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Volumetric Textural Analysis of Colorectal Masses at CT Colonography:

Differentiating Benign versus Malignant Pathology and Comparison with Human Reader Performance

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Abstract

Rationale and Objectives—To (1) apply a quantitative volumetric textural analysis (VTA) to colorectal masses at CT colonography (CTC) for differentiation of malignant and benign lesions and (2) to compare VTA with human performance.

Materials and Methods—A validated, quantitative VTA method was applied to 63 pathologically-proven colorectal masses (mean size, 4.2 cm; range, 3–8 cm) at non-contrast CTC in 59 adults (mean age, 66.5 years; range, 45.9–91.6 years). 51% (32/63) of the masses were invasive adenocarcinoma and the remaining 49% (31/63) were large benign adenomas. Three readers with CTC experience independently assessed the likelihood of malignancy using a 5-point scale (1=definitely benign, 2=probably benign, 3=indeterminate, 4=probably malignant, 5=definitely malignant). Areas under the ROC curve (AUC) and accuracy levels were compared.

Results—VTA achieved optimal sensitivity of 83.6% versus 91.7% for human readers ($P=0.034$), with specificities of 87.5% and 77.4%, respectively ($P=0.007$). No significant difference in overall accuracy was seen between VTA and human readers (85.5% vs 84.7%, $P=0.753$). The ROC AUC for differentiating benign and malignant lesions was 0.936 for VTA and 0.917 for human readers.

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Intra-class correlation coefficient among the human readers was 0.76, indicating good to excellent agreement.

Conclusion—Volumetric textural analysis demonstrates excellent performance for distinguishing benign from malignant colorectal masses (> 3 cm) at CTC, comparable yet potentially complementary to experienced human performance.

Keywords

CT colonography; texture analysis; colorectal cancer

Introduction

Colorectal cancer (CRC) remains a major public health issue in the United States, with recent figures estimating nearly 135,000 new diagnoses and 50,000 deaths per year.¹ Fortunately, CRC is generally believed to begin as a benign colorectal polyp, with most requiring many years to progress to invasive cancer.² Detection and removal of these benign precursors prior to malignant transformation through screening programs remains the cornerstone of CRC prevention.³ Over the last 10–15 years, CT colonography (CTC) has emerged as a validated CRC screening tool, recently gaining US Preventative Services Task Force (USPSTF) approval as a recommended CRC screening test.^{4,5} CTC is comparable in effectiveness to traditional optical colonoscopy (OC) for the detection of advanced colorectal neoplasia,^{6–9} and has the advantages of being non-invasive, cost-effective,^{10,11} and less operator-dependent.¹²

Historically, distinguishing large benign colorectal precursor mass lesions from truly invasive malignant cancers has presented a challenge, both at CTC as well as OC. A large degree of overlap exists between large advanced benign and malignant lesions with regard to observable features of lesion appearance (e.g., size and morphology). Consequently, the standard of care for screening CTC is to send all large polyps (diameter ≥ 10 mm) for polypectomy, whereas management of small (6–9 mm) lesions can be individualized between polypectomy and CTC surveillance.^{13,14} The standard of care for screening OC has generally been to remove all polyps, regardless of size, although some have deviated from this practice. However, recent studies have reinforced that not all benign neoplastic polyps—even those of identical histological subtype—present the same risk for growth and malignant transformation,^{15–18} and the search for novel methods to predict polyp behavior remains an active area of research.

