JOP. J Pancreas (Online) 2006; 7(6):584-592.

REVIEW

Contrast-Enhanced Ultrasound in the Diagnosis of Pancreatic Tumors

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Summary

Echo-enhanced ultrasound is a newly available imaging modality for the evaluation of pancreatic lesions. Neoplasms of the pancreas tend to have a characteristic vascularization pattern. Adenocarcinomas are often hypovascularized as compared to the surrounding tissue. On the other hand, neuroendocrine tumors are hypervascularized lesions. Masses associated with pancreatitis have a different vascularization pattern depending on the degree of inflammation and necrosis. Cystadenomas frequently show many vessels along fibrotic strands. Data from prospective studies have demonstrated that based on these imaging criteria, the sensitivity and the specificity of echo-enhanced sonography in diagnosing the degree of differentiation of pancreatic masses are equal to, or greater than, 85% and 90%, respectively. In conclusion, pancreatic tumors have a different vascularization pattern in echo-enhanced ultrasound. These characteristics can be used with high a diagnostic accuracy for differentiation.

Introduction

The most common pancreatic tumors are adenocarcinomas and pancreatitis-associated masses. Neuroendocrine lesions, cystic tumors and metastases to the pancreas occur less frequently. The differentiation of pancreatic tumors is important for therapeutic planning and for the evaluation of the prognosis but this difficult with current imaging techniques, even when a combination of various diagnostic procedures is employed. Although histology or cytology obtained from fine needle biopsy or surgery is the standard of reference, especially in the differential diagnosis between pancreatitis-associated lesions and adenocarcinomas, needle biopsy can produce false results due to sampling error. Endoscopic retrograde (ERCP) and magnetic resonance cholangiopancreatography (MRCP) are the current imaging standards for the differential diagnosis of pancreatic lesions [1, 2, 3, 4, 5]. With conventional transabdominal ultrasound, there are no characteristic findings for the differentiation of pancreatic masses and its diagnostic accuracy is less than 70% [6, 7, 8, 9]. Echo-enhanced ultrasound has been proposed as a valuable technique for the differentiation of liver lesions [10, 11, 12, 13, 14, 15]. We and others have demonstrated that echo-enhanced ultrasound is a valuable imaging method to evaluate pancreatic tumors [16, 17, 18, 19, 20]. In this review, we present a practical approach for the use of echo-enhanced sonography in the differential diagnosis of pancreatic masses.

Technical Aspects of Echo-Enhanced Ultrasound

All patients are first investigated by conventional sonography using a dynamic sector scanner. Special patient preparation is

not necessary. When using echo-enhanced sonography, the pulse inversion technique or the power-Doppler mode under the conditions of 2nd harmonic imaging are available. At present, the pulse inversion mode is used more frequently than 2nd harmonic imaging.

When performing echo-enhanced sonography with pulse inversion, 2.4 mL SonoVue® (Bracco Spa, Milan, Italy) are injected intravenously, and the mechanical index varies from 0.1 to 0.2 (low mechanical index procedure). The investigation can be done in real time and lasts approximately two minutes.

Echo-enhanced power Doppler sonography starts immediately after the injection of 4 g Levovist® (Schering AG, Berlin, Germany) at a 300 mg/mL concentration. Intermittent sweeps have to be carried out and the investigation lasts also approximately two minutes. One focus zone with depth adapted to the area of interest and a mechanical index of 0.8 to 1.3 (high mechanical index procedure) should be used.

Table 1. Criteria for pancreatic tumor differentiation with conventional ultrasound, unenhanced power Doppler sonography and echo-enhanced ultrasound [9, 16].

