Title

Serrated lesions in colorectal cancer screening: detection, resection, pathology and surveillance

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Key messages box

- Colorectal cancer can occur by more than one molecular pathway. The serrated pathway probably accounts for 20-30% of colorectal cancer
- Histopathological nomenclature for serrated lesions is variable internationally. We suggest the terms hyperplastic polyp (HPs), sessile serrated polyp (SSP), and traditional serrated adenoma (TSA) to describe these lesions.
- Colonoscopy is the best detection tool for serrated polyps but detection rates are variable.
- Chromoendoscopy and slower withdrawal time are the only interventions that have been demonstrated to increase serrated lesion detection. High definition endoscopy and right colon retroflexion may have a role.
- All polyps proximal to the recto-sigmoid junction should be removed. A benchmark rate of 4.5% for detection of proximal serrated lesions (HPs plus SSPs proximal to splenic flexure) in screening has been suggested for U.S. based colonoscopic screening, but implementing a target for serrated lesions in clinical practice is currently impractical.
- DNA based detection significantly augments serrated lesion detection in stool based screening programmes
- There are limited data to guide surveillance after resection of serrated lesions; however the logic behind surveillance for serrated lesions is consistent with that for conventional adenomas

INTRODUCTION

A strong evidence base supports colorectal cancer screening. Interruption of the adenoma-carcinoma sequence by endoscopic polypectomy has been considered the key step to prevent the development of colorectal cancer[1]. Higher adenoma detection rates (ADRs) at colonoscopy have a linear correlation with lower post colonoscopy colorectal cancer (PCCRC) rates and death from PCCRC[2]. However, colonoscopy is not as effective in colorectal cancer prevention in the right colon as in the left[3-5]. Interval cancers are often right sided and hypermethylated, not consistent with an origin in conventional adenomas[4]. Recent molecular approaches to colorectal cancer indicate there are three or more distinct molecular pathways to colorectal cancer, including a pathway arising through serrated lesions[6 7].

Serrated lesions pose multiple challenges in clinical practice, particularly with regard to detection. Sessile serrated polyps (SSPs), the most important subset of the serrated class of lesions, are endoscopically subtle lesions distributed predominantly in the right colon. SSPs are often flat and have minimal discoloration compared to the background mucosa. These lesions are challenging to detect by any method, including colonoscopy. SSPs are also more challenging to completely resect using standard polypectomy techniques compared to conventional adenomas[8]. Finally, there are few observational data to guide development of post-polypectomy surveillance guidelines after resection of serrated lesions.

In this review we aim to clarify for clinicians the role of serrated lesions in colorectal cancer screening, and the practical issues that flow from our current understanding of their importance**.**

TERMINOLOGY

There are two major classes of polyps and flat lesions in the colorectum. The best known class is the conventional adenomas. Conventional adenomas are uniformly dysplastic, and pathologically the degree of dysplasia is characterized as high or low grade. Conventional adenomas can also be characterized pathologically as tubular or villous. Conventional adenomas are widely understood to be pre-malignant lesions, with the risk of cancer development increasing in lesions that are larger, or having high grade dysplasia or villous elements[9].

The serrated class of colorectal lesions is distinct from the conventional adenomas. The World Health Organization (WHO) recommended that the serrated class has three major subtypes termed: 1) hyperplastic polyps (HPs) 2) sessile serrated adenoma/sessile serrated polyp and 3) traditional serrated adenoma (TSA)[10]. The WHO considers the terms sessile serrated adenoma (SSA) and sessile serrated polyp (SSP) to be synonymous and interchangeable. However, in this review we will utilize only the "SSP" term, and we recommend that the term "SSA" be abandoned in clinical practice. The term "SSA" had value when first introduced because the word "adenoma" in the term gave importance to the lesion[11]. However, the overwhelming majority of SSAs have no dysplastic component. Since all conventional adenomas are dysplastic, the term SSP more accurately distinguishes this generally non-dysplastic lesion from the conventional adenoma. Similarly, the endoscopic surface features of SSP are very similar to HPs and very distinct from conventional adenomas[12]. Finally, the ADR has emerged as the most important quality indicator in the technical performance of colonoscopy[13]. Clinicians given a pathology report of "SSA" often believe these lesions should be counted toward the ADR (understandably so when the term SSA includes the word "adenoma"), when guidelines clearly indicate the basis and history for why they are not counted

toward ADR[13]. Thus, based on pathology, endoscopic surface features, and clinical measurements of quality, the term SSA is misleading and confusing and the term SSP more accurately relates the position of this lesion in the distinct serrated class (Table 1)[10].

Table 1: Recommended classification of colorectal polyps and flat lesions[10]

Conventional adenomas
All conventional adenomas can be characterized by their degree of dysplasia (high or low) and tubular vs. villous histology
Serrated lesions
Hyperplastic polyps
Sessile serrated polyp
Sessile serrated polyp without cytological dysplasia Sessile serrated polyp with cytological dysplasia
Traditional serrated adenoma

A distinct and important but small subset of SSPs do contain a region of dysplasia that histologically appears to be a region of conventional adenoma within the SSP. In the past such lesions were often called "mixed hyperplastic-adenomatous polyps." The term "SSP with cytological dysplasia" accurately reflects the mixed histology of this lesion which is considered a more advanced lesion in the polyp-cancer sequence than the much more common "SSP without cytological dysplasia"[10].

The traditional serrated adenoma (TSA) is a rare lesion located primarily in the left colon and rectum[14 15]. TSA is the only member of the serrated class that is uniformly dysplastic.

Among the two classes of colorectal polyps and flat lesions, only the HP of the serrated class is considered to lack malignant potential (Table 2). HPs can be subclassified into goblet cell rich type, microvesicular and mucin-poor[10], but this sub-classification is not emphasized here because it lacks clinical relevance and is not used by pathologists in clinical practice. However, clinicians may benefit from understanding that the microvesicular subtype is distributed toward

the proximal colon relative to the goblet cell rich subtype, and the microvesicular type accounts for much of the poor agreement among pathologists in differentiating SSP from HP in clinical practice[16 17].

The terms “polyp”, “flat lesion” and “depressed lesion” are defined in the Paris classification and are descriptions of endoscopic lesion shape[18]. The use of term “polyp” in the names of different histologic classes of colorectal lesions does not imply that the lesions in that class are all “polypoid” i.e. Paris 0-1p (pedunculated) or 0-1s (sessile) in the Paris classification system. For example, conventional adenomas may be polyps, flat lesions, or depressed lesions, and SSPs are either sessile or flat (Table 2).

Table 2. Clinical features of the major classes of colorectal lesions (conventional adenomas and the serrated class)

Lesion	Frequency in screening[19]	Colonic distribution[14 15]	Dysplastic	Malignant potential	Shape	Surface features[12]
Conventional adenomas	~50%	Throughout	Y	Y	Usually sessile or flat 5-10% pedunculated < 1% depressed	Rich in blood vessels surrounding pits Pits of variable size and shape, often tubular
Serrated class						
Hyperplastic polyp	~30%	Mostly distal	N	N	Sessile or flat	No surface vessels or only a few lacy vessels Pits of relatively uniform size and shape
Sessile serrated polyp		Mostly proximal				
• Without cytological dysplasia	3-8%		N	Y		
• With cytological dysplasia	< 1%		Y	Y		May have surface features of both the serrated class and the conventional adenomas
Traditional serrated adenoma	rare	Mostly distal	Y	Y	Sessile or pedunculated	Villiform

KEY MOLECULAR ASPECTS

Every cancer is unique from a molecular perspective, but there are three general molecular pathways to CRC[20]. The most common is the Chromosomal Instability (CIN) pathway which develops through conventional adenomas and accounts for perhaps 65-70% of CRCs. Vogelstein developed the concept of chromosomal instabilities leading to progressive accumulation of sporadically acquired mutations in tumor suppressor genes and oncogenes, resulting in development of a conventional adenoma and its transition over many years from low to high grade dysplasia and then invasive cancer[9].

