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CLINICAL INVESTIGATION INTERVENTIONAL ONCOLOGY

# Real-Time US-$^{18}$FDG-PET/CT Image Fusion for Guidance of Thermal Ablation of $^{18}$FDG-PET-Positive Liver Metastases: The Added Value of Contrast Enhancement

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**Abstract**

*Purpose* To assess the feasibility of US-$^{18}$FDG-PET/CT fusion-guided microwave ablation of liver metastases either poorly visible or totally undetectable with US, CEUS and CT, but visualized by PET imaging.

*Materials and Methods* Twenty-three patients with 58 liver metastases underwent microwave ablation guided by image fusion system that combines US with $^{18}$FDG-PET/CT images. In 28/58 tumors, $^{18}$FDG-PET/CT with contrast medium (PET/CECT) was used. The registration technical feasibility, registration time, rates of correct targeting, technical success at 24 h, final result at 1 year and complications were analyzed and compared between the PET/CT and PET/CECT groups.

*Results* Registration was successfully performed in all cases with a mean time of 7.8 + 1.7 min (mean + standard deviation), (4.6 + 1.5 min for PET/CECT group versus 10.9 + 1.8 min for PET/CT group, $P < 0.01$). In total, 46/58 (79.3%) tumors were correctly targeted, while 3/28 (10.7%) and 9/30 (30%) were incorrectly targeted in PET/CT and PET/CECT group, respectively ($P < 0.05$). Complete ablation was obtained at 24 h in 70.0% of cases ($n = 40$ tumors), 23/28 (82.1%) in the PET/CECT group and 17/30 (56.7%) in the PET/CT group ($P < 0.037$). Fourteen tumors underwent local retreatment (11 ablations, 2 with resection and 1 with stereotactic body radiation therapy), while 4 tumors could not be retreated because of distant disease progression and underwent systemic therapy. Finally, 54/58 (93.1%) tumors were completely treated at 1 year. One major complication occurred, a gastrointestinal hemorrhage which required surgical repair.

*Conclusions* Percutaneous ablation of $^{18}$FDG-PET-positive liver metastases using fusion imaging of real-time US and pre-acquired $^{18}$FDG-PET/CT images is feasible, safe and effective. Contrast-enhanced PET/CT improves overall ablation accuracy and shortens procedural duration time.

**Keywords** Thermal ablation · Fusion imaging · Liver · Metastasis · Ultrasound · PET

**Abbreviations**

| | |
|---|---|
| CECT | Contrast-enhanced computed tomography |
| CEUS | Contrast-enhanced ultrasound |
| CT | Computed tomography |
| $^{18}$FDG-PET | $^{18}$Fluorodeoxyglucose positron emission tomography |
| MRI | Magnetic resonance imaging |
| PET | Positron emission tomography |

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| | |
|---|---|
| US | Ultrasound |
| SBRT | Stereotactic body radiation therapy |

## Introduction

Image-guided thermal ablations are gaining an increasingly important role in the management of patients with liver metastases [1]. However, in some cases ablation cannot be performed due to the poor conspicuity of the target lesion at ultrasound (US) [2–4]. Fusion of US with other imaging modalities such as computed tomography (CT) or magnetic resonance imaging (MRI) has been demonstrated to be feasible and effective for treating liver lesions not well visible at US, enabling the treatment of a larger patients population [2, 4–6]. However, in rare cases liver metastases are inconspicuous at contrast-enhanced CT (CECT) imaging and are only visualized at MRI or PET/CT [7–9]. Fusion of US with MRI has been already described [2, 6]. If MRI is not available, PET/CT can be used as the imaging modality to guide ablations [10–12]. Recently, several reports described interventional procedures in the liver performed in PET/CT scanners, using direct PET acquisition for targeting and monitoring of the procedures [11, 13–20]. However, this solution requires a complex environment that is foreign to and often distant from the typical interventional suite. Additionally, although the radiation exposure can be similar to fluoroscopy procedures when some technical concerns are applied, it is substantially increased for both patient and operators in comparison with standard US guidance. Moreover, economic and time costs of performing an interventional liver procedure in a typical diagnostic PET/CT suite can also be considerable [14, 15].

One potential solution to surmount these problems would be to perform interventional procedures in an US interventional suite using fusion of the pre-acquired PET/CT images with real-time US [2, 5].

