CURRICULUM BASED CLINICAL REVIEWS

Curriculum review: serrated lesions of the colorectum

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ABSTRACT

Colorectal cancer (CRC) is the second leading cause of death from cancer in the UK. Sporadic CRC evolves by the cumulative effect of genetic and epigenetic alterations. Typically, over the course of several years, this leads to the transformation of normal colonic epithelium to benign adenomatous polyp, low-grade to high-grade dysplasia and finally cancer—the adenoma-carcinoma sequence. Over the last decade, the serrated neoplasia pathway which progresses by methylation of tumour suppressing genes has been increasingly recognised as an important alternative pathway accounting for up to 30% of CRC cases. Endoscopists should be aware of the unique features of serrated lesions so that their early detection, appropriate resection and surveillance interval can be optimised.

INTRODUCTION

This review addresses the 2010 specialty training curriculum for gastroenterology ([figure 1](#)), focusing on understanding the pathological and genetic features of serrated colorectal lesions. Particular attention has been given to the clinical aspects relevant to trainees and established gastroenterologists including endoscopic detection, management and surveillance.

Terminology and epidemiology

Serrated lesions (SL) of the colorectum are a heterogeneous group encompassing hyperplastic polyps (HP), sessile serrated lesions (SSL) and traditional serrated adenomas (TSA). SLs are characterised histologically by a saw-toothed appearance of the crypt epithelium. In the last decade, they have been characterised by their morphological and molecular profiles into different subsets with varying risk of malignant transformation. The 2010 WHO classification for SLs categorises them into three groups; HPs, sessile serrated adenoma/polyp (SSA/P)

and TSAs. The British Society of Gastroenterology (BSG) highlights limitations of this classification including the fact that not all SSLs have cytological atypia and not all are polypoid and instead recommend using the term 'SSL with or without dysplasia'.¹

The prevalence of these lesions is difficult to determine due to highly variable and inconsistent diagnostic criteria, evolving nomenclature and variation in detection rates among endoscopists. SLs account for 11%–53% of all polyps detected at colonoscopy in screening populations. HPs are the most common accounting for 83%–96% of all SLs. TSAs are the least common accounting for 1%–7% of SLs.¹ In one study including 1910 colonoscopy screening patients the SSL prevalence was 8.1%. Of these, 5%–8% contained cytological dysplasia, the more advanced subtype.²

The distribution of SLs varies according to the subtype, with HPs and TSAs located most frequently in the distal colorectum, while SSLs are found predominantly in the proximal colon.³

Subtypes of SLs

Hyperplastic polyps

HPs are characterised by elongation of the crypts with variable degrees of serration. The crypts are straight and symmetrical and crypt bases are narrow. As with all SLs, serrations are present in the luminal aspects of the epithelium. Endoscopically HPs tend to be diminutive (<5 mm), pale and sessile with a type 2 (asteroid or star-shaped) Kudo pit pattern ([figure 2](#)).⁴ They can be further divided into three groups: microvesicular HP (MVHP), goblet cell rich HP (GCHP) and mucin poor HP, the clinical relevance of which remains to be elucidated. Although HPs are not thought to have malignant potential, there has been some suggestion, although

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Large Intestinal Tumours

To recognise the presentation of colorectal tumours, how they are diagnosed and managed.		
Knowledge	Assessment Methods	GMP
Knows the pathology of benign and malignant tumours of the colon and rectum	SCE	1
Has awareness of the molecular genetics of colorectal carcinogenesis and the adenoma-carcinoma sequence	SCE	1
Knows the range of predisposing conditions including inherited syndromes and acquired colonic diseases	SCE	1
Knows the range of clinical presentation and the means of diagnosis, investigation, management and follow-up	CbD, mini-CEX, SCE	1
Knows the strategy for prevention including procedures for screening	CbD, SCE	1

Figure 1 The Joint Royal Colleges of Physicians Training Board 2010 gastroenterology curriculum—competencies for colorectal tumours.

unproven, that MVHPs may progress to SSLs which do have malignant potential.³

Sessile serrated lesions

SSLs are characterised by the presence of a disorganised and distorted crypt growth pattern seen in the

lower third of the crypts. Unlike HPs, the proliferative zone is not straight but displaced laterally (figure 2).⁵ The crypts are therefore dilated and branched and may be filled with mucin resulting in a mucous cap which is often an endoscopic clue for an underlying SSL.

