Medical Ultrasonography
2009, Vol. 11, no. 4, 37-45

Contrast-enhanced ultrasonography of the pancreas – current state of the method, indications, performance, limitations

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Abstract

Contrast-enhanced ultrasonography is a relatively new technique, currently used for liver tumors diagnosis. Contrast agents are composed of stabilized micro-bubbles that fill the vascular supply. Lately, the method has also been used in the assessment of pancreatic disorders. Pulse inversion harmonic imaging allows the assessment of the hypervascularised masses as neuroendocrine tumors, of the hypoperfused masses as adenocarcinomas or of the necrotic areas in acute pancreatitis. Also, this technique allows a better assessment of the pancreatic tumors resectability and the identification of septa inside cystic lesions. In addition, it is highly accurate in detecting liver metastases. Contrast-enhanced ultrasound may represent a convenient alternative to contrast CT for selected cases.

Keywords: Contrast enhanced ultrasonography, pancreas, pancreatitis, neoplasm

Rezumat

Ecografia cu substanţă de contrast este o tehnică relativ nouă, folosită în mod curent în diagnosticul tumorilor hepatice. Agenţii de contrast sunt compuşi din microsfere stabilizate care umplu patul vascular. In ultimul timp metoda este folosită şi în evaluarea patologiei pancreatice. Utilizarea tehnicilor **armonice** de inversie a pulsului a permis evaluarea maselor hipervascularizate cum sunt tumorile neuroendocrine, a celor hipovascularizate cum sunt adenocarcinoamele sau a ariilor necrotice din pancreatita acută. De asemenea această tehnică permite o mai bună apreciere a rezecabilităţii tumorilor pancreatice şi a septelor din interiorul leziunilor chistice. In plus are o mare acurateţe în detectarea metastazelor hepatice. Ecografia cu substanţă de contrast poate reprezenta în cazuri selecţionate o bună alternativă la tomografia computerizată cu substanţă de contrast.

Cuvinte cheie: ecografie cu substanţă de contrast, pancreas, pancreatită, neoplasm

List of abbreviations

CAUS – contrast agents used in ultrasonography
CEUS – contrast-enhanced ultrasonography
CT – computed tomography
ERCP – endoscopic retrograde cholangiopancreatography
MRCP – magnetic resonance retrograde cholangiopancreatography
US – ultrasonography

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Introduction

Pancreatic diseases, both inflammation, acute or chronic, and neoplasms, represent an important health problem [1]. The diagnosis of pancreatic diseases is mostly based on sectional images – CT, MRI, US – which attempt to identify any alterations as early as possible, so that therapy, costs and patient's suffering to be minimal. *Spiral CT* assesses the pancreatic tumors and its extensions and the parenchymatous necrosis, vascular complications and serous collections in cases of acute pancreatitis, being considered the gold standard for such disorders [2]. The technique has the disadvantage of using an iodine contrast substance, which is good for assessing circulation but is nephrotoxic. Moreover, they can also affect pancreatic microcirculation, as evidenced by experimental

studies [3]. Other techniques are *endoscopic retrograde cholangiopancreatography (ERCP)* and *MRI cholangiopancreatography (MRCP)*, each of them with limitations regarding the diagnosis of masses, being either invasive, or with low specificity [4]. *Ultrasound examination* is the first method used in the assessment of abdominal pain and abdominal emergencies. Nowadays there are high-resolution portable equipments in emergency units, in gastroenterology units, independently from medical imaging departments. Non-invasive and non-radiating, it is easily accepted by patients and has proven to be a very good diagnostic tool if performed by an expert. Ultrasonography is an extension of the clinical examination, often shortening the diagnostic time [5,6].

The most common cases of acute pancreatitis are mild to moderate, with reversible edema. However, 10-25% of patients will develop necrosis, pseudocysts and infections, a complex management being required: surgery, endoscopy and/or radiology [7,8]. The US diagnosis is based on: pancreatic parenchyma enlargement, non-homogeneous parenchyma (not characteristic), and intra abdominal collections [9]. The color Doppler association allows vascular pseudoaneurysms and venous thromboses detection, without evidencing pancreatic microcirculation. Therefore the identification of the ischemic and necrotic areas in acute pancreatitis is not possible with conventional equipment [10]. US allows the detection of pancreatic tumors over 10 mm, especially when they are hypoechogenic or cystic. At this size, the US image is not characteristic and does not discriminate between adenocarcinoma and other tumors such as microcystic adenoma, focal pancreatitis, cystic adenoma, cystic mucinous neoplasm and intraductal mucinous tumors [11]. The disadvantages of this technique are the difficulty of a complete examination in overweight patients, operator dependence, and low reproducibility. The newer imaging techniques as endoscopic ultrasonography and intraductal US are not used in routine examinations or emergencies assessment. [12,13].

