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# Real-Time 3D Virtual Target Fluoroscopic Display for Challenging Hepatocellular Carcinoma Ablations Using Cone Beam CT

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**Abstract**

Three-dimensional virtual target fluoroscopic display is a new guidance tool that can facilitate challenging percutaneous ablation. The purpose of this study was to assess the feasibility, local efficacy, and safety of liver ablation assisted by three-dimensional virtual target fluoroscopic display. Sixty-seven hepatocellular carcinomas (mean diameter: 31 mm, range: 9-90 mm, 24 $\geq$ 30 mm, 16 of an infiltrative form) in 53 consecutive patients were ablated using irreversible electroporation (n = 39), multibipolar radiofrequency (n = 25), or microwave (n = 3) under a combination of ultrasound and three-dimensional virtual target fluoroscopic display guidance because the procedures were considered to be unfeasible under ultrasound alone. This guidance technology consisted of real-time fluoroscopic three-dimensional visualization of the tumor previously segmented from cone beam computed tomography images acquired at the start of the procedure. The results were assessed by cross-sectional imaging performed at 1 month and then every 3 months in the event of complete ablation. Factors associated with overall local tumor progression (initial treatment failure and subsequent local tumor progression) were assessed using a logistic regression model. Sixty-one (91%) tumors were completely ablated after 1 (n = 53) or 2 (n = 8) procedures. After a median follow-up of 12.75 months (1-23.2) of the 61 tumors displaying imaging characteristics consistent with complete ablation at 1 month, local tumor progression was observed in 9, so the overall local tumor progression rate was 22.3% (15 of 67). Under multivariate analysis, dome locations and infiltrative forms were associated with local tumor progression. No major complications occurred. Three-dimensional virtual target fluoroscopic display is a feasible and efficient image guidance tool to facilitate challenging ablations that are generally considered as infeasible using ultrasound alone.

**Keywords**

hepatocellular carcinoma, ablation, guidance, cone beam CT, fluoroscopy, fusion imaging

**Abbreviations**

3D-VTFD, three-dimensional virtual target fluoroscopic display; CBCT, cone beam CT; CT, computed tomography; HCC, hepatocellular carcinoma; IRE, irreversible electroporation; mbpRFA, multibipolar radiofrequency ablation; MR, magnetic resonance; MRI, magnetic resonance imaging; MWA, microwave ablation; ROI, region of interest; US, ultrasound.

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## Introduction

Ablation is a therapeutic option for hepatocellular carcinoma (HCC) $\leq$5 cm or up to 3 tumors $\leq$3 cm, in patients with cirrhosis who are not eligible for resection or liver transplantation.[1] However, in practice, many of these patients are still treated with palliative options because ablative procedures are considered to be too challenging, given the location or conspicuity of the tumor under standard imaging guidance such as

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ultrasound (US) or computed tomography (CT).[2-4] In 1 tertiary center, up to 32% of patients eligible for ablation according to current guidelines were considered not to be suitable for such curative treatment because the procedure was deemed too dangerous using conventional US or CT guidance alone.[5] Moreover, whatever the visibility of the target with any imaging modality, in the case of some liver tumors located in the hilum or dome and requiring ablation, multiprobe techniques such as irreversible electroporation (IRE) or multibipolar radiofrequency ablation (mbpRFA)[6,7] could be used. The safety and efficacy of such problematic multineedle insertions could be improved through the easier three-dimensional (3D) assessment of the arrangement of applicators than that currently provided by standard cross-sectional imaging, that is, US and CT. Using modern angiographic rooms equipped with CT-like imaging capabilities or cone beam CT (CBCT), operators have reported improvements in their success rates with hyperselective endovascular treatments for HCC.[8,9] Cone beam CT has also proved its ability to assess the completeness of percutaneous ablation.[10]

We hypothesized that CBCT-enhanced fluoroscopic imaging could also facilitate challenging liver ablations, overcoming common technical limitations such as poor tumor visibility or a complex spatial relationship between multiple probes and the target. The principal concept underlying this proposed new guidance technique consists in the real-time overlay of a 3D virtual target on live fluoroscopy. This target can be created from a preablative intravenous contrast-enhanced liver CBCT, either alone if the tumor is visible or combined with pretherapeutic conventional cross-sectional images such as CT or magnetic resonance (MR). We refer to this technique as 3D virtual target fluoroscopic display (3D-VTFD). During the present study, we assessed the feasibility and safety of 3D-VTFD in guiding challenging percutaneous ablations of HCC.

