PET/MR Versus PET/CT Imaging: Impact on the Clinical Management of Small-Bowel Crohn’s Disease

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Abstract

Background and Aims: The aim of this study was to compare the accuracy and clinical impact of hybrid positron emission tomography [PET]/magnetic resonance-enterography [MR-E] and PET/computed tomography-enterography [CT-E] in patients with Crohn’s disease [CD].

Methods: A total of 35 patients with symptomatic small-bowel CD who were scheduled to undergo operation were evaluated before operation by same-day PET/CT-E and PET/MR-E. PET/MR-E was also compared with MR-E alone. Imaging accuracy for detecting pathological sites and discriminating between fibrotic and inflammatory strictures was assessed. Treatment was adjusted according to imaging findings and change in medical/surgical strategy was also evaluated.

Results: PET/CT-E, PET/MR-E, and MR-E were equally accurate in detecting CD sites. PET/MR-E was more accurate in assessing extra-luminal disease \( p = 0.002 \), which was associated with higher need for stoma \( p = 0.022 \) and distant localisation \( p = 0.002 \). When the latter was observed, laparoscopy was started with hand-assisted device, reducing operative time \( p = 0.022 \). PET/MR-E was also more accurate in detecting a fibrotic component compared with PET/CT-E \( p = 0.043 \) and with MR-E \( p = 0.024 \). Fibrosis was more frequently classified as inflammation with MR-E \( p = 0.019 \). Out of 8 patients with predominantly inflammatory CD who received medical treatment, 6 [75\%] remained surgery free. Overall, 29 patients received surgery. At median follow-up of 9 [6–22] months, no recurrences occurred in either the medical or the surgical group.

Conclusions: Preoperative PET/MR-E imaging is highly accurate for assessing CD lesions before operation and contributed to clinical management of patients with small-bowel CD more often than PET/CT-E.

Key Words: Crohn’s disease; diagnosis; surgery; magnetic resonance imaging; fibrosis; inflammation; pathology
1. Introduction

Crohn’s disease [CD] is a chronic granulomatous inflammatory bowel disease with a tendency toward remission and relapse. Patients with penetrating or fibrostenosing CD have higher need for surgery, disease recurrence, and mortality. Cross-sectional imaging is important in guiding treatment of CD, and each modality has specific advantages and drawbacks. PET/CT and PET/MR combines the morphological and physiological patterns provided by CT and MR, respectively, with the metabolic activity obtained by FDG-PET, as a single test. Although no studies have investigated the impact of PET/MR for the evaluation of CD, the advantages from the use of this hybrid technique may be expected.

In this study we prospectively assessed the effectiveness of PET/MR-enterography [MR-E] compared with PET/CT enterography [CT-E] in evaluating small-bowel CD and in determining its relevance on clinical management of patients with CD.

2. Materials and Methods

All patients with active CD observed between October 2012 and September 2014 were considered for inclusion. All patients gave their written informed consent for study enrolment. The study algorithm is depicted in Figure 1.

2.1. Inclusion and exclusion criteria

Patients included in the study underwent clinical assessment by a gastroenterologist and a surgeon with inflammatory bowel disease [IBD] expertise. Subjects ≥ 18 years old who were candidates for surgery for small-bowel CD were enrolled. Exclusion criteria were: perianal CD; pregnancy; known diabetes mellitus or blood glucose levels greater than 140 mg/dl [7.77 mmol/l]; non-diagnostic PET/MR image quality; or contraindication to MR imaging including incompatible metallic hardware or devices; ocular metallic foreign bodies; claustrophobia. The latter was considered an exclusion criterion for final data evaluation, but the rate of patient withdrawal was used to assess tolerability of the procedure.

