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CLINICAL INVESTIGATION INTERVENTIONAL ONCOLOGY

Real-Time US-CT/MRI Image Fusion for Guidance of Thermal Ablation of Liver Tumors Undetectable with US: Results in 295 Cases

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Abstract
Purpose This study was designed to assess feasibility of US-CT/MRI fusion-guided ablation in liver tumors undetectable with US.
Methods From 2002 to 2012, 295 tumors (162 HCCs and 133 metastases; mean diameter 1.3 ± 0.6 cm, range 0.5–2.5 cm) detectable on contrast-enhanced CT/MRI, but completely undetectable with unenhanced US and either totally undetectable or incompletely conspicuous with contrast-enhanced US (CEUS), were treated in 215 sessions using either internally cooled radiofrequency or microwave with standard ablation protocols, guided by an image fusion system (Virtual Navigation System, Esaote S.p.A., Genova, Italy) that combines US with CT/ MRI images. Correct targeting and successful ablation of tumor were verified after 24 hours with CT or MRI.
Results A total of 282 of 295 (95.6 %) tumors were correctly targeted with successful ablation achieved in 266 of 295 (90.2 %). Sixteen of 295 (5.4 %) tumors were correctly targeted, but unsuccessfully ablated, and 13 of 295 (4.4 %) tumors were unsuccessfully ablated due to inaccurate targeting. There were no perioperative deaths. Major complications were observed in 2 of the 215 treatments sessions (0.9 %).
Conclusions Real-time virtual navigation system with US-CT/MRI fusion imaging is precise for targeting and achieving successful ablation of target tumors undetectable with US alone. Therefore, a larger population could benefit from ultrasound guided ablation procedures.

Keywords Real-time virtual navigation · Liver malignancies · Percutaneous thermal ablation · Ultrasonography · Image fusion

Introduction

Thermal ablation has been validated as a treatment for hepatocellular carcinoma (HCC) and unresectable liver

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metastases [1–14]. An essential premise to achieve good results with percutaneous ablation therapies is the availability of precise and reliable imaging techniques for accurate pre-procedural planning, intraprocedural targeting, and postprocedural assessment of the therapeutic success [5, 6, 8, 10, 14]. Ultrasound (US) is actually the most widely diffused imaging technique for guiding percutaneous ablations, because it allows for real-time visualization of the needle insertion and monitoring of the procedure and does not require ionizing radiation [3–5, 8–18]. Moreover, a not negligible number of liver tumors are clearly visualized on computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET) but are completely undetected with US due to their location, small size, or echogenicity [16–20]. When contrast-enhanced US (CEUS) is available and achieves good visibility of the target, ablation can be performed under the guidance of real-time CEUS [21–24]. However, there are some cases in which even with CEUS the tumor cannot be visualized or its conspicuity is incomplete rendering the target only partially assessable, for example in the case of small HCCs, which often are not sufficiently hypoechoic in the delayed phase of contrast-enhanced US to enable safe and accurate targeting. Accordingly, the use of a virtual navigation system that combines real-time procedural US with reconstructed CT or MRI or even FDG-PET images can potentially increase detectability and conspicuity of tumors and allow more precise targeting and monitoring [25–38]. Moreover, validation of this technique has been reported for small series of patients [26, 28, 33–36]. Accordingly, the purpose of this study was to assess the feasibility of US-CT/MRI fusion-guided ablation in liver tumors undetectable with conventional US and insufficiently detected with CEUS in a large series of patients.

Table 1 Demographics, pathological diagnosis, lesion dimension and location, type of percutaneous treatment, and type of fusion guidance in 295 liver tumors in 175 patients

Demographics	
Age (yr)	66 ± 12.3
Sex (M/F)	113/62
Pathology	
HCCs	162
Metastases	133
Breast	24
Colon	74
Stomach	7
Other	28
Size	
Mean maximum diameter (cm)	1.3 ± 0.6
<1.5	215
>1.5	80
Liver segment	
1	4
2	30
3	15
4	53
5	32
6	47
7	35
8	79
Treatment	
RFA	171
MWA	124
Imaging guidance	
US-CT fusion	239
US-MRI fusion	56

HCC hepatocellular carcinoma; *M* males; *F* females; *RFA* radiofrequency ablation; *MWA* microwave ablation

Materials and Methods

Patients

Our database of patients who underwent percutaneous thermal ablation of liver malignancies was retrospectively reviewed. From December 2002 to December 2012, 987 patients (1,581 tumors) were treated. Institutional Review Board approval was obtained, and patients' informed consent was waived.