## Materials and Methods

### Patients and Tumors

Our retrospective study was approved by our local ethics committee, and informed written consent from the patients was waived. Between January 2014 and January 2015, fifty-three patients (mean age 66.6 [11.8] years; range: 40.5-89.2 years; 9 women), with a total of 67 HCC tumors (mean diameter 31 [21] mm; range: 9-90 mm, 24 $\geq$ 30 mm), underwent 75 percutaneous ablations (including 8 repeated procedures because of incomplete ablation) under US (Logiq E9; GE Healthcare, Chalfont St Giles, United Kingdom) and 3D-VTFD guidance in our angiography suite (Innova IGS540; GE Healthcare). The choice of 3D-VTFD rather than standard US guidance alone was decided upon because of poor visibility of the tumor and/or the planning of problematic needle punctures with US alone and/or a need for easy 3D real-time visualization of the geometrical arrangement of several applicators. Our center has more than 10 years' experience in the intensive use of multiapplicator ablative techniques under US guidance alone for the treatment of liver tumors that are beyond the standard technical limits of feasibility, including locally advanced stages.[7,11] Indeed, all 67 tumors were located at a hazardous site, either in the hepatic hilum (n = 26) or at the periphery, or at the dome of the liver abutting critical extrahepatic structures (n = 41). Thirty-two tumors could not be visualized under US alone, even when combined with pretherapeutic images. The characteristics of the patient population are detailed in Table 1.

**Table 1.** Characteristics of 53 Patients With 67 HCCs Treated With Percutaneous Ablation Under 3D-VTFD Guidance.

| | |
|---|---|
| Age (years)[a] | 68.3 (40.2-89.2) |
| Female gender | 9 (17%) |
| Body mass index (kg/m$^2$)[a] | 25.1 (17.5-35.9) |
| Number of tumors/patient: 1/2/3 | 42 (79.2%)/8 (15.1%)/3 (5.7%) |
| Diameter of tumor (mm)[b] | 31 (21) [9-90] |
| Tumor diameter $\geq$ 30 mm | 24 (35.8%) |
| Infiltrative form | 18 (26.9%) |
| Location of tumor H/P/D | 26 (38.8%)/27 (40.3%)/14 (20.9%) |
| Not visualized under ultrasound | 32 (47.8%) |
| Not visualized on preablative CBCT[c] | 22 (32.8%) |

Abbreviations: 3D-VTFD, 3D virtual target fluoroscopic display; CBCT, cone-beam CT; CT, computed tomography; D, dome; H, hilar; HCC, hepatocellular carcinoma; MRI, magnetic resonance imaging; P, peripheral.
[a]Median (range).
[b]Mean (standard deviation) [range].
[c]In these cases segmentation of the targeted tumor was performed on recorded fusion images of CBCT and pretherapeutic CT or MRI acquisitions.

### Ablation Techniques

Most ablations relied on multielectrode technologies (64/67) such as IRE or mbpRFA. Forty-five IRE procedures, including 6 repeated after primary incomplete ablations, were performed using 3 to 6 19-G electrodes (median: 4; NanoKnife, Angiodynamics, Amsterdam, Netherlands).[12] Twenty-seven mbpRFA procedures were performed using from three to six 15-G electrodes (median: 5; Celon-power, Olympus, Teltow, Germany), including 2 secondary procedures (1 mbpRFA and 1 IRE).[7] Three microwave ablation (MWA) procedures were performed using a 16-G antenna (Acculis; Angiodynamics;[13] Table 2).

