Almost One-Third of Large Sessile Serrated Polyps Are Missed on CT Colonography

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ABSTRACT

Background: *Nearly one-third of colorectal cancers (CRC) arise via the serrated pathway. CT colonography (CTC) is a CRC screening examination. Endoscopic detection of sessile serrated polyps (SSPs) varies widely; it is unknown whether CTC effectively detects SSPs. The aim of this study is to determine whether CTC detects SSPs at an institution that performs a large volume of CTC.*

Methods: *We conducted a search of pathology records to identify serrated polyps (SPs) from 2005 to 2012. We extracted demographic data from the electronic health records (EHRs) of subjects with an SSP and examined endoscopy reports for location and size of each SSP. We identified subjects with a CTC within 1 year prior to the colonoscopy that found an SSP, and determined if the CTC identified the SSP.*

Results: *Our search found 3978 subjects with SP over the 7-year period. Seven hundred thirty-two subjects had at least 1 SSP. Eighty-two subjects had CTC done within 1 year prior to the colonoscopy that identified SSP. Seventy-nine subjects' polyps were identified on CTC. CT colonography was done an average of 38 ± 54 days prior to colonoscopy. One hundred fifteen SSPs were identified endoscopically. A total of 48.7% of all SSPs were identified via CTC; larger SSPs were more likely to be seen on CTC ($P < .001$), and 69.6% of SSPs larger than 10 mm were found via CTC. Proximal SSPs were more often identified than distal SSPs ($P = .005$).*

Conclusion: *Given the miss rate for SSPs on CTC, endoscopists should be vigilant about examining the proximal colon in subjects referred after CTC, even if the imaging does not reveal a proximal polyp.*

Keywords: *Colon cancer screening, sessile serrated polyps, computed tomography colonography, polyps*

INTRODUCTION

Colorectal carcinoma (CRC) represents the third most common fatal malignancy, with 136 830 new cases annually and 50 310 deaths estimated in 2014.[1] The current screening and detection guidelines target conventional adenomas that progress via biallelic APC inactivation and abrogation of the Wnt/β-catenin pathway via the suppressor pathway leading to carcinoma.[2] The adenomatous pathway accounts for only 60% of colorectal adenocarcinomas; a large percentage of the remaining 40% can be accounted for by the progression of serrated lesions.[3,4] Both the American College of Gastroenterology and the US Multi-Society Task Force on Colorectal Cancer endorse the use of computed tomographic colonography (CTC) for colorectal cancer screening.[5] There are limited data on the detection of serrated lesions by CTC.

BACKGROUND

Vogelstein et al.,[2] in 1990, established the role of adenomas in the development of colorectal cancer. Current screening programs are based on this evidence and are generally successful in preventing carcinomas arising via the adenomatous pathway.[6] The term sessile serrated lesion was introduced in 1990 after analysis of polyps that shared features of hyperplastic polyps (HPs) and adenomas.[7] They were initially termed serrated adenomas, but are now more commonly known as sessile serrated polyps (SSPs).[8] Regular reporting of these lesions began in 2007

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when SSPs were described as different from conventional adenomas and HPs.[9] SSPs are typically right-sided (proximal to the splenic flexure), larger than 1 cm, and may appear poorly circumscribed on endoscopy (sometimes mimicking normal enlarged folds).[10] The reported incidence of SSPs in the population varies from 1% to 4% and they represent 1-9% of all polyps.[11-17] SSPs typically show abnormal architectural features such as L- or T-shaped crypts, prominently dilated crypts, and serrations that extend to the crypt base.[18]

Histologic findings differentiating a HP from an SSP can be subtle, and it can be difficult to tell the lesions apart even for pathologists with a special interest in gastrointestinal pathology.[19,20] A secondary analysis of the PRESEPT trial data showed that the detection rate of proximal serrated lesions differed significantly between centers (0-9.8%, $P < .0001$) and that pathologists at some centers never identified proximal serrated lesions at all.[21] A recent study where previously designated right-sided HPs were re-examined by blinded pathologists showed that 30-64% of right-sided HPs were reclassified as SSPs, from 2009 to 2012. During that study period, there was an increase in SSPs diagnosed (0 in 2009, 32 in 2010, 83 in 2011, and 134 in 2012).[22] A prospective study of 111 patients with HPs larger than 5 mm found on screening colonoscopy showed that, after histologic re-examination, 28.8% had their polyps reclassified as SSPs, and that 26.1% of patients with high-risk SSP had appropriate follow-up surveillance recommended.[23]

