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Optimal Endoscopic Treatment and Surveillance of Serrated Polyps

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Abbreviations:

- 1) SSL: Sessile serrated lesion
- 2) SSP: Sessile serrated polyp
- 3) NBI: Narrow band imaging
- 4) NICE: NBI International Colorectal Endoscopic classification
- 5) SPS: Serrated Polyposis Syndrome
- 6) EMR: Endoscopic mucosal resection
- 7) ND-SP: Non dysplastic serrated polyp
- 8) TSA: Traditional serrated adenomas
- 9) USTF:US Multi-society task force
- 10) ESGE :European Society of Gastrointestinal Endoscopy
- 11) BSG : British society of Gastroenterology
- 12) HR: Hazard ratio
- 13) CI: Confidence Interval
- 14) OR: Odds ratio
- 15) LST: Laterally spreading tumour

Introduction:

Colorectal cancer is one of the leading causes of mortality around the world. It is the fourth most common cancer worldwide accounting for 6.1% of total cancers diagnosed and second leading cause of cancer related death, after lung cancer, in world¹. In United Kingdom, bowel cancer is the 4th most common cancer accounting for 12% of all new cancer diagnosis.

Overall, serrated polyps contribute to 20-30% of sporadic colorectal cancers². Although serrated lesions are thought to be less common in Asian populations, a number of studies from Korea and Hongkong have suggested similar rates to Western cohorts^{3,4,5}. Failure to detect sessile serrated lesions (SSL) is thought to be one of the reasons for interval colorectal cancer⁶ and the failure of screening colonoscopy in preventing right sided colon cancers⁷. One of the reasons behind this is that SSL are difficult to detect or visualize during endoscopy due to flat shape and pale or translucent appearance⁸ and are often incompletely resected⁹. These issues have implications on what should be the optimal endoscopic treatment and surveillance of serrated polyps which remains area of active research. Through this review, we attempt to address this contentious issue through available literature and evidence.

Sessile serrated polyps and their endoscopic detection

Lesion of the serrated class include Sessile serrated polyps along with hyperplastic polyps and traditional serrated adenomas form heterogeneous group¹⁰. Sessile serrated polyps can be further characterized on basis on endoscopic, histological and molecular features. Endoscopic assessment of SSP is challenging. They are often subtle, pale in appearance and are frequently masked by mucous cap¹¹. Features suggestive of SSL rather than hyperplastic polyp include dark spots within pits, indistinct boarder, a cloud-like or bosselated surface and irregular shape [Ref: Hazewinkel Y, Lopez-Ceron M, East JE, et al. Endoscopic features of sessile serrated adenomas: validation by international experts using high-resolution white-light endoscopy and narrow-band imaging. *Gastrointest Endosc*

2013;77:916–24. AND East JE, Vieth M, Rex DK Serrated lesions in colorectal cancer screening: detection, resection, pathology and surveillance Gut 2015;64:991-1000] Dysplastic lesions have transition from flat to nodular, sessile or depressed area ;type III–V pit pattern and NICE 2 ¹².

They are more common in the right side of colon where less good preparation can make detection challenging. Detection can be improved by withdrawing slowly, using high definition colonoscope¹³ and chromoendoscopy (dye spray)^{14,15,16,17} (Table 1). Some early data suggests the use of Endocuff may support SSL (SSA/P) detection with a 15% detection rate with Endocuff versus a 3% rate with standard colonoscopy($p=0.001$).¹⁸ A colonoscope with a large balloon at the bending section which slows withdrawal and compresses folds (G-EYE colonoscope; Smart Medical Systems Ltd, Ra'anana, Israel) also improved Serrated lesion detection rates in a large randomised controlled study, 2.7% versus 0.8 % $p=0.036$ ¹⁹.A study that looked at Narrow Band Imaging (NBI; Olympus, Japan) for serrated polyp detection suggested a statistical trend toward improved detection with a mean number of serrated lesions proximal to the sigmoid of 0.51 with NBI versus 0.39 for white light, $p=0.085$ ²⁰. A subsequent meta-analysis of NBI for detection of non-adenomatous (serrated) lesions suggested significantly improved detection with either first or second generation “Bright” NBI²¹. With increasing use of NBI, the Workgroup on serrated polyps and Polyposis (WASP) – has described classification (also called WASP) for distinguishing between hyperplastic and adenomatous/serrated polyps at endoscopy²²; (Flowchart 1). In WASP classification , criterion like ‘ dark spots inside crypt’ are more reliable than criterion ‘irregular shape’.

