Serrated polyps

IJspeert, J.E.G.

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Serrated neoplasia — role in colorectal carcinogenesis and clinical implications

J.E.G. IJspeert, L. Vermeulen, G.A. Meijer, E. Dekker

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ABSTRACT

Colorectal cancer (CRC) is considered a heterogeneous disease, both regarding pathogenesis and clinical behaviour. Four decades ago, the adenoma–carcinoma pathway was presented as the main pathway towards CRC, a conclusion that was largely based on evidence from observational morphological studies. This concept was later substantiated at the genomic level. Over the past decade, evidence has been generated for alternative routes in which CRC might develop, in particular the serrated neoplasia pathway. Providing indisputable evidence for the neoplastic potential of serrated polyps has been difficult. Reasons include the absence of reliable longitudinal observations on individual serrated polyps that progress to cancer, a shortage of available animal models for serrated polyps and challenging culture conditions when generating organoids of serrated polyps for in vitro studies. However, a growing body of circumstantial evidence has been accumulated, which indicates that ≥15% of CRCs might arise through the serrated neoplasia pathway. An even larger amount of post-colonoscopy colorectal carcinomas (carcinomas occurring within the surveillance interval after a complete colonoscopy) have been suggested to originate from serrated polyps. The aim of this Review is to assess the current status of the serrated neoplasia pathway in CRC and highlight clinical implications.
INTRODUCTION

Colorectal cancer (CRC) is one of the most common causes of cancer-related morbidity and mortality in both Europe and the USA. CRC arises through precursor lesions, often referred to as polyps, and the timely detection and resection of these lesions is vital in preventing CRC. A decade ago, the general consensus was that conventional adenomas (further referred to as adenomas)—lesions characterized by typical intestinal type dysplasia—were the only precursor lesions that would develop into CRC (the adenoma–carcinoma pathway). By contrast, hyperplastic polyps typically observed in the rectum were believed to remain benign, which meant they could be left in situ. Over the past 15 years, this view has changed drastically, mostly due to the advent of more-flexible colonoscopes. Previously, only the distal part of the large bowel was accessible for endoscopes, but modern equipment, with more flexibility and higher resolution, and a stronger emphasis on quality assurance during colonoscopies have unveiled a wider morphological spectrum of serrated lesions. Another impetus for the paradigm change ensued from closer examination of serrated polyposis syndrome (SPS) and the finding that affected patients demonstrated an increased risk of CRC development.

Nowadays, CRC is considered a heterogeneous disease—from carcinogenesis to tumour maintenance and therapy—which has introduced many strategic changes in prevention and treatment of CRC. The latest WHO guideline published in 2010 recognizes an overarching group of serrated polyps, which can be divided into sessile serrated adenomas or polyps (SSA/Ps), traditional serrated adenomas (TSAs) and hyperplastic polyps (Figure 1). At least a subset of these lesions has been suggested to also harbour malignant potential and can progress to cancer through the alternative serrated neoplasia pathway; in particular, the association between SSA/Ps and CRC has been documented.

Although an extensive amount of research has been performed in the past decade to elucidate the development of serrated lesions and the pathogenesis of the serrated neoplasia pathway, many questions remain unanswered. Longitudinal observations on individual serrated lesions that eventually progress to cancer are scarce and existing studies are subject to major bias. Furthermore, only a few animal models for serrated lesions have been generated, and attempts to culture serrated lesions as organoids for in vitro studies were unsuccessful. However, a growing body of circumstantial evidence has been accumulated, indicating that ≥15% of all CRCs arise through the serrated neoplasia pathway. An even larger amount of post-colonoscopy colorectal carcinomas—cancers that occur within the surveillance interval after a complete colonoscopy—are suggested to originate from serrated polyps. The aim of this Review is to present an overview of the existing literature documenting the association between serrated polyp subtypes and CRC occurrence to consolidate current knowledge about the serrated neoplasia pathway, its associated risks and clinical implications.
CLASSIFICATION OF SERRATED POLYPS

