

Review Article

Screening, management and surveillance for the sessile serrated adenomas/polyps

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Abstract: The incidence and mortality rates from right-sided colorectal cancers (CRCs) have not decreased, compared with the significant reduction of CRCs in the left colon in recent years. It is likely that a significant proportion of right-sided CRCs evolve from undetected sessile serrated adenomas/polyps (SSA/Ps) in the primary colonoscopy. Increasing evidences suggest that SSA/Ps are high-risk lesions, with 15% of the SSA/P patients developing subsequent CRCs or adenomas with high-grade dysplasia. However, there are many issues in the screening, management and surveillance of SSA/Ps. Based on new evidences, this review addresses major issues in the diagnostic criteria for the serrated polyps of the colorectum, new endoscopic techniques (high-resolution magnifying endoscopy, narrow-band imaging, autofluorescence imaging, confocal laser endoscopy, and endocytoscopy) for the realtime identification of SSA/Ps, and the management of SSA/Ps by endoscopic mucosal resection, endoscopic sub-mucosal dissection or surgical resection in practice.

Keywords: Serrated polyp, sessile serrated adenomas/polyps, screening, management, surveillance

Introduction

Although there is a significant reduction of colorectal cancers (CRCs) in the left colon, the incidence and mortality rates from right-sided CRCs have not decreased in recent years [1, 2]. It is very likely that a significant proportion of these cancers evolve from undetected sessile serrated adenomas/polyps (SSA/Ps) in the primary colonoscopy [3]. It's believed that up to 20% of all CRCs arise through a serrated polyp-neoplasia pathway [4-6].

Serrated polyps of the colorectum are histologically classified into hyperplastic polyps (HPs), traditional serrated adenomas (TSAs), and SSA/Ps [7-9]. All these serrated lesions are characterized by the saw-toothed architecture of epithelium [10, 11]. HPs account for 70-95% of all serrated polyps and are located usually in the left colon [12]. HPs used to be defined as benign lesions without neoplastic potential. However, it has been suggested that right-sided microvesicular HP may be a precursor to more advanced SSA/P [9, 13]. TSAs was first described by Longacre and Fenoglio-Preiser

[14] in 1990, which exhibit cytologic dysplasia reminiscent of classical adenomas and a serrated architecture resembling HPs. TSAs are found mainly in the left colon and considered to be a lesion of minor importance because of its low prevalence [15]. It's claimed that the subsequent cancer risk rate of TSA equals that of traditional adenomas [16, 17].

The entity of SSA/P was established and started to be recognized in the pathology community after about 2005 [8]. SSA/P cytologically resembles HP but is distinguished from HP on the basis of crypt dilation, branching, and horizontal spreading (**Figure 1**) [18]. Moreover, SSA/Ps are mainly found in the right colon and typically larger than HPs, representing 5-25% of serrated polyps [7, 12, 19, 20].

SSA/Ps are recognized as high-risk lesions with fast progression

Increasing evidences suggest that SSA/Ps are high-risk lesions, with 15% of the SSA/P patients developing subsequent CRCs or adenomas with high-grade dysplasia (HGD) [16, 21,

