Combined Ultrasound and Computed Tomography Guidance in Radiofrequency Ablation for Hepatocellular Carcinoma Reduces Local Recurrence Rate

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Abstract. *Background/Aim: In radiofrequency ablation (RFA) treatment of hepatocellular carcinoma (HCC), the therapeutic effect depends on the appropriate position of the electrode. To improve the accuracy of the electrode needle position, we currently perform RFA with combined ultrasound sonography (US) and computed tomography (CT) guidance. The purpose of this study was to evaluate the effectiveness of this US/CT-guided RFA method. Patients and Methods: This retrospective study recruited 97 patients with single tumors treated with transcatheter arterial chemoembolization and monopolar RFA between January 2013 and December 2017. Among these, 50 patients were treated with RFA under US/CT guidance (US/CT-guided group) and 47 were treated with RFA under US guidance alone (US-guided group). We analyzed the efficacy of US/CT guidance compared with US guidance alone. Results: The 1-, 2-, and 3-year local recurrence rates for the US/CT-guided and US-guided groups were 4.1%, 6.3%, and 8.6%, and 19.6%, 31.6%, and 41.9%, respectively. The local recurrence rate was lower in the US/CT-guided group (p=0.0030). Cox proportional hazards model for multivariate analysis demonstrated that the independent risk factors associated with local recurrence were tumor size (p=0.0028) and US/CT guidance (p=0.0037). Conclusion: US/CT-guided RFA for HCC reduced the local recurrence rate compared with US-guided RFA alone.*

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the third leading cause of cancer death (1). Percutaneous radiofrequency ablation (RFA) has been widely performed for small HCCs since RFA was recommended as a treatment option in the 2005 guidelines issued by the American Association for the Study of Liver Diseases (2). Several randomized controlled trials have also been conducted on the efficacy of treatment for HCCs with surgical resection *versus* RFA, although the specific techniques of RFA differ between institutions and the outcomes of tumors treated with RFA vary, with the local recurrence rate ranging from 1.7% to 20.8% after 5 years of treatment (3-11).

RFA is generally performed under ultrasound sonography (US) or computed tomography (CT) guidance to puncture the electrode needle either into the target tumor or nearby, both of which have advantages and disadvantages. US guidance provides a real-time visualization of the tumor and electrode needle, but this method is largely dependent on patient factors and is affected by the costal bone or air in the lung and gastrointestinal tract. While fusion imaging with CT, magnetic resonance imaging (MRI), or contrast-enhanced ultrasonography is effective for clear tumor detection and accurate electrode needle positioning, ultrasound images lack objectivity and reproducibility, making it difficult to retrospectively confirm that the technique was performed properly (12-16). However, CT guidance in RFA provides better detection of tumors and the electrode needle, although radiation exposure is required and is easily affected by the respiratory motion of the patient.

We performed RFA under US guidance alone until October 2015. For more precise treatment, RFA has been

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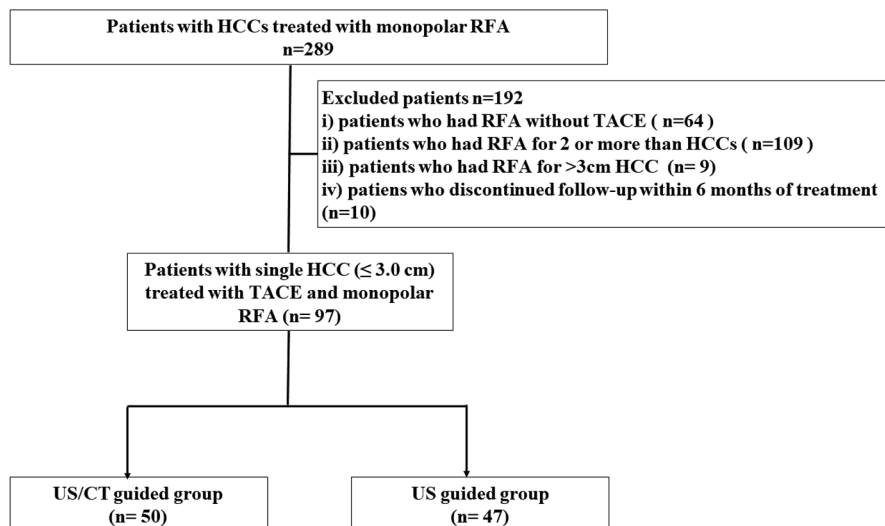
Figure 1. *Patient flow chart. RFA: Radiofrequency ablation; HCC: hepatocellular carcinoma; CT: computed tomography; US: ultrasound sonography; TACE: transcatheter arterial chemoembolization.*

performed with combined US and CT guidance since November 2015. The purpose of this study was to evaluate the efficacy of combined US and CT (US/CT) guidance compared with US guidance alone in RFA.

