Risk factors of recurrence after transarterial chemoembolization for early stage hepatocellular carcinoma

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Abstract

Background: Radiofrequency ablation (RFA) is a standard therapy for the treatment of hepatocellular carcinoma (HCC) numbering 3 or fewer tumors of up to 3 cm (early stage HCC); when RFA is unsuccessful or unfeasible, transcatheter arterial chemoembolization (TACE) has often been performed. However, little information about the outcome of TACE for early stage HCC has been reported and it is hard to decide whether to perform additional treatment following TACE in these difficult conditions. The aim of this study was to determine the risk factors of local or intrahepatic distant recurrence after TACE in early stage HCC.

Methods: Among 1,560 newly diagnosed HCC patients who were admitted to Okayama University Hospital, 43 early stage HCC patients who received only TACE of at least one nodule were enrolled in this study. We analyzed the risk factors for local and distant recurrence by Cox proportional hazard model.

Results: The local recurrence rates and intrahepatic distant recurrence rates at 3 months, 6 months, and 1 year were 18.6%, 33.4%, and 61.8%, and 2.8%, 2.8%, and 10.2%, respectively. Among 12 parameters examined,

heterogeneous lipiodol uptake (risk ratio 3.38; 95% confidence interval 1.14-10.60) and high serum des-gamma-carboxy prothrombin (DCP) (2.58; 1.03-7.14) were significantly correlated with local recurrence, and multiple tumors (10.64; 1.76-93.75) was significantly correlated with intrahepatic distant recurrence.

Conclusions: Heterogeneous lipiodol uptake, high serum DCP and multiple tumors are risk factors for recurrence in patients with early HCC who have undergone palliative TACE.

Keywords: hepatocellular carcinoma, small HCC, TACE, early stage HCC

Introduction

Hepatocellular carcinoma (HCC) has become increasingly detected at an early stage with the growing use of surveillance systems. The guidelines established by the American Association for the Study of Liver Disease (AASLD) [1], European Association for the Study of the Liver (EASL) [2], and the Japanese "Evidence-Based Guidelines" recommend local treatment [3-4], such as radiofrequency ablation (RFA) or operation, for HCCs numbering 3 or fewer tumors of up to 3 cm with good liver functional reserve and performance status. Additionally, RFA combined with transcatheter arterial chemoembolization (TACE) has been reported to be an efficient and safe treatment that provides an overall survival rate similar to those achieved with surgical resection [5-7]. If HCC is hypervascular tumor, most cases of HCCs numbering 3 tumors or fewer of up to 3 cm are often subjected to sequential TACE followed by RFA, percutaneous ethanol injection therapy (PEIT), or operation regardless of the size because TACE is expected to enhance the efficacy of local therapy by reducing arterial blood flow [8].

Occasionally, several factors such as poor liver functional reserve, difficult location for RFA treatment, and presence of severe associated diseases in the

elderly or those rejecting treatment result in the selection of only TACE, even in candidates for local therapies. TACE is known to be effective for inoperable HCC [9-10]; however, little information has been reported about TACE for early stage HCC and it is hard to decide whether to perform additional treatment following TACE in these difficult conditions.

The objective of this retrospective cohort study was to determine whether only TACE for HCC numbering 3 tumors or fewer of up to 3 cm could control HCC by revealing the recurrence rate and the risk factors of local or intrahepatic distant recurrence in such cases.

Subjects and Methods

Patients

Patients were enrolled from among 1,560 newly diagnosed HCC patients who were admitted to Okayama University Hospital between 2002 and 2010. Inclusion criteria were as follows: (1) no previous treatment of HCC, (2) 3 or fewer nodules of up to 3 cm (early stage HCC), (3) at least one nodule treated only by TACE as an initial treatment, (4) no planned local treatment performed such as RFA, PEIT, or operation within 30 days of TACE, (5) no vascular invasion, and (6) no extrahepatic metastasis. Exclusion criteria were (1) complete cures of all nodules with RFA, PEIT, or operation and (2) follow-up period less than 1 year. Finally, 43 patients was selected and enrolled in this study. Of these patients, 6 died in the follow-up period. Five of these died due to liver disease and 1 died of heart failure. Informed consent was obtained from all patients in this study for the use of their clinical data. The study protocol conformed to the ethical guidelines of the World Medical Association Declaration of Helsinki and was approved by the ethical committee of the institute (approval # 458).