A second major pathway is designated the Lynch pathway and is based in inherited mutation in one or more of four DNA-mismatch repair genes (MLH1, MSH2, MSH6, PMS2)[21]. The Lynch pathway, like the CIN pathway, develops through conventional adenomas, but accounts for only about 3% of CRCs. Tumors in Lynch Syndrome consistently demonstrate mutation in short repeating sequences of DNA called microsatellites and Lynch tumors thus carry a phenotype termed microsatellite instability (MSI). Clinically, MSI appears to be associated with more rapid transformation of adenoma to cancer, and this observation underlies the recommendation to perform colonoscopy at closer intervals than are needed to intercept cancers passing through the CIN pathway[21].

For this review the third major molecular pathway is of primary interest, since the precursor lesion is serrated. Tumors in this pathway have higher levels of methylation relative to tumors in the other pathways, and the pathway is most often designated the CpG-island methylator phenotype (CIMP) pathway[20], though reference to the “serrated pathway” or “hypermethylated pathway” is also made. DNA-methylation changes cytosin in CpG islands

into methylcytosin, which in excess may inactivate the promoter regions of tumour suppressor genes (e.g. p16, PTEN, E-cadherin, ER, AR, MLH1)[22]. This event represents epigenetic gene inactivation. About half of tumors in the CIMP pathway have MSI, which results from epigenetic inactivation of MLH1, one of the same mismatch repair genes that when mutated in the germ line results in Lynch Syndrome. Because CIMP pathway tumors are considerably more common than Lynch tumors, CIMP tumors account for about 80% of the CRCs with MSI. The CIMP or "serrated" pathway probably accounts for 20-30% of colorectal cancer [23-25]. Clinicians encountering MSI in tumors may need to differentiate the underlying cause of MSI as CIMP vs. Lynch if the affected mismatch repair gene is MLH1. This differentiation can be accomplished by testing the tumor for hypermethylation, or by testing the tumor for mutation in the BRAF oncogene. BRAF mutation is characteristic of CIMP cancers as well as many SSPs and HPs[26].

Variable molecular profiles for TSAs have been described, and include the recent finding that TSAs are the sporadic equivalent of hereditary mixed polyposis syndrome, driven by aberrant epithelial GREM1 expression[27].

CLINICAL ASPECTS OF THE PATHOLOGY OF SERRATED LESIONS

Many aspects of the histologic criteria used to classify subtypes of colorectal polyps by pathologists lack validation, and also are subject to substantial interobserver variation among pathologists even when those pathologists are using identical diagnostic criteria. These limitations apply to dysplasia grade and the presence of villous elements in conventional

adenomas[28]. Clinicians should understand that similar limitations affect the serrated class of colorectal lesions.

First, the agreement between pathologists is low to moderate when differentiating HP (Figure 1a) from SSP[16 17]. The main histologic criteria for diagnosis of SSP are listed in Table 3[29]. The clinical significance of these diagnostic criteria is not validated. Important features that identify the SSP include lateral growth of crypts at the base, dilation in the lower third of crypts, and hyperserration of the crypt bases, sometimes with branching (Figure 1b). Low interobserver variation results when the diagnostic features of SSP are not pronounced or affect only one or a few crypts. To extend the clinical difficulties for clinicians, a multicenter study showed that some pathologists never use the term "serrated" in a pathology report, calling all lesions in the serrated class HPs[17]. Because SSPs are associated with larger size and proximal location compared to HPs, some experts have advocated that lesions larger than 1 cm in size removed from the proximal colon and called "HP" by pathologist should be treated as SSP by clinicians with regard to surveillance[30]. This seems particularly reasonable if the institutional pathologists rarely make an SSP determination.

Table 3. Main histologic diagnostic criteria for sessile serrated polyps (at least 2 out of the 4 criteria for diagnosis in at least 2 crypts not necessarily neighbouring)*

- Hyperserration, serration in the lower third of the crypts with and without branching of the crypts
- T- and L-shaped crypts above the muscularis mucosae
- Inverted crypts (pseudoinvasion) below the muscularis mucosae
- Columnar dilation in the lower third

*Modified from Aust et al.[29] and does not include the "side criteria" in that reference

Clinicians should discuss terminology with their pathologists (Table 1). We recommend that all SSPs be designated by pathologists as “without” or “with” cytological dysplasia. A focus of cytological dysplasia generally appears to be a region of conventional adenoma within a lesion that is otherwise SSP (Figure 1c). Microdissection studies indicate that the dysplastic portion is more likely to demonstrate MSI[31], suggesting that the SSP with cytological dysplasia is an advanced lesion for which an endoscopist should be sure of complete resection. When cytological dysplasia is identified, it may be described as high grade or low grade, but the significance of this designation in SSPs with cytological dysplasia is uncertain. Clinicians should treat any dysplasia in an SSP as a more advanced lesion than an SSP without cytological dysplasia.

The TSA is a rare lesion compared to HP and SSP. Because the TSA is dysplastic and may be villiform histologically (Figure 1d), it is likely commonly mistaken for a conventional tubulovillous adenoma, though TSAs have specific features such as eosinophilic cytoplasm and crypt building.

DETECTION OF SERRATED LESIONS DURING COLONSOCOPY

Endoscopic appearance of serrated lesions

HPs are typically ≤5 mm in size, located in the recto-sigmoid, are hemi-spherical, often paler than the background mucosa and usually have either no visible blood vessels or have fine, threadlike branching vessels across their surface[12] (Figure 2). SSPs are similar in color and vessel distribution to HPs, but in contrast to HPs have larger mean size, are distributed toward

the proximal colon, have a cloud-like or bossellated surface[32], an irregular surface[32], a mucus cap[33], and indistinct edges[32 34] (Figure 2). Large black pits on the surface of a serrated lesion predict SSP over HP[32] (Figure 2). Serrated lesions may be recognized by distortion of a fold edge or disruption of the vascular pattern of the normal colonic mucosa[34] (Figure 4).

Colonoscopic prevalence rate of serrated polyps in screening populations

Prevalence rates of proximal colon serrated lesions (HPs plus SSPs) vary between centers[17] and between operators within centers[35 36], with one U.S. centre reporting a range of 1-18% among 15 endoscopists performing screening colonoscopy[36]. A Dutch screening study with five endoscopists showed a range of 6-22%[37]. The combination of a high detecting colonoscopist and an experienced GI pathologist revealed an SSP prevalence rate of 8.1% in a series of 1910 screening colonoscopies , 0.6% of which had cytological dysplasia[19].

Many researchers have chosen to consider all right sided serrated lesions (HPs plus SSPs) as the outcome measure because of the unreliable differentiation of HP from SSP by pathologists. Prevalence rates of proximal serrated lesions are higher in FOBT based colonoscopy programs because they are associated with advanced conventional adenomas that are detected by FOBT[38-41]. Prevalence rates of proximal serrated lesions vary worldwide from 2.8 to 13% (Netherlands, Spain, USA, Hong Kong, Korea)[17 36-40 42-45]. There is also variation between centers within these estimates with one study of 32 US and German centers reporting a range of 0-9.8%[17]. There may also be differing rates of serrated lesions related to ethnicity, with higher rates reported in Caucasian patients in autopsy studies[46].

Serrated polyposis syndrome in screening

Serrated lesions are often multiple and if in sufficient numbers and size can meet the criteria for serrated polyposis syndrome (SPS, previously called hyperplastic polyposis syndrome; WHO definition, Box 1)[47]. SPS increases future CRC risk, with Boparai et al. reporting a 7% risk at 5 years[48]. In FOBT based screening the prevalence of SPS may exceed 1:300 (Table 4[36 49-52]) making this an important syndrome for screening colonoscopists to recognize in these programmes, and again highlighting the association between serrated polyps and advanced adenomas[50 51]. The rates in colonoscopy based programmes are approximately 1: 2000 (Table 4).

