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EDITORIAL

Serrated pathway: Alternative route to colorectal cancer

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Abstract

Serrated polyps have been an area of intense focus for gastroenterologists over the past several years. Contrary to what was thought before, a growing body of literature indicates that these polyps can be precursors of colorectal cancer (CRC). Most of these lesions, particularly those in the proximal colon, have so far been under-recognized and missed during colonoscopy, qualifying these lesions to be the main cause of interval cancers. It is estimated that 10%-20% of CRCs evolve through this alternative, serrated pathway, with a distinct genetic and epigenetic profile. Aberrant DNA methylation plays a central role in the development of this CRC subtype. This characteristic molecular background is reflected in a unique pathological and clinical manifestation different from cancers arising *via* the traditional pathway. In this review we would like to highlight morphological, molecular and clinical features of this emerging pathway that are essential for gastroenterologists and may influence their everyday practice.

Key words: Serrated pathway; DNA methylation; Hyperplastic polyps; Serrated adenomas; Colorectal cancer; Endoscopic surveillance

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INTRODUCTION

It is being increasingly recognized that colorectal cancer (CRC) is not a single disease, but rather a heterogeneous disorder including a collection of many distinct diseases with diverse molecular background and clinicopathological manifestations. According to the adenoma-carcinoma sequence proposed by Vogelstein *et al*[1] adenomatous polyps have long been considered as the sole preneoplastic lesions leading to CRC. On the other hand, hyperplastic polyps (HP) often found in the distal colon, until recently have been considered innocuous lesions, despite some contradictory opinions[2,3]. This common view has recently been challenged, as it turned out that these polyps along with other similar lesions commonly termed "serrated polyps" can be precursors to CRC[4,5].

The aim of this article is to provide a thorough clinicopathologic overview of this emerging pathway in colorectal carcinogenesis and help to understand how this accumulating data can be translated into clinical management strategies and better clinical outcomes.

CLASSIFICATION OF SERRATED POLYPS

General features of serrated polyps

The term "serrated polyp" contains a wide variety of colonic lesions and broadly refers to HP and different serrated adenomas. The main histological feature of serrated polyps is the infolding of the crypt epithelium[5], that is represented as a serrated or saw-toothed appearance in longitudinal section and a stellate or starlike appearance on cross section (Figure 1). The molecular basis for this histological feature has been attributed to decreased apoptosis[6-8] that is caused by the activated

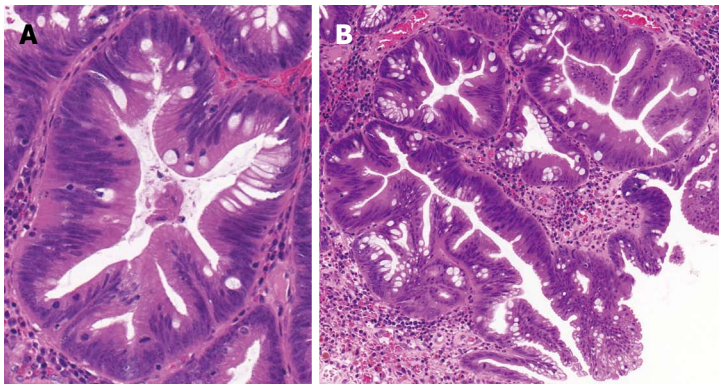

Figure 1 Microscopic features of serrated polyps. A: On cross section serrated crypt shows a stellate or starlike appearance; B: In longitudinal section a characteristic serrated or saw-toothed appearance can be seen.

mitogen activated protein kinase (MAPK)-ERK pathway that is induced by either *BRAF* or *KRAS* mutation (Figure 2). Inhibited apoptosis leads to the accumulation of non-proliferating cells. Serration is a general characteristics of this pathway from HP all the way to serrated adenocarcinoma (SAC)[9].

Hyperplastic (non-dysplastic) aberrant crypt foci

The earliest known microscopical precursors to CRC are mucosal abnormalities termed aberrant crypt foci (ACF). ACF can be further subclassified into two categories: dysplastic and hyperplastic[10,11] (also called as heteroplastic or non-dysplastic). Dysplastic ACFs, often termed as microadenomas, have been associated with sporadic adenomas arising *via* the traditional pathway[12,13]. Hyperplastic ACF may be serrated or non-serrated[11]. They are very frequent; almost every individual over 50 has at least one ACF in the distal colorectum[14]. Serrated hyperplastic ACF has a higher frequency of *BRAF* mutations, than non-serrated ACF, whereas non-serrated ACF has a higher frequency of *KRAS* mutations, than serrated ACF[11,15]. This finding supports the idea that these lesions are potentially initiating step on the serrated pathway to CRC[15], however their high frequency imply that only a small fragment progresses to HP or more advanced lesions of the serrated pathway[9]. *BRAF* and *KRAS* (mutually exclusive) mutations induce the activation of the MAPK-ERK pathway leading to decreased apoptosis and an initial burst of MAPK-ERK-dependent proliferation, leading to the formation of hyperplastic crypts. This uncontrolled proliferation is counteracted by a protective phenomenon called oncogene-induced senescence that is driven by telomere attrition, that triggers the induction of tumor suppressors including *p16*[16] or *IGFBP7*[17] (insulin-like growth factor binding protein 7), similarly as it was described in melanocytes. Hyperplastic crypts may remain dormant for prolonged periods due to the induction of crypt senescence[8] (Figure 2).

HP

HPs are the most common (80%-90%) and the best described serrated polyps. They occur most frequently in the distal colon and the rectum; they are usually slightly elevated, diminutive polyps, less than 5 mm in size. Key morphological features include elongated crypts with serration limited to the upper half of the crypt, with lack of cytologic or architectural dysplasia. These alterations can be seen only in the upper third or only on the surface of the crypts[18]. The proliferative zone may be expanded, but usually confined to the crypt base. The nuclei are small, uniform and basally placed[18], the cytoplasm is eosinophilic. If surface epithelium is not present for histological evaluation, a thickened basal membrane and muscularis mucosae with short smooth muscle extensions into the basal part of the mucosa ("comb-like" appearance) can be helpful hints to identify HP[19] (Table 1).

