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MINIREVIEWS

Dynamic contrast enhanced ultrasound in gastrointestinal diseases: A current trend or an indispensable tool?

Mattia Paratore, Matteo Garcovich, Maria Elena Ainora, Laura Riccardi, Antonio Gasbarrini, Maria Assunta Zocco

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Mattia Paratore, Matteo Garcovich, Maria Elena Ainora, Laura Riccardi, Medicina Interna e Gastroenterologia, CEMAD Digestive Disease Center, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome 00168, Italy

Antonio Gasbarrini, Maria Assunta Zocco, Medicina Interna e Gastroenterologia, CEMAD Digestive Disease Center, Università Cattolica del Sacro Cuore, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome 00168, Italy

Corresponding author: Matteo Garcovich, MD, PhD, Research Scientist, Staff Physician, Medicina Interna e Gastroenterologia, CEMAD Digestive Disease Center, Fondazione Policlinico Universitario A. Gemelli IRCCS, Largo A. Gemelli 8, Rome 00168, Italy.
matteogarcovich@yahoo.it

Abstract

Contrast enhanced ultrasound (CEUS) has been widely implemented in clinical practice because of the enormous quantity of information it provides, along with its low cost, reproducibility, minimal invasiveness, and safety of the second-generation ultrasound contrast agents. To overcome the limitation of CEUS given by the subjective evaluation of the contrast enhancement behaviour, quantitative analysis of contrast kinetics with generation of time-intensity curves has been introduced in recent years. The quantification of perfusion parameters [named as dynamic-CEUS (D-CEUS)] has several applications in gastrointestinal neoplastic and inflammatory disorders. However, the limited availability of large studies and the heterogeneity of the technologies employed have precluded the standardisation of D-CEUS, which potentially represents a valuable tool for clinical practice in management of gastrointestinal diseases. In this article, we reviewed the evidence exploring the application of D-CEUS in gastrointestinal diseases, with a special focus on liver, pancreas, and inflammatory bowel diseases.

Key Words: Quantitative perfusion analysis; Gastrointestinal diseases; Time-intensity curve; Multiparametric ultrasound

Core Tip: Contrast-enhanced ultrasound (CEUS) has been widely implemented in clinical practice in recent years. Despite its several advantages, the qualitative evaluation of this exam and the lack of objectivity could lead to variability between different operators and ultrasound equipments. Dynamic-CEUS (D-CEUS) with the measurement of perfusion parameters is aimed at overcoming this important limitation. The purpose of this review is to explore the usefulness of D-CEUS in gastroenterological diseases.

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INTRODUCTION

Contrast enhanced ultrasound (CEUS) has been widely implemented in clinical practice as a result of the enormous quantity of information it provides, along with its low cost, reproducibility, minimal invasiveness, and safety of the second-generation ultrasound contrast agents (UCAs)[1-4]. Despite its numerous advantages, one of the most significant limitations of CEUS is the subjective evaluation of contrast enhancement related behaviour of the explored tissues[5]. In recent years, dynamic-CEUS (D-CEUS) has been explored to overcome this limitation.

D-CEUS represents the quantitative analysis of UCA-kinetics in a specific region of interest (ROI)[6]. This technique allows two types of analysis in the examined tissue: Disruption-replenishment analysis and wash-in/wash out analysis[7]. The first analysis consists in the evaluation of microbubbles replacement after destroying them with high mechanical index. Requiring the continuous intravenous infusion over five to twenty minutes of UCA, the disruption-replenishment analysis are infrequently used due of their complex methodology[8]. Consequently, the second form of analysis is more frequently employed in clinical practice. It consists of measuring the average intensity of a ROI following a bolus injection of UCA and generating a time-intensity curve (TIC). Hence, multiple parameters are derived from the TIC to quantitatively characterize the different stages of the wash-in and wash-out phases. The fundamental parameters derived from TIC are summarized in Table 1[9,10] and a schematic representation of TIC is shown in Figure 1. Generally, these parameters are obtained from different softwares and might consequently have varying nomenclature but can be divided into two categories: Amplitude parameters and time parameters. These criteria reflect various vascularization features: Amplitude parameters are mainly related to blood volume in the ROI, while blood flow is mostly correlated with time parameters[11]. Tracking microbubbles circulation provides the spatial representation of blood flow patterns and the derivation of parametric values of tissue perfusion since microbubbles strictly remain within the vasculature compartment[12].

Examining the pros and cons, D-CEUS is a widely accessible, radiation-free, non-nephrotoxic and cost-effective technique that allows objective enhancement quantification, image comparison, real-time evaluation of the microcirculation perfusion by a strictly intravascular blood pool agent. This is crucial after the introduction of updated response evaluation criteria in solid tumor (RECIST) criteria based on tumour perfusion as D-CEUS potentially enables the monitoring of changes in vascularization even shortly after tumor treatment[13,14]. According to current European Federation for Ultrasound in Medicine and Biology recommendations, D-CEUS is useful for quantifying tumor enhancement objectively, to characterize focal lesions and evaluate the therapeutic response[7]. In contrast, D-CEUS should ideally be uniform regardless of the ultrasound equipment, data collecting, and analysis software, as different approaches and technical issues may influence the results' validity. Lastly, the technical limitations of the method must be addressed, particularly in the abdomen, where intestinal, respiratory, and probe motion artefacts could make this exam challenging, as well as the patient's ability to accomplish the instructions based on his mental and physical state[15].

The first D-CEUS examination was performed on oncological renal illness more than two decades ago [16]. Since then, this technique has spread to several medical specialties, especially in the gastroenterological setting and not only for oncological diseases. In this review we summarize the evidence exploring the application of D-CEUS in gastrointestinal diseases.