As a reference, 171 less technically demanding percutaneous ablations in 118 patients (3 IRE, 148 mbpRFA, and 20 MWA) were performed during the same period using US as the only imaging guidance. The characteristics of the patients and tumors treated under US alone are described in Supplemental Material 1.

In our institution, all liver ablations are performed under general anesthesia which includes tracheal intubation and complete muscle relaxation with curare.

### Three-Dimensional Virtual Target Fluoroscopic Display Protocol

The patients were all in the decubitus position. Special care was taken to center the liver as close as possible to the C-arm rotation axis so as to ensure adequate coverage of the region

**Table 2.** Technical Data on 75 Percutaneous Ablative Procedures Performed Under 3D-VTFD to Treat 53 Patients With 67 HCCs.

| | |
|---|---|
| No. of IRE/mbpRFA/MWA procedures | 45/27/3 |
| No. of repeated IRE/mbpRFA/MWA procedures | 6/2/0 |
| No. of applicators per IRE/mbpRFA/MWA[a] procedure | 4 (3-6)/5 (3-6)/1 |
| Time of positioning per applicator for IRE/mbpRFA/MWA (minutes)[a] | 12.5 (2.5-35)/11.5 (2-26)/3.5 (2-6) |

[a]Median (range).
Abbreviations: 3D-VTFD, 3D virtual target fluoroscopic display; HCC, hepatocellular carcinoma; IRE, irreversible electroporation; mbpRFA, multibipolar radiofrequency ablation; MWA, microwave ablation.

of interest (ROI) during CBCT acquisition. Curare-induced total muscle relaxation enabled a reproducible chest position at the end of the expiratory phase when the ventilator was switched off. Two hundred ninety-one or 582 projections were acquired during a 200° C-arm rotation at a rotation speed of 20°/s or 10°/s, respectively. The raw data sets were transferred for reconstruction to an external workstation (Advantage Workstation 4.6; GE Healthcare). Cone beam CT were acquired after the injection of 1.5 mL/kg contrast medium (Iobitridol; Xenetix, Guerbet, Aulnay-sous-Bois, France) in the antecubital vein. For the 30 (61.2%) patients with a hypervascular HCC pattern on pretherapeutic images, the preablative CBCT was acquired during the arterial phase using cadenced fluoroscopic bolus tracking in the abdominal aorta (Figure 1; Supplemental Materials 2 and 3). For the 19 (39.8%) patients with hypovascular tumor on pretherapeutic images, preablative CBCT was acquired 70 seconds after the intravenous injection of contrast medium at 2 to 3 mL/s (Figure 2). Once located on preablative CBCT images, the tumor was segmented manually using a commercially available workstation (Advantage Workstation; GE Healthcare; Figure 1) to create a virtual target. To enable real-time visualization of the tumor location, the virtual target was overlaid (Innova Vision; GE Healthcare) onto live fluoroscopic images, automatically following the table and C-arm movements (Figure 1, Supplemental Material 4). When the tumor was not visible on preablative CBCT images (n = 12; 17.9%), pretherapeutic CT or MR images were first of all combined with CBCT (Automated Registration; GE Healthcare; Figure 3). The tumor was then segmented on the workstation using spherical or free-hand ROIs placed on the CBCT volume, fused with the pretherapeutic images with the help of anatomical landmarks. The preferred anatomical landmark used to coregister images was the local vascular tree portion (arterial or portal) around the tumor.

The definition of skin entry points and the advancement of applicators were ensured under US guidance until the forward applicator track became insufficiently visible. Punctures were then guided under 3D-VTFD (Figure 1). At each step of the procedure, the accuracy of the trajectory was checked on at least two 3D-VTFD orthogonal projections and adjusted if required. Because there was no compensation for respiratory motion, the needle trajectories on 3D-VTFD were assessed at the same expiratory position of the diaphragm as during CBCT acquisition. For IRE and mbpRFA, the geometrical arrangement of electrodes was also verified systematically and then readjusted if necessary using at least 2 orthogonal projections (Figure 1; Supplemental Material 4).

