

## Contrast-enhanced ultrasonography with intraarterial administration of SonoVue for guidance of transarterial chemoembolization: An initial experience.

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### Abstract

**Aims:** To describe the technique and to evaluate the feasibility of contrast-enhanced ultrasound with intraarterial administration of echo-enhancer (i.a CEUS) as a method for guidance of transarterial chemoembolization (TACE).

**Patients and methods:** Twelve patients with 17 target liver tumors underwent superselective TACE, guided with i.a CEUS. After microcatheter placement in a (sub)segmental artery suspected as a tumor feeder, a diluted suspension of SonoVue was injected through the microcatheter, and imaging of the target tumor was performed with a low mechanical index technique and with contrast-specific software. If intraarterial injection of SonoVue was associated with immediate, strong tumoral enhancement, the injected artery was considered as tumor-feeding and TACE was performed, otherwise another artery was evaluated.

**Results:** From 25 segmental or subsegmental arteries evaluated i.a CEUS confirmed that 16 arteries were actually tumor feeders and unequivocal excluding 4 arteries as a tumor arterial supply. The remainder 5 arterial branches could not be safely characterized due to artifacts or technical limitations. In 8 patients in which tumoral vascular supply could not be elucidated by angiography alone, i.a CEUS increased the accuracy of superselective embolization, and provided other clinically relevant information in 2 of these patients. No adverse effects were observed.

**Conclusions:** For guidance of superselective TACE i.a CEUS is a safe and feasible method.

**Keywords:** transarterial chemoembolization, contrast-enhanced ultrasonography, liver tumors

### Introduction

Contrast-enhanced ultrasonography (CEUS) is a flexible and versatile adjunct to many liver oncologic interventions, playing an important role in therapeutic planning, intervention guidance and post-treatment evaluation [1]. Although the vast majority of the respective applications of CEUS require intravenous administration

of the echo-enhancer, techniques based on intraarterial or intraportal injection of the echo-enhancer have also emerged. Initial experience has demonstrated that these techniques are safe and feasible and can increase the diagnostic yield of CEUS, or facilitate certain liver interventions [2-4].

In our institution we routinely use CEUS for immediate and for short-term assessment of the efficacy of transarterial chemoembolization (TACE) of liver tumors [5,6]. Recently, we have utilized CEUS with the intraarterial administration of echo-enhancer (i.a CEUS) for the guidance of TACE. We herein describe the technique and evaluate the feasibility of i.a CEUS guidance of TACE, with a special focus on tumor targeting and on the identification of tumor feeders.

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## Material and method

### *Patients and tumors*

In this prospective study 12 patients (9 men, 3 women; mean age: 70 years; range: 54–82 years) were included. Seven patients were affected by hepatocellular carcinoma (HCC), 4 patients by liver metastases from colorectal cancer and one by cholangiocarcinoma. Eight patients had solitary lesions. A total of 17 target tumors were chosen for treatment with superselective (segmental and/or subsegmental) TACE. The longest diameter of the target tumors lesions ranged from 1.9–8.1 cm (mean: 4 +/-2.12 cm).

All patients provided a written informed consent both for TACE and for i.a CEUS. This study was approved by the institutional review board (the Ethical Committee) of our hospital.

### **Chemoembolization**

Selection criteria (fulfilled by all patients) as well as the basic technique of chemoembolisation were similar to those described in a previous work [5]. Segmental or subsegmental arteries considered as probable tumor feeders were superselectively catheterized with a microcatheter (2.7 Fr. Progreat, Terumo, Europe, N.V, or 3.0 Fr. Microferret, Cook, Europe) and digital subtraction angiography (DSA) was performed during manual injection of 2-3 ml of non-ionic contrast medium (iodine concentration; 300 mg/ml). If tumor blush was angiographically detected, the respective vessel was unequivocally characterized as tumor-feeding and TACE was performed. If no tumor stain was present on DSA, further evaluation with i.a CEUS was carried out.

The chemoembolic mixture consisted of a suspension of preloaded, drug-eluting microspheres (DC-Beads Biocompatibles Ltd, Surrey, UK). Each patient received 2-4 ml of DC beads (diameters: 100-300  $\mu$ m and 300-500  $\mu$ m). For TACE of HCC and of cholangiocarcinoma, DC Beads were preloaded with doxorubicin (Adriblastina, Pfizer Italia S.r.l., Nerviano, Milano, Italy) at a dose of 25-37.5 mg drug/ml of hydrated beads. For TACE of metastases, DC Beads were preloaded with irinotecan (Campto, Aventis Pharma, Dagenham, UK) at a dose of 50 mg drug /ml of hydrated beads.