Patients and Methods

Patients. This single-center retrospective study analyzed the efficacy of US/CT guidance in RFA at our hospital between January 2013 and December 2017. Two hundred eighty-nine patients with HCCs were treated with monopolar RFA. HCC was diagnosed based on the typical imaging pattern on three-phase contrast-enhanced CT (CECT) or ethoxybenzyl diethylenetriamine pentaacetic acid-enhanced magnetic resonance imaging (EOB-MRI). Inclusion criteria were as follows: a) Patients with a single HCC of ≤3 cm in maximum diameter on CT/MRI images; b) Child–Pugh class A or B liver disease; and c) conventional transcatheter arterial chemoembolization (TACE) conducted before RFA. Exclusion criteria were as follows: a) patients who had RFA without TACE; b) patients who had RFA for two or more HCCs; c) patients who had RFA for >3 cm HCC; and d) patients who discontinued follow-up within 6 months of treatment. We excluded 192 patients, and 97 patients were finally enrolled in this study. Of these, 50 patients were treated RFA under US/CT guidance (US/CT-guided group) and 47 were treated with RFA under US guidance alone (US-guided group) (Figure 1).

The present study was conducted in accordance with the guidelines of the Declaration of Helsinki and was approved by the Aso Iizuka Hospital Ethics Committee (approval no. 22075). The need for written informed consent was waived by Aso Iizuka Hospital Ethics Committee because of the retrospective nature of this study.

Conventional transarterial chemoembolization. TACE was performed by hepatologists or radiologists with sufficient experience. After identifying the feeder arteries via catheterization of the celiac artery and superior mesenteric, common hepatic, lobar, and segmental hepatic arteries, selective catheterization was performed with microcatheters, and a mixture containing 2-4 ml iodized oil (Lipiodol, Guerbet Group, Villepinte, France) and 10-20 mg Epirubicin (Pfizer, New York, NY, USA) were infused under fluoroscopic and CT guidance with a mixture containing 0.9-1.5 mm or 1.8-2.6 mm porous gelatin particles (Gelpart; Nipponkayaku, Tokyo, Japan).

Radiofrequency ablation procedure and assessment of the technical success. RFA was performed under intravenous and local anesthesia 1-3 days after TACE by hepatologists with sufficient experience. Depending on the location of the tumor, the artificial ascites technique was used to improve tumor visibility and reduce the risk of thermal injury to the abdominal wall. All patients were treated using a monopolar RFA system (Cool-Tip RF Ablation System, Covidien, Dublin, Ireland) with a single electrode needle (17-gauge electrode with 2- or 3-cm exposed metallic tips). Intravenous and local anesthesia was administered under monitoring. The electrode needle was inserted in the supine position under US guidance. US scans were obtained using Hitachi Prosound Alpha 7 (Hitachi Aloka Medical, Tokyo, Japan) with a 6-1 MHz abdominal intercostal convex probe (UST-9133).

Treatment procedures differed before and after November 2015. Until October 2015, RFA was performed under US guidance (US-guided group). CECT was performed the day after RFA to enable the assessment of treatment efficacy by 3-6 hepatologists. If residual tumor was suspected, additional RFA was performed on the following day or later. Since November 2015, RFA has been used in the treatment room where CT could be undertaken without moving the patient in the supine position (US/CT-guided group). The electrode needle was inserted into the tumor under US guidance. Plain CT was performed immediately after insertion of the electrode needle to confirm its position, and if necessary, the electrode needle position was adjusted. Because detailed CT images

are not required for positional confirmation, the patient's exposure dose could be reduced to one-third of that of a normal plain scan by suppressing the bulb dose and limiting the area of imaging. CECT was performed after the ablation, and if insufficient margins were determined by the operator, additional RFA was performed on the spot (Figure 2). After the procedure was finished, the CT images were reviewed by 3-6 hepatologists to assess ablation lesions.

