The value of Contrast-Enhanced Ultrasound in the characterization of vascular pattern of solid pancreatic lesions

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Abstract

The aim of our study was to evaluate the accuracy of CEUS in the characterization of pancreatic solid lesions, considering cross sectional imaging techniques (CE-CT/MRI) as the “gold standard” methods. **Material and methods:** We performed a retrospective, monocentric study that included 91 solid pancreatic lesions which were evaluated by CEUS and by a second-line contrast imaging technique (CT or MRI), considered as the reference method. **Results:** The rate of a conclusive diagnosis based on a typical enhancement pattern was 94% (78/83 cases). In 72 cases out of 83 (86.7%) there was a perfect concordance between CEUS and the “gold-standard” imaging method (CE-CT/MRI). In our study, 88% (73/83) of the pancreatic lesions were categorized as malignant due to their typical wash-out aspect in the late phase. The overall accuracy of CEUS for the differential diagnosis of solid pancreatic tumors was approximately 81%. The accuracy of CEUS for the diagnosis of hypoenhancing pancreatic tumors was approximately 89.1%; while for the diagnosis of hyperenhancing pancreatic tumors it was approximately 72.8%. **Conclusion:** CEUS allows the differentiation between hypo- vs. hyperenhancing pancreatic solid lesions, with a considerable diagnostic accuracy, a fundamental step in the precise diagnosis of pancreatic tumors.

Keywords: CEUS, enhancement pattern, pancreatic tumors, cross sectional imaging techniques

Introduction

More and more pancreatic lesions (symptomatic or not) are being detected due to recent advancement of imaging technology. Differentiation between various types of pancreatic tumors is crucial for the patients' prognostic. Since surgical resection offers the best chance for long-term survival and in order to avoid unnecessary laparotomies, the characterization of pancreatic masses based on imaging modalities is mandatory, but still challenging [1].

Conventional B-mode ultrasound (US) is a preferred imaging method in the screening for pancreatic lesions [2] because of its relatively low cost, readily available exami-

nation [3] and, not the least, because it is a non-invasive method. Until now, due to its accessibility and its ability to perform a rapid scan of the whole abdomen and pelvis, the main diagnostic method for pancreatic lesions had been contrast enhanced – computer tomography (CECT). Magnetic resonance imaging (MRI), which showed a higher specificity and sensitivity in the detection and staging different types of pancreatic lesions, is more expensive and not so widely available. The introduction of contrast-enhanced ultrasound (CEUS) has improved the diagnostic accuracy of US and extended its value [3,4]. The innovative use of CEUS for the study of the pancreas created the need for a precise definition of the most dynamic features of pancreatic masses (solid and cystic) [5]. Thus, CEUS can aid in the differential diagnosis of pancreatic tumors [4] and can provide dynamic information, with a high temporal and spatial resolution, concerning macro and micro-circulation of focal lesions and normal parenchyma [3,6]. Its high capability in showing tumoral microcirculation also makes CEUS accurate in the study

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of neoangiogenesis [5,7]. But CEUS has the disadvantage of being an operator-dependent method, and also its accuracy is influenced by the patients' acoustic window, an important aspect to be taken into consideration when evaluating a pancreatic lesion.

Currently, a number of published papers describe the CEUS enhancement pattern of the most common benign and malign pancreatic lesions [3,8-14].

The **aim** of our study was to evaluate the accuracy of CEUS in the characterization of pancreatic solid lesions, considering CECT/MRI as the "gold standard" methods.

Material and methods

We performed a retrospective, monocentric study that included 91 solid pancreatic lesions which were evaluated in our Department during a 50 months period, between October 2009 and December 2013.

Patients

We included in our study patients older than 18 years, in whom focal solid pancreatic masses were found and could not be characterized by US alone. In each patient the following characteristics were documented: indication for CEUS and a short history regarding pancreatic diseases or pancreatic malignancy. Each patient underwent a B-mode US examination, followed in the same session by a CEUS examination. CE-CT or MRI exam were available in each patient and considered as the "gold standard" for establishing the final diagnosis.

Exclusion criteria were: absence of the gold standard method (CE-CT/MRI); a characterized pancreatic lesion before the present study; inconclusive aspect in CE-CT/MRI; difficulties in CEUS examination due to the lesion's location (tail of the pancreas, improper acoustic window); subjects with a recent myocardial infarction; class III/IV cardiac insufficiency; significant rhythm disorders; pregnant women.

The study was conducted in full accordance with the Declaration of Human Rights (Helsinki, 1975) and with its further revisions (2000 revision-Edinburgh), and was approved by the local ethical committee. Patients gave their written consent prior examination.

