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Original Article

Transcatheter Arterial Chemoembolization to Reduce Size of Hepatocellular Carcinoma before Radiofrequency Ablation

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Transcatheter arterial chemoembolization (TACE) is often performed before radiofrequency ablation (RFA) for the treatment of early-stage hepatocellular carcinoma (HCC). TACE prior to RFA can expand the ablated area and reduce the tumor size, facilitating complete ablation. However, the factors correlated with size reduction remain uncertain. The aim of this study was to identify the factors associated with size reduction by TACE and develop a formula to predict the reduction rate. A total of 100 HCC patients treated with TACE followed by RFA at least 20 days later were enrolled. The tumor size was measured at the time of TACE and RFA, and correlations between the reduction rate and 13 clinical factors were examined. A formula to predict the reduction rate was built using the factors obtained by the analysis. Reduction in the tumor size was observed in 69 nodules, and the median reduction rate was 16.2%. A multivariate regression analysis revealed that a large tumor size ($p < 0.01$) and a long interval between the therapies ($p = 0.01$) were factors for a high tumor reduction rate, with tumor size more strongly related to the degree of reduction. A size reduction of more than 10% can be expected by waiting 20 days after TACE when the size of the tumor at TACE is over 25 mm in diameter. The tumor size at TACE and the interval between TACE and RFA were closely correlated with HCC size reduction by TACE.

Key words: hepatocellular carcinoma, transcatheter arterial chemoembolization, radiofrequency ablation, interval, size reduction

Hepatocellular carcinoma (HCC) is the sixth-most common neoplasm and the third-most frequent cause of cancer death. More than 700,000 HCC patients are newly diagnosed globally each year [1]. More patients are being diagnosed in the early stage thanks to the accumulation of knowledge about risk factors and the increasing prevalence of HCC surveillance. The Japanese Clinical Practice Guidelines recommends radiofrequency ablation (RFA) or surgical resection for the treatment of early-stage HCC. However, surgical liver resection carries serious risks, such as deterioration of liver function.

RFA is thought to be an effective treatment because of its high tumor control rate and low invasiveness. The survival rates of patients who achieve complete ablation are comparable to those in patients resected by surgery [2, 3]. In addition, RFA combined with TACE has been

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reported to contribute to an improved recurrence-free survival rate and treatment time [4-10]. The advantages of TACE are tumor necrosis by chemotherapy and occlusion of the feeding artery flow by embolization, which lead to tumor reduction or extension of the ablation area due to less heat loss by convection [11]. In most previous reports on combination therapy, the interval between TACE and RFA has been within 2 weeks [5, 8, 12-15]. While prolongation of the interval might lead to a reduction in the size of HCC, no studies have examined the effect of a longer interval between the two therapies.

In this study, we analyzed the factors correlated with the reduction in the size of HCC after TACE and tried to predict the reduction rate.

Methods

Patients. This retrospective study was conducted at the Department of Gastroenterology and Hepatology, Okayama University, Japan. From January 2001 to December 2014, a total of 1358 HCCs were treated with combination therapy of TACE and RFA. The diagnosis of HCC was confirmed pathologically or based on the findings of typical radiological features using contrast-enhanced computed tomography (CT) or dynamic magnetic resonance imaging (MRI) [16].

The eligibility criteria were as follows: a single tumor ≤ 5 cm in diameter, or 3 or fewer nodules ≤ 3 cm in diameter; a Child-Pugh grade A or B; sufficient iodized oil accumulation at the lesions treated with TACE; lesion visibility on abdominal ultrasonography (AUS); and RFA performed more than 20 days after TACE. All patients in this study provided informed consent for the use of their clinical data in the analysis. This study was approved by our institutional review board (No. 1609-501) and was conducted according to the Helsinki Declaration. Ultimately, 100 patients were enrolled in this study (Fig. 1).

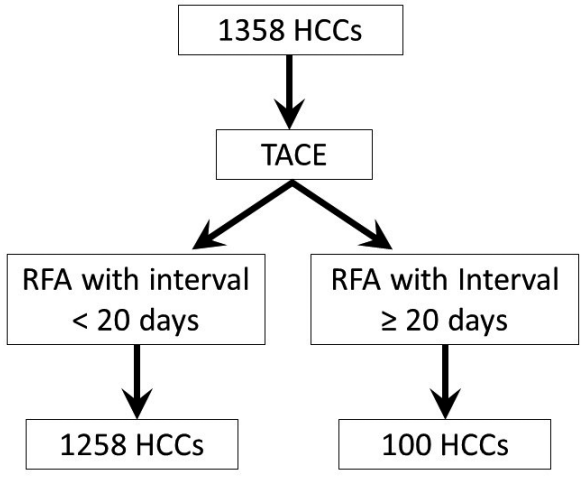

Fig. 1 Enrollment process of patients. 1358 HCCs were treated with TACE and RFA in Okayama University Hospital from January 2001 to December 2014. One hundred patients were satisfied with the eligibility criteria.

