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Contrast-Enhanced Ultrasonography Better Identifies Pancreatic Tumor Vascularization than Helical CT

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Key Words
Pancreatic tumors · Contrast-enhanced ultrasonography · Helical computed tomography · Angiogenesis · Microvessel density

Abstract
Background: Contrast-enhanced ultrasonography (CEUS) is a recently introduced field of ultrasonography (US). To assess the ability of CEUS to identify the vascularization of solid pancreatic tumors in comparison to helical CT. ***Methods:*** Forty-two resected pancreatic tumors, found at US, were studied with CEUS and helical CT. The tumor enhancement at CEUS was scored in comparison to the baseline aspect of the lesion and/or the extralesional pancreatic parenchyma together with the adjacent vessels during the dynamic study. All the lesions underwent pathological examination using H&E stains and CD34 markers with an evaluation of the microvessel density (MVD). The correlation of CEUS and helical CT with the MVD of the lesions was established with Spearman's test. ***Results:*** The correlation of CEUS with the MVD of the lesions was significantly superior (Rs = 0.914; $p < 0.0001$) to that of helical CT (Rs = 0.635; $p < 0.0001$). ***Conclusions:*** CEUS is better than helical CT in the identification of the vascularization of solid pancreatic tumors. CEUS, when the pancreatic gland is optimally visualized, should be therefore considered a complementary imaging modality in the characterization of pancreatic tumors. CEUS can be a valid onco-imaging modality for quantifying tumoral vascularization in a noninvasive and accurate way.

Introduction

Angiogenesis is the formation of new microvessels [1–3]. Microcirculation is the network of vessels with a diameter smaller than 100 μm, thus below the resolution power of angiography [4]. The progressive trespassing of this limit depends on the technological development of imaging techniques and modalities. Identification and characterization of tumors may depend on the correct identification of degree and features of vascularization at imaging. The necessity of imaging techniques that are able to quantify tumoral vascularization in a noninvasive, accurate and repeatable way is also a consequence of the development of anti-angiogenic therapies [5, 6].

Contrast-enhanced ultrasonography (CEUS) is a recently introduced field of ultrasonography (US). Second-generation contrast media are stable microbubbles of gas with a diameter around 3 μm [7]. Nondestructive low mechanical index enhanced ultrasound with the continu-

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ous observation of the dynamic phases allows real time evaluation of tumoral perfusion. Technological developments have improved the spatial resolution of ultrasound [8]. CEUS with the use of microbubbles, a blood-pool contrast medium, could therefore play an important role in onco-imaging. Through pathological analysis and correlation, we compared CEUS and contrast-enhanced helical CT in the assessment of the vascularization of solid pancreatic lesions.

Materials and Methods

In the course of 2003 we studied prospectively with CEUS and helical CT 111 solid pancreatic lesions found at basal US. Of these lesions 42 were then resected and pathological examination of the resected specimens was performed, with histological diagnosis and quantification of tumoral vascularization. A prospective comparison between imaging (CEUS and helical CT) and pathology in the identification of the vascularization of pancreatic tumors was thus possible. The resected lesions were located at the pancreatic head or in the uncinate process in 29 cases and in the pancreatic body-tail in 13 cases. The resected lesions' dimensions ranged from 1.5 to 11 cm. The resected pancreatic tumors were 39 primitive neoplastic lesions of the pancreas (11 ductal adenocarcinomas well/moderately differentiated, 4 poorly differentiated adenocarcinomas, 1 acinar cell carcinoma, 2 solid and papillary epithelial tumors and 21 endocrine tumors) and 3 secondary neoplastic lesions (2 metastases from renal carcinoma and 1 from melanoma).

