



Serrated Mucosal Lesions of the Large Bowel

Introduction: Recent advances in molecular biology, detailed microscopic and clinico-pathologic studies have highlighted a number of morphologically distinct colorectal polyps which share a serrated architecture and exhibit a range of features. Some of these serrated polyps are now recognised as being part of the relatively recently recognised serrated polyp-colorectal neoplasia pathway. This is an evolving concept and this pathway to colorectal neoplasia accounts for approximately 15% of sporadic (nonsyndromic) colorectal adenocarcinomas. (Reference 1)

The aim of this article is to discuss the pathology, reporting terminology, clinical behaviour and recommendations for management. The key points are summarised in Table 1.

Table 1

Summary of Key Points

- Large bowel polyps which share a common, serrated (saw toothed) architecture secondary to inhibition of apoptosis
- Reclassified on the basis of recent microscopic and molecular biology studies
- 'Newly recognised' lesion; sessile serrated adenoma - SSA (synonym, sessile serrated polyp – SSP)
- SSA previously grouped with hyperplastic polyps and now an entity in its own right.
- SSA are sessile lesions, with predilection for right colon
- The proximal location, sessile nature and poorly defined borders of SSA can make colonoscopic resection difficult, particularly for large lesions
- Mixed serrated polyps (SSA and dysplastic component) may have microsatellite instability and some lesions rapidly progress to adenocarcinoma
- Mixed serrated polyps require complete resection by whatever means (endoscopic or open resection)
- Patients who have had SSA and mixed serrated polyps require on going colonoscopic surveillance

The Serrated Architecture

These polyps exhibit significant crowding of the epithelium, giving rise to a serrated architecture, characterised by 'saw-toothed' infolding of the epithelium (micro-papillary, star shaped appearance).

Normal glands are characterised by proliferation in the proliferative compartment of the glands and an unusual form of apoptosis located at the gland/luminal surface, called 'anoikis', with programmed exfoliation of epithelial cells. This group of serrated mucosal lesions share inhibition of programmed cell death and loss of cells from the epithelial surface. As a consequence, with on going proliferation there is significant crowding of epithelial cells and resulting serrated architecture. In addition, in some of these lesions there is disorder of the proliferative zone, increased proliferation and 'dysmaturation' of the cells. References (1, 2, 3, 6)

Classification of Serrated Lesions

A number of sessile lesions and polyps with serrated architecture have been identified and are classified in Table 2.

Hyperplastic polyps of usual type may be sub-classified on the basis of the dominant lining epithelium. However, at this stage this does not appear to be of prognostic significance or influence management and they are not sub-classified in routine histopathology reports.

Table 2

Terminology for Reporting Serrated Lesions of the Large Bowel

1. Hyperplastic Polyp
 - Microvesicular (MVHP)
 - Goblet Cell (GCHP)
 - Mucin Poor (MPHP)
2. Sessile Serrated Adenoma (Sessile Serrated Polyp)
3. Traditional Serrated Adenoma
4. Mixed Serrated Polyp
 - Mixed sessile serrated adenoma and adenomatous polyp
 - Mixed sessile serrated adenoma and traditional serrated adenoma

