High-risk metachronous polyps are more frequent in patients with traditional serrated adenomas than in patients with conventional adenomas: a multicenter prospective study

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Background and Aims: Although the malignant progression of serrated polyps has been clearly documented, the malignant potential of the traditional serrated adenoma (TSA) subtype has not been established. We compared the prevalence of metachronous polyps in surveillance colonoscopies between patients with TSA and those with conventional adenomas (CAs).

Methods: Four hundred twenty patients were diagnosed with TSAs by current diagnostic criteria at 10 tertiary care university hospitals in Korea from January 2003 to December 2005; 186 patients who received surveillance colonoscopy after removal of initial polyps were enrolled. During the same time period, 372 age- and sex-matched patients diagnosed with CAs were used as a control group.

Results: TSA patients had a significantly higher recurrence rate of colorectal polyps compared with CA patients (66.1% vs 43.5%, respectively). TSA patients had a greater number (3 vs 2) and larger size (8.6 ± 5.7 vs 6.3 ± 5.2 mm) of recurrent polyps compared with CA patients. TSA patients also had a higher rate of CA (54.8% vs 37.9%), serrated adenoma (14.0% vs. 0.8%), and hyperplastic polyp (33.3% vs. 13.7%) recurrence compared with CA patients. TSA patients had significantly greater odds of having a recurrent high-risk polyp than CA patients (odds ratio, 2.37; 95% confidence interval, 1.55-3.63).

Conclusions: In comparison with patients with CAs, patients with TSAs have a higher metachronous occurrence rate of all polyp subtypes including CAs, serrated adenomas, and hyperplastic polyps. Moreover, the presence of TSAs is an independent predictor of a high-risk polyp occurrence. (Gastrointest Endosc 2015;82:1087-93.)

Conventional adenomas (CAs) are major precursor lesions of colorectal cancer (CRC). However, the importance of serrated polyps, a heterogeneous group of lesions that include hyperplastic polyps (HPs), sessile serrated adenomas (SSAs), traditional serrated adenomas (TSAs), and mixed hyperplastic adenomatous polyps (MHAPs) with variable malignant potential, has been recognized recently because of their possible contribution to interval cancer. Serrated polyps are epithelial lesions that demonstrate a "saw-toothed" or serrated appearance on histologic

Abbreviations: CA, conventional adenoma; CRC, colorectal cancer; HP, hyperplastic polyp; MHAP, mixed hyperplastic adenomatous polyp; SSA, sessile serrated adenoma; TSA, traditional serrated adenoma.

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sections because of infolding of the crypt epithelium. Subtypes of serrated lesions are generally identified by cytologic and architectural features and by the location and extent of the proliferative zone.[1,2]

In the serrated neoplasia pathway, sessile serrated polyps bearing *BRAF* mutations are precursors of high-frequency microsatellite instability and/or CpG island methylation phenotype–high CRCs.[3] TSAs are precursor lesions of CpG island methylation phenotype–low and microsatellite-stable cancers and are associated with *KRAS* mutations and silencing of the DNA repair gene methylguanine methyltransferase by promoter hypermethylation.[4] Because genetic and epigenetic studies on TSAs have been limited to small case numbers and the relationship of genetics to histology has not been well studied,[5] the role of TSAs in the serrated neoplasia pathway is unclear.[6]

Most studies suggest that serrated adenomas have significant malignant potential and are associated with increased development of metachronous polyps, synchronous advanced conventional neoplasias, and CRC compared with CAs.[7-9] Although the malignant progression of serrated adenomas, especially the relationship between SSAs and interval cancer, has been underlined, the malignant potential of TSAs has not been well established. Some authors indicate that SSAs are more likely to progress to CRC than TSAs.[1] However, only a few small studies have compared the malignant potential between CAs and TSAs, and results have been conflicting.[1,10-12] Current guidelines for serrated polyps recommend a 3-year colonoscopic surveillance interval in TSA cases, but the quality of evidence supporting this recommendation is low.[13,14]

Furthermore, the prevalence, characteristics, classification, and significance of serrated adenomas as a sporadic lesion were not well recognized until 2003, when their histologic features were formally analyzed.[6] Because of interobserver variation in pathologic interpretation, few studies have carefully categorized serrated polyps based on histology and included a sufficient long-term follow-up. Therefore, little is known about the relative risk of malignancy or the relative rate of neoplastic development and progression in TSAs.

The purpose of this study was to compare the risk of metachronous polyp occurrence during surveillance between TSAs and CAs after removal of the initial polyps. We used the prospective patient cohort of our previously published study, in which all polyps were reclassified into TSAs or SSAs by specialized GI pathologists, to reduce interobserver variability in the initial diagnosis.[15]

METHODS

Patients

In an earlier study, we researched clinicopathologic findings from 727 Korean patients with 753 colorectal serrated polyps diagnosed at 14 tertiary hospitals between January 2003 and December 2005.[15] The initial pathologic diagnoses of the 753 polyps were found to be TSAs in 717 cases (95.2%), SSAs in 32 (4.3%), and MHAPs in 4 (.5%). All polyps were re-examined for TSAs, SSAs, MHAPs, and HPs by 6 specialized GI pathologists using revised diagnostic criteria.[6,15,16] Among the 753 polyps, 420 polyps (55.8%) were reclassified into TSAs, 56 polyps (7.4%) into SSAs, 20 (2.7%) into MHAPs, 154 (20.4%) into CAs, and 103 (13.7%) into HPs.

For the current study, we inspected the surveillance colonoscopic report and clinical data of 186 patients who had been diagnosed with TSAs during this re-examination and had received a surveillance colonoscopy at least 6 months after their baseline colonoscopy at 10 tertiary hospitals. In this study, we selected only colonoscopic cases that had cleaning above a fair degree and succeeded in cecal intubation. The timeline for the surveillance colonoscopy was chosen in consideration of lesion size, shape, location, and so on. Many surveillance colonoscopies were performed after approximately 1 to 3 years, based on consensus opinion on surveillance intervals after endoscopic resection of serrated lesions.[17] We collected data from 372 age- and sex-matched patients with CAs from the same tertiary center during that same period to use as a control group. This study was approved by the institutional review boards of all hospitals.

Assessment of clinical outcomes

Clinical outcomes were evaluated according to polyp number, size of the largest polyp, pathologic parameters in adenomatous polyps, and rates of CA and serrated polyp occurrence on the surveillance colonoscopy. Findings on all colonoscopies for 1 patient were combined to score the incidence rate of polyps. We also compared the incidence of high-risk polyps, defined as an adenoma $\geq$ 10 mm in size, with a villous component, high-grade dysplasia or carcinoma, or existence of 3 or more adenomas, between the groups.[17,18] In addition, we compared polyp occurrence rate and risk factors of high-risk polyp development on surveillance colonoscopy between the TSA group and a high-risk CA subgroup (indicated by the presence of high-risk polyps on initial colonoscopy).

Statistical analysis

Continuous variables were presented as median (range) or mean $\pm$ standard deviation and compared using 2-sample *t* tests. Categorical variables were compared using the χ^2 test or the Fisher exact test. Logistic regression analysis was performed to identify predictive variables for high-risk polyp occurrence. $P < .05$ was considered to be statistically significant. Statistical analyses were performed using SPSS 12.0 for Windows (SPSS Inc, Chicago, Ill).