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Detective flow imaging *versus* contrast-enhanced EUS in solid pancreatic lesions

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ABSTRACT

Background and objectives: Detective flow imaging EUS (DFI-EUS) is a new technology that detects fine vessels and low-flow velocity without contrast agents, used in real time during EUS, with a better resolution compared to usual technologies such as color Doppler and eFLOW. The aim of this study was to compare DFI-EUS with contrast-enhanced EUS (CE-EUS) for the evaluation of vascularization in solid pancreatic lesions.

Methods: We included patients who had a pancreatic mass visualized by EUS, with recorded images of their assessment in DFI-EUS and CE-EUS techniques and a histological diagnosis confirmed malignant tumors or a minimum of 1-year follow-up for benign lesions.

Results: Of the 107 patients included in this retrospective single-center study, the histological diagnosis revealed 69 cases (64.5%) of pancreatic adenocarcinoma, 18 cases (16.8%) of neuroendocrine tumors (NETs), and 10 cases (9.3%) of metastases from nonpancreatic cancers. A smaller proportion (9.4%) exhibited other lesions. As a result, the incidence of intralesional microvascularization was 43.9% with DFI-EUS and 48.6% with CE-EUS, indicating a positive correlation between the 2 techniques ($P = 0.0001$). Compared to CE-EUS, DFI-EUS exhibited sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of 88.5%, 98.2%, 97.9%, and 90%, respectively, for the detection of intralesional vessels.

Conclusions: The novel technique DFI-EUS demonstrates a remarkable correlation with CE-EUS, exhibiting high sensitivity and specificity for the assessment of microvascularization in solid pancreatic lesions. This method eliminates the need for a contrast agent, thus carrying no risk of adverse effects.

Key words: Detective flow imagine EUS; Doppler EUS; Pancreatic cancer; Solid pancreatic lesions; Contrast-enhanced EUS

INTRODUCTION

EUS is one of the most reliable, efficient, and radiation-free modality for the detection of pancreatic lesions.[1,2]

EUS can detect small pancreatic masses with a sensitivity of over 80%, which is higher than those with the other imaging methods: ultrasound (17%–70%), computed tomography (CT) (33%–75%), and positron emission tomography (50%).[3] However, it is difficult to distinguish pancreatic cancer from other diseases on EUS imaging alone. Indeed, the specificity of EUS for the diagnosis of malignant pancreatic diseases is reported as 53%, with a sensitivity of 95%.[2]

A large number of studies have demonstrated that EUS and their related techniques, including contrast-enhanced EUS (CE-EUS), EUS elastography, and EUS-FNA, now play an important role in the clinical evaluation and diagnosis of pancreatic lesions.[2,4]

The technique of CE-EUS allows characterization, differentiation, and staging of focal pancreatic masses. The development of contrast-enhanced low mechanical index harmonic imaging techniques used in real time during EUS allows perfusion imaging and the quantification of intensity of the contrast signal through time-intensity curve analysis.[5,6] This method suggests the diagnosis of pancreatic adenocarcinoma visualizing the lesion as hypoenhanced as compared to the rest of the parenchyma.[6,7] The sensitivity and the specificity of this technique for the diagnosis of pancreatic adenocarcinoma range between 89%–96% and 64%–100% respectively.[8–14] On the other hand, chronic pancreatitis and neuroendocrine tumors (NETs) could be shown as isoenhanced or hyperenhanced.[6] In addition, CE-EUS can help to identify the EUS-FNA target leading to a reduced requirement for repeated FNA.[2]

The evaluation of vascularity has been worthwhile in the approach to differential diagnosis in pancreas lesions. In this context, color-Doppler EUS (CD-EUS), power Doppler EUS, or e-FLOW EUS may be useful for observing vascularity in real time.[15–18] In the last few years, a new tool has developed for assessment of the vascularization in EUS, without the need of the injection of contrast. Detective flow imaging (DFI-EUS) is an advanced imaging technology for highly dynamic visualization of low velocity blood flow

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below the previous detection threshold in the conventional color methods, with a high frame rate. The unique algorithm displays clear and accurate information on blood perfusion with greater resolution and sensitivity.[17]

At the moment, there are 2 studies that have analyzed the utility of DFI-EUS in the pancreatobiliary lesions.[17,19]

The present study compares DFI-EUS and CE-EUS to detect microvascularity in the assessment of solid pancreatic lesions.

MATERIALS AND METHODS

Study design

The aim of this retrospective study was to assess the accuracy of DFI-EUS compared with CE-EUS for the evaluation of solid pancreatic lesions.

