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Contrast-enhanced ultrasound in oncology

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Abstract

In patients with known malignant disease, 51% of liver lesions less than 1.5 cm turn out to be benign. Whether the probability of malignancy is high or low, further investigations are often necessary to definitely exclude malignancy. Contrast-enhanced ultrasonography has a prominent role in lesion characterization with a diagnostic accuracy comparable with computed tomography and magnetic resonance imaging. Anti-angiogenic treatment is common in most oncological institutions and the response evaluation is a new challenge with a research focus on the change in tumour vasculature and perfusion. In planning biopsies, CEUS can identify necrotic and viable areas of tumours and improve the diagnostic accuracy.

Keywords: *Contrast-enhanced ultrasound; CEUS; dynamic contrast-enhanced ultrasound; cancer; characterization.*

Introduction

In patients with known malignant disease, 51% of liver lesions less than 1.5 cm turn out to be benign[1]. Whether the probability of malignancy is high or low, further investigations are often necessary to definitely exclude malignancy. Contrast-enhanced ultrasonography (CEUS) has a prominent role in lesion characterization with a diagnostic accuracy comparable with computed tomography (CT) and magnetic resonance imaging (MRI). The EFSUMB guidelines cover the oncological applications for CEUS[2].

Anti-angiogenic treatment is common in most oncological institutions and the response evaluation is a new challenge with a research focus on the change in tumour vasculature and perfusion. In planning biopsies, CEUS can identify necrotic and viable areas of tumours and improve the diagnostic accuracy[3].

Most of the literature deals with CEUS of the liver and the major experience is based on data from this organ. However, CEUS has also been reported in the evaluation of focal pathology in other organs. CEUS is a fast, cheap and widely used technique in most oncological centres with the additional benefit of lack of nephrotoxicity and radiation.

The contrast

The ultrasound contrast is capsule-stabilized microbubbles with a high-molecular-weight gas, which has low solubility in blood and is consistent with the ultrasound pulses. SonoVue (Bracco, SpA, Italy) is the sole ultrasound contrast approved for extra-cardiac use in the European Union. The shells are flexible and the bubbles are roughly the size of erythrocytes, which makes transpulmonary and peripheral capillary pass possible. Ultrasound contrast is an exclusively real blood pool agent and contrary to normal tissue, has non-linear scatter at low mechanical index (MI). The non-linear response of the bubbles occurs when the expansion of the bubble exceeds the compression induced by the ultrasound wave. This non-linear oscillation emits strong multiples (harmonics) of the insonated frequencies, most likely as a guitar string. Normal tissue at low MI will contribute with no or a minimal fraction of harmonics. Low MI will prevent bubble destruction and real-time scanning is possible for up to 5 minutes. At higher MIs the shell will rupture and the harmonics from normal tissue will increase substantially. Ultrasound contrast is inexpensive compared with CT and MRI, with a vial price of approximately 100 euros, lasting for 2–4 examinations within 6 h.

Equipment

In contrast imaging, the technique and equipment are designed to detect the characteristic signals from the microbubbles as non-linear scatters, exclude the non-linear components from the tissue and the equipment

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and cancel all linear signals in a manner such that bubbles are preserved. The asymmetric oscillation emits heavily non-linear signals, which can be identified by designed software as bubble-specific signals. To minimize the non-linear signals from the native tissue, a low MI technique is mandatory because the non-linear component from native tissue increases the higher the MI. The reduction of the non-linear component induced in the equipment is an on-going process for all manufacturers.

Lesion characterization

Correct staging is crucial in the decision-making process of cancer treatment. In the staging phase, CT, MRI and positron emission tomography (PET)/CT frequently disclose additional lesions of unknown genesis. Whether the probability of malignancy is high or low, further investigations are often necessary to definitely exclude malignancy. In these cases additional fine-needle aspiration, CT or MRI might be necessary. A major part of these more expensive or invasive procedures can frequently be replaced by CEUS.