	B-mode sonography	Unenhanced power Doppler sonography	Echo-enhanced ultrasound
Ductal carcinoma	• low-echo pattern • lobulated margins • dilated Wirsung's duct • vascular infiltration • metastases	• no tumor vessels detectable	• poorly vascularized tumor • marginal tumor vessels
Pancreatitis (chronic and acute)	• low-echo pattern • lobulated margins • thrombosis • necrotic areas • dilated Wirsung's duct • calcifications	• vessels rarely detectable	• vascularization depending on inflammation and necrosis • acute edematous pancreatitis: hypervascularized • chronic pancreatitis: hypo-vascularized
Neuroendocrine tumor	• low-echo pattern • sharply delineated round margins • no dilated Wirsung's duct • vascular infiltration rare • metastases	• tumor vessels rarely detectable	• highly vascularized tumor
Cystadenoma	• small cystic areas (often <3 cm) • spoke-like pattern of fibrotic strands with small calcifications • no dilated Wirsung's duct	• no tumor vessels detectable	• highly vascularized tumor arteries along the fibrotic strands
Cystadenocarcinoma	• large cystic areas (often >5 cm) • solid areas • no dilated Wirsung's duct • metastases	• tumor vessels with chaotic pattern rarely detectable	• poorly and chaotic vascularized solid areas
Pseudocyst	• often shows echo-free pattern • sharply delineated wall • features of acute and/or chronic pancreatitis • signs of bleeding and/or calcifications • bowel infiltration is possible	• tumor vessels rarely detectable in “young cysts”	• “young cysts” (few weeks of age) often show a highly vascularized wall • “old cysts” (few months of age) often show a poorly vascularized wall
Metastasis of a renal cell carcinoma	• low-echo pattern • lobulated margins	• tumor vessels rarely detectable	• highly vascularized tumor
Lymphoma	• low-echo pattern • sharply delineated round margins • no dilated Wirsung's duct	• no tumor vessels detectable	• differently vascularized tumor masses

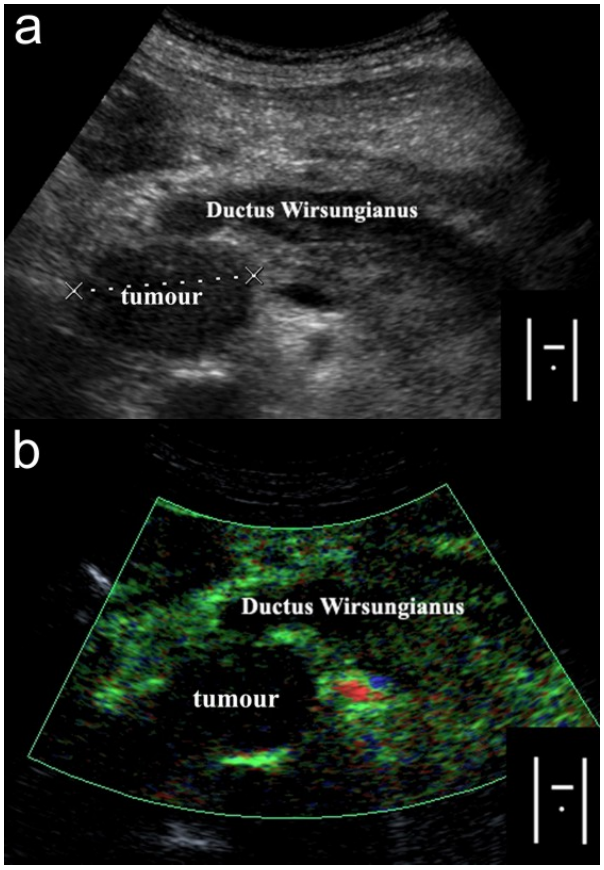

Figure 1. Pancreatic adenocarcinoma at conventional (**a.**) and echo-enhanced sonography (**b.**). **a.** Low-echo tumor with lobulated margins and dilatation of Wirsung's duct. **b.** Poorly vascularized lesion compared to the surrounding tissue.

Criteria for Pancreatic Tumor Differentiation

Criteria for the differentiation of pancreatic masses by conventional and echo-enhanced sonography have recently been published (Table 1) [9, 16].

