Multiple antenna placement in microwave ablation assisted by a three-dimensional fusion image navigation system for hepatocellular carcinoma

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\section*{ABSTRACT}

\textbf{Purpose:} This study was conducted to compare a three-dimensional (3D) fusion image navigation system (FINS) with ultrasound (US) for guiding percutaneous microwave ablation (PMWA) for treatment of hepatocellular carcinoma (HCC).

\textbf{Materials and methods:} This is a retrospective, non-randomized, comparative study. Our team developed a 3D FINS and used it to guide PMWAs for HCCs in 19 patients (3D group) and compared the results to those of 24 PMWAs guided by US (US group). The complete ablation rate of the first session, the local tumor progression (LTP), intrahepatic recurrence and disease-free survival were compared between the groups.

\textbf{Results:} The 3D FINS was successfully applied in all 19 patients. The mean size of HCCs was 4.14 cm \pm 0.95 in 3D the group and 4.07 cm \pm 0.91 in the US group. Major complications were identified in 5.3\% in the 3D group and 4.2\% in the US group (\(p = .865\)). Average time of image fusion was 404.53 \pm 161.84 s. There were more antenna insertions in the 3D group (3.68 \pm 1.57) than in the US group (2.71 \pm 1.12) (\(p = .02\)). The complete ablation rate of the first session was higher in the 3D group (94.7\%) than in the US group (62.5\%) (\(p = .034\)). The mean follow-up period was 11.4 months \pm 4.9 in the 3D group and 9.8 months \pm 5.5 in the US group. There were no significant differences in technique efficacy rate and LTP rate between the two groups.

\textbf{Conclusions:} The 3D FINS could be a safe, feasible and effective technique for guiding PMWA of HCC, which could help an operator improve the complete ablation rate of the first session.

\section*{Introduction}

Image-guided percutaneous microwave ablation (PMWA) therapy is a relatively new technology that was been developed in the 21st century [1–4]. PMWA therapy is minimally invasive, with results comparable to those of hepatectomy [5–9]. PMWA therapy has been most widely used for the ablation of hepatocellular carcinomas (HCCs) [10–12]. A high rate of recurrence seems to be a common problem. Several studies have shown that tumor size is an independent risk factor for tumor recurrence [11–14] because large HCCs need to be treated with a larger ablation necrotic area. If the tumor is larger than 3.0 cm in diameter, a single microwave antenna for ablation may not be sufficient. Therefore, several microwave antennae are necessary to ensure an effective treatment. The ablation thermal field should cover the tumor completely in three-dimensional (3D) space, while the surrounding vital structures, such as the bile duct, large blood vessels and gastrointestinal tract, should not be damaged.

Ultrasound (US) with no radiation, high image resolution and real-time imaging speed has been the most common imaging modality for guiding ablation [15–17]. However, US is only a two-dimensional (2D) image. The operator plans the placement of the multiple microwave (MW) antennae only based on a mentally reconstructed 3D image, which is neither objective nor precise. Inaccurate ablation planning could lead to incomplete ablation, which would increase the rate of local tumor recurrence especially for large tumors. To overcome these drawbacks, 3D imaging was studied in a series of studies [18–25], but most of the studies were focused on applying this technique to either the preablation plan or postablation evaluation. In this study, we applied a self-developed real-time 3D fusion image navigation system (FINS) to guide PMWA for large HCCs and evaluated its safety and efficiency.
Materials and methods

Self-developed 3D FINS

In previous studies [26–30], our research group developed and presented a 3D navigation software system that was applied to perform relevant experimental studies. These previous studies demonstrated that the navigation software could satisfy the clinical requirements of effectiveness, stability and security. Based on the previous studies, we developed a real-time 3D FINS. This system can fuse US images with reconstructed 3D computed tomography (CT) images, monitor and display the process of MW antenna puncture in 3D perspectives and provide operators with 3D views of the anatomical relationships between lesions and surrounding vital structures.

The 3D FINS was developed by connecting open-source software libraries [26]. It used the Medical Imaging Interaction Toolkit (MITK) as a framework providing image processing tools for the image-guided navigation system and used the Image-Guided Surgery Toolkit (IGSTK) as a library that provided the basic components of the system for location, tracking and registration. The functional modules comprised the segmentation module, measurement module, volume visualization module, registration module, preablation planning module, navigation module and postablation evaluation module.