Diagnosis

HCC was diagnosed in accordance with AASLD guidelines. The diagnostic criteria for HCC via imaging were based on hyperattenuation at the artery phase, hypoattenuation at the portal phase by dynamic computed tomography (CT) or magnetic resonance imaging (MRI), and tumor stain on angiography. Sonazoid ultrasonography (US) and/or Gadolinium ethoxybenzyl magnetic resonance imaging (Gd-EOB-MRI) was performed in 30 (69.8%) cases. When we could not diagnose HCC by only imaging, fine needle biopsy using abdominal US was performed as histological proof (3 cases). Recurrence of HCC was diagnosed in the same way at the initial diagnosis.

Treatment

TACE was performed using the Seldinger technique followed by arterial embolization. After introducing a 4-Fr catheter through the femoral artery, hepatic arteriography and superior mesenteric arterial portovenography were performed to evaluate portal flow and location of tumors. When portal flow was sufficient, a 1.8-Fr or a 2.0-Fr microcatheter was placed in the feeding arteries at the closest point from the HCC. An emulsion consisting

of 30 to 60 mg of epirubicin (Kyowa-Hakko, Japan) and 2 to 6 ml of iodized oil (Lipiodol Ultrafluid; Terumo, Japan) was injected into the artery supplying blood to the tumor, followed by embolization with 1mm gelatin sponge particles (Gelfoam; Nihonkayaku, Japan). After embolization, CT angiography was performed to determine the extent of vascular occlusion and to assess blood flow in other arterial vessels. Patients were observed carefully, and analgesia (Pentazocine; Astellas, Japan) was administered if necessary.

Lipiodol uptake was divided into two groups of homogeneous and heterogeneous by plain CT after TACE. Homogeneous was defined by complete uptake of lipiodol in the tumor without any defect, and CT value in these cases was over 200 Hounsfield Unit. The rest was considered as heterogeneous. Two experienced investigators (K.N. and H.O.) reviewed the images of CT and evaluated the lipiodol uptake. If the two investigators had different diagnoses, they discussed the difference and reached agreement.

Follow up

Patients were assessed every one to three months by serum biochemistry, dynamic CT, dynamic MRI, or US. Local recurrence was defined as the appearance of viable tumor in contact with or inside the treated area. Intrahepatic distant recurrence was defined as the occurrence of a new HCC in the liver that did not meet the definition of local recurrence. When recurrence was detected, TACE, RFA, PEIT, or surgical resection was performed depending on the condition of the recurrence and background liver function. Patients were followed until loss to follow up, death, or January 31, 2011.

Statistical analysis

The following 12 parameters were used for analyzing the risk factors for recurrence: age, sex, viral markers (hepatitis B virus surface antigen and hepatitis C virus antibody), alcohol intake, liver function, size of tumors, number of tumors, location of tumors (within 10 mm of the surface of the liver or not), serum tumor markers (alpha-fetoprotein (AFP) and des-gamma-carboxy prothrombin (DCP)), and the status of lipiodol uptake.

Recurrence rates were estimated using the Kaplan-Meier method and

differences between groups were compared using the log-rank test. The Cox proportional hazard model was used to analyze the predisposing factors for recurrence. All statistical analyses were performed using JMP version 9 (JMP Japan, Tokyo, Japan). All reported P values are 2-sided, with $P<0.05$ considered statistically significant.

Results

Patient background

A total of 43 patients met the criteria of this study. The total number of HCC nodules was 54. There were 27 males (63%) and 16 females (37%) aged 50-85 years (mean: 71 years), and 34 patients (79%) were infected with hepatitis C virus and 6 (14%) with hepatitis B virus. Twenty-three patients (53%) were habitual drinkers. Thirty-four patients (79%) had a single tumor in the initial treatment. Thirty-six patients (84%) had recurrence (Table 1). Eleven (26%), 23 (53%), and 9 (21%) patients were treated with only TACE because of poor liver functional reserve, difficult location for RFA, and old age, respectively. Among 11 patients who had poor liver function, 1 patient was Child C and 10 patients was Child B. Although the Japanese guideline for treatment of HCC indicates that RFA/Operation was recommended for the treatment of small HCC with Child A/B stage, these 10 Child B patients had worse condition like uncontrollable ascites or low albumin so that it was quite difficult to perform RFA/Operation. Among 23 patients who had difficult location for RFA, the nodules were located beside portal vein in 5 patients, digestive tract in 4 patients, gallbladder in 4

patients, inferior vena cava in 3 patients, collateral veins on the surface of liver in 3 patients, bile duct in 3 patients, and beside heart in 1 patient.