In 2010, the WHO published a statement paper on sporadic serrated polyps and SPS.\textsuperscript{10} Sporadic serrated polyps are defined as a heterogeneous group of lesions morphologically characterized by a serrated ("saw-tooth" or stellate) architecture of the epithelium that lines the colonic crypts and are subdivided into SSA/Ps, TSAs and hyperplastic polyps (Figure 1).\textsuperscript{10}

![Figure 1](image_url)  
**Figure 1** | Representative endoscopic images of serrated lesion subtypes.  
\(a\) | Hyperplastic polyp.  
\(b\) | Sessile serrated adenoma or polyp.  
\(c\) | Sessile serrated adenoma or polyp with dysplasia.  
\(d\) | Traditional serrated adenoma.

Hyperplastic polyps

Hyperplastic polyps are the most prevalent subtype of serrated polyps, accounting for ~60–75% of all serrated lesions.\textsuperscript{31,32} An endoscopy-based study has shown that ~25% of average-risk individuals harbour at least one hyperplastic polyp in their colon, most often located in the left-sided colon.\textsuperscript{31} Hyperplastic polyps are most often diminutive in size, rarely grow larger than 5 mm, and usually present a flat or sessile morphology.\textsuperscript{31,33} On the basis of mucin type, hyperplastic polyps can be subclassified into microvesicular hyperplastic polyps (MVHPs), goblet-cell-rich hyperplastic polyps
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(GCHPs) and mucin-poor hyperplastic polyps (MPHP). MVHPs account for up to 60% of hyperplastic polyps, are more often located in the right-sided colon and almost always have molecular similarities to SSA/Ps. GCHPs make up ~30% of hyperplastic polyps, are always located in the left-sided colon and have some molecular similarities to TSAs. MPHPs are rare and the clinical relevance of these lesions seems to be minor.

Histopathologically, all three hyperplastic polyp subtypes are characterized by elongation of the intestinal crypts, with serration of the upper half of the crypt. The lower half of the crypt is narrow and does not show any serration. The proliferation zone of the crypts is located uniformly in the basal part of the crypt. Cytological dysplasia does not occur in any subtype of hyperplastic polyps (Figure 2).

**Sessile serrated adenomas or polyps**

SSA/Ps are the second most prevalent subtype of serrated polyps, accounting for 20–35% of all serrated lesions. In European clinical practice, SSA/Ps are also often referred to as sessile serrated lesions, as they do not harbour any adenomatous changes and most often are flat rather than polypoid. Currently, the prevalence of SSA/Ps is thought to be higher than documented in the literature a few years ago. This underestimate might be due to the fact that, back then, endoscopists often neither detected nor removed these subtle lesions, and pathologists classified most of the lesions now known as SSA/Ps as hyperplastic polyps, especially if only biopsy samples were taken.

Endoscopy-based studies have shown that up to 16% of patients with an average risk of CRC have at least one SSA/P, whereas up to 12% of all detected lesions are regarded as SSA/Ps. The average diameter of SSA/Ps is described to be 5 mm, and most SSA/Ps are smaller than 10 mm in diameter. SSA/Ps can be subclassified into SSA/Ps without dysplasia (referred to as SSA/Ps) and SSA/Ps with dysplasia. Two studies published in 2014 have assessed the proportion of SSA/Ps with dysplasia, reporting that ~20–30% of all SSA/Ps harbour a dysplastic component. Both studies might have overestimated the proportion of SSA/Ps with dysplasia, because they only reported a fairly low number of SSA/Ps, which potentially causes a bias. SSA/Ps and SSA/Ps with dysplasia are similar in size; both polyp subtypes were equally frequently measured to be <6 mm in a study published in 2014. SSA/Ps are more often located in the right-sided colon, but 20–40% are also situated distally. Similarly to hyperplastic polyps, SSA/Ps usually show a flat or sessile morphology.

