Heterogeneity of colorectal adenomas, the serrated adenoma, and implications for screening and surveillance

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Abstract

Current algorithms for screening and surveillance for colon cancer are valuable, but may be limited by the underlying nature of the targeted neoplastic lesions. Although part of the success of adenoma removal relates to interruption of so-called “adenoma-carcinoma sequence”, an alternate serrated pathway to colon cancer may pose difficulties with the ultimate results achieved by traditional colonoscopic methods. The endpoint carcinoma in this unique pathway may be derived from a dysplastic serrated adenoma. These tend to be located primarily in the right colon, especially in females, and are frequently associated with co-existent colon cancer. Unfortunately, however, there are few, if any, other identifiable risk factors, including age or family history of colon polyps or colon cancer. Moreover, this alternate serrated pathway may itself also be quite biologically heterogeneous as reflected in sessile serrated adenomas (SSA) with virtually exclusive molecular signatures defined by the presence of either BRAF or KRAS mutations. Screening algorithms in the future may need to be modified and individualized, depending on new information that likely will emerge on the natural history of these biologically heterogeneous lesions that differ from traditional adenomatous polyps.

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INTRODUCTION

Clinician endoscopists have witnessed an evolution in the application of the colonoscope. Initially, it was used primarily as an investigative modality to explore patient symptoms (abdominal pain, diarrhea, bleeding). Later, it also became widely applied as a therapeutic tool, particularly for removal of colorectal neoplasms. Now, colonoscopy has increasingly been used to screen for colon polyps and cancer in those with few or no symptoms demanding peace of mind. As a result, various agencies have developed (and promoted) guidelines for use that might aid in this endeavour, largely based on various risk factors, including familial colon polyps and cancers. For some, these are described as “evidence-based” with the goal of being “cost-effective” for an increasingly scarce service resource. These guidelines have also been based, at least in part, on the “Vogelstein” hypothesis that colon cancer results from a multistage and sequential series of mutational events that proceed from a benign adenomatous proliferation of altered epithelial cells to an increasingly larger and more complex invasive neoplastic (and even metastatic) lesion or lesions, the so-called “polyp-cancer sequence”[1]. Reasonably, interruption of this sequence could be accomplished by an intervening polypectomy and reduce the individual's risk for colon cancer. Recent information emphasizing the heterogeneous nature of these precursor colon epithelial polyps has suggested that this perspective may be an oversimplification of a more difficult problem.

TRADITIONAL ADENOMAS AND SCREENING

Although different degrees of altered cytological
differentiation and atypia have often been described for individual polyps, recognition that colon polyp heterogeneity might have some prognostic clinical significance has traditionally been limited to discerning the degree of villous architectural change in the resected polyp (as opposed to tubular change), estimating polyp size (or more precisely, dimension) along with the number of colon polyps (albeit macroscopically visible). Any one (or more) of these has been considered by some to warrant alteration in the general guideline leading to shortened intervals of screening and/or surveillance, particularly if there were multiple polyps of large size that were histologically complex, primarily with villous architecture. Other factors may have also been entered into the equation in the mind of the practicing clinician including a background of chronic inflammatory bowel disease, certain ethnic or racial backgrounds, and, likely, individual financial means to facilitate performance of the actual screening procedure.

ALTERNATE SERRATED PATHWAY

More recently, there has also been increased recognition that the serrated polyp (including the hyperplastic polyp (HP) with its serrated morphological features) may be more than a simple clinically innocuous bystander in the process of cancer development[3].

These polyps appear quite distinct from traditional adenomatous polyps and may also exhibit morphological and molecular heterogeneity. Recent evidence suggests that some subtypes may pose a substantive potential risk for eventual malignant transformation. As such, it appears that this serrated pathway may represent an alternate road to development of colon cancer with potentially important implications for the “guideline approach” to screening and surveillance for colon neoplastic lesions.

Some of the difficulty in this area relates to the pathological terminology along with evolution in methods of classification of serrated lesions that reflects the so-called “saw-tooth” architectural appearance of this polyp group[4]. Moreover, distinction between different forms of serrated polyps and interobserver agreement among expert pathologists may be limited[5]. It appears that HPs are the most common type and these have been further sub-divided into microvesicular, goblet-cell rich and mucin-poor types. Other kinds of serrated polyps include sessile serrated adenomas (SSA), traditional serrated adenomas (TSA) and mixed polyps containing components of sessile serrated and tubular adenomas. Significant differences in the expression of specific genetic and molecular markers have also been shown between SSA and TSA[6]. While HPs seem to remain small and localized to the distal colorectum, other serrated polyps may progress to cancer through an apparently unique pathway. An early recognized form of this entity, initially labeled “hyperplastic polyposis” or “serrated adenomatous polyposis”, consisted of larger sessile polyps developing mainly in the right colon. These were associated with synchronous colon cancer in over 50%[7]. For TSA, dysplasia or intramucosal carcinoma were also noted in almost 50%[8]. Of note, about 10% of all colon polyps may be SSA type and about 15% have multiple lesions, based on detection with magnification chromoendoscopy[9]. Most were located in the right colon, particularly in females, however, there was no correlation with age or personal or family history of colon polyps or colon cancer[10]. Other characteristics of SSA are listed in Tables 1 and 2.

