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Update on the serrated pathway to colorectal carcinoma

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Summary Adenocarcinoma of the large intestine can no longer be considered one disease but rather a family of diseases with different precursor lesions, different molecular pathways, and different end-stage carcinomas with varying prognoses. Approximately 60% of colorectal carcinomas arise from conventional adenomas via the suppressor pathway leading to microsatellite stable carcinomas. These carcinomas represent the pathway that has been the target of screening and prevention programs to date. However, approximately 35% of carcinomas arise along the serrated pathway developing from the precursor lesion known as the sessile serrated adenoma (also referred to as the sessile serrated polyp). Sessile serrated adenomas/polyps lead to carcinomas with extensive CpG island promoter methylation (CpG island methylated phenotype positive carcinomas), which can be either microsatellite unstable high or microsatellite stable. The remaining 5% of carcinomas arise from conventional adenomas in patients with germ line mutations of mismatch repair genes (Lynch syndrome), leading to CpG island methylated phenotype negative microsatellite unstable carcinomas. Carcinomas arising from sessile serrated adenomas/polyps are not prevented by removing conventional adenomas and hence may be missed in routine screening programs. In addition, a subset of these lesions may potentially progress rapidly to carcinoma; hence, it is likely that these lesions will require a different screening strategy from that used for conventional adenomas. This article reviews the various pathways to colorectal carcinoma with emphasis on the serrated pathway and evaluates the implications of this pathway for colorectal carcinomas screening programs.

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1. Introduction

Colorectal carcinoma is a major health issue in the United States, representing the second most commonly fatal malignancy after lung. Although it is often assumed that almost all colorectal carcinomas arise from conventional adenomas via the suppressor pathway initiated with a mutation of the APC gene (the Fearon-Vogelstein model), it is now clear that this pathway accounts for only approximately 60% of colon carcinoma [1,2]. Most of the remaining 40% is accounted for by the more recently described serrated pathway leading to CpG island methylated phenotype (CIMP+) carcinoma (approximately 35%), with the remaining 5% arising via the mutator pathway in Lynch syndrome [2]. Trying to understand the multiplicity of pathways is confused by a plethora of overlapping ways to describe these pathways and cancers. Pathways have been defined by the presumed initiating factor (ie, suppressor [chromosome instability] versus mutator [microsatellite instability] pathways) and by the presumed precursor lesions (ie, conventional adenoma-carcinoma sequence versus the serrated pathway). A commonly utilized subdivision into microsatellite stable (MSS) carcinomas (which represent both suppressor pathway carcinomas arising either sporadically or
in familial adenomatous polyposis as well as approximately 60% of CIMP+ carcinomas arising along the serrated pathway) and microsatellite instable high (MSI-H) carcinomas (by convention usually referred to as “MSI” carcinoma without the “high” or “-H” descriptor), which represent all carcinomas in Lynch syndrome arising via the mutator pathway, as well as approximately 40% of sporadic CIMP+ carcinomas, is useful for detecting patients with Lynch syndrome but still represents a phenotypic end stage of differing pathways. All of these different descriptions overlap to some degree. The conventional APC initiated adenoma-carcinoma pathway leads to FAP and sporadic CIMP− colon cancers arising via the suppressor pathway as well as cancers in Lynch syndrome arising along the mutator pathway. The alternate serrated pathway leads to CIMP+ carcinomas either by a mutator pathway (leading to sporadic MSI+CIMP+ carcinomas) or a pathway (details of which are still unknown) that leads to MSS CIMP+ carcinomas. In addition, there remain probable other pathways to colorectal carcinomas that have not yet been well worked out, including MSI-low (MIS-L) carcinomas and carcinomas associated with mutation of the MYH gene, both of which may have some relationship to the serrated pathway. These various pathways and their overlaps are summarized in Fig. 1. Current thinking regarding colorectal pathways was recently summarized in review by the late Jeremy Jass, and this article is recommended reading for anyone wishing to understand the multiple pathways to colorectal carcinoma [2].

