REVIEW

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Sessile Serrated Adenomas: How to Detect, Characterize and Resect

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Serrated polyps are important contributors to the burden of colorectal cancers (CRC). These lesions were once considered to have no malignant potential, but currently up to 30% of all CRC are recognized to arise from the serrated neoplasia pathway. The primary premalignant lesions are sessile serrated adenomas/polyps (SSA/Ps), although traditional serrated adenomas are relatively uncommon. Compared to conventional adenomas, SSA/Ps are morphologically subtle with indistinct borders, may be difficult to detect endoscopically, are more prevalent than previously thought, are associated with synchronous and metachronous advanced neoplasia, and have a higher risk of incomplete resection. Although many lesions remain "dormant," progressive disease is associated with the development of dysplasia and more rapid progression to CRC. As a result, SSA/Ps are strongly implicated in the development of interval cancers. These factors represent unique challenges that require a meticulous approach to their management. In this review, we summarize the contemporary literature on the characterization, detection and resection of SSA/Ps. **(Gut Liver 2017;11:747-760)**

Key Words: Sessile serrated adenoma; Detection; Endoscopic imaging; Histology; Endoscopic resection

INTRODUCTION

Sessile serrated adenomas/polyps (SSA/Ps), hyperplastic polyps (HPs) and traditional serrated adenomas (TSAs) form a heterogeneous group of lesions known as serrated polyps.[1,2] These lesions share a common serrated or 'saw-toothed' histological appearance of their epithelial crypts, with each subtype being defined by specific architectural features, location and extent of the proliferative zone. The classification of serrated polyps has evolved over time, reflecting advances in our understanding of their histopathological, morphological and molecular features (Table 1).[3,4] Before the turn of the century, virtually all serrated polyps were called HPs, as these lesions were believed to have no risk of malignancy and therefore were of little clinical significance.[5,6] We now also know SSA/Ps and TSAs have the po-

Table 1. Endoscopic, Histologic, and Molecular Features of Sessile Serrated Adenoma/Polyps

	Endoscopic	Histologic	Molecular
Nondysplastic	Flat (0-IIa/0-IIb) morphology	Saw-toothed architecture of crypt epithelium	*BRAF* V600E mutation
	Pale colour, indistinct borders	Boot shaped crypts +/– goblet/mucinous	CIMP-high
	Mucous cap, surrounding rim of debris/stool	cells at base	*MLH1* promotor methylation
	Type II-0 pit pattern	Pseudoinvasion	*KRAS* mutations (infrequent)
Dysplastic	Transition from flat to nodular, sessile or	Adenomatous dysplasia* (most common)	Reduced expression of *MLH1*
	depressed area	Serrated dysplasia† (less common)	Microsatellite instability
	Type III–V pit pattern		Silencing of other tumor
	NICE 2, Sano II on NBI		suppressor genes‡

CIMP, CpG island methylator phenotype; NICE, narrow band imaging (NBI) international colorectal endoscopic classification.
*Characterized by elongated penicillate nuclei with hyperchromasia, nuclear pseudostratification and amphophilic cytoplasm;[3] †Characterized by cells with a more cuboidal shape and eosinophilic cytoplasm, enlarged vesicular nuclei and prominent nucleoli;[3] ‡Including *p16INK4a*, *IGFBP7* and *MGMT*.[4]

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tential for dysplasia and subsequent malignant transformation, and account for up to 30% of all colorectal cancers (CRC).[2] The World Health Organization (WHO) classification, last updated in 2010, standardized terminology and definitions of serrated lesions.[1] However, the detection of SSA/Ps may be hampered due to a range of factors. These polyps are usually found in the right colon where bowel preparation can be poor, have a flat morphology with indistinct borders, pale surface and may be concealed by a mucous cap or stool debris.[2,5,7] As a result, SSA/Ps may be easily missed or be inadequately resected, contributing to the development of interval cancers.[8-10] Recognizing these lesions as important cancer precursors, knowledge regarding their identification and management is paramount for all endoscopists.

SCALE OF THE PROBLEM: IMPORTANCE OF SESSILE SERRATED ADENOMAS

Previous studies reported SSA/P prevalence of between 0.6% and 5.3%, probably reflecting differences in endoscopic detection and variations in histological definitions.[11-15] Recent work, however, suggests the prevalence may be higher. For example, a single center 4-year European study in a screening population of 3,364 patients with 4,251 resected and histologically confirmed polyps found 399 of these lesions were SSA/Ps.[16] The prevalence of SSA/Ps overall was 8.2%, increasing to 9.0% in patients older than 50 years. Per-polyp analysis showed the typical SSA/P was sessile or flat, 5 mm in size and located in the right colon. The higher prevalence of SSA/Ps in this study was favored by involvement of an expert pathologist, high adenoma detection rate (ADR) (median 38.5%) amongst endoscopists, and good quality bowel preparation (median Boston Bowel Preparation score, 8; 90% ≥6), signifying the importance of pairing both quality indicators of colonoscopy and pathological expertise in the diagnosis of these lesions.[16]

Despite an overall improvement in recognition of SSA/Ps, wide variation in SSA/P detection rates amongst endoscopists is reported by some studies.[16-18] For example in the aforementioned study by Ijspeert *et al*.[16] the SSA/P detection rate ranged between 2.5% and 13.6%. A similar SSA/P detection range (1% to 18%) was reported in another study involving tertiary center gastroenterologists, with the odds of detecting at least one proximal serrated polyp for individual endoscopists ranging from 0.05 to 0.67 compared to the highest level detector.[17] Misclassification of these lesions amongst pathologists could account for some of this difference. In a study of 1,910 average risk patients undergoing screening colonoscopy, the prevalence of SSA/Ps rose from 1.5% to 8.1% after all polyps in the serrated class were reassessed by an expert pathologist.[19] A multicenter study of 350 serrated polyps from 5,778 detected lesions, found the number of serrated lesions per colonoscopy ranged between 0.00 and 0.11, with some centers' pathologists having never identified proximal serrated lesions as SSA/Ps.[20] These data suggest enhanced awareness, education and training are necessary for both endoscopists and pathologists alike to improve outcomes in these areas.