At our institution, patients with a single HCC up to 5 cm, or up to five HCCs ≤3 cm and no contraindications are considered for percutaneous ablation. Patients with metastases are considered for percutaneous ablation if they have up to five liver lesions ≤5 cm and are considered not resectable or at high surgical risk or refuse surgery. Discussion with the referring physician and surgical evaluation are always performed before enrolling a patient for percutaneous ablation.

Of 1,581 tumors, 295 (18.6 %) (162 HCCs and 133 metastases) with a mean diameter of 1.3 ± 0.6 cm (mean ± standard deviation; median 1.2 cm; range 0.5–2.5 cm) in 175 of 987 (17.7 %) patients (113 males and 62 females, aged 66 ± 12.3 years) were considered not treatable with US- and/or CEUS-guidance by interventional radiologists with greater than 15 years' experience (L.C., T.I., L.S.). For this reason, they underwent treatment guided by real-time virtual navigation system with US-CT/MRI fusion imaging, based on the visualisation of the tumors on CT or MRI. A total of 215 treatment sessions were performed; 182 tumors were considered not treatable with US- and/or CEUS-guidance because of insufficient conspicuity/distinction in their echogenicity from

surrounding tissue or a lack of detection, because they were located in an area not accessible to US. Baseline characteristics of these patients are summarized in Table 1.

Technique

Pre-Procedural Examinations

CEUS was performed by one of three interventional radiologists (L.C., T.I., L.S.) using ultrasound machines with contrast-specific software (MyLab 70 XVG and MyLab Twice, Esaote S.p.A., Genova, Italy) and a bolus of 2.4 ml of microbubble contrast agent (Sonovue, Bracco Imaging, Milan, Italy).

CT examinations were performed with 40-slice scanner (Somatom Sensation 40, Siemens Healthcare, Erlangen, Germany) after intravenous injection of 100–120 ml of contrast agent (Iomeron 350, Bracco Imaging, Milan, Italy). Scans were obtained during expiration breath-hold, in arterial (using a bolus tracking technique; 15–25 sec delay), portal venous (75 sec), and delayed (180 sec) vascular phases, with the following scanning parameters: 120 kVp, 200 mAs with care dose 4D, 2.5-mm slice thickness.

MRI scans were performed on 1.5 T system (Magnetom Avanto, Siemens Healthcare), employing a SENSE body coil. Our protocol included: T2 true fast imaging with steady state precession, breath-hold, coronal and axial planes, section thickness 6 mm; T1 spoiled gradient echo in-opp phase, axial plane; T1 volume interpolated fat-sat gradient echo, coronal and axial planes, 3-mm slice thickness; breath-hold axial single-shot echo planar (EPI) DWI, b factors 50/400/800 sec/mm^2, 2-mm section thickness. Then, 0.1-mmlo/kg body weight of Gd-EOB-DTPA (Primovist, Schering, Berlin, Germany) was administered with an infusion rate of 1 ml/sec, and T1 volume interpolated fat-sat imaging sequences were acquired with 2-mm slice thickness. The first post-contrast (arterial phase) sequences were started manually using bolus tracking at the time when contrast agent reached the thoracic aorta. Four subsequent acquisition intervals were placed between arterial and portal venous phase (20 s) and between portal venous and equilibrium phase (40 s). Finally, T1 spoiled gradient echo fat–sat sequences were acquired 20 min after contrast material administration at the hepatocellular phase.

