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Contrast-enhanced sonography *versus* biopsy for the differential diagnosis of thrombosis in hepatocellular carcinoma patients

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Abstract

AIM: To clarify which method has accuracy: 2nd generation contrast-enhanced ultrasound or biopsy of portal vein thrombus in the differential diagnosis of portal vein thrombosis.

METHODS: One hundred and eighty-six patients with hepatocellular carcinoma and portal vein thrombosis underwent in blinded fashion a 2nd generation contrast-enhanced ultrasound and biopsy of portal vein thrombus; both results were examined on the basis of the follow-up of patients compared to reference-standard.

RESULTS: One hundred and eight patients completed the study. Benign thrombosis on 2nd generation contrast-enhanced ultrasound was characterised by progressive hypoenhancing of the thrombus; in malignant portal vein thrombosis there was a precocious homogeneous enhancement of the thrombus. On follow-up there were 50 of 108 patients with benign thrombosis: all were correctly diagnosed by both methods. There were 58 of 108 patients with malignant thrombosis: amongst these, 52 were correctly diagnosed by both methods, the remainder did not present malignant cells on portal vein thrombus biopsy and showed on 2nd generation contrast-enhanced ultrasound an inhomogeneous enhancement pattern. A new biopsy during the follow-up, guided to the area of thrombus that showed up on 2nd generation contrast-enhanced ultrasound, demonstrated an enhancing pattern indicating malignant cells.

CONCLUSION: In patients with hepatocellular carcinoma complicated by portal vein thrombosis, 2nd generation contrast-enhanced ultrasound of portal vein thrombus is very useful in assessing the benign or malignant nature of the thrombus. Puncture biopsy of thrombus is usually accurate but presents some sampling errors, so, when pathological results are required, 2nd generation contrast-enhanced ultrasound could guide the sampling needle to the correct area of the thrombus.

Key words: Hepatocellular carcinoma; 2nd generation contrast enhanced ultrasound; Contrast enhanced sonography; Malignant thrombosis; Portal vein biopsy

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INTRODUCTION

About 20% of patients at first access visit to a specialized centre for the care of hepatocellular carcinoma (HCC)[1] are in need of differential diagnosis between be-

nign portal vein thrombosis (PVT) or malignant thrombosis. The nature of the thrombus can have a significant impact on treatment. In particular, because the prevalence of tumor recurrence is nearly 100%, patients who have HCC and proven neoplastic vascular thrombus are not candidates for any treatment[2-5]. Malignant PVT can occur in patients with cirrhosis, with or without the presence of parenchymal HCC, because there is the possibility of intravascular first growth of this neoplasm[6]. Thrombi have been studied in an effort to determine imaging characteristics that could be used to distinguish benign from malignant thrombi[7-11]. Unfortunately, the imaging characteristics tend to overlap, in particular on computer tomography (CT) or magnetic resonance imagine (MRI) exams only the feature of thrombus-tumor continuity is widely accepted as a reliable indicator of thrombus malignancy[12,13]. In patients where percutaneous ablation of HCC is the therapy of choice, the technique of reference throughout the world for differentiating benign from malignant PVT is percutaneous fine needle biopsy (FNB) of the thrombus[14]. Given the obvious clinical utility of a reliable non-invasive technique for diagnosis of malignant PVT, the limitation of previous imaging studies and an opportunity at our institutions to perform a reasonably large prospective study with cytopathologic correlation in all patients, we undertook an investigation to compare Contrast-Enhanced Sonography (CEUS) and portal vein FNB of thrombus in differentiating benign from malignant thrombosis.

MATERIALS AND METHODS

The study protocol which was fully concordant with ethical principles of the Declaration Helsinki was approved by the institutional ethic committee. A written informed consent was obtained from each patient.

Patients

From January 2001 to February 2006, we enrolled consecutively 256 cirrhotic patients with HCC and PVT (Table 1). The major part of these patients were not eligible for surgical resection/liver transplantation, the others refused intervention. We restricted analysis only to patients without direct contiguity between the thrombus and HCC and considering also the patients drop out on follow-up we completed the study in 108 patients. Clinical and ultrasonography (US) details of these patients are displayed in Table 2.

