Serrated polyps of right colon: guilty or innocent?

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Abstract

In recent years a lot of interest has been focused on a specific category of polyps, the so-called serrated polyps which until recently were categorized with the hyperplastic or mixed polyps and were thought to have no risk of malignant transformation. Recently though, the serrated pathway of carcinogenesis was discovered and destroyed this myth. It is believed that up to one third of all colorectal cancers arise through the serrated pathway; these cancers occur more often in the proximal colon and have specific molecular characteristics. Specific subtypes of serrated polyps (mainly the sessile serrated adenomas/polyps) are thought to be precursor lesions of these cancers. The prevention of these cancers is a challenge for gastroenterologists because their location and endoscopic characteristics renders them difficult to detect. Also, although there is a clear need for creating a specific post-polypectomy surveillance program for these lesions, to date there have been no guidelines for surveillance with a high level of evidence. In this article the main molecular, endoscopic, histological and epidemiologic characteristics of these lesions are presented, as well as recommendations for surveillance.

Keywords Serrated polyps, sessile serrated polyps, traditional serrated adenoma, colorectal cancer, surveillance

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Introduction

The term serrated polyps was used for the first time in 1990 by Longacre and Fenoglio- Preiser and until recently this category of polyps was included in a larger group that was called "hyperplastic" or "mixed hyperplastic/adenomatous" polyps [1]. At the same time it was believed that these polyps had no potential for malignant transformation and for that reason they did not require polypectomy or surveillance. However, in recent years, after the discovery of the "serrated pathway" of carcinogenesis, specific groups of these polyps have been incriminated as precursor lesions of colorectal cancer (CRC).

Molecular features of the serrated pathway of carcinogenesis

There are at least three basic molecular pathways of CRC development: 1) the pathway of chromosomal instability (CIN) which is responsible for 70-85% of CRCs [2] and is associated

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with conventional adenomas; in this pathway there are common mutations of the *APC (adenomatous polyposis coli)* gene as well as mutations at the *KRAS* oncogene and *β-catenin* (*CTNNB1*) [3,4]; 2) the pathway of CpG (Cytosine Guanine phosphodiester bond) island methylator phenotype (CIMP) which is the second main pathway of sporadic CRC development and includes sporadic CRCs with high microsatellite instability (MSI-H); in this pathway common mutations of the *BRAF* gene are observed and in a smaller percentage of the *KRAS* oncogene [3]; and 3) the pure MSI pathway which is caused by mutations in the *mismatch repair* gene (*MMR*). The hereditary non-polyposis colorectal cancer (HNPCC) syndrome occurs through the pure MSI pathway [3].

The serrated pathway of carcinogenesis is actually the pathway of the CIMP [3].

Classification of serrated polyps

In 2010 the World Health Organization (WHO) published a classification for serrated polyps (Table 1) [5]. The subtypes of these serrated lesions have different molecular features (mutations) and also different potential for malignant transformation to CRC.

Hyperplastic polyps (HP) are very common, of small size (<5 mm) and they are more often located in the distal colon and rectum. Endoscopically they are identified by their smooth, symmetrical and pale appearance as well as by their tendency to disappear with air insufflation [6,7]. Histologically they are characterized by straight crypts, without branching, while they

Table 1 WHO classification of serrated polyps-lesions

Non-dysplastic	Dysplastic
1. Hyperplastic polyps	3. Sessile serrated adenoma, dysplastic
1a. Goblet cell serrated polyp	
1b. Microvesicular serrated polyp	
2. Sessile serrated adenoma/polyp (also known as sessile serrated lesion)	4. Traditional serrated adenoma

show minimal cellular atypia. HPs are subcategorized in two histological subtypes: goblet cell serrated polyps (GCSP), which usually have *KRAS* mutations, and it is unknown whether they can evolve to more progressive lesions; and microvesicular serrated polyps (MVSP), which have *BRAF* mutations as well as increased susceptibility to hypermethylation (CIMP). It seems that the MVSPs are probably evolving to SSA/Ps, especially when they are located to proximal colon [8,9].

