Anatomic Distribution of Sessile Serrated Adenoma/Polyp With and Without Cytologic Dysplasia

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● *Context.*—Sessile serrated adenomas/polyps (SSA/Ps) have been increasingly studied during the last 10 years. However, their detailed anatomic distribution pattern has not been studied, especially given newer (broader) criteria for the diagnosis.

Objectives.—To characterize the anatomic distribution of SSA/P with and without cytologic dysplasia and to assess the demographics of these patients in a nationwide database.

Design.—We retrospectively analyzed the database of Miraca Life Sciences Research Institute for a 1-year period. Patients with a diagnosis of SSA/P, SSA/P with low-grade cytologic dysplasia (SSA/P-LGD), SSA/P with high-grade cytologic dysplasia (SSA/P-HGD), or SSA/P with adeno-carcinoma (SSA/P-ACA) were retrieved, and patients' age, sex, and specific anatomic location were analyzed.

Results.—A total of 11 201 patients were identified, of which 10 646 (95.0%) had SSA/P, 514 (4.6%) had SSA/P-LGD, 39 (0.35%) had SSA/P-HGD, and 2 (0.018%) had SSA/P-ACA. All SSA/Ps and more advanced lesions were significantly more common in the proximal colon—SSA/P (61.2%), SSA/P-LGD (61.2%), SSA/P-HGD (80%), and SSA/P-ACA (100%)—than in either the transverse (18.8%, 17.8%, 10.0%, and 0%, respectively) or the distal (19.9%, 21.0%, 10.0%, and 0%, respectively) colon, P < .001. Sessile serrated adenoma/polyp with cytologic dysplasia was most commonly found in the ascending colon (LGD, 31.6%) and cecum (HGD, 37.5%). Advanced SSA/Ps were disproportionally more common among older women.

Conclusions.—Sessile serrated adenomas/polyps with and without cytologic dysplasia and carcinoma are predominantly found in the cecum and ascending colon, whereas there is low prevalence in both the transverse and distal colon. Confirmation of previously published data regarding demographics of advanced lesions among a different cohort and including newer (broader) criteria suggests these criteria are valid.

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Colorectal cancer (CRC) is the third most common cancer diagnosed in men and women and is the third leading cause of cancer death in the United States.[1–3] About 80% to 85% of CRCs are thought to arise from preexisting adenomas resulting from the Adenoma Polyposis Coli (APC) gene mutation through the chromosome instability pathway.[4,5] The remaining 15% to 20% of CRCs are believed to develop through the microsatellite instability pathway, as exemplified by the 3% to 5% of CRC patients with Lynch Syndrome and the 10% to 12% of CRC patients with epigenetic alteration or epigenetic instability due to CpG island methylator phenotype and hypermethylation, both manifested as microsatellite instability pathway cancers.[5–8] Screening colonoscopy with polyp removal is an effective method to reduce the incidence of and mortality from CRC.[9,10] In the United States, although the age-adjusted incidence of distal colon cancer has steadily decreased from 1976 to 2005, the incidence of right-sided colon cancers remains unchanged,[11] likely at least in part because of underdetected and/or underdiagnosed sessile serrated adenomas/polyp (SSA/P).

At this institution, Lash et al[12] previously reported on a different cohort of patients with SSA/Ps and found that they were more prevalent in women in the right colon (including transverse colon), and that SSA/Ps with cytologic dysplasia and carcinoma occurred disproportionately among older women and over a long period of time, based on median age. The current study is designed to further characterize the specific anatomic distribution of SSA/P with and without cytologic dysplasia. Also, recently updated criteria[8] have resulted in classifying what was previously considered "borderline or indeterminate" serrated polyp as true SSA/P, and the authors also wanted to determine whether this more inclusive group of SSA/P shares the same distribution and demography.

