Computed tomography-guided radiofrequency ablation of the retained iodized oil after simultaneous combination with transarterial embolization in small recurrent or residual hepatocellular carcinoma

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A R T I C L E I N F O

A B S T R A C T

Objective: To assess the clinical efficacy and safety of transarterial embolization (TAE) in simultaneous combination with computed tomography (CT)-guided radiofrequency ablation (RFA) for recurrent or residual hepatocellular carcinoma (HCC), and to determine the risk factors influencing local tumor progression following this procedure.

Methods: One hundred eighteen patients with recurrent or residual HCC (tumor size, 10–30 mm) underwent RFA. During the 19-month follow-up, 59 patients received RFA only (RFA group), and the remaining 59 received RFA immediately after TAE (TAE + RFA group). All patients were followed up to observe the short-term therapeutic effects and complications. The cumulative local tumor progression rates in both groups were calculated using unpaired Student's t tests and the Kaplan-Meier method.

Results: The rate of major complications was 5.08% in the TAE + RFA group and 3.39% in the RFA group. The overall response rate was 96.61% in the TAE + RFA group and 79.66% in the RFA group ($P = 0.008$). The disease control rate was significantly higher in the TAE + RFA group than in the RFA group (94.92% vs. 79.66%, $P = 0.024$). The median time to local tumor progression was 4.8 months in the RFA group and 9.6 months in the TAE + RFA group. The cumulative local tumor progression rate at 1 year was 10.60% in the RFA group and 23.60% in the TAE + RFA group ($P = 0.016$).

Conclusion: TAE in simultaneous combination with CT-guided RFA was effective and safe against recurrent or residual HCC. Local tumor progression can be minimized by the complete ablation of targeted iodized oil deposits after simultaneous TAE.

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common malignant tumor and the third leading cause of cancer deaths worldwide.[1] Even when compared to surgical resection, radiofrequency ablation (RFA) is widely accepted as an effective treatment for patients with early stage HCC.[1] Therefore, RFA is generally considered a first-line treatment for small recurrent or residual HCC. Computed tomography (CT) is one of the most common guidance methods for RFA of HCC. In particular, the residual or recurrent marginal tumors after transarterial chemoembolization (TACE) or transarterial embolization (TAE) in patients with HCC are occasionally difficult to differentiate on ultrasound images from areas using iodized oil retention.[2] Moreover, recurrent or residual HCC typically shows multiple small-sized lesions. Generally, non-contrast images are used for CT guidance, and these cannot precisely identify the tumor focus. Even when using contrast-enhanced CT images, the

contrast agent is not retained throughout the RFA procedure. Therefore, when RFA is performed under CT guidance, the iodized oil retained from a prior TACE or TAE is commonly used as a targeting marker.[3] After TACE, the main artery supplying the tumor may be occluded. The subsequent RFA is thus more effective and reflects minimized heat loss by convection.[4] Moreover, TACE combined with RFA has demonstrated synergistic cytotoxic effects in HCC,[5] and studies have shown that this combination provides better efficacy than does RFA alone.[6]

Furthermore, the effectiveness of a combination therapy comprising various treatment options, including TACE, RFA, microwave ablation, percutaneous ethanol injection, and radiation therapy,[7,8] has recently been reported. The combined use of TACE or TAE with RFA is applicable for recurrent or residual HCC.[6] However, compared to TAE, TACE increases the risk of liver damage or liver failure, especially in patients with cirrhosis. To our knowledge, studies on RFA performed in the area around the retained iodized oil immediately after TAE for recurrent or residual HCC have rarely been reported. Therefore, in the present retrospective study, we examined whether the iodized oil retained from a previous TAE (performed 1–2 days before) is useful as a targeting marker to minimize the recurrence rate and prolong progression-free survival in patients with small recurrent or residual HCC lesions (size range, 1–3 cm).

Materials and methods

Patient selection

We reviewed the medical records of patients with recurrent or residual HCC from the database at Sun Yat-sen University Cancer Center (Guangzhou, China) from January 1, 2015 to July 31, 2016. The following eligibility criteria were used to select the patients: 1) diagnosis of HCC based on the American Association for the Study of Liver Diseases guidelines[9,10]; 2) recurrent or residual HCC after surgery or ablation; and 3) tumor nodules (≤10) between 1 and 3 cm in size. All patients with general contraindications for RFA or other procedures (Child-Pugh classification grade C, prothrombin activity < 40%, uncontrolled ascites, extrahepatic metastasis, vascular invasion, and previous or simultaneous malignancies) were excluded from the present study.

