

# Usefulness of endoscopic ultrasound for perianal fistula in Crohn's disease.

## *Papel da ultrassonografia endoscópica na avaliação da fistula perianal na doença de Crohn.*

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### A B S T R A C T

**Objective:** to determine the role of endoscopic ultrasonography (EU) in comparison with nuclear magnetic resonance imaging (MRI) and examination under anesthesia (EUA) in the management of patients with perianal fistulizing Crohn's disease. **Methods:** we conducted a cross-sectional, observational study with patients with perianal Crohn's disease evaluated at a tertiary center in Curitiba, Paraná, Brazil, from February 2016 to March 2017. All patients underwent EU, MRI and EUA. We evaluated the degree of agreement between the three methods by obtaining the Kappa coefficient. A Kappa value of 0.7 or greater indicated good agreement. We used the Friedman's non-parametric test to compare the number of fistulous paths detected in each modality. We set the level of statistical significance at  $p < 0.05$ . **Results:** we included 20 patients. There was agreement between the three exams in 11 patients. The level of Kappa agreement between the three exams was 0.53 (moderate -  $p < 0.001$ ). There was no statistically significant difference in relation to the number of fistulous trajectories detected in the three exams ( $p = 0.641$ ). EU failed to identify a fistulous pathway in three patients; MRI failed in three; and EUA failed in two. **Conclusion:** EU was comparable to MRI and EUA for the evaluation of perianal fistulizing Crohn's disease, and can be considered a valid exam for preoperative investigation of such patients.

**Keywords:** Crohn Disease. Rectal Fistula. Endosonography. Magnetic Resonance Imaging.

### INTRODUCTION

Crohn's disease is an autoimmune and chronic condition that can affect any segment of the gastrointestinal tract. The formation of fistulous pathways is observed in 12% of patients with small bowel involvement, in 41% with colonic disease without rectal involvement, and in 92% of individuals with perianal disease<sup>1</sup>.

Perianal fistulizing disease is one of the most debilitating clinical conditions associated with Crohn's disease, and has a cumulative incidence of 20 to 26%<sup>1-3</sup>. It is associated with poor quality of life, fecal incontinence and postoperative recurrence. Its treatment requires accurate evaluation of the fistulous path. The treatment goals are prevention of sepsis, reduction of perianal secretion and, if possible, healing of the fistulous path. Failure to identify a fistulous path results in inadequate treatment.

In patients with Crohn's disease with superficial and simple perianal fistula, identification of the fistulous pathway is usually possible through examination under anesthesia (EUA). However, for complex and recurrent fistulas, the European Crohn's and Colitis Organization (ECCO)<sup>4</sup> and the American Gastrointestinal Association (AGA)<sup>5</sup> recommend imaging examinations, such as nuclear magnetic resonance imaging (MRI) and endoanal ultrasonography. Other exams, such as contrast injection through the fistulous path under fluoroscopy and computed tomography, display low accuracy. Fistulography provides little information about the relationship of the fistulous pathway and the sphincter anatomy<sup>6</sup>. Computed tomography has a significantly lower accuracy<sup>7</sup> compared with endoanal ultrasonography in patients with Crohn's disease. Transperineal ultrasonography, an examination using a linear and convex transducer, has

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been described in small series as a painless method, and an accurate alternative to evaluate perianal fistulas in Crohn's disease. However, the visualization of deeper planes is limited and, therefore, presents a low sensitivity for the detection of abscesses and extra- or suprasphincteric fistulas<sup>8-10</sup>.

Therefore, MRI and endoanal ultrasonography are the preferred modalities for evaluating perianal fistulizing disease. Endoanal ultrasonography is a method that allows the evaluation of the anal canal with a delicate transducer, which can be rigid or flexible (endoscopic ultrasonography - EU). This transducer has a smaller caliber and is capable of providing an endoscopic view, which may be an advantage in patients with inflammation and rectal stenosis due to severe Crohn's disease. Thus, EU makes it possible to evaluate the anatomy of the perianal region and the rectal mucosa, especially in cases with intense inflammatory activity, in addition to identifying the fistulous pathways. However, its role in the evaluation of perianal fistulizing Crohn's disease is still not well established due to the small number of investigations. The aim of this study was to verify the role of EU in relation to MRI and EUA in the evaluation of patients with perianal fistulizing Crohn's disease.