LIVER DISEASES

In liver diseases, D-CEUS has been explored primarily for its usefulness in characterizing focal liver lesions (FLLs). Several applications of D-CEUS in predicting biological behaviour, differential diagnosis, and prognosis have been explored. These studies are summarized in Table 2, and Figure 2 illustrates the

Table 1 Dynamic contrast-enhanced ultrasound parameters in time-intensity curve

Abbreviation	Parameter	Definition	Unit
AT	Arrival time	Time from administration of UCA to the beginning of the curve	s
AUC or WiWoAUC	Area under the curve or wash-in and wash-out area under the curve		AIU
FT	Fall time	Time from PE to point where tangent of descending curve across x-axis	s
IMAX or MI	Maximum intensity	Maximum intensity of the curve	AIU
MTT	Mean transit time	Mean time taken by contrast to pass through the ROI	s
PE	Peak enhancement	Maximum intensity of the curve	AIU
PI	Peak intensity	Maximum intensity of the curve	AIU
Pw	Slope coefficient of wash-in	Coefficient of the enhancement wash-in slope	AIU × s
RT	Rise time	Time from PE to point where tangent of ascending curve across x-axis	s
TPI or TTP or TP	Time to peak	Time from the beginning of the curve to peak	s
WiAUC	Wash-in area under the curve	AUC from the beginning of the curve to PE	AIU × s
WoAUC	Wash-out area under the curve	AUC from the PE to the end of the curve	AIU × s
WiR	Wash-in rate	Tangent at the ascending part of the curve	AIU × s
WoR	Wash-out rate	Tangent at the descending part of the curve	AIU × s

AIU: Absolute intensity unit; ROI: Region of interest; UCA: Ultrasound contrast agent.

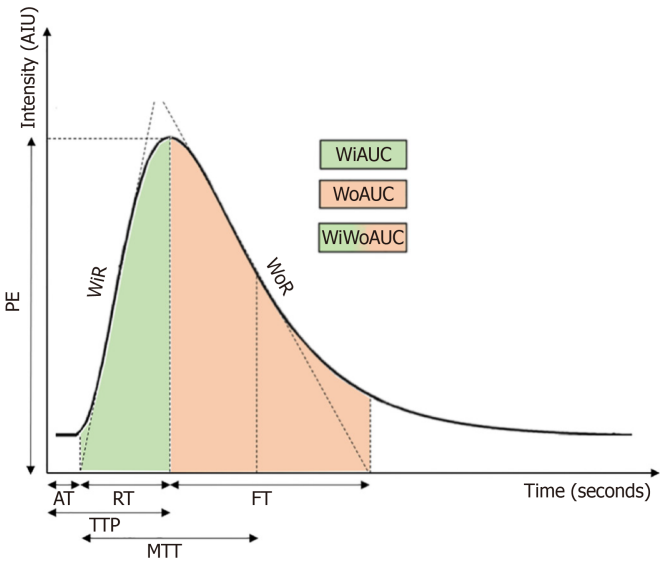

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Figure 1 Time-intensity curve and derived parameters. AIU: Absolute intensity unit; AT: Arrival time; FT: Fall time; MTT: Mean transit time; PE: Peak enhancement; s: Second; TTP: Time to peak; WiAUC: Wash-in area under the curve; WiR: Wash-in rate; WiWoAUC: Wash-in and wash-out area under the curve; WoAUC: Wash-out area under the curve; WoR: Wash-out rate; RT: Rise time.

use of D-CEUS to characterize liver lesions.

Table 2 Dynamic contrast-enhanced ultrasound and liver diseases

Ref.	Study design/number of patients	Object of D-CEUS	Population/groups	Machine/UCA/software	Significant results ($P < 0.05$)
Wildner *et al*[31], 2022	Prospective/17	Melanoma liver metastasis	Patients with melanoma liver metastasis treated with sorafenib/Responders' *vs* non-responders	Sequoia 512/SonoVue/Qontrast	Increase of MTT and TTP is associated with response to treatment and prognosis
Gu *et al*[30], 2022	Retrospective/97	HCC	Patients with HCC underwent thermal ablation	Acuson Sequoia, Phillip EpiQ7/SonoVue/VueBox	WiAUC, WoAUC, and WiWoAUC ratios between HCC and surrounding parenchyma before ablation were predictors of survival
Huang *et al*[18], 2022	Prospective/120	HCC	Patients with HCC underwent biopsy/Low-Ki-67 *vs* high-Ki-67	Logiq E9/Sonazoid/NovoUltrasound Kit	PE difference between HCC and distal liver parenchyma was different in the Kupffer phase
Li *et al*[22], 2022	Retrospective/31	HCC	Patients with HCC underwent surgery/MVI-positive *vs* MVI-negative	Phillip EpiQ7/Sonazoid/built-in auto contrast software	None of the D-CEUS parameters was related to MVI
Zocco *et al*[28], 2013	Prospective/46	Liver parenchyma	Cirrhotic patient underwent HVPG/clinically significant portal hypertension *vs* severe portal hypertension	iU22/SonoVue/QLAB	Negative correlation between PI, Pw and HVPG. Positive correlation with MTT. AUROC of 1.00 for PI < 23.3 AIU to predict clinically significant portal hypertension
Dong *et al*[21], 2021	Retrospective/16	HCC	Patients with HCC underwent surgery/MVI-positive *vs* MVI-negative	Acuson Oxana, Logiq E9, Siemens Acuson Sequoia/SonoVue, Lumason/VueBox	WiAUC and WoAUC were higher in MVI positive group
Schwarz *et al*[24], 2021	Retrospective/139	Focal liver lesion	Patients with diagnosed focal liver lesion/malignant versus benign	Acuson Sequoia, S2000 or S3000 and Phillip EpiQ7/SonoVue/VueBox	RT and late phase ratio were different between malignant and benign liver lesion
Xuan *et al*[19], 2021	Retrospective/128	HCC	Patients with HCC underwent biopsy or surgery/highly-differentiated *vs* moderate-differentiated *vs* poorly-differentiated	-/SonoVue/-	RT and MTT increased from poorly- to moderate- to highly-differentiated. Enhancement rates decreased from poorly- to moderate- to highly-differentiated
Amadori *et al*[32], 2018	Prospective/37	CRC Liver metastasis	Patients underwent chemotherapy/chemotherapy *vs* chemotherapy plus bevacizumab	iU22 vision 2008/SonoVue/QLAB	Reduction of PI and AUC and increase of TPI correlated with higher PFS in chemotherapy plus bevacizumab group
Wildner *et al*[25], 2019	Prospective/148	Focal liver lesion	Patients with focal liver lesion and subsequent final diagnosis/HCC, CCC, PCA, CRC, BC, MM, FNH	Sequoia 512/SonoVue/VueBox	Higher PE and WiWoAUC in HCC than CRC. Lower Relative intensity signal for PCA and CRC compared to HCC at 30 and 120 s after PE
Mogensen *et al*[33], 2017	Prospective/12	CRC liver metastasis	Patients underwent chemotherapy/chemotherapy *vs* chemotherapy plus bevacizumab	Logiq E9/SonoVue/VueBox	Early changes of PE correlate with tumor shrinkage at CT scan
Zocco *et al*[28], 2013	Prospective/28	HCC	Patients treated with sorafenib/Responders' *vs* non-responders	iU22/SonoVue/QLAB	PI, Pw and AUC 10% decrease correlate with response to therapy. AUC 10% decrease and increased/unchanged TPI and MTT are associated with longer survival. Decrease of Pw is associated with PFS
Zhan *et al*[20], 2019	Prospective/35	HCC	Patients with HCC underwent microwaves ablation	Acuson Sequia/Sonovue/SonoLiver	Positive correlation between MVD, VEGF and IMAX; negative correlation

