Research Article

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Real-time US-CT/MR fusion imaging for percutaneous radiofrequency ablation of hepatocellular carcinoma

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Background & Aims: Although ultrasonography (US) guided radiofrequency ablation (RFA) is a commonly used treatment option for early hepatocellular carcinoma (HCC), inconspicuous tumors on US limits its feasibility. Thus, we prospectively determined whether real-time US-CT/MR fusion imaging can improve the technical feasibility of RFA compared with B-mode US, and help predict local tumor progression after RFA in patients with HCC.

Methods: A total of 216 patients with 243 HCCs ⩽5 cm referred for RFA were prospectively enrolled. Prior to RFA, the operators scored the visibility of tumors, and technical feasibility on a 4-point scale at both B-mode US and fusion imaging. RFA was performed with a switching monopolar system using a separable cluster electrode under fusion imaging guidance. Technique effectiveness, local tumor progression and intrahepatic remote recurrences were evaluated.

Results: Tumor visibility and technical feasibility were significantly improved with fusion imaging compared with B-mode US (p <0.001). Under fusion imaging guidance, the technique effectiveness of RFA for invisible tumors on B-mode US was similar to those for visible tumors (96.1% *vs.* 97.6%, p = 0.295). Estimated cumulative incidence of local tumor progression at 24 months was 4.7%, and previous treatment for other hepatic tumors (p = 0.01), higher expected number of electrode insertions needed and lower technical feasibility scores (p <0.01) on fusion imaging were significant negative predictive factors for local tumor progression.

Conclusion: Real-time fusion imaging guidance significantly improved the tumor visibility and technical feasibility of RFA in patients with HCCs compared with B-mode US, and low feasibility scores on fusion imaging was a significant negative predictive factor for local tumor progression.

Lay summary: US/CT-MR fusion imaging guidance improved the tumor visibility and technical feasibility of RFA in patients with HCCs. In addition, fusion imaging guided RFA using multiple electrodes demonstrated a high technique effectiveness rate and a low local tumor progression rate during mid-term follow-up.

Clinical trial number: ClinicalTrials.gov number, NCT02687113.

Introduction

Percutaneous image guided radiofrequency ablation (RFA) is now widely performed in patients with early stage hepatocellular carcinomas (HCCs). It is a minimally invasive local treatment option in those who are considered unsuitable for surgical resection [1,2] as recommended by the American Association for the Study of Liver Disease (AASLD) and European Association for the Study of the Liver–European Organization for Research and Treatment of Cancer (EASL–EORTC) [3,4]. Indeed, several previous studies have demonstrated that RFA was able to achieve a significant extension of the life expectancy of patients with small HCCs (<3 cm), with better cost effectiveness over surgery and other interventional procedures [5–8]. However, RFA is not always feasible in all cases, with approximately 15–45% of tumors deemed infeasible owing to the inconspicuousness of tumors, the inadequacy of electrode paths, and the vulnerability of organs to collateral thermal damage [9,10]. Thus, various imaging techniques are used today as guidance tools that can assist in the pre-treatment ultrasonography (US) assessment of RFA. Ideally, the best guidance tool should provide not only good delineation of target tumors, but also of critical structures that might be at risk of injury during the ablative procedure [11]. Furthermore, it would also need to play a critical role in facilitating electrode placement into the tumor and provide accurate real-time monitoring and control throughout the procedure [11,12].

At present, pre-treatment US assessment is often used with RFA as a guidance tool, particularly in Asia and Europe, in order to determine the feasibility of RFA and to plan ablation strategies, including the route to take and to decide the overlapping ablation plan [9,10,13]. However, in cases with inconspicuous tumors on conventional US, contrast-enhanced ultrasound (CEUS), contrast-enhanced computed tomography, or magnetic resonance imaging (MRI) can also be used. Nevertheless, it can still often be difficult to perform ablation due to the short durations of the different

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vascular phases with CEUS, the lack of real-time imaging guidance with conventional CT and MRI machines, and due to concerns over increased radiation exposure with CT fluoroscopy [14,15]. Therefore, to overcome these problems, real-time-fusion of sonography and CT or MR images using an electromagnetic tracking system has been introduced for percutaneous liver biopsy and RFA of hepatic tumors [12,16–19]. Previous studies [18,20] dealing with this technique have demonstrated that fusion imaging can indeed increase the feasibility of RFA for HCCs invisible on conventional US by improving the conspicuity of HCCs. However, most studies dealing with these techniques have been retrospective with vague inclusion criteria, and have only evaluated the technical value of fusion techniques in the detection of tumors.

Therefore, the purpose of this prospective study was to determine whether fusion imaging guidance can improve the technical feasibility of percutaneous RFA compared with B-mode US guidance, and to determine the predictors of local tumor progression (LTP) after fusion imaging guided RFA in patients with HCC.