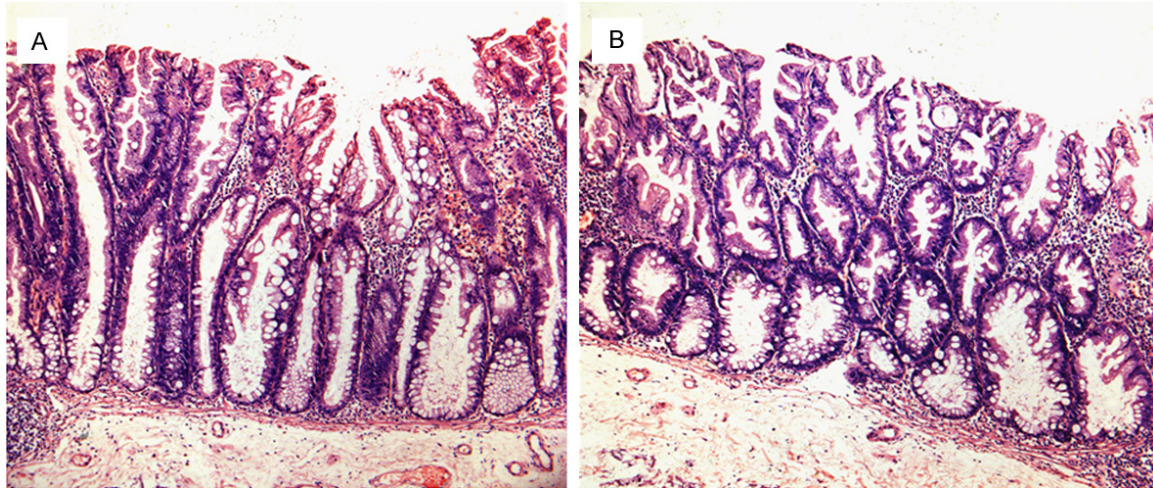


Figure 1. Histologic features of sessile serrated adenomas/polyps. The architecture of the crypts is distorted, seen as basal crypt dilatation and crypt branching. Hematoxylin and eosin (H&E) staining, 200 × magnification.

22]. SSA/Ps have been considered to be precursor of some microsatellite-instability (MSI)-high carcinomas of the proximal colon [8]. Furthermore, the neoplastic progression within this pathway is faster than within the classical adenoma–carcinoma sequence [16, 22]. Oono et al [23] reported a case of a SSA/P showing rapid transformation into a submucosal invasive carcinoma in a short period of 8 months. Nevertheless, the natural history and biologic behavior of SSA/P remains unknown.

Standardized criteria for histopathological diagnosis of SSA/Ps are needed

Recent investigations have identified the SSA/Ps as a clinically distinct subgroup and a potential precursor for MSI CRCs, underlining the necessity of identifying them correctly [24–26]. It has become increasingly important to reproducibly distinguish SSA/P from innocent HP, because patients with SSA/P need more aggressive treatment and vigilant clinical monitoring. However, the distinction between SSA/P and HP may be difficult, as SSA/P closely resembles HP [24, 27]. Moreover, there is considerable variation in histologic interpretation for SSA/P by pathologists [28]. Diagnostic criteria and nomenclature for these serrated lesions of the colorectum are not uniform and, therefore, somewhat confusing.

In 2008, the diagnostic criteria and nomenclature for the serrated polyps of the colorectum was proposed by the consensus conference of

the Working Group of Gastroenterological Pathology of the German Society of Pathology [29]. An expert panel from USA stated in 2010 that serrated lesions of the colorectum should be classified pathologically according to the World Health Organization criteria as HP, SSA/P with or without cytological dysplasia, and TSA [12]. According to their proposal, crypts in the SSA/Ps appear dilated and/or branched at the basal portion of the polyp, particularly in the horizontal plane, which leads to the formation of “boot,” “L,” or “anchor”-shaped crypts. The basal half of the crypts often contain excessive serration and mature goblet cells and mucinous cells. Other common cytological features include various degrees of nuclear atypia, dystrophic goblet cells, and an absence of neuroendocrine cells [12].

Given the facts that SSA/Ps were not well recognized by some pathologists and endoscopists, especially those in developing countries [30], standardized diagnostic criteria and terminology for SSA/Ps should be formulated to improve interobserver agreement among pathologists.

Endoscopic diagnosis for SSA/P is facing great challenge

There is a significant reduction of CRCs in the left colon because of the widespread use of screening colonoscopy [1, 2]. However, the incidence and mortality rates from right-sided CRCs have not decreased [1, 2, 31]. These can-