Recurrence rate

Local recurrence and intrahepatic distant recurrence were observed in 29 patients and 14 patients, respectively, and in these cases, 7 involved both local and intrahepatic distant recurrences at the same time.

The total recurrence rates at 3 months, 6 months, and 1 year were 20.9%, 35.3%, and 68.5%, respectively. The local recurrence rates and intrahepatic distant recurrence rates at 3 months, 6 months, and 1 year were 18.6%, 33.4%, and 61.8%, and 2.8%, 2.8%, and 10.2%, respectively (Fig. 1). Thirteen patients had local recurrences within 180 days. Eleven patients and 11 patients received RFA and TACE for the therapy of local recurrence, respectively. Eight patients, 5 patients, and 1 patient received RFA, TACE, and PEIT for the therapy of intrahepatic distant recurrence, respectively. No difference of the therapies was observed between the local recurrence group and the distant recurrence group.

Factors related to local recurrence

Among 12 factors analyzed, heterogeneous lipiodol uptake (risk ratio 3.19; 95% confidence interval 1.41-7.90; P=0.004) and high serum DCP (2.37; 1.06-5.83; 0.034) were correlated with local recurrence by univariate analysis. The factor of location was not associated with local recurrence on univariate analysis. Factors exhibiting significance in the univariate analysis and reported to be correlated with recurrence, namely, DCP, age, number of HCC, liver function, size of HCC, extent of lipiodol uptake, HCV, and location of HCC, were further analyzed using the Cox multivariate proportional hazard model [11-20]. On multivariate analysis, only heterogeneous lipiodol uptake (risk ratio 3.38; 95% confidence interval 1.14-10.60; P=0.027) and high serum DCP (2.58; 1.03-7.14; 0.042) were significantly correlated with local recurrence (Table 2).

Factors related to intrahepatic distant recurrence

In the same way, among 12 factors analyzed, the factor of multiple tumors (3.98; 1.02-13.50; 0.047) was correlated with intrahepatic distant recurrence by univariate analysis. On multivariate analysis with serum DCP, age,

tumor number, Child-Pugh score, tumor size, lipiodol uptake, HCV, and tumor location, multiple tumors (10.64; 1.76-93.75; 0.010) was significantly correlated with recurrence (Table 3).

Discussion

While RFA is considered as the first choice for the treatment of early stage HCC, TACE could be another option when RFA is unsuccessful or unfeasible. Livraghi et al. reported that RFA was not feasible in 6.0% of patients because of a high-risk tumor location or poor detection on ultrasonography [21]. However, it is hard to decide to treat these patients with additional locoregional therapy because there have been few reported studies examining the outcomes of these patients in detail.

In this study, the clinical course of 43 patients treated with palliative TACE for HCC numbering 3 tumors or fewer of up to 3 cm was examined. Over 80% of the patients (36/43, 84%) had recurrence and most of them (29/36, 80%) exhibited local recurrence. The rate was higher than that of local ablation. The recurrence rates of the patients treated with RFA/operation at 3 months, 6 months, and 1 year in our institution during the same period were 2.8%, 9.6%, and 24.5%, respectively.

Cases with heterogeneous lipiodol uptake and high serum DCP were significantly correlated with local recurrence, whereas multiple tumor was significantly correlated with intrahepatic distant recurrence.

The risk factors for recurrence after TACE in patients with HCC have been described in several reports. These include extent of lipiodol uptake, location of HCC, size of HCC, tumor markers, viral markers, number of HCC, age, and liver function [11-20]. However, most of these studies were on TACE for advanced HCC. In this study, we examined the risk factors for early stage HCC and revealed that only the extent of lipiodol uptake and serum DCP level were correlated with local recurrence, which is the most common type of recurrence after TACE. In cases of early stage HCC, most HCC might be highly differentiated and less invasive so that the tumor can be controlled merely by complete obstruction of blood supply. Then, only high DCP is an additional risk factor because HCC with high DCP showed a poorer differentiation grade [22]. The results suggested that it is better to treat early stage HCC showing high serum DCP as well as incomplete lipiodol uptake not only with TACE but also with additional locoregional treatment if possible.

