Contrast-Enhanced Ultrasound in Assessing Therapeutic Response in Ablative Treatments of Hepatocellular Carcinoma

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Abstract

Percutaneous ablative methods guided by imaging techniques are considered nowadays curative treatment for early HCC in patients who are not candidates for liver transplantation and surgical resection. The final goal of all ablative treatments is to achieve complete destruction of neoplastic tissue by disruption of tumor vascularity. The best way to demonstrate the efficacy of any ablative methods noninvasively is to demonstrate that the blood supply has been disrupted both inside and at the periphery of the tumor by means of imaging methods. Contrast-enhanced ultrasound (CEUS) with second generation contrast agents is almost as sensitive as CT (considered to be the gold standard) in depicting the residual tumor after an ablation. Moreover, CEUS can be used before ablation to plan the treatment, during the procedure to guide the needle insertion, or immediately after to determine whether the tumor has been ablated or needs additional treatment which can be performed in the same session

Key words

Hepatocellular carcinoma – percutaneous ablative treatment – contrast enhanced ultrasound – treatment response.

Introduction

Hepatocellular carcinoma (HCC) usually appears as the most severe complication of liver cirrhosis and constitutes the major cause of death in these patients. Detection of HCC in early stages, as an expected consequence of screening programs is of crucial importance because the treatment in this stage can provide a survival rate above 50% at 5 years. Several curative options are available for the treatment of early HCC: liver transplantation, surgical resection and percutaneous ablative therapy [1, 2].

The aims of percutaneous treatment is to achieve a complete necrosis of the tumoral tissue and a safety margin of nontumoral tissue around the tumor without damaging the liver function. Necrosis may be obtained chemically (by injection of ethanol or acetic acid) or thermally with radiofrequency (RFA), laser or microwave ablation [3, 4]. Complete necrosis can be achieved in 80-98% of HCCs of less than 3 cm in diameter whereas in tumors measuring 3-5 cm the complete ablation rate is much lower (65%)[5,6].

Assessment of treatment response in percutaneous ablation

The final goal of all ablative treatments is to achieve complete destruction of neoplastic tissue by disruption of tumor vascularity. The best way to demonstrate the efficacy of any ablative methods noninvasively is to demonstrate that the blood supply has been disrupted both inside and at the periphery of the tumor by means of imaging methods [7].

CT after administration of a contrast agent is the most used imaging technique in the evaluation of the efficacy after percutaneous ablation of HCC [7-10]. Dynamic MRI with gadolinium is increasingly used, the advantages over CT being the lack of radiation and high sensitivity in the detection of vascularization, especially in small tumors [11].

The diagnostic criterion of a complete response is the absence of tumoral enhancement reflecting tissue necrosis. The residual tumor is defined as the presence of enhancing areas inside the treated lesion reflecting remaining vascularization of viable neoplastic tissue [12]. The necrotic areas visualized as areas without perfusion on CT or MRI match with coagulation zones on pathology [13].

The ability to detect residual disease immediately after ablation would be of extreme importance allowing retreatment in the same session and therefore, reducing the

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number of incomplete ablations. It has been demonstrated that the initial complete response to ablation is associated with an improved survival in cirrhotic patients with early HCC[14].

As percutaneous ablations are usually performed using US guidance it would be convenient to evaluate the response after treatment with US. Although it can assess the changes in echogenicity and tumor size after ablation, conventional US cannot differentiate between a completely treated tumor and a residual or recurrent one [10]. Color and Power Doppler US with or without the use of first generation contrast agents are not sensitive enough to differentiate vascularized viable tumor from ablated tissue [15-18].

The introduction of second generation contrast agents (SGCA) together with contrast software operating at a very low mechanical index allows the detection of intratumoral microvasculature in real time with high sensitivity [8,10]. It has been proved that contrast – enhanced ultrasound (CEUS) has a very high accuracy in the detection of the typical hypervascularization of HCC in the arterial phase, some studies suggesting that it is even more accurate than CT in demonstrating the intratumoral vessels [19-20].

Role of CEUS in evaluating ablative treatment results

Having an excellent accuracy in depicting the microvascularization of an HCC nodule, CEUS has been used to assess intratumoral vascularization after the ablative treatment. Complete response is considered as the absence of contrast enhancement during both the arterial and portal phase reflecting coagulative and vascular necrosis (Fig.1). Treatment failure is defined as persistence of areas of focal enhancement as a sign of the presence of well-perfused residual tumor (Fig. 2). The residual tumor maintains the enhancement pattern depicted in the pretreatment studies.