Materials and methods

Patients

Our institutional review board approved this prospective study, and written informed consent was obtained from all patients prior to RFA treatment. Between March 2013 and January 2015, a total of 380 patients with at least one liver tumor were referred to our department for percutaneous RFA. The inclusion criteria for percutaneous RFA were as follows: (1) pathologic or typical imaging based diagnosis of HCC; (2) no more than four tumors, with at least one tumor having a maximum diameter of less than 5.0 cm; (3) the absence of injury in the blood vessel and adjacent organ, nodal metastases or distant metastasis; (4) Child-Pugh grade A or B liver function status; (5) the absence of intractable ascites and uncorrectable coagulopathy; (6) prothrombin activity above 40% and a platelet count of more than 500,000/L; and (7) patients who are unsuitable for, or those refusing partial hepatectomy [11]. Among the 341 patients who satisfied inclusion criteria, 125 patients were excluded from the study for the following reasons: (a) patients refused to be included in this study (n = 106); (b) were already enrolled in another prospective study (n = 19). Finally, the remaining 216 patients with 243 HCCs measuring less than 5 cm in diameter comprised our study population (Fig. 1).

HCCs were diagnosed using one of the following criteria: (1) liver biopsies with pathologic confirmation (27 tumors) or (2) typical imaging features, i.e., arterial enhancement followed by portal/delayed washout at dynamic contrast-enhanced CT or MRI (216 tumors) as described by the AASLD guidelines or Liver Imaging Reporting and Data System (LI-RADS) [4,21]. The baseline characteristics of all study patients are summarized in Table 1 with more detailed patient characteristics described in the Supplementary material.

Conventional US and real-time US-CT/MRI fusion imaging

In general, at pre-treatment US assessment US, the operator assessed whether the target tumors were conspicuous enough for RFA to be effective, determined a safe needle path for RFA, and detected the risk of injury of other organs adjacent to the nodules [22]. One experienced ablation specialist (J.M.L with 18 years of clinical experience performing percutaneous ablations) and one of the three clinical fellows carried out the assessments. Tumor visibility, presence of a safe access route, expected number of electrode insertions needed, and the technical feasibility of RFA on B-mode US alone and on US-CT/MR fusion imaging, respectively, were determined while referencing previous CT or MR studies [13]. Detailed descriptions of the conventional US and CT/MRI fusion imaging techniques are provided in the Supplementary material.

Evaluation of tumor visibility, safe access route, technical feasibility and planning ablation

US visibility of the target tumor was graded by the operator on a four-point scale. Thereafter, the operator assessed the presence of a safe access route for electrode placement according to the presence of intrahepatic vessels (>3 mm) or at risk of organ injury adjacent to the RFA zone using a three-point scale. Next, the operators graded their degree of confidence regarding technical feasibility on a four-point scale using a combination of the tumor visibility score and the score of

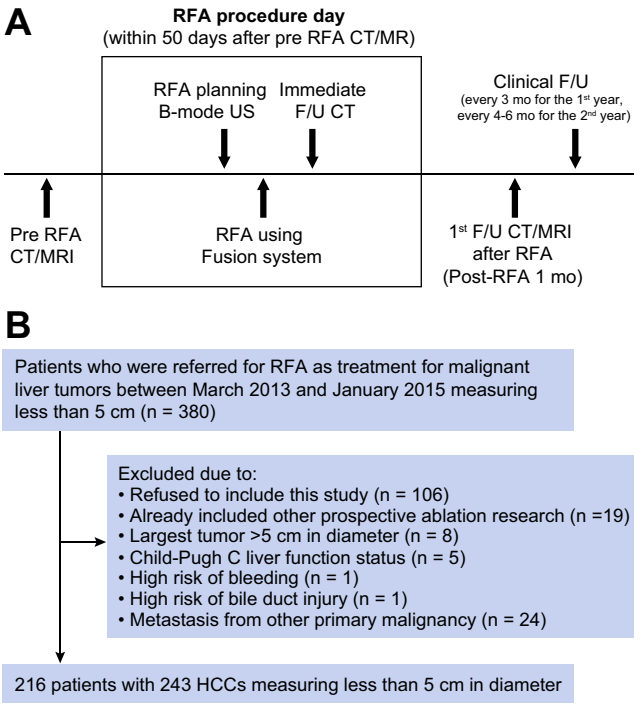

Fig. 1. Study protocol and flowchart. (A) Schedule shows protocol of US/CT-MR fusion imaging guidance RFA procedure and intervals between pre-procedure examinations, treatment and follow-up. (B) Flowchart showing the consequences of the study flow. RFA, radiofrequency ablation; HCC, hepatocellular carcinoma; F/U, follow-up; mo, month.