One advantage CTC may hold as a CRC screening test lies in the ability to extract quantitative information from the CT data set, even retrospectively. Analysis of this quantitative data may allow for improved characterization beyond the subjective visual interpretation of a human reader. Recent innovations have taken advantage of the ability of CT to resolve different density arrangements at relatively high three-dimensional (3D) spatial resolution to quantitatively evaluate the texture of colorectal polyps using volumetric data,¹⁹ which represents a significant improvement upon prior textural evaluation methods which were limited to two-dimensional (2D) space. As such, a mathematically-based, quantitative volumetric textural analysis (VTA) method for distinguishing non-neoplastic

hyperplastic polyps from neoplastic adenomas was developed and underwent preliminary validation,²⁰ but has not yet focused on distinguishing benign from malignant neoplastic masses (ie, advanced adenoma vs. invasive cancer), and also has lacked comparison against human readers. Therefore, our aims in this study are to (1) apply higher-order volumetric textural analysis to colorectal masses (≥ 3 cm) at CT colonography (CTC) for differentiation between malignant and benign, and (2) to compare volumetric textural analysis with subjective human performance.

Materials and Methods

This HIPAA-compliant retrospective study was approved by the institutional review boards of the participating institutions. The need for signed informed consent was waived. This study was performed without industrial sponsorship or support.

Patient Selection

Retrospective review of a database of adult patients undergoing first-time CTC from April 2004 through October 2012 was performed. All patients with colonic masses detected at CTC, defined as ≥ 3 cm in maximum diameter, with available histopathology correlation were identified. These patients comprised the study cohort.

CTC Protocol

The CTC technique used at our institution has been described in detail elsewhere.²¹ In summary, patients undergo a low-volume bowel preparation on the evening prior to CTC using a cathartic cleansing agent. Sodium phosphate was the standard cathartic from 2004–2008, but was replaced by magnesium citrate thereafter.²² Oral contrast material tagging of residual fluid and fecal material was achieved with 2.1% weight per volume barium sulfate and diatrizoate (Gastrografin, Bracco). During the CTC examination, colonic insufflation was maintained using automated continuous carbon dioxide delivered through a small flexible rectal catheter.²³ Patients were routinely scanned in both supine and prone positions, with decubitus positioning as needed.²⁴ Images were acquired with 8-to-64-section multi-detector CT scanners using 1.25-mm collimation, 1-mm reconstruction interval, 120 kV_p, and either a fixed tube current-time product (50–75 mAs) or tube-current modulation (range, 30–300 mA). Clinical interpretation of CTC examinations at our institution is performed using combined two-dimensional and three-dimensional reconstructions (Figure 1) for initial lesion detection and two-dimensional cross-sectional images for confirmation, with all studies interpreted using a dedicated CTC software system (Viatronix V3D Colon).

CT Image Reconstruction and Analysis for Human Readers

Three human readers with formal training and experience in CTC interpretation were recruited for lesion analysis, including a senior radiology resident, an abdominal imaging fellow, and a fellowship-trained abdominal imaging radiologist with six years of attending experience. For each patient, readers were provided all originally acquired 2D CTC series (including supine, prone, and decubitus series where acquired) reconstructed with 1.25-mm slice thickness at 1-mm intervals, as well as the reconstruction of the supine series with 5-mm slice thickness at 3-mm intervals generally used to evaluate for extracolonic findings.

Patients were presented to readers in a random order. Readers were aware that patients all had confirmed masses (≥ 3 cm), but were otherwise blinded to all other patient history, including pathology results. Readers were provided with the location of each mass, including a description of colonic segment and image numbers, to aid in localizing the lesion. Readers were informed of cases in which the patient had multiple masses, and were provided with the location of each distinct lesion. Readers were informed in advance that all lesions in question were either noninvasive benign but advanced adenomas (including lesions with HGD) or invasive adenocarcinomas.

