Predisposing factors for hepatocellular carcinoma recurrence following initial remission after transcatheter arterial chemoembolization

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Abstract. Hepatocellular carcinoma (HCC) is prone to recurrence following curative treatment. The purpose of the present study was to identify the predisposing factors of HCC recurrence following complete remission achieved by transarterial chemoembolization (TACE). A retrospective cohort study of 70 consecutive patients with HCC who underwent TACE as the initial treatment was conducted. The patients were divided into two groups according to their 1-year disease-free survival (DFS) status; the early recurrence group (ER group; n=32), with HCC recurring within 1 year of initial TACE; and the non-early recurrence group (NER group; n=38), who did not experience recurrence within 1 year. The parameters identified as significantly associated with DFS time on univariate analysis were aspartate aminotransferase (AST), alanine aminotransferase and α-fetoprotein levels, as well as the tumor number (P=0.003, P=0.027, P=0.002 and P=0.005, respectively). Multivariate analysis revealed that AST levels and tumor number were significantly associated with a shorter DFS period (P=0.009 and P=0.038, respectively). The Mantel-Haenszel test revealed a significant trend of decreasing DFS with increasing tumor number. Among the patients with HCC in the ER group, locoregional recurrence occurred more frequently in those who received TACE alone compared with those treated with TACE combined with radiofrequency ablation treatment. In summary, multinodularity of HCC is the most potent predictive factor for the recurrence of HCC within 1 year of initial TACE.

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Introduction

Hepatocellular carcinoma (HCC) is the sixth most common type of cancer worldwide (1), and develops in patients with chronic liver disease and cirrhosis (2). The treatment of HCC depends on its stage of progression (3). Surgical resection remains the mainstay of potentially curative therapy, but the majority of patients with HCC have passed the opportunity for treatment with surgery at the time of diagnosis (4,5).

Transcatheter arterial chemoembolization (TACE) is an essential treatment option for patients with HCC who cannot be treated with other potentially more effective therapies, including surgical resection or local ablative therapies, and is the standard of care for patients with noninvasive multinodular tumors at an intermediate stage (6,7). However, the long-term outcomes of patients treated with TACE are not entirely satisfactory, mainly due to the low tumor necrosis rates (8) and high recurrence rates (6).

Radiofrequency (RF) ablation (RFA) represents a safe and effective first-line locoregional treatment for HCCs with three tumors or fewer, of ≤3 cm in size (3,9). Despite the high complete necrosis rate of RFA, early local or distant tumor recurrence within 1 year may still occur (10). TACE combined with RFA can enhance the advantages of each individual treatment (8) and increase their cooperative effect, demonstrating the potential benefits of a multidisciplinary approach for advanced HCC (11,12). Furthermore, the combination therapy of RFA and TACE has been shown to be superior to TACE or RFA alone in increasing locoregional control and improving the curative effect and survival time in patients with advanced HCC (13,14). However, the risk factors for tumor recurrence following treatment of HCC have not yet been clarified in detail.

The aims of the present study were to identify the characteristics of HCC associated with recurrence following successful initial treatment with TACE, and to compare the recurrence patterns between patients with HCC who received TACE alone and those treated with TACE combined with RFA treatment.

Materials and methods

Study design. The present study was a retrospective cohort study performed at a single center. The medical records of 357 patients treated with TACE between June 2009 and June 2013 at Nara Medical University (Kashihara, Japan) were reviewed (Fig. 1). Of these, 70 patients were initially treated with TACE and subsequently observed over a 1-year period. These patients were divided into two groups according to DFS status at 1 year: The early recurrence (ER) group (recurrence within 1 year after initial TACE; n=32) and the non-early recurrence (NER) group (no recurrence within 1 year after initial TACE; n=38). Of the 32 patients in the ER group, 5 did not achieve a complete remission (CR), with 2 succumbing to HCC. Of the 38 patients in the NER group, 1 succumbed to HCC, while 15 did not experience a recurrence of HCC for >1 year after the initial TACE. The degree of lipiodol retention in the tumor within 1 week of TACE was routinely evaluated by multi-detector row computed tomography (MDCT). RFA was administered if MDCT and contract-enhanced ultrasonography (CE-US) detected a residual viable tumor. The study was approved by the local ethics committee of Nara Medical University (Nara, Japan) and written informed consent was obtained from all patients prior to treatment.