Box 1: WHO definition of serrated polyposis syndrome 2010 [47]*

A	At least five serrated polyps proximal to the sigmoid colon, two of which are greater than 10 mm in diameter
B	Any number of serrated polyps occurring proximal to the sigmoid colon in an individual who has a first-degree relative with serrated polyposis
C	More than 20 serrated polyps of any size distributed throughout the colon

*Serrated lesion refers to any combination of hyperplastic polyps and sessile serrated polyps

Table 4: Serrated polyposis syndrome prevalence in population based screening by modality

Author	Screening modality	**n/pop**	**% (95% CI)**	**Ratio**
Lockett [49]	Flexible sigmoidoscopy	12/ 40674	0.029% (0.02-0.05)	1:3000
Orlowska [52]	Colonoscopy	28/50148	0.056% (0.04-0.09)	1:1791
Kahi [36]	Colonoscopy	3/6681	0.04% (0.01-0.014)	1:2227
Biswas [50]	FOBT (Guaiac)	5/755	0.66% (0.24-1.52)	1:151
Moreira [51]	FOBT (FIT)	8/2355	0.34% (0.17-0.67)	1:294

CI, Confidence interval

FOBT, Faecal occult blood test
FIT, Faecal immunochemical test

Serrated polyp miss rates

Few direct measures of serrated lesion miss rates are not available. Harrison et al. in 2004 found a miss rate for "hyperplastic" polyps of 59% (13/22, 100 patients examined) in the proximal colon[53]. Wide variation in detection[17 35 36] implies large miss rates, as does the increased rate of hypermethylated cancers among post-colonoscopy cancers. Endoscopists using chromoendoscopy find twice the serrated lesions and more proximal serrated lesions as the same endoscopists using white light, indicating that lesions were missed with white light[54-56]. Heresebach et al. determined an overall miss rate overall for hyperplastic polyps of 31% vs. 20% for adenomas[57]. These data indicate that miss rates for serrated lesions may be higher than for conventional adenomas, consistent with their subtle endoscopic appearance.

TECHNOLOGIES AND TECHNIQUES TO IMPROVE SERRATED POLYP DETECTION

Bowel preparation Few studies have had detection of serrated lesions as a primary outcome. Bowel preparation quality does not have the impact on detection of serrated lesions that has been documented for conventional adenomas[58 59]. In a Dutch screening study quality of bowel preparation was not associated with lower proximal serrated lesion detection rates, multivariate odds ratio 0.98 (95% CI 0.92-1.05)[37]. In a U.S. registry based study serrated polyp detection rates were similar for optimal (excellent or good) vs. fair bowel preparation, with an odds ratio of 0.75 (95% CI 0.31-1.80) for poor prep vs. optimal prep for proximal

serrated polyp detection[60]. This effect may result from a thicker mucus cap on serrated lesions with lower preparation quality.

Withdrawal time

Two studies indicate that longer withdrawal time is important for serrated lesion detection. In the same Dutch screening cohort, longer withdrawal time had an odds ratio of 1.12 for detection of serrated lesions, identical to that for conventional adenoma detection[37]. Analysis of data from the New Hampshire colonoscopy registry reports an incidence rate ratio of 1.77 for each minute beyond 6 minutes withdrawal time to a maximum at 9 minutes, slightly higher than that seen for conventional adenomas at 1.50[61].

High definition

In a cohort study, detection rates for proximal hyperplastic polyps and for large (≥10mm) hyperplastic polyps were not different[62]. In a Dutch screening cohort use of high definition or wide angle colonoscopes did not improve proximal serrated polyp detection, multivariate odds ratios 1.07 and 1.30 respectively[37]. High definition compared to standard definition colonoscopy provided only a marginal incremental yield in polyp detection rates of 3.8% (95% CI 1-6.7%) in a meta-analysis suggesting that a major benefit is unlikely[63].

Chromoendoscopy

Chromoendoscopy consistently improves adenomatous as well as non-adenomatous polyps detection rates, with the vast majority of the latter being serrated lesions. A summary of four studies performed between 2002 and 2006, prior to general appreciation of the importance of serrated polyps, suggested an approximate doubling of hyperplastic or non-adenomatous polyp detection from 23 to 45%, and from 9 to 16% when only the proximal colon was considered[56].

More recent studies have confirmed this result and effect size in multicentre studies from Germany (46.2 vs 29.5% serrated lesions, rectum excluded, p<0.001)[55] and the U.S. (high definition colonoscopes; mean non-neoplastic lesions per patient 1.8 vs 1.0, P<0.001)[54]. The use of chromoendoscopy to increase yield of serrated polyps in the right colon is currently being trialed in an FOBT positive screening population (CONSCOP Study; ClinicalTrials.gov identifier: NCT01972451).

Narrowed spectrum endoscopy

Narrow band imaging (NBI) showed promise in a single centre, single operator study for detection of serrated lesions in the setting of serrated polyposis syndrome[64]; however, a multicentre study from the same group did not confirm this benefit[65]. Four different meta-analyses of NBI vs. white light, including more than 3,000 patients, have failed to show improvements in adenoma or polyp detection rates, suggesting a benefit for serrated polyps is unlikely[66]. Similarly, there is no clear benefit for either flexible spectral imaging color enhancement (FICE, Fujinon)[67-69], or iSCAN (Pentax) with tone enhancement[70-72].

Anti-spasmodics

Hyoscine butyl bromide (Buscopan) increased polyp detection in the right colon, 0.43 vs. 0.31, p=0.01 in one randomized controlled trial[73]; however, a metaanalysis that included this study found no increase in polyp detection rate overall (OR1.09 95% CI 0.91-1.31)[74].

Wide angle and proximal colon retroflexion

Proximal colon retroflexion showed a modest increase in proximal serrated lesion detection, although this gain might have been achieved with a repeated examination in the forward view[75]. In a tandem study the Third Eye Retroscope detected 77 vs. 58 non-adenomatous

polyps, but in the right colon this was only 19 versus 22 non-adenomatous polyps, so better detection of clinically relevant serrated lesions was not shown[76]. Other novel devices to reveal more mucosa have been recently reported such as G-Eye, Full Spectrum Endoscopy and Third Eye Panoramic Device[77 78]; however no current studies report data that allow assessment of proximal serrated lesion detection rates.

Bench marks for serrated lesion detection rates

Benchmarks for lesion detection remain a challenge as a link to important clinical outcomes often requires time to become apparent. Post-colonoscopy colorectal cancer rates are an ideal target for quality improvement but are expensive to measure and fail to detect poor performers early in their experience[79]. A Polish screening study validated ADR as a concept associated with CRC prevention[38 40 80]. A larger cohort from the U.S. found that improvements in ADR above the original recommended thresholds led to additional gains in cancer prevention[2]. Initial data suggested that ADR and detection of proximal serrated lesions, those found proximal to the splenic flexure, are highly correlated (R=0.7)[36]; however, three recent studies found lower correlations (R=0.04-0.43)[17 43 81]. Therefore, reaching current ADR targets may not lead to adequate serrated detection. Kahi and colleagues examined serrated detection in a cohort of 15 endoscopists for whom the ADR and proximal serrated lesion detection rates were known. They drew a line from the US Multi-Society Task Force ADRs for men (25%) and women (15%) to the regression line and found the equivalent proximal serrated detection rate to be 4.5% for both men and women[36]. For programs based on FOBT, where the higher rate of advanced neoplasia should be associated with higher proximal serrated detection rates, the benchmark may need to be higher[41]. One FOBT based program reported a rate of 8%[39].

While 5% might be a reasonable target for practitioners wanting to check their detection of total proximal colon serrated lesions (HPs plus SSPs), widespread use of this or any proximal colon serrated lesion target would be complicated to institute, since it could be easily corrupted by inclusion of more distal colon serrated lesions (which mostly lack significance).