Table 1. Baseline characteristics and technical variables of 243 tumors in 216 patients with HCCs treated with radiofrequency ablation.

Baseline characteristics	Numbers of cases
Age (years)*	65 (30–85)
Gender (men/women)	160/56
Liver cirrhosis (yes/no)	180/36
Etiology of liver disease (none/alcoholic/HBV/HCV/HBV + HCV)	12/12/162/26/4
Child-Pugh class (A/B)	205/11
No. of tumors (single/two/three)	193/19/4
Tumor size (mm)*	15 (3–50)
Tumor location (right hemiliver/left hemiliver)	196/47
Previous hepatic therapy (OP/RFA/PEI/TACE/OP + RFA/OP + TACE/RFA + TACE/RFA + PEI/PEI + TACE/RFA + TACE + PEI/none)	10/28/9/37/7/2/16/4/11/4/88
Technical variables	**Numbers of cases**
Interval between CT/MRI and RFA (days)*	16.04 (0–49)
Artificial ascites (none/used)	116/100
Mean time of RFA (min/lesion)*	11.7 (5–16)
Immediate re-RFA+	6 (2.5%)

Data are numbers of cases unless specified otherwise.
HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; TACE, transarterial chemoembolization; PEI, percutaneous ethanol injection; RFA, radiofrequency ablation.
* Data are mean values (range).
+ Data are number of cases (percentage).

Table 2. Scoring criteria for evaluation of tumor visibility, safety access route, and technical feasibility for radiofrequency ablation.

Visibility
Invisible
Poor - partially visible even in deep inspiration, or tumors with poor conspicuity
Fair - visible with an indistinct margin
Good - clearly visible tumor with a distinct margin
Safe access route
Poor - presence of HA, PV or HV (>3 mm) along the path or index tumor abutting the dangerous organ
Fair - any vessels 1–2 mm away from the expected path or index tumor away from the dangerous organ within 1–2 mm
Good - any vessel more than 3 mm away from the expected path or index tumor more than 3 mm away from the dangerous organ
Technical feasibility
Not feasible - invisible tumor, or a poor safe access route
Equivocally feasible - partially visible tumor or tumors with poor conspicuity and a fair safe route
Fairly feasible - fair tumor conspicuity and a fair safe access route
Definitely feasible - confident in identifying the index tumor and presence of a good safe access route

HA, hepatic artery; PV, portal vein; HV, hepatic vein.

the safety access route. Detailed criteria regarding the evaluation of tumor visibility, the safety access route, and technical feasibility for RFA are described in Table 2. Interobserver agreement between experienced an ablation specialist and one clinical fellow was also evaluated.

The basic criteria for the feasibility of percutaneous RFA was based on the safety of the procedure and the likelihood of complete ablation of the target tumors [23] (Fig. 2). When registration was good, feasibility determined not only virtual target tumor on US images but also anatomical landmarks adjacent to the target tumor such as portal or hepatic venous branches, focal hepatic lesions, and the liver configuration. Therefore, even invisible tumors were able to be scored as being equivocally feasible (Fig. 3, Supplementary Fig. 1). However, if registration images were not able to provide good registration of hepatic vessels between US and CT/MR, invisible tumors were regarded as not being feasible for RFA. Finally, the expected number of electrode insertions needed so as to achieve complete ablation of the target tumors was recorded.

RFA procedures

An experienced ablation specialist (J.M.L) with 18 years of experience in RFA and a clinical fellow or a senior resident performed the RFA procedures on an inpatient basis. In brief, under guidance of real-time fusion imaging, RFA was performed using the switching monopolar technique with a separable clustered electrode (Octopus electrodes; STARmed, Goyang, Kyunggi, Korea) and a 200 W multichannel generator (VIVA RF System, STARmed). We terminated the procedure when complete coverage of the target tumor with a sufficient safety margin (>5 mm) was achieved by echogenic bubbles on real-time fusion US-CT/MR [24]. At the end of the RFA procedure, the electrode path was cauterized during retraction of the electrode. Detailed description of the RFA procedure is provided in the Supplementary material.

Assessment of RFA treatment response and complications

Immediate follow-up

Immediately after the RFA procedures, all patients underwent contrast-enhanced liver CT including unenhanced, arterial and portal venous phases, in order to assess the technical success of the procedure and the development of major complications. According to the immediate CT results, response to RFA was classified as either a case of technical success or failure according to the criteria defined in literature [25–28]. In cases of incomplete ablation, another session of RFA was performed immediately after CT to achieve complete ablation on the same day.

Follow-up

Follow-up contrast-enhanced liver CT or MR scans were performed in all patients 1 month after treatment, and follow-up liver CT or MRI scans and serum alpha-fetoprotein (AFP) checkups were performed every 3 months for the first year, and then every 4–6 months for the second year [1]. On the basis of the one-month follow-up CT or MR results, the technique effectiveness was determined according to the parameters reported in literature [1].