Although higher bowel preparation quality has previously not been shown to be associated with improved serrated lesion detection, a recent meta-analysis suggests that use of split dose

Commented [de1]: Ref 14 is the same as ref 12

bowel preparation does seem to improve serrated lesion detection ,relative risk 2.48 (95% CI: 1.21-5.09)²³.

Endoscopic treatment methods:

The choice of endoscopic resection for any polyp revolves around two principles; safety and recurrence. Recurrence depends heavily on completeness of endoscopic resection. Size more than 10 mm and SSP are two strongest predictors of incomplete endoscopic resection^{poli,CARE}. Hence, removal of SSP of size over 10mm requires expertise. Cold snare polypectomy is the preferred method for removal of SSP less than 10mm. Relatively little data specific to serrated lesions is available; however in cases series of small polyps which are predominantly adenomatous, cold snaring is a very safe and efficacious method and performs better than cold forceps polypectomy method^{24,25}. Rates of complications with cold snare polypectomy are very low and intra procedural bleeding, 1.8% in one large series, is usually controlled with injection or endoscopic clipping^{huric,CONSCOP}. Perforations , which are more of concern with hot snare, are exceptionally rare with cold snare. Majority of the bleed with cold snare are immediate and self limiting.

Thin wire (0.30mm) snares have been shown more effective than thick wire (0.47mm) snares in achieving complete endoscopic and pathologic excision. Horiuchi *et al.* showed , in a prospective randomized controlled trial of 210 polyps, that thin wire snares have significantly more complete pathological resection as compared to thick wire snare (91% vs 79%, p value = 0.02)²⁶. In another study Din *et al.* showed there was significantly endoscopic complete resection(90.2% vs 73.3%, p <0.05) and non significant higher trend for complete pathological excision(73.3 % vs 65.2%, p = 0.4) with thin wire snares²⁷. Injection can be helpful to help grasp some normal mucosa around the edges of these flat lesions to maximise

chances of comprehensive resection, and adding methylene blue or indigo carmine to the injection fluid and provide contrast to see the edges of the lesion more clearly (Figure 1)

Endoscopic Mucosal Resection (EMR) of large serrated lesions:

For lesions greater than 10mm, endoscopic mucosal resection (EMR) is the preferred technique. It is important to carefully inspect larger lesion as they have more chance to have dysplasia which may appear as subtle change in surface of polyp in form of nodularity, elevation or depression with or without adenomatous pit pattern²⁸. EMR is safe and efficacious method of removing larger (>10mm) sessile serrated polyps. SSPs are easier to remove by endoscopic resection as compared to adenomas as they do not have submucosal fibrosis and are loosely attached to deeper layers making lifting easy after injection. Rao et al²⁹ showed, in a large cohort of 251 SSP(>10 mm), EMR could safely remove polyps with only 3.6% recurrence rate after mean follow up of 17.8 ± 15.4 months. All recurrences (median size 4mm) could be managed by endoscopic resection.

In a large cohort of laterally spreading tumours (LST) > 20mm, Pellise et al³⁰ showed EMR could successfully remove SSP as compared to adenomas with similar adverse events and less bleeding. The same study showed significantly lower rates of recurrence with SSP at 6 months (6.3% vs 16.1%) and 12 months (7.0% vs 20.1%) compared to adenomatous lesions. EMR does have associated complications which involve bleeding (1 in 10 to 1 in 30)³¹, perforation (1 in 100) and post polypectomy syndrome (1 in 200)³². Given the risks of resection of flat lesion in the right colon, some authors have suggested that the risks of resection may outweigh the cancer prevention benefits; however we would suggest that cold snare piecemeal EMR is a safe and effective way to resect these larger right sided serrated lesions. Three recent studies have reported cold snare pEMR data, with or without injection to lift the lesion, with acceptable rates of recurrence and low complication rates (Table 2),

and it seems likely that cold snare pEMR will become the standard of care for resection of these lesions in the future^{33,34,35}.

