Computed Tomographic Enterography Adds Information to Clinical Management in Small Bowel Crohn's Disease

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Background: CT enterography yields striking findings in the bowel wall in Crohn's disease. These images may help to evaluate whether small bowel narrowing results from active disease requiring anti-inflammatory therapy. However, the clinical relevance of these images is unknown. It is also not known if these radiologic findings correlate with objective biomarkers of inflammation.

Methods: In a blinded and independent evaluation, IBD subspecialty gastroenterologists reviewed clinical data, and CT radiologists reviewed CT enterography scans of 67 consecutive patients with Crohn's disease and suspicion of either small bowel inflammation or stricture. Comparisons were made between (1) clinical and radiologic assessments of inflammation and stricture, (2) clinical assessments before and after computed tomographic enterography (CTE) reports were revealed, and (3) radiologic findings and objective biomarkers of inflammation.

Results: (1) Individual CTE findings correlated poorly (Spearman's rho < 0.30) with clinical assessment; (2) clinicians did not suspect 16% of radiologic strictures, and more than half the cases of clinically suspected strictures did not have them on CTE; (3) CTE data changed clinicians' perceptions of the likelihood of steroid benefit in 41 of 67 cases; (4) specific CTE findings correlated with CRP, and a distinct set of CTE findings correlated with ESR in the subset of patients who had these biomarkers measured.

Conclusions: CTE seems to add unique information to clinical assessment, both in detecting additional strictures and in changing clinicians' perceptions of the likelihood of steroids benefiting patients. The biomarker correlations suggest that CTE is measuring real biologic phenomena that correlate with inflammation, providing information distinct from that in a standard clinical assessment.

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Crohn's disease of the small intestine is frequently manifested by abdominal pain. However, it is often not clear, despite careful clinical evaluation, whether this pain is caused by inflammation, by stenosis and upstream dilation, or by a combination of inflammation and stricture. Ideally, diagnostic assessment could differentiate which process is predominant, and therapy could be directed at either inflammation (e.g., steroids, infliximab) or stricture (e.g., dilation, strictureplasty, or resection). Small bowel follow-through can define the extent and severity of narrowing, but it provides little data on whether narrowing results from inflammation of the wall of the intestine. Similarly, endoscopy only assesses the superficial mucosa and does not evaluate the transmural inflammation in Crohn's disease. A diagnostic tool that allows imaging of the entire wall may add additional clinical information and enable physicians to make more informed treatment decisions for their patients with Crohn's disease and abdominal pain.

Computed tomographic enterography (CTE) has been recently applied to the study of Crohn's disease. This rapid, high-resolution scan captures far more detail than a standard CT and has revealed new findings of unknown significance in Crohn's disease. By using low-density "negative" oral contrast and 1.25-mm slices, more information can be obtained from the bowel wall. Wold et al demonstrated that this method was feasible and tolerated by patients and did not miss fistulas in 23 cases.[1] A study by Guidi et al of 35 patients with Crohn's disease showed a positive correlation between activity seen on CTE and CDAI of more than 150 (active disease) and a correlation between an elevated ESR and the presence of fistulas.[2]

The inflammatory markers erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are not well understood in Crohn's disease despite their frequent use. Neither ESR nor CRP is consistently elevated in active disease, yet both are correlated with disease activity. In addition, they do not always correlate with each other. Guidi's data suggest that ESR may correlate with the breaching of the bowel wall by the disease process. Other studies[3] have suggested that elevated CRP correlates with responsiveness to medications that reduce leukocyte attachment to blood vessel endothelium.

Although CTE produces remarkable images, we do not know whether the information gained adds to clinical deci-

sion making, or if we are simply spending valuable health care dollars for very nice pictures. We do not know if CTE is able to detect unsuspected strictures or to affect management in meaningful ways. We do not know if CTE correlates with objective biomarkers of inflammation like ESR and CRP. Therefore, we designed a retrospective, blinded evaluation study to test the following hypotheses:

1. CTE findings correlate well with clinical ratings of inflammation ($r > 0.7$);
2. CTE detects additional strictures beyond those suspected by clinicians;
3. CTE results lead to changes in the clinical likelihood of benefit from steroids; and
4. CTE findings correlate ($r > 0$) with objective laboratory markers of inflammation (ESR, CRP).