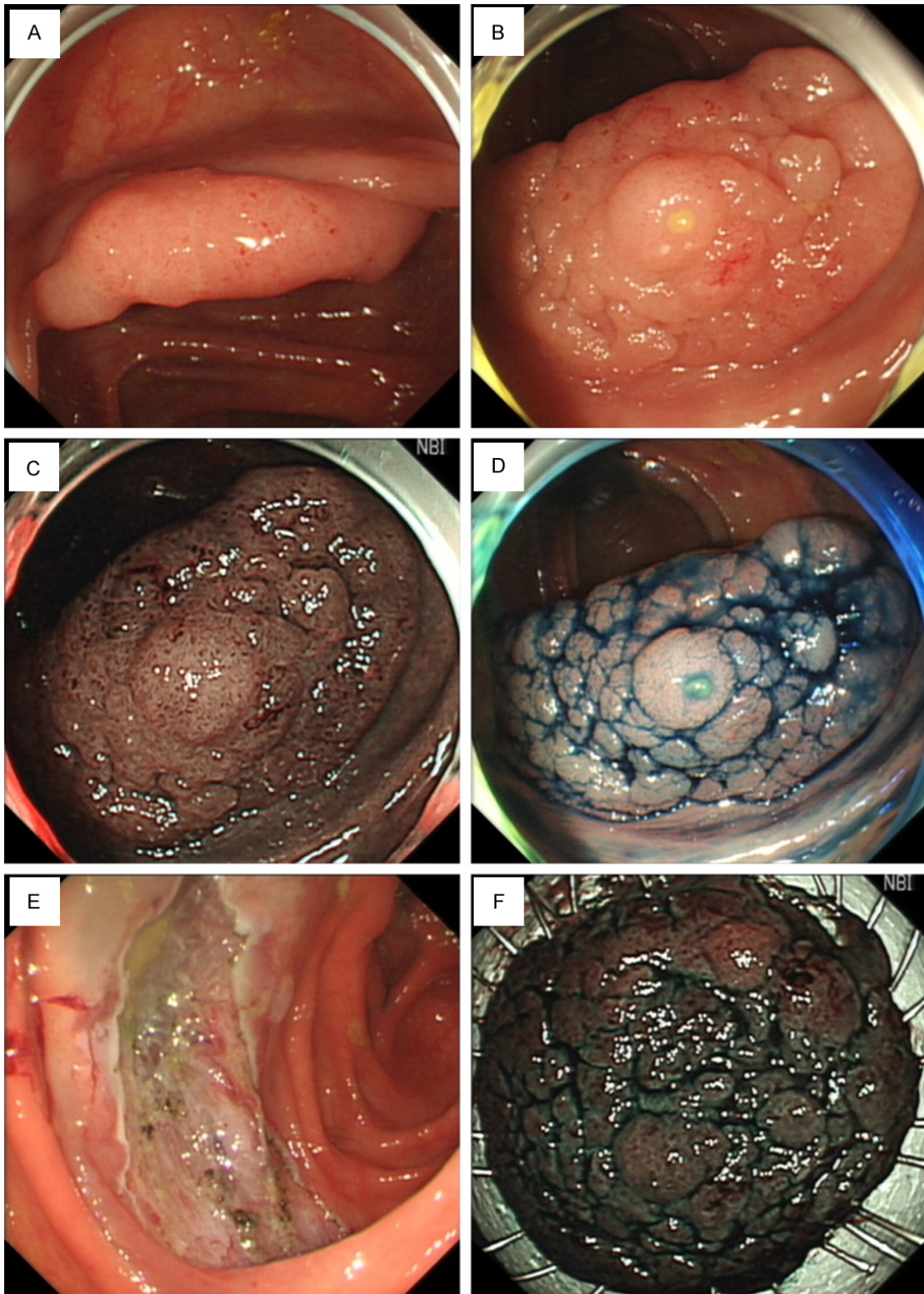


Figure 2. Endoscopic appearance and endoscopic submucosal dissection (ESD) procedure for a 12-mm SSA/P on the ascending colon. Characteristic appearance of flat sessile serrated adenoma/polyp of the proximal colon using standard white light (A) and retroflex view with magnifying endoscopy (B), including indistinct edges and color

similar to the surrounding normal mucosa. SSA/P typically has a weak/normal vascular pattern intensity seen using narrow-band imaging (C). Chromoendoscopy using 0.2% indigo carmine clearly delineated the margins of the lesion (D). Submucosal dissection using a small tip insulation-tipped diathermic knife was performed. Artificial ulcer was seen after ESD (E). Appearances of the resected tumor (F).

cers are predominantly located in the proximal colon and are usually CpG island methylator phenotype (CIMP)-high and MSI-high [15]. Moreover, previous studies reported that CRCs after colonoscopy were more likely to occur in proximal colon compared with the distal part [1, 2, 32-34]. A plausible explanation for this observation is that a significant proportion of these right-sided CRCs may evolve from undetected SSA/Ps [3].