					between MVD and TTP. TTP was an independent predictor of OS
Wildner *et al*[26], 2014	Prospective/43	HCC, ICC	Patient with proven HCC and ICC	Acuson Sequoia 512/SonoVue/VueBox	FT and MTT were lower in ICC than HCC. Relative signal intensity was lower in ICC than HCC in all time point after PE
Frampas *et al*[69], 2013	Prospective/19	HCC	Patients with HCC treated with sorafenib or sunitinib/RECIST progressor *vs* non-progressor	Aplio XV/SonoVue/Vascular Recognition Imaging" mode	AUC decrease ≥ 40% correlated with RECIST non-progression
Lassau *et al* [29], 2011	Prospective/42	HCC	Patients with HCC treated with Bevacizumab	Aplio scanner/SonoVue/Contrast Harmonic Imaging-Quantification software	AUC, WiAUC, WoAUC and TPI decrease correlate with tumor response. TPI decrese correlate with PFS. AUC and WoAC decrease correlate with OS

AIU: Arbitrary intensity unit; AUC: Area under the curve; AUROC: Area under the receiver operating characteristic; BC: Breast cancer; CCC: Cholangiocarcinoma; CRC: Colorectal cancer; CT: Computed tomography; D-CEUS: Dynamic contrast-enhanced ultrasound; FNH: Focal nodular hyperplasia; HCC: Hepatocellular carcinoma; HVPG: Hepatic vein portal pressure; MM: Malignant melanoma; MTT: Mean transit time; MVD: Microvascular density; MVI: Microvascular invasion; OS: Overall survival; PCA: Pancreatic adenocarcinoma; PE: Peak enhancement; PFS: Progression free survival; PI: Peak intensity; Pw: Slope coefficient of wash-in; RECIST: Response evaluation criteria in solid tumors; RT: Rise time; TPI: Time to peak intensity; TTP: Time to peak; UCA: Ultrasound contrast agent; WiAUC: Wash-in area under the curve; WoAUC: Wash-out area under the curve; WiWoAUC: Wash-in and wash-out area under the curve.

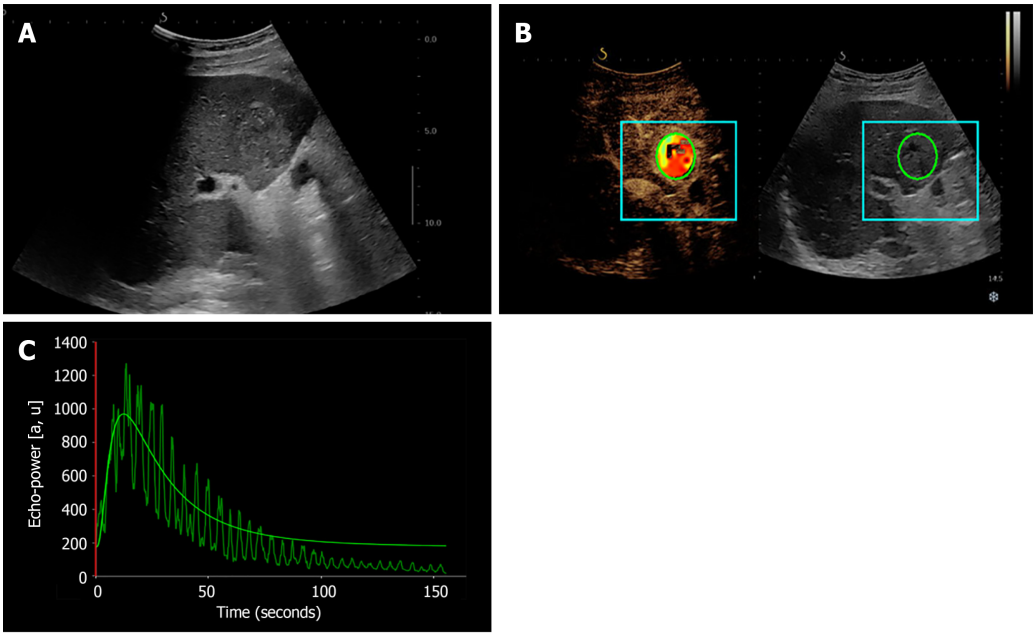

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Figure 2 Dynamic contrast-enhanced ultrasound and time-intensity curves of the liver. A: Hypoechoic mass (hepatocellular carcinoma) of IV liver segment visualized in B-mode ultrasound; B and C: Contrast-enhanced ultrasound with corresponding time-intensity curve of the liver mass.

Biological behaviour

The vascular structure of a tumour lesion is closely associated with microscopic features such as the degree of differentiation, the proliferation index and growth rate, the presence of necrosis, the angiogenesis and the vascular invasion[17]. Therefore, the analysis of vascularization parameters could be different according to each of the aforementioned characteristics.

Huang *et al*[18] investigated the correlation between perfusion parameters and Ki-67 in hepatocellular carcinoma (HCC) patients. Prospective analysis of one hundred twenty patients showed that the peak enhancement (PE) difference between HCC and distal liver parenchyma in the Kupffer phase was significantly higher in low Ki-67 (< 10%) group compared to high Ki-67 (≥ 10%) group, probably due to lower concentration of Kupffer cells in poorly differentiated neoplasms[18]. Supporting this, differences in D-CEUS parameters were found among HCC differentiation classes. Specifically, rise time (RT) and time to peak (TTP) demonstrated a significant positive correlation with differentiation degree, whereas

enhancement rate was significantly higher in lesions with less differentiation[19].