2.2. PET/CT-E protocol

Patients fasted for at least 6h before imaging. On the day of imaging, blood glucose level was assessed with a blood glucose meter [OneTouch Vita, LifeScan, Milpitas, CA] to ensure that it was less than 140 mg/dl [7.77 mmol/l] and all patients started drinking a biphasic oral contrast solution consisting of 4 vials of 58.30 g macrogol 4 000 plus 0.020 g symethicon [Selg-esse1000, Promefarm, Milan, Italy] diluted in 4 l of water, followed by intravenous injection of 18F-FDG (mean dose, 4.44 MBq per kilogram of body weight ± 1 [range, 370–400 MBq]). PET/CT-E studies were acquired with a 64-detector row scanner [Gemini TF, Philips, Best, The Netherlands] with time-of-flight capabilities, and began 60 min after FDG injection. Patients were scanned in the supine position, with the entire abdomen and pelvis covered.

2.3. PET/MR-E protocol

PET/MR-E was performed after PET/CT scan, as previously described. Five minutes before the start of PET/MR acquisition, 20 mg of Joscine N-butilbromure [Buscopan, Boehringer Ingelheim, Milan, Italy] were injected intravenously in all patients. PET/MR studies were acquired with a Biograph mMR scanner [Siemens Healthcare] using two 12-channel body coils combined to form a multichannel abdominal and pelvic coil by using total imaging matrix technology. PET/MR imaging began a mean of 80 min ±12 after FDG injection. Patients were scanned from level of the mid thigh through to the diaphragm, using a dedicated protocol that included MR sequences acquired simultaneously with PET [co-acquired sequences] and MR sequences run after completion of the PET data acquisition, including contrast-enhanced coronal acquisitions. The co-aquired part of the protocol ensures temporal and spatial matching of MR and PET information, a feature unique to PET/MR; and the stand-alone MR sequences were subsequently co-registered and fused with the PET data.

2.4. Image evaluation

PET/CT-E and PET/MR-E images were fused by and evaluated at a dedicated workstation [Extended Brilliance, Philips and Syngo.via, Siemens Healthcare, respectively] by consensus agreement of two expert readers (one radiologist [MS, OAC] and one nuclear medicine physician [AC, EN]). Every hybrid study was evaluated as a whole. Readers were blind to clinical history and previous imaging. Two separate teams were formed and assigned to either PET/CT-E or PET/MR-E reading. Those assigned to PET/CT-E did not look at the same-day PET/MR-E, and vice versa. After completion of the reports, the two separate teams met to compare the findings. ‘Additional findings’ were subdivided in intestinal, extra-luminal, or extra-intestinal and distant from CD site, and the surgical team evaluated their clinical relevance. The surgeons received three distinct medical reports [i.e. whole body PET, PET/CT-E, and PET/MR-E]. Each abdominal lesion detected was tested with PET and the maximum standard uptake value [SUV max] was reported, and a whole-body PET scan with specific report was used to disclose unexpected, distant malignancies.

For both image modalities, accepted criteria for the evaluation of CD patients were used. The SUV was recorded and compared with clinical findings, seeking for discrimination ability between inflammatory and fibrotic lesions. Differences between PET/CT-E and PET/MR-E in terms of reliability in relation to surgical and histological findings were recorded [e.g. disease patterns and localisation], seeking for findings affecting the clinical management. A certain degree of inflammation is always observed, even in severely fibrotic segments, and hence it was anticipated that no purely fibrotic site could have been identified. The two different reading teams [PET/CT-E and PET/MR-E] independently classified each detected site as purely inflammatory, fibrotic with slight inflammation, fibrotic with moderate-to-extensive inflammation, or unclassified.

2.5. Treatment and follow-up

Figure 1 depicts the criteria for treatment and management of patients. Patients with both asymptomatic and symptomatic strictures classified as purely inflammatory or fibrotic with moderate-to-extensive inflammation, and those with asymptomatic bowel thickening with marked inflammation, were deemed manageable with medical treatment. The decision was made after a complete clinical and serological assessment. These patients were observed after 2–3 days and again after 1–2 weeks. A final decision upon continuing conservative treatment or undergoing surgery was made jointly by the gastroenterologist and surgeon. Decision to operate was made according to clinical variables and combined functional and morphological imaging data. Surgery was performed by a senior surgeon [FS] with a resident [GP] within 8 weeks from imaging.
Clinical Impact of PET/MR in CD

Symptomatic CD patients

Clinical examination
Blood sampling
-/- US -/- Endoscopy

Candidate to immediate surgery?