Electromagnetic tracking device

The NDI Aurora 6 DOF (NDI, Waterloo, ON, Canada) electromagnetic tracking devices were used for image fusion, which comprised an electromagnetic field generator, a system control unit, sensor interface units and sensors (25 mm disc, standard; Figure 1(a)). The first sensor was attached to the US probe (Figure 1(b)). The second sensor was attached to the tail of the MW antenna (Figure 1(c)). The computer was connected to the electromagnetic tracking device through a universal serial bus port. By calibrating the sensors, probe and MW antenna, the computer acquired and displayed information on real-time position and orientation of the US probe and the MW antenna. The accuracy and methods of calibration were verified in our previous studies [26,28–30]. To avoid interference and disturbance of the magnetic field, metallic material was forbidden between the transmitter and the receiver.

Microwave ablation

The KY-2000 MW unit (Kangyou Medical, Nanjing, China) was used for ablation with 100 W of power at 2450 MHz. The needle antenna was 1.9 mm in diameter (15 gauge) and 18 cm long. There were dual channels in the antenna shaft through

Figure 1. The electromagnetic tracking devices.
which distilled water was circulated using a peristaltic pump to continuously cool the shaft to prevent overheating.

**US and CT apparatus**

An Acuson Sequoia 512 scanner (Signature 10.2; Siemens Medical Solutions, Mountain View, CA, USA) with 3.5- to 5.0-MHz curved array of multifrequency transducers was used for guiding the ablation and image fusion. In some special cases in which the image quality was poor on the gray-scale US, contrast-enhanced (Sonovue; Bracco, Milan, Italy) US was used for guidance [31]. Contrast-enhanced (iopromide, Ultravist 300; Schering, Berlin, Germany) multi-detector CT (Lightspeed 16; GE Medical Systems, Milwaukee, WI, USA) was performed before PMWA using a section 1.5 mm thick, a pitch of 1.35:1.0, 120 kV and 250 mA.

**Methods**

**Study design**

This is a retrospective, nonrandomized, comparative study conducted by the Chinese PLA General Hospital (28 Fuxing Road, Beijing, China). The study was approved by the institutional review board.

Between August 2013 and October 2015, 19 patients diagnosed with HCC were treated by PMWAs with the guidance of the 3D FINS (3D group). The inclusion criteria were as follows: (1) single nodule, (2) nodule diameter from 3.0 to 8.0 cm, (3) Child-Pugh class A or B and (4) no evidence of extrahepatic metastases or vascular invasion. The exclusion criteria were as follows: (1) previous treatment for HCC, (2) prothrombin time of more than 25 s, prothrombin activity lower than 40% and platelet count lower than 40 $\times$ 10$^9$/L and (3) presence of vascular invasion or extrahepatic metastases. All patients in the 3D group also had high quality contrast enhanced (CE) CT DICOM data.

For patients in the US group, using the same inclusion and exclusion criteria, 24 patients were selected who were treated by PMWAs with the guidance of US only (US group). The case selection flow chart is shown in Figure 2.

**Image data preprocessing**

The 3D images were reconstructed by two radiologists (ZDZ, ZM) with 6 years’ experience of processing image data. The reconstruction steps were as follows: First, the CE-CT DICOM data were imported into the 3D image navigation software. Second, the contours of the liver, tumor, skeleton, portal vein, hepatic vein and intrahepatic duct were semiautomatically extracted from the original CT image using the segmentation module (Figures 3 and 4). The software also provided operators with the ability to perform various operations on the 3D models, such as hiding, visualizing, rotating, scaling and moving, and could visually display the tumor size and the distance between the tumor and the surrounding tissue (Figures 5 and 6) [27,28].

**Image registration**

The image registration was performed by one radiologist (ZDZ) with 6 years’ experience in processing image fusion. The Aurora electromagnetic tracking system was positioned and enabled (Figure 7). The inner fiducially point method was used for registration of the 3D reconstructed CT image space, electromagnetic space and real-time US space. Briefly, four inner fiducial markers (often at the bifurcation of the portal vein) were selected and marked both on the US image and the CT image. The software calculated the registration error based on the root mean square (RMS) between the inner fiducial points in the US image and in the 3D CT image. When the RMS was smaller than 10, which represents high quality registration, image registration was considered to be complete [27].

