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Added value of intravenous contrast-enhanced ultrasound for characterization of cystic pancreatic masses: a prospective study on 37 patients

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Abstract

The aim of this study was to evaluate the added value of contrast-enhanced ultrasound (CEUS) in the pancreatic cystic mass (PCM) diagnosis by using a qualitative and quantitative analysis in order to make a relevant characterization. **Patients and method:** Between December 2008 and November 2011, 37 patients with PCM discovered at ultrasound examination were prospectively followed. A qualitative and quantitative CEUS analysis was performed in order to differentiate etiologies of the PCM. In the quantitative analysis several parameters were followed: Peak Intensity (PI), Time to Peak (TTP), maximum ascending gradient (GRAD), Time to maximum gradient (TTG) and Area Under the Curve (AUC). Normalized ratios were also calculated. In all patients a definite cytological or histological diagnosis was obtained. **Results:** Thirty-seven patients were studied: 12 with pancreatitis-associated pseudocyst and 25 with cystic tumors (10 serous cystic adenoma, 5 mucinous cystic adenoma, 6 cystadenocarcinomas, 2 solid pseudopapillary tumors and 2 intraductal papillary mucinous neoplasms). There was a significant difference of the nAUC and nTTP between pseudocyst and cystic tumors, p=0.03 and p=0.01, respectively. A normalized TTP value above 7 sec was suggestive for the diagnosis of pseudocysts with 79.16 % accuracy. There was a significant difference of nTTP and nTTG between the benign and malignant lesions. nTTP < 9 sec and nTTG < 8.5 sec rules out malignant cysts in almost 90% of cases. **Conclusion:** The CEUS is useful in the diagnosis of PCM. The quantitative analysis of the enhancement of the cystic wall may discriminate the different types of the PCM.

Keywords: pancreas, cystic tumors, pseudocysts, contrast-enhanced ultrasound, quantitative analysis

Introduction

Ultrasonography (US) is a widely available imaging method with good diagnostic performance in detecting pancreatic masses and in the discrimination of cystic masses from solid tumors [1]. The US resolution allows the detection of the focal lesions greater than 10 mm, especially if they are cystic or hypoechogenic. However, at this size, the ultrasound image is not characteristic for the different types of masses and tumors, which may have the same aspect [2]. Color Doppler ultrasound only contributes to the detection of the vascular pseudoaneurysm or venous thrombosis [3]. Circulation model assessment of pancreatic masses using a contrast agent could be useful in practice for the characterization and discrimination of pancreatic masses [4,5].

The i.v. contrast enhanced ultrasound (CEUS) was initially developed for the hepatic masses characterization [6-8], but its applications were extended to pancreatic diseases [9,10]. There are studies that show the useful-

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ness of the procedure in characterizing solid pancreatic tumors and the performances of CEUS are encouraging as an alternative to the CT scan for pancreatic neoplasms [11,12].

Pancreatic cystic masses (PCM) found at 1% of the population [13] are represented by pancreatic pseudocysts (80-85% of cases) and cystic neoplasms. PCM may benefit from CEUS in order to differentiate between different etiologies.

The aim of this study was to evaluate the added value of CEUS in the PCM diagnosis by using a qualitative and quantitative analysis in order to make a relevant characterization.

Material and methods

Between December 2008 and November 2011, 41 patients with undetermined PCM of any size detected by transabdominal US were prospectively included in our study. Patients were enrolled after giving their written informed consent and the study was designed according to the ethical guidelines issued by the 2000 revision (Edinburgh) of the 1975 Declaration of Helsinki, being approved by the Ethical Committee of the University.

The exclusion criteria were: allergies to the i.v. contrast agent, inadequate ultrasound quality, lack of precision of quantitative measurements due to out-of-plane movements. Patients with obvious clinical or imaging signs of pancreatic malignancy (metastatic disease, organ invasion), or acute pancreatitis were also excluded, to reveal just the performance of the proposed method in differencing those diseases. According to these exclusion criteria four patients were finally excluded from the study (2 with inadequate ultrasound quality and 2 with lack of precision of quantitative measurements due to out-of-plane movements).