Development of hepatic tumor recurrence during the follow-up period, if any, was assessed and was further defined into LTP, intrahepatic distant recurrence (IDR) or extrahepatic metastasis (EM) according to the criteria defined in the

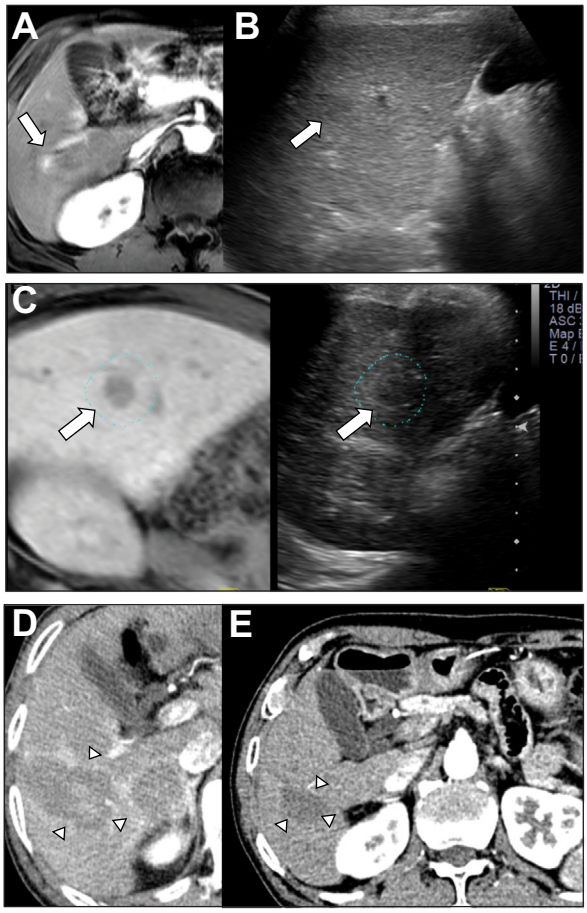

Fig. 2. A 68-year-old man with a 1.1 cm HCC and hepatitis B virus-related cirrhosis who had no history of local treatment. (A) Arterial phase CT image shows a small hypervascular HCC (arrow) in segment VI of the liver. (B) B-mode sonogram shows a small, hypoechoic HCC (arrow) in segment VI. (C) US image (right) and corresponding hepatobiliary phase (HBP) phase MR image (left) obtained with the real-time fusion technique simultaneously show the target tumor (arrow) and the presence of a good safe access route. The operator scored a high confidence score for the technical feasibility of RFA (definitely feasible) in this case. (D) Arterial phase CT image obtained immediately after RFA shows an ablation zone (arrowheads) in segment VI, encompassing the target tumor with a sufficient ablative margin. (E) Arterial phase CT image obtained 24 months after RFA shows shrinkage of the ablation zone (arrowheads) in segment VI, without local tumor progression. (This figure appears in colour on the web.)

