European Journal of Radiology 84 (2015) 1666–1674

Contents lists available at ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

Contrast enhanced ultrasound in the evaluation and percutaneous treatment of hepatic and renal tumors

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ARTICLE INFO

Article history:
Received 29 April 2015
Received in revised form 13 May 2015
Accepted 3 June 2015

Keywords:
Contrast enhanced ultrasound
Hepatocellular carcinoma
Liver metastases
Ablation therapy
Renal cell carcinoma
Diagnostic imaging

ABSTRACT

Image-guided percutaneous ablation techniques are increasingly being used for the treatment of malignant tumors of the liver and kidney. Contrast enhanced ultrasound (CEUS) is a real-time dynamic imaging technique that plays an important role in the pre-, intra-, and post-procedural management of these patients. This review will focus on the role of CEUS in the evaluation of patients undergoing treatment with percutaneous ablation for hepatic or renal tumors.

1. Introduction

Contrast enhanced ultrasound (CEUS) is a contrast harmonic imaging technique that allows to detect and characterize focal lesions by assessing their microvascularization with a second generation contrast material (SonoVue, Bracco, Milano, Italy) at a low mechanical index (MI < 0.2) [1].

Ultrasound contrast materials have an excellent safety profile with adverse reactions much lower than that reported for other radiologic or magnetic resonance contrast agents [2]. There is no evidence of organ damage, such as nephrotoxicity that is an important safety concern with computed tomography (CT) iodinated contrast agents [3].

Percutaneous image-guided ablation techniques are widely applied for the treatment of tumors in different organs, such as liver and kidney when surgery is not indicated. The most widely accepted consensus guidelines for treatment of hepatocellular carcinoma (HCC) and renal cell carcinoma (RCC) now include ablative therapies as first- or second-line therapy. For HCC, the Barcelona Clinic Liver Cancer (BCLC) staging system recommends thermal ablation as a curative treatment in very early (0) and early (A) stages [4]. Excellent local tumor control and improved survival rates have been achieved in selected patients with colorectal or breast liver metastases [5,6]. For the treatment of RCC, the European Association of Urology (EAU) guideline recommends the use minimally invasive therapies, including percutaneous ablation, in high-risk surgical candidates [7].

Percutaneous ablation relies on imaging at every step of the process in order to detect, guide, and confirm complete tumor coagulation. Contrast enhanced computed tomography (CECT) or contrast enhanced magnetic resonance imaging (CEMRI) are the reference standards for staging of liver and kidney tumors prior to

Abbreviations: BCLC, Barcelona clinic liver cancer; HCC, hepatocellular carcinoma; RCC, renal cell carcinoma; CECT, contrast enhanced computed tomography; CEMRI, contrast enhanced magnetic resonance imaging; US, ultrasound; CEUS, contrast enhanced ultrasound; EFSUMB, European federation of societies for ultrasound in medicine and biology; TACE, transarterial chemoembolization; PEI, percutaneous ethanol injection.

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http://dx.doi.org/10.1016/j.ejrad.2015.06.004
0720-048X/

ablative therapy, and for assessing the completeness of ablation at the end of the procedure and during the follow-up. In Europe and Asia, ultrasound (US) is the imaging modality most often used to guide applicator placement [5,6,8]. Ideally, ultrasound could also be used to detect residual unablated tissue which could then be re-targeted for coagulation during a single treatment session.

CEUS is a real-time dynamic imaging technique that plays an important role in the management of patients treated with ablation for malignant tumors [2]. Due to the capability to accurately depict tumor vascularity, CEUS can be used to detect and characterize tumors, guide the placement of ablation devices when tumors are not visible at conventional grey-scale US, and to follow up patients during the immediate and delayed post-ablation periods. According to the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) guidelines [2], the use of CEUS in patients treated with ablation therapy is recommended in the following situations:

a **Pretreatment evaluation**, including characterization of suspected malignant abdominal tumors and treatment planning to assess number and size of the lesions;
b **CEUS-guidance during ablation** in lesions not visible by conventional US;
c **Periprocedure evaluation** performed immediately or within 24 h after ablation;
d **Follow-up**, when CECT or CEMRI are contraindicated or inconclusive.

This review will focus on the role of CEUS in the evaluation of patients undergoing percutaneous treatments for hepatic and renal tumors.