### Assessment of 3D-VTFD Effectiveness and Safety

The efficiency of 3D-VTFD guidance was measured by: its technical success rate (percentage of ablation procedures completed), the time required for punctures, radiation exposure per puncture, the efficacy of primary and secondary ablations (percentage of complete ablations assessed at 1 month using CT or magnetic resonance imaging [MRI] after 1 or 2 procedures), local tumor progression rate as previously defined,[14] overall local tumor progression rate (primary failure of ablation and local tumor progression occurring during follow-up), and finally the rate of complications was recorded (according to the grading determined by the Society of Interventional Radiology grading).[14] Patients were followed up every 3 months with triple phase-enhanced CT or MRI.

### Statistical Analysis

A mixed logistic regression model was used to determine factors associated with tumor progression. To control confounders, the variables with $P \leq .2$ were integrated in the multivariate model. The factors associated with tumor progression were determined using stepwise regression to $P < .05$.

## Results

### Technical Success and Duration of Electrode Positioning

No technical failures were observed. The positioning time for single electrodes averaged 12.5 minutes with IRE and 11.25 minutes with mbpRFA (Table 2). The median radiation exposure per puncture was 3.13 (3.46) mSv (0.40-19.5).

### Primary and Secondary Efficacy

Thirty of the 39 tumors treated with IRE appeared to be completely ablated after a single procedure. Complete ablations were achieved in 7 further tumors after the procedure was repeated (6 with IRE and 1 with mbpRFA). The primary and secondary efficacy of IRE was therefore 76.9% and 94.8%, respectively (Table 2).

Twenty of the 25 tumors treated with mbpRFA appeared to be completely ablated after a single procedure. Complete ablation of another tumor was achieved after mbpRFA was repeated. The primary and secondary efficacy of mbpRFA was therefore 80% and 84%, respectively (Table 2).

The 3 tumors treated with MWA appeared to be completely ablated after a single procedure (Table 2). Thus the overall primary and secondary efficacy of ablation reached 79.1% (53/67) and 91% (61/67), respectively.