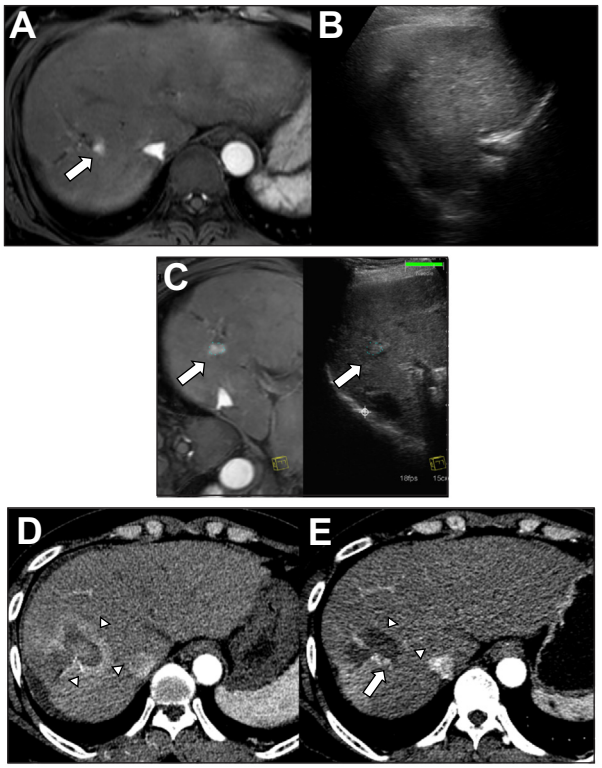

Fig. 3. A 66-year-old man with a 1.5 cm HCC and hepatitis B virus-related cirrhosis, who had a previous history of receiving RFA and transarterial chemoembolization for other HCCs. (A) Arterial phase CT image shows a hypervascular HCC (arrow) in segment VIII of the liver. (B) B-mode sonogram does not show a definite HCC nodule in segment VIII of the liver. Diffuse coarse liver echo is demonstrated, suggestive of cirrhosis. (C) Real-time fusion US image (right) and corresponding MR image (left) show both the target tumor (arrow) and presence of the segmental branch of PV along the planned access route. The reviewer scored a low confidence score for technical feasibility (equivocally feasible). (D) Arterial phase CT image obtained immediately after RFA shows a non-enhancing ablation zone (arrowheads) encompassing the target tumor with a sufficient ablative margin in segment VIII, which was regarded as a case of technical success. (E) Arterial phase CT image obtained 21 months after RFA shows shrinkage of the ablation zone (arrowheads) in segment VIII, but an enhancing nodular lesion along the posterior margin of the ablated lesion (arrow) is seen, suggestive of marginal recurrence of HCC due to the heat sink effect from the adjacent portal vein branch. (This figure appears in colour on the web.)

literature [1]. Evaluation of complications after RFA is described in detail in the Supplementary material.

Statistical analysis

The Mann Whitney *U* test and Fisher's exact test were used for comparison of B-mode US and fusion imaging as well as invisible and visible lesions on B-mode US. The Cohen κ value for agreement between two readers was calculated for tumor visibility, assessment of safety route, expected number of electrode insertions needed, technical feasibility in both B-mode and fusion system. The guidelines of Landis and Koch were followed in interpreting κ values: poor (κ <0.20), fair (κ = 0.21–0.40), moderate (κ = 0.41–0.60), good (κ = 0.61–0.80), and excellent (κ = 0.81–1.00) [29].

The cumulative incidences of LTP, IDR and EM at 6, 12, and 24 months were evaluated using the Kaplan-Meier method.

Univariate and multivariate analyses were performed to determine significant clinical and biological parameters able to predict LTP. All statistical analyses were done using SPSS version 21 (SPSS, Chicago, IL, USA). Detailed description of the statistical analysis is described in the Supplementary material.

Results

Comparison between fusion imaging and B-mode US for tumor visibility and technical feasibility

Compared with B-mode US alone, real-time US-CT/MR fusion significantly improved the tumor visibility score and operator's confidence for technical feasibility (p <0.001): 2.09 ± 1.01 *vs.* 2.54 ± 1.02 and 2.36 ± 1.02 *vs.* 3.54 ± 0.55. On B-mode US, there were 76 invisible tumors (76/243, 31.2%). However, on real-time fusion imaging, 30 (30/76, 39.5%) of those 76 lesions became visible.

In terms of technical feasibility, among the 243 tumors, 60 tumors were scored as not treatable (score 1) owing to invisible tumors, low conspicuity of anatomic landmarks (n = 46) or inadequate safety access route (n = 14) on B-mode US alone. After applying CT/MRI fusion imaging, operator's confidence regarding feasibility was upgraded in all 60 tumors from not feasible to equivocally (n = 42) or fairly (n = 16) feasible when registration quality for peritumoral anatomic landmarks such as segmental portal or hepatic veins, focal liver lesions, or the liver contour was good. The overall mean technical feasibility grade of RFA increased from 2.36 ± 1.02 to 3.54 ± 0.55 after the fusion system was applied (p <0.001) (Supplementary Table 1). However, there were no statistical differences in terms of the assessment of the safety route and the expected number of electrode insertions between US alone and fusion imaging. Interobserver agreement (κ) were good (range: 0.63–0.79) in all parameters not only B-mode but also fusion system. More detailed value Cohen κ values for interobserver agreement listed in Supplementary Table 2.

Comparison between invisible tumors and visible tumors on B-mode US

Among the 243 HCCs, 167 (68.8%) lesions were detected on B-mode US, while 76 (31.2%) HCCs were not well visualized on B-mode US because of underlying diffuse liver disease with steatosis or multiple regenerative nodules or patient obesity (n = 29), overlapping lungs, ribs or gastric gas (n = 19) or previous percutaneous treatments (n = 28) (RFA in 7 cases, transarterial chemoembolization [TACE] in 19 cases, and percutaneous ethanol injection [PEI] in 2 cases). The mean size of the invisible HCCs (1.48 ± 0.55 cm) was significantly smaller than that of visible HCCs (2.05 ± 0.73 cm) (p <0.001) (Table 3). Invisible tumors showed a significantly lower grade of operator's confidence in technical feasibility (p <0.001) on both B-mode US and fusion imaging, with occurrences of more frequent access route changes (p <0.001) (Fig. 3, Supplementary Fig. 1). However, fusion guided RFA achieved comparable technique efficacy between invisible tumors (73/76, 96.0%) and visible tumors (163/167, 97.6%) (p = 0.295).