Because most screening and intervention programs for colon carcinoma have been directed toward the elimination of conventional adenomas, it would appear that at best a 65% reduction in colorectal carcinoma can be expected by our current approach. Eliminating the other 35% will require a better understanding of the serrated pathway and precursor lesions of the serrated pathway, mainly the lesion known as the sessile serrated adenoma (SSA; AKA sessile serrated polyp) and the less common traditional serrated adenoma (TSA). This review will focus on these lesions and current controversies related to them.

2. Molecular mechanisms of carcinomas development via the serrated pathway

Developing a management scheme for dealing with serrated lesions requires an understanding of the underlying mechanism of molecular carcinogenesis. The basic
mechanism for the suppressor pathway to colon carcinoma begins with a mutation of the APC tumor suppressor gene, which allows unregulated proliferation of epithelial suppressor gene cells with the formation of a lesion conventionally known as an "adenoma" (these APC-related adenomas will be referred to as "conventional adenomas" throughout this review; they are commonly subdivided into tubular, tubulovillous, and villous types, and with these designations, the term conventional is understood and need not be applied in daily practice). This proliferative population then undergoes additional mutations, presumably in a relatively random order, with the eventual progression of a small subset of conventional adenomas to carcinoma with intermediate stages showing increasing degrees of dysplasia. With the exception of conventional adenomas arising in Lynch syndrome, which appear to progress rapidly to carcinoma, the most conventional adenomas never progress and those that do require many years (probably 10 or more) to develop into malignancy. Hence, screening programs periodically removing conventional adenomas can be very successful in preventing MSS carcinomas arising via the suppressor pathway.

The mechanism of the most common carcinomas arising via the serrated pathway appears to begin with an activating mutation of the BRAF gene, a gene which when mutated inhibits normal apoptosis of colonic epithelial cells. Lesions bearing the BRAF mutation develop into serrated lesions that are mainly either microvesicular hyperplastic polyps (MVHP) or sessile serrated adenomas/polyps (SSA/P, see terminology, below) [3]. These lesions are prone to methylation of the CpG island promoter regions resulting in the epigenetic silencing of a number of genes. It is presumed that the specific genes silenced may be random events. The specific gene silenced determines what happens with a lesion. The most well characterized epigenetic silencing in these lesions is that of the hMLH1 gene, which is the gene silenced in sporadic MSI carcinomas. The hMLH1 gene is one of the mismatch repair genes, and when silencing occurs, these lesions become MSI and are prone to the development of additional mutations at a rapid rate, similar to what happens to conventional adenomas in patients with Lynch syndrome. Although in most (although unfortunately not all) lesions it appears that methylation of hMLH1

Fig. 2  Representation of the serrated pathway to MSI-H carcinoma. This sequential pathway involves slow and rapid steps. The origin of SSA/P remains debatable. It is possible that SSA/P arises directly from normal mucosa or SSA/P might develop from a preexisting MVHP; hence, the arrows for these steps are dotted.
is a late event, occurring in all likelihood many years after the lesion initially develops, once hMLH1 is inactivated, there is rapid development of cytological dysplasia (see terminology, below) followed by potentially rapid development of frank malignant transformation. The rate of progression of these lesions has an important impact on screening strategies, discussed below. Carcinomas arising via this pathway are CIMP+ MSI carcinomas. The specific molecular events leading to the development of CIMP+ MSS carcinomas are not nearly as well characterized as that for CIMP+ MSI carcinomas but presumably involve epigenetic silencing of other genes leading to carcinoma via as yet undefined pathways. A simplified diagram of the serrated pathway to CIMP+ MSI carcinoma is shown in Fig. 2.

There may be several more serrated pathways not related to the BRAF gene mutation. Several types of serrated polyps, including goblet cell–rich hyperplastic polyps (GCHP) and TSA, are mutated at the Kras gene rather than the BRAF gene (4, 5). There is currently no known direct role of GCHP in carcinogenesis; however, it is clear that TSA may develop into carcinoma, although there has been some controversy as to the type of carcinoma. It has been suggested that MSI-L carcinomas may develop in these lesions after methylation of the MGMT gene or possibly secondary to partial methylation of hMLH1. Finally, there is a recent report of multiple serrated polyps in patients with MYH polyposis associated with Kras mutations; however, this remains to be confirmed and the molecular mechanisms evaluated [6].