Patients

We enrolled randomly patients who have had the exploration of a pancreatic lesion with DFI-EUS and CE-EUS, between August 2021 and December 2022 at the digestive Endoscopy Unit of the Institut Paoli Calmettes in Marseille, France.

We included patients older than 18 years, having a mass pancreatic visualized by EUS, with recorded images of the assessment of DFI-EUS and CE-EUS, and having the histological diagnosis confirming the etiology of the malignant tumors or a follow-up of a minimum 1 year for benign lesions.

When a negative biopsy was no sufficient to rule out the diagnostic, we performed a second biopsy, and if it was negative as well, the patient was followed for a minimum of 1 year to evaluate signs of progression with CT scanner to eliminate a probable cancer or regression of the lesions, considering to have a benign pancreatic inflammation.

The criteria of exclusion were as follows: cyst lesions, lesions with a size nonmeasurable with EUS, patients without biopsies of the lesion, and patients lost in the follow-up.

All data from the patients (sex, age, and diagnosis) were recovered from the electronic medical records.

EUS imaging techniques

The endoscopy explorations were performed by 5 experienced sonographers with the endoscopes EG38UJ10 and EG34UJ10 (Pentax Medical, France) and ultrasound-equipped (ARIETTA 850; FUJIFILM Medical Co., France).

According to the services protocol, all the endoscopies were performed under general anesthesia by Propofol without orotracheal intubation; some exceptions were required for the anesthesiologist at the moment of the endoscopy.

Once the pancreatic lesion was detected in B mode, the evaluation of their localization, size, and the involvement with others anatomic structures were performed. Subsequently, the assessment of the vasculature was carried out by the technique of DFI-EUS followed by CE-EUS.

The parameters/settings employed for the DFI-EUS were the following: dynamic range, 85; transmission frequency, 65 MHz; and color gain, 65 MHz. The mechanical index was set at 0.15.

The CE-EUS was performed by SonoVue (Bracco, Milan), a second-generation ultrasound contrast agent. It contains sulfur hexafluoride (a gas) as microbubbles in a suspension that is made up into a solution. The administration of the CE-EUS was made by bolus intravenous, of 8 mL of the solution, followed by a flush of 10 mL saline solutions, undertaken by a nursery specializing in endoscopy. The time of the observation of the lesion is at least 2 minutes counting from the moment of the flash, having a peak maximum of enhancement in around 30 seconds, to evaluate if there is hyperenhancement or hypoenhancement of the lesions, compares with the rest of the parenchyma. All EUS data were stored in a recording system.

Histological samples

The histological confirmation of the pancreatic masses was done by EUS-FNA, with a 20- or 22-gauge needle, delivered by the endoscopist criteria at the moment of the EUS. In the cases that hepatic lesions were visualized during the EUS, a biopsy was made as well and analyzed in a different pot.

Interpretation of images

All the photos and videos of the EUS were read at the same time by 2 endoscopists (V.M. and M.G.) to determine if within the lesions had or had not microvessels, visualized by the tool DFI-EUS (defining it as "positive" or "negative") and also by CE-EUS (establishing an hyperenhancement as "present" or an hypoenhancement as "absent") [Figure 1].

Statistical analysis

The analysis was performed with BM SPSS Statistics V22.0. Quantitative variables were expressed as mean and ranges, and categorical variables were expressed as percentages. A *P* value less than 0.05 was considered statically significant.

RESULTS

A total of 127 patients were initially selected, of whom 20 were subsequently excluded (14 due to cystic lesions, 3 not biopsied, and 3 lost to follow-up). Of the 107 patients included, 53% were males and 47% were females. The median age was 67.6 years (interquartile range [IQR] 35–90 years).

The pancreatic lesions were located more frequently in the head (41.1%), followed by the body (26.2%) and the tail (24.3%), and 8.4% were in the uncinate process. The mean size of the lesions was 28.5 mm (5–115 mm [SD = 16.1]).

After the EUS-FNA, the histological diagnosis revealed 69 cases (64.5%) of pancreatic adenocarcinoma, 18 cases (16.8%) of NETs, 10 cases (9.3%) of metastases from nonpancreatic cancers, 5 (4.7%) benign lesions (3 cases of inflammatory/tumor-like lesions in patients with chronic pancreatitis and 2 case of accessory spleen), and 3 (2.8%) cases of acinar cell carcinoma, and 2 cases exhibited as a lymphoma and an adenosquamous cell carcinoma, representing 1.9% of the cases. Regarding the classification of the NETs,[20] we found that two cases were grade 3, three were grade 2, twelve were grade 1, and one was not classifiable.

