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Review Article

Diagnosis, epidemiology and management of serrated polyposis syndrome: a comprehensive review of the literature

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Abstract: Serrated polyp associated colorectal cancer (CRC) develops from an alternative mechanism of colorectal carcinogenesis and accounts for 10-15% of all CRC. Serrated polyposis syndrome (SPS) occurs infrequently and is characterized by the occurrence of multiple serrated polyps (hyperplastic polyps, sessile serrated lesions and traditional serrated adenomas) throughout the colon and/or rectum and has been strongly associated with development of CRC. However, SPS is frequently unrecognized, due to application failure of the WHO criteria regarding diagnosis and/or missed serrated polyps during endoscopy. The management of SPS requires surveillance at regular intervals and removal of large serrated polyps. Endoscopic resection suitability and technique depends on lesion size and the endoscopist's experience. In this manuscript, we present an update regarding SPS epidemiology, molecular characteristics, management, surveillance strategies and endoscopic resection techniques.

Keywords: Serrated polyposis syndrome, colorectal cancer, surveillance, sessile serrated lesions

Introduction

Colorectal cancer (CRC) is the most frequent cancer of the digestive system and the third most common malignancy worldwide, with estimated 140,750 new cases and approximately 50,000 deaths in the United States in 2018 [1], while genetic and environmental factors seem to participate in CRC development.

Colorectal cancer occurs through two pathways. The colorectal adenoma-carcinoma sequence represents the predominant process by which CRC originates [2] and it refers to the development of CRC from a precursor dysplastic polypoid adenomatous lesion. The risk of CRC development from an adenoma has been associated with the size of the adenoma and the growth pattern (villous adenoma, tubular adenoma or tubulovillous adenoma) [3]. In addition, several genetic alterations have been linked to CRC processing via colorectal adenoma. Microsatellite instability, KRAS mutation, APC mutation and loss, and Tumor Protein 53 mutation and loss are well studied and documented [4].

On the other hand, a minority of CRC seems to develop from serrated polyps, whereas the serrated mechanism may be culpable for the origin of 10-15% of all CRC [5]. Serrated polyps represent a miscellaneous group of polyps with specific histologic, morphologic and molecular genetics features, which include the following three subsets: hyperplastic polyps, sessile serrated lesions (otherwise known as sessile serrated polyps/adenoma) and traditional serrated adenomas [6]. In particular, hyperplastic polyps represent the most common subgroup of serrated polyps and are frequently flat, <5 mm in size and situated mainly in the distal colon. Moreover, endoscopically they are identified as lesions with a pale color or a color approximating to the normal mucosa and their boundaries are not always distinct.

Sessile serrated lesions represent 3% to 9% of all serrated polyps, are flat and most frequently found proximately to the splenic flexure [7]. Endoscopically, these lesions also have a pale color that is approximating to that of hyperplastic polyps. However, they have yellowish thick mucus, known as "mucous cap". In addition,

the use of magnifying endoscopy with narrow-band imaging (NBI) and/or chromoendoscopy seems to be effective in differentiating sessile serrated lesions and hyperplastic polyps. In serrated polyp lesions, magnifying NBI shows varicose microvascular vessels and dark spots inside the crypts, while the use of magnifying chromoendoscopy detects the type II-open pit pattern [8].

On the other hand, traditional serrated adenomas are frequently detected in the distal colon, represent polypoid or pedunculated with reddish villous lesions and account for less than 1% of serrated polyps [9, 10]. The latter two subsets of serrated polyps are mainly associated with CRC development [11]. Also, the term "mixed polyp" is used in the rare cases of polyps with serrated and adenomatous features [12].

Histological characteristics of colorectal serrated lesions include serrated morphology of the crypt epithelium, non-uniform distribution of crypts, dilated crypt bases, horizontal extension of crypt bases, branched crypts and dysmaturation of crypts [13, 14]. According to WHO diagnostic criteria, at least two adjacent crypts or at least three crypts should demonstrate one or more of aforementioned histological characteristics to establish a diagnosis of sessile serrated lesion [15]. The estimated prevalence of serrated polyps on the general population ranges from 15.1% to 32.4% [16, 17].

Several molecular alterations have been described in serrated carcinoma. Mutations of BRAF or KRAS genes, overexpression of GTPase RAC1b, the CpG island methylation phenotype and microsatellite instability seem to participate in serrated pathway of CRC [18]. Serrated polyposis syndrome (SPS) is characterized by the development of multiple serrated polyps in the colon and/or rectum and seems to be associated with a higher risk of CRC development, requiring surveillance in order to detect and resect potential precancerous lesions.