Albumin-bilirubin (ALBI) score. We evaluated liver function using the ALBI score, which was calculated as follows:

ALBI score=log10(T-Bil[mg/dl]×17.1)×0.66+(ALB[g/dl]×10)×−0.085, where T-Bil is total bilirubin and ALB is serum albumin level (17).

Follow-up. Patients treated with RFA were followed up every 3 months by imaging examinations including CECT or EOB-MRI. Local recurrence was defined as the appearance of viable intrahepatic tumors within or at the periphery of the original ablated lesion.

Statistical analysis. Data are presented as medians (interquartile ranges). Statistical analyses were performed using the Kaplan–Meier method, log-rank test, and Cox proportional hazards regression analysis using JMP statistical software (version 11.0 for Windows; SAS Institute, Inc., Cary, NC, USA). Statistical significance was set at $p<0.05$.

Results

Patient characteristics. Patient characteristics in the US/CT-guided and US-guided groups are shown in Table I. Of 97 patients, 50 patients were treated with RFA under US/CT guidance (US/CT-guided group) and 47 patients with US guidance (US-guided group). Serum protein-induced vitamin K absence or antagonist-II (PIVKA-II) levels in the US/CT-guided group were significantly higher than those in the US-guided group (p=0.0239). There were no significant differences in age, sex, tumor size, Child–Pugh score, ALBI score, tumor location, and serum α-fetoprotein (AFP) level. The median follow-up periods were 3.1 years in the US/CT-guided group and 2.8 years in the US-guided group (p=0.8426).

Therapeutic outcomes after RFA. Complete ablation was determined when there was a sufficient ablation area around the tumor and no viable lesion of tumor enhancement. Forty-six cases (92.0%) in the US/CT-guided group were assessed for complete ablation compared with 39 cases (82.9%) in the US-guided group (p=0.2244). One of 50 patients (2.0%) in the US/CT-guided group and 2 of 47 patients (4.2%) in the US-guided group had major complications. There were no differences in the complete ablation and complication rates between the two groups (p=0.6100).

Local recurrence rate. Twenty-seven patients had local recurrence. Figure 3A shows a Kaplan–Meier analysis of the cumulative local recurrence in all patients. The 1-, 2-, and 3-year local recurrence rates for all patients were 11.6%, 17.2%, and 25.4%, respectively. Figure 3B shows the

A

B

C

Figure 2. *Radiofrequency ablation (RFA) procedure in the ultrasound sonography (US)/computed tomography (CT) guided group. CT scan prior to RFA after transcatheter arterial chemoembolization showed hepatocellular carcinoma that had lipiodol accumulation. CT scan was used to evaluate the correct position of the electrode needle. Contrast-enhanced CT scan after RFA showed ablated tumor with no viable lesions. CECT: Contrast-enhanced computed tomography.*

cumulative incidence of local recurrence in the US/CT-guided and US-guided groups. Local recurrence was identified in 7 patients (16.2%) in the US/CT-guided group and in 20 patients (58.7%) in the US-guided group during the follow-up periods. The 1-, 2-, and 3-year local recurrence rates for the US/CT-guided group and the US-guided group were 4.1%, 6.3%, and 8.6% and 19.6%, 31.6%, and 41.9%, respectively. The local recurrence rate was lower in the US/CT-guided group (p=0.0021).

Table I. *Baseline characteristics of patients.*

Characteristics	All	US/CT guided group	US guided group	*p*-Value
Number	97	50	47	
Age, years	75 (67-80)	76.5 (67-80)	73 (66-80)	0.5876
Sex, n (male/female)	63/34	31/19	32/15	0.6706
Tumor size, cm	1.7 (1.4-2.0)	1.6 (1.3-1.9)	1.7 (1.4-2.0)	0.1603
Etiology				0.1253
HBV	17 (17.5%)	12 (24.0%)	5 (10.6%)	
HCV	52 (53.6%)	27 (54.0%)	25 (53.2%)	
NBNC	28 (28.8%)	11 (22.0%)	17 (36.2%)	
Child-Pugh score (5/6/7/8/9)	56/27/8/3/3	32/12/4/1/1	24/15/4/2/2	0.7262
Plt (×10^4/mm^3)	11.7 (8.6-16.8)	12.0 (9.1-15.1)	11.1 (8.1-17.5)	0.4770
Alb, g/dl	3.6 (3.2-4.0)	3.7 (3.4-4.2)	3.5 (3.2-3.8)	0.1065
T.Bil, g/dl	0.8 (0.6-1.2)	0.8 (0.6-1.1)	0.8 (0.5-1.3)	0.8449
ALBI score	−2.34 (−2.65 to −1.99)	−2.38 (−2.79 to −2.04)	−2.25 (−2.59 to −1.94	0.1951
Tumor location, n (%)				0.8569
Periportal	14 (14.4%)	8 (16.0%)	6 (12.8%)	
Perivenous	10 (10.3%)	4 (8.0%)	6 (12.8%)	
Subphrenic	26 (26.8%)	14 (28.0%)	12 (25.5%)	
Others	47 (48.5%)	24 (48.0%)	23 (48.9%)	
Tumor marker				
AFP, ng/ml	6.9 (3.3-26.3)	7.2 (3.3-34.3)	6.3 (3.3-18.4)	0.3863
PIVKA-II, mAU/ml	20.0 (13.8-44.5)	30.0 (15.0-93.0)	17.0 (12.0-35.0)	0.0239
Follow up duration (years)	3.0 (1.9-4.3)	3.1 (2.1-3.8)	2.8 (1.2-5.0)	0.8426