Sessile serrated adenomas (polyps, lesions- SSA/P) are flat, sessile lesions. They tend to be larger than HPs. They are commonly located in the proximal colon and are usually covered by a mucous layer which is often difficult to be removed despite washing (mucous cap) [9]. Histologicaly they are differentiated from HPs from the presence of architectural changes of the crypts (inverted T- and L- shaped crypt bases) [10] and they also have various degrees of nuclear atypia [8]. They are characterized by mutations of the *BRAF* gene and from high levels of CIMP (CIMP-H). These lesions can evolve to SSA with dysplasia (SSADs) [11].

SSADs display morphological characteristics of SSAs and proportional distribution, and are also characterized by *BRAF* mutations and CIMP-H state [8]. They are responsible for a large percentage of sporadic MSI-H CRCs (epigenetic silencing of the DNA *MMR* gene *hMLH1* by promoter methylation) [9]. This category of polyps was until recently named "mixed hyperplastic/adenomatous" polyps [8].

Traditional serrated adenomas (TSAs) are rarer than SSA/Ps. They are most often located to the distal colon, and are usually pedunculated and present with tubulovillus architecture [9]. They are more often characterized by *KRAS* mutations [12]. The TSAs are also precancerous lesions and have various degrees of cellular atypia. TSAs and SSADs can present conventional adenoma-like dysplasia as well as serrated dysplasia [8].

The basic theory for evolution of serrated lesions from HPs to CRC is shown in Fig. 1 [11,13-15]. The evolution of a GCSP to TSA has not been documented and the precursor lesion of TSA has not yet been determined [8].

Wnt signaling in serrated pathway of carcinogenesis

About 90% of all sporadic CRCs occur through activation of the Wnt signaling pathway. In the pathway of CIN the result of the *APC* or *CTNNB1* mutations is the activation of the

Wnt signaling pathway. In the normal state the APC protein forms a complex with the key effector β-catenin [4]. When this APC protein function is lost, the β-catenin is translocated from the lateral membrane to the nucleus. There it promotes the transcription of multiple genes involved in tumor growth and invasion [4].

The role of Wnt signaling pathway is controversial in the serrated pathway of carcinogenesis. Although *APC* and *CTNNB1* mutations are very rare in serrated lesions, there is evidence that Wnt signaling activation contributes to progression of serrated lesions to CRC through mechanisms other than *APC* and *CTNNB1* mutations [4]. Recent studies have shown that promoter hypermethylation of the *mutated in colorectal cancer* gene (*MCC,* a candidate tumor suppressor gene) leads to loss of action of MCC protein which normally acts as suppressor of the Wnt signaling pathway by interacting with β-catenin [4,16,17]. This was observed especially in MSI-H/CIMP+ sporadic CRCs and in their precursor lesions mainly SSAs and right-sided HPs, indicating that MCC promoter hypermethylation may be a Wnt signaling activating event in the serrated pathway of carcinogenesis [4,16,17]. It must be stated though, that MCC promoter hypermethylation
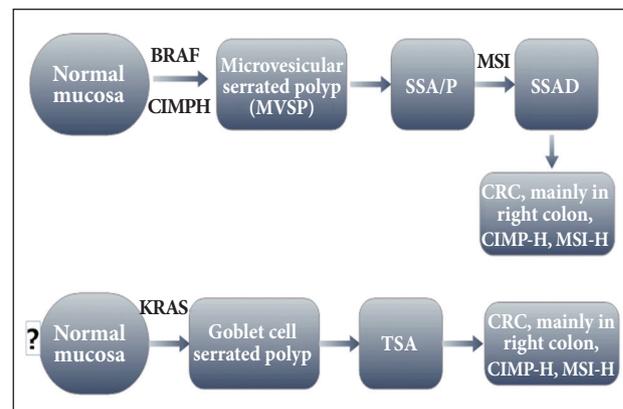