The use of contrast agents has determined further improvement of the diagnostic accuracy.

Contrast agents (CAUS) are stabilized gas microbubbles with a diameter less than 10 microns. They are injected into the systemic circulation, pass through the pulmonary capillary circulation and reach the organ vascular supply and remain at this level, unlike the contrast agents used in CT or MRI. Based on the Doppler principle and secondary harmonics, the micro-bubble are detected following vibration and bursting and increasing the signal-to-noise ratio. The contrast agents are non-embolizing and non-toxic and only mild adverse reactions are recorded [14,15]. The main indications of the method are the qualitative and quantitative assessment of parenchyma perfusion and optimal visualization of slow blood flow in small vessels difficult to assess by Doppler ultrasound. While a large number of studies have been showing the CAUS usefulness in liver tumors assessment, studies regarding pancreatic disorders are scant and inconclusive [16]. For pancreatic diseases studies on CEUS are still undergoing [17].

There are several types of contrast agents on the European market, among which Optison (GE Healthcare) and Luminity (Bristol Myers Squibb), with cardiac applications, and Levovist (Schering) and SonoVue (Bracco) for abdominal organs.

The SonoVue (Bracco) substance is a second generation contrast agent used with modern ultrasound equipment. Echoes are received in a wide range of values concomitant with pulse inversion, which improves discrimination between non-linear micro-bubble and linear tissue echoes. Lowering the mechanical index (acoustic pressure of the ultrasounds emitted by the transducer), the bubbles can be distinctly visualized concomitant with the parenchyma extraction from the image, resulting an improved visualization of the vascular supply in real time, during a longer period (range of minutes).

The information is obtained and analyzed during the procedure, which makes it a "real-time" examination. An important limitation of the method is the situation when conventional US examination fails to detect the lesion. However, in overweight patients tissue harmonics may be used to enhance the image quality [18].

Contrast-enhanced examination of the pancreas has been recently introduced [19,20] and it's main indications are acute pancreatitis, pancreatic tumors and pseudotumours.

Examination technique. The ultrasound examination of the pancreas consists of two phases:

(a) *native phase* regarding the area of interest selection (details of the parenchyma structure, presence of a defined lesion, its texture, overall pancreatic echoes, collections, Wirsung duct, cysts or calcifications), the study of fluid collections in acute pancreatitis (peripancreatic, omental sac, supra- or submesocholic level, pleura and pericardium), signs of vascular thrombosis (in inflammations) or vascular invasions (neoplasia), involvement of other solid organs (ischemia, metastases) and

(b) *contrast phase* regarding the assessment of the enhancement pattern of the pancreatic vascular supply. Concomitantly, the operator should assess the retroperitoneal vessels permeability (thrombosis or vascular invasion), the liver vascular supply and the possible existence of hepatic metastasis. The amount of CAUS

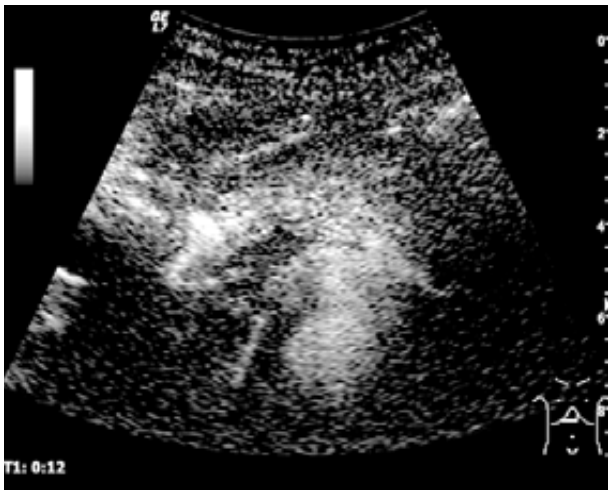


Fig 1. Acute edematous pancreatitis. Hyperechogenicity after SonoVue administration is to be noted!

injected is a standard one (2.4 ml/patient, regardless of body weight), or adapted to each individual, always followed by 10 ccm saline injection. The US equipment is set for a contrast examination program which produces a suppression of the tissue echoes and detects the microbubbles harmonic echoes. The mechanical index is set at 0.09-0.11, while the focus is positioned below the area of interest in order to avoid the bursting of the bubbles. Due to the entirely arterial pancreatic vascularization, the CEUS phases are easy to identify: arterial/early 10 – 30 seconds (concomitant with the abdominal aorta, and venous/late 30 – 120 seconds interval (contrast agent noted in the splenic and mesenteric veins). The assessment of enhanced pattern in the interest area is made using the normal pancreatic parenchyma as reference. The examination must include the scanning of the liver and spleen in order to detect small metastatic lesions (over 90-120 seconds).