**PMWA**

PMWAs were performed by two interventional radiologists with 20 years’ experience in liver ablation. The procedure was conducted under intravenous anaesthesia with a combination of propofol (Diprivan; Zeneca Pharmaceuticals, Wilmington, DE, USA) and ketamine (Shuanghe Pharmaceuticals, Beijing, China). The microwave ablation (MWA) unit allows for a maximum of two antennae for simultaneous ablation. For tumors $>3.0$ cm, multiple insertions of antennae were needed. For the US group, PMWAs were guided by US image only. The operator planned the multiple insertions of the MW antennae according to a reconstructed 3D image built mentally. For the 3D group, PMWAs were guided by both US image and 3D fusion image. The operator could directly observe the 3D anatomic information, rotate the 3D image as needed to choose the optimum puncture route, monitor and display the process of puncture on 3D views (Figure 6). The output power of ablation was 50–60 W. The time of net ablation was $\sim$6–8 min at each site. After the first session of PMWA, contrast-enhanced US was initially used to evaluate the range of necrosis, which determined
whether another session of ablation was needed within 3 days [32].

**Efficacy assessment and follow-up**

The therapeutic efficacy and follow-up results were assessed by two radiologists with contrast-enhanced imaging (i.e., contrast-enhanced CT or contrast-enhanced MRI) after treatment. The image fusion time was defined as the time from the patient entering the operating room to the end of registration (only in the 3D navigation group). The number of antenna insertions was defined as the sum of the number of each antenna insertion at the end of the session. The time of average antenna placement was defined as the total time needed for the operation minus the time of ablation, divided by the number of antenna insertions.
Technical outcome and response were defined using the International Working Group on image-guided tumor ablation standardized definitions [33]. The complete ablation rate of the first session was defined as complete ablation of the macroscopic tumor proved by contrast-enhanced US within 3 days after the first session of ablation. Technique effectiveness was defined as complete ablation of the macroscopic tumor proved by imaging follow-up 1 month after ablation. Local tumor progression (LTP) was defined as an incompletely treated tumor that continued to grow, or a new tumor (or satellite tumors) growing at the original site at follow-up. The common toxicity criteria of the National Cancer Institute and the Clavien-Dindo classification of surgical complications to index pain and postoperative morbidity were used [34,35].

The follow-up period was calculated from the beginning of PMWAs in all patients. Contrast-enhanced CT or MRI was routine examination in follow-up. The first follow-up was conducted after 1 month and afterwards every 3 months in the first year. From the second year, the follow-up was conducted every 6 months. Patients with LTP or intrahepatic recurrence were treated with appropriate therapies following American Association for the Study of Liver Disease (AASLD) guidelines and the Japan guidelines for HCC [36,37].

Statistical analyses
Data were analyzed using SPSS 20.0 for windows (SPSS Inc., Chicago, IL, USA). Continuous data were expressed as the
mean ± standard deviation (SD). The Student’s t test was used to compare continuous variables. Comparisons of proportions were undertaken using the two-sided Pearson’s Chi-square test, Fisher’s exact test, or the Kruskal-Wallis test. The Kaplan-Meier curves, which included LTP, intrahepatic recurrence and disease-free survival, were created and compared using the log-rank test. \( p < .05 \) was considered statistically significant.

**Results**

Between August 2013 and October 2015, 43 patients who conformed to the inclusion criteria and exclusion criteria were involved in this study. Nineteen PMWAs were guided by the 3D FINS (3D group) and 24 by US only (US group). The mean size of HCC was 4.14 cm ±0.95 in the 3D group and 4.07 cm ±0.91 in the US group. The baseline characteristics of all patients are shown in Table 1. The 3D FINS successfully fused the reconstructed 3D CT image with the real time US image in all 19 patients (8–10, Supplementary materials 1 and 2). The mean time ± SD for image fusion was 404.53 ± 161.84 s (198–900 s). The number of antenna insertions in the 3D group was more than that in the US group (3.68 ± 1.57 [2–6] vs. 2.71 ± 1.12 [2–6]; \( p = .02 \)). The average time for antenna placement in the 3D group was shorter than that of the US group (306.16± 48.88 s (230–420) vs. 521.04± 143.91 s (330–810), \( p < .0001 \)). A significantly higher rate of complete ablation of the first session was observed in the 3D group compared with the US group (18/19 94.7% vs. 15/24 62.5%, \( p = .034 \)). One case in the 3D group and nine in the US group achieved complete ablation after the second PMWA session. There were no significant differences (\( p = .777 \)) in the technique effectiveness between the 3D group (94.7%, 18/19) and US group (87.5%, 21/24). The specific details are shown in Table 2.