## **METHODS**

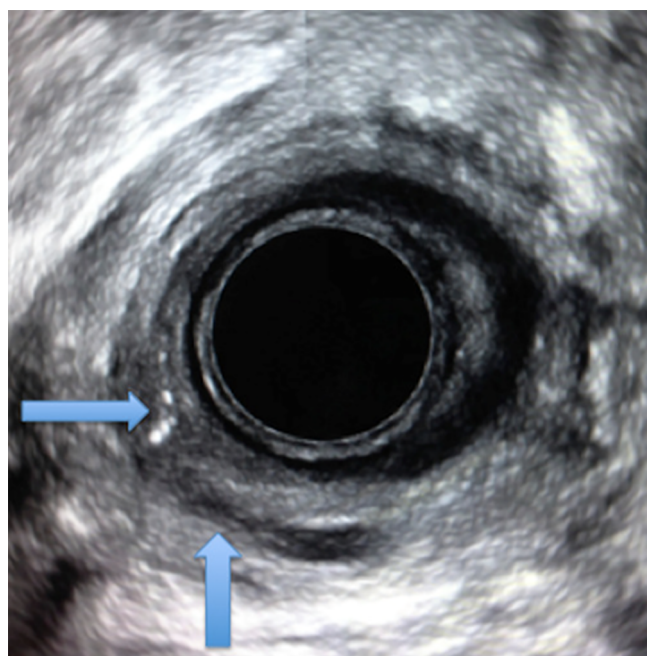
We conducted an observational, cross-sectional study of patients with perianal fistulizing Crohn's disease under follow-up at the Department of Coloproctology, Hospital de Clínicas, Federal University of Paraná. This study was approved by the Ethics in Research Committee of the institution (CAAE nº 53417816.0.0000.0096). We obtained a signed informed consent form from all patients. All procedures involving patients in this study were in accordance with the recommendations of the Declaration of Helsinki, 1964. All patients were attended between February 2016 and January 2017,

and submitted to EU, MRI and EUA for evaluation of perianal fistulizing Crohn's disease. Each examiner was blinded to the results of the previous exams.

We obtained the following demographic and clinical data: age, gender, time of Crohn's disease diagnosis, medications in use, technique and number of previous interventions, and clinical symptoms (pain, pruritus, fecal incontinence and anal secretion). We clinically evaluated all patients using the PDAI (Perianal Disease Activity Index)<sup>11</sup> and the Harvey-Bradshaw<sup>12</sup> scales. Exclusion criteria were age less than 18 years and anal stenosis that did not allow insertion of the EU transducer.

We performed The EU exam using the Fuji 8000 processor with EG530UR2 radial transducer, with a 360° angle, 8cm long, and 7-12 MHz frequency. All exams were performed with the patient in left lateral decubitus, under deep sedation with intravenous propofol.

At EU, the fistulous trajectories presented a typical hypoechoic tubular image, sometimes with hyperechogenic foci inside it, corresponding to air bubbles (Figure 1).



**Figure 1.** Endoscopic ultrasonography with a typical hypoechoic tubular image corresponding to the fistulous path. Hyperechoic foci correspond to air bubbles (arrows).

We performed MRI using the Signa HDX 1.5 Tesla device. Intravenous injection of gadolinium was administered at the discretion of the radiologist. The EUA was conducted in the operating room, with the patient in lithotomy position and under spinal anesthesia. The surgeon was initially blinded to the MRI and EU results, and assessed the anatomy of the fistula with the aid of a stilet. After the complete evaluation of the fistulous trajectory, the findings of MRI and EU were informed to the surgeon before the surgical treatment was performed.

For the three examination modalities, the fistulous trajectory was classified according to the Parks<sup>13</sup> and the American Gastroenterological Association (AGA) classifications<sup>5</sup>. Parks's classification distinguishes fistulas in five types: superficial, intersphincteric, transsphincteric, suprasphincteric, and extrasphincteric. The AGA classification distinguishes fistulas in "simple" and "complex". The simple one is defined as low (superficial, intersphincteric or transsphincteric), has a single external orifice, and no perianal complications. The complex fistula, on its turn, is high (intersphincteric, transsphincteric, extrasphincteric or suprasphincteric) and may present several external orifices or be associated with perianal abscess, anal stricture, proctitis or communication with the vagina or bladder. Secondary pathways, rectovaginal fistula and presence of proctitis have also been reported.