Contrast-enhanced US examination must follow a set of principles: (a) examination consist of "real-time" follow-up of the vascular filling and its subsequent wash-out; (b) each area of interest will require different administration of the contrast agent; (c) video clips should be recorded on the hard disk of the equipment, at precise times, identification and analysis of wash-out curves being easier on the records, in the patient's absence; (d) total time of examination is about 10 minutes, which will include the examination of the specific area as well as the neighboring parenchymatous organs (liver, spleen).

Applications of CEUS in pancreatic diseases

Acute pancreatitis. In acute edematous pancreatitis the filling of the vascular supply is diffuse, leading to an overall increase of echogenicity [21] (fig1).

This part of the examination represents a true "parenchymography". There is a sinusoidal filling of the vascular supply which leads to a late enhancement of the pancreas, about 3-5 minutes from the i.v. administration of the contrast agent, thus improving the conventional ultrasound image. In severe forms of pancreatitis, CEUS allows the identification of ischemic areas and, thus improves the assessment of the parenchymal necrosis (fig 2).

The CEUS performance in the diagnosis of severe acute pancreatitis is very good compared to the CT Balthazar score (82% sensitivity, 89% specificity; positive predictive value: 95%, negative predictive value: 67%) [18] in a study of 31 patients with acute pancreatitis. The CEUS advantages include the non-radiation character, lower cost and utility for the patients in which contrast

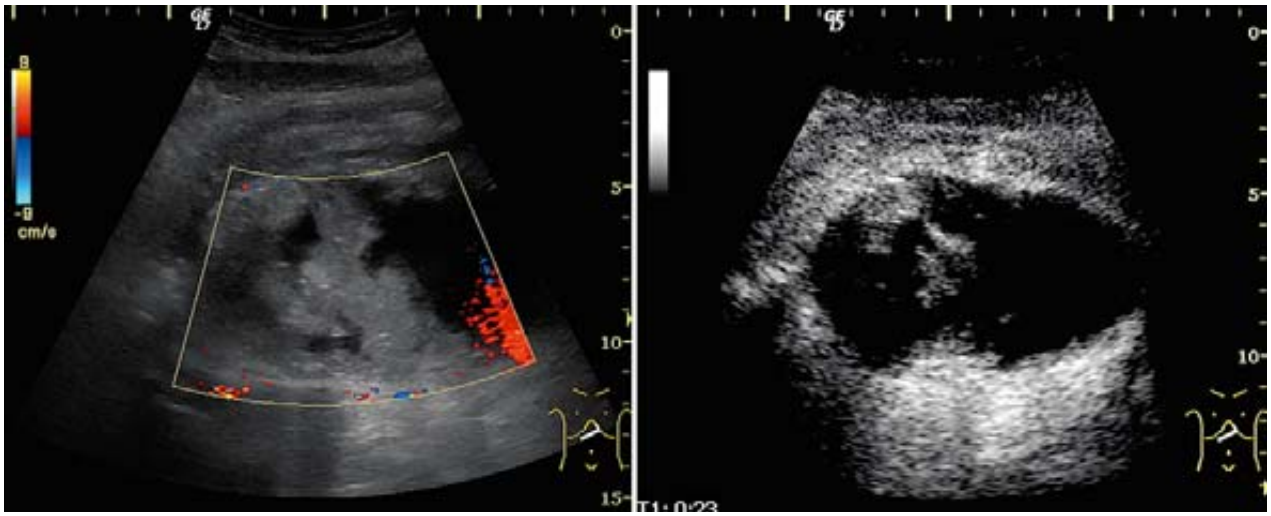


Fig 2. Severe necrotic pancreatitis.