On the other hand, intrahepatic distant recurrence was observed in cases with multiple tumors, indicating that some of these tumors were intrahepatic metastases and that undetectable small HCC might have

already existed.

Meta-analysis showed that chemoembolization could improve the survival of well-selected patients with unresectable HCC [23]; in addition, there is a report that the effect was observed even in HCC with poor liver function [24]. However, the efficacy of TACE for HCC at an early stage has not been well elucidated. Although we could not show the survival benefit of TACE in early stage HCC, to the best of our knowledge, this is the first report about the outcome of TACE for HCC numbering 3 tumors or fewer of up to 3 cm.

While new technologies such as artificial pleural effusion, ascites or Real-time Virtual Sonography (RVS) increase the number of patients eligible for RFA, the age of HCC patients gradually increases so that more patients would be excluded from observation when considering the treatment guideline algorithm of HCC owing to the presence of complications and poor performance status, among other factors. Eventually, we could not avoid facing the selection of TACE instead of RFA and operation. This study helped us to decide if additional treatment should be considered according to the treatment algorithms even in cases with difficult conditions.

In conclusion palliative TACE for HCC numbering 3 tumors or fewer of up

to 3 cm could be effective. Lipiodol uptake, serum DCP and number of tumors (≥2) are the most important factors to control these HCC numbering 3 tumors or fewer of up to 3 cm with palliative TACE. Heterogenous uptake should not be left untreated after TACE as much as possible.

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Table 1　Clinical background of 43 patients

Demographic variables		
Sex (male)		27 (63%)
Age (years)		71 (50-85)
Etiology	HCV	34 (79%)
	HBV	6 (14%)
	HCV+HBC	2 (4.7%)
	Alcohol	23 (53%)
	Unknown	1 (2%)
Tumor size (mm)		18 (6-30)
Number of tumors	1	34 (79%)
	2	7 (16%)
	3	2 (5%)
Location (distance from surface of the liver)	≤10 mm	28 (65%)
Recurrence	local	22 (52%)
	distant	7 (16%)

	local+distant	7 (16%)
	no recurrence	7 (16%)
Lipiodol uptake	homogeneous	23 (53%)
	heterogeneous	20 (47%)
AFP (ng/mL)		124.1 (1.6-1539)
DCP (mAU/mL)		157.7 (12-3450)
Total bilirubin (mg/dL)		1.09 (0.37-3.13)
Albumin (g/dL)		3.47 (2.4-4.42)
ALT (IU/L)		43.5(13-147)
AST (IU/L)		55.2(23-119)
Child-Pugh score	(A/B/C)	32/10/1

Numbers in the tables are shown as median (range) unless otherwise noted.

HCV, positive for hepatitis C virus antibody; HBV, positive for hepatitis B virus antigen; AFP, alpha-fetoprotein; DCP, des-gamma-carboxy prothrombi; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Table 2　Risk factors for local recurrence after TACE

Variables	Univariate		Multivariate	
	Risk ratio (95% CI)	P-value	Risk ratio (95% CI)	P-value
AFP (>10 ng/mL)	1.46(0.69-3.23)	0.328		
DCP (>28 mAU/mL)	2.37(1.06-5.83)	0.034*	2.58(1.03-7.14)	0.042*
Age (≥75 years)	1.04(0.50-2.24)	0.900	1.16(0.42-3.11)	0.769
Tumor number (≥2)	1.72(0.66-4.04)	0.249	1.18(0.37-3.26)	0.759
Child-Pugh score (≥7)	1.25(0.51-3.74)	0.650	1.65(0.60-5.43)	0.347
Tumor size (≥20 mm)	1.58(0.74-3.37)	0.230	1.66(0.70-3.94)	0.245
Lipiodol uptake (heterogeneous)	3.19(1.41-7.90)	0.004*	3.38(1.14-10.60)	