ENDOSCOPIC RESECTION OF SERRATED POLYPS

Endoscopic resection is recommended for all polyps proximal to the sigmoid colon, all lesions in the rectosigmoid colon >5 mm in size, and for conventional adenomas in the rectosigmoid of any size[30]. The overwhelming majority of serrated lesions ≤ 5 mm in the rectosigmoid are hyperplastic and not SSPs, and rectosigmoid SSPs ≤ 5 mm in size with cytological dysplasia are extremely rare. Therefore serrated lesions ≤ 5 mm in size located in the rectosigmoid colon remain the single group of colorectal polyps for which avoidance of resection is appropriate[20 30 82]. Identifying this group of lesions and selecting them to be left in-situ requires endoscopic estimation of pathology in real-time during colonoscopy[12]. Experts can exclude conventional adenoma by endoscopic criteria in the rectosigmoid with > 95% accuracy[83].

In a recent study of polyps 5 to 20 mm in size, predictors of incomplete resection were the endoscopist, increasing polyp size and serrated histology[8]. The overall rate of incomplete resection of serrated lesions was 32% compared to 7% for conventional adenomas[8]. SSPs are characteristically flat or sessile and have indistinct edges compared to hyperplastic polyps and to conventional adenomas[31 32]. The impact of indistinct edges on incomplete resection

is readily understood, but can be overcome by endoscopic mucosal resection employing a contrast agent in the submucosal injection fluid and a high definition colonoscope[84]. This combination provides excellent delineation of the lesion edges, thereby enabling complete resection (Figure 3). Inclusion of a margin of normal tissue and the use of snare resection for the entire lesion, with reservation of ablative techniques only for sections that can't be snared, helps ensure lesion eradication[84]. Adherence to these principles is associated with cure rates of endoscopic resection of serrated lesions equal to those for conventional adenomas[84].

Serrated lesions treated with endoscopic mucosal resection techniques are more often resectable en bloc (as opposed to piecemeal) compared to conventional adenomas of equal size[84].

The frequent location of large serrated lesions in the cecum and ascending colon is not a deterrent to their endoscopic resection. There is currently no published evidence that the complication rate of endoscopic resection of serrated lesions is higher than for conventional adenomas; however concerns have been raised due to the high complication rate seen in a large cohort from pre-2005 describing a subgroup of patients with large sessile lesions resected in the right colon[85 86].

Resection of serrated lesions by endoscopic mucosal resection is facilitated by use of a stiff snare, which allows the endoscopist to effectively grip the normal mucosa around the lesion and achieve a clear margin (Figure 3). Once the snare is closed on tissue, the snare can be squeezed very tightly before application of electrocautery with less risk of mechanical tissue tearing relative to conventional adenomas. This may be the result of more submucosal fat under serrated lesions compared to conventional adenomas. Some experts recommend tight

snare closure before application of cautery to increases current density, speed transection during cautery application, and potentially limit thermal injury to the submucosa[87].

EFFICACY OF OTHER TECHNIQUES (NON-ENDOSCOPIC) FOR DETECTION OF SERRATED POLYPS

When used for screening, flexible sigmoidoscopy generally leads to colonoscopy based on detection of any adenoma or detection of advanced or multiple adenomas[88 89]. As such, flexible sigmoidoscopy can detect some proximal cancers and advanced conventional adenomas, with the fraction of advanced proximal lesions detected generally low and dependent on the criteria by which colonoscopy is indicated[88 89]. One study found that conventional adenomas in the distal colon did not predict advanced serrated neoplasms (SSPs $\geq$ 1 cm)[90]. Therefore available evidence indicates flexible sigmoidoscopy lacks value for identifying important proximal colon serrated lesions.

Available evidence suggests detection of serrated lesions by CT colonography is lower than for conventional adenomas[91-93]. Studies of CT colonography directly targeting SSPs are not available. Only one trial of capsule colonoscopy directly assessed performance for serrated lesions, and sensitivity was substantially lower than for conventional adenomas[94].

Serrated polyps have no or very few blood vessels on the surface[12], and they rarely show hemorrhage pathologically [94 95], suggesting they may not be detected by fecal immunochemical testing (FIT). Only one study has directly measured FIT performance for serrated lesions, and the sensitivity of FIT was 5%[96]. This sensitivity equaled the false

positive rate of FIT, indicating no sensitivity of FIT for serrated lesions[96]. Fecal DNA testing includes assays for hypermethylation, and detected 40% of serrated lesions ≥ 1 cm in size[96]. The incremental gain in sensitivity of fecal DNA compared to FIT was much larger for serrated lesions than for conventional adenomas and cancers[96].

SURVEILLANCE FOR SERRATED POLYPS AFTER COLONOSCOPY

Surveillance for serrated lesions after colonoscopy is controversial because there are not proven benefits and cost-effectiveness is not established. The guaiac-based FOBT NHS bowel cancer screening program in England does not endorse surveillance after resection of serrated lesions, citing lack of evidence. Schreiner et al. re-analyzed data collected from 1994-1997 in the U.S. Veterans Affairs study group to show that patients who had a proximal serrated lesion alone had an increased risk of future colorectal neoplasia, and those with a serrated lesion and an advanced adenoma had a higher risk of neoplasia and advanced neoplasia at follow up[97]. Recent data from a Norwegian flexible sigmoidoscopy based study from an earlier time in which large "hyperplastic" were not considered pre-malignant suggests that patients with serrated polyps ≥10 mm in size had a future colorectal cancer risk equivalent to having an advanced adenoma, supporting recent guideline recommendations for surveillance of patients with serrated lesions[98]. Other circumstantial evidence supports surveillance including: over-representation of the serrated pathway[4] in interval cancers and high rates of residual neoplasia after resection of serrated polyps[8].

Given this circumstantial evidence, some but not all editorialists, GI societies, and some international guideline groups have offered guidelines on surveillance (Table 5)[30 82 99-

101] that are broadly consistent, though the European IARC guidelines make no recommendation.

Table 5. Cross tabulation of recommendations for surveillance intervals after detection of serrated lesions.

Terdiman, McQuaid[99]	**US Multi-society taskforce[30]**	**AJG working group[20]**	**ESGE[100]**	**European Union / IARC[101]**	**Surveillance interval, years**
Hyperplastic (serrated) polyposis syndrome	Serrated polyposis syndrome	Serrated polyposis syndrome	N/A	N/A	1
Serrated polyp proximal to splenic flexure, ≥ 10 mm in size, or with cytological dysplasia at any location*	Sessile serrated adenoma/polyp ≥10 mm, sessile serrated adenoma/polyp with dysplasia, or traditional serrated adenoma	SSA/P or TSA ≥10mm or 3 or more in number. Two or more SSA/P 10mm in size† or any SSA/P with dysplasia†	Serrated polyps ≥ 10 mm, or with cytological dysplasia at any size*	-	3
-	Sessile serrated adenoma/polyp <10 mm with no dysplasia	≥4 HPs any size proximal to sigmoid , or any proximal HP >5mm in size, or 1-2 SSPs or TSAs <10mm	-	-	5
Distal serrated polyp < 10 mm	-	HP <10mm in recto-sigmoid, or ≤3 HP≤5mm proximal to sigmoid	Serrated polyp <10 mm with no dysplasia	All serrated lesions of any size without adenomatous dysplasia (no recommendation for surveillance)	10 (routine screening)

* This proposed strategy considers hyperplastic polyps, sessile serrated adenomas/polyps, and traditional serrated adenomas as serrated polyps.
†1-3 years recommended depending on clinical circumstances. SPS should be considered.

CONCLUSIONS AND FUTURE DIRECTIONS

Colonoscopy is currently not as effective at preventing CRC arising from the serrated pathway compared to CRC arising via the conventional adenoma-carcinoma sequence. However, all other screening methods are less effective than colonoscopy for detection of serrated lesions. With increased understanding of the importance and appearance of serrated lesions, and improved pathological sub-typing, detection of serrated lesions is likely to improve. The balance between the risks and costs of resection and the benefits for CRC prevention remain uncertain[85]. High quality prospective studies are needed to inform surveillance guidelines which are currently based on low or very low quality evidence. The recognition of a new pathway to CRC outside the traditional adenoma-carcinoma sequence gives researchers and clinicians a chance to further improve CRC prevention by optimizing screening to meet this new challenge.