CT scan if feasible

SURGERY

EXCLUDED FROM ANALYSIS

Patients unable to tolerate MRI or cooperate

Localized ileocaecal disease?
Complications?

"Pure" inflammation
Fibrosis +/- minimal inflammation

Start or modify medical treatment
2/3 days

Symptoms persist?

1/2 weeks

Symptoms persist?

Fibrosis +/- moderate/extensive inflammation

Follow-up +/- maintenance therapy

Clinical Exam
Endoscopy at 6 month FU

Follow-up +/- maintenance therapy

"Pure" inflammation
Fibrosis +/- moderate/extensive inflammation

Start or modify medical treatment
2/3 days

Symptoms persist?

1/2 weeks

Symptoms persist?

Fibrosis +/- minimal inflammation

SURGERY [within 8 weeks from imaging]

PATHOLOGY ASSESSMENT

PATHOLOGY ASSESSMENT

Figure 1. Study algorithm and treatments. *In patients with purely inflammatory disease, and in those with fibrotic strictures with a moderate-to-extensive inflammatory component [as suggested by imaging findings], administration of anti-inflammatory therapy was considered. Patients without obstructive symptoms were approached with oral steroids. Patients with symptoms of obstruction were hospitalised and approached as described in the surgery section of this figure [see †]. They received intravenous steroids first and, if steroid refractory or dependent, biologics were considered. All decisions were made in multidisciplinary collaboration of gastroenterologist and surgeons. †Patients with confirmed intestinal obstruction were hospitalised. In case of complete bowel obstruction, they received nasogastric tube decompression, bowel rest, intravenous fluids, and electrolyte replacement. Those with suspected sepsis also received antibiotics. Prophylactic perioperative antibiotics and low molecular weight heparin were delivered as previously described. 45

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Preoperatively, imaging reports were read and the surgical team evaluated images. Every site classified as pathological by the imaging specialists was checked and the predicted pattern [inflammatory versus fibrotic] recorded. An accurate inspection of the entire bowel was always performed. Grossly pathological segments were identified and localisation was compared with imaging findings. Macroscopic features were noted [inflammatory versus fibrostenosing appearance]. Inflammatory segments were defined as areas of thickening and serosal hypervascularisation, with or without fat wrapping. Fibrosis was defined as rigidity and shortening of the involved segment. Concomitant findings were noted [e.g. fistulae and abscesses]. After the resection, the specimen was opened and the presence of mucosal alterations was checked. When strictureplasty procedures were performed, a full-thickness biopsy of the involved segment was always collected and sent to pathology. All areas of pathological PET accumulation were inspected. All patients included in analysis were followed up for a minimum of 6 months after imaging. Visits were carried out according to current practice of the clinicians, and included an ileocolonoscopy.

2.6. Histopathology
Pathological examination was the reference standard. The pathologists were blind to radiological and intra-operative findings. The resected specimens were sampled in multiple diseased sections. Length of abnormal segments was measured. Inflammation and fibrosis were graded as follows: 0 = none/mild; 1 = moderate; 2 = severe. Segments were defined as prevalently inflammatory or fibrotic, accordingly.

2.7. Statistical analysis
The discriminatory ability of PET/CT-E for CD patterns is lower than 15%24 compared with 88–92%25,26 of MR-E. Given that most previous studies used 1.5 T-MR and no PET/MR-E studies are available, by assuming a 70% increase with 3.0 T PET/MR-E compared with PET/CT-E, we planned enrolment of at least 10 patients per predominant pattern [fibrosis with slight inflammation versus inflammatory], receiving both imaging studies and undergoing surgery overall, in order to reject the null hypothesis that fibrosis detection rates were equal with power of 80% and a type I error probability of 5%. We also planned enrolment of at least five patients managed medically. Continuous and categorical data were analysed by Mann-Whitney and Fisher’s exact test, respectively. The reference standard [histopathology] was applied for sensitivity analysis. Receiver operating characteristic [ROC] curves were plotted and the area under the curve [AUC] was calculated to compare the diagnostic performance of the tests.27 A quantification of the extent of fibrosis/inflammation was attempted by means of SUV values, obtaining cut-off values to optimise the sensitivity and the specificity for fibrosis with 1000 bootstrap 95% confidence interval [CI].28 The results are reported with standard error [SE] and 95% CI.27,28 P-values < 0.05 were considered statistically significant. The data were analysed with the GraphPadPrism [version 5.00 for Windows, GraphPad Software, San Diego, CA, USA] and MedCalc® [Version 14.8.1 MedCalc Software bvba, Ostend, Belgium] statistical software.