### **TACE guidance with i.a CEUS**

The location of the tumor was identified with gray-scale ultrasonography, immediately prior to the echo-contrast study. i.a CEUS required administration of an echo-enhancer through the microcatheter and imaging of the area of the target tumor with a dedicated, contrast specific, technique.

The echo-enhancer utilized in this study was a sus-

pension of microbubbles of sulphur hexafluoride (SonoVue, Bracco, Milan Italy). The ratio of dilution of SonoVue and the rate of injection varied in the first 4 patients; however, in the last 8 patients, the following protocol was applied: 0.5 ml of the suspension of SonoVue were diluted with 1.5 ml of solution of sodium chloride 0.9%, in a 2.5 ml syringe and was manually injected through the microcatheter, at a rate of 0.5 ml/second. The microcatheter was flushed with heparinized saline, both prior to, and after injection of the echo-enhancer to prevent mixing of the microbubbles with iodine contrast or with the chemoembolic mixture.

Scanning of the target tumor and of the surrounding liver parenchyma was initiated immediately after the injection of SonoVue and lasted for 15-20 seconds. Imaging technique was the same as with CEUS after intravenous SonoVue: a low-mechanical index (MI: 0.08-0.11) was utilized and scanning parameters were optimized, to facilitate detection of the microbubbles in the area of the tumor and to minimize background echoes. If intraarterial injection of SonoVue was followed by tumoral enhancement, the respective artery was considered to be the tumor feeding. On the contrary, if i.a CEUS resulted in (sub)segmental enhancement of uninvolved liver parenchyma, the respective artery was considered as normal (non-tumor feeding).

The i.a CEUS was performed with a Esaote Megasp GPX (Esaote, Genoa, Italy) or with a Philips HD11 XE (Philips Ultrasound, Andover, MA, USA) ultrasonographic units with convex, 2.5-5 MHz probes. The unit was transferred in the angiographic suite and positioned next to the right-upper side of the angiographic table. Intra-procedural CEUS required cessation of fluoroscopy, elevation of the image intensifier and removal of the sterile drapes from the right upper quadrant of the patient's abdomen.

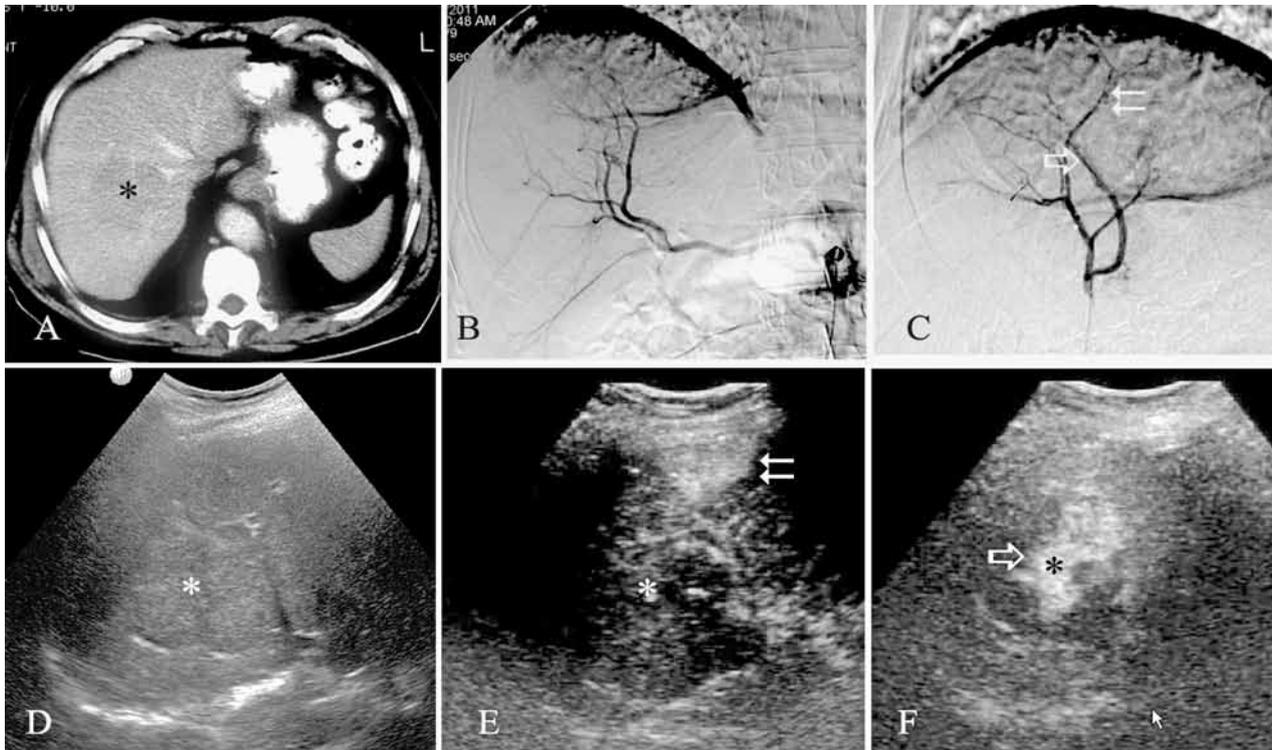
All i.a CEUS studies were performed by the same radiologist (HM) with 7 years experience in CEUS imaging and 4 years experience in liver interventions. All TACE treatments were performed by KM (20 years experience in liver interventions) and HM. After each session of TACE, these two radiologists decided in consensus on the following issues: the efficacy of i.a CEUS in identifying tumor feeders; the clinical relevance of additional i.a CEUS findings; the impact of i.a CEUS on treatment outcome. The procedural delay caused by i.a CEUS and the safety of this technique were also evaluated.