Purpose of this narrative review is to present the updated diagnostic criteria of SPS, the prevalence of SPS and analyze the association between SPS and CRC in order to emphasize the significance of SPS diagnosis and increase endoscopists' awareness. Also, a great emphasis has been placed on presentation of management, including surveillance strategies of SPS and endoscopic resection techniques of serrated polyps.

Literature research

We have performed an in-depth review of the literature in PubMed to identify articles about epidemiology, diagnosis and management of serrated polyposis syndrome, using the following search string: ("serrated polyposis syndrome") AND ("diagnosis" OR "prevalence" OR "management" OR "molecular characteristics" OR "treatment"). Only articles in English were reviewed. Furthermore, we reviewed the guidelines of gastroenterology societies about management of SPS.

Diagnosis

According to the updated diagnostic criteria of World Health Organization (WHO) 2019, a diagnosis of SPS is made if any of the two following criteria are fulfilled: i) Presence of at least 5 serrated lesions/polyps proximal to the rectum, all being 5 mm in size, with 2 being 10 mm in size. ii) >20 serrated lesions/polyps of any size distributed throughout the large bowel, with 5 being proximal to the rectum [19].

However, until recently the most studies about SPS have applied the WHO's 2010 diagnostic criteria. According to them, the patients with SPS meet any of the three following criteria [20]: i) At least 5 serrated polyps are proximal to the sigmoid colon and 2 of which are greater than 10 mm in diameter. ii) Any number of serrated polyps occurring proximal to the sigmoid colon in an individual who has a first-degree relative (FDR) with serrated polyposis. iii) More than 20 serrated polyps of any size distributed throughout the colon.

The major differences about WHO's 2010 and 2019 criteria are that the criterion II of WHO's 2010 criteria has been abandoned, diminutive serrated polyps proximal to the rectum are not included in criterion I and the old criterion III of WHO's 2010 diagnostic criteria requires the presence of at least 5 serrated polyps proximal to the rectum. Arguments for updating the diagnostic criteria seem to be the high prevalence of proximal serrated polyps, which ranges between 4.7% and 12% in general population

and endoscopic surveillance of FDR of patients with SPS is recommended [19].

However, diagnostic criteria are not systematically applied by endoscopists, resulting in unrecognized SPS [21]. Noteworthy, due to flat morphology serrated polyps are not easily distinguishable, particularly in proximal colon and high quality bowel preparation is mandatory for adequate detection [22]. In view of a retrospective study with 5,000 patients, diagnosis of SPS in 25 patients according to the WHO's 2010 criteria was made. Nevertheless, in 6 patients, no previous diagnosis of SPS had been established, resulting in a miss-rate of 24%. The major reasons were unavailable pathology reports, no application of diagnostic criteria and polyps removed before establishment of the WHO criteria [23]. Hence, a single screening colonoscopy may be not sufficient enough to identify all patients with SPS [24].

The development of new endoscopic tools and techniques may improve serrated polyps' detection. Chromoendoscopy have been documented to improve the detection rate of serrated lesions compared to standard colonoscopy [25]. In a prospective randomized trial with 1008 individuals, the use of colonoscopy with continuous 0.4% indigo carmine spraying during extubation, seemed to contribute to increased overall detection rate of adenomas (0.95 versus 0.66 per patient), flat adenomas (0.56 versus 0.28 per patient) and serrated lesions (1.19 versus 0.49 per patient) ($P< 0.001$) compared to standard colonoscopy [26]. Also, according to a multicenter randomized controlled trial, prolonging withdrawal time from 6 to 9 minutes may contribute to increased detection of serrated polyps [27].

Furthermore, the use of NBI appears to increase the detection rate of serrated polyps in comparison with white light colonoscopy [28]. Additionally, adjunctive use of chromoendoscopy may offer improved diagnostic accuracy to distinguish sessile serrated polyps/adenomas from hyperplastic polyps compared to the use of NBI alone [29]. Retroflexion in the right colon after repeated forward-view examinations may lead to mild improved detection of serrated lesions [30]. Full-spectrum endoscopy (FUSE) offers a panoramic 330 degree view of the colon lumen, while standard endoscopy provides 170 degree field of view [31]. However, a recent study suggested that FUSE does not improve the detection of serrated polyps than standard forward-viewing colonoscopy [32]. Furthermore, a recent meta-analysis demonstrated that the use of antispasmodic agent hyoscine butylbromide does not increase the rate of polyp detection during colonoscopy [33]. In addition, the use of a mucosal exposure device (AmlifEYE) to the tip of colonoscope may improve the serrated polyp detection rate, as compared to the standard colonoscopy (37.6% vs 20.1%, $P<0.001$) [34].