The US examination performed on Logiq 7 BT 07 (GE) equipment followed: detection and characterization of PCM (size, location, content assessment and walls), and evaluation of the unaffected pancreatic parenchyma.

CEUS examination was performed on the same equipment with the multifrequency broadband convex transducer and consisted of the i.v. injection of 2.4 ml SonoVue (Bracco, Italy) followed by 10 cc saline solution in accordance with recent recommendations [14]. A single ultrasound expert blind to the final diagnosis made all CEUS examinations. The mechanical index was set at a value of 0.09 - 0.11. The area of interest was represented by: cystic lesion, its walls, an arterial vessel (aorta and /or superior mesenteric artery) and normal pancreatic parenchyma as reference.

The qualitative analysis was based on the following: the PCM wall filling, the persistence of the contrast agent in the PCM and the washout of the contrast agent. All these data were compared to the normal pancreatic parenchyma.

The quantitative analysis consisted of automatic plotting of time / intensity curves (TIC) in selected 5 mm areas situated in PCM, in the lesion wall and a proximity artery. The curves were drawn using the Origin 8 software. Following parameters were calculated: Peak Intensity (PI), Time to Peak (TTP), maximum ascending gradient (GRAD), Time to maximum gradient (TTG) and Area Under the Curve (AUC). Normalized ratios (nParam) were also calculated after the following formula: Normalized Param = (Param. wall – Param. cavity)x(Param. artery/Param. wall). The significance of these parameters is shown in table I.

In all patients, a definite cytological or histological diagnosis was obtained by endoscopic ultrasonography guided fine-needle aspiration (EUS-FNA) using a 22 G needle (28 patients) or surgical pancreatic resection (9 patients). In patients with benign cytology or histology a follow-up examination of at least six months was documented also. Clinical and laboratory examinations as well as CT scans and endoscopic ultrasound were per-

Table I. The significance of TIC parameters

Parameter	Formula	Significance
Peak Intensity (PI)	Max(I(t))	Maximum enhancement inside the ROI = curve's *peak*
Time to Peak (TTP)	t_m for which I(t)=Max	Time of maximum enhancement ~ *Speed* of the blood in the region
Area Under the Curve (AUC)	$\int I(t)dt$	Total enhancement inside the ROI ~ *Volume* of blood transiting the region
Maximum Ascending Gradient (GRAD)	Max(I'(t))	Maximum acceleration during in-fill ~ arterial *compliance*
Time to GRAD (TTG)	t_g for which I'(t)=Max	The time of maximum acceleration

formed as part of the clinical work-up in all patients and not for the purpose of this study. CT native and contrast enhanced scans were acquired with Siemens Somatom Emotion 16 CT Scanner (Siemens Medical Solutions, Germany) and EUS examination with a linear echoendoscope (GF-UCT 140 AL 5, Olympus) in conjunction with Aloka Alpha 10 ultrasound unit, the patient being under slight sedation.

Statistical analysis was performed using the SPSS 13.0 package (SPSS Inc., Chicago, USA). Results were expressed as mean ± SD, unless otherwise specified. Sensitivity (Se), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV), and Acc – accuracy (Acc) were calculated. T - Student's two-sample test and Fischer's two-sample variance test were used for comparing quantitative and variables. The most commonly used index of accuracy is the area under the Receiver Operator Curve curve (AUROC), with values close to 1 indicating higher diagnostic accuracy.

Results

In the final analysis 37 patients (15 men, 22 women; mean age, 51.3 ± 16.9 years) were included. The final diagnosis was: 12 pancreatitis-associated pseudocysts and 25 cystic tumors (10 serous cystic adenoma, 5 mucinous cystic adenoma, 6 cystadenocarcinomas, 2 solid pseudopapillary tumors and 2 intraductal papillary mucinous neoplasms - IPMN). The mean size of the PCM was 52.3± 24.6 mm [between 15mm (serous cystic adenoma) and 90 mm (solid pseudopapillary tumor)], 17 PCM being localized in the pancreatic head, 12 in the body, and 8 in the pancreatic tail.

