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Whole tumor ablation of locally recurred hepatocellular carcinoma including retained iodized oil after transarterial chemoembolization improves progression-free survival

Dong Ho Lee · Jeong Min Lee [1,2] · Pyo Nyun Kim [3] · Yun-Jin Jang [3] · Tae Wook Kang [4] · Hyunchul Rhim [4] · Jung Wook Seo [5] · Young Joon Lee [6]

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Abstract

Objectives To evaluate and compare clinical outcomes of two different radiofrequency ablation (RFA) methods for locally recurred hepatocellular carcinoma (LrHCC) after locoregional treatment.

Methods Our institutional review board approved this study with a waiver of informed consent. A total of 313 patients previously treated with transarterial chemoembolization (TACE) ($n = 167$) and RFA ($n = 146$) with a single LrHCC ≤ 3 cm was included from five tertiary referral hospitals. RFA was done for LrHCCs using either viable tumor alone ablation (VTA) method (VTA: $n = 61$ in the TACE group and $n = 127$ in the RFA group) or whole tumor ablation (WTA) method which includes both viable tumor and retained iodized oil or previously ablated zone (WTA: $n = 106$ in the TACE group and $n = 19$ in the RFA group). Local tumor progression (LTP)-free survival as well as progression-free survival (PFS) were estimated using the Kaplan-Meier method, and prognostic factors were evaluated using the Cox proportional hazards regression model.

Results In 167 patients with LrHCC who underwent TACE, the 5-year LTP-free survival after RFA was significantly higher with the VTA method than with the WTA method (26.9% vs. 87.8%; $p < 0.001$; hazard ratio (HR) = 8.53 [4.16–17.5]). The estimated 5-year PFS after RFA for LrHCC after TACE using the VTA method was 5.7%, which was significantly lower than that with the WTA method (26.4%) ($p = 0.014$; HR = 1.62 [1.10–2.38]). However, in 146 patients with LrHCC after initial RFA, there were no significant differences in cumulative incidence of LTP ($p = 0.514$) or PFS ($p = 0.905$) after RFA between the two ablation methods.

Conclusions For RFA of LrHCC after TACE, the WTA method including both viable tumor and retained iodized oil could significantly lower LTP and improve PFS than VTA.

Key Points

- *Whole tumor ablation (WTA) could provide significantly better local tumor control for locally recurred HCC (LrHCC) after TACE than viable tumor alone ablation (VTA).*
- *WTA for LrHCC after TACE could also provide significantly better progression-free survival than VTA.*
- *Regarding LrHCC after RFA, VTA would provide a comparable clinical outcome to WTA.*

Keywords Hepatocellular carcinoma · Ablation techniques · Progression-free survival · Chemoembolization · Therapeutic

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✉ Jeong Min Lee
jmsh@snu.ac.kr

[1] Department of Radiology, Seoul National University Hospital, 101 Daehangno, Jongno-gu, Seoul 110-744, South Korea

[2] Institute of Radiation Medicine, College of Medicine, Seoul National University, Seoul, South Korea

[3] Department of Radiology and Research Institute of Radiology, University of Ulsan, Asan Medical Center, Seoul, South Korea

[4] Department of Radiology, Samsung Medical Center, School of Medicine, Sungkyunkwan University, Seoul, South Korea

[5] Department of Radiology, Inje University Ilsan Paik Hospital, Goyang, South Korea

[6] Department of Radiology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, South Korea

Abbreviations

AFP	Alpha-fetoprotein
CI	Confidence interval
CT	Computed tomography
EM	Extrahepatic metastasis
HCC	Hepatocellular carcinoma
HR	Hazard ratio
IDR	Intrahepatic distant recurrence
LrHCC	Locally recurred hepatocellular carcinoma
LTP	Local tumor progression
MR	Magnetic resonance
PFS	Progression-free survival
RFA	Radiofrequency ablation
TACE	Transarterial chemoembolization
US	Ultrasound

Introduction

Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related death worldwide [1]. Among various treatment modalities, radiofrequency ablation (RFA) has emerged as an effective locoregional treatment option and a first-line treatment option in patients with small HCCs less than 3 cm in size and portal hypertension, providing comparable overall survival outcomes to surgical resection [2–5]. Transarterial chemoembolization (TACE), on the other hand, has been the standard treatment modality for Barcelona Clinic Liver Cancer (BCLC) stage B HCC patients according to current HCC management guidelines proposed by the European Association for the Study of the Liver (EASL) and American Association for the Study of Liver Diseases (AASLD) [6, 7]. However, in real clinical practice, TACE is the most frequently used first treatment option for HCCs in North America, Europe, China, and South Korea, regardless of stage [8].

One of the most important limitations of locoregional treatment such as RFA or TACE is its frequent local tumor recurrence, even after achievement of initial complete tumor control. With RFA, the reported 5-year cumulative incidence of local tumor progression (LTP) has been approximately 20–25% [2, 4, 5] which is significantly higher than that of surgical resection. Thus, considering the frequent incidence of LTP after locoregional treatment for HCC, early detection and effective treatment for recurrent tumors are of crucial importance in the management of patients with HCC. In this regard, several previous studies have been reporting that RFA can provide effective tumor control for locally recurred HCCs (LrHCCs) after both TACE [9, 10] and RFA [2–5].

In planning RFA for LrHCC after locoregional treatment, two ablation methods are possible with differences in their ablation coverage: one is ablation for only the viable tumor portion (i.e., local tumor recurrence itself alone) and the other is ablation for both the viable tumor portion and the previously treated area (Fig. 1). Indeed, Kim et al [11] previously reported that when they performed RFA for LrHCC after TACE, RFA of the whole tumor including both the viable tumor and retained iodized oil could provide better tumor control compared with RFA of the viable tumor alone. However, this study was only a single-center retrospective study with a small study population, and the results of the study have not yet been validated in another cohort. Furthermore, it is not yet certain whether whole tumor ablation can result in the same clinical outcome as above in patients with LrHCC after RFA.