Study design

Diagnosis of HCC was made according to the guidelines drawn up the Barcelona 2000 EASL Conference[15]. These guidelines suggest that in a liver cirrhosis setting HCC may be diagnosed by coincidental findings in at least two imaging modalities (spiral CT and Doppler US or MRI) that should reveal arterial hypervascularity or in the case of combined criteria (spiral CT with alfa-fetoprotein levels > 400 ng/mL). US guided biopsy should be performed in those cases in which the above-mentioned criteria are not satisfied[15]. Pathological diagnosis of HCC was made according to the International Working Party criteria[16]. The thrombi were detected on routine sonographic and CT examination. Spiral CT was performed in a range of one month before or after color Doppler US. In patients after diagnosis of HCC, in order to characterize PVT, we performed both CEUS and portal FNB; according to the results of portal FNB patients were evaluated for potential percutaneous ablation of HCC. Study design is displayed in Figure 1. Patients underwent first CEUS then portal FNB on the same occasion carried out by two separate operators; the operator that performed PVT FNB was blinded to the results of CEUS. Patients without malignant cells on FNB underwent percutaneous treatment; the others underwent supportive care. Results of baseline CEUS were evaluated in blind fashion on the basis of the evolution

Table 1 Enrollment design

Contents	
Inclusion criteria	Presence of one to three focal HCC Presence of intra-vascular[1] portal vein thrombosis Child-Pugh class A or B
Patients initially enrolled	Men: 190 Women: 66
Excluded for US evidence direct HCC portal vein invasion	70
Drop out on follow-up	78 (42%)
Died	30
Liver could not be adequately visualized	9
Patients studied	Mean age: 66 ± 6 Men: 82 Women: 26

[1]Not US features of infiltration of perivascular parenchyma: intact vessel wall.

Table 2 Principal clinical/ultrasound features of patients

Clinical data	Results
Child A/B	44/64
Etiology	
HCV related	58
HBV related	23
Alcohol related	12
Mixed etiology	15
Number of HCC nodules	
Single nodule	10
Median size	44 mm (range 40-75 mm)
Two nodules	22
Median size	41 mm (range 33-68 mm)
Three nodules	76
Median size	39 mm (range 32-67 mm)
Topography of portal vein thrombosis	
In right or left but not in the main portal vein	80 (74%)
In main, right and left portal vein	14 (13%)
In right or left and main portal vein	12 (11%)
In main portal vein	2 (1.8%)
Complete or incomplete vessel occlusion of on power-color-Doppler	
A complete occlusion of the portal vessel	99 (91%)
Incomplete thrombosis lumen	9 (9%)

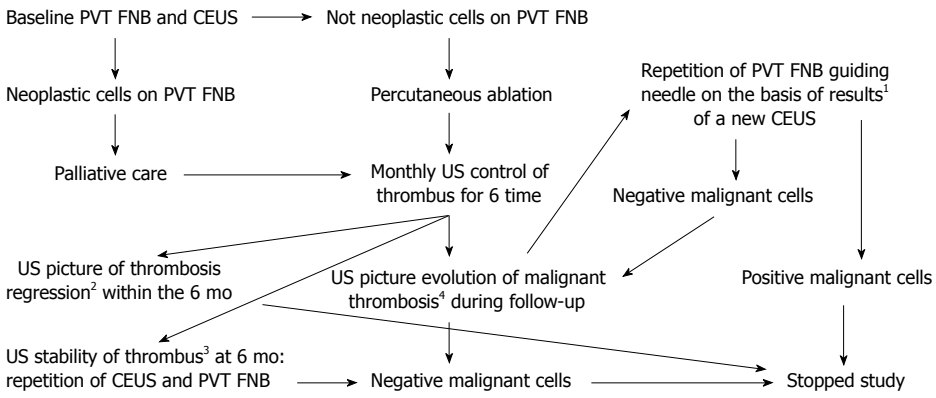

Figure 1 Study design. PVT FNB: Portal vein thrombus fine needle biopsy; CEUS: 2nd generation Contrast-Enhanced US (CEUS) of thrombus; [1]Guiding needle on portion of thrombus showing on CEUS precocious iso or hyperenhancement pattern; [2]No increase in size and distribution with preservation of vessel wall or recanalization/shrinkage, or disappearance of a PVT within the 6 mo of follow-up were accepted as proof of a benign portal vein thrombus; [3]No change in feature of thrombus and in the diameter of the segment of involved vein at 6 mo of follow-up; [4]Increase in size with infiltration of perivascular parenchyma and interruption of vessel wall was US features indicative of malignant thrombosis.