Readers were instructed to classify all lesions as either “benign” (advanced adenoma) or “malignant” (invasive cancer) based on CTC imaging appearance using a 5-point scale: 1=definitely benign, 2=likely benign, 3=indeterminate, 4=likely malignant, 5=definitely malignant. Readers were instructed to focus on the lesion of interest and immediate surrounding tissues, including pericolonic fat, mesentery, and local lymph nodes, while specifically ignoring the liver and other solid organs in order to avoid bias in evaluation of the colorectal masses from possible distant metastases. While there are no published formal criteria for differentiating malignant from benign colorectal masses, readers took into account a number of imaging features associated with colorectal cancer.^{25–27} These features were used in combination to assign a likelihood score of 1 to 5, as above, and include lesion morphology (longitudinal and circumferential extent, or “footprint”), degree of luminal narrowing, lesion “shouldering”, lesion ulceration/necrosis, extramural extension/invasion, adjacent fat stranding, and regional lymphadenopathy. Following lesion classification by all readers, diagnostic performance was computed and compared to VTA. Inter-observer agreement was also calculated.

Volumetric Textural Analysis (VTA)

Volumetric textural feature extraction and analysis was performed using a previously validated expansion of the Haralick model²⁸ from 2D to 3D space, and has been thoroughly described elsewhere.^{19,20} The original Haralick model described a mathematical method for extracting textural features from pixelated greyscale 2D images. Haralick, et al. originally defined a set of 14 measures of texture derived from analyzing variations in greyscale tone (analogous to Hounsfield Unit) of the neighboring pixels surrounding a given pixel within the image. These features generally related to visually perceived characteristics of an image such as homogeneity, contrast, and complexity, as well as perceived organized structure within the image. Each of the 14 measures is calculated along four directions (represented as lines at 0°, 45°, 90°, and 135° from the reference pixel, Figure 2), and for each feature a mean value (reflecting the overall average for the image) and a range of values (reflecting spatial variation across the image) are computed, giving a total of 28 textural features (14 means and 14 ranges, termed “Haralick features” in the literature) for quantitative characterization of the texture of a defined 2D image.

The original Haralick model was limited to 2D data sets. Here, we apply a previously validated expansion of the original model for application to 3D images comprised of voxels of varying grayscale tone.¹⁹ Instead of eight neighboring pixels in 2D space, each voxel in 3D space has 26 neighbors, corresponding to a total of 13 directions (instead of four) along

which features can be computed (Figure 2). Additionally, the expansion to three dimensions allows the introduction of 16 additional textural measures (in addition to the original 14 determined by Haralick), resulting in a total of 30 measures. Furthermore we apply a validated method for amplifying 3D textural features which incorporates measurements from first and second-order derivative images (termed *gradient* and *curvature images*, respectively) in addition to the original image (termed the *intensity* or *density image*).^{19,20}

One potential source of error in the extraction of these textural measures in 3D space as compared to 2D space arises from the spatial variation of colon lesions and orientations in 3D space, as the original Haralick model of averaging textural measures across four directions was designed for textural analysis of a rectangular array of pixels. Because colon lesions are not perfect spheres (and certainly not perfect cubes), the use of mean and range Haralick features over the 13 3D directions may not adequately reflect the volumetric texture of the mass. To address this spatial variation, we employ principal component analysis (PCA), specifically using the Karhunen-Loève (KL) transformation, to the data set to eliminate possible correlation among the individual textural measures.²⁰ Application of the KL transformation to each of the 30 textural measures in each of the 13 3D spatial directions yields a total of 390 textural features per image; when the method is applied to each of the *density*, *gradient*, and *curvature* image sets, a total of 390×3 or 1170 individual textural features for lesion classification are extracted. In addition to being analyzed independently, the features from each of the image sets may be combined (*density-gradient*, *density-curvature*, *gradient-curvature*, or *density-gradient-curvature*) in an attempt to find the most predictive set of textural features.

Prior studies applied this method to colorectal polyps of known histology and used the random forest (RF) strategy²⁹ to determine which of the volumetric textural features were most predictive of polyp histology by varying sensitivity and specificity and performing receiver operating characteristic (ROC) analysis, using multiple runs with threshold averaging. This volumetric modified Haralick method with textural feature amplification and PCA was applied to the 63 masses in the current study. Unpublished preliminary VTA data for this cohort demonstrated that features extracted from the *gradient* (first-order derivative) image set yielded the optimal balance of sensitivity and specificity for lesion classification. Therefore, the model was run 100 times using *gradient* textural features alone, and an ROC curve was generated using threshold averaging.