The technical feasibility of real-time US fusion with pre-acquired PET/CT images has been reported in phantom/animal model, and for the guidance of percutaneous biopsies and ablations in a few patients—all of which were performed with non-contrast-enhanced CT imaging [21–23]. However, these reports highlighted both the difficulties in obtaining accurate fusion given limited anatomic landmarks and the need for larger clinical series in which liver ablations are performed using fusion imaging of real-time US and pre-acquired PET/CT images to better evaluate the utility of this technique.

Given previous successes in an improved US-CT fusion system based upon identification of intrahepatic vessel bifurcations [2, 21], we hypothesized that the incorporation of CECT images would further enable better imaging fusion based upon vessel conspicuity and render this fusion technique more practical. Accordingly, the aim of our work was to assess the feasibility and effectiveness of fusion imaging using real-time US and pre-acquired $^{18}$FDG-PET/CT in a clinical series of patients undergoing microwave (MWA) ablation of liver metastases. We further compared results in the group of patients treated with US-PET/CT fusion and patients treated with US-PET/CECT fusion.

## Methods

### Patient Population

Institutional review board (IRB) approval was obtained. Informed consent was obtained from all individual participants included in the study. We retrospectively evaluated data of 23 patients (13 males/10 females, mean age 62.8 ± 9 years) with 58 liver metastases treated between December 2012 and January 2017 (mean number of tumors per patient; 2.52, median: 2, range 1–14). Patients' characteristics are reported in Table 1, and number of tumor treatment sessions per patient in Table 2. Patients were selected to undergo thermal ablation with PET/CT image fusion with real-time US when accurate targeting of the metastasis was considered by the interventional radiologist to be extremely challenging or impossible to achieve with conventional US, CT or CECT image guidance alone (deep-located targets, poor acoustic window, isoechoic tumors or a combination of such situations). Accordingly, over the study period, 58 FDG-avid liver metastases (mean maximum diameter ± standard deviation 19 ± 9 mm) underwent ablation with fusion imaging of real-time US and pre-acquired $^{18}$FDG-PET/CT images over 30 treatment sessions. Number of lesions and treatment sessions per patient are reported in Table 2. This included three tumors unsuccessfully ablated using conventional imaging guidance and one case of local tumor progression after previous percutaneous thermal ablation. In total, 28/58 (48.3%) tumors were treated using US fused with PET/CECT and 30/58 (51.7%) underwent US fusion with conventional PET/CT. Tumors were equivalent in the two groups with respect to size (2.0 ± 0.8 cm vs. 1.9 ± 0.9 cm, respectively) and other demographic characteristics (Table 1). Six metastases were located in segment II, 1 in segment III, 10 in segment IV, 10 in segment V, 6 in segment VI, 9 in segment VII and 16 in segment VIII.

### Technique

#### *Pre-Procedural Examinations*

In this series, two PET/CT scanners were used. In 21 cases, PET/CT was performed using a Biograph 6 True Point

**Table 1** Data of 23 patients treated with US-PET/CT-guided liver thermal ablation

| | Overall ($n$ = 58) | PET/CECT group ($n$ = 28) | PET/CT group ($n$ = 30) |
|---|---|---|---|
| Patients | 23 | 12 | 11 |
| Sessions | 30 | 13 | 17 |
| Gender | 13M/10F | 7M/4F | 6M/6F |
| Age (years) | 45–81 (mean 62.8) | 45–76 (mean 62.5) | 48–81 (mean 62.1) |
| Primary cancer | | | |
| Colon | 32 | 16 | 16 |
| Rectum | 6 | 2 | 4 |
| Ileal carcinoid | 8 | 3 | 5 |
| Pancreas | 4 | 2 | 2 |
| Breast | 4 | 2 | 2 |
| Stomach | 3 | 3 | 0 |
| GIST | 1 | 0 | 1 |
| Numbers of tumors | 58 | 28 (48.3%) | 30 (51.7%) |
| Tumor size (cm)* | 0.6–4.5 (1.9 ± 0.86) | 1.0–4.0 (2.0 ± 0.79) | 0.6–4.5 (1.9 ± 0.94) |

*Data are expressed as range (mean ± standard deviation)

**Table 2** Number of lesions and treatment sessions per patient

| Lesions ($n$ = 58) | Patients ($n$ = 23) | Treatment sessions ($n$ = 30) |
|---|---|---|
| 1 | 10 | 1 |
| 2 | 7 | 1 or 2 |
| 3 | 4 | 1 |
| 8 | 1 | 3 |
| 14 | 1 | 5 |