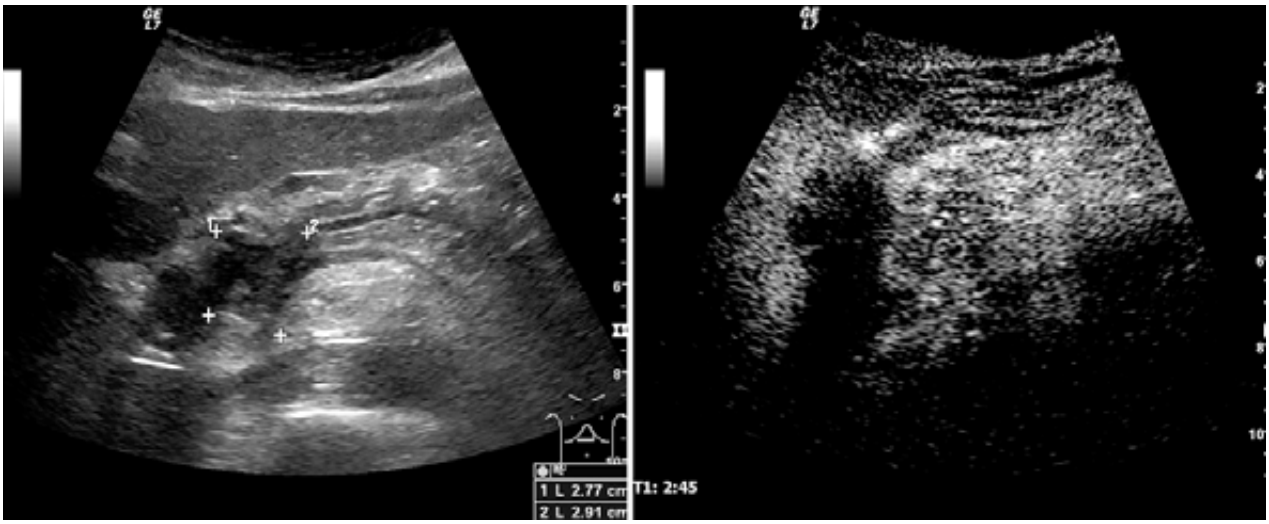


Fig 3. Pseudotumoral chronic pancreatitis (head) (left – conventional US, right- CEUS – 165 sec after injection of SonoVue).

CT is contraindicated – renal failure, iodine contrast allergy and pregnancy [18].

Pancreatic pseudotumours. They represent well delimited areas of pancreatic inflammation and interstitial fibrosis. They occur after repeated bouts of acute alcoholic pancreatitis or in chronic alcoholic or autoimmune pancreatitis. Similarly to tumors, they compress the pancreatic duct or the retroperitoneal organs (vessels, duodenum, nerves). Differential diagnosis with neoplasm is difficult due to similarities [22]. At conventional ultrasound examination they appear as an imprecise, hypoechoic tumor mass. Following contrast administration there is a slow and diffuse enhancement of the pseudo-tumor in over 90% of cases [21], similar in pattern and intensity with the normal parenchyma, thus excluding the presence of tumors (fig 3).

The extent of contrast enhancement is in inverse proportion to the duration and intensity of the inflammatory process, which might represent an indirect sign of the degree of fibrosis and the presence of parenchyma inflammation and necrosis [21]. The technique diagnostic accuracy regarding pancreatic tumors is: 88.6% sensitivity, 97.8% specificity, 91.2% positive predictive value, 97.1% negative predictive value, general accuracy 96% [21].

Pancreatic masses. Their behavior after contrast i.v. administration is defined in relation to the initial aspect of the tumor and the normal neighboring parenchyma. It may be hypoechogenic, isoechogenic or hyperecogenic [11]. *Adenocarcinoma* presents as a hypoechoic mass at conventional ultrasound. Following the contrast agent administration, the signal appears in the large tumor arteries at 9 – 11 seconds, followed by a slow and diffuse filling of the vascular supply, reaching a maximum intensity at 20 – 30 seconds. Filling is non-homogeneous, while the overall enhancement remains low compared to the surrounding parenchyma, which leads to a hypovascular pattern (fig 4).

It is found in 90% of the cases of adenocarcinoma [24,25] and is independent of the contrast agent, 1st generation (Levovist, Schering), or second generation (SonoVue, Bracco). The cause of this filling pattern is the poor vascularity and the fibrous content of the tumor, which further slows the filling [25]. The enhancement pattern differences delineates better the tumor margins, which is more common in hypoechoic adenocarcinomas compared to the isoechoic tumors, thus increasing the diagnostic accuracy (fig 5).