Regarding the pure vascular features of tumors, Zhan *et al*[20] demonstrated that histological determined microvessel density and vascular endothelial grow factor stain positively correlated with maximum intensity (MI), while microvessel density negative correlated with TTP[20]. This suggested that D-CEUS parameters could provide a reliable characterization of the microvascular scaffold of lesions. In another study Dong *et al*[21] perform a retrospective analysis of D-CEUS characteristics of HCC to investigate the capability to predict microvascular invasion in a cohort of 16 patients who underwent subsequent surgery. They found that wash-in area under the curve (WiAUC) and wash-out area under the curve (WoAUC) were significantly higher in microvascular invasion positive group ($P < 0.05$), especially when the ROI was positioned in the marginal area of the lesion. This phenomenon is likely to be attributed to the formation of arteriovenous fistulas during vascular invasion, which leads to an increase in blood flow[21]. In contrast, using different UCA, Li *et al*[22] found no correlation between quantitative parameters and microvascular invasion in thirty-one resected HCCs[22]. One of the most significant differences between second-generation UCAs is their resistance to US wave pressure, which could explain this apparent contradiction in results[23].

This evidence suggests that D-CEUS may serve as a biomarker of the biological behaviour and microscopic characteristics of HCC, detecting the abnormal vascularization characteristics that developed as the disease progressed.

Differential diagnosis

Quantitative analysis of perfusion parameters demonstrated a promising potential to distinguish between benign and malignant FLLs. In a retrospective study including one hundred and thirty-nine FLLs of which forty-four benign and ninety-five malignant, benign lesions showed a significantly higher late-phase ratio (ratio between signal intensities of lesion and surrounding tissue in late phase, LPR) compared to malignant counterpart, showing an area under the curve (AUC) of 0.9, with maximal sensitivity (100%) but low specificity (56.8%). Interestingly, the difference in LPR remains significant also comparing hypoechoic haemangiomas to malignant lesions, suggesting the ability to distinguish a real wash-out from other phenomena. Although RT demonstrated a lower AUC (0.58) for distinguishing benign from malignant lesions, it demonstrated outstanding accuracy (AUC: 0.91) when applied to the distinction between haemangioma and malignancy. Furthermore, considering only benign lesions, haemangioma and adenoma displayed longer mean RT values than other benign lesions[24]. This suggests that quantitative analysis could increase the diagnostic accuracy between benign liver lesions and in challenging situations, such as benign lesions with moderate hyperenhancement (*e.g.*, thrombosed haemangioma) or modest hypoenhancement in late phase (*e.g.*, certain subtypes of hepatic adenoma).

D-CEUS might be helpful to differentiate hypervascular tumours like HCC from other malignant liver lesions that are predominantly necrotic and hypovascular. Wildner *et al*[25], analysing D-CEUS parameters in HCC and different secondary liver lesions showed that PE normalized for parenchyma signal and wash-in-wash-out area under the curve (WiWoAUC) were significantly higher in HCC compared to colorectal cancer (CRC) metastasis and relative signal intensity at 30 and 120 s after PE was significantly lower for pancreatic adenocarcinoma and CRC liver metastasis compared to HCC[25]. These results clearly suit to the hypervascular nature of HCC in contrast to the more necrotic and weakly centrally vascularized secondary liver lesions of other primitive cancers. While arterial phase parameters are significantly different between HCC and CRC metastatic liver masses, their applicability to differentiate HCC from other primary intrahepatic malignancies is unfitted. Previously, the same authors had investigated the differences between HCC and intrahepatic cholangiocellular carcinoma (ICC) showing no significant differences in arterial phase parameters while ICC group showed lower values of mean transit time (MTT) and fall time in portal and venous phase. Furthermore, relative signal intensity was significantly lower in ICC compared to HCC in all time points after PE at 40 s, 80 s, 100 s and 120 s[26]. Actually, the main difference between HCC and ICC at CEUS is the early and marked wash-out in portal phase for ICC[4]. Objective quantification of the wash-out phenomenon using D-CEUS could improve the diagnostic accuracy of differentiating lesions with similar portal and late phase hypoenhancement.

Prognosis prediction

One of the most promising applications of D-CEUS is the assessment of liver tumour response to treatment, particularly in HCC where chemotherapy regimens are mostly based on vascular-targeting agents[27]. To this purpose, Zocco *et al*[28] investigated the role of D-CEUS to early detect vascular changes in HCC patients treated with sorafenib and to predict response to therapy and prognosis. The results showed that a decrease in AUC, peak intensity (PI), and slope of wash-in (Pw) between T0 (baseline) and T1 (after fifteen days of therapy) was significantly associated with response to therapy assessed with RECIST criteria after two months of treatment. Furthermore, 10% decrease in AUC was significantly associated with longer survival as increased/unchanged of time to PI (Tp) and MTT, while a Pw reduction was significantly associated with progression-free survival (PFS)[28]. Similar results were obtained by Lassau *et al*[29] considering patients with advanced HCC treated with bevacizumab. D-CEUS was performed before treatment and at days 3, 7, 14, and 60 after treatment; and every 2 mo

thereafter. Interestingly, the results showed that very early changes in D-CEUS characteristics correlated with response to therapy and prognosis. Particularly, the decreases in AUC, AUC during wash in, AUC during washout, and time to PI (TPI) at day 3 were significantly associated with RECIST response at 2 mo. Furthermore, PI, AUC and AUC during washout changes at day 3 were correlated with PFS and overall survival (OS)[29]. These results suggest that effects of antiangiogenetic treatments can be early assessed quantifying the perfusion parameters and could allow for a tempestive intervention when relative prognosis is unfavourable.

D-CEUS could also have a role in predicting the prognosis of HCC patients who received loco-regional treatments. In HCC patients undergoing microwave ablation, TTP evaluated before the procedure was confirmed as an independent predictor of OS[20]. Similarly, the WiAUC, the WoAUC and the WiWoAUC ratio between HCC lesion and surrounding liver parenchyma evaluated before thermal ablation were significantly associated with survival[30]. As a consequence, quantitative perfusion evaluation might provide additional information useful to plan treatment procedures.