HPs usually occur a decade earlier (in the fifth and the sixth decade) than adenomatous polyps[20]. Several risk factors have been linked with the prevalence of serrated polyps including cigarette smoking, alcohol consumption, obesity and low-folate intake[20,21], whereas regular nonsteroidal anti-inflammatory drug use, hormone replacement therapy, and high calcium intake have been associated with reduced risk[20]. It is of note that besides smoking, all other factors have also been linked to adenoma formation *via* the traditional pathway[9,20]. This observation gained further importance when it was discovered that smoking is only a strong risk factor for those CRCs that exhibit a unique molecular phenotype [CpG island methylator phenotype (CIMP)] linked to sessile serrated pathway[22,23].

Subclassification of HP

Based on the epithelial mucin content, Torlakovic *et al*[19] histologically subclassified HPs into three categories: goblet cell-rich, microvesicular, and mucin-poor.

Microvesicular hyperplastic polyp (MVHP), also called type 2 HP, is the most common type and the typical representation of HPs encountered in the distal colon. It is characterized by large microvesicular mucin-containing epithelial cells in the upper half of the crypt, reduced goblet cells compared to normal colonic mucosa, and goblet cell abnormalities. MVHP shows prominent serration mostly in the upper half of the crypt and it has a large proliferative zone, which may take up the basal half of the mucosa. Nuclear stratification is present, but it is not prominent. The overall architecture is slightly distorted and minimal to mild crypt dilatation is present. Almost all MVHPs are slightly thicker than surrounding normal colonic mucosa. At the molecular level, MVHPs

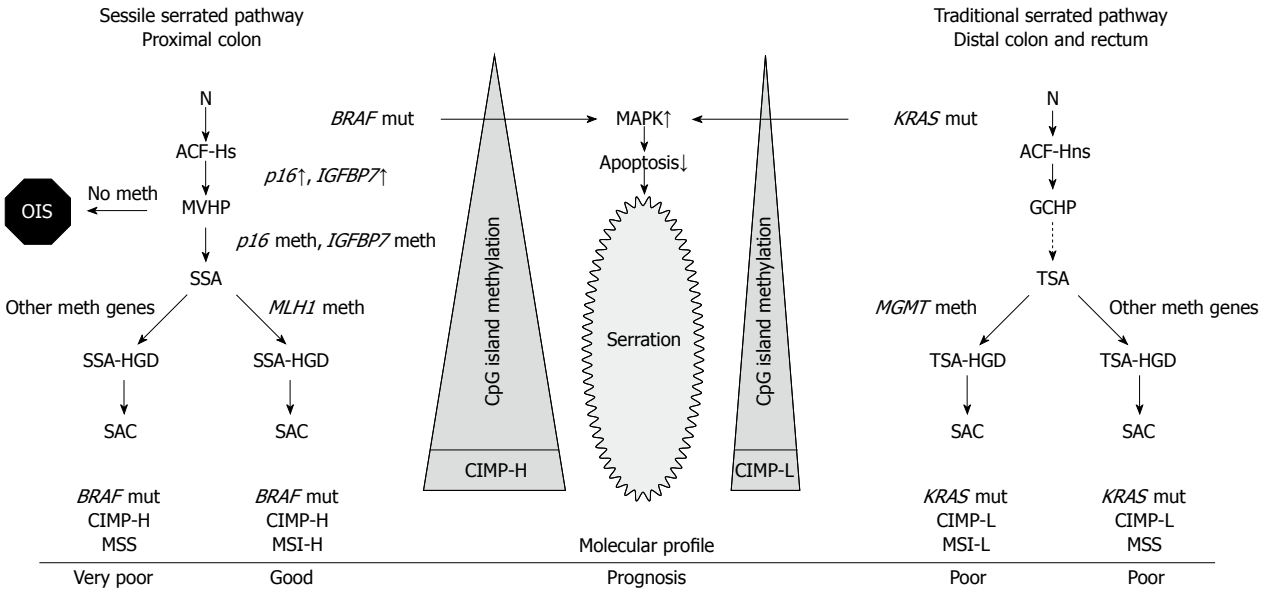

Figure 2 Schematic representation of the sessile and traditional serrated pathways. N: Normal mucosa; ACF-Hs: Serrated hyperplastic-type aberrant crypt focus; ACF-Hns: Non-serrated hyperplastic-type aberrant crypt focus; MVHP: Microvesicular hyperplastic polyp; OIS: Oncogene-induced senescence; GCHP: Goblet cell-rich hyperplastic polyp; SSA: Sessile serrated adenoma; TSA: Traditional serrated adenoma; SSA-HGD: Sessile serrated adenoma with high grade dysplasia; TSA-HGD: Traditional serrated adenoma with high grade dysplasia; SAC: Serrated adenocarcinoma; *IGFBP7*: Insulin-like growth factor-binding protein 7; MAPK: Mitogen activated protein kinase-ERK pathway; *MLH1*: MutL homolog 1; *MGMT*: O-6-methylguanine-DNA methyltransferase; CIMP-H: CpG island methylator phenotype-high; CIMP-L: CpG island methylator phenotype-low; MSI-H: High-level microsatellite instability; MSI-L: Low-level microsatellite instability; MSS: Microsatellite stable.

commonly (80%) exhibit *BRAF* V600E mutation[24], where valine is substituted for glutamic acid. As it was discussed above, this induces MAPK-ERK pathway that is followed by oncogene-induced senescence that includes overexpression of growth control genes *p16* and *IGFBP7* holding the cells in a dormant state. Aberrant CpG island methylation of the promoter region of *p16* and *IGFBP7* bypasses this dormant state[8] and drives MVHPs further to the next stage of serrated polyp progression, namely sessile serrated adenoma[9]. CpG island methylation is more pronounced in proximal MVHPs than in those located distally[25,26] (Figure 2).

Goblet cell-rich hyperplastic polyp (GCHP), also known as type 1 HP, is most commonly found in the distal colon, and is probably the most under-recognized variant. As its name implies this subtype is abundant of large, mature, distended goblet cells in the upper half of enlarged crypts and surface epithelial cells. Surface serrations are less prominent than in MVHP. Nuclear atypia is generally not present, but nuclei are slightly enlarged. *KRAS* mutations (in codon 12 and 13) were detected in almost half of these lesions[24,27], whereas *BRAF* mutations were rarely detected[27]. Successor lesions of GCHPs were rarely observed and it is open question whether they are self-limiting[9,24] or progress to advanced *KRAS*-mutated serrated polyps, presumably traditional serrated adenomas (TSA)[28] (Figure 2).

The mucin-poor hyperplastic polyp is the rarest form, almost absent of goblet cells. It has prominent nuclear atypia, hyperchromatic nuclei, lack of mucin, therefore it is considered to be a reactive version of MVHP with unknown clinical significance[29].