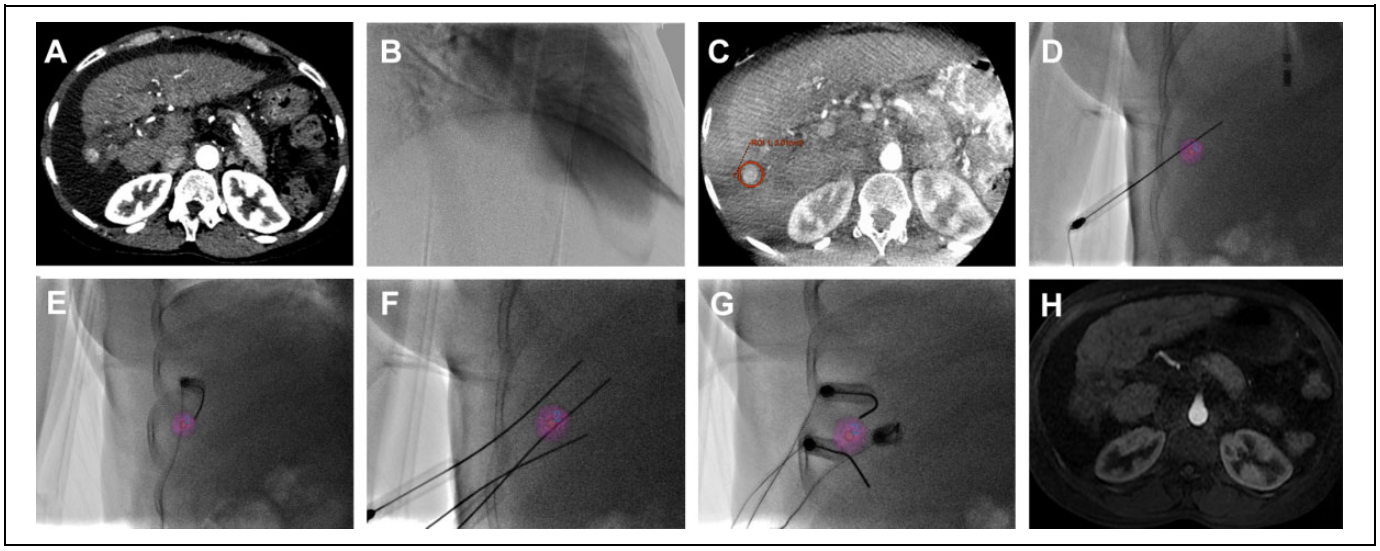


**Figure 1.** Irreversible electroporation ablation of a hypervascular tumor not visualized with US using 3D-VTFD from segmented CBCT acquired at the arterial phase of liver enhancement after the intravenous injection of iodinated contrast medium. A, Axial pretherapeutic CT of the liver acquired at the arterial phase after the intravenous injection of iodinated contrast medium revealing a small subcapsular hypervascular nodule in segment 6. Note the ascites linked to advanced cirrhosis which was the reason for choosing IRE for ablation. B, Cadenced subtracted lateral fluoroscopic images acquired following the intravenous injection of iodinated contrast medium which tracked the arrival of the bolus in the abdominal aorta (see also Supplemental Materials 2). C, On the 291 projections acquired at the liver arterial phase during 200° C-arm rotation at a speed of 20°/s (see also Supplemental Materials 2) the hyperattenuating tumor is segmented on CBCT images using a spherical tool. D to G, The target is then exported on a fluoroscopic image to provide the operator with a real-time 3D display as a function of the C-arm position. Fluoroscopic shots with different c-arm positions enable sequential guidance of the insertion of the 3 IRE probes and finally verify their geometrical arrangement. Continuous fluoroscopic acquisition can also be used to monitor needle progression or to check the geometrical arrangement of probe positioning (see Supplemental Materials 3). H, One month after the procedure, an axial MR T1-weighted image acquired at the arterial phase of an intravenous gadolinium contrast injection reveals a hypointense area encompassing the tumor boundaries and indicative of a complete response. 3D-VTFD indicates 3D virtual fluoroscopic target display; CBCT, cone beam CT; CT, computed tomography; IRE, irreversible electroporation; MR, magnetic resonance; US, ultrasound.