All patients with a solid pancreatic mass found at baseline US underwent CEUS and helical CT within 2 weeks. All CEUS exams were performed on the same diagnostic ultrasound system, Sequoia 512 6.0 (Acuson, Mountain View, Calif., USA) and recorded on VHS and magnetic-optic disk. Harmonic microbubble-specific imaging with low acoustic ultrasound pressure (2–4 MHz Coherent Contrast Imaging; Mechanical Index <0.2; 12–13 frames/s) was used. A 2.4-ml bolus of contrast medium, SonoVue® (Bracco, Milan, Italy), was injected i.v. followed by a 5-ml bolus of saline solution. Insonation of the pancreatic lesion was continuous with dynamic observation of the shift from the unenhanced phase to the contrast-enhanced phase. The definition of the arterial phase was possible when observing hyperechogenity of the aorta or other big perilesional arteries. Venous phase was defined when the splenomesenteric-portal tree became hyperechoic. All CT studies were performed with a Somatom Plus 4 (Siemens; Erlangen, Germany) helical scanner, with a scanning time of 0.75 s, collimation of 5 mm and table feed of 7.5 mm per gantry rotation. Images were reconstructed at 5-mm intervals. Patients received 130 ml of intravenous contrast medium iopromide (Ultravist 370, Schering AG, Germany) administered by EnVision CT injector (Medrad, USA) at a rate of 4 ml/s. Contrast-enhanced phases were obtained with a start delay of 30 s for the pancreatic phase and 80 s for the venous phase.

All CEUS exams were performed by the same radiologist resulting technically adequate in all cases. Lesional enhancement was evaluated with a separate and independent review of the recorded exam by two radiologists; any disagreement was solved by means of consensus after discussion. For the evaluation of lesional enhancement we considered the baseline aspect of the tumor and/or the extralesional pancreatic parenchyma together with the adjacent vessels during the dynamic study. The pancreatic tumors studied were then classified at CEUS into 4 groups according to the lesional enhancement in the arterial contrast-enhanced phase. The 4 categories of enhancement in the arterial phase at CEUS were: hypoechoic lesions almost without enhancement = 1; isoechoic lesions with enhancement similar to that of the adjacent parenchyma = 2; slightly hyperechoic lesions with enhancement slightly superior to that of the adjacent parenchyma = 3; hyperechoic lesions with enhancement similar to that of arteries = 4.

The lesional enhancement on CT scans was reviewed independently by two radiologists, who were blinded to the results of US, and any disagreement was solved by means of consensus after discussion. For the evaluation of lesional enhancement we considered the basal aspect of the tumor and the extralesional pancreatic parenchyma together with the adjacent vessels in the enhanced phases. Pancreatic tumors in our series were then classified at CT into 4 groups according to the enhancement in the pancreatic phase. The 4 categories of enhancement in the arterial phase at CT were: hypodense lesions almost without enhancement = 1; isodense lesions with enhancement similar to that of the adjacent parenchyma = 2; slightly hyperdense lesions with enhancement slightly superior to that of the adjacent parenchyma = 3; hyperdense lesions with enhancement similar to that of arteries = 4.

Pathological examination was performed on all lesions by the same pathologist, blinded to the results of CEUS and helical CT. In our protocol, histological sections were prepared with H&E stains and with an endothelial immunohistochemical marker (CD34). Histological sections were examined first with low magnification (20–40×). The vessel counts were assessed in the three areas of the tumor with the highest number of capillaries and small venules, as described by Kuwahara et al. [9] and Tanigawa et al. [10]. All lesions were evaluated qualitatively and quantitatively for lesional vascularization. Qualitative evaluation of the lesional vascularization was based on the ratio between fibrosis or desmoplastic reaction in the lesion and size and organization of intralesional vessels related to the architecture of the neoplastic tissue, which is a consequence of the histotype. Quantitative evaluation of the lesional vascularization was performed comparing the number and size of the lesional vessels to that of the perilesional pancreatic parenchyma present in the resected specimen. Considering qualitative and quantitative features together, a mean vascular density value was assigned to each lesion from the comparison with the adjacent pancreatic parenchyma, whose vascularization grade was arbitrarily chosen as 2 in a range from 1 to 4. Lesions with less vessels were assigned a numeric value of 1. Lesions with slightly or frankly more vessels were assigned values of 3 or 4, respectively. We therefore classified the pancreatic lesions into 4 groups: lesions with less vascularization than extralesional pancreas = 1; lesions with vascularization equal to that of extralesional pancreas = 2; lesions with vascularization slightly superior to that of extralesional pancreas = 3; lesions with vascularization markedly superior to that of extralesional pancreas = 4.

The ability of imaging (CEUS and helical CT) in identifying the vascularization of solid pancreatic lesions was assessed calculating the correlation coefficient (Rs) between enhancement categories at imaging and vascularization groups at pathology by using Spearman's test. Comparison between imaging (CEUS and helical CT) and pathology was possible for all the resected tumors (fig. 1). Therefore 42 comparisons were performed.