Detecting active inflammation and fibrosis in pediatric Crohn’s disease: prospective evaluation of MR-E and CT-E

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Abstract

Symptoms of Crohn’s disease (CD) can be due to active inflammation or fibrosis. Differentiating these based on clinical presentation, endoscopy, laboratory parameters, and clinical scoring methods can be inaccurate and/or invasive. As therapy decisions are often directed based on whether active disease or fibrosis is present, a reliable and non-invasive test to distinguish these two etiologies would be a powerful clinical tool. CT enterography (CT-E) and MR enterography (MR-E) are two non-invasive imaging modalities tailored to evaluate the small bowel. The purpose of our study was to compare the ability of MR-E and CT-E to assess for active inflammation and mural fibrosis in patients with known CD as compared to a histologic reference standard. After obtaining MR-E and CT-E on the same day, a total of 61 histologic samples were obtained from twelve subjects aged 12–20 years via full-thickness bowel resection or endoscopy. These were evaluated by the pathologist for active inflammation and fibrosis. We found that while CT-E and MR-E were similar in their accuracies of depicting active inflammation, MR-E was significantly more sensitive in detecting fibrosis. Because of this and the lack of ionizing radiation from MR-E, we believe that MR-E rather than CT-E should serve as the primary imaging modality for the assessment of CD pediatric patients with non-acute clinical exacerbations.

Key words: Crohn’s disease—Fibrosis—MR enterography (MR-E)—CT enterography (CT-E)

Crohn’s disease (CD) is a chronic relapsing transmural inflammatory disorder of the gastrointestinal tract affecting approximately 600,000 people worldwide with 25% to 30% of all Crohn’s patients being younger than 20 years of age [1, 2]. The inflammatory process of Crohn’s disease is thought to arise from altered gut mucosal immunity leading to cytokine overproduction and increased bowel wall leukocyte infiltration [3]. Longstanding bowel inflammation and tissue remodeling over time can lead to mural collagen deposition and intestinal fibrosis, causing fixed luminal narrowing and obstruction [4]. Four major subtypes of Crohn’s disease have been described and include active inflammatory, fibrostenotic, fistulizing/perforating, and reparative/regenerative. Accurate classification is important for guiding therapeutic decision-making [5].

Deciding if a Crohn’s disease patient’s symptoms are related to active inflammation or fibrosis is of utmost importance as this directs therapy [6]. For active inflammation, a host of anti-inflammatory drugs are effective therapeutic choices including corticosteroids, aminosalicylates, and immunomodulatory drugs such as azathioprine, methotrexate, and anti-TNF-α antibodies [7]. Fibrosis, in contrast, is an irreversible sequela of chronic inflammation and is therefore unresponsive to medical therapy; mechanical treatments including balloon dilation, stricturoplasty, and bowel resection are usually required for symptomatic relief [8].

Crohn’s disease activity is difficult to evaluate by patient symptomatology alone. As a result, various methods have been used to gauge disease activity including optical and wireless capsule endoscopic visualization, endoscopic biopsy grading, clinical scoring methods such as the Crohn’s disease activity index (CDAI), and serum inflammatory markers such as ESR and CRP. These methods, however, are imperfect. Although Crohn’s disease most frequently affects the small bowel, optical endoscopy is unable to visualize lesions...
between the proximal jejunum and terminal ileum. Endoscopic biopsies, when technically feasible, demonstrate high accuracy for detecting active inflammation but are invasive. In addition because they only sample the mucosa, they cannot evaluate the deeper bowel wall layers where collagen deposition in fibrosis occurs. Wireless capsule endoscopy can evaluate the entire small bowel but does not allow for histologic sampling. It is associated with a significant capsule retention rate (up to 13%) in CD patients and is therefore contraindicated in patients with suspected small bowel obstruction [9]. CDAI is the best known clinical index for Crohn’s disease but is rarely used in clinical practice because of its subjectivity and labor-intensiveness (including 13 different clinical criteria and a 7 day patient symptom log). Serum inflammatory markers show incomplete correlation with disease activity and infer rather than visualize a specific bowel lesion. If uncertainty persists in regards to the nature of a lesion (active inflammation vs. fibrosis), a 5–10 day steroid trial may be undertaken. However, most patients in this scenario have already failed previous steroid therapy, so a lack of steroid-responsiveness is not informative. In addition, clinical and serum assessment of Crohn’s disease would likely have difficulty in distinguishing fibrosis only from remission, as both states would be characterized by lack of active inflammation. A test that can identify mural fibrosis that warrants surgical intervention in patients with Crohn’s disease is needed.

