Abstract

The aim of this study was to summarize the spectrum of pancreatic pathology assessed by contrast enhanced ultrasound (CEUS) in a single Gastroenterology Center and to emphasize its accuracy in assessing two of the most important pancreatic lesions: solid tumors and necrotic lesions in acute pancreatitis. Material and methods: Our retrospective study included 197 patients with pancreatic lesions (de novo pancreatic masses; acute, severe pancreatitis; other pathologies) evaluated by CEUS from October 2009 to May 2013, in which a reference method (contrast CT/MRI) was available. Results: A conclusive diagnosis was established according to the EFSUMB Guidelines in 87.8% of the 197 cases. In 87.3% cases there was a perfect concordance between CEUS and the reference method (contrast CT/MRI). 95 examinations were made for pancreatic solid masses: 41.1% (39) were hypoenhanced, 34.7% (33) were hyperenhanced, and 20% (19) were isoenhancing – chronic pancreatitis and autoimmune pancreatitis – while in 4.2% (4) cases CEUS was inconclusive. 60 examinations were made in severe acute pancreatitis and in 50% (30) cases pancreatic necrosis was diagnosed. 42 examinations were performed for other lesions: 64.2% (27) pancreatic pseudocysts, 11.9% (5) cystic tumors, 23.8% (10) other pathologies (abscesses, fibrosis, etc). CEUS accuracy for solid tumors was 92.9%. For necrotic lesions the accuracy was 97.4%. Conclusions: CEUS has turned to be a good method for the characterization of different pancreatic pathologies and for evaluating acute pancreatitis. CEUS was conclusive in 90% cases and it should be considered as a first line imaging method in clinical practice.

Keywords: contrast-enhanced ultrasound, pancreatic tumors, acute pancreatitis

Introduction

Over the years, Contrast Enhanced Ultrasound (CEUS) has gained an important place in the characterization of pancreatic lesions, leading to improvement of its diagnostic capability.

Pancreatic lesions are found more and more often due to the widespread use of imaging modalities, especially B-mode ultrasound – widely spread in clinical practice due to its accessibility and also due to its accuracy. B-mode ultrasound is quite sensitive in detecting pancreatic lesions by an experimented examiner, but it is not specific enough. B-mode ultrasound can visualize a pancreatic mass or alterations of pancreatic parenchyma during pancreatitis but, unfortunately, many lesions cannot be characterized only by B-mode ultrasound [1].

CEUS has the main advantage to be a real-time investigation method, being able to evaluate tumor enhancement, filtering the background tissue signals [2-4]. It is a sensitive method that evaluates the vascularization of pancreatic lesions: solid and cystic [3,5] and also the viability of pancreatic tissue and of pancreatic masses. Its high ability to visualize microcirculation makes CEUS accurate in the study of neoangiogenesis [6] and also for noninvasive prognostic stratification of pancreatic adenocarcinoma and for the evaluation of chemotherapeutic effects [7-10].

CEUS is the only real-time method that allows a complete evaluation of the enhancement of pancreatic lesions during the dynamic phases [11]. Aided by ultrasound contrast agents it is now possible to investigate not only the vascularization of pancreatic lesions, but also their
specific perfusion. The usefulness of this technique for the diagnosis of pancreatic pathology is summarized in the Guidelines of the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) issued in 2008 and updated in 2011 [3,12].

The purpose of this study was to summarize the spectrum of pancreas pathology assessed by CEUS in a single Gastroenterology Center with extensive experience in ultrasound and to interpret the results according to the typical patterns presented in the EFSUMB Guidelines from 2008 updated in 2011 [3,12]. We also want to emphasize the accuracy of CEUS in detecting two of the most important pancreatic lesions: solid pancreatic tumors and necrotic lesions in acute pancreatitis. Lastly, we wanted to underline the importance of using CEUS for the diagnosis of pancreatic lesions from a financial point of view. In this respect we performed a cost effectiveness analysis of using CEUS alone and CEUS plus CT/MRI in inconclusive cases, versus CT/MRI for all cases.