About 77% of the tumors with negative resection margins presented a hypovascular filling pattern in a

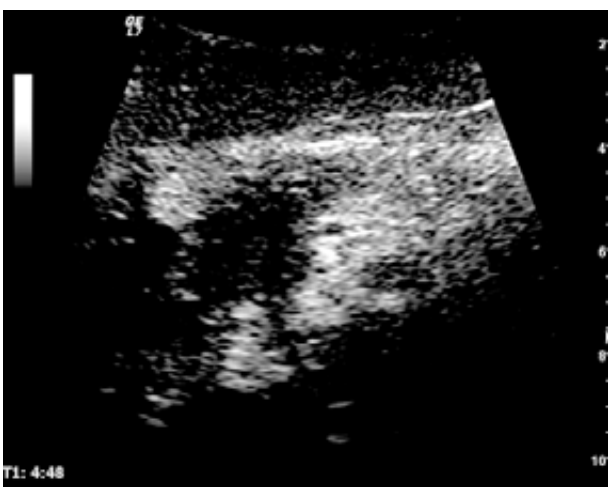


Fig 4. Pancreatic adenocarcinoma – hypovascular pattern.

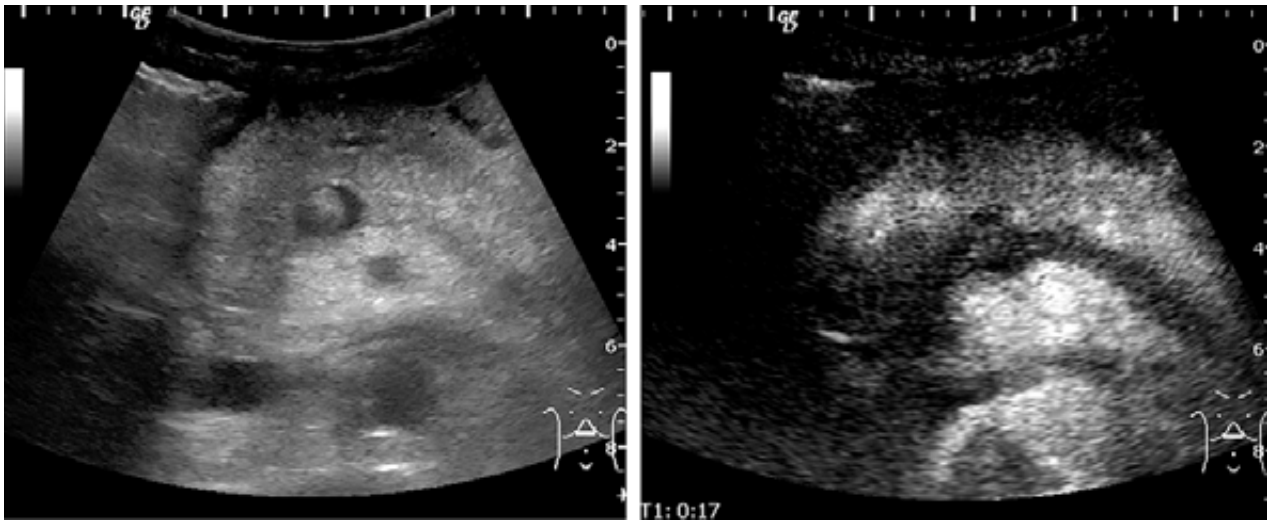


Fig 5. Optimization of the ultrasound image and evidence of the tumoral delineation before and after contrast administration in a case of adenocarcinoma of the head of the pancreas.

group of 67 cases of pancreatic adenocarcinoma assessed by this technique and subsequently resected. Only 50% of the tumors with positive resection margins had this filling pattern [26].

The enhancement pattern might lead to an increased echogenicity similar to normal pancreas parenchyma (isoechogenic filling pattern) in 10% of the cases. This pattern might also occur in chronic pancreatitis, thus leading to differential diagnostic errors [11]. In all cases retroperitoneal vascularization is better emphasized and arterial invasion becomes clear

Kitano classified the pancreatic tumors according to the vascular pattern and behavior after contrast injection: type I – no vessels in the arterial time and no enhancement on the perfusion image; type II – a few vessels and scattered signal intensity increase in the hypo vascular area on the perfusion image, vascularization less intense than in the neighboring pancreatic parenchyma; type III – vascularization similar to the neighboring parenchyma and homogeneous signal intensity increase on the perfusion image; type IV – abundant vessels in the arterial time and hypervascularization on the perfusion image [17]. Most of the adenocarcinomas belong to types I and II (hypo vascular tumors), while the other pancreatic tumors are iso- or hypervascular (fig 6).