There were no perioperative deaths in either group in 90 days. The mean postoperative hospital stay was 3.84 ± 1.21 day (3–7) in the 3D group and 3.58 ± 1.1 d (3–7) in the US group (\( p = .419 \)). Postablation pain (grade 1–2) was observed in 42% of patients in the 3D group and 25% in the US group (\( p = .236 \)). Pain was relieved with a short course of nonsteroidal anti-inflammatory medication. Six patients (31.6%) in the 3D group and five patients (20.8%) in the US group had fever lasting 12–72 h after ablation, all of which self-resolved (\( p = .653 \)). The overall morbidity rate of

**Table 1. Clinical characteristics of patients in 3D group and US group.**

| Parameter             | 3D group | US group | \( p \) |
|-----------------------|----------|----------|--------|
| No. of patients       | 19       | 24       | .183   |
| Mean age (y)\(^{a}\)  | 61.26 ± 9.86 (44–75) | 57.39 ± 9.42 (42–77) | .183 |
| M/F ratio             | 15/4     | 16/8     | .057   |
| Tumor size (cm)\(^{a}\) | 4.14 ± 0.95 (3–6.3) | 4.07 ± 0.91 (3–6.3) | .793 |
| Liver cirrhosis       |          |          | .673   |
| Child A               | 15       | 19       | .590   |
| Child B               | 2        | 4        |        |
| No cirrhosis          | 2        | 1        |        |
| Hepatitis             |          |          |        |
| HBV                   | 14       | 17       |        |
| HCV                   | 3        | 6        |        |
| No Hepatitis          | 2        | 1        |        |

\(^{a}\)Data are means ± SD; data in parentheses are ranges.

**Figure 7.** The three-dimensional fusion image navigation system in operation.

![Figure 7](image-url)
postprocedure complications was 57.9% in the 3D group and 41.6% in the US group ($p = .453$). The specific details are shown in Table 3. The major complication (Clavien-Dindo class 3a) rate was 5.3% in the 3D group and 4.2% in the US group ($p = .865$). The pleural effusion (Clavien-Dindo class 3a) of two patients required pleural drainage.

The mean follow-up period was 11.4 months ±4.9 (range, 2.3–19.6 months) in the 3D group and 9.8 months ±5.5 (range, 0.9–17.2 months) in the US group. At the time of follow-up, the LTP rate was 10.5% in the 3D group and 25% in the US group. The Kaplan-Meier curves of LTP between the two groups showed no significant difference with a Log-Rank test ($p = .206$) (Figure 10a). Two patients in the 3D group who had LTP were successfully retreated by PMWAs guided by US. In the US group, four patients who had LTP were successfully retreated by US guided PMWAs. Two patients who had LTP were treated by transcatheter hepatic arterial chemoembolization. The 1 year cumulative intrahepatic tumor recurrence rates were 16.1% in the 3D group and 24.4% in the US group. The Kaplan-Meier curves of intrahepatic tumor recurrence between the two groups showed no significant difference with a Log-Rank test ($p = .603$) (Figure 10b). The two groups demonstrated similar rates of overall HCC recurrence and cumulative disease-free survival ($p = .444$) (Figure 10c,d). At the time of follow-up, one patient died because of hemorrhage from esophageal-fundic varices.

**Discussion**

Choosing the right image modality is essential for guiding PMWA procedures. Although US is adequate for most small HCCs, it might be inadequate for large lesions that need several MW antenna placements for ablation or lesions that have complicated anatomical relationships with surrounding vital structures. However, 3D imaging can provide the operator with different views to observe the anatomical relationships between the lesion and surrounding vital structures and assist in guiding more accurate spatial placement of the MW antenna. Maier-Hein, L’s group has reported the application of 3D reconstruction of preoperative imaging in laparoscopy surgery [38] and computer-assisted trajectory planning for percutaneous needle insertions with an electromagnetic track [39]. Audigier, C’s team has reported a multiphysics model of liver tumor radiofrequency ablation by multimodal fusion images. Although several studies have reported the use of 3D imaging in surgery [18–25], there are few comparative clinical studies on real-time 3D fusion image navigation used in PMWA. Here, we have described the safety and effectiveness of combining 3D reconstructed images with US imaging to facilitate PMWA.

With regard to the safety of 3D FINS guided PMWA, our study showed no perioperative mortality. The incidence of postoperative complications was 57.9% in the 3D group and 41.6% in the US group ($p = .453$), with major complication (Clavien-Dindo classes 3a) rates <5%. These values are comparable to the safety profiles found in previous clinical ablation studies [2,40]. In our study, only two cases (5%) required an invasive procedure (pleural drainage).