Box 2: Key research questions for serrated lesions in colorectal cancer screening

- What is the risk of future neoplasia and colorectal cancer after resection of SSPs
- Should SSP risks be combined with adenoma risk or additive to adenoma risk for surveillance?
- Is surveillance for serrated lesions cost effective?
- What chemopreventive measures would reduce the development and growth of serrated lesions and associated cancers?
- Is better detection of serrated lesions linked to clinical outcomes?
- What tools will increase the detection of serrated lesions at colonoscopy and by other screening methods?

- What biomarkers can select patients at high risk of serrated lesions?
- How can we teach community based endoscopists to effectively recognize and safely resect SSPs?
- How can we integrate SSP into current paradigms for "optical biopsy" at colonoscopy?
- How can we decrease interobserver variability between pathologists assessing SSPs?
- How can we link specific molecular changes suggestive of pre-malignant potential in SSPs to pathological features?

Figure legend

Figure 1a. Hyperplastic polyp with saw-tooth protrusions of the epithelium into the glandular lumen and eosinophilic cytoplasm. Goblet cells are present but do not reach the basal compartment. The basal zone shows increased proliferative changes with hyperchromatic but not pleomorphic nuclei.

Figure 1b. Sessile serrated polyp with saw-tooth protrusions of the epithelium into the glandular lumen comparable to hyperplastic polyps but focally with a more complex architecture and T or L shaped glands (black arrow) and dilated glands (yellow arrow) at the base of the lesion just above the muscularis mucosae. Goblet cells reach the base of the lesion in contrast to a hyperplastic polyp.

Figure 1c. Sessile serrated polyp with cytological dysplasia (low-grade). Black rectangle surrounds most of the dysplastic portion.

Figure 1d. Traditional serrated adenoma showing the typical micro acini or microglandular foci and also eosinophilic cytoplasm. Nuclei are hyperchromatic, stratified and palisading, depicting the classical intestinal dysplasia in combination with serration of the tubular glands. This demonstrates a mixture of a distinct subtype of serrated lesion with intestinal dysplasia.

Figure 2a. Typical sigmoid colon hyperplastic polyps (arrows) in narrow band imaging. No blood vessels are visible. The uniform pattern of black dots represent pits.

Figure 2b. Sessile serrated polyp. Some of the mucus cap remains (orange arrows). One edge is indistinct (yellow arrow).

Figure 2c. The same lesion seen in Figure 2b, now shown in narrow band imaging. Arrows point to the large dark pits that predict sessile serrated polyp over hyperplastic polyp. The “cloud-like” surface is evident on the left.

Figure 2d. The lesion seen in 2a and 2b after submucosal injection with hydroxyethyl starch containing indigo carmine. Arrows show the excellent delineation of the lesion edges by the contrast agent.

Figure 2e. A sessile serrated polyp in narrow band imaging. Arrows designate the visible edge. The rectangle encloses a section with numerous large dark pits. The irregular surface of the lesion favors sessile serrated polyp over hyperplastic polyp.

Figure 2f. A sessile serrated polyp in white light. Arrows delineate the lesion edges. The main clue to the recognition is that the lesion obscures the normal colonic vascular pattern.

Figure 2g. A very large sessile serrated polyp with the appearance of redundant folds. Yellow arrows mark the lesion edges. The left edge is not visible in the frame. Orange arrows mark areas of residual mucus cap after washing.

Figure 2h. A sessile serrated polyp with cytological dysplasia. The black rectangle encloses a portion of the lesion with endoscopic features of a conventional adenoma (numerous blood vessels surrounding white pits, which are often tubular, but quite variable in shape). The

yellow rectangle encloses a portion of the lesion characterized by uniformly distributed black dots, typical of a serrated lesion.

Figure 3a. A sessile serrated polyp with adherent mucus cap. Arrows mark the edges.

Figure 3b. The same lesion seen in Figure 3a after washing the mucus cap. The edges are less well defined.

Figure 3c. The lesion after injection with hydroxyethyl starch containing indigo carmine. The edges are now well defined (arrows).

Figure 3d. A stiff snare is used to facilitate capture of a margin of normal tissue (arrows) around the lesion.

Figure 3e. The snare is closed very tightly before application of electrocautery. Note the large injection mound. The small red nodule (arrow) is an intramucosal hemorrhage in normal tissue and can be ignored. Larger lesions are resected piecemeal using the same principles.

Figure 3f. The defect after transection. The blue color in the submucosa indicates limited thermal injury. The contrast agent and high definition permit visualization of a tiny nodule of residual serrated tissue (arrow) that requires further snaring or ablation.

References

1. Bond JH. Clinical evidence for the adenoma-carcinoma sequence, and the management of patients with colorectal adenomas. Seminars in gastrointestinal disease 2000;**11**(4):176-84
2. Corley DA, Jensen CD, Marks AR, et al. Adenoma detection rate and risk of colorectal cancer and death. N Engl J Med 2014;**370**(14):1298-306 doi: 10.1056/NEJMoa1309086[published Online First: Epub Date]|.
3. Baxter NN, Goldwasser MA, Paszat LF, et al. Association of colonoscopy and death from colorectal cancer. Ann Intern Med 2009;**150**(1):1-8
4. Nishihara R, Wu K, Lochhead P, et al. Long-term colorectal-cancer incidence and mortality after lower endoscopy. N Engl J Med 2013;**369**(12):1095-105 doi: 10.1056/NEJMoa1301969[published Online First: Epub Date]|.
5. Baxter NN, Warren JL, Barrett MJ, et al. Association between colonoscopy and colorectal cancer mortality in a US cohort according to site of cancer and colonoscopist specialty. J Clin Oncol 2012;**30**(21):2664-9 doi: 10.1200/JCO.2011.40.4772[published Online First: Epub Date]|.
6. Jass JR, Iino H, Ruszkiewicz A, et al. Neoplastic progression occurs through mutator pathways in hyperplastic polyposis of the colorectum. Gut 2000;**47**(1):43-49 doi: 10.1136/Gut.47.1.43[published Online First: Epub Date]|.
7. Torlakovic E, Skovlund E, Snover DC, et al. Morphologic reappraisal of serrated colorectal polyps. Am J Surg Pathol 2003;**27**(1):65-81
8. Pohl H, Srivastava A, Bensen SP, et al. Incomplete polyp resection during colonoscopy-results of the complete adenoma resection (CARE) study. Gastroenterology 2013;**144**(1):74-80 e1 doi: 10.1053/j.gastro.2012.09.043[published Online First: Epub Date]|.
9. Vogelstein B, Fearon ER, Hamilton SR, et al. Genetic alterations during colorectal-tumor development. N Engl J Med 1988;**319**(9):525-32 doi: 10.1056/NEJM198809013190901[published Online First: Epub Date]|.
10. Snover D, Ahnen DJ, Burt RW, Odze RD. Serrated polyps of the colon and rectum and serrated polyposis. In: Bosman FT, Carneiro F, Hruban RH, Theise ND eds. WHO Classification of Tumours of the Digestive System: LYON: IARC 2010:160-5
11. Torlakovic E, Snover DC. Serrated adenomatous polyposis in humans. Gastroenterology 1996;**110**(3):748-55
12. Hewett DG, Kaltenbach T, Sano Y, et al. Validation of a simple classification system for endoscopic diagnosis of small colorectal polyps using narrow-band imaging. Gastroenterology 2012;**143**(3):599-607 e1 doi: 10.1053/j.gastro.2012.05.006[published Online First: Epub Date]|.
13. Rex DK, Schoenfeld PS, Cohen J, et al. Quality indicators for colonoscopy. Gastrointest Endosc 2015;**81**(1):31-53 doi: 10.1016/j.gie.2014.07.058[published Online First: Epub Date]|.
14. Chetty R, Hafezi-Bakhtiari S, Serra S, et al. Traditional serrated adenomas (TSAs) admixed with other serrated (so-called precursor) polyps and conventional adenomas: a frequent occurrence. J Clin Pathol 2015 doi: 10.1136/jclinpath-2014-202827[published Online First: Epub Date]|.
15. Miwa S, Mitomi H, Igarashi M, et al. Clinicopathologic differences among subtypes of serrated adenomas of the colorectum. Hepato-gastroenterology 2005;**52**(62):437-40

