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ORIGINAL ARTICLE

Intraoperative ultrasonography in patients undergoing surgery for Crohn's disease. Prospective evaluation of an innovative approach to optimize staging and treatment planning

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Abstract

Percutaneous ultrasonography (perc-US) and magnetic resonance enterography (e-MR) are the present standards for staging patients with Crohn's disease (CD). However, intraoperative data still have some discrepancies with preoperative ones. The contribution of intraoperative ultrasonography (IOUS) has never been evaluated. Sixty-five consecutive patients scheduled for ileal/colonic resection for CD between 2010 and 2014 were prospectively enrolled. All patients had perc-US, e-MR and IOUS. Data from different imaging modalities were compared. The reference standard was the final pathology. Surgery was scheduled because of intestinal obstruction ($n=31$ patients), inflammatory mass ($n=21$), fistula ($n=10$), or abdominal pain/sepsis ($n=3$). Fourteen (21.5%) patients had a major discrepancy between preoperative and intraoperative data that required a modification of the surgical planning (five additional ileal lesions, three unknown ileo-sigmoid fistulas, and six not confirmed CD sites). IOUS correctly staged CD in all but one patients (missed ileo-colonic fistula). Pathology data differed from Perc-US data in 13 (20%) patients, from e-MR data in 14 (21.5%), and from IOUS data in one (1.5%). The sensitivity of Perc-US, e-MR and IOUS was: for the identification of CD sites 84.2%, 86.1%, and 100%; for the identification of stenoses 86.8%, 86.8%, and 100%; for the identification of fistulas 75.0%, 81.3%, and 93.8%, respectively. IOUS contributed to the surgical planning in 8 (12.3%) patients. IOUS is a safe, feasible and easy-to-perform procedure that optimizes staging of CD and, in some patients, helps to better define the treatment strategy. It could be helpful to face complex disease presentations on the basis of objective and reproducible data.

Keywords Intraoperative ultrasonography · Crohn's disease staging and surgery · Intestinal fistula · Intestinal stenosis · Inflammatory disease of the bowel · Percutaneous ultrasonography · Magnetic resonance enterography

Introduction

Crohn's disease (CD) is an inflammatory disease of the bowel with a recurrent and progressive evolution that is associated with poor quality of life and disability [1, 2]. The persistent transmural inflammation often determines intestinal complications, such as stenoses and fistulas [1–4]. Surgery is only indicated in symptomatic patients non-responsive to medical treatments or in patients with complications, but most of the patients will require at least one surgical intervention during their lifetime [1–4].

Through the last decades, diagnosis and staging of CD had an extraordinary evolution. Percutaneous ultrasonography (perc-US) and magnetic resonance enterography (e-MR) are the present standards, while endoscopy has a limited role [5]. Perc-Us and e-MR allow to predict the intestinal wall

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characteristics, the presence of complications (mainly stenoses and abdominal collections), a mesenteric thickening, the presence of enlarged lymph nodes, and the required surgical treatment with good sensitivity and specificity. Perc-Us data may even be used to predict relapse [6].

Notwithstanding those progresses, intraoperative data still have some discrepancies with preoperative ones in terms of CD extension, number of lesions, and evidence of fistulas [5, 7–10]. Visual inspection, manual palpation and dissection allow to define the adequate treatment, but the presence of a severe inflammation and of CD complications may lead to a difficult and inaccurate assessment. Even in complex disease presentations, the CD staging is paramount to maximize a bowel-sparing surgery in the perspective of future recurrences [1].

Intraoperative ultrasonography (IOUS) is the standard in liver surgery. It allows to identify liver anatomy, to complete tumor staging and to guide liver resection [11–13]. Theoretically, IOUS could offer the same advantages in patients with CD, but it has never been evaluated. The aims of the present study were: (1) to verify the feasibility and safety of intraoperative bowel ultrasonography in patients with CD; (2) to elucidate the contribution of IOUS to the identification of CD sites, to the diagnosis of stenoses and fistulas, and to the definition of the surgical planning; (3) to compare the performances of IOUS with those of the preoperative imaging modalities (perc-US and e-MR).

Materials and methods

All the consecutive patients scheduled for an ileal and/or colonic resection for CD at the authors' center between January 2010 and April 2014 were prospectively considered for the present study. Patients undergoing both a first resection and a redo surgery were considered. Exclusion criteria were: no completion of the preoperative staging required by the study protocol (perc-US and e-MR); technical problems precluding IOUS; patient's refusal. A laparoscopic resection was not an exclusion criterion, provided that a complete abdominal exploration was feasible and a laparoscopic IOUS was performed. The study was approved by the local ethical committee. Informed consent was obtained from each included patient.