Considering non-HCC malignant liver lesions, different studies evaluated D-CEUS modifications to predict early response to therapies. In patients with liver metastasis of melanoma treated with sorafenib, TTP and MTT increased significantly in responders group at 15 and 56 d assessment[31]. Furthermore, CRC-metastatic patients treated with chemotherapy plus bevacizumab showed changes in derived PI, TPI and AUC at day 15 that were significantly correlated with PFS, however these modifications were not related with tumor response or survival[32]. In contrast, Mogensen *et al*[33] observed a significant association between PE early variation and computed tomography (CT) dimensional tumour decrease in patients treated with chemotherapy plus bevacizumab[33]. Variability in these results could be explained by limitations of 2-dimensional imaging techniques used in all the discussed studies. In the future, 3-dimensional D-CEUS might provide a more accurate evaluation of entire tumor features[34].

Non-oncological hepatic application of D-CEUS

Despite most studies primarily focused on neoplastic liver disease, the application of quantitative analysis of perfusion parameters has also been explored in chronic liver disease. The TICs of the liver parenchyma can provide information's of intrahepatic blood flow and, indirectly, of portal vein pressure, either that could be altered by liver fibrosis.

In the past, different studies evaluated transit time between vessels to estimate the intrahepatic blood flow and to assess liver fibrosis stage. It was showed that hepatic vein transit time decreased as severity of histologically proved chronic hepatopathy increased, thus allowing diagnosis of severe fibrosis with an accuracy of 79%[35,36]. In addition, hepatic vein arrival time and intrahepatic transit time were correlated with hepatic venous pressure gradient (HVPG), with an area under the receiver operating characteristic (AUROC) of 0.97 for HVPG > 10 mmHg and 0.94 for HVPG > 12 mmHg, respectively[37, 38].

Recently, perfusion parameters analysis of liver parenchyma showed a decrease of amplitude-parameters and an increase of time-dependent parameters according to grade of portal pressure assessed with HVPG. Interestingly, PI resulted significantly negative correlated with portal hypertension and showed high accuracy (100% for both specificity and sensitivity) to predict clinical significant portal hypertension using a cut-off of 23.3 dB in patients with liver cirrhosis[39].

PANCREATIC DISEASES

Existing evidence about the usefulness of D-CEUS for pancreatic diseases is very limited and is resumed in Table 3. Characterization and differential diagnosis of benign and malignant pancreatic lesions are the focus of the available research. Figure 3 depicts an example of D-CEUS in pancreatic disease.

One of the first studies regarding the perfusion analysis of pancreatic cancer was conducted by D'Onofrio *et al*[40]. Prospectively, ten patients with suspected pancreatic ductal adenocarcinoma (PDAC) (as confirmed by histology) underwent CEUS with subsequent quantitative perfusion analysis. The results showed a significant difference in PE and ascending curve between PDAC and normal pancreatic parenchyma, providing an objective quantification of enhancement for the assessment of pancreatic lesion[40].

Chronic pancreatitis (CP), localized autoimmune pancreatitis (AIP), and paraduodenal pancreatitis can present CT and magnetic resonance imaging abnormalities identical to PDAC and, vice versa, potentially resectable malignant lesions can be misdiagnosed due to their similarities with benign masses[41]. In such instances, D-CEUS may reveal the pathophysiological differences between highly vascularized inflammatory lesions and essentially necrotic malignant masses, enabling a correct differentiation between benign lesions and cancer. To compare CP to PDAC, Kersting *et al*[42] performed D-CEUS in sixty undetermined pancreatic lesions that were histologically characterized as PDAC (fourty-five) or inflammatory lesion in CP (fifteen). The grouped analysis of TICs showed that TTP and arrival time were significantly prolonged in PDAC compared to CP. On the contrary, no differences were detected in MI and AUC between the two pathological conditions[42]. Regarding AIP, D-CEUS with quantitative analysis has the potential to make pre-operative differential diagnosis between focal-type

Table 3 Dynamic contrast-enhanced ultrasound and pancreatic diseases

Ref.	Study design/number of patients	Object of D-CEUS	Population/groups	Machine/UCA/Software	Significant results ($P < 0.05$)
Yang *et al* [47], 2023	Retrospective/42	pNET	Patients with histopathologically proved pNET/G1, G2, G3, pNEC	Acuson Sequoia, Acuson Oxana2/SonoVue/VueBox	rPE, rMTT and rAUC were higher in pNETs G1/G2 than G3/pNECs
Zhang *et al* [45], 2020	Prospective/11	LAPC	Patient with LAPC underwent chemoradiotherapy	Acuson Oxana2/SonoVue/SonoLiver	MI decreased after chemoradiotherapy
Vitali *et al* [43], 2015	Prospective/20	PC, focal AIP	Patients with diagnosis of AIP *vs* histologically proved PC	Acuson Sequoia 512, S200/SonoVue/VueBox	The difference in PE (dPE) between lesion and surrounding parenchyma in AIP was lower compared to dPE in PC
D'Onofrio *et al*[40], 2014	Prospective/10	Suspected PDAC	Patients with suspected and then histologically proved PDAC	Acuson S2000/SonoVue/VueBox	PE and ascending curve values were different between lesion and adjacent parenchyma
Kersting *et al* [42], 2009	Prospective/60	Undefined pancreatic lesion	Patients with undefined pancreatic lesion underwent biopsy/PDAC *vs* CP	Sonoline Elegra/SonoVue/Axius ACQ	TTP and AT were longer in PDAC compared to focal masses in CP

AIP: Autoimmune pancreatitis; AT: Arrival time; CP: Chronic pancreatitis; D-CEUS: Dynamic contrast-enhanced ultrasound; LAPC: Local advanced pancreatic cancer; MI: Maximum intensity; PC: Pancreatic cancer; PDAC: Pancreatic ductal adenocarcinoma; PE: Peak enhancement; pNET: Pancreatic neuroendocrine tumor; pNEC: Pancreatic neuroendocrine carcinoma; rAUC: Relative area under the curve; rMTT: Relative mean transit time; rPE: Relative peak enhancement; TTP: Time to peak; UCA: Ultrasound contrast agent.