Epidemiology

Due to frequent failure to recognize SPS, the true prevalence of SPS is not clear yet and to our knowledge, all studies about epidemiology of SPS have used WHO's 2010 diagnostic criteria. Colonoscopy screening programs have documented a prevalence of SPS below 0.1% which ranges from 0.014% to 0.056% (**Table 1**) [35-40]. In patients undergoing screening programs for CRC based on fecal immunochemical test (FIT) and fecal occult blood test (FOBT), the estimated prevalence of SPS is higher and ranges between 0.31% and 0.66% (**Table 2**) [41-43]. Despite the higher specificity of FIT compared to guaiac FOBT for CRC detection, advanced adenomas or other adenomas [44], the sensitivity of FIT for serrated polyps detection is shown to be low. In a prospective study of 6198 patients, the sensitivity of FIT for serrated polyps was 12.3%, 6.2% and 6.2%, at cutoffs of 10, 15 and 20 μg hemoglobulin/gr feces, respectively [45].

The mean age of patients with SPS at diagnosis is approximately 50 years, with no significant age differences between Western and Asian countries. On the other hand, males have a higher risk for SPS in Asia, while in Western countries no predominance has been documented [46].

Association of SPS with colorectal cancer and extra-colonic malignancy

The association between CRC and SPS has been documented in several studies. In a retrospective study from the Netherlands with 77 SPS patients, CRC was detected in 35% (27/77) of patients during surveillance of 5.6 years, while the cumulative incidence was 6.5% after a median follow-up period of 1.3 years [47].

Table 1. Prevalence of serrated polyposis syndrome on population-based screening programs for colorectal cancer

Study	Origin of study	Number of patients	Endoscopy	Number of patients with SPS	Prevalence of SPS
Orlowska J et al. [36]	Poland	50,148	Colonoscopy	28	0.056%
Kahi CJ et al. [37]	USA	6,681	Colonoscopy	3	0.04%
Lockett MJ et al. [38]	United Kingdom	40,674	Flexible sigmoidoscopy	12	0.029%
Kim HY [39]	Korean	53,842	Colonoscopy	12	0.022%
Miwata T et al. [40]	Japan	73,608	Colonoscopy	10	0.014%

Table 2. Prevalence of serrated polyposis syndrome in patients with FIT or FOBT positive

Study	Origin of study	Number of patients	Screening modality	Number of patients with SPS	Prevalence of SPS
Moreira L et al. [41]	Spain	2,355	FIT positive	8	0.34%
Colussi D et al. [42]	Italy	3,906	FIT positive	12	0.31%
Biswas S et al. [43]	United Kingdom	755	guaiac FOBT positive	5	0.66%

Similarly, in a recent multicentre study with 434 SPS patients from Europe, 29.3% (127/434) of patients were diagnosed with CRC. After the removal of all lesions >5 mm in size, surveillance was performed in 260 patients, with a median interval between colonoscopies of 1.2 years. The 5-year cumulative incidence of CRC during endoscopic surveillance was 1.5% (95% CI; 0-3.7) [48]. In another retrospective multicentre study from Spain, 47 of 296 SPS patients (15.8%) developed CRC. The cumulative CRC risk in SPS patients with no prior history of CRC was 1.9% after a mean follow-up period of 4.9 years [49]. The development of CRC in patients with SPS is shown to be associated with dysplastic serrated polyps (OR: 2.07, 95% CI: 1.28-3.33), advanced adenomas (OR 2.3, 95% CI: 1.47-3.67) and/or combined WHO's 2010 criteria 1 and 3 (OR: 1.6, 95% CI: 1.04-2.51), while a history of smoking was correlated with decreased risk of CRC development (OR: 0.36, 95% CI: 0.23-0.56) [48]. A recent single-center cohort of SPS patients with over 10 years of prospective follow-up studied the natural disease course and long-term outcomes of SPS under surveillance and demonstrated a cumulative 5-year CRC incidence of 1%, with a median follow-up of 47 months [50]. These studies demonstrate that SPS is a significant risk factor of CRC development and the cumulative 5 year incidence is approximately 1.5%. However, WHO's 2010 diagnostic criteria were used and there were no epidemiologic data with updated criteria.