Differentiation between a benign and malignant lesion in the liver is most often possible due to the difference in wash-in and wash-out profiles. Each microbubble gives rise to a signal from the vascular space and focus is particular for the first 2–3 s of early arterial enhancement (10–30 s), in the portal phase (30–120 s) and in the late phase (>120 s). Benign lesions such as simple cysts, haemangioma, focal nodular hyperplasia, focal fatty sparring and focal fatty infiltration are often easily identified by CEUS (Fig. 1). CEUS has a diagnostic accuracy that matches CT and MRI and in several benign lesions as precise as biopsy[4–10]. The diagnostic accuracy for B-mode ultrasonography is in the range of 49–51% and a substantial improvement in diagnostic accuracy is reported to 85–89% for CEUS[11–13]. In a meta-analysis, the diagnostic value of CEUS was not found to be significantly different from contrast-enhanced CT and contrast-enhanced MRI[14].

In the characterization process, only lesions with a classic contrast presentation in arterial, portal and late phases can justify the characterization as final. On the other hand, most clinicians will accept multiple lesions in a patient with well-known malignant disease as metastasis if a rapid or marked wash-out is present in portal and late phases. If only a single lesion with malignant appearance is identified, biopsy is still mandatory.

CEUS seems to be helpful in characterization of lesions in the spleen[15], prostate[16], breast[17,18], sentinel lymph nodes in breast cancer[19] and pancreas[20], but cannot reliably distinguish between benign and malignant focal renal lesions[21,22]. The role of CEUS in these organs has to be ruled out in future studies.

Lesion detection

Response evaluation in cancer treatment is performed according to the RECIST criteria[23]. In version 1.0 ultrasound follow-up is allowed in superficial lesions and in version 1.1 ultrasound follow-up is not allowed at all. However, CEUS might be used in non-protocol enrolled patients, who are not appropriate for MRI or CT contrast media as an alternative to non-enhanced CT or MRI. Other candidates for CEUS are patients with previous cancer who present clinical or para-clinical signs of relapse. In prospective studies, a sensitivity and specificity for detection of metastatic liver lesions by CEUS has been reported in the range of 0.79–0.80 and 0.95–0.98, respectively[10,24]. In the study by Larsen[25] Multidetector CT had a non-significant higher sensitivity in the detection of liver metastases compared with CEUS.

Perfusion imaging

The introduction of targeted treatment, such as tyrosine kinase inhibitors, has increased the focus of dynamic contrast-enhanced ultrasonography (DCE-US) as an additional tool in the assessment of changes in tumour perfusion. The RECIST criteria are not suited for early response evaluation, since a pronounced decrease in vasculature and perfusion might be present without any change in tumour size. In gastrointestinal tumours (GIST) treated with imatinib, De Giorgi et al.[26] demonstrated response after 2 weeks by DCE-US and after 9 months by CT according to the RECIST criteria. Lassau et al.[27] identified responders 1–2 weeks after treatment of GIST, hepatocellular carcinoma (HCC) and renal cell carcinoma (RCC) and the results correspond in RCC and HCC with progression-free-survival (PFS) and overall-survival (OAS). Williams et al.[28] found no correlation between change in DCE-US parameters and PFS after 2 weeks of treatment and the DCE-US data could not predict long-term assessment of best response.

Another aspect is the demonstration of therapeutic resistance to anti-angiogenic treatment, which is well known to develop in a percentage of patients, which has been demonstrated by DCE-US in 15% of patients after 1 year and 39% after 2 years[29].

Image perfusion can be demonstrated by Doppler ultrasonography and DCE-US. Doppler ultrasonography has limitations and can only demonstrate blood flow in vessels down to 2 mm in size. Medium-sized tumour vessels are in the range of 20–39 μm and tissue movement due to respiration and cardiovasculature dependent movements will exceed the signals from these vessels. The echo signals from the blood can be enhanced up to a 1000-fold by injection of a standard dose of microbubbles, which allows direct visualization of flow in vessels down to 50 μm. The quantification of large, medium and small-size tumour vessels can be demonstrated in

