Pancreatology

Pancreatology 2011;11(suppl 2):20–27
DOI: 10.1159/000323480

Published online: April 5, 2011

Transabdominal Contrast-Enhanced Ultrasonography of Pancreatic Cancer

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Key Words
Contrast-enhanced ultrasonography · Cystic pancreatic lesions · Pancreatic ductal adenocarcinomas · Pseudocysts · Ultrasonography

Abstract
Since its introduction, contrast-enhanced ultrasonography (CEUS) has significantly extended the value of ultrasonography (US). CEUS can be used to more accurately determine pancreatic lesions compared to conventional US or to characterize lesions already detectable by US. Thus, CEUS can aid in the differential diagnosis of pancreatic tumors. Using US contrast media, it is possible to visually detect microvessels in the majority of pancreatic ductal adenocarcinomas. Thus, the use of quantitatively evaluated transabdominal CEUS can help in the differentiation of patients with mass-forming pancreatitis from patients with pancreatic adenocarcinomas. In neuroendocrine pancreatic tumors, different enhancement patterns can be observed in relation to the tumor mass: larger ones show a rapid early enhancement sometimes combined with necrotic central structures, and smaller ones disclose a capillary-blush enhancement. Pseudocysts, the most widespread cystic lesions of the pancreas, are not vascularized. They do not show any signal in CEUS and remain entirely anechoic in all phases, while true cystic pancreatic tumors usually have vascularized septa and parietal nodules. In summary, CEUS is effective for differentiating solid pancreatic tumors in most cases. CEUS is safe and cost effective and can better discriminate solid from cystic pancreatic lesions, thereby directing further imaging modalities.

Introduction

Pancreatic carcinoma is an aggressive and devastating disease. It is characterized by invasiveness, rapid progression and profound resistance to treatment. Only 10–20% of patients with pancreatic cancer are diagnosed with tumors suitable for surgical resection, the only cure. Imaging of pancreatic tumors employs various techniques such as B-mode ultrasound (US), color Doppler sonography, endoscopic US, computed tomography (CT) and magnetic resonance imaging (MRI). Unfortunately, in up to 30% of patients determined to have a resectable tumor by preoperative imaging the lesion is deemed unresectable during surgery [1, 2].

US is usually the first approach to investigation due to its relatively low costs, noninvasiveness, and general availability. B-mode US allows for the identification of focal lesions, even small ones of ~1 cm in diameter, which

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are usually hypoechoic or cystic. Nevertheless, among these hypoechoic lesions, B-mode US is unable to discriminate adenocarcinomas from islet cell tumors or even rarer diseases, such as microcystic adenomas or focal pancreatitis. The advantages of CT and MRI include the ability to assess more lesion types during different dynamic phases.

Since its introduction in 1995, contrast-enhanced US (CEUS) has offered a wide array of diagnostic possibilities and has significantly extended the value of US. It has already proven to be a competent tool for evaluating the liver. However, other organs, particularly the pancreas, can be examined during continuous US imaging [3]. CEUS can be used to improve the visualization of pancreatic lesions compared to conventional US or to characterize lesions already detectable by US. CEUS provides high contrast and spatial resolution. Utilizing microbubbles, which represent an inherent contrast medium in the blood pool, perfusion of a tissue can be visualized without motion artifacts. Also, tumor enhancements can be seen more clearly by deleting background tissue signals and permitting dynamic observations in the same plane [3–5]. Together, these abilities make CEUS a sensitive imaging technique for estimating the vascularity of pancreatic lesions. Neoangiogenesis and residual tumors can be precisely studied to assess treatment response because CEUS can visualize tumor vascularization [4–9]. In addition, it has been reported that CEUS imaging is superior to helical CT regarding the identification of pancreatic tumor vascularization [7].

Using US contrast media, it is possible to visually detect microvessels in the majority of pancreatic ductal adenocarcinomas (PDACs). A previous study found a sensitivity of 95% for the detection of carcinomas [10]. However, using this technology, the subjective assessment of the degree of vascularization still remains problematic because the examiner must make a judgment based on a personal impression of brightness and contrast compared to the surrounding tissue. In addition, interindividual comparisons are not possible using this method. However, software algorithms can be used to quantify changes in contrast intensity. Thus, objective information can be obtained for the entire contrast-enhanced examination. In one of our recently published studies [11], the use of quantitatively evaluated transabdominal CEUS enabled the differentiation of patients with mass-forming pancreatitis from patients with pancreatic adenocarcinomas. Thus, CEUS can notably improve the accuracy of US, leading to a better recognition and description of pancreatic lesions [4–9]. Additionally, *endoscopic* CEUS has also been described as a useful tool for the differential diagnosis of pancreatic lesions in patients with chronic pancreatitis [12–14].

Compared to CT and MRI, the CEUS technique is simple and inexpensive. It is noninvasive and can be accomplished in an outpatient setting. It can also be performed on patients with renal failure or patients allergic to iodine contrast agents [3, 15]. Contrary to the contrast agents used in CT or MRI, US contrast agents are generally well tolerated. In a study of >23,000 applications of US contrast agents, only 29 cases of adverse events were reported, and these were mostly minor complaints such as rash or pruritus. Of all the adverse events, only 2 anaphylactic reactions were graded as serious, and both resolved completely without permanent damage [16]. Thus, CEUS is generally contraindicated in patients who may develop fatal anaphylactic reactions, e.g. in patients with a history of unstable cardiac conditions.

At present, the application of CEUS is not part of the regular diagnostic routine applied for pancreatic cancer. It may be a tool for evaluating pathologic changes in pancreatic cancer and may provide useful information for staging before treatment [17].

Technical Background

Harmonic imaging with low acoustic pressure US is necessary for CEUS. Immediately after the injection of a second-generation contrast medium, the dynamic surveillance of the contrast-enhanced phases begins (early arterial, arterial, pancreatic, and late). Sulfur hexafluoride microbubbles can enter the microcirculation because of their low mean diameter of 2.5 μm [3]. The enhancement peaks between 15 and 20 s after the injection of the contrast medium. Pancreatic parenchymography is earlier and shorter than that of the liver due to the absence of portal venous blood supply. Afterwards, there is a progressive washout of contrast medium, with a loss of gland echogenicity [3]. According to our previous research, the mean arrival time in healthy volunteers is 14 s; the time to reach peak intensity was measured at 22 s, and the maximum intensity was 5.3 dB on average [11]. These times can be considerably longer when measuring the contrast phase in pancreatic tumors or chronic pancreatitis. However, technical problems such as restricted image resolution of deep regions and poor sonographic imaging of the pancreas due to overlying abdominal gas or fat can often impair the contrast-enhanced evaluation of the pancreas [3, 5].