The qualitative analysis is summarized in table II. Thus, in the case of the pancreatitis-associated pseudocyst, regardless of the localization, the color Doppler signal was absent in the walls but an intense enhancement in the walls and in the pseudocystic proximity was found at CEUS examination (fig 1).

Also, no parietal Doppler signal was detected in cystic adenomas, but CEUS examination showed a low intensity enhancement with a different behavior depending on the cystic content. If serous, the enhancement was present in the walls and septa (fig 2) and if mucinous, the enhancement was present in walls and intraparietal nodules (fig 3).

The cystadenocarcinomas showed a chaotic vascular Doppler signal in the wall and intense enhancement in the arterial time with rapid washout in the CEUS examination (fig 4).

The quantitative analysis. The TIC aspects were consistent with the visual findings (table III): 1. Intense uptake in the arterial phase and persistence of enhancement in the venous phase for the pancreatitis-associated pseudocyst; 2. Moderate uptake in the arterial phase especially in the intraparietal nodules and a slow washout

Table II. The qualitative CEUS analysis of wall's microcirculation of the PCM

Diagnostic	Conventional US	Doppler US	CEUS
Pseudocyst (n = 12)	Transonic lesion, net separation, irregular internal contour, containing fluid or semifluid, sometimes internal septa.	Without intracystic or parietal circulatory signal	Intense enhancement of the cystic wall and surrounding parenchyma
Serous cystic adenoma (n = 10)	Unique/ multiple transonic lesions; usually small; thin septas inside	Without intracystic or parietal circulatory signal	Low intensity enhancement of the cystic walls and septas
Mucinous cystic adenoma (n = 5)	Unique transonic lesion; usually big; nodules in the cystic walls	Without intracystic or parietal circulatory signal	Low intensity enhancement of the cystic walls and nodules
Cystadenocarcinomas (n = 6)	Hypo or anechoic lesion; moderate or large dimensions; without Wirsung duct dilatation	Without intralesional circulatory signal; rarely circulator signal may be present in the wall	Intense enhancement in the arterial time with rapid washout; metastasis may be detected more accurate
Solid pseudopapillary tumor (n = 2)	Encapsulated mixed tumor (solid and liquid)	Arterial signal in the parenchymal part	Intense and homogenous enhancement of the parenchymal part; moderate and tardive washout; peripheral rim enhancement
Intraductal papillary mucinous tumor (n=2)	Mixed tumor developed inside the main pancreatic duct or branches, with retrograde dilation; may have parietal nodules and septae.	Without intracystic or parietal circulatory signal	Low intensity enhancement of the cystic walls and nodules

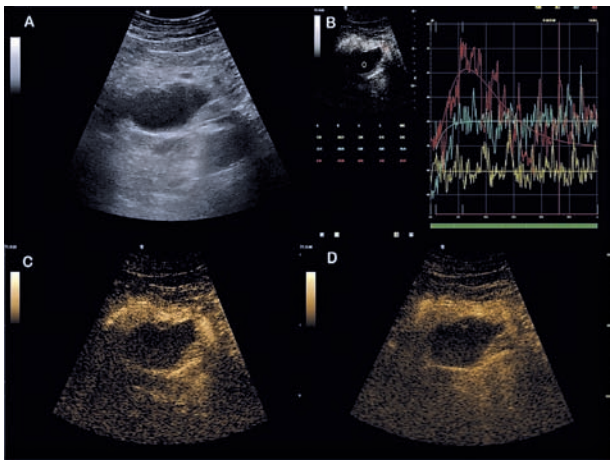

Fig 1. Pancreatic pseudocyst. Native image (A), TIC curve (B) arterial (C) and venous phase enhancement (D). There was an intense arterial enhancement inside the wall and the surroundings of the cyst, with a slow wash-out in the venous phase.