3. Precursor lesions of the serrated pathway

As recently as 2003, all of the various serrated lesions were considered hyperplastic or “metaplastic” polyps, and their malignant potential was not well recognized, but it is now generally recognized that these lesions represent a complex family of lesions differing in their specific underlying mutation and degree of methylation [3-5, 7-11]. As yet unknown factors lead to alterations in the location of the proliferative zone as well as differences in the anchoring of crypts within the lesions, leading to a wide range of histological appearances [10]. It is mainly architectural alterations resulting from these abnormalities of proliferation that allow distinction of the different categories of polyps. A summary of the current classification of serrated polyps (based on the fourth edition of the World Health Organization [WHO] blue book to be published in 2010 [11]) is shown in Table 1. A diagrammatic representation of the proliferative zone abnormalities and resultant architectural changes of the various serrated lesions is shown in Fig. 3.

Although there is now general consensus on the importance of the serrated lesions in the development of carcinomas, and the general categories of lesions are accepted, challenges remain. Included among these are issues related to terminology, diagnostic criteria, and natural history, which affects management decisions.

4. Terminology and diagnostic criteria

Details of the histological appearance of these lesions have been reviewed extensively elsewhere [7-11] and will not be repeated here except to provide a brief review and introduction into current issues.

Although the terminology is not perfect because these lesions are not truly “hyperplastic” or “metaplastic,” the term hyperplastic polyp (HP) has been retained for the most indolent form of serrated lesions [11]. These lesions are characterized by variably prominent serrations occurring in crypts that are generally straight and demonstrate more or less normal localization of the proliferative zone to the base of the crypts (Figs. 3A and 4). HPs are subdivided based on the mucin content, with those demonstrating exclusively goblet cell mucin being termed GCHP, those with small droplet (microvesicular) mucin either alone or intermixed with goblet cells being called MVHP, and those with no mucin being designated mucin poor HPs (MPHP). GCHPs

Fig. 3 Graphic representation of the putative sequence for the development of serrated lesions based on the location of the proliferative zone. All 3 lesions begin with normal mucosa in which the proliferative zone (indicated by the thick line) is located at the lower third of the crypt, and cells mature toward the lumen (arrow). The double thin line represents the muscularis mucosae. A, HP. The proliferative zone remains in the lower portion of the crypt, occupying up to half of the length of the crypt. Cells continue to mature toward the surface (arrow), but because of delayed apoptosis, the cells tend to pile up, leading to serrations. B, SSA/P. The proliferative zone is located at various locations throughout the crypt length. This allows maturing cells to move toward the lumen but also toward the base of the crypt (arrow), which leads to distorted and dilated crypts since the muscularis mucosae blocks the downward growth of the crypts. C, TSA. The proliferative zone is also variably located, but small ectopic crypts develop from the side of the original crypt. These miniature crypts create a complex growth pattern. (adapted from Reference [10]).
A

Normal crypt.
Proliferation occurs at the base of the crypts and cells mature toward the lumen (arrow)

Hyperplastic polyp with expanded proliferative zone. Maturation continues toward the lumen with decreased apoptosis creating serrations.

B

Normal crypt

Early stage of SSA/P with movement of proliferative zone to side of crypt (dotted arrow) and bidirectional maturation (solid arrow)

Progression of SSA/P with downward growth of mature epithelium leading to distorted crypt

C

Normal crypt

Early stage of TSA with proliferative zone on side of crypt. Outward growth creates ectopic crypt (arrow)

Fully developed TSA with multiple ectopic crypts lining villi
are found almost exclusively in the left colon and commonly demonstrate Kras mutations, whereas MVHP, which is still predominantly left-sided but with more rightsied lesions than GCHP, tends to be BRAF mutated \[4\]. MPHP appears to represent a damaged MVHP with reactive change, but this category is rare and has not been well studied. It has been suggested that MVHP may act as a precursor to the more advanced and clearly premalignant SSA/P, in large part because they share the BRAF mutation and a propensity to methylation, although this has not been proven and perhaps is of more theoretical than practical significance. Very rarely will one encounter a MVHP that demonstrates cytological dysplasia resembling conventional adenoma, and hence, it is possible that MVHP may occasionally become methylated at a gene critical for carcinogenesis, as occurs in SSA/P, and hence may progress to malignancy without an intervening SSA/P.