This implies that all SSA/Ps should be accurately identified during colonoscopy. These serrated lesions, however, are susceptible to being easily missed because of their flat morphology and unremarkable color. Some endoscopists, having discriminated a polyp as HP, may intentionally not biopsy and remove the polyp owing to past training suggesting that HPs carry no risk of malignancy.

Accurate and real-time recognition of SSA/Ps might aid endoscopists in selecting a polypectomy technique resulting in a complete resection, whereas HP-appearing lesions can be removed with lower risk techniques [35]. However, the detection of SSA/Ps was considerably variable and endoscopist-dependent [24, 36-38]. There is a clear relationship between the endoscopist specialty and the risk of interval cancer after colonoscopy [36, 39-41]. Thus, recognition of SSA/Ps by colonoscopist may improve SSA/P detection and eventually decrease right-sided CRCs.

Introduction of new endoscopic techniques improved ability to identify SSA/Ps in realtime

Recently, new endoscopic techniques for reaching histologic diagnoses without taking biopsy samples have been introduced. These newly developed endoscopic techniques, such as high-resolution endoscopy, high-magnification endoscopy, narrow-band imaging (NBI), auto-fluorescence imaging, confocal laser endoscopy (CLE), and endocytoscopy, have led to many clinical studies focusing on conventional adenomas [42-44]. These techniques may be promising tools for making decisions regarding therapeutic strategies for serrated polyps.

However, systematical studies of these new endoscopic techniques characterizing the endoscopic features of SSA/Ps have not been fully elucidated.

Magnifying chromoendoscopy

Once a mucosal abnormality has been detected during standard colonoscopy, target chromoendoscopy with magnification is performed for confirming the surface structure, perimeter shape, and mucosal crypt (pit) pattern of the lesion in detail. The pit patterns were usually categorized according to Kudo's classification [45]. Pit Type I and II lesions were classified as non-tumor lesions (normal colon and HP), while the pit Types III, IV and V were considered as neoplastic lesions.

Type II pits are indicative of benign HPs and are, however, also observed in neoplastic SSA/Ps. Recently, a more detailed investigation by Kimura et al [46] introduced a novel pit pattern as a predictive feature for SSA/Ps: Type II -Open (Type II-O) [46]. The pits of this Type II-O pattern are wider and more rounded in shape than Type II from Kudo's classification. The Type II-O pattern has been proved to be characteristic of SSA/Ps with magnifying chromoendoscopy in another study (sensitivity 83.7%, specificity 85.7%) [47]. Moreover, Nakao et al [48] reported that when pit dilatation (II-dilatation pit) were used for the differential diagnosis of SSA/P from HP, the sensitivity, specificity and accuracy were 80%, 72%, and 78%.

Narrow-band imaging

Magnifying endoscopy with narrow-band imaging (ME-NBI) is a novel endoscopic imaging technology that enhances structural visualization and the microvessels on the tumor surface [49]. NBI has the advantage of being able to gain images immediately by the operator at the touch of a button, avoiding the need for bothersome chromoendoscopy. It has now replaced the major role of chromoendoscopy worldwide because of its convenience and simplicity, although magnifying chromoendoscopy had been a reliable diagnostic tool [49].

Sessile serrated adenomas/polyps

Table 1. Clinical features of serrated lesions of the colorectum[†]

Classification	Prevalence	Distribution	Malignant potential
Hyperplastic polyp	Very Common	Mostly distal	Very low
Sessile serrated adenoma/polyp	Common	80% proximal	
No dysplasia			Low
Dysplastic			Significant
Traditional serrated adenomas	Uncommon	Mostly distal	Significant

[†], revised from Lieberman et al [79].