This distinction among these HP variants is primarily of theoretical importance, and an area of academic interest with little or no clinical importance at the moment. However, the distinction between HPs and more advanced lesions is of cardinal clinical importance[28] (Table 1).

PRECURSOR LESIONS TO SERRATED ADENOCARCINOMA

Serrated adenomas

In their landmark paper from 1990, Longacre and Fenoglio-Preiser[30] retrospectively overviewed 18 000 colorectal polyps and identified 110 (0.6%) as serrated adenomas. In 2003, Torlakovic *et al*[19] further divided serrated adenomas into two categories, TSA (those originally described by Longacre and Fenoglio-Preiser) and a new group identified as sessile serrated adenomas (SSAs), lesions with a serrated morphology without cytologic dysplasia.

Sessile serrated adenoma

SSAs are thought to be the second most common form of serrated polyps representing about 20% of all serrated polyps[18,19,31], however more recent studies have shown decreased prevalence (3%-8%)[32,33]. As mentioned above, before 2003 SSAs were labeled as "HP"[34]. It was demonstrated in a recent case series that according to the new WHO classification for serrated colonic polyps[35] a considerable proportion of HPs (especially those greater than 5 mm) were reclassified as SSAs[36].

Still today it is hard to distinguish SSAs from HPs, as

there are only subtle differences, and SSAs lack the typical features (such as cytologic dysplasia) of traditional adenomas. SSAs tend to locate in the proximal colon, but they can also be encountered in the distal colon (Table 1).

The microscopical features of SSAs were first described by Torlakovic and Snover[37] in their landmark paper in 1996, then the term was reintroduced in 2003[19,31]. Microscopically, most characteristic features include horizontal crypt extensions (inverted T- or L- shape) at the crypt bases, crypt branching, crypt invaginations and inverted crypts beneath the mucosal muscle layer (pseudoinvasion), mature goblet cells at the crypt bases, dilation in the lower crypts, serration throughout the crypt length, extending into the lower third of the crypt as well[18,38]. The proliferation zone can extend to the basis of the crypt. SSAs can exhibit mild nuclear atypia, but always lack cytologic dysplasia.

Endoscopically, SSAs are flat or slightly elevated, malleable lesions with irregular borders and may be covered with a thin layer of yellowish mucus giving them a pale appearance[28,38]. They are usually larger than 5 mm in diameter. Their surface is smooth or granular[28], sometimes resembling a prominent mucosal fold. These features altogether make it difficult to detect and remove completely with conventional white-light endoscope, therefore advanced, image-enhanced endoscopy techniques including traditional or virtual magnifying chromoendoscopy are needed. Chromoendoscopy is an image-enhanced endoscopic technique that highlights differences in colonic mucosa based on structural patterns, so-called "pit patterns". In a recent magnifying endoscopy study a new Type Ⅱ open-shape pit pattern (Type Ⅱ-O) was described and shown highly predictive of SSAs (with a sensitivity of 65.5% and a specificity of 97.3%). Progression of SSAs to more advanced lesions was associated with additional morphological changes, including the Type Ⅲ, Ⅳ and Ⅴ pit patterns[39] (Table 1).

On a molecular level, SSAs exhibit *BRAF* mutation and high level of CpG island methylation, supporting the hypothesis that they represent an intermediate stage between MVHPs and sporadic CIMP-H cancers. It was shown that SSAs can progress to dysplasia (SSA with high grade dysplasia, SSA-HGD) and then to CIMP-H cancers. Methylation and consequential loss of expression of *MLH1* (a major DNA mismatch repair gene) is thought to drive this transformation. Impaired mismatch repair leads to high level of microsatellite instability (MSI-H) (Figure 2). It was hypothesized that this malignant progression can occur at faster rate than that observed in the lesions emerging *via* the traditional pathway[40]. This is based on the observation that SACs are more prevalent than SSA-HGD[31,32,38]. The exact time of progression from SSA to SAC is unknown. In a recent case report an untreated SSA was described to transform into an early submucosal invasive cancer in a period of 8 months[41]. These data further underline the need for improved detection of these lesions.

Traditional serrated adenoma

TSAs were first described by Longacre and Fenoglio-Presier[30] in 1990. As mentioned above, until 2003 they were termed serrated adenomas when Torlakovic *et al*[19] divided serrated adenomas to SSA and TSA. In 2008 the same group further characterized these lesions[42]. TSAs represent the rarest subtype of serrated lesions, with a frequency of 1%-6%[18]. Similar to the majority of serrated lesions (unlike SSAs), TSAs have a predilection for the distal colon and the rectum. Macroscopically they resemble traditional adenomas, as having a pedunculated, polypoid appearance. Cytologic dysplasia (90% low-grade and 10% high-grade[18]), as their name implies, is a major feature of TSAs (Table 1).

In 2008, Torlakovic *et al*[42] proposed ectopic crypt formation as decisive morphological criterion for diagnosing TSAs. Ectopic crypts are newly formed aberrant crypts that lost their anchoring to the underlying muscular layer of mucosa[18]. Other characteristics include diffuse eosinophilic cytoplasm, mucosal bridges and protrusions resembling tennis-racquets[42]. On a molecular level, TSAs are frequently *KRAS* mutants; however they can exhibit *BRAF* mutation, and also lack both mutations.

Filiform serrated adenoma is an unusual, less aggressive variant of traditional serrated adenoma, with morphological features similar to TSA[43]. Unlike TSA, filiform SA is composed predominantly of prominent, thin, elongated filiform projections lined by neoplastic epithelium with a serrated contour[44].

Mixed polyps

Mixed polyps are combinations of traditional adenomas and serrated lesions. They are postulated to be the result of collision tumors[45] and successors of SSAs. It is not encouraged to use this term as it does not disclose the preinvasive nature of these lesions[18]. Still, "mixed polyp" is a widely used term and when used it is recommended to describe the components of these lesions (*e.g.*, TSA and traditional adenoma *etc.*)[18].