Endoscopic submucosal dissection (ESD) of large serrated lesions:

Large sessile serrated lesions are predominantly right sided, as compared to adenomatous laterally spreading tumours (LSTs) which have propensity for being left sided or rectal. The risk of recurrence in large SSLs is lower than equivalent adenomatous lesions, and the risk of invasive cancer is also lower for a lesion of equivalent size [ref 30]. ESD has been described in management of large serrated lesion³⁶; however, it has its own technical challenges e.g. the flap of sessile serrated lesions is thin and floppy making it difficult to manoeuvre using standard gravity based positioning during ESD. Therefore the advantages of use of ESD for which are perhaps clearest for large rectal lesions where the risk of recurrence or invasion is high, and the consequences of a perforation are lower, are inverted for serrated lesions which are technically difficult to resect, occur in the thin walled right colon, and are low risk for recurrence or invasion [Ref: Repici A Gastrointest Endosc. 2013 Jan;77(1):96-101 AND Clin Gastroenterol Hepatol. 2019 Jan;17(1):16-25.e1. doi: 10.1016/j.cgh.2018.07.041. Epub 2018 Aug 2. AGA Institute Clinical Practice Update: Endoscopic Submucosal Dissection in the United States. Draganov PV1, Wang AY2, Othman MO3, Fukami N4. AND Endoscopy. 2017 Mar;49(3):270-297. doi: 10.1055/s-0043-102569. Epub 2017 Feb 17 Colorectal polypectomy and endoscopic mucosal resection (EMR): European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. Ferlitsch M1,2, Moss A3,4, Hassan C5, Bhandari P6, Dumonceau JM7, Paspatis G8, Jover R9, Langner C10, Bronzwaer M11, Nalankilli K3,4, Fockens P11, Hazzan R12, Gralnek IM12, Gschwantler M2, Waldmann E1,2, Jeschek P1,2, Penz D1,2, Heresbach D13, Moons L14, Lemmers A15, Paraskeva K16, Pohl J17, Ponchon T18, Regula J19, Repici A20, Rutter MD21, Burgess NG22,23, Bourke MJ22,23.]. We therefore recommend cold snare pEMR for large SSLs, and would only consider ESD for a

lesion assessed as high risk for early sub-mucosal invasion. Traditional serrated adenomas (TSA) are morphologically much more similar to LSTs, are predominantly found in the rectum and may be good targets for ESD. In a large Korean cohort of sessile serrated polyp/adenoma with dysplasia/adenocarcinoma, ESD was used as resection method in 3.8% of patients for SSP ≥ 20 mm³⁷.

Surveillance

Due to lack of prospective and controlled data, most of the recommendations and guidelines are based on expert opinion and observational data. Table 3 summarises the current US Multi-society task force³⁸, ESGE (European Society of Gastrointestinal Endoscopy)³⁹ and BSG position statement guidance on surveillance for serrated polyps (Table 3); however more recently data has become available both on the comparative risk of small and advanced serrated lesions versus adenomas and whether serrated lesions and adenomas should be treated separately or together.