For statistical analysis, we described the number of perianal fistulae identified in terms of frequency and percentage. We used the Kappa coefficient to evaluate the degree of agreement between the evaluation of the fistulous pathway by EU, MRI and EUA. For each two exams, we considered the null hypothesis as zero Kappa coefficient (absence of agreement). We considered

a Kappa value  $\geq 0.7$  as a good agreement, and  $\leq 0.4$  indicated poor agreement. We used the Friedman's non-parametric test to compare the number of fistulous trajectories identified in each exam. Values of  $p < 0.05$  indicated statistical significance. We analyzed all data using the software Stata/SE v.14.1.

## RESULTS

We selected 21 patients with perianal fistulizing Crohn's disease followed up at Hospital das Clínicas for the study. Of these, we included 20, seven men and 13 women, aged 19 to 64 years (mean  $39 \pm 11.45$  years). We excluded one patient because of anal stenosis that prevented the introduction of the EU transducer.

Patients had a diagnosis of Crohn's disease between one and 28 years (mean 10.4). Five patients (25%) had undergone abdominal surgery: three ileocelectomies and two total colectomies. Sixteen patients (80%) had already been operated on for perianal fistula, perianal abscess or anal stricture, ranging from one to eight interventions. All patients were on drug treatment. Fifteen patients (75%) were on biologic therapy (infliximab or adalimumab), eight on combined azathioprine and biological therapy, four on azathioprine monotherapy, and one on methotrexate. The main symptoms were anal secretion (11 patients), pain (9), pruritus (8), bleeding (6) and fecal incontinence (6). The average Harvey-Bradshaw scale was 2.8 and the mean PDAI was 5.4. Seven patients had proctitis. In the evaluation of EUA, MRI and EU of the 20 patients, six (30%) had simple fistula and 14 (70%) had complex ones. As to the fistulous trajectories, ten patients had only one, six had two, three had three, and one patient had four, totaling 35 detected perianal fistulouspaths (Tables 1 and 2).

**Table 1.** Parks classification for the 20 patients with perianal fistulizing Crohn's disease.

Parks classification	Number of fistulous paths
Transsphincteric	16
Intersphincteric	2
Extrasphincteric	1
Suprasphincteric	7
Retovaginal	7
Superficial	2
Total	35

**Table 2.** Number of fistulous paths per patient

Number of paths	Number of patients
1	10
2	6
3	3
4	1
Total	20

MRI failed to identify two rectovaginal fistulas and one transsphincteric pathway in the anterior midline. EU did not identify a supralevator abscess and two transsphincteric pathways - one lateral and one posterior. Both the MRI and the EU of one patient were not able to show the horseshoe transsphincteric fistulous trajectory in the posterior midline, which was diagnosed only under examination under anesthesia. EUA was not able to identify the fistulous trajectory in only two patients (10%), one with a rectovaginal fistula, and the other with a suprasphincteric abscess. Both paths have been identified both by EU and by MRI, and detected in the EUA only after the surgeon became aware of the other exams' results. In the other 18 cases, all the fistulous pathways detected by MRI and EU were also identified by the surgeon, who was not aware of the results of the imaging tests.

There was agreement between MRI, EU and EUA in 55% (11/20) of the cases (Table 3). In the other 45% (9/20), there was agreement in at least two exams. There was fistula identification failure in three patients with EU, in three patients

with MRI, in two patients with EUA, and in one patient with EUA and MRI. All fistulous pathways detected by EU and MRI were confirmed by EUA. There were no conflicts in the findings regarding the fistulous trajectories erroneously diagnosed in the three exams.

When comparing the three exams in patients with a single fistulous trajectory, there was agreement in seven of the ten patients; in those with more than one fistulous path, agreement occurred in only four of the ten individuals. When comparing MRI and EU, there was agreement in 14 patients (70%). In three cases (15%), the MRI identified more pathways than the EU, and in the other three cases (15%), the EU identified more pathways than the MRI. The estimated Kappa coefficient was 0.54 (95% CI: 0.27-0.81) with statistical significance ( $p < 0.001$ ).

In the comparison between MRI and EUA, there was agreement in 14 patients (70%). In four of them (20%) the EUA identified more paths than the MRI, and in the other two (10%) the MRI identified more paths than the EUA.

