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Impact of an ultrasound-guided radiofrequency ablation training program on the outcomes in patients with hepatocellular carcinoma

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Education

Abstract
Purpose: The aim of this study was to retrospectively evaluate the impact of a training program on the safety and efficacy of percutaneous ultrasound-guided radiofrequency ablation (RFA) for the treatment of hepatocellular carcinoma (HCC).
Materials and methods: A total of 227 patients with 296 HCC nodules who underwent percutaneous RFA with or without transcatheter arterial chemoembolization at our institution were included. There were 163 men and 64 women with a mean age of 74.2 ± 8.3 (SD) years (range: 41—89 years). Percutaneous ultrasound-guided RFA was performed by three trainees (205 HCC nodules in 157 patients) or a mentor (91 HCC nodules in 70 patients) after preprocedural preparation including planning ultrasonography. We compared background-related, tumor-related, and treatment-related factors, and local recurrence and complication rates between the trainee group and the mentor group. Similarly, we compared these variables among the years 2015, 2016, and 2017 for trainee group.
Results: The proportion of easy-to-treat tumors in the trainee group (109/205; 53.2%) was greater than that in the mentor group (33/91; 36.3%) ($P = 0.020$). No significant differences were observed in procedure difficulty among the years 2015, 2016, and 2017 for trainee group (easy-to-treat HCC nodules: 25/47; 53.2% vs. 39/79; 49.4% vs. 45/79; 57.0%. $P = 0.775$). The local recurrence rate in the trainee group was 8.8% (18/205 HCC nodules) which was equivalent to 7.7% in the mentor group (7/91 HCC nodules). No significant differences were observed in local recurrence rate (8.8% vs. 7.7%, respectively; $P = 0.621$) and major complication rate (1.3% vs.

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1.4%, respectively; $P = 0.999$) between the trainee group and the mentor group. No significant differences were observed in local recurrence rates ([5/47; 10.6%] vs. [11/79; 13.9%] vs. [2/79; 2.5%]) ($P = 0.109$) and major complication rates ([1/36; 2.8%] vs. [1/62; 1.6%] vs. [0/59; 0%]) ($P = 0.701$) between the years 2015, 2016, and 2017 for trainee group.

Conclusion: A well supervised training program that includes planning ultrasonography fosters the efficacy and treatment quality of RFA for HCC.

Hepatocellular carcinoma (HCC) is one of the most common malignancies in the world and has a high mortality rate [1]. Most patients with HCC are not good candidates for surgical resection because of compromised liver function and other contraindications. Therefore, an effective locoregional therapy is necessary for many patients with HCC.

Percutaneous radiofrequency ablation (RFA) has become established as an effective treatment for small HCC. RFA is currently considered to have a local antitumor effect, leading to a lower local recurrence risk [2,3]. RFA is generally safe and minimally invasive, although numerous reports have been published on the complications associated with RFA [4,5]. RFA is an operator-dependent procedure. Its outcomes vary among operators, probably related to operator experience [2—11]. Normally, training and treatment quality of interventional procedures are inversely related to the quality of treatment by beginners typically inferior to seasoned practitioners even though the entire procedure must be performed effectively and safely by trainees. However, few reports are available regarding RFA training and education for mastering the procedural technique for beginners [12].

The aim of the present study was to retrospectively assess the training efficacy and treatment quality of RFA for HCC by comparing effectiveness and safety between the trainee group and the mentor group.

Materials and methods

This retrospective study was approved by the Institutional Review Board and all participants provided informed consent.

Patient selection and indications for RFA

From April 2015 to March 2018, 248 patients with HCC from our institution who were potential candidates to RFA were initially identified. The indications of RFA for HCC were three or fewer HCC nodules, with each nodule ≧5 mm and ≦30 mm in diameter and a Child-Pugh score of A or B. An exception was made for four patients (2 patients with Child-Pugh class C because of good general condition and 2 patients with HCC of 32 mm in diameter). The laboratory criteria for RFA include a total bilirubin concentration < 3 mg/dL, platelet count > $5 \times 10^4/\mu L$, and a prothrombin time > 50%. Patients with prior bilio-enteric anastomosis or sphincterotomy, central HCC close to the hepatic hilum, pacemakers, refractory ascites, portal vein tumor thrombi, or extrahepatic metastases were excluded. Transcatheter arterial chemoembolization (TACE) before RFA was performed in patients with hypervascular HCC of 20—30 mm in diameter.