Methods

All the studied lesions respected the same approach: standard US and CEUS in the same session, followed by CT/MRI. CEUS examinations were performed in a highly experienced center, by 4 experienced physicians, 2nd and 3rd level according to the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) classification of expertise levels. CEUS was performed on an Accuson S2000 US system (Siemens, Er-

Fig 1. Hypoechoic lesion in the pancreatic head. Dilated Wirsung duct (B-mode ultrasound).

Fig 2. Hypoechoic lesion in the pancreatic tail (B-mode ultrasound).

langen, Germany) with a low mechanical index: 0.09 to 0.11. Firstly a standard US examination was performed and the pancreatic lesions' size, location and pattern were documented (fig 1, fig 2). Afterwards, a CEUS was performed in the same session only for the assessment of "de novo" solid pancreatic masses (undetermined new pancreatic mass, not characterized by another imaging method). We did not include into the study cystic lesions (anechoic in B-mode ultrasound); mixed, solid-anechoic lesions; nor the lesions (solid and/or cystic) detected during an acute pancreatitis.

Real-time observation of the lesion's blood perfusion was no less than 120s, during which the patient was instructed to maintain smooth breathing. Dynamic images were preserved for later analysis. A 2.4 ml bolus of second generation contrast agent – sulphur hexafluoride filled microbubbles with a phospholipid peripheral shell (SonoVue, Bracco SpA, Milan, Italy) – was injected in an antecubital vein, followed by a 10 ml bolus saline solution. A "real-time", dynamic observation of the contrast enhanced phases – arterial (early stage of enhancement, until 30 seconds) and late (delayed stage of enhancement, 30-45 until 120 seconds following contrast injection) – began immediately after the contrast bolus [2,3,15]. Considering the surrounding pancreatic parenchyma as control, the enhancement and wash-out of the contrast agent in the lesion was observed.

Table I. Criteria used for pancreatic tumor differentiation in US [6,18] and CEUS [16]:

Pancreatic lesion	B-mode ultrasound	CEUS
Ductal carcinoma	Low echo pattern Lobulated margins Dilated Wirsung's duct	Typically hypoenhanced
Pancreatitis (chronic, autoimmune)	Low- echo pattern Lobulated margins Thrombosis Dilated Wirsung's duct Calcifications	Autoimmune pancreatitis presents as isoenhanced; chronic pancreatitis as isoenhanced.
Neuroendocrine tumors	Low echo pattern Sharply delineated Wirsung duct no-dilated	Typically hyperenhanced

According to the enhancement pattern as compared to the surrounding pancreas, the lesion was categorized as hyper-, hypo- or isoenhancing: 1) Homogenous hyper-enhancement: the whole lesion enhanced homogeneously

Fig 3. Hypoenhanced lesion in the pancreatic body – arterial phase (arrows).

Fig 4. Hypoenhanced lesion in the pancreatic body – arterial phase.

Fig 5. Hyperenhanced lesion in the pancreatic body – arterial phase

following the contrast bolus; 2) Heterogeneous hyper-enhancement: the pancreatic lesion enhanced inhomogeneously following the contrast bolus; 3) Isoenhanced: the lesion's enhancement was similar to the surrounding pancreatic parenchyma; 4) Hypoenhancement: the lesion enhanced less than the surrounding parenchyma; 5) Wash-out: loss of enhancement in the late phase, preceded by hypo-, hyper- or isoenhancement in the arterial phase (fig 3-5).

A CEUS final diagnosis was established after the contrast agent completed its course by comparing the enhancement pattern with the typical one described in the EFSUMB guidelines from 2008, updated in 2011 [16,17]. We compared the results of the enhancement pattern in our study with a second line contrast imaging method (CT/MRI), considered to be the reference method, and identified the accuracy of CEUS in the characterization of solid pancreatic masses.

The criteria used for pancreatic tumor differentiation in US [6,18] and CEUS [16], are presented in Table I.

Statistical analysis

Data were collected and analyzed using the SPSS v.17 software suite (SPSS Inc. Chicago, IL, USA). Data are presented as mean $\pm$ standard deviations for continuous variables with Gaussian distribution. For analyzing the diagnosis quality of pancreatic CEUS we used sensitivity (Se – the number of true positive divided to the total number of positives), specificity (Sp – the number of true negatives divided to the total number of negatives), positive predictive value (PPV – the number of true positives divided to the total number of positives at test) and negative predictive value (NPV – the number of true negatives divided tot the total number of negatives at the test). Accuracy was defined as the percentage of correctly classified patients from the total analyzed ones. A value of $p < 0.05$ was considered statistically significant and was taken into consideration.