Interestingly, SSLs can have foci of MVHP like morphology with straight crypts which has been suggested as evidence of progression of MVHP to SSL. Alternatively, MVHP-like features could simply be part of the histologic spectrum of SSLs.⁶ The BSG recommends using the 2010 WHO criteria to diagnose a SSL. Three crypts or at least two adjacent crypts must show one or more of the following features; irregular distribution of crypts, dilation of crypt bases, serration at crypt bases, branched crypts, horizontal extension of crypt bases, dysmaturation of the crypts and herniation of crypts through the muscularis mucosa.¹

	Hyperplastic Polyp	Sessile Serrated Lesions	Traditional Serrated Adenoma
Frequency	80–90%	15–20%	1–6%
Localisation	More frequent in left colon and rectum	More frequent in proximal colon	More frequent in left colon and rectum
Morphology	Slightly elevated	Flat or sessile	Protuberant and/or pedunculated
Size	Usually <5mm	Usually >5mm	Usually >5mm
Kudo Pit Pattern
	Type II ("asteroid" shape)	Type II-O ("open" shape)	Type IV ("pinecone" shape)
Histology	Elongated, symmetrical crypts	Horizontal extension of crypt bases with L or inverted T-shape	Ectopic crypt formation
Malignant Potential	Not considered precancerous	Yes	Yes

Figure 2 Summary of features characterising the three subtypes of serrated lesions. images adapted from Ishigooka *et al* and Snover.^{4,5}

Figure 3 Two SSLs with dysplasia viewed under white light (left) and narrow-band imaging (NBI) (right). Top: flat elevated lesion (Paris IIa) with clouded surface. Bottom: flat elevated lesion with sessile component (Paris IIa +Is) and indistinctive border. The dysplastic portions (red box) appear darker under NBI with Kudo type III–IV pits.

SSLs occur more commonly in the right colon and are at least as common in women as they are in men.³ They can have flat or sessile morphology but are more likely to be flat in the proximal colon. Kimura *et al* reported a novel type II-O or ‘open-shape’ Kudo pit pattern (figure 2) which has been demonstrated to have a high specificity for SSLs.⁷

Cytological dysplasia is not present in uncomplicated SSLs, however SSLs with foci of conventional (tubular or tubulovillous) adenoma-like dysplasia may represent progression towards carcinoma (figure 3). Microdissection studies indicate that the dysplastic portion is more likely to demonstrate microsatellite instability,⁸ suggesting that SSLs with dysplasia are advanced lesions for which an endoscopist should be sure of complete resection to reduce the risk of post-colonoscopy colorectal cancer (CRC). The significance of the grade of dysplasia in SSLs has not been fully evaluated. There is increasing evidence that these lesions may behave more aggressively than conventional adenomas thus ‘SSL with dysplasia’ is the preferred term. It should be noted that true ‘collision tumours’ comprising conventional adenoma and SSL are exceedingly rare.

Traditional serrated adenomas

TSA are the rarest SL, characterised by complex villous growth patterns and abundant eosinophilic cytoplasm. Luminal infoldings perpendicular to the main axis of the crypts called ectopic crypt foci are thought to be related to loss of normal anchorage of crypts to the underlying muscularis mucosae.⁶ They tend to be protuberant or pedunculated, left sided lesions with Kudo type IV, pinecone-like pit pattern

(figure 2) and are often reddish in colour.⁴ Their molecular and pathological features are not as clearly characterised as SSLs.

Genetics

Mutations in tumour suppressor genes and oncogenes result in development of conventional adenoma and its transition over many years from low-grade to high-grade dysplasia and then invasive cancer. This sequential accumulation of genetic mutations and chromosomal instability causes microsatellite stable (MSS) tumours.

In contrast, the serrated neoplasia pathway progresses by the methylation of promoter regions of tumour suppressing genes (eg, MLH1). Methylation involves the addition of a methyl group (CH₃) to the cytosine nucleotide in a CpG dinucleotide. Excess methylation results in gene inactivation. This epigenetic silencing of gene function does not involve changes in the DNA sequence itself but leads to the CpG island methylator phenotype (CIMP). MSS and unstable tumours (MSI) can result depending on the genes silenced as the lesions progress.¹

Both the serrated and Lynch pathways can lead to microsatellite instability high (MSI-H) tumours but where the Lynch pathway involves germline mutations of mismatch repair genes, oncogenic mutation of the BRAF gene and the development of the CIMP is a characteristic molecular feature of the serrated pathway.⁹ Comparatively little is known about the traditional serrated pathway leading to TSAs but evidence is accumulating that this is a distinct molecular subtype with varying levels of CIMP positivity.