MATERIALS AND METHODS
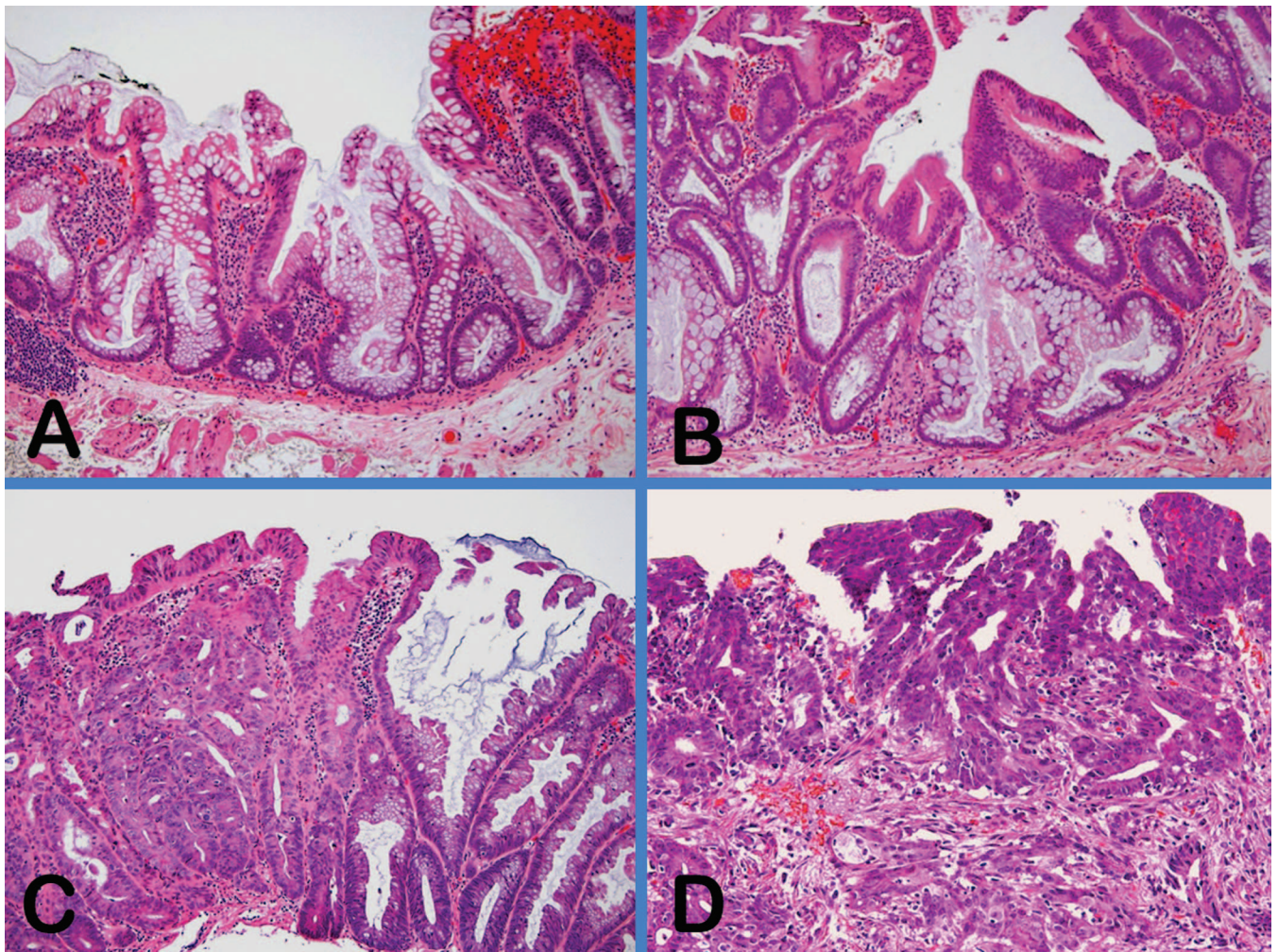
Study Design and Database

This retrospective study was conducted at Miraca Life Sciences Research Institute (Irving, Texas) and was approved by the Miraca Institutional Review Board. Miraca Life Sciences is a national specialized anatomic pathology laboratory that includes a large subspecialty gastrointestinal pathology practice. It receives speci-

Figure 1. A, Sessile serrated adenoma/polyp (SSA/P) showing abnormal dilation with inverted T- or L-shaped crypts. B, SSA/P with low-grade cytologic dysplasia with abnormal dilation, nuclear pseudostratification, and hyperchromasia (upper portion of the specimen). C, SSA/P with high-grade cytologic dysplasia characterized by dysplastic glandular epithelium with increased cytologic pleomorphism and architectural complexity, including cribiforming (left of the specimen). D, SSA/P with adenocarcinoma with angulated dysplastic glands surrounded by desmoplasia (hematoxylin-eosin, original magnification ×10).

mens primarily from community-based ambulatory endoscopy and surgery centers throughout the United States.