Figure 1 Schematic illustration of serrated pathway of carcinogenesis

?: It has not been established that Goblet cell serrated polyps can evolve to TSAs and this pathway is only theoretical

SSA/P, sessile serrated adenoma/polyp; SSAD, sessile serrated adenoma with dysplasia; CRC, colorectal cancer; MSI, microsatellite instability; CIMPH, CpG island methylator phenotype high; MSI-H, microsatellite instability high; TSA, traditional serrated adenoma; MSI-L, microsatellite instability low; MSS, microsatellite stable

was not so frequent in TSAs and left-sided HPs further suggesting the different behavior of these serrated lesions [16].

Epidemiology of serrated polyps

The epidemiologic data on serrated polyps originate mainly from the era when they were characterized as hyperplastic or mixed; at present a large number of studies are being conducted worldwide in order to determine the epidemiologic characteristics of the specific groups of serrated polyps.

It seems that approximately 25-50% of white men have one or more serrated lesions (totally, not specific groups) [18-25]. It also seems that their total prevalence increases only minimally with age in comparison to conventional adenomas whose prevalence increases significantly with age [8,26]. Serrated polyps are located in their majority in the sigmoid and rectum, but their distribution varies according to their histological type. HPs account for 70-95% of all serrated polyps and are located mainly in the left colon [8]. SSA/Ps account for 5-25% of serrated polyps and are usually found in the right colon, being typically larger than HPs [8], and with a tendency to present more often in women [27]. TSAs are rarer than SSA/Ps, with a prevalence 2-3.5% and are found mainly in the left colon [4,9]; they are also larger in size than HPs [9].

Clinical significance

It is believed that approximately one third of CRCs develop through the serrated pathway of carcinogenesis [28-34]. A retrospective analysis of these percentages shows an increase during the last decade [8,9]. This observation of course does not mean an increase in the absolute number of these CRCs, but rather a relative increase, due to a simultaneous decrease in the malignancies which develop from conventional adenomas as a result of screening colonoscopies and polypectomies.

Recent studies have shown that the age-adjusted incidence and mortality rates from right-sided CRCs have not decreased, despite the widespread use of screening colonoscopy [35,36]. In addition, "interval cancers" are a very important problem, they are defined as cancers that are diagnosed within 5 years after a negative complete colonoscopy [9]. These cancers represent 2-6% of all CRCs. They are located more often in the proximal colon and they are usually CIMP-H and MSI-H [9]. Therefore, it is very probable that a significant proportion of these cancers evolve from undetected SSAs in the primary colonoscopy.

There is also a question about the rapid progression of SSADs from the time they enter the MSI-H state. This arises from the behavior of adenomas in HNPCC syndrome which are also MSI-H and present a rapid evolution to CRC [9].

In addition, some preliminary studies show that these CIMP+, MSI-H cancers may not be responsive to chemotherapy with 5-fluorouracil and this seems to be associated with hypermethylation. This information could be critical in the choice of chemotherapeutic treatment, especially considering recently developed new inhibitors of DNA methylation [37].

Unfortunately, there is an important problem in the detection of these lesions and this is caused mainly by their endoscopic features. The commonest serrated lesions, the HPs, are flat, small (<5mm) and usually flatten with air insufflation [8,9]. As for the larger and more dangerous lesions, the SSA/Ps, they have the same color as the neighboring mucosa, they are frequently covered by a mucus layer (mucus cap), they have a weak vascular net in comparison to classic adenomas and they are frequently located, as was mentioned before, in the right colon which in many cases is not properly prepared [8,9]. All of these features make their detection difficult and this fact is more probably related to the relative increase of CIMP-H, MSI-H cancers. TSAs, on the other hand, are more frequently located in the left colon, tend to be larger than SSA/Ps, and in many cases are pedunculated, a fact that renders their detection easier [8,9].