SSA/Ps are also associated with synchronous advanced neoplasia in the colon.[13,21-25] In an early study of 3,121 asymptomatic patients undergoing screening colonoscopy, those with at least one proximal serrated polyp were more likely than those without, to have synchronous advanced neoplasia (17.3% vs 10.0%; odds ratio [OR], 1.90; 95% confidence interval [CI], 1.33 to 2.70), particularly in patients with serrated polyps ≥10 mm in size (OR, 3.14; 95% CI, 1.59 to 6.20).[21] Furthermore detection of proximal serrated polyps at baseline examination was associated with an increased risk of interval neoplasia on subsequent surveillance colonoscopy.[21] Other subsequent large studies have reported similar findings.[13,22,24] Recently, a systematic review and meta-analysis of nine studies with 34,084 participants and overall serrated polyp prevalence of 15.6% showed that serrated polyps were associated with a more than 2-fold increased risk of detection of synchronous advanced neoplasia (OR, 2.05; 95% CI, 1.38 to 3.04).[25] Individuals with proximal and large serrated polyps had the highest risk (OR, 2.77; 95% CI, 1.71 to 4.46 and OR, 4.10; 95% CI, 2.69 to 6.26, respectively).[25] Thus, there is strong data supporting carefully searching for synchronous lesions whenever an SSA/P is detected, and particularly if it is large.

SSA/Ps are associated with increased risk for CRC, including interval cancers.[2,26-28] Approximately 30% of all CRC is believed to develop along the serrated neoplasia pathway,[2,29] and although polypectomy reduces CRC incidence,[30,31] the imperfect protection of colonoscopy against right colon CRC[32,33] may be accounted for by failed detection or inadequate resection of SSA/Ps.[10] A recent Danish case-control study of 272,342 individuals and 2,045 cases of CRC showed those with a history of SSA/Ps had a significantly increased risk of CRC than patients without these polyps.[27] The CRC risk was particularly elevated in patients with proximal SSA/Ps (OR, 12.42; 95% CI, 4.88 to 31.58), SSA/Ps with dysplasia (OR, 4.76; 95% CI, 2.59 to 8.73) and females with SSA/Ps (OR, 5.05; 95% CI, 3.05 to 8.37).[27] The CRC risk was significantly elevated for those patients with TSAs (OR, 4.84; 95% CI, 2.36 to 9.93) and for conventional adenomas (OR, 2.51; 95% CI, 2.25 to 2.80).[27] Further implicating SSA/Ps, interval cancers also commonly occur in the right colon,[32,34] have the CpG island methylator phenotype (CIMP) with microsatellite instability (MSI), and activating mutations of the BRAF gene more often than noninterval CRC.[35]

SERRATED POLYPOSIS SYNDROME

Serrated polyposis syndrome (SPS) is characterized by multiple, large and/or proximal serrated polyps. Diagnosis is based upon satisfaction of one or more of the following WHO criteria

(1) at least five serrated polyps proximal to the sigmoid colon, two of which are larger than 10 mm; (2) any number of serrated polyps proximal to the sigmoid colon in a patient with a first degree relative with SPS; or (3) greater than 20 serrated polyps of any size, distributed throughout the colon.[36] Patients with SPS have an increased risk of CRC, with a recent study reporting a standard incidence ratio of CRC in patients with SPS of 18.72 (95% CI, 6.87 to 40.74), and a lifetime CRC risk of up to 50%.[37,38] Although SPS has features of being a hereditary condition including familial clustering and increased risk of CRC amongst relatives, no germline mutations have been identified. Nonetheless, screening colonoscopy is recommended for first degree relatives, beginning at 40 years of age or 10 years younger than the age at diagnosis of the youngest affected relative.[2,39] Management strategies focus on completely resecting all proximal polyps followed by annual surveillance,[39] although a consensus on risk-stratified management (e.g., based upon polyp burden, location, histology and presence of dysplasia) of SPS is still pending. Two recent multicenter series from Spanish and Dutch-British cohorts of patients with SPS managed by intensive endoscopic surveillance showed a 1.5% to 1.9% absolute 5-year CRC risk estimate,[40,41] less than previously expected. These results indicate that in SPS patients without CRC, early recognition and treatment of serrated polyps is imperative, and that protection from CRC by colonoscopic surveillance in dedicated centers is feasible.[42]

CHARACTERIZATION OF SESSILE SERRATED ADENOMAS

1. The serrated neoplasia pathway

Carcinogenesis in SSA/Ps is believed to progress through a unique epigenetic pathway. This involves hypermethylation of CpG islands (CIMP) on the promotor regions of tumor suppressor genes, in which a cytosine (C) is followed by a guanine (G) nucleotide linked by a phosphodiester bond (CpG).[43] Epigenetic silencing of the DNA mismatch repair (MMR) gene *MLH1* through promotor hypermethylation leads to the MSI phenotype, and leaves the cell vulnerable to mutations in genes controlling cell growth.[44-46] Notably, although *MLH1* methylation occurs in early SSA/Ps, only reduced or loss of gene expression, which requires extensive methylation, is associated with dysplasia and progression to malignancy.[3] This is supported by the observation that variably decreased *MLH1* expression is seen in dysplastic areas of SSA/Ps, with loss of expression in invasive MSI-high CRC.[47] The CIMP status of a lesion can be determined by assessment of a panel of 5 or 6 MMR genes, in which promotor hypermethylation of three or more genes is considered CIMP-high.[35] SSA/Ps, especially those with dysplasia, are considered the probable precursors to sporadic CIMP-high, MSI-high CRC given the similarities in their molecular profiles including hypermethylation of MMR genes *MLH1*, and of other tumor suppressor genes such as *p16INK4a*, *IGFBP7* and *MGMT*.[48-51] Activation of the *BRAF* oncogene (*BRAF* V600E mutation) is also a feature of the serrated neoplasia pathway[52,53] and is closely associated with CIMP-high CRC.[43,54] *BRAF* regulates cell proliferation, differentiation and survival, and is hypothesized to have a role in early serrated polyp development.[4,55]

2. Histopathological features

Sporadic serrated polyps are characterised by a serrated architecture of the epithelium that lines the colonic crypts, thought to result from decreased epithelial cell apoptosis.[56] The subtypes of serrated lesions may be distinguished by the location and extent of the proliferative zone.[29] The specific causes of these changes are presumed to result from epigenetic alterations in genes responsible for cell proliferation and differentiation,