While other more sensitive tests, such as CO2 double-contrast barium enteroclysis or capsule endoscopy can detect subtle mucosal abnormalities and are therefore considered very sensitive for the initial diagnosis of Crohn’s disease [10], CT enterography (CT-E) and MR enterography (MR-E) are two non-invasive imaging modalities tailored to evaluate small bowel abnormalities using a large volume of oral contrast. They are used both in the initial diagnosis and follow-up of patients with Crohn’s disease. Studies in adult patients with CD have demonstrated MR-E to be comparable to CT-E for detecting active small bowel inflammation [11–13]. MR-E is also a promising imaging modality for detecting mural fibrosis, given its superior soft tissue contrast for bowel wall tissue characterization. Few studies in the literature have directly assessed the ability of imaging studies to detect bowel fibrosis. One recent paper compared standard CT with positive oral contrast to MR-E in pediatric CD patients and showed that MR-E was highly accurate in detecting active inflammation [14]. In addition, in the absence of co-existing active inflammation, MR-E also demonstrated high accuracy for detecting mural fibrosis. However, given that CT-E is one of the most commonly performed imaging modalities for CD evaluation, an important unanswered question is to compare the ability of MR-E to CT-E to detect active inflammation and mural fibrosis.

The purpose of this study is to prospectively compare the ability of MR-E and CT-E to assess disease activity (active inflammation and mural fibrosis) in patients with known Crohn’s disease compared with a histologic reference standard.

Materials and methods

IRB, HIPAA compliance and consent

This prospective, single institution study was conducted with Institutional Review Board approval and in accordance with the Health Insurance Portability and Accountability Act. Informed consent from the subject’s guardian and assent were obtained for subjects between age 10 and 18. Informed consent was obtained from subjects greater than 18 years of age.

Inclusion and exclusion criteria

All enrolled patients were scheduled to undergo CT-E for symptoms including abdominal pain, change in bowel habits, fever, and leukocytosis. As part of our study, all subjects additionally underwent an MR-E immediately after the CT-E. A primary inclusion criterion was patient age 18 years or younger; patients older than 18 were eligible if they continued to receive medical care from a pediatric gastroenterologist. Study exclusion criteria included inability to undergo MRI without sedation, the presence of MRI-incompatible metallic hardware, and renal impairment (estimated glomerular filtration rate < 60 mL/min/1.73 m²). A total of 23 subjects were enrolled in the study. For analysis of disease activity, we only included the 12 subjects who subsequently underwent surgical bowel resection or endoscopic biopsy within 7 weeks of the imaging studies.

Image acquisition

A single common oral contrast prep was administered to patients beginning one hour before the CT-E examination. This consisted of both 900 mL of dilute barium and sorbitol (VoLumen E-Z EM, Lake Success, NY) to facilitate bowel distention as well as 300 mL of superparamagnetic iron oxide particles to alter bowel lumen MRI signal intensity (GastroMARK; Mallinckrodt, St. Louis, MO). With this preparation, the lumen of the bowel appears fluid density on CT images. On MRI, the bowel lumen is hypointense on both T1 and T2 images, increasing the sensitivity for detecting active inflammation of the bowel wall which appears bright on T1 post contrast images and T2 weighted images.

CT-E was performed on a 16 detector helical scanner (GE Lightspeed; Milwaukee, WI). Standard departmental radiation dose reduction techniques, including auto-mA tube current modulation and weight-based modulation of tube current, voltage, and noise index, were used. Intravenous contrast (Isovue 370) was
injected and images were acquired in the portal venous phase. Images were acquired at 5 mm slice thickness followed by reconstruction to 2.5 mm for axial image interpretation. Coronal and sagittal reformats were obtained.

