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Findings in the Distal Colorectum Are Not Associated With Proximal Advanced Serrated Lesions

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BACKGROUND & AIMS: **Serrated lesions are an important contributor to colorectal cancer (CRC), notably in the proximal colon. Findings in the distal colorectum are markers of advanced proximal adenomatous neoplasia. However, it is not known whether they affect the odds of advanced proximal serrated lesions.**

METHODS: **We performed a retrospective cross-sectional study of data from 1910 patients (59.3 ± 8.0 years, 53.8% female) who underwent an average-risk screening colonoscopy from August 2005 through April 2012 at Indiana University Hospital and an associated ambulatory surgery center. Colonoscopies were performed by an endoscopist with high rates of detection of adenomas and serrated polyps. Tissue samples of all serrated polyps (hyperplastic, sessile serrated adenoma/polyp [SSA/P], or traditional serrated adenoma) proximal to the sigmoid colon and serrated polyps >5 mm in the rectum or sigmoid colon were reviewed by a gastrointestinal pathologist and reclassified on the basis of World Health Organization criteria. Advanced serrated lesion (ASL) was defined as SSA/P with cytologic dysplasia, SSA/P ≥10 mm, or traditional serrated adenoma. Advanced conventional adenomatous neoplasia (ACN) was defined as tubular adenoma ≥10 mm, villous histology, high-grade dysplasia, or cancer. The prevalence of proximal ASL and ACN was calculated on the basis of distal colorectal findings. Multivariable logistic regression analysis was performed to determine the age-adjusted and sex-adjusted odds of advanced proximal adenomatous and serrated lesions. Secondary analyses were performed to examine the effect of variable ASL definitions.**

RESULTS: **Fifty-two patients (2.7%) had proximal ASL, and 99 (5.2%) had proximal ACN. Of the 52 patients with proximal ASL, 27 (52%) had no distal polyps. Of the 99 patients with proximal ACN, 40 (40%) had no distal polyps. Age and type of distal adenomas were significantly associated with proximal ACN. There were no significant associations between distal polyp type and proximal ASL. In secondary analyses, distal SSA/Ps ($P = .008$) but not distal hyperplastic polyps or conventional adenomas were associated with any proximal SSA/P.**

CONCLUSIONS: **The findings at flexible sigmoidoscopy that traditionally serve as indications for colonoscopy (conventional adenomas) are likely to be ineffective for detection of proximal ASL. This finding, plus the observation that most patients with proximal ASL have no distal polyps, favors screening colonoscopy over sigmoidoscopy, especially in the elderly. The observation that non-advanced distal SSA/Ps are associated with any proximal SSA/P warrants further study.**

Keywords: Early Detection; Colorectal Neoplasms; Sigmoidoscopy; Colonoscopy.

Abbreviations used in this paper: **ACN, advanced conventional adenomatous neoplasia; ASL, advanced serrated lesion; CRC, colorectal cancer; HP, hyperplastic polyp; SSA/P, sessile serrated polyp; SSA/P-CD, sessile serrated polyps with cytologic dysplasia; TA, tubular adenoma; TSA, traditional serrated adenoma; WHO, World Health Organization.**