Twenty-five patients were excluded and 227 patients with a total of 296 HCC nodules were ultimately included. There were 163 men and 64 women with a mean age of 74.2 ± 8.3 (SD) years (range: 41—89 years) who underwent percutaneous RFA alone (215 nodules) or in combination with TACE (81 nodules) at our institution. Fig. 1 is a flowchart of patients who were considered for this study.

Diagnosis of HCC

The diagnosis of HCC was based on imaging findings and tumor marker serum level (*i.e.*, alpha-fetoprotein [AFP], protein induced by vitamin K absence II [PIVKAII]). Biopsy was not performed for all patients. Imaging findings consisted in well-established criteria including hyperenhancement during the arterial phase and washout during the portal-venous phase on computed tomography (CT) and/or magnetic resonance imaging (MRI) [13]. Nodules displaying a hypointense, hypovascular pattern in a cirrhotic liver on during the hepatocyte phase after intravenous administration of gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA, Primovist®, Bayer Yakuhin) was diagnosed as a well-differentiated HCC [14,15].

CT examinations were obtained using LightSpeed® VCT or Ultra 8® (GE Healthcare) units. After unenhanced CT images, contrast-enhanced axial images were obtained at 40 seconds (arterial phase), 90 seconds (portal-venous phase), and 3 minutes (delayed phase) after intravenous administration of 100 mL of iopamidol (Iopamiron 300®, Bayer Yakuhin) or iohexol (Omnipaque 300®, GE Healthcare). MRI examinations were obtained a 1.5- or 3-Tesla (Magnetom® Avanto or Skyra, Siemens Healthineers). Two-dimensional T2-weighted turbo spin-echo and T1-weighted (in-phase and out-of-phase) sequences were obtained. After intravenous administration of 0.1 mmoL/kg of Gd-EOB-DTPA, three-dimensional volumetric interpolated breath-hold (3D VIBE) sequences were obtained in the axial and coronal planes during the arterial phase (20—40 seconds), portal-venous phase (60—80 seconds), delayed phase (100—120 seconds), and

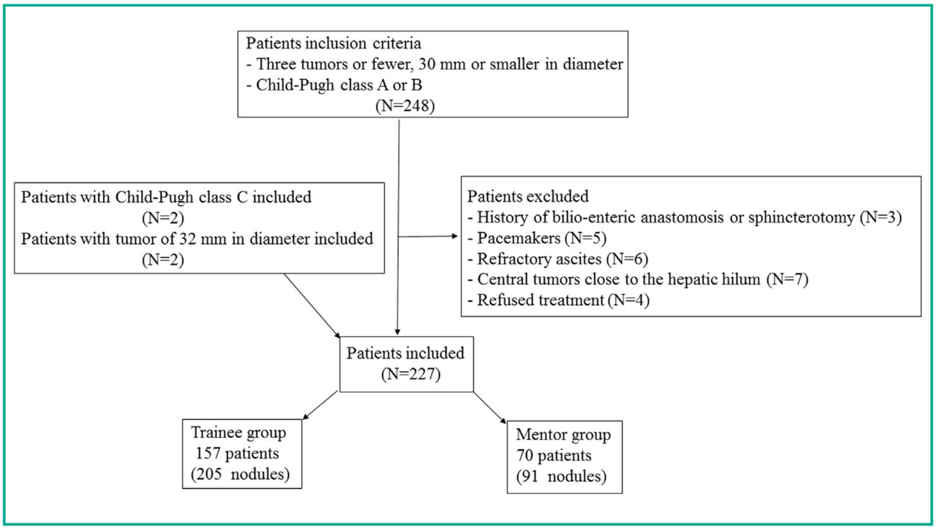

Figure 1. Flowchart of patients who were considered for this study.

hepatocyte phase (10 and 20 minutes). Diffusion-weighted MRI sequences were also obtained.

Training program and procedure details

Percutaneous RFA was performed by a mentor (A.O.) who had 25 years of experience in ultrasound-guided interventional procedures including more than 500 RFA interventions and three RFA beginner trainees (R.T.T., G.Y., K.M.) who graduated from medical school on March 2013 at our hospital. The trainees and mentor strictly performed pre-RFA assessment including patient evaluation with imaging and clinical data, and pre-RFA ultrasound planning. Ultrasound examinations were performed using an Aplio® i-800 (Toshiba). Virtual ultrasound with image fusion from CT or MRI data was used for all patients. Pre-RFA ultrasound planning lasted at least 30 minutes.