Diagnosis of HCC. The diagnosis of HCC was confirmed without biopsy in patients with chronic liver disease and cirrhosis who had a tumor that exhibited a typical vascular pattern on dynamic imaging modalities [such as contrast-enhanced MDCT (CE-MDCT) and gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA)-enhanced magnetic resonance imaging (MRI)], in accordance with the practice guidelines of the Japan Society of Hepatology (15). However, if the vascular profile on imaging was not characteristic, or if a nodule was detected in a healthy normal liver, supplementary tests, including Gd-EOB-DTPA-enhanced MRI, CE-US, computed tomography (CT) angiography and liver tumor biopsy, were considered. All patients were examined by CE-MDCT or Gd-EOB-DTPA-enhanced MRI every 2 or 3 months after initial TACE.

TACE. The procedure for TACE has previously been described in detail (16). Briefly, a single femoral approach was used, following Seldinger's technique (17), by inserting a 4-Fr catheter (RH-6SP0061i; Terumo Medical Corporation, Tokyo, Japan) over a 5-Fr introducer sheath into the celiac artery, using superior mesenteric artery angiography as well as selective hepatic arteriography to identify tumor feeders. The artery was selectively catheterized with a microcatheter/microguidewire system and embolized with a mixture of epirubicin with iodized oil (lipiodol; Laboratoire Andre Guerbet, Aulnay-sous-Bois, France). The feeders were then embolized with gelatin sponge pledgets (Cutanplast; Mascia Brunelli S.p.A, Milan, Italy) until complete stasis of the blood flow was detected by angiography. Collateral artery embolization was performed if branches such as the phrenic artery and internal thoracic artery were engaged in the tumor blood supply. Post-TACE cone-beam CT was performed to assess the extent of lipiodol uptake in the tumor at the end of TACE.

Percutaneous RFA. RFA of HCC was performed using the Cool-tip™ RF system (Integra Burlington MA, Inc., MA, USA). RFA with ultrasound guidance was conducted under general and local anesthesia, using a 3.5-MHz probe with an incorporated guide and a 17-gauge cooled-tip electrode (Cool-tip; Valleylab, Burlington, MA, USA) with a 2- or 3-cm exposed portion. This system consisted of an RF generator to produce a current of 480 kHz at a maximal power of 200 W, a single-electrode RFA, a water-pumping machine and return grounding pads. The RFA started at a low power (40 or 60 W) and increased by 10 W/min, and the delivery of RF energy was automatically modulated according to the tissue impedance around the electrode. Tumor ablation continued at maximum power until the tissue impedance increased to the point at which the power output fell rapidly (the 'break'). The treatment response was assessed based on CE-MDCT or CE-US performed within 1 week of RFA treatment.

Assessment and follow-up. The Response Evaluation Criteria in Solid Tumors (RECIST) criteria (18) are recommended for evaluating treatment efficacy in clinical trials and practice. The response to treatment was assessed by CE-MDCT according to the RECIST criteria at 4 weeks post-TACE or within 1 week of RFA, and additional RFA was performed until no residual viable tumor was detectable. Following the final treatment session, patients were evaluated every 3 months for 2 years and followed up every 6 months thereafter by CE-MDCT or CE-MRI. The primary end-point was the HCC DFS period following initial TACE.

Statistical analysis. Categorical variables were analyzed using the Mantel-Haenszel test. Bivariate analyses of nominal parameters were performed using the χ^2 test. Univariate and multivariate logistic regression analyses were conducted to assess the effect of different parameters on HCC recurrence following initial TACE. Data are presented as the mean ± standard deviation. $P<0.05$ was considered to indicate a statistically significant difference. All statistical analyses were performed using IBM SPSS statistics version 22 (IBM Corp., Armonk, NY, USA).