Recent studies have shown that NBI can predict the histology of serrated polyps in real-time with good accuracy. Uraoka et al [50] have reported that NBI is superior to white light imaging (WLI) for detection of flat and diminutive lesions. Hazewinkel et al [35] provided a systematic validation of novel endoscopic features of SSA/Ps using high-resolution white-light endoscopy (HR-WLE) and NBI. In their study, four endoscopic features were independently associated with SSA/P histology: a cloud-like surface and indistinctive borders were predictive features on both HR-WLE and NBI, whereas dark spots and an irregular shape were predictive characteristics solely on NBI. A combination of these features might aid endoscopists in differentiating premalignant SSA/Ps from innocuous HPs using NBI with a high diagnostic accuracy [35]. Another clinical study showed that the red cap sign (mucous layer under NBI) and II-dilatation pit visible under ME-NBI were the most reliable criteria to differentiate SSA/Ps from HP [48].

Endocytoscopy

Recently, Kutsukawa et al [51] introduced a new endoscopic technique named endocytoscopy, which can reliably distinguish the different types of serrated polyps. According to their study, SSA/P can be distinguished endocytoscopically from HP by the shape of the lumens. The presence of star-like lumens was characteristic of HPs, the oval lumens was characteristic of SSA/Ps, both with high sensitivity and specificity [51]. Moreover, endocytoscopy can approach the pathology through visualization of the morphology of cells and nuclei, and can thus realize realtime pathology predictions.

However, compared with NBI, endocytoscopy requires dye spraying before observation, and its use is very limited to a few institutions. Further prospective investigations are manda-

tory to confirm the effectiveness of this technique, although endocytoscopy might be a promising tool for differentiating among different types of serrated polyps.

Confocal laser endoscopy (CLE) and autofluorescence imaging (AFI)

CLE is a newly developed endoscopic technology and today commercially available. Based on tissue fluorescence using local and/or intravenous contrast agents, CLE can generate high-quality images comparable with traditional histology [52, 53]. Xie et al [54] reported that the sensitivity and specificity of real-time CLE in identifying colonic adenomas were 93.9% and 95.9%, respectively, compared with histological results. However, realtime CLE to characterize the endoscopic features of SSA/Ps have not been reported.

Nakao et al [48] reported that, using AFI, a magenta color was observed in 32% of HPs and 44% of SSA/Ps. When AFI color changes were used to differentiate between the HPs and SSA/Ps, the sensitivity, specificity, and diagnostic accuracy of SSA/P diagnosis were 43%, 68%, and 52%, respectively. However, the diagnostic accuracy of HP and SSA/P with AFI was not satisfactory.

SSA/Ps should be eradicated completely once found

The therapeutic goal of SSA/P is to achieve the most effective treatment and the least postoperative complications with the simplest method. It's recommended that all polyps should be removed except the small HPs (<5 mm) in rectum or sigmoid [12, 36, 55-57]. The National Polyp Study Group of the USA reported that resection of all neoplastic polyps led to a 76-90% reduction in the incidence of CRCs and a subsequent 53% reduction in mortality [58,

Table 2. Recommendations for surveillance intervals of serrated polyps[†]

Baseline colonoscopy	Recommended surveillance interval (y)
Hyperplastic polyps	
small (<10 mm) in rectum or sigmoid	10
Sessile serrated adenoma/polyps	
<10 mm with no dysplasia	5
≥10 mm	3
with dysplasia	3
Traditional serrated adenomas	3
Serrated polyposis syndrome	1
Conventional adenomas	
1-2 small (<10 mm) tubular adenomas	5-10
3-10 tubular adenomas	3
>10 adenomas	<3

[†], revised from Lieberman et al [79].

59]. Experts endorsed that all serrated lesions of the proximal colon should be removed as accurately as possible, whatever the pathologic interpretation [12, 60, 61].

However, Endoscopic resection of large SSA/Ps remains challenging because of its technical difficulty and high complication rate [36, 39, 62]. These lesions are usually managed by endoscopic mucosal resection (EMR), endoscopic sub-mucosal dissection (ESD) or surgical resection in practice.