Therefore, the purpose of this retrospective multicenter study was to evaluate and compare the clinical outcomes of two different RFA methods for LrHCCs after locoregional treatment.

Patients and methods

Patients

This retrospective multicenter study was approved by the institutional review board of five university-affiliated hospitals, and the requirement for written informed consent was waived. The inclusion criteria for this study were the following: (a) a single LrHCC after either RFA or TACE equal to or less than 3 cm in size treated by RFA, (b) initial presentation of three or fewer HCCs equal to or less than 3 cm that were initially treated by RFA or TACE and achieved complete response on follow-up imaging, (c) no extrahepatic metastasis nor vascular invasion, (d) Child-Pugh class A or B liver function, (e) no concomitant serious medical disease such as malignant tumors other than HCC, and (f) available medical records and follow-up imaging studies after RFA for LrHCC. The diagnosis of LrHCC was made by non-invasive imaging criteria proposed by the EASL consisting of arterial hyperenhancement followed by washout on the portal venous/delayed phase adjacent to the previously treated area [12, 13]. Between January 2010 and December 2014, we initially found 335 patients who underwent RFA for a single LrHCC after either RFA or TACE from five tertiary referral hospitals (Seoul National University Hospital, Asan Medical Center, Samsung Medical Center, Inje University Ilsan Paik Hospital, and Seoul St. Mary's Hospital), and each patient was treated at each center. Among them, 22 patients were excluded from this study for the following reasons: concomitant malignant disease other than HCC ($n = 11$; gastric cancer, $n = 6$; breast cancer, $n = 2$; pancreatic cancer, $n = 1$; lung cancer, $n = 1$; and lymphoma, $n = 1$), immediate follow-up loss after RFA for LrHCC ($n = 5$), more than three HCCs at the time of initial HCC diagnosis ($n = 4$), and the presence of segmental portal vein invasion at the time of initial diagnosis of HCC ($n = 2$). The remaining 313 patients comprised our

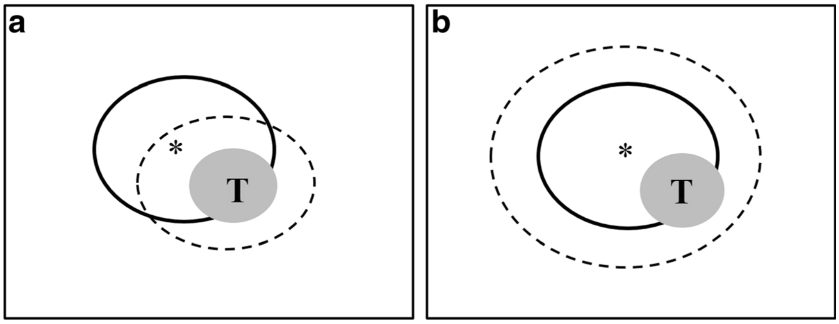


Fig. 1 Diagrams showing the coverage of the ablation method. **a** Viable tumor alone ablation method, in which ablation was done only for the viable tumor portion (T) around the retained iodized oil/previous ablated zone (asterisk). **b** Whole tumor ablation method including viable tumor and retained iodized oil/previous ablated zone, in which ablation was done for both the viable tumor portion (T) and retained iodized oil/ previous ablated zone (asterisk). Dashed circle, intended ablation zone

final study population. Among the 313 participating patients, LrHCC was diagnosed by using dynamic liver CT in 142 patients (45.4%) and gadoxetic acid-enhanced MR in 171 patients (54.6%). We then divided our study patients into two patient groups according to the type of locoregional treatments before RFA: patients with a single LrHCC from the TACE group ($n = 167$) and patients with a single LrHCC from the RFA group ($n = 146$) (Fig. 2). We also searched and recorded the location of LrHCC seen on imaging study, and the tumor location was further defined into four groups: perivascular, subcapsular, non-perivascular and non-subcapsular, and perivascular and subcapsular [14]. The baseline characteristics of all patients are summarized in Table 1.

Ablation method

A multidisciplinary team including radiologists, hepatologists, liver surgeons, and radiation oncologists has been holding a regular meeting for discussion regarding the choice of HCC treatment method in each patient, and RFA was chosen for treatment of LrHCC through the discussion in a multidisciplinary team. In this study, two different ablation methods were used for the RFA of LrHCCs after either RFA or TACE. One was ablation for the viable tumor portion alone (VTA), and the other was whole tumor ablation (WTA) including both the viable tumor portion and previously treated area or areas with retained ionized oil (Fig. 1) [11]. As there have been no guidelines or recommendations for RFA of LrHCC after locoregional treatment during the study period, selection between the two ablation methods was generally made according to the operator's preference. In our study, both VTA and WTA methods were used to do RFA for LrHCC in five participating centers, and there were no significant differences in the distribution of ablation methods among the five participating centers ($p = 0.496$). RFA procedures with assessment of treatment outcome are given in the supplementary data.

Immediate after RFA, contrast-enhanced computed tomography (CE-CT) was performed in all patients to assess its technical success (i.e., whether the target tumor was completely ablated or not) [13] as well as to detect any possible procedure-related complications such as bleeding. When a viable residual tumor was seen at the site of the original tumor on the CT scan immediately obtained after RFA, an additional ablation session was done to achieve complete ablation of the target tumor, if feasible [14, 15]. All patients underwent follow-up contrast-enhanced liver CT or magnetic resonance (MR) imaging 1 month after RFA to determine technical effectiveness: when an arterial-enhancing foci of tissue showing washout on portal venous or delayed-phase images at the site of the original tumor was seen on 1-month follow-up images, it was classified as treatment failure [13, 16]. For patients who experienced treatment failure, possible treatment methods including surgical resection, repeated ablation, liver transplantation, TACE, or radiation therapy were considered. For patients who achieved treatment success defined as the absence of enhancing tumor tissue at the site of the original tumor on 1-month follow-up images, follow-up contrast-enhanced CT or MR imaging was made every 2 months to 3 months during the first year, and every 3 months to 6 months during the second year [15]. Thereafter, when no tumor recurrence was observed, the follow-up schedule was maintained the same as that of the surveillance program for liver cirrhosis (i.e., US with 6-month intervals).