## Results

A total of 25 arteries (7 segmental, 18 subsegmental) were studied with i.a CEUS. On the basis of the afore-

mentioned criteria, 16 arteries were characterized as tumor feeders, while 4 arteries were considered as non-tumor feeding vessels (table I, fig 1).

It was deemed that i.a CEUS had a positive impact on the treatment outcome in 8/12 patients (66.6%): By confidently identifying tumor feeders, i.a CEUS redu-



**Fig 1.** i.a CEUS-guided TACE of a solitary metastasis (\*). The lesion is hypovascular on contrast-enhanced CT prior to treatment (A). Tumor feeders cannot be confidently identified on the angiogram of the replaced right hepatic artery (B), or on the super-selective angiogram (C). Two subsegmental arteries (double arrow and open arrow, respectively on C) were suspected as tumor feeders. Tumor location was initially identified with unenhanced US (D). Injection of SonoVue in the first subsegmental artery (double arrow, C) resulted in the enhancement of the non-tumorous liver (double arrow, E). Injection of SonoVue in the other subsegmental artery (open arrow, C) resulted in strong intralésional enhancement (open arrow, F). This artery was embolised.

Table I. Summary of the studied tumors, tumor feeders and i.a CEUS findings.

Patient no	Tumor type	Tumor(s) number	Number of studied arteries	Identification of tumor feeders with i.a CEUS	Impact on treatment outcome
1	HCC	1	1	Unsuccessful (unknown reason)	N
2	HCC	1	2	Unsuccessful (acoustic shadowing)	N
3	Meta	1	2	Successful (1F, 1NF)	Y
4	CCC	1	2	Successful (2F)	Y
5	HCC	1	2	Unsuccessful (deep location)	N
6	HCC	1	2	Successful (2F)	N*
7	HCC	1	1	Successful (1F)	Y
8	Meta	2	2	Successful (2F)	Y
9	Meta	2	3	Successful (2F, 1NF)	Y
10	HCC	3	4	Successful (3F, 1NF)	Y
11	HCC	2	2	Successful (2F)	Y
12	Meta	1	2	Successful (1F, 1NF)	Y

HCC- hepatocellular carcinoma, Meta- liver metastasis, CCC- cholangiocellular carcinoma, F- confirmed tumor feeder, NF- confirmed non-tumor feeder, N- no, Y-yes