of thrombus on follow-up and were not decisive for the therapeutic management of patients. All patients after CEUS and PVT FNB were followed up for 6 mo; they underwent monthly US examination by an operator that was blinded to CEUS and PVT FNB initial results. We considered as the reference standard of benign or malignant thrombosis the US evolution of thrombus in combination with concordant cytology on new PVT FNB: i.e. no increase in size and distribution with preservation of vessel wall or recanalization/shrinkage, or disappearance of a PVT within the sixth months of follow-up were accepted as proof of a benign portal vein thrombus. However, in cases of stability of thrombi with no change in diameter of the segment of involved vein at 6 mo of follow-up, patients were resubmitted to CEUS and PVT FNB; in absence of malignant cells at this cytological examination, thrombus was definitively considered benign. Our reference standard of malignant thrombosis was increase in size on US, with or without infiltration of perivascular parenchyma and interruption of vessel wall at any time point during the follow-up. In the presence of such evolution of the US picture, CEUS and PVT FNB were repeated with guidance of the needle biopsy to thrombus areas with enhancing pattern allowing for the search for malignant cells; in presence of these, patients stopped the follow-up and thrombus was definitively considered malignant. Patients that died on follow-up without definitive diagnosis were considered drop outs. Specimens were obtained with a 22-Gauge Chiba needle in all patients; needles are manufactured with a removable occlusive stylet. The same biopsy technique described by others[14] was used in all patients. A positive result was considered if the biopsy specimen contained hepatocytes that had malignant features.

Baseline and contrast-enhanced harmonic ultrasound

An Aloka-Prosounds-5500-model equipped with a multifrequencies 2-6 MHz sector probe, was used. Contrast-enhanced imaging was performed according to the protocol used for the Bracco-SonoVue preclinical trial[17]. Examination was performed with low acoustic power (mechanical index under 0.01). SonoVue (BR1; Bracco, Milan, Italy)[18,19] consisted of sulfur-hexafluoride (SF_6) vapor-filled and phospholipid-stabilized microbubbles with a diameter uniformly smaller than 8 μm; these microbubbles circulate in the intravascular space crossing pulmonary and systemic capillary circulation[20,21]. 2.5 mL of contrast-agent were administered for each patient. Thanks to its ability to avoid destruction of bubbles, the low mechanical index technique allows identification of the entire vascular phase of contrast agent perfusion, consisting of the arterial phase (15-30 s after injection of agent), the portal phase (30-60 s after injection of agent) and the late parenchymal phase[22-24]. Positive arterial enhancement of the thrombus was defined as a greater hyperechogenicity of the vascular bed-occupying lesion in comparison to the surrounding liver parenchyma detected during the arterial phase. Two independent highly experienced readers firstly performed off-site assessments of the videotapes in a computer-generated randomised order. The readers were blinded to all clinical and pathological information as to the nature of the analysed thrombi.

Statistical analysis

Sensitivity, specificity, positive and negative predictive values of CEUS and PVT FNB were obtained for diagnosis of the nature of the thrombus; we considered as reference standard the US picture evolution of thrombus on follow-up, with a new PVT FNB as above decrypted accordingly to obtain definitive cytological confirmation.

RESULTS

On follow-up we identified 58 of 108 patients (53.7%) with malignant thrombosis and 50 (46.3%) with benign thrombosis. Figure 2 displayed results of combined tests: in 50 of 56 patients without malignant cells on first PVT FNB, benign PVT was characterized on CEUS by a diffuse homogeneous hypoenhancing pattern and this appearance was persistent compared with the adjacent liver, also during late phase (Figure 3A-C). In the follow up of