In our study, the complete ablation rate of the first session was higher in the 3D group than that in the US group. Two reasons were speculated. First, with the 3D fusion image, the operator could observe the lesion from different views and plan for more antenna placements to ensure...
complete ablation. Second, when the ablation started, the lesion quickly changed into hyperecho, which affected second antenna placement guided by US only.

The LTP rate (10.5%) in the 3D group was lower than that in the US group (25%), but no statistically significant differences were found between two groups. The first reason might be the sample size. This study is a preliminary clinical application. The sample size is small. Large sample data may find a significant difference between the groups in the future. The second reason for this result might be related to our treatment protocol. After the first session of PMWA, contrast-enhanced US was used within 3 days to evaluated the range of necrosis, which determined whether another session of ablation was needed. Repeated ablations could represent a potential confounder for interpreting LTP data.

Consider the selection of image modality for reconstructing the 3D image. The raw DICOM CT data was better than other images. Compared with MRI, CT may have more advantages in constructing the new 3D image because the skeleton and important pipeline structures can be extracted from the CT image but not MRI, meanwhile volume rendering can be performed only on the CT image.

With regard to the deviation of image fusion, image registration is an important step for fusion of the 3D reconstructed CT and US images. The main reasons that might affect image registration were as follow: first, breathing could cause movement of the liver and generate deviation. Respiratory liver motion seems to be a common problem for liver image registration. Several studies have attempted to solve this problem. Maier-Hein, L’s group has reported a respiratory liver motion simulator for liver interventions [41] and real-time compensation of tissue shift with electromagnetic organ tracking in image-guided surgery [42]. Preusser, T’s team has reported a spatio-temporal liver motion prediction system from motion tracked on MR thermometry images [43] and a model-based software for FUS in moving abdominal organs [44]. In our research, we matched each inner fiducial point at the end of inspiration to reduce the
respiratory motion deviation. Second, the process of marking each inner fiducial point might generate the deviation. In our experience, the bifurcation of the portal vein was a good inner fiducial point that could be easily found on both US and CT images and could reduce registration deviation.

There were some limitations to our study. First, this was a preliminary study. The sample size is small and the follow-up time is short. Second, the lack of randomization could cause a selection bias for grouping. Finally, as previously described, repeated ablations received by patients could represent a potential confounder for some survival data.

Figure 10. The Kaplan-Meier curves.
Table 2. Comparison of ablation results in 3D group and US group.

| Parameter                        | 3D group   | US group   | p-value |
|----------------------------------|------------|------------|---------|
| Fusion time (s)                  | 404.53 ± 161.84 (198–900) | NA         |         |
| Injections                       | 3.68 ± 1.57 (2–6) | 2.71 ± 1.12 (2–6) | .020    |
| The time of average antenna placement (s) | 306.16 ± 48.88 (230–420) | 521.04 ± 143.91 (330–810) | .000    |
| The complete ablation rate of the first session | 94.7% (18/19) | 62.5% (15/24) | .034    |
| The technique effectiveness rate | 94.7% (18/19) | 87.5% (21/24) | .777    |
| LTP rate                         | 10.5% (2/19) | 25% (6/24)  | .206    |
| The 1.0-year intrahepatic tumor recurrence rate | 24.5% | 24.4% | .603 |
| The 1.0-year disease-free survival rate | 63.9% | 62.0% | .444 |

*Data are means ± SD; data in parentheses are ranges.

Table 3. Clavien-Dindo classification of complications in 3D group and US group.

| Complications            | 3D group (n = 19) | US group (n = 24) | p     |
|--------------------------|-------------------|-------------------|-------|
| Intraperitoneal bleeding | 2 0 0 1 0 0 .42   | 2 0 0 1 0 0 .422  |       |
| Pleural effusion         | 3 1 1 5 2 1 .707 | 3 1 1 5 2 1 .707 |       |
| Jaundice                 | 2 0 0 1 0 0 .422 | 2 0 0 1 0 0 .422 |       |
| Ascites                  | 2 0 0 2 0 0 .808 | 1 0 0 0 0 0 .261 |       |
| Hematuria                | 1 0 0 0 0 0 .261 | 1 0 0 0 0 0 .261 |       |

Clavien-Dindo 3a consider as major complication.

Conclusions
The 3D FINS is a safe, feasible and effective technique for guiding PMWA of HCC, which could help an operator improve the complete ablation rate of the first session.

Disclosure statement
No potential conflict of interest was reported by the authors.

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