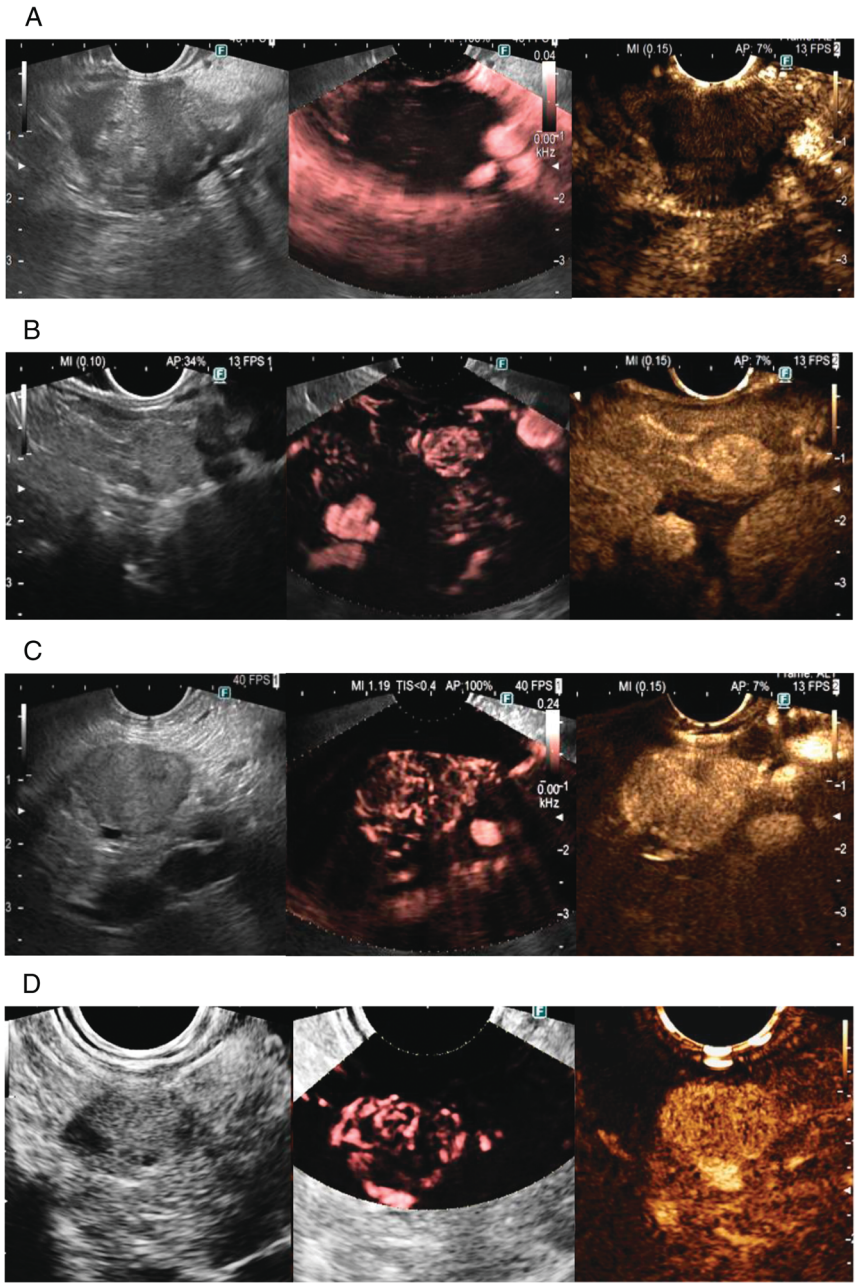

Figure 1. Examples of endosonographic images showing pancreatic lesions, from the left to the right, in B-mode, DFI-EUS, and CE-EUS. (A) A case of pancreatic adenocarcinoma. (B) A case of neuroendocrine tumor. (C) A case of pancreatic metastasis. (D) A case of accessory spleen. CE-EUS: contrast-enhanced EUS; DFI-EUS: detective flow imaging EUS.

Concerning the 10 cases of metastases, 6 were from kidney cancer, and the rest were from hepatocellular carcinoma (CHC), lung cancer, thyroid cancer, and leiomyosarcoma.