CT colonography performs well as a screening exam for adenomas. It is very effective at detecting colorectal cancer,[24] is >90% sensitive for finding adenomas larger than 8 mm, and 88.7% sensitive for finding adenomas larger than 6 mm.[25,26] CT colonography offers a number of advantages over colonoscopy; there is no need for sedation, it is non-invasive, there is a low risk for perforation, and it provides rapid imaging of the colon. Flat polyps may be a source of false-negative CTC examinations.[27] In a study comparing the detection of polypoid lesions to flat lesions of the colon on CTC, 80.0% of flat lesions larger than 6 mm were found on CTC compared to 86.2% of polypoid lesions.[28] Another study which examined the characteristics of flat lesions found that 79% of the flat lesions found showed contrast coating on CTC.[29] However, neither of these studies identified the histology of these flat lesions, so conclusions about the detection of SSPs are limited to date. The aims of our study were to evaluate the detection rate of SSP on CTC at a facility that has conducted over 16 000 CTCs, and to determine whether the location or size of SSPs affects the detection rate of SSP on CTC.

MAIN POINTS

- *CT Colonography (CTC) discovered fewer than half of all sessile polyps (SSPs) seen on colonoscopy in our study.*
- *Even for large (>1 cm) lesions, CTC missed nearly one-third of all SSPs in this study.*
- *Our findings support the US Multi-Society Task Force recommendation that CTC be used as a second-tier test in those unwilling or unable to undergo a first-tier test.*

MATERIALS AND METHODS

This is a retrospective review examining all serrated polyps (SPs) removed during colonoscopy between January 1, 2005, and January 1, 2012, at 3 centers: All centers are academic, tertiary-care military treatment facilities that serve active duty service members, retirees, and their dependents. All colonoscopies were performed with CF or PCF-180 colonoscopes (Olympus, Tokyo, Japan) with high-definition monitors. Endoscopists included 16 attending gastroenterologists, 10 fellows in gastroenterology, and 8 surgeons. The Institutional Review Boards of all centers approved this study. CT colonography preparation was done with 1000 mL of MoviPrep (Salix, North Carolina, USA), 300 mL of oral 2% barium, and 120 mL of GastroView (Mallinkrodt, Dublin, Ireland). All CTCs were done with a 64-channel scanner and with mechanical CO_2 insufflation. Scans were done in supine and prone positions, with a total radiation dose of 3-6 mSv. Three-dimensional reconstruction was done on all CTC images, with evaluation of both proximal and distal "fly through" images and verification on 2D images.

We searched the pathology tissue bank's Composite Health Care System electronic health record (EHR) for all biopsy reports that included the words "serrated," "hyperplastic," "sessile serrated," "SSA," or "SSP." Polyp location, size, histology, and the histology of other polyps removed during the same procedure were noted. The locations and sizes of polyps were determined by the specimen labels reported in the pathology requests, and confirmed by examining the original endoscopic reports in Provation (Wolters Kluwer, Philadelphia, PA). The original slides of each polyp were pulled from our pathology storage and a pathologist reviewed all HPs using the World Health Organization classification for SPs.[30] The pathologist either confirmed the initial histologic diagnosis or reclassified the lesion as an SSP.

We cross-referenced all patients with an SSP against all patients at our facility that had a CTC completed, to generate a list of patients who had both an SSP found on colonoscopy and a CTC conducted. Patient selection was limited to those who had their CTCs within 1 year prior to the removal of an SSP. We chose a 1-year cut-off, given that a short follow-up period would identify lesions that are "missed" rather than polyps that were interval growths. In selected patients, we examined CTC reports for location of all polyps seen. We then identified whether the CTC detected the SSPs, and in those same patients, determined whether the CTC also detected the patients' tubular adenomas (TAs). Data were collated and analyzed using the statistical software package IBM SPSS Statistics 21.0 (IBM, Armonk, New York). Fisher's exact test and chi-squared test were used for statistical analysis for between-group comparisons of categorical data. A probability value of less than.05 was considered statistically significant.

RESULTS

We initially identified 3978 colonoscopies during the study period that found a serrated polyp. Of these, 728 colonoscopies found an SSP. In the same study period, our facility conducted 16 293 CTCs. In the study, 119 patients had at least 1 SSP and had a CTC conducted. Of these, 82 patients had a CTC within 1 year prior to SSP resection.

