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Volumetric growth rates of sessile serrated adenomas/polyps observed in situ at longitudinal CT colonography

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Abstract

Objective Sessile serrated adenomas/polyps (SSA/Ps) are now recognized as potential cancer precursors, but little is known about their natural history. We assessed the in vivo growth rates of histologically proven SSA/Ps at longitudinal CT colonography (CTC) and compared results with non-advanced tubular adenomas (TAs).

Methods We identified a cohort of 53 patients (mean age, 54.8 ± 5.5 years; M:F, 26:27) from one center with a total of 58 SSA/Ps followed longitudinally at CTC (mean follow-up interval, 5.3 ± 1.9 years). Initial and final size measurements were determined using dedicated CTC software. Findings were compared with 141 non-advanced TAs followed at CTC (mean, 4.1 ± 2.3 years) in 113 patients (mean age, 56.8 ± 6.9 years).

Results SSA/Ps were more often flat (62% [36/58] vs. 14% [20/141], $p < 0.0001$) and right-sided (98% [57/58] vs. 46% [65/141], $p < 0.0001$) compared with TAs. Initial average diameter was greater for SSA/Ps (9.3 mm vs. 6.3 mm; $p < 0.0001$). Mean annual volumetric growth was + 12.7%/year for SSA/Ps vs. + 36.4%/year for TAs ($p = 0.028$). Using a previously defined threshold of + 20% increase in volume/year to define progression, 22% (13/58) of SSA/Ps and 41% (58/141) of TAs progressed ($p = 0.014$). None of the SSA/Ps had dysplasia or invasive cancer at histopathology.

Conclusions Sessile serrated adenoma/polyps demonstrate slower growth compared with conventional non-advanced tubular adenomas, despite larger initial linear size. This less aggressive behavior may help explain the more advanced patient age for serrated pathway cancers. Furthermore, these findings could help inform future colonoscopic surveillance strategies, as current guidelines are largely restricted to expert opinion related to the absence of natural history data.

Key Points
• *Sessile serrated adenoma/polyps (SSA/Ps) tend to be flat, right-sided, and demonstrate slower growth compared with conventional non-advanced tubular adenomas.*
• *This less aggressive behavior of SSA/Ps may help explain the more advanced patient age for serrated pathway cancers.*

Keywords CT colonography · Virtual colonoscopy · Polyps · Natural history

Abbreviations
CTC   CT colonography
HGD   High-grade dysplasia
OC   Optical colonoscopy
SSA/P Sessile serrated adenoma/polyp
TA   Tubular adenoma
TSA   Traditional serrated adenomas

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Introduction

In the past, nearly all serrated colorectal lesions were considered to be hyperplastic polyps with no malignant potential. However, serrated lesions are now subdivided into three categories: hyperplastic polyps, traditional serrated adenomas (TSAs), and sessile serrated adenomas/polyps (SSA/Ps). Although alternative terminology has been used, based on the 2010 WHO Classification of Tumors of the Digestive

System, this third category is given the designation of sessile serrated adenoma/polyp [1–3]. Of greatest clinical relevance, SSA/Ps are now widely considered to have malignant potential and may even account for 15–30% of sporadic colon cancers [1, 2, 4]. Sessile serrated lesions provide an alternative pathway to cancer that is characterized by mutations in *BRAF* and epigenetic methylation that silences *MLH1* and inactivates mismatch repair activity, leading to cancers with microsatellite instability [1, 2, 5].

Beyond single case reports of individual dysplastic serrated lesions left in situ [6, 7], very little is known of the actual natural history or malignant potential of SSA/Ps. Although some have suggested that these sessile serrated lesions more rapidly progress to cancer [8–11], the preponderance of indirect data seem to favor a more indolent course. Serrated pathway cancers tend to present at a more advanced patient age, and the high-grade dysplasia and invasive cancer rates for large SSA/Ps are considerably lower compared with conventional colorectal neoplasms of a similar diameter [4, 12, 13]. However, because these right-sided serrated polyps have been under-recognized and were frequently missed until recently, they are nonetheless presumed to represent a disproportionate percentage of missed or "interval" cancers, possibly related to late phase acceleration in a minority of cases [14, 15].