TAE and RFA procedures

In the TAE + RFA group, TAE was performed by injecting iodized oil (Lipiodol; Guerbet, France) into the hepatic artery. Therefore, residual or recurrent enhancing targeted tumors were indicated by the iodized oil. CT-guided RFA was performed using a 64 multidetector-row CT scanner (Brilliance CT Big Bore; Philips Medical Systems, the Netherlands). Analgesia was achieved via the intravenous administration of remifentanil (2–3 ng/mL target concentration infusion) and local injection of 5–15 mL of 1% lidocaine. Subsequently, the electrode was inserted towards the area of iodized oil retention. We used internally cooled, 17-gauge, 15-cm-long, single RF electrodes with a 2- or 3-cm-long exposed metallic tip (Cool-tip; Covidien, Boulder, CO). The RF energy was delivered in the impedance control mode for 12–16 min,[11] depending on the size of the index tumors. During RFA, the goal was to achieve complete ablation of the iodized oil-marked tumor and create an ablative margin of at least 0.5 cm of normal liver parenchyma. When necessary, multiple overlapping applications were performed.

Follow-up

Laboratory tests, including α-fetoprotein (AFP), albumin, bilirubin, aspartate aminotransferase, and alanine aminotransferase level measurements; prothrombin time test; and liver dynamic CT or magnetic resonance imaging (MRI), were performed every 3–4 weeks to evaluate treatment response and conserved liver function. A second RFA session was performed only when the tumor was found to be residual according

to the analysis of contrast-enhanced MR or CT images. Contrast-enhanced MRI or CT was performed monthly and repeated three times after treatment; scans were subsequently performed every 3 months after the last examination. Follow-up began at the time of diagnosis of small recurrent or residual HCC and ended at the time of death or the last follow-up ending on January 31, 2017.

Evaluation of clinical efficacy

Technical success was assessed on the basis of the analysis of immediate post-RFA CT images. Primary technique effectiveness was evaluated using dynamic MRI or CT performed 1 month after RFA or the combination of TAE and RFA. The primary study endpoint was local tumor progression. At the time of dynamic liver MRI or CT, local tumor progression was defined as the observation of a new enhancing lesion within or adjacent to the ablation site.[11] A distant metastasis was defined as the observation of a new HCC in the liver distant from the treated nodule or in extrahepatic regions.

Treatment response was evaluated using contrast-enhanced CT or MRI based on the modified Response Evaluation Criteria in Solid Tumors.[12] A complete response (CR) was defined as the disappearance of any intratumor arterial enhancement in all lesions. A partial response (PR) was defined as a ≥30% decrease in the sum of the diameters of viable (contrast enhancement in the arterial phase or portal venous phase) lesions. Progressive disease (PD) was defined as an increase of ≥20% in the sum of the diameters of viable lesions. Stable disease (SD) included cases that did not qualify as either PR or PD. The overall response rate (ORR) was defined as CR plus PR, and the disease control rate (DCR) was defined as CR plus PR and SD. If patients remained progression free at their last follow-up visit, then the data on the duration of local tumor progression time were censored at the time of the last radiographic assessment. Complications were classified as major or minor, according to the definitions of the Society of Interventional Radiology.[11,13]

Statistical analysis

Statistical analyses were performed using Pearson's X^2 test, Fisher's exact test, the Mann-Whitney U test, or the Kruskal-Wallis test, as appropriate. The cumulative rate of local tumor progression was estimated using the Kaplan-Meier method. All statistical tests were two-sided, and $P<0.05$ was considered significant. The analyses were performed using SPSS for Windows, Version 16.0 (SPSS Inc., Chicago, IL) by applying the Common Terminology Criteria for Adverse Events v3.0.[14]

Results

Patient and tumor characteristics

Baseline patient and tumor characteristics are summarized in Table 1. No significant intergroup differences were observed in age, sex, etiology, serum AFP level, Child-Pugh score, size of viable tumor, and tumor number. The technical success rate was 100.0% (270/270 targeted tumors). The median time interval between TAE and CT-guided RFA was 0.8 days (range, 0–2 days). The follow-up periods ranged from 3.0 to 36.5 months after RFA (median = 13.3 ± 7.3 months). During the follow-up period, 62 patients received RFA only (RFA group), while 63 received RFA immediately after TAE (TAE + RFA group). In the RFA group, 134 sessions of RFA were performed. However, 8 sessions were excluded because they involved metastatic tumors other than HCC. The remaining 126 CT-guided RFA sessions were performed in 59 patients. In the TAE + RFA group, 160 sessions of CT-guided RFA were performed. However, 11 sessions were excluded because of a lack of iodized targeted tumors, and another 5 sessions were excluded because the targeted tumors did not show typical arterial enhancement and were followed by delayed washout on dynamic contrast-enhanced CT or MRI performed for the

diagnosis of residual or recurrent HCC.[9] The retained iodized oil was used as an anatomic landmark to place the electrode in the remaining 144 RFA sessions included in the present study. These 144 CT-guided RFA sessions were performed in 59 patients. Demographic findings of the patients are summarized in Table 2.