The Miraca Life Sciences database was queried for SSA/P with and without cytologic dysplasia and adenocarcinoma from January 1, 2009, to December 31, 2009, including patients' demographics, clinical information, endoscopic findings, specimen sites, and corresponding pathologic findings. Specimen sites of SSA/P with cytologic dysplasia and/or carcinoma were then confirmed manually.

The pathologic criteria for the diagnosis of SSA/Ps were based on Torlakovic and Snover,[13] Torlakovic et al,[14] and Snover et al[15] regarding morphologic reappraisal of serrated colorectal polyps. Cytologic dysplasia was assessed based on previously described criteria[16–18] and was routinely confirmed at the daily departmental consensus conference (examples are demonstrated in Figure 1). The diagnosis of SSA/P with dysplasia or carcinoma required the presence of dysplasia/carcinoma in the same tissue fragment(s) as the SSA/P.

Our SSA/P group included 4541 patients (42.7%) with polyps that were originally classified as "borderline or indeterminate" serrated polyps, a classification based on more conservative criteria existing at that time,[19] typically because of a limited number of basally dilated glands in an otherwise sessile serrated configura-

tion. A recent expert consensus recommendation has defined SSA/P more liberally, requiring only "a single crypt with unequivocal dilatation, distortion, and/or horizontally branched crypt." Based on these newly published criteria, the formerly designated "borderline or indeterminate" serrated polyp would be classified as SSA/P.[8] Traditional serrated adenomas, hyperplastic polyps, and tubular adenomas were not included in this study.

The patients were then subgrouped and analyzed by age, sex, degree of cytologic dysplasia, and anatomic site.

Study Definition of Anatomic Sites of the Colon

In this study, anatomic sites were based on their original specimen requisitions submitted by endoscopists, except when specimens (164 patients; 1.46%) were labeled by the distance from the anal verge. For these, the anatomic site was "translated" into a specific site based on the following: <15 cm (rectum), 15 to 17 cm (recto-sigmoid), 17 to 57 cm (sigmoid), 57 to 82 cm (descending), 82 to 132 cm (transverse), 132 to 147 cm (ascending), and 150 cm (cecum). Those requisitions that failed to provide clearly written specimen site information, those specimens that were labeled as "random," and those specimens without any specific designation were all designated as "not otherwise specified."

Statistical Analysis

All quantitative data were summarized by mean and standard deviation (mean ± SD), and count data were given their corresponding percentage (%). The collected quantitative and count data were then subgrouped and analyzed using Student t test or χ^2 test. A P value less than or equal to .05 was considered to be significant. All statistical analyses were performed using SigmaStat 3.5 software (San Jose, California).

RESULTS

Patients' Demography

A total of 11 201 patients (6.3%) with 13 072 SSA/P specimens were identified among 178 963 patients (49.6% women; mean age 59.3 ± 13.3 years, ranging from 3 months to 106 years) who received colonoscopy, with a total of 180 948 colonoscopy specimens dating from this period of time in our database. Among them, 10 646 patients (95.0%) had SSA/P, 514 patients (4.6%) had SSA/P with low-grade cytologic dysplasia (SSA/P-LGD), 39 patients (0.35%) had SSA/P with high-grade cytologic dysplasia (SSA/P-HGD), and 2 patients (0.018%) had SSA/P with adenocarcinoma (SSA/P-ACA).

There were more women than men in all studied groups: 4965 men (46.6%) versus 5681 women (53.4%) had SSA/P; 209 men (40.7%) versus 305 women (59.3%) had SSA/P-LGD; 11 men (28.2%) versus 28 women (71.8%) had SSA/P-HGD, and the 2 patients with SSA/P-ACA were both women (100%). The mean age differences of SSA/P with and without cytologic dysplasia were significant in SSA/P (60.8 ± 11.2 years), SSA/P-LGD (65.6 ± 11.1 years), and SSA/P-HGD (69.9 ± 9.3 years; Table 1). The mean age differences of patients with SSA/P versus LGD and LGD versus HGD were 4.8 and 4.3 years, respectively (total, 9.1 years). Further, the percentage of women among each advancing lesion was significantly and increasingly higher than men.