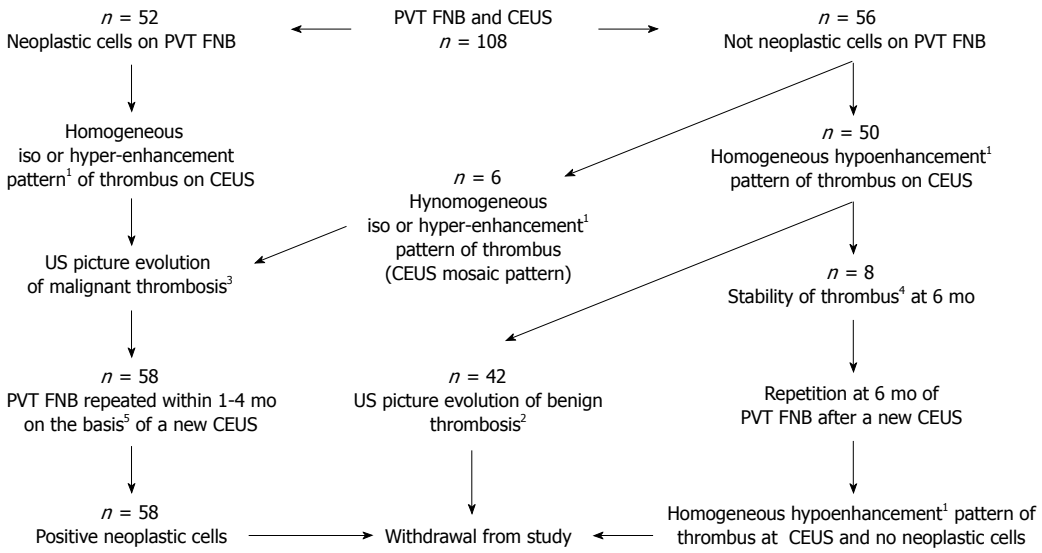

Figure 2 Summary of combined test results. [1]Iso, hyper, or hypoenhancement pattern of thrombus compared to the surrounding parenchyma; [2]Reference standard of benign thrombosis is a US evidence of evolving thrombus: no increase in size or distribution with vessel wall preservation or recanalization/shrinkage, or disappearance of a PVT within the 6 mo of follow-up were accepted as evidence of a benign portal vein thrombus; [3]Us image of evolution, indicating malignant thrombosis: increase in size with infiltration of perivascular parenchyma and interruption of vessel wall was US features of malignant thrombosis; [4]No change in thrombus image and in the diameter of the segment of vein involved at 6 mo of follow-up; [5]PVT FNB were repeated guiding the needle to the thrombus territories with enhancing pattern.

these patients we observed 16 spontaneous disappearances of thrombi after treatment of HCC, 26 recanalization with shrinkage of thrombi and 8 cases of stability of thrombi with no change in diameter of the segment of involved vein. These benign PVT patients were resubmitted to CEUS and PVT FNB at 6 mo with the same combined results as at the start (Figure 2). In 6 patients of 56 without malignant cells on FNB (false negative on PVT FNB), CEUS showed no homogeneous arterial enhancement of some small portions of thrombus. On follow-up the thrombus of these patients showed intravascular spread with growth in maximal diameter of the involved segments of the portal branch from a mean of 8 mm to a mean of 14 mm, with interruption of the vessel wall in 3 patients; we repeated CEUS and guided a new portal FNB to areas of thrombus that showed an enhancing pattern, obtaining positive results for malignant hepatocytes. The islands of neoplastic tissue were located at baseline CEUS as corresponding to the anterior wall of right branch in 1 case, corresponding to and mainly in the centre of the vessel in 3 cases, and corresponding to the posterior wall of left portal branch in 2 cases; they measured between 9 mm and 15 mm in length. In all 6 cases there was a complete thrombosis, involving the portal trunk and both branches, which measured in length between 18 mm and 27 mm. We retrospectively called the CEUS appearance of these cases "mosaic picture" of neoplastic thrombus (Figure 4A and B).

There were 52 patients (Figure 2) with the presence of malignant cells on the baseline portal FNB: these showed on follow-up growth in diameter and intravascular spread of PVT within 1-4 mo. The repetition of PVB FNB in all these patients, with an US picture evolution of malignant thrombosis on the basis of a new CEUS, always confirmed the diagnosis (not false-negative). Typical malignant PVT had an unequivocal appearance at CEUS: during the arterial phase intense and diffuse homogeneous contrast enhancement (Figure 5A and B) was seen, followed or not by a washout of contrast material from the thrombus; the appearance was iso or hyperechoic in arterial phase and hypo or isoechoic during the late phase (Table 3). Sensitivity, specificity, positive and negative predictive value of PVT FNB and CEUS were the same for both, respectively: 89.6%, 100%, 100%, 89.2%. These