Many studies have suggested that FDR of patients with SPS may carry an elevated risk of CRC development. In a Dutch population-based study, FDR of SPS patients have been associated with an increased chance of both CRC and SPS development than the general population [relative risk (RR): 5.4, 95% CI: 3.7-7.8] [51]. Additionally, a multicentre study from New Zeeland, Canada, Australia and USA showed that the FDR have a higher risk for CRC development in comparison with general population [standardized incidence ratio: 5.16, 95% (3.70-7.30)] [52]. Consequently, endoscopic surveillance could benefit FDR of SPS patients.

Furthermore, several studies have reported that individuals with SPS are associated with an increased chance of developing extra-colonic malignancy. Up to 54% of individuals with SPS appear to have a family history of extracolonic cancer [53] whereas up to 24% of SPS patients develop an extra-colonic malignancy [54]. In addition, the reported relative risk and the standard incidence ratio (compared to the SEER population) for extra-colonic cancers was 0.69% (95% CI, 0.36-1.33) and 31.2 (95% CI, 14.96-57.37), respectively [55, 56].

A recent multicentre cohort study with Hodgkin lymphoma survivors has demonstrated high prevalence of SPS compared to the healthy population (6% vs 0%) [57]. However, these patients were treated with abdominal radiotherapy and/or procarbazine and the impact of

Table 3. Presentation of serrated polyposis syndrome associated molecular alterations

SPS-associated molecular alterations
√ BRAF mutation
√ KRAS mutation
√ Absence of MLH1 immunostaining
√ Microsatellite instability
√ CpG island methylator phenotype

chemo- and radiotherapy on serrated pathway was not clarified.

Molecular features of colonic neoplasms in SPS

The molecular characteristics of SPS are not fully identified, with a wide variety of molecular alterations associated with SPS (**Table 3**). In our knowledge, only a single meta-analysis has focused on molecular alterations in SPS. It has shown that BRAF mutation coexists in 73% (95%, CI: 65%-80%) of serrated polyps, 0% (95%, CI: 0%-3%) of conventional adenomas and 49% (95%, CI: 33%-64%) of CRC in SPS patients. On the other hand, KRAS mutation occurs in 8% (95%, CI: 5%-11%) of serrated polyps, 3% (95%, CI: 0%-13%) of conventional adenomas and 6% (95%, CI: 0%-13%) of CRC. MLH1 immunostaining is absence in 3% (95%, CI: 0%-10%) of serrated polyps and 53% (95%, CI: 36%-71%) of CRC. Additionally, microsatellite instability is present in 40% (95%, CI: 18%-64%) of CRC in SPS [58]. Furthermore, the presence of CpG island methylator phenotype (CIMP-high), which leads to the inactivation of several tumor suppressor genes, has been associated with SPS [59], while germline RNF43 mutations seem to be rarely detected (2%) in patients with SPS [60].

Management of SPS

Surveillance strategies: Management of SPS is a debated topic and requires colonoscopy surveillance at regular intervals and removal of precursor CRC lesions. In 2015, the American College of Gastroenterology published guidelines for the gastrointestinal cancer syndromes, recommending that SPS surveillance should require colonoscopy in 1-3 years intervals and the resection of all polyps >5 mm in size. Moreover, in cases of inability for adequate surveillance and removal of polyps, colectomy and ileorectal anastomosis should be considered [61]. On the other hand, the British Society of Gastroenterology in 2017 recommended shorter intervals (one or two yearly colonoscopy) for endoscopic surveillance and the removal of polyps >5 mm. After piecemeal endoscopic mucosal resection (pEMR) of a serrated lesion >20 mm, evaluation of the polypectomy site within 2-6 months is suggested. Surgery (segmental colectomy, total colectomy with ileorectal anastomosis or proctocolectomy) should be considered, when lesions are not amenable to endoscopic resection due to their number, size or site [14]. Similarly, according to Spanish [62] and Dutch [63], individuals with SPS should undergo colonoscopy every 1-2 years. However, many authors support that in cases of SPS without CRC, less intensive surveillance could be applied, due to low risk of CRC in this subgroup of SPS patients [64].

Colonoscopy should be recommended in FDR of individuals with SPS: 1) at the age of 40 years, 2) at the same age as youngest diagnosis of SPS in family, or 3) 10 years younger than earliest CRC diagnosis in FDR with SPS. In cases of no polyp detection, colonoscopy should be performed every 5 years. If multiple adenomas or proximal serrated polyps are detected, colonoscopy should be considered every 1-3 years [65, 66].