Surveillance for Small <10mm serrated lesions

The BSG position statement on serrated polyps in the colorectum recommended no surveillance for patients with one or more serrated lesions <10mm in size who do not meet the criteria for serrated polyposis syndrome^{EAST,BSG}, although US MSTF guidelines suggests 5 yearly surveillance for 1-2 serrated lesions <10mm in size. There are as yet no prospective data to validate this recommendation. Schreiner et al report in a US cohort from more than a decade ago, 248 / 3121 patients (7.9%) had at least 1 proximal non dysplastic-serrated polyp (ND-SP). They were more likely than patients with no proximal non dysplastic- serrated polyp to have advanced neoplasia (17.3% vs 10.0%). During surveillance, 39 patients with

baseline proximal ND-SP and no neoplasia were more likely to have neoplasia compared with subjects who did not have polyps, OR, 3.14. Among patients with advanced neoplasia at baseline, those with proximal ND-SP (n = 43) were more likely to have advanced neoplasia during surveillance, OR, 2.17⁴⁰. A US, pathology based case-control study suggested that the rate of CRC was significantly higher in sessile serrated adenomas than in patients with adenomas or hyperplastic polyps over 13 years follow up (12.5% versus 1.8% versus 1.8% respectively)⁴¹. All serrated lesions with subsequent cancer were <10mm in size; however some SPS patients and patients with TSA were included and it is not clear whether SSAs were resected comprehensively and not just biopsied. In a large Danish case control cohort, which reanalysed pathological samples using modern definitions of serrated polyps, serrated lesions alone were broadly risk equivalent to adenomas alone for future cancer risk without considering size⁴². Given that nonadvanced serrated lesions appear risk equivalent to non-advanced adenomas, their surveillance should be equivalent, with no surveillance recommended by the BSG position statement or ESGE and that patients should return to population screening.

Surveillance for advanced serrated lesions (SSL =>10mm, SSL with dysplasia or traditional serrated adenoma)

The BSG position statement on serrated polyps in the colorectal recommends one off surveillance colonoscopy at 3 years for patients with an advanced serrated lesion, defined as a sessile serrated lesion (SSL) =>10mm, SSL with dysplasia and traditional serrated adenomas^{EAST,BSG}, in line with US MSTF recommendation, and broadly with ESGE recommendation (Table 3). No prospective data to validate this recommendation exists; however a number of lines of evidence are strongly suggestive that future CRC risk is increased by these lesions to

a level consistent with that post advanced adenoma detection. In a Norwegian flexible sigmoidoscopic screening study (NORCCAP), large ≥ 10 mm hyperplastic (serrated) lesions were associated with the same future colorectal cancer risk as advanced adenomas, increased 3-4 fold versus no polyps⁴³. A large Danish cohort which reanalysed pathological samples using modern definitions of serrated polyps, traditional serrated adenomas and SSL with dysplasia had an almost 5-fold higher risk of future CRC^{ERICHSONR,GASTRO}.

Serrated polyposis syndrome surveillance

Serrated polyposis syndrome (SPS) is common in bowel cancer screening programmes which use gFOBT or FIT as a screening test, with estimates of SPS prevalence ranging from 1:150-1:300^{44,45}. A recent Spanish FIT based cohort followed up all their patients with proximal serrated polyps, tripling the number of additional cases of SPS, for a final prevalence of 1:100⁴⁶. Therefore, especially when using FIT in bowel cancer screening, colonoscopists should be alert to a diagnosis of SPS.

US MSTF and ESGE recommend surveillance period of 1 year and 3 years respectively (Table 3). The BSG position statement on serrated polyps in the colorectal recommended 1-2 yearly surveillance for patients meeting the WHO criteria for serrated polyposis syndrome^{EAST,BSG}. This recommendation was on the basis that in early cohorts, future risk of CRC was elevated at as much as 7% at 5 years^{47,48}; however in larger cohorts with rigorous surveillance performed every 1-2 years, with all lesions larger than 5mm in size resected, at academic centres, the risk appeared much lower with CRC only diagnosed at 1.9 cases per 1000 years of patient follow up^{49,50}. Recent data suggests once the colon is cleared, follow up can be safely deferred to 2 years^{51,52}.

The risk for patient who are first degree relatives of patients with SPS also appears elevated between 3 to 5 fold compared to the general population ^{BPOP,RAI GUT, 53,54} and screening colonoscopy is recommended for this group, with subsequent colonoscopies determined by polyp burden. Surveillance should then be performed every 5 years if no polyps are found.