Fusion imaging guided RFA: treatment success, technique effectiveness, and complications

Technical success

For the treatment of the 243 HCCs, a total of 249 RFA sessions were performed (one session in 237 tumors and two sessions in six tumors). The mean time per lesion needed for RFA was 11.7 min (range, 5–16 min). Technical success was achieved in all patients including six patients who underwent two sessions at immediate follow-up CT or MRI.

Table 3. Comparison of basic tumor characteristics, treatment variables of RFA and technique efficacy between invisible and visible groups on B-mode ultrasound.

Characteristics	Invisible (n = 76)	Visible (n = 167)	*p* value
Age (years)*	62.94 (30–81)	62.5 (33–85)	0.722
Gender (male/female)	50/26	132/33	0.853
Etiology of liver disease (alcohol/HBV/HCV/none)	5/59/10/2	9/116/24/18	0.619
Child-Pugh score (A/B)	72/4	160/7	0.876
Previous treatment (none/yes)	34/42	54/113	0.042
Artificial ascites (not used/used)	45/31	89/78	0.826
Tumor location (left/right)	12/64	33/134	0.898
Size of tumor (mm)+	1.48 ± 0.55	2.05 ± 0.73	<0.001
Safety route assessment - B mode+	2.26 ± 0.78	2.11 ± 0.74	0.091
Safety route assessment - fusion imaging+	2.25 ± 0.79	2.10 ± 0.73	0.092
Expected number of electrode insertions needed - B mode+	1.22 ± 0.44	1.31 ± 0.51	0.127
Expected number of electrode insertions needed - fusion imaging+	1.20 ± 0.4	1.37 ± 0.67	0.038
Technical feasibility - B mode+	1.37 ± 0.6	2.88 ± 0.79	<0.001
Technical feasibility - fusion imaging+	3.14 ± 0.47	3.75 ± 0.46	<0.001
Route change (yes/no)	92/4	106/79	<0.001
Technique efficacy (success/fail)+	73/3	163/4	0.295

Data are numbers of cases unless specified otherwise.
* Mean values (range).
+ Mean ± standard deviation.

Technique efficacy

Technique efficacy assessed by one-month follow-up imaging obtained after complete ablation via RFA was achieved in 236 out of 243 tumors (97.1%). Incomplete ablation was observed in seven of 243 nodules (2.9%), including four nodules located in an area difficult to ablate (closely abutting the hepatic veins [HV] or portal veins [PV]), one nodule larger than 3 cm in diameter, and two nodules associated with a serum AFP level higher than 200 ng/ml. Of the seven patients with incomplete ablation, one underwent hepatic resection and the remaining six patients were treated with TACE.

Complications

There were no procedure-related deaths observed in this study, while major complications developed in four patients (1.9%, 4/216): two hepatic abscesses requiring percutaneous drainage, one peri-hepatic hematoma requiring percutaneous drainage after liquefaction and one hemopericardium, which was treated conservatively leading to complete recovery 15 days after RFA.

Follow-up and outcome after RFA

The median follow-up period was 19.2 months (range, 6–29 months). During follow-up, two patients died due to liver failure (n = 1), or upper gastrointestinal bleeding (n = 1). The estimated 6-, 12-, and 24-month overall recurrence-free survival rates were 98.2%, 86.0%, and 75.8%, respectively.

LTP

Of the 236 tumors in which technique efficacy was achieved at CT or MRI one-month after ablation, LTP developed in 17 tumors (17/236, 7.2%). The cumulative incidence of LTP was estimated as 1.1%, 3.2%, and 4.7% at 6-, 12-, and 24-months, respectively. Among the 17 patients with LTP of HCC, eight were treated

Table 4. Univariate and multivariate cox survival analysis of the predictors for local tumor progression in 243 HCCs after successful RFA.

Characteristic	Univariate analysis			Multivariate analysis		
	RR	95% CI	*p* value	RR	95% CI	*p* value
Age	0.99	0.95–1.05	0.91			
Tumor location (left/right)	0.89	0.29–2.75	0.85			
Tumor size	1.52	0.82–2.81	0.19			
Liver cirrhosis (yes/no)	2.59	0.34–19.54	0.36			
Child-Pugh class (A/B)	5.1	1.16–22.4	0.03			
Previous treatment (none/yes)	4.24	1.26–14.78	0.02	7.12	1.52–33.34	0.01
Artificial ascites (not used/used)	0.98	0.38–2.54	0.97			
Tumor visibility - B mode	3.61	0–4.01	0.32			
Tumor visibility - fusion imaging	4.33	0–5.91	0.13			
Safety root assessment - B mode	1.77	0.36–6.3	0.38			
Safety root assessment - fusion imaging	1.947	0.43–8.80	0.24			
Expected number of electrode insertions needed - B mode	1.17	0.41–3.34	0.89			
Expected number of electrode insertions needed - fusion imaging	53.04	5.86–480.21	0.04	150.72	10.60–2142.08	<0.01
Technical feasibility - B mode	2.67	0.32–22.37	0.14			
Technical feasibility - fusion imaging	10.889	1.26–93.95	0.03	20.76	2.02–213.44	0.01
Route change (yes/no)	1.818	0.59–5.65	0.30			

RR, relative risk; CI, confidence interval.