SERRATED ADENOCARCINOMA

Morphologic features

SAC, a special subtype of colorectal adenocarcinomas morphologically and histochemically resembling serrated polyps, was first described by Jass and Smith in 1992[46]. The relationship between serrated adenomas and SAC were further confirmed by Mäkinen *et al*[47], then histological characteristics of SAC were described[48] and reviewed by the same group[38]. Based on these seminal reports, most important diagnostic criteria of SAC include epithelial serrations, eosinophilic and abundant cytoplasm with vesicular nuclei, chromatin condensation and lack of necrosis. SAC was further classified into three major growth patterns. The most common (70%) serrated pattern contains mature, abundant, mucus-producing epithelium with well-preserved polarity, very similar to serrated

polyps[38]. The mucinous pattern (43%) strongly overlaps with the first group, and is characterized by eosinophilic papillary rods (93%) and eosinophilic cell balls floating in the mucus[38]. The least common (7%) trabecular pattern is a feature of poorly differentiated SACs, where serrated structures are absent and cancer cells grow in a trabecular pattern, but still these cases show eosinophilic epithelium with vesicular nuclei, uncharacteristic of poorly differentiated traditional CRCs[38].

Molecular features

Gene expression profiling study by Laiho *et al*[49] provided molecular evidence that SAC is a biologically distinct subclass of CRC. Comparison of SAC and conventional CRCs revealed 201 differentially expressed genes. Three potential candidates were identified that can be involved in the oncogenesis of SAC: Ephrin receptor B2 (*EPHB2*), hypoxia-inducible factor 1-alpha (*HIF1a*) and patched (*PTCH*) appeared as genes important for the oncogenesis of serrated CRC. *EPHB2* and *PTCH* expression are decreased in SAC compared to conventional CRC. On the other hand, constitutive overexpression of *HIF1a*, a major proangiogenic factor, can be the cause of infrequent necrosis seen in SAC[50]. Activating mutations of oncogenic *BRAF* and *KRAS* are common findings in SAC[26]. As mentioned above, these mutually exclusive mutations induce MAPK-ERK pathway that leads to the inhibition of apoptosis resulting in serrated appearance. Accumulation of CpG island methylation in the promoter regions and consequential silencing in key proapoptotic and tumor suppressor genes, such as *p16* or *IGFBP7* sets up a vicious circle. It is well established that methylation of *MLH1* leading to MSI-H phenotype (closely linked with the sessile serrated pathway) and methylation of *MGMT* leading to MSI-L are the main inducing factors in the malignant progression of serrated adenomas (Figure 2).

It is generally thought that CpG island hypermethylation is confined to the serrated pathway (CIMP)[51,52], however a recent study showed that sporadic CRCs and precursors arising *via* the traditional adenoma-carcinoma pathway also have a characteristic DNA methylation pattern different from those evolving through the serrated pathway[53].

Clinical characteristics

SAC predominantly locates to cecum (52%) and rectum (33%)[47]. It is estimated that 16% of proximal CRCs are SACs, whereas this proportion in the distal colon is only 6%[48]. It is hypothesized that proximal SACs (mostly MSI-H) arise from SSAs and distal SACs (MSI-L and MSS) originate from TSAs[38] (Figure 2). While serrated adenomas are more common in males, SACs are almost twice (1.9 : 1) as common in females, than in males[48]. The higher risk of malignant progression of serrated adenomas to SAC in (elderly) women was explained with postmenopausal estrogen deficiency and decreased folate level, however this needs to be further investigated[38].

The prognosis of SAC seems to be defined by its molecular profile (Figure 2). *BRAF*-mutated, microsatellite-stable cancers in the proximal colon confer a very poor survival[54] with adverse histological features such as lymphatic and perineural invasion and high tumor budding[55]. On the other hand, *BRAF*-mutated cancers with MSI-H phenotype (sporadic MSI-H CRCs) have a favorable prognosis[56].

SERRATED POLYPOSIS: A GENETIC PREDISPOSITION SYNDROME

Serrated polyposis, formerly called hyperplastic polyposis, is a rare form of intestinal polyposis, initially described in 1970 by Goldman *et al*[2]. Current diagnostic criteria, manifested in 2010[35], include (1) at least five serrated polyps proximal to the sigmoid colon with two or more of these being > 10 mm; (2) any number of serrated polyps proximal to the sigmoid colon in an individual who has a first-degree relative with serrated polyposis; and (3) > 20 serrated polyps of any size distributed throughout the colon (not all in the rectum).

Although serrated polyposis provided the first evidences for the malignant potential of serrated polyps, it is still one of the most under-recognized and poorly understood intestinal polyposis syndrome. This is probably due to its rarity (1 in 3000)[57], but also to the phenotypic plasticity[58] and overlapping clinical phenotypes within this disorder[59]. However, based on clinical observations including earlier onset of CRC, multiple cancers, increased individual and familial risk, accumulating evidence indicates that serrated polyposis is a genetic predisposition syndrome to CRC and probably confers also an increased risk for some extracolonic cancers[60].

IMPLICATIONS FOR MANAGEMENT OF SERRATED POLYPS

It is imperative to detect and completely remove serrated lesions, as majority of these lesions tend to progress, and contribute to the development of interval cancers. Data on the natural history of serrated polyps is limited, only retrospective studies with small sample size[61] are currently available. High risk serrated polyps are frequently flat and associated with synchronous advanced colorectal neoplasms[62]. Magnifying chromoendoscopy can facilitate to differentiate between serrated polyps, but it is still difficult to distinguish between SSA and typical HP[63]. Both endoscopists and pathologists should know the most important features in order to detect and diagnose these lesions (Table 1).

To date, no consensus guidelines exist on the management of serrated polyps, but new guidelines including recommendations for management and follow-up of serrated polyps are expected to be available in the near future. With the exception of small and diminutive HPs in the rectosigmoid, that confer no malignant potential,

Table 1 Most important features of serrated polyps[18,19,38,39,62]

	Sessile serrated adenoma	Traditional serrated adenoma	Hyperplastic polyps
Location	Proximal	Distal	Distal
Macroscopic characteristics	Sessile, flat, covered with mucus, poorly defined borders	Protruding, pedunculated	Flat
Color	Normochromatic, pale	Reddish	Pale
Size	> 5 mm	> 5 mm	< 5 mm
Molecular features	*BRAF* mt	*KRAS* mt	
Histological characteristics	Dilated, branched serrated crypts at the bottom	Prominent crypt serration, ectopic crypt formation	Serrations at the top
Pit pattern	Open-shape (type II-O)	Fern or pinecone-like	Starlike (type II)
Precursor	MVHP	GCHP	ACF
Malignant potential	+++	++	-
CIMP status	CIMP-H	CIMP-L	
MSI status	MSI-H or MSS	MSI-L or MSS	MSS
Gender predominance	Female	Male	Male
Dysplasia	Absent	Present	Absent
Ectopic crypt formation	Absent	Present	Absent

MVHP: Microvesicular hyperplastic polyp; GCHP: Goblet cell-rich hyperplastic polyp; ACF: Aberrant crypt focus; CIMP-H: CpG island methylator phenotype-high; CIMP-L: CpG island methylator phenotype-low; MSI-H: High-level microsatellite instability; MSI-L: Low-level microsatellite instability; MSS: Microsatellite stable.