MATERIALS AND METHODS

Study Design

The study design is presented diagrammatically in Figure 1. To summarize, retrospective independent evaluations of anonymized clinical information were performed by IBD subspecialists (P.H. and E.M.Z.) blinded to the CTE findings, and retrospective independent evaluations of the CT enterography scans were performed by 2 CT radiologists (J.F.P. and L.P.S.) blinded to the clinical information. Both the clinical and radiologic evaluators reached consensus on the ratings, which were used in all statistical analyses. Repeat evaluations were done by the clinical evaluators after the CTE reports were revealed. Biomarkers (C-reactive protein, Westergren erythrocyte sedimentation rate) were recorded if measured in the 2 weeks before CTE. Statistical comparisons of (1) clinical rating of inflammation with radiologic rating of severity, (2) clinical rating of stricture likelihood with radiologic presence of stricture, (3) clinical rating of likelihood of steroid response before CTE reports were revealed to clinicians with that after CTE reports were revealed to clinicians, and (4) CTE radiologic findings with biomarkers were performed. Examples of these radiologic findings in Figure 2.

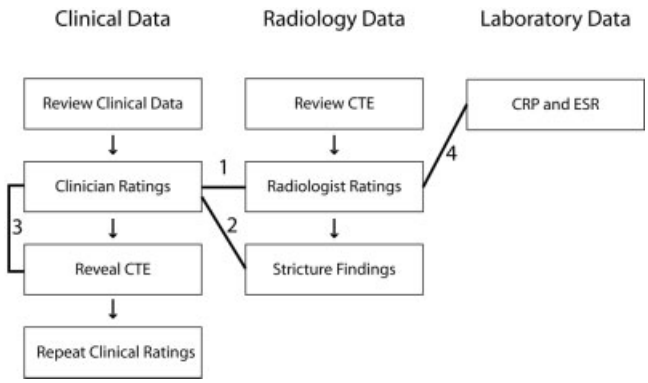

FIGURE 1. Study design. The subjects were evaluated independently by IBD subspecialty physicians blinded to the CTE findings and by CT radiologists blinded to the clinical findings. The IBD subspecialists reviewed anonymized packets of clinical information, including clinic notes, hospital notes, laboratory tests, endoscopy reports, pathology reports, and small bowel follow-through reports, if available, from the 6 months before the CT enterography date. The clinicians then independently rated the overall severity of inflammation (0–3), likelihood of stricture (1–5), and likelihood of response to steroids (1–5). Then the 2 clinicians came to a consensus to produce a single rating for statistical analysis. Then the results of the CTE report were revealed to the clinicians, and the 3 ratings of overall severity of inflammation, likelihood of stricture, and likelihood of response to steroid were repeated. Independently, the CT radiologists, blinded to the clinical data, rated 6 items in the images of the terminal ileum on a severity scale of 0 to 3 (none, mild, moderate, severe): mucosal enhancement, bowel vascularity, bowel wall thickening, fat stranding, local fluid (edema), and bowel fat. A global rating of severity on a scale of 0 to 3 was also recorded. In addition, possible strictures were measured, and the most narrow lumen diameter in millimeters and the proximal bowel diameter (at greatest dilation) in millimeters were recorded. For purposes of this study, a true stricture was defined as a luminal narrowing to less than 6 mm in the ileum with proximal dilation to 3 times the diameter of the narrowing. Four comparisons were made: (1) between the ratings of the clinician and the radiologist on inflammation and global severity, (2) between the clinicians' prediction of strictures and the radiologic presence of strictures, (3) between the clinicians' ratings before and after CTE data were revealed, and (4) between the radiologic findings and biomarkers of inflammation (Westergren erythrocyte sedimentation rate, C-reactive protein).

Patient Population

Sixty-seven consecutive patients with Crohn's disease and a suspicion of small bowel narrowing or inflammation on their requisition for a CTE (abdominal pain, vomiting, or some other stated reason for concern for small intestinal stricture or inflammation) were selected for retrospective evaluation. CTEs were obtained between October 2002 and March 2004. One patient appeared twice in the dataset because of a second CTE performed for clinical reasons during the review period.