Once our patient cohort was identified, supine and prone DICOM series from CTC (1.25 mm collimation, reconstructed at 1 mm intervals) were loaded into our VTA software. Colorectal masses were then visually confirmed and a 3D region of interest was semi-automatically segmented, with initial segmentation performed automatically and segmentation margins adjusted manually (Figure 3). Once segmented, VTA of the colonic masses was performed as described.

Statistical Analysis

The modified Wald method was used to calculate confidence intervals for proportions. The *t*-test was used to assess differences in continuous variables and Pearson's χ^2 or Fisher's exact test was used, where appropriate, to assess differences in categorical variables. Intra-

class correlation coefficient was calculated following two-factor ANOVA to assess inter-observer agreement. A two-tailed P-value <0.05 was used as the criterion for statistical significance. ROC curves for human readers were constructed using Microsoft Excel (Microsoft Excel 2010, Microsoft Corporation, Redmond, WA) and areas under the curve (AUC) were calculated using the trapezoidal rule described by Hanley and McNeil.^{30,31}

Results

Retrospective database review yielded 32 distinct pathologically-proven adenocarcinomas of the colon and rectum in 28 patients measuring 3 cm in size. Mean ($\pm$ SD) age in this patient group was 68.9 ± 14.2 years (range 45–91 years) with 11 men and 17 women. Mean ($\pm$ SD) adenocarcinoma diameter at CTC was 4.4 ± 1.3 cm (range, 3.0–8.0 cm) with N=15 lesions located in the right colon (defined as cecum, ascending, or transverse colon) and N=17 in the left colon (descending, sigmoid, or rectum).

From the same time period, 31 distinct pathologically-proven benign neoplastic masses (advanced adenomas measuring 3 cm) from 31 different patients were also identified for evaluation. Histologic subtypes included N=5 villous adenomas (3 with HGD), N=21 tubulovillous adenomas (4 with HGD), N=3 serrated adenomas (1 with HGD), and N=2 tubular adenomas. Mean ($\pm$ SD) age in this patient group was 64.3 ± 10.3 years (range 51–86 years) with 19 men and 12 women. Mean ($\pm$ SD) advanced adenoma diameter at CTC was 4.0 ± 1.2 cm (range, 3.0–8.0 cm) with 17 lesions located within the right colon and 16 in the left colon. No significant difference among these metrics was seen between the adenocarcinoma and advanced adenoma groups (Table 1).

ROC analysis for human readers generated AUC values of 0.869 for Reader 1, 0.960 for Reader 2, and 0.928 for Reader 3, with a pooled AUC value of 0.917. By comparison, the calculated AUC value for the VTA ROC curve was 0.936 (Figure 4).

Using a threshold for malignancy of 3 (indeterminate or worse) on the five-point scale, the pooled sensitivity for human readers was 91.7% (88/96) compared with a sensitivity of 83.6% (2675/3200) for VTA ($P=0.034$) based on the optimized threshold from the ROC curve. Pooled specificity for human readers was 77.4% (72/93) compared with an optimized specificity of 87.5% (2713/3100, $P=0.007$) for VTA. The relative increase in specificity and decrease in sensitivity for VTA compared with human readers was statistically significant. Similarly, pooled human reader positive predictive value (PPV) and negative predictive value (NPV) were 80.7% (88/109) and 90.0% (72/80), respectively, compared with values of 87.4% (2675/3062, $P=0.057$) and 83.8% (2713/3238, $P=0.165$) for VTA at the optimal threshold, neither of which was statistically significant, although both were trending towards significance. Finally, pooled human accuracy of 84.7% (160/189) and VTA accuracy of 85.5% (85.5%) were comparable ($P=0.753$), with no statistically significant difference seen. Diagnostic performance for individual readers, as well as pooled data and VTA, are summarized in Table 2. Intra-class correlation coefficient among the readers was 0.76 with 95% CI [0.65, 0.83], indicating good to excellent agreement.