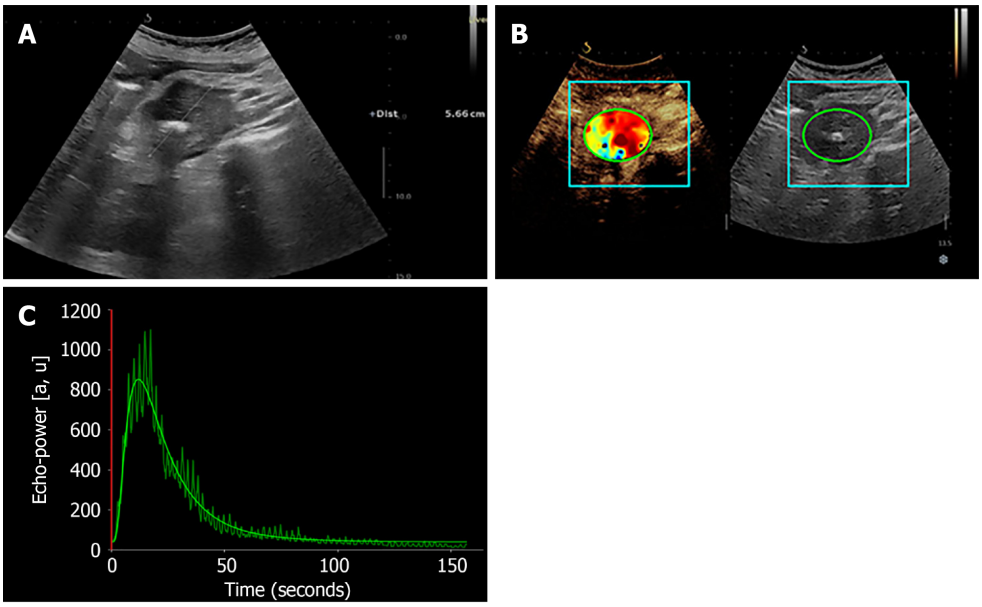

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Figure 3 Dynamic contrast-enhanced ultrasound and time-intensity curves of the pancreas. A: Hypoechoic mass (adenocarcinoma) of pancreatic head in B-mode ultrasound; B and C: Contrast-enhanced ultrasound with corresponding time-intensity curve of the pancreatic lesion.

AIP and PDAC non-invasively. Vitali *et al*[43] compared D-CEUS parameters of three patients with focal AIP with seventeen PDAC patients. Specifically, the difference between PE of PDAC and circumjacent normal parenchyma was significantly lower as compared to AIP. Significant was also the difference between wash in index perfusion (WiPI = WiAUC/RT) of PC and AIP[43]. In another study, TICs of AIP lesions showed delayed and higher enhancement compared to PDAC. Among all CEUS perfusion parameters, ratio of PE, WiAUC, wash-in rate (WiR), WiPI, WoAUC, WiWoAUC, and wash-out rate (WoR) between pancreatic lesion and surrounding normal pancreatic tissue were significantly higher in AIP lesions than PDAC lesions[44]. In cases of diffuse AIP, quantitative perfusion analysis is not suggested since there is no healthy parenchyma for comparison, which is necessary to enhance the

comparability of the results regardless of exam- or patient-related factors[42].

Similarly to perfusion analysis for malignant liver lesions, D-CEUS could be considered to evaluate the response to therapies in PDAC. Recently, Zhang *et al*[45] investigated the role of D-CEUS to monitor the response to chemoradiotherapy in eleven patients with local advanced pancreatic cancer. They performed D-CEUS at baseline and after four weeks of therapy and analyzed the variation of TICs and related parameters. The rising and falling slope rates of TICs diminished after four weeks, and the percentage of MI decreased significantly compared to the surrounding normal parenchyma[45]. Since MI is related to tumour microvascular density, its reduction is coupled with a decrease in lesion blood perfusion, and the quantification of this consequence might reflect the objective efficacy of chemotherapy.

Lastly, D-CEUS could provide information in other types of pancreatic tumors. It has been proven that pancreatic neuroendocrine tumors (pNETs) with different histopathological grades have differences in tumor microvascular perfusion[46], therefore Yang *et al*[47] analyzed the correlation between perfusion analysis and histopathological grades of pNETs. In forty-two patients, the TICs shape of grade 1 (G1)/grade (G2) lesions were significantly different compared to TICs of grade 3 (G3)/pancreatic neuroendocrine carcinomas (pNECs). Significant differences were revealed at relative RT, relative MTT and relative AUC which were higher in G1/G2 than G3/pNECs. ROC analysis showed that relative AUC had the higher accuracy to distinguish the two groups[47]. The D-CEUS analysis and quantitative parameters have the potential value to non-invasively predict the biological behaviour of pNETs.

INFLAMMATORY BOWEL DISEASES

Table 4 summarizes the evidence regarding the role of D-CEUS in inflammatory bowel diseases, and Figure 4 depicts a TIC derived from intestinal wall examination. These studies are mainly focused on Crohn's disease (CD).

D-CEUS and inflammatory/fibrotic disease

TICs represent the perfusion of a tissue, and we would expect a difference in perfusion parameters not only when comparing fibrosis to inflammation, but also when considering various degrees of inflammation.

Girlich *et al*[48] described for the first time the difference in perfusion parameters between CD and healthy gut. As expected, the differences were substantially with significantly higher PE and regional blood volume, and longer TTP of thickness bowel wall of CD patients[48]. In another study, the same authors investigated the correlation between perfusion parameters and histopathological characteristics of the gut wall in surgically treated CD patients, confirming that TTP was negatively correlated with the histological inflammatory score[49]. Similarly, a higher PE, regional blood flow and regional blood volume, and shorter TTP were significantly correlated with high vascular density defined as the presence of more than two hundred sixty five vessels per field on histological examination[50]. On the contrary, Ripollés *et al*[51] showed a non-significant association of TTP with inflammatory or fibrosis histological score, however they used different histological scores and had longer time between CEUS and surgery (34.5 ± 17.3 *vs* 4.7 ± 4.7 d)[51].

To assess the differences between fibrotic or inflammatory CD, Nylund *et al*[52] compared sixteen patients with fibrotic disease undergoing surgery to seventeen patients with medically treated active inflammatory disease. In inflammatory disease, the blood volume and blood flow were significantly higher compared to fibrotic disease, while MTT was not significantly different between the two groups. Interestingly, blood volume/bowel wall thickness ratio showed a high accuracy to predict surgery[52]. Similarly, Quaia *et al*[53] found a significant difference in blood volume related parameters (PE, AUC, WiAUC, WoAUC, WiR and, WiPI) between fibrotic strictures and inflammatory strictures among patients with CD, with the latter having higher values. However, TTP showed no significant differences between the two groups[53]. These findings imply that D-CEUS can detect the microvascular differences between fibrotic and inflammatory tissue and allows non-invasive differentiation of CD phenotypes.