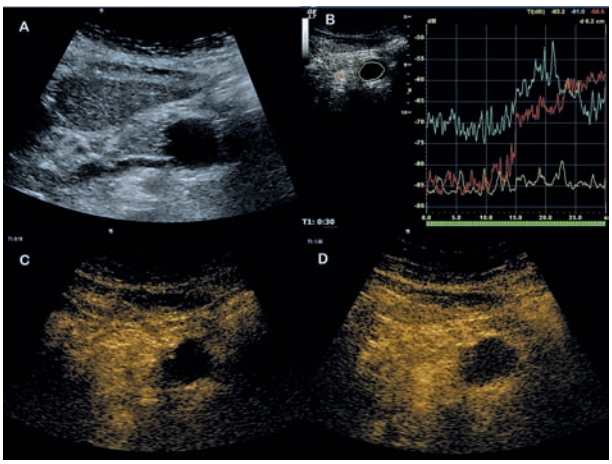

Fig 3. Mucinous cystadenoma. Native image (A), TIC curve (B) arterial (C) and venous phase enhancement (D). There was a mild enhancement in the arterial phase inside the wall nodules and a slow wash-out during the venous phase.

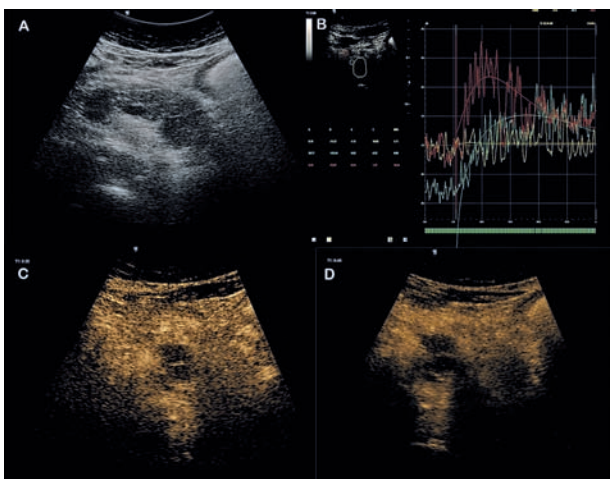

Fig 2. Multilocular serous cystadenoma. Native image (A), TIC curve (B) arterial (C) and venous phase enhancement (D). Contrast enhancement was low inside the walls and septa.

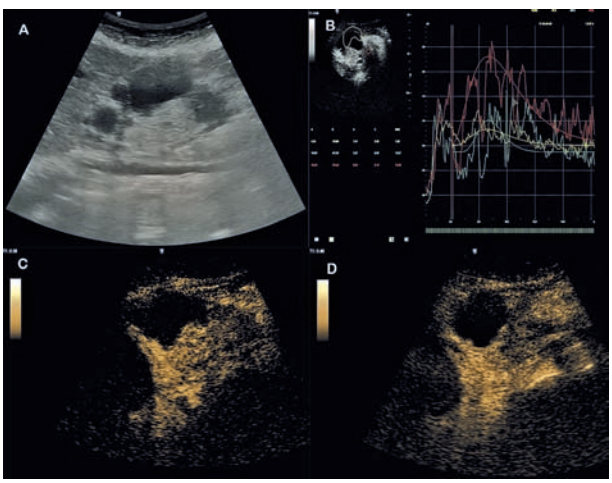

Fig 4. Mucinous cystadenocarcinoma. Native image (A), TIC curve (B) arterial (C) and venous phase enhancement (D). The tumor tissue enhances intensely in the arterial phase, but washes out quickly in the venous phase.

for mucinous cystic adenomas; 3. Non-homogeneous and asymmetrical enhancement with accelerated washout for cystadenocarcinomas.