Discussion

Subjective distinction between colorectal masses that represent benign but likely premalignant neoplastic masses versus adenocarcinoma can present a diagnostic challenge, as observable features such as size and morphology overlap considerably between the two groups. At this time, reliably distinguishing cancer from benign precursor lesions can only be accomplished at pathology—after the lesion has been completely removed at colonoscopy or, more often, at surgery. Developing methods of accurate noninvasive prediction of the malignant status of a lesion prior to resection may lead to opportunities for better treatment planning prior to any intervention, including whether or not to pursue neoadjuvant treatment, more aggressive resection, or nodal dissection.

The results of our volumetric textural analysis study demonstrated comparable but complementary diagnostic performance of VTA when compared to human readers. With an optimized performance threshold based on the ROC curve, VTA was approximately 8% less sensitive (91.7% human vs 83.6% VTA) but 10% more specific (77.4% vs 87.5%) when compared with pooled human reader data, with similar patterns seen for predictive values. However, the overall accuracy between human readers and VTA was remarkably similar (84.7% vs 85.5%). This complementary performance could potentially be harnessed to improve the overall evaluation. Furthermore, our data seems to indicate that the discrepancy between sensitivity and specificity among human readers is likely a real phenomenon (i.e. human readers overall may be more sensitive than specific), as inter-observer agreement was found to be in the good-to-excellent range (intra-class correlation coefficient 0.76).

As current standard of care for colorectal masses of the size evaluated in this study is endoscopic evaluation and/or surgical resection in almost all cases, we recognize that there are limits to the clinical application of this technology. However, while not yet feasible for clinical use, there are numerous opportunities for the application of VTA to the assessment of colorectal neoplasms. While endoscopic evaluation (generally including biopsy) and surgical resection are standard of care for lesions of this size, there are lesions which are unreachable by endoscopy, sometimes due to colon anatomy or stricture. Endoscopic biopsy may also undersample larger lesions, and consequently some colorectal masses determined to be benign at endoscopic biopsy are found to have a malignant focus at surgical resection. Given that the surgical approach can vary based on the advanced knowledge of benign versus malignant pathology, other methods of predicting histology could influence patient management. Furthermore, it may be a surprise to some that roughly half of all neoplastic colorectal masses (> 3 cm) may be benign, as seen in our series. As such, determining malignant status is far from a foregone conclusion. Ultimately, VTA may have a greater impact on smaller colorectal polyps not immediately destined for removal (lesions 6–9 mm in diameter); while this current study does not directly address the application of our VTA method to these smaller polyps, we assert that predicting malignant histology in smaller lesions will likely be more challenging than in larger lesions. Therefore, confirming adequate performance of VTA in predicting malignant histology in larger lesions is a logical precursor.

Additionally, emerging novel theories of colorectal tumorigenesis postulate that multiple driver mutations occur early—possibly before a polyp is detectable—as opposed to the classic stepwise adenoma-carcinoma sequence in which mutations drive the transition from one pathological state to the next.^{16,32} The existence of very early punctuated mutational events implies that some polyps may be “born to be bad”. Furthermore, prior research suggests that polyps occurring synchronously with cancers may share mutational features with the associated cancer.³³ As such, CT textural analysis could potentially uncover more ominous features in some benign polyps and masses, and might help to reveal the patient’s overall risk of cancer.