US-CT/MRI Imaging Fusion

US scanners (MyLab 70 XVG and MyLab Twice, Esaote S.p.A., Genova, Italy) with 3.5-MHz convex probe provided with needle guidance device and dedicated built-in hardware and software (Virtual Navigator, Esaote, Genova, Italy) were used. Hardware included a magnetic field transmitter, fixed to the operation table and placed close to the right upper quadrant of the patient abdomen (Ascension Technology Corporation, Burlington, USA) and two electromagnetic sensors, one applied to the US probe and one attached to the handle or, from 2010, secured to the hub (VirtuTrax, CIVCO Medical Solutions, Kalona, IA) of the ablation applicator (Fig. 1). This commercially available system enables position and orientation in space of the US

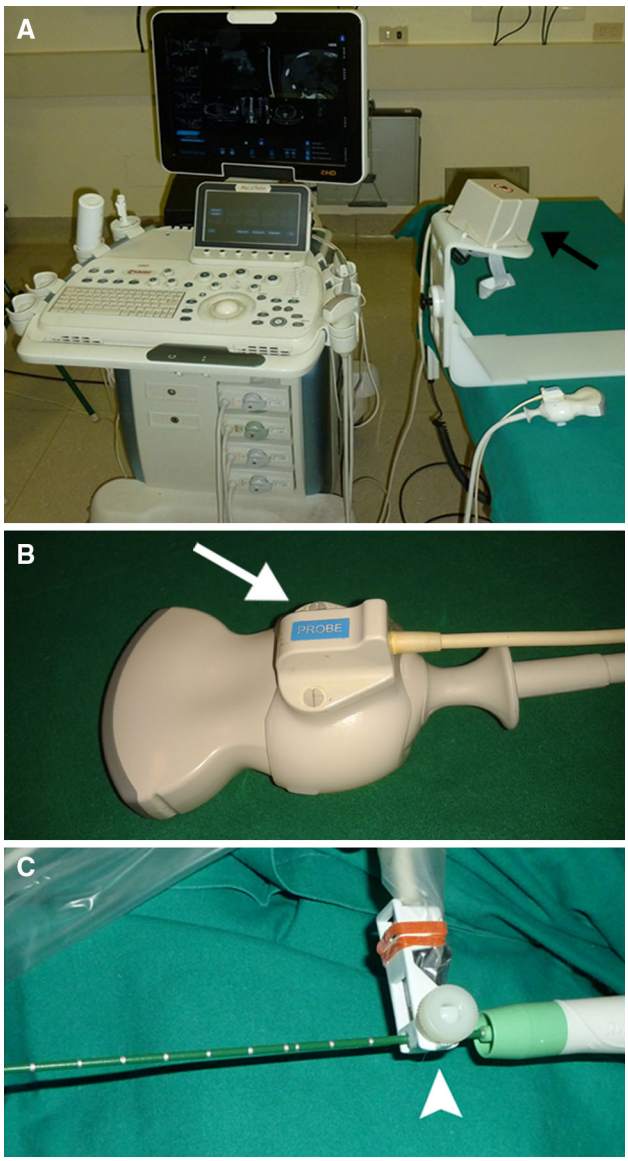

Fig. 1 Virtual navigation system for real-time US-CT/MRI image fusion. The system is made of an US scanner (Mylab Twice, Esaote, Genova, Italy) with a dedicated built-in hardware and software (Esaote, Genova). An electromagnetic tracking system integrated in the workstation consists of a magnetic field transmitter (*black arrow*, **A**), fixed to the operation bed at the right upper quadrant of the abdomen, and two electromagnetic sensors, one applied to the convex ultrasound probe (*white arrow*, **B**), and one mounted on ablation applicator (*arrowhead*, **C**)