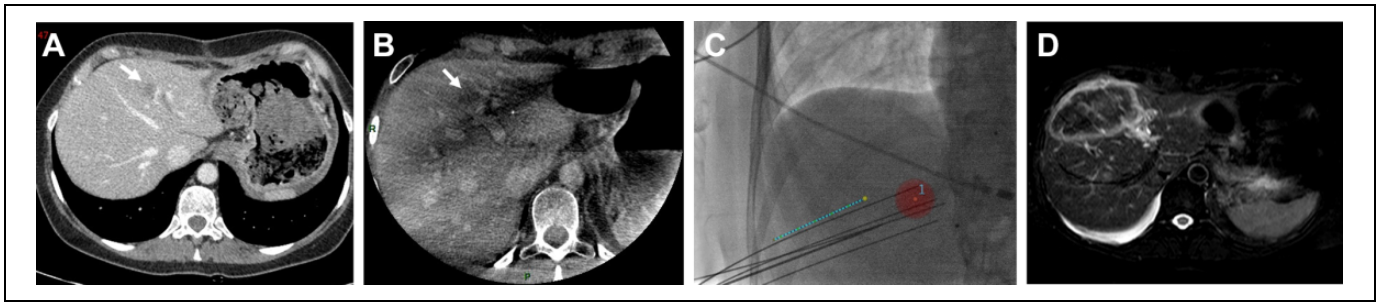


**Figure 2.** Irreversible electroporation ablation of a hypovascular tumor not visualized with US using 3D-VTFD from segmented CBCT acquired at the portal phase of liver enhancement after the intravenous injection of iodinated contrast medium. A, Axial pretherapeutic CT of the liver acquired at the portal phase after the intravenous injection of iodinated contrast medium revealing a small subcapsular hypovascular nodule in segment 3 (arrow). B, Cone beam CT acquisition 70 seconds after the intravenous injection of iodinated contrast medium at a speed of 20°/s shows the tumor (C) that is segmented for 3D-VTFD used to insert 4 probes. D, One month after the procedure, axial T2-weighted MR images reveal an isointense area surrounded by a hyperintense rim encompassing the tumor boundaries and indicative of a complete response. 3D-VTFD indicates 3D virtual target fluoroscopic display; CBCT, cone beam CT; CT, computed tomography; MR, magnetic resonance.

## *Local and Overall Tumor Progression Rates*

After a median follow-up of 12.75 months (1-23.2), local progression was observed in 9/61 tumors (14.6%). Therefore, taking account of the 6 tumors that were incompletely ablated after the initial course of treatment, the global local tumor progression rate was 22.3% (15/67). A hepatic dome location and infiltrative form were associated with overall local tumor progression (Table 3).

