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PREVENTION AND EARLY DETECTION (R BENAMOUZIG, SECTION EDITOR)

The Importance of Increased Serrated Polyp Detection Rate

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Abstract Based on the World Health Organization (WHO) criteria, serrated lesions were classified as sessile serrated adenoma/polyp (SSA/P), traditional serrated adenoma (TSA), and hyperplastic polyp (HP). Large serrated lesions are found to be associated with advanced colonic adenoma in the colon. Serrated lesions of the colorectum are believed to account for 15–20 % of all colorectal cancers via the "serrated neoplastic pathway" with SSA/P being the main precursor lesion. Serrated lesions are also thought to account for around 30 % of cancers that develop after a negative colonoscopy or the interval cancers. While serrated lesions are often flat or sessile and inconspicuous on conventional white light colonoscopy, missed lesions are not uncommon. Increased detection of serrated lesions may potentially reduce the incidence and mortality of colorectal cancers, especially the risk of interval cancers. Further research shall be directed to improve detection of serrated lesions by colonoscopy.

Keywords Serrated lesion · Sessile serrated adenoma/polyp · Colonoscopy · Colorectal cancer

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Introduction

Colorectal cancer (CRC) is a major cause of cancer-related morbidity and mortality worldwide. In the USA, it is the third most common diagnosed cancer and third leading cause of cancer death [1]. Although CRC is generally considered to be a western disease, the incidence of CRC is also rising at an alarming rate in many Asian countries. CRC has emerged as the top cancer in Korea with the highest age-standardized incidence rate in the world (45 per 100,000 population) [2].

Conventionally, CRC was believed to develop through the adenoma-carcinoma sequence with the continuous accumulation of genetic alterations [3]. Recently, evidence showed that around 10–20 % of CRCs developed through an alternative pathway called the serrated neoplastic pathway that arise from serrated lesions [4]. Certain subtypes of serrated lesions, such as sessile serrated adenoma/polyp (SSA/P), are considered to have higher potential for malignant transformation.

Serrated neoplastic pathway is also considered to have an important role in patients who developed CRCs after colonoscopy, often called postcolonoscopy/interval cancers [5–10]. Thus, identification and complete removal of these lesions appears to be instrumental in reducing CRC development. This review will discuss the pathology of serrated lesions, the association of serrated lesions with advanced neoplasia, and suggest ways to improve detection of these lesions.

Clinicopathologic Presentation of Serrated Lesions

Serrated polyps are a group of heterogeneous lesions which are characterized by the serrated ("saw-tooth") architecture of epithelium that lines the colonic crypts. There was much confusion in the nomenclature in the past. In 2010, the World

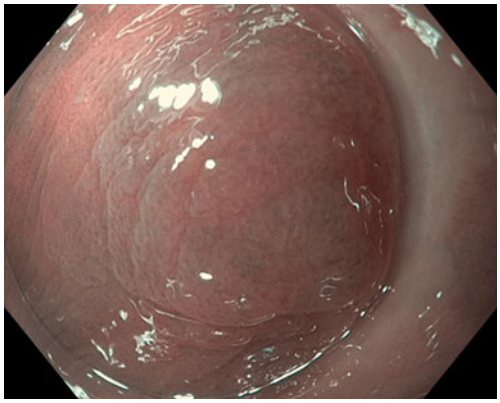

Fig. 1 Sessile serrated adenoma/polyp examined under narrow band imaging: the polyp is flat, has an indistinctive border and a cloud-like surface

Health Organization published a statement to standardize the terminology and diagnostic criteria of sporadic serrated lesions [11]. Serrated lesions are now classified into hyperplastic polyp (HP), sessile serrated adenoma or polyp (SSA/P), and traditional serrated adenoma (TSA).

Hyperplastic polyp is the most prevalent subtype of serrated lesions. Around one-quarter of average-risk individuals have at least one hyperplastic polyp in the colon. They are characterized by elongation of intestinal crypts, with serration of the upper half of the crypt. Cytological dysplasia does not occur in HPs. Microvesicular hyperplastic polyps (MVHPs) and goblet cell hyperplastic polyps (GCHPs) are the two most common subtypes of HPs. Both are more often located in the distal colon [12, 13].

