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Clinical Significance of Serrated Polyps of the Colon

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INTRODUCTION

The recognition of a putative hyperplastic polyp- serrated adenoma-adenocarcinoma pathway to colorectal cancer (CRC) has challenged the fundamental view that colon adenocarcinomas arise only from conventional adenomas. This article reviews the historical description of the serrated polyp pathway and compares the histologic and endoscopic appearance of serrated polyps to that of traditional adenomas and hyperplastic polyps (HPs). The proposed molecular mechanism of malignant transformation from the hyperplastic polyp into a colorectal carcinoma (CRC) via a serrated polyp will be reviewed with the caveat that the story is rapidly evolving. Given the shift in the paradigm of the precancerous lesion to include a subset of serrated polyps, recommendations for colonoscopic polypectomy and surveillance for serrated neoplasia will be reviewed.

BRIEF HISTORY

Until the late 1990s colorectal polyps were generally divided into two major subtypes: hyperplastic polyps and adenomatous polyps. Although a continuum between the two was proposed as early as 1970, it was generally held that these two subtypes were unique and had separate outcomes [1,2]. Despite scattered objections over the next 30 years, the consensus opinion was that adenomatous polyps were the precursor of colorectal cancer while hyperplastic polyps were considered to be non-neoplastic hyperproliferations with little clinical significance [3]. The historical highlights of this paradigm shift are of interest for this review.

Goldman initially proposed a morphological continuum between hyperplastic polyps and adenomatous polyps in 1970 and suggested that hyperplastic polyps may represent the precursor of some neoplastic adenomas [1]. Throughout the following decades recurring suggestions of some sort of a relationship between hyperplastic polyps and colorectal cancer appeared [4]. These included isolated reports of foci of cancers occurring within HPs and the association of a high risk of CRC in individuals with multiple HPs. Observational epidemiologic studies also reported substantial overlap in the risk factors for hyperplastic polyps, adenomas and colorectal cancer; smoking, alcohol, obesity, and low folate intake were associated with both HPs and adenomas whereas calcium intake, non-steroidal anti-inflammatory drugs and hormone replacement therapy were associated with protection for both [5]. The presence of distal hyperplastic polyps at sigmoidoscopy was reported to be a modest risk factor for colorectal cancer and some putative biomarkers of colorectal cancer were strongly expressed in hyperplastic polyps [6,7]. Despite these suggestions the

prevailing view held that HPs were innocuous hyperproliferations until detailed histologic studies began to suggest otherwise.

In 1984, Urbanski described a polyp with mixed morphology, having features of both a hyperplastic polyp and adenomatous polyp that was adjacent to and appeared to give rise to a colonic adenocarcinoma [8]. Around the same time, Jass and colleagues termed a similar lesion an “atypical metaplastic polyp.” In 1990, Longacre and Fenoglio-Preiser first used the term “serrated adenoma” to describe a serrated polyp that had rather uniform dysplastic cytology [9]. The term “serrated” came from the observation of the saw tooth-shaped infoldings of the surface and crypt epithelium of these polyps that was similar to that of HPs. In this landmark report, the authors identified 110 serrated adenomas by retrospectively reviewing 18,000 polyps [9]. In 2003, Torlakovic et al. suggested that serrated polyps be further divided into two groups, traditional serrated adenomas (TSA) for those initially described by Longacre et al [8] and a new category termed the sessile serrated adenoma (SSA) for lesions that had serrated histology but did not have uniform cytologic dysplasia [10]. In retrospect, it appears that SSAs had been previously grouped with HPs by most pathologists. SSAs could have subtle cytologic areas of atypia but if they had features of SSA with distinct foci of unequivocal dysplasia they were termed mixed polyps (MPs). In this review, we will use the terms HP, TSA, SSA and MP whenever the data allows and will use the term serrated polyp or serrated neoplasia to refer to the entire group.