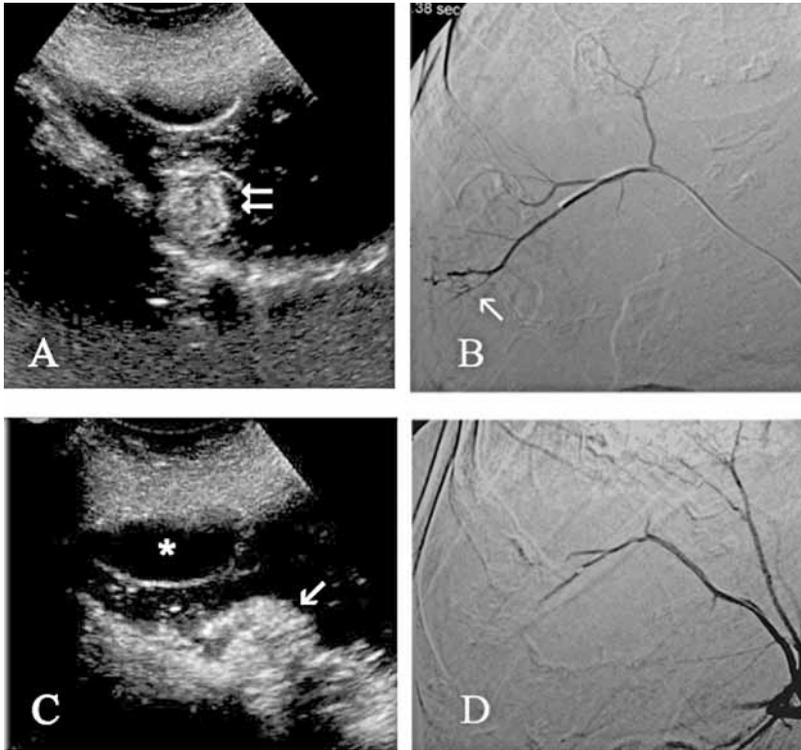
\* this tumor had a very complex vascular supply with multiple potential feeders and investigation of each probable tumor feeder with i.a CEUS was deemed impractical

ced the need for additional angiographic studies and by detecting non-tumoral arteries, i.a CEUS reduced the risk of non-target embolization. In 2 of these 8

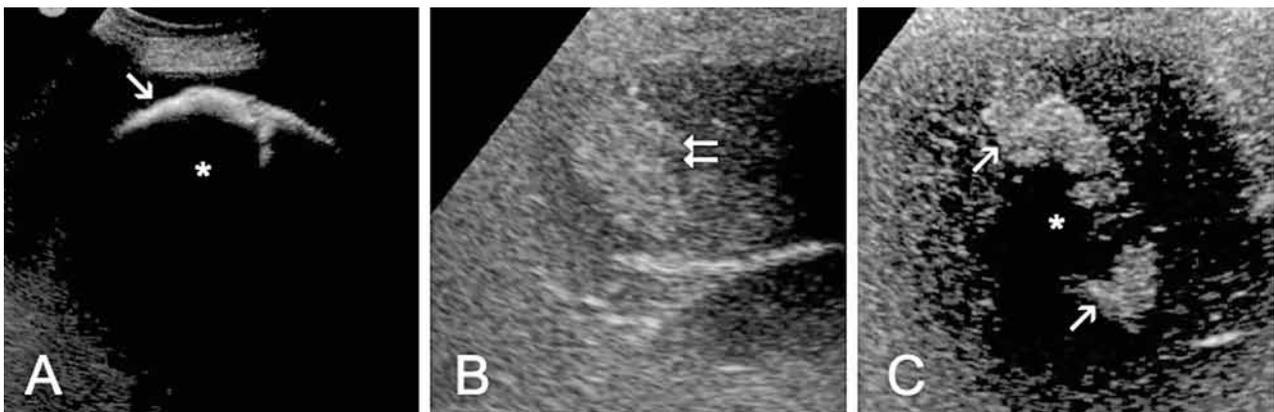
patients, i.a CEUS provided additional useful information. In the first patient, injection of SonoVue in a segmental artery resulted in tumoral enhancement, but also in enhancement of a large part of liver parenchyma around the tumor. This prompted to a more distal (subsegmental) placement of the microcatheter, in order to minimize damage in the non-tumorous liver. In the second patient with a small HCC located close to the gallbladder, i.a CEUS confirmed that the gallbladder derived no vascularity from the tumor feeder, which was subsequently embolised (fig 2).

In 3 patients with HCC, 5 probable tumor feeders could not be confidently characterized with i.a CEUS due to artifacts or technical errors. Artifacts and ancillary findings of i.a CEUS are depicted in fig 3.

All i.a CEUS studies were well tolerated and no adverse effects were observed. All patients were discharged the day after TACE and no complications were observed. The duration of the sonographic study of each potential tumor feeder (including dilution of the echo-enhancer, preparation of the scanning field, injection, scanning, and on-site evaluation) did not exceed 5 minutes.