Distribution in the Colon

Sessile serrated adenoma/polyps with and without cytologic dysplasia or carcinoma occurred throughout the entire colon but were concentrated in certain areas (graphically demonstrated in Figure 2; Table 2). Sessile serrated adenoma/polyp was significantly more prevalent in the proximal colon than the transverse and distal colon (Figure 3): 61.2% versus 18.8% in the transverse colon ($P < .001$) and 19.9% in the distal colon ($P < .001$). There was no statistical difference in the prevalence of SSA/P in the transverse versus distal colon ($P = .08$).

The distribution of SSA/P-LGD in the colon was similar to SSA/P: 61.2% SSA/P-LGD in the proximal colon versus 17.8% in the transverse colon ($P < .001$) and 21.0% in the distal colon ($P < .001$). There was no significant difference between the prevalence of SSA/P-LGD in the transverse and distal colon ($P = .31$). Among them, there were 18 patients (18 of 514; 3.5%; men, n = 6; women, n = 12; average age, 65.7 years) with ≥2 SSA/P-LGDs (one patient had 4 SSA/P-LGDs and the remaining had 2 SSA/P-LGDs), which showed as having a similar distribution: cecum (4; 10.5%), ascending (10; 26.3%), hepatic-flexure (6; 15.8%), transverse (10; 26.3%), splenic-flexure (1; 2.6%), descending

Figure 2. *Mapping of sessile serrated adenoma/polyp (SSA/P), SSA/P with low-grade cytologic dysplasia (SSA/P-LGD), and SSA/P with high-grade cytologic dysplasia (SSA/P-HGD). All occurred throughout the colon but are more concentrated in the proximal colon. Abbreviation: F, flexure.*

Table 2. Anatomic Location of Sessile Serrated Adenoma/Polyp (SSA/P) and More Advanced Lesions in the Colon
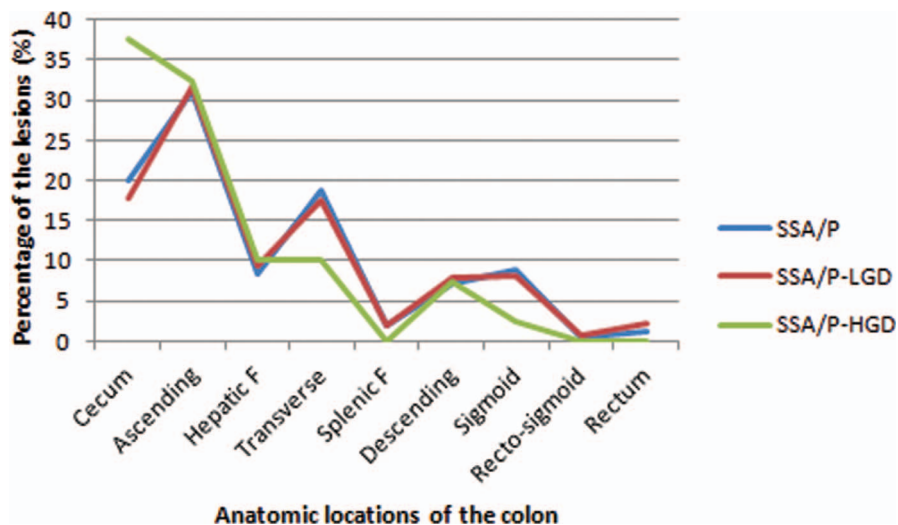
Locations	SSA/P, No. (%)	SSA/P-LGD, No. (%)	SSA/P-HGD, No. (%)	SSA/P-ACA, No. (%)	Total, No. (%)
Cecum	2509 (20.1)	95 (17.8)	15 (37.5)	1 (50.0)	**2620** (20)
Ascending	3895 (31.2)	169 (31.6)	13 (32.5)	1 (50.0)	**4078** (31.2)
Hepatic flexure	1045 (8.4)	50 (9.4)	4 (10.0)	0	**1099** (8.4)
Transverse	2333 (18.7)	94 (17.6)	4 (10.0)	0	**2431** (18.6)
Splenic flexure	243 (1.9)	10 (1.9)	0	0	**253** (1.9)
Descending	882 (7.1)	42 (7.9)	3 (7.5)	0	**927** (7.1)
Sigmoid	1107 (8.9)	43 (8.1)	1 (2.5)	0	**1151** (8.8)
Rectosigmoid	57 (0.46)	4 (0.7)	0	0	**61** (0.5)
Rectum	157 (1.3)	12 (2.2)	0	0	**169** (1.3)
Labeled "right"	135 (1.1)	9 (1.7)	0	0	**144** (1.1)
Labeled "left"	22 (0.2)	0	0	0	**22** (0.2)
NOS/random	111 (0.9)	6 (1.1)	0	0	**117** (0.9)
Total	**12 496**	**534**	**40**	**2**	**13 072**
Proximal colon[a]	7584 (61.2)	323 (61.2)	32 (80)	2 (100)	**7941** (61.3)
Transverse	2333 (18.8)	94 (17.8)	4 (10.0)	0 (0)	**2431** (18.8)
Distal colon[b]	2468 (19.9)	111 (21.0)	4 (10.0)	0 (0)	**2583** (20.0)
Total[c]	**12 385**	**528**	**40**	**2**	**12 955**