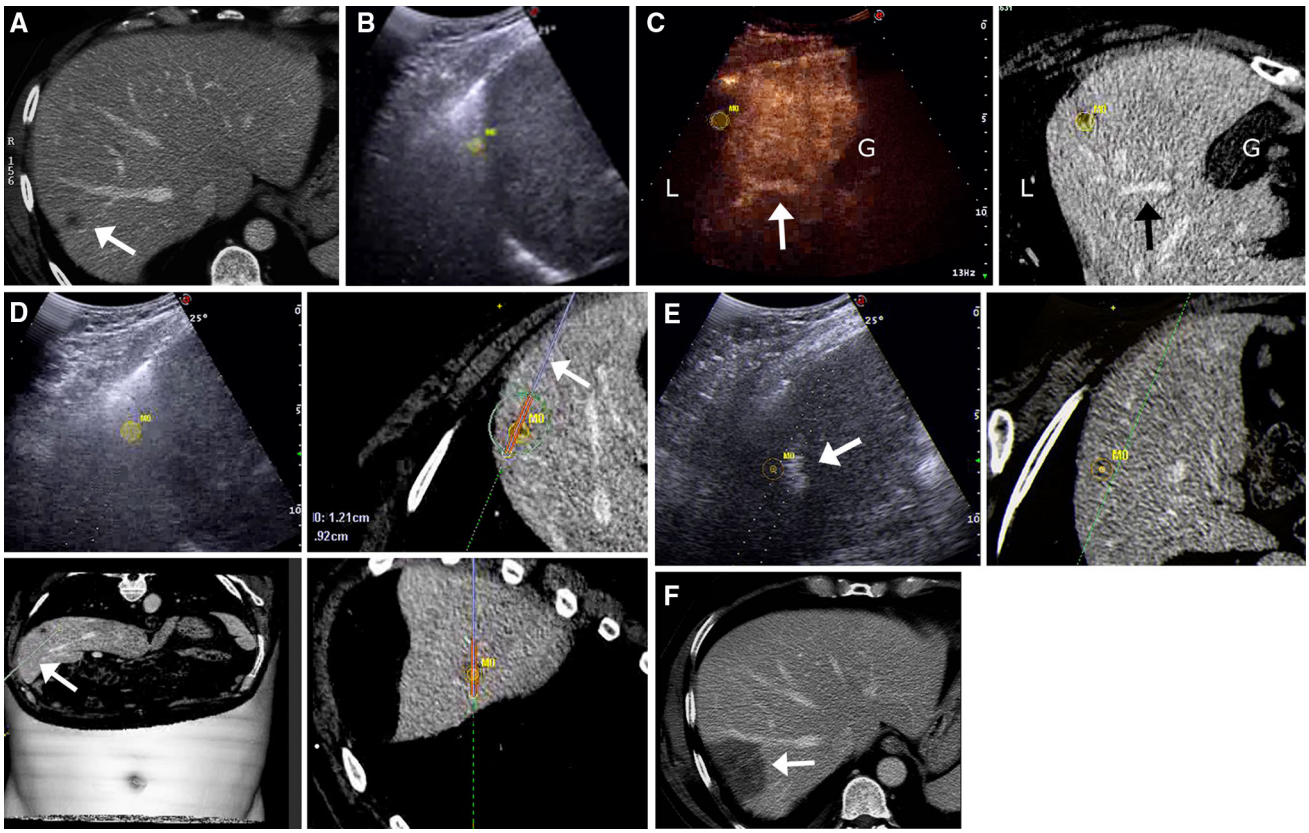

Fig. 2 Real-time, US-CT image fusion for guidance of thermal ablation of colorectal liver metastasis detected by contrast-enhanced CT (*arrow*, **A**), but undetectable by US and CEUS (*left side*, **B**), being hidden by air lung due to its location. With image fusion the lesion is clearly seen on CT (*right side*, **B**) (*yellow circle* virtual target; *L* lung; *G* gallbladder; *arrow* portal vein branch). Radiofrequency electrode is inserted into the target under the guidance of CT scan as a reference (*right side*, **C**) and completely blind for US (*left side*, **C**). The "real" electrode is not visible on US both before (*left side*, **C**) and during ablation (*left side*, **D**) (*arrows* gas formation during ablation), whereas the "virtual" electrode is visible on CT (*arrows* in **C**) (*yellow circle* virtual target). 24-hour, follow-up, contrast-enhanced CT demonstrates correct targeting and successful ablation of the lesion (**E**)

probe in space to be determined in relation to the transmitter and generates real-time matched US-CT/MRI images.

Prior to ablation, CT/MRI data were transferred in DICOM format to the US system. Series to be used for fusion imaging were selected case by case, based on the criteria of optimal display of target lesions and detectability of adjacent or intervening blood vessels.

Registration of US with the cross-sectional imaging modality (CT or MRI) was performed starting from a reference plane (usually the plane crossing the umbilicus) as detected by both modalities. Initially, image fusion was further refined by subsequently identifying 4–5 concordant internal anatomic markers (e.g., vessel bifurcations) on both the US and the CT/MRI study with slight manual adjustments (fine tuning) by the operator to ensure total alignment of the images. More recently, only one anatomic marker was needed for acceptable image registration with "fine tuning" technique no longer required. Correct registration can be realized in approximately 5–20 min. Once registration was finalized, the system simultaneously displayed in real-time US scans on one side of the screen and CT/MRI reconstructed scans on the other side (Fig. 2).