CEUS detects small (< 2 cm) pancreatic tumors with a sensitivity similar to endoscopic ultrasound (95%) and higher than CT (68%) [17]. In another study Dietrich *et al.* showed that poor vascularization as a sign of adenocarcinoma has a 90% sensitivity and 100% specificity [25]. Exploration of intratumoral circulation may represent an indicator of the efficiency of chemotherapy in patients with adenocarcinoma. The technique is sufficiently sensitive to discriminate between patients with abundant tumor vascularization associated with better response to therapy and patients with hypovascularized tumors, with lower therapeutic efficiency and unfavorable prognosis [27].

Neuroendocrine tumours are very small in size (in about 50-70% of the cases the insulinoma diameter is less than 1.5 cm), hypo- or iso-echogenic, and almost impossible to detect by conventional ultrasound [28-30]. They usually have a very rich vascularization. Following CEUS, the arterial phase is characterized by a rapid and marked enhancement [31], with a hyperechogenic pattern compared to the surrounding parenchyma. The tumor might be homogeneous or non-homogeneous, depending on the presence of necrotic or cystic areas. During the venous phase the contrast is washed out, leading to a hypoechogenic pattern compared to the surrounding parenchyma. The examination may be performed percutaneously, or during an intraoperative angiography; tumors of up to 1 cm might be detected [29]; studies have reported a sensitivity of 94%, specificity 96%, positive predictive value of 75% and negative predictive value of 99% [32] (fig 7).

Pancreatic metastases are rare. The most frequent cases of pancreatic metastasis occur in renal carcinoma. CEUS might demonstrate the hypervascular pattern of thist pancreatic leions, and sometimes also detects the presence of liver metastases [33,34] (fig 8).

Cystic tumours present a particular filling pattern, but the definite diagnosis requires integration of CT and MRI findings [11]. *Microcystic adenoma* appears as a well delineated mass with small cysts inside. Following contrast administration septa are enhanced, the tumor showing a