In the first period, the trainees selected mainly easy-to-treat HCC nodules, and moderate- and difficult-to-treat HCC nodules were usually handled by the mentor. Difficulty was classified as easy-to-treat, moderate-to-treat, or difficult-to-treat HCC nodules. Difficult-to-treat tumors included:

- failure to detect a nodule by usual ultrasound due to tumor location (*e.g.*, below the diaphragm or left edge of the left lobe);
- inability to perform RFA with usual methods because of the proximity of the tumor to other vital organs (*e.g.*, the heart and the digestive tract);
- lack of clarity on ultrasound because of obesity or cirrhosis or;
- long route of needle insertion (> 10 cm).

Easy-to-treat HCC nodules were defined as clearly visible nodules located within 5 cm from the surface of the liver. All other HCC nodules were defined as moderate-to-treat. Gradually, the trainees also performed the procedure on moderate- and difficult-to-treat tumors. The mentor always supervised the trainees during all the procedures. When a trainee hesitated during an actual procedure when inserting an electrode needle, the mentor relieved the trainee. The method was an intended countermeasure for keeping the quality of the treatment. Ten nodules were thus shifted to the mentor group during the early period of 2015.

The RFA schedule was as follows. On Day 1, pre-RFA planning ultrasound was performed again by the trainee and mentor as a final confirmation after hospitalization. On Day 2, the RFA procedure was performed. A 17-Gauge, cooled-tip electrode with a 2- or 3-cm exposed tip was attached to a 200-W radiofrequency generator (Covidien). Sonazoid®-enhanced ultrasound-guided RFA was performed for HCC nodules that were not depicted on unenhanced ultrasound. In a subset of patients, artificial ascites was produced using 5% glucose solution to prevent thermal injury of the gastrointestinal tract during RFA of HCC nodules close to the gastrointestinal tract. Following RFA, tract ablation was performed during needle withdrawal. On Day 3, laboratory tests were performed.

Follow-up, definitions, data collection and analysis

Post RFA imaging evaluation included contrast-enhanced CT or MRI one to three days after RFA. The evaluation immediately after RFA was classified into three patterns as follows: Pattern 1 corresponded to a 5 mm or larger ablative margin around the entire HCC nodule indicating absolutely curative ablation. Pattern 2 corresponded to an ablative margin around the HCC nodule, but less than 5 mm in diameter in some places indicating relatively curative ablation. Pattern 3 corresponded to an HCC nodule which was not entirely ablated, indicating non-curative ablation. When ablation was found to be non-curative, an additional RFA session was performed until curative ablation was confirmed on contrast-enhanced CT. Patients were followed at our outpatient clinic every 3—4 months with serum AFP and PIVKAII, as well as with ultrasound, CT or MRI. When recurrence was observed, appropriate treatment was immediately performed.

All patients were divided into two groups according to who actually inserted the electrode needle: the trainee group (205 nodules in 157 patients) and the mentor group

(91 nodules in 70 patients). Background-related variables were investigated in the two groups included: age, sex, background liver disease, platelet, prothrombin time, albumin, total bilirubin, alanine aminotransferase, Child-Pugh classification, presence of chronic kidney disease, and use of antithrombotic drugs. Tumor-related factors (nodules) included: location, size, and vascularity (hypo or hyper). Treatment-related factors (nodules) included: the combination of TACE, the use of a 2- or 3-cm needle, the number of insertions and RFA sessions, the use of Sonazoid®, the number of sessions, ablation time (in minutes), difficulty to treat (easy/moderate/difficult), and image evaluation immediately after RFA (absolutely curative or relatively curative). All clinical data were retrospectively collected in a computerized database. We defined an RFA session as a single intervention episode that consisted of one or more ablations performed on a single tumor. We compared background-related, tumor-related, and treatment-related factors between the trainee group and the mentor group.

We defined local recurrence as the presence of an enhanced nodule adjacent to the ablated area after RFA by dynamic CT or MRI. Recurrence time was defined as the interval between the date of the last RFA and the detection of the local recurrence. A recurrence that was distant from the ablated area in the same segment was not included as a local recurrence.

Major complications were defined as those that if left untreated might threaten the patient's life, lead to substantial morbidity and disability, or result in a lengthened hospital stay. Major complications included hemothorax, pneumothorax, hemoperitoneum, biliary injury, liver abscess, gastrointestinal perforation, liver infarction, neoplastic seeding, and hemobilia. All other complications were considered minor. Minor complications included pain, fever, and asymptomatic pleural effusion and ascites. The severity of the complications was graded according to the CIRSE classification system for complications [16]. Local recurrence and complication rates after RFA were compared between the trainee group and the mentor group.

We also compared background-related, tumor-related, and treatment-related factors, and local recurrence and complication rates after RFA among the years 2015, 2016, and 2017 for trainee groups (Japan fiscal year; April 1st to March 31st).