MR-E was performed on either a 1.5T or 3T scanner (Siemens Magnetom; Malvern, PA) utilizing a Total Imaging Matrix whole-body surface coil design. Subjects were placed supine on the MRI scanner table and 3-plane localizer images were obtained to evaluate bowel distension as well as patient positioning. Sequences obtained included coronal and axial single shot T2 weighted images with Half-Fourier acquisition (HASTE; this sequence is especially tailored to evaluate the bowel wall), coronal balanced steady-state free precession (True-FISP; this sequence is especially tailored to evaluate for mesenteric changes), axial fast recovery T2 (RESTORE) with fat suppression, dynamic 3D volumetric T1 fat-suppressed gradient echo breath hold (VIBE) with images acquired before as well as 1, 3, and 5 min after intravenous Gadopentetate dimeglumine administration, and high resolution post-contrast 2D T1 fat-suppressed spoiled gradient echo images. The average MR-E exam lasted 45 min. All imaging examinations were performed between 2007 and 2010.

Histologic evaluation of bowel inflammation
A total of 61 bowel segments were obtained from twelve subjects in the study, who had histologic bowel sampling performed within 7 weeks of imaging. Seven bowel segments were from endoscopic mucosal biopsies and 54 bowel segments were from full-thickness bowel excision. A single gastrointestinal pathologist, blinded to the imaging findings, original specimen interpretation and clinical history, assessed all histologic specimens. For surgical excisions, all specimens were sectioned at 5 or 10 cm intervals to obtain the bowel segments included. All bowel resection segments were evaluated for the presence or absence of active inflammation and mural fibrosis. All endoscopic mucosal biopsies were evaluated for active inflammation, but not fibrosis.

Active inflammation by histology consisted of neutrophilic infiltration of intestinal crypts (cryptitis and/or crypt abscess), erosion, ulcer, and fissure and/or abscess formation on H&E staining. Of those, the presence of cryptitis and/or crypt abscess was considered to be the minimal requirement for the diagnosis of active inflammation in this study. Mural fibrosis was defined as collagen fiber replacement involving at least one bowel layer (Table 1).

### Image Interpretation

Bowel segments were selected for imaging-pathologic correlation from each subject based on the locations of either the endoscopic biopsy or bowel resection specimens that were stained for histologic analysis. The location of each bowel segment was determined by the gross pathology and operative/endoscopic note description of relationship to known anatomic landmarks (distance from ileocecal valve, appendix, and/or anal canal). Two pediatric radiologists independently reviewed the CT-E and MR-E images of each bowel segment, blinded to the histologic result, and made an assessment of bowel inflammatory activity (normal, active inflammation, or fibrosis if applicable).

CT-E features of active inflammation included avid enhancement of an abnormally thickened (>3 mm but well distended) loop of bowel, submucosal edema and/or adjacent mesenteric inflammation (fat stranding, enlarged lymph nodes, prominent vasa recta). MR-E criteria for active inflammation included progressive transmural enhancement with an early mucosal component, adjacent mesenteric inflammation, and T2 hyperintensity of the bowel wall (relative to adjacent muscle; see Table 1; Figures 1, 2).

A loop of bowel was considered to meet imaging criteria for fibrosis on CT-E if it was abnormally thickened with minimal enhancement, demonstrated fatty infiltration of the submucosa (the so-called “fat-halo” sign), no adjacent mesenteric inflammation, was featureless in appearance, and/or demonstrated upstream bowel dilatation. MR-E criteria for fibrosis included bowel wall thickening without or with only mild transmural enhancement, lack of adjacent mesenteric inflammation, T2 iso- or hypointensity compared to adjacent muscle, anti-mesenteric pseudosacculation and/or upstream bowel dilatation (see Table 2) [15–18].

### Statistical analysis

Contingency tables were also constructed for comparing the ability of MR-E and CT-E to assess bowel inflammatory activity compared with histologic reference. McNamer’s test was performed to analyze the sensitivity

| Table 1. Criteria used to judge active inflammation in thickened loops of bowel by histology, MR-E and CT-E |
|---------------------------------------------------------|----------------------------------------------------------|----------------------------------------------------------|
| Pathology                                               | MR-E                                                     | CT-E                                                     |
| Neutrophilic infiltration of intestinal crypts          | Avid enhancement especially with an early mucosal component | Avid enhancement                                        |
| Adjacent mesenteric inflammation*                      | Adjacent mesenteric inflammation*                        |
| T2 hyperintense bowel wall (c/w adjacent muscle)       |                                                          |

*Adjacent mesenteric inflammation includes prominent mesenteric lymph nodes, engorgement of the vasa recta, fat stranding
and specificity differences of CT-E and MR-E for depicting acute inflammation and fibrosis. A Fisher’s exact test was performed to detect a statistical difference between the overall accuracy of CT-E and MR-E.