Sessile serrated adenoma/polyps are the second commonest subtype of serrated lesions. It is usually flat or sessile and located in the proximal colon [13], which accounted for around 20–35 % of all serrated lesions. In SSA/P, the abnormal architecture characteristics are secondary to abnormal proliferation. Crypt proliferation leads to increase in crypts being asymmetric of T-shape or inverted L-shape. The other histological features are hyperserration throughout the base or in the crypts and muscle pseudoinvasion [4, 14]. SSA/Ps can be further subdivided into SSA/Ps without dysplasia and SSA/Ps with dysplasia, which is likely to indicate a more aggressive behavior [11]. Dysplastic component is present in around 15–30 % of SSA/Ps [12, 15, 16].

Traditional serrated adenoma is a rare subtype of serrated lesions. The term "serrated adenoma" was first introduced by Longacre et al. in 1990 [17]. It accounted for <1 % of serrated lesions and are most often located in the distal colon. Unlike SSA/Ps, TSA can be sessile or pedunculated. TSA has complex and distorted tubulovillous and villous configuration. Prominent serration and ectopic crypt foci are the other histological characteristics of TSA. Dysplasia is present by definition [18•, 19]. These features could allow distinction of TSA from other serrated lesions.

In contrast, hyperplastic polyposis syndrome (HPS), or serrated polyposis syndrome (SPS), is a rare form of polyposis syndrome, which was associated with even higher risk of CRCs. Torlakovic et al. showed that the polyps in patient with HPS are more similar to serrated adenomas rather than conventional HPs, further suggesting the link between serrated adenomas and cancer [20].

Serrated Neoplastic Pathway

CRCs develop through accumulation of genetic alteration and molecular changes. There are at least three proposed molecular mechanisms of colorectal tumorigenesis: chromosomal instability, defective mismatch repair gene leading to microsatellite instability (MSI) and epigenetic DNA promoter hypermethylation leading to CpG island methylator phenotype (CIMP). The serrated neoplastic pathway is often referred to as CIMP pathway or the sporadic MSI pathway [18•]. Hypermethylation of CpG islands in the promotor regions of the tumor suppressor genes and mutation of *BRAF* proto-oncogene are the most important molecular alterations in this pathway [13]. Hypermethylation of CpG island within the promotor region leads to reduced expression of a gene [21], and in the case of tumor suppressor genes, promotes carcinogenesis. To determine the CIMP status, a panel of five genes will be assessed and hypermethylation of at least three genes is considered to be CIMP-high [22]. *BRAF* functions as a molecular switch in the MAPK/ERK pathway, which regulates cell proliferation, differentiation, and survival. Mutation in *BRAF* will result in uncontrolled cell proliferation leading to neoplastic process [23, 24]. The mechanism leading to CIMP-high/positive status is not fully understood, but *BRAF* mutation may have a role [13]. Evidence showed that *BRAF* mutations are strongly associated with CIMP status in CRC [24, 25].

CIMP-high, *BRAF* mutant CRC was hypothesized to arise and progress through this sequence: colonic mucosa to MVHP, to SSA/P (or colonic mucosa directly to SSA/P), to SSA/P with dysplasia, then to CRC. This is based on the relative prevalence of *BRAF* mutation and CIMP-high phenotype in various serrated lesions [13, 26–28]. However, direct evidence to confirm the hypothesis does not exist.

TSA is less common than SSA/P and there is few data on its molecular profile. TSA is group of more heterogeneous lesion in terms of morphology and molecular characteristics. The frequency of *KRAS* and *BRAF* mutations varied among different subtypes of TSA. The mechanism of progression of TSA to carcinoma and the association with serrated neoplastic pathway is largely unclear [29, 30].

Detection of Serrated Lesions

Polyp Characteristics

Hyperplastic polyps are usually diminutive in size and most frequently found in the rectosigmoid colon, which are usually sessile or flat with a pale color. Small (<5 mm) hyperplastic polyps in the rectosigmoid colon are common and are generally considered to be benign [13]. On the other hand, SSA/Ps and TSA deserve more attention because of their malignant potential.

Pereya et al. showed that a vast majority (94 %) of SSA/Ps was located in the right-sided colon. Around half of the SSA/Ps is flat. Similar findings were reported in other studies. SSA/Ps are typically larger than HPs. The average size of SSA/Ps is 10.3 mm and 14 % of lesions are greater than or equal to 20 mm [31•, 32, 33].