Perhaps the most persistent and perplexing issue regarding serrated lesions is the fact that there remains no consensus on the best terminology for the lesion known variably in the literature as sessile serrated adenoma (SSA), sessile serrated polyp (SSP), or serrated polyp with abnormal proliferation. The term SSA was the first term used for this lesion, and a majority of the current literature is written using the term SSA; however, there is a second large group who prefers SSP. The term serrated polyp with abnormal proliferation is rapidly losing favor. The rationale for the use of “polyp” rather than “adenoma” for this lesion revolves around a concern that use of “adenoma” will cause confusion with conventional adenomas arising via the APC mutation pathway, despite the fact that most authors in the field accept that these lesions are functionally premalignant and hence “neoplastic.” In the practice of this author, who has used the term SSA since 1996, confusion with conventional adenomas has not been an issue with our gastroenterologists, who seem to have no difficulty understanding the difference between SSA, tubular adenoma, tubulovillous adenoma, and villous adenoma once they are familiar with the concept. Many authors believe that SSA is the best term because it reflects the premalignant potential of this lesion in the serrated pathway and is likely to lead to more appropriate management that other more noncommittal terms. Nonetheless, consensus has not been reached, and the upcoming fourth edition of the WHO classification of tumors of the digestive trace will reflect that at the current time either term is acceptable as long as it is recognized that SSA and SSP are referring to the same lesion \[11\]. For clarity sake, SSA/P will be used throughout this article. Unfortunately, there are still some pathologists who continue to use the term hyperplastic polyp or variant hyperplastic polyp for these lesions, a most unfortunate fact given the considerable management differences between HP and SSA/Ps. The use of the “hyperplastic polyp” for these lesions should be avoided.

SSA/P is characterized mechanistically by movement of the proliferative zone away from its usual location in the base of the crypts, resulting in maturation, which may develop toward the base of the crypts leading to distortion of the crypt architecture, commonly with dilated, L, inverted T, or anchor-shaped crypts with mature cells where the proliferative zone normally is located (as evidenced by mucinous differentiation as well as marking for cytokeratin 20 (Figs. 3B and 5) \[10\]). The crypts still retain their “attachment” or orientation toward to the muscularis mucosae, however, and are arranged perpendicular to the muscularis mucosae. SSA/P in its earliest stage does not manifest dysplasia resembling conventional adenoma, although with progression toward carcinomas, such dysplasia develops.

There has been variation regarding the best term for lesions that combine the features of SSA/P with areas of frank cytological dysplasia that resemble conventional adenomas (Fig. 6). These lesions have in most of the older

**Fig. 4** Microvesicular hyperplastic polyp. Note that the crypts are relatively straight with narrow bases (×40). Also, see Fig. 3A.

**Fig. 5** SSA/P without cytological dysplasia. Compared to the HP, the overall architecture is distorted with variably shaped crypts and mature cells at the base of the crypts (×40). Also, see Fig. 3B.
literature been called mixed HP-TA, and with the recognition of SSA/P, it turned out that the serrated portion of most of these mixed lesions was in reality SSA/P, leading to the use of the term mixed SSA/P-TA for these lesions [7]. However, it is currently felt that this term is misleading because the cytologically dysplastic part of these polyps is not a conventional TA from a molecular perspective and probably has a more aggressive course than conventional TA. As noted above, conventional TA is a lesion that starts with an APC mutation, acquires addition mutations over time, and eventually, in a small number of cases and generally over the course of 10 years or more, becomes malignant. SSA/P with cytological dysplasia, on the other hand, in some cases (ie, in the case of lesions developing into MSI carcinomas) represents the development of microsatellite instability in the lesion and hence is creating a lesion with a propensity to develop into carcinoma with high frequency and rapidity (see Fig. 2 and discussion above). These lesions are not APC mutated and probably require considerably more aggressive follow-up than conventional adenomas. Hence, “SSA/P with cytological dysplasia” is the preferred term for this lesion, and the term mixed SSA/P-TA or HP-TA is no longer considered acceptable.