Table 3 Contingent tables

Group	Results
Patients studied on follow-up	108
Malignant thrombosis	58 (53.7%)
Benign thrombosis	50 (46.3%)
Presence of neoplastic cells on PVT FNB[1]	
True positive	52 (48.1%)
False positive	0
Not neoplastic cells on baseline PVT FNB	
False negative	6[2] (5%)
True negative	50 (46.3%)
Iso-hyper-enhancement pattern[1] on CEUS and mosaic pattern	
True positive	58
Precocious isoenhancement pattern	21
Precocious hyperenhancement pattern	31
Mosaic pattern[3]	6
False positive	0
Hypoenhancement patternc on CEUS	
False negative	0
True negative	50 (46.3%)

Sensitivity, specificity, positive and negative predictive value of CEUS: All 100%. [1]Iso-hyper-hypoenhancement pattern of thrombus respect to surround parenchyma; [2]False negative patients on portal vein FNB were the same with mosaic pattern on CEUS; [3]Hynomogeneous iso-hyperenhancement of thrombus.

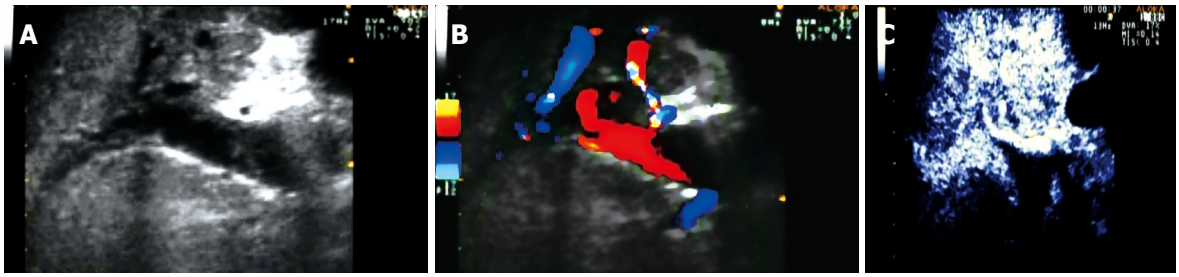

Figure 3 Benign thrombus. A: On sonography lumen of portal vein is partially filled with hypoechoic material representing occlusive thrombus; B: Color Doppler ultrasound reveals color signals only within a portion of portal lumen; C: Contrast-enhanced sonography scan during portal phase reveals uniformly non-enhancing area within portal vein, perfectly reproducing the benign thrombus.

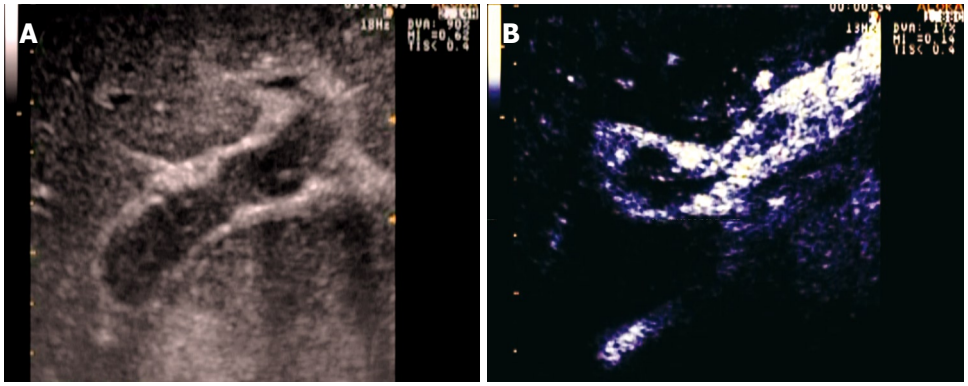

Figure 4 Malignant mosaic thrombus. A: Sonography scan reveals isoechoic area within portal lumen representing thrombus; B: Contrast enhanced sonography scan during late arterial phase reveals thrombus as predominantly enhancing area, indicative of arterial neovascularization (malignant thrombosis) with some non-enhancing areas of the thrombus (mosaic pattern).