One of the distinctive features of SSA/P is the presence of a mucus cap, which comprised of a layer of mucus adherent to the surface of the lesion, giving the lesion a yellow or rust color on white light endoscopy. This feature was considered the most prevalent distinctive feature of SSA/Ps and it is present in around 40–60 % of SSA/Ps [18•, 31•, 32, 34, 35]. Apart from the presence of mucus cap, peripheral rim of debris or bubbles and lesions obscuring underlying submucosal blood vessel and nodular surface are also distinctive features of SSA/Ps [32]. Other endoscopic features that are independently associated with SSA/Ps are lesions in the proximal colon, flat morphology, and red-colored surface [31•]. [15]. Unlike SSA/Ps, TSAs are usually located in the distal colon. They are often >5 mm and can be pedunculated or sessile [13].

Ways to Improve Detection of Serrated Lesions

Apart from conventional white light colonoscopy, the use of image enhanced colonoscopy such as narrow band imaging (NBI) can enhance the visibility of SSA/Ps (Fig. 1). Hazewinkel et al. showed that cloud-like surface, indistinct border, irregular shape, and dark spots inside crypts are independent predictors of SSA/Ps on NBI examination. Combining these endoscopic features on NBI examination, the accuracy of differentiating SSA/Ps from HPs is 93 % [36•]. A Dutch group developed the "Workgroup serrAted polypS and Polyposis (WASP)" classification for optical diagnosis of different polyps including adenoma, SSA/Ps, and HPs. It combined the NBI International Colorectal Endoscopic classification and criteria for differentiation of SSA/Ps described by Hazewinkel et al. [36•] in a stepwise approach. The use of NBI and the WASP classification may improve the diagnostic accuracy of serrated lesions by colonoscopy. It is especially useful in determining whether a diminutive lesion can be left in situ safely as the negative predictive value for diminutive neoplastic lesions (adenoma and SSA/Ps) was 91 % [37].

Type II Kudo pit pattern is frequently described in SSA/Ps [32, 33]. A Japanese group proposed a new Type II open-shape pit pattern (Type II-O). This is similar to the conventional Type II pattern, but the pits are wider and more roundish in shape. This pit pattern is highly predictive of SSA/Ps with specificity of 97.3 % [38]. Recent evidence showed that combination of NBI with optical magnification can allow for more detailed examination of polyps and are potentially useful to discriminate SSA/Ps from other lesions [39, 40].

These lesions, such as SSA/Ps, are easily masked by feces, debris, or non-transparent fluid in the colon [33], which illustrates the importance of satisfactory bowel preparation. A recent retrospective study showed that cap-assisted colonoscopy detected more significant serrated polyps (defined as SSA/Ps, TSA, proximal HPs and HPs ≥ 1 cm) than colonoscopy performed without a cap [41].

In real-life clinical practices, the detection rates of serrated lesions can be highly variable and operator dependent. A study showed that the detection rates for proximal serrated lesions ranged from 0–9.8 % in different centers. Another study from the Netherlands showed that the detection rate of proximal serrated polyps differed significantly among endoscopists, ranging from 6 to 22 % [42, 43]. In order to increase the detection rate of serrated lesions, endoscopists should have training on the features of these lesions. As there is a strong correlation between adenoma detection rates and detection rates of serrated lesions [44, 45], endoscopist could measure their adenoma detection rates as a surrogate marker for detection of serrated lesions. One recent study showed that longer withdrawal time was also associated with higher detection rate of proximal serrated lesions [46].