Complications

Major complications were defined as events leading to substantial morbidity and disability, increasing the level of care, resulting in a substantially lengthened hospital stay, or requiring a blood transfusion or an interventional drainage procedure. All other complications were considered minor. The major and minor complications are summarized in Table 2. Minor complications such as fever, pain, and pleura-related complications, including pneumothorax, pleural effusion, hydro-pneumothorax, and a diaphragm defect, occurred in 45 patients (38.14%). Major complications were observed in five patients (4.24%), and no complication led to mortality. In three patients with major complications, intra-ablation massive liver hemorrhages occurred, while the other two patients showed intercostal artery bleeding. Emergency surgery was required in all five patients.

Local tumor progression rate

The mean follow-up periods of the RFA and TAE + RFA groups were 13.2 months (range, 3.4–36.5 months) and 13.4 months (range, 3.0–30.0 months), respectively ($P = 0.910$). During follow-up, tumor relapse was observed in 63 of the 118 patients with HCC (53.3%), with 39 patients (66.1%) in the RFA group and 24 patients (40.7%) in the TAE + RFA group. The ORR was 96.61% in the TAE + RFA group and 79.66% in the RFA group ($P = 0.008$), as shown in Table 3. The DCR was significantly higher in the TAE + RFA group than in the RFA group (94.92% vs. 79.66%, $P = 0.024$). The median time until local tumor progression was 4.8 and 9.6 months, respectively, in the RFA and TAE + RFA groups. The cumulative local tumor progression rate at 1 year was 10.6% in the RFA group and 23.6% in the TAE + RFA group. Local tumor progression rates were significantly lower in the TAE + RFA group ($P = 0.016$) (Fig. 1). During follow-up, 45 of the 118 patients showed new lesions at another liver site after RFA. Among these 45 patients, 25 received repeat RFA, 20 received TACE, and 2 underwent surgical resection of the new lesions.

The images acquired in a 52-year-old man (RFA group) with HCC and a recurrent lesion adjacent to the inferior vena cava are shown in Fig. 2. The patient was diagnosed with recurrent HCC on the basis of contrast-enhanced MRI and a high level of serum AFP (51.61 ng/mL; normal value, 25.0 ng/mL). The MR images showed a liver lesion (arrow in A) with a maximal diameter reaching 10 mm. The contrast-enhanced CT images acquired during RFA showed a low-intensity lesion (arrow in B)

Table 1
Baseline characteristics of patients with small recurrent or residual HCC in the TAE + RFA group and RFA group.

Parameter	Total (n = 118)	TAE + RFA (n = 59)	RFA (n = 59)	P
Median age (range)	58 (36–81)	59 (41–79)	57 (36–81)	/
Sex (male/female)	103/15	52/7	51/8	0.782
Etiology	/	/	/	/
HBV	87	46	41	0.296
Liver cirrhosis	48	28	20	0.134
AFP (>20 ng/mL)	103	50	53	0.407
Child-Pugh class (A/B)	99/19	48/11	51/8	0.452
Tumor size	/	/	/	0.851
≥1 cm, ≤2 cm	71	36	35	/
>2 cm, ≤3 cm	47	23	24	/
Tumor number (single/ multiple)	50/68	36/23	26/33	0.065

HCC, hepatocellular carcinoma; TAE, transarterial embolization; RFA, radio-frequency ablation; HBV, hepatitis B virus; AFP, α-fetoprotein.

Table 2
Complications associated with CT-Guided radiofrequency ablation of small recurrent or residual tumor lesions.