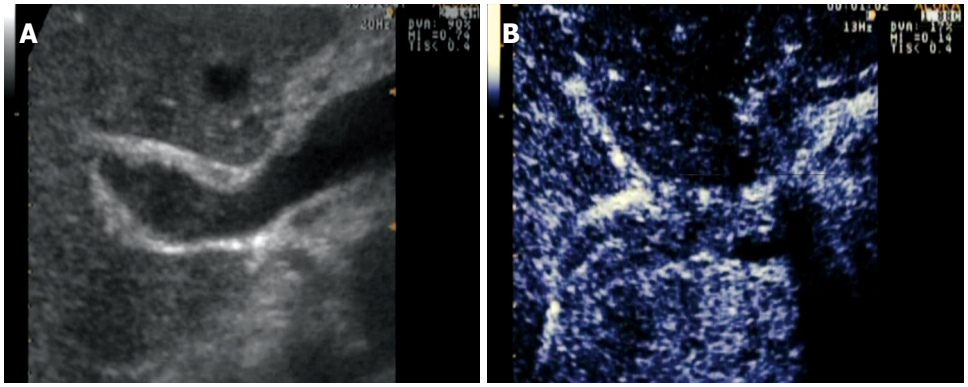

Figure 5 Malignant thrombus. A: sonography reveals echogenic area (thrombus) within vessel lumen; B: during arterial phase of contrast-enhanced sonography the diffusely enhanced area representing thrombus with internal neovascularity.

values coincided for both techniques because, as shown in Table 3, the false-negative patients on baseline CEUS and PVT FNB were the same. On the other hand, if we retrospectively admitted the mosaic picture of enhancement (the picture of the 6 false-negative patients on CEUS) as an alternative, but possible, picture of appearance of malignant PVT on CEUS, and considering that prospectively no false-positive or false-negative results were given, 100% of sensitivity and specificity were obtained for this technique.

DISCUSSION

In previous studies, we[25] and others[26] have described the usefulness and superiority of contrast-enhanced sonography with respect to sonography and color Doppler sonography in the detection and characterisation of thrombus. Here our study differs in two points: (1) we systematically compared in blinded fashion the validity of portal FNB with respect to contrast enhancement of portal thrombus; (2) we excluded from our study patients with evidence of continuity between thrombus and tumor tissue (most of patients in study of Rossi *et al*[26]) a feature considered diagnostic of malignant thrombosis both on sonography[26], and on helical TC/MRI imaging[12,13].

CT remains the primary imaging technique for staging HCC and identifying PVT[27]. MRI also appears to be a promising tool[28]. Although the capacity for CT to show main or lobar PVT is well established, controversy surrounds radiologists' ability to use CT to consistently differentiate between malignant and simple thrombi[3,7,27]. This reluctance to stage possible portal vein invasion by CT/MRI alone has perhaps been appropriate given the lack of a formal study in the literature that compares the imaging characteristics of proven benign and malignant thrombi. It was shown that tumor thrombus neovascularity may also be identified, with variable accuracy, by color Doppler

sonography[29-34]. Now the use of CEUS permits us to study in real time micro-vascular architecture of each thrombus, searching for global arterial enhancement typical of HCC neovascularity. The interpretation of results is based on general characteristics of enhancing/hypoenhancing of thrombus after administration of contrast ultrasound agent. The sensitivity of CEUS is better with respect to Doppler sampling of intrathrombus vessels; there are in fact technical limits of Doppler sampling due to the small diameter of vessels of the microvascular architecture of neoplastic tissue[35].

We deduced that homogeneous hypoenhancement of the thrombus on CEUS with respect to the surrounding parenchyma is diagnostic for benign thrombosis. Significantly, benign PVT does not show enhancement at any time after ultrasound contrast agent administration. The homogeneous enhancement of thrombus on CEUS must be considered diagnostic for malignant thrombosis. In particular, the appearance of malignant PVT can be precociously hyperechoic or isoechoic with respect to the surrounding parenchyma: this picture could be due to diffuse arterialization of surrounding liver parenchyma, a pathophysiological phenomenon secondary to the same thrombosis.