Table 2 Colonoscopic management and surveillance strategies for serrated polyps based on experts' opinion and current literature[28,34,51,63]

Serrated polyp	Intervention	Surveillance interval
Hyperplastic polyp in the rectosigmoid	No surveillance recommended	Screening colonoscopy at 10 yr
SSA without dysplasia	Endoscopic resection (EMR)	< 3 lesions, < 1 cm: 5 yr ⩾ 3 lesions, ⩾ 1 cm: 3 yr
SSA with dysplasia	Endoscopic resection (EMR)	Complete: 2-6 mo Incomplete: Segmental colectomy
TSA	Endoscopic resection (cold-snare)	Complete: 3 yr Incomplete: Segmental colectomy
Serrated polyposis	Endoscopic resection	Follow-up colonoscopy at 6-12 mo Children: screening at an age 10 yr younger than index case
Serrated polyposis in first-degree relative	Screening at an age 10 yr younger	Follow-up colonoscopy at 12 mo

SSA: Sessile serrated adenoma; TSA: Traditional serrated adenoma; EMR: Endoscopic mucosal resection.

all other serrated polyps should be endoscopically removed. If endoscopic resection cannot be implemented, then segmental colectomy is advised[51]. There is no consensus among experts on the optimal post-polypectomy surveillance intervals, however because of lack of data and presumed faster progression rate a more intensive surveillance is recommended (Table 2).

Due to their sessile nature, SSAs are difficult to detect and remove endoscopically. For the removal of flat SSAs endoscopic mucosal resection (EMR) is the method of choice[34]. It is recommended to use a chromoendoscopy contrast dye (either onto the surface or injected submucosally) to define the border of the lesion, lifting it, then snare removing *in toto* or in multiple sessions[28,34]. It is important to note that because of the thin wall of proximal colon (where SSAs typically locate[65]), this difficult technique is even more challenging, as one has take the complications of EMR (bleeding, perforation, incomplete resection) into account and it is advised to use argon plasma coagulation to reduce the risk of complications and recurrence[34,66].

CONCLUSION

It is getting generally accepted that CRC is a heterogeneous disease. Serrated pathway is serrated pathway is a rapidly evolving concept in colorectal carcinogenesis and it is postulated that 10%-20% of CRCs arise *via* this alternative pathway. In the past two decades since its original description our knowledge of morphologic and molecular alterations of serrated lesions has greatly expanded and these lesions are getting increasingly recognized. A major challenge is how to translate these new findings into clinical practice and how to determine appropriate surveillance intervals in order to avoid interval cancers. Further investigation is needed to better characterize natural history, optimize management and improve clinical outcomes.

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REFERENCES

1 **Vogelstein B**, Fearon ER, Hamilton SR, Kern SE, Preisinger AC, Leppert M, Nakamura Y, White R, Smits AM, Bos JL. Genetic alterations during colorectal-tumor development. *N Engl J Med* 1988; **319**: 525-532 [PMID: 2841597 DOI: 10.1056/NEJM198809013190901]

2 **Goldman H**, Ming S, Hickock DF. Nature and significance of hyperplastic polyps of the human colon. *Arch Pathol* 1970; **89**: 349-354 [PMID: 5435674]

3 **Jass JR**. Relation between metaplastic polyp and carcinoma of the colorectum. *Lancet* 1983; **1**: 28-30 [PMID: 6129371 DOI: 10.1016/S0140-6736(83)91564-7]

4 **Young J**, Jenkins M, Parry S, Young B, Nancarrow D, English D, Giles G, Jass J. Serrated pathway colorectal cancer in the population: genetic consideration. *Gut* 2007; **56**: 1453-1459 [PMID: 17566021 DOI: 10.1136/gut.2007.126870]

5 **Snover DC**. Update on the serrated pathway to colorectal carcinoma. *Hum Pathol* 2011; **42**: 1-10 [PMID: 20869746 DOI: 10.1016/j.humpath.2010.06.002]

6 **Tateyama H**, Li W, Takahashi E, Miura Y, Sugiura H, Eimoto T. Apoptosis index and apoptosis-related antigen expression in serrated adenoma of the colorectum: the saw-toothed structure may be related to inhibition of apoptosis. *Am J Surg Pathol* 2002; **26**: 249-256 [PMID: 11812948 DOI: 10.1097/00000478-200202000-00013]

7 **Higuchi T**, Jass JR. My approach to serrated polyps of the colorectum. *J Clin Pathol* 2004; **57**: 682-686 [PMID: 15220357 DOI: 10.1136/jcp.2003.015230]

8 **Carragher LA**, Snell KR, Giblett SM, Aldridge VS, Patel B, Cook SJ, Winton DJ, Marais R, Pritchard CA. V600EBraf induces gastrointestinal crypt senescence and promotes tumour progression through enhanced CpG methylation of p16INK4a. *EMBO Mol Med* 2010; **2**: 458-471 [PMID: 20941790 DOI: 10.1002/emmm.201000099]

9 **O'Brien MJ**. Hyperplastic and serrated polyps of the colorectum. *Gastroenterol Clin North Am* 2007; **36**: 947-968, viii [PMID: 17996799 DOI: 10.1016/j.gtc.2007.08.007]

10 **Chan AO**, Broaddus RR, Houlihan PS, Issa JP, Hamilton SR, Rashid A. CpG island methylation in aberrant crypt foci of the colorectum. *Am J Pathol* 2002; **160**: 1823-1830 [PMID: 12000733 DOI: 10.1016/S0002-9440(10)61128-5]

11 **Suehiro Y**, Hinoda Y. Genetic and epigenetic changes in aberrant crypt foci and serrated polyps. *Cancer Sci* 2008; **99**: 1071-1076 [PMID: 18384435]

12 **Nucci MR**, Robinson CR, Longo P, Campbell P, Hamilton SR. Phenotypic and genotypic characteristics of aberrant crypt foci in human colorectal mucosa. *Hum Pathol* 1997; **28**: 1396-1407 [PMID: 9416697 DOI: 10.1016/S0046-8177(97)90230-6]