Association of Serrated Lesions With Advanced Neoplasia

Multiple studies have demonstrated that serrated lesions, especially the large or proximal serrated lesions, are associated with advanced colonic neoplasm [12, 47–53, 54•]. In a large cohort of asymptomatic average-risk subjects undergoing screening colonoscopy, the presence of large (≥1 cm) serrated polyp was found to be an independent predictor of advanced colorectal neoplasia with an odds ratio (OR) of 3.24. Both right and left-sided serrated polyps were associated with advanced colorectal neoplasia [47]. Another study involving 5059 average-risk patients undergoing screening colonoscopy showed that 6.5 % patients had proximal serrated polyps while 1.8 % patients had large (≥1 cm) serrated polyps. Large serrated polyps were associated with advanced colorectal neoplasia (OR 2.49), regardless of their proximal (OR 4.15) or distal (OR 2.61) locations [51]. There were similar results with studies involving Asian patients. A study involving 1282 Chinese patients undergoing screening colonoscopies showed that the

presence of advanced neoplasia was associated with the presence of large or proximal serrated polyps (OR 1.8) [52]. Another study involving average-risk Chinese undergoing colonoscopy showed that the independent predictors of synchronous advanced colorectal neoplasia were the presence of SSA (OR 4.52), proximal serrated polyps (OR 2.23), hyperplastic polyps (OR 1.66), and the presence of three or more serrated polyps (OR 4.86) [53].

A multicenter study in Japan showed that the presence of large (≥10 mm) serrated polyps was associated with both advanced neoplasia (OR 4.01) and CRC (OR 3.34) [48]. Schreiner et al. showed that the presence of proximal serrated polyp is associated with higher chance of interval neoplasia at surveillance colonoscopy (OR 3.14) [55]. Although there is considerable heterogeneity among these studies, a recent meta-analysis confirmed the association between proximal and large serrated polyps with advanced neoplasia [54•].

Association of Serrated Lesions With Cancer

The natural history of serrated polyp is uncertain. However, there were case reports describing the rather unexpected rapid development of CRCs from serrated lesions. Two Japanese case reports described progression of a 15-mm ascending colon SSA into cancer in 8 months [56] and a 20-mm SSA with severe dysplasia progressed to adenocarcinoma in 2 years [57]. On the other hand, some evidences showed that serrated lesions progressed slowly and some serrated lesions might not turn malignant even left in situ for a median of 11 years [58]. A study that evaluated 2416 SSAs showed that the median age of patient increases in the following order: SSA without dysplasia (61 years), SSA with low-grade dysplasia (66 years), SSA with high-grade dysplasia (72 years), and SSA with adenocarcinoma (76 years). Based on this, the authors indirectly concluded that SSA progressed to cancer in a stepwise manner in a period over 10–15 years [16]. A case series showed that serrated adenocarcinoma was often accompanied by synchronous residual serrated adenomas and remote serrated adenoma, suggesting a possible etiological link between serrated adenoma and serrated adenocarcinoma [59].

Although evidence showed that some serrated lesions may not progress to cancer, its presence was associated with a higher risk of CRC. A large population-based trial involving 12,955 patients screened with flexible sigmoidoscopy showed that those with large serrated polyps, as compared to those without polyps, have higher risk of developing CRC (hazard ratio of 2.5) over a median of 10.9 years [58]. Hiroaka et al. showed that the presence of large, serrated polyps was associated with synchronous CRC (OR 3.34) [48].

The risk of CRCs varies in patients harboring different types of serrated lesions. A study showed that the incidence of subsequent CRCs was significantly higher in patients with SSAs at baseline than those with HPs at baseline (12.5 vs 1.8 %). In this study, 15 % of patients with SSA at baseline developed subsequent CRCs or adenomatous polyps with high-grade dysplasia [60].

Interval Cancers

There are overwhelming evidences that colonoscopy and polypectomy significantly reduce the incidence and mortality of CRC. However, recent studies showed that the protection may be more prominent for left side than right side colonic cancer. In fact, some studies showed that there may be no significant protection from right-side cancer by colonoscopy [61–65].

SSA/P, an important precursor lesion in serrated pathway, is more often diagnosed in the proximal colon. SSA/P is often flat and inconspicuous on endoscopy [49, 66] and can be easily missed. With increased recognition in the recent years, the reported prevalence of SSA/Ps has increased, indicating some of these lesions were missed in the past [44, 67, 68]. Pohl et al. showed that around one third of SSA/Ps and almost half of the serrated lesions of 10–20 mm were incompletely resected [69•]. An endoscopist may also fail to correctly size the entire polyp because of the indistinct border, resulting in incomplete removal. Snare polypectomy may also be inadequate in the larger, sessile/flat lesions, leaving residual tissue. More specialized technique such as endoscopic mucosal resection (EMR) may be required for complete removal of these lesions. Even with endoscopic mucosal resection, residual polyp was identified in 8.7 % of patients with SSA/Ps [70]. As the growth rate of serrated lesions is variable, some of these residual lesions may potentially grow into malignant tumor before the usual surveillance interval.