- An adenocarcinoma presents at B-mode ultrasound with a low-echo pattern and lobulated margins. The Wirsung's duct is dilated (Figure 1a). At echo-enhanced sonography, the lesion is, in most cases, poorly vascularized (Figure 1b).
- In contrast to adenocarcinomas, neuroendocrine tumors and metastases of renal cell carcinomas show sharply delineated margins, and the Wirsung's duct is usually not dilated (Figure 2a). Hypervascularization after the injection of an echo-enhancer is a characteristic sign of these masses (Figure 2b).
- In particular, the differential diagnosis of adenocarcinomas and pancreatitis-associated masses is notoriously problematic since both tumors can appear as low-echo and lobulated lesions with dilatation of Wirsung's duct. The vascularization of pancreatitis-associated tumors depends on the degree of inflammation and necrosis. Acute edematous lesions are generally hypervascularized (Figure 3). On the other hand, necroses or chronic pancreatitis-associated masses are mostly hypovascularized.
- Cystic pancreatic neoplasms are rare. While serous microcystic adenomas are characterized by small cystic areas and highly vascularized fibrotic strands (Figure 4), cystadenocarcinomas consist of large cysts and poorly vascularized solid areas. Pseudocysts show an echo-free pattern and a sharply delineated wall. In cases of chronic

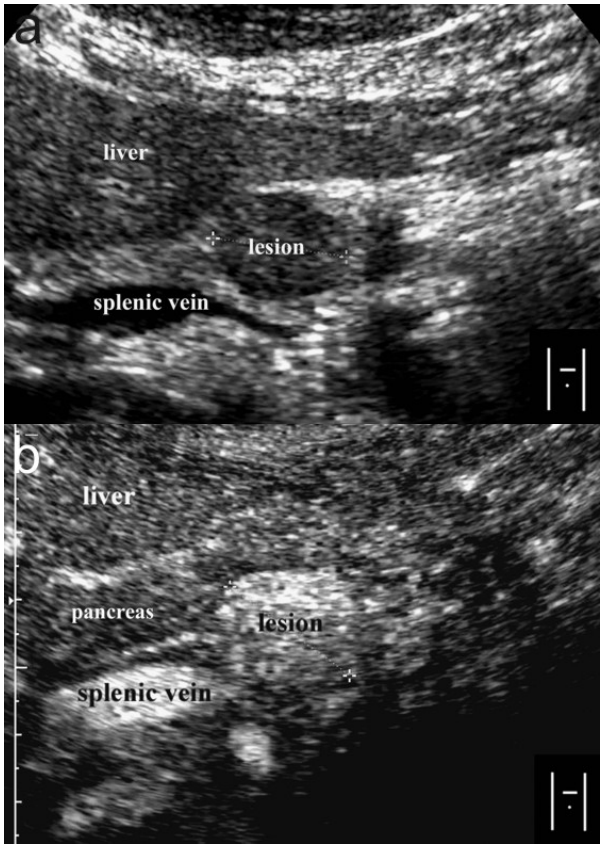

Figure 2. Pancreatic metastasis of a renal cell carcinoma at conventional (**a.**) and echo-enhanced sonography (**b.**). **a.** Low-echo mass with sharply delineated margins without dilatation of Wirsung's duct. **b.** Highly vascularized lesion compared to the surrounding tissue.