Results

Clinical characteristics of patients. Baseline characteristics of the enrolled 70 patients are summarized in Table I. The patient group included 51 males (73%) and 19 females (27%), and the mean age was 70.5±8.9 years. A total of 54 patients (77%) were classified as having Child-Pugh class (19) A cirrhosis, and 16 (23%) patients were classified as having class B cirrhosis. At the initial diagnosis, the mean tumor number was 2.3±2.1, and 8 patients (11%) had multiple lesions. The mean serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were 53.3±43.4 and 40.3±36.4 IU/l, respectively. The mean α-fetoprotein (AFP) level was 1,450.0±7,430.0 ng/ml.

Risk factors associated with HCC recurrence. Univariate and multivariate analyses were performed to identify predictive risk factors for HCC recurrence through comparisons between the ER and NER groups. Univariate analysis revealed that the levels of AST, ALT and AFP, as well as tumor number,

Table I. Baseline characteristics of the patients (n=70).

Variable	Value
Age, years[a]	70.5±8.9 (49-83)
Sex, n	
Male	51
Female	19
Etiology, n	
HBV	12
HCV	37
Others	21
Child-Pugh classification, n	
A	54
B	16
TNM stage, n	
I	20
II	29
III	19
IV	2
Tumor size, cm[a]	3.4±3.1 (0.7-20.0)
Tumor number[a]	2.3±2.1 (1-9)
Aspartate transaminase, IU/l[a]	53.3±43.4 (12-285)
Alanine aminotransferase, IU/l[a]	40.3±36.4 (11-236)
α-fetoprotein, ng/ml[a]	1,450.0±7,430.0 (1.7-56,831.6)
Protein induced by vitamin K absence/antagonist-II, mAU/ml[a]	3,342.0±10,537.0 (7.0-66,753.0)

[a]Mean ± standard deviation (range). TNM, tumor-node-metastasis; HBV, hepatitis B virus; HCV, hepatitis C virus.

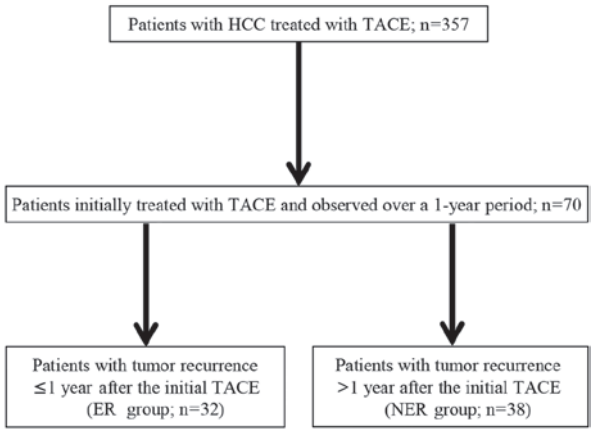

Figure 1. Schematic flowchart of the study design. A retrospective review of medical records was conducted for 357 patients with HCC treated with TACE. Of these, 70 patients were initially treated with TACE and observed over a 1-year period. These patients were divided into two groups according to their disease-free survival status at 1 year: The ER group (recurrence within 1 year of the initial TACE; n=32); and the NER group (no recurrence within 1 year of the initial TACE; n=38). HCC, hepatocellular carcinoma; TACE, transcatheter arterial chemoembolization; ER, early recurrence; NER, non-early recurrence.

were associated with early HCC recurrence following TACE (Table II). The ER and NER groups did not differ significantly in terms of mean age, sex ratio, tumor etiology, Child-Pugh classification, tumor stage, mean tumor size or levels of protein induced by vitamin K absence/antagonist-II. Multivariate logistic regression analysis indicated that AST levels [odds ratio (OR), 1.069; P=0.009] and tumor number (OR, 1.661; P=0.038) were independent risk factors associated with HCC recurrence following initial TACE (Table III).