Statistical analysis

Quantitative variables were expressed as mean ± standard deviation (SD) and ranges. Qualitative variables were

Table 1 Characteristics of 227 patients who underwent percutaneous ultrasound-guided radiofrequency ablation of hepatocellular carcinoma.

	Trainee group(n = 157)	Mentor group(n = 70)	P value
Age (years)	74.1 ± 8.3 [50—89]	74.5 ± 8.4 [41—88]	0.704
Sex			0.686
Man	114/157 (72.6%)	49/70 (70.0%)	
Woman	43/157 (27.4%)	21/70 (30.0%)	
Underlying liver disease			0.154
HBV	18/157 (11.5%)	8/70 (11.4%)	
HCV	79/157 (50.3%)	38/70 (54.3%)	
NBNC	60/157 (38.2%)	22/70 (31.4%)	
HBV & HCV	0/157 (0%)	2/70 (2.9%)	
Platelet ($\times 10^4/\mu L$)	12.9 ± 6.4 [3.4—59.7]	13.0 ± 7.5 [2.8—50.9]	0.881
Prothrombin time (%)	81.3 ± 16.8 [11.6—111.6]	78.0 ± 18.6 [12.7—112.3]	0.189
Albumin (g/dL)	3.7 ± 0.5 [2.2—4.7]	3.7 ± 0.5 [2.6—4.5]	0.974
Total bilirubin (mg/dL)	0.79 ± 0.58 [0.2—4.1]	0.85 ± 0.72 [0.3—5.4]	0.516
ALT (U/L)	36.9 ± 27.1 [7—157]	36.6 ± 23.4 [8—112]	0.943
Child-Pugh score			0.591
A	144/157 (91.7%)	64/70 (91.4%)	
B	11/157 (7.0%)	6/70 (8.6%)	
C	2/157 (1.3%)	0/70 (0%)	
Chronic kidney disease	10/157 (6.4%)	4/70 (5.7%)	0.999
Antithrombotic therapy	27/157 (17.2%)	7/70 (10.0%)	0.161

Quantitative variables are expressed as mean ± standard deviation; numbers in brackets are ranges. Qualitative variables are expressed as proportions; numbers in parentheses are percentages. HBV: hepatitis B virus; HCV: hepatitis C virus; NBNC: nonHBV; nonHCV: ALT: alanine aminotransferase.

expressed as raw numbers, proportions, and percentages. Comparisons of variables between the groups were performed using Chi[2] (χ^2) test, Student-*t*- test, Fisher exact test, and one-way analysis of variance (Anova). The cumulative local recurrence rate between the trainee group and the mentor group was calculated using the Kaplan-Meier method and compared using the log-rank test. A P value < 0.05 was considered to indicate statistical significance. All statistical analyses were performed using SPSS software program, version 22.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

There were no significant differences in background-related factors (Table 1) and tumor-related factors (Table 2) between the trainee group and the mentor group. There were significant differences regarding the use of additional TACE, Sonazoid® use, and difficulty levels between the two groups. In the trainee group, Sonazoid® was less frequently used and the number of difficult-to-treat HCC nodules was lower compared with those in the mentor group (Table 2).

The cumulative local recurrence rate was 8.8% (18/205) in the trainee group and 7.7% (7/91) in the mentor group (Fig. 2) with no significant differences between the two groups (P = 0.621). The follow-up period after RFA ranged from 41 to 1215 days, with a mean duration of 554 ± 316 (SD) days. There were 21 patients eliminated (29 nodules) due to death occurring from other diseases and hospital transfers.

In the present study, 3/227 patients (1.3%) had major complications, including pneumothorax and rapid portal-venous recurrence in the trainee group and intraperitoneal bleeding in the mentor group. The pneumothorax and intraperitoneal bleeding were promptly identified and treated appropriately with thoracic drainage and transcatheter arterial embolization, respectively. A patient with rapid recurrence of portal-venous tumor thrombus two months after RFA had surgical resection that showed recurrence of tumor thrombus in the distal area but no local recurrence in the ablated area. All complications corresponded to Grade 3 in CIRSE classification system for complications [16]. The major complication rates in the trainee group were similar to those in the mentor group either on a per patient basis (2/157; 1.3% vs. 1/70; 1.4%) (P = 0.999) or on a per HCC nodule basis (2/205; 1.0% vs. 1/91; 1.1%) (P = 0.999). During the follow-up periods, there were no periprocedural and delayed complications such as biloma, liver atrophy, liver infarction, diaphragmatic injury, and peritoneal dissemination.