TACE procedure. TACE was performed using the Seldinger technique followed by arterial embolization. After introducing a 3- or 4-Fr catheter through the femoral artery, hepatic arteriography and superior mesenteric arterial portovenography were performed to evaluate portal flow and the location of the tumors. When the portal flow was deemed sufficient, a 1.8- or 2.0-Fr microcatheter was placed in the feeding arteries. An emulsion consisting of 30-60 mg of epirubicin (Kyowa-Hakko, Tokyo, Japan) and 2-6 mL of iodized oil (Lipiodol Ultrafluid; Terumo, Tokyo, Japan) was injected into the artery supplying blood to the tumor, followed by embolization with 1-mm gelatin sponge particles (Gelfoam; Nihonkayaku, Tokyo, Japan). After embolization, CT angiography was performed to determine the extent of vascular occlusion.

Measurement of tumor size. We measured the maximum tumor size just before TACE and RFA. Before TACE, we measured the diameter of the tumor on CT during hepatic arteriography (CTHA). At RFA we measured the diameter of the tumor by AUS. After treatment, all patients received follow-up every 3-6 months during follow up period by blood testing and dynamic contrast-enhanced CT or AUS.

Statistical analysis. The following parameters were used to analyze the factors involved in tumor reduction: age, sex, viral markers (hepatitis B virus surface antigen and hepatitis C virus antibody), Child-Pugh grade, size of tumors, number of tumors, interval between TACE and RFA, total bilirubin and albumin (Alb) levels, platelet (PLT) count, prothrombin time (PT), and levels of α-Fetoprotein (AFP) and des-gamma-carboxy prothrombin (DCP). Cut-off values were defined by median or standard values. The baseline characteristics are presented as medians and ranges. The change in the tumor size between therapies was analyzed by a paired *t*-test. The least squares

method was performed to analyze the factors involved in tumor reduction.

Variables with a p-value < 0.05 in a univariate comparison were subjected to a multivariate regression analysis. The predictive tumor reduction rate was estimated using a multivariate regression model. All of the significance tests were two-sided, and differences with a p-value < 0.05 were considered significant. Statistical analyses were performed using JMP 11.0 (SAS Institute, Cary, NC, USA).

Results

Factors for tumor reduction after TACE. The patient characteristics are shown in Table 1. The median tumor diameter at TACE was 17.8 mm (range, 3.8-42.5 mm), and the median interval between TACE and RFA was 42 days (range, 21-643 days). The median reduction rate was 16.2%. Tumor size was reduced, unchanged, and increased in 69%, 3%, and 28% of the patients, respectively (Fig. 2). Univariate analysis revealed that the factors related to tumor reduction after TACE were the tumor size at TACE and the interval between the therapies ($p < 0.01$ and $p = 0.02$, respectively) (Table 2). A multivariate analysis with the factors showing a p-value < 0.05 in the univariate analysis revealed that both the tumor size at TACE and the interval between the therapies remained significant factors in the multivariate analysis ($p < 0.01$ and $p = 0.01$, respectively).

Construction of a formula predicting tumor reduction rate. To predict the tumor reduction rate, we constructed a formula based on the results of the least-square method using the 2 factors above, as follows:

Tumor reduction rate (%) = [tumor size at TACE (mm) × 1.1] + [interval between the therapies (days) × 0.06] − 17

A clear correlation was observed between the measured reduction rate and the predictive reduction rate (Fig. 3, $R^2 = 0.23$, $p < 0.001$). Table 3 shows the calculated reduction rate. The reduction rate largely depended on the tumor size at TACE. For initially small tumors (≤ 20 mm in diameter), the size reduction rate was within 10%. Conversely, over 10% size reduction was expected for larger tumors (≥ 25 mm) over 20 days after TACE. The 1-year local recurrence rate after the combination therapy was 3.2%.

Table 1 Clinical profile of 100 patients

Characteristic	Value
Age (years old)	70.5 (28–85)
Sex (male/female)	77/23
Etiology (HBV/HCV/HBV + HCV/others)	12/79/1/8
Child-Pugh class (A/B)	76/24
Tumor size at TACE (mm)	17.8 (3.8–42.5)
Tumor number (1/≥2)	78/22
Interval between therapies (days)	42 (21–643)
AST (IU/L)	47 (18–165)
ALT (IU/L)	39 (11–201)
Total bilirubin (mg/dL)	0.76 (0.3–2.4)
Albumin (g/dL)	3.6 (2–4.5)
Prothrombin time (%)	93 (59–130)
PLT (/μL)	10.9 (2.8–32.9)
AFP (ng/mL)	16.8 (2–5131)
DCP (mAU/mL)	59 (8.2–451)
	Median (range)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; PLT, platelet; AFP, alpha-fetoprotein; DCP, des-gamma-carboxy prothrombin.