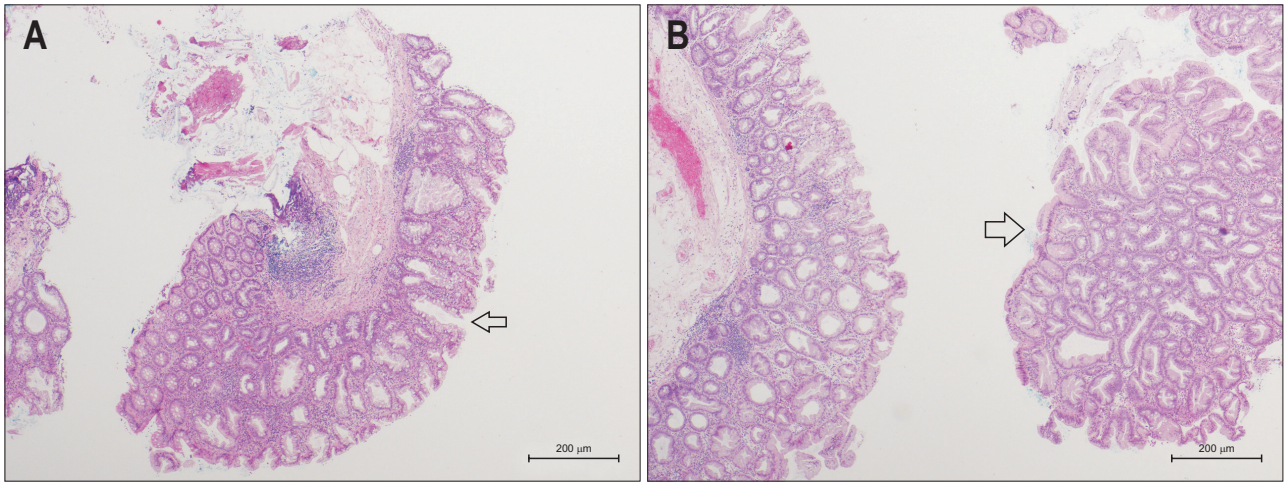

Fig. 1. Histologic features of sessile serrated adenomas/polyps (SSA/Ps). (A) A serrated adenoma (SSA/P) without dysplasia showing the classical features of broad bases and dilated crypts (arrow). H&E stained, low power magnification. (B) An SSA/P with mild dysplasia is shown in the right-side specimen (arrow). The glandular architecture and surface epithelium of the dysplastic component resembles a conventional adenoma. The left-sided specimen is nondysplastic. H&E stained, low power magnification.

as well as genetic changes such as mutations in *BRAF*.[2] SSA/Ps are characterised by distorted crypt growth and dilatation of the crypt base, leading to the formation of 'boot' or 'L' or 'anchor'-shaped crypts (Fig. 1).[2,6] The basal aspect of the crypt may contain hyper-serration, mature goblet cells and mucinous cells, which are responsible for the excessive mucin frequently seen within the dilated crypts and on the surface of the lesion. Recently, an expert consensus panel recommended that one unequivocal architecturally distorted crypt base was sufficient to diagnose an SSA/P.[2] Pseudoinvasion below the muscularis mucosae, also known as displaced crypts, also often occurs in SSA/Ps.[57] SSA/Ps are not typically dysplastic, although cytological dysplasia resembling conventional adenoma with frequent loss of expression of *MLH1* on immunohistochemistry may develop in some lesions and potentially progress quickly to invasive malignancy.[3,14]

3. Endoscopic features of sessile serrated adenomas

SSA/Ps are most commonly located in the right colon, have a sessile or flat morphology sometimes resembling prominent mucosal folds, pale in colour similar to the surrounding mucosa and with indistinct borders (Fig. 2). About two-thirds of lesions are covered by a tenacious mucous cap (Fig. 3), with less common signs including a rim of stool debris, alteration of fold contour, interrupted underlying mucosal pattern and a dome shaped protuberance.[58] Because of these features, the endoscopic appearance of SSA/Ps may be subtle and even large lesions may be missed without careful attention from the endoscopist. It is prudent to note the location of the polyp before washing off the mucous cap as the SSA/P may be difficult to discern afterwards.[2] Other factors associated with SSA/Ps include female sex, smokers with more than a 20 pack year history, diabetes and obesity.[59,60]

SSA/Ps are identified endoscopically by a Type II open-shape (II-0) pit pattern (sensitivity 65.5%, specificity 97.3% using magnification and indigo carmine chromoendoscopy).[61] On narrow band imaging (NBI), other endoscopic predictors of SSA/Ps include a cloud-like surface, indistinct borders, irregular shape, and dark spots inside the crypts.[62] A recent systematic review and meta-analysis assessing the utility of image enhanced endoscopy in differentiating SSA/Ps from nonneoplastic tissue showed 80% sensitivity for magnification-NBI, 60% for NBI, 49% for autofluorescence, and 47% for flexible spectral imaging color enhancement.[63] In head to head comparisons with white light endoscopy (WLE), only NBI and magnification-NBI demonstrated significantly greater sensitivity.[63] The NBI International Colorectal Endoscopic (NICE) classification based upon lesion colour, vessel appearance and surface pattern distinguishes

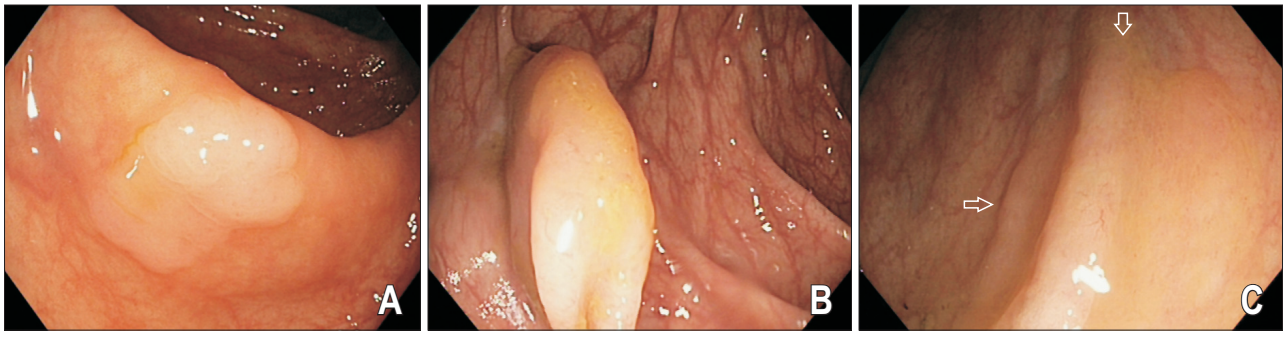

Fig. 2. (A-C) Endoscopic appearance of nondysplastic sessile serrated adenomas/polyps (SSA/Ps). SSA/Ps are often found in the right colon, are morphologically flat and pale, have a color similar to the surrounding mucosa and have indistinct borders (arrows). Detection requires good bowel preparation and a high index of suspicion.