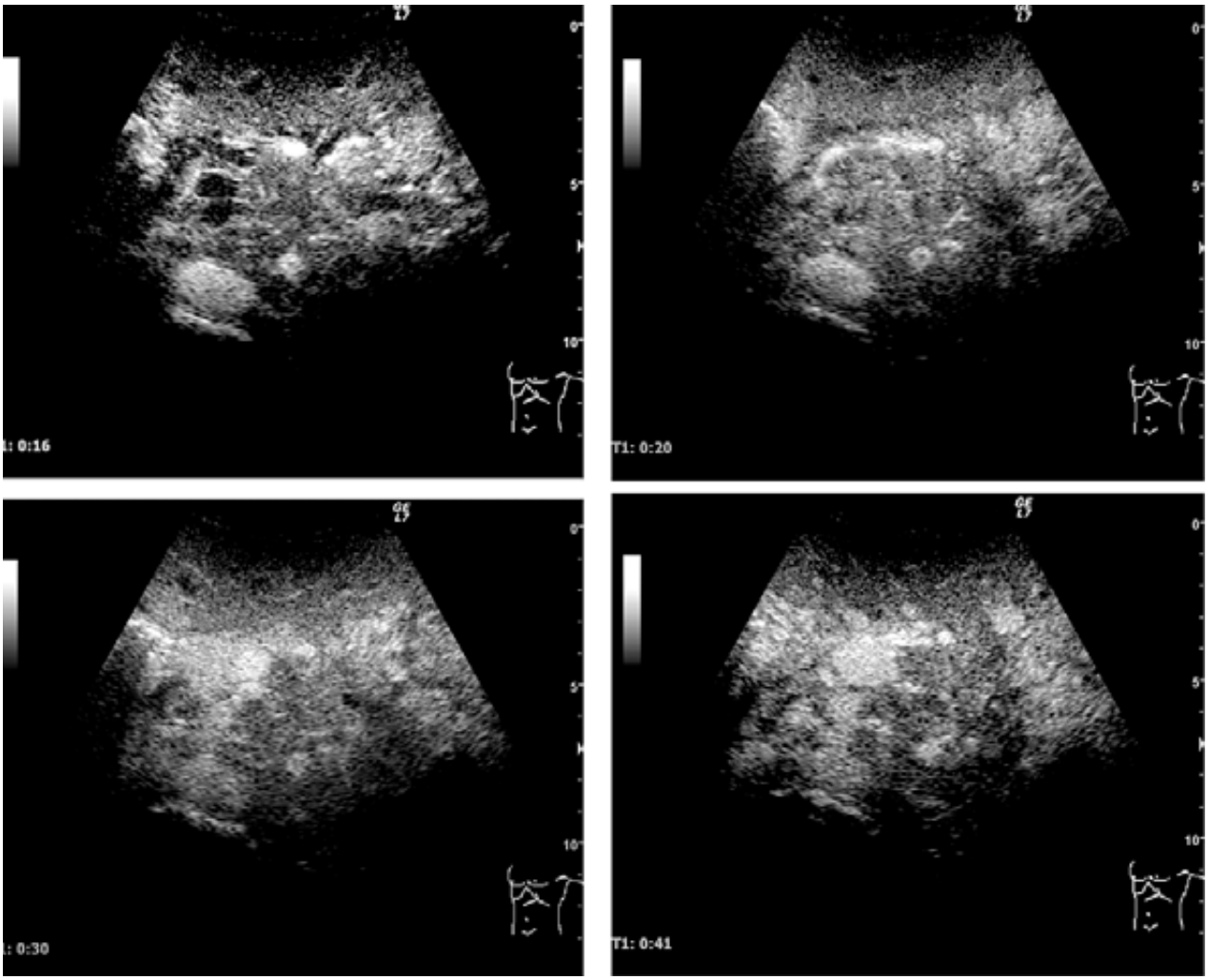


Fig 6. Pancreatic adenocarcinoma - hypervascular pattern.



Fig 7. Neuroendocrine tumor (gastrinoma).

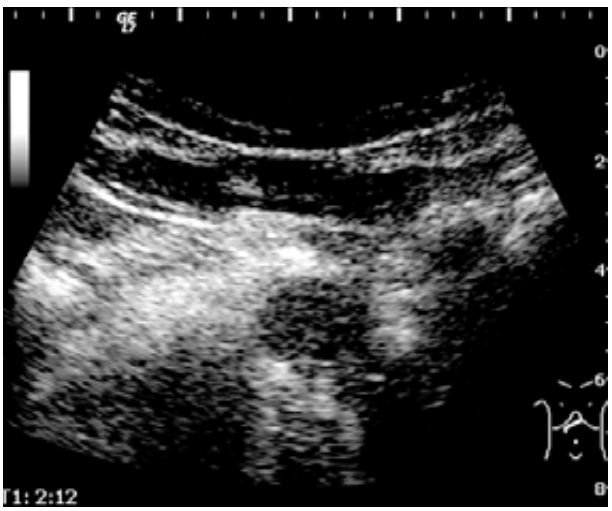


Fig. 8. Metastases in the pancreatic head (gastric neoplasm).

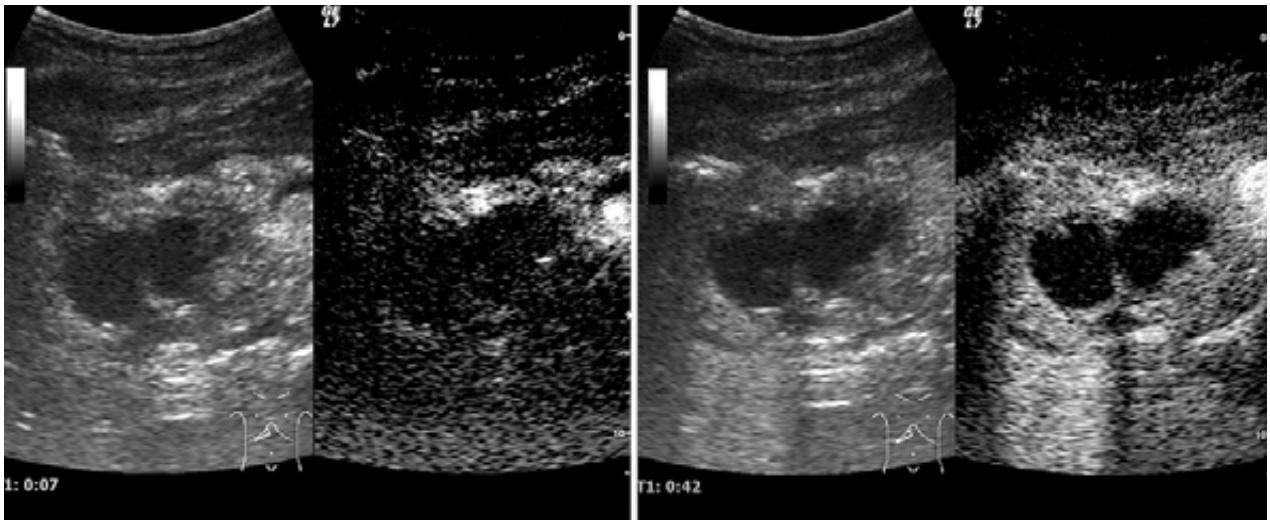


Fig 9. Pancreatic cystic tumor.