Table II. Patients' characteristics

Median age (years)	63.7± 9.8
Gender	
– women	49 (59%)
– men	34 (41%)
Reference Method (CT/MRI)	67 (80.7%) cases with CT 16 (19.3%) cases with MRI
CEUS diagnosis:	
– hypoenhanced tumors	39 (47%)
– hyperenhanced tumors	31 (37.3%)
– isoenhanced tumors	13 (15.7%)
Final diagnosis by CT/MRI:	
– hypoenhanced tumors	36 (43.3%)
– hyperenhanced tumors	28 (33.7%)
– isoenhanced tumors	12 (14.5%)
– homogenous pancreatic tissue	2 (2.4%)
– solid-cystic tumors	5 (6.1%)

Results

We investigated 91 CEUS examinations in 91 patients. Of the whole investigated group we excluded 8 cases (5 cases in which the gold-standard method, CE-CT/MRI, was not available and 3 cases in which the lesion, located in the tail of the pancreas, was not clearly seen due to a poor ultrasound window). Thus, 83 lesions in 83 patients were included in the final analysis. The patients' characteristics are presented in Table II.

The pancreatic lesions' aspect in standard US is detailed in Table III.

The rate of a conclusive diagnosis based on a typical enhancement pattern was 94% (78/83 cases). In 72 cases out of 83 (86.7%) there was a perfect concordance between CEUS and the "gold-standard" imaging method (CE-CT/MRI). In our study, 88% (73/83) of the pancre-

atic lesions were categorized as malignant due to their typical wash-out aspect in the late phase.

The performance of CEUS for the differential diagnosis of solid pancreatic tumors is presented in table IV.

Discussions

The main imaging methods used for the assessment of pancreatic lesions are US, CE-CT or MRI. Conventional US is the preferred first-line method since it is noninvasive, simple and inexpensive. However, its quantitative diagnostic ability is limited [2]. Major limitations are the occasionally restricted image resolution due to the lesions' location (especially in the pancreatic tail) and to the poor sonographic visualization of the gland, due to overlying abdominal gas or to large amounts of abdominal fat [5].

In the last years, CEUS became a validated imaging technique for the assessment of pancreatic pathology. The main advantage of CEUS, as compared to other imaging techniques, is the ability to obtain a dynamic study, a real-time observation of blood perfusion of the lesion. With high spatial and temporal resolution for a relatively long time after microbubbles bolus, CEUS tends to gain lot of confidence in the characterization of pancreatic lesions [2,19]. Due to the fixed time of scanning, CE-CT/MRI cannot capture a transient enhancement. Besides, it is difficult for CE-CT/MRI to reflect the full-time phase blood supply of tumor [2].

When a pancreatic tumor has been detected, an immediate and correct differential diagnosis is mandatory to direct appropriate management [3]. CEUS is able to provide a rapid assessment of the pancreatic lesion's pat-

Table III. Pancreatic lesions' characteristics in standard ultrasonography (83 lesions).

Size n (%)	Location n (%)	Aspect in US n (%)
<2cm: 3 (3.6%)	Head: 53 (63.8%)	Hyperechoic: 4 (4.8%)
2-5cm: 59 (71.1%)	Isthm: 12 (14.5%)	Hypoechoic: 47 (56.6%)
>5cm: 9 (10.8%)	Body: 7 (8.5%)	Hypo-hyperechoic: 3 (3.6%)
Not recorded: 12 (14.5%)	Body-Tail: 4 (4.8%)	Mixed: 3 (3.6%)
	Tail: 1 (1.2%)	Hypo-anechoic: 5 (6.1%)
	Procesus uncinatus: 4 (4.8%)	Isoechoic: 17 (20.5%)
	Not recorded: 2 (2.4%)	Not recorded: 4 (4.8%)

n – number of lesions

Table IV. Performance of CEUS for the differential diagnosis of solid pancreatic tumors

	Overall (all tumors)		Hypoenhancing tumors		Hyperenhancing tumors	
	%	95% CI	%	95% CI	%	95% CI
Sensitivity	90.7	85.3 to 96.2	92.2	87.9 to 96.6	79.8	65.7 to 93.9
Specificity	90	84.6 to 95.5	86.4	78.1 to 94.7	97.8	95.9 to 99.8
Positive Predictive Value	87.2	80.4 to 94.1	88.7	81.8 to 95.7	75.7	51.7 to 99.7
Negative Predictive Value	95.4	91.5 to 99.3	94.2	88.8 to 99.6	96.5	93.6 to 99.5

CI- confidence interval

tern and to improve the solid lesion characterization, thus making possible a differential diagnosis. The most common solid pancreatic tumors are adenocarcinomas. Neuroendocrine lesions and metastases in the pancreas occur less frequently [18].