Clinical Evaluation

The IBD subspecialist clinicians (blinded to CTE results) evaluated all 67 subjects based on anonymized packets of clinical data from the 6 months before CTE, which included (if available): clinic notes, hospital notes, laboratory tests, endoscopy reports, pathology reports, and small bowel follow-through reports. The evaluations included (1) a rating of inflammation on a scale of 0 to 3 (none, mild, moderate, severe), (2) a rating of the likelihood of the presence of a clinically significant stricture on a scale of 1 to 5 (very unlikely, unlikely, not sure, likely, very likely), and (3) a rating of the likelihood of clinical response to steroids on a scale of 1 to 5 (very unlikely, unlikely, not sure, likely, very likely). Consensus ratings were reached and recorded, and

then CTE reports were revealed. Ratings were repeated independently, and post-CTE consensus ratings were reached.

Radiologic Evaluation

The 2 CT radiologists independently evaluated 58 of the CTE scans while blinded to the clinical data, including determining if luminal narrowing was present. If such narrowing were found, each radiologist independently measured the smallest diameter and the largest proximal dilation, both in millimeters. Consensus was reached on each measurement, and a narrowing was only considered a true radiologic stricture if both the luminal diameter was less than 6 mm and the proximal dilation was at least 3 times the diameter of the smallest luminal narrowing.

For 47 of the CTE scans, independent ratings of individual findings were made on a scale of 0 to 3 (none, mild, moderate, severe). The findings recorded were mucosal vascularity, bowel wall thickening, mucosal enhancement, localized fluid (edema), extraluminal gas, fat stranding, bowel fat, fat proliferation, lymphadenopathy, feces sign, fistulas, and a global assessment. Consensus ratings were reached and recorded for each finding.

Biomarker Data

As this was a retrospective study, it was only sporadically that these assays had been performed within 2 weeks of the date of the CTE. As (1) the choice to perform these assays may not have been random, and (2) these assays were performed in only a small number of our 51 subjects, we evaluated correlations of radiologic findings with these biomarkers as an exploratory, hypothesis-generating endpoint.

Ethical Considerations

Institutional review board approval for this retrospective review of data already collected for clinical reasons was obtained (IRB no. 2003-0306). As it was impracticable to contact and obtain consent from all 67 patients to review data retrospectively, a waiver of the requirement for informed consent was approved by the institutional review board.

Statistical Methods

SAS 9.1 (Cary, NC) was used for the statistical analysis of the correlation between clinical assessment of inflammation and CTE findings, with Spearman's rho calculated for each pairwise correlation and an alternative hypothesis of rho = 0. The same statistical approach was used for the correlations between CTE findings and biomarkers (CRP and ESR). A kappa statistic with a 95% confidence interval was calculated for the agreement between clinically suspected strictures (likelihood = likely or very likely) and radiographically defined strictures. A change in the likelihood of steroid benefit was defined as a change of at least 1 unit on a likelihood scale of 1 to 5, and simple proportions and percentages were calculated for the frequency of changes in this likelihood after CTE reports were revealed.

RESULTS

CTE Findings Are Not Equivalent to Clinical Assessment

We initially tried to determine whether CTE was merely replicating and reinforcing the clinical impression. If CTE measures the same information, then it is not likely to contribute significantly to clinical decision making. We found that the CTE findings of mucosal enhancement, mucosal vascularity, bowel wall thickening, fat stranding, localized fluid (edema), bowel fat, fat proliferation, extraluminal gas, lymphadenopathy, fistulas, feces sign, and the radiologists' global assessment all correlated poorly with the clinicians' ratings of inflammation (Table 1). No individual finding had a correlation greater than 0.30 (Spearman's rho). We attempted to use multiple regression modeling to combine these radiologic ratings and predict the clinical rating of inflammation and could predict no more than 27% of the variance in clinical ratings with the best model.