A recent paper that looked at patients with multiple serrated polyps and adenomas, not quite meeting the criteria for SPS also noted that their risk for CRC was equivalent to patients who met the WHO definition of SPS, and that their first degree relatives also had an elevated risk of CRC, comparable to the risk for FDRs of SPS ^{patients^{EGOVIL,GASTRO}}.

Surveillance when serrated lesions and adenomas are found together

In previous guidelines it was not possible to comment on how to assign surveillance intervals when serrated lesions occurred together with adenomas and whether risk, and therefore surveillance intervals, should be considered separately for each polyp class or if their risk was additive. At that time, each polyp class was considered separately and the shortest surveillance interval was ^{used^{EAST,BSG}}. There has been recent data on the future risk when adenomas and serrated lesions are found together. The risk of finding an advanced adenoma at surveillance had an odd ratio for future risk with synchronous advanced adenomas and serrated lesions at index exam four-fold higher than for advanced adenomas alone. A further similar study from Korea presented in abstract form suggests additive risk between adenomas and sessile serrated lesion with the risk of advanced colorectal neoplasia at 3 years follow up for adenoma with synchronous serrated polyp being 17.9% versus 10.7% for adenoma alone ($p<0.001$)⁵⁵. Audit data from an Australian colorectal cancer surveillance programme with 2157 patient followed up for a median of 50 months found additive risk of advanced neoplasia when serrated lesion and adenomas were found together (high-risk adenoma: hazard ratio (HR) = 2.04 (95% CI 1.70-2.45); high-risk SSP + adenoma HR = 3.20 (95% CI

1.31-7.82); low-risk SSP + adenoma: HR = 2.20 (95% CI 1.03-4.68))⁵⁶. Older data from the 1990s when serrated lesions were less recognised both endoscopically and pathologically is supportive but less definitive.

Conclusion:

Adequate resection technique and appropriate surveillance of serrated polyps is of utmost importance as they are a major reason behind interval cancers and failure of screening colonoscopy in preventing right sided colon cancers. Their identification is difficult and challenging but is aided by increased withdrawal time and chromoendoscopy. Cold resection techniques are safe and effective and are increasingly supported by larger cases series data. Surveillance strategies, on the other hand, are currently predominantly based on expert opinion and observational data; however new case series are becoming available to make these recommendations more evidence based.

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Figure legend

Figure 1. Cold snare lift and EMR of small sessile serrated lesion.

1a. 5mm serrated polyp seen in ascending colon

1b. Lesion seen with NBI and close focus, note small black dots within pits suggestive of sessile serrated lesion

1c. Lesion lifted with fluid containing methylene blue as contrast agent to clarify lesion edges

1d. Lesion grasped with thin wire cold snare, note additional normal mucosa snared to ensure complete excision.

1e. Post-resection defect seen with close focus after washing, note normal mucosal clearly seen around edges confirming excision.

References:

¹⁾ Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394-424.

²) Snover DC. Update on the serrated pathway to colorectal carcinoma. Hum Pathol.2011;42:1-10.

³) Lee CK, Kim YW, Shim JJ, Jang JY. Prevalence of proximal serrated polyps and conventional adenomas in an asymptomatic average-risk screening population. Gut Liver 2013 ;7:524-31.

⁴) Min YW, Lee JH, Lee SH et al.Prevalence of proximal colon serrated polyps in a population at average risk undergoing screening colonoscopy: a multicenter study. Clin Res Hepatol Gastroenterol. 2012;36:604-8.

⁵) Leung WK, Tang V, Lui PC. Detection rates of proximal or large serrated polyps in Chinese patients undergoing screening colonoscopy. J Dig Dis. 2012 ;13:466-71.

⁶) Cooper GS, Xu F, Barnholtz Sloan JS, Schluchter MD, Koroukian SM. Prevalence and predictors of interval colorectal cancers in medicare beneficiaries. Cancer 2012;118:3044-52.