The differentiation between pancreatitis-associated pseudocyst and cystic tumors: The AUC of pseudocystic wall enhancement was significantly lower than for cystic adenomas, -3153.75 dBxS vs. -3457.05 dBxs (p=0.05). The use of normalization in relation to the cavities of cystic lesions emphasized this difference, 632.9 dBxs vs. 846.05 dBxs (p=0.03). The diagnosis of pseudocysts was consistent with a cut-off value of nAUC below 825 dBxs, with Se=73.15%, Sp=72.21% and AUROC=0.75 (95%CI=0.50).

The nTTP in the wall was shorter when compared with cystic tumors and pseudocysts, 3,05 sec. vs. 8,36 sec., respectively (p=0.01). The diagnosis of a pseudocyst was supported above the cut-off of 7 sec, with AUROC =0.77 (95% CI=0.43), Se=73.54%, Sp=83.72%, PPV=80,64% and NPV=77.24% and accuracy=79.16%.

*The differentiation between benign and malignant cystic tumors:*The nTTP and nTTG were significantly lower in the benign lesions, 4.7 sec vs. 10.6 sec (p<0.01)

Table III. TIC parameters in different types of PCM (pseudocysts vs. cystadenomas and Malign vs benign lesions)

	nPI (dB)		**nTTP (s)**		**nAUC (dBxs)**		**nGRAD**		**nTTG (s)**	
	Median	95%CI	Median	95%CI	Median	95%CI	Median	95%CI	Median	95%CI
Pseudocyst	7,63	5,74	8,36	5,31	632,93	453,32	0,29	0,46	1,74	5,98
Cystadenomas	7,76	4,42	3,05	6,94	846,05	233,63	0,11	0,20	6,05	5,98
p	0,45		**0,01**		**0,05**		0,1		0,09	
Malignant lesion	10,76	5,61	10,62	11,27	778,94	341,18	0,13	0,35	9,66	10,58
Benign lesion	7,04	4,35	4,68	3,32	805,98	287,32	0,14	0,27	3,99	3,32
p	0,13		**<0,01**		0.47		0,49		**0,03**	

nPI – normalized peak intensity, nTTP – normalized time to peak, nAUC – normalized area under curve, nGRAD = normalized maximum ascending gradient, nTTG – normalized time to GRAD

and 3.99 sec vs. 9.66 sec (p=0.03), respectively. The cut-off value for malignancy for TTP was 9 sec, with AUROC=0.764 (95% CI= 0.42) Se = 73.7%, Sp = 81.3%, PPV=60.3%, NPV=89.7%, accuracy= 78.8% (p=0.01. For TTG the cut-off value was 8.5 sec, with Se = 87.7%, Sp = 65.3%, PPV = 62.3%, NPV = 89.7%, accuracy = 72.2%; AUROC = 0.79 (95% CI=0.41) (p=0.01).

Discussions

In our study we used the numerical analysis of TIC parameters measured within the cyst walls of PCMs. The values were normalized according to the same parameters measured within the cystic cavities and inside a neighbouring artery. Significant statistical differences between pseudocysts and cystic tumors regarding nAUC and nTTP were observed. Also, significant statistical differences were observed between benign and malignant/borderline cystic tumors, regarding nTTP and nTTG.

The accuracy of different imaging techniques in the diagnosis and evaluation of PCM is limited to a maximum 60 % and may achieve 80 % using EUS –FNA [15]. The malignancy of the cystic tumors may be difficult to establish even using the intratumoral genetic markers [16]. Thus the differentiation of pseudocyst and benign cystic neoplasia from malignant cystic (or mixed solid-cystic) neoplasia of the pancreas remains up today, despite improved technology, a challenging and still incompletely resolved problem. The gold standard still remains surgery with pathological examination of histological specimens.