FIGURE 2. Typical findings of CT enterography in Crohn's disease. These images illustrate the findings identified by the 2 radiologists reviewing the CTEs, including: (A) mucosal enhancement, recognized by the bright density arising from the bowel mucosa surrounded by the bowel wall; (B) increased mesenteric vascularity, recognized by the engorged vasculature associated with the abnormal bowel; (C) bowel wall thickening, recognized by the thickened bowel, wall which normally measures less than 3 mm thick (the bowel wall is the same density as the pelvic musculature); (D) extraluminal fluid, recognized by extraluminal fluid (outside the bowel loops) surrounded by an irregular wall and mesenteric stranding; (E) mesenteric stranding, recognized by ill-defined haziness in the mesentery, which has a brighter density than mesenteric fat; (F) extraluminal gas, recognized by very low-density foci outside the bowel loops (gas is lower density than fluid); (G) fatty proliferation, recognized by prominent fat displacing bowel loops toward the periphery of the abdomen (fat is lower density than fluid and mesenteric stranding); (H) lymph node enlargement, recognized by the abnormal soft-tissue masses in the mesentery, measuring at least 1 cm; (I) feces sign, recognized by intraluminal solid material intermixed with gas in the small bowel (normally seen in the colon and rectum, but when seen within a loop of small bowel suggests poor transit time through the involved bowel segment); and (J) bowel fat, recognized by the crescentic low attenuation in the bowel wall, indicating fat (unlike mesenteric fat, this finding is adjacent to the bowel mucosa and is confined to the bowel wall).

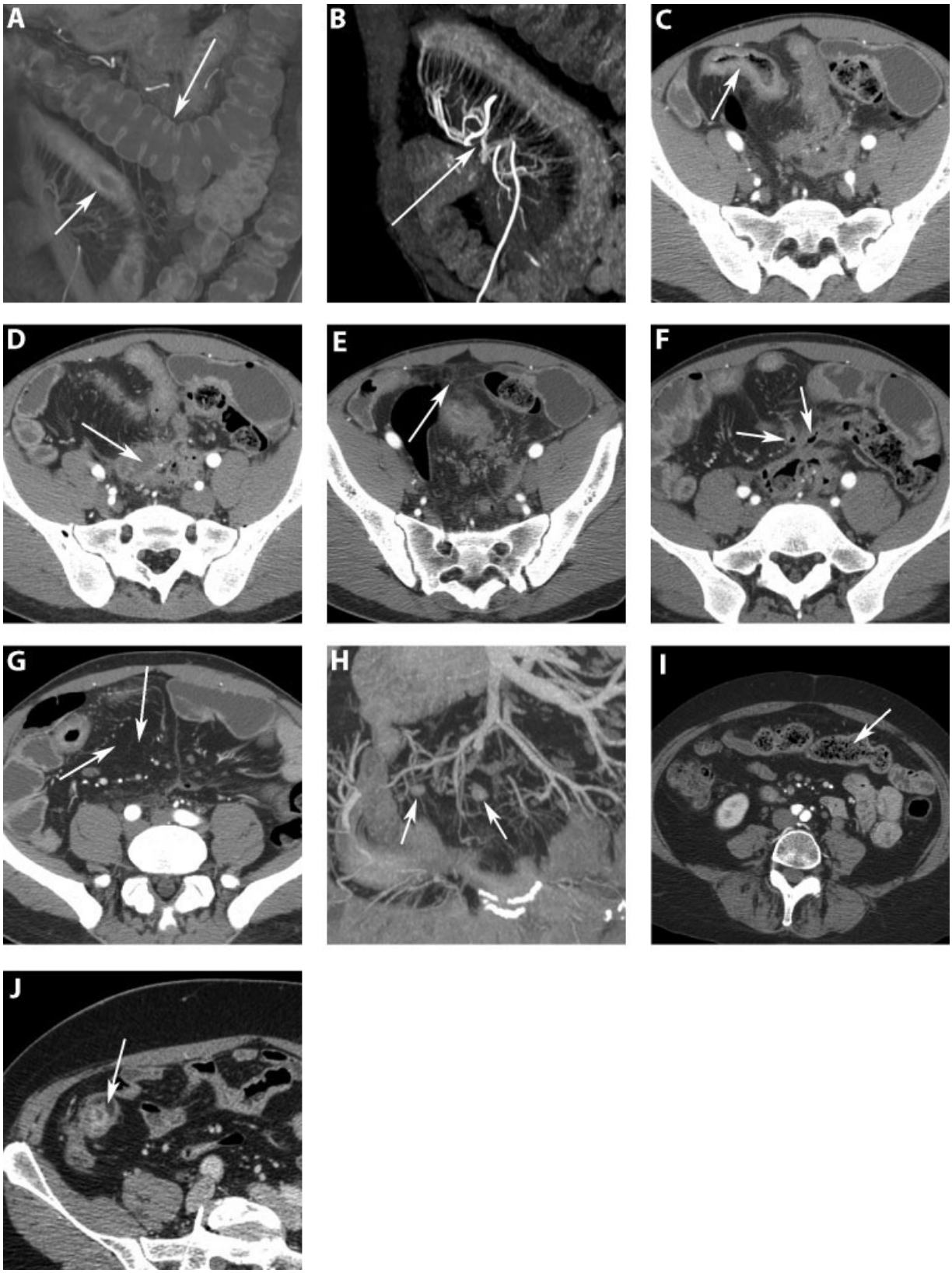

FIGURE 2

TABLE 1. Spearman Correlation between CTE Findings and Clinician Assessment of Inflammation Is Poor ($n = 46$)