⁷) Singh H, Nugent Z, Demers AA, Kliwer EV, Mahmud SM, Bernstein CN. The reduction in colorectal cancer mortality after colonoscopy varies by site of the cancer. Gastroenterology. 2010 ;139:1128-37.

⁸) Kahi CJ, Hewett DG, Norton DL, Eckert GJ, Rex DK. Prevalence and variable detection of proximal colon serrated polyps during screening colonoscopy. Clin Gastroenterol Hepatol. 2011 ;9:42-6.

⁹) Pohl H, Srivastava A, Bensen SP et al. Incomplete polyp resection during colonoscopy- results of the complete adenoma resection (CARE) study.Gastroenterology. 2013 ;144:74-80.

¹⁰) Rex DK, Ahnen DJ, Baron JA, et al. Serrated lesions of the colorectum: review and recommendations from an expert panel. Am J Gastroenterol 2012;107:1315-1329.

¹¹) Bouwens MW, van Herwaarden YJ, Winkens B et al. Endoscopic characterization of sessile serrated adenomas/polyps with and without dysplasia. Endoscopy 2014;46:225-35.

¹²) Ma MX, Bourke MJ. Sessile Serrated Adenomas: How to Detect, Characterize and Resect. Gut Liver. 2017 ;11:747-760.

¹³) Roelandt P, Demedts I, Willekens H et al. Impact of endoscopy system, high definition, and virtual chromoendoscopy in daily routine colonoscopy: a randomized trial. Endoscopy. 2019;51:237-243.

¹⁴) Michael X. Ma , Michael J. Bourke. Sessile Serrated Adenomas: How to Detect, Characterize and Resect. Gut and Liver 2017;11:747-60.

-
- ¹⁵) East JE, Atkin WS, Bateman AC et al. British Society of Gastroenterology position statement on serrated polyps in the colon and rectum. *Gut*. 2017;66:1181-96.
- ¹⁶) Hurt C, Ramaraj R, Farr A et al; CONSCOP Clinical Research Consortium. Feasibility and economic assessment of chromocolonoscopy for detection of proximal serrated neoplasia within a population-based colorectal cancer screening programme (CONSCOP): an open-label, randomised controlled non-inferiority trial. *Lancet Gastroenterol Hepatol*. 2019;4:364-375.
- ¹⁷) Repici A, Wallace MB, East JE et al. Efficacy of Per-oral Methylene Blue Formulation for Screening Colonoscopy. *Gastroenterology*. 2019 ;156:2198-2207.
- ¹⁸) Baek MD, Jackson CS, Lunn J et al. Endocuff assisted colonoscopy significantly increases sessile serrated adenoma detection in veterans. *J Gastrointest Oncol*. 2017;8:636-42
- ¹⁹) Shirin H, Shpak B, Epshtein J et al. G-EYE colonoscopy is superior to standard colonoscopy for increasing adenoma detection rate: an international randomized controlled trial (with videos). *Gastrointest Endosc*. 2019;89:545-553.
- ²⁰) Rex DK, Clodfelter R, Rahmani F et al. Narrow-band imaging versus white light for the detection of proximal colon serrated lesions: a randomized, controlled trial. *Gastrointest Endosc*. 2016;83:166-71.
- ²¹) Atkinson NSS, Ket S, Bassett P et al. Narrow-band Imaging for Detection of Neoplasia at Colonoscopy: a Meta-analysis of Data From Individual Patients in Randomized Controlled Trials. *Gastroenterology*. 2019 . pii:S0016-5085(19)35708-7. [Epub ahead of print]
- ²²) IJspeert JE, Bastiaansen BA, van Leerdam ME et al; Dutch Workgroup serrated polyps & Polyposis (WASP). Development and validation of the WASP classification system for optical diagnosis of adenomas, hyperplastic polyps and sessile serrated adenomas/polyps. *Gut*. 2016;65:963-70.
- ²³) Zawaly K, Rumbolt C, Abou-Setta AM et al. The Efficacy of Split-Dose Bowel Preparations for Polyp Detection: A Systematic Review and Meta-Analysis. *Am J Gastroenterol*. 2019 Mar 11. doi:10.14309/ajg.0000000000000155. [Epub ahead of print]
- ²⁴) Repici A, Hassan C, Vitetta E et al. Safety of cold polypectomy for <10mm polyps at colonoscopy: a prospective multicenter study. *Endoscopy*. 2012 ;44:27-31.
- ²⁵) Lee CK, Shim JJ, Jang JY. Cold snare polypectomy vs. cold forceps polypectomy using double-biopsy technique for removal of diminutive colorectal polyps: a prospective randomized study. *Am J Gastroenterol* 2013;108:1593-1600.