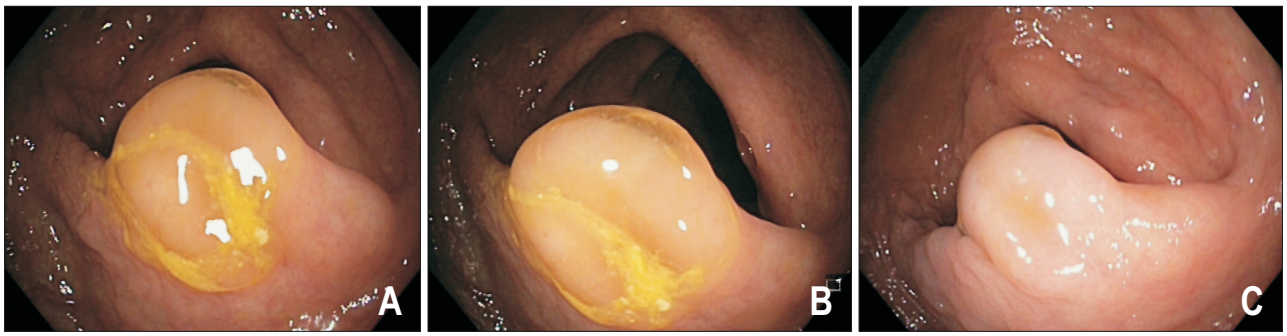

Fig. 3. Sessile serrated adenomas/polyp (SSA/P) before and after cleaning of the mucous cap. This nondysplastic SSA/P is covered by a tenacious mucous cap with a surrounding rim of stool (A, B). The lesion becomes less conspicuous (C) upon cleansing and can potentially be mistaken for a prominent mucosal fold.

hyperplastic from adenomatous polyps,[64] however, does not accurately diagnose SSA/Ps.[65] To improve the endoscopic identification of SSA/Ps using NBI, the NICE classification was combined with the criteria for differentiation of SSA/Ps[62] to form the recently proposed Workgroup Serrated Polyps and Polyposis (WASP) classification.[66] In the first validation phase using this classification, the accuracy of optical diagnosis for SSA/Ps versus non-SSA/Ps with high confidence amongst a cohort of 10 gastroenterologists was 0.83 (95% CI, 0.75 to 0.91) rising to 0.93 (95% CI, 0.87 to 0.98) after completion of a standardised WASP training module.[66] Although promising, further validation of the WASP criteria in prospective trials is awaited before its routine implementation to daily practice. In practice and with experience, the recognition of SSA/Ps and their differentiation from adenomas is usually not challenging.[67]

Whereas nondysplastic SSA/Ps have a relatively homogeneous appearance, progression to more advanced lesions with dysplasia (SSA/P-D) is associated with accumulation of aberrant DNA methylation and additional lesion changes resembling that of a conventional adenoma (Fig. 4).[61,67,68] The identification of an endoscopically apparent transition point between two differing surface patterns within a lesion should alert the endoscopist to an SSA/P harbouring dysplasia. The dysplastic component is usually a small (1 to 5 mm) centrally or peripherally located nodule, and occasionally minimally elevated or depressed area within the lesion.[67] Examination of the surface pit pattern with WLE and NBI often reveals two distinct patterns corresponding to the different histology, with the dysplastic component exhibiting a type III (tubular or roundish pits) or type IV (branched or gyrus-like pits) pattern.[67] With NBI, the area of dysplasia is darker due to more abundant and thicker surface capillaries in keeping with a NICE 2 or Sano II vascular pattern, compared with the relatively hypovascular background pattern of the nondysplastic SSA/P.[67] Once dysplasia develops, transformation to invasive cancer can be rapid and may occur even when lesions are small.[67,69] Large (≥20 mm) SSA/Ps may more frequently harbour dysplasia, and was present in 32.4% of all such lesions referred for endoscopic mucosal resection (EMR) in a prospective multicenter study of large laterally spreading lesions (LSLs).[68] Multivariable analysis revealed SSA/P-D were significantly associated with increasing age (OR, 1.69 per decade; 95% CI, 0.19 to 2.40), increasing lesion size (OR, 1.90 per 10 mm; 95% CI, 1.30 to 2.78), an "adenomatous" pit pattern (Kudo III, IV or V) (OR, 3.98; 95% CI, 1.94 to 8.15) and any 0-Is component within an SSA/P (OR, 3.10; 95% CI, 1.19 to 8.12).[68]

DETECTION OF SESSILE SERRATED ADENOMAS

Endoscopic detection of SSA/Ps can be assisted by high definition (HD) endoscopes, chromoendoscopy and/or image enhancement, adoption of quality criteria for colonoscopy and possibly use of ancillary devices. High definition scopes deliver better image quality and brighter illumination, and their use improves the detection of both adenomas and SSA/Ps.[70] In another study, the combination of HD colonoscopes with chromoendoscopy (0.4% indigo carmine) during scope withdrawal increased the overall detection rate for adenomas (0.95 vs 0.66 per patient) and serrated lesions (1.19 vs 0.49 per patient) (p<0.001)