Table 2 Tumor-related and treatment-related factors of 296 nodules of hepatocellular carcinoma.

	Trainee group(n = 205)	Mentor group(n = 91)	P value
Segmental location of HCC			0.698
S1	4/205 (2.0%)	2/91 (2.3%)	
S2	12/205 (5.9%)	7/91 (7.8%)	
S3	17/205 (8.3%)	4/91 (4.5%)	
S4	28/205 (13.6%)	13/91 (14.3%)	
S5	28/205 (13.6%)	13/91 (14.3%)	
S6	38/205 (18.5%)	17/91 (18.8%)	
S7	35/205 (17.1%)	16/91 (17.8%)	
S8	43/205 (21.0%)	19/91 (20.2%)	
Size (mm)	13.9 ± 5.1 [5—30]	13.9 ± 5.7 [5—32]	0.973
Vascularity on arterial phase			0.279
Hypovascular	40/205 (19.5%)	13/91 (14.3%)	
Hypervascular	165/205 (80.5%)	78/91 (85.7%)	
Combination with TACE	49/205 (23.9%)	32/91 (35.2%)	0.045
Needle size			0.649
2 cm	156/205 (76.1%)	67/91 (73.6%)	
3 cm	49/205 (23.9%)	24/91 (26.4%)	
Number of insertions and ablations	1.04 ± 0.22 [1—3]	1.09 ± 0.32 [1—3]	0.128
Use of Sonazoid®	36/205 (17.6%)	32/91 (35.2%)	0.001
Number of sessions	1.06 ± 0.26 [1—3]	1.08 ± 0.27 [1,2]	0.574
Time of ablation (minute)	6.1 ± 2.1 [2—14]	6.3 ± 2.9 [2—18]	0.483
Difficulty			0.020
Easy	109/205 (53.2%)	33/91 (36.3%)	
Moderate	85/205 (41.4%)	49/91 (53.8%)	
Difficult	11/205 (5.4%)	9/91 (9.9%)	
Image evaluation after RFA			0.147
Absolutely curative	176/205 (85.9%)	72/91 (79.1%)	
Relatively curative	29/205 (14.1%)	19/91 (20.9%)	

Quantitative variables are expressed as mean ± standard deviation; numbers in brackets are ranges. Qualitative variables are expressed as proportions; numbers in parentheses are percentages. TACE: transcatheter arterial chemoembolization; RFA: radiofrequency ablation.

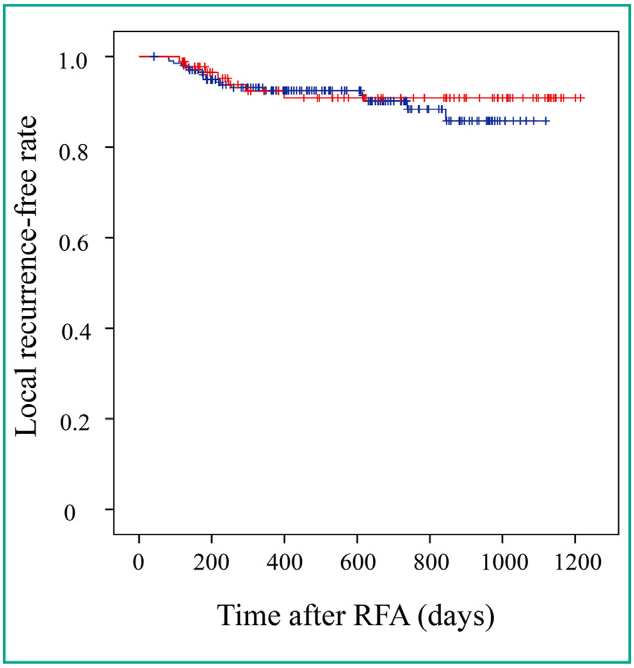

Figure 2. Graph shows cumulative local recurrence rate using the Kaplan-Meier method in the trainee and mentor groups. Blue line corresponds to the Trainee group (205 HCC nodules). Red line corresponds to the Mentor group (91 HCC nodules). There was no significant difference in the local recurrence rate between the two groups ($P = 0.621$). The follow-up period ranged from 41 to 1215 days (mean: 554 days). The 21 eliminated patients (29 HCC nodules) consisted of 18 patients (25 HCC nodules) in the trainee group and 3 patients (4 HCC nodules) in the mentor group.