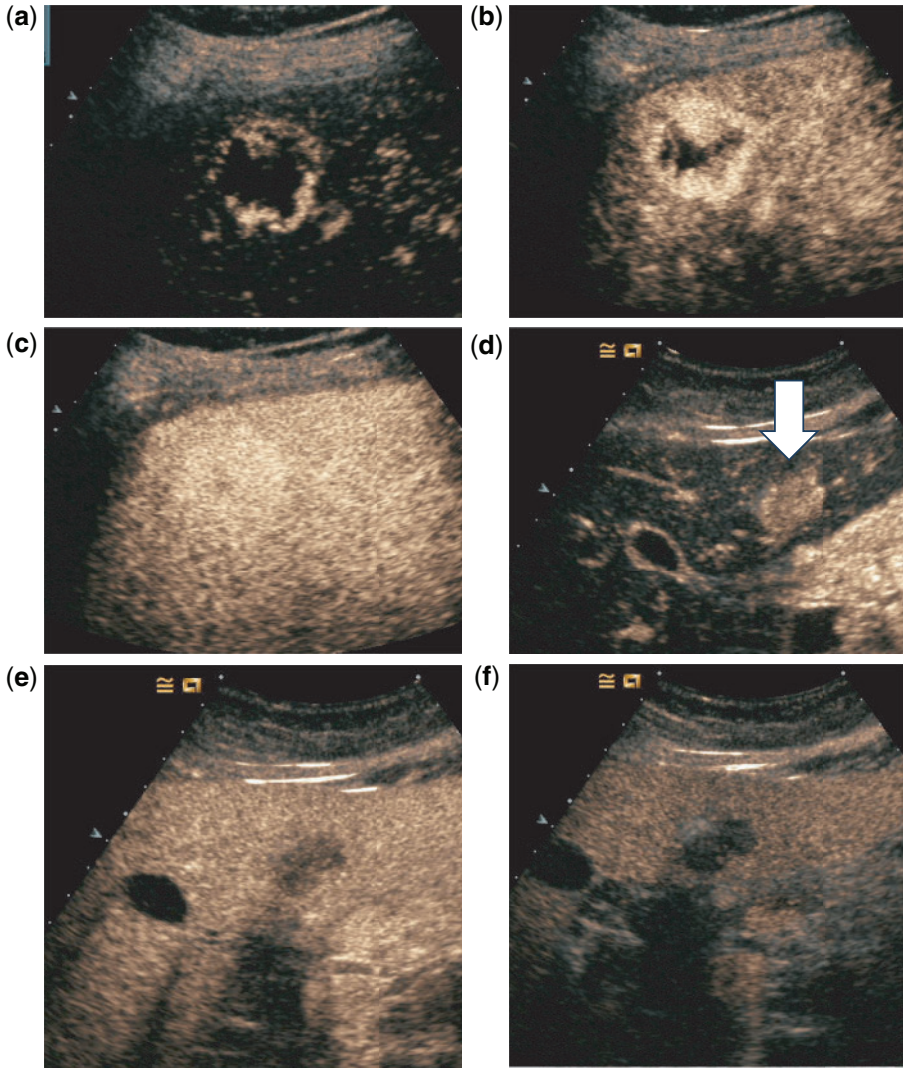

Figure 1 **(a) Globular enhancement in the initial early arterial phase and (b) progressive filling is evident for haemangioma. (c) In the portal and late phases, the haemangioma will most often stay hyper- or iso-intense. These findings are different in malignant tumours characterized by hypervascular metastases in (d) arterial, (e) portal and (f) late phase. Note early portal wash-out and marked wash-out in the late phase, characteristic for malignant lesions.**

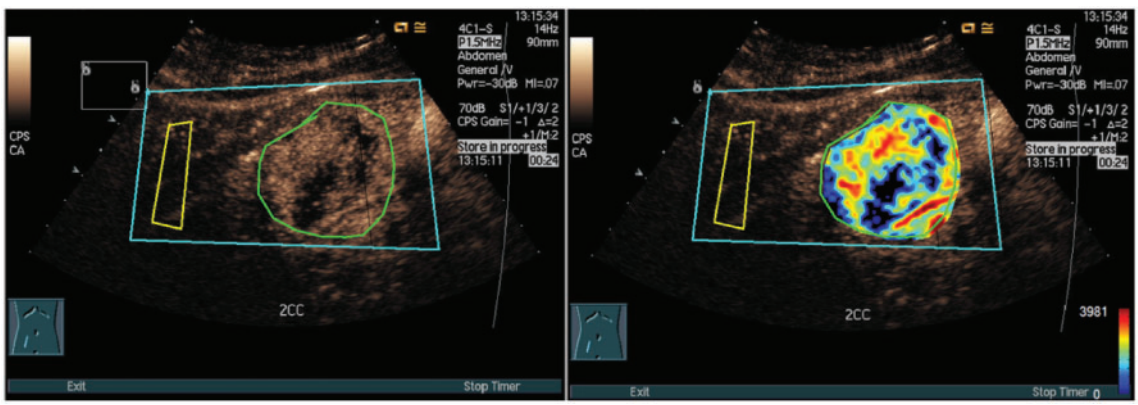

Figure 2 **Contrast-enhanced tumour and the corresponding parametric image, which demonstrates the peak enhancement, pixel by pixel in the tumour. Note the necrotic areas, coloured dark blue. The colour range goes from no enhancement (dark blue) to highest enhancement (dark red).**