2.8. Ethicl Considerations
The study protocol was approved by the institutional review board and met the guidelines of good clinical practice.

3. Results
A total of 48 consecutive patients with established CD were considered for inclusion. Eight patients were excluded from the study and three were diagnosed with other conditions being responsible for their symptoms. The latter included one patient with imaging modalities, clinical examination and endoscopy consistent with ulcerative colitis, one with intestinal malrotation, and another one with a pancreatic cyst adenoma. Two patients with negative examinations did not require any treatment.

In all, 35 patients undergoing same-day PET/CT-E and PET/MR-E were included [Table 1]. Eight patients were deemed manageable with medical treatment, of whom two subsequently needed surgery. The latter were added to the 27 remaining patients undergoing surgery. Hence, the final study population for primary aims

Table 1. Demographical data and disease features of 35 included patients. Values are median [range] and n [%].

| Age, years | 39 [18–63] |
| Male gender, n | 14 [40] |
| Concomitant medications, n | 11 [31.4] |
| - none | 2 [5.7] |
| - corticosteroids | 13 [37.1] |
| - 5-ASA | 11 [31.4] |
| - AZA/6-MP/MTX | 3 [8.6] |
| - IFX/ADA | 9 [25.7] |
| Previous surgery for CD | 8 [1–42] |
| Disease duration, years | 5-ASA 13 [37.1] |
| BMI, kg/m² | 20 [15–26] |
| Smoking habit, n | 11 [31.4] |
| - never | 8 [22.9] |
| - current | 16 [45.7] |
| - discontinued | 8 [22.9] |
| Familial, n | 5 [14.2] |

- 5-ASA, 5-aminosalicylic acid derivatives; 6-MP, 6 mercaptopurine; ADA, adalimumab; AZA, azathioprine; BMI, body mass index; CD, Crohn’s disease; EIMs, extra-intestinal manifestations; IFX, infliximab; MTX, methotrexate.

3 Patients may have been taking more than one medication.

Table 2. Surgical details of 29 patients undergoing operation. Values are median [range] and n [%].

| Weeks between imaging and surgery | 3 [1–8] |
| CRP, mg/l | 10 [3–80] |
| Median operative time, min | 110 [60–190] |
| Surgical approach | 5-ASA 13 [37.1] |
| - hand-assisted laparoscopy | 7 [24.1] |
| - laparoscopy | 6 [20.7] |
| - laparotomy | 11 [38] |
| - laparoscopy converted to laparotomy | 5 [17.2] |
| Procedure performed³ | 9 |
| - resection | 8 |
| - ileocaecal resection | 7 |
| - ileocolic anastomosis resection | 3 [10.3] |
| Length of resection, cm | 16 [5–38] |
| Primary stoma³ n | 3 |
| Major postoperative complications, n | 5 in 4 patients [17.2] |

CRP, C-reactive protein.

³ Patients may have received more than one procedure, not all detected sites required surgical treatment.

³ Excluding the one who received a stoma for postoperative complications.
Comprised 29 patients [median age 38 years, range 18–65, 11 men]. Surgical data are depicted in Table 2. Five major complications occurred in four patients [17%], of whom one required reoperation with ileocolonic anastomosis disconnection and stoma fashioning. At a median follow-up of 9 months [range 6–22], no recurrence was observed in either the medical or the surgical group.