An electronic "virtual" target was manually applied to the tumor seen on CT or MRI scans and immediately an analogous target was automatically applied by the machine to the corresponding anatomical area on US scans. The most suitable path to the target, selected by the operator, was automatically applied both on US and CT/MRI scans.

Ablation Procedures

Treatments were performed under general anaesthesia. Radiofrequency (RFA) ablations were performed with a 200 W generator and single, 2–3-cm tip, 17-gauge, monopolar, cooled-tip electrodes (Covidien, Boulder, CO). For microwave (MWA) ablations, a high-power (140 W, 2.45 GHz) microwave generator (AMICA, HS Hospital Service, Aprilia, Italy) with 14-gauge, internally cooled, coaxial antennas was used. Applicator insertions were

performed at ventilator-driven expiration or temporary cessation of ventilation by the anaesthesiologist. During insertion of the electrode/antenna, and throughout the ablation procedure, the system automatically showed a virtual needle on the CT/MRI scans (Fig. 2).

Postablation Targeting and Technical Success

Accuracy of targeting and success of ablation were assessed at 24 hours with dynamic CT or MRI scans. Tumor was considered correctly targeted when the center of the ablated zone was located within 5-mm range from the ideal target point preoperatively established and successfully ablated when the nonenhancing necrotic volume covered the whole tumor and a margin of at least 5 mm of hepatic tissue all around the tumor ("ablative safety margin") [39–41]. Complete ablation was defined as absence of contrast enhancement in the tumor at 3–4 months.

Data Analysis

Technical feasibility, rate of correctly targeted and successfully ablated at 24 hours tumors, and rate of complications were evaluated. Number of correctly targeted tumors and of tumors incorrectly targeted was compared according to pathology (HCC vs. metastases), method of guidance (US/CT fusion vs. US/MRI fusion), and ablative technique (RFA vs. MWA) using Fisher's exact test. Mean dimension of correctly targeted tumors was compared with mean dimension of tumors not correctly targeted using Mann–Whitney *U* test. Target tumor distribution in liver segments was compared between correctly targeted tumors and tumors not correctly targeted using χ^2 test. Analysis was performed using GraphPad Prism 5 software (GraphPad, La Jolla, CA).

Results

Real-time fusion imaging was technically feasible and enabled to perform ablations successfully in all cases. Successful ablation was achieved in 266 of 295 (90.2 %) tumors. Sixteen of 295 (5.4 %) tumors were correctly targeted, but the necrosis volume size was insufficiently large to cover the whole tumor volume and the ablative margin, resulting in incomplete ablation. In the remaining 13 of 295 (4.4 %) cases, the distance between ablated volume center and ideal target point preoperatively established was greater than 5 mm, ranging from 8 to 16 mm (11 ± 3 mm) with this considered as unsuccessful ablation deriving from incorrect targeting. Mean size of noncorrectly targeted lesions was 1.2 ± 0.5 cm (mean ± standard deviation). One tumor was located at S1, one at S2, two at S4, three at S7, and five at S8. Of the 29 unsuccessfully ablated tumors, 11 (37.9 %) underwent successful percutaneous ablative retreatment, 8 (27.6 %) underwent chemoembolization, and 10 (34.5 %) had disease progression before the time of planned retreatment and underwent chemotherapy or palliative therapy. At 3–4 months complete ablation was achieved in 250 of 277 (90.3 %) tumors, including the 11 tumors that were retreated and excluding the 18 tumors could not be retreated with percutaneous ablation. No differences were found in correct targeting between patients treated with MWA (119/124, 96.0 %) and patients treated with RFA (163/171, 95.3 %; $p = 1.000$), nor between patients with HCC (155/162, 95.7 %) and patients with metastases (127/133, 95.5 %; $p = 1.000$) (Table 2).