The usual appearance of residual unablated tumor is an irregular, eccentric or nodular peripheral enhancement (Fig. 2) [8-10]. Sometimes, especially in HCCs treated with PEI, an enhancement in some septa inside the nodule may be seen or a vessel passing through the nodule (Figs 3, 4).

In large tumors, incomplete ablations may appear as enhanced areas especially localized near the border (Fig. 5). In order to correctly evaluate the treatment efficacy a review of preablation and postablation images is mandatory to compare the diameters of ablation zone with those of the tumor before treatment [10].

Accuracy of CEUS, timing of examination and limitations of the technique

At 1 month after ablation, CEUS with second generation contrast agents is almost as sensitive as CT (considered to be the gold standard) in depicting the residual tumor [2, 4, 8, 21, 22]. The accuracy in these studies range from 91% [8] to 100% [21]. These results seem to be very relevant since contrast enhanced CT, used in almost all studies as

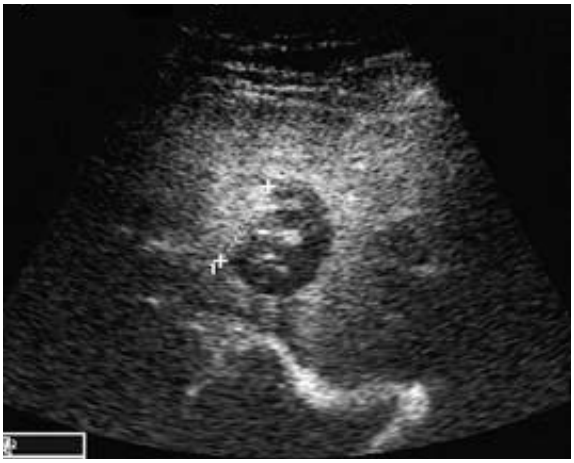

Fig 2. Residual tumor in a 60-year old man with HCC treated with PEI. Arterial phase CEUS image obtained 24 hours afer PEI shows peripheral nodular enhancement suggesting residual tumor.

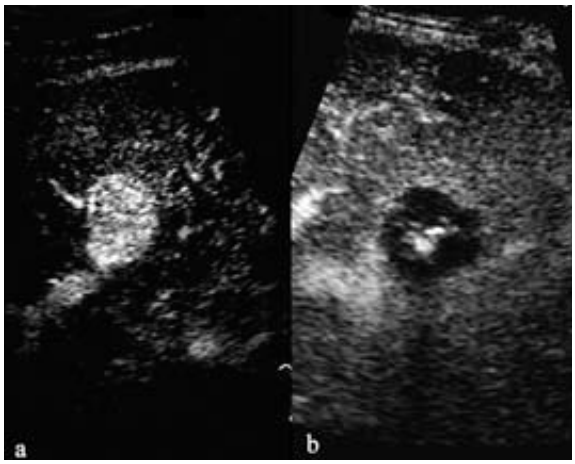

Fig 1. Early HCC treated by PEI in a 65-year old man. a) Arterial phase CEUS image before PEI shows homogeneous enhancement of the tumor; b) 24 hours after treatment, in arterial phase no enhancement is seen inside the tumor, compatible with complete response.

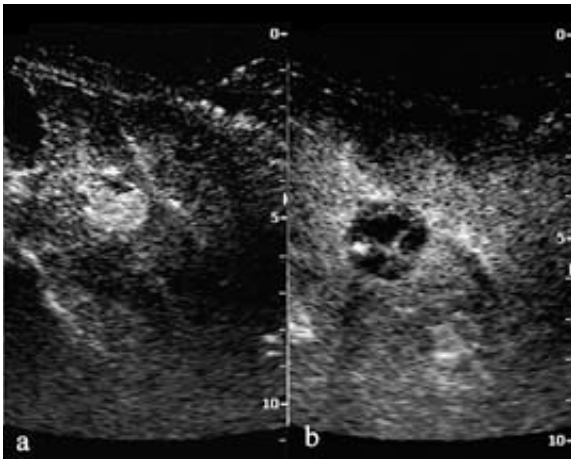

Fig 3. Incomplete ablation in an early HCC in a 62 year old woman treated with PEI. a) Arterial phase CEUS image before PEI shows inhomogenuous enhancement of the tumor; b) persistence of enhancement in arterial phase along some septa (»). Note that the rest of nodule is not enhancing.