Therefore, it is possible that the same factors regarding the quality of colonoscopy and the detection of flat neoplasms of the colon, such as bowel preparation, time of withdrawal, thoroughness during examination and endoscopist's experience also apply for the detection of SSA/Ps. Results from recent studies [38,39] indicate that the real prevalence of serrated lesions is probably higher than believed and also indicate that the detection of serrated lesions varies and depends on the endoscopist. Using adjuvant methods, as chromoendoscopy and narrow band imaging (NBI) may help improve the detection of SSA/Ps although their effectiveness has not as yet been established [8,40].

It must be also emphasized that due to difficulties in histological classification of serrated lesions by pathologists, on many occasions there is a misclassification of these lesions and underestimation of their malignant potential. For that reason some experts suggest that all serrated lesions in proximal colon larger than 10 mm should be regarded as SSA/Ps even if histology reports HPs [41].

The features of serrated lesions are summarized in Table 2.

Table 2 Features of serrated lesions

	Shape	Median size	Prevalence	Location	Malignant potential
HP	Flat, sessile	Small, often ≤5mm	Very common	Distal colon	No
SSA/P	Flat, sessile	Larger than HPs	Common	Proximal colon	Yes
TSA	Sessile, pedunculated	Larger than HPs	Rare	Distal colon	Yes

HP, hyperplastic polyp; SSA/P, sessile serrated adenoma/polyp; TSA, traditional serrated adenoma

Inflammatory bowel disease (IBD)-associated serrated lesions

It is well known that IBD (ulcerative colitis and Crohn's disease) is associated with increased risk of development of CRC. For that reason all patients with IBD (except for patients with proctitis) must undergo a control colonoscopy 6-8 years after the beginning of the disease symptoms and then according to risk stratification must enter a surveillance program for CRC [42]. The main pathway for CRC development in IBD is that of chromosomal instability but with a main difference compared to the pathway of sporadic CRC. In sporadic CRC there are usually APC gene mutations but in IBD-associated carcinogenesis these mutations are less frequent and the most common mutation is that of tumor suppressor gene *p53* [43]. Approximately 80% of identified *p53* mutations are transition mutations and appear to be strongly associated with inflammation-induced and oxidative stress-induced DNA damage [43].

Interestingly, in 2007 Bossard *et al* conducted a study in 91 samples from 36 patients with IBD-associated neoplasia and revealed the existence of pre-neoplastic serrated lesions in the inflammatory mucosa of IBD [44]. These lesions had the same molecular characteristics as sporadic SSA/Ps and HPs (*BRAF* mutations) and accounted for 6.9% of all pre-neoplastic lesions in inflammatory mucosa. This percentage is actually lower than that found in the general population but this may be due to sample size. Thus, the serrated pathway of carcinogenesis may be involved as an alternative secondary pathway in IBD-related carcinogenesis [44].

This observation raises questions about whether detection of serrated lesions (especially of non-dysplastic lesions such as HPs and SSA/Ps) should change the surveillance program of IBD patients. Until now there are no guidelines or suggestions about this, and further studies are warranted in order to fully assess their potential risk for carcinoma development in IBD patients. Of course, these lesions should be removed according to the same principles regarding sporadic serrated lesions.

Risk factors for developing serrated lesions

Data about the risk factors of developing serrated lesions are inadequate and further investigation is required in order to determine risk factors about the specific groups of serrated lesions. Until now, only correlation regarding smoking habits has been determined for serrated lesions, both in the right and left colon [45-47]. Physical activity and folate intake have been found to have a reverse relationship with the development of serrated lesions in the left colon, but this has not been confirmed for the right colon [45-47]. Series studying alcohol consumption, calcium intake and non steroidal anti-inflammatory drugs have been inconclusive [47]. Obesity, high dietary fat intake, total energy intake and consumption of red meat seem to increase the risk of development of serrated lesions mainly in the left colon, but this has not been confirmed for right colon serrated lesions (SSA/Ps) [47].