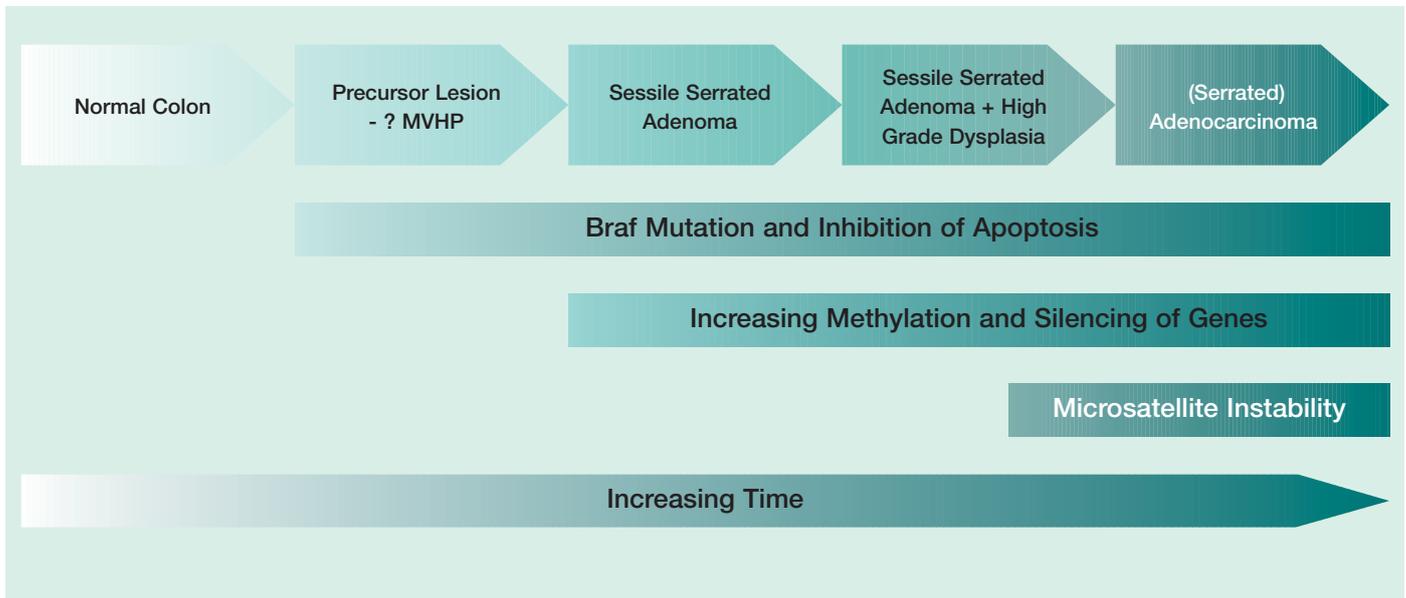
There is current debate regarding the classification and terminology of the 'newly recognised' lesions with serrated features. The term sessile serrated adenoma (sessile serrated polyp) is used for serrated lesions which fulfil certain morphologic criteria, as defined later in this article. These lesions are distinct from traditional serrated adenomas and conventional adenomatous polyps (which may exhibit tubular, tubulovillous and villous architecture). The term sessile serrated adenoma has generated discussion in the literature, with some experts believing that this term is potentially confused with 'conventional' adenomatous polyps, and in view of this, some authors prefer to use the term sessile serrated polyp. The term sessile serrated adenoma has merit in view of the relatively recently recognised progression of some of these polyps to





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Figure 1 Serrated Polyp Neoplasia Pathway



adenocarcinoma and the need for resection of these polyps. Finally, there is a group of polyps which display mixed features; these were previously regarded as mixed hyperplastic and either adenomatous or traditional serrated adenomas. With our new knowledge and appreciation of these lesions, most mixed lesions are sessile serrated adenomas with associated adenomatous polyps or traditional serrated adenomas, rather than hyperplastic polyps.

Patients with the hyperplastic polyposis syndrome have a reported prevalence of adenocarcinoma of up to 50%. The WHO definition of hyperplastic polyposis is an individual with: a) 5 or more hyperplastic polyps proximal to the sigmoid colon of which 2 are ≥ 1 cm, b) any number of hyperplastic polyps proximal to the sigmoid colon if the person has a first degree relative with hyperplastic polyposis and c) more than 30 hyperplastic polyps of any size and any location.

Review of hyperplastic polyposis syndrome colectomy specimens reveals a range of polyps, including hyperplastic polyps, sessile serrated adenomas and traditional serrated adenomas.

Molecular Biology

The likely multi-step sequence of molecular events (References 1, 2, 7) leading to the formation of serrated polyps and progression to malignancy is summarised in Figure 1 and below.

- BRAF mutation, leading to inhibition of apoptosis and cellular 'longevity'
- With longevity there is increased potential for methylation of Cytosine phospho Guanine (CpG) islands, leading to CpG island methylation phenotype (CIMP).

- Methylation silences genes in the absence of mutation ('epigenetic silencing')
- A number of genes are methylated, including DNA mismatch repair genes (hMLH1 and occasionally hMSH2) and the DNA repair gene O6-methylguanine-DNA methyltransferase (MGMT).
- Methylated mismatch repair genes lead to microsatellite instability (MSI); MSI-CIMP carcinoma.
- If non mismatch repair oncogenes are methylated then the tumour is microsatellite stable (MSS); MSS-CIMP carcinoma.