Study protocol

The study protocol entailed:

- Step 1: Preoperative assessment. All the enrolled patients had preoperative perc-US and e-MR. Total colonoscopy was not mandatory.
- Step 2: Surgical exploration (open or laparoscopic). The whole abdominal cavity, the small bowel, and the colon were completely explored. The disease extension was assessed by visual inspection and manual palpation before and after lysis of adhesions and intestinal mobilization.
- Step 3: IOUS. It was performed before any dissection and mobilization.
- Step 4: Treatment. Definition and execution of the adequate surgical procedure.
- Step 5: Data analysis. Comparison of preoperative data (perc-US and e-MR) and of intraoperative data (inspection, palpation and IOUS) with pathology data (reference for the standard).

Data were prospectively registered in the appropriate form after each step. The data derived from surgical exploration and manual palpation were separately registered from the data derived from IOUS. Any bowel alteration identified at the preoperative imaging, at intraoperative exploration, or at IOUS was considered except for benign asymptomatic lesions (e.g., colonic diverticulosis and Meckel diverticulum). The reference for the standard was the final pathology examination in all patients. Pathologists were blinded to both the clinical and the intraoperative data.

According to the Buderer's formula [14], 34 patients were needed to demonstrate a 90% sensitivity of IOUS in CD site detection with an α error = 0.05 and a marginal error of 0.1. Considering an expected prevalence of stenosis of 80%, the number of patients to enroll was 48.

IOUS was performed by LV, MM and FB. The surgical team has a wide experience in perc-US (perioperative management of surgical patients and outpatients clinic for the follow-up of cancer patients) and IOUS (regularly performed during liver resections). Since 1999, gastroenterologists regularly perform perc-US. The two teams (gastroenterologists and surgeons) jointly developed the protocol for IOUS in patients with CD.

IOUS technique and details

The technique of IOUS was standardized as follows: evaluation of the normal ileal and colonic wall; identification and characterization of known CD lesions; exploration of all the bowel segments and characterization of any new lesion.

The ProSound Alpha 5sv or the ProSound Alpha 7 ultrasound system (Hitachi Aloka Medical, Tokyo, Japan) was utilized. IOUS was performed with a linear multi-frequency (5–10 MHz) transducer (UST-579T-7.5, Hitachi Aloka Medical, Tokyo, Japan). Laparoscopic IOUS was performed with a multifrequency (5–10 MHz) flexible linear-array laparoscopic transducer (UST-5536-7.5; Hitachi Aloka Medical, Tokyo, Japan). A control handle at the proximal handheld

end of the probe enabled to move up and down the distal intra-abdominal end. The US probes were sterilized by a sterilization system based on hydrogen peroxide gas plasma (STERRAD®, ASP, Roma, Italy).

Patient management

The authors' institution is a tertiary referral center for CD. A multidisciplinary committee including surgeons, gastroenterologists, endoscopists and radiologists systematically discussed the management of every patient. Surgery was scheduled in patients with symptomatic CD non-responsive to medical therapy or in patients with complicated CD (i.e., intestinal obstruction, abdominal collections, or fistulas).

A laparoscopic approach was scheduled whenever possible. The preoperative diagnosis of complicated CD or a redo surgery were not absolute contraindications to a laparoscopic approach. A pure laparoscopic approach was routinely adopted for left colonic CD. In patients with ileal, ileocecal or right colonic CD, a laparoscopic-assisted approach including laparoscopic mobilization followed by mini-laparotomy and open resection and anastomosis was performed.

Statistical analysis

Continuous variables were compared between groups using the unpaired t test or Mann–Whitney *U* test, as appropriate. Categorical variables were compared using the Fisher's exact test. A P value < 0.05 was considered statistically significant for all tests. Per-patient and per-lesion analyses were performed to assess performances of perc-US, e-MR and IOUS.

Results

Between January 2010 and April 2014, 132 patients with a preoperative diagnosis of CD underwent surgery at the authors' center. Sixty-seven patients were excluded because of an incomplete preoperative staging or because of technical problems precluding IOUS. Overall, 65 patients were prospectively enrolled.