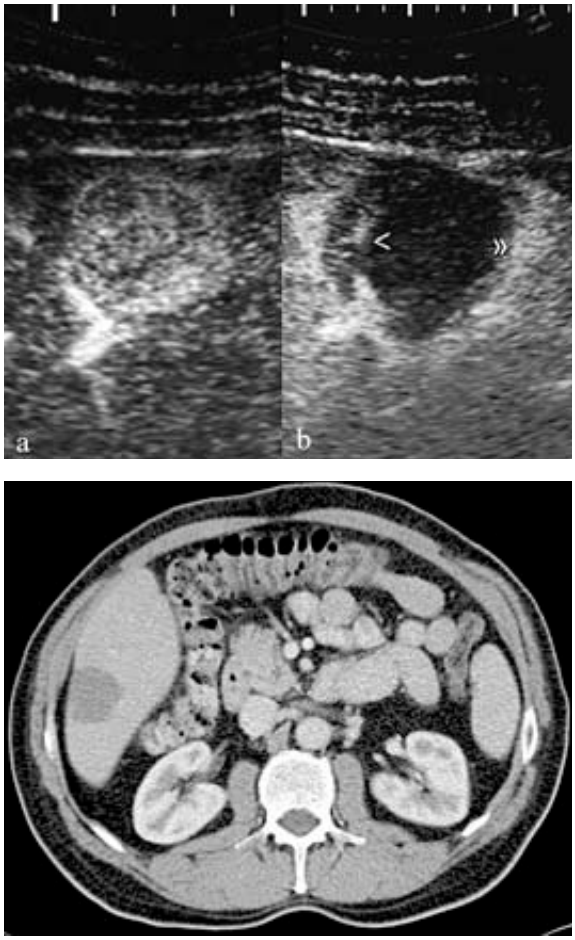

Fig 4. 59-year-old man after RFA of HCC. a) Arterial-phase CEUS obtained 24 h after procedure illustrates difficulty in interpreting these studies due to reactive marginal hypervascularity (») and residual vessel traversing ablation zone (<). b) Arterial-phase CT scan obtained at 4-week follow-up shows no enhancement in the treated area.

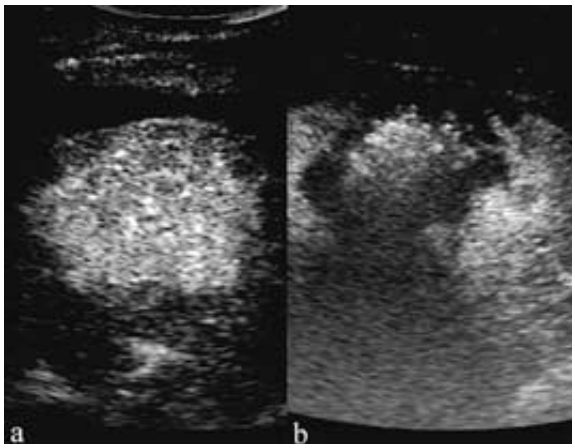

Fig 5. Incomplete ablation in a large HCC treated by PEI. a) Arterial phase CEUS image before PEI shows inhomogeneous enhancement of the tumor; b) arterial phase CEUS image obtained 24 hours afer PEI shows large areas of nodular enhancement suggesting residual tumor. Note the gas inside the tumor making the correct evaluation of the posterior margin of the ablated tumor difficult.

the gold standard in assessing the ablation results has not in fact a 100% accuracy. Thus, marginal recurrence may occur 3-7 months after ablation in 7-9 % of patients with negative CT scans at 2-4 weeks [8]. This relatively high local recurrence rate may be explained by the persistence of microscopic neoplastic foci within or around the tumor that cannot be visualized with imaging methods [15]. CEUS has a 83% sensitivity in detecting residual tumors even when compared with histopathological findings [13]. Following these excellent results some authors have suggested that CEUS should be the first imaging technique to evaluate the initial response and CT and MRI should be reserved for follow-up at 3 months (Fig. 6) [10]. This approach would have several advantages as both the ablation and evaluation of efficacy could be done by the same operator using the same equipment, thus avoiding more expensive methods.