Histopathologically, SSA/Ps are characterized by distorted crypts, which are often dilated towards the base, and have abnormal shapes, including L-shapes or inverted T-shapes. Pseudoindentation below the muscularis mucosae, also referred to as displaced crypts, is often seen in SSA/Ps. In addition, differentiated and serrated epithelium is present in the lower half of the intestinal crypt, unlike in hyperplastic polyps, and the proliferation zone has often shifted from the basal part to the side of the crypt (Figure 2).
CHAPTER 1

Traditional serrated adenomas

TSAs are a rare subtype of serrated polyps, accounting for <1% of all serrated lesions. TSAs are often >5 mm and most often located in the distal part of the colon. Unlike hyperplastic polyps and SSA/Ps, TSAs usually have a sessile or pedunculated shape. Histologically, TSAs often possess a complex and distorted tubulovillous or villous configuration. Prominent serration and diffuse cytoplasmic eosinophilia are also often present in TSAs. Other histopathological characteristics include aberrant crypt formation in the form of lateral budding of crypts, and a ‘tennis racquet’ shape of the tips of the villi. By definition, TSAs demonstrate dysplasia, usually as mild nuclear atypia with elongated penicillate nuclei and reduced differentiation (that is, less mucin formation), causing the typical eosinophilic cytoplasm (Figure 2). The fact that these lesions can progress to cancer has been well documented.

Although SSA/Ps and TSAs share some similarities, the differences are striking. Therefore, histopathological differentiation of SSA/Ps and TSAs is thought to be reasonably easy. More difficulties can be expected in the histological differentiation between TSAs and tubulovillous adenomas. As a result of the increased awareness of serrated lesions, a substantial number of lesions that would have been classified previously as tubulovillous adenomas are now recognized.
as TSAs. In fact, it is important to realize that the classification of serrated lesions implies an attempt to define sharp margins in a morphological continuum. This morphological heterogeneity, which is equally evident during the progression to cancer, has also been demonstrated in the literature. 

**Differentiation between polyp subtypes**

Differentiation between SSA/Ps and hyperplastic polyps can sometimes be challenging because lesions might present with features of a hyperplastic polyp in one crypt, whereas a neighbouring crypt has features of SSA/P. Small-sized or superficial tissue samples further complicate a distinction. The dilemma mainly results from the fact that morphological features are part of a continuous spectrum rather than discrete entities. In an attempt to facilitate discrete ‘calling’ in this spectrum of morphological changes, classification criteria have been proposed somewhat arbitrarily, but seem to work in practice. According to the WHO, a lesion should be classified as an SSA/P if more than two or three contiguous crypts demonstrate features of a SSA/P. Aust et al. have proposed that this diagnosis applies (according to histopathology results) if at least two of the four most important diagnostic features are demonstrated in at least two different colonic crypts: hyperserration or serration in the lower third of the crypts (with and without branching); T-shaped and L-shaped crypts above the muscularis mucosae; displaced crypts below the muscularis mucosae; and columnar dilatation in the lower third of the crypts (with or without mucus).

**Serrated polyps and colorectal cancer**

The development of CRC from serrated polyp precursors has only been widely accepted as a separate entity in the past decade. However, the earliest evidence of the association between serrated polyps and CRC was published in the 1970s and 1980s. Of particular relevance has been the recognition of SPS, characterized by the presence of multiple serrated polyps throughout the colorectum in affected individuals, and an elevated lifetime risk of CRC of up to 50%. Subsequent studies showed that CRC development via the serrated neoplasia pathway predominated over the conventional adenoma–carcinoma pathway in these patients, which suggested a link between serrated polyps and CRC. A substantial amount of research has been performed to deepen the understanding of the serrated neoplasia pathway and to further elaborate the actual risk of CRC in individuals with sporadic serrated polyps.