Association between tumor number and recurrence patterns with DFS period following initial TACE. Of the 70 patients, 32 had a single nodule, 20 had two nodules, 7 had three nodules and 11 had four or more nodules. The mean HCC DFS periods for patients with one, two, three and four or more nodules were 19.8, 13.4, 9.1 and 7.4 months, respectively. The χ^2 test for trend demonstrated an inverse association between tumor number and DFS period in these patients (Fig. 2). Recurrence within 1 year of TACE was documented in 27 patients, including distant recurrence in 11 (41%) of these patients, and locoregional recurrence in 16 (59%) patients. Recurrence after 1 year was documented in 22 patients, including distant recurrence in 17 (77%) of these patients and locoregional recurrence in 5 (23%) patients. The association between recurrence patterns of HCC and DFS following initial TACE was also analyzed. A χ^2 test revealed that, among all patients with recurrence, the proportions of locoregional and distant recurrence differed significantly between the ER group and the NER group (P<0.05), with a greater proportion of regional recurrence observed in the ER group (Fig. 3).

Comparison of HCC recurrence patterns between combined TACE and RFA treatment and TACE alone. In the ER group (n=32), 5 patients underwent TACE and RFA and the remaining 27 patients received TACE alone. In the NER group, all 38 patients received TACE alone. No locoregional recurrence was observed following treatment with a combination of TACE and RFA. Of the 11 patients who experienced distant recurrence in the ER group, 7 (64%) patients had undergone a combination of TACE and RFA and 4 (36%) patients received TACE alone. A χ^2 test revealed that the combination treatment of TACE and RFA was associated with a significantly lower locoregional recurrence rate compared with TACE treatment alone in patients of the ER group (P<0.05; Fig. 4). Patients treated with TACE alone had a higher incidence of distant recurrence compared with those treated with combination therapy.

Discussion

TACE is a well-established procedure that offers a palliative survival benefit for patients with HCC that is unresectable or not suitable for local ablative treatment (20). Several case-control and retrospective studies have revealed a benefit of TACE for patient survival when comparing TACE-treated patients with untreated or historical controls (the patients with unresectable HCC received conservative treatment) (9,20). It has been a challenge for patients with advanced HCC to maintain a CR following TACE due to extracapsular invasion of HCC and residual viable cancer cells around the fibrous capsules

Table II. Baseline characteristics of the patients.

Variable	Early recurrence group (n=32)	Non-early recurrence group (n=38)	P-value[a]
Age, years[b]	69.5±9.0 (50-83)	71.3±8.8 (49-82)	0.354
Sex, n			0.865
Male	23	28	
Female	9	10	
Etiology, n			0.871
HBV	5	7	
HCV	18	19	
Others	9	12	
Child-Pugh classification, n			0.695
A	24	30	
B	8	8	
TNM stage, n			0.555
I	7	13	
II	13	16	
III	11	8	
IV	1	1	
Tumor size, cm[b]	4.4±4.2 (1.7-20.0)	2.6±1.3 (0.7-6.6)	0.153
Tumor number[b]	3.0±2.7 (1-9)	1.6±0.9 (1-4)	0.005
Aspartate transaminase, IU/l[b]	69.8±57.4 (24-285)	39.4±18.1 (12-96)	0.003
Alanine aminotransferase, IU/l[b]	50.2±46.2 (11-236)	32.1±22.9 (13-126)	0.027
α-fetoprotein, ng/ml[b]	3144.6±10,836.0 (2.3-56,831.6)	22.7±35.2 (1.7-144.2)	0.002
Protein induced by vitamin K absence/antagonist-II, mAU/ml[b]	6,396.5±14,871.0 (7.0-66,753.0)	646.9±1,291.0 (8.0-5,845.0)	0.053

[a]P-values represent comparisons between the early recurrence group and the non-early recurrence group. [b]Mean ± standard deviation (range). TNM, tumor-node-metastasis; HBV, hepatitis B virus; HCV, hepatitis C virus.

Table III. Multiple logistic regression analysis of risk factors for recurrence within 1 year of initial transcatheter arterial chemoembolization for hepatocellular carcinoma.