No procedure-related deaths occurred. Minor complications occurred in 9 of 215 (4.2 %) sessions (small pleural effusions in 5 and minimal ascites in 4) and major complications in 2 of 215 (0.9 %). One patient developed right

Table 2 Results of ablative treatment of 295 liver tumours targeted by the guidance of real time US-CT/MRI image fusion: comparison among different groups

	Correct targeting ($n = 282$, 95.6 %)	Inaccurate targeting ($n = 13$, 4.4 %)	*P*
Pathology			
HCCs (n = 162)	155 (95.7 %)	7 (4.3 %)	1.000
Metastases (n = 133)	127 (95.5 %)	6 (4.5 %)	
Guidance			
US/TC fusion (n = 239)	230 (96.2 %)	9 (3.8 %)	0.279
US/MRI fusion (n = 56)	52 (92.9 %)	4 (7.1 %)	
Ablative technique			
RFA (n = 171)	163 (95.3 %)	8 (5.7 %)	1.000
MWA (n = 124)	119 (96.0 %)	5 (4.0 %)	
Lesion's dimension (cm)	1.3 ± 0.6[a]	1.2 ± 0.5[a]	0.971
Liver segment			
I (n = 4)	3	1	0.223
II (n = 30)	29	1	
III (n = 15)	15	0	
IV (n = 53)	51	2	
V (n = 32)	31	1	
VI (n = 47)	47	0	
VII (n = 35)	32	3	
VIII (n = 79)	74	5	

HCC hepatocellular carcinoma; *CT* computed tomography; *MRI* magnetic resonance imaging; *RFA* radiofrequency ablation; *MWA* microwave ablation

[a] Data are given as mean ± standard deviation

colon wall perforation 24 hours after the procedure and underwent surgery. A second patient developed an anterior abdominal wall hematoma and prolonged hospitalization with no repair treatment required.

Discussion

During the past 15 years, image-guided thermal ablation has been increasingly used for the treatment of neoplastic diseases because of its low invasiveness, efficacy, repeatability, and low cost [1–14].

The importance of imaging for success and safety of percutaneous ablations is crucial. US is currently the most widely used method of guidance for percutaneous ablations of abdominal organs [3–5, 8–18]. However, compared with contrast-enhanced, cross-sectional modalities (e.g., CT and MRI), US has less contrast resolution and can be limited by the presence of aerated lung parenchyma and bone. Thus, tumors easily seen with CT or MRI may be inconspicuous (insufficient distinction in its echogenicity from surrounding liver tissue) or undetectable (located in an area inaccessible to US) with conventional US [16–20]. In a recent series [19], Kim et al. reported a 25.3 % rate of undetectable target tumors on the pretreatment planning US, with tumor size, distance between the tumor and the diaphragm, liver cirrhosis, and macronodular cirrhosis representing statistically significant factors affecting US detection at multivariate analysis. Compared with US, CEUS has been reported to increase lesion conspicuity, and consequently may be helpful in targeting tumors not well seen on US [21–24]. However, some tumors may not be sufficiently and thoroughly seen even with CEUS and poor conspicuity has been reported as a major cause of mistargeting [20]. Accordingly, there is a growing interest for guidance methods that combine the advantages of different imaging modalities. Although systems for real-time image fusion of US and CT have been commercially available for some years, only recently reports of their accuracy and efficacy have been published, most often in mixed populations of patients [25–37]. In our study, we fused real-time US and CT/MRI scans in the interventional room using one reference axial plane and increasingly fewer internal anatomical marker and less and less manual fine tuning. The accuracy of the system used in our study was previously tested in an animal setting [42].

At our institution, all patients with liver tumors for which percutaneous thermal ablation is indicated as the treatment of first choice undergo preprocedural liver US, CEUS, and contrast-enhanced CT or MRI. When the target tumor is visible in its entirety with unenhanced US, ablation is routinely performed under US-guidance with CEUS routinely used immediately afterwards for assessment of the volume of necrosis achieved [21, 43]. When the target tumor is partially or completely undetectable with unenhanced US and thoroughly visible in its full conspicuity with CEUS, ablation is performed under the guidance of real-time CEUS. However, there are many cases when the tumor is not visible with unenhanced US and either completely undetectable or partially conspicuous with CEUS. For these patients, performing ablation under the guidance of virtual navigation with real-time fusion imaging system has been reported in small series of patient [26, 28, 33–36].