**Results**

**Demographics/histologic sampling**

All subjects included in this analysis underwent histologic bowel sampling within 7 weeks of the imaging studies (range 3–46 days; mean 18.6 days, median 19 days). Seven subjects were male; five of the subjects were female (range 12 years 3 months to 20 years 6 months, mean 16 years 10 months; median 17 years 2 months). For surgical resection segments from 8 patients, the length of resected specimen ranged between 2 cm (done for ileal diversion) and 39 cm with an average length of 27 cm. All sites of surgical resection included the distal ilium and proximal colon. A total of 54 segments were obtained for full-thickness histologic analysis of active inflammation and fibrosis. Seven additional endoscopic mucosal biopsies from 4 patients were included in the analysis of active inflammation only. All endoscopic biopsies included were obtained from either the terminal ileum or rectum because of the well-defined location that could be correlated with imaging.

**Histologic assessment**

Of 54 full-thickness segments, 27 demonstrated active inflammation, 26 demonstrated fibrosis, 22 exhibited both active inflammation and mural fibrosis, 5 with active inflammation only, 4 with mural fibrosis only, and 23 with neither active inflammation nor fibrosis. Of 7 additional biopsy samples, 5 demonstrated active inflammation, and 2 did not. Given the mucosal depth of endoscopic sampling, fibrosis could not be assessed.

**Imaging evaluation of active inflammation**

CT-E and MR-E assessment of active bowel inflammation was performed and compared with histologic reference.
We evaluated 61 total bowel segments, with 54 having a surgical excision reference and 7 having an endoscopic biopsy reference. Imaging evaluation of all bowel segments with histologic reference was performed, with the radiologist being blinded to the histologic result. MR-E demonstrated an 87.5% (28/32) sensitivity and 79.3% (23/29) specificity for active inflammation compared with histologic reference, while CT-E demonstrated a 100% (32/32) sensitivity and 62.1% (18/29) specificity for active inflammation. Accuracy for detecting active inflammation was 83.6% (51/61) for MR-E and 81.9% (50/61) for CT-E. Overall, there was no significant difference between CT-E and MR-E in sensitivity ($p = 0.125$) or specificity ($p = 0.226$) for detecting active inflammation. There was no difference in the accuracy of CT-E and MR-E ($p = .38$; see Table 3; Figure 3).

## Fibrosis

CT-E and MR-E assessment for bowel fibrosis was also performed, with comparison to histologic reference. For this analysis, we only included the 54 bowel segments that had full-thickness bowel excision as the histologic

![Fig. 2. Active inflammation by CT-E and MR-E in a 13 year old male. Axial CT (A, B) show avid enhancement of the thickened distal ilium (thin arrows). Additionally, there is engorgement of the adjacent vasa recta (open arrow) and adjacent ascites (thick arrow). Corresponding axial T1 FS post-contrast (C) and FRSE T2 FS (D) shows avid enhancement, T2 hyperintensity of the bowel wall (thick arrow) and adjacent ascites (open arrow).](image)

### Table 2. Histologic, MR-E and CT-E criteria used to judge fibrosis in thickened bowel loops

<table>
<thead>
<tr>
<th>Pathology</th>
<th>MR-E</th>
<th>CT-E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collagen deposition within at least one layer of bowel wall</td>
<td>Non-Avidly enhancing T2 iso to hypointense to adjacent muscle Lack of adjacent mesenteric inflammation</td>
<td>Non avidly enhancing Fatty Halo Lack of adjacent mesenteric inflammation Featureless bowel</td>
</tr>
</tbody>
</table>

### Table 3. Accuracy, sensitivity and specificity of CT-E and MR-E in detecting active disease compared to the histologic gold standard