Abbreviations: NOS, not otherwise specified; SSA/P, sessile serrated adenoma/polyp; SSA/P-ACA, SSA/P with adenocarcinoma; SSA/P-HGD, SSA/P with high-grade cytologic dysplasia; SSA/P-LGD, SSA/P with low-grade cytologic dysplasia.

[a] Proximal colon includes: cecum, ascending, hepatic flexure and labeled "right" colon biopsies.
[b] Distal colon includes: splenic flexure, descending, sigmoid, recto-sigmoid, rectum and labeled "left" colon biopsies.
[c] Numbers of SSA/P and more advanced lesions labeled as "NOS/Random" were not included in the classification of proximal, transverse, and distal colon.

(2; 5.3%), sigmoid (4; 10.5%), rectosigmoid (0; 0%), and rectum (1; 2.6%).

Sessile serrated adenoma/polyp–HGD and SSA/P-ACA also had distribution patterns similar to their less advanced counterparts: 80% of SSA/P-HGDs and 2 SSA/P-ACAs were both in the cecum/ascending colon ($P < .001$), whereas 10.0% of SSA/P-HGDs were evenly distributed in the transverse and the distal colon (Figure 3). As with SSA/P, the prevalence of SSA/P with cytologic dysplasia and carcinoma showed a similarly low prevalence in the transverse and distal colon relative to the proximal colon ($P < .001$).

The most likely specific site to harbor an SSA/P-HGD was the cecum (15 of 40; 37.5%), and the highest prevalence of SSA/P-LGD was in the ascending colon (169 of 534; 31.6%), shown in Table 2. One SSA/P-ACA was found in the cecum, and the other was located in the ascending colon.

COMMENT

It is now understood that serrated polyps have molecular and clinical attributes that differ from nonserrated adenomas.[6–8,20] The serrated polyp family members include the microvesicular hyperplastic polyp, goblet cell–rich hyperplastic polyp, traditional serrated adenoma, filiform serrated adenoma, and SSA/P. The prevalence of SSA/P ranges from 0.6% to 9% of all colonic polyps,[12,21–24] and reported risk factors for SSA/P include older age, female sex, smoking, diabetes mellitus, and obesity.[12,25,26]