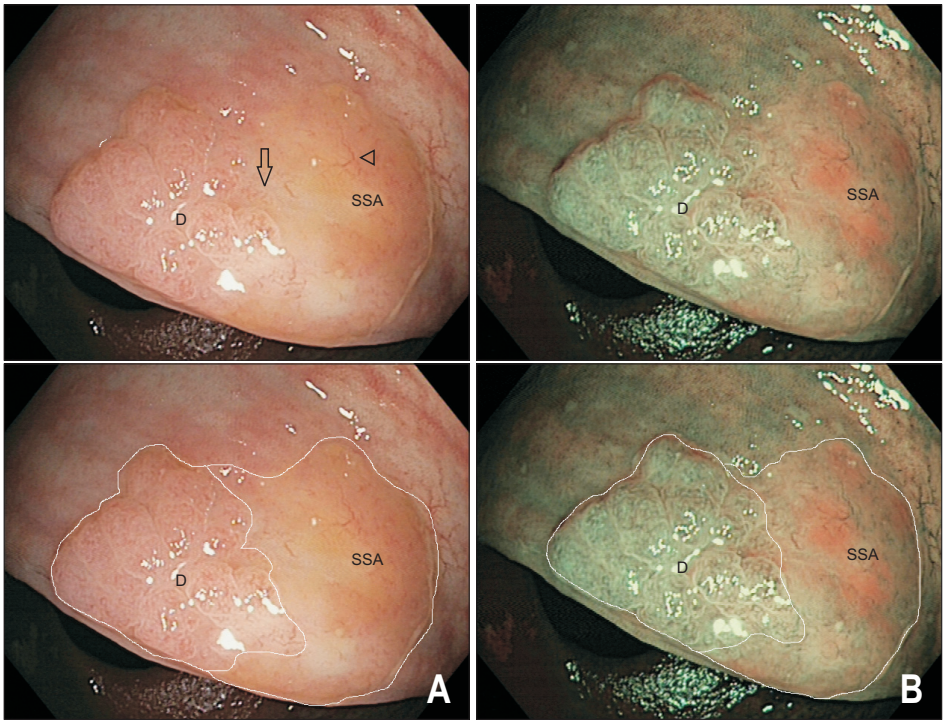

Fig. 4. Endoscopic appearance of sessile serrated adenomas/polyps (SSA/Ps) with dysplasia. A 20 mm SSA/P-D viewed under white light (A) and narrow band imaging (B) with and without the dysplastic (label D) and nondysplastic (label SSA) components outlined. The lesion has developed a raised, nodular component on the left-hand aspect with a type IV surface pit pattern indicative of dysplastic transformation (label D). The nondysplastic component of the lesion (label SSA) is pale with relatively hypovascular background surface markings and is covered by a thin layer of stool debris (arrowhead). Note there is an obvious transition zone from the nondysplastic flat SSA/P to the area of dysplasia (arrow). The lesion and a rim of normal tissue were removed *en bloc* by endoscopic mucosal resection; histology confirmed a completely resected SSA/P with mild dysplasia.

compared with standard colonoscopy.[71] Potential drawbacks included longer procedural times and additional cost of chromoendoscopic dye. The utility of NBI compared with HD-WLE for detecting serrated lesions was assessed in a randomized controlled trial of 800 patients.[72] Although more proximal colon serrated lesions were detected by NBI than HD-WLE (204 vs 158), this did not achieve statistical significance.[72] Similarly, a randomized multicenter trial found no significant difference in polyp miss rates using HD-WLE or NBI in patients with SPS.[73]

The detection of SSA/Ps in CRC screening programs was assessed in a multicenter retrospective series of over 70,000 colonoscopies, reporting significant association with caecal intubation rate (OR, 3.75; 95% CI, 2.22 to 6.34), presence of at least one advanced adenoma (OR, 2.08; 95% CI, 1.86 to 2.33) and ADR.[74] In this study, no association between faecal immunochemical test (FIT) and detection of SSA/Ps was found.[74] Similar outcomes were reported from a prospective population screening study of over 6,000 patients, finding FIT detected SSA/Ps with significantly lower sensitivity than conventional adenomas.[75] In a multicenter study of almost 8,000 colonoscopies, serrated polyp detection increased with each minute of withdrawal time above 6 minutes, with maximal benefit at 9 minutes (incident rate ratio, 1.77; 95% CI, 1.15 to 2.72).[76] Other studies have also demonstrated the benefits of a longer withdrawal technique,[18] including second looks and retroflexion in the right colon,[77] with careful cleaning and meticulous mucosal examination for the detection of SSA/Ps.

Adequacy of bowel preparation is well documented for optimising detection of conventional adenomas as well as for SSA/Ps. One study reported overall SSA/P detection of 4.6% versus 12.0% (OR, 0.37; 95% CI, 0.15 to 0.87) and 1.5% versus 7.9% (OR, 0.19; 95% CI, 0.05 to 0.81) in the right colon for intermediate quality preparation versus high quality preparation, respectively.[78] This study also showed that any level of preparation below high quality was associated with a significant decrease in SSA/P detection, whereas intermediate quality preparation was still adequate for adenoma detection.[78] Split dose bowel preparation improves colonic cleansing and detection of conventional adenomas.[79,80] In a prospective randomised trial of 341 patients, split dose bowel preparation also improved SSA/Ps detection relative to single dose regimens (9.9% vs 2.4%, p=0.004), with improved patient tolerance and quality of preparation.[81]

Ancillary devices used with the aim of improving mucosal examination and polyp detection include disposable attachments to the colonoscope such as transparent caps and Endocuff (ARC Medical Design, Leeds, UK), accessory video processors such as Third Eye® Retroscope® and Third Eye® Panoramic™ (Avantis Medical Systems, Sunnyvale, CA, USA), and specialised colonoscopes such as Full Spectrum Endoscopy® (EndoChoice Inc., Alpharetta, GA, USA), Extra-Wide-Angle-View colonoscope (Olympus, Tokyo, Japan), NaviAid™ G-EYE™ balloon colonoscope (SMART Medical Systems Ltd., Ra'anana, Israel).[82-84] Distal attachment caps have not demonstrated improved polyp detection,[85] whereas the others have shown promise but are either technically intensive and/or associated with significant additional cost. A recent review based on observational data suggested use of Endocuff may result in higher ADR (35.4% to 53.5%), particularly for polyp detection in the right colon.[83] However, a multicenter randomised trial did not demonstrate Endocuff identified an increased number of patients with one or more adenomas relative to conventional colonoscopy.[86] Taking everything together, meticulous examination technique, high quality bowel preparation and use of HD scopes remain the key to optimising SSA/P detection. Endoscopists with high ADRs are unlikely to gain significant improvements in ADR by using the additional technologies and ancillary devices currently available.