<table>
<thead>
<tr>
<th>Active disease</th>
<th>Accuracy</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT-E</td>
<td>81.9%</td>
<td>100%</td>
<td>62.1%</td>
</tr>
<tr>
<td>MR-E</td>
<td>83.6%</td>
<td>87.5%</td>
<td>79.3%</td>
</tr>
</tbody>
</table>

The differences were not statistically significant.
Table 4. Accuracy, sensitivity and specificity of CT-E and MR-E in detecting fibrosis disease compared to the gold standard of a full-thickness histologic examination

<table>
<thead>
<tr>
<th>Fibrosis</th>
<th>Accuracy</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT-E</td>
<td>55.6%</td>
<td>42.3%</td>
<td>67.9%</td>
</tr>
<tr>
<td>MR-E</td>
<td>80.8%</td>
<td>57.1%*</td>
<td>82.1%</td>
</tr>
</tbody>
</table>

* MR-E was significantly ($p = 0.039$) more sensitive than CT-E in detecting fibrosis

reference for fibrosis. MR-E demonstrated 80.8% (42/54) accuracy, 73.1% (19/26) sensitivity, and 82.1% (23/28) specificity for depicting fibrosis compared with full-thickness histologic reference. CT-E demonstrated 55.6% (30/54) accuracy, 42.3% (11/26) sensitivity, and 67.9% (19/28) specificity for fibrosis. MR-E’s sensitivity for fibrosis detection was statistically higher compared to CT-E (McNemar’s test $p = 0.039$) but was not significantly more specific ($p = 0.289$). MR-E superior accuracy compared to CT-E approached statistical significance ($p = .058$ one tailed Fisher’s exact test; see Table 4; Figure 4).

Discussion

Disease activity is a critical determinant of the therapeutic approach to patients with Crohn’s disease, highlighting the need for an accurate and non-invasive method of characterizing Crohn’s disease activity. This
would help to identify those who, because they have active inflammation, require initiation or modification of medical treatment. The vast majority of prior studies examining imaging evaluation of Crohn’s disease focus on distinction between active and inactive disease. Accurate detection of inactive disease is clinically useful because it prevents unnecessary administration of immunosuppressive and biologic therapies that are expensive and have significant toxicities. However, accurate imaging detection of mural fibrosis is just as important, not only because it is refractory to medical therapy [19], but also because it is an indication for mechanical therapy via endoscopy or surgery. Because endoscopic techniques cannot assess the submucosal layers that accumulate collagen during the fibrotic process, cross-sectional imaging studies such as CT-E and MR-E are better suited for this task. The purpose of our study was to prospectively compare CT-E and MR-E for detection of active inflammation and fibrosis in pediatric Crohn’s disease patients compared to a histologic reference. To our knowledge, this is the first prospective imaging study for detection of Crohn’s fibrosis. In addition, this is the first prospective comparison of CT-E and MR-E in pediatric Crohn’s disease.

CT-E is widely available, easy to perform and interpret, and capable of detecting mucosal and submucosal disease making it a well-established imaging modality in Crohn’s disease [20, 21]. Previous studies in adult patients have shown CT-E to demonstrate high accuracy for detecting active inflammation [22]. Its ability to evaluate fibrosis has, to our knowledge, never been examined in a prospective fashion but it is thought to be less reliable for demonstrating bowel fibrosis [23] because of the relatively poor CT soft tissue contrast. No prospective studies have demonstrated increased risk of cancer in people receiving <100 mSv of cumulative radiation dose, calling into doubt the BIER VII supported linear non-threshold model in favor of threshold-quadratic model [24]. But it must be noted that compared with adults, children are more sensitive to the effects of radiation given their body habitus, rapid cell division, and longer latency period for cancer development [25]. Supporting this is a recent retrospective study by Pearce et al. in Lancet raising concern that, although small in