**Fig 2.** i.a CEUS-guided TACE of a small HCC. On CEUS with i.v. SonoVue prior to TACE (A), the lesion shows early enhancement (double arrows). On the super-selective angiogram (B), there are only faint signs of neovascularity (arrow). i.a CEUS through the artery catheterized in (B), shows definite, strong tumoral enhancement (arrow, C). The neighboring gallbladder (\*) shares no vascularity with the tumor. TACE was safely performed through the selected artery. D: post TACE angiogram.



**Fig 3.** Artifacts and ancillary findings of i.a CEUS. A: Accumulation of microbubbles at the superficial parts of the liver (arrow) obscures the deepest portions of the liver due to acoustic shadowing (\*). B: Persistent "pooling" of microbubbles in a liver subsegment, probably due to forceful injection, appears as a pseudolesion (double arrow). C: Unexplained, preferential early enhancement of the peritumoral liver (arrows), instead of the tumor (\*).

## Discussions

Identification of the appropriate tumor feeders is of crucial importance in superselective (chemo) embolization. Successful subsegmental TACE in patients with HCC is associated with a high degrees of tumor necrosis, low recurrence rates and prolonged survival [7,8]. On the contrary, inappropriate selection and subsequent TACE of a normal artery adjacent to the tumor will only result in damage of the uninvolved liver parenchyma. Angiographic detection of tumor feeders may be challenging in small and hypovascular tumors, with little or no tumor blush on DSA, or in tumors with a complex vascular supply. Additional difficulties are to be expected, when target tumors are located near vital organs (eg. gallbladder); the latter may be inadvertently embolised, even after superselective catheterization, if the gallbladder shares small arterial branches with the treated neoplasm.

Cone-beam computed tomographic guidance of TACE represents a sophisticated and efficient solution for the aforementioned problems [9]. However, this technique requires expensive and not widely available equipment (i.e an angiographic unit with a flat-panel detector); it is also associated with radiation exposure and with iodine contrast injection.

Contrast-enhanced US with intraarterial injection of echo-enhancer may be a promising alternative for guidance of superselective TACE. In the past, microbubbles of carbon-dioxide injected through angiographic catheters were used as a sonographic contrast agent, to reveal tumors inconspicuous on DSA and to facilitate targeting of feeders for TACE [10]. However, in this approach, conventional (B-mode) sonography was utilized to detect the microbubbles. Intraprocedural imaging based on intraarterial application of modern (2<sup>nd</sup> generation) echo-enhancers along with the dedicated, contrast-specific software is likely to provide a more clear and detailed visualization of micro- and macro-circulation. Intraarterial administration of SonoVue during TACE was originally proposed by Schacherer et al, who used "sono-hepatic-arteriography" to detect lesions inconspicuous on other modalities and to assess the efficacy of TACE [2]. In our study, we used a similar technique as a guiding tool, to facilitate selection of the correct tumor feeders, when angiographic identification of them was not straightforward. By correlating the sonographically evident tumoral enhancement with angiography, 80% of the studied arteries were confidently characterized as tumor-, or non-tumor feeding, thus increasing the accuracy of TACE and avoiding non-target embolization. Moreover, by depicting in real time the vascular territory of each injected vessel, i.a CEUS provided information re-

garding the extent of expected tissue necrosis (in case of embolization) and regarding potential involvement of adjacent vital organs. Other advantages of i.a CEUS include the lack of radiation or iodine load to the patient, the short examination time and the acceptable cost (only a small part of the content of each 4.8 ml-vial of the echo-enhancer is required for an intraarterial injection).

Clearly, i.a CEUS guidance is not free of limitations. Artifacts and technical issues may impair detection of tumor feeders. For example, similar to other applications of CEUS, evaluation of multiple, hyperechoic or deeply seated tumors may be problematic [10,11]. Moreover, the clinical impact of i.a CEUS largely depends on the skill and on the experience of the operator, who has only a few minutes to acquire and interpret CEUS images, to correlate them with DSA and to make therapeutic decisions.

In **conclusion** i.a CEUS guidance is feasible, safe and potentially useful in selected cases of TACE, in which targeting of tumor feeders cannot be safely accomplished on an angiographic basis alone. Further research is required, to optimize and standardize this technique and to demonstrate the clinical benefits of guided TACE in terms of tumor response and patients' survival.

**Conflict of interest:** none

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