(Siemens Medical Solutions, Knoxville, TN) scanner. CT was acquired with 130 kV, 120mAs and 2.5 mm slice thickness; immediately after CT, PET images of the same volume were obtained for 2-min acquisitions at each level. The global PET/CT acquisition time was 20 min. $^{18}$FDG was intravenously administered 1 h prior to PET acquisition at the dosage of 4 MBq/Kg. In 2 cases, PET was performed using a General Electric Discovery CT/PET 690 (General Electric Healthcare, Waukesha, WI) scanner.

From November 2013, CECT was acquired after initial PET acquisition in 13/30 procedures (corresponding to 48.3% of tumors treated). Scans were obtained after intravenous injection of 100–120 ml of contrast agent (Iomeron 350, Bracco Imaging, Milan, Italy) during expiration breath hold, in arterial (35 s delay) and portal venous (75-s delay) vascular phases, with the following scanning parameters: 130 kVp, 120 mAs and 2.5 mm slice thickness. This technique was used for a total of 28 tumors from 12 patients (7 males/5 females; 62.8 ± 8.6 years).

*US-CT/PET Fusion*

US scanners (MyLab Twice and MyLab Nine, Esaote SpA, Genova, Italy) with dedicated built-in hardware and software for image fusion (Virtual Navigator, Esaote, Genova, Italy) were used. The system included a magnetic field transmitter (Ascension Technology Corporation, Burlington, USA) and two electromagnetic sensors applied to the US probe and to the hub of the ablation applicator, respectively (VirtuTRAX, CIVCO Medical Solutions, Kalona, IA).

Prior to ablation, PET/CT data were transferred in DICOM format to the US system. Registration of US and CT images was performed starting from a reference plane (usually the plane crossing the umbilicus) and an internal anatomic landmark (i.e., the distal portion of the main portal vein as it enters the liver). Subsequent refinements to the image fusion displayed were made by generating additional anatomic landmarks when further alignment was needed. When fusion included non-enhanced CT images, only gross liver and other organ contour could be used, whereas CECT imaging enabled co-registering using one to three bifurcations of intrahepatic blood vessels, as previously reported [21]. Registration was considered sufficiently precise to safely perform ablation when visualized discrepancies between the fused US and CT images were less than 3 mm. PET images were then overlaid to US and CT images using an additional iteration of fusion. Contrast-enhanced US (CEUS) using 2.4–4.8 ml of microbubble contrast agent (Sonovue, Bracco Imaging, Milan, Italy) was performed before and immediately after ablation, with CEUS volumes overlaid to PET images to preliminarily assess the success of ablation—including determination as to whether or not an ablative margin of at least 5 mm was achieved.

**Table 3** Results of fusion process and treatment outcome of 58 liver lesions treated with US-PET/CT and US-PET/CECT-guided thermal ablation

| | Overall ($n$ = 58) | PET/CECT group ($n$ = 28) | PET/CT group ($n$ = 30) | $P$ value |
|---|---|---|---|---|
| Fusion process | | | | |
| Synchronization time (min) | 2–14 (mean 7.8) | 2–8 (mean 4.6) | 6–14 (mean 10.9) | < 0.001 |
| Correct targeting | 46 (79.3%) | 25 (82.1%) | 21 (70%) | 0.105 |
| Treatment outcome | | | | |
| Complete ablation | 40 (70.0%) | 23 (82.1%) | 17 (56.7%) | 0.037 |
| Incomplete ablation | 18 (30%) | 5 (17.9%) | 13 (43.3%) | 0.037 |
| Correct targeting | 6 (10.3%) | 2 (7.2%) | 4 (13.3%) | 0.671 |
| Incorrect targeting | 12 (20.6%) | 3 (10.7%) | 9 (30%) | 0.105 |

*Ablation Procedure*

Ablations were performed by two interventional radiologists (blinded for review) with more than 20-year experience performing thermal ablations. Treatments were performed under general anesthesia (48/58 procedures) or moderate sedation (10/58 procedures). Briefly, ablations were performed using a high-power (140 W, 2.45 GHz) MWA generator (AMICA, HS Hospital Service, Aprilia, Italy) with 14-gauge, internally cooled, coaxial antennas. MWA energy was applied for 4–10 min per ablation.