**Table 3.** Comparative analysis of the number of fistulous trajectories detected per patient with perianal fistulizing Crohn's disease in EU, MRI and EUA.

Patient	Number of paths identified			Exams compared		
	EU	MRI	EUA	EU x MRI	EU x EUA	MRI x EUA
1	1	1	1	Agreed	Agreed	Agreed
4	2	2	2	Agreed	Agreed	Agreed
5	1	1	1	Agreed	Agreed	Agreed
6	2	2	2	Agreed	Agreed	Agreed
9	1	1	1	Agreed	Agreed	Agreed
11	2	2	2	Agreed	Agreed	Agreed
13	1	1	1	Agreed	Agreed	Agreed
14	2	2	2	Agreed	Agreed	Agreed
17	1	1	1	Agreed	Agreed	Agreed
18	1	1	1	Agreed	Agreed	Agreed
20	1	1	1	Agreed	Agreed	Agreed
2	2	2	3	Agreed	EUA > EU	EUA > MRI
7	3	3	2	Agreed	EUA < EU	EUA < MRI
10	2	2	1	Agreed	EUA > EU	EUA < MRI
8	2	1	2	MRI < EU	Agreed	EUA > MRI
16	1	0	1	MRI < EU	Agreed	EUA > MRI
19	1	0	1	MRI < EU	Agreed	EUA > MRI
3	2	4	4	MRI > EU	EUA > EU	Agreed
12	0	1	1	MRI > EU	EUA > EU	Agreed
15	2	3	3	MRI > EU	EUA > EU	Agreed
				Agreed: 14 (70%)	Agreed: 14 (70%)	Agreed: 14 (70%)
				MRI > EU: 3 (15%)	EUA > EU: 4 (20%)	EUA > MRI: 4 (20%)
				MRI < EU: 3 (15%)	EUA < EU: 2 (10%)	EUA < MRI: 2 (10%)

The estimated Kappa coefficient of agreement was 0.54 (95% CI: 0.25-0.77) with statistical significance ( $p < 0.001$ ).

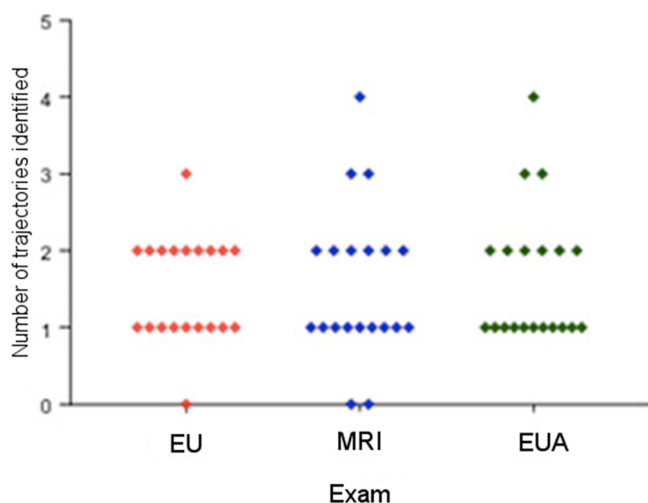
There was agreement in 14 patients (70%) when comparing EUA and EU. In four cases (20%), the EUA identified more fistulous trajectories than the EU, and in the other two patients (10%), the EU identified more fistulous trajectories than the EUA. The estimated Kappa coefficient of agreement was 0.51 (95% CI: 0.258-0.83), with statistical significance ( $p = 0.001$ ).

When comparing the findings of the three exams (EU, MRI and EUA), the Kappa coefficient of

agreement was estimated to be 0.53, with statistical significance ( $p < 0.001$ ). There was no statistically significant difference in relation to the number of trajectories detected in the three exams -  $p = 0.641$  (Table 4, Figure 2).

**Table 4.** Number of fistulous trajectories detected by examination in patients with perianal fistulizing Crohn's disease.

Exam	N	Average	Median	Minimum	Maximum
EU	20	1.5	1.5	0	3
MRI	20	1.5	1	0	4
EUA	20	1.6	1	1	4



**Figure 2.** Comparison of the number of perianal fistulous pathways detected by examination in patients with perianal fistulizing Crohn's disease. Each point corresponds to one fistulous path.