Clinical, Pathologic and Molecular Features

The key features of the various sessile serrated lesions are listed in Tables 3 and 4. Table 3 includes the frequency of the different types of serrated colorectal polyps identified in a series of 1250 polypectomy specimens (excluding patients with known colorectal cancer, familial polyposis and inflammatory bowel disease). (Reference 9) Normal colonic mucosa and various serrated mucosal lesions are illustrated in Figures 2 to 6.

The majority of the sessile serrated adenomas are located in the right colon and some have poorly defined borders, which can make colonoscopic resection technically difficult and at times hard to guarantee.

Sessile serrated adenomas (SSA) exhibit a range of microscopic architectural and cytologic features, related to decreased apoptosis, changes in the proliferative compartment, abnormal cellular maturation (dysmaturation) and abnormal mucin production, including the formation of gastric mucin. (References 2, 3, 6)



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SSA Architectural Features

- Serration, including extension into the crypt bases
- Increased surface villosity or papillarity
- Branched, dilated and horizontally orientated crypts (flask, T and L shaped glands)
- Increased gland:stroma ratio (> 50%)
- Glands herniating through muscularis mucosae into submucosa
- Prominent adipose tissue in underlying submucosa

SSA Cellular Features

- Hyperchromasia in mid to upper crypt
- Mitoses in mid to upper crypt (not at the base) and asymmetry of the proliferative zone
- Cells in upper crypt with enlarged vesicular nuclei and prominent nucleoli
- Mucin may be seen in basal crypt cells (either goblet cells or cells resembling gastric foveolar epithelium).
- Dystrophic goblet cells
- Increased mucin production – both intracellular and luminal

Table 3. Clinical and Macroscopic Features of Serrated Lesions

Polyp Type	Frequency	Location	Macroscopic Appearance
Hyperplastic Polyps	23.8%	Predominantly rectosigmoid	Usually <5mm, symmetrical and uniform
Traditional Serrated Adenoma	1.9%	Distal colon and rectum	Pedunculated or broad based polypoid lesion
Sessile Serrated Adenoma	2.2%	Pan colonic with a distinct preference for the proximal colon	Slightly elevated, irregular borders and may be covered with mucus
Mixed Serrated Polyp	0.8%	Majority in proximal colon	Variable, ranging from slightly elevated, sessile to polypoid

Table 4. Microscopic and Molecular Classification of Serrated Lesions of the Large Intestine

Polyp Type	Gland Architecture	Cellular Features	BRAF Mutation	Level of CpG Island Methylation	Microsatellite Status
Hyperplastic Polyp (GHP)	Straight crypts, narrow bases, little serration	Mucin in goblet cells	Kras mutation	Low	Presumed MSS
Hyperplastic Polyp (MHP)	Straight crypts, narrow bases, prominent serration	Minimal cytoplasmic mucin	Unknown	Unknown	Unknown
Hyperplastic Polyp (MVHP)	Straight crypts, narrow bases, prominent serration	Mucin in small droplets Pencil nuclei,	Present	Low	Presumed MSS
Traditional Serrated Adenoma	Complex serration, Often villiform	Eosinophilic cytoplasm	Present	Intermediate	MSS
Sessile Serrated Adenoma	Serration, broad bases, complex architecture, mucinous epithelium at gland base	May have vesicular nuclei and slight chromatin irregularity	Present	High	MSS
Mixed Serrated Polyp	Serration, variable shapes, including broad bases, complex architecture	Variable including TSA and adenomatous features	Present	High, including methylation of hMLH1 or MGMT	May be MSI