*Data Analysis and Endpoint Definition*

Registration technical feasibility, registration time, rate of correct targeting, technical success, final result at 1 year and complications were evaluated.

Technical feasibility was defined as the ability to achieve correct registration between real-time US and PET/CT images sufficiently to perform the ablation as preoperatively planned. Registration time was calculated from the beginning of the fusion images process to the achievement of a precise enough fusion for performing the procedure. Correct targeting was defined as the center of the ablated zone being located within 5-mm range from the ideal target point preoperatively established. Technical success of ablation was assessed 24 h after ablation by comparing results to a repeat PET/CT. Successful ablation was defined as a hypodense and photopenic necrotic volume encompassing the entire tumor and at last an additional 5-mm periablational margin [24–27]. Final result was defined as the absence of FDG uptake in the tumor at the last time of follow-up (> 1 year in all cases). Complications were recorded and classified according to the CIRSE classification system [28].

Continuous variables were expressed as mean ± SD, categorical variables displayed as frequencies, and the appropriate parametric (Student's $t$ test) or nonparametric test (Mann–Whitney $U$ test or Chi-square test) was used to assess significance of the differences between subgroups. A $P$ value of less than 0.05 was considered statistically significant. Analysis was performed using GraphPad Prism 5 software (GraphPad, La Jolla, CA).

## Results

Registration was successfully performed in all procedures with a mean time of 7.8 + 1.7 min (mean + standard deviation). Significantly shorter registration times were noted for the ablations performed with fusion imaging using PET/CECT (4.6 ± 1.5 min, 2.0–8.0 min range) compared with the ablations performed with fusion imaging and PET/CT without contrast enhancement (10.9 ± 1.8 min, 6–14 min range; $P < 0.001$) (Table 3). Fusion imaging enabled sufficient detection of targets to permit the performance of the planned ablation in all the 30 sessions (Fig. 1).

Full ablation results are reported in Table 3. Complete ablation was obtained from a single ablation session in 70.0% of cases ($n$ = 40 tumors), including 23/28 (82.1%) in the PET/CECT group and 17/30 (56.7%) in the PET/CT group ($P < 0.037$). This procedure resulted in an incomplete ablation in 6 cases (2/28 cases [7.2%] in the PET/CECT group and 4/30 [13.3%] in the PET/CT group). Incorrect targeting occurred in 7 cases (12.1%), 3/28 (10.7%) in PET/CECT group and 4/30 (30%) in PET/CT group. Five tumors (8.6%), located in the liver dome (two in segment VIII, three in segment IVa) and all of which belonging to the PET/CT group, were completely missed during the first ablation session and subsequently retreated using PET/CECT guidance achieving complete ablation (Fig. 2). For the remaining 13 (22.4%) incompletely ablated tumors, successful retreatment was achieved with repeat ablation ($n$ = 6), surgical resection ($n$ = 2) or