The immediate assessment of therapy efficacy would be of crucial importance since retreatment can be performed in the same session in case there is any residual tumor [7, 9]. Unfortunately, the absence of enhancement immediately after the ablation (or in the following 24-48 hours) does not always indicate a complete ablation and cannot exclude the presence of viable tumoral tissue that will lead to a recurrence

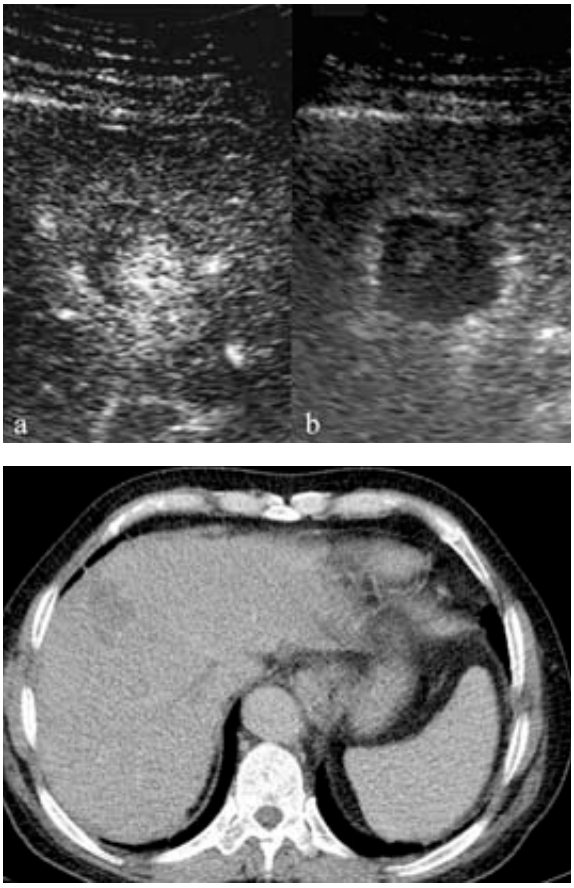

Fig 6. A 3.5 cm HCC treated with RFA in a 72 year old patient. a) Arterial phase CEUS image before RFA shows inhomogeneous enhancement of the tumor; CEUS (b) and arterial-phase CT (c) scans obtained at 4-week follow-up show no enhancement in the treated area.

over time. The sensitivity of CEUS in early assessment of efficacy is as low as 27-60% and specificity is not 100% [2,8]. Thus, if CEUS shows no vascularity in the treated lesion immediately after treatment, an imaging method (CEUS or CT) should be performed at 1 or 3 months to confirm ablation success [10]. CT performed at 24 hours after therapy has even a lower sensitivity (20%) than CEUS which, in fact, precludes its use in clinical practice [2].

The poor results of CEUS and CT during the first days may be explained by: a) vascular abnormalities around the treated lesion (peripheral hyperemia, arteriovenous fistula); b) presence of gas inside the tumor; c) difficulty to scan lesions (too deep located or in a fatty liver) and d) uncooperative patient (in case of immediate postablative assessment) [2, 7-10].

Peripheral hyperemia is a common, transient finding after percutaneous ablation reflecting peritumoral inflammation secondary to thermal damage. It disappears after 1-2 months and may be encountered both on CEUS and CT exams. The peripheral enhancement at the borders of the ablation zones may be misjudged as peripheral residual tumor (Fig.7). There are some characteristics of the enhancement which may help in the differentiation (Table I)[2, 8, 10].

It is important to evaluate the necrotic area both in arterial and parenchymal phase to assess if the size of necrosis is larger (0.5-1.0 cm) than the initial tumor, thus achieving a correct safety margin necessary to assure a low recurrence rate [23, 24].

The presence of gas inside the treated tumor is one of the main limitations of CEUS after ablation. During RF ablation gas forms as a result of cavitation, while in PEI bubbles of gas are injected with the alcohol [2, 8-10]. When the treated tumor contains gas it displays a marked hyperechogenicity with important distal shadowing that hinder correct evaluation of the posterior margin of the ablated tumor (Fig.5). It is advisable to wait 20-40 minutes to perform an acceptable CEUS study, but a proper examination can be done only after 12-24 hours [8, 10].

With all these mentioned limits, an early assessment of success after the theoretical end of an ablative treatment

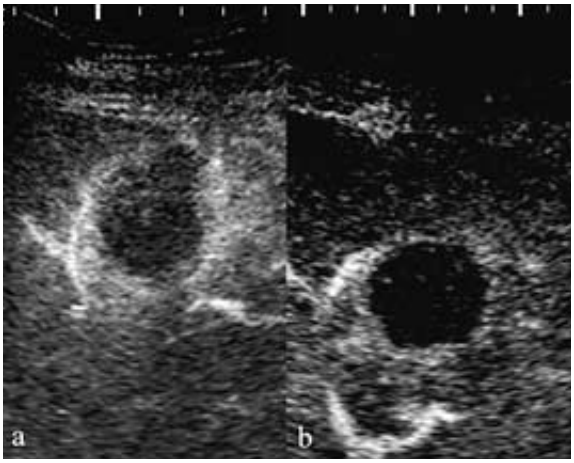

Fig 7. A 48-year-old man after RFA of HCC. a) Arterial-phase enhanced sonogram obtained immediately after ablation depicts a rindlike marginal reactive hypervascularity; b) Arterial-phase enhanced sonogram obtained at 4-week follow-up depicts no marginal reactive hypervascularity .