Preoperative patients characteristics

Among the 65 included patients, 39 were male (60%). The median age was 42 years (range 15–79). The median Harvey–Bradshaw Index (HBI) was 8 (range 2–18), > 7 in 37 (56.9%) patients. The indications to surgery were as follows: intestinal obstruction in 31 patients; abdominal inflammatory mass in 21; intestinal fistula in 10; abdominal pain in two; and sepsis in one. Overall, 24 (36.9%) patients presented with recurrent CD. Patients' characteristics are summarized in Table 1.

All patients had preoperative perc-US and e-MR. Total colonoscopy was performed in 22 (33.8%) patients. Perc-US and e-MR had a concordant assessment of the disease extension in 62 (95.4%) patients: CD of the ileum in 31 patients; of the ileocecal area in 12; of the left colon in two; of both the ileum and the colon in three; and of the ileo-colonic anastomosis in 14 (including three with additional ileal lesions). In three patients perc-US and e-MR were discordant. In all cases, e-MR diagnosed an ileal + colonic involvement (ileal CD extended to the cecum in one, ileum + transverse colon in one, and ileum + sigmoid colon in one), while perc-US diagnosed an ileal-only disease.

Stenoses were evident in 61 (93.8%) patients. Fifteen (23.1%) patients had a preoperative diagnosis of intestinal fistula: entero-enteral fistula in eight, entero-cutaneous fistula in four, ileo-colonic fistula in two (transverse colon and left colon, respectively), and ileo-vaginal fistula in one.

Table 1 Patients' characteristics

Age, years	42 (15–79)
Male sex	39 (60%)
Must score	
Well nourished	37 (57%)
Risk of malnutrition	8 (12%)
Malnourished	20 (31%)
Disease presentation	
Acute disease	20 (31%)
Recurrent disease	24 (37%)
Active medical treatments	57 (88%)
Mesalazine	33 (51%)
Immunosuppressive therapies	18 (28%)
Remicade	12 (18%)
Steroids	4 (6%)
Harvey bradshaw index	8 (2–18)
Index > 7	37 (57%)
Indications to surgery	
Intestinal obstruction	31 (48%)
Abdominal inflammatory mass	21 (32%)
Intestinal fistula	10 (15%)
Abdominal pain	2 (3%)
Sepsis	1 (2%)
Preoperative imaging	
Percutaneous US	65 (100%)
MR enterography	65 (100%)
Total colonoscopy	22 (34%)
Abdominal CT	6 (9%)

Continuous variables are reported as median (range)

US ultrasonography, *MR* magnetic resonance, *CT* computed tomography

Perc-US failed to identify two ileo-colonic fistulas detected by e-MR.

Surgical exploration

Twenty (30.8%) patients had a discrepancy between preoperative and intraoperative data. Of those, 14 (21.5%) patients had major discrepancies that required an intraoperative modification of the planned surgical procedure. In 8 (12.3%) patients the CD was more extended than expected: five patients had additional skip ileal lesions; and three had an ileo-sigmoid fistula, associated with sigmoid CD in one (preoperative diagnosis of ileal-only CD). In three (4.6%) patients the CD disease was less extended than expected: in one patient an ileal lesion was not identified; in one patient an ileo-ileal fistula was not confirmed; in one patient an ileo-sigmoid fistula and a sigmoid CD were not confirmed. In three (4.6%) patients the preoperative diagnosis of CD was not confirmed (preoperative diagnosis was CD of the ileum in two and CD of the ileo-colonic anastomosis in one). Six (9.2%) patients had a minor discrepancy between preoperative and intraoperative data: three had a colonic involvement more extended than expected (two had a CD extended to the right colon instead of an ileo-cecal CD, and one had an involvement of the transverse colon instead of an isolated recurrence of the ileo-colonic anastomosis); three had a more limited CD (isolated ileal CD without colonic involvement). Discrepancies between preoperative imaging and surgical exploration are summarized in Fig. 1.

IOUS contribution to CD staging

IOUS correctly identified the extension of CD in all but one (98.5%) patients. In one patient IOUS failed to identify an ileo-colonic fistula. IOUS correctly identified all the CD sites and stenoses (complete agreement with pathology data). The median intestinal wall thickness was 2 mm (range, 1–4) in normal tracts vs. 9 mm (4–18) in CD tracts, $p < 0.0001$. Some examples of IOUS images are reported in Fig. 2.