Our technical success rate in a previously "inaccessible" population of tumors is similar to that (92.8–100 %) reported in groups of cases ablated under direct visualization by US, CT, or MRI [5, 8–11, 20, 42].

Some papers dealing with thermal ablation of liver tumors guided by real-time virtual navigation systems have been published [25–37]. Few of them deal with ablation of tumors undetectable with US. Liu et al. [36] performed MWA for 18 HCCs (0.9–3.8 cm in diameter) with technical success rate of 94.4 % (17/18 tumors) evaluated with intravenous contrast-enhanced CT or MRI 1 month after ablation. Nakai et al. [37] performed RFA for 20 HCCs (1.8–3.2 cm in diameter) in the CT suite with a technical success rate of 90 % (17/20 tumors), evaluated by CT immediately performed during ablation. Compared with these studies, in our much larger series (295 tumors undetectable with B-mode US) of smaller targets (mean diameter of 1.3 ± 0.6 cm), we achieved a similarly high technical success rate (90.2 %).

In our series, 16 of 295 (5.4 %) tumors were precisely targeted but unsuccessfully completely ablated. One of the advantages of real-time image fusion systems is the possibility to better assess treatment result comparing ablated area on US and tumor on CT or MRI in cases of target tumors undetectable for isoechogenicity with surrounding liver parenchyma. However, in tumors hidden by the presence of aerated lung parenchyma (Fig. 2), in addition to the usual factors that may determine some unpredictability of every ablation treatment (e.g., heat-sink effect), the amount of energy deposited may be insufficient, because it is impossible to monitor precisely the ablation volume development through the extent of gas produced by ablation and to perform an adequate postablation assessment of the necrosis size with CEUS.

In the remaining 13 (4.4 %) tumors, inaccurate targeting can likely be ascribed to patient respiration movements, needle bending, organ deformation or incorrect coregistration of US and CT or MRI. Although few in number, these technical failures highlight that precision of registration and organ motion are critical problems to tackle by precise attention to technical detail.

The very low major complications rate (0.9 %) reported in our study compares favourably with that of many literature

publications dealing with thermal ablations performed under direct visualization of thermal applicators during the whole procedure [1, 3, 5–11, 44, 45]. This may be due to the high anatomical definition of CT and MRI, the correct choice of the safest path to the target and the real-time control of the entire procedure (and particularly of the most risky phase—the initial puncture) provided by US.

In our series, 295 of 1,581 tumors (18.6 %) were undetectable at US or not sufficiently visible at CEUS and considered untreatable with conventional US guidance. Such a high percentage of tumors undetectable at US is justified by the fact that, being a major referral center, patients with hardly accessible lesions are sent to us from other centers for evaluation and, if feasible, treatment (Table 2).

Based largely upon the addition of the image-fusion, this leads one to appreciate that most patients referred to us successfully underwent even technically tough thermal ablations in the sonographic room of our center using a simple, low-cost (approximately $150,000 for an US machine equipped with navigator system), widely available and safe modality. Without this advance, many of these patients would have been otherwise referred to either other, more invasive treatments (such as surgical resection) or to thermal ablations guided by more complex, expensive, and potentially harmful (due to the use of radiation) imaging modalities (CT and MRI). Accordingly, additional patient populations with liver tumors undetectable with US and CEUS can benefit from accurate US-guided ablative treatments thanks to the real-time virtual navigation system with fusion imaging.

The major limitation of our study is that it was a retrospective single-centre study limited to ablation of liver tumors with a solitary primary end-point of assessing the technical success of ablations. Accordingly, for liver malignancies we advocate future studies that could enable to go beyond our aims and determine whether real differences in long-term local control and survival will be possible. In addition, with further technological improvements such image-guidance systems will likely expand our ability to apply ablation and other interventional procedures to additional patient populations.

Conflict of interest Giovanni Mauri, Luca Cova, Stefano De Beni, Tiziana Ierace, Tania Tondolo, Anna Cerri, and Luigi Solbiati have nothing to disclose. S. Nahum Goldberg has sponsored research and consulting for AngioDynamics, Marlborough, MA, and Cosman Company, Burlington, MA, USA.

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