Regarding the three trainee groups, there were no significant differences in background-related variables among the different years (Table 3). Significant differences were observed in segmental location of HCC nodules ($P = 0.027$) and TACE was less frequently used in the year 2017 compared to years 2015 and 2016 (Table 4). No significant differences in local recurrence rates were observed between the year 2017 (5/47; 10.6%) and the years 2015 (11/79; 13.9%) and 2016 (2/79; 2.5%) ($P = 0.109$) (Fig. 3). Similarly, no significant differences in major complication rates were observed between the year 2017 and the years 2015 and 2016 either on a per patient basis ([1/36, 2.8%] vs. [1/62, 1.6%] vs. [0/59, 0%], respectively) ($P = 0.701$) and on a per HCC nodule basis ([1/47, 2.1%] vs. [1/79, 1.3%] vs.[0/79, 0%], respectively) ($P = 0.702$).

Discussion

In the present study, we showed that a well supervised training program that includes a careful distribution of tasks promotes the efficacy and safety of RFA for HCC. This is to our knowledge, the first study that examined the efficacy of training and treatment quality of RFA for HCC on the treatment outcome.

Various studies have shown that the incidence of local recurrence after RFA ranges from 1.7% to 21% [2,3,6,8—10]. In the present study, the cumulative local recurrence rate was 8.8% in the trainee group and 7.7% in the mentor group. In addition, there were no statistical differences between the trainee group and the mentor group. These rates were similar to those reported in previous studies.

The major complication rate of percutaneous RFA ranges between 1.5% and 10.6% [3—5,7,10,11]. The major complication rate in the present study was 1.3% and lower than those reported in previous studies. In addition, there were no statistical differences between the trainee group and the mentor group. Studies on RFA training for beginners are rare [12]. Several studies demonstrated that there is a significant learning curve in performing RFA for liver tumors [17—20]. A high complete ablation and low complication rate could be achieved with the accumulated experience from the first 50 RFA interventions for liver tumors by a specialized team [17]. If inexperienced trainees perform RFA procedures, the local recurrence rates might be higher and this situation must be avoided. In the present study, there were no significant differences in the rates of local recurrence and those of complications between the trainee group and the mentor group, and among the 2015, 2016, and 2017 trainee groups.

Our results suggest that well monitored trainees could perform RFA procedures effectively and safely as in the present study. Possible reasons for this are as follows: The trainees performed screening ultrasonography once a week for training because ultrasound is fundamental for RFA. RFA is an intervention that needs preprocedural preparation and rehearsal by planning ultrasound. The trainees prepared and rehearsed the RFA procedure. Careful planning of the site and the angle of the needle probe placement before RFA is essential to obtain adequate margins [7] and helps ensure relatively low rates of local recurrence and complications even in the trainee group. This is particularly important when the tumor is difficult to visualize. The mentor supervised all the above procedures including the actual RFA procedure performed by the trainees.

In the first period, the trainees selected mainly tumors that were easy-to-treat. Gradually, the trainees performed the procedure for moderate- and difficult-to-treat tumors. Therefore, there was a significant difference in difficulty between the trainee group and the mentor group. This was not a selection bias, but an intended countermeasure. On the other hand, there was no significant difference in difficulty or in the local recurrence and major complication rates among the years 2015, 2016, and 2017 trainee groups. These results suggest that a well supervised training program fostered effective and safe RFA procedures after the initial period regardless of the distribution of patients.

In addition to RFA, image-guided thermal ablation of liver tumors includes microwave ablation and cryoablation. Furthermore, irreversible electroporation, a relatively new ablation technique with a nonthermal mechanism, has emerged [21]. Irreversible electroporation is a suitable technique for central tumors that are close to the hepatic hilum and are contraindicated for thermal ablation. However, a training program for irreversible electroporation has to be developed.

In our study, several differences were observed between trainees and mentor groups. A difference was observed in the use of Sonazoid®. This was because the mentor usually performed RFA for tumors that were difficult to visualize for which enhanced ultrasound is useful [22]. For percutaneous procedures, guiding tools are of outmost importance [23]. In

Table 3 Background-related variables for patients in the trainee group on a year-to-year analysis.