Serrated polyposis syndrome (SPS)

This syndrome, previously known as hyperplastic polyposis syndrome, is characterized by the presence of multiple serrated (typically SSA/Ps and/or HPs) colorectal polyps. Actually, it was studies in patients with this syndrome that indicated that SSA/Ps may be precursors of CRC.

Recently, WHO published the updated criteria for determining this syndrome and diagnosis can be made if any of the following three criteria is met [5,48]: 1) at least 5 serrated polyps located proximal of sigmoid colon, two of them must be larger than 10 mm; 2) any number of serrated polyps located proximal of sigmoid colon in person with first-degree relatives with diagnosed SPS; or 3) >20 serrated polyps distributed throughout the colon.

SPS has been associated with increased incidence of CRC. In published studies, almost 25-70% of patients with SPS had CRC at diagnosis or during follow up [40]. In larger series with patients who met the WHO criteria for SPS, 35% had CRC (28.5% in first endoscopy and 6.5% during mean follow up of 5.6 years) [49-52]. In these studies, the increased number of polyps and the presence of SSA/Ps or TSAs were associated with the presence of CRC [49-52]. Also, first-degree relatives of patients with SPS presented increased risk of developing CRC and SPS in comparison to the general population [53].

The presence of this syndrome does not seem to differ between the two sexes. The median age at diagnosis is 44-62 years and ranges from 10 to 90 years. Also, these patients commonly develop synchronous conventional adenomas [49,54,55].

It must be emphasized that this syndrome is perhaps underdiagnosed since many small serrated lesions may be missed during colonoscopy; NBI and chromoendoscopy seem to significantly reduce polyp miss rates in patients with SPS [56].

The surveillance of these patients can be performed according to the following model: 1) colonoscopy with chromoendoscopy every 1-2 years with endoscopic removal of all polyps; 2) if the removal of all polyps is not possible because of their size or number, or if cancer is found, then colectomy with ileorectal anastomosis should be performed; and 3) in first-degree relatives of patients with SPS screening colonoscopy with chromoendoscopy, if possible, should be offered every 1-2 years from 10 years younger than the index case [40].

If segmental colectomy is performed for SPS, then postoperative endoscopic surveillance every 6-12 months of the retained colorectum should be initiated and this also applies for screening rectum in case of ileorectal anastomosis because recurrence of CRC postoperatively in retained colorectal segments occurs rapidly [57,58].

Rate of progression of serrated lesions to CRC

The rate of progression of serrated lesions to CRC has not yet been determined and possibly depends on if and when

these lesions enter the MSI-H state. There are reports for evolution of SSA/Ps to CRC in only 8 months [59]. Also, the observation that these CIMP-H, MSI-H CRCs are actually more prevalent than SSADs with high-grade dysplasia supports the theory that the rate of progression of serrated lesions to CRC is faster than that of conventional adenomas [60]. Data from a recent study comparing apoptotic index of SSA/Ps and conventional tubular adenomas (TAs) showed that the mitotic index in both groups is similarly high but the apoptotic index in SSA/Ps is statistically significantly lower in SSA/Ps than in TAs, also indicating that SSA/Ps may have faster rate of progression to CRC due to large imbalance between apoptosis and mitosis [61]. On the contrary, in a study with a large number of patients (2139 patients with SSA/Ps) the median age of patients with SSA/Ps, SSADs and SSA/Ps with cancer was calculated and was found to be 61, 66 and 76 years of age respectively, indicating that probably the evolution from SSA/Ps to CRC takes about 15 years [62]. Thus, at least until now, there is no clear evidence about the rate of progression of serrated lesions to CRC and this fact raises questions and problems about the optimal interval of follow-up colonoscopies in patients with polypectomy of serrated lesions in the primary colonoscopy. One thing is certain, that these lesions (especially SSA/Ps in right colon and TSAs) are precancerous lesions and these patients must enter a surveillance program.