Resection techniques of serrated polyps: Endoscopic removal of serrated polyps is depended on the location and their size as well as the endoscopists' experience (**Table 4**). Based on size, serrated lesions may be classified as small (<10 mm), large (10-20 mm) and larger (>20 mm) serrated [67].

Cold snare polypectomy represents an approach with high effectiveness and safety for subcentimetric serrated polyps, while the post-polypectomy bleeding risk is low [68]. Moreover, cold snare polypectomy seems to be more effective in comparison with cold forceps polypectomy for the resection of diminutive colorectal polyps (≤5 mm), regarding complete resection [69]. According to a recent meta-analysis, both cold snare polypectomy and hot snare polypectomy appear to have same effectiveness and safety for removal diminutive (≤ 5 mm) or small polyps (6-10 mm), regarding complete resection rate and bleeding [70]. However, the clinical guidelines of the European

Table 4. Presentation of appropriate endoscopic resection techniques depending on the size of serrated lesion and their major characteristics

Small serrated lesions (<10 mm)	Large serrated lesions (10-20 mm)	Larger serrated lesions (>20 mm)
Cold snare polypectomy	**Endoscopic mucosal resection (EMR)**	**Piecemeal endoscopic mucosal resection (pEMR)**
Recommended resection technique High rate of complete resection Low rate of post-polypectomy bleeding	Recommended resection technique Low rates of incomplete resection Very low rates of complications	Higher recurrence rates of lesion than EMR and ESD Evaluation of the polypectomy site within 2-6 months is suggested
Hot snare polypectomy	**Hot snare polypectomy**	**Endoscopic mucosal resection (EMR)**
High rate of complete resection Low rate of post-polypectomy bleeding	Higher rates of incomplete resection	Higher recurrence rates of lesion than ESD
Cold forceps polypectomy		**Endoscopic submucosal dissection (ESD)**
Appropriate for lesions <5 mm Lower rate of complete resection in compared to other both techniques		Lower recurrence rates of lesion High endoscopic experience is required Higher cost

Society of Gastrointestinal Endoscopy (ESGE) suggests the use of cold snare polypectomy for resection of sessile polyps 6-9 mm in size because of higher safety, despite the lack of evidence comparing efficacy with hot snare polypectomy [71].

Endoscopic mucosal resection (EMR) is considered as the first-line endoscopic technique for removal of large serrated lesions (10-20 mm) [67]. Many studies have suggested that EMR is associated with a safe and effective removal of large and flat colorectal polyps [72]. In a retrospective study from 2 centers, 251 serrated polyps with mean size of 15.9 mm were removed by EMR from the proximal colon. Of these lesions, only 3.6% had local recurrence, which was detected after 17.8 (± 15.4) months, with a median size of 4 mm. During post-polypectomy period, no cases of perforation, bleeding or advanced colon cancer were reported [73]. On the other hand, a prospective study with 356 polypectomies by hot snare demonstrated higher rates of incomplete resection regarding large (10-20 mm) compared to small (5-9 mm) neoplastic polyps (17.3% vs 6.8%), and for sessile serrated adenomas/polyps compared to conventional adenomas (31.0% vs 7.2%) [74].

Larger serrated lesions (>20 mm) can be removed by EMR, piecemeal EMR (pEMR) or endoscopic submucosal dissection (ESD), depending on the size and the endoscopist's experience. In a prospective multicenter study, all cases of large (>20 mm) serrated sessile adenomas/polyps could be removed by EMR and the cumulative recurrence rate was 6.3% at 6 months and 7.0% from 12 months and onwards [75]. A retrospective study compared the outcomes and complications of ESD, hybrid ESD, pEMR and EMR for laterally spreading tumors larger from 20 mm. Local recurrence rates in cases with curative resection by ESD, hybrid ESD, EMR and pEMR were 0%, 0%, 1.4% and 12.1%, respectively, while there were no differences in perforations rates, demonstrating that the safety of ESD and hybrid ESD is similar to EMR and pEMR, while ESD and hybrid ESD may offer en bloc resection without local recurrence [76].

Conclusion

SPS remains an underestimated and undetected condition, which is strongly associated with CRC development via the serrated pathway. Increased awareness, use of new endoscopic techniques, such as chromoendoscopy and application of WHO's criteria are required for timely identification of patients with SPS. Moreover, surveillance at regular intervals and removal of precursor CRC lesions are mandatory for the management of SPS.

Disclosure of conflict of interest

None.

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