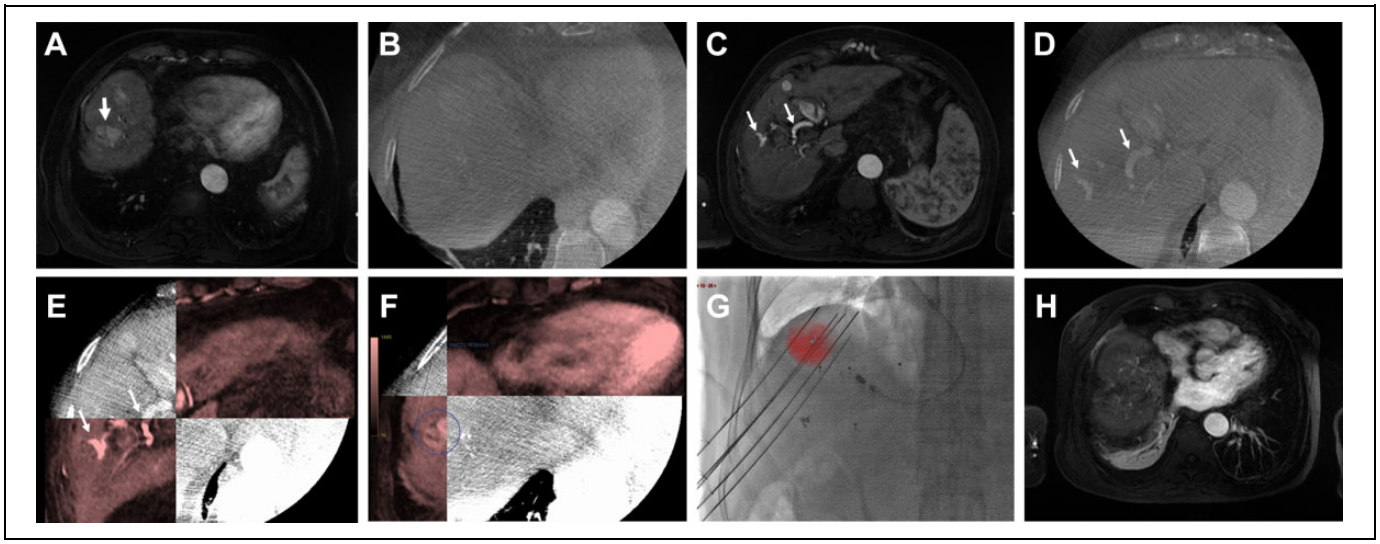


**Figure 3.** Irreversible electroporation ablation of a hypervascular tumor not visualized with US and CBCT acquired at the arterial phase of liver enhancement after the intravenous injection of iodinated contrast medium using 3D-VTFD from segmented pretherapeutic MR images fused with CBCT. A, Axial pretherapeutic MR of the liver determined at the arterial phase after the intravenous injection of gadolinium contrast medium revealing a subdiaphragmatic hypervascular nodule in segment 8 (arrow). The hyperintense area on the front of the tumor is above the paraumbilical portal vein. B, On CBCT acquired at the arterial phase following an intravenous injection of iodinated contrast medium, the tumor is insufficiently visible to be segmented. C, On MR images, below the level of the tumor, the hepatic arterial tree appears to be markedly enhanced (arrows) like (D) on CBCT (arrows). E, Magnetic resonance and CBCT volumes are fused using the arterial tree as a landmark for coregistration (arrows). F, The tumor is then segmented in the CBCT volume using superimposed MR as a tracing image. G, Segmentation is exported to a fluoroscopic screen for 3D-VTFD guidance of the 5 IRE probe insertions. H, One month after the procedure, an axial MR T1-weighted image acquired at the arterial phase of an intravenous injection of gadolinium contrast medium reveals a hypointense area encompassing the tumor boundaries and indicative of complete response. 3D-VTFD indicates 3D virtual fluoroscopic target display; CBCT, cone beam CT; CT, computed tomography; IRE, irreversible electroporation; MR, magnetic resonance; US, ultrasound.

**Table 3.** Factors Associated With Overall Local Tumor Progression After Percutaneous Treatment Under 3D-VTFD Guidance of 67 HCCs in 53 Patients.

| | Univariate Analysis | | Multivariate Analysis | |
|---|---|---|---|---|
| | OR (95% CI) | *P* | OR (95% CI) | *P* |
| Body mass index > 25kg/m$^2$ | 0.559 (0.187-1.669) | .3 | | |
| Age ≥ 65 years | 1.577 (0.530-4.694) | .4 | | |
| Not visualized under ultrasound | 0.825 (0.283-2.406) | .7 | | |
| Not visualized on preablative CBCT | 1.375 (0.471-4.017) | .6 | | |
| Number of electrodes > 3 | 2.917 (0.843-10.095) | .07 | | |
| IRE/mbpRFA technique | 0.835 (0.280-2.488) | .7 | | |
| More than one ablative procedure | 0.672 (0.126-3.574) | .6 | | |
| Tumor location | | .03 | | .04 |
| Dome versus peripheral | 8 (1.626-39.354) | | 8.244 (1.592-42.680) | |
| Hilar versus peripheral | 4.235 (0.997-17.999) | | 3.032 (0.666-13.814) | |
| Diameter of tumor > 3 cm | 1.064 (0.367-3.084) | .9 | | |
| Infiltrative form | 3.9 (1.228-12.391) | .02 | 3.846 (1.067-13.864) | .04 |

Abbreviations: 3D-VTFD, 3D virtual target fluoroscopic display; CI, confidence interval; HCC, hepatocellular carcinoma; CBCT, cone beam CT; CT, computed tomography; IRE, irreversible electroporation; mbpRFA, multibipolar radiofrequency ablation; OR, odds ratio.

### *Complications*

Two minor complications occurred (2/75; 2.7%): 1 pneumothorax which did not require drainage in the case of a dome-located HCC treated with IRE, and 1 case of jaundice which resolved itself within 2 weeks in a patient who had undergone a large mbpRFA for an infiltrative tumor. No major complications or procedure-related deaths occurred.