Progression of SSLs to cancer

Studies have demonstrated that in patients with SSLs, the detection of synchronous and metachronous neoplastic lesions may be more likely.³ SSLs are therefore thought to represent a mucosal field defect, altering the colonic milieu in a way that promotes colorectal carcinogenesis.

SSLs without dysplasia are much more common than SSLs with dysplasia, and tend to arise in younger patients, suggesting a long dwell time prior to development of dysplasia. In contrast, the mean age and distribution of SSLs with dysplasia and SSLs with cancer are very similar, suggesting a rapid transition from dysplasia to malignancy. One study indicated a mean dwell time of 17 years before the development of dysplasia and then rapid conversion to carcinoma.¹⁰

The rapid progression of lesions via the serrated pathway has been further supported by the finding that many cancers identified in between endoscopic screening examinations do not have a genetic makeup consistent with an origin in conventional adenoma. In one study, CRC diagnosed within 5 years after colonoscopy was more likely than cancer diagnosed after that period to have CIMP and microsatellite instability,¹¹

Figure 4 The WASP classification for optical diagnosis of hyperplastic polyps, sessile serrated lesions and adenomas based on the NBI International Colorectal Endoscopic criteria and the Hazewinkel criteria in a stepwise approach.

suggesting the serrated pathway may be involved in the development of post-colonoscopy CRC.

Improving detection of SLs

SSLs can be subtle with paucity of surface vasculature and hidden under a mucous cap. The presence of adherent mucous should alert the endoscopist to the possibility of an underlying SL. Due to their flat morphology and indistinct borders, special care is needed to ensure their accurate identification and delineation. The use of newer colonoscopes with an auxiliary water channel allows endoscopists to easily wash away surface mucus and stool and make a close assessment of pit patterns using near focus or magnification.

Optimising the bowel preparation in the right colon is important as this is where SSLs frequently occur. Split-dose preparations have been shown to increase SSL detection rate and should be utilised over traditional evening before dosing.¹²

The use of high-definition colonoscopes, and an optimal withdrawal time of 9 min¹³ have been shown to increase the detection rate for SLs. Data from the CONSCOP trial has shown chromocolonoscopy took an average of 6.3 min longer than standard white light colonoscopy but the proximal SL detection rate was significantly higher in the chromocolonoscopy arm.¹⁴ Advanced imaging techniques such as narrowed spectrum endoscopy (NBI, FICE, i-SCAN), also known as virtual chromoendoscopy help facilitate the endoscopic differentiation of colonic polyp subtypes. In a multivariate analysis by Hazewinkel *et al*, the presence of indistinctive borders, cloud-like surface, irregular shape and dark spots inside the crypts were

independent predictors of SSLs with an 89% sensitivity and 96% specificity.¹⁵ Thickened surface capillary vessels with branching seen during NBI with optical magnification has also been shown to improve positive predictive value of identifying SSLs.¹⁶

The NBI International Colorectal Endoscopic criteria divide polyps into type 1 (hyperplastic), type 2 (adenoma) and type 3 (deep submucosal invasive cancer). However, optical diagnosis could misclassify SSLs as unimportant if they resemble HPs. The WASP classification system was therefore developed for endoscopic differentiation of adenomas, HPs and SSLs <10 mm (figure 4).¹⁷

Distinguishing HPs from SSLs is also difficult histologically with considerable inter-observer variation. Retrospective studies have shown when blinded to previous histologic and clinical information, reinterpretation of previously described HPs as SSLs occurs frequently. Size >5 mm and location in the right colon were independent predictors of reclassification in one study.¹⁸

Serrated polyposis syndrome

If SLs are present in sufficient numbers and size they may fulfil the WHO criteria (box 1) of a serrated polyposis syndrome (SPS).¹⁹ SPS is important to recognise as it incurs a higher risk of CRC, although the magnitude remains uncertain.

Although the prevalence of SPS is not known, population estimates have traditionally been low, with figures of 1 in 3000 quoted. It has been shown however, in screening cohorts the prevalence may be significantly higher.

Box 1 WHO criteria for serrated polyposis syndrome

1. At least five serrated lesions (SLs) proximal to the sigmoid colon, two of which are ≥ 10 mm in diameter.
2. Any number of SLs proximal to the sigmoid colon in an individual who has a first-degree relative with serrated polyposis.
3. Twenty or more SLs of any size throughout the colon (outside of the rectum).