Material and methods

Our retrospective study included all patients with pancreatic pathology evaluated by CEUS in the Department of Gastroenterology and Hepatology, Timișoara, Romania, between October 2009 and May 2013.

Patients

The inclusion criteria were: patients (older than 18 years), discovered in B-mode ultrasound with visible, undetermined, pancreatic lesions. For each patient the following characteristics were documented: indication for CEUS, a short history regarding recent pancreatitis or other pancreatic diseases, pancreatic malignancy. Each patient underwent a B-mode examination, followed in the same session by a CEUS examination. Contrast enhanced CT or MRI were available in each patient and considered as reference methods for the final diagnosis.

Exclusion criteria were: subjects with a recent myocardial infarction, class III/IV cardiac insufficiency, significant rhythm disorders, pregnant women, absence of contrast enhanced CT/MRI as reference method, inconclusive aspect in CT/MRI (4 cases out of 197 in our study).

The study protocol was approved by the Ethical Committee and was in accordance with the Helsinki Declaration from 1975. Informed consent from every patient was obtained before examination.

We divided the studied lesions into 3 subgroups: **Group 1** - de novo pancreatic masses (solid masses) – a newly diagnosed solid lesion that could not be characterized by B-mode ultrasound alone (fig 1, fig 2); **Group 2**...
Contrast Enhanced Ultrasonography study

The size, ultrasound pattern and location of each pancreatic lesion were documented after B-mode examination. The examinations were performed by experienced physicians (2nd and 3rd level according to EFSUMB classification of expertise levels), using a convex probe with low mechanical index (0.09-0.11) in order to minimize microbubble disruption. 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- standard protocol [13].

The examinations were performed in fasting patients in supine position. Dynamic observation of the contrast enhanced phases: arterial (early stage of enhancement, until 30 seconds) and late (delayed stage of enhancement) began immediately after the contrast bolus. The contrast study for each patient lasted 5 minutes following the bolus injection and was documented by photos and video-clips no longer than 30s that included: B-mode examination, the arterial and late phases. The contrast vascular patterns were defined by comparing the enhancement behavior of the pancreatic lesion to the surrounding pancreatic parenchyma. Subsequently we reviewed the images for a correct placement of the regions of interest and further interpretation. We interpreted the lesions as hyperenhanced (the whole lesion enhanced homogenously), isoenhanced (the lesion’s enhancement was similar to the surrounding pancreatic parenchyma), hypoenhanced (the lesion enhanced less than the surrounding parenchyma) (fig 5, fig 6), unenhanced (the pancreatic lesion did not enhance at all) (fig 7-9) and with or without wash-out (loss of contrast agent in the late phase, preceded by hypo-, hyper- or isoenhancement in the arterial phase).
A CEUS final diagnosis was established after the contrast agent completed its course and the enhancement pattern was assessed according to the EFSUMB 2008 and 2011 Guidelines [3,12]:

Adenocarcinomas typically show poor enhancement during all phases, being hypoenhanced due to the desmoplastic reaction, with a relatively poor mean vascular density and perfusion.

The neuroendocrine tumors are hyperenhanced, they show rapid and intense enhancement during the early dynamic phases, followed by wash-out in the late phase.

Pseudocysts are always completely avascular, being homogeneously unenhanced during CEUS examination.

Serous cystadenomas show enhancement of the internal septa and of the cystic wall, with better identification of the lesion’s multilocular architecture. CEUS is useful not only in the differential diagnosis of serous cystadenomas, but also in the long-term follow-up.

Mucinous cystic tumors appear as round macrocystic lesions, with particulate content, irregular thick walls and internal inclusions which enhance during CEUS. Generally, these tumors have vascularized septa and parietal nodules.

Acute pancreatitis appears as hyperenhanced following contrast agent, with different enhancement intensity. In acute severe pancreatitis, CEUS is able to detect necrotic regions, which appear as unenhancing (avascular).