THE SPECTUM OF SERRATED POLYPS OF THE COLON

The spectrum of serrated polyps of the colon has been defined and distinguished by their histologic features and the endoscopic and molecular features were subsequently linked to the histology. At the outset, it is important to note that there is at best only moderate inter-observer agreement among pathologists in the diagnosis of and distinction among the various types of serrated polyps [11]. In one study, the concordance was only moderate and it improved only slightly after the pathologists agreed on the primary features they would use to make a diagnosis of the various types of serrated polyps. The greatest variability was in the distinction between HPs and SSAs. Although the variability in the histologic diagnosis of serrated neoplasia clouds the clinical and molecular analyses of these lesions, a generally accepted picture of the serrated neoplasia pathway seems to be emerging.

HISTOLOGY

The four commonly accepted histological variants of serrated polyps of the colon include the hyperplastic polyp (HP), the sessile serrated adenoma (SSA), the mixed polyp (MP) (Fig 1) and the traditional serrated adenoma (TSA). In addition, some adenocarcinomas of the colon have a prominent serrated appearance and have been termed serrated adenocarcinomas [12]. The histologic and molecular similarities of these lesions have led to the concept of a serrated polyp-carcinoma sequence (HP-SSA-MP-serrated CRC) that is histologically and molecularly distinct from the traditional adenoma-carcinoma sequence. It is becoming increasingly important to distinguish the members of the serrated polyp pathway because it seems almost certain that a subset of HPs or SSAs, particularly large right sided lesions give rise to more advanced serrated lesions included adenocarcinomas and thus should be managed like adenomas. There is also growing evidence that the serrated polyp-carcinoma sequence may have a distinct natural history and that cancers arising through this pathway may have a different prognosis and response to therapy than cancers arising through the traditional adenoma-carcinoma sequence.

Hyperplastic polyps

In contrast to the normal colon which consists of smooth surfaced, regularly spaced test-tube like crypts HPs typically retain non-branched but convoluted crypts that have an epithelium with a sawtooth pattern of infoldings (serrations) in the upper half of the crypt [15]. This serrated pattern gives a stellate-like appearance to HP glands cut in cross section (Fig 1). The serrated pattern is thought to be due to a relatively normal rate and regulation of proliferation in the crypt base with a failure of normal apoptosis and release of epithelial cells at the upper crypt and surface mucosa. This unbalanced rate of proliferation and cell loss results in the accumulation of non-proliferating cells in the upper crypt with infolding to allow more surface area for the retained cells. HPs are the most common of the serrated neoplasia of the colon accounting for about 80–90% of all serrated polyps and about 10–15% of all polyps of the colon [16]. HPs are typically diminutive (80–90% <5mm) and located in the distal colon (75–80% in the rectosigmoid) [17].

HPs have been subclassified into goblet cell rich and microvesicular types of serrated polyps (GCSP and MVSP respectively) based on the cellular mucin distribution. It is not totally clear if this distinction is very clinically useful but molecular features of these two types of lesions suggest that the microvesicular subset of HPs (Fig 1) could be the precursors to some of the more advanced serrated polyps described below [15].

Sessile Serrated Adenomas

Sessile serrated adenomas (SSAs) are thought to account for about 20% of all serrated neoplasia of the colon and about 10% of all colonic polyps [17]. SSAs share the serrated crypt architecture with HPs but the serrations tend to be more exaggerated and extend to the crypt base (Fig 1). The gross architecture of the SSA crypt also differs from that of typical HPs; SSA crypts are often dilated and extend laterally to grow parallel to the muscularis mucosae forming either an inverted T or L shaped crypt [18,19]. SSAs do not have classic dysplasia, they may have mild cytologic atypia but even this is not required for the diagnosis. One hallmark of SSAs is that they have abnormal patterns of proliferation and differentiation with proliferating cells extending to upper levels of the crypt and differentiated goblet cells found at the crypt base (this abnormality led some authors to call these lesions Sessile Adenomas with Abnormal Proliferation [20]). SSAs tend to be flat, are commonly found in the proximal colon (75% proximal to splenic flexure), and when found are typically larger than the usual HP (64% >5mm and 17% >10 mm in one large series) [18].