Interval cancers shared similar biology with serrated lesions such as CIMP status and MSI [71, 72]. Around 30 % of interval cancers are thought to originate from serrated lesions. A study showed that CIMP positive status was present in 57 % of interval cancers, as compared to 33 % of non-interval cancers ($p = 0.004$) [72]. In another study, MSI was found in 30.4 % of interval cancers compared to 10.3 % of non-interval cancers ($p = 0.03$). After adjusting for age, interval cancers were 3.7 times more likely to have MSI than are non-interval cancers [71]. The similarity of biology in serrated lesions and interval cancers suggested that serrated neoplastic pathway may have important role in the development of these cancers.

The nomenclature and diagnostic criteria of serrated lesions are evolving over the years, which lead to inconsistency on

reporting of different serrated lesions. Payne et al. showed that the reporting rate of SSA/Ps is highly variable among different centers, ranging from 0–9.8 %. Some pathologists never reported proximal serrated lesions such as SSA/Ps, even in high-volume centers [42]. Another study showed that around one third of the HPs (>5 mm) diagnosed between 2003 and 2008 could be reclassified as SSA/Ps after a review in 2011 [73]. Underreporting of important precursor lesions, such as SSA/Ps, could potentially lead to inappropriate surveillance interval, thus contributing to postcolonoscopy/interval cancers.

Current Management Strategy

Owing to the malignant potential, it is recommended that all serrated lesions proximal to the sigmoid colon should be fully resected. In addition, all serrated lesions of greater than 5 mm in size in the rectosigmoid region should also be resected [18•].

As the natural history of different types of serrated lesions is largely unclear, surveillance recommendations are mainly based on expert opinion [18•, 74, 75]. The current recommended surveillance intervals for various serrated lesions by the U.S. Multi-Society Task Force Guideline (2012) and the expert consensus opinion by Rex et al. were summarized in Table 1, which are largely dependent on the size, multiplicity, and the histology of the serrated lesions..

Table 1 Current recommended surveillance intervals for different serrated lesions

	Year	Serrated lesions	Surveillance interval
US Multi-Society Task Force [74]	2012	• SSA/P <10 mm, without cytologic dysplasia	5 years
		• SSA/P, ≥10 mm • SSA/P with cytological dysplasia	3 years
		• TSA	
		• Serrated polyposis syndrome	1 years
Expert consensus opinion by Rex et al. [18•]	2012	• Any number of HPs, <10 mm, in rectosigmoid	10 years
		• ≤3 HPs, ≤5 mm, proximal to sigmoid	
		• ≥4 HPs, any size, proximal to sigmoid • ≥1 HPs, >5 mm, proximal to sigmoid	5 years
		• <3 SSA/P or TSA, <10 mm	
		• 1 SSA/P or TSA, ≥ 10 mm • ≥3 SSA/P or TSA, < 10 mm	3 years
		• ≥2 SSA/P, ≥ 10 mm • Any number of SSA/P with dysplasia	1–3 years

Conclusion

Serrated neoplastic pathway is now generally considered to be another important pathway of colorectal carcinogenesis. Certain subtypes of serrated lesions, large SSA/Ps and TSAs, are of higher malignant potential. While there are increasing evidences that these lesions are associated with advanced neoplasia and CRCs, high-quality longitudinal studies on the natural history of serrated lesions are lacking. Some of the sessile lesions, such as SSA/Ps, are often difficult to detect because of its unique endoscopic features. Increased recognition and awareness among endoscopist is necessary to improve the detection rate. Newer techniques such as NBI and magnification endoscopy can help better characterize the lesion and improve detection. Accurate pathological diagnosis is of equal importance, and appropriate surveillance interval can then be recommended. As serrated lesions contribute to a significant proportion of CRCs, especially proximal CRCs and interval cancer, increased detection and complete removal of these precursor lesions will be the key to further enhance the efficacy of colonoscopy in preventing CRCs.

Compliance with Ethical Standards

Conflict of Interest Yuk Fai Lam and Wai K. Leung declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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