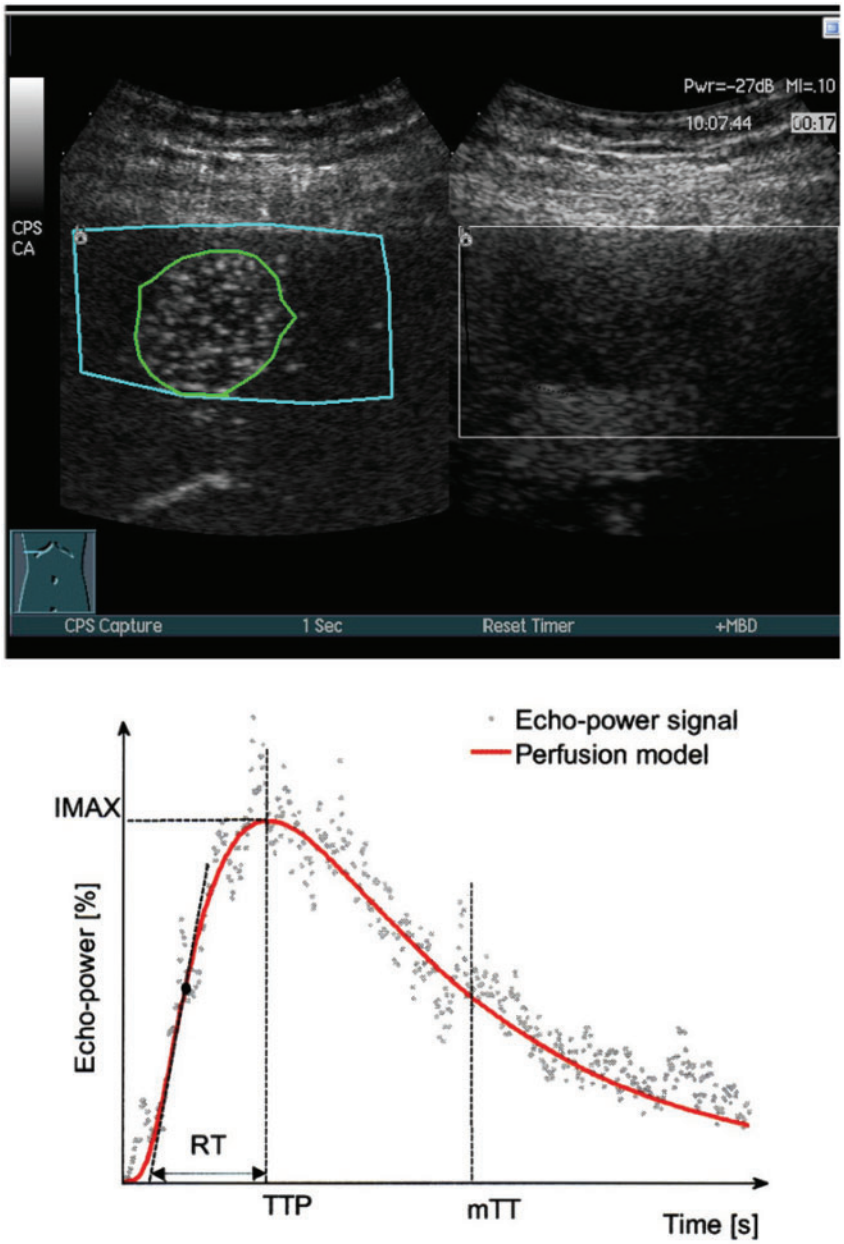

Figure 3 **Time–intensity-curves following contrast injection can objectively determine parametric values as rise-time (RT), peak enhancement (I-Max), time to peak, mean transit time (mTT) and area under the curve.**

flash replenishment techniques, where contrast enhancement is measured at low MI at different time points following a destructive, high MI, flash pulse[30] reflecting the initial filling of larger tumour vessels and over time successive filling of smaller and smaller vascular beds until the entire vascular space is contrast enhanced.