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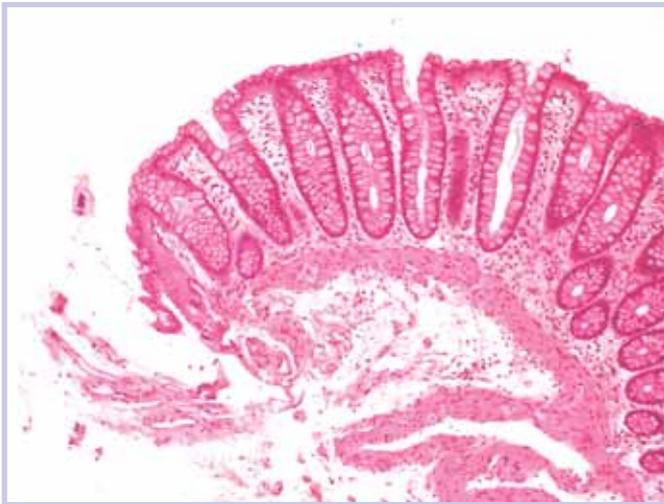


Figure 2 Normal Colonic Mucosa.

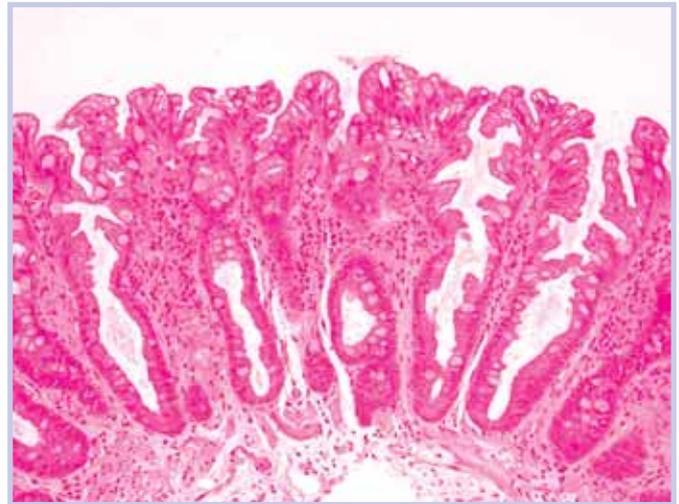


Figure 3 Hyperplastic Polyp.

Sessile Serrated Adenoma Cancer Risk

There is definite risk of progression to colorectal adenocarcinoma, based upon indirect and direct evidence, including small adenocarcinomas arising within sessile serrated adenomas. What is unclear at this stage is the magnitude of the risk and how rapidly a sessile serrated polyp will progress to cancer. In one study of 106 sessile serrated adenomas (91 patients), 19 polyps preceded the onset of MSI – H adenocarcinomas by less than 3 years. (Reference 4)

Recommendations for Management and Follow-up of Serrated Lesions

The development of firm guidelines has been hampered by lack of data, evolving terminology and lack of prospective studies. As our knowledge of the molecular biology, morphology and clinical behaviour of these lesions progresses, more precise prognostic features and consensus management guidelines will evolve. Until more is known a shorter surveillance interval with follow-up colonoscopy in one year is advised for incompletely excised sessile serrated adenomas. The guidelines (References 2, 3, 6) are detailed in Table 5.

Table 5. Recommendations for Management of Serrated Lesions of the Large Intestine

Lesion	Frequency
Hyperplastic Polyp	Continue with current management
Sessile Serrated Adenoma (without dysplasia)	If possible recommend complete endoscopic removal. For adequately biopsied but incompletely removed polyps (because of size or location), recommend watchful waiting with follow-up colonoscopy and biopsy/resection in 1 year, to monitor possible progression to dysplasia. For patients declining repeated colonoscopy, consider surgical excision for large lesions, even in the absence of dysplasia. If no residual lesion, suggest on going surveillance as per tubular adenoma protocol.
Sessile Serrated Adenoma (with dysplasia – mixed polyps)	Complete resection, by whatever means is required, since these lesions are potentially MSI and prone to rapid progression to adenocarcinoma. Adequacy of excision may be uncertain endoscopically due to the frequent poor demarcation and sessile nature of these polyps. Therefore, for lesions ‘completely resected endoscopically,’ recommend follow up colonoscopy in 1 year to review the biopsy site and exclude local recurrence. If no residual lesion, suggest on going surveillance as per tubular adenoma protocol.
Traditional Serrated Adenomas	The dysplastic appearing epithelium warrants applying tubular adenoma management guidelines.