16. Khalid O, Radaideh S, Cummings OW, et al. Reinterpretation of histology of proximal colon polyps called hyperplastic in 2001. World J Gastroenterol 2009;**15**(30):3767-70 doi: 10.3748/wjg.15.3767[published Online First: Epub Date]|.
17. Payne SR, Church TR, Wandell M, et al. Endoscopic detection of proximal serrated lesions and pathologic identification of sessile serrated adenomas/polyps vary on the basis of center. Clin Gastroenterol Hepatol 2014;**12**(7):1119-26 doi: 10.1016/j.cgh.2013.11.034[published Online First: Epub Date]|.
18. The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon: November 30 to December 1, 2002. Gastrointest Endosc 2003;**58**(6 Suppl):S3-43
19. Abdeljawad K, Vemulapalli KC, Kahi CJ, et al. Sessile serrated polyp prevalence determined by a colonoscopist with a high lesion detection rate and an experienced pathologist. Gastrointest Endosc 2014 doi: 10.1016/j.gie.2014.04.064[published Online First: Epub Date]|.
20. 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**(9):1315-29 doi: 10.1038/ajg.2012.161[published Online First: Epub Date]|.
21. Giardiello FM, Allen JI, Axilbund JE, et al. Guidelines on genetic evaluation and management of Lynch syndrome: a consensus statement by the U.S. Multi-Society Task Force on Colorectal Cancer. Gastrointest Endosc 2014;**80**(2):197-220 doi: 10.1016/j.gie.2014.06.006[published Online First: Epub Date]|.
22. Jass JR. Classification of colorectal cancer based on correlation of clinical, morphological and molecular features. Histopathology 2007;**50**(1):113-30 doi: 10.1111/j.1365-2559.2006.02549.x[published Online First: Epub Date]|.
23. Samowitz WS, Albertsen H, Herrick J, et al. Evaluation of a large, population-based sample supports a CpG island methylator phenotype in colon cancer. Gastroenterology 2005;**129**(3):837-45 doi: 10.1053/j.gastro.2005.06.020[published Online First: Epub Date]|.
24. Hawkins N, Norrie M, Cheong K, et al. CpG island methylation in sporadic colorectal cancers and its relationship to microsatellite instability. Gastroenterology 2002;**122**(5):1376-87 doi: 10.1053/gast.2002.32997[published Online First: Epub Date]|.
25. Toyota M, Ahuja N, Ohe-Toyota M, et al. CpG island methylator phenotype in colorectal cancer. Proc Natl Acad Sci U S A 1999;**96**(15):8681-6
26. Kambara T, Simms LA, Whitehall VL, et al. BRAF mutation is associated with DNA methylation in serrated polyps and cancers of the colorectum. Gut 2004;**53**(8):1137-44 doi: 10.1136/gut.2003.037671[published Online First: Epub Date]|.
27. Davis H, Irshad S, Bansal M, et al. Aberrant epithelial GREM1 expression initiates colonic tumorigenesis from cells outside the stem cell niche. Nat Med 2015;**21**(1):62-70 doi: 10.1038/nm.3750[published Online First: Epub Date]|.
28. Lasisi F, Mouchli A, Riddell R, et al. Agreement in interpreting villous elements and dysplasia in adenomas less than one centimetre in size. Dig Liver Dis 2013;**45**(12):1049-55 doi: 10.1016/j.dld.2013.05.014[published Online First: Epub Date]|.
29. Aust DE, Baretton GB, Members of the Working Group GIPotGSoP. Serrated polyps of the colon and rectum (hyperplastic polyps, sessile serrated adenomas, traditional serrated adenomas, and mixed polyps)-proposal for diagnostic criteria. Virchows Arch 2010;**457**(3):291-7 doi: 10.1007/s00428-010-0945-1[published Online First: Epub Date]|.

30. Lieberman DA, Rex DK, Winawer SJ, et al. Guidelines for colonoscopy surveillance after screening and polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology 2012;**143**(3):844-57 doi: 10.1053/j.gastro.2012.06.001[published Online First: Epub Date]|.
31. Tadepalli US, Feihel D, Miller KM, et al. A morphologic analysis of sessile serrated polyps observed during routine colonoscopy (with video). Gastrointest Endosc 2011;**74**(6):1360-8 doi: 10.1016/j.gie.2011.08.008[published Online First: Epub Date]|.
32. 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**(6):916-24 doi: 10.1016/j.gie.2012.12.018[published Online First: Epub Date]|.
33. Rex DK, Rahmani EY. New endoscopic finding associated with hyperplastic polyps. Gastrointest Endosc 1999;**50**(5):704-6
34. Sweetser S, Smyrk TC, Sinicrope FA. Serrated colon polyps as precursors to colorectal cancer. Clin Gastroenterol Hepatol 2013;**11**(7):760-7; quiz e54-5 doi: 10.1016/j.cgh.2012.12.004[published Online First: Epub Date]|.
35. Hetzel JT, Huang CS, Coukos JA, et al. Variation in the detection of serrated polyps in an average risk colorectal cancer screening cohort. Am J Gastroenterol 2010;**105**(12):2656-64 doi: 10.1038/ajg.2010.315[published Online First: Epub Date]|.
36. Kahi CJ, Li X, Eckert GJ, et al. High colonoscopic prevalence of proximal colon serrated polyps in average-risk men and women. Gastrointest Endosc 2012;**75**(3):515-20 doi: 10.1016/j.gie.2011.08.021[published Online First: Epub Date]|.
37. de Wijkerslooth TR, Stoop EM, Bossuyt PM, et al. Differences in proximal serrated polyp detection among endoscopists are associated with variability in withdrawal time. Gastrointest Endosc 2013;**77**(4):617-23 doi: 10.1016/j.gie.2012.10.018[published Online First: Epub Date]|.
38. Alvarez C, Andreu M, Castells A, et al. Relationship of colonoscopy-detected serrated polyps with synchronous advanced neoplasia in average-risk individuals. Gastrointest Endosc 2013;**78**(2):333-41 e1 doi: 10.1016/j.gie.2013.03.003[published Online First: Epub Date]|.
39. Pullens B, Dekker E, Ellis AJ, et al. Impact of the consideration of serrated polyps to the interval of colonoscopic surveillance in the NHS Bowel Cancer Screening Programme. Colorectal Dis 2014;**16**(9):O320-6 doi: 10.1111/codi.12607[published Online First: Epub Date]|.
40. Ng SC, Ching JY, Chan VC, et al. Association between serrated polyps and the risk of synchronous advanced colorectal neoplasia in average-risk individuals. Aliment Pharmacol Ther 2015;**41**(1):108-15 doi: 10.1111/apt.13003[published Online First: Epub Date]|.
41. Li D, Jin C, McCulloch C, et al. Association of large serrated polyps with synchronous advanced colorectal neoplasia. Am J Gastroenterol 2009;**104**(3):695-702 doi: 10.1038/ajg.2008.166[published Online First: Epub Date]|.
42. Anderson JC, Butterly LF, Goodrich M, et al. Differences in detection rates of adenomas and serrated polyps in screening versus surveillance colonoscopies, based on the new hampshire colonoscopy registry. Clin Gastroenterol Hepatol 2013;**11**(10):1308-12 doi: 10.1016/j.cgh.2013.04.042[published Online First: Epub Date]|.
43. Lee CK, Kim YW, Shim JJ, et al. Prevalence of proximal serrated polyps and conventional adenomas in an asymptomatic average-risk screening population. Gut