Satisfaction of any one of the three criteria qualifies for a diagnosis of serrated polyposis syndrome.

Although multiple genes have been associated with a SPS phenotype (eg, *MUTYH*, *SMAD4*, *PTEN*), a clear genetic aetiology has not yet been defined for SPS. The average age of diagnosis is usually more than 50 years. There have not been any clear associations with extra-colonic cancer.

First degree relatives of individuals with SPS have a fivefold increase in their lifetime risk for developing CRC, justifying the recommendations by one expert panel for 5 yearly surveillance colonoscopies from the age of 40, or from an age that is 10 years younger than the earliest age at which SPS was diagnosed in the family.⁶

Endoscopic management

HPs 3 mm or smaller are often removed with biopsy forceps. Lesions displaying features of a SSL should be resected in entirety. SSLs are hypovascular, which makes cold snare resection (CSR) a safe, time efficient and user friendly method of resection.

Endoscopic mucosal resection (EMR) involves submucosal lifting to promote a complete and safe en bloc resection and is the widely adopted technique for resection of larger lesions. Where possible polyps < 20 mm in size should be resected en bloc; however, this may be a challenge for SLs in the right colon where the wall is thinner and easily damaged by diathermy during polypectomy, carrying a risk of delayed bleeding, perforation and postpolypectomy syndrome. Currently, CSR is considered the preferred technique to resect small polyps. A recent case series reported preliminary experience in achieving complete resection of large SSLs using a cold piecemeal EMR technique.²⁰ Twenty-nine SSLs, ranging between 10 and 30 mm were lifted using submucosal injection and resected piecemeal using a 9 mm snare (Exacto; US Endoscopy, Mentor, Ohio, USA). Complete endoscopic resection was achieved in all cases. Minor oozing was noted in almost all cases; however, no haemostatic interventions were required. There were no adverse events during or after resection.

There has been attention to promote cost-effective measures in colonoscopy screening and surveillance

Serrated surveillance flowchart

Figure 5 2017BSG algorithm for serrated lesion surveillance.

Diminutive (< 5 mm) HPs in the rectosigmoid are not thought to be risk markers for future CRC. It is currently unclear whether proximal small HPS or SSLs are markers for future CRC risk. CRC, colorectal carcinoma; HP, hyperplastic polyp; SSL, sessile serrated lesion.

including implementing a ‘resect and discard’ strategy for diminutive (< 5 mm) polyps. The potential for translating this strategy into clinical practice largely depends on the accuracy of determining the histology of a polyp immediately on detection. Recent guidance from the National Institute for Health and Care Excellence recommend using virtual chromoendoscopy to assess polyps of 5 mm or less during colonoscopy, instead of histopathology, to determine whether they are adenomatous or hyperplastic, only if high-definition colonoscopes are used and the operator is accredited to use the technique under a national accreditation scheme.²¹ It should be noted this practice has not yet been widely adopted.

Surveillance of SLs

In the absence of high-quality prospective data, the BSGs position statement on serrated polyps provides clinical guidance on surveillance strategies following detection of SLs (figure 5). There is evidence that larger lesions (≥ 10 mm) are predictive of neoplasia, a one-off surveillance colonoscopy is therefore recommended for these lesions at 3 years. Given the elevated CRC risk in patients who meet criteria for SPS, the BSG recommends annual or 2 yearly colonoscopic surveillance for this cohort. There is currently no evidence to support extracolonic cancer surveillance for SPS.

The CARE study suggested that rates of incomplete resection are four times higher for SLs than for adenomas and interval cancers are more likely to be derived from the serrated pathway.²² The BSG therefore suggests a site check at 2–3 months for lesions ≥ 20 mm in size after piecemeal EMR resection.¹

CONCLUSION

SSLs, particularly those with foci of cytological dysplasia, are considered the likely precursor lesions

to sporadic MSI-H colon cancer through a molecular pathway characterised by CIMP positivity—the serrated pathway. Effective colonoscopy requires understanding the typical appearance of SLs, followed by accurate identification, delineation and resection of these lesions. Endoscopic clearance using standardised EMR and effective surveillance is important to mitigate the threat of post-colonoscopy CRC, highlighting the importance of high-quality baseline examination and referral to a centre with expertise in SPS when needed.

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