In the analyses of the endosonographic images, we found that the presence of the intralesional vascularity with DFI-EUS was positive in 47 (43.9%) of the patients, and it was negative in 60 (56.1%). On the other hand, the assessments of the same lesions by CE-EUS showed that 48.6% had a hypersignal intralesional (present) and 51.4% had hypoenhancement (absent) [Figure 2].

Comparing both techniques, we observed that of the 60 patients in which DFI were negative, CE-EUS had an agreement in 90% (P = 0.0001). In the negative cases evaluated by DFI-EUS, all of them had an hyperenhancement in CE-EUS, considered as positive for the last technique [Figure 3]. This difference occurred in a total of 7 patients, and the lesions were correlated with 6 adenocarcinomas and 1 NET in the results of histology.

Taking CE-EUS as a technique of references for the assessment of microvasculature in solid pancreatic lesions, this study found that

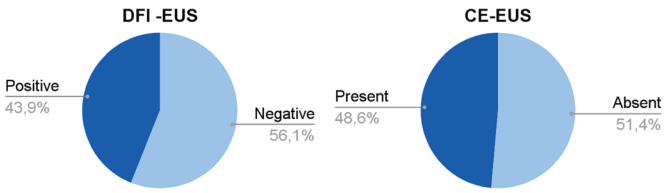

Figure 2. Evaluation of the microvascularity with DFI-EUS and CE-EUS in solid pancreatic lesions. CE-EUS: contrast-enhanced EUS; DFI-EUS: detective flow imaging EUS.

DFI-EUS has an accuracy for detecting intralesional vasculature of 93.5%, with a sensitivity of the method of 88.5% and a specificity of 98.2%; the positive predictive value and the predictive negative value are 97.9% and 90.0%, respectively [Table 1].

In addition, we subanalyzed the value of DFI-EUS compared to CE-EUS based on the histological diagnosis separately. Due to the number of cases, we selected the 3 most common diagnoses; as result, we found that the correlations between the 2 techniques were statistically significant for all of them: pancreatic adenocarcinoma (P = 0.0001), NET (P = 0.004), and metastasis (P = 0.002) [Table 2]. The sensitivity and specificity of DFI-EUS for the adenocarcinoma, compared with CE-EUS, were 73.7% and 98.0% respectively; the PPV was 93.3%, and the NPV was 90.7%. In contrast, we found that the value of the new technology was 100% equal to the technique with contrast in the assessment of the metastases. On the other hand, the NET showed a sensitivity of 94.1%, a specificity of 100.0%, a PPV of 100%, and an NPV of 50% [Table 3].

DISCUSSION

In the prospective study of Yamachita et al. that evaluated 33 patients, the detection of vessel in intraductal papillary mucinous neoplasm (IPMN) and gallbladder had showed that DFI-EUS was superior to e-FLOW EUS.[18]

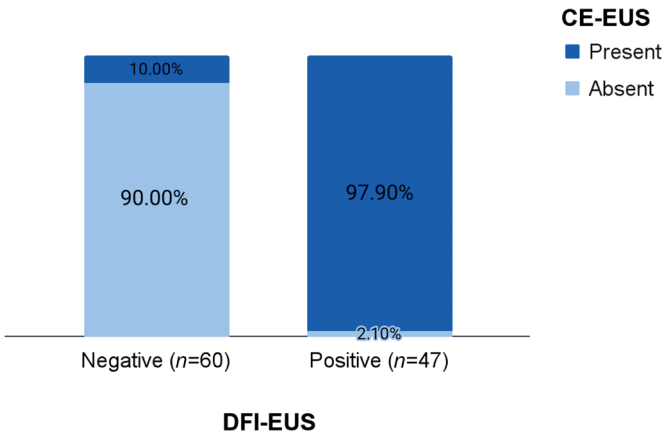

Figure 3. Comparison between DFI-EUS with CE-EUS in the assessments of solid pancreatic lesions. CE-EUS: contrast-enhanced EUS; DFI-EUS: detective flow imaging EUS.

Table 1

Accuracy of DFI-EUS compared with CE-EUS for the evaluation of the vasculature in solid pancreatic lesions.

Parameters	Values %	95% CI	
		Lower limit	Upper limit
Correctly diagnosed patients	93.5	86.5	97.1
Sensitivity	88.5	75.9	95.2
Specificity	98.2	89.0	99.9
Positive predictive value	97.9	87.3	99.9
Negative predictive value	90.0	78.8	95.9

CE-EUS: contrast-enhanced EUS; CI: confidence interval; DFI-EUS: detective flow imaging EUS.