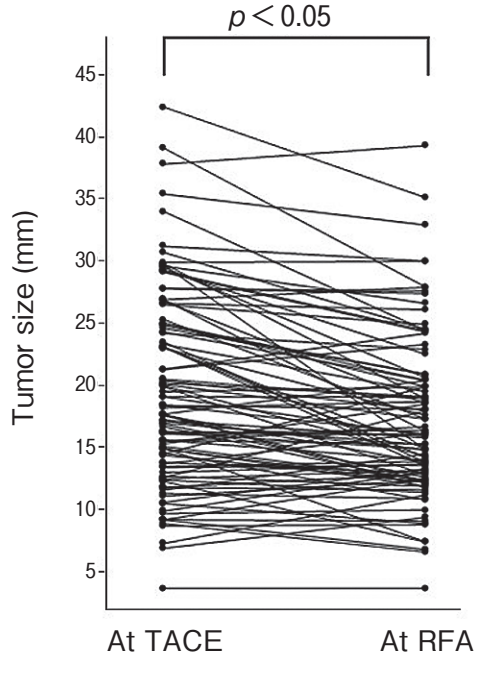

Fig. 2 Change in tumor size between therapies. Tumor size was reduced, unchanged and increased in 69%, 3%, and 28% of the patients, respectively. The median reduction rate in all nodules was 16.2% ($p < 0.05$).

Table 2 Factors related with size reduction

		Number of patients (n)	Tumor reduction rate (%) (median, range)	Univariate *p*-value	Multivariate *p*-value
Age	≥70	54	11.1 (−37.0–41.4)	0.16	
	<70	46	6.6 (−52.7–50.3)		
Sex	male	77	8.0 (−52.7–50.3)	0.47	
	female	23	13.9 (−24.8–39.5)		
HCV	+	80	8.0 (−42.5–50.3)	0.25	
	−	20	9.1 (−52.7–50)		
HBV	+	13	13.9 (−52.7–25.6)	0.19	
	−	87	8.0 (−42.5–50.3)		
Child-Pugh grade	A	76	10.3 (−52.7–50.3)	0.82	
	B	24	6.6 (−35.5–39.5)		
Tumor size at TACE	≥17 mm	57	16.0 (−15.2–50)	<0.01	<0.01
	<17 mm	43	0 (−52.7–50.3)		
Interval between TACE and RFA	≥40 days	51	15.0 (−52.7–50.3)	0.02	0.01
	<40 days	49	1.7 (−42.5–39.5)		
T-bil (mg/dl)	≥1.0	28	7.9 (−35.7–50.3)	0.96	
	<1.0	72	10.1 (−52.7–50)		
Albumin (g/dL)	≥3.5	59	13.9 (−52.7–50)	0.54	
	<3.5	41	6.0 (−42.5–50.3)		
Prothrombin time (%)	≥100	36	9.1 (−32–36.5)	0.90	
	<100	64	8.0 (−52.7–50.3)		
PLT (/μL)	≥150000	32	4.8 (−20.8–36.5)	0.80	
	<150000	68	11.1 (−52.7–50.3)		
AFP (ng/mL)	≥20	48	5.7 (−42.5–39.3)	0.16	
	<20	52	14.4 (−52.7–50.3)		
DCP (mAU/mL)	≥50	52	9.0 (−37.0–50.3)	0.21	
	<50	47	8 (−52.7–50)		

HCV+, positive for hepatitis C virus antibody; HBV+, positive for hepatitis B virus antigen; PLT, platelet count; AFP, alpha-fetoprotein; DCP, des-gamma-carboxy prothrombin.

Discussion

Our analysis showed that tumor reduction after TACE was observed in 69% of the nodules, and the median reduction rate was 16.2%. The factors related to tumor reduction were tumor size at TACE and the interval between TACE and RFA. Tumor size at TACE was particularly strongly related to the reduction. If the tumor size was ≥25 mm, the predicted reduction rate was over 10% at RFA.