**The serrated neoplasia pathway**

Although pathogenesis via the serrated neoplasia pathway shows multiple similarities with the traditional adenoma–carcinoma sequence, tumour development in the former is suggested to be an independent pathway to CRC (Figure 3). The most pronounced molecular alteration associated with the serrated neoplasia pathway is a mutation in the BRAF proto-oncogene. Additionally, hypermethylation of CpG islands (described in detail later) on the promoter regions of tumour
suppressor genes is also common, and subsequently leads to the silencing of these genes. An example of such a tumour suppressor gene is the mismatch repair gene MLH1. The silencing of this gene will result in sporadic microsatellite instability, comparable to hereditary microsatellite instability in patients with Lynch syndrome.11,26,61 For this reason, the serrated neoplasia pathway is often referred to as the CpG island methylation phenotype (CIMP) pathway or the sporadic microsatellite instability pathway. However, these three pathways do not seem to be 100% identical and interchangeable use of these terms should be done with caution. Importantly, CIMP is also seen in a minority of adenomas, and promoter methylation is observed, to some extent, in most adenomas.14,62,63

![Normal Mucosa](image1)

**Figure 3** | A global and simplified model of the serrated neoplasia pathway. Pathway depicted is based largely on evidence from mouse models. Abbreviations: CIMP, CpG island methylation phenotype; CRC, colorectal cancer; MSI, microsatellite instability; MSS, microsatellite stable; MVHP, microvesicular hyperplastic polyp; SSA/P, sessile serrated adenoma or polyp; SSA/P-D, sessile serrated adenoma or polyp with dysplasia.

**CpG island methylation phenotype**

Although the CIMP as a concept has become quite popular in CRC literature, the story is not as straightforward as it seems.64 CpG island methylation is a physiological mechanism to regulate gene expression; CpG islands are dense cytosine clusters followed by a guanine nucleotide, often occurring in the promoter region of genes.65 Aberrant hypermethylation of CpG islands in the promoter region of a gene can result in its silencing. This CIMP-dependent inactivation of tumour suppressor genes is commonly seen in CRC.26 The number of genes affected by CpG island hypermethylation differs from tumour to tumour and varies widely. The fact that CpG promoter hypermethylation is a common event in colorectal tumour formation has led to the recognition of the DNA methylation status as a
sensitive biomarker for early detection of CRCs from stool samples, both derived from the serrated neoplasia pathway as well as from the adenoma–carcinoma pathway. In practice, the CIMP status of a lesion is determined by the assessment of the promoter methylation status of a panel of five genes, in which hypermethylation of at least three genes is considered to be CIMP-high and methylation of one or two genes is considered CIMP-low. CIMP-high tumours have been strongly associated with the serrated neoplasia pathway, but the oncogenesis of CIMP-low CRCs is less well understood. Importantly, CIMP positivity is determined based on an arbitrary threshold in the magnitude of epigenetic changes present in a tumour sample. In addition, different panels of genes have been suggested to aid in the assessment of the CIMP status. Essentially, discrete classes are assigned to a continuous spectrum, similarly to the issue of morphological classification we discussed earlier. Moreover, it is important to realize that the molecular mechanism by which CIMP positivity develops has not yet been fully resolved, although increased DNA binding of the transcriptional repressor MAFG caused by a \textit{BRAF} mutation might be an important factor. The silencing of other tumour suppressor genes, such as \textit{p16INK4a}, \textit{IGFBP7} and \textit{MGMT}, might also have a prominent role in the development of CIMP-high tumours.

\textbf{BRAF mutations}

One of the key players in the serrated neoplasia pathway is the \textit{BRAF} proto-oncogene. The most common \textit{BRAF} mutation is a hotspot mutation in codon 15 that results in a Val600Glu amino acid change (\textit{BRAF} V600E). \textit{BRAF} functions as a molecular switch in the RAS–RAF–MEK–ERK pathway, often referred to as the MAPK/ERK pathway, which regulates vital processes in human cells controlling proliferation, differentiation and survival. A mutation in \textit{BRAF} will therefore result in uncontrolled cell division and contribute to the neoplastic process, comparable to the effects of a \textit{KRAS} mutation, which is common in adenomas. Because \textit{BRAF} and \textit{KRAS} are part of the same pathway, mutations in these genes are mutually exclusive in colorectal neoplasms. In many instances, \textit{BRAF} mutations and CIMP coincide in CRC. \textit{BRAF} mutations were found in 77% of CIMP-high, 18% of CIMP-low and 0% of CIMP-negative CRCs. \textit{KRAS} mutations, on the other hand, were reported in 1.5% of CIMP-high, 43% of CIMP-low and 29% of CIMP-negative CRCs. Another study states an odds ratio of 203 when comparing \textit{BRAF} mutations in CIMP-high with CIMP-low or CIMP-negative CRC. This study, however, used CIMP as an intermediate marker for serrated polyps and did not examine the serrated phenotype directly.