3.1. Detection of disease, and discrimination between inflammation and fibrosis

Both PET/CT-E and PET/MR-E detected 26 out of 31 [85%] pathological sites identified and treated by surgery. The median delay between examination start [60 min after tracer administration] and CT scan detection of pathological sites was 61.5 min [range 36–171]. The median delay between PET/CT-E examination start and PET/MR-E detection of pathological sites was 104 min [range 75–205]. For the localisation of detected segments, no significant differences between the two modalities were observed [Table 3]. ROC curves comparison for discriminating segments with or without fibrosis are depicted in Supplementary Figure, [available as Supplementary data at ECCO-JCC online]. AUCs were 0.51 [SE 0.098, 95% CI 0.31–0.71] for PET/CT-E and 0.77 [SE 0.085, 95% CI 0.56–0.91] for PET/MR-E [p = 0.007]. Morphological data were implemented with findings of PET scans for both modalities, aiming at increasing fibrosis detection and assessment of inflammatory extent. We observed a linear positive correlation between the values of maximum SUV and the

Table 3. Results of PET/CT and PET/MR in 29 patients undergoing surgery. The benchmark for comparison was surgery with histopathology confirmation. Values are median [range] and n [%].

<table>
<thead>
<tr>
<th></th>
<th>PET/CT</th>
<th>PET/MR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detected strictures or bowel thickening, n</td>
<td>26/31 [84.8]</td>
<td>26/31 [84.8]</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>- duodenum</td>
<td>1/2 [50]</td>
<td>1/2 [50]</td>
<td></td>
</tr>
<tr>
<td>- small bowel</td>
<td>9/11 [81.8]</td>
<td>10/11 [91]</td>
<td></td>
</tr>
<tr>
<td>- terminal ileum/caecum/ileocolonic anastomosis</td>
<td>16/16 [100]</td>
<td>15/16 [93.7]</td>
<td></td>
</tr>
<tr>
<td>- colon</td>
<td>1/2 [50]</td>
<td>1/2 [50]</td>
<td></td>
</tr>
<tr>
<td>Additional extra-intestinal or distant from CD-involved sites findings</td>
<td>15</td>
<td>23</td>
<td>0.0038</td>
</tr>
<tr>
<td>- gallbladder fundal adenomyomatosis</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>- gallbladder stones</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>- benign liver cysts</td>
<td>3</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>- liver angiomata</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>- benign kidney cysts</td>
<td>3</td>
<td>2</td>
<td></td>
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<tr>
<td>- duplicated renal vein</td>
<td>1</td>
<td>0</td>
<td></td>
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<tr>
<td>- inhomogeneous endometrium stripe</td>
<td>0</td>
<td>1</td>
<td></td>
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<tr>
<td>- ovary haemorrhagic cysts</td>
<td>1</td>
<td>1</td>
<td></td>
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<tr>
<td>- vertebral angiomas</td>
<td>1</td>
<td>1</td>
<td></td>
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<tr>
<td>- physiological thymus uptake</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>- vertebral uptake</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>- caecum polyps</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>- sigmoid pseudo-diverticulum</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>- caecum pseudo-diverticulum</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>- ileoileal intussusception</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Findings changing the management, n</td>
<td>2</td>
<td>6</td>
<td>0.060</td>
</tr>
<tr>
<td>Additional intestinal extra-luminal findings</td>
<td>17</td>
<td>26</td>
<td>0.0017</td>
</tr>
<tr>
<td>- intramural abscess</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>- phlegmon</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>- fistula</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>- hypertensive mesentery</td>
<td>4</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>- mesenteritis with mesenteric retraction</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>- mesenteric adenopathy</td>
<td>9</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>- free fluid in abdomen</td>
<td>1</td>
<td>1</td>
<td></td>
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<tr>
<td>Preoperative classification of detected strictures or bowel thickening compared with pathology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- purely inflammatorya</td>
<td>8/10 [80]</td>
<td>8/10 [80]</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>- detected</td>
<td>6/8 [75]</td>
<td>7/8 [87.5]</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>- Fibrotic or mixedb</td>
<td>18/21 [85.7]</td>
<td>18/21 [85.7]</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>- predominant feature not stated</td>
<td>5/18 [27.8]</td>
<td>12/18 [66.7]</td>
<td>0.043</td>
</tr>
<tr>
<td>- undetected fibrosis</td>
<td>16/21 [76.1]</td>
<td>9/21 [42.8]</td>
<td>0.038</td>
</tr>
</tbody>
</table>