Mixed Polyps

Mixed polyps (MPs) differ from HPs and SSAs in that they have distinct areas that have the appearance of SSAs and separate distinct areas that display unequivocal dysplasia [16] as shown in Fig 1. In one colonoscopic series, MPs accounted for about 2% of all colonic polyps and 4% of all serrated neoplasia of the colon [17]. MPs are now commonly thought to be SSAs that have developed focal dysplasia that is similar to that seen in traditional colonic adenomas and the dysplastic foci are thought to be the immediate precursors of a unique subset of colorectal adenocarcinomas.

Traditional Serrated Adenomas

As noted above, the term serrated adenoma was coined in 1990 by Longacre and Fenoglio-Preiser [9] to describe what are currently termed traditional serrated adenomas (TSAs). TSAs are thought to be uncommon lesions accounting for less than 1% of all colonic polyps and about 2% of all serrated neoplasia of the colon [17]. TSAs share the same serrated crypt architecture with HPs and SSAs but also contain unequivocal cytologic dysplasia throughout

the polyp. These cytologic features include nuclear hyperchromasia, nuclear elongation, nuclear stratification, prominent nucleoli and hypereosinophilic cytoplasm [19]. TSAs may have tubular, tubulovillous or villous histology and, like SSAs, they have loss of orientation in the basal crypts as well as detachment of the crypt from the muscularis mucosae. This crypt architecture can give TSAs a villiform appearance when viewed at low power. In their original description Longacre et al [9] reported that 37% of TSAs had significant dysplasia; and 11% contained areas of intramucosal carcinoma strongly suggesting that these lesions, although uncommon, could be a precursor of some colorectal cancers [9]. The molecular studies presented below suggest that if TSAs are CRC precursors their molecular pathway is divergent from that of SSAs.

ENDOSCOPIC APPEARANCE

Hyperplastic polyps

HPs are most frequently seen in the distal colon [21]. Distal HPs are typically diminutive sessile polyps ranging from 1–5 mm in size and rarely reach a size greater than 1 cm. Classically distal HPs are described as looking like pearl-colored dew drops on the colonic mucosa. HPs tend to flatten and are more difficult to see when the lumen is fully distended. Newer high-definition endoscopes with narrow band imaging or other similar adaptations as well as chromoendoscopy have described the surface of HPs as having crypt openings that are larger than the surrounding normal crypts with either rounded or stellate shaped lumens [22]. The stellate appearing crypts (also called asteroid crypt pattern) have been said to be seen in the microvesicular type HP and the rounded pattern in goblet cell type HPs [23]. These advances as well as newer techniques such as optical coherence tomography and autofluorescence promise to make the endoscopic diagnosis of HPs feasible but currently polypectomy and histology is the standard method for diagnosis of HPs. HPs in the proximal colon are, on average, larger than the typical diminutive distal HP which has suggested the possibility that proximal HPs may, as a group, have a different clinical significance than the typical distal HP.

Sessile Serrated Adenomas

Endoscopically SSAs are on average larger than HPs with more than half > 5mm and 15–20% > 10 mm in size. In one endoscopic series of 91 serrated adenomas, the size ranged from 0.1 cm to 5.5 cm [24]. SSAs are most commonly found in the proximal colon (75% proximal to splenic flexure in one series) [17]. SSAs usually appear flat to sessile with a soft, smooth appearing surface and are often covered with mucus giving them a yellow appearance initially [15]. Once the mucus is washed off the underlying polyp may be similar in color to the adjacent mucosa or have a reddish appearance. Iwabuchi et al., for example, reported that 60% of cases of serrated adenomas had a “reddish” appearance [25]. The surface characteristics of SSAs when viewed by chromoendoscopy or NBI are similar to those of microvesicular HPs with enlarged stellate shaped pit pattern [26].