\section*{MOLECULAR ALTERATIONS AND CANCER PROGRESSION}

Several studies have evaluated the molecular characteristics of adenomas and serrated polyps to clarify which lesions are the main precursors of CIMP-high and/or \textit{BRAF}-mutant CRCs (Table 1). In these studies, a \textit{BRAF} mutation was found in 0–2% of adenomas, 0–23% of GCHPs, 53–76% of MVHPs, 50–85% of SSA/Ps and 57–100% of SSA/Ps with dysplasia. The same studies showed that the presence of a CIMP-high phenotype increased sequentially in MVHPs, SSA/Ps and SSA/Ps with
CHAPTER 1

dysplasia, whereas adenomas and GCHP rarely harboured a CIMP-high phenotype in most studies. Combined MLH1 hypermethylation and microsatellite instability was hardly demonstrated in any precursor subtype, except for SSA/Ps with dysplasia.

These results have led to the hypothesis that CIMP-high, BRAF-mutant CRCs arise from serrated lesions through the following sequence: colonic mucosa to MVHP, to SSA/P, to SSA/P with dysplasia, to CRC (Figure 3). SSA/Ps have also been hypothesized to originate directly from the colonic mucosa, without MVHPs as an intermediate stage. On the basis of these results, BRAF mutations were suggested to have a role in early serrated polyp development, whereas biallelic methylation and subsequent silencing of MLH1 contributes to the transition from polyp to cancer. However, evidence to confirm these hypotheses does not yet exist. Several studies have suggested that tumours with microsatellite instability, CIMP and BRAF mutations increase gradually along the distal to proximal axis, similar to SSA/Ps, suggesting an association between both entities.

Studies on carcinoma progression originating from TSAs have demonstrated that this progression is heterogeneous, both on a morphological and a molecular level. In particular, the frequency of BRAF and KRAS mutations varied substantially between different subtypes of TSAs during cancer progression. However, in this Review we will not further elaborate on the morphological and molecular characteristics of TSAs, since little is known about this subject and the association with the serrated neoplasia pathway is largely unclear.

Table 1 | Molecular characteristics of colonic polyp subtypes

<table>
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<th>TVA n (%)</th>
<th>MLH1-H</th>
<th>MSI-H</th>
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<th>SSA/P n (%)</th>
<th>SSA/P-O n (%)</th>
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### Serrated neoplasia—role in colorectal carcinogenesis and clinical implications