CTE Finding	Correlation with clinical inflammation rating (0–3)*
Mucosal enhancement	0.17
Mucosal vascularity	0.13
Bowel wall thickening	0.09
Localized fluid (edema)	0.27
Fat stranding	−0.01
Extraluminal gas	0.20
Fat proliferation	−0.14
Lymphadenopathy	0.12
Fistulae	0.29
Feces sign	0.17
Bowel fat	−0.19
Radiologists' global assessment	0.16

*Pearson's rho with clinical inflammation ratings of none, mild, moderate, or severe (0–3).

Clinicians Suspect Most True Strictures, But Suspect Many More

We then assessed whether clinicians suspected most or all of the CTE-identified true strictures. By requiring upstream dilation to be at least 3 times the minimum luminal stricture diameter on the CTE, we used a strict endpoint for stricture as our gold standard. Strictures clinically identified as either "possible" or "likely" were defined as clinical suspicion of stricture. According to this definition, the clinicians suspected 84% (16 of 19) of the CTE-identified strictures. However, the clinicians' suspicion of stricture was not very specific, as 17 of 33 subjects in whom strictures were suspected did not have them by these criteria. We found that the overall agreement between clinicians' assessment and the CTE-identified true strictures was poor, with a kappa of 0.34 (95% CI 0.13–0.55; Table 2). CTE was able to identify an additional 3 unsuspected strictures and was able to demonstrate there was not a radiologically significant stricture in more than half the subjects with suspected strictures in this study sample.

CTE May Change Steroid Use

We then simulated a clinical situation, in which clinicians made their assessment of the patient's likelihood of response to steroids based on available clinical data, and then revealed the findings of the CTE. We then determined whether the CTE findings changed the clinicians' perceived likelihood of steroid benefit for the patient. We found the CTE findings changed the perceived likelihood of steroid benefit in 41 of 67 cases (61%) (Table 3). This was not unidirectional. After the CTE information was revealed, steroids were rated more likely to help in 18 cases, and less likely to help in 23 cases. In 9 cases, the rating changed at 2 levels on the 5-point likelihood scale, 5 with increased likelihood of steroid benefit, and 4 with decreased likelihood.

TABLE 2. Agreement between Clinician Assessment of Likelihood of Strictures and Presence of Radiologic Strictures ($n = 58$)

Clinical likelihood of stricture	Radiologic stricture	
	Present	Absent
Very unlikely or unlikely	22	33
Not sure, likely, or very likely	17	16

Kappa = 0.34 (95% CI: 0.13–0.55).

CTE Findings Correlate with Objective Biomarkers

In an exploratory data analysis, we looked at the cases in which either a CRP or ESR was drawn within 2 weeks of the CTE scan. A limited number of subjects had timely biomarkers available (CRP: $N = 9$; ESR: $N = 27$), and they were not a random selection, so this analysis can only be used to generate hypotheses for future, more definitive studies. We found that mucosal vascularity and global enhancement correlated with CRP and that extraluminal findings (extraluminal gas, localized fluid) seemed to correlate with ESR (Table 4). Several findings were negatively correlated with ESR, including fat proliferation, feces sign, mucosal enhancement, and bowel wall thickening.

DISCUSSION

We found that CTE identifies findings clearly different from, and perhaps complementary to, those identified through clinical assessment. CTE seems to add useful information about stricture detection and changes simulated clinical de-

TABLE 3. Effect of CTE Findings on Clinicians' Perceived Benefit of Steroid Use ($n = 67$)

Likelihood before CTE	Likelihood after CTE			
	Very unlikely	Not likely	Not sure	Likely
Very unlikely	7	4	4	0
Not likely	15	7	7	1
Not sure	3	3	7	2
Likely	0	1	1	5

Weighted kappa = 0.32 (95% CI: 0.14–0.49).