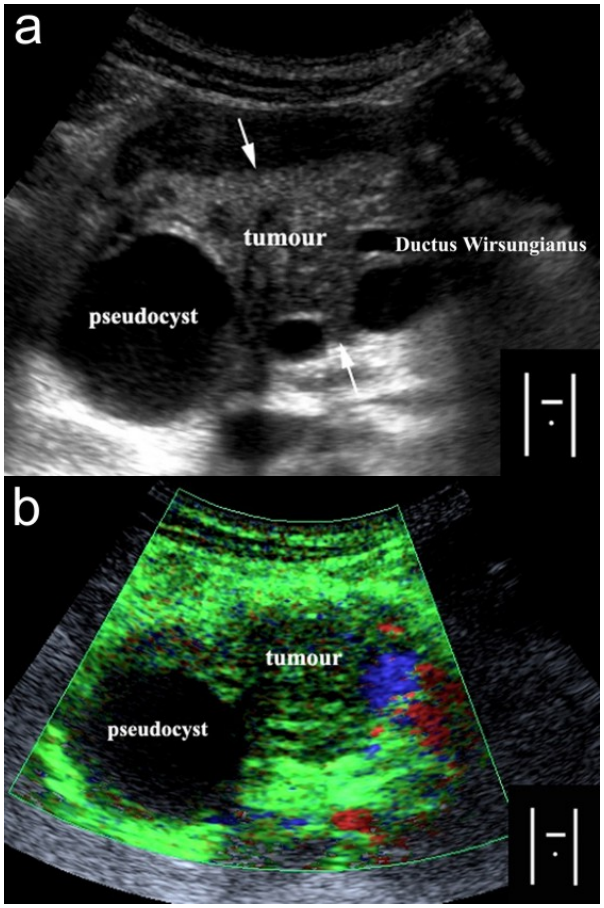

Figure 3. Pancreatitis-associated lesion at conventional (**a.**) and echo-enhanced sonography (**b.**). **a.** Lobulated mass (arrows) with a small pseudocyst. **b.** Highly vascularized lesion compared to the surrounding tissue.

pancreatitis, the remaining pancreatic parenchyma may display features of chronic inflammation such as calcifications and a dilated Wirsung's duct. After the injection of an echo-enhancer, the wall of the pseudocysts is highly ("young cyst") or poorly ("old cyst") vascularized.

Results of Echo-Enhanced Ultrasound in the Differentiation of Pancreatic Tumors

Several studies have demonstrated that echo-enhanced sonography is a valuable method

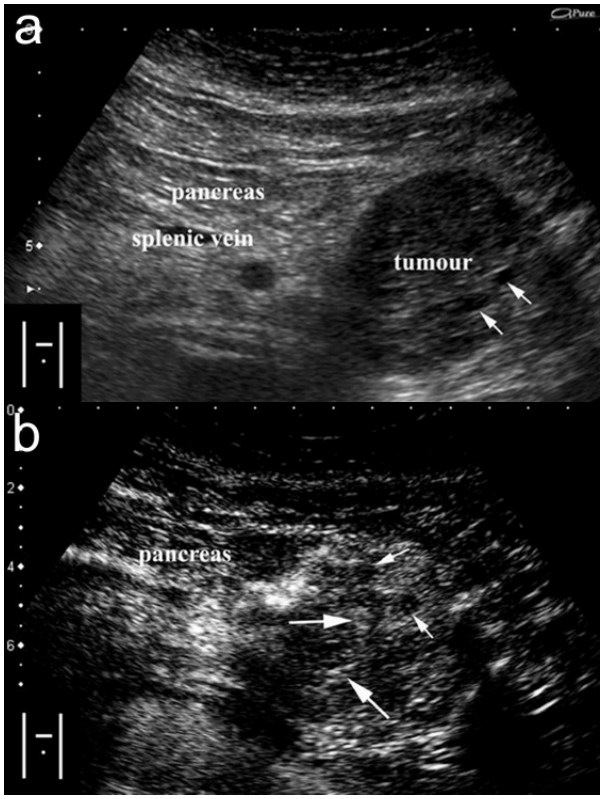

Figure 4. Serous cystadenoma at conventional (**a.**) and echo-enhanced sonography (**b.**). **a.** Tumor at the pancreatic tail with small cystic areas (small arrows) and thin fibrotic strands. **b.** Highly vascularized tumor arteries (large arrows) along the fibrotic strands.

for the evaluation of pancreatic lesions (Table 2) [16, 17, 18, 19, 20]. Similar to conventional ultrasound, operator dependency, flatulence, obesity, deep lesions, and tumors in the pancreatic tail are limitations of this procedure.

In a study published in 2002 [17], only 57% of the adenocarcinomas were correctly classified by conventional and unenhanced ultrasound. However, with echo-enhanced sonography, 87% of the masses could be differentiated (P=0.0001). Two out of 47 carcinomas were interpreted erroneously as pancreatitis-associated masses.

Table 2. Results of echo-enhanced sonography for the differentiation between pancreatic tumors.