Complication	Total (n = 118)	TAE + RFA (n = 59)	RFA (n = 59)
*Major complication	5	3	2
Pneumothorax	3	2	1
Massive hemorrhage	2	1	1
†Minor complication	45	17	28
Pneumothorax	13	5	8
Minimal intraperitoneal hemorrhage	11	4	7
Pleural effusion	6	2	4
Pain	15	6	9

Note: *Major pneumothorax necessitates the insertion of a chest tube or percutaneous chest drain. †Minor pneumothorax does not require any treatment.
CT, computed tomography; TAE, transarterial embolization; RFA, radio-frequency ablation.

adjacent to the inferior vena cava. When positioning the needle electrode into the liver, the tumor was difficult to identify and distinguish from the inferior vena cava (arrow in C), because the contrast agent was excreted from the liver. During CT-guided RFA, we only located the tumor on the basis of the neighboring anatomic landmarks, and we were unsure whether any tumor tissue was left behind (arrow in D) after RFA. One month later, contrast-enhanced MR images showed a residual lesion adjacent to the last RFA area (arrows in E and F) in this patient.

Fig. 3 shows the contrast-enhanced MR images acquired in a 47-year-old man (TAE + RFA group) diagnosed with recurrent HCC. The MR images showed a liver lesion (arrow in A) with a maximal diameter reaching 10 mm. The plain CT images acquired before TAE showed a low-intensity lesion (arrow in B) adjacent to the heart. One day after TAE, the amount of lipiodol (arrow in C) deposited in the tumor was seen in the images, and the lipiodol in the normal liver could help easily distinguish between the liver and heart on the plain CT images acquired during RFA. CT-guided RFA with an overlapping technique was performed for the residual tumor in the liver (arrow in D). After the combination of TAE and RFA, the liver lesions showed complete necrosis (arrows in E and F) on contrast-enhanced MR images, and the serum AFP levels decreased to normal. No recurrence was observed on the basis of image analysis and serum AFP levels during the 2-year follow-up period.

Discussion

RFA is generally considered a first-line treatment for small HCC and is comparable to hepatic resection in terms of overall survival, as evidenced in numerous studies; however, tumor recurrence due to incomplete ablation is a negative prognostic factor for patient survival.[15,16] Thus, to minimize the recurrence rate and prolong survival, the combined use of TACE with RFA has been applied.[17] After TACE, the main artery supplying the tumor may be occluded. Hence, subsequent RFA is more effective and reflects minimized heat loss by convection.[18] Moreover, TACE combined with RFA has shown synergistic cytotoxic effects in

Table 3
Short-term response of patients with HCC in the TAE + RFA group and RFA group (cases).

	CR	PR	SD	PD	ORR (%)	DCR (%)
TAE + RFA	44	12	1	2	96.61	94.92
RFA	33	14	0	12	79.66	79.66
P	/	/	/	/	0.008	0.024

Short-term response was calculated from the first day of treatment until 3 months after the last treatment.
HCC, hepatocellular carcinoma; TAE, transarterial embolization; RFA, radiofrequency ablation; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; DCR, disease control rate; ORR, overall response rate.
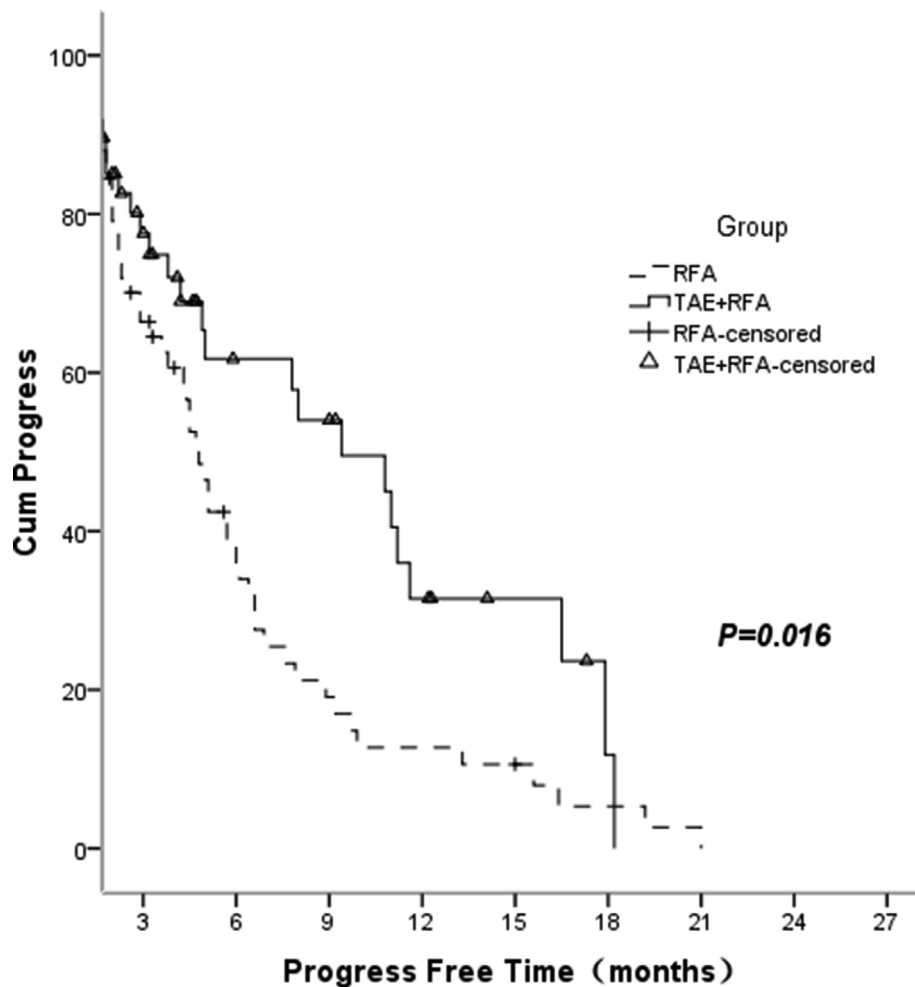
Fig. 1. The cumulative progression-free survival (PFS) in patients with hepatocellular carcinoma (HCC). The graph shows the PFS rates of patients with HCC in the transarterial embolization plus radiofrequency ablation (TAE + RFA) group and the RFA group. Differences between the groups are compared using the Kaplan-Meier method ($P = 0.016$).