## DISCUSSION

The evaluation of perianal fistulizing Crohn's disease is challenging, even for experienced surgeons. Accurate diagnosis is essential for effective treatment. The anatomy of the fistulous path, its relationship with the sphincter muscles, and the identification of collections are key components for treatment planning. Failure to detect any of these components results in improper handling and fistula recurrence. Patients with perianal fistulizing Crohn's disease often have complex fistulas, which represented more than 75% of the cases in this sample, an incidence similar to those presented by Orsoni<sup>14</sup> and Lahat<sup>15</sup>, of 69% and 75%, respectively.

The management of perianal fistulizing Crohn's disease has changed considerably in the last decades after the spread of the use of biological therapy, such as infliximab and adalimumab. Although these medications cause closure of the external orifice and help in the resolution of drainage of purulent secretion through the anus, the fistulous pathway remains inflammatory and leads to fistula recurrence<sup>16-18</sup>. Therefore, to plan the best treatment, it is recommended to perform imaging

in the evaluation of patients, especially those with complex perianal fistula<sup>4,5</sup>.

In this study, of the ten patients with a single fistulous path, there was agreement between EU, MRI and EUA in seven cases. For the other ten patients who had more than one fistulous trajectory, there was agreement between the three exams in only four cases. The high incidence of complex fistulas and the low agreement in the findings between different methods reinforce the importance of imaging tests in patients with perianal fistulizing Crohn's disease.

Pelvic MRI is recommended as an initial examination to evaluate fistulizing perianal disease, as it is an accurate and non-invasive method<sup>4</sup>. Its sensitivity in identifying the anatomy of the fistula varies from 46% to 100%<sup>19-21</sup>. In this study, MRI was able to detect seven cases of suprasphincteric fistulas, including one that was not detected by EUA. MRI was also more accurate than EUA in the detection of supra and extrasphincteric fistulas in the study by Linniss *et al.*<sup>22</sup>, with 35 patients. In a meta-analysis, Siddiqui *et al.*<sup>20</sup> also demonstrated that MRI is more sensitive than endoanal ultrasonography for evaluation of suprasphincteric fistulas. In the present study, MRI failed to identify the fistulous trajectory in four cases (20%): two rectovaginal fistulas, one transsphincteric in the anterior midline and the other transsphincteric in horseshoe in the posterior midline. In three of the four cases, MRI was not able to identify previous fistulas, which may suggest a limitation of this technique in the evaluation of anterior, anovaginal, superficial and short fistulous trajectories, as already reported in the literature<sup>23</sup>. However, one limitation of the present study was the fact that eight patients did not receive intravenous contrast, which may have interfered with their diagnosis.

In the examination under anesthesia, the anatomy of the fistulous trajectory is evaluated by means of rectal touch, with the aid of a stylet.

Hardened tissue with inflammation, suprasphincteric or ischiorectal abscess, and scars from previous surgical procedures make it difficult to identify the fistulous path. Despite these limitations, in the hands of experts, its accuracy reaches 91%<sup>19</sup> and the test is defined as the gold standard in most studies<sup>20</sup>. In the present study, EUA was able to identify fistulous pathways in 90% of patients. In both cases where it failed, both the MRI and the EU identified the paths. This information is corroborated by the literature, with reports that two of the three studied exams are sufficient to reach 100% accuracy in the evaluation of perianal fistulas in Crohn's disease<sup>19</sup>.

Endoanal ultrasonography, in experienced hands, provides information equivalent to that of MRI<sup>4</sup> and has a sensitivity of 82% to 87% in evaluating perianal fistulous pathways in Crohn's disease<sup>7,14,20</sup>. In general, transanal ultrasonography is performed with a rigid transducer, but endoscopic ultrasound has also been used for the same purpose and has a similar sensitivity (91%)<sup>15,19,24</sup>. Schwartz *et al.*<sup>19</sup> evaluated 32 patients with perianal Crohn's disease with endoscopic ultrasonography. They compared the findings with those of MRI and EUA. The accuracy of the three modalities was  $\geq 85\%$ , and when two of these tests were associated, the accuracy reached 100%.