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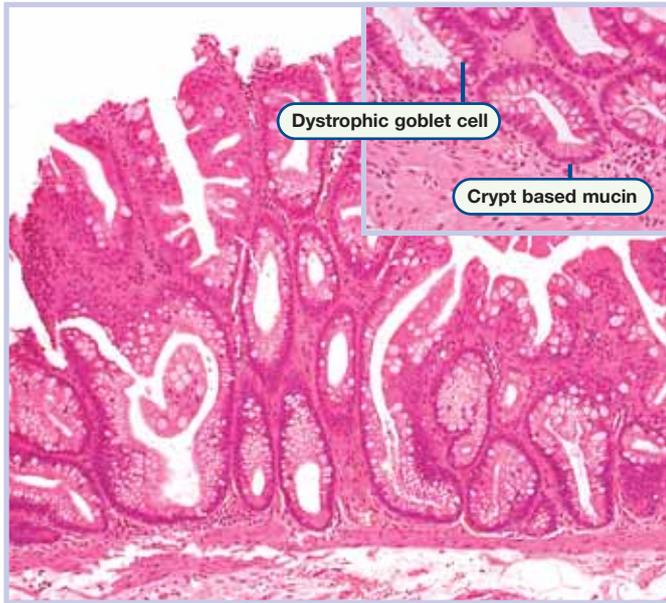


Figure 4 Sessile Serrated Adenoma with dilated, broad crypts including L shaped crypt.

Insert showing crypt based mucin and dystrophic goblet cells.

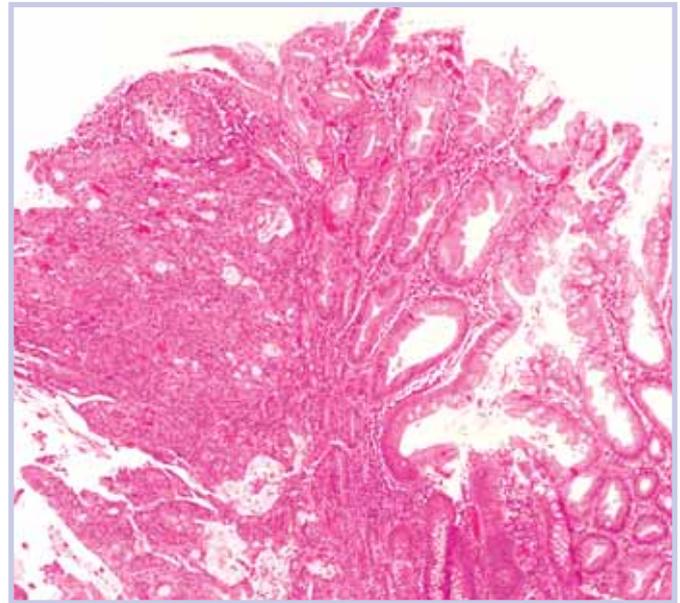


Figure 5 Adenocarcinoma arising in Sessile Serrated Adenoma.

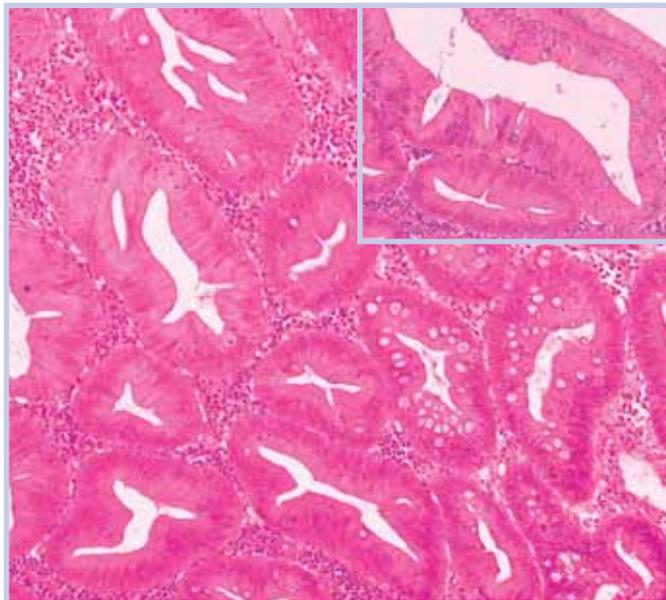


Figure 6 Traditional Serrated Adenoma.

Insert showing high magnification.

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