Lesion	Sensitivity	Specificity	PPV	NPV
Adenocarcinoma [17] (137 patients investigated)	87%	94%	89%	93%
Pancreatitis [17] (137 patients investigated)	85%	99%	97%	94%
Neuroendocrine tumor [18, 19] (138 patients investigated)	94%	96%	76%	99%
Cystic tumor [20] (31 patients investigated)	95-100%	92-100%	95-100%	92-100%

Of the pancreatitis-associated tumors, 85% were diagnosed correctly by echo-enhanced sonography. Four out of 41 benign tumors were falsely classified as ductal carcinomas. All of them showed necrotic tissue at histology.

Another study showed good results of echo-enhanced ultrasound in the differentiation of neuroendocrine pancreatic tumors [18]. Table 2 demonstrates that, with this procedure, a sensitivity of 94% and a specificity of 96% was achieved. Other reports have confirmed these good results [19]. On the other hand, it was shown that the overall sensitivity of somatostatin receptor scintigraphy in the differential diagnosis of neuroendocrine pancreatic tumors is less than 55% [18].

Furthermore, a recently published study showed that echo-enhanced sonography can differentiate cystic neoplasms from pseudocysts [20]. However, one out of 10 cystadenomas was misdiagnosed as a cystadenocarcinoma and *vice-versa*. The morphological variability of these cystic lesions at conventional ultrasound and the difficulties in the evaluation of the vascularization of cystic masses seem to be responsible for the false results.

Discussion

There is no ideal diagnostic procedure to differentiate between pancreatic tumors. The gold standard is histology, obtained either through image-guided fine needle biopsy or surgery. However, especially when evaluating pancreatitis-associated lesions and adeno-carcinomas, needle biopsy can produce false negative results due to sampling error. ERCP is the standard for diagnostic imaging, but has an increased risk of complications, the most important being pancreatitis [21, 22]. MRCP (including magnetic resonance tomography) has a sensitivity (about 80%) and specificity (about 90%) similar to ERCP for detecting pancreatic cancer or chronic pancreatitis [1, 2, 3, 4, 5]. However, this procedure is expensive and available only in large medical centers. In some studies evaluating pancreatic tumor differentiation with computed tomography, endoscopic ultrasonography and positron emission tomography, sensitivities and specificities of more than 90% were observed [23, 24, 25, 26]. However, in these studies, only a small number of patients were investigated. In most cases, computed tomography and endoscopic ultrasonography are unable to differentiate between pancreatic tumors satisfactorily but may be the best methods to stage for resectability and to detect metastases [27, 28, 29].

There are no characteristic signs to differentiate between the various pancreatic lesions when using conventional trans-abdominal ultrasound. In particular, the differentiation of adenocarcinoma from chronic pancreatitis is notoriously problematic [9, 16].

Some years ago, the angiographic vascular-ization pattern was reported to be helpful to differentiate between pancreatic tumors [30, 31, 32]. Whereas ductal carcinomas are characterized by their hypovascularization, neuroendocrine tumors were found to be hypervascularized. However, the diagnostic accuracy of angiography is low because it is impossible to investigate the macroscopic tumor features.

Unenhanced power Doppler sonography also allows the investigation of the vascularization pattern of tumors by ultrasound. For instance, there are good results for diagnosing the degree of differentiation of hepatocellular carcinomas using this method [13, 33]. However, in the differential diagnosis of pancreatic masses, no diagnostic advantage of this method was observed in comparison to conventional ultrasound. This might be explained by the low sensitivity of unenhanced power Doppler sonography for detecting low blood flow velocity or small vessels and the existence of multiple tissue artifacts [9, 10].

The sensitivity of power Doppler sonography can be increased by echo-enhancers, such as Levovist®. This preparation consists of microbubbles of air which enhance the Doppler signal at 20-30 dB [10, 34, 35]. With echo-enhanced power Doppler sonography, however, the signal intensity from flowing

blood is much lower as compared to that of moving solid structures, such as tissue movements. Thus, 2nd harmonic imaging was developed to overcome these difficulties. This method is based on the property of microbubbles to resonate and emit harmonic waves in an ultrasound field with a frequency of 1-5 MHz. If the harmonic frequency is to be detected at twice the transmitted frequency, the procedure is called 2nd harmonic imaging. Tissue particles have fewer 2nd harmonic waves than microbubbles; therefore, the signals of echo-enhancers become more distinguishable [10].