Comparison with the reference standard (Table 2)

First, the capability of perc-US, e-MR and IOUS to globally assess the disease was considered (per-patient analysis). In comparison with the pathology data, perc-US data were incorrect in 23 (35.4%) patients, e-MR data in 22 (32.8%) and IOUS data in one (1.5%). Major discrepancies occurred in 13 (20%), 14 (21.5%), and one (1.5%) patients, respectively ($p < 0.05$ IOUS vs. perc-US/e-MR). Perc-US and e-MR had both underestimation and overestimation of

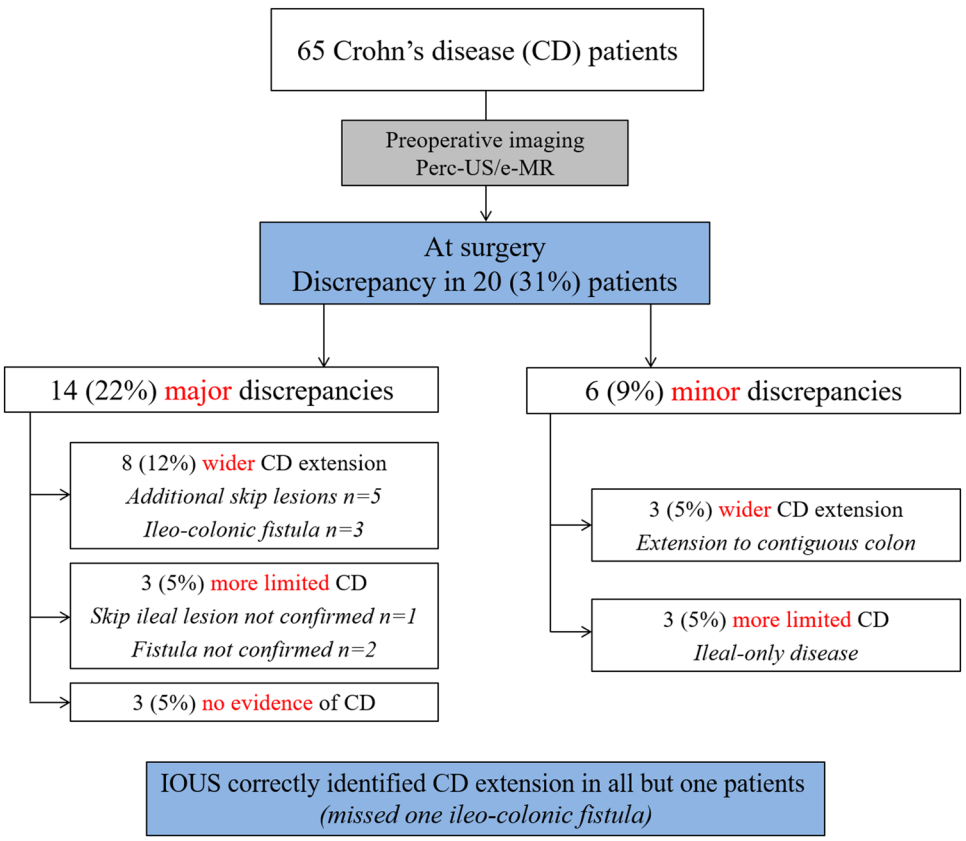

Fig. 1 Extension of CD: discrepancies between preoperative imaging and intraoperative data

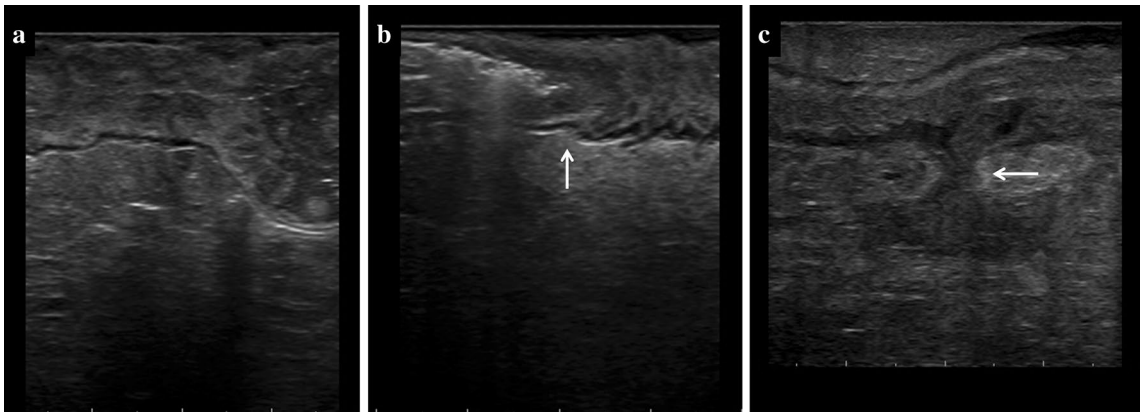

Fig. 2 Intraoperative ultrasonography in patients affected by Crohn's disease (CD): **a** CD of the ileum with severe thickening of the ileal wall; **b** the transition (arrow) from the normal ileal wall (left side) to the thickened wall due to CD (right side); **c** a fistula (arrow) across the right colonic wall affected by CD