Endoscopic mucosal resection (EMR)

Most SSA/Ps can be successfully eradicated using the technique of EMR. Nowadays, EMR is a commonly used technique for removing SSA/Ps, but with some rate of local residual and recurrent neoplasia [63]. Recently, researchers [15, 64] proposed that the preferred method for removing large sessile polyps should be submucous injection and resection (injection-assisted polypectomy, IAP), which can effectively reduce the complications and the recurrence rate. Binmoeller et al [65] developed a novel method of water immersion (“under-water”) EMR (UEMR) that enables complete removal of large sessile colorectal polyps without submucosal injection. This new technique was safe in a large patient cohort, and appears to have a very low recurrence rate.

Some investigators have reported that endoscopic piecemeal mucosal resection (EPMR) is

a safe procedure for large sessile polyps [66]; however, this approach remains controversial because of the high possibility of coexisting malignancy and a high recurrence rate [67]. Studies have shown that EPMR for sessile polyps was associated with residual polyps in up to 55% of the cases [68]. In a study of long-term follow-up of large sessile adenomas (>2 cm) after EPMR, 17.6% had macroscopically evident residual adenoma at follow-up [69]. Thus, close follow-up endoscopic examinations after EPMR are necessary for early detection of recurrence [67].

Endoscopic submucosal dissection (ESD)

EMR is a useful therapeutic technique for flat polyps of the colorectum. However, for large sessile tumors, EPMR has the disadvantages of difficult pathological evaluation, risk of residual tumor and local recurrence [70]. ESD has recently been introduced by expert endoscopists for en bloc resection of large sessile polyps [71]. It provides a good pathologic assessment of polyps and has a higher initial cure rate [72]. Recent study reported that ESD showed no local recurrence, in comparison with the high recurrence rate associated with EPMR [73], thus verifying the usefulness in local cure of ESD for large sessile polyps (**Figure 2**).

However, this technique has a long procedure time and frequent complications, and is not currently widely used because of its technical difficulty [74, 75]. Nowadays, through technical improvements, many centers have started trying to perform colorectal ESDs [73, 76-78]. As experience with the technique improves, ESD may gradually replace EPMR and radical colon resection in the treatment of large sessile polyps like SSA/Ps [76, 77].

Surgical resection

Surgical resection of colon containing a serrated lesion is almost unnecessary, but is appropriate when a serrated lesion cannot be endoscopically removed. Surgical resection may also be indicated when there are multiple large

serrated lesions or cancers in the proximal colon [12].

Surveillance of SSA/Ps

Colonoscopic surveillance intervals should be based on evidence showing that interval examinations prevent interval cancers and cancer-related mortality [79]. The US and British guidelines on postpolypectomy surveillance were issued in 2006 and 2002, respectively [80, 81]. However, these guidelines did not comment on surveillance intervals for proximal serrated polyps.

Recently, based on new evidence, the guidelines were updated to address the surveillance of serrated polyps. The clinical features of serrated polyps of the colorectum were summarized in **Table 1**. The US guideline in 2012 suggests that size (>10 mm), histology (an SSA/P is a more significant lesion than an HP; an SSA/P with cytological dysplasia is more advanced than an SSA/P without dysplasia), and location (proximal to the sigmoid colon) are risk factors associated with CRC [79]. An SSA/P ≥ 10 mm and with cytological dysplasia should be managed like high-risk adenomas. Serrated polyps that are <10 mm and do not have cytological dysplasia may have lower risk and can be managed like low-risk adenomas [79]. However, this recommendation is based on low-quality evidence and will require updating when new data emerge [79]. Nevertheless, the British guideline in 2010 did not comment on surveillance intervals for proximal serrated polyps [82].

The serrated lesions of the proximal colon may biologically differ from distal lesions, and progress to malignancy more rapidly than the classical adenoma [16, 22]. Thus, compared with traditional adenomas, SSA/Ps may need vigilant clinical monitoring, and may have shorter follow-up intervals for surveillance. However, there is currently insufficient evidence to support this practice. The 2012 US recommendations for surveillance intervals in individuals with serrated polyps were summarized in **Table 2**.

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Disclosure of conflict of interest

None.

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