In the past years there have been studies that demonstrate the utility of CEUS in the diagnosis of solid pancreatic tumors [9,17], or contrast enhance EUS [18]. However, there are only few published studies regarding the CEUS diagnosis of the PCM [2,17,19]

For PCM the CEUS demonstrated the ability to improve the delineation and characterization of pancreatic lesions [20], the evidence of the wall vascularization being the main criteria of CEUS differentiation between the pseudocysts and the cystic tumors [17,21]. Given the perilesional inflammation, the pseudocysts have an intense wall enhancement but with a washout comparable with the normal pancreatic tissue. The cystic benign tumors have similar enhancement behavior with pseudocysts but the TTP curves were significantly different. By using the TTP curves we were able to differentiate pseudocysts from cystic benign tumors with accuracy comparable with intracystic liquid analysis. The diagnosis of the cystic tumor by using CEUS may be easier when there are septa or the aspect is microcystic [10,11,17]. All the studies published so far have taken into consideration the global contrast enhancement at the level of cystic walls, septa and parietal nodules, but no individual quantitative analysis was performed at those sites so far. In the case of cystic tumors without specific aspect, the analysis of the enhancement curves may be a very useful tool in the diagnosis.

In our study a normalized TTP above 7 sec and AUC value below 825 dBxs was associated with a pseudocyst diagnosis with great accuracy. This finding could add an important value to the differential diagnosis between pseudocysts and other cystic tumors that can be very difficult.

The major concern in the management of PCM is the malignancy detection. Contrary to the solid malignant tumors, which have reduced and inhomogeneous enhancement in the arterial phase [11], the cystic malignant tumors have a different CEUS behavior. The cys-

tadenocarcinomas have inhomogeneous and accelerated enhancement in the arterial phase followed by a rapid washout in the late arterial phase. This finding was confirmed with the TIC analysis.

The quantitative analysis showed that a normalized TTP above 9 sec is suggestive for a malignant lesion with 78% accuracy and NPV of almost 90%. The same results were found for the TTG analysis. Interestingly the TTG was not significant in the differentiation between pseudocysts and cystic tumor, but it has demonstrated good performance in the differentiation of malignant tumors. The good results of TTP and TTG in malignancy detection consist of a high NPV. Therefore, in the evaluation of a PCM if it is nTTP<9 sec and nTTG <8.5 sec, a malignant cyst can be ruled out. Moreover, if the malignant etiology is ruled out, the differentiation between pseudocysts and other cystic tumors may be made if TTP is more than 7 sec and the AUC is below 825 dBxs.

To our knowledge this is the first report of the use of TIC of CEUS in the diagnosis of the PCM. This analysis is more difficult than in the case of solid pancreatic tumors. More studies and a large number of patients are required.

In order to obtain values less dependent on patient-related conditions and US settings, we used for the first time in CEUS analysis, a complex normalization process of the TIC parameters, taking into account data from three different regions. By adding the quantitative analysis to the CEUS procedure we aimed at a diminution of the operator subjectivity in the PCM evaluation.

The major limit of our study is the reduced number of patients with PCM, including only 12 pseudocysts and 25 cystic tumors. Thus, we were challenged for the quantitative analysis of PCM to find a single, common and relevant denominator which has been considered the contrast-enhancement within the cystic wall. This focusing of the study on the behavior of the cystic wall was also in order to simplify the quantitative analysis, a time consuming post-processing technique. Nevertheless, the need of a standardization has imposed the use of a constant size of samples, which we have arbitrarily chosen to be 5 mm, size which may not be appropriate in all individual situations (e.g. thin cystic walls, or, for further studies, thin septa or nodes within the PCM). By choosing smaller samples, the number of subjects rejected from our study may have increased due to out-of-plane movements, increasing the errors of the method we proposed.

Conclusions

Qualitative and quantitative CEUS analysis may be useful in the differentiation of pancreatic cystic masses. This noninvasive method has the great advantage of repeatability, which is important in the PCM patients' follow-up. A normalized "time to peak" above 7 sec. and an area under curve value below 825 dBxs is associated with a pseudocyst diagnosis. Cystadenocarcinomas have inhomogeneous and accelerated enhancement in the arterial phase followed by a rapid washout in the late arterial phase. A value of nTTP inferior to 9 sec and nTTG inferior to 8.5 sec. can rule out a malignant cyst.

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Conflict of interest: none

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