and liver 2013;**7**(5):524-31 doi: 10.5009/gnl.2013.7.5.524[published Online First: Epub Date]|.
44. 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**(9):466-71 doi: 10.1111/j.1751-2980.2012.00621.x[published Online First: Epub Date]|.
45. 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. Clinics and research in hepatology and gastroenterology 2012;**36**(6):604-8 doi: 10.1016/j.clinre.2011.12.016[published Online First: Epub Date]|.
46. Jass JR, Young PJ, Robinson EM. Predictors of presence, multiplicity, size and dysplasia of colorectal adenomas. A necropsy study in New Zealand. Gut 1992;**33**(11):1508-14
47. Bosman FT, World Health Organization., International Agency for Research on Cancer. *WHO classification of tumours of the digestive system*. 4th ed. Lyon: International Agency for Research on Cancer, 2010.
48. 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**(8):1094-100 doi: 10.1136/gut.2009.185884[published Online First: Epub Date]|.
49. Lockett MJ, Atkin WS. Hyperplastic polyposis: Prevalence and cancer risk. Gut 2001;**48**:A4-A4
50. Biswas S, Ellis AJ, Guy R, et al. High prevalence of hyperplastic polyposis syndrome (serrated polyposis) in the NHS bowel cancer screening programme. Gut 2013;**62**(3):475 doi: 10.1136/gutjnl-2012-303233[published Online First: Epub Date]|.
51. Moreira L, Pellise M, Carballal S, et al. High prevalence of serrated polyposis syndrome in FIT-based colorectal cancer screening programmes. Gut 2013;**62**(3):476-7 doi: 10.1136/gutjnl-2012-303496[published Online First: Epub Date]|.
52. Orlowska J, Kiedrowski M, Kaminski FM, et al. Hyperplastic polyposis syndrome in asymptomatic patients: the results from the colorectal-cancer screening program. Virchows Archiv 2009;**455**:47-47
53. Harrison M, Singh N, Rex DK. Impact of proximal colon retroflexion on adenoma miss rates. Am J Gastroenterol 2004;**99**(3):519-22 doi: 10.1111/j.1572-0241.2004.04070.x[published Online First: Epub Date]|.
54. Kahi CJ, Anderson JC, Waxman I, et al. High-definition chromocolonoscopy vs. high-definition white light colonoscopy for average-risk colorectal cancer screening. Am J Gastroenterol 2010;**105**(6):1301-7 doi: 10.1038/ajg.2010.51[published Online First: Epub Date]|.
55. Pohl J, Schneider A, Vogell H, et al. Pancolonic chromoendoscopy with indigo carmine versus standard colonoscopy for detection of neoplastic lesions: a randomised two-centre trial. Gut 2011;**60**(4):485-90 doi: 10.1136/gut.2010.229534[published Online First: Epub Date]|.
56. East JE, Saunders BP, Jass JR. Sporadic and syndromic hyperplastic polyps and serrated adenomas of the colon: classification, molecular genetics, natural history, and clinical management. Gastroenterol Clin North Am 2008;**37**(1):25-46, v doi: 10.1016/j.gtc.2007.12.014[published Online First: Epub Date]|.
57. Heresbach D, Barrioz T, Lapalus MG, et al. Miss rate for colorectal neoplastic polyps: a prospective multicenter study of back-to-back video colonoscopies. Endoscopy 2008;**40**(4):284-90 doi: 10.1055/s-2007-995618[published Online First: Epub Date]|.
58. Froehlich F, Wietlisbach V, Gonvers JJ, et al. Impact of colonic cleansing on quality and diagnostic yield of colonoscopy: the European Panel of Appropriateness of

Gastrointestinal Endoscopy European multicenter study. Gastrointest Endosc 2005;**61**(3):378-84
59. Lebwohl B, Kastrinos F, Glick M, et al. The impact of suboptimal bowel preparation on adenoma miss rates and the factors associated with early repeat colonoscopy. Gastrointest Endosc 2011;**73**(6):1207-14 doi: 10.1016/j.gie.2011.01.051[published Online First: Epub Date]|.
60. Anderson JC, Butterly LF, Robinson CM, et al. Impact of fair bowel preparation quality on adenoma and serrated polyp detection: data from the New Hampshire Colonoscopy Registry by using a standardized preparation-quality rating. Gastrointest Endosc 2014;**80**(3):463-70 doi: 10.1016/j.gie.2014.03.021[published Online First: Epub Date]|.
61. Butterly L, Robinson CM, Anderson JC, et al. Serrated and adenomatous polyp detection increases with longer withdrawal time: results from the New Hampshire Colonoscopy Registry. Am J Gastroenterol 2014;**109**(3):417-26 doi: 10.1038/ajg.2013.442[published Online First: Epub Date]|.
62. East JE, Stavrindis M, Thomas-Gibson S, et al. A comparative study of standard vs. high definition colonoscopy for adenoma and hyperplastic polyp detection with optimized withdrawal technique. Aliment Pharmacol Ther 2008;**28**(6):768-76 doi: 10.1111/j.1365-2036.2008.03789.x[published Online First: Epub Date]|.
63. Subramanian V, Mannath J, Hawkey CJ, et al. High definition colonoscopy vs. standard video endoscopy for the detection of colonic polyps: a meta-analysis. Endoscopy 2011;**43**(6):499-505 doi: 10.1055/s-0030-1256207[published Online First: Epub Date]|.
64. Boparai KS, van den Broek FJ, van Eeden S, et al. Increased polyp detection using narrow band imaging compared with high resolution endoscopy in patients with hyperplastic polyposis syndrome. Endoscopy 2011;**43**(8):676-82 doi: 10.1055/s-0030-1256447[published Online First: Epub Date]|.
65. Hazewinkel Y, Tytgat KM, van Leerdam ME, et al. Narrow-band imaging for the detection of polyps in patients with serrated polyposis syndrome: a multicenter, randomized, back-to-back trial. Gastrointest Endosc 2014 doi: 10.1016/j.gie.2014.06.043[published Online First: Epub Date]|.
66. Ket SN, Bird-Lieberman EL, East JE. Electronic imaging to enhance lesion detection at colonoscopy. Gastrointest Endosc Clin N Am In press
67. Pohl J, Lotterer E, Balzer C, et al. Computed virtual chromoendoscopy versus standard colonoscopy with targeted indigocarmine chromoscopy: a randomised multicentre trial. Gut 2009;**58**(1):73-8 doi: 10.1136/gut.2008.153601[published Online First: Epub Date]|.
68. Chung SJ, Kim D, Song JH, et al. Comparison of detection and miss rates of narrow band imaging, flexible spectral imaging chromoendoscopy and white light at screening colonoscopy: a randomised controlled back-to-back study. Gut 2014;**63**(5):785-91 doi: 10.1136/gutjnl-2013-304578[published Online First: Epub Date]|.
69. Aminalai A, Rosch T, Aschenbeck J, et al. Live image processing does not increase adenoma detection rate during colonoscopy: a randomized comparison between FICE and conventional imaging (Berlin Colonoscopy Project 5, BECOP-5). Am J Gastroenterol 2010;**105**(11):2383-8 doi: 10.1038/ajg.2010.273[published Online First: Epub Date]|.
70. Testoni PA, Notaristefano C, Vailati C, et al. High-definition colonoscopy with i-Scan: better diagnosis for small polyps and flat adenomas. World J Gastroenterol