The overall accuracy of CEUS for the differential diagnosis in solid pancreatic masses was 81% in our study, a result slightly lower than in the Pancreatic Multicenter Ultrasound Study (PAMUS) in which the overall accuracy was 91.7% [3]. Previous studies report CEUS accuracies for the diagnosis of pancreatic solid lesions ranging from 83% to 92% [20,21]. The overall accuracy might be higher in PAMUS since pancreatitis lesions were also included in the group of solid pancreatic lesions, with a strong accuracy of 96.7%. In our study we only included only solid pancreatic tumors and excluded patients with pancreatitis.

The diagnostic accuracy of CEUS in hypoenhancing pancreatic lesions was 89.1% in our study, which was consistent with the results of studies by Yan et al and D'Onofrio et al [19,20]. In particular, in PAMUS [3] ductal adenocarcinomas were correctly identified with an accuracy of 87.8% based on the hypoenhancing aspect at CEUS. In five series that included more than fifty ductal adenocarcinomas proven by pathological exam, the tumor was reported to be hypovascular in 73-93% of the cases [10-12,16,22]. Our results are slightly better, possibly due to the fact that the gold standard method in our study was an imaging technique, not pathology.

In our study, 3 lesions described by CEUS with hypoenhancing pattern had a discordant aspect in the gold standard method: hyperenhancing (2 lesions) and iso-enhancing (1 lesion). An explanation may be the presence of distorted tumor vessels, of abnormal structures and vascular fistula caused by carcinoma invasion, so that the contrast agent has an inhomogeneous distribution, with a rapid wash-out [2].

Even if the accuracy of CEUS in characterizing hypovascular pancreatic lesions is high when compared with CE-CT/MRI, CEUS alone is not enough for a correct tumor staging. To assess tumor resectability, contrast enhanced CT/MRI are needed for a more accurate evaluation of the local extension and metastatic spread [6], even if in the same CEUS session we can examine the liver in the late phase to search for metastases. Thus, the most important role of CE-CT/MRI is to search for a possible invasion of the adjacent vessels.

CEUS also seems very accurate in detecting the hyperenhancing pattern of a pancreatic lesion. In the present study, the accuracy of CEUS in characterizing hyperenhancing lesions was 72.8%, similar to the one published by Serra et al [23] – 73.8%; but slightly lower

than in the PAMUS, in which the accuracy was 90.5% [3]. This might be due to the small number of hyperenhancing lesions identified by CE-CT/MRI (28 cases) and also because we couldn't verify the imaging results with a more sensitive method (pathology). In PAMUS, most of the neuroendocrine tumors had a hyperenhancing pattern, but some lesions also presented a hypoenhancing or iso-enhancing pattern, depending on the amount of stroma within a tick and hyalinized lesion. In our study 3 lesions interpreted by CEUS as hyperenhancing, were described as hypoenhancing in CE-CT/MRI, a situation also described in PAMUS [3].

By combining both methods (CEUS and CE-CT/MRI), a higher accuracy in detecting a neuroendocrine tumor, or in characterizing the extent of an adenocarcinoma can be expected. As stated in PAMUS, CEUS can improve the accuracy of the ultrasound study of pancreatic masses, obtaining faster diagnosis (immediate diagnosis of ductal adenocarcinoma). CEUS could also play a further role, subject for additional investigations, and act as a problem solving method: uncertain hypervascularity, or doubtful septa enhancement in a lesion [3]. Here is the place where the second imaging method and or histology interfere.

In the iso-enhancing group, 7 lesions turned to be chronic pancreatitis, even though in CEUS they presented a delayed wash-out and 2 lesions were autoimmune pancreatitis. The other 3 lesions were interpreted by CE-CT/MRI as iso-enhancing tumors with rapid wash-out.

A major limitation of the present study is that the reference method was not the pathology but an imaging technique. That's why we defined each lesion as being hypo, hyper or iso-enhancing and why we couldn't establish a firm diagnosis (adenocarcinoma, neuroendocrine tumor). The reference method, CE-CT/MRI, also described the lesions' enhancement pattern, and not the histological diagnosis. Nevertheless, our results were similar to the ones presented in published studies, where histology was considered the "gold standard" method.

Others limitations of the present study are the operator-dependency of US/CEUS and the fact that CE-CT/MRI were performed in different centers and interpreted by different examiners.

Conclusions

CEUS allows with a considerable diagnostic accuracy the differentiation between hypo- vs. hyperenhancing pancreatic solid lesions, which is a fundamental step in the precise diagnosis of pancreatic tumors. Thus, CEUS proved to be highly concordant (almost 87%) with a second-line cross sectional imaging method for the diagno-

sis of pancreatic solid lesions, proving its high accuracy of almost 81%.

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Conflict of interest: none

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