2. Liver

2.1. Pretreatment evaluation

Imaging of liver malignancies with CEUS relies on the histological and vascular features of the different tumors. HCC generally arises in patients with a background of chronic liver disease through a multistep process. A subset of regenerative nodules develops into dysplastic nodules which can harbor small foci of well-differentiated HCC. This manifests on CEUS as a small area of intranodular vascularity during the hepatic arterial phase with portal phase and late phase wash-out [9].

Surveillance strategies for HCC in at-risk populations are aimed at detecting HCC during the early stages, and is recommended to be performed with conventional US every 6 months. According to the EFSUMB guidelines, CEUS is not recommended for surveillance of cirrhotic patients if the target is not visible during the B-mode evaluation. The main reason for this is the short duration of the arterial phase during which time it is not possible to adequately survey the entire liver. In half of cases of early HCC, there is an absence of wash-out during the portal and delayed phases which, while longer in duration, are also not ideal for detecting early HCC [2].

CEUS has prognostic significance for the efficacy of both ablation and intra-arterial treatments. When ablation is not indicated and alternative therapies such as transarterial chemoembolization (TACE) or percutaneous ethanol injection (PEI) are considered, the assessment of vascular conspicuity of HCC with CEUS is predictive of treatment success. For ablation, Maruyama et al. have reported that the quantitative assessment of CEUS findings of HCC during the arterial phase before ablation is predictive for distant recurrence [10].

The typical enhancement pattern of liver metastases at CEUS in the arterial phase is variable, and depends on the primary tumor cell type [11,12]. Hepatic metastases also typically demonstrate rapid wash-out, within 30–40 s after injection, which becomes more apparent in the portal and late phases. Tumors that are hypovascular by CECT and CEMRI tend to be hypoenhancing at CEUS in the arterial phase, whereas hypervascular metastases are typically hyperenhancing. Even hypovascular liver metastases can demonstrate a peripheral hypervascular halo during the arterial phase. The marked washout in the late phase, which lasts up to 4–5 min, aids detection of even very small metastases (less than 5 mm in size) with accuracy at least comparable to CECT and CEMRI [2,13–15]. The enhancement pattern of liver metastases with CEUS is especially helpful because the echogenicity of metastases on conventional grey-scale US may be similar to that of the background liver, making detection without contrast material difficult.

In the pretreatment staging of liver metastases, CEUS can play an important role in determining the eligibility of the patients for ablation due to the ability to detect small satellites and additional small metastases not visible with other imaging modalities [14–16] (Fig 1)**.** CEUS is also very accurate in defining the true size of liver metastases due to the hypervascular halo often seen during the arterial phase only. This halo corresponds to a chronic inflammatory infiltrate without evidence of tumor infiltration [13,17]. In order to reduce the possibility of recurrence – due to the risk of promoting neovascularization and production of tumoral growth factors – the hypervascular halo should be included in the treatment volume during the planning for ablation procedures.

2.2. CEUS guidance ablation

The success of percutaneous ablation relies on precise targeting via an imaging technique. Typically, B-mode US is used to insert the applicator into the targeted tumor. To achieve this end however, the ability to visualize the tumor is mandatory. In certain situations, tumor visualization can be particularly difficult. For example, metastases may become more difficult to detect after the administration of chemotherapy. Local recurrences (both HCC and metastases) can also be problematic to visualize, particularly discriminating between the viable and non-viable components of the tumor. In both of these cases, CEUS can facilitate needle positioning by detecting the area of viable/recurrent tumor. Of note, the use of CEUS in this setting is superior for liver metastases due to the prolonged wash-out period in the portal venous and late post-vascular phases. For HCC, the use of CEUS for targeting viable tumor can be more challenging due to the transient nature of the hyperenhancement during the arterial phase and the lack of wash-out in 25–42% of small tumors [18].

2.3. Periprocedure efficacy assessment

There are a number of interstitial ablative procedures in use today for the treatment of liver tumors, including chemical ablation (e.g., ethanol or acetic acid) and thermal therapies (e.g., radiofrequency, laser, microwave, focused ultrasound, and cryoablation). Chemical ablation is generally limited to the treatment of small HCC, or for HCC in locations near vulnerable structures such as major bile ducts. Thermal therapies are utilized both for HCC and liver metastases. Tumors are usually targeted for ablation therapies using US-guidance, thus it is highly convenient to use the same imaging modality for assessing the efficacy of the treatment immediately post-procedure. The one exception to this is the use of CEUS immediately after chemical injection.

In fact the hyperechogenicity determined by the chemical agents such as ethanol or acetic acid and the gas bubbles created