2012;**18**(37):5231-9 doi: 10.3748/wjg.v18.i37.5231[published Online First: Epub Date]|.
71. Hong SN, Choe WH, Lee JH, et al. Prospective, randomized, back-to-back trial evaluating the usefulness of i-SCAN in screening colonoscopy. Gastrointest Endosc 2012;**75**(5):1011-21 e2 doi: 10.1016/j.gie.2011.11.040[published Online First: Epub Date]|.
72. Hoffman A, Loth L, Rey JW, et al. High definition plus colonoscopy combined with i-scan tone enhancement vs. high definition colonoscopy for colorectal neoplasia: A randomized trial. Dig Liver Dis 2014;**46**(11):991-6 doi: 10.1016/j.dld.2014.07.169[published Online First: Epub Date]|.
73. Corte C, Dahlenburg L, Selby W, et al. Hyoscine butylbromide administered at the cecum increases polyp detection: a randomized double-blind placebo-controlled trial. Endoscopy 2012;**44**(10):917-22 doi: 10.1055/s-0032-1310009[published Online First: Epub Date]|.
74. Rondonotti E, Zolk O, Amato A, et al. The impact of hyoscine-N-butylbromide on adenoma detection during colonoscopy: meta-analysis of randomized, controlled studies. Gastrointest Endosc 2014;**80**(6):1103-12 e2 doi: 10.1016/j.gie.2014.05.319[published Online First: Epub Date]|.
75. Chandran S, Parker F, Vaughan R, et al. Right-sided adenoma detection with retroflexion versus forward-view colonoscopy. Gastrointest Endosc 2014 doi: 10.1016/j.gie.2014.08.039[published Online First: Epub Date]|.
76. Leufkens AM, DeMarco DC, Rastogi A, et al. Effect of a retrograde-viewing device on adenoma detection rate during colonoscopy: the TERRACE study. Gastrointest Endosc 2011;**73**(3):480-9 doi: 10.1016/j.gie.2010.09.004[published Online First: Epub Date]|.
77. Gralnek IM, Siersema PD, Halpern Z, et al. Standard forward-viewing colonoscopy versus full-spectrum endoscopy: an international, multicentre, randomised, tandem colonoscopy trial. Lancet Oncol 2014;**15**(3):353-60 doi: 10.1016/S1470-2045(14)70020-8[published Online First: Epub Date]|.
78. Gralnek IM, Suissa A, Domanov S. Safety and efficacy of a novel balloon colonoscope: a prospective cohort study. Endoscopy 2014;**46**(10):883-7 doi: 10.1055/s-0034-1377968[published Online First: Epub Date]|.
79. Morris EJ, Rutter MD, Finan PJ, et al. Post-colonoscopy colorectal cancer (PCCRC) rates vary considerably depending on the method used to calculate them: a retrospective observational population-based study of PCCRC in the English National Health Service. Gut 2014 doi: 10.1136/gutjnl-2014-308362[published Online First: Epub Date]|.
80. Kaminski MF, Regula J, Kraszewska E, et al. Quality indicators for colonoscopy and the risk of interval cancer. N Engl J Med 2010;**362**(19):1795-803 doi: 10.1056/NEJMoa0907667[published Online First: Epub Date]|.
81. Sanaka MR, Gohel T, Podugu A, et al. Adenoma and sessile serrated polyp detection rates: variation by patient sex and colonic segment but not specialty of the endoscopist. Dis Colon Rectum 2014;**57**(9):1113-9 doi: 10.1097/DCR.0000000000000183[published Online First: Epub Date]|.
82. 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**(9):1315-29; quiz 14, 30 doi: 10.1038/ajg.2012.161[published Online First: Epub Date]|.
83. Hewett DG, Huffman ME, Rex DK. Leaving distal colorectal hyperplastic polyps in place can be achieved with high accuracy by using narrow-band imaging: an observational

study. Gastrointest Endosc 2012;**76**(2):374-80 doi: 10.1016/j.gie.2012.04.446[published Online First: Epub Date]|.
84. Burgess NG, Nanda KS, Williams SJ, et al. 505 Comparison of Large Sessile Serrated Adenoma Characteristics With Conventional Advanced Mucosal Neoplasia Resected by Wide Field Endoscopic Mucosal Resection in a Multicenter Prospective Cohort. Gastrointestinal Endoscopy 2013;**77**(5):AB157 doi: 10.1016/j.gie.2013.04.091[published Online First: Epub Date]|.
85. Hoff G, Bretthauer M, Garborg K, et al. New polyps, old tricks: controversy about removing benign bowel lesions. BMJ 2013;**347**:f5843 doi: 10.1136/bmj.f5843[published Online First: Epub Date]|.
86. Heldwein W, Dollhopf M, Rosch T, et al. The Munich Polypectomy Study (MUPS): prospective analysis of complications and risk factors in 4000 colonic snare polypectomies. Endoscopy 2005;**37**(11):1116-22 doi: 10.1055/s-2005-870512[published Online First: Epub Date]|.
87. Klein A, Bourke MJ. Advanced polypectomy and resection techniques. Gastrointest Endosc Clin N Am in press
88. Atkin WS, Edwards R, Kralj-Hans I, et al. Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial. Lancet 2010;**375**(9726):1624-33 doi: 10.1016/S0140-6736(10)60551-X[published Online First: Epub Date]|.
89. Schoen RE, Pinsky PF, Weissfeld JL, et al. Colorectal-cancer incidence and mortality with screening flexible sigmoidoscopy. N Engl J Med 2012;**366**(25):2345-57 doi: 10.1056/NEJMoa1114635[published Online First: Epub Date]|.
90. Kahi CJ, Vemulapalli KC, Snover DC, et al. Findings in the Distal Colorectum Are Not Associated With Proximal Advanced Serrated Lesions. Clin Gastroenterol Hepatol 2014 doi: 10.1016/j.cgh.2014.07.044[published Online First: Epub Date]|.
91. Pickhardt PJ, Choi JR, Hwang I, et al. Nonadenomatous polyps at CT colonography: prevalence, size distribution, and detection rates. Radiology 2004;**232**(3):784-90 doi: 10.1148/radiol.2323031614[published Online First: Epub Date]|.
92. Johnson CD, Chen MH, Toledano AY, et al. Accuracy of CT colonography for detection of large adenomas and cancers. N Engl J Med 2008;**359**(12):1207-17 doi: 10.1056/NEJMoa0800996[published Online First: Epub Date]|.
93. Zalis ME, Blake MA, Cai W, et al. Diagnostic accuracy of laxative-free computed tomographic colonography for detection of adenomatous polyps in asymptomatic adults: a prospective evaluation. Ann Intern Med 2012;**156**(10):692-702 doi: 10.7326/0003-4819-156-10-201205150-00005[published Online First: Epub Date]|.
94. Rex DK, Adler SN, Aisenberg J, et al. Accuracy of Capsule Colonoscopy in Detecting Colorectal Polyps in a Screening Population. Gastroenterology doi: 10.1053/j.gastro.2015.01.025[published Online First: Epub Date]|.
95. Waldock A, Ellis IO, Armitage NC, et al. Histopathological assessment of bleeding from polyps of the colon and rectum. J Clin Pathol 1989;**42**(4):378-82
96. Imperiale TF, Ransohoff DF, Itzkowitz SH, et al. Multitarget stool DNA testing for colorectal-cancer screening. N Engl J Med 2014;**370**(14):1287-97 doi: 10.1056/NEJMoa1311194[published Online First: Epub Date]|.
97. Schreiner MA, Weiss DG, Lieberman DA. Proximal and large hyperplastic and nondysplastic serrated polyps detected by colonoscopy are associated with neoplasia. Gastroenterology 2010;**139**(5):1497-502 doi: 10.1053/j.gastro.2010.06.074[published Online First: Epub Date]|.

98. Holme O, Bretthauer M, Eide TJ, et al. Long-term risk of colorectal cancer in individuals with serrated polyps. Gut 2014 doi: 10.1136/gutjnl-2014-307793[published Online First: Epub Date]|.
99. Terdiman JP, McQuaid KR. Surveillance guidelines should be updated to recognize the importance of serrated polyps. Gastroenterology 2010;**139**(5):1444-7 doi: 10.1053/j.gastro.2010.09.024[published Online First: Epub Date]|.
100. Hassan C, Quintero E, Dumonceau JM, et al. Post-polypectomy colonoscopy surveillance: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy 2013;**45**(10):842-51 doi: 10.1055/s-0033-1344548[published Online First: Epub Date]|.
101. Atkin WS, Valori R, Kuipers EJ, et al. European guidelines for quality assurance in colorectal cancer screening and diagnosis. First Edition--Colonoscopic surveillance following adenoma removal. Endoscopy 2012;**44 Suppl 3**:SE151-63 doi: 10.1055/s-0032-1309821[published Online First: Epub Date]|.