	Year 2015(36 patients)	Year 2016(62 patients)	Year 2017(59 patients)	*P* value
Age (years)	72.3 ± 10.0 [50–87]	74.3 ± 7.9 [53–88]	74.9 ± 7.5 [57–89]	0.329
Sex				0.619
Man	24/36 (66.7%)	47/62 (75.8%)	43/59 (72.9%)	
Woman	12/36 (33.3%)	15/62 (24.2%)	16/59 (27.1%)	
Underlying liver disease				0.086
HBV	1/36 (2.8%)	9/62 (14.5%)	8/59 (13.5%)	
HCV	25/36 (69.4%)	29/62 (46.8%)	25/59 (42.4%)	
NBNC	10/36 (27.8%)	24/62 (38.7%)	26/59 (44.1%)	
HBV & HCV	0/36 (0%)	0/62 (0%)	0/59 (0%)	
Platelet ($\times 10^4/\mu L$)	12.9 ± 6.2 [4.9–28.5]	11.9 ± 4.4 [4.1–26.6]	13.9 ± 8.1 [3.4–59.7]	0.219
Prothrombin time (%)	79.0 ± 18.2 [11.6–111.6]	81.6 ± 19.6 [12.9–111]	82.4 ± 12.3 [43.9–107]	0.628
Albumin (g/dL)	3.7 ± 0.5 [2.7–4.6]	3.7 ± 0.5 [2.2–4.7]	3.7 ± 0.5 [2.5–4.5]	0.957
Total bilirubin (mg/dL)	0.74 ± 0.36 [0.3–2.2]	0.73 ± 0.64 [0.2–4.1]	0.88 ± 0.62 [0.2–4]	0.331
ALT (U/L)	35.8 ± 25.9 [10–102]	39.1 ± 30.0 [7–157]	35.1 ± 24.9 [7–137]	0.700
Child-Pugh score				0.231
A	33/36 (91.7%)	60/62 (96.8%)	51/59 (86.4%)	
B	3/36 (8.3%)	1/62 (1.6%)	7/59 (11.9%)	
C	0/36 (0%)	1/62 (1.6%)	1/59 (1.7%)	
Chronic kidney disease	2/36 (5.6%)	4/62 (6.5%)	4/59 (6.8%)	0.972
Antithrombotic therapy	6/36 (16.7%)	8/62 (12.9%)	13/59 (22.0%)	0.411

Quantitative variables are expressed as mean ± standard deviation; numbers in brackets are ranges. Qualitative variables are expressed as proportions; numbers in parentheses are percentages. HBV: hepatitis B virus; HCV: hepatitis C virus; NBNC: nonHBV, nonHCV; ALT: alanine aminotransferase.

Table 4 Comparison of tumor-related and treatment-related variables on a per HCC nodule analysis and year-by-year analysis in the trainee group.

	Year 2015(47 HCC nodule)	Year 2016(79 HCC nodule)	Year 2017(79 HCC nodule)	*P*-value
Segmental location of HCC				0.027
S1	0/47 (0%)	2/79 (2.5%)	2/79 (2.5%)	
S2	2/47 (4.3%)	2/79 (2.5%)	8/79 (10.1%)	
S3	2/47 (4.3%)	6/79 (7.6%)	9/79 (11.4%)	
S4	5/47 (10.6%)	17/79 (21.5%)	6/79 (7.6%)	
S5	7/47 (14.9%)	9/79 (11.4%)	12/79 (15.2%)	
S6	16/47 (34.0%)	9/79 (11.4%)	13/79 (16.5%)	
S7	7/47 (14.9%)	12/79 (15.2%)	16/79 (20.3%)	
S8	8/47 (17.0%)	22/79 (27.9%)	13/79 (16.4%)	
Size (mm)	13.9 ± 5.0 [8–30]	13.8 ± 5.2 [5–30]	14.1 ± 5.0 [6–30]	0.921
Vascularity on arterial phase				0.818
Hypovascular	8/47 (17.0%)	17/79 (21.5%)	15/79 (19.0%)	
Hypervascular	39/47 (83.0%)	62/79 (78.5%)	64/79 (81.0%)	
Combination with TACE	14/47 (29.8%)	24/79 (30.4%)	11/79 (13.9%)	0.030
Needle size				0.182
2 cm	32/47 (68.1%)	59/79 (74.7%)	65/79 (82.3%)	
3 cm	15/47 (31.9%)	20/79 (25.3%)	14/79 (17.7%)	
Number of insertions and ablations	1.02 ± 0.15 [1,2]	1.04 ± 0.25 [1–3]	1.05 ± 0.22 [1,2]	0.766
Use of Sonazoid®	7/47 (14.9%)	15/79 (19.0%)	14/79 (17.7%)	0.842
Number of sessions	1.04 ± 0.21 [1,2]	1.06 ± 0.28 [1–3]	1.06 ± 0.22 [1,2]	0.888
Time of ablation (minute)	6.3 ± 2.2 [2–10]	6.4 ± 2.3 [2.5–14]	5.8 ± 1.8 [2–2]	0.184
Difficulty				0.775
Easy	25/47 (53.2%)	39/79 (49.4%)	45/79 (57.0%)	
Moderate	20/47 (42.6%)	34/79 (43.0%)	31/79 (39.2%)	
Difficult	2/47 (4.2%)	6/79 (7.6%)	3/79 (3.8%)	
Image evaluation after RFA				0.643
Absolutely curative	39/47 (83.0%)	67/79 (84.8%)	70/79 (88.6%)	
Relatively curative	8/47 (17.0%)	12/79 (15.2%)	9/79 (11.4%)	

Quantitative variables are expressed as mean ± standard deviation; numbers in brackets are ranges. Qualitative variables are expressed as proportions; numbers in parentheses are percentages. TACE: transcatheter arterial chemoembolization; RFA: radiofrequency ablation.