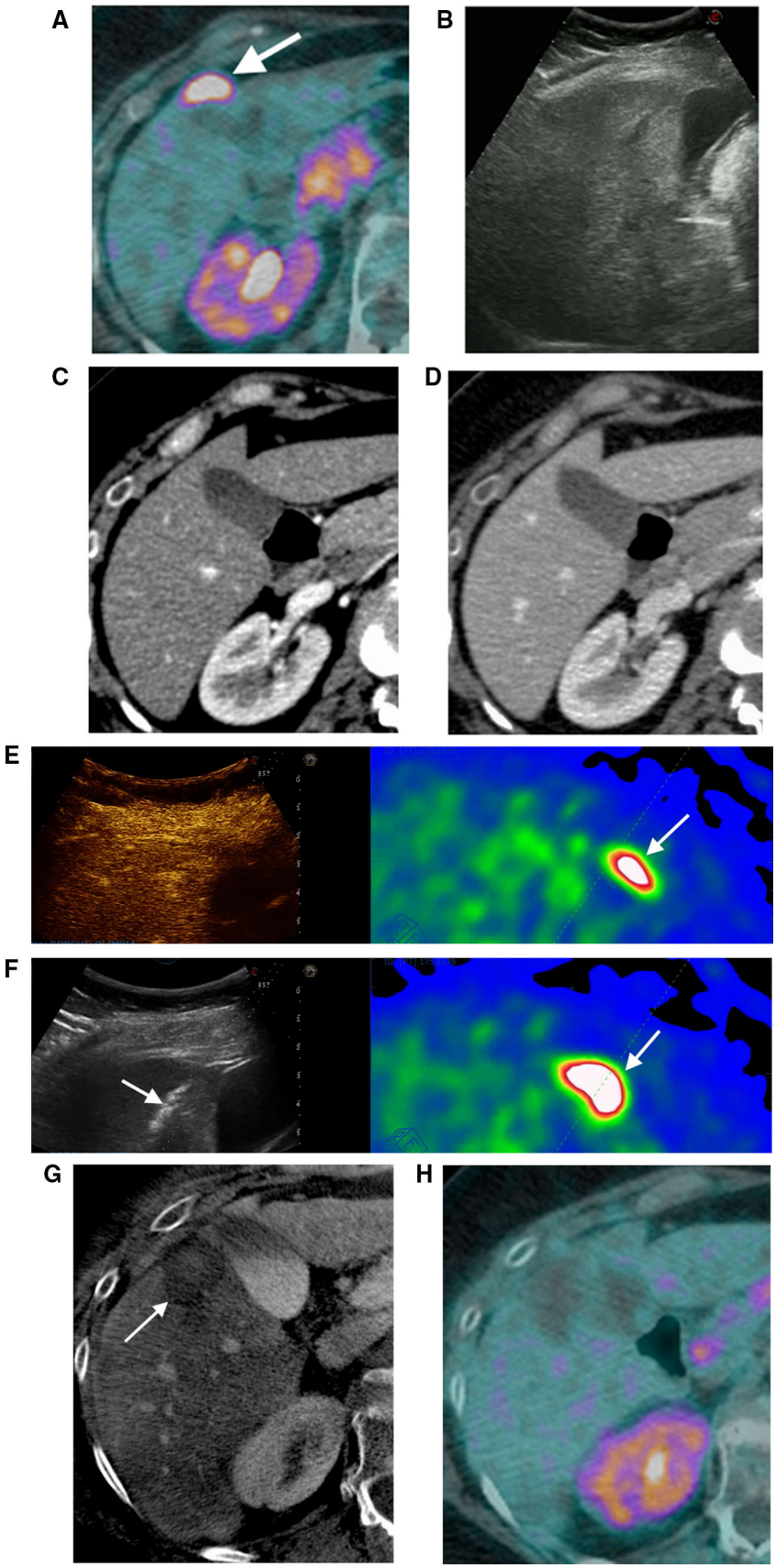


**Fig. 1** Sixty-eight-year-old female patient with [18]FDG-PET-positive solitary intrahepatic metastasis from ileal carcinoid (1.8 cm) in segment IVb (arrow), adjacent to the gallbladder (**A**). This tumor was not identified by conventional US (**B**) and CECT in either the arterial (**C**) or venous (**D**) phases. **E** Registration of real-time US and [18]FDG-PET with CECT (arrow) and verification that CEUS also could not detect the tumor were performed. **F** Ablation with MWA antenna (arrow) was performed using only PET co-registered with US for guidance (curved arrow). **G** Immediately after ablation, contrast-enhanced cone-beam CT shows a large ablation volume (arrow). **H** On three-month follow-up [18]FDG-PET did not show any uptake in the area of ablation