is very important since it may allow detection of areas not covered by the treatment which will need a second insertion. Scanning immediately after the procedure is potentially the most clinically relevant application of enhanced sonography in percutaneous ablation [8]. Although the sensitivity is only 60% the specificity is high enough (94%) to be clinically useful. Thus, in patients with residual tumor, CEUS may facilitate the insertion of the needle in the untreated area and end the ablation at the time of initial therapy (Fig.8)[7-9]. Using this approach, it is possible to decrease the rate of partial necrosis in treated HCCs from 16.1 % to 3.8 % [7].

Role of CEUS in long term follow up

A reasonable protocol in the follow-up of patients after percutaneous ablation implies the use of CEUS at 1 month to detect residual disease, CT and/or MRI being used at 3 months to detect marginal recurrence [10,25]. A close two-year follow-up, with an imaging method (including CEUS) performed every 3 months, is mandatory in patients treated for HCC to detect recurrence, satellites or seeding (Fig.9) [25-26]. In the long time follow-up enhanced helical CT

Table I. Characteristic features of peritumoral enhancement and peripheral residual disease useful in the differentiation

Characteristics/ Finding		Peritumoral inflammation	Peripheral residual disease
Peripheral enhancement	Pattern	Diffuse, homogeneous	Focal, irregular, heterogeneous
	Thickness	Uniform, rind like, 4-5 mm thick	More 7-8 mm
Pattern of enhancement	Arterial phase	Hyperenhancing	Hyperenhancing (sometimes weak and transient)
	Portal venous and late phase	Hyperenhancing or isoenhancing	Hypoenhancing (wash out) (as win the preablated nodule)
Size of the unenhanced area (in respect with initial lesion)		Larger than the initial lesion	The same as the initial lesion
		Hyperenhancing area lies inside the border of initial tumor	Hyperenhancing area lies outside the border of initial tumor

(or dynamic gadolinium enhanced MRI) is the mainstay for imaging of treated patients and the detection of local or remote intrahepatic and extrahepatic relapse [9].

Other applications of CEUS in percutaneous ablative methods

According to the Guidelines for the use of contrast agents in ultrasound developed in 2004 and updated in 2008 [24], CEUS plays several other roles in monitoring ablation.

Treatment planning

Before ablation it is advisable to scan the entire liver with conventional US and CEUS and to store digitally the images and movie clips. A careful comparison with CT or MRI result is mandatory to maximize lesion detection. A careful mapping of the tumor for location, number and size is essential to evaluate the feasibility of the treatment. Tumor diameter should be measured with 3D or 4D ultrasound. In cases when the tumor borders are not well delineated with conventional US and CEUS and conventional US provides different identification of the borders, volume calculation should be performed with CEUS [9,24,27].

Lesion targeting

Continuous mode CEUS allows real time targeting of lesions not well delineated on conventional ultrasound. Needle insertion is performed during the phase of maximum lesion conspicuity, namely for HCC in arterial phase. This approach is considered mandatory in case of: a) small HCC detected by CT or MRI but not visible or with conventional US in a inhomogeneous cirrhotic liver [28]; b) isoechoic HCC with margins which cannot be exactly delineated with US; c) areas of residual untreated or locally recurrent tumor which display a typical enhancement in the arterial phase at an early assessment (Fig.8)[9]. Using CEUS as guidance for ablation instead of conventional US, the complete necrosis rate after 1 session has increased from 65% to 94.7 % [29].

Targeting the untreated area during ablative session is now facilitated by equipment which displays both the CEUS image in one half screen and the fundamental US image in the other half screen (Fig.8) [9, 10, 24].