Recommendations regarding removal of serrated lesions

According to the recommendations proposed by Douglas *et al* (2012), all serrated lesions should be removed, with the exception of minimal (<5 mm) lesions in sigmoid and rectum from which random biopsies should be obtained [8].

The general principles regarding polypectomy of serrated lesions are the same as those regarding polypectomy of conventional adenomas. There are some difficulties in the removal of serrated lesions arising from the fact that these lesions are sessile and flat, and also because some times their borders are not clear since they have similar color with the neighboring mucosa [8,9]. In this case, the use of adjuvant techniques such as chromoendoscopy, NBI or high resolution endoscopy may be necessary [8,40].

Snaring of large serrated lesions may actually be easier than snaring conventional flat adenomas and the fulcrum technique may be used in cases where the space is too tight or the polyp very flat [8,63]. Also, the submucosal injection of solution may actually make snaring more difficult for these lesions [8].

If piecemeal technique is used for large lesions, then colonoscopy should be repeated after 3-6 months in order to confirm the total removal of the lesion [40].

Surgical resection of the colon is rarely necessary, but in case of serrated lesions that cannot be removed endoscopically or in case of multiple large serrated lesions in proximal colon then surgery is the only option [8,40].

Surveillance of patients after polypectomy of serrated lesions

As it was mentioned before, surveillance of patients with serrated lesions is necessary after polypectomy, but to date there are no specific guidelines for this surveillance and those existing have a low level of evidence. Table 3 outlines recommendations from an expert consensus published in the American Journal of Gastroenterology in June 2012 [8]. These recommendations are based on a risk stratification of these lesions which is presented in Fig. 2 [8]. This stratification is based on the fact

Table 3 Expert consensus [from ref 8]

Histologic type	Size	Number	Location	Recommended interval of surveillance/years
HP	<10 mm	Any number	Rectosigmoid	10
HP	≤ 5 mm	≤3	Proximal of sigmoid	10
HP	Any	≥4	Proximal of sigmoid	5
HP	> 5 mm	≥1	Proximal of sigmoid	5
SSA/P or TSA	<10 mm	<3	Anywhere	5
SSA/P or TSA	≥10 mm	1	Anywhere	3
SSA/P or TSA	<10 mm	≥ 3	Anywhere	3
SSA/P	≥10 mm	≥ 2	Anywhere	1-3
SSA/P with dysplasia	Any	Any number		1-3

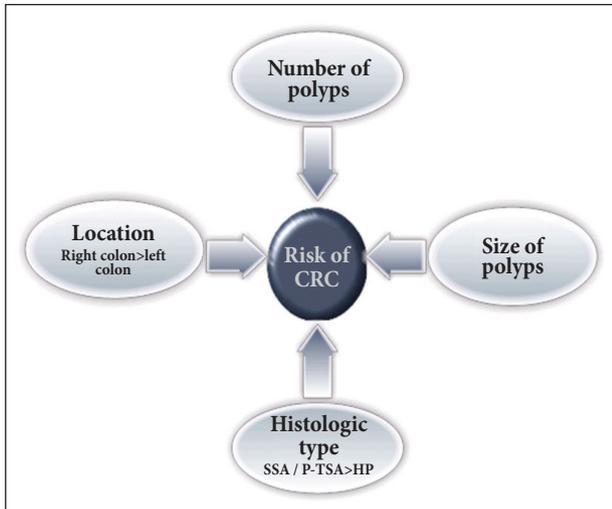*HP, hyperplastic polyp; SSA/P, sessile serrated adenoma/polyp; TSA, traditional serrated adenoma*

were published in 2012 to the former guidelines, indicated that this strategy may be cost-effective and potentially cost-saving [65].