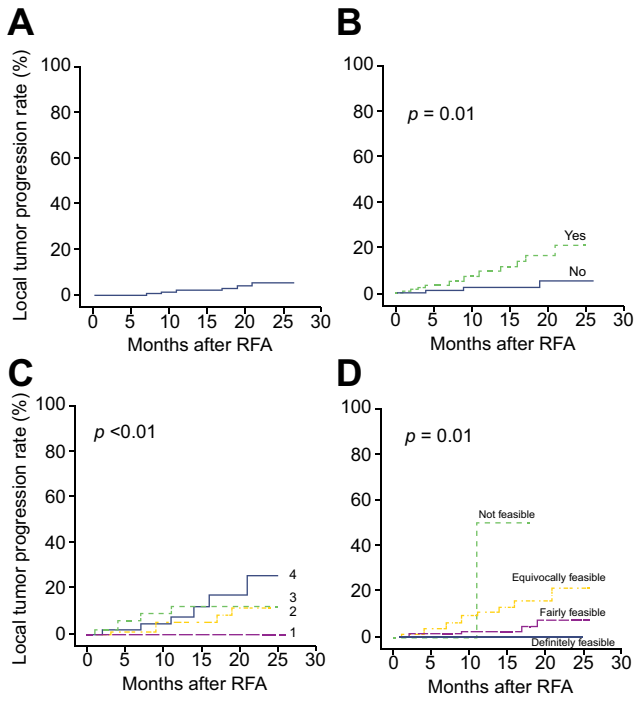

Fig. 4. Cumulative local tumor progression rates after RFA. The 6-, 12-, and 24-month local tumor progression rates are 1.1%, 3.2%, and 4.7%, respectively (A). Significant risk factors for local tumor progression after percutaneous RFA for HCC included previous treatment history ($p = 0.01$) (B), expected number of electrode insertions needed on US-CT/MRI fusion imaging ($p < 0.01$) (C), and operator's confidence in technical feasibility on US-CT/MRI fusion imaging ($p = 0.01$) (D) as demonstrated using the Kaplan-Meier method and log-rank test. Risk ratio was analyzed using the stepwise Cox proportional hazard regression model. (This figure appears in colour on the web.)

successfully with repeat RFA, two underwent hepatic resection and 7 patients were treated with TACE. The mean time to LTP was 10.96 months (range, 2–24 months). The prognostic factors affecting LTP-free survival of HCC are summarized in Table 4. At univariate analysis for HCC, Child-Pugh score ($p = 0.03$), previous local treatment for HCC ($p = 0.02$), expected number of electrode insertions needed ($p = 0.04$) and confidence in technical feasibility ($p = 0.03$) on fusion imaging were significant predictive factors for the development of LTP (Table 4). At multivariate analysis, on the other hand, previous local treatment for HCC ($p = 0.01$), expected number of electrode insertions needed ($p < 0.01$) and operator's confidence in technical feasibility ($p < 0.01$) on fusion imaging were significant predictive factors for the development of LTP (Fig. 4).

IDR and EM

Thirty-four of the 216 patients (15.7%) developed IDR, and were treated via the following methods: TACE (n = 18), RFA (n = 10), ethanol injection therapy (n = 4), and liver transplantation (n = 2). The estimated 6-, 12-, and 24-month cumulative incidences of IDR were 8.1%, 17.6%, and 21.1%, respectively. During the follow-up period, EM to lymph nodes in the hepatoduodenal ligament area developed in one patient (0.5%, 1/216) 16 months after RFA, and was treated with radiation therapy. The estimated 6-, 12-, and 24-month cumulative incidences of EM were 0%, 1.1%, and 2.3%, respectively.