Data are expressed as median (interquartile range). HBV: Hepatitis B virus; US: ultrasound sonography; CT: compute tomography; HCV: hepatitis C virus; Plt: platelet count; Alb: albumin; T.Bil: total bilirubin; ALBI score: albumin-bilirubin score; AFP: α-fetoprotein; PIVKA-II: protein induced vitamin K absence or antagonist-II.

Table II. *Factors associated with local hepatocellular carcinoma recurrence after radiofrequency ablation.*

	Univariate			Multivariate		
	HR	95%CI	*p*-Value	HR	95%CI	*p*-Value
Age	0.98	0.95-1.03	0.4336			
Sex: Male	0.98	0.41-2.15	0.9568			
Child-Pugh score	1.02	0.64-1.48	0.9266			
Tumor size	3.35	1.63-6.71	0.0013	2.98	1.47-5.83	0.0028
Alfa-fetoprotein	1.00	0.99-1.00	0.1188			
PIVKA-II	1.00	1.00-1.00	0.4790			
US/CT guidance	0.26	0.10-0.62	0.0017	0.29	0.10-0.68	0.0037

PIVKA-II: Protein induced by vitamin K absence or antagonist-II; US: ultrasound sonography; CT: computed tomography.

Factors for local recurrence. Table II details the factors associated with local recurrence. Potential predictive factors were age, sex, Child–Pugh score, tumor size, AFP, PIVKA-II, and use of US/CT guidance. Tumor size [*p*=0.0028; hazard ratio (HR)=2.98; 95% confidence interval (CI)=1.47-5.83] and use of US/CT guidance (*p*=0.0037; HR=0.29; 95%CI=0.10-0.68) were independently related to the local recurrence on multivariate analysis.

Discussion

This study demonstrated that combined US and CT guidance reduced the local recurrence rate compared with US guidance. This result suggests that US guidance alone may not enable placement of the electrode needle in an accurate position to provide a sufficient ablation area. The background liver in which HCC has formed is almost
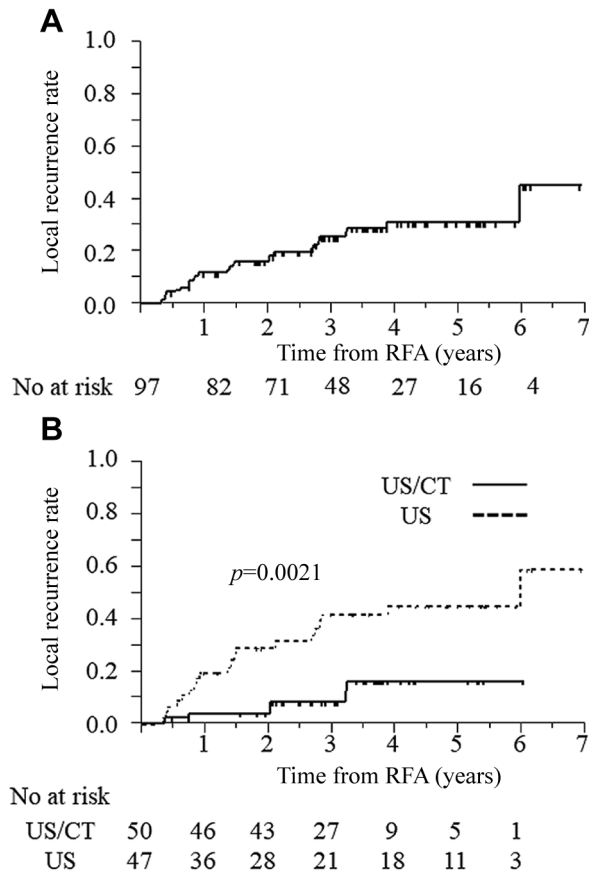
Figure 3. *Kaplan–Meier estimates of the cumulative incidence of local recurrence and overall survival. Significant differences were determined by the log-rank test. A) All patients. B) Ultrasound sonography/computed tomography (US/CT)-guided group and US-guided group.*