HCC,[17,19] and studies have shown that this combination provides better efficacy than does RFA alone.[20,21] Numerous studies have examined the efficacy and safety of TACE combined with RFA in the treatment of HCC and have concluded that, compared to RFA alone, TACE combined with RFA could significantly improve survival rates. Previously published results[22] on CT-guided RFA showed that it was a safe and effective procedure in cases of residual or recurrent HCC around retained iodized oil after TACE. However, a meta-analysis showed that, compared with RFA alone, TACE combined with RFA showed no survival benefit when used for treating patients with small HCC (<3 cm). This result may reflect the fact that RFA is consistently performed 2–4 weeks after TACE, and viable HCC can remain unchanged in size or even grow, indicating that adding TACE to RFA is redundant in producing the assessed outcome.[23,24] Moreover, the drawback of RFA alone is that only those lesions visualized by imaging can be treated, and hence, potential microscopic lesions in the vicinity of the main lesion may be left untreated.

Therefore, in the present study, we retrospectively reviewed whether the combination of RFA and previous TAE (performed 1–2 days before) could minimize the recurrence rate and prolong progression-free survival owing to the retained iodized oil in recurrent or residual small HCC lesions (size range, 1–3 cm). In the present study, we compared the efficacy of the simultaneous combination of TAE with RFA to that of RFA alone for the treatment of small recurrent or residual HCC tumors. During a mean follow-up period of 10.1 months (range, 3.0–36.5 months) after RFA, tumor relapse was observed in 63 (53.3%) patients with HCC. The overall local tumor progression rate in all 118 tumors at 1 year was

18.1% over a median local tumor progression period of 5.7 months.

Joon-Il Choi et al.[22] evaluated the efficacy of CT-guided RFA for recurrent or residual HCC around the retained iodized oil after TACE in 64 patients with 75 viable HCC lesions. In that study, the incidence of local tumor progression was 17.5% and 37.5% at 1 and 2 years, respectively. The higher local tumor progression rate observed in the present study might be attributed to the differences in sample size (n = 118 vs. n = 88) or tumor number (68/118, 57.6% in our study).

We observed significantly higher local tumor progression rates when only RFA was performed for active tumor lesions rather than when TAE combined with RFA was performed for recurrent or residual tumors with retained iodized oil. These findings suggest that examinations based on contrast imaging underestimate the viable tumor component of the treated lesions.[10] Thus, the rate of local HCC progression can be reduced by routinely performing RFA using the retained iodized oil.