TABLE 4. Spearman Correlation of CTE Findings with Objective Biomarkers

CTE finding	Correlation with CRP (n = 9)	Correlation with ESR (n = 27)
Mucosal enhancement	0.10	−0.35
Mucosal vascularity	0.38	−0.23
Bowel wall thickening	0.00	−0.36
Localized fluid (edema)	0.00	0.22
Fat stranding	0.04	0.06
Extraluminal gas	0.00	0.31
Fat proliferation	−0.21	−0.39
Lymphadenopathy	0.02	−0.06
Fistulas	0.29	−0.03
Feces sign	0.05	−0.36
Bowel fat	−0.77	−0.19
Radiologists' global assessment	0.26	−0.26

cision making about steroid use. Thus, CTE seems to be a useful tool in the evaluation of patients with Crohn's disease and abdominal pain.

Patients with Crohn's frequently develop abdominal pain as a result of bowel narrowing. Commonly used imaging modalities such as SBFT identify narrowing but do not demonstrate whether the narrowing is due to inflammation and tissue edema or whether it is fibrotic. Clinical response to an empiric trial of potent anti-inflammatory therapy including steroids or infliximab is often used to provide a clue about the nature of the narrowing. As Crohn's is a transmural disease, it should not be too surprising that being able to image the full thickness of the bowel wall adds information to the assessment of these patients. Our finding that CTE does not simply recapitulate clinical assessment and is able to identify unsuspected strictures supports this idea.

Our exploratory analysis of biomarkers that might correlate with CTE found an apparent correlation of CRP with vascular and intrabowel findings and of ESR with extraluminal findings. These hypotheses need to be tested in larger prospective studies. If proven, they may provide new insight as to the meaning and clinical implications of elevated expression of these markers in Crohn's patients.

Because CRP has been shown to be elevated in coronary artery disease, it is tempting to speculate that the correlation between CRP and both increased vascularity and mucosal enhancement means the CTE findings are detecting inflammation at the vascular level. Many studies have connected vascular inflammation and abnormalities in vascular function to the pathogenesis of inflammatory bowel disease.[4–7] CTE may offer a noninvasive way to detect vascular abnormalities in Crohn's disease that was not previously available. Findings similar to ours, of elevated CRP correlating with increased vascularity detected on CTE, were observed in a study designed with this correlation as a primary endpoint.[8] However, a different study, which used either SBFT or CTE to detect radiologic abnormalities in Crohn's disease, did not find a correlation with CRP.[9] A study by Guidi et al[2] showed that ESR was correlated with fistulas, similar to our finding of a correlation between extraintestinal manifestations and ESR, but we had too few fistulas to report any correlation.

This study had several limitations. Because of the retrospective character of the study, bias in assessment was a possibility. We minimized this by blinding the radiologists to the clinical data and blinding the clinicians to the CTE data in the initial assessment. Also because this was a retrospective study, we had incomplete data on many patients. Some patients had not had a recent CRP or small bowel follow-through. Others had not had a recent endoscopy with biopsy at the time of CTE. This limitation made the clinical assessment a bit more true to practice, where complete data are rarely available. However, the clinical assessment also lacked direct physical assessment, and it is not clear that reading notes, lab reports, and radiologic reports accurately simulates clinical assessment in actual practice. The biomarkers we chose to evaluate have been measured infrequently, so the correlations found should be conservatively considered as hypothesis-generating.

From this study we have learned that CTE offers new, complementary information about symptoms of obstruction in Crohn's disease, rather than merely confirming and reinforcing the clinical impression. Our finding is supported by the results of the recent study by Bodily et al, which showed that quantitative measurement of mural attenuation on CTE was highly correlated with histologic findings of inflammation.[10] In addition to detecting mucosal inflammation, CTE seems to be able to detect functionally significant and clinically unsuspected strictures and to rule out significant strictures in many patients in whom they are suspected. The simulation of clinical decision making about steroid benefits in the present study suggests CTE may also be able to change clinical management in this group of patients. However, to prove the value of CTE in the clinical assessment of Crohn's disease, we need prospective studies that can determine whether the information gained from CTE actually changes clinical decision making and clinical outcomes. Future research should also address whether vascular findings on CTE are truly detecting vascular dysfunction and whether ESR is truly a marker of Crohn's disease activity extending beyond the serosa.

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