RFA at the time of puncture followed by CT to confirm the needle tip. Our institution adopted this technique and compared it with US-guided RFA. Furthermore, unlike other studies, US/CT-guided RFA is not limited to difficult locations, such as under a dome. Usually, CT-guided RFA is chosen only in special circumstances, such as when the target tumor cannot be detected by US. We perform all RFA cases under US/CT guidance, even if the tumor can be easily detected by US. CT-guided RFA following TACE has the advantage of delivering additional treatment before CECT because it is possible to roughly estimate the ablation area by confirming the position of the deposited lipiodol and the electrode needle.

US techniques in RFA therapy are largely dependent on the experience and skills of the operators, but the use of CT guidance provides immediate feedback to the operators with reproducible and multidimensional information. Another advantage of US/CT-guided RFA is that it might reduce the burden of patients treated with RFA. This is because in US-guided RFA, CT imaging is performed the day after RFA, and if additional ablation is needed, two or more RFA sessions are performed in one hospitalization. In contrast, in US/CT-guided RFA, CECT is taken *in situ* after RFA so that additional ablation can be performed immediately if any residual tumor is present. Complications due to RFA were few and not significant in both groups; however, the US/CT-guided group was able to detect and deal with adverse events more quickly because the CT scan was performed without moving the patient into the supine position after RFA.

Several studies have reported that larger HCCs are associated with a higher local recurrence rate (29-32). In these reports, multivariate analysis revealed tumor size as one of the independent risk factors for local recurrence.

Study limitations. First, it was retrospective. All US-guided RFAs were performed before October 2015, and most US/CT-guided RFAs were performed after November 2015. Therefore, it is possible that the technology has improved over time and that the US/CT-guided group had better outcomes. Second, all patients enrolled in this study were from a single institution. A large-scale randomized controlled trial needs to be performed to validate our results. Furthermore, there was no difference in the complete ablation rate between groups, but the reason for the difference in the local recurrence rate was unclear. A previous study revealed that a safety margin of 5 mm or more contributed to local recurrence (33). In the present study, an ablation margin of 5 mm or more was not defined as complete ablation, and no viable tumor within the ablated lesion was defined as complete ablation. We compared the minimum diameter of the ablation margins of the two groups, but there was no difference. However, this was a measurement of horizontal section images only, and it was necessary to measure coronal and sagittal section images.

always cirrhotic with coarse parenchyma, making it difficult to delineate the tumor itself by US, and if obesity and fatty liver is added, it becomes even more difficult to visualize (2, 18-23). Therefore, we have introduced US/CT-guided RFA.

Some institutions have tried to overcome this limitation of US-guided RFA with their own innovations, such as real-time virtual sonography or contrast-enhanced ultrasound sonography (24, 25). CT-guided RFA is also often used and has been reported to be useful in cases in which US-guided RFA alone is insufficient for ablation or complications, such as lung injury, under the right lobe dome (26, 27).

However, Kan *et al*. reported the usefulness of US/CT-guided RFA over CT guidance for HCC under the right lobe dome only (28). They explained that CT-guided RFA is relatively time-consuming and is a non-real-time dynamic observation, which may cause lung injury or damage to major organs; thus, it is more effective to use US-guided

Conclusion

In conclusion, our study demonstrated that combined US- and CT-guided RFA reduced local recurrence.

Conflicts of Interest

All Authors declare no competing interests in relation to this study.

Authors' Contributions

S.N., A.K., and K.T. designed the study. S.N., A.K., K.T., K.K., and Y.M. assisted with data analyses. S.N. wrote the initial draft of the manuscript. K.T. contributed to the analysis and interpretation of the data. M.Y., A.M., and K.M. assisted in the preparation and critical review of the manuscript. All Authors approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

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