RESECTION OF SESSILE SERRATED ADENOMAS

Complete polyp resection is the fundamental principle governing treatment of SSA/Ps. All serrated lesions except for diminutive rectosigmoid lesions should be removed.[2] However, endoscopic detection and resection of SSA/Ps is hampered by their predominantly flat morphology, inconspicuous surface features and indistinct borders. Once detected, these lesions can be excised endoscopically utilizing similar principles to those for resection of conventional adenomas. The Complete Adenoma Resection (CARE) study assessed the incomplete resection rate (IRR) of polyps by immediate biopsy of the resection margins in 1,427 patients undergoing colonoscopy with at least one nonpedunculated polyp. The study found that SSA/Ps were more likely to be incompletely resected than conventional adenomas (31% vs 7.2%, p<0.001), and that the IRR rose to 47.6% for larger (10 to 20 mm) SSA/Ps.[10] In this study, the two strongest associations for IRR were increasing polyp size (relative risk [RR], 2.1; 95% CI, 1.13 to 3.86 for lesions 10–20 mm vs 5–9 mm), and SSA/P diagnosis (RR, 3.74; 95% CI, 2.04 to 6.84).[10] Significant variation in rates of complete resection were also observed amongst endoscopists,[10] indicating that careful attention to polypectomy technique is essential to achieving satisfactory outcomes, and particularly for SSA/Ps.

1. Removal of small sessile serrated adenomas (<10 mm)

Cold snare polypectomy (CSP), when performed correctly, is ideal for removal of diminutive and small SSA/Ps up to 10 mm in size, due to its efficacy and safety.[87-89] CSP is superior to cold forceps polypectomy with regard to completeness of excision of small and diminutive polyps.[88-90] Hot forceps polypectomy is associated with high rates of deep tissue injury, poor histological specimens, residual tissue, and is now strongly discouraged.[91,92] The principle of CSP is to ensure that complete polyp removal

is achieved with a 1 to 2 mm margin of normal tissue.[92,93] Our recommended approach to CSP is described in Table 2.

The efficacy of CSP using thin wire snares has been assessed by a number of studies, although none have solely included SSA/Ps. In one study, completeness of excision based on endoscopic imaging was significantly higher with thin wire (0.30 mm) than thick wire (0.47 mm) snares (90.2% vs 73.3%, p<0.05), with a trend towards higher complete pathological excision (73.3% vs 65.2%, p=0.4).[94] Another prospective randomized controlled trial of 210 lesions resected by CSP found complete pathological resection was significantly greater with thin wire than thick wire snares (91% vs 79%, p=0.015), particularly for polyps 8 to 10 mm in size.[95]

The risk of complications related to CSP such as perforation and clinically significant bleeding is extremely low.[87] The rate of perforation is negligible as the closed snare is unable to cut through muscularis propria, and its occurrence has mostly been associated with lesions removed using electrocautery (hot snare polypectomy, HSP).[96,97] Furthermore, compared with HSP, CSP has similar rates of complete polyp resection, shorter procedure time and no increase in clinically significant bleeding.[98-100] Protrusions within the cold snare defect occur in approximately one in six cases, and may create concern for incomplete resection, however, these do not contain residual polyp nor are they associated with adverse outcomes.[101] Immediate bleeding after CSP is common, but is typically self-limited and without risk of ongoing or delayed bleeding.[99]

2. Removal of large sessile serrated adenomas (10–20 mm)

EMR is the first-line therapy for LSLs. The supporting data is mostly based on resection of conventional adenomas,[92,102,103] however, studies have also shown large (≥10 mm) SSA/Ps can be adequately treated by EMR (Fig. 5).[104-107] HSP is highly operator dependant and may be inadequate for resection of SSA/Ps. For example, the CARE study showed wide inter-operator variability in efficacy of HSP with almost half of the lesions 10 to 20 mm in size incompletely resected using this technique.[10] Large SSA/Ps are also more likely to harbor dysplasia, which may be subtle, and these lesions should be carefully examined prior to removal, particularly with respect to their surface pattern and peripheral extent, to ensure complete resection. As mentioned above, dysplasia is manifest as a transition point with a change in surface appearance from the usual flat SSA/P morphology to a nodular or minimally elevated or depressed area within the lesion, along with an "adenomatous" (type III–IV) pit pattern.[67] The safety and efficacy of endoscopic resection for large SSA/Ps was demonstrated in a 2 center retrospective study of 199 patients with 251 proximal colon SSA/Ps measuring 10 mm or larger removed by EMR.[104] After mean follow-up of 17.8±15.4 months, five patients (3.6%; 95% CI, 0.5% to 6.7%) developed local recurrence with a median size of 4 mm.[104] The recurrences were all cured endoscopically. There were no complications and no high grade dysplasia or advanced CRC following the index colonoscopy.[104]

The median size of large SSA/Ps tend to be smaller than that of adenomatous LSLs. SSA/Ps seem to be relatively loosely attached to the deeper mural layers, usually lift easily and are not associated with submucosal fibrosis.[107] As such, SSA/Ps are generally easier to remove by EMR than adenomatous LSLs. Nonetheless, EMR is associated with risks such as perforation (1% to 2%), post polypectomy syndrome (0.5%) and clinically significant post EMR bleeding (6% to 11%).[102,108-110] Therefore, it may be beneficial to remove large SSA/Ps by piecemeal CSP, achieving complete excision whilst mitigating many of the adverse effects of EMR (Fig. 6). In a pilot study of 15 patients with adenomatous colonic polyps (mean size, 20 mm; range, 10 to 45 mm) removed by piecemeal CSP using a stiff thin wire snare, technical success was 100%, with no perforation, no post pol-

Table 2. Technical Tips for the Removal of SSA/Ps (<10 mm) by Cold Snare Polypectomy

1. Position the lesion in the 5 to 6 o'clock position.
2. Place the catheter of the opened snare on normal mucosa 1 to 2 mm distal to the lesion with the snare tip 1 to 2 mm proximal to the lesion. Stiff thin-wire snares are likely more effective.
3. Anchor the catheter in place on the mucosa by downward angulation of the scope tip (pushing forward on the up/down wheel).
4. Close the snare, capturing the polyp with a margin of normal tissue. Avoid excessive distention of the colon as tension on the wall will cause the closing snare to slide over the mucosa, impeding tissue capture. If this occurs, gently deflating the lumen during snare closure may be helpful.
5. Small flat nonpolypoid lesions (Paris 0-IIa and 0-IIb morphology) can be difficult to capture. A suction pseudopolyp technique, whereby the lesion is aspirated into the suction channel of the colonoscope and continuous suction applied for 5 seconds whilst the colonoscope is gently retracted, allows formation of a pseudopolyp to facilitate subsequent resection. This has been shown to be a safe, effective and reproducible therapy for removal of these lesions.[111,112]
6. Expand the mucosal defect following polypectomy by water jet irrigation. This distends the defect and its edges, facilitating inspection for residual polyp tissue.