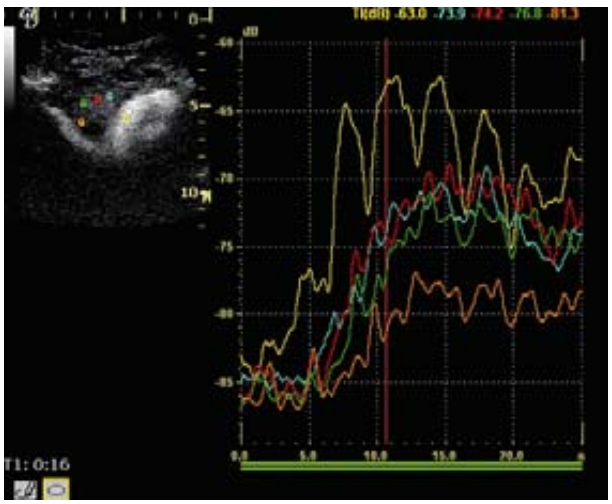


Fig 10. Intrapancreatic varices.

honeycomb pattern [35]. *Pancreatic pseudocyst* is better diagnosed at contrast administration with the enhancement of the surrounding parenchyma . Peripheral circulatory signal might by more enhanced in older pseudocysts [30, 36]. *Mucinous cystadenomas* are characterized by cystic areas separated by septa, with parietal nodules and papillary wall protrusions. The parietal nodules might not be detected by conventional US due to the rich mucinous content. Also, the differential diagnosis with large pseudocysts might be difficult. Following CEUS there is an increase of the parietal nodule and intracystic septa vascular signal intensity, allowing the differential diagnosis with pseudocysts (fig 9).

Mucinous intraductal papillary tumours are rarely detected at ultrasound. They appear as a non-homogeneous mass just below a dilated duct when they are large. CEUS might show the intraductal growth [31]. However, for most cystic masses CEUS is not sufficient for the differential diagnosis, CT and MRI being also required [11].

Intrapancreatic circulation abnormalities are rare. Among these, there are intrapancreatic varices caused by high portal hypertension. They appear as intrapancreatic hypoechogenic areas corresponding to the dilated vessels completely filled during CEUS venous phase (fig 10).

Diagnostic improvement and added value of the technique. The results of the studies on CEUS used for the diagnosis of pancreatic diseases are presented in Table 1,

Table 1. The contribution of CEUS in the diagnosis of pancreatic diseases.

Disease	Author	Sensitivity	Specificity	PPV	NPV
Acute pancreatitis	Rickes, 2002, 2006	82.85%	89.99%	95.97%	67.94
Pseudotumours	D'Onofrio, 2006	88.6%	97.8%	91.2%	97.8%
Adenocarcinoma	Rickes, 2002	87%	94%	89%	93%
Neuroendocrine tumors	Rickes, 2003	94%	96%	76%	99%
Cystic tumors	Rickes, 2004	95 – 100%	92 – 100%	95 – 100%	92 -100%

and they demonstrate high values of the sensitivity, specificity, positive and negative predictive values in the diagnosis of acute pancreatitis, pancreatic pseudotumors, adenocarcinoma, neuroendocrine tumors and cystic tumors. The liver examination in the late phase significantly increases the performance of the ultrasound technique in detecting liver metastases – competitive with CT and MRI.

The limits of CEUS in pancreatic disorders are due to the tumors with similar macroscopic appearance, such as cystic tumors. The technique is useful only when the interest area is also well delineated at conventional ultrasonography.

Conclusions

Contrast-enhanced ultrasonography of the pancreas represents a new development of conventional ultrasonography. Its main indications are the assessment of the solid tumors according to the enhancement pattern following the contrast agents injection, and the differential diagnosis between pseudotumoral chronic pancreatitis and pancreatic adenocarcinoma. The technique might improve the tumor staging through a more precise delineation of the resection margins. The neuroendocrine tumors pattern after the contrast administration is highly characteristic increasing the diagnostic accuracy. In acute pancreatitis the method is useful for the identification of the necrotic areas and for the differentiation of pancreatic pseudocysts from cystic neoplasms due to the vascularized septa.

Acknowledgements

The authors would like to thank Mrs. Sasz Jako for her contribution to this study.

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