Tumor progression which appeared during the follow-up period was also evaluated and classified into three categories including LTP, intrahepatic distance recurrence (IDR), and extrahepatic metastasis (EM). LTP was defined as the reappearance of enhancing tumor tissue showing washout on portal venous or delayed-phase images adjacent to the ablation zone after achievement of treatment success, and IDR was defined as the appearance of one or more HCC lesions apart from the treated site [16].

Statistical analysis

To compare the baseline characteristics between the two ablation methods, we used Fisher's exact test for categorical variables and the Mann-Whitney U test for continuous variables.

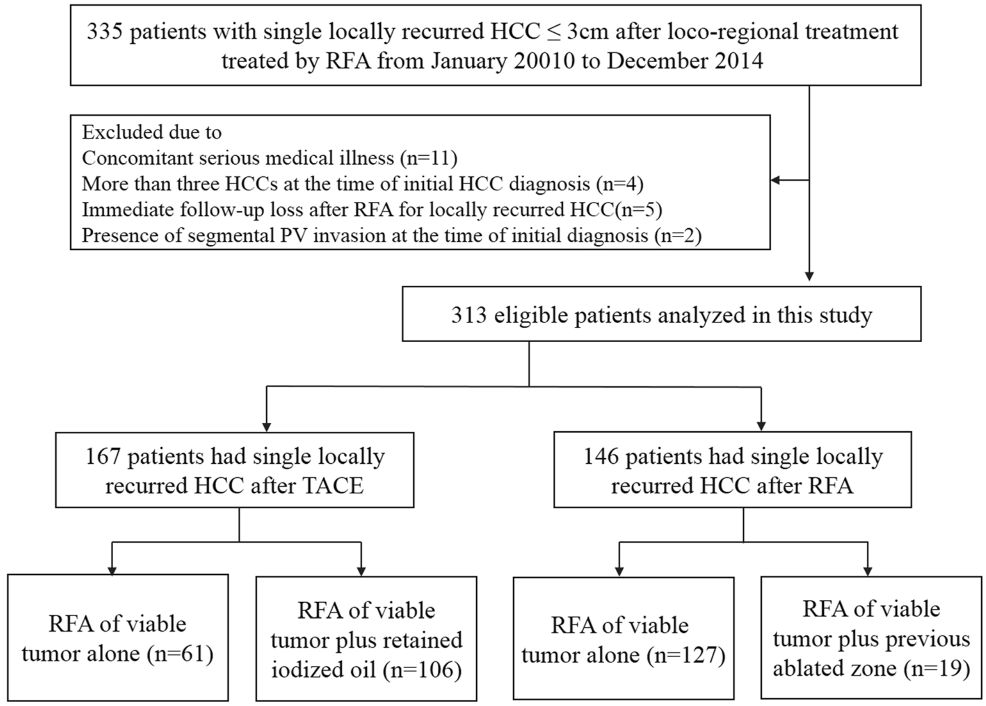


Fig. 2 Flow diagram summarizing the patient enrollment process of this study

Overall survival was defined as the interval between the date of RFA for locally recurred HCC and death or the date of the last follow-up visit prior to September 30, 2017. Progression-free survival (PFS) was defined as the interval between the date of RFA for LrHCC and the first date of any type of HCC progression including LTP, IDR, or EM or the last follow-up date in cases of no progression. Survival curves were estimated using the Kaplan-Meier method. Patients who underwent liver transplantation during the follow-up period after RFA for LrHCC were censored from our study at the date of their transplantation. The cumulative incidence of each type of recurrence, i.e., LTP, IDR, and EM, was also estimated using the Kaplan-Meier method.

To determine significant clinical and biological parameters able to predict overall patient survival, PFS, and cumulative incidence of recurrence, we used univariate and multivariate Cox proportional hazards regression models. First, a univariate Cox proportional hazards model was fitted to each variable. After that, all variables with a p value < 0.05 were included for the multivariate Cox proportional hazards regression model in order to evaluate their value as independent predictors. All statistical analyses were performed using SPSS (version 22).

After the initial analysis, we used propensity score analysis to adjust potential biases caused by the differences in baseline characteristics between the two ablation methods using a multivariate logistic regression model using the following baseline characteristics: age, gender, etiology of liver disease, initial tumor size, viable tumor size, serum alpha-fetoprotein (AFP) level, serum albumin and total bilirubin levels, prothrombin activity, tumor location, and diagnosis method for LrHCC. After that, one-to-one match using the nearest-neighbor matching method with the caliper width set at 0.10 was obtained. The PFS as well as cumulative incidence of recurrence were compared between the two ablation methods after propensity score matching.

Results

Patient characteristics according to the two ablation methods

Baseline characteristics of the two patient groups using the two different ablation methods are summarized in Table 1. In the "LrHCCs after TACE" group which included 167 patients, there were no significant differences in baseline characteristics between the two ablation methods. Similarly, in the baseline characteristics of the "LrHCCs after RFA" group which included 146 patients, there were no significant differences between the two ablation methods.