²⁶⁾ Horiuchi A, Hosoi K, Kajiyama M, Tanaka N, Sano K, Graham DY. Prospective, randomized comparison of 2 methods of cold snare polypectomy for small colorectal polyps. *Gastrointest Endosc* 2015;82:686-92.

²⁷⁾ Din S, Ball AJ, Riley SA, Kitsanta P, Johal S. Cold snare polypectomy: does snare type influence outcomes? *Dig Endosc* 2015;27:603-8.

^{28)} Nanda KS, Tutticci N, Burgess N, Sonson R, McLeod D, Bourke MJ. Caught in the act: endoscopic characterization of sessile serrated adenomas with dysplasia. *Gastrointest Endosc* 2014;79:864-70.

^{29)} Rao AK, Soetikno R, Raju GS et al . Large Sessile Serrated Polyps Can Be Safely and Effectively Removed by Endoscopic Mucosal Resection. *Clin Gastroenterol Hepatol*.2016;14:568-74.

^{30)} Pellise M, Burgess NG, Tutticci N et al. Endoscopic mucosal resection for large serrated lesions in 2017 ;66:644-53.

^{31)} Burgess NG, Metz AJ, Williams SJ et al. Risk factors for intraprocedural and clinically significant delayed bleeding after wide-field endoscopic mucosal resection of large colonic lesions. *Clin Gastroenterol Hepatol*. 2014 ;12:651-61.

^{32)} Cha JM, Lim KS, Lee SH et al. Clinical outcomes and risk factors of post-polypectomy coagulation syndrome: a multicenter, retrospective, case-control study. *Endoscopy*.2013;45:202-7.

^{33)} Tate DJ, Awadie H, Bahin FF et al. Wide-field piecemeal cold snare polypectomy of large sessile serrated polyps without a submucosal injection is safe. *Endoscopy*.2018;50:248-52.

^{34)} Rameshshanker R, Tsiamoulos Z, Latchford A, Moorghen M, Saunders BP. Resection of large sessile serrated polyps by cold piecemeal endoscopic mucosal resection: Serrated COld Piecemeal Endoscopic mucosal resection (SCOPE). *Endoscopy*. 2018;50:E165-E7

³⁵⁾ Piraka C, Saeed A, Waljee AK, Pillai A, Stidham R, Elmunzer BJ. Cold snare polypectomy for non-pedunculated colon polyps greater than 1 cm. *Endosc Int Open*. 2017;5:E184-E9.

^{36)} Kondo S, Mori H, Nishiyama N et al. Case of pediatric traditional serrated adenoma resected via endoscopic submucosal dissection. *World J Gastroenterol*. 2017;23:4462-6

^{37)} Kim KH, Kim KO, Jung Y et al.Clinical and endoscopic characteristics of sessile serrated adenomas/polyps with dysplasia/adenocarcinoma in a Korean population: A Korean Association for the Study of Intestinal Diseases (KASID) multicenter study. *Sci Rep*. 2019;9:3946.