Focal mass-forming pancreatitis and autoimmune pancreatitis have been reported to have similar enhancement pattern with that of the normal pancreatic parenchyma.

A CEUS examination was considered conclusive if the lesion had a typical pattern according to the EFSUMB Guidelines and inconclusive if the enhancement pattern didn’t correspond. The diagnosis established by CEUS was compared with the diagnosis found by contrast CT/MRI, which were considered to be the reference methods.

Cost-analysis

We designed a cost-effectiveness analysis algorithm inspired by the study by Şirli et al [13]. Three scenarios were compared: the first one in which CEUS was used as a first line imaging method, followed by contrast enhanced CT/MRI only in inconclusive cases; the second scenario in which contrast enhanced CT was used as a first line imaging method in all cases; and the third scenario in which contrast enhanced MRI was used as a first line imaging method in all cases. We used the prices of CEUS, CT and MRI practiced in our home town Timişoara, Romania: 42 Euros for CEUS; 65 Euros for contrast enhanced CT; 150 Euros for contrast enhanced MRI.

Cost-effectiveness analysis

Data were collected and analyzed using the SPSS v.17 software suite (SPSS Inc. Chicago, IL, USA). Data are presented as mean ± standard deviations for continuous variables with Gaussian distribution, median (interquartile range) for continuous variables without Gaussian distribution, or percentages for categorical variables. Prevalence is expressed as number of positive cases, divided to the total number of the groups components; the lower and upper limits of the 95% confidence intervals (CI), used to estimate the prevalence, were calculated according to Wilson’s procedure for variables with Poisson 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 to the total number of negatives at the test). Accuracy is defined as the percentage of correct classified patients from the total analyzed ones.

Results

We identified 277 CEUS pancreatic examinations in 277 patients during the studied period that fulfilled the inclusion criteria. Of all cases, 77 were excluded for not having CT/MRI as a reference method and 3 cases for being CEUS failures – 2 due to paravenous injection and 1 because the lesion was situated too deep (in the pancreatic tail) and we were not able to visualize it properly. Finally 197 lesions in 197 patients fulfilled all criteria (Table I).

The rate of conclusive diagnosis based on typical enhancement pattern according to the EFSUMB Guidelines

Table I. Characteristics of the lesions (197) evaluated by B-mode ultrasound.

<table>
<thead>
<tr>
<th>Size of lesion</th>
<th>Number of lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2cm</td>
<td>7</td>
</tr>
<tr>
<td>2-5 cm</td>
<td>100</td>
</tr>
<tr>
<td>&gt;5 cm</td>
<td>41</td>
</tr>
<tr>
<td>Not recorded</td>
<td>49</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Aspect in B-mode ultrasound</th>
<th>Number of lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoechoic</td>
<td>91</td>
</tr>
<tr>
<td>Hyperechoic</td>
<td>6</td>
</tr>
<tr>
<td>Mixed (hypo-hyper-anechoic)</td>
<td>3</td>
</tr>
<tr>
<td>Solid-cystic (hypo-anechoic)</td>
<td>21</td>
</tr>
<tr>
<td>Isoechoic</td>
<td>31</td>
</tr>
<tr>
<td>Anechoic</td>
<td>33</td>
</tr>
<tr>
<td>Anechoic with internal septa</td>
<td>9</td>
</tr>
<tr>
<td>Not recorded</td>
<td>3</td>
</tr>
</tbody>
</table>
was 87.8% (173 cases). In 172 cases out of 197 (87.3%) there was a perfect concordance between CEUS and a second line imaging method (contrast enhanced CT/MRI) (Table II).

In the first group, 95 CEUS examinations were performed for the assessment of solid pancreatic lesions. A positive diagnosis was established following CEUS in 83.1% cases. The spectrum of the solid masses included: 41.1% hypoenhanced, 34.7% hyperenhanced, and 20% isoenhancing lesions – including chronic pancreatitis and autoimmune pancreatitis – while in 4.2% cases CEUS was inconclusive. CEUS accuracy for the diagnosis of solid tumors was 92.9% (Table III).