Progression outcome in patients with locally recurred HCCs after TACE

There was no significant difference in treatment success as well as overall survival between the two ablation methods, and detailed information was given in the supplementary data. LTP developed in 40 patients after a mean and median follow-up period of 41.7 ± 21.5 months and 40.0 months,

Table 1 Baseline patient characteristics between the two ablation methods

Parameters	RFA for locally recurred HCC after TACE ($n = 167$)			RFA for locally recurred HCC after RFA ($n = 146$)		
	Viable tumor alone ($n = 61$)	Whole tumor ablation ($n = 106$)	p value*	Viable tumor alone ($n = 127$)	Whole tumor ablation ($n = 19$)	p value*
Age (years, mean ± SD)	61.6 ± 9.71	61.4 ± 10.3	0.871	62.8 ± 9.13	67.0 ± 12.8	0.184
Gender (n, M:F)	46:15	78:28	0.856	107:20	16:3	1.000
Etiology, n (%)						
HBV	54 (88.5)	88 (83.0)	0.682	95 (74.8)	12 (63.1)	0.501
HCV	6 (9.9)	13 (12.3)		17 (13.4)	5 (26.3)	
Alcoholic	1 (1.6)	4 (3.8)		10 (7.9)	1 (5.3)	
Others	0 (0.0)	1 (0.9)		5 (3.9)	1 (5.3)	
Child-Pugh class (A:B)	58:3	103:3	0.670	114:13	18:1	0.695
Initial tumor size	2.22 ± 0.59	2.14 ± 0.74	0.792	1.85 ± 0.94	1.97 ± 0.84	0.455
Viable tumor size	1.49 ± 0.66	1.45 ± 0.55	0.807	1.42 ± 0.49	1.31 ± 0.38	0.474
Albumin (mg/dL)	3.76 ± 0.40	3.78 ± 0.51	0.584	3.79 ± 0.55	3.77 ± 0.52	0.867
Total bilirubin (mg/dL)	0.80 ± 0.40	0.91 ± 0.47	0.150	0.97 ± 0.75	0.89 ± 0.39	0.731
Prothrombin activity (INR)	1.10 ± 0.11	1.14 ± 0.14	0.139	1.15 ± 0.21	1.11 ± 0.11	0.744
AFP (ng/mL)	167.7 ± 214.3	50.5 ± 149.1	0.429	170.5 ± 988.3	53.2 ± 76.4	0.110
Tumor location, n (%)						
Perivascular	17 (27.9)	23 (21.7)	0.278	20 (15.8)	4 (21.1)	0.858
Subcapsular	18 (29.5)	33 (31.1)		50 (39.4)	7 (36.8)	
Non-perivascular and non-subcapsular	23 (37.7)	49 (46.3)		44 (34.6)	7 (36.8)	
Perivascular and subcapsular	3 (4.9)	1 (0.9)		13 (10.2)	1 (5.3)	
Diagnostic method, n (%)						
CT	32 (52.5)	50 (47.2)	0.525	51 (40.2)	9 (47.4)	0.621
MR	29 (47.5)	56 (52.8)		76 (59.8)	10 (52.6)	

TACE transarterial chemoembolization, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *INR* international normalized ratio, *AFP* alpha-fetoprotein, *RFA* radiofrequency ablation, *CT* computed tomography, *MR* magnetic resonance imaging

*p values were determined with the Mann-Whitney U test for continuous values and Fisher's exact test for categorical values

respectively, and was treated by the following: repeated RFA ($n = 6$), TACE ($n = 31$), liver transplantation ($n = 1$), surgical resection ($n = 1$), and best supportive care (BSC) ($n = 1$). The estimated LTP-free survival rates after RFA for LrHCC after TACE was 84.4%, 76.1%, and 67.5% at 1 year, 3 years, and 5 years, respectively. Predictive factors for the development of LTP after RFA for LrHCC after TACE are summarized in Table 2. Viable tumor size ($p = 0.029$, hazard ratio (HR) = 1.96, 95% confidence interval (CI) = 1.26–3.04) and ablation method ($p < 0.001$, HR = 8.53, 95% CI = 4.16–17.5) were significant affecting factors for the development of LTP after RFA for LrHCC after TACE. The 1-year, 3-year, and 5-year LTP-free survival rates were 67.2%, 49.9%, and 26.9%, respectively, in the 57 patients treated by the VTA method. However, the 1-year, 3-year, and 5-year LTP-free survival rates were 94.0%, 90.6%, and 87.8%, respectively, in the 105 patients treated by the WTA method (Figs. 3a and 4). The cumulative incidences of IDR, as well as EM, were not significantly different between the two ablation methods ($p = 0.917$ for IDR and $p = 0.104$ for EM).

The estimated 1-year, 3-year, and 5-year PFS rates after RFA in the 167 patients who had LrHCC after TACE were 58.2%, 23.8%, and 19.0%, respectively. Predictive factors for PFS are summarized in Table 3. Ablation method ($p = 0.014$, HR = 1.62, 95% CI = 1.10–2.38) and serum AFP level ($p = 0.015$, HR = 1.01 per 100 units, HR = 1.01–1.01) were shown to be significant predictive factors for PFS. The estimated 1-year, 3-year, and 5-year PFS rates were 48.5%, 11.5%, and 5.7%, respectively, in the 61 patients treated with the VTA method, whereas the rates were 63.9%, 31.4%, and 26.4%, respectively, in the 106 patients treated using the WTA method (Fig. 5a).