PET, positron emission tomography; MR, magnetic resonance; CT, computed tomography; CD, Crohn’s disease.

aNo signs of fibrosis observed at imaging with inflammatory grade 1 or 2 and fibrosis grade 0 at pathology.

bSigns of fibrosis observed at imaging with fibrosis 1 or 2 grade and inflammation grade 1 or 2 at pathology.
degree of inflammation as reported by the pathologist. By choosing a cut-off value of 2.95 maximum SUV, the PET scan had 82% sensitivity and 88% specificity in identifying a fibrotic component [≤ 2.95] with mild inflammation [AUC 0.904, SE 0.059, 95% CI 0.72–0.98, \( p < 0.0001 \)]. When comparing severely fibrotic segments plus mild inflammation \( [n = 7] \) with purely inflammatory and fibrotic plus moderate to severe inflammation, the cut-off for fibrosis was 1.46 [95% CI ≤ 0.81–≤ 1.46] and more accurate [100% sensitivity, 83% specificity, AUC 0.944, SE 0.045, 95% CI 0.77–0.99, \( p < 0.0001 \)] [Supplementary Figure 2, available as Supplementary data at ECCO JCC online]. Although the two imaging modalities had similar detection rates [Table 3], PET/MR-E was significantly more accurate in indentifying a fibrotic component [67% versus 28%, \( p = 0.043 \)]. Extra-luminal disease detection was increased by PET/MR-E compared with PET/CT-E [26 versus 17, \( p = 0.002 \)], resulting in higher reliability of preoperative fibrosis prediction \( [p < 0.05] \). Specifically, intramural disease was better assessed with PET/MR-E, as well as the involvement of the mesentery of the diseased segment. An ileocolic fistula was missed at PET/CT-E.

### 3.2. Impact of imaging on clinical and surgical management

PET/MR-E detected more extra-intestinal findings or conditions affecting bowel segments distant from those involved by CD compared with PET/CT-E [23 versus 15, \( p = 0.004 \)], and were associated with a trend toward a modification of management. In detail, PET/MR-E identified a case of gallbladder adenomyomatosis that required cholecystectomy, and caecum polyps that were removed with endoscopic polypectomy at the time of surgery in a patient undergoing small-bowel resection. Both imaging procedures detected pulmonary tuberculosis in a patient exposed to a long course of biological and immunosuppressant medications, requiring specific treatment before surgery. An old lady was found with inhomogeneous endometrium stripe at PET/MR-E, requiring gynaecologist consultation. PET/MR-E identified an ileoileal intussusception in a patient found with an ileal polyp at surgery. Non-specific colonic uptake was observed in up to 12 patients overall [33%], but had no practical implications in clinical management.

Based on clinical conditions and PET/CT-E and PET/MR-E findings, eight patients were treated medically. After 2 weeks of follow-up, two patients [25%] required surgery. They were found to have active inflammation and severe fibrosis. In these two, PET/MR-E and PET/CT-E were in agreement in one patient preoperatively diagnosed with purely inflammatory CD, whereas in the other one PET/MR-E identified a fibrotic component but the patient refused surgery, and both imaging modalities missed a stricture located in the small bowel. The remaining six [75%] patients [Figure 2] were disease free at last available follow-up. One patient had a relapse requiring hospitalisation, but none required further surgery. These patients are on maintenance treatment; 6-month follow-up endoscopy was performed in five [83.3%] of these patients, and was unremarkable.

The 12 patients diagnosed with fibrosis with slight inflammation by PET/MR-E were offered straight surgery. Pathology confirmed the diagnosis. One patient diagnosed with fibrosis by PET/CT-E scan was actually found with inflammatory CD.