Mixed Polyps

The endoscopic appearance of MPs has not been well differentiated from that of SSAs described above. Some serrated adenomas have been reported to have the characteristic cerebriform pattern of an adenomatous polyp as well as the stellate crypt pattern of SSAs.

Traditional Serrated Adenomas

TSAs have not been separated from other serrated neoplasia in most of the large endoscopic descriptions of these lesions but TSAs are described as having an endoscopic appearance more like standard colonic adenomas. They are said to be more commonly reddish in color and to be more protuberant or pedunculated than SSAs [27–29]. The endoscopic surface

appearance of TSAs is not well characterized but is also thought to be similar to that of colonic adenomas [30] with tubular or cerebriform crypt openings.

THE SERRATED POLYP-CARCINOMA SEQUENCE

Several converging lines of evidence suggest that there is in fact a serrated polyp-carcinoma sequence. A number of histologic associations and correlations have suggested such a pathway but the most compelling reason to think that serrated polyps are the precursors to some colon cancers comes from the distinct molecular similarity between a sizable subset of colorectal cancers and serrated polyps of the colon, particularly with SSAs.

Histologic Associations

Some colonic adenocarcinomas have a distinct serrated mucosal surface similar to that seen in serrated polyps suggesting the possibility of a pathogenic relationship. More convincing is the evidence of residual serrated neoplasia at the periphery of some colonic adenocarcinomas, particularly those in the proximal colon. Makinen et al., for example, reported serrated neoplasia adjacent to about 6% of colorectal cancers and importantly noted that there was typically a transition zone containing definite cytologic dysplasia between what appeared to be a non-dysplastic SSA and the cancer [31]. This suggested the possibility that the focal dysplasia might occur in SSA giving rise to MPs which might, in turn, be the histologic immediate precursor of a subset of colonic cancers. Conversely, foci of high grade dysplasia and invasive cancer can be found in lesions that otherwise meet the histologic criteria for MPs. High-grade dysplasia has been observed in up to 11% of MPs. Both cancers with residual SSA or MP at their periphery and MPs with high grade dysplasia or focally invasive cancer are reported to occur more commonly in the proximal colon and adenocarcinomas of the cecum and ascending colon have been reported to have serrated features more commonly (up to 16%) than those in the distal colon and rectum. Finally, an increased frequency of serrated neoplasia have been reported in colonic resections of the subset of microsatellite unstable colorectal cancers (see below) than in microsatellite stable CRC suggesting the possibility of a precursor relationship for serrated neoplasia and this subset of CRCs. Taken together these histologic associations have been cited to support the concept that SSAs and MPs could be the precursor of proximal serrated adenocarcinomas of the colon.

Histology of “Hyperplastic Polyposis”

Histologic analyses of polyps in a familial CRC syndrome have also supported the concept of a serrated polyp-carcinoma sequence. The term SSA was coined in 1996 by Torlakovic and Snover when they carefully examined the histology of polyps in a series of patients with what was then called Hyperplastic Polyposis (currently termed Serrated Adenomatous Polyposis by some authors) [32]. This familial syndrome is characterized by numerous serrated polyps of the colon and is now known to be associated with an increased colon cancer risk. The association of SSAs with a premalignant familial polyposis syndrome is reminiscent of the association of colonic adenomas with Familial Adenomatous Polyposis and provides strong support for a role for SSAs as a CRC precursor.

Molecular Correlations

The most compelling evidence supporting the concept of a serrated neoplasia pathway to colorectal cancer that is distinct from the classical adenoma-carcinoma sequence comes from a unique molecular profile of a subset of colorectal cancers and some serrated polyps of the colon. The three central molecular components of this profile that separate it from the CRCs of the classic adenoma-carcinoma sequence include microsatellite instability, mutations in the B-RAF oncogene and epigenetic silencing of many genes through

hypermethylation of their promoter region a characteristic termed the CpG island methylator phenotype (CIMP).