-
- ³⁸) Lieberman DA, Rex DK, Winawer SJ, Giardiello FM, Johnson DA, Levin TR. Guidelines for colonoscopy surveillance after screening and polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer. *Gastroenterology*. 2012 ;143:844-57.
- ³⁹) Hassan C, Quintero E, Dumonceau JM et al. Post-polypectomy colonoscopy surveillance: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. *Endoscopy*. 2013;45:842-51.
- ⁴⁰) Schreiner MA, Weiss DG, Lieberman DA. Proximal and large hyperplastic and nondysplastic serrated polyps detected by colonoscopy are associated with neoplasia. *Gastroenterology*. 2010;139:1497-502.
- ⁴¹) Lu FI, van Niekkerk de W, Owen D, Tha SP, Turbin DA, Webber DL. Longitudinal outcome study of sessile serrated adenomas of the colorectum: an increased risk for subsequent right-sided colorectal carcinoma. *Am J Surg Pathol*. 2010;34:927-34.
- ⁴²) Erichsen R, Baron JA, Hamilton-Dutoit SJ et al. Increased Risk of Colorectal Cancer Development Among Patients With Serrated Polyps. *Gastroenterology*. 2016;150:895-902.
- ⁴³) Holme Ø, Bretthauer M, Eide TJ et al. Long-term risk of colorectal cancer in individuals with serrated polyps. *Gut*. 2015 ;64:929-36.
- ⁴⁴) Biswas S, Ellis AJ, Guy R, Savage H, Madronal K, East JE. High prevalence of hyperplastic polyposis syndrome (serrated polyposis) in the NHS bowel cancer screening programme. *Gut*. 2013;62:475.
- ⁴⁵) Moreira L, Pellisé M, Carballal S et al. High prevalence of serrated polyposis syndrome in FIT-based colorectal cancer screening programmes. *Gut*. 2013 ;62:476-7.
- ⁴⁶) Rivero-Sanchez L, Lopez-Ceron M et al. Reassessment colonoscopy to diagnose serrated polyposis syndrome in a colorectal cancer screening population. *Endoscopy*. 2017 ;49:44-53.
- ⁴⁷) Boparai KS, Mathus-Vliegen EM, Koornstra JJ et al. Increased colorectal cancer risk during follow-up in patients with hyperplastic polyposis syndrome: a multicentre cohort study. *Gut*. 2010 ;59:1094-100.
- ⁴⁸) Edelstein DL, Axilbund JE, Hyland LM et al. Serrated polyposis: rapid and relentless development of colorectal neoplasia. *Gut*. 2013 ;62:404-8.
- ⁴⁹) Carballal S, Rodríguez-Alcalde D, Moreira L et al. Colorectal cancer risk factors in patients with serrated polyposis syndrome: a large multicentre study. *Gut*. 2016 ;65:1829-37.
- ⁵⁰) Jspeert JE, Rana SA, Atkinson NS et al. Clinical risk factors of colorectal cancer in patients with serrated polyposis syndrome: a multicentre cohort analysis. *Gut*. 2017;66:278-84.

⁵¹) MacPhail ME, Thygesen SB, Patel N, Broadley HM, Rex DK. Endoscopic control of polyp burden and expansion of surveillance intervals in serrated polyposis syndrome. *Gastrointest Endosc.* 2018 ; S0016-5107:33287-5.

⁵²) Bleijenberg AG, IJspeert JE, van Herwaarden YJ et al. Personalised surveillance for serrated polyposis syndrome: results from a prospective 5-year international cohort study. *Gut.* 2019. pii: gutjnl-2018-318134.

⁵³) Win AK, Walters RJ, Buchanan DD et al. Cancer risks for relatives of patients with serrated polyposis. *Am J Gastroenterol.* 2012 ;107:770-8.

⁵⁴) Egoavil C, Juárez M, Guarinos C et al. Increased Risk of Colorectal Cancer in Patients With Multiple Serrated Polyps and Their First-Degree Relatives. *Gastroenterology.* 2017;153:106-12.

⁵⁵) Park SK, Park D, Yang HJ, Jung YS. Serrated Polyps and the Risk of Metachronous Advanced Colorectal Neoplasia. Oral presentation, KSAID conference(April 2018).

⁵⁶) Symonds E, Anwar S, Young G et al. Sessile Serrated Polyps with Synchronous Conventional Adenomas Increase Risk of Future Advanced Neoplasia. *Dig Dis Sci.* 2019;64:1680-1685.