One of the mechanisms behind this reduction is the level of development of tumor vessels. Bigger tumors have more abundant blood flow, which facilitates the dispersal of anticancer agents or gelatin sponge particles. Consequently, larger tumor size leads to more effective necrosis measures and subsequent tumor reduction. In contrast, the relationship between the degree of tumor reduction and the interval between

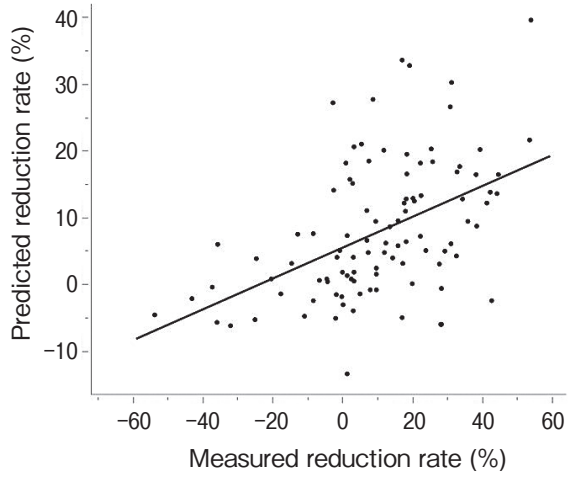

Fig. 3 Relationship between the measured reduction rate and the predictive reduction rate. A clear correlation was observed between the measured reduction rate and the predicted reduction rate.

Table 3 Expected reduction of tumor size after TACE

Tumor diameter at TACE	Days after TACE			
	20	40	60	80
15 mm	1% (0.1 mm)	2% (0.3 mm)	3% (0.5 mm)	4% (0.6 mm)
20 mm	6% (1.2 mm)	7% (1.5 mm)	9% (1.7 mm)	10% (2.0 mm)
25 mm	11% (2.9 mm)	13% (3.2 mm)	14% (3.5 mm)	15% (3.8 mm)
30 mm	17% (5.2 mm)	18% (5.5 mm)	20% (5.9 mm)	21% (6.2 mm)
35 mm	23% (7.9 mm)	24% (8.4 mm)	25% (8.8 mm)	26% (9.2 mm)

therapies was relatively weak. No significant further tumor reduction was achieved with an interval over 20 days. Indeed, the difference in the predicted size reduction between 20 days and 80 days after TACE was only about 1 mm. This implies that most tumor reduction mainly occurs within the first 20 days after TACE. At our institute, RFA is usually performed 7 days after TACE. We preliminary measured the size of tumors treated by TACE and RFA at a 7-days interval (n = 10). Tumor size reduction was observed in only 4 patients, and the median change rate of all 10 patients was a 2.5% increase. Therefore, the bulk of the reduction in patients with at least a 20-day interval may have occurred between 7 and 20 days after TACE. Altogether, our data suggest that 20 days might be a sufficient interval for tumor reduction.

Although a greater tumor reduction can be expected by extending the interval, waiting too long might increase the risk of tumor re-enlargement and local recurrence. In the present study, however, over two-thirds of the tumors achieved a size reduction following TACE, and the 1-year local recurrence rate was 3.2%, which was as low as that found in our previous report in which most patients were treated by RFA at 7 days after TACE [17]. These results indicated that a greater-than-20-day interval did not increase the risk of local recurrence, so long as sufficient iodized oil accumulation during TACE was achieved. Obtaining these promising results requires the accumulation of iodized oil, since insufficient iodized oil accumulation is a risk factor of recurrence after TACE, as we reported previously [18].

In most previous studies, RFA has been performed about one week after TACE. In the present study, we found that small HCCs (≤ 20 mm in diameter) did not shrink in size, regardless of the interval after TACE; in the case of small lesions, then, it is therefore better to perform RFA soon after TACE, as in most studies. Conversely, waiting somewhat longer might be better for HCCs ≥ 25 mm, as we can expect substantial size reduction, thereby facilitating ablation of the tumor without increasing the risk of local recurrence.

Several limitations associated with the present study warrant mention. First, this is a retrospective study, and the number of patients who underwent TACE and RFA with a long interval between them was limited. Second, patient selection bias might exist. We usually have a long interval between TACE and RFA in the case of patients who need physical recovery after TACE. So, a patient's condition might be related to the change of tumor size. Third, in this study we measured the tumor size based on CT and AUS scans. The difference in the modality may have influenced the perceived tumor size. Finally, we did not examine the degree of tumor reduction in patients who were treated by RFA between 7 and 20 days after TACE, which might be when the bulk of tumor reduction occurs.

In conclusion, the tumor size at TACE and the interval between TACE and RFA were correlated with tumor reduction after TACE. In particular, large tumors (≥ 25 mm) had a potential size reduction of ≥ 10% if RFA was delayed slightly after TACE, without increasing the local recurrence rate. These findings suggest that waiting 7-20 days after TACE might be a useful strategy for RFA when treating large tumors.

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