Our preliminary collaborative work in CT textural analysis using the described methodology has also demonstrated utility in differentiating neoplastic polyps (adenomas) from non-neoplastic lesions (e.g., hyperplastic polyps).^{19,20} Combining VTA with other strategies, including surveillance of volumetric polyp growth rates and mutational profiles assessing for genomic and epigenomic changes,^{15,16} may one day lead to a more comprehensive evaluation of colorectal neoplasia, including a more sophisticated assessment of risk posed to the patient that goes beyond simple measures of tumor size and histology. Furthermore, in addition to the primary tumor, these tools may also have a role in the evaluation of metastatic disease in these patients.

We acknowledge some limitations specific to this study, beyond the general limitations of application of VTA technology to evaluation of colorectal masses, as discussed above. Perhaps the most significant limitation is our use of investigational software for VTA analysis which is not commercially available; consequently, wider study and application of our findings are not feasible at this time, nor is direct clinical application. Furthermore, this retrospective analysis was performed using data gathered from a single Midwest U.S. center and results may not necessarily generalize to dissimilar populations, although we feel our patient population is typical for a CRC cohort. Additionally, in this study we limited our analysis to proven adenocarcinomas and benign masses that were ≥ 3 cm in diameter, and did not address lesions of similar histology which may be smaller. Further evaluation of VTA in the assessment of smaller lesions (both cancers and benign) is a clear future direction of research.

In conclusion, volumetric textural analysis demonstrates excellent performance for distinguishing benign from malignant colorectal masses (≥ 3 cm) at CTC, comparable yet potentially complementary to experienced human reader performance.

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References

1. Howlader NNA, Krapcho M, Miller D, Bishop K, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975–2013, National Cancer Institute Bethesda, MD, http://seer.cancer.gov/csr/1975_2013/, based on November 2015 SEER data submission, posted to the SEER web site, April 2016.
2. Muto T, Bussey HJR, Morson BC. Evolution of Cancer of Colon and Rectum. *Cancer* 1975;36:2251–70. [PubMed: 1203876]
3. Winawer SJ, Zauber AG, Ho MN, et al. Prevention of colorectal cancer by colonoscopic polypectomy. *New England Journal of Medicine* 1993;329:1977–81. [PubMed: 8247072]
4. Bibbins-Domingo K, Grossman DC, Curry SJ, et al. Screening for Colorectal Cancer: US Preventive Services Task Force Recommendation Statement. *Jama* 2016;315:2564–75. [PubMed: 27304597]
5. Lin JS, Piper MA, Perdue LA, et al. Screening for Colorectal Cancer: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. *Jama* 2016;315:2576–94. [PubMed: 27305422]
6. Graser A, Stieber P, Nagel D, et al. Comparison of CT colonography, colonoscopy, sigmoidoscopy and faecal occult blood tests for the detection of advanced adenoma in an average risk population. *Gut* 2009;58:241–8. [PubMed: 18852257]
7. Johnson CD, Chen M-H, Toledano AY, et al. Accuracy of CT colonography for detection of large adenomas and cancers. *New England Journal of Medicine* 2008;359:1207–17. [PubMed: 18799557]
8. Kim DH, Pickhardt PJ, Taylor AJ, et al. CT colonography versus colonoscopy for the detection of advanced neoplasia. *New England Journal of Medicine* 2007;357:1403–12. [PubMed: 17914041]
9. Pickhardt PJ, Choi JR, Hwang I, et al. Computed tomographic virtual colonoscopy to screen for colorectal neoplasia in asymptomatic adults. *New England Journal of Medicine* 2003;349:2191–200. [PubMed: 14657426]
10. Hassan C, Zullo A, Laghi A, et al. Colon cancer prevention in Italy: Cost-effectiveness analysis with CT colonography and endoscopy. *Digestive and Liver Disease* 2007;39:242–50. [PubMed: 17112797]
11. Pickhardt PJ, Hassan C, Laghi A, Zullo A, Kim DH, Morini S. Cost-effectiveness of colorectal cancer screening with computed tomography colonography - The impact of not reporting diminutive lesions. *Cancer* 2007;109:2213–21. [PubMed: 17455218]
12. Pooler BD, Kim DH, Hassan C, Rinaldi A, Burnside ES, Pickhardt PJ. Variation in Diagnostic Performance among Radiologists at Screening CT Colonography. *Radiology* 2013;268:127–34. [PubMed: 23449954]
13. Pickhardt PJ. CT Colonography for Population Screening: Ready for Prime Time? *Dig Dis Sci* 2015;60:647–59. [PubMed: 25492504]
14. Zalis ME, Barish MA, Choi JR, et al. CT colonography reporting and data system: A consensus proposal. *Radiology* 2005;236:3–9. [PubMed: 15987959]
15. Pickhardt PJ, Kim DH, Pooler BD, et al. Assessment of volumetric growth rates of small colorectal polyps with CT colonography: a longitudinal study of natural history. *Lancet Oncol* 2013;14:711–20. [PubMed: 23746988]
16. Sievers CK, Zou LS, Pickhardt PJ, et al. Subclonal diversity arises early even in small colorectal tumours and contributes to differential growth fates. *Gut* 2016.
17. Olson TJP, Hadac JN, Sievers CK, et al. Dynamic Tumor Growth Patterns in a Novel Murine Model of Colorectal Cancer. *Cancer Prevention Research* 2014;7:105–13. [PubMed: 24196829]
18. Sottoriva A, Kang H, Ma ZC, et al. A Big Bang model of human colorectal tumor growth. *Nature Genetics* 2015;47:209–+. [PubMed: 25665006]
19. Song BW, Zhang GP, Lu HB, et al. Volumetric texture features from higher-order images for diagnosis of colon lesions via CT colonography. *International Journal of Computer Assisted Radiology and Surgery* 2014;9:1021–31. [PubMed: 24696313]
20. Hu YF, Liang ZR, Song BW, et al. Texture Feature Extraction and Analysis for Polyp Differentiation via Computed Tomography Colonography. *IEEE Transactions on Medical Imaging* 2016;35:1522–31. [PubMed: 26800530]