In the second group, 60 CEUS examinations were performed in patients with severe acute pancreatitis, with a conclusive diagnosis in 95% of the cases. Pancreatic necrosis was found by CEUS in 50% cases. The accuracy of CEUS for detecting pancreatic necrosis in severe acute pancreatitis was 97.4% (Table IV).

In the third group 42 CEUS examinations were performed for other pancreatic lesions: 76.2% for cystic lesions: 64.2% for pancreatic pseudocysts, 12% for cystic tumors; and 23.8% for other pathologies (abscesses, fibrosis, etc).

Cost-analysis

First scenario: CEUS performed in all cases as first line imaging method followed by contrast enhanced CT/MRI for inconclusive cases. The total cost of CEUS in all 197 cases was 197x42 Euros=8.274 Euros. In 24 cases CEUS was inconclusive. The costs of contrast enhanced CT or MRI in the inconclusive cases were: for CT 24x65=1.560 Euros and for MRI 24x150=3.600 Euros, respectively. If CEUS is followed by CT in inconclusive cases the cost would be 8.274+1.560=9.834 Euros. If CEUS is followed by MRI in inconclusive cases the cost would be 8.274+3.600=11.874 Euros.

Second scenario in which contrast enhanced CT is performed as a first line imaging method in all cases, the total cost would be 197x 65 = 12.805 Euros.

Third scenario in which contrast enhanced MRI is performed as a first line imaging method in all cases the total cost would be 197x 150 = 29.550 Euros.

Discussions

Conventional B-mode ultrasound is a widely performed, relatively low cost and readily available examination for pancreatic study [2], commonly used especially as first line imaging method. Unfortunately, even if B-mode ultrasound is able to identify pancreatic lesions, it is not able to establish a final diagnosis in the majority of cases (for instance it can’t differentiate an adenocarcinoma from a neuroendocrine tumor or from pseudotumoral chronic pancreatitis). CEUS takes advantage of its special features: high contrast and spatial resolution, the use of a blood-pool microbubble contrast medium and the real time, dynamic evaluation of tumor enhancement [15]. The introduction of microbubble contrast agents has improved the diagnostic accuracy of B-mode ultrasound.
In our study we encountered a wide spectrum of pancreatic lesions, in accordance with the pancreas pathology described in published papers [4,15-17]. In 2006, Rickes et al underlined the importance of CEUS in the diagnosis of pancreatic tumors [17]. They presented the ability of CEUS to characterize pancreatic lesions. D’Onofrio underlined in 2010 [15] the innovative use of CEUS for the study of the pancreas and its ability to describe dynamic features of solid and cystic masses. They demonstrated that CEUS has a large applicability in pancreatic pathology: in acute pancreatitis (it improves the detection and delimitation of necrotic areas), in the differential diagnosis of pseudocysts and pancreatic cystic tumors; in differentiating a mass forming chronic pancreatitis or autoimmune pancreatitis, from a solid tumor (adenocarcinoma or neuroendocrine tumor); it also improves the characterization of cystic lesions. Later, in 2011, D’Onofrio et al published a study [16] that included 1439 lesions and demonstrated the accuracy of CEUS in describing pancreatic pathology: solid lesions (adenocarcinomas, neuroendocrine tumors, pancreatitis) and cystic lesions (tumors, pseudocysts).

Similar to the PAMUS study [16] in which the accuracy of CEUS for the diagnosis of solid pancreatic lesions was 91.7%, in our study the accuracy was 92.9%. The result is better due to the high concordance rate between CEUS and the second line diagnostic method used in our study. Our reference method was an imaging one, not histology, as stated in the PAMUS’ study. We observed that in our study the Se, Sp, PPV and accuracy for a positive diagnosis range around 93% (for lesions with a typical enhancement pattern according to the EFSUMB Guidelines). These results are almost the same as those published by Dietrich et al. [18]. Considering histology as a reference method Dietrich demonstrated that CEUS had 93.8% accuracy for the characterization of solid pancreatic lesions (duetal adenocarcinomas and non-duetal adenocarcinomas). Thus we can be very confident in our results and conclude that for a positive diagnosis of pancreatic lesions it is sufficient to perform a CEUS examination after a standard B-mode ultrasound exam.