Concerning the choice of surgical approach, among patients suitable for minimally invasive surgery, those with multiple disease localisations and/or PET/MR-E evidence of significant involvement of the mesentery received hand-assisted laparoscopy \( \text{ab initio} \) [17%] [Figure 3, Figure 4]. Compared with those who needed either conversion to midline laparotomy or subsequent application of the hand-assisted device during laparoscopy, this significantly decreased median operative time [80 min, range 70–110 versus 120 min, range 90–190, \( p = 0.022 \)].

Patients with PET/MR-E findings of phlegmon and intramural abscesses were more likely to receive a stoma [67% versus 4%, \( p = 0.022 \)].

Extra-luminal septic findings at either PET/MR-E or PET/CT-E were associated with a trend toward higher rates of major postoperative complications, but the latter identified fewer lesions resulting in a non-significant association [50% versus 9%, \( p < 0.05 \) and 67% versus versus 13%, \( p = 0.068 \)].

One patient was not able to cooperate and another one was unable to stay in the MR system, resulting in an overall withdrawal of 7% [3 out of 45 both PET/MR and PET/CT scan performed].

We also compared PET/MR-E with MR-E alone. They were equally accurate in detecting CD sites, but MR-E missed the fibrotic component more often [17/21 versus 9/21, MR-E versus PET/MR-E, \( p = 0.024 \)]. A higher rate of strictures classified as ‘inflammatory’ with MR-E alone were eventually found to have grade 1–2 fibrosis [7/10 versus 1/10, MR-E versus PET-MR-E, \( p = 0.019 \)].

### 4. Discussion

This study compared the capability of PET/CT-E and PET/MR-E in detecting inflammation and fibrosis and their clinical relevance in patients with CD. PET/CT-E and PET/MR-E were comparable for disease detection overall, but MR morphological data combined with PET were more reliable in predicting fibrosis. PET/MR-E addressed better the extra-luminal disease, allowing for more appropriate strategy planning. These features were associated with postoperative complications and need for stoma, and were useful to optimise the surgical approach, also reducing operative time. We identified a cut-off maximum SUV value to detect fibrotic sites with minimal inflammation. A relationship between maximum SUV values and degree of inflammation as graded by the pathologists was also observed. Combined functional, morphological, and clinical data allowed for identifying patients as candidate for either medical or early surgical approach. The patient withdrawal rate for PET/MR-E was below 7%.

Fibrosis is a major challenge in CD, resulting from a complex interaction between environmental agents and the immune system of...
Clinical Impact of PET/MR in CD

No validated biomarkers of intestinal fibrosis are available, and no medical treatment can reverse it.3,4,31 Stricture dilation and surgery are the only measures to relieve symptoms,3,4,5,6,33 but many patients need repeated treatments over time.5,33 Current cross-sectional imaging techniques do not permit an accurate distinction between inflammation and fibrosis,18 although this is useful to guide the management of small-bowel CD.1,2 A diagnostic delay is often observed in stricturing CD, and it is associated with higher need for repeated surgery and lower quality of life.5

MR-E is a radiation-free alternative tool non-inferior to CT-E in stricturing and active CD.18,25 Contradictory findings are reported in assessing fibrosis and need for surgery in CD.19,22 Rimola et al.34 suggested that the percentage of contrast \[p < 0.01\] and late enhancement \[p < 0.01\] could ease the detection of severe fibrosis, but their model needs prospective validation.14 Metabolic and molecular imaging procedures have been validated for monitoring disease activity and relapse of various malignancies15,35 and inflammatory conditions.3,4,5,6,33 PET/CT-E,25 correlates well with active inflammation. Jacene et al.9 suggested that quantitative PET data obtained with PET/CT-E helped in identifying fibrostenosing lesions. In the present study, segments with intense fibrosis and minimal inflammatory component did not exceed 1.46 maximum SUV, and this may guide treatment [Figure 1].