Microsatellite Instability

About 80% of colorectal cancers are thought to originate through what is called the chromosomal instability (CIS) pathway characterized by mutational events leading to activation of oncogenes and inactivation of tumor suppressor genes as classically described by Vogelstein et al [33]. The classic adenoma carcinoma sequence is the histologic counterpart of the CIS pathway and Familial Adenomatous Polyposis is a hereditary example of this pathway. A distinct type of colon cancer was subsequently characterized in Lynch Syndrome, another hereditary colon cancer syndrome also called Hereditary Non-Polyposis Colorectal Cancer or HNPCC.

Lynch syndrome cancers are characterized by microsatellite instability (MSI) due to an inactivating germ line mutation in one of several genes required for DNA mismatch repair. The DNA mismatch repair system is essential for correction of DNA mismatches that occur during DNA replication and these mismatches are particularly prone to occur in areas of repetitive nucleotide sequences (mono-, di-, tri- or larger nucleotide repeats). Microsatellite unstable cancers are characterized by alterations in the size of these repetitive nucleotide sequences in DNA from the cancer compared to that in the normal mucosa and they do not typically have markers, such as aneuploidy, that are usually associated with the CIS pathway. Thus, colorectal cancers can be divided into two broad groups: microsatellite stable (MSS) CRCs arising largely through the classic adenoma-carcinoma sequence and microsatellite instable (MSI) CRSs arising through a serrated polyp-carcinoma sequence. The CIS molecular pathway accounts for the large majority of CRCs but the MSI pathway accounts for about 15% of all CRCs.

It soon became clear that most microsatellite unstable CRCs were not due to Lynch Syndrome but arose in subjects without a strong family history of CRC. Microsatellite instability in these sporadic cancers did not occur as a result of mutations in the DNA mismatch repair genes but rather through an epigenetic process of hypermethylation and silencing of one of the DNA mismatch repair genes hMLH-1 (more about this hypermethylation process below). It was subsequently shown that these two classes of microsatellite unstable CRCs could be distinguished by the presence of activating mutations in an oncogene B-RAF in sporadic MSI cancers but not in Lynch syndrome cancers.

B-RAF/KRAS Mutations

The finding of B-RAF mutations in microsatellite unstable CRCs was of considerable interest because the B-RAF protein is immediately downstream from KRAS in a kinase pathway known to be important for growth factor signaling and the KRAS gene was known to be one of the most commonly mutated oncogenes in the classic CIS pathway/adenoma carcinoma sequence. Conceptually, mutational activation of both KRAS and B-RAF would be redundant as they would both result in activation of the same signaling system. In fact, mutations in these two genes appear to be mutually exclusive in human CRCs. B-RAF mutations appear to be largely confined to the subset of sporadic microsatellite unstable CRCs. Neither microsatellite stable cancers nor Lynch syndrome cancers commonly have B-RAF mutations. Importantly standard colonic adenomas rarely have B-RAF mutations suggesting that the colonic adenoma is not likely to be the precursor of sporadic MSI CRCs.

CpG Island Methylator Phenotype (CIMP)

The finding that microsatellite instability in sporadic CRCs was due to hypermethylation of the DNA mismatch repair gene hMLH-1 rather than to mutational inactivation linked these

tumors to an epigenetic process of gene silencing termed CIMP [34]. CIMP refers to non-random hypermethylation of promoter regions of numerous genes including several known to be important tumor suppressor and DNA repair genes. Hypermethylation of some genes is known to occur with increasing age and does not appear to be related to cancer risk but methylation of others is strongly associated with cancer independent of age and this cancer-associated hypermethylation has been termed CIMP. Such hypermethylation of promoter regions is known to result in gene silencing. As such, this mechanism can result in epigenetic inactivation of genes that is functionally comparable to the mutational inactivation of tumor suppressor genes or DNA repair genes seen in the CIS pathway and Lynch Syndrome respectively.