Discussion

Our study demonstrated that real-time US-CT/MR fusion imaging significantly improved tumor visibility and operator's confidence in the technical feasibility of RFA compared with conventional US (2.36 ± 1.023 *vs.* 3.54 ± 0.547, $p < 0.01$). In addition, real-time fusion imaging guided, percutaneous RFA using a separable clustered electrode was able to achieve high technique efficacy (97.1%) as well as low LTP rates (1.1%, 3.2%, and 4.7% at 6, 12 and 24 months respectively). Our results regarding the LTP rate are superior to those demonstrated in previous studies using multiple electrode RFA (2-year LTP rate, 10%) under the guidance of conventional US [28,30]. We attribute the comparative superiority of our results to the allowance of easier planning for the adequate electrode path via better demonstration of vessels, bile ducts as well as a virtual tumor margin, and the easier perception allowed of the relationship between at risk of injury structures or organs abutting the expected ablation zone with fusion imaging than with B-mode US [31–33]. Although other guiding techniques such as CT or MRI could also be used to improve the feasibility of percutaneous RFA by improving the visibility of tumors and vessels or bile duct in the liver, however, conversion of CT or MRI may lead to increased radiation or lack of real-time imaging capability [10]. Considering that real-time multimodality fusion imaging only requires an additional procedure time of less than 5 min for registration and could be easily equipped in any US room where RFA procedures are performed [20], real-time multimodality fusion imaging may be a cost effective, practical guidance tool for RFA, especially where US is already widely used as a guidance modality for RFA.

We also found that among 243 HCCs visible on CT or MRI, B-mode US was able to detect 167 (68.8%) lesions, while 76 (31.2%) lesions were not well visualized. More importantly, we achieved comparable technique efficacy of RFA in invisible tumors under the guidance of fusion imaging (96.0% *vs.* 97.6%, $p = 0.295$), although those invisible tumors or tumors with poor conspicuity on conventional US showed significantly lower confidence of technical feasibility for RFA ($p < 0.001$). Until now, although there have been a few sporadic studies reporting the value of real-time fusion imaging guidance for RFA of tumors with poor conspicuity or invisible tumors [34–38], they were all retrospective studies or had a small number of study patients and demonstrated only the technical feasibility of real-time fusion imaging. Based on our study results, which addressed these issues, we believe that real-time fusion imaging can be a valuable tool in planning RFA in patients with invisible or poorly visible tumors on B-mode US, and that it can also expand the technical feasibility of RFA in patients with HCC.

According to our multivariate analysis, it was revealed that a history of previous local treatment for other hepatic tumors ($p = 0.01$), higher expected number of electrode insertions needed and lower operator's confidence in technical feasibility ($p < 0.01$) on real-time fusion imaging were significantly negative predictive factors for the development of LTP. Previously known risk factors for LTP included large tumor size, infiltrating tumor morphology, insufficient ablative margins, blood vessels close to the tumor, subcapsular tumor location, subphrenic tumor location, poor histologic grade and history of previous treatments [37,39–44]. In our study, the higher expected number of electrode insertions needed may represent the difficulty in creating a sufficient ablation volume so as to ensure entire coverage of

the targeted zone, three dimensionally, with a single placement of an electrode, owing to large tumor size, vicinity to large vessels, poor delineation of margins or the non-spherical shape of target tumors [45,46]. Furthermore, our study demonstrated a relationship between LTP and operator's confidence in technical feasibility. Given that the operator would have considered these aforementioned known predictive factors of LTP when grading the feasibility score, we can deduce that operator's confidence was the most important predictive factor for LTP. Thus, we believe that more precise delineation of the target tumor and at risk of injury structures using fusion imaging would be helpful for lowering the development of LTP.

There were a few limitations in our study. First, despite the fact that it was a prospective study, it was only a single arm, single center study and there was no control group in which RFA was performed with conventional US guidance only. Thus, further randomized controlled trials might be necessary to confirm the value of fusion imaging guidance in improving the therapeutic results of RFA. Second, as the follow-up period in our study was relatively short with a median of only 19.2 months, our mid-term outcomes at 2 years need to be cautiously interpreted. Finally, some of the criteria for tumor visibility and technical feasibility contain subjective judgments. Until now, there has been no objective grading system to assess the feasibility of sonography-guided percutaneous RFA of HCC. Therefore, we attempted to use objective estimations of technical feasibility after referencing previous studies [9,10,13,16]. Yet, in this era of the standardization of imaging guided tumor ablation, further investigation of a more objective classification of feasibility is warranted to provide predictive indicators of successful ablation without LTP [47].

In conclusion, real-time US/CT-MR fusion imaging guidance improved tumor visibility and the technical feasibility of RFA in patients with HCCs compared with B-mode US, and fusion imaging guided RFA using multiple electrodes demonstrated a high technique effectiveness rate and a low LTP rate.

Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

Authors' contributions

All authors contributed to and approved the final version of this manuscript. Su Joa Ahn: Analyzed and interpreted the data, drafted the manuscript, performed statistical analysis. Jeong Min Lee: Orchestrated the study concept and design, acquired data, performed critical revision of the manuscript and supervised the overall study. Dong Ho Lee, Jung-Hwan Yoon, Yoon Jun Kim, Jeong-Hoon Lee, Su Jong Yu, Joon Koo Han: acquired clinical data, assisted in the critical revision of the final manuscript.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jhep.2016.09.003.

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