TAE and RFA are minimally invasive options that provide an appropriate balance between tumor treatment efficacy and preservation of quality of life.[19,24] Performing TAE prior to RFA also has several advantages. First, iodized oil can be used to demarcate the range of the tumors. Second, as the hepatic artery is the primary source of blood supply to an HCC lesion, the occlusion of hepatic arterial flow using TAE can reduce the cooling effect of the hepatic blood flow on RFA. Therefore, subsequent RFA can induce a larger area of necrosis.[21,22] This finding is important because recurrent tumors commonly occur in the liver remnants near the RFA-ablated region.[3,15] Third, the lipiodol used in TAE can improve the likelihood of detection and control of invisible
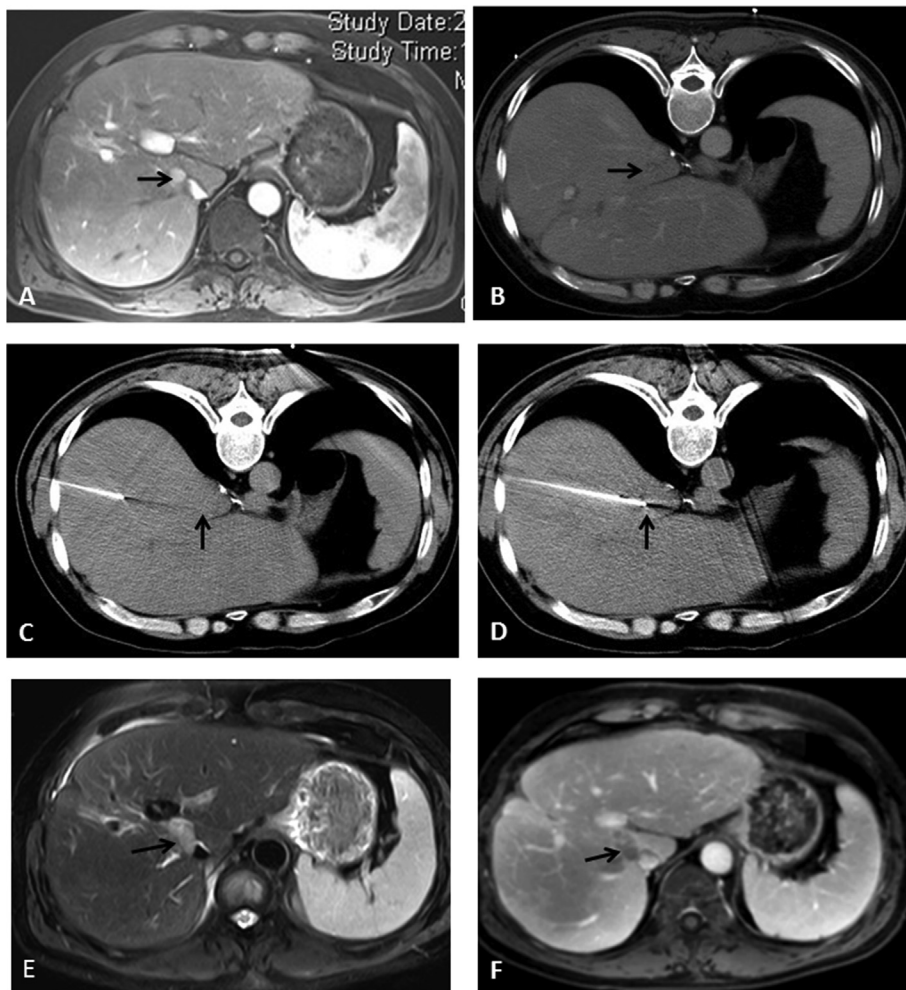
Fig. 2. The images of a 52-year-old man with hepatocellular carcinoma (HCC) and a recurrent lesion adjacent to the inferior vena cava (radiofrequency ablation [RFA] group). A 52-year-old man was diagnosed with recurrent HCC on the basis of contrast-enhanced magnetic resonance imaging (MRI) findings and a high level of serum α-fetoprotein (AFP) (51.61 ng/mL; normal value, 25.0 ng/mL). The MR images show a liver lesion (arrow in A) with a maximal diameter reaching 10 mm. The contrast-enhanced computed tomography (CT) images acquired during RFA show a low-intensity lesion (arrow in B) adjacent to the inferior vena cava. When positioning the needle electrode into the liver, the tumor is difficult to identify and distinguish from the inferior vena cava (arrow in C) because the contrast