21. Pickhardt PJ. Screening CT colonography: How I do it. *American Journal of Roentgenology* 2007;189:290–8. [PubMed: 17646453]
22. Borden ZS, Pickhardt PJ, Kim DH, Lubner MG, Agriantonis DJ, Hinshaw JL. Bowel Preparation for CT Colonography: Blinded Comparison of Magnesium Citrate and Sodium Phosphate for Catharsis. *Radiology* 2010;254:138–44. [PubMed: 20032148]
23. Shinnars TJ, Pickhardt PJ, Taylor AJ, Jones DA, Olsen CH. Patient-controlled room air insufflation versus automated carbon dioxide delivery for CT colonography. *American Journal of Roentgenology* 2006;186:1491–6. [PubMed: 16714635]
24. Buchach CM, Kim DH, Pickhardt PJ. Performing an additional decubitus series at CT colonography. *Abdominal Imaging* 2011;36:538–44. [PubMed: 21184064]
25. Horton KM, Abrams RA, Fishman EK. Spiral CT of Colon Cancer: Imaging Features and Role in Management. *RadioGraphics* 2000;20:419–30. [PubMed: 10715340]
26. Iyer RB, Silverman PM, DuBrow RA, Charnsangavej C. Imaging in the Diagnosis, Staging, and Follow-Up of Colorectal Cancer. *American Journal of Roentgenology* 2002;179:3–13. [PubMed: 12076894]
27. Nerad E, Lahaye MJ, Maas M, et al. Diagnostic Accuracy of CT for Local Staging of Colon Cancer: A Systematic Review and Meta-Analysis. *American Journal of Roentgenology* 2016;207:984–95. [PubMed: 27490941]
28. Haralick RM, Shanmugam K, Dinstein I. Textural Features for Image Classification. *Ieee Transactions on Systems Man and Cybernetics* 1973;SMC3:610–21.
29. Breiman L. Random forests. *Machine Learning* 2001;45:5–32.
30. Hanley JA, McNeil BJ. The Meaning and Use of the Area Under a Receiver Operating Characteristic (ROC) Curve. *Radiology* 1982;143:29–36. [PubMed: 7063747]
31. McNeil BJ, Hanley JA. Statistical Approaches to the Analysis of Receiver Operating Characteristic (ROC) Curves. *Medical Decision Making* 1984;4:137–50. [PubMed: 6472062]
32. Sievers CK, Grady WM, Halberg RB, Pickhardt PJ. New insights into the earliest stages of colorectal tumorigenesis. *Expert Rev Gastroenterol Hepatol* 2017 (in press).
33. Yang CY, Tseng JY, Chen CF, et al. Genome-wide copy number changes and CD133 expression characterized distinct subset of colon polyps: differentiation between incidental polyps and cancer-associated polyps. *International Journal of Colorectal Disease* 2015;30:1617–26. [PubMed: 26206347]