13 **Takayama T**, Ohi M, Hayashi T, Miyanishi K, Nobuoka A, Nakajima T, Satoh T, Takimoto R, Kato J, Sakamaki S, Niitsu Y. Analysis of K-ras, APC, and beta-catenin in aberrant crypt foci in sporadic adenoma, cancer, and familial adenomatous polyposis. *Gastroenterology* 2001; **121**: 599-611 [PMID: 11522744 DOI: 10.1053/gast.2001.27203]

14 **Stevens RG**, Swede H, Rosenberg DW. Epidemiology of colonic aberrant crypt foci: review and analysis of existing studies. *Cancer Lett* 2007; **252**: 171-183 [PMID: 17182176 DOI: 10.1016/j.canlet.2006.11.009]

15 **Rosenberg DW**, Yang S, Pleau DC, Greenspan EJ, Stevens RG, Rajan TV, Heinen CD, Levine J, Zhou Y, O'Brien MJ. Mutations in BRAF and KRAS differentially distinguish serrated versus non-serrated hyperplastic aberrant crypt foci in humans. *Cancer Res* 2007; **67**: 3551-3554 [PMID: 17440063 DOI: 10.1158/0008-5472.CAN-07-0343]

16 **Michaloglou C**, Vredeveld LC, Soengas MS, Denoyelle C, Kuilman T, van der Horst CM, Majoor DM, Shay JW, Mooi WJ, Peeper DS. BRAFE600-associated senescence-like cell cycle arrest of human naevi. *Nature* 2005; **436**: 720-724 [PMID: 16079850 DOI: 10.1038/nature03890]

17 **Wajapeyee N**, Serra RW, Zhu X, Mahalingam M, Green MR. Role for IGFBP7 in senescence induction by BRAF. *Cell* 2010; **141**: 746-747 [PMID: 20510919 DOI: 10.1016/j.cell.2010.05.014]

18 **Aust DE**, Baretton GB. Serrated polyps of the colon and rectum (hyperplastic polyps, sessile serrated adenomas, traditional serrated adenomas, and mixed polyps)-proposal for diagnostic criteria. *Virchows Arch* 2010; **457**: 291-297 [PMID: 20617338 DOI: 10.1007/s00428-010-0945-1]

19 **Torlakovic E**, Skovlund E, Snover DC, Torlakovic G, Nesland JM. Morphologic reappraisal of serrated colorectal polyps. *Am J Surg Pathol* 2003; **27**: 65-81 [PMID: 12502929 DOI: 10.1097/00000478-200301000-00008]

20 **Morimoto LM**, Newcomb PA, Ulrich CM, Bostick RM, Lais CJ, Potter JD. Risk factors for hyperplastic and adenomatous polyps: evidence for malignant potential? *Cancer Epidemiol Biomarkers Prev* 2002; **11**: 1012-1018 [PMID: 12376501]

21 **Kearney J**, Giovannucci E, Rimm EB, Stampfer MJ, Colditz GA, Ascherio A, Bleday R, Willett WC. Diet, alcohol, and smoking and the occurrence of hyperplastic polyps of the colon and rectum (United States). *Cancer Causes Control* 1995; **6**: 45-56 [PMID: 7718735 DOI: 10.1007/BF00051680]

22 **Samowitz WS**, Albertsen H, Sweeney C, Herrick J, Caan BJ, Anderson KE, Wolff RK, Slattery ML. Association of smoking, CpG island methylator phenotype, and V600E BRAF mutations in colon cancer. *J Natl Cancer Inst* 2006; **98**: 1731-1738 [PMID: 17148775 DOI: 10.1093/jnci/djj468]

23 **Limsui D**, Vierkant RA, Tillmans LS, Wang AH, Weisenberger DJ, Laird PW, Lynch CF, Anderson KE, French AJ, Haile RW, Harnack LJ, Potter JD, Slager SL, Smyrk TC, Thibodeau SN, Cerhan JR, Limburg PJ. Cigarette smoking and colorectal cancer risk by molecularly defined subtypes. *J Natl Cancer Inst* 2010; **102**: 1012-1022 [PMID: 20587792 DOI: 10.1093/jnci/djq201]

24 **O'Brien MJ**, Yang S, Mack C, Xu H, Huang CS, Mulcahy E, Amorosino M, Farraye FA. Comparison of microsatellite instability, CpG island methylation phenotype, BRAF and KRAS status in serrated polyps and traditional adenomas indicates separate pathways to distinct colorectal carcinoma end points. *Am J Surg Pathol* 2006; **30**: 1491-1501 [PMID: 17122504 DOI: 10.1097/01.pas.0000213313.36306.85]

25 **O'Brien MJ**, Yang S, Clebanoff JL, Mulcahy E, Farraye FA, Amorosino M, Swan N. Hyperplastic (serrated) polyps of the colorectum: relationship of CpG island methylator phenotype and K-ras mutation to location and histologic subtype. *Am J Surg Pathol* 2004; **28**: 423-434 [PMID: 15087661]

26 **Yang S**, Farraye FA, Mack C, Posnik O, O'Brien MJ. BRAF and KRAS Mutations in hyperplastic polyps and serrated adenomas of the colorectum: relationship to histology and CpG island methylation status. *Am J Surg Pathol* 2004; **28**: 1452-1459 [PMID: 15489648 DOI: 10.1097/01.pas.0000141404.56839.6a]

27 **Spring KJ**, Zhao ZZ, Karamatic R, Walsh MD, Whitehall VL, Pike T, Simms LA, Young J, James M, Montgomery GW, Appleyard M, Hewett D, Togashi K, Jass JR, Leggett BA. High prevalence of sessile serrated adenomas with BRAF mutations: a prospective study of patients undergoing colonoscopy. *Gastroenterology* 2006; **131**: 1400-1407 [PMID: 17101316 DOI: 10.1053/j.gastro.2006.08.038]

28 **Huang CS**, Farraye FA, Yang S, O'Brien MJ. The clinical significance of serrated polyps. *Am J Gastroenterol* 2011; **106**: 229-240; quiz 241 [PMID: 21045813 DOI: 10.1038/ajg.2010.429]

29 **Arnold CA**, Montgomery E, Iacobuzio-Donahue M. The serrated pathway of neoplasia: new insights into an evolving concept. *Diagn Histopathol* 2011; **17**: 367-375 [DOI: 10.1016/j.mpdhp.2011.06.006]