The other term that has had some controversy is that of the “traditional” serrated adenoma (TSA). This lesion is one of several forms of serrated lesions that fit the definition of “serrated adenoma” proposed in the seminal article by Longacre and Fenoglio-Prieser in 1990 [12]. The definition provided initially for “serrated adenoma” was that a “serrated adenoma” was a lesion with dysplasia (and hence “adenoma” by conventional criteria in use at the time) but which showed an overall serrated configuration. Unfortunately, this definition is overly broad and can be used to describe what are now known to be 3 or possibly 4 different lesions (SSA/P, SSA/P with cytological dysplasia, TSA, and conventional APC adenomas with a serrated growth pattern). Recognizing this, in 2003, it was suggested that the most unique of this group, and the one member of this group which did not have a better name, should be recognized as a separate entity, and the term traditional serrated adenoma was recommended (because it was thought that this lesion was the one member of this group that was most easily recognized by most pathologists, and the one that at the time was probably most commonly being called “serrated adenoma,” in large part because at the time SSA/P was still being called HP by most pathologists, and SSA/P with cytological dysplasia was being called mixed HP-TA.) [3]. It is of some interest along these lines that a recent reproducibility study identified this lesion as the one with the best kappa statistic of the various serrated lesions, supporting our contention that most pathologists already know how to recognize this lesion [13].

There does continue to be some variation in the diagnosis of TSA, however, in large part because of recent suggestions for expansion of the diagnostic criteria [10]. The original definition of TSA was a very simplistic one, with the most notable feature being the presence of a peculiar type of atypical cell characterized by relatively abundant eosinophilic cytoplasm resembling that of an oncocyte, with elongated nuclei (typically not hyperchromatic) often located in the mid portion of the cell and with little or no pseudostratification and with little proliferative activity as determined by mitotic count or Ki67 immunoreactivity [3,7,10]. This cell was considered by many as being “dysplastic” and therefore was often equated with the “dysplasia” of conventional adenomas. Given the lack of proliferative activity (as well as the lack of APC mutations) in these cells, they are not likely to have the same neoplastic potential as conventional dysplasia and are better considered...
a metaplastic or possibly senescent cell. Although this cell
type was originally considered a sine qua non for the diagnosis
of TSA, it is now apparent that this cell type can be seen in a
variety of circumstances including in small areas of
otherwise typical SSA/P, in some conventional adenomas
(APC-related) and sometimes even in reactive mucosa. An
immunohistochemical analysis of proliferation and matura-
tion in serrated lesions has pointed out that a more likely
diagnostic abnormality in TSA is the presence of small
ectopic crypts created by apparent loss of anchoring of the

crypt bases to the muscularis mucosae [10] (Figs. 3C and 7).
These ectopic crypts demonstrated strong CK20 staining in the
luminal portions and Ki67 staining in the deeper aspects,
hence recapitulating small crypts except that the base of the
crypts was free floating in the lamina propria of villi rather
than sitting on (or being “anchored to”) the muscularis
mucosae. We now feel that these ectopic crypts are probably
the best defining feature of TSA, although most TSAs will
also have the atypical eosinophilic cell noted above. These
ectopic crypts are not present in all areas of all TSAs but
should be present at least focally. Often TSA will have large
areas with the metaplastic eosinophilic cells described above,
but using these diagnostic criteria, a TSA can also be
composed mainly of goblet cells. Whether these different cell
types have any molecular or prognostic implications is also
not known. The lesion described as “filiform” serrated
adenoma is probably synonymous with TSA or represents a
subset of TSA and may provide less confusing terminology
(see Table 2) [14].