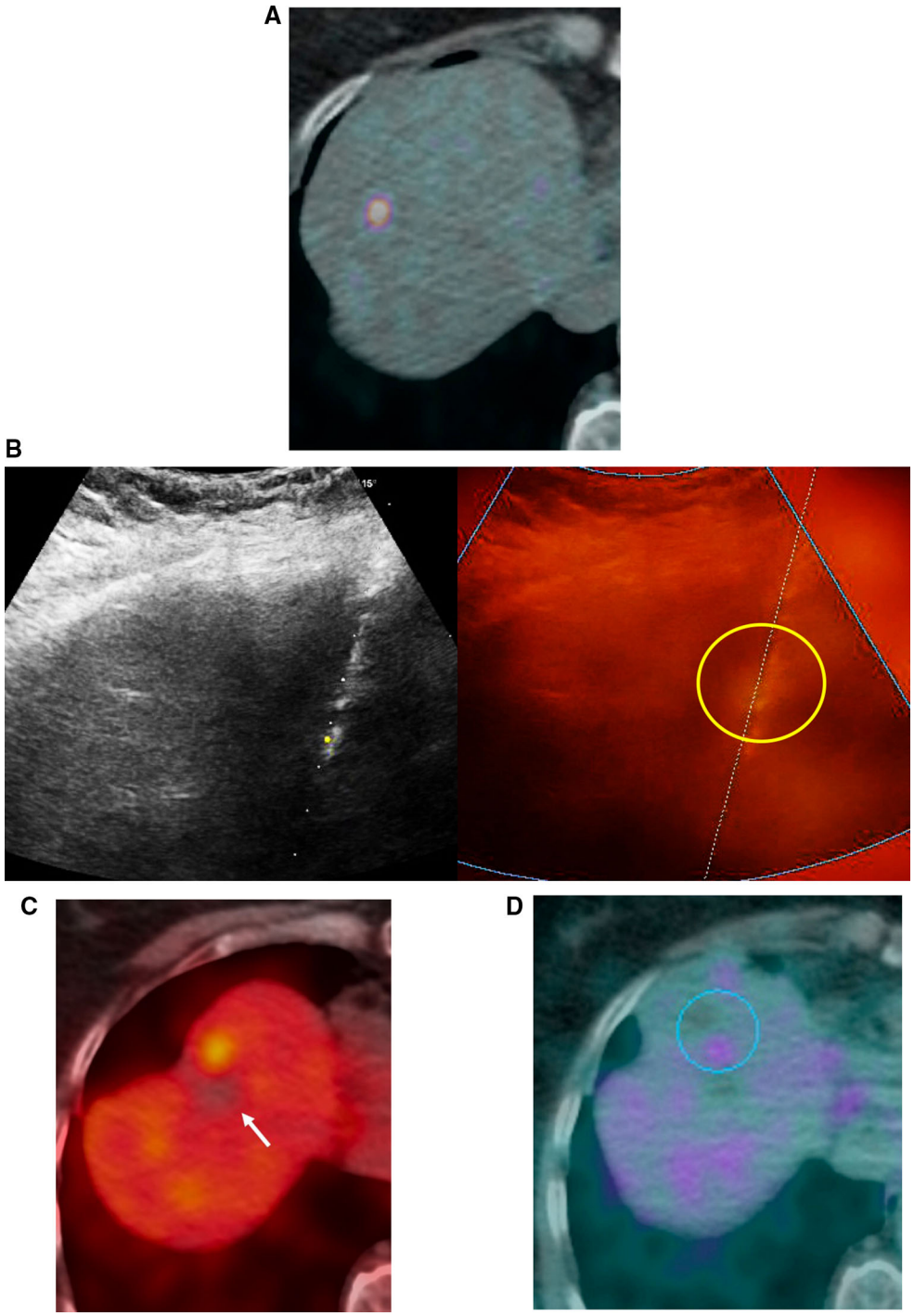


**Fig. 2** In a 71-year-old male patient with history of colon cancer, a solitary, 1.0-cm metastasis is identified on [18]FDG-PET (**A**) within segment VIII, but undetectable on US, CEUS and CECT. After fusion of real-time US with [18]FDG-PET/CT without contrast enhancement, the MWA antenna (yellow circle) is inserted into the target with intercostal approach (**B**). On 24-h follow-up [18]FDG-PET, the ablation area is visible as a photopenic defect (arrow), but the tumor has not been targeted and remains [18]FDG avid and viable, anteriorly to the coagulation zone (**C**). Four weeks later, the tumor is retreated using [18]FDG PET/CT guidance with contrast enhancement, achieving complete ablation (**D**)

stereotactic body radiation therapy (SBRT) ($n = 1$) or could not benefit from further local treatment due to distant disease progression ($n = 4$). Successfully ablated tumors had significantly smaller mean diameter (18 ± 6 mm; mean ± standard deviation) than unsuccessfully ablated tumors (mean diameter of 28 ± 10 mm; mean ± standard deviation) ($P = 0.022$). Small pleural effusion occurred after 3/58 (5.2%) ablations. One patient (1.7%) in PET/CT

group suffered from a gastrointestinal hemorrhage that required surgical repair. No procedure-related deaths or other major complications occurred.

At 12-month PET/CT follow-up, 54/58 (93.1%) targeted tumors were completely treated of which 51/58 (87.9%) were achieved with thermal ablations only.