30 **Longacre TA**, Fenoglio-Preiser CM. Mixed hyperplastic adenomatous polyps/serrated adenomas. A distinct form of colorectal neoplasia. *Am J Surg Pathol* 1990; **14**: 524-537 [PMID: 2186644 DOI: 10.1097/00000478-199006000-00003]

31 **Goldstein NS**, Bhanot P, Odish E, Hunter S. Hyperplastic-like colon polyps that preceded microsatellite-unstable adenocarcinomas. *Am J Clin Pathol* 2003; **119**: 778-796 [PMID: 12817424 DOI: 10.1309/DRFQ0WFUF1G13CTK]

32 **Higuchi T**, Sugihara K, Jass JR. Demographic and pathological characteristics of serrated polyps of colorectum. *Histopathology* 2005; **47**: 32-40 [PMID: 15982321 DOI: 10.1111/j.1365-2559.2005.02180.x]

33 **Tannapfel A**, Neid M, Aust D, Baretton G. The origins of colorectal carcinoma: specific nomenclature for different pathways and precursor lesions. *Dtsch Arztebl Int* 2010; **107**: 760-766 [PMID: 21085545]

34 **East JE**, Saunders BP, Jass JR. Sporadic and syndromic hyperplastic polyps and serrated adenomas of the colon: classification, molecular genetics, natural history, and clinical management. *Gastroenterol Clin North Am* 2008; **37**: 25-46, v [PMID: 18313538 DOI: 10.1016/j.gtc.2007.12.014]

35 **Snover D**, Ahnen D, Burt R, Odze RD. Serrated Polyps of the Colon and Rectum and Serrated Polyposis. WHO Classification of Tumours of the Digestive System. 4th ed. Lyon: IARC, 2010

36 **Fidalgo CA**, Santos L, Rosa I, Fonseca R, Lage P, Claro I, Chaves P, Dias Pereira A. Hyperplastic polyp? The impact of the new classification for serrated polyps. *Gut* 2011; **60** Suppl 3: A306

37 **Torlakovic E**, Snover DC. Serrated adenomatous polyposis in humans. *Gastroenterology* 1996; **110**: 748-755 [PMID: 8608884 DOI: 10.1053/gast.1996.v110.pm8608884]

38 **Mäkinen MJ**. Colorectal serrated adenocarcinoma. *Histopathology* 2007; **50**: 131-150 [PMID: 17204027 DOI: 10.1111/j.1365-2559.2006.02548.x]

39 **Kimura T**, Yamamoto E, Yamano HO, Suzuki H, Kamimae S, Nojima M, Sawada T, Ashida M, Yoshikawa K, Takagi R, Kato R, Harada T, Suzuki R, Maruyama R, Kai M, Imai K, Shinomura Y, Sugai T, Toyota M. A novel pit pattern identifies the precursor of colorectal cancer derived from sessile serrated adenoma. *Am J Gastroenterol* 2012; **107**: 460-469 [PMID: 22233696 DOI: 10.1038/ajg.2011.457]

40 **Sheridan TB**, Fenton H, Lewin MR, Burkart AL, Iacobuzio-Donahue CA, Frankel WL, Montgomery E. Sessile serrated adenomas with low- and high-grade dysplasia and early carcinomas: an immunohistochemical study of serrated lesions "caught in the act". *Am J Clin Pathol* 2006; **126**: 564-571 [PMID: 16938659 DOI: 10.1309/C7JE8BVL8420V5VT]

41 **Oono Y**, Fu K, Nakamura H, Iriguchi Y, Yamamura A, Tomino Y, Oda J, Mizutani M, Takayanagi S, Kishi D, Shinohara T, Yamada K, Matumoto J, Imamura K. Progression of a sessile serrated adenoma to an early invasive cancer within 8 months. *Dig Dis Sci* 2009; **54**: 906-909 [PMID: 18688718 DOI: 10.1007/s10620-008-0407-7]

42 **Torlakovic EE**, Gomez JD, Driman DK, Parfitt JR, Wang C, Benerjee T, Snover DC. Sessile serrated adenoma (SSA) vs. traditional serrated adenoma (TSA). *Am J Surg Pathol* 2008; **32**: 21-29 [PMID: 18162766 DOI: 10.1097/PAS.0b013e318157f002]

43 **Yantiss RK**, Oh KY, Chen YT, Redston M, Odze RD. Filiform serrated adenomas: a clinicopathologic and immunophenotypic study of 18 cases. *Am J Surg Pathol* 2007; **31**: 1238-1245 [PMID: 17667549 DOI: 10.1097/PAS.0b013e31802d74c0]

44 **Ha SY**, Lee SM, Lee EJ, Kang SY, Jang KT, Park CK, Kim JY, Kim YH, Chang DK, Kim KM. Filiform serrated adenoma is an unusual, less aggressive variant of traditional serrated adenoma. *Pathology* 2012; **44**: 18-23 [PMID: 22157687 DOI: 10.1097/PAT.0b013e32834d7bbf]

45 **Jass JR**, Whitehall VL, Young J, Leggett BA. Emerging concepts in colorectal neoplasia. *Gastroenterology* 2002; **123**: 862-876 [PMID: 12198712 DOI: 10.1053/gast.2002.35392]

46 **Jass JR**, Smith M. Sialic acid and epithelial differentiation in colorectal polyps and cancer--a morphological, mucin and lectin histochemical study. *Pathology* 1992; **24**: 233-242 [PMID: 1289763 DOI: 10.3109/00313029209068874]

47 **Mäkinen MJ**, George SM, Jernvall P, Mäkelä J, Vihko P, Karttunen TJ. Colorectal carcinoma associated with serrated adenoma--prevalence, histological features, and prognosis. *J Pathol* 2001; **193**: 286-294 [PMID: 11241406 DOI: 10.1002/1096-9896(2000)9999:]

48 **Tuppurainen K**, Mäkinen JM, Junttila O, Liakka A, Kyllönen AP, Tuominen H, Karttunen TJ, Mäkinen MJ. Morphology and microsatellite instability in sporadic serrated and non-serrated colorectal cancer. *J Pathol* 2005; **207**: 285-294 [PMID: 16177963 DOI: 10.1002/path.1850]