Recently, the new contrast agent SonoVue® has been used more frequently for echo-enhanced sonography. Furthermore, 2nd harmonic imaging has partially been replaced by the pulse inversion imaging technique. With this new procedure, more favorable results can be achieved than with 2nd harmonic imaging. With 2nd harmonic imaging, it is impossible to separate the transmitted and the received harmonic signal completely due to limited bandwidth. However, pulse inversion imaging avoids these bandwidth limitations by using characteristics specific to the microbubble vibrations to subtract rather than filtering out the fundamental vibrations. Because this imaging transmits two reciprocal pulses, leading to the subtraction of fundamental signals, it allows the use of broader transmission and receiving bandwidths for improved resolution and can provide increased sensitivity to contrast [36]. However, the comparative results of large prospective studies are lacking.

Characteristic signs of pancreatic tumors at echo-enhanced sonography have been published [9, 16]. Similar to their angiographic features, ductal carcinomas and the solid areas of cystadenocarcinomas were found to be hypovascularized. In contrast, neuroendocrine tumors and the solid parts of cystadenomas are mostly hypervascularized. Pancreatitis-associated masses show different patterns of vascularization depending on inflammation, fibrotic scars, and the extent of necrosis [9, 16].

The results of the studies of Table 2 demonstrate that, with the combination of echo-enhanced sonography and 2nd harmonic or pulse inversion imaging, a higher percentage of ductal carcinomas, pancreatitis-associated masses, and neuroendocrine and cystic tumors can be classified correctly.

However, conventional ultrasound, unenhanced and echo-enhanced sonography must not be used as separate imaging techniques. Conventional ultrasound is the basic sonographic method and tumor differentiation is hardly possible with echo-enhanced ultrasound alone. Echo-enhanced sonography offers more diagnostic criteria than conventional ultrasound alone. Therefore, all sonographic procedures should be combined.

Echo-enhanced sonography has a similar accuracy in diagnosing pancreatic carcinoma as compared to ERCP and MRCP [1]. With respect to the differentiation of pancreatitis-associated tumors, the sensitivity of echo-enhanced power Doppler sonography seems to be slightly lower while the specificity is somewhat higher as compared to ERCP and MRCP [1]. Necroses and fibroses are major problems for the differential diagnosis of ductal carcinomas and pancreatitis-associated masses. Since both tissues are not vascularized, necrotic pancreatitis may be falsely interpreted as ductal carcinoma. On the other hand, it is possible to find inflammation in the surrounding tissue of an adenocarcinoma leading to the suspicion of pancreatitis.

Echo-enhanced sonography displayed, above all, a high sensitivity and specificity in differentiating between neuroendocrine tumors. Whereas endoscopic ultrasonography is of great value for localizing neuroendocrine pancreatic tumors [37], echo-enhanced sonography could become the new standard of reference for their differentiation by using imaging procedures.

However, there are reports of false results involving echo-enhanced sonography due to hypervascularized metastases of a renal cell carcinoma. Hypervascularization of metastases from renal cell carcinomas has

also been observed in angiographic studies [38, 39]. This phenomenon is based on a well-vascularized stroma.

Cystic pancreatic masses are often associated with multiple artifacts at sonography. Although it is difficult to investigate the vascularization pattern of the solid tumor parts, the present results demonstrate the higher diagnostic value of echo-enhanced sonography as compared to conventional or unenhanced ultrasound [40]. However, MRCP seems to be more useful in the differential diagnosis of cystic pancreatic tumors [41, 42].

Furthermore, a recently published study showed that echo-enhanced sonography also produces excellent results in the staging of acute pancreatitis severity [43]. This procedure is cheaper and has fewer contraindications than computed tomography.

The successful treatment of pancreatic tumors requires a highly sensitive and specific diagnostic procedure. Echo-enhanced sonography is a powerful tool which may satisfy this requirement. New ultrasound procedures such as pulse inversion and vascular recognition imaging offer higher imaging quality. However, histology is the standard of reference for the definitive diagnosis of pancreatic lesions.

Keywords Cell Differentiation; Pancreatic Neoplasms; Ultrasonography

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