### Study

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*In addition, molecular characteristics of serrated CRCs were examined by O’Brien et al. and found no mutations in KRAS (n = 0/10 [0%]), a high number of mutations in BRAF (n = 9/11 [82%]), presence of a CIMP-H phenotype (n = 9/10 [90%]), MLH1 hypermethylation (n = 5/10 [50%]) and MSI-H (n = 9/11 [82%]). Abbreviations: –, not applicable; CIMP-H, CpG island methylation phenotype-high; CRC, colorectal carcinoma; GCHP, goblet-cell-rich hyperplastic polyp; HPV, hyperplastic polyp; MSI-H, microsatellite instability; MVHP, microvesicular hyperplastic polyp; SSA/P, sessile serrated adenoma or polyp with dysplasia; TA, tubular adenoma; TSA, traditional serrated adenoma; TVA, tubulovillous adenoma; Unspecif., unspecified.*
Although the neoplastic potential of a subset of serrated polyps is generally accepted, the long-term risk of CRC in patients with serrated polyps is still largely unknown. Similarly, there is no consensus about the natural development of different serrated polyp subsets. International guidelines for surveillance intervals after the detection of serrated lesions are, therefore, mainly based on expert opinion, and recommendations differ widely.\textsuperscript{33,36,92} In many cases, patients also harbour more than one type of lesion (for instance, adenomas and serrated polyps) and might therefore be susceptible to different risks.\textsuperscript{31} In addition, little evidence exists that polypectomy of colonic lesions contributes to reduced mortality from CRC.\textsuperscript{93} This matter has led to a critical reappraisal of post-polypectomy surveillance policies in combination with efforts to start studies that will provide more evidence for the usefulness of polypectomy followed by the most optimal surveillance interval. So far, four studies have been published that assess the natural development of serrated polyps and/or the risk of future cancer in these patients.\textsuperscript{17–20} Owing to the amount of bias in all these studies, the external validity is hard to assess. Lazarus et al.\textsuperscript{19} demonstrated in 2005 that 5\% (2 of 38) of patients with a SSA/P with dysplasia developed CRC during long-term follow-up, compared with 2.2\% (3/138) of patients with adenomas. They also demonstrated that the mean growth rate of SSA/Ps with dysplasia (3.04 mm per year) was comparable to adenomas (2.79 mm per year) and faster than that of hyperplastic polyps (1.36 mm per year). The time frame during which the patients were monitored, however, was not declared in this study. All detected polyps were removed during initial colonoscopy and all lesions detected in follow-up colonoscopies were regarded as newly developed lesions. In another retrospective study published in 2010, Lu et al.\textsuperscript{17} demonstrated that CRC developed in 12.5\% (5 of 40) of patients with SSA/Ps after a median follow-up time of 7.2 years. The incidence of a newly developed CRC was substantially higher in patients with SSA/Ps than in a control group of patients with hyperplastic polyps (1 of 55; 1.8\%) or adenoma (1 of 55; 1.8\%). A third study demonstrated that, after a 5 year follow-up, 3.03\% (1 of 33) of patients with a SSA/P or SSA/P with dysplasia at baseline developed CRC.\textsuperscript{20} Another study by Holme et al.\textsuperscript{18} showed that the presence of a large serrated polyp was an independent risk factor for CRC, comparable to the risk of having an advanced adenoma. Furthermore, the authors showed that, after a median follow-up time of 11 years, none of the 23 large serrated polyps that were detected and left in situ developed into CRC. All studies were based on colonoscopy data, performed during an era when serrated polyps were not regarded as neoplastic. Therefore, the majority of serrated polyps might not have been detected, described and/or removed and analyses were probably performed on a minority of individuals of interest. For these reasons, more high-quality evidence is needed to quantify the exact CRC risk for patients with serrated polyps.

### PRECLINICAL MODELS

Several preclinical mouse models have been developed to simulate the serrated neoplasia pathway.\textsuperscript{21–24} None of these models fully recapitulate the features of human disease, both in terms of
molecular alterations and tumour phenotype. Nevertheless, these models have been instrumental in resolving the causal relationships between molecular aberrations and histopathological features. Bennecke et al. provided evidence that expression of oncogenic Kras specifically in intestinal epithelial cells induces the transformation of normal mucosa into serrated hyperplasia in the mouse colon. Subsequent loss of p16INK4a expression led to metastasized cancer. This model shows that activation of the MAPK cascade might indeed be the initiating event in serrated carcinogenesis. Loss of p16INK4a, for instance due to hypermethylation, is suggested to be responsible for the transition from serrated polyp to CRC. These results were confirmed in a second mouse model by Carragher et al. Induction of BrafVal600Glu expression in mice led to the formation of hyperplastic crypts in the small intestines. These hyperplastic crypts then remained dormant for prolonged periods and, as a result, the mice survived for >20 weeks. Only after p16INK4a had been silenced through enhanced CpG methylation of exon 1 invasive tumours were detected in the small intestines. The involvement of p16INK4a in tumour progression was further corroborated by combining BrafVal600Glu expression with genetic inactivation of the Ink4a/Arf locus, which resulted in rapid development of aggressive tumours. During these experiments, none of the mice survived past 6 weeks. An even more accurate recapitulation of the human condition is achieved by stringent intestine-specific expression of mutant Braf from the endogenous locus in mice, which limits extraintestinal tumour formation warranting premature termination. This model not only exhibits intestinal hyperplasia but also spontaneous malignant progression following mutations in tumour suppressor genes and the occurrence of microsatellite instability, independently of artificial Ink4a/Arf inactivation. Studies in which adenomas were cultured in vitro as organoids have improved our understanding of chromosomal-instability-related progression to CRC. To our knowledge, in vitro studies culturing serrated polyps as organoids have not yet been reported. As a consequence, preclinical organoid models for the serrated neoplasia pathway are still lacking.