CIMP status of tumors is measured by assessing the methylation status of a set of these cancer-associated genes in the tumor to that found in normal tissue. The reason that some people develop CIMP is not known but could be due to a genetic predisposition to environmental factors thought to affect DNA methylation (alcohol, folate status). Strong CIMP positivity (termed CIMP-High) is unusual in either chromosomal instability-type CRCs or in Lynch cancers. Lower levels of CIMP (CIMP-L) can be seen, however, in the former and this clouds the strict linkage of CIMP to microsatellite unstable B-RAF mutated CRCs. Interesting CIMP can be found not only in cancers but in the normal appearing mucosa of some subjects with CIMP positive CRCs [35] suggesting the possible use of CIMP status as a biomarker of risk.

The clustering of MSI due to hypermethylation of hMLH-1, B-RAF mutations and CIMP-High status thus defines a molecular subset of CRCs and the lack of these markers in classic adenomas of the colon and their presence in some serrated polyps is at the core of the concept of a serrated polyp-carcinoma sequence.

Model of a Molecularly Defined Serrated Polyp-Carcinoma Sequence

The concept of the serrated polyp-carcinoma sequence is that sporadic MSI CRCs have a molecular profile that is similar to that of some serrated polyps and quite distinct from that of standard colonic adenomas. The molecular profile of serrated polyps and traditional colonic adenomas is compared in Table 1. As noted above, sporadic MSI CRCs have B-RAF mutations and high levels of CIMP. Standard adenomas do not typically have any of these 3 markers whereas MPs have been reported to have all three. SSAs and some HPs have both B-RAF and CIMP without MSI [35]. These molecular similarities along with the histologic similarities described above have led to the hypothesis of a putative HP-SSA-MP-MSI CRC pathway depicted in Fig 1. This hypothesis does not suggest that all HPs are at risk for progression to cancer but that large and right sided HPs and SSAs should be viewed as a putative cancer precursor. If HPs are integral to this pathway it suggests that, as a group, HPs in the proximal and distal colon are either fundamentally different from the outset or variations in local factors lead to different risks of progression since large HPs, SSAs and MSI CRCs are all more common proximally. It is important to note that some experts in the field are not convinced that the HP is part of this pathway and they suggest that SSAs can arise de novo.

If the SSA appears to have the greatest molecular similarity to sporadic MSI CRCs, where then does the TSA fit into the picture? TSAs differ from SSAs in that they more commonly have K-RAS than B-RAF mutations. They do frequently have CIMP but they don't typically have hypermethylation of hMLH-1 but more commonly have hypermethylation of another DNA repair gene MGMT (O6-methylguanine-DNA methyltransferase). The molecular profile of TSAs is more heterogeneous but overlaps to some extent with that reported for SSAs and standard colonic adenomas. It is not clear if this heterogeneity is due to the variability in the histologic classification of TSA in the reported studies or if the molecular

pathway to TSAs is intrinsically heterogeneous. Although there is substantial histologic and molecular evidence that TSAs can progress to CRCs that typically have CIMP and low levels of microsatellite instability but the precursors for TSAs are not clear. Since some HPs do share the molecular features (K-RAS mutations and CIMP) of TSAs (Table 1) it has been suggested that the TSA pathway could diverge from the SSA pathway on the basis of K-RAS vs. B-RAF mutations and hMLH-1 vs. MGMT hypermethylation within subsets of HPs or SSAs [23]. There is, as yet, no general agreement about the precursor, if any, of the TSA.