Because it is smaller in size than the rigid apparatus, EU can be performed in patients with some degree of rectal stenosis. This method also allows endoscopic examination of the rectal mucosa, detection of proctitis and visualization of the internal orifice of the fistulous path. Despite being a high-cost exam, endoscopic ultrasonography is more popular than rigid endoanal transducers in large tertiary endoscopy centers. EU is considered an invasive exam, which can cause pain or discomfort for the patient, and it is recommended to be carried out under sedation.

In patients with stenoses that do not allow transposition of the device into the EU, it provides limited information, and MRI is an alternative for imaging in these cases.

The present study demonstrated that EUA has a moderate Kappa agreement coefficient in relation to EU and MRI in the evaluation of perianal fistulizing Crohn's disease. Portilla *et al.*<sup>25</sup> found 81% agreement between endoanal ultrasonography and EUA, a value higher than that reported in the present study (70%)<sup>15,16</sup>.

The findings described here suggest that EU is less sensitive with posterior and suprasphincteric trajectories. Limitations have already been presented in the identification of extra-frontiers and suprasphincteric trajectories - regions where an adequate coupling with the transducer surface is difficult - when examining the lateral and distal trajectories of the midline<sup>20,22,25</sup>. In this study, EU did not identify a supralevator abscess and three transsphincteric (two lateral and one posterior) fistulous trajectories, detected by both MRI and EUA. In our patients, EU was the only method capable of detecting a rectovaginal fistula.

EU has the limitation of being an operator-dependent exam. Experienced ultrasonographers are particularly important in the examinations of patients undergoing multiple surgeries due to fibrosis and distortion of the anatomy. In the present study, a single sonographer with experience of more than 400 endoscopic ultrasound examinations performed all exams. However, he had limited experience in the identification of perianal fistulous trajectories. With greater experience, one can project an improvement of the method's sensitivity. Injection of hydrogen peroxide into the external orifice may aid in the identification of the fistulous path<sup>26</sup>, but this procedure was not adopted in the routine of this study to simplify the procedure.

Another limitation of this study is the absence of intravenous contrast injection in eight patients submitted to MRI, which makes it difficult to differentiate between active inflammation and fibrosis, especially in cases of complex fistulas, and may contribute to a lower sensitivity of this method. This study had a limited number of patients, which affected the statistical analysis and prevented the evaluation of the sensitivity and specificity of the methods.

In summary, EU is safe, simple and effective, and allows adequate assessment of

perianal fistula pathways in Crohn's disease. It is as a valid alternative method in the examination of complex perianal fistulas. The method is limited when evaluating suprasphincteric and distal trajectories of the anal border. Further studies are needed to confirm these findings. A cost-effectiveness comparison between EU and other imaging modalities such as MRI and endoanal ultrasound with the rigid transducer may be useful in determining its role in the management of perianal fistulas in patients with Crohn's disease.

## R E S U M O

**Objetivo:** determinar o papel da ultrassonografia endoscópica (UE) em relação à ressonância magnética nuclear (RMN) e ao exame sob anestesia (ESA) no manejo de pacientes com doença de Crohn fistulizante perianal. **Métodos:** estudo observacional transversal com pacientes com doença de Crohn perianal, avaliados em um centro terciário de Curitiba, Paraná, Brasil, de fevereiro de 2016 a março de 2017. Todos os pacientes foram submetidos à UE, RMN e ESA. O grau de concordância entre os três métodos foi avaliado através da obtenção do coeficiente de Kappa. Um valor de Kappa de 0,7 ou maior indicou boa concordância. O teste não paramétrico de Friedman foi utilizado para comparar o número de trajetos fistulosos detectados em cada modalidade. Considerou-se o nível de significância estatística como  $p < 0,05$ .

**Resultados:** vinte pacientes foram incluídos. Houve concordância entre os três exames em 11 pacientes. O nível de concordância de Kappa entre os três exames foi 0,53 (moderado) ( $p < 0,001$ ). Não houve diferença estatisticamente significativa em relação ao número de trajetos fistulosos detectados nos três exames ( $p = 0,641$ ). Houve falha na identificação de um trajeto fistuloso em três pacientes com a UE, em três pacientes com a RMN e em dois pacientes com o ESA. **Conclusão:** a UE foi comparável à RMN e ao ESA para avaliação da doença de Crohn fistulizante perianal, e pode ser considerada um exame válido para investigação pré-operatória desses pacientes.

**Descritores:** Doença de Crohn. Fistula Retal. Endossonografia. Imagem por Ressonância Magnética.

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