As in DCE-CT and DCE-MRI time–signal curves can be created following DCE-US. From these curves, an estimation of perfusion can be performed. Advantages of the technique are that the microbubbles serve as a real blood pool agent with no limitations in the number of samples and the temporal resolution (more than 20 frames per second) compared with DCE-CT and DCE-MRI.

The signal displayed on the monitor is logarithmic, compressed to provide a video output suitable for diagnostic purposes. However, native linear data is a more precise method for evaluation of perfusion, either as native data before logarithmic compression or by re-linearization of logarithmic compressed data. The refilling process is fit into a mathematical model: $I = A(1-e^{-\beta t})$, where I is the signal intensity, A is the plateau level of the time–intensity curve (TIC) and relates to the fractional blood volume, β is the slope of the wash-in curve and relates to the relative blood velocity of the inflow, and t is the time. From the TIC data, semi-quantitative values can be estimated as: time to peak,

peak intensity, mean transit time (MTT) and the area under the curve (AUC), which reflects the total vascular volume of the examined area (Fig. 3). The tissue perfusion is expressed as total blood volume, which is identical to AUC divided by the MTT. Intra-observer variability is substantial in the estimation of semi-quantification perfusion parameters. The lowest variability, less than 15.79%, was found by AUC and the area under the wash-out curve[31]. The MTT and arrival time seem to be important parameters. In breast cancers, the MTT and arrival time seem to be shorter than in benign masses[19,32], but an overlap exists. In metastatic liver disease, an increase in arterial supply and intrahepatic shunts results in a reduced transit time in metastatic disease[33,34].

Parametric images can be performed as a pixel-by-pixel demonstration of semi-quantitative parameters, e.g. peak enhancement, time to peak or MTT (Fig. 2).

CEUS and biopsy

For malignant abdominal tumours, sensitivities over 90% in ultrasonography-guided biopsies have been reported[35–38]. Limitations to success rely on how well the tumour is identified on US, the location, extent of necrosis and reactive fibrotic tissue within the tumour. CEUS often identifies the tumour invisible on B-mode scan and the necrotic and viable tumour parts by contrast enhancement. Using a split screen, both the contrast and the B-mode images are visible, optimal for CEUS-guided biopsy. The diagnostic accuracy with CEUS-guided biopsy from liver tumours increased from 87 to 95.3%[2]. In lung tumours, the necrotic areas can be identified and the discrimination between tumour and atelectasis is possible[39]. The accuracy also seems to increase in CEUS-guided biopsies from prostate adenocarcinoma[40–42] and is expected to increase in retroperitoneal tumours.

CEUS and radiofrequency ablation

Response evaluation after chemotherapy of liver lesions is according to RECIST performed by either CT or MRI. No evidence-based response criteria are available for interventional tumour treatment. However, CEUS is used in the planning of the procedure, during treatment, immediately after as quality assessment of the ablation and in many institutions as follow-up for recurrence[43]. Frieser et al.[44] reported CEUS performed equally to CT and MRI in the follow-up of patients treated for liver tumours by radiofrequency ablation (RFA). Further, promising results are reported in the follow-up CEUS following RFA of RCC[45].

Targeted microbubbles

In research, microbubbles targeted to the angiogenic vasculature have been developed for imaging of oncological disease. The drugs are targeted toward trans-membrane receptor proteins[46,47] through monoclonal antibodies and receptor-specific peptides, growth factor receptors such as $VEGF_2$, that are signalling factors for angiogenic activity[48,49] or expressed genes on activated endothelial cells, which can become overexpressed in the immature tumour vasculature due to tumour necrosis factors[50]. Research on drug-loaded microbubbles with and without a targeted technique is in progress and the future will show the implications in cancer patients.

Key points

- CEUS is an inexpensive, fast and easy way to characterize lesions in cancer patients. In many institutions, the technique has replaced biopsy and multiphase contrast-enhanced CT and MRI.
- Advantages of the DCE-US technique are that the microbubbles serve as a real blood pool agent and with no limitations in the number of samples and the temporal resolution compared with DCE-CT and DCE-MRI.
- DCE-US seems to be valuable in the prediction of responders in anti-angiogenic treatment, response evaluation following interventional image-guided cancer treatment and in optimization of US-guided biopsies.
- Targeted microbubbles may change the method of diagnosis and treatment.

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