Progression outcome in patients with locally recurred HCC after RFA

There was no significant difference in treatment success as well as overall survival between the two ablation methods, and detailed information was given in the supplementary data. LTP developed in 37 patients after a mean and median follow-up period of 43.2 ± 20.3 months and 42.0 months, respectively,

Table 2 Cox analysis of predictors for the development of local tumor progression after RFA for locally recurred HCC after locoregional treatment in which treatment success was achieved

Characteristic	RFA for locally recurred HCC after TACE ($n = 162$)						RFA for locally recurred HCC after RFA ($n = 141$)					
	Univariate			Multivariate			Univariate			Multivariate		
	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value
Gender (male)	0.92	0.45–1.86	0.805				1.17	0.49–2.79	0.731			
Age (per 1 year)	1.00	0.97–1.03	1.00				1.02	0.99–1.05	0.327			
Viable tumor size (cm)	1.75	1.10–2.78	0.018	1.96	1.26–3.04	*0.029*	2.78	1.45–5.31	0.002	2.78	1.45–5.31	*0.002*
Ablation method	7.91	3.87–16.1	< 0.001	8.53	4.16–17.5	*< 0.001*	1.41	0.50–3.98	0.514			
Serum albumin (mg/gL)	0.47	0.25–0.90	0.022	0.78	0.35–1.74	0.549	0.85	0.47–1.56	0.603			
Total bilirubin (mg/dL)	1.69	0.85–3.37	0.138				0.67	0.34–1.33	0.257			
Prothrombin activity (INR)	1.33	0.12–15.1	0.816				2.50	0.61–10.2	0.201			
Serum AFP (ng/mL)	1.01	1.01–1.01	< 0.001	1.00	0.99–1.01	0.558	1.01	1.01–1.01	0.001	1.01	1.01–1.01	*0.003*
Tumor location	0.77	0.53–1.11	0.160				0.93	0.64–1.35	0.694			
Diagnostic method	0.63	0.34–1.15	0.132				0.85	0.45–1.62	0.623			

p values less than 0.05 are in italics

RFA radiofrequency ablation, *TACE* transarterial chemoembolization, *HR* hazard ratio, *CI* confidence interval, *INR* international normalized ratio, *AFP* alpha-fetoprotein (per 100 units)

and was treated by the following: repeated RFA ($n = 10$), TACE ($n = 21$), surgical resection ($n = 4$), radiation therapy ($n = 1$), and BSC ($n = 1$). The estimated LTP-free survival rates after RFA for LrHCC after initial RFA were 87.5%, 74.3%, and 68.4% at 1 year, 3 years, and 5 years, respectively. Predictive factors for the development of LTP after RFA for LrHCCs after initial RFA are summarized in Table 2. Viable tumor size ($p = 0.002$, HR = 2.78, 95% CI = 1.45–5.31) and serum AFP level ($p = 0.003$, HR = 1.01 per 100 units, 95% CI = 1.01–1.01) were demonstrated to be significant affecting factors for the development of LTP after RFA for LrHCC after initial RFA. The 1-year, 3-year, and 5-year LTP-free survival rates were 85.5%, 74.4%, and 67.0%, respectively, in the 122 patients treated with the VTA method, while the 1-year, 3-year, and 5-year LTP-free survival rates were 100.0%, 72.7%, and 72.7%, respectively, in the 19 patients treated with the WTA method: this difference was not statistically significant ($p = 0.514$) (Fig. 3b). The cumulative incidence of IDR, as well as EM, was also not significantly different between the two ablation methods ($p = 0.615$ for IDR and $p = 0.935$ for EM).

The estimated 1-year, 3-year, and 5-year PFS rates after RFA in the 146 patients who had LrHCC after RFA were 57.5%, 31.3%, and 25.5%, respectively. Predictive factors for PFS are summarized in Table 3. Serum AFP level ($p = 0.015$, HR = 1.01 per 100 units, HR = 1.01–1.01) was shown to be the only significant predictive factor for PFS. The estimated 1-year, 3-year, and 5-year PFS rates were 55.9%, 31.8%, and 28.7%, respectively, in the 127 patients treated with the VTA method and 67.7%, 28.2%, and 15.0%, respectively, in the 19 patients treated using the WTA method: this difference was not significant ($p = 0.905$) (Fig. 5b).

Result after propensity score matching

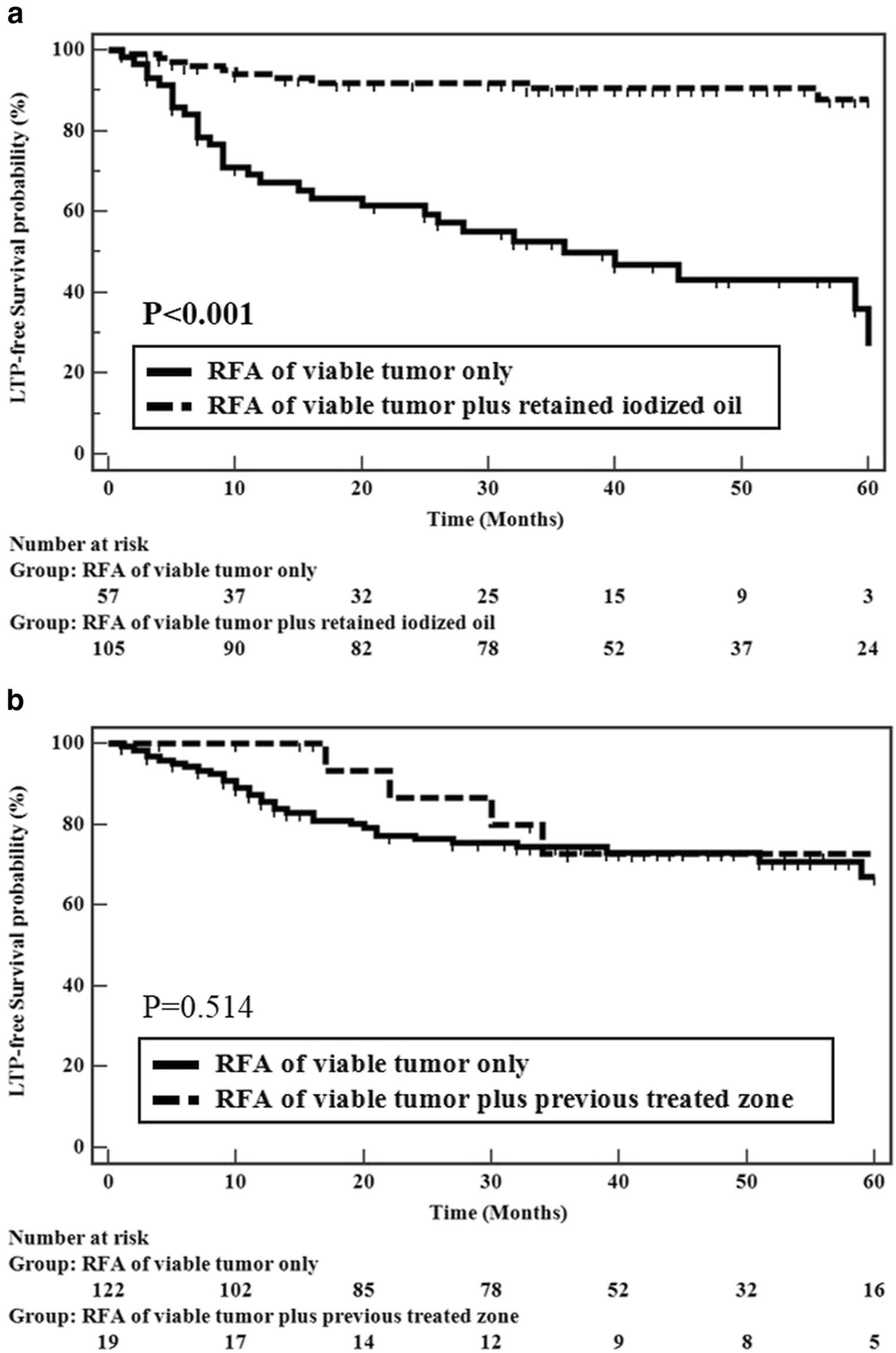
Patients with locally recurred HCC after TACE