The importance of the "serrated" pathway with SSA/P and more advanced lesions is now recognized. Patients with SSA/Ps are more likely to have a greater polyp burden, have other synchronous and metachronous neoplasms, and are believed to represent the precursor to about 15% to 30% of sporadic CRCs.[6,20] Therefore, it is recommended from a recent expert consensus review that all proximal serrated
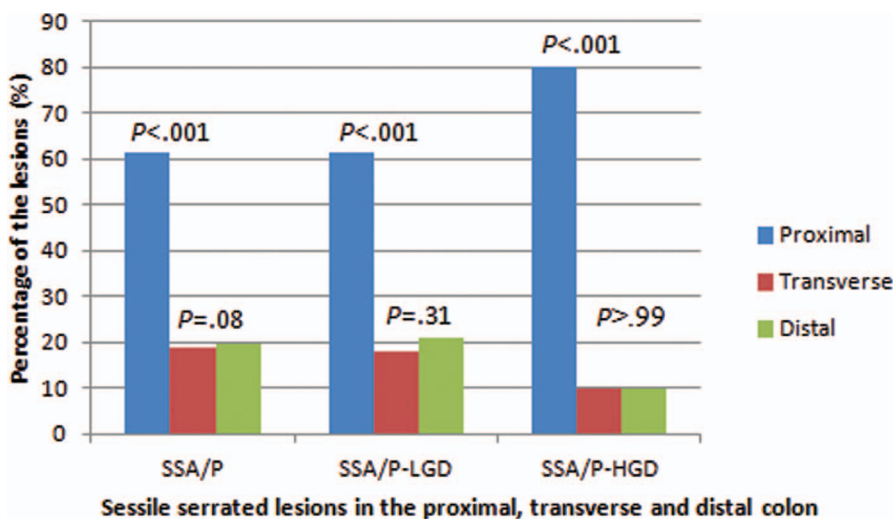
Figure 3. Distribution of sessile serrated adenoma/polyp (SSA/P) and more advanced lesions in the colon. The graph highlights the concentration in the proximal colon (P < .001). Compared with the proximal colon, both transverse and distal colon show a similarly low prevalence of SSA/P with and without cytologic dysplasia. Abbreviations: SSA/P-HGD, SSA/P with high-grade cytologic dysplasia; SSA/P-LGD, SSA/P with low-grade cytologic dysplasia.
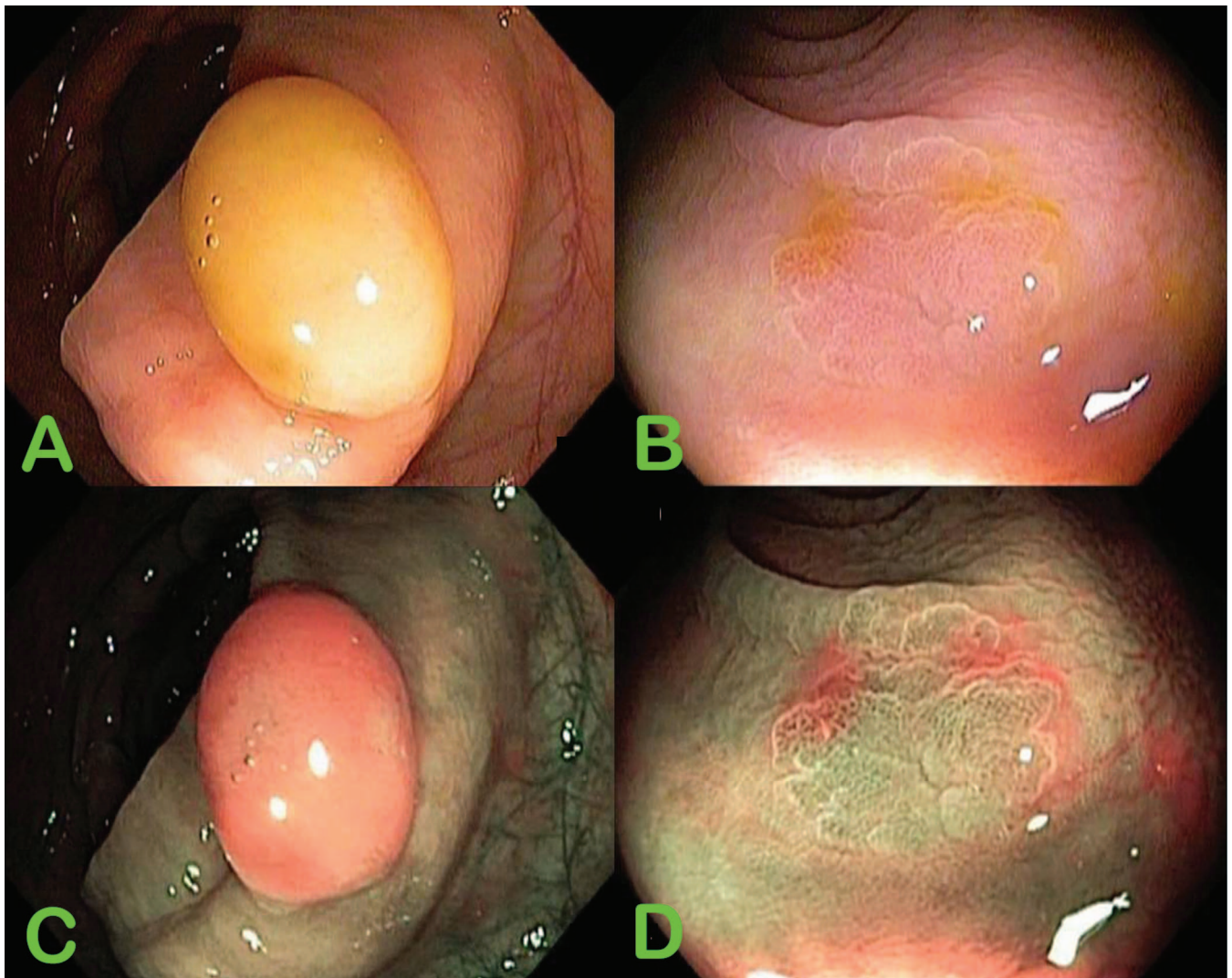
Figure 4. *Endoscopic images of 2 sessile serrated adenomas/polyps (SSA/Ps) under white light (A and B) and narrow banding imaging (C and D): a mucus-covered polypoid SSA/P in the ascending colon (A and C) and another flat SSA/P in the cecum (B and D).*