agent is immediately excreted from the liver. During CT-guided RFA, we can only locate the tumor by using the neighboring anatomic landmarks. Moreover, we are unsure whether any tumor tissue is left behind (arrow in D) after RFA. One month later, contrast-enhanced MR images show a residual lesion adjacent to the last RFA area (arrows in E and F) in this patient.
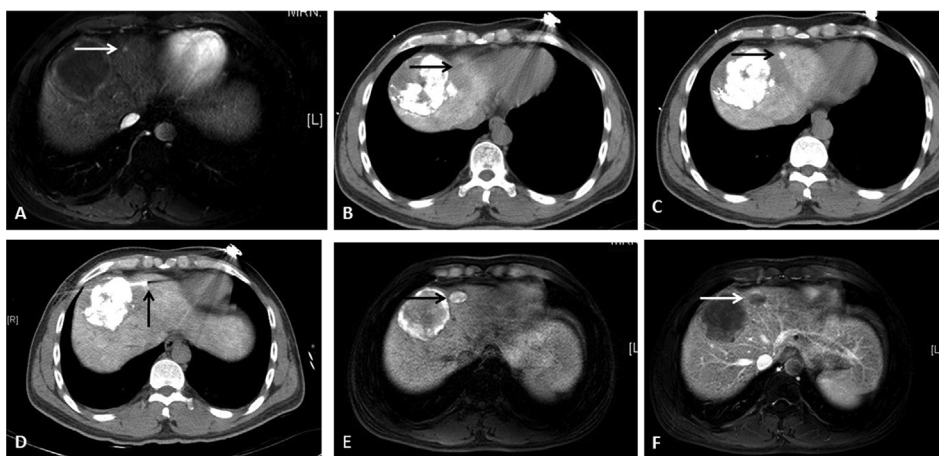
Fig. 3. The images of a 47-year-old man with recurrent small hepatocellular carcinoma (HCC) (transarterial embolization plus radiofrequency ablation [TAE + RFA] group). A 47-year-old man was diagnosed with recurrent HCC on the basis of contrast-enhanced magnetic resonance imaging (MRI) scanning. The MR images show a liver lesion (arrow in A) with a maximal diameter reaching 10 mm. The plain computed tomography (CT) images acquired before TAE show a low-intensity lesion (arrow in B) adjacent to the heart. One day after TAE, the amount of lipiodol (arrow in C) that was deposited in the tumor is seen in the images. Moreover, the lipiodol in the normal liver can help easily distinguish between the liver and heart on the plain CT images acquired during RFA. CT-guided RFA with an overlapping technique is performed on the residual tumor in the liver (arrow in D). After combination therapy using TAE and RFA, the liver lesions show complete necrosis (arrows in E and F) on the contrast-enhanced MR images, and the serum α-fetoprotein (AFP) levels decrease to normal levels. No recurrence occurred on the basis of imaging analyses and serum AFP levels during the 2-year follow-up period.