After propensity score matching, 45 patients were selected in each ablation method. There was no significant difference in baseline characteristics after propensity score matching (Table E1). The estimated 1-year, 3-year, and 5-year progression-free survival rates in the 45 patients treated by the WTA method were 53.7%, 31.7%, and 22.2%, respectively, and were significantly higher than those of 43.4%, 11.0%, and 5.5%, respectively, in the 45 patients treated by the VTA method ($p = 0.041$). The 1-year, 3-year, and 5-year LTP-free survival rates were 65.5%, 49.1%, and 30.9%, respectively, in the 45 patients treated by the VTA method. However, the 1-year, 3-year, and 5-year LTP-free survival rates were 92.8%, 90.2%, and 90.2%, respectively, in the 45 patients treated by the WTA method: this difference was statistically significant ($p < 0.001$). The cumulative incidences of IDR, as well as EM, were not significantly different between the two ablation methods ($p = 0.864$ for IDR and $p = 0.242$ for EM).

Patients with locally recurred HCC after RFA

After propensity score matching, 17 patients were selected in each ablation method. There was no significant difference in baseline characteristics after propensity score matching (Table E1). The estimated 1-year, 3-year, and 5-year progression-free survival rates in 17 patients treated by the WTA method were 64.7%, 29.4%, and 15.7%, respectively, and were not significantly different

Fig. 3 Local tumor progression (LTP)-free survival. **a** LTP-free survival after RFA for locally recurred HCC after (**a**) TACE and (**b**) RFA was compared between the two ablation methods



from those of 50.7%, 38.0%, and 22.8%, respectively, in the 17 patients treated by the VTA method ($p = 0.664$). The 1-year, 3-year, and 5-year LTP-free survival rates were 81.9%, 68.3%, and 68.3%, respectively, in the 17 patients treated with the VTA method, while the 1-year, 3-year, and 5-year LTP-free survival rates were 100.0%, 78.6%, and 70.7%, respectively, in the 17 patients treated with the WTA method: this difference was not statistically significant ($p = 0.626$). The cumulative incidence of IDR, as well as EM, was also not significantly different between the two ablation methods ($p = 0.982$ for IDR and $p = 0.328$ for EM).