MANAGEMENT

In an ideal world, recommendations about management of serrated neoplasia of the colon would be based upon an understanding of the natural history and overall malignant potential of the various types of serrated polyps. Unfortunately such detailed information is not yet available and there are no controlled studies of follow-up intervals of serrated neoplasia of the colon. Thus, attempts to define the natural history of these lesions have been indirect and largely done prior to the routine distinction between SSAs and TSAs. Lazarus et al. [26] compared the rate of metachronous neoplasia and cancer in subjects with serrated polyps without dysplasia (HPs and some SSAs likely included in this group), serrated adenomas with dysplasia (some SSAs and TSAs) or admixed polyps (MPs) to those with conventional adenomas. They reported that the subjects with non-dysplastic serrated polyps as their most advance index polyp most commonly had similar metachronous lesions (>90%), those with dysplastic SAs most commonly had dysplastic SAs (75%) and those with MPs or conventional adenomas most commonly had conventional adenomas (70–90%) as their most advanced metachronous lesion. Although they had little power for a cancer endpoint they found no difference in the rate of metachronous CRC in those with SAs vs. conventional adenomas in their series. The authors tried to estimate the mean growth rate of the SAs with dysplasia and concluded it was slightly more rapid than that of conventional adenomas and 3 times more rapid than non-dysplastic serrated polyps [43]. Goldstein et al. [27] reported that the interval between the diagnosis of a SSA and a subsequent microsatellite unstable CRC was directly proportional the average size of the SSA and was 3 years in 82%, 6 years in 55% and 10 years in 28% of cases [40]. These data suggest that surveillance colonoscopy intervals for SSAs should be at least as frequent as those recommended for conventional adenomas. Despite the relative lack of data, the following management recommendations seem reasonable based on current knowledge.

Perform careful colonoscopy

Undetected lesions have been cited as the most common cause of interval advanced adenomas and cancers in patients undergoing surveillance colonoscopy after polypectomy [44]. Miss rates may be higher for SSA than for adenomas since they are often flat (or become flat with air insufflation), right sided, sometimes are covered with mucus and may be more difficult to distinguish from the surrounding normal mucosa with standard white light colonoscopy. These lesions can also be missed on colonoscopy because of poor prep or inattention to the areas behind folds where flat lesions could be obscured [45]. Thus, good quality patient preparation, careful visualization during white light colonoscopy and the availability of some technology to help define the surface characteristics and borders of a polyp (chromoendoscopy, NBI or something similar) when necessary is essential for the identification and characterization of these lesions. Monitoring of cecal intubation rates, adenoma detection rates and withdrawal times seem like a reasonable recommendation that might decrease routine colonoscopic miss rates [46,47].

Remove all colonic polyps completely whenever feasible

The recommendations of the Multi-Society Task Force on Colorectal Cancer states that “polypectomy should be performed on all polyps identified during colonoscopy, with the exception of multiple small (usually 1–5 mm) hyperplastic-appearing (pale, sessile, sometimes disappearing with air insufflation) polyps in the rectosigmoid. These polyps may be sampled with biopsy forceps and otherwise left *in situ*.” [48]. Since incomplete polypectomy has been cited as one of the most likely causes of interval advanced adenomas and cancers [44], this recommendation should be strengthened to include that assurance of complete polypectomy is an integral part of high quality colonoscopy. This addition is particularly relevant to SSAs since their recurrences is thought to be related to incomplete excision as seen by frequent positive margins at the time of excision [24]. Complete excision could be aided by the routine use of a snare technique with care to include a margin of normal mucosa in the polypectomy specimen rather than multiple biopsies for small (< 1cm) colonic polyps. Similarly, cauterization of the edges of polypectomy sites after removal of larger sessile polyps can decrease the rate of incomplete resections. Although many pathologists do not routinely report whether the resection margins of colonic polyps are free of residual neoplasia, this information should be requested after resection of large polyps and routine re-examination of the large (>2cm) polypectomy sites is recommended [49]. Just as occasionally required for complete removal of conventional adenomas, surgical resection should be considered for removal of large proximal SSAs, MPs and TSAs if repeat attempts at colonoscopic polypectomy fail particularly if high grade dysplasia is present.