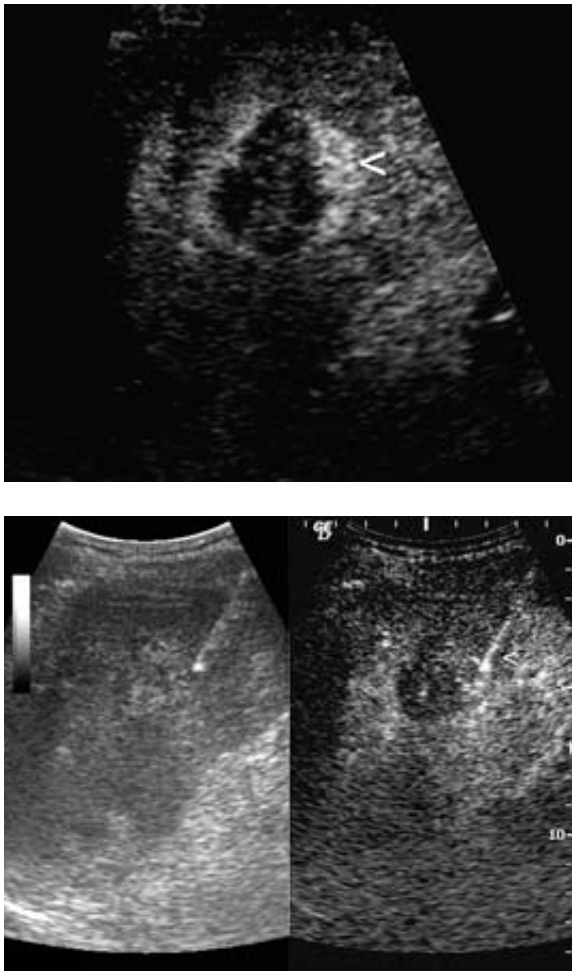

Fig 8. Large HCC treated by intraoperative RFA in a 69 year old man. a) Arterial phase CEUS image obtained 30 days after RFA shows peripheral nodular enhancement suggesting residual tumor (<); b) PEI ablation was then performed guided by CEUS. Note the tract of the needle targeting the untreated area (>). The equipment displays both the CEUS image in right half screen and the fundamental US image in the left half screen.

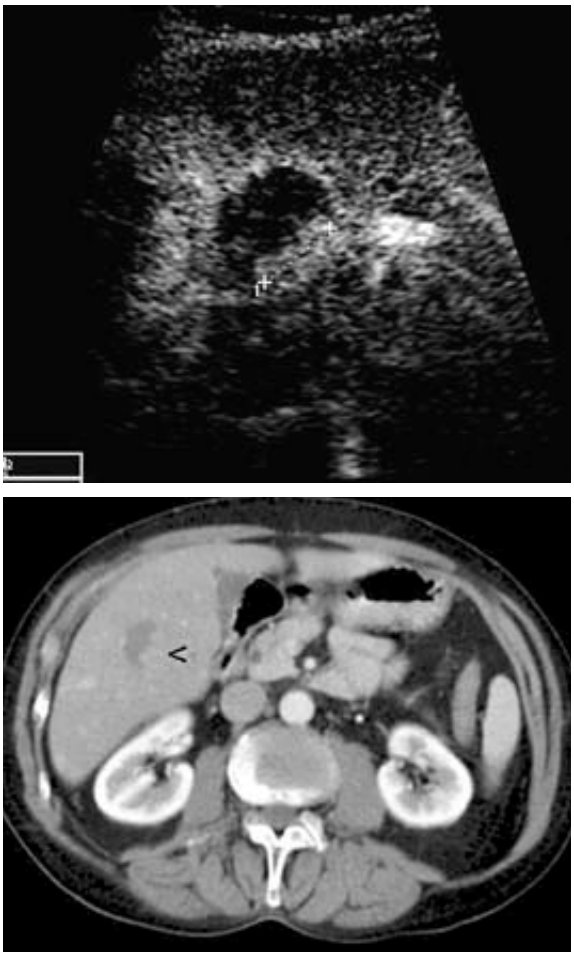

Fig 9. Recurrence after 1 year in a 3 cm HCC previously treated by PEI. a) Arterial phase CEUS image shows a peripheral, nodular enhancement in the area of previously treated tumor b) Arterial-phase CT scan obtained confirms the peripheral recurrence (<) detected by CEUS.

Conclusions

Contrast enhanced ultrasound with second generation contrast agents is an established imaging method to assess the efficacy of ablative treatment. Its high accuracy in depicting the residual tumor with no adverse effects makes it one of the methods of choice to evaluate treatment response at one month. Its use immediately after ablation allows the detection of a persistent viable tumor and retreatment in the same session with huge impact in both recurrence and survival rates and cost.

Conflicts of interest

No conflicts to declare.

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