Fig. 1—. Large tubulovillous adenoma at CT colonography.

3D CTC image from asymptomatic 74-year-old woman shows a lobulated polypoid mass in the sigmoid colon that measures 3 cm. This corresponds to the middle 2D image on the bottom row in Fig. 3, and proved to be a tubulovillous adenoma.

Fig. 2—. Expansion of Haralick Model from 2D to 3D Space.

The left image illustrates Haralick's original four directions (0° , 45° , 90° , 135° from the center reference pixel) used for calculation of textural measures in 2D space. Expansion to 3D space, illustrated on the right, allows for thirteen directions (from the center reference voxel) to be used in calculation of textural measures.

Fig. 3—. CT colonography images showing semi-automated segmentation.

Collage of CTC images showing the colorectal masses that were segmented semi-automatically for volumetric textural analysis. Four of these cases were adenocarcinoma (the top left image and the entire middle row). The remaining masses were all benign tubulovillous adenomas (TVA). Note the middle image of the bottom row corresponds to the lesion presented in Figure 1.

Fig. 4—. ROC curves for human readers versus volumetric textural analysis. ROC curves demonstrating performance of volumetric textural analysis (VTA) versus individual and pooled human readers.

Table 1:

Comparison of Adenocarcinoma and Advanced Adenoma Cohorts

Metric	Adenocarcinoma Cohort	Advanced Adenoma Cohort	P-value	All Patients
Number of patients	28	31	-----	59
Mean patient age [$\pm$ SD] (years)	68.9 $\pm$ 14.2	64.3 $\pm$ 10.3	0.157	66.5 $\pm$ 12.4
Patient ratio (male:female)	11:17	19:12	0.121	40:39
Number of lesions	32	31	-----	63
Mean lesion diameter [$\pm$ SD] (cm)	4.4 $\pm$ 1.3	4.0 $\pm$ 1.2	0.223	4.2 $\pm$ 1.3
Lesion location ratio (right colon:left colon)	15:15	17:16	1.000	32:31

Table 2:

Diagnostic Performance of Human Readers and VTA

Metric	Reader 1	Reader 2	Reader 3	All Readers	VTA	P-value
Sensitivity	84.4% (27/32)	96.9% (31/32)	93.8% (30/32)	91.7% (88/96)	83.6% (2675/3200)	0.034
Specificity	74.2% (23/31)	77.4% (24/31)	80.6% (25/31)	77.4% (72/93)	87.5% (2713/3100)	0.007
PPV	77.1% (27/35)	81.6% (31/38)	83.3% (30/36)	80.7% (88/109)	87.4% (2675/3062)	0.057
NPV	82.1% (23/28)	96.0% (24/25)	92.6% (25/27)	90.0% (72/80)	83.8% (2713/3238)	0.165
Accuracy	79.4% (50/63)	87.3% (55/63)	87.3% (55/63)	84.7% (160/189)	85.5% (5388/6300)	0.753