Even large right-sided SSA/Ps are typically subtle at endoscopy, given their flat, pale, and inconspicuous appearance [1, 2]. However, one feature that can augment detection is the tenacious mucus cap overlying most of these serrated polyps [16]. This key feature can also be leveraged at CT colonography (CTC), where the use of a dual-tagging regimen consisting of oral barium and iodinated contrast results in surface coating of this mucus cap in the majority of cases [17]. The CTC program at our academic center provides for a unique clinical opportunity to investigate changes in polyps over time at serial examinations.

The purpose of this study was to determine the growth rates of histologically proven sessile serrated adenomas/polyps (SSA/Ps) followed in vivo at CTC prior to endoscopic resection and compare these results with non-advanced tubular adenomas (TAs).

Methods

Patient cohorts and CTC protocol

This HIPAA-compliant study was approved by the Institutional Review Board at the University of Wisconsin. Although some of the earlier patients provided signed informed consent for CTC polyp surveillance, signed consent was no longer obtained once this approach became an accepted clinical practice at our institution. For these latter cases, the need for signed informed consent was waived for retrospective review. In addition, some lesions were first discovered at routine CTC screening surveillance, with retrospective identification on the initial screening CTC. The need for consent was also waived for these patients.

Asymptomatic patients undergoing CTC screening at our center between 2004 and 2017 were eligible for potential inclusion in this study if a CTC-detected polyp subsequently removed at colonoscopy was identifiable on at least two separate CTC examinations performed over time. The primary study cohort included patients with histologically proven SSA/Ps (Figs. 1 and 2). From over 300 patients with proven SSA/Ps detected at CTC and subsequently removed at colonoscopy, a subset of 53 patients had more than one CTC study over time where the lesions were evident. Cases were excluded if the lesion was only visible on the final CTC before polypectomy, or if the patient underwent only a single CTC screening study. A consecutive comparison cohort over the same interval that consisted of all available cases of histologically proven non-advanced tubular adenomas (TAs) measuring 6–9 mm at the time of initial CTC was included. Adenomas with villous histology or high-grade dysplasia (HGD) were excluded, as these histologically advanced polyps demonstrate more aggressive growth [18]. The inclusion/exclusion criteria were otherwise the same for this control group.

The CTC technique employed for bowel preparation, colonic distention, and CT scanning at our center has changed very little over time and was previously published [19–22]. In particular, all patients receive a cathartic bowel preparation with dual oral contrast tagging, consisting of dilute 2% barium and water-soluble iodinated contrast. All CTC studies were prospectively interpreted by experienced abdominal radiologists using dedicated software (V3D Colon, Viatronix). A combined 2D-3D polyp search in at least two different patient positions was performed in all CTC cases. These technical features of cathartic preparation, dual oral contrast tagging, and combined 2D-3D review are of particular relevance for the detection of flat colorectal lesions [17, 23–25]. Polyps removed at optical colonoscopy were sent for histopathological review.