These patients were 65.9% male and 67.1% Caucasian, with a mean age of 61.8 ± 10.3 years (see Table 1 for complete demographics). Of these 82 patients, 79 patients had at least 1 polyp identified on CTC. Two patients had a negative CTC, but had a subsequent colonoscopy because they were part of a prospective study comparing CTC to colonoscopy for detection of adenomas. The third patient had a suboptimal CTC (CTC Reporting and Data System Classification C0), and was referred for colonoscopy for adequate screening. The CTCs were performed a mean of 38.4 ± 54.2 days prior to colonoscopy, with 28% of the CTCs done on the same day as the colonoscopy. Thirty-eight colonoscopies had withdrawal time documented; the average withdrawal time during these procedures was 27.2 ± 16.0 minutes. The cecum was reached in 95% of the procedures. Ninety-six percent of procedures had an adequate (excellent, good, or fair) preparation.

Table 1. Patient Characteristics (n = 82)

Male	65.8%
Race	
Caucasian	67.1%
Black	8.5%
Hispanic	0.0%
Asian	1.2%
Undeclared	23.2%
Mean age, years ± SD	61.8 ± 10.3
Family history of colon cancer	2.4%
Active smoking	18.3%
Active alcohol use	36.6%

A total of 115 SSPs were found on colonoscopy in these 82 patients. We found that CTC detected 48.7% of SSPs seen endoscopically. Larger SSPs were more likely to be found on CTC ($P < .0001$), with 69.7% of the 33 polyps sized 10 mm or larger detected on CTC (Figure 1). When limiting analysis to SSPs larger than 5 mm, proximal SSPs were more likely to be found than distal SSPs ($P = .005$), with 90.9% of the 11 cecal SSPs found on CTC, and 28.6% of the 7 SSPs distal to the splenic flexure found on CTC (Figure 2).

A total of 74 TAs were found on colonoscopy in these 82 patients. TAs were more likely to be detected on CTC than SSPs (54.1% vs 48.7%, $P = .565$), although this was not statistically significant. When limiting analysis to those polyps larger than 5 mm (for which CTC should be sensitive, given previous studies), TAs were more likely to

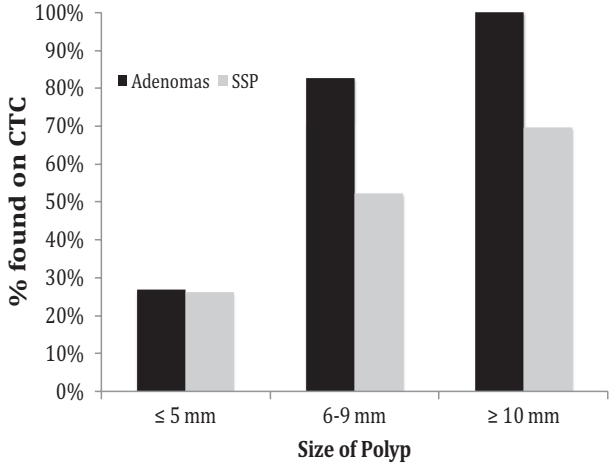

Figure 1. Larger sessile serrated polyps (SSPs) were more likely to be found on CT colonography (CTC) than smaller SSPs ($P = .001$). Sessile serrated polyps were found at lower rates on CTC than tubular adenomas (TAs) of the same size.

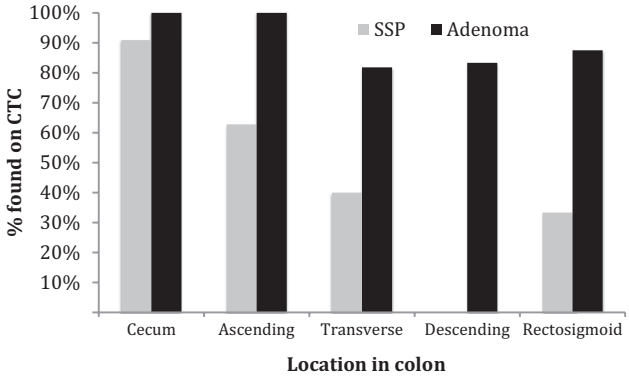

Figure 2. Proximal SSPs were more likely to be found on CTC than distal SSPs (P = .023).

be found than SSPs on CTC (87.9% vs 59.7%, P = .007). TAs larger than 9 mm were more likely to be found than SSPs larger than 9 mm (100% vs 69.7%, P = .084).

The time elapsed from CTC to colonoscopy did not significantly affect the detection of SSPs larger than 5 mm (P = .476), with 52.0% of SSP larger than 5 mm missed on CTCs done on the same day as colonoscopy, and 63.5% of SSPs larger than 5 mm missed on CTCs done more than 48 hours (but less than 12 months) prior to colonoscopy.

There was no significant difference in detection of SSPs between the first half of our study (prior to 2008) and the second half of our study (after 2008) (P = .112). This is despite increasing recognition of SSPs at our institution; the total number of SSPs found at our institution grew from 82 SSPs found on colonoscopy in 2005 versus 209 SSPs found on colonoscopy in 2011.