micrometastases in the liver, even when the lesions are solitary and small. Most importantly, for small HCC lesions adjacent to the heart, large blood vessels, intrahepatic bile duct, gallbladder, diaphragm, or other important tissues, the safety and quality of RFA for liver tumors would be limited. However, our study highlights the advantages of the simultaneous combination of TAE and RFA for small HCC.

The principal limitation of the present study was its retrospective and nonrandomized design. Thus, a prospective and randomized controlled trial is required to draw definitive conclusions regarding the clinical efficacy of TAE and RFA for the elimination of viable tumors. In addition, several patients included in this study did not undergo contrast-enhanced MRI, which may be better than contrast-enhanced CT for detecting tumor recurrence after TAE.[9,25]

In conclusion, in the treatment of viable tumors after TAE in patients with recurrent or residual small HCC, subsequent RFA using the retained iodized oil may reduce the rates of local tumor progression to a greater extent than would RFA of viable tumors alone. The current study suggests that a previous TAE (performed 1–2 days before) combined with RFA using the retained iodized oil can maximize patient benefits when an initial RFA procedure is performed on a viable tumor.

Conflicts of interest/financial disclosures

All authors have declared there are no financial conflicts of interest regarding this work.

References

1. Torre LA, Bray F, Siegel RL, et al. Global cancer statistics. *CA A Cancer J Clin*. 2012; 65:87–108, 2015.
2. Min JH, Lee MW, Rhim H, et al. Recurrent hepatocellular carcinoma after transcatheter arterial chemoembolization: planning sonography for radio frequency ablation. *J Ultrasound Med*. 2011;30:617–624.
3. Kim JH, Kim PN, Won HJ, et al. Viable hepatocellular carcinoma around retained iodized oil after transarterial chemoembolization: radiofrequency ablation of viable tumor plus retained iodized oil versus viable tumor alone. *AJR Am J Roentgenol*. 2014;203:1127–1131.
4. Rossi S, Garbagnati F, Lencioni R, et al. Percutaneous radio-frequency thermal ablation of nonresectable hepatocellular carcinoma after occlusion of tumor blood supply. *Radiology*. 2000;217:119–126.
5. Au JS, Frenette CT. Management of hepatocellular carcinoma: current status and future directions. *Gut Liver*. 2015;9:437–448.
6. Dong W, Zhang T, Wang ZG, et al. Clinical outcome of small hepatocellular carcinoma after different treatments: a meta-analysis. *World J Gastroenterol*. 2014;20: 10174–10182.
7. Lan T, Chang L, Rahmathullah MN, et al. Comparative efficacy of interventional therapies for early-stage hepatocellular carcinoma: a PRISMA-compliant systematic review and network meta-analysis. *Medicine (Baltim)*. 2016;95. e3185.
8. Qi X, Zhao Y, Li H, et al. Management of hepatocellular carcinoma: an overview of major findings from meta-analyses. *Oncotarget*. 2016;7:34703–34751.
9. Furlan A, Marin D, Cabassa P, et al. Enhancement pattern of small hepatocellular carcinoma (HCC) at contrast-enhanced US (CEUS), MDCT, and MRI: intermodality agreement and comparison of diagnostic sensitivity between 2005 and 2010 American Association for the Study of Liver Diseases (AASLD) guidelines. *Eur J Radiol*. 2012;81:2099–2105.
10. Bruix J, Sherman M, Llovet JM, et al. Clinical management of hepatocellular carcinoma. Conclusions of the barcelona-2000 EASL conference. European association for the study of the liver. *J Hepatol*. 2001;35:421–430.
11. Ahmed M, Solbiati L, Brace CL, et al. Image-guided tumor ablation: standardization of terminology and reporting criteria–a 10-year update. *J Vasc Intervent Radiol*. 2014; 25:1691–1705.
12. Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. *Semin Liver Dis*. 2010;30:52–60.
13. Burke DR, Lewis CA, Cardella JF, et al. Quality improvement guidelines for percutaneous transhepatic cholangiography and biliary drainage. Society of Cardiovascular and Interventional Radiology. *J Vasc Intervent Radiol*. 1997;8: 677–681.
14. Trotti A, Colevas AD, Setser A, et al. CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. *Semin Radiat Oncol*. 2003; 13:176–181.
15. Livraghi T, Meloni F, Di Stasi M, et al. Sustained complete response and complications rates after radiofrequency ablation of very early hepatocellular carcinoma in cirrhosis: is resection still the treatment of choice? *Hepatology*. 2008;47: 82–89.
16. N'Kontchou G, Mahamoudi A, Aout M, et al. Radiofrequency ablation of hepatocellular carcinoma: long-term results and prognostic factors in 235 Western patients with cirrhosis. *Hepatology*. 2009;50:1475–1483.
17. Yamakado K, Nakatsuka A, Ohmori S, et al. Radiofrequency ablation combined with chemoembolization in hepatocellular carcinoma: treatment response based on tumor size and morphology. *J Vasc Intervent Radiol*. 2002;13:1225–1232.
18. Rossi S, Garbagnati F, Lencioni R, et al. Percutaneous radio-frequency thermal ablation of nonresectable hepatocellular carcinoma after occlusion of tumor blood supply. *Radiology*. 2000;217:119–126.
19. Abdelsalam ME, Murthy R, Avritscher R, et al. Minimally invasive image-guided therapies for hepatocellular carcinoma. *J Hepatocell Carcinoma*. 2016;3:55–61.
20. Morimoto M, Numata K, Kondou M, et al. Midterm outcomes in patients with intermediate-sized hepatocellular carcinoma: a randomized controlled trial for determining the efficacy of radiofrequency ablation combined with transcatheter arterial chemoembolization. *Cancer*. 2010;116:5452–5460.
21. Kim JW, Kim JH, Won HJ, et al. Hepatocellular carcinomas 2-3 cm in diameter: transarterial chemoembolization plus radiofrequency ablation vs. radiofrequency ablation alone. *Eur J Radiol*. 2012;81:e189–e193.
22. Koh YH, Choi JI, Kim HB, et al. Computed tomographic-guided radiofrequency ablation of recurrent or residual hepatocellular carcinomas around retained iodized oil after transarterial chemoembolization. *Korean J Radiol*. 2013;14:733–742.
23. Woo S, Lee JM, Yoon JH, et al. Small- and medium-sized hepatocellular carcinomas: monopolar radiofrequency ablation with a multiple-electrode switching system-mid-term results. *Radiology*. 2013;268:589–600.
24. Ni JY, Liu SS, Xu LF, et al. Meta-analysis of radiofrequency ablation in combination with transarterial chemoembolization for hepatocellular carcinoma. *World J Gastroenterol*. 2013;19:3872–3882.
25. Shim JH, Lee HC, Kim SO, et al. Which response criteria best help predict survival of patients with hepatocellular carcinoma following chemoembolization? A validation study of old and new models. *Radiology*. 2012;262:708–718.