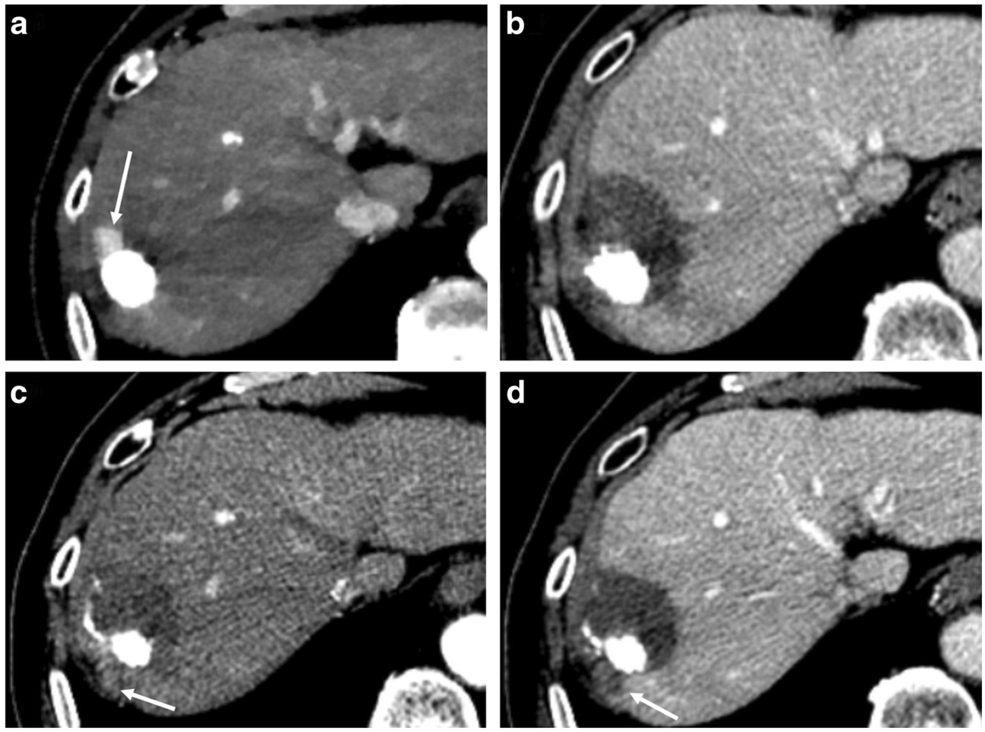


Fig. 4 Development of local tumor progression of RFA for locally recurred HCC after TACE. **a** Contrast-enhanced arterial phase axial CT image shows a 1.5-cm enhancing nodular lesion anterior to the retained iodized oil (arrow), suggesting locally recurred HCC. **b** RFA was done for this locally recurred HCC using the viable tumor alone ablation method; thus, the posterior part of the retained iodized oil was not covered by the ablation zone. **c** Contrast-enhanced arterial phase axial CT image obtained 9 months after RFA shows a 1.2-cm faint enhancing nodular lesion posterior to the retained iodized oil (arrow). **d** Washout is noted on the portal venous phase image (arrow), suggesting the development of local tumor progression

Discussion

In our study, the LTP-free survival rates after using the WTA method for LrHCC after TACE was significantly lower than that using the VTA method ($p < 0.001$, HR = 8.53, 95% CI = 4.16–17.5). In addition, the WTA method also provided significantly better PFS after RFA for LrHCCs after TACE compared to the VTA method ($p = 0.014$, HR = 1.62, 95% CI = 1.10–2.38) due to the significantly lower rate of LTP. Our study results are well correlated with the results of a previous study done by Kim et al [11] in which the WTA method including both the viable tumor and iodized oil-laden portion demonstrated better local tumor control compared with the VTA method in patients with LrHCC after TACE. Our study results could be explainable by the results of previous studies showing that complete tumor necrosis could be obtained in only about half of HCCs treated with TACE on histopathologic examination [17, 18]. In addition, another previous

Table 3 Cox analysis of predictors for progression-free survival after RFA for locally recurred HCC after locoregional treatment

Characteristic	RFA for locally recurred HCC after TACE (*n* = 167)						RFA for locally recurred HCC after RFA (*n* = 146)					
	Univariate			Multivariate			Univariate			Multivariate		
	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value
Gender (male)	0.88	0.59–1.31	0.523				0.79	0.44–1.42	0.429			
Age (per 1 year)	1.02	1.01–1.04	0.035	1.02	0.99–1.04	0.052	1.00	0.98–1.02	0.826			
Viable tumor size (cm)	1.29	0.96–1.72	0.087				1.36	0.92–2.02	0.122			
Ablation method	1.72	1.20–2.46	0.003	1.55	1.05–2.29	*0.026*	0.97	0.56–1.67	0.905			
Serum albumin (mg/gL)	0.66	0.45–0.97	0.032	0.81	0.52–1.27	0.363	0.72	0.49–1.07	0.104			
Total bilirubin (mg/dL)	1.32	0.87–2.03	0.197				1.24	0.93–1.65	0.150			
Prothrombin activity (INR)	1.47	0.35–6.19	0.596				1.72	0.70–4.23	0.235			
Serum AFP (ng/mL)	1.01	1.01–1.01	0.010	1.01	1.01–1.01	*0.008*	1.01	1.01–1.01	0.008	1.01	1.01–1.01	*0.008*
Tumor location	0.86	0.69–1.07	0.166				0.86	0.68–1.08	0.190			
Diagnostic method	0.63	0.44–0.90	0.011	0.69	0.47–1.01	0.056	1.05	0.70–1.56	0.818			

p values less than 0.05 are in italics

RFA radiofrequency ablation, *TACE* transarterial chemoembolization, *HR* hazard ratio, *CI* confidence interval, *INR* international normalized ratio, *AFP* alpha-fetoprotein (per 100 units)