Although eosinophilic metaplastic cells often make up a
considerable portion of TSAs, atypical cells with many of
the morphological attributes of conventional dysplasia (ie,
hyperchromasia, pseudostratification and increased prolifer-
ative activity) do occur in TSA, probably as part of
conversion toward malignancy (Fig. 8). The molecular
characteristics of these cells (eg, mutation and methylation
status) have not been well characterized, however, and there
has been essentially no discussion of the terminology of this
converted lesion in the literature. Trying to be analogous to
SSA/P, it would probably be appropriate to refer to these
lesions as “TSA with conventional cytological dysplasia,”
despite the fact that this is somewhat cumbersome. The
specific mechanism of carcinogenesis in TSA is currently
not well known and is discussed briefly above under

![Fig. 8](image)

**Fig. 8** TSA with conventional dysplasia. This TSA has
cytological dysplasia similar to that seen in conventional adenomas
in the right portion of the photo. In this particular case, the dysplasia
is high grade with a cribriform pattern of growth. There was
invasive carcinoma elsewhere in this polyp (X40).

### Table 2 Proposal for a semimolecular classification of colorectal polyps

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<td>CIMP-adenomas, BRAF type</td>
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<td>Hyperplastic polyp</td>
<td>SSA/P without cytological dysplasia</td>
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“molecular mechanisms of carcinomas development via the serrated pathway.”

5. The role of SSA/P in carcinogenesis and its effect on management of these lesions

As noted in the introduction, it is now generally recognized that “colon cancer” comprises a family of diseases with various molecular pathways. There is now no question that SSA/P is the immediate precursor lesion to sporadic CIMP+MSI carcinomas. SSA/P is likely the precursor lesion to CIMP+MSS carcinomas as well. Combined, CIMP+MSI and CIMP+MSS carcinomas account for approximately 35% of all colorectal carcinoma; hence, these are very important lesions to recognize and deal with if one wants to reduce the risk of colon carcinoma through screening. Unfortunately, we are still somewhat impaired in our understanding of the natural history of serrated lesions because of a lack of longitudinal studies, and current recommendations for management are based in large part on our understanding of the molecular mechanisms of the pathway and on observational studies including recent data on the frequency of serrated pathway–associated carcinomas presenting as interval cancers in screening programs.

One important difference in screening for serrated lesions (as opposed to screening for conventional adenomas) results from the fact that the CIMP+MSI pathway may be a rapidly progressive pathway, much more rapid than carcinogenesis via the conventional APC pathway, as described above. Recent analysis of “interval carcinomas” occurring in screening populations has indicated that these cancers are disproportionately MSI [15]. One possible reason for this is that some of these lesions may become malignant very rapidly, with their entire lifespan fitting in the 5 or 10 years between screening examinations. Another potential reason that should not be overlooked, however, is that SSA/P is a very subtle lesion and may be difficult to identify on endoscopic examination, especially for an endoscopist who is not experienced with recognizing the subtle changes that might indicate the presence of a lesion (especially adherent stool or mucin that must be washed off to visualize the lesion). Therefore, interval MSI cancers might also occur because SSA/Ps are being missed. It turns out that interval cancers are not only disproportionally CIMP+MSI, but they are also disproportionally CIMP+MSS [16]. Because there is no a priori reason to suspect that CIMP+MSS development has the same potential rapid progression as seen with CIMP+MSI carcinoma, this finding would bolster the theory that some of the issue related to interval cancers involves failure to identify the underlying lesion. Regardless of the reason, this apparent enhancement of interval cancers with CIMP+ carcinomas arising via the serrated pathway has significant implications on the appropriate interval for rescreening patients with a known SSA/P.

Our past recommendations had suggested that the most worrisome lesions of this group, and the lesion with the most pressing need for close surveillance, were the SSA/Ps with cytological dysplasia, since these lesions have the potential to rapidly progress to carcinoma [7,8]. We still maintain that any lesion with this histology should be removed entirely by whatever means necessary and that the patient undergo repeat endoscopy no longer than a year after initial excision (if the endoscopist is comfortable that the lesion has been entirely removed) or sooner if there is any question about adequacy of excision. TSAs, either with or without changes of conventional dysplasia, are probably best treated as conventional adenomas because they do not lead to the development of MSI carcinomas, and hence, there is no reason to suspect that they might be more aggressive than other lesions. In addition, because they tend to occur in the rectosigmoid region and are usually well-circumscribed protruding lesions, surveillance and removal tend to be easier. The real management issue is for SSA/P without cytological dysplasia because these are the most common lesions and are the ones that are most difficult to visualize and remove.