**CLINICAL IMPLICATIONS**

Owing to the molecular homogeneity of CIMP-high, BRAF-mutant CRCs and serrated lesions, it has been suggested that ≥15% of CRCs arise through the serrated neoplasia pathway. Both CIMP and microsatellite instability are more frequently found in post-colonoscopy CRC, consistent with a major role of the serrated neoplasia pathway in these tumours. A potential reason could be that the serrated neoplasia pathway results in accelerated carcinogenesis, comparable to tumour development in patients with Lynch syndrome. However, other studies have suggested a fairly slow disease progression, in which the median transformation time from SSA/P to CRC takes up to 15 years. A second reason for the high rate of post-colonoscopy CRC could be because serrated polyps can be easily missed during colonoscopy, probably due to their flat or sessile morphology, inconspicuous colour and camouflage by a mucus cap. Several studies have shown that the detection rate of serrated polyps differs widely among endoscopists. The individual detection
rate of proximal serrated polyps, for instance, varied from 1–20% between different endoscopists, indicating a high miss-rate of clinically relevant serrated polyps among low detectors. A third reason for their relatively large contribution to post-colonoscopy CRC could be that serrated polyps are more often incompletely resected than adenomas, due to the difficulty to demarcate their indistinct borders.27

To prevent CRC derived from serrated polyps, more awareness has to be created among endoscopists regarding the neoplastic threat of serrated polyps. Furthermore, endoscopists should receive specific training on how to increase their detection rate and how to radically resect serrated polyps for secondary prevention. A study by Hazewinkel et al.99 has shown that when endoscopists are well trained and colonoscopies performed according to quality standards, post-colonoscopy CRC can be prevented, even in patients with SPS.

Future studies will have to be designed to validate the effect of training on the detection rate of serrated polyps and the occurrence of interval cancers. Finally, a benefit could be gained from primary prevention, such as targeted lifestyle advice for patients with an increased risk of developing CRC.100 Association studies have shown that smoking behaviour especially seems to be related to the occurrence of serrated polyps.101,102 However, no evidence exists for the value of lifestyle advice in primary prevention of these lesions or serrated adenocarcinomas.

CONCLUSIONS

Careful clinical and histological observations combined with an increased understanding of tumour biology and genomics has led to the acknowledgement of a broader diversity in the pathogenesis of CRC. This progress has resulted in the recognition of the serrated pathway as an alternative to the traditional adenoma–carcinoma sequence. Although substantial progress in our knowledge has been made compared with a decade ago, substantial gaps remain. Much of the data represents cross-sectional observational associations and only limited high-quality, longitudinal data in combination with high-quality endoscopic, histopathological and molecular data are available, which confronts us with serious limitations in understanding this pathway. Nonetheless, this latter situation is not unique to serrated lesions, but also applies to the adenoma–carcinoma sequence concept. Establishing such datasets is a prime challenge to take this field further. In addition, there are hurdles to overcome in model systems, both in animals and human organoids, to further unravel biological mechanisms underlying the disease that might enable us to translate this knowledge into better diagnostic and therapeutic strategies to improve patient outcomes.
REFERENCES


43. Tsai JH, et al. Traditional serrated adenoma has two pathways of neoplastic progression that are distinct from the sessile serrated pathway of colorectal carcinogenesis. Mod Pathol 2014;27:1375–85.


Serrated neoplasia—role in colorectal carcinogenesis and clinical implications