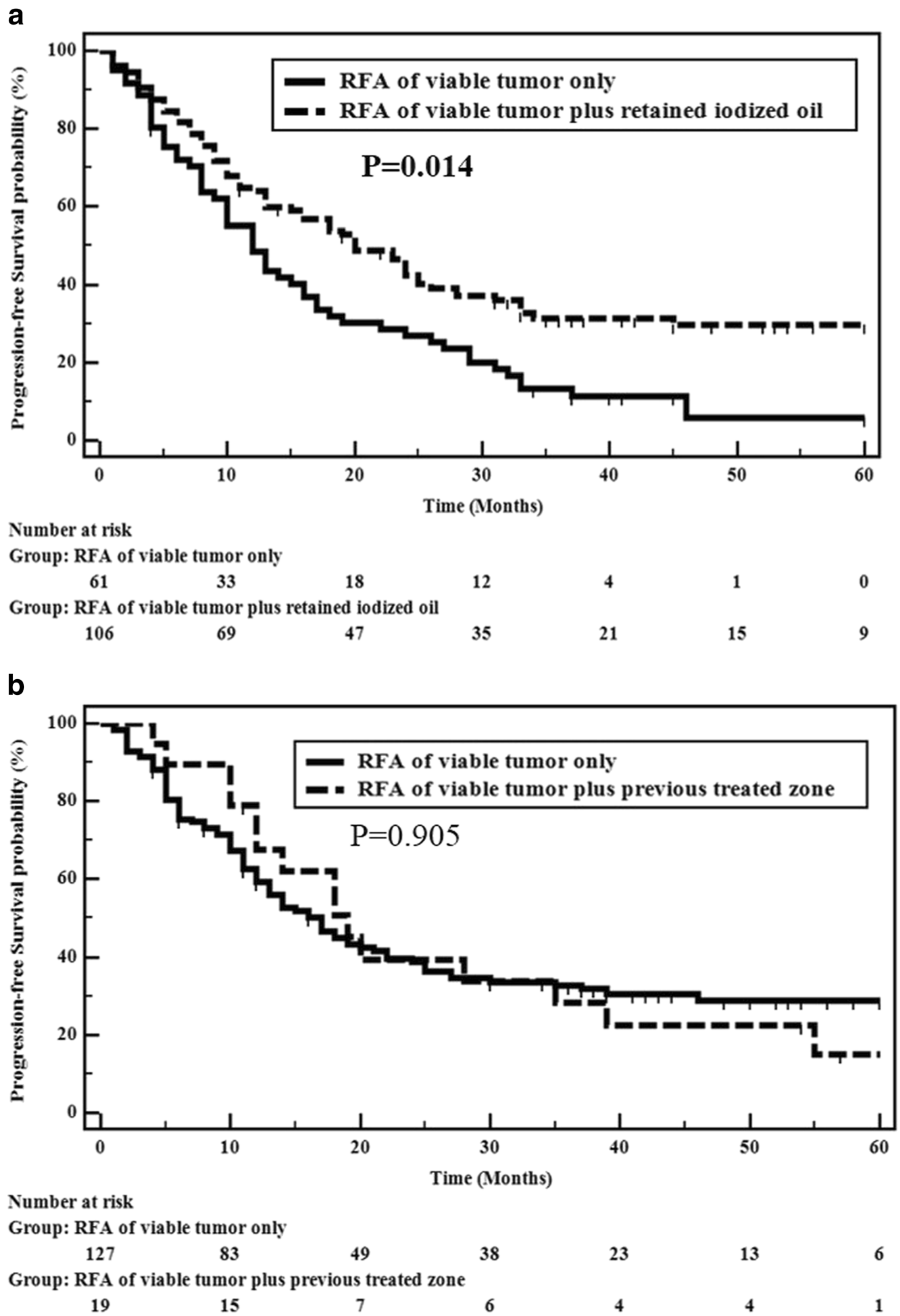


Fig. 5 Progression-free survival after RFA for locally recurred HCC. Kaplan-Meier estimation of the progression-free survival of RFA for locally recurred HCC after (**a**) TACE and (**b**) RFA was compared between the two ablation methods

study by Kim et al [19] reported that 12.8% of HCCs treated by TACE showing compact iodized oil uptake without evidence of contrast enhancement on follow-up imaging study had a viable HCC portion within the tumor on histopathologic examination of the specimen obtained after liver transplantation. Indeed, assessment of the therapeutic efficacy of TACE for HCC using contrast-enhanced CT or detection of small HCC foci around the compact iodized oil uptake may be limited due to the high density of iodized oil uptake within the tumor [20, 21]. The use of the WTA method including the viable tumor portion as well as retained iodized oil may eradicate these potential small foci of HCC and would provide significantly better local tumor control in RFA for LrHCC after TACE, as shown in our study results.

Of interesting note is that in patients with LrHCC after initial RFA, the WTA method including both the viable tumor portion and previously ablated zone did not provide better local tumor control than the VTA method. These different results in patients with LrHCC after RFA compared with patients with LrHCC after TACE could be attributed to the histopathological findings of the non-enhancing area on CT or MRI after RFA [22–24]: the majority of the non-enhancing area seen on imaging studies after RFA for HCC revealed no evidence of a viable tumor portion on histopathologic examination. Therefore, we may consider the non-enhancing area of the ablated zone after RFA to be completely necrotic, and thus, the possibility of developing LTP from these non-enhancing areas of the ablated zone could be quite low. Considering the results of our study, in regard to RFA treatment for LrHCC after locoregional treatment of either RFA or TACE, we cautiously suggest that the WTA method including both the viable tumor and retained iodized oil should be considered for the RFA treatment of LrHCC after TACE, if feasible, as this ablation method can provide a significantly better clinical outcome regarding local tumor control and PFS after RFA. However, in patients with LrHCC after initial RFA, the VTA method would be sufficient as both ablation methods may provide a comparable clinical outcome. We believe that the WTA method for LrHCC after TACE should be preferred in patients with well-conserved liver function as it would provide significantly better local tumor control than the VTA method, as shown in our study results.

Several limitations of our study need to be mentioned. The main limitation of this study is its retrospective non-randomized design, which may involve unavoidable selection bias. In particular, the choice of the ablation method for the RFA treatment of LrHCC was made according to the operator's preference. However, during our study period, there was no consensus guideline and/or recommendations for RFA treatment of LrHCC after locoregional treatment including RFA and TACE. In addition, there were no significant differences in patient characteristics between the two ablation methods in our study. Even though a double-blinded, randomized controlled trial may be the best way to compare the two treatment strategies, implementation of a double-blinded, randomized controlled trial for interventional procedures such as RFA is often difficult owing to concerns of the multiplicity and heterogeneity of technologies [25].

Nevertheless, to validate our study results and to more confirmatively establish the guidelines regarding the RFA treatment method for LrHCC, further studies with a prospective design and a large number of patients are warranted. Furthermore, as we enrolled patients from five different tertiary referral hospitals, there was heterogeneity in the RFA technique and equipment used as well as in the follow-up period even though the operators in this study held a regular joint meeting to share their RFA experience over the duration of the study, and this would be another limitation. In addition, we only included patients with LrHCCs treated by RFA, and although RFA is the most widely used thermal ablation modality, this may be another limitation of our study. Indeed, more recently, microwave ablation (MWA) has emerged as a newly introduced thermal ablation technique which may have theoretical merits over RFA including better heat conduction and faster ablation times with a larger ablation volume [26].

In conclusion, for the RFA treatment of LrHCC after TACE, ablation of both the viable tumor and retained iodized oil may provide a significantly lower LTP rate as well as better PFS than ablation of the viable tumor alone.

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Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Jeong Min Lee.

Conflict of interest The authors declare that they have no competing interests.

Statistics and biometry No complex statistical methods were necessary for this paper.

Informed consent Written informed consent was waived by the Institutional review board.

Ethical approval Institutional review board approval was obtained.

Methodology
• Retrospective
• Observational
• Performed at five institutes

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