Lower FDG uptake was associated with failure of medical therapy in a retrospective series.38 Although not clearly stated by the authors, one could argue that these lesions were predominantly fibrotic and, therefore, fit in with our finding correlating the SUV value with the extent of inflammation. Lenze et al.24 found that the discriminatory ability between CD patterns of PET/CT-E and MR-E did not significantly differ [53% versus 57%], and both were unable to identify fibrostenotic lesions.24

Scanners able to co-acquire PET and MR images have been developed.15,37 We found that the higher image quality of 3.0T-MR combined with quantitative PET had greater discriminatory ability between CD patterns than PET/CT-E [Table 3]. Improving the overall detection of pathological segments represents room for improvement for both PET/CT-E and PET/MR-E. Notwithstanding, adding PET metabolic data to MR-E should be considered as adjunctive to endoscopy and pathology, aiming at defining the reference standard for fibrosis research in stricturing CD.11 The combined features of these techniques could ease the detection of truly intestinal fibrosis without inflammation.18,31,34

This study has limitations. First, the number of patients is relatively low. However, this is the first study directly comparing PET/CT-E and PET/MR-E in CD patients, and their clinical relevance. No quantitative scores were used to grade inflammation or fibrosis according to the features of MR-E and CT-E, but no validated tools are currently available. Balloon dilation alone40 or with anti-inflammatory drugs injection41,42 was not considered. These approaches require expertise. Comparisons with ultrasound findings were not performed, but it is currently not possible to distinguish between inflammation and fibrosis with this technique. No validated anatomo-pathological scoring systems are available to grade fibrosis.31 Given the lack of a validation panel, our choice of cut-offs could have influenced the risk of over-fitting. PET/MR-E is expensive and unfeasible in patients needing emergency surgery. PET/MR-E acquire functional and morphological data simultaneously, providing qualitative and quantitative information.15,32 A direct comparison between PET/MR-E and MR-E alone found that MR-E was less accurate in detecting fibrosis. This would have delayed surgery. Last, hybrid PET/MR-E allows for testing each suspected bowel thickening to assess local inflammation with a single examination. This is not possible with serological or stool tests.
Strengths of this study consist of its prospective nature, the use of a 3.0 T MR scanner, the simultaneous acquisition of PET and MR images, the reference used for comparisons, and the endoscopic assessment for the group managed medically. Fused images were recorded and available during the same examination, avoiding misregistration of PET and MR images due to unavoidable dislocation of organs. The literature lacks assessment of MR-E and CT-E sensitivity and specificity using surgical pathology as reference. We retrieved pathological data from the entire specimen, allowing the pathologists to accurately evaluate all CD features along the diseased segment [extra-intestinal and extra-luminal].

Our observations have practical implications [Figure 1]. Inflammation and fibrosis are intertwined in inflammatory bowel diseases. Diseased CD segments show all disease patterns at pathology, meaning that a minimum degree of inflammation is found in fibrotic segments, and vice versa. Fibrosis is closely and positively related to inflammation, suggesting that it may not be relevant to make an exclusive distinction between patients with either inflammatory or fibrotic pattern. In any event, PET combined with high quality anatomical MR data may represent an ideal tool to differentiate between prevalently fibrotic segments [unlikely to respond to medical treatment] and those with an active inflammation with or without fibrosis [suitable for conservative treatment before surgery]. The latter could be approached with anti-inflammatory medications, aiming at reducing transmural oedema, postponing or avoiding surgery. As for MR-E, young patients would be the ideal candidates for PET/MR-E disease assessment. The proposed approach could avoid predictably ineffective exposure to medical drugs and achieve ideal surgical timing, eventually reducing complications.

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Conflict of Interest
All authors have no conflict to declare.

Author Contributions
GP: planned and conducted the study, interpreted and analysed data, drafted the article, and approved the final draft submitted. EN: planned and conducted the study, interpreted and analysed data, drafted the article, and approved the final draft submitted. OAC: planned and conducted the study, interpreted data, and approved the final draft submitted. SC: conducted the study, interpreted data, and approved the final draft submitted. FPD: conducted the study and approved the final draft submitted. MS: planned and conducted the study, interpreted data, drafted the article, and approved the final draft submitted. AC: planned and conducted the study, interpreted data, drafted the article, and approved the final draft submitted. FS: planned and conducted the study, interpreted and analysed data, drafted the article, and approved the final draft submitted.

Supplementary Data
Supplementary data are available at ECCO-JCC online.

References
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