In our study we observed a very good accuracy of CEUS for detecting necrotic lesions in acute pancreatitis (97.4%). Similar results were obtained by Ripolles et al [19] who found that CEUS had 86% sensitivity and 97% specificity for detecting severe acute pancreatitis. In this study a significant correlation between CT and CEUS was found for the CT severity index, extent of necrosis and Balthazar grade. The study confirmed the value of CEUS in detecting pancreatic necrosis and as a predictor of severity in an episode of acute pancreatitis [19]. Thus, according both to Ripolles’ study and to our own, CEUS is comparable to CT in detecting pancreatic necrosis, as well as for predicting its clinical course. Repeated CT would be too irradiant for the patient. The medical world is concerned more and more about exposure to ionizing radiation. Also, unlike contrast enhanced CT/MRI, CEUS can be safely used in patients with acute/chronic renal failure [20], while the adverse events following ultrasound contrast agents are rare and mild [19,21] as compared to other contrast imaging techniques [22].

Considering all these facts we can sustain the use of CEUS as a first line imaging method for the detection of necrotic lesions and follow-up of acute, severe pancreatitis, of course only in cases in which the pancreas is well seen by standard B-mode ultrasound, since a disadvantage of CEUS is that not always a good ultrasound window is available for the examination of the pancreas, especially in acute pancreatitis. Current clinical guidelines established the use of contrast CT as the gold standard method for the diagnosis and evaluation of patients with acute pancreatitis, with a high degree of accuracy in detecting necrosis. Indeed, CT permits a complete evaluation of the peripancreatic, retroperitoneal region. However, CEUS is useful where CT is contraindicated, or in patients who want to avoid extra radiation dose. To conclude, CEUS can be used as a follow-up imaging method in patients with an initial CT staging at admission [19].

As demonstrated by our study, the strategy in which CEUS is used as a first line imaging method in all pancreatic lesions found by B-mode ultrasound followed by contrast enhanced CT/MRI only in inconclusive cases, is less expensive than the strategies in which contrast enhanced CT or MRI are used as first line imaging methods. The savings of CEUS as a first line imaging method as compared to CT amounted to 2971 Euros, and as compared to MRI as first line imaging method to 17676 Euros. The results in our study are in line with other published studies [14,15] CEUS is a cost-efficient method as a first line diagnosis as compared to first line contrast-CT or first-line MRI [14].

Even if in all cases presented in our study a reference method was available, one of the weak points of the study was that the reference method was not histology for pancreatic masses. All the tumors’ characterization was in fact made according to the enhancement pattern following contrast, but a firm diagnosis could not be established, that is why we avoided describing a tumor as being an adenocarcinoma, or a neuroendocrine tumor.

For malignant tumors, even if CEUS detects with high accuracy the hypoenhancing pattern – consistent with ductal adenocarcinoma in 87.8% of cases; and hyperenhancing pattern – consistent with neuroendocrine tumors in 90.5% cases [16], CEUS is not sufficient to
characterize the tumor. To assess tumor resectability, contrast enhanced CT/MRI are needed for a more accurate evaluation of the local extension and metastatic spread [23].

Conclusions

CEUS has been proven to be an accurate method for the characterization of pancreatic masses (solid tumors) and for evaluating the presence and extension of necrosis in acute pancreatitis. In our study, according to the EF-SUMB Guidelines, CEUS was conclusive in almost 90% of cases and therefore it should be considered as a first line imaging method for pancreatic lesions. Last but not least, CEUS is a cost-effective method for the assessment of pancreatic lesions.

Conflict of interest: none

References