Sample fields of diminutive polyps of the rectosigmoid

The exception to the recommendation for complete polypectomy cited above that multiple small hyperplastic-appearing polyps in the rectosigmoid may be sampled, is based on the acceptance that diminutive HPs of the distal colon are not a significant precursor lesion for CRC. Since it is not yet possible to reliably distinguish diminutive HPs from diminutive adenomas, sampling of such lesions is important. If the sampled polyps are adenomas, SSAs or TSAs, it would be appropriate to repeat an exam of the rectosigmoid and remove the residual polyps.

Base surveillance on histology of the removed polyp(s)

After careful detection and complete removal of colonic polyps, surveillance recommendations can be made based upon the histologic classification of the removed lesions. The presence of only diminutive HPs in the rectosigmoid is not thought to predict an increased subsequent risk of CRC so screening and surveillance intervals should not be changed by this finding. Although recommendations may change as we learn more about the other types of colonic serrated polyps, it seems reasonable now to follow these lesions in a manner similar to traditional adenomatous polyps because of their putative risk of progression to microsatellite unstable colorectal carcinoma [50]. Surveillance intervals for completely removed large HPs and SSAs without dysplasia can be similar to those for small tubular adenomas (5–10 years) although 5 year intervals seem prudent initially since the natural history of these lesions is unclear. Recommended surveillance intervals after completely removed serrated adenomas with dysplasia (MPs and TSAs) or for more 3 or more large HPs or SSAs are similar to those for advanced adenomas (3 years).

CONCLUSIONS

The serrated polyp-carcinoma sequence appears to be a genuine pathway to CRC based on molecular and histological characteristics and is an important alternative model of carcinogenesis that invites further research. The polyps of this pathway which have the potential of developing into sporadic MSI carcinomas must be identified and treated with

careful colonoscopy (good patient prep, sufficient withdrawal times, and complete polypectomy). With further work to develop greater uniformity in histologic diagnosis and information on the natural history of serrated adenomas, evidence-based treatment and surveillance guidelines may be modified but it seems reasonable to follow large right sided HPs, SSAs, MPs and TSAs in a manner similar to the current follow up of conventional adenomas.

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Figure 1.

The histology and schematic of the serrated polyp-carcinoma sequence. Diagram shows the putative (?s represent areas of greatest uncertainty) progression of a subset of hyperplastic polyps (HPs), which are typically (+) CIMP and (+) BRAF, into a Sessile Serrated Adenoma (SSA) that may have hypermethylation of the DNA mismatch repair gene hMLH1 gene and subsequently into a Mixed Polyp that more often has hypermethylation of hMLH1 and may show evidence of microsatellite instability particularly in areas of high grade dysplasia that are thought to progress to microsatellite unstable colorectal carcinomas. The origin of the Traditional Serrated Adenomas is less clear; some authors have proposed that these polyps arise from a subset of sessile serrated adenomas or from a subset of HPs such as the goblet cell-rich HPs based on their higher frequency of K-ras rather than BRAF mutations and the higher frequency of hypermethylation of another DNA repair gene MGMT rather than hMLH-1. Photographs courtesy of Russell Nash M.D.

Table 1

The differences between the molecular profile of serrated polyps and traditional colonic adenomas (approximate percentages). Standard adenomas contain low amounts of CIMP and BRAF whereas MPs have been reported high amounts, suggesting that these lesions are mutually exclusive. SSAs and MPs share similar differences, thus supporting the serrated adenoma-carcinoma sequence.

	CIMP-H	BRAF	K-RAS	MSI
TA	18%	26%	<1%	13%
HP	52%	65%	30%	30%
SSA	68%	75%	10%	29%
MP	75%	85%	8%	82%
Sporadic CRC	40%	76%	29%	15%