Table 2 Comparison of performances of perc-US, e-MR and IOUS, per-lesion analysis

	Perc-US (%)	E-MR (%)	IOUS (%)
Identification of CD sites			
Sensitivity	84.2	86.1	100
Positive predictive value	93.4	93.5	100
Accuracy	79.4	81.3	100
Identification of stenoses			
Sensitivity	86.8	86.8	100
Specificity	50.0	50.0	–
Positive predictive value	95.2	95.2	100
Negative predictive value	25.0	25.0	–
Accuracy	83.8	83.8	100
Identification of fistulas			
Sensitivity	75.0	81.3	93.8
Specificity	98.0	95.9	100
Positive predictive value	92.3	86.7	100
Negative predictive value	92.3	94.0	98.0
Accuracy	92.3	92.3	98.5

the CD, while IOUS had a single case of underestimation (missed ileo-colonic fistula).

Second, the capability of the three imaging modalities to identify the CD sites was analyzed (per-lesion analysis). Sensitivity of perc-US, e-MR and IOUS was 84.2, 86.1, and 100%, respectively; accuracy was 79.4, 81.3, and 100%, respectively. Similar data were observed for the identification of CD stenoses: sensitivity of perc-US, e-MR and IOUS was 86.8, 86.8, and 100%, respectively; accuracy was 83.8, 83.8, and 100%, respectively. Finally, the diagnosis of fistula was considered. Sensitivity of perc-US, e-MR and IOUS was 75.0, 81.3, and 93.8%; positive predictive value was 92.3, 86.7, and 100%; accuracy was 92.3, 92.3, and 98.5%, respectively.

IOUS contribution to the surgical planning

Manual palpation and dissection allowed to define surgical treatment in most cases. Nevertheless, in some patients IOUS data contributed to the choice of the most appropriate treatment. In two patients with multiple ileal stenoses (> 10 CD sites), IOUS allowed to discriminate the ileal tracts to resect, those to treat with a strictureplasty (the severity of stenosis and the endoluminal fluid transit were evaluated by IOUS for every single lesion), and those not to treat. In three patients with intraoperative detection of ileo-colonic fistula, IOUS helped to decide the need for a colonic resection on the basis of the colonic wall alterations (only one patient had colonic resection). Finally, in three patients with no macroscopic evidence of CD, IOUS confirmed a normal intestinal wall reassuring about no resection.

Surgical procedures and operative outcomes

One (1.5%) patient had pure laparoscopic resection (left colonic resection). Forty-four (67.7%) patients had laparoscopic-assisted surgery. Conversion to open surgery occurred in three (6.7%) patients because of bulky masses or fistulas. No complications related to IOUS occurred. Operative mortality was nil and overall morbidity rate was 20% (13 patients). Severe morbidity occurred in eight patients (12.3%): six anastomotic leaks and two bleedings requiring reoperation.

Discussion

The present analysis is a pilot study about the role of IOUS in patients with CD. Even if the majority of patients with CD can be adequately managed without IOUS, our data showed that IOUS has a strong reliability in CD staging, higher than preoperative imaging (perc-US and e-MR), and may give a contribution to surgical planning in patients with complex disease presentation.

During the last decades, IOUS progressively became part of surgical practice. Liver surgery was the first setting in which IOUS gained consensus [11–13]. To date, whenever a liver resection is scheduled, IOUS is an essential tool to elucidate anatomy, to disclose tumor nodules, to analyze their relationship with intrahepatic vessels, and to define the most appropriate resection [11–13]. Recently, IOUS application has been extended to biliary and pancreatic surgery [15–17]. Since early '90s, the authors extensively adopted IOUS in HPB surgery and repeatedly reported its benefits and applications [13, 15, 18–20]. This positive feeling with IOUS combined with the wide experience of gastroenterologists in perc-US for CD led the authors to explore the role of IOUS in CD.