This study exposes that the novel technique DFI-EUS has high sensitivity and specificity (88.5% and 98.2%, respectively) compared with CE-EUS for the assessment of microvasculature in the lesions, with the highest capacity predictive seen in the metastases from nonpancreatic cancers, probably due to the hypervascularization of these lesions, principally of the renal cell adenocarcinoma.

In one meta-analysis, the pooled sensitivity of CE-EUS for the differential diagnosis of pancreatic adenocarcinomas was 94% (95% CI, 0.91–0.95), and the specificity was 89% (95% CI, 0.85–0.92).[16] We found that the sensitivity and specificity of DFI for the adenocarcinoma were 73.7% and 98.0%, respectively.

Because DFI-EUS is a tool that does not need the administration of a contrast agent, their application has no risk of adverse product-related events as compared with CE-EUS. Most adverse reactions reported in the literature by SonoVue were mild, including skin erythema, tachycardia, and palpitations. However, their incidence of severe event adverse is between 0.0086% and 0.9%, including anaphylactic shock and death. Furthermore, CE-EUS has a limited time in the image window due to the administration of the intravenous product; in contrast, this restriction does not exist by the technique DFI, enabling a second evaluation if needed. Another advantage of DFI-EUS is that it could be implemented to observe one or more lesions in the same patient, in real time, which allows the study of hepatic lesions in the case suspected. As it happens with conventional Dopplers, the tool DFI does not have good resolution in lesions that are located at more than a certain distance from the transducer. Finally, it must be taken into account that DFI is only compatible with ARIETTA endoscopes of the last generation.

Nevertheless, this retrospective single-center study has certain limitations. The imaging registration was not standardized. There was

Table 2

Correlation of the detections of the microvasculature of solid pancreatic lesions comparing DFI-EUS versus CE-EUS in relation with the histological diagnoses.

Histology	n	DFI-EUS		CE-EUS		P-value
		Negative	Positive	Absent	Present	
Adenocarcinoma	69	54	15	50	19	0.0001
NET	18	2	16	1	17	0.004
Metastases	10	1	9	1	9	0.002

CE-EUS: contrast-enhanced EUS; DFI-EUS: detective flow imaging EUS; NET: neuroendocrine tumor.

Table 3

Accuracy of DFI-EUS compared with CE-EUS in the assessments of the microvasculature according to the histological diagnoses.

Histologie (*n*)	Correctly diagnosed (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Adenocarcinoma (69)	91.3% (81.4–96.4)	73.7% (48.6–89.9)	98.0% (88.0–99.9)	93.3% (66.0–99.7)	90.7% (78.9–96.5)
NET (18)	94.4% (70.6–99.7)	94.1% (69.2–99.7)	100% (5.5–89.2)	100% (75.9–99.4)	50% (2.7–97.3)
Metastases (10)	100% (65.5–99.1)	100% (62.9–99.0)	100% (5.5–89.2)	100% (62.9–99.0)	100% (5.5–89.2)

CE-EUS: contrast-enhanced EUS; CI: confidence interval; DFI-EUS: detective flow imaging EUS; NET: neuroendocrine tumor.

a possibility of discrepancy in their interpretation and also a disagreement between the operators.

CONCLUSIONS

The novel technique DFI-EUS demonstrates a remarkable correlation with CE-EUS, exhibiting high sensitivity and specificity for the assessment of microvascularization in solid pancreatic lesions, with a superiority in the hypervascular lesions. This method eliminates the need for a contrast agent, thus carrying no risk of adverse effects, and additionally, it allows for the evaluation across multiple lesions in the same patient. Assessing the cost-benefit ratio of DFI-EUS would be of interest to determine its utility in recommendations for the evaluation of solid pancreatic lesions.

Conflicts of Interest

Marc Giovannini is a Founding Editor-in-Chief of the journal. The article was subjected to the standard procedures of the journal, with a review process independent of the editors and their research group. The other authors declare that they have no conflict of interest.

Author Contributions

All authors contributed to the study conception and design. The concept was developed by [Fabrice Caillol et Marc Giovannini]. Material preparation and data collection were performed by [Maria Victoria Mulqui, Fabrice Caillol, Jean Philippe Ratone, Solène Hoibian, Yanis Dahel, Élise Meunier Clément Archimbaud and Marc Giovannini]. Data and image analysis was performed by: [Maria Victoria Mulqui and Marc Giovannini]. The first draft of the manuscript was written by [Maria Victoria Mulqui] and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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