Discussion

Despite the efforts made through screening with colonoscopy and polypectomy (when necessary), although there is a significant decrease of CRCs of the left colon, this does not apply to CRCs of the right colon. CRCs of the right colon seem to express specific molecular features (CIMP-H, MSI-H), different from those of conventional adenomas. At present, interest has been shifted to studying these cancers since they constitute a challenge regarding optimal CRC prevention. These CRCs seem to have as precursor lesions serrated polyps, until recently included in the "innocent group" of HPs. At present, the malignant potential of these lesions has been recognized. The rate of their progression to CRC has not as yet been determined, but there is a theory that these lesions may actually present with a faster progression rate than conventional adenomas. WHO published in 2010 the classification of these lesions (Table 1) and according to the studies performed to date it seems that the most "dangerous" are the SSA/Ps. They are usually flat, sessile and tend to be located in right colon, often making their endoscopic detection difficult. TSAs also present malignant potential although they are rare and localized mostly in the left colon in comparison to SSA/Ps. Generally, TSAs present molecular characteristics, distribution and behavior closer to that of conventional adenomas. In addition, the increased risk for CRC development has been recognized in patients with SPS and their first-degree relatives, and recently WHO published the updated criteria for diagnosis of this syndrome. In conclusion, it seems that all these lesions should be endoscopically removed, perhaps with the exception of multiple small lesions in the rectosigmoid (but random biopsies must be obtained from these lesions) and these patients should enter a surveillance program. The interval of the surveillance has not yet been optimally determined, but it seems that if the lesions are multiple, large, proximal to sigmoid, with histology revealing SSA/Ps or TSAs and, if dysplasia exists, then the surveillance must be stricter and more frequent. Recent data also indicate that the strategy of surveillance including SSA/Ps as precursors is indeed cost-effective and potentially cost-saving. A serrated pathway of carcinogenesis has also been implicated in IBD-associated carcinogenesis and questions are raised also about surveillance in IBD patients with serrated lesions. Thus, it is necessary for gastroenterologists to familiarize themselves with these new data which change the perception held until recently that these polyps were innocent and did not need surveillance. It is also important for gastroenterologists to optimize their ability to detect these lesions especially in the right colon where the conditions are not always ideal (mainly regarding bowel preparation). Proper education of pathologists is also

Figure 2 Risk stratification for CRC

CRC, colorectal cancer; SSA/P, sessile serrated adenoma/polyp; TSA, traditional serrated adenoma; HP, hyperplastic polyp

that the size, the number, the histological type and the location of the lesions are related with the risk of progression to CRC [8]. In Table 4 the recommendations from US Multi-Society Task Force on Colorectal Cancer are presented, that were also published in 2012, but as reported by the authors the quality of evidence upon which the recommendations were based is low [41]. In addition, there is nothing mentioned in these recommendations about the number of serrated lesions and how this number may influence the interval of surveillance. Finally, in the European guidelines published in 2012 in Endoscopy on behalf of the European Committee, there is only a small report regarding serrated lesions which states that the same surveillance program that exists for classic adenomas should be followed (level of evidence VI-C) [64].

Finally, data from a recent study which estimated the incremental cost-effectiveness ratio for colonoscopy comparing the new recommendations of US Multi-Society Task Force on Colorectal Cancer which included evaluation of SSA/Ps and

Table 4 US multi-society task force on colorectal cancer

Serrated lesions	Recommended interval of surveillance/years
SSA/P <10 mm without dysplasia	5
SSA/P ≥ 10 mm	3
or	
SSA/P with dysplasia	
or	
TSA	
Serrated polyposis syndrome	1

SSA/P, sessile serrated adenoma/polyp; TSA, traditional serrated adenoma

very important and necessary since they carry the burden of histological identification of these lesions and classification of the specific types. Finally, more studies are needed in order to determine risk factors for the development of serrated lesions as well as their rate of progression to CRC, since this may change the time interval of surveillance.

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