Regarding ulcerative colitis (UC), only one prospective study investigated the relationship between perfusion parameters and histopathological findings. In this study, TTP/Peak(%) showed a strong negative correlation with histopathological inflammatory activity score[54].

D-CEUS and clinical outcomes

Given the negative correlation with inflammation, Peak% > 40.5% and TTP < 35 seconds had a high positive predictive value (94%) and a high negative predictive value (92.3%) for active disease, respectively[50].

It has also been shown that the evaluation of PE and AUC is a useful tool to assessing the severity of CD when the ultrasound global assessment and colorDoppler imaging criteria are indeterminate. Particularly, PE > 23 dB showed a sensitivity and specificity of 90% and 89.5%, respectively, to distinguish moderate from severe disease[55]. Using this cut-off to identify patients with severe disease, Wilkens *et*

Table 4 Dynamic contrast-enhanced ultrasound and inflammatory bowel diseases

Ref.	Study design/number of patients	Object of D-CEUS	Population/groups	Machine/UCA/Software	Significant results ($P < 0.05$)
Laterza *et al* [60], 2021	Prospective/44	CD	Patients with CD treated with anti-TNFα/responders *vs* non-responders	iU22/SonoVue/QLAB	Correlation between decrease in PI, AUC, Pw, and MTT and response to therapy
Goertz *et al* [57], 2018	Prospective/18	CD and UC	Patients with CD or UC treated with vedolizumab/responders *vs* non-responders	Acuson S2000/SonoVue/VueBox	WiR was lower in responders' group after 14 wk
Wilkens *et al* [56], 2018	Retrospective/104	CD	Patients with severe CD underwent CEUS/normal *vs* atypical intensity decline on CEUS	iU22/Definity/QLAB	AUC, wash-out time, and intensity at 60s and 120s were higher in atypical decline group and this correlated with bad outcomes
Quaia *et al*[53], 2017	Prospective/65	CD	Patients with CD with terminal ileal loop stricture histologically characterized/inflammatory *vs* fibrostenotic disease	iU22/SonoVue/VueBox	PE, WiR, WiPI, AUC, WiAUC and WoAUC were higher in inflammatory group compared to fibrostenotic gruoup. TTP was not different between the two groups
Medellin-Kowalewski *et al*[55], 2016	Retrospective/127	CD	Patients with CD underwent US and CEUS	iU22/Definity/QLAB	PE correlate with wall thickness
Quaia *et al*[61], 2016	Prospective/50	CD	Patient with CD underwent medical treatment/responders *vs* non-responders	iU22/SonoVue/VueBox	Changes in PE, WiR, WoR, WiPI, AUC, WiAUC, and WoAUC from baseline to six weeks after therapy differed between responders and non-responses
Socaciu *et al* [58], 2015	Prospective/38	CD and UC	Patients with CD or CU candidate for medical treatment	Logiq 7/SonoVue/SonoLiver	Logarithm of AUC correlated with endoscopic improvement in both diseases
Saevik *et al* [59], 2014	Prospective/14	CD	Patients with CD started medical treatment/remission *vs* treatment failure	Logiq E9/SonoVue/VueBox	PE, WiR, WoR, and WiAUC were different between two groups at 1 mo of treatment
Romanini *et al* [50], 2014	Prospective/33	CD	Patients with CD undergoing colonoscopy and biopsy	Sequoia 512/SonoVue/Qontrast	Correlation between high vascular density and Peak% and regional blood flow
Ripollés *et al* [51], 2013	Prospective/25	CD	Patients with CD undergoing elective bowel resection/inflammatory *vs* fibrostenotic disease	Aplio 80/SonoVue/Software in Aplio 80 system	The percentage of increase in contrast enhancement of the bowel wall in inflammatory lesions was greater than fibrotic lesions
Nylund *et al* [52], 2013	Prospective/33	CD	Patient with CD underwent surgery or medical treatment/inflammatory *vs* fibrostenotic disease	Logiq E9/SonoVue/Custom software	Blood flow and blood volume were higher in the medical group compared to surgery group
Girlich *et al* [54], 2012	Prospective/11	UC	Patients with UC undergoing endoscopy	Logiq E9/SonoVue/Qontrast	Negative correlation between TTP/Peak% and histopathological score
Girlich *et al* [49], 2011	Prospective/20	CD		Logiq 9/SonoVue/Qontrast	Negative correlation between TTP and histopathological score. Positive correlation with single items of the score
Girlich *et al* [48], 2009	Prospective/20	CD	Patients with active CD *vs* healthy volunteers	Logiq 9/SonoVue/Qontrast	Higher PE and regional blood volume and shorter TTP in CD

AUC: Area under the curve; CD: Crohn's disease; CEUS: Contrast-enhanced ultrasound; D-CEUS: Dynamic contrast-enhanced ultrasound; MTT: Mean transit time; PE: Peak enhancement; PI: Peak intensity; Pw: Slope coefficient of wash-in; TNF-α: Tumor necrosis factor-α; TTP: Time to peak; UC: Ulcerative colitis; UCA: Ultrasound contrast agent; US: Ultrasound; WiAUC: Wash-in area under the curve; WiPi: Wash-in ratio index; WiR: Wash-in rate; WoR: Wash-out rate.