SSA/Ps, sessile serrated adenoma/polyps.

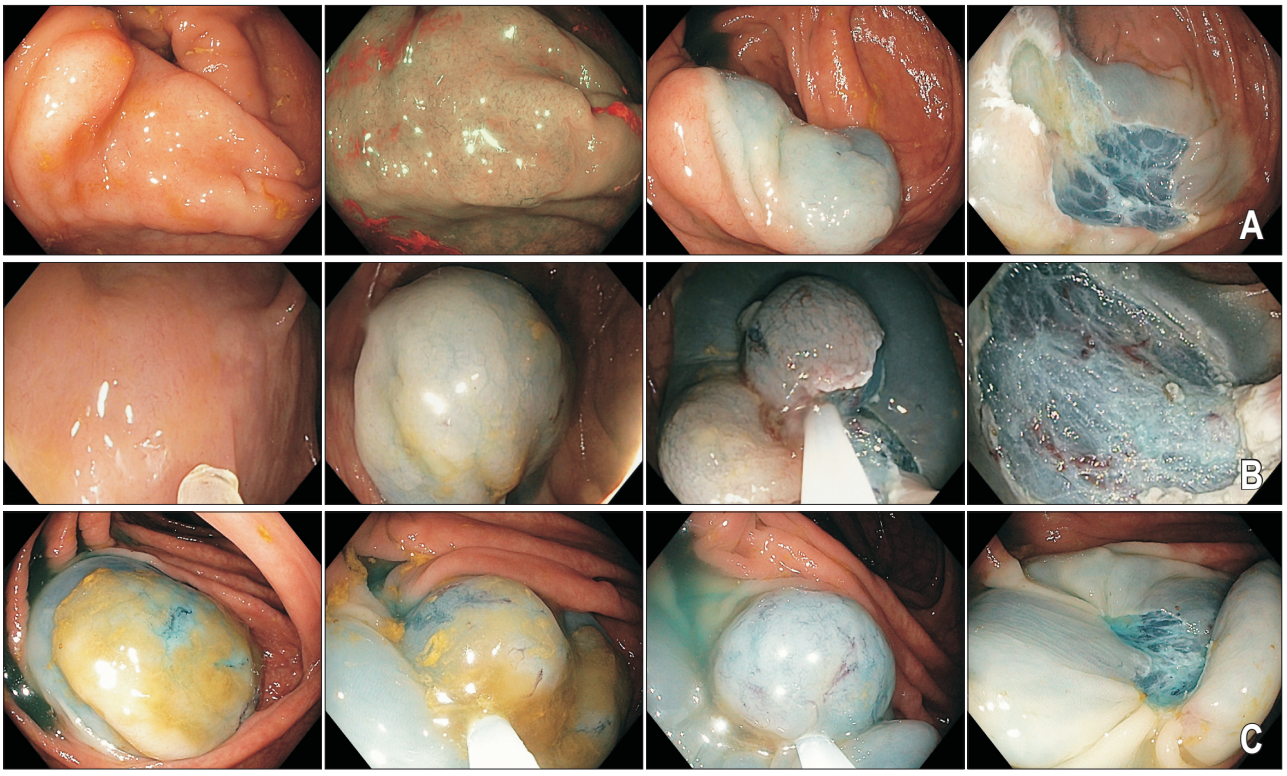

Fig. 5. Endoscopic mucosal resection of sessile serrated adenomas/polyps (SSA/Ps). (A-C) Note the inconspicuous appearance of all three lesions despite their larger sizes. Submucosal chromogelofusine injection assists with delineating the peripheral extent of the lesion. A margin of normal tissue should be captured during mucosal resection. Thermal ablation of the resection margins with snare tip soft coagulation (effect 4, 80W; VIO 300D; Erbe) reduces the risk of lesion recurrence.

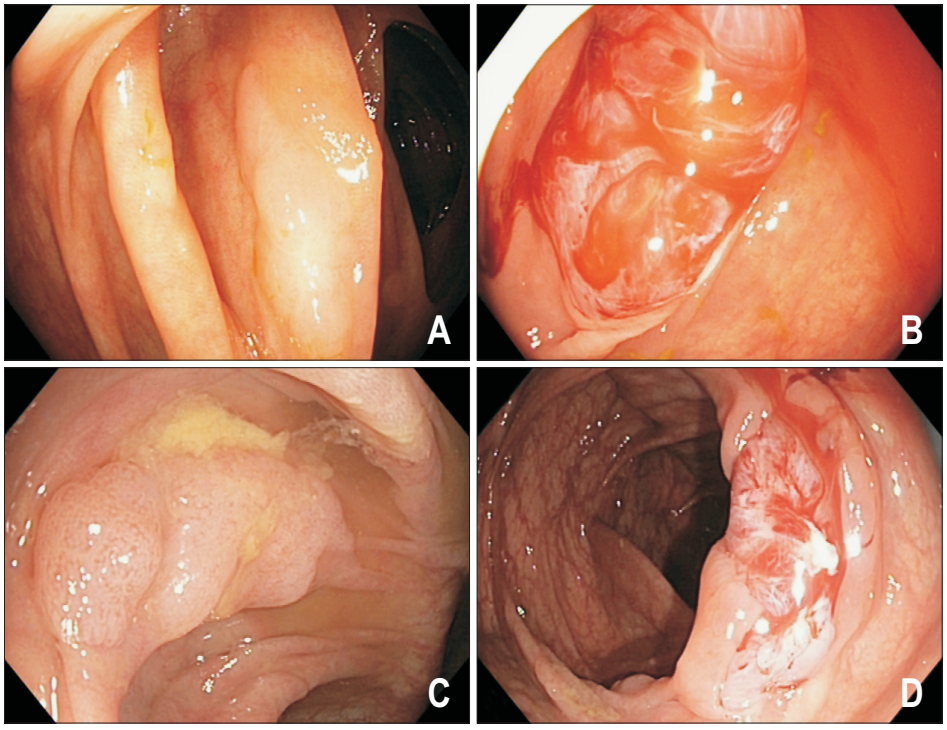

Fig. 6. Piecemeal cold snare polypectomy of sessile serrated adenomas/polyp (SSA/P). Larger (10 to 15 mm) SSA/Ps (A, C) removed by piecemeal cold snare polypectomy (B, D).