## Discussion

Percutaneous thermal ablation has been validated for the treatment of a large variety of tumors in a wide range of organs [1, 4, 29, 30]. Yet, whatever the ablation modality and technique used, a crucial point of every percutaneous thermal ablation is the availability of precise and reliable imaging techniques for guiding the treatment. US and CT are by far the most widely used imaging techniques for guiding percutaneous thermal ablations [31]. US affords the operator the advantage of real-time visualization during the needle insertion, while CT offers a larger field of view and the potential to visualize targets beyond bone and air. However, in some cases tumor targets may not be visible under both US and CT due to low soft tissue contrast resolution for both imaging methods. The use of contrast medium to increase the conspicuity of the target tumor may be helpful for both modalities [32, 33]. Moreover, some tumors may be better identified with other imaging modalities, such as MRI or PET. In these cases, some investigators have proposed performing the ablations under direct MRI or PET/CT guidance [3, 13, 34, 35]. However, this requires resources that may not be widely available including a dedicated MRI or PET/CT interventional room, dedicated materials such as non-magnetic devices for MRI-guided procedures, not to mention the increased environment complexity and higher costs in comparison with standard US- or CT-guided procedures.

Fusing pre-acquired PET images to the guiding image technique obviates $^{18}$FDG administration to the patient during the procedure, with a consequent reduction in radiation exposure for patient and operator and a resultant reduction of costs. Moreover, this approach lowers the procedural time, by avoiding the necessity of a second PET/CT acquisition after needle placement. For our approach, we performed ablations in the US interventional room using internal anatomic landmarks to achieve a precise co-registration between the pre-acquired PET/CT images and US, then performing ablation under US real-time monitoring.

Here, our experience further confirms the utility of virtual navigation using fusion imaging of real-time US and pre-acquired $^{18}$FDG-PET/CT images, as both feasible and effective in guiding thermal ablation of liver metastases that are positive at $^{18}$FDG-PET but are poorly visible or completely undetectable at conventional imaging [17]. We also demonstrate that contrast-enhanced CT can dramatically improve the utility of the procedure.

Our study documents significant improvements in outcomes when contrast-enhanced CT is part of the fusion process. We attribute this finding in large part to iodinated contrast ability to provide a large number of precise anatomic landmarks in proximate vicinity to the target tumor. Although some incomplete ablations were noted even in the PET/CECT group, there was no case of completely missing a targeting once CT contrast was incorporated into our protocol. Hence, the use of contrast-enhanced imaging is highly desirable whenever possible.

The major limitation of our study is that it was a retrospective study and limited to ablation of a small number of PET-positive liver metastases. Moreover, we did not perform biopsy of the ablation margins, which would have proved complete ablation, besides of representing an independent predictor of local tumor progression [26, 36, 37]. Furthermore, the 5-mm margin chosen for this study may represent another limitation compared to potentially selecting a larger 1-cm margin [19, 25]. Moreover, a large variety of primary tumors were included in our series, with a wide range of tumor and margin sizes. Additionally, we did not stratify results based on minimal margin size given the need for a much larger sample size. Thus, further studies are needed, in particular comparing this method with procedures performed under direct PET/CT guidance, for the evaluation of clinical impact and cost efficiency in larger series.

In conclusion, percutaneous thermal ablations of $^{18}$FDG-PET-positive liver metastases with fusion imaging of real-time US and pre-acquired $^{18}$FDG-PET/CT images is clinically feasible and may facilitate ablation that would be challenging or impossible with conventional imaging guidance. Utilization of CT contrast medium is highly recommended to boost tumor targeting, to achieve successful ablation and to optimize procedural times. Moreover, the time needed for co-registration with real-time US for fusion imaging can be halved when PET/CECT is used. Owing to this simple, low-cost and potentially widely available modality, we were able to treat even tumors poorly visible at conventional imaging with US guidance serving as the only "real-time" imaging modality.

### Compliance with Ethical Standards

**Conflict of interest** The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article. Giovanni Mauri received consultancy fee from Elesta Srl, speaker honorarium from Guerbet and travel support from RGG. S. Nahum Goldberg performs unrelated consulting for Angiodynamics and Cosman Instruments.

**Ethical Approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

**Informed Consent** Informed consent was obtained from all individual participants included in the study.

**Consent for Publication** Consent for publication was obtained from all individual participants included in the study.

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