Variable	P-value	Odds ratio	95% confidence interval
Aspartate transaminase	0.009	1.069	1.017-1.125
Alanine aminotransferase	0.220	0.916	0.270-1.001
α-fetoprotein	0.142	2.961	0.740-6.372
Tumor number	0.038	1.661	1.029-2.680

subsequent to TACE (21). Complications associated with TACE, including an impaired hepatic functional reserve, support the use of RFA rather than repeated TACE treatments (22,23). Emerging evidence suggests that a combination of TACE and RFA exerts a synergistic anticancer activity against HCC, particularly for larger lesions that do not respond sufficiently to either TACE or RFA treatments alone (24-26). An analysis of the factors that carry a high risk of early recurrence following TACE may improve the selection of patients suited to a combination of TACE with RFA.

In the present study, the clinical courses of 70 patients with HCC treated with TACE, and the different risk factors associated with HCC recurrence following initial remission after TACE, were examined. To the best of our knowledge, this is the first study to show that tumor number is the most important risk factor for recurrence within 1 year of initial TACE. The findings of the present study demonstrated an inverse association between tumor number and DFS time following initial TACE. Consistent with the present study, several previous studies have identified tumor number as a predictor of intrahepatic recurrence following initial TACE for HCC (27-31). Recurrence following initial remission by TACE has been more often reported in patients with multinodular-type HCC and with portal vein thrombosis (32). By contrast, Matsuda *et al* (33) conjectured that tumor multiplicity was not associated with 1-year HCC recurrence

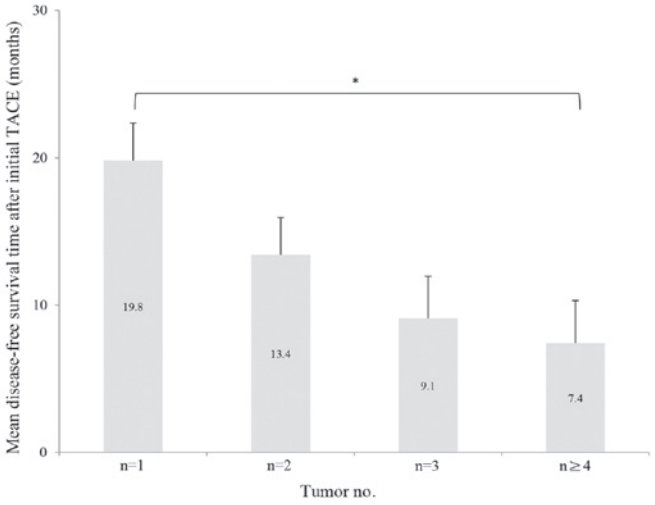

Figure 2. Association between tumor number and DFS period following initial TACE in patients with hepatocellular carcinoma. An inverse association was observed between tumor number and DFS time. *P<0.05, Mantel-Haenszel test. DFS, disease-free survival; TACE, transcatheter arterial chemoembolization.

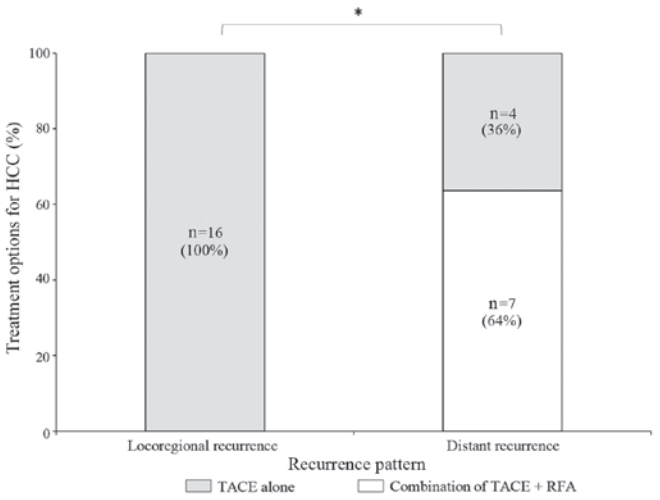

Figure 4. Comparison of recurrence patterns of HCC between patients that received a combination of TACE and RFA and those treated with TACE alone. Among the patients with HCC recurrence within 1 year of initial TACE, locoregional recurrence occurred more frequently in those who received TACE alone compared with those treated with TACE combined with RFA treatment. *P<0.05 (χ^2 test). RFA, radiofrequency ablation; TACE, transcatheter arterial chemoembolization; HCC, hepatocellular carcinoma.