The surgical approach to CD patients has to combine two separate aims: the resolution of symptoms (patients scheduled for surgery are either complicated or symptomatic) and a bowel-sparing policy in view of future recurrences [1]. Accordingly, both an accurate assessment of the extension of CD and a precise surgical planning are paramount.

Perc-US, CT and e-MR are the present standards for non-invasive diagnosis and staging of CD [5]. They achieved excellent results in the diagnosis of CD site (sensitivity 70–90% and specificity 85–95%) and of CD complications (70–90 and 85–100%, respectively) [8, 9, 21–25]. Similar data were observed in the present analysis. However, sensitivity of non-invasive imaging modalities decreases in most complex disease presentations, such as in presence of fistulas (70–75% for both Perc-US, and CT, and e-MR) [5, 7–10]. The present series confirmed also those data: sensitivity of perc-US and of e-MR in fistula detection was 75% and 81%, respectively. Overall, preoperative imaging may underestimate the severity of CD in up to one-fourth of patients. IOUS performed much better: its data were concordant with pathology data in all but one patients (vs. 65% for perc-Us and e-MR data, major discrepancy in 20% of cases); IOUS identified all CD lesions and stenoses (vs. 85–88% of the other imaging modalities) and 94% of fistulas (vs. 75–80%). An intraoperative imaging modality was compared with non-invasive preoperative ones. Nevertheless, the present data suggest that IOUS (a natural evolution of perc-US) can be consistently a new reference standard for imaging in CD, exactly as hepatic IOUS became a standard in liver diseases.

The second issue to consider is the surgical planning. In patients with CD, surgeons are used to modify the scheduled treatment on the basis of intraoperative findings. Nevertheless, some situations can be difficult to manage even after laparotomy, e.g., multiple CD localizations or inflammatory masses involving contiguous organs. In the present series, IOUS impacted the surgical strategy exactly in the most complex scenarios. In patients with multiple CD localizations, surgeons must decide which lesions should be treated and which treatment should be performed (strictureplasty vs. resection). IOUS allowed to assess the severity of stenoses on the basis of objective data (the lumen diameter and the transit of fluid) and to decide the treatment on the basis of reproducible criteria. In patients with a suspected fistula, IOUS allowed to confirm it before any dissection, and to identify bowel tracts to resect. Finally, IOUS was useful in patients with overestimation of CD severity at preoperative imaging. We decided not to perform resection according to objective criteria (intestinal wall thickness and fluid transit). In the present series, about 10% of patients benefited from IOUS exploration. In high-volume centers, specialized in CD surgery, it could represent a non-negligible number of patients.

A major criticism can be advanced: CD patients are worldwide treated without IOUS achieving excellent results. Even if palpation and dissection are helpful, IOUS offered additional data that contributed to the surgical decision. Of note, IOUS was always performed before dissection and manipulation. Objective measures provided by IOUS could optimize the standardization and the rationalization of the surgical strategy. IOUS could be even more relevant in laparoscopic procedures where tactile feedback is lacking. In the presence of large inflammatory masses, IOUS may help to recognize anatomy. Some authors reported a risk of misdiagnosis of endometriosis as CD [26–28]. The two diseases have similar production of proinflammatory cytokines and, in some patients, may have similar macroscopic features, but require different treatments [29–31]. IOUS could be useful in this difficult differential diagnosis. Future studies should analyze if IOUS data in patients with CD are associated with their outcomes, with the effectiveness of medical treatments or with the recurrence risk.

This is a monocenter analysis including a limited number of patients. External validation by large series is needed to completely ascertain the clinical impact of IOUS in patients affected by CD and to recommend it in daily practice. The learning curve of IOUS was not assessed. In the authors center, where perc-US for CD and IOUS in HPB surgery are routinely performed, the IOUS program for CD was quickly developed and standardized thanks to a strict cooperation between gastroenterologists and surgeons.

In conclusion, a new tool in CD management is outlined. IOUS is a safe, feasible and easy-to-perform procedure that

allows to optimize staging of CD. In some patients, IOUS data may even refine treatment strategy. In referral centers, IOUS can be helpful to face complex disease presentations on the basis of objective and reproducible data.

Compliance with ethical standards

Conflict of interest The authors have no source of funding and no conflict of interest to declare.

Ethical approval The study was approved by the local ethical committee.

Informed consent Informed consent was obtained from each included patient.

Research involving human participants and/or animals All the procedures performed in the present study involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments. No animal was involved in the present study.

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