## Discussion

We report here on our initial experience with 3D-VTFD guidance in the context of particularly challenging percutaneous

ablations of HCC using IRE or mbpRFA multiprobe technologies. Without suffering any technical failures, we achieved a 91% success rate of complete ablations, while subsequent local tumor progressions occurred in 14.6% of cases after a median follow-up of 12.7 months. Global local tumor progression in our study reached 22.3%, which is slightly higher than the rates typically reported (lower than 20%) after standard singleprobe percutaneous treatments.[15] Furthermore, this rate of incomplete local tumor control appeared to be clearly higher than the 3% and 9.2% that we had previously reported in larger cohorts of patients treated with multiprobe technology (mbpRFA) for treatment-naive HCC within the Milan criteria.[16,17] However, these discrepancies in terms of the completeness of tumor ablation cannot be attributed to a potentially poorer efficacy of 3D-VTFD when compared to US guidance alone, because all the procedures performed during this study had indeed been considered by skilled operators as being unfeasible under US alone because of the combination of challenging conditions involving tumor characteristics such as a lack of visualization under US, problematic locations, locally advanced stages, and the need to use complex multiprobes for ablative technologies such as IRE or mbpRFA. Thus, in our cohort, 47.8% of tumors were poorly visible with US, 35.8% were larger than 3 cm, 26.9% were infiltrative, and 96% of the ablative procedures used multiprobe technologies. In these particularly challenging conditions, univariate and multivariate statistical analysis showed that a dome location and infiltrative form were independent factors associated with overall local tumor progression, but not size or visibility under US. In a routine clinical setting, such challenging conditions often lead to a shift from a curative to a palliative approach, especially in the case of intra-arterial treatments.[3,4] So, in this clinical context, the local tumor control that we achieved using 3D-VTFD guidance appeared clearly to be much better than what could be expected with endoarterial strategies.[2]

A lack of lesion visibility under US was the most common reason to use 3D-VTFD. In such circumstances, CT is often suggested as an alternative method for guidance. Unfortunately, most small liver tumors are also poorly visualized on unenhanced CT images, and their visibility is improved too transiently with the intravenous injection of iodinated contrast medium to guide the punctures. Other techniques have been proposed to overcome this problem. The arterial ethiodized oil tagging (Lipiodol, Guerbet LLC, Villepinte, France) of poorly visible HCC has been implemented prior to ablation,[9,18] but not all HCC nodules display clear Lipiodol uptake, and to date, Lipiodol tagging has been performed during a separate procedure.[18] The real-time fusion of US with pretherapeutic CT or MR 3D data is another attractive option.[19] However, as with 3D-VTFD, liver misregistration may occur because of the liver deformation induced both by pressure of the US probe and also by probes insertions themselves.[20] The advantage of 3D-VTFD is that it is currently the only guidance modality that can provide a real-time image of the geometrical arrangement of applicators near the target. This is key information in the case of challenging ablations requiring multiprobe technologies. In this case, the wide space available around the patient in the angiography suite is appreciated, unlike the small room in which the CT scan gantry is housed. It is also worth noting that no major complications occurred during this study, despite the complexity of the cases under treatment.

The 3D-VTFD technique is currently limited by a lack of compensation for motion when the patient breathes. This limitation is mitigated in the case of the so-called "no-touch" technologies that do not require precise intratumorous punctures.[11] Another source of target misregistration is displacement of the tumor induced at electrode insertion, particularly in the left liver lobe, when the simultaneous use of US is highly recommended.

In conclusion, when dealing with challenging liver ablations, advanced guidance methods such as 3D-VTFD could enable a curative option in patients whom percutaneous ablation under conventional guidance (CT or US alone) would otherwise be contraindicated because of poorer visibility of the tumor and/or a complex location. The combination of 2 real-time imaging modalities (US and 3D-VTFD guidance) used during our study produced some promising results in terms of safety and efficacy when considering the complexity of the cases. Further comparative studies with a longer follow-up in more homogeneous patient groups are now essential in order to clarify the role of this new modality for the guidance of percutaneous ablation.

## Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Olivier Seror is consultant for General Electric Healthcare and Angiodynamics.

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## Supplemental Material

Supplemental material for this article is available online.

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