49 **Laiho P**, Kokko A, Vanharanta S, Salovaara R, Sammalkorpi H, Järvinen H, Mecklin JP, Karttunen TJ, Tuppurainen K, Davalos V, Schwartz S, Arango D, Mäkinen MJ, Aaltonen LA. Serrated carcinomas form a subclass of colorectal cancer with distinct molecular basis. *Oncogene* 2007; **26**: 312-320 [PMID: 16819509 DOI: 10.1038/sj.onc.1209778]

50 **García-Solano J**, Pérez-Guillermo M, Conesa-Zamora P, Acosta-Ortega J, Trujillo-Santos J, Cerezuela-Fuentes P, Mäkinen MJ. Clinicopathologic study of 85 colorectal serrated adenocarcinomas: further insights into the full recognition of a new subset of colorectal carcinoma. *Hum Pathol* 2010; **41**: 1359-1368 [PMID: 20594582 DOI: 10.1016/j.humpath.2010.04.002]

51 **Leonard DF**, Dozois EJ, Smyrk TC, Suwanthanma W, Baron TH, Cima RR, Larson DW. Endoscopic and surgical management of serrated colonic polyps. *Br J Surg* 2011; **98**: 1685-1694 [PMID: 22034178 DOI: 10.1002/bjs.7654]

52 **Patai AV**, Molnár B, Kalmár A, Schöller A, Tóth K, Tulassay Z. Role of DNA methylation in colorectal carcinogenesis. *Dig Dis* 2012; **30**: 310-315 [PMID: 22722557 DOI: 10.1159/000337004.]

53 **Patai AV**, Galamb O, Kalmár A, Wichmann B, Valcz G, Patai A, Leiszter K, Tóth K, Tulassay Z, Molnár B. Non-sequential DNA methylation alterations in the adenoma-dysplasia-carcinoma sequence in the distal colon. *Gut* 2011; **60** Suppl 3: A76

54 **Samowitz WS**, Sweeney C, Herrick J, Albertsen H, Levin TR, Murtaugh MA, Wolff RK, Slattery ML. Poor survival associated with the BRAF V600E mutation in microsatellite-stable colon cancers. *Cancer Res* 2005; **65**: 6063-6069 [PMID: 16024606 DOI: 10.1158/0008-5472.CAN-05-0404]

55 **Pai RK**, Jayachandran P, Koong AC, Chang DT, Kwok S, Ma L, Arber DA, Balise RR, Tubbs RR, Shadrach B, Pai RK. BRAF-mutated, microsatellite-stable adenocarcinoma of the proximal colon: an aggressive adenocarcinoma with poor survival, mucinous differentiation, and adverse morphologic features. *Am J Surg Pathol* 2012; **36**: 744-752 [PMID: 22314188 DOI: 10.1097/PAS.0b013e31824430d7]

56 **Samowitz WS**, Curtin K, Ma KN, Schaffer D, Coleman LW, Leppert M, Slattery ML. Microsatellite instability in sporadic colon cancer is associated with an improved prognosis at the population level. *Cancer Epidemiol Biomarkers Prev* 2001; **10**: 917-923 [PMID: 11535541]

57 **Lockett MJ**, Atkin WS. Hyperplastic polyposis: prevalence and cancer risk. *Gut* 2001; **48** Suppl 1: A4

58 **Roberts A**, Nancarrow D, Clendenning M, Buchanan DD, Jenkins MA, Duggan D, Taverna D, McKeone D, Walters R, Walsh MD, Young BW, Jass JR, Rosty C, Gattas M, Pelzer E, Hopper JL, Goldblatt J, George J, Suthers GK, Phillips K, Parry S, Woodall S, Arnold J, Tucker K, Muir A, Drini M, Macrae F, Newcomb P, Potter JD, Pavluk E, Lindblom A, Young JP. Linkage to chromosome 2q32.2-q33.3 in familial serrated neoplasia (Jass syndrome). *Fam Cancer* 2011; **10**: 245-254 [PMID: 21165777]

59 **Kalady MF**, Jarrar A, Leach B, LaGuardia L, O'Malley M, Eng C, Church JM. Defining phenotypes and cancer risk in hyperplastic polyposis syndrome. *Dis Colon Rectum* 2011; **54**: 164-170 [PMID: 21228663 DOI: 10.1007/DCR.0b013e3181fd4c15]

60 **Jarrar AM**, Church JM, Fay S, Kalady MF. Is the phenotype

mixed or mistaken? Hereditary nonpolyposis colorectal cancer and hyperplastic polyposis syndrome. *Dis Colon Rectum* 2009; **52**: 1949-1955 [PMID: 19934914 DOI: 10.1007/DCR.0b013e3181b5450c]

61 **Teriaky A**, Driman DK, Chande N. Outcomes of a 5-year follow-up of patients with sessile serrated adenomas. *Scand J Gastroenterol* 2012; **47**: 178-183 [PMID: 22229626 DOI: 10.3109/00365521.2011.645499]

62 **Rondagh EJ**, Masclee AA, Bouwens MW, Winkens B, Riedl RG, de Bruïne AP, de Ridder R, Kaltenbach T, Soetikno RM, Sanduleanu S. Endoscopic red flags for the detection of high-risk serrated polyps: an observational study. *Endoscopy* 2011; **43**: 1052-1058 [PMID: 21971921 DOI: 10.1055/s-0030-1256770]

63 **Kashida H**, Ikehara N, Hamatani S, Kudo SE, Kudo M. Endoscopic characteristics of colorectal serrated lesions. *Hepatogastroenterology* 2011; **58**: 1163-1167 [PMID: 21937375 DOI: 10.5754/hge10093]

64 **Terdiman JP**, McQuaid KR. Surveillance guidelines should be updated to recognize the importance of serrated polyps. *Gastroenterology* 2010; **139**: 1444-1447 [PMID: 20875785 DOI: 10.1053/j.gastro.2010.09.024]

65 **Gurudu SR**, Heigh RI, De Petris G, Heigh EG, Leighton JA, Pasha SF, Malagon IB, Das A. Sessile serrated adenomas: demographic, endoscopic and pathological characteristics. *World J Gastroenterol* 2010; **16**: 3402-3405 [PMID: 20632442 DOI: 10.3748/wjg.v16.i27.3402]

66 **Brooker JC**, Saunders BP, Shah SG, Thapar CJ, Suzuki N, Williams CB. Treatment with argon plasma coagulation reduces recurrence after piecemeal resection of large sessile colonic polyps: a randomized trial and recommendations. *Gastrointest Endosc* 2002; **55**: 371-375 [PMID: 11868011 DOI: 10.1067/mge.2002.121597]

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