In our study, in order to obtain an accurate differential diagnosis as to the nature of a PVT, we utilized as gold-standard methods the prospective evaluation of the thrombus with, in most cases, a concordant cytology on PVT FNB repetition. We in fact were uncertain about the validity of using only baseline portal FNB to determine diagnosis because of the not optimal sensitivity of the method. The possibility of sampling error could result in both false-positive and false-negative diagnoses for malignant PVT. Because a benign thrombus does not contain hepatocytes, specimens that include cells from the periportal hepatic parenchyma or hepatocytes picked up during passage of the biopsy needle through the liver could lead to false-positive diagnoses of malignant tumor. We prevented false-positive diagnoses by using a biopsy needle with an occlusive stylet, keeping the stylet tightly seated until the needle tip was detected inside the portal vein and performing the biopsy under continuous sonographic visualization with the needle tip kept within the lumen of the portal vein at all times during passages. In our study no diagnosis of malignant tumor on FNB PVT was false-positive indicating that the invasive procedure is maximally specific. False-negative diagnoses for malignant cells could be produced if the portion of a malignant portal vein thrombus from which a specimen was obtained failed to contain malignant hepatocytes. We tried to prevent false-negative diagnoses by performing the biopsy on the portal vein thrombus by sampling the longest possible segment of a portal vein thrombus. We obtained anyway 6 false-negative results for malignant thrombi. In all 6 cases the appearance on CEUS was as an inhomogeneous enhancement of the thrombus; we called the CEUS appearance of these cases "mosaic-picture" of neoplastic thrombus. We were unhappy about the false-negative results of portal FNB derived from sampling the non-neoplastic portion of the thrombus; we repeated portal FNB within 1-4 mo guiding the biopsy on results of the CEUS (FNB of enhancing part of thrombus) and obtained malignant cells. We supposed that the echotexture of malignant thrombus on CEUS was not homogeneous in these 6 patients because there were some occult islands of neoplastic tissue in the thrombus that after administration of ultrasound contrast agent showed as enhancing patterns with respect to the diffuse hypoenhancing of the remaining benign thrombus. Probably in these cases the phenomena of benign thrombosis was superimposed on the initial neoplastic invasion of the portal vein. So CEUS of portal vein thrombi appears as a diagnostic procedure more accurate than "blind" portal FNB in the diagnosis of malignant thrombosis with regard to the possibility of giving a panoramic vision of the thrombus without the sampling-error of "blind" portal FNB. So it is reasonable, when cytology confirmation of malignant thrombosis is needed, that portal FNB can be guided on the result of CEUS in order to reduce false-negative results due to casual sampling.

In conclusion, CEUS of portal thrombus is more accurate than biopsy of thrombus for making the differential diagnosis as to the nature of the thrombus. CEUS of portal thrombus is a reliable diagnostic tool for assessing non-invasively the nature of the PVT. This procedure is usually accurate but presents some sampling errors linked to the 'blind' biopsy of the thrombus.

COMMENTS

Background

About 20% of patients at first access visit to a specialized centre on the care of hepatocellular carcinoma need differential diagnosis between benign portal vein thrombosis (PVT) or malignant thrombosis. Patients who have hepatocellular carcinoma and proven neoplastic vascular thrombus are not candidates for any treatment: in these cases the prevalence of tumor recurrence is nearly 100%.

Research frontiers

The world technique of reference for differentiating benign from malignant PVT is the invasive percutaneous fine needle biopsy (FNB) of the thrombus. Given the obvious clinical utility of a reliable non-invasive technique for the diagnosis of malignant PVT, the authors undertook an investigation to compare Contrast-Enhanced Sonography (CEUS) and portal vein FNB of thrombus for differentiating benign from malignant thrombosis.

Innovations and breakthroughs

For the first time, the authors systematically compare in blinded fashion the validity of portal FNB with respect to non-invasive contrast enhancement of portal thrombus in order to differentiate benign from malignant thrombosis.

Applications

CEUS of portal thrombus is more accurate than biopsy of thrombus for making differential diagnosis of the nature of the thrombus. CEUS of portal thrombus is a reliable diagnostic tool for assessing non-invasively the nature of PVT.

Terminology

CEUS consists of an ultrasound exam which is performed after parenteral administration of an ultrasound contrast. The CEUS in this study consists of sulfurhexafluoride (SF_6) vapor-filled and phospholipid-stabilized microbubbles with a diameter uniformly smaller than 8 μm; these microbubbles circulate in the intravascular space crossing pulmonary and systemic capillary circulation.

Peer review

This paper addresses the value of II Generation CEUS in non-invasive differential diagnosis of benign from malign portal vein thrombosis. The manuscript is interesting.

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