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Colorectal cancer (CRC) is preventable and is one of few cancers for which there is considerable evidence that screening is effective and cost-effective.[1,2] Colonoscopy allows the detection and removal of precursor polyps during the same session and is the final common pathway for other screening modalities; these characteristics have contributed to its position as the dominant CRC screening modality in the United States. However, colonoscopy requires considerable human and financial resources,[3,4] and the need to balance these constraints with effectiveness has increased interest in strategies where colonoscopy is used selectively after initial testing with one of the other modalities. Sigmoidoscopy is an attractive option because it is more straightforward to perform, is less burdensome, and is associated with lower risk for harm than colonoscopy. Randomized controlled trials[5–7] and meta-analyses[8,9] have shown that flexible sigmoidoscopy decreases CRC incidence and mortality, supporting its endorsement by major guideline organizations.[1] Sigmoidoscopy effectively decreases distal CRC incidence and mortality; however, its effect on right-sided CRC depends on the colonoscopy referral strategy in place. The 4 large randomized trials of screening sigmoidoscopy[5–7,10] have used different criteria to refer patients to colonoscopy, but all are based on the premise that the risk of advanced neoplasia in the proximal colon can be predicted according to findings in the distal colon, allowing the adjudication of colonoscopy referrals based on the presence and characteristics of polyps found at sigmoidoscopy.[11] In this context, the term *advanced neoplasia* has been used to refer mainly to lesions on the spectrum of the adenoma-carcinoma sequence, including invasive cancer and advanced adenomas (size $\geq$10 mm or presence of high-grade dysplasia or significant villous components on histology). Indeed, the studies that supported this approach[12–15] were performed at a time when it was thought that the great majority of colon cancers arose from precursor conventional adenomas via the chromosomal instability pathway. However, it is now recognized that nearly one-third of CRCs arise through the serrated pathway, which is characterized by mutations in the BRAF gene, high levels of methylation of promoter CpG islands (CIMP-high), and in which the sessile serrated adenoma/polyp (SSA/P) is the principal precursor lesion.[16–18] Serrated lesions can be challenging to visualize because of their subtle morphologic characteristics and are more likely to be overlooked than conventional adenomas.[19,20] These features likely account for the fact that the serrated pathway is a disproportionate contributor to interval CRC (CRC diagnosed relatively soon after colonoscopy). Cancers associated with the serrated pathway tend to occur in the proximal colon, and their molecular signature overlaps significantly with interval CRC.[21–23] The study of serrated lesions has been complicated by evolving definitions and nomenclature, leading to significant interobserver variability in the histologic differentiation of subtypes of serrated polyps, notably between SSA/P and hyperplastic polyps (HPs). The World Health Organization (WHO) has recently updated the classification of serrated colorectal lesions.[18]

Although it is recognized that distal colorectal adenomas are a marker of advanced proximal conventional adenomatous neoplasia, it is not known whether the same applies to important proximal serrated lesions, specifically those higher-risk serrated lesions that warrant more intensive surveillance.[16,24] This issue is of relevance for CRC screening strategies that use sigmoidoscopy as the initial test and refer patients to colonoscopy on the basis of distal findings. Such approaches are based on the assumption that the relevant target proximal colon lesions are predominantly adenoma-based, an assumption that does not take into account serrated lesions and their significant contribution to the pathogenesis of CRC. To help understand whether distal colorectal findings are predictive of advanced serrated lesions in the proximal colon, we analyzed data from a large group of average-risk patients who had undergone screening colonoscopy by an endoscopist with high detection rates of adenomatous and serrated polyps, which was combined with review of histology by an expert pathologist with specific interest in serrated polyps, using the WHO consensus guidelines.

Methods

This was a cross-sectional study conducted at Indiana University Hospital and an associated ambulatory surgery center in Indianapolis, Indiana. The study was approved by the Institutional Review Board of Indiana University Health. We reviewed a prospectively updated electronic database for all patients $\geq$50 years old who underwent an average-risk screening colonoscopy between August 2005 and April 2012 by an endoscopist with documented high adenoma and serrated polyp detection rates (D.K.R.). The colonoscopy database contains information regarding patient demographics and number, location, size, shape, and histopathology of resected polyps. Patients who underwent colonoscopy for any indication other than screening (diagnostic colonoscopy for evaluation of symptoms or occult bleeding, history of inflammatory bowel disease, family history of familial adenomatous polyposis, surveillance colonoscopy after polypectomy or CRC resection) were excluded. The proximal colon was defined as cecum, ascending colon, and transverse colon and the distal colon as splenic flexure, descending colon, sigmoid colon, and rectum. During the interval in which the