Our original recommendations were relatively leisurely regarding this group, with recommendations to remove the lesion if possible or, if the lesion was not easily resected via the endoscopy, to do surveillance at annual intervals to liberally biopsy the lesion and look for cytological dysplasia that would then accelerate the need to remove the lesion [7,8]. If the lesion was completely removed, then we suggested reversion to “standard” adenoma surveillance intervals. Given the recent data regarding CIMP+ and interval cancers, however, this may not be an adequate strategy. Personal observations by myself and others (Kenneth Batts, MD, personal communications) would indicate that often patients with one SSA/P will harbor others, either synchronously or metachronously. This seems especially true for large lesions found in the right colon. When the criteria for “serrated polyposis” (formerly known as “hyperplastic polyposis”) are met ([1] at least 5 serrated polyps proximal to the sigmoid colon with 2 or more of them larger than 10 mm, [2] any number of serrated polyps proximal to the sigmoid colon in an individual who has a first-degree relative with serrated polyposis, or [3] more than 20 serrated polyps of any size, but distributed throughout the colon ), the situation is more defined, and close surveillance with possible colectomy is considered [11]. However, the criteria for serrated polyposis are at this point still entirely arbitrary, and therefore, it is possible if not probable that the finding of multiple SSA/Ps of any size or location may be adequate to recommend more frequent surveillance. As noted above, the issue with SSA/P may be 2-fold—potential rapid progression to carcinoma and incomplete removal. To prevent interval cancers, therefore, shortened interval surveillance may be appropriate.
Reasonable risk factors suggesting the need for short interval reendoscopy would include size of lesions (lesions smaller than 1 cm may not be as important), location of lesions (right sided lesions may be more important), and age (older patients being more prone to SSA/P as well as to sporadic MSI carcinomas), in addition to number of lesions. A reasonable strategy, and one we are currently recommending, would be to repeat surveillance at 1 year for anyone with 2 or more completely removed SSA/Ps greater than 1 cm and determine future screening based on these findings. If there is any significant risk that a lesion was not completely removed, repeat endoscopy at a shorter interval may well be indicated. If additional SSA/Ps are identified at 1 year, annual surveillance (at least until there is a negative colonoscopy) would seem reasonable. If screening at 1 year is clear of lesions, then extension of the interval to 2 to 3 years would seem appropriate.

6. Proposed solutions to ongoing issues

As noted above, perhaps the more important issues regarding serrated lesions involve appropriate management, although terminology remains an issue as well. The management issue is amenable to further clinicopathological studies focusing on natural history, not only for the more common SSA/P but also for TSA, since we know the least about that lesion. Additional molecular characterization of specific genetic changes resulting in CIMP+MSS carcinomas and for carcinomas arising in TSA will also be valuable in this regard, since this information may help determine the best surveillance and prevention strategies.

Regarding the terminology issues, at the current time, there appears to be a stalemate between the proponents of SSA and those for SSP. Much of this problem exists because of the traditional use of the term adenoma not as a generic family of lesions (ie, polyp with premalignant potential) but rather for a specific subset of adenomas, that is, adenomas predominantly arising along the suppressor pathway initiated with APC mutations. Perhaps it is time for gastrointestinal pathologists to consider reclassification of adenomas on a semimolecular basis, realizing that it is not practical to perform molecular testing on all lesions removed as adenomas. We could, however, alter our terminology to indicate the likely molecular aspects of adenomas, something that would point out the potential molecular difference and would at a minimum have an educational effect if not a direct management effect. It might also be advisable to eliminate the term adenoma from terminology given the long history of using this word only for precursor lesions to non-CIMP carcinomas (ie, APC-related carcinomas arising via the suppressor pathway and MSI carcinomas arising via MMR mutations in Lynch syndrome); however, finding a convenient shorthand substitute will be difficult. Nonetheless, as a starting point, a suggestion for a semimolecular classification is proposed in Table 2.

References