DISCUSSION

Studies suggest that SSPs may progress to malignancy at a higher rate than do conventional adenomas.[31-33] This rapid progression, combined with low rates of endoscopic detection and incomplete resection, make SSPs a likely source of interval cancers between colonoscopies. Improved detection of these lesions is essential to an effective colon cancer screening program.

Our data suggest that SSPs, even large ones, are poorly detected on CTC. CT colonography is an effective tool to detect adenomas; a sensitivity of over 90% for adenomas larger than 1 cm implies that we should hope for the same detection rate for SSPs. This did not bear out in our data that showed a significantly lower rate of detection of SSPs. The higher rate of detection of larger SSPs is intuitive, given that previous studies on CTC show that larger adenomas are found at higher rates than smaller adenomas. The higher rate of detection in the proximal colon may be explained by both endoscopist and radiologist bias; radiologists may be more likely to look for flat polyps in the right colon, and endoscopists are also evolving to spend more time in the right colon looking for such lesions through second examinations or ascending colon retroflexion.[34] CT colonography may have difficulty detecting SSPs because these lesions are often flat instead of polypoid, and detection of these lesions on endoscopy is often aided by visualization of a change in mucosal characteristics. Adequate colon preparation and distension for the CTC, while improving the quality of exam in all cases, may be particularly necessary in the detection of flat lesions.[28] Despite advances in detection of SSPs on CTC, the best available data suggest a detection rate of 3.1%.[35] Colonoscopy, on the other hand, detects SSPs at nearly double that rate, at 6%.[38]

However, our data do not suggest that CTC is a poor CRC screening tool. No cancers were found on colonoscopy that were missed on CTC. In addition, 79/82 (95.1%) of CTCs led to colonoscopies to remove polyps, suggesting that CTC performs well as an exam intended to screen for those patients who need a colonoscopy.

Our study has many strengths. Three experienced radiologists read all CTCs at an institution that has read over 16 000 CTCs in the past decade. All polyps were found on colonoscopy less than 10 months after the CTC, with a large portion of these found on the same day as the colonoscopy. This implies that these polyps were not interval growths between 2 examinations but were likely present during the CTC. With a retrospective pathologic review of polyps, we were able to identify extra SSPs that were not originally labeled as such, extending our cohort to 82 patients.

There are some limitations to our study. We were limited to using colonoscopy as a gold standard to find SSPs, and the existing literature suggests that endoscopists vary significantly in their detection of SSPs. A recent study of a prospectively enrolled database of screening comparing CTC to colonoscopy showed that colonoscopy was 5.5 times more likely to find SSPs than CTC.[36] However, in our study, we have also compared this detection rate against the TA detection rate for validation. Endoscopist adenoma detection rate and colonoscopy withdrawal times were often unavailable, given the period of study (these were not commonly recorded in the early half of our

study period), so we do not have a reliable way to assess the quality of colonoscopy. In addition, a recent study shows that 21.5% of negative follow-up colonoscopies after CTC are false negatives.[37] This may lead to an underestimation of endoscopic polyp detection, and suggests that our 69.7% detection rate of CTC for large SSPs is falsely high. The study was underpowered to assess if there were demographic factors that led to missed polyps. Given the retrospective nature of our study, we used the results of the gold standard study (colonoscopy) to identify true positives and false negatives of the test study (CTC), so we were not able to do a sensitivity, specificity, or predictive value analysis, given that we do not have a rate of true negatives or of false positives. This could be accomplished by a prospective study examining SSP detection in CTC with immediate follow-up colonoscopy in all cases.

CONCLUSION

Our data show that CTC detection of SSPs is poor, but that CTC remains a good cancer screening test and a good study to identify patients who need a colonoscopy. Given the miss rate for SSPs, endoscopists should be vigilant about examining the proximal colon for SSPs in subjects referred for polypectomy after CTC, as even imaging does not identify a proximal polyp.

Ethics Committee Approval: The Institutional Review Board (IRB) of Walter Reed National Military Medical Center (WRNMMC) approved this study.

Informed Consent: The IRB of WRNMMC deemed that no informed consent was needed as all data was de-identified.

Peer-review: Externally peer-reviewed.

Author Contributions: Singla – Data analysis, manuscript drafting and revision. Kemp – Analysis of pathological samples, revision of manuscript. Cirigliano – revision of manuscript, Boblele, revision of manuscript, Veerappan – Study concept, manuscript revision, Young- study concept, data analysis, manuscript revision.

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