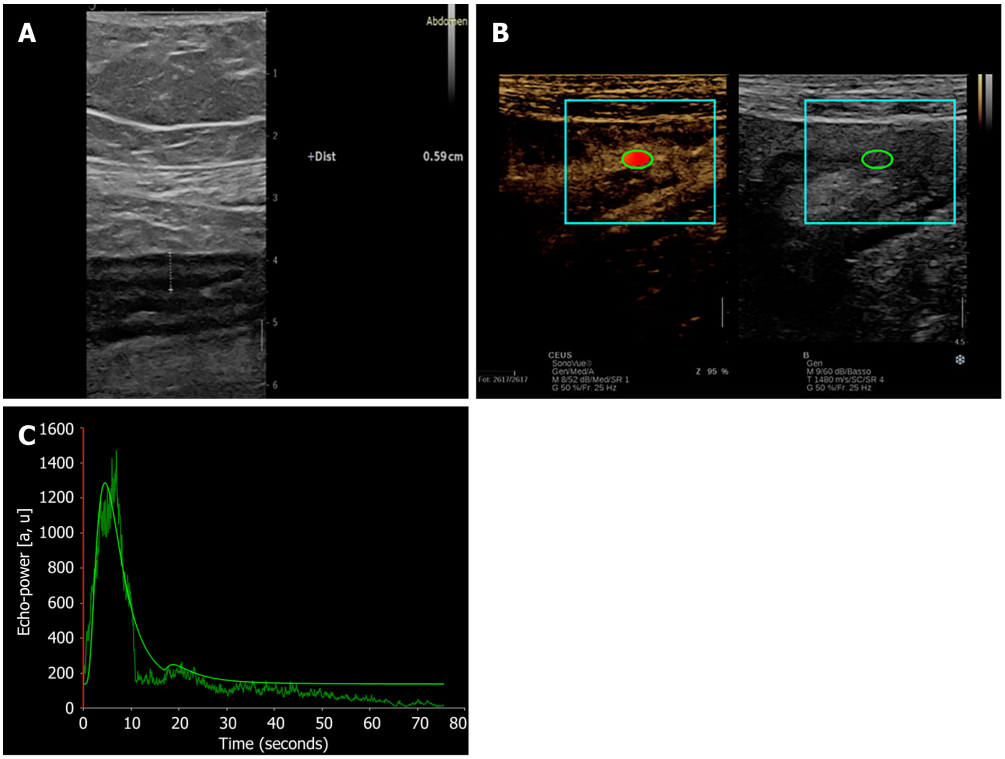

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Figure 4 Dynamic contrast-enhanced ultrasound and time-intensity curves of the bowel wall. A: B-mode ultrasound features of ileal bowel wall thickening in Crohn's disease; B and C: Contrast-enhanced ultrasound with corresponding time-intensity curve of the bowel wall thickening.

al[56] investigated the clinical outcomes in twenty patients with severe disease in whom they observed an atypical, prolonged intestinal washout due to the stuck bubble phenomenon (AUC > 20000 AIU) compared to patient with severe disease and AUC < 20000 AIU (control group). They found a significative higher rate of surgery and a trend toward more combination therapies in study group. Interestingly, they ascribed the stuck bubbles phenomena to the attachment of microbubbles to active leukocytes on the endothelium; if confirmed, this might be utilized as a tool for targeted therapy[56].

Assessment of perfusion parameters is important for identifying disease status, as well as monitoring and predicting the efficacy of therapies. Indeed, D-CEUS measurements changed significantly between clinical- and endoscopic-assessed responders and non-responders with CD and UC following treatments[57,58]. In a prospective study, Saevik *et al*[59] included fourteen patients with acute CD who started treatment with steroids or tumor necrosis factor-α (TNF-α) inhibitors. CEUS was performed before starting therapy and at one, three and twelve months. At one month, the differences between patients who achieved clinical remission and those who had treatment failure during the follow-up period were significant. Particularly, PE, WiAUC, WiR and WoR was significantly lower in effective treatment group[59]. The reduction in perfusion parameters could be related to a decrease in inflammation and, thus, a treatment response. Recently, it was demonstrated that the reduction in PI, AUC, Pw, and MTT was higher in patients responding to anti-TNF-α therapy after two weeks than in patients who relapsed within six months of treatment initiation, who displayed not only a lower early reduction in perfusion parameters but also an increase in PI after twelve weeks[60]. Changes in quantitative perfusion analysis parameters between baseline and six weeks after therapy initiation distinguished responders from non-responders defined by clinical and endoscopic evaluation at twelve weeks[61]. This highlights the potential for D-CEUS to detect therapy-induced modifications in the pathologic bowel wall and support clinicians in disease management.

OTHER GASTROINTESTINAL DISEASES

The investigation of perfusion parameters with D-CEUS could be an informative tool in the diagnosis and prognosis of other gastrointestinal diseases, such as gastric cancer[62]. In a prospective study including forty-three patients with advanced gastric cancer, Joo *et al*[63] showed a good feasibility of CEUS (88.4%) and a significant difference in PI and AUC according to differentiation status of the tumor. Localization in the upper stomach and an ulcerated phenotype were the limiting variables for D-CEUS feasibility[63]. Regarding the CRC, the difference in AUC was significantly related with tumor

necrosis and T stage[64], suggesting a possible role of D-CEUS in predicting tumor microenvironment characteristics and behavior. Furthermore, dynamic contrast enhanced endoscopic ultrasound (D-CE-EUS) showed a significant correlation between RT and vessel density in patients with left side colonic tumors[65], indicating that perfusion analysis might be useful to predict outcomes of antiangiogenic treatment as Lassau *et al*[66] has showed in a multicentric study including over one thousand D-CEUS evaluations in more than five hundred patients with solid tumor treated with antiangiogenic therapy [66]. In particular, D-CEUS blood volume related parameters showed significant early changes in gastrointestinal stromal tumours treated with masitinib, predicting positron emission tomography-CT outcome[67].

Concerning non-neoplastic bowel diseases, different studies described the CEUS aspects of various inflammatory bowel diseases, including abscesses, acute appendicitis, diverticulitis, vascular bowel disease, such as intestinal ischemia, and graft *vs* host disease[68]. To the best of our knowledge, no specific study employing D-CEUS in the aforementioned conditions has been published yet; however, it would be desirable to investigate the potential usefulness of quantitative perfusion analysis in predicting pathological features and prognosis also in this field.

CONCLUSION

The quantification of perfusion parameters in CEUS has several applications in gastrointestinal neoplastic and inflammatory disorders. Everything that is visible with ultrasound can be measured, and this has allowed D-CEUS to be employed within the pancreas and digestive system in addition to the liver evaluation. The objective assessment of tissue perfusion is crucial for the evaluation of all disorders in which the vascular component plays a key pathophysiological role, such as malignant tumours and inflammatory bowel disease. However, the limited availability of large studies and the heterogeneity of the technologies employed have precluded the standardization of this approach which potentially represents a valuable tool for clinical practice in management of gastrointestinal diseases.

FOOTNOTES

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Country/Territory of origin: Italy

ORCID number: Mattia Paratore 0000-0002-7546-8041; Matteo Garcovich 0000-0002-5805-7953; Maria Elena Ainora 0000-0001-5847-1065; Laura Riccardi 0000-0001-6249-0314; Antonio Gasbarrini 0000-0003-4863-6924; Maria Assunta Zocco 0000-0002-0814-9542.

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