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**Fig. 4.** Discordant findings of active inflammation per CT but fibrosis per MRI; corresponding histologic specimen showed fibrosis. Axial CT-E (A) of the abdomen from a 16 y/o F shows an enhancing and thickened loop of distal ilium (thin arrows) with adjacent mesenteric stranding, which by CT criteria represented active inflammation. Two axial T2 HASTE images (B and C) show that this loop of bowel (thin arrows) is T2 isointense to adjacent muscle meeting MRI criteria for fibrosis. Additionally, there is upstream bowel dilation. The corresponding pathologic specimen (D) showed collagen deposition in the submucosa consistent with fibrosis.
absolute risk (1 case of brain tumor and 1 case of leukemia per 10,000 head CTs) there remains concern that diagnostic radiation in children may be associated with a non-zero cancer risk [26]. While a single CT-E exposes the patient to 3–10 mSv of radiation, Crohn’s patients often undergo multiple CTs given the chronic and relapsing nature of their disease. One study showed that CTs accounted for 84.7% of Crohn’s patients’ total diagnostic radiation exposure. The cumulative effective dose (CED) in one study of 399 CD patients exceeded 75 mSv in 15.5% of patients [27]. Although there have been recent advances and continue to be further research into CT dose reduction, a critical component of radiation reduction is to decrease the number of CT scans performed.

Concern over the potential radiation risks of CT has spurred the development and implementation of MR-E for Crohn’s disease evaluation. Previous studies in adult Crohn’s disease patients have demonstrated MR-E to be comparable to CT-E for detection of terminal ileum active inflammation, and prevailing thought is that substitution of MR-E for CT-E in appropriate clinical situations could lead to substantial reduction in radiation exposure. To our knowledge, a true imaging advantage of MR-E over CT-E for bowel evaluation in CD had not been demonstrated before this study. The superior soft tissue contrast of MRI relative to CT and its ability to dynamically assess bowel wall enhancement at multiple time points, have raised hopes that MR-E could accurately detect bowel fibrosis. By comparing MR-E and CT-E to a full-thickness surgical and endoscopically obtained histologic reference standard specimens, we determined that MR-E was significantly more sensitive than CT-E in depicting of fibrosis and similar in its depiction of active inflammation. By combining the lack of ionizing radiation with more accurate determination of fibrosis, we feel that MR-E can be used as the primary imaging modality in imaging non-acute but symptomatic pediatric Crohn’s patients. However, other factors must be considered including cost, scan time, patient compliance, and speed of interpretation (Table 5).

### Study limitations

This study was limited by a relatively small number of patients, as we limited our study to include patients who had histologic sampling performed within 7 weeks of imaging. However, in our study we were able to identify a total of 61 bowel segments for imaging-histologic correlation, including 54 full-thickness histologic specimens for fibrosis assessment. In addition, there was a variable latency between imaging and histologic sampling with a maximum delay of up to 46 days. Because the majority of patients in the study underwent open surgical resection, there needed to be flexibility in surgical scheduling to accommodate both the surgeons and the patients.

### Summary statement

MR-E is comparable to CT-E for detection of Crohn’s disease imaging features and active inflammation but is superior in the detection of fibrosis. This distinction is clinically useful as active inflammation is treated medically and fibrosis is treated surgically. MR-E additionally lacks ionizing radiation. We believe that MR-E rather than CT-E should serve as the primary imaging modality for assessment of CD patients with non-acute clinical exacerbations.

### Acknowledgments

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### References


### Table 5. Factors to consider when deciding to use CT-E or MR-E

<table>
<thead>
<tr>
<th></th>
<th>CT-E</th>
<th>MR-E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average time to complete examination</td>
<td>2 min</td>
<td>45 min</td>
</tr>
<tr>
<td>Cost of examination</td>
<td>+</td>
<td>+ +</td>
</tr>
<tr>
<td>Sedation needed</td>
<td>No</td>
<td>Occasionally in small children*</td>
</tr>
<tr>
<td>Time to perform examination</td>
<td>10 min</td>
<td>20 min</td>
</tr>
<tr>
<td>Radiation dose</td>
<td>3–10 mSv</td>
<td>None</td>
</tr>
<tr>
<td>Accuracy for detecting active inflammation</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Accuracy for detecting mural fibrosis</td>
<td>Fair</td>
<td>High</td>
</tr>
<tr>
<td>Image quality</td>
<td>Typically good with high spatial resolution</td>
<td>Variable depending on oral contrast bowel distention and patient motion</td>
</tr>
</tbody>
</table>

* Sedation was not required for any of the patients enrolled in our study.