Polyp assessment

Polyp measurement analysis was performed independently by two co-authors (PJP and BDP) on separate cases, each with extensive experience interpreting CTC (> 1000 cases each), as well as with performing linear and volumetric polyp measurements. Maximal linear size was obtained using a validated approach that combines 2D and 3D assessment with electronic calipers [26]. Polyp volume was derived using a validated tool (V3D Colon, Viatronix) that automatically segments the lesion but allows the user to appropriately adjust the included volume on each individual 2D slice (Fig. 2) [27]. Direct lesion matching between the initial and follow-up CTC studies was reconfirmed to ensure the same polyp was being assessed.
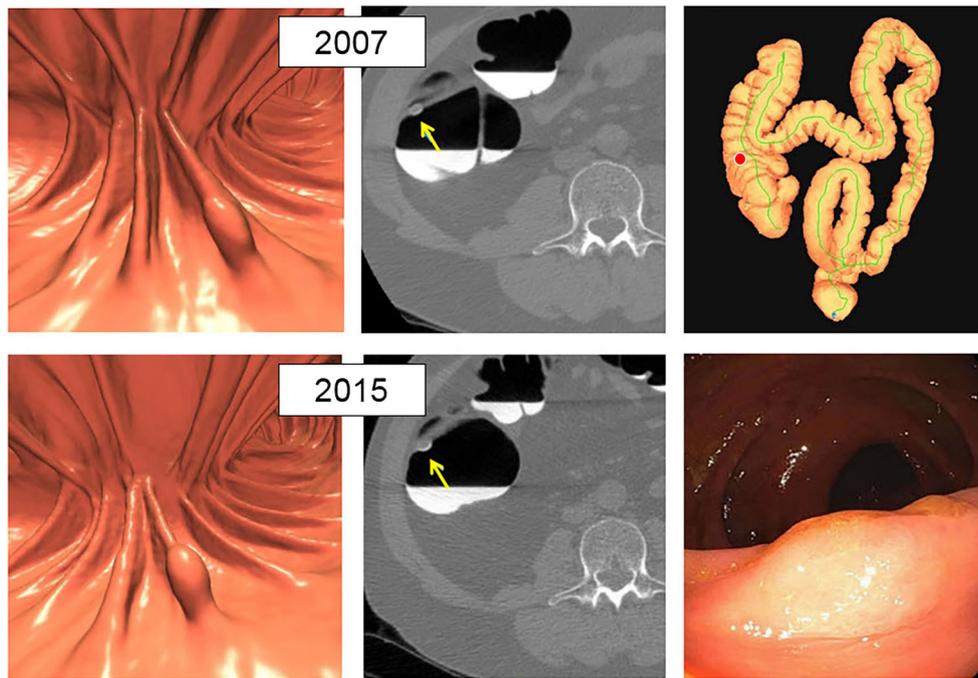
Fig. 1 Slow growth of flat right-sided sessile serrated adenoma/polyp over 8 years in asymptomatic man who was 52 years old at the time of initial CTC screening. Top row from 2007 shows 3D endoluminal (left), 2D axial (middle), and 3D colon map (right) images from screening CTC. Flat lesion on a fold demonstrates only minimal surface tagging of oral contrast on 2D (yellow arrow). Red dot on the colon map shows polyp location in ascending colon. This lesion was not identified prospectively on this initial study. Follow-up CTC 8 years later (bottom row) shows the same lesion, now with more obvious surface tagging (yellow arrow). The lesion is more conspicuous on 3D due to the thicker contrast coat, but had only grown slightly over this time interval, with a linear increase of 0.9 mm (from 8.8 to 9.7 mm) and a 6.8% annual increase in volume. The lesion was confirmed and resected at same-day colonoscopy (right). Pathology proved to be sessile serrated adenoma/polyp without cytologic dysplasia

Fig. 2 Volume measurement of sessile serrated adenoma/polyp at CTC in asymptomatic woman who was 53 years old at initial screening. 2D images (top row) for follow-up CTC 5 years after the initial screening show a sessile polyp in the ascending colon (blue arrow). The image on the right shows the semi-automated segmentation of the polyp (in red) for volume assessment. The 3D endoluminal image on the lower left shows the same segmented lesion. The lower right image shows the same lesion at initial CTC screening 5 years earlier. The lesion had slowly enlarged from 8.8 to 10.3 mm, with an annual volume increase of 12.8%
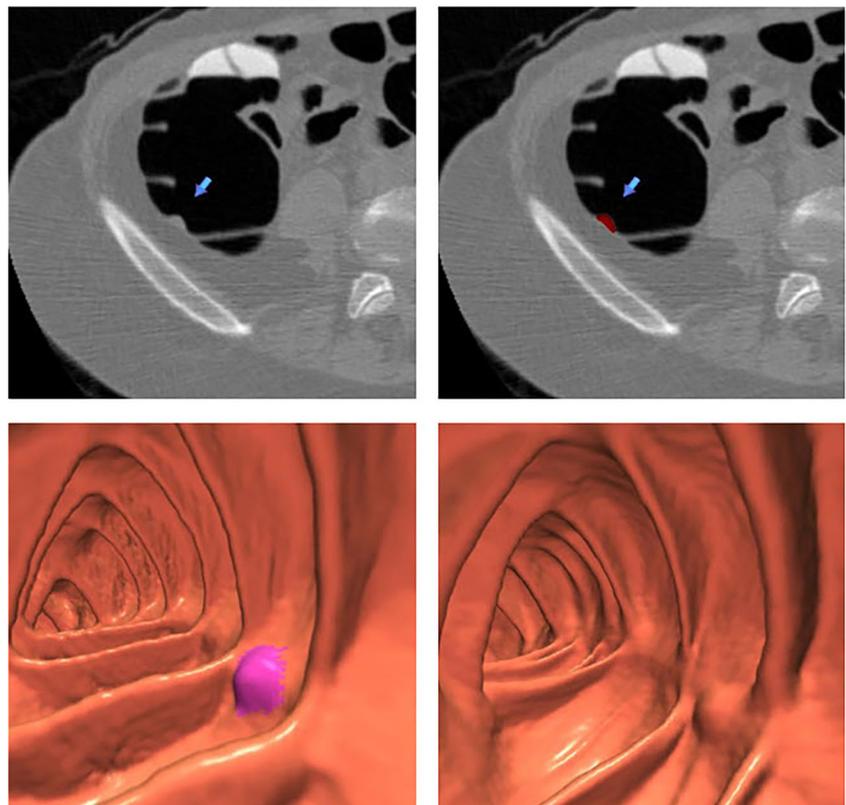
Great care was taken to obtain the final CTC-based size measures on optimal and comparable series between the two studies. In our experience, the 3D endoluminal view provides the best visual assessment for interval change, supplemented by the 2D views, which is then confirmed best by volumetric comparison. Not infrequently, changes in linear size may poorly reflect the actual changes in these 3D lesions, whereas volumetric assessment tends to capture these changes.