ypectomy syndrome and only one delayed bleeding episode in a patient on warfarin.[113] A subsequent study involving 30 sessile colonic polyps ≥10 mm in size treated by piecemeal CSP also found this technique to be feasible, with no significant adverse events.[114] At first follow-up after 6 months, 20% of patients had small volume residual tissue, and all cases were treated endoscopically.[114] Although piecemeal CSP appears effective and safe for resection of large SSA/Ps, particularly those 10 to 20 mm in size, prospective studies are awaited to determine the long term durability of this technique, and whether risks of complications such as bleeding are truly reduced.

3. Removal of larger sessile serrated adenomas (>20 mm)

EMR of larger SSA/Ps (>20 mm) is safe and effective, with comparable recurrence rates to that seen with similar sized conventional adenomas (8.7% vs 11.1%, p=0.8).[105] A recent multicenter, prospective cohort of 2,000 LSLs ≥20 mm (median size 35 mm) comprising 323 SSA/Ps and 1,527 adenomas, showed large SSA/Ps could be successfully removed by EMR in almost all cases.[107] The study reported EMR of these lesions compared with adenomatous LSLs, was easier to perform, with less intraprocedural bleeding and similar rates of significant adverse events.[107] Cumulative recurrence rates at 6 and 12 months for SSA/Ps was significantly less compared with adenomas (6.3% and 7.0% vs 16.1% and 20.4%, p<0.001, respectively). Subgroup analysis by lesion size revealed an 8-fold increased risk of recurrence for 20 to 25 mm adenomatous LSLs versus SSA/Ps, but no significant difference in risk between lesion types in larger lesion groups.[107] The technique of EMR for removal of LSLs including large SSA/Ps has been described,[92,115,116] and key aspects are summarized in Table 3.[117,118]

SURVEILLANCE

Recommendations for colonoscopy surveillance intervals in patients with SSA/Ps follow similar principles to that of conventional adenomas, and are based upon lesion number, size and histology, albeit with some caveats. Although guidelines exist,[2,39,119] these are largely based upon observational data and expert opinion, as prospective, controlled data on the natural history of SSA/Ps is lacking. Major European and North American societal guidelines are largely congruent and recommend the following intervals of colonoscopy surveillance: 5 years for patients with a single SSA/P without dysplasia <10 mm in size, 3 to 5 years for patients with <3 SSA/Ps without dysplasia each <10 mm in size, 3 years for patients with ≥3 SSA/Ps without dysplasia each <10 mm in size, and 3 years for patients with "high risk" lesions (any lesion ≥10 mm in size or with dysplasia).[39,119] Lesions removed piecemeal may warrant early follow-up colonoscopy at 6 months given the potential for incomplete resection, although this area requires much further systematic study to optimise techniques and quantitate the risks.

Recent expert consensus guidelines advocate a slightly more aggressive surveillance recommendation, suggesting an interval colonoscopy in 1 to 3 years after resection of any SSA/P with dysplasia or after resection of ≥2 SSA/Ps of ≥10 mm in size.[2] These recommendations are based upon the observation that interval CRC are more likely right sided, colonoscopy is less effective at preventing proximal CRC, and the greater variability in detection of SSA/Ps compared with conventional adenomas.[2] Other guidelines do not make any specific recommendations with respect to serrated lesions, instead treating such lesions the same as conventional adenomas.[120]

CONCLUSIONS

As our understanding of the biological behaviour of SSA/Ps improves, we increasingly recognise the clinical significance of these lesions, in particular their potential to progress to CRC and role in development of interval cancers. SSA/Ps can be

Table 3. Technical Tips for the Removal of larger SSA/Ps by Endoscopic Mucosal Resection

1. Carefully inspect the lesion for features of dysplasia and peripheral extent. Use of high definition scopes with or without chromoendoscopy or NBI may assist. Dye based submucosal lift solution for EMR aids in delineating the lesion's peripheral extent.[107]
2. Ensure snare captures a peripheral rim of 1 to 2 mm normal mucosal tissue around the polyp. Utilize EMR rather than hot snare polypectomy for SSA/Ps 10 to 20 mm as this has higher rates of complete polyp resection. Piecemeal cold snare polypectomy is an alternative technique.
3. Firmly anchor the snare catheter in normal tissue 1 to 2 mm front of the polyp, and allow the polyp to fall into the open snare by deflating the lumen. With further deflation, close the snare to capture the polyp, but do not close completely.
4. At this point, we prefer to take control of the snare from the assistant, closing to within 1cm. Mobility of the captured tissue relative to the adjacent bowel wall is assessed, followed by tissue resection with electrocautery (EndoCut Q, effect 3, cut duration 1, cut interval 6; VIO 300D; Erbe).
5. Carefully assess the resection margins to assess for residual polyp. Defect expansion with water jet irrigation may assist inspection. Residual polyp can be subtle and further resections can be performed to remove suspect tissue.
6. Recurrence after EMR can be reduced by ablating the resection margins with snare tip soft coagulation (effect 4, 80W) by a light touch technique.
7. Referral to a center with expertise in advanced polypectomies is recommended if there is insufficient local expertise in EMR.[117,118]

SSA/Ps, sessile serrated adenoma/polyps; NBI, narrow band imaging; EMR, endoscopic mucosal resection.

difficult to identify and use of HD colonoscopes, quality bowel preparation, meticulous mucosal examination and withdrawal technique are the factors most likely to improve their detection. Each lesion should be carefully assessed to determine its peripheral extent and localise any dysplastic areas. Like all adenomatous colorectal polyps, complete endoscopic resection is the key to successful eradication of SSA/Ps. Lesions ≤10 mm in size are suitable for removal by CSP. Lesions 10 to 20 mm in size may be removed by either piecemeal CSP or EMR. Larger lesions are currently best removed by EMR. Improved detection, accurate characterisation and safe and complete resection of SSA/Ps are imperative to optimising patient outcomes and reducing the incidence of CRC.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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