MOLECULAR HETEROGENEITY OF SSA TYPE POLYPS

The molecular heterogeneity of lesions in this alternate serrated pathway has been nicely reviewed elsewhere by O’Brien[11]. The carcinomas that occur demonstrate microsatellite instability (MSI-high) due to hMLH1 inactivation and consequent DNA mismatch repair (MMR). In addition, heterogeneity is evident in that some carcinomas are also microsatellite stable (MSS or MSI-low). The pathway is believed to originate in a HP, or precursor aberrant crypt focus, and progresses through an intermediate disordered type of HP that eventually becomes dysplastic (dysplastic serrated polyp), and ultimately to a serrated adenocarcinoma[12]. Definition of the phenomenon of epigenetic mutagenesis by CpG-island methylation and its key role in sporadic MSI colorectal carcinomas have been stated to be at the molecular genetic core of this newly defined serrated

Table 1 Comparison of SSA and TSA to TA-TVA-VA polyps

| Location     | SSA           | TSA           | TA-TVA-VA |
|--------------|---------------|---------------|-----------|
| Right colon  | Throughout, 60% left | Throughout, 60% left |       |
| Shape        | Flat          | Pedunculated  | Pedunculated |
| Cytodysplasia| Minimal       | Present       | Present   |
| Growth       | Bottom-up     | Bottom-up     | Top-down |
| Serration    | Present       | Present       | Absent   |
| Basal crypt  | Dilation      | Dilation absent| Dilation may |
| Horizontal crypts | Present | Absent | May be present |
| Branched crypts | Present | Absent | May be present |
| Basal serration | Present | Absent | Absent |
| Nuclear shape | Round or oval | Tall columnar | Tall columnar |
| Cytoplasm    | Eosinophilic  | Eosinophilic  | Basophilic |

Table 2 Comparison of SSA polyps and HP polyps

| Location     | SSA           | HP            |
|--------------|---------------|---------------|
| Right colon  | SSA           | Rectosigmoid  |
| Shape        | Flat          | Pedunculated or flat |
| Size         | > 5 mm        | < 5 mm        |
| Cytologic dysplasia | Minimal | Absent |
| Basal crypt dilation | Yes | No |
| Horizontal crypts | Yes | No |
| Branched crypts | Yes | No |
| Basal crypt serration | Yes | No |
| Nuclear shape | Round to oval | Flat or low columnar |
| Cytoplasmic eosinophilia | Prominent | Not prominent |

SSA: Sessile serrated adenoma; TSA: Traditional serrated adenoma; TA: Tubular adenoma; TVA: Tubulovillous adenoma; VA: Villous adenoma. Adapted from Li and Burgart[10].
FUTURE SCREENING FOR COLON POLYPS

The high proportion of SSA is noteworthy as these are not exactly rare and most disconcerting is that routine colonoscopy may not be adequate for their detection[11,12].

Moreover, there does not appear to be a definite profile of high risk for this SSA type that might actually lead to initiation of the screening process, particularly family history[3]. Thus, current screening algorithms may not be adequate for detection. Moreover, hyperplastic/serrated polyposis has also been observed in patients with chronic inflammatory bowel disease[14]. A prudent approach has been suggested to include complete resection and surveillance examinations as often as the intervals defined for the more traditional adenomatous polyps but this approach is not necessarily reflective of the natural biological history of these lesions. A prudent colonoscopist will also emphasize prior to embarking on a screening procedure with the patient that small lesions may not be readily detectable. While still the gold standard for polyp detection, colonoscopic procedures have a definitive “miss rate” so that it can come close to, but does not appear able to reach perfection. Recent comparative and prospective studies using pan-colonic narrow-band imaging suggest that its use for surveillance of even small adenomas may be superior to conventional colonoscopy and equivalent to chromoendoscopy[15-18]. More widespread application of these evolving technologies in the future may also impact on the detection of serrated adenomas and current screening and surveillance guidelines.

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