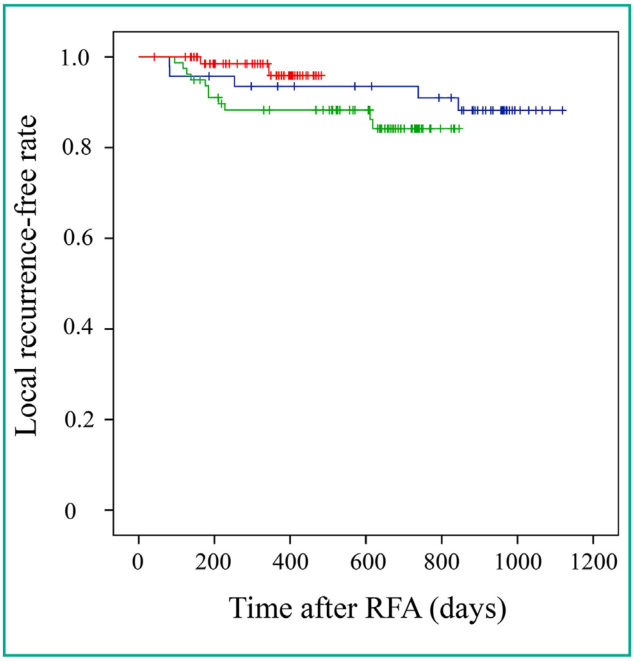

Figure 3. Graph shows cumulative local recurrence rate using the Kaplan-Meier method in the trainee group during the years 2015, 2016, and 2017. Blue line corresponds to 2015 trainee group ($n = 47$ HCC nodules). Green line corresponds to 2016 trainee group ($n = 79$ HCC nodules). Red line corresponds to 2017 trainee group ($n = 79$ HCC nodules). There was no significant difference in the local recurrence rate among the three groups ($P = 0.109$). The 18 eliminated patients (25 nodules) in the trainee group consisted of 8 patients (10 nodules) in the 2015 trainee group, 8 patients (12 nodules) in the 2016 trainee group, and 2 patients (3 nodules) in the 2017 trainee group.

addition, there was a difference in the use of TACE between the two trainee and mentor groups and among the three trainee groups, although there was no significant difference in tumor size. The possible reason for this discrepancy is unknown. The reason for a difference in locations (S1-8) among the three trainee groups is also unknown.

The present study had several limitations. First, this study was a retrospective analysis. Second, we could not investigate the long-term outcomes. Long-term observation may reveal an increase in the local recurrence rate and delayed onset of complications, such as biloma, liver atrophy, liver infarction, diaphragmatic injury, and peritoneal dissemination. Third, some patients were eliminated (21/227: 9.3%) as they died due to other diseases or were transferred to another hospital.

In conclusion, a carefully monitored training program that includes treatment planning, ultrasonographic evaluation, and identification of patients according to the disease characteristics allows effective training of the clinicians and maintenance of RFA quality for HCC.

Human and animal rights

The authors declare that the work described has been carried out in accordance with the Declaration of Helsinki of the World Medical Association revised in 2013 for experiments involving humans.

Informed consent and patient details

The authors declare that this report does not contain any personal information that could lead to the identification of the patient(s).

The authors declare that they obtained a written informed consent from the patients and/or volunteers included in the article. The authors also confirm that the personal details of the patients and/or volunteers have been removed.

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Contribution of authors

All authors attest that they meet the current International Committee of Medical Journal Editors (ICMJE) criteria for Authorship.

Rieko Takai Takamatsu: conceptualization, methodology, formal analysis, investigation, resources, data curation, writing-original draft, writing-review and editing, visualization and project administration.

Akihiro Okano: conceptualization, methodology, formal analysis, investigation, resources, data curation, writing-review and editing, supervision and project administration.

Go Yamakawa: investigation, resources and data curation.

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Hitoshi Obayashi: conceptualization, methodology, formal analysis and data curation, visualization.

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Disclosure of interest

The authors declare that they have no competing interest.

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