO n (%)	SSA, Reclassified per 2019 WHO n (%)	HP, Reclassified per 2019 WHO n (%)	Control group n (%)	SEER
No. of patients	249	21 (8)	228 (92)	48 (19)	201 (81)	393	100,000
CRC							
Yes	5 (2.0)	2 (9.5)	3 (1.3)	2 (4.2)	3 (1.5)	0 (0)	39 (0)
No	244 (98.0)	19 (90.5)	225 (98.7)	46 (95.8)	198 (98.5)	393 (100)	99961 (100)
P value	0.0087 vs Control	0.0025 vs Control	0.0049 vs Control	0.0116 vs Control	0.0384 vs control	n/a	n/a
	<0.0001 vs SEER	<0.0001 vs SEER	0.0001 vs SEER	0.0002 vs SEER	0.0001 vs SEER		
		0.0581 vs HP		0.241 vs HP			

cally but was measured under the light microscopy in our study. Left-sided serrated polyps <5 mm were 100% true HPs. On the other hand, one should be aware that not all large, serrated polyps were SSA, since our data showed that serrated polyps larger than 5 mm had only 46% chance of SSAs, and 54% chance of HPs. When surgical pathologists diagnose the serrated polyps, some might use the polyp size and location to adjust the diagnosis of SSA that has borderline or subtle histological features at the deep crypts. Others might review multiple tissue sections to find unequivocal crypt distortion to render the final diagnosis of SSA. This interpersonal variation may partially explain why interobserver concordance among pathologists for diagnosing SSAs is currently suboptimal.

Recent studies have suggested that some biomarkers such as MUC6, Annexin 10, Hes1, and Progastrin may be helpful to distinguish SSA from HP [29-31]. Although the expression of some biomarkers was higher in SSA than HP, these markers seemed to show suboptimal specificity for SSA, since some HPs also expressed these markers.

Interestingly, among the 5 patients who developed CRC, one patient with SSA and one patient with HP showed MMR deficiency with concurrent loss of MLH1 and PMS2 in the tumor cells, suggesting that these two tumors have similar genetic pathway. Molecular studies and/or next generation sequencing (NGS) have been performed in serrated polyps in the literature [10, 29, 30], and to our knowledge, molecular tests are still not cost-effective for daily practice. Even HPs harbor similar genetic alterations seen in SSAs such as *BRAF* and less frequently *KRAS* mutations [10, 32, 33], supporting the hypothesis that HPs and SSAs are a heterogenous group of precursors of CRC in the same "serrated pathway" [34]. In other words, HPs are mostly early serrated neoplasm carrying less genetic mutations, whereas SSA are late and more advanced lesions harboring more mutations, although large-size HPs also exist. Interestingly, our data showed that not only patients with SSA increased the rate of developing metachronous CRC, but patients with sporadic HPs also had a higher risk of metachronous CRC compared to the control group and general US population with average risk. It is a reasonable argument that patients with only HP(s) on the initial colonoscopy can still have CRC through other high-risk precursor lesions newly developed during the regular interval before the follow-up surveillance colonoscopy.

The 2019 5th edition of WHO classification of the serrated polyps is less stringent requiring only one crypt (rather than three crypts in 2010 4th edition WHO) with unequivocal architectural distortion for the diagnosis of SSA. The 2019 WHO criteria will certainly increase the frequency of pathological diagnosis of SSA that was previously insufficient for the diagnosis. This official change reflects the importance and awareness of recognizing more serrated polyps as precursors of developing CRC. Then the remaining question needs to be addressed is: what would be the best strategy to manage the sporadic HPs among the same family of serrated polyps?

The risk for malignant transformation in traditional adenomatous polyps has been well recognized [35, 36], and post-polypectomy surveillance interval for these traditional adenomas has been well-established. In addition, polyp number, size, and "advanced histology" of the traditional adenoma have been accepted as additional criteria to consider for the post-polypectomy surveillance intervals. For example,

5-10 small adenomas (<10 mm), adenomas over 10 mm, or those with high-grade dysplasia ("advanced histology") have short interval of 3 years [20, 34, 35], while 1-2 small tubular adenomas (<6 mm) may not be associated with significantly increased risk for cancer after polypectomy and an interval of 7-10 years is currently recommended [37, 38]. With recent advancement of research, SSA has been recognized as an important precursor of CRC in a different genetic pathway. In the 2020 guideline, post-polypectomy surveillance interval for 1-2 SSAs (<10 mm) is 5-10 years, slightly shorter than 1-2 small traditional adenomas. Patients with large HPs >10 mm are recommended to have follow-up surveillance in 3-5 years. However, the guideline recommendation for patients with <20 small (<10 mm) HPs remains the same as normal colonoscopy without any adenomatous polyp (10 years) [38]. Interestingly, Hamoudah T and colleagues have shown similar findings to our data in a retrospective cohort of 482 patients who had proximal small HPs, and results showed that patients with proximal small HPs had significantly higher rate of synchronous advanced neoplasm than patients without any proximal HPs [39]. Our data showed that 2 patients with SSA developed CRC at shorter intervals of 2.5 and 7 years, and 3 patients with HP(s) developed CRC at longer intervals of 7, 10.3, and 11.9 years. Our study added another line of evidence that patients with HP alone may have above-average risk of developing metachronous CRC and small HPs may not be ignored as innocent finding. It is tempting to suggest that small HPs regardless of their anatomic site are mostly small and may be analogous to the sporadic small incipient adenomas with a relatively lower cancer risk and can be followed-up similarly as small traditional adenomas, while SSAs and larger HPs are similar to large traditional adenomas and associated with higher risk for CRC that require closer follow-up.

Conclusion

More and more data suggest that all serrated polyps including small HPs carry significant genetic mutations and should be considered as neoplastic growth at different stage of progression, and therefore are associated with a spectrum of risk of developing metachronous CRC or synchronous advanced neoplasia. The risk of CRC from sporadic HPs is higher than traditionally thought. Post-polypectomy surveillance for non-syndromic patients with HPs may follow that of sporadic traditional adenomas in future practice, given their low but above-average risk of developing CRC. In addition, documentation of any polyp size during endoscopy becomes a trend and may prove critical for surveillance guidelines for all precursors of CRC. We understand the limitation of our study due to relatively small size of this cohort. More investigations from other institutions and prospective studies may be necessary to provide more evidence for this conclusion.

Acknowledgements

We are grateful for Alexa M. Buskey from the University of Vermont Medical Center (UVM) and Cara Strock and Karen Dresser from the University of Massachusetts (UMASS) Memorial Health Care for their technical support. Initial work was supported by the internal research fund at the Department of Pathology and Laboratory Medicine at UVM.

This project was approved by Institutional Review Board at UVM (IRB # CHRMS: 16-603) and at UMASS IRB# H00022173).

Disclosure of conflict of interest

None.

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