polyps, proximal polyps >10 mm diagnosed as hyperplastic polyp, serrated lesions proximal to the sigmoid colon, and serrated lesions in the rectosigmoid colon >5 mm be completely removed when possible.[8,27,28]

This study specifically maps the anatomic location of SSA/P with and without cytologic dysplasia or carcinoma (beyond the broad categories "right" and "left" colon), including previously considered "borderline or indeterminate" serrated polyp. We found that right-sided SSA/P and more advanced lesions were concentrated in the cecum and ascending colon, with the distribution in the transverse colon matching the low rate in the distal colon. As mentioned, this study included a large group of previously designated "borderline or indeterminate" serrated polyps that, according to updated criteria, should be considered true SSA/Ps. This cohort, using newer, more inclusive criteria for SSA/P, featured the same demographic and anatomic distribution described previously.[12] This study also confirmed, on a 5-fold larger cohort, the key elements of the previous findings from this institution regarding a separate group of SSA/Ps,[12] specifically an approximately 5-year

difference between the mean ages for each progressive stage from SSA/P to SSA/P-HGD, as well as the female and right-sided predominance. Such confirmation of a different cohort of patients not only confirms the prior data but also indicates that the newer criteria for SSA/P (inclusive of the formerly designated "borderline or indeterminate" serrated polyp) appear to be valid.[8]

In this study, our data also show that 18 patients (3.5%) had multiple synchronous SSA/P-LGD. This subgroup with multiple lesions showed a similar female predominance (67%) and mean age (65.7 years) as that of the general SSA/P-LGD group. Although this group of patients might meet the criteria of serrated polyposis syndrome,[6,29–31] we do not have sufficient clinical data to determine the prevalence of serrated polyposis syndrome in our cohort.

After excluding patients who had previously been designated as having "borderline or indeterminate" serrated polyp, the prevalence of SSA/P with LGD, HGD, and CRC in our cohort (7.7%, 0.59%, and 0.03%, respectively) was still lower than the reported rates in the prior study from this institution (12%, 2%, and 1%).[12] We believe that the

differences of prevalence of SSA/P with cytologic dysplasia and carcinoma between the 2007 study and this study are due to not only more inclusive pathologic criteria but also increased recognition of more subtle (and therefore likely nondysplastic) SSA/Ps by endoscopists. The endoscopic appearance of SSA/P is shown in Figure 4.

It is worth mentioning that the low rate of diagnosis of invasive CRC arising in the background of SSA/P in this study is most likely due to the fact that biopsy specimens are limited in quantity and often do not demonstrate both carcinoma and the preexisting SSA/P.

In conclusion, SSA/P with and without cytologic dysplasia or carcinoma occurs most commonly in the cecum and ascending colon, and occurs similarly less frequently in the transverse and distal colon. Highly advanced SSA/Ps (SSA/P-HGD and SSA/P-ACA) are also most commonly found in the cecum and ascending colon. The inclusion of recently published, more inclusive criteria of patients with SSA/P does not appear to alter the age and sex relationships previously reported. Further, based on mean ages, neoplastic progression from SSA/P to SSA/P-LGD and then to SSA/P-HGD appears to take about 5 years for each step. Advanced lesions occur increasingly and disproportionately among older women. The increased number of patients with the diagnosis of SSA/P is likely due to increased awareness by both endoscopists and pathologists. Endoscopic screening and detection of SSA/P and more advanced lesions need to be focused on high-risk groups (older women) and high-risk locations (cecum and ascending colon).

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