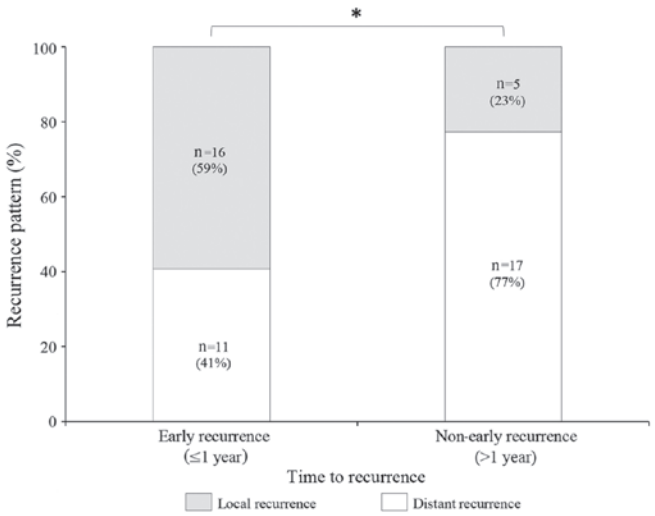

Figure 3. Association between patterns of hepatocellular carcinoma recurrence and disease-free survival time following initial TACE. Among patients with recurrence, the proportion of observed locoregional recurrence was higher in patients with recurrence ≤1 year after initial TACE than in those with recurrence >1 year after initial TACE. *P<0.05 (χ^2 test). TACE, transcatheter arterial chemoembolization.

status. It has also been reported that the risk factors for early HCC recurrence subsequent to achieving CR by TACE included large tumor size, non-compact lipiodol uptake and an AFP concentration >20 ng/ml, but not tumor number (34). This discrepancy may be explained in part by the different treatment modalities and the baseline characteristics of the patients with HCC between studies. HCC often consists of different cell types, including moderately differentiated and undifferentiated carcinoma (35,36), which is not eligible for TACE due to its hypovascularity. Early recurrence following a CR achieved by TACE may be mainly attributed to residual tumors that were undetectable on angiography. The distribution of lipiodol uptake determined by tumor differentiation and the blood vessel network have been shown to affect the local recurrence rate and long-term outcome in patients with HCC (37,38). Furthermore, consistent with the present study, a previous study showed that local recurrence developed more frequently in patients with early recurrence (≤1 year) compared with those with late recurrence (>1 year) (27). These results indicated that early recurrence is associated with local recurrence arising from limitations of the radiological evaluation of tumor response, and remnant tumors can develop and be recognizable by imaging modalities over time.

In combined treatment with TACE and RFA, the main roles of TACE are to counteract the heat-sink effect of hepatic blood flow by hepatic artery embolization (39) and to reduce the portal venous flow by filling the peripheral portal vein around the HCC (40). TACE can also lead to ischemic edema, which may enlarge the area of tumor necrosis induced by RFA (24). The combination of TACE and RFA generally results in complete tumor remission if the liver function reserve is sufficiently maintained post-TACE (12). No local HCC recurrence was observed in patients treated with a combination of TACE and RFA in the present study. The combination of TACE and RFA has significant advantages in terms of local tumor control and longer patient survival compared with TACE alone (41,42). These findings reinforce the notion that the combination of TACE and RFA resulted in a more efficient microscopic local tumor response compared with TACE alone.

The present study had a number of limitations. First, it was conducted in a single center and the sample size of patients with HCC recurrence was small. Second, there may have been unexpected factors that effected the probability of therapeutic response and recurrence. Third, patients who were lost to follow-up within 1 year and those who succumbed to the disease were excluded from the analysis, since the presence of early recurrence could not be confirmed; this may have led to selection bias.

In conclusion, multinodularity of HCC is an independent risk factor for 1-year recurrence of HCC in patients with initial

remission following TACE. In particular, in patients who developed early recurrence, intrahepatic local recurrence more frequently occurred in HCC patients who received TACE alone compared with those treated with TACE combined with RFA treatment, which indicated that the combination treatment of TACE and RFA may be beneficial in preventing early recurrence of HCC.

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