We have previously studied observer agreement for both polyp linear size and volume measurements [27, 28] and have demonstrated the advantage of using polyp volume over linear size to discern interval change [27]. Furthermore, we have previously utilized these validated measurement techniques for investigating polyp growth rates [18]. The current investigation focuses on polyp behavior (of serrated lesions) and not on measurement technique or inter-observer differences. For pedunculated polyps, the stalk was excluded from the measurement. Any contrast cap was also excluded from the measurements. Lesion morphology (sessile, flat, or pedunculated) and colonic segmental location at CTC were recorded for each polyp. Flat lesions were differentiated from sessile lesions by their plaque-like morphology and were typically raised ≤ 3 mm from the mucosa [29]. Pedunculated lesions were characterized by a stalk. Histologic specimens from all available sessile serrated tissue were retrospectively reviewed by an experienced GI pathologist (KAM), who confirmed the histologic diagnosis and specifically assessed for the presence of cytologic dysplasia (low-grade and high-grade) and invasive cancer. Polyps classified as SSA/P contained at least two consecutive crypts demonstrating basal crypt dilation with lateral spread of the crypt bases, along with saw-tooth serrations of the surface epithelium.

Statistical analysis

Initial and final polyp diameters and volumes, in conjunction with the time interval between CTC scans, were used to derive annualized growth rates. As previously defined, thresholds of ± 1.0 mm per year in diameter and $\pm 20\%$ change per year in polyp volume were primarily used to categorize lesions as growing, stable, or regressing [18]. Other varying threshold definitions for linear and volumetric change were considered in a sensitivity analysis.

Data were collated and analyzed in Microsoft Excel 2016 (Microsoft). The SSA/P and TA cohorts were compared according to lesion size, morphology, location, and growth rates. In addition, the subset of TAs located in the right colon (cecum, ascending, and transverse colon) were separately compared to the SSA/P cohort. Fischer's exact test was used to assess for the differences in categorical variables while Student's t test was used to assess for the differences in continuous variables. A value of $p < 0.05$ was used for statistical significance.

Results

The final SSA/P cohort consisted of 58 lesions in 53 patients (mean age at initial CTC, 54.8 ± 5.5 years; M:F, 26:27). The mean ($\pm$ SD) follow-up interval between the initial and final CTC was 5.3 ± 1.9 years (range, 1.0–9.8 years). The available TA control group consisted of 141 polyps without advanced histology in 113 patients (mean age at initial CTC, 56.8 ± 6.9 years; M:F, 69:44), with a mean follow-up interval of 4.1 ± 2.3 years (range, 0.7–10.7). Table 1 shows the morphology and segmental location of the SSA/P and TA lesions under surveillance. As expected, sessile serrated polyps were much more likely to be flat (non-polypoid) in morphology than TAs (62% [36/58] vs. 14% [20/141], $p < 0.0001$) and were more likely to be located in the right colon (98% [57/58] vs. 46% [65/141], $p < 0.0001$).

Table 2 provides detailed information on polyp size and growth rates for both the SSA/P and TA cohorts. Case examples of SSA/Ps are shown in Figs. 1 and 2. Although the initial mean diameter of the serrated lesions was significantly greater than the TAs (9.3 mm vs. 6.3 mm, $p < 0.0001$), the initial mean volumes were similar (66 mm^3 vs. 63 mm^3, $p = 0.668$), reflecting the flat (non-polypoid) morphology of the former. The average change in diameter for SSA/Ps was 1.5 mm, corresponding to 0.3 mm/year of growth, which was the same for TAs (0.3 mm/year, $p = 0.922$). However, the mean volume change for SSA/Ps was significantly less at only 2.4 mm^3/year, compared with 10.9 mm^3/year for TAs ($p = 0.046$), again reflecting the flat/non-polypoid nature of the SSA/P cohort (Fig. 3).

Mean ($\pm$ SD) linear percentage change per year for SSA/Ps was less than for TAs ($+ 3.8 \pm 6.5\%$/year vs. $+ 6.3 \pm 15.8\%$/year), but the difference was not statistically significant ($p = 0.246$). The difference in the mean volume change per year, however, was statistically significant ($+ 12.7 \pm 23.1\%$/year vs. $+ 36.4 \pm 80.0\%$/year; $p = 0.028$). Using the defined threshold of ± 1.0-

Table 1 Segmental location and polyp morphology of SSA/Ps and TAs

	SSA/P ($n = 58$)	TA ($n = 141$)
Segmental location		
Cecum	12 (20.7%)	6 (4.3%)
Ascending	38 (65.5%)	29 (20.6%)
Transverse	7 (12.1%)	30 (21.3%)
Descending	1 (1.7%)	9 (6.4%)
Sigmoid	0	43 (30.5%)
Rectum	0	24 (17.0%)
Right-sided	57 (98.3%)	65 (46.1%)
Polyp morphology		
Flat (non-polypoid)	36 (62.1%)	20 (14.2%)
Sessile	21 (36.2%)	109 (77.3%)
Pedunculated	1 (1.7%)	12 (8.5%)

Table 2 Polyp sizes and growth rates for the SSA/P and TA cohorts

	SSA/P ($n = 58$)	TA ($n = 141$)	p value
Polyp diameter			
Initial CTC (mean ± SD)	9.3 ± 3.6 mm	6.3 ± 1.7 mm	$p < 0.0001$
Final CTC (mean ± SD)	10.9 ± 3.8 mm	7.6 ± 2.3	$p < 0.0001$
	$p = 0.0217$	$p < 0.0001$	
Polyp volume			
Initial CTC (mean ± SD)	66.1 ± 48.7 mm^3	62.6 ± 53.5 mm^3	$p = 0.668$
Final CTC (mean ± SD)	86.6 ± 53.5 mm^3	107.2 ± 124.8 mm^3	$p = 0.227$
	$p = 0.0330$	$p < 0.0001$	
Follow-up interval			
mean ± SD	5.3 ± 1.9 years	4.1 ± 2.3 years	$p = 0.001$
Change in diameter			
Δ/year (mean ± SD)	0.3 ± 0.4 mm/year	0.3 ± 0.7 mm/year	$p = 0.922$
Δ%/year (mean ± SD)	3.8 ± 6.5%/year	6.3 ± 15.8%/year	$p = 0.246$
Change in volume			
Δ/year (mean ± SD)	2.4 ± 10.3 mm^3/year	10.9 ± 31.5 mm^3/year	$p = 0.046$
Δ%/year (mean ± SD)	12.7 ± 23.1%/year	36.4 ± 80.0%/year	$p = 0.028$

mm change in diameter per year, polyp progression, stability, and regression were seen in 2 (3.4%), 56 (96.6%), and 0 (0%) of 58 SSA/Ps and in 16 (11.3%), 116 (82.3%), and 9 (6.4%) of 141 non-advanced TAs. Similarly, using ± 20% change in volume per year, progression, stability, and regression were seen in 13 (22.4%), 43 (74.1%), and 2 (3.4%) of 58 SSA/Ps, respectively, and in 57 (40.4%), 73 (51.8%), and 11 (7.8%) of 141 non-advanced TAs, respectively. Of note, using these annualized volumetric change criteria, a significantly lower percentage of SSA/Ps were noted to progress (22.4%) compared with that of TAs (40.4%, $p = 0.022$). Using an alternative threshold of ± 0.5-mm change in diameter per year, progression, stability, and regression

were seen in 14 (24.1%), 43 (74.1%), and 1 (1.7%) SSA/Ps and in 43 (30.5%), 82 (58.2%), and 16 (11.3%) non-advanced TAs. Using an alternative volume threshold of ± 10% change per year, progression, stability, and regression were seen in 27 (46.6%), 26 (44.8%), and 5 (8.6%) SSA/Ps, respectively, and in 79 (56.0%), 46 (32.6%), and 16 (11.3%) non-advanced TAs, respectively.

Due to the propensity for SSA/Ps to be located in the right colon (cecum, ascending, transverse), an additional sub-analysis comparing SSA/Ps with only right colon TAs ($n = 65$) was performed and yielded similar results. SSA/Ps were again more likely to be flat (62% [36/58] vs. 18% [12/65], $p < 0.0001$) with greater initial diameter (9.3 mm vs. 6.5 mm, $p < 0.0001$) but with similar initial volume (66 mm^3 vs. 60 mm^3, $p = 0.501$). Patterns of change were also similar, with no significant difference in linear growth (+ 3.8 ± 6.5%/year vs. + 5.8 ± 16.8%/year, $p = 0.396$), but with significantly greater volume change for TAs (+ 12.7 ± 23.1%/year vs. + 37.5 ± 85.6%/year, $p = 0.035$).

At histology, none of the sessile serrated lesions demonstrated low-grade dysplasia, high-grade dysplasia, or invasive cancer. By definition, all non-advanced TAs contain low-grade dysplasia.

Discussion

The serrated pathway of carcinogenesis is a recently recognized pathway that is now estimated to account for perhaps 15–30% of all colorectal cancer [1, 2]. Sessile serrated adenomas/polyps (SSA/Ps) are predominantly flat in morphology and overwhelmingly right-sided in location. In comparison, hyperplastic polyps are typically left-sided (primarily rectosigmoid), comprise 70–95% of all colorectal serrated polyps, and have no

Mean Annual Volume Change
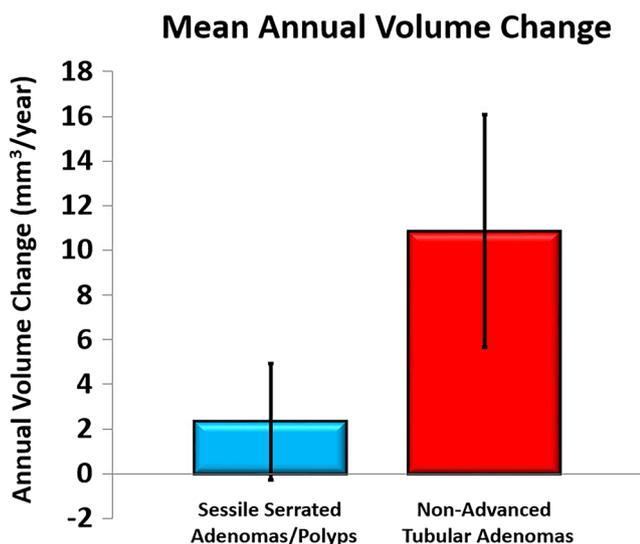
Fig. 3 Bar graph showing the mean annual volume increase for all sessile serrated adenoma/polyps ($n = 58$) versus the non-advanced tubular adenomas ($n = 141$). Error bars indicate the 95% confidence intervals

malignant potential. Also of note, TSAs are quite rare, more commonly left-sided, and may carry a mixture of BRAF and, to a lesser extent, KRAS mutations [30].

Until recently, these subtle SSA/Ps lesions were commonly missed or mischaracterized [31, 32]. The recognition of the mucus cap over the surface of these lesions has led to improved detection rates at both colonoscopy and CTC [16, 17, 23]. To date, however, very little is known about the natural history of sessile serrated lesions, necessitating expert panel recommendations in lieu of evidence [1, 2]. Because these precursors appear to give rise to a disproportionate percentage of interval cancers after negative colonoscopy, some have inferred a more aggressive growth pattern for SSA/Ps [8–11], whereas others posit a less aggressive course related to missed lesions on prior exams.

Our findings provide direct evidence for a more indolent course for typical SSA/Ps, at least early on, with volumetric growth rates that are significantly less than small non-advanced tubular adenomas despite excluding histologically advanced adenomas (i.e., those with a villous component or HGD) in the control group, which are typically more aggressive. Furthermore, none of the serrated lesions, which averaged > 10 mm in linear size at resection, showed either low-grade or high-grade dysplasia (or invasive cancer) at histology, despite a mean in vivo surveillance interval greater than 5 years. To our knowledge, this is the first report on the in vivo behavior of sessile serrated adenomas/polyps, beyond isolated individual case reports [6, 7].

The less aggressive behavior that we have observed over time with SSA/Ps aligns with prior static histology data, which is indirect but supportive. In a large histopathology series of > 2400 SSA/Ps, the average patient age with SSA/Ps harboring no dysplasia, low-grade dysplasia, high-grade dysplasia, and cancer was 61, 66, 72, and 76 years of age, respectively [12]. This more advanced age among patients with serrated pathway cancers aligns with our finding of slower growth. Perhaps a small subset of these serrated lesions subsequently undergo a rapid transition to cancer following an extended indolent phase [11]. Another histopathology study found dysplasia in only 2% of sessile serrated lesions [13]. The absence of dysplasia in our series likely reflects both the younger age profile of our cohort and the low baseline rate of cytologic dysplasia in SSA/Ps. In contrast, all conventional adenomas demonstrate at least low-grade dysplasia. Rates of HGD and cancer are also much lower in serrated polyps compared with conventional adenomas. One colonoscopy series consisting of large SSA/Ps (mean size, 2.9 cm) found invasive cancer in only 3.9% cases, and HGD in another 3.3%, [33] which is considerably lower than in conventional colorectal neoplasms of a similar size [34].

Since all detected colorectal polyps are generally resected at colonoscopy, this precludes longitudinal observation of in situ behavior. CTC, however, has the ability to non-invasively observe and measure colorectal polyps in vivo over time,

providing unique insights into their natural history [18]. Because anatomic localization at CTC is so precise, confirmation of the same lesion on studies separated in time is more straightforward (Figs. 1 and 2). In contrast to colonoscopy, where there may be some question as to whether a specific location between two exams is maintained, there is high confidence in spatial localization at CTC. Furthermore, while careful size measurement using calibrated probes at colonoscopy can match closely with CTC size measurement [35], estimated sizes used in typical clinical practice at colonoscopy are less reliable. Beyond linear assessment, volumetric measurement of polyps at CTC provides for a much more sensitive and useful indicator of interval change over estimated linear size at colonoscopy [18, 27]. The interaction of colorectal lesion volume and diameter depends upon the lesion morphology; that is, more polypoid lesions will have more tissue volume for a given linear size compared with flat lesions. Based on our experience to date, we surmise that lesion volume, reflecting actual tissue bulk, is a more clinically relevant biomarker than linear size. This may explain in part why large flat lesions such as SSA/Ps and more conventional carpet lesions (adenomatous laterally spreading tumors) are more often benign for a given linear size relative to non-polypoid colorectal tumors [24, 29].

It is not yet widely appreciated that, with proper technique and understanding, CTC can effectively detect sessile serrated lesions [17, 23, 31]. As with optical colonoscopy, some SSA/Ps went unrecognized at CTC in early practice, whereas others were detected yet misclassified as large right-sided hyperplastic polyps at histology [36]. However, CTC detection rates have increased as general awareness has grown. In our experience, CTC detection rates for non-diminutive SSA/Ps appear to be comparable to the reported colonoscopic detection rates [12, 17, 37]. The initial prevalence rate of non-diminutive SSA/Ps at CTC screening we reported was comparable to a large colonoscopy-based series by Lash et al (1.4% vs. 1.2%), with similar age and gender profiles in the two cohorts [12, 17]. As awareness of these characteristic lesions has grown, prevalence at both CTC and colonoscopy is likely to increase. We have now identified hundreds of non-diminutive sessile serrated lesions at screening CTC at our center that were subsequently removed at colonoscopy and confirmed at histopathology. Contrast coating of the mucus cap covering these lesions greatly aids in their detection at CTC, and the lack of oral contrast tagging will predictably results in lower detection rates [31]. In general, we feel that optimized CTC technique is critical for reliable detection of these often subtle flat lesions, including cathartic preparation with dual oral contrast tagging and combined 2D-3D assessment. This has important implications for alternative CTC techniques, including the use of a noncathartic preparation, foregoing oral contrast tagging, and primary 2D detection strategies. A number of SSA/Ps followed in our study were actually missed at the initial CTC screening study [38], generally due to the early lack of

recognition of the findings. Nonetheless, despite the typically large linear lesion size of these missed lesions, our current study shows that they grew very little over 5 years or more, and none progressed to cytologic dysplasia or cancer.

Missed serrated polyps may largely explain the decreased protective effect of colonoscopy from right-sided cancer that has been previously reported [15, 39–41]. Interval (or missed) cancers following a negative colonoscopy are thrice as likely to occur in the proximal colon than non-interval cancers. Furthermore, these "interval cancers" are four times more likely to be CIMP-high and/or MSI, both of which are recognized features of the serrated pathway to cancer [14, 40–42]. As such, it appears likely that the serrated pathway has disproportionately contributed to interval or missed cancers, possibly through accelerated growth in a subset of older patients. Interval cancers after negative CTC also tend to be right-sided, with an overall rate that is similar to or slightly lower than colonoscopy [43]. Because CTC allows for retrospective review, it was shown that missed lesions were present on review in over 90% of these interval cancers. This provides further support that interval cancers are much more likely to be from longstanding missed lesions and not from rapidly growing de novo tumors [44].

We acknowledge limitations to our study. This is a single-center experience with a relatively small patient cohort limited in part by the relatively low prevalence of SSA/Ps. Nonetheless, this may represent the first series of in vivo observation of sessile serrated lesions. Despite a relatively long follow-up interval (> 5 years on average), the timeframe for progression from no dysplasia to cancer in serrated lesions may be on the order of 15–20 years. It is possible that much a much longer observation period would be required to demonstrate more rapid progression in a subset of older individuals. We did not perform testing for MSI, CIMP, or *BRAF* on all resected SSLs in this series, but these findings have been well documented by others. Going forward, we plan to pursue epigenetic and genetic (whole genome or exome) investigations on a subset of these resected lesions to correlate with observed growth rates [45–47]. Finally, because we have previously shown that approximately 10% of colorectal polyps may completely regress at CTC follow-up [18], it is possible that we have overestimated the overall rate of progression, as we have no way to account for any serrated lesions that resolved.

In conclusion, sessile serrated adenomas/polyps followed in situ at longitudinal CTC demonstrated overall slower growth compared with small conventional non-advanced tubular adenomas, despite larger initial linear size of the former. This less aggressive behavior may help explain the more advanced patient age for serrated pathway cancers. As expected, SSA/Ps are typically right-sided and flat. Our longitudinal results may help inform future colonoscopic surveillance protocols related to SSA/Ps, as current guidelines are largely restricted to expert opinion related to the absence of natural history data.

Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Perry J. Pickhardt.

Conflict of interest The authors of this manuscript declare relationships with the following companies: Dr. Pickhardt is advisor to Bracco; shareholder in SHINE, Elucent, and Cellectar.

Statistics and biometry One of the authors has significant statistical expertise (BDP). However, no complex statistical methods were necessary for this paper.

Informed consent Written informed consent was obtained from all subjects (patients) in this retrospective study by the Institutional Review Board.

Ethical approval Institutional Review Board approval was obtained.

Study subjects or cohorts overlap Some study subjects or cohorts have been previously reported in Kim DH, Matkowskyj KA, Lubner MG, Hinshaw JL, Muñoz del Rio A, Pooler BD, Weiss JM, Pickhardt PJ. Serrated polyps at CT colonography: prevalence and characteristics of the serrated polyp spectrum. Radiology 2016;280:455–463. However, that study was simply cross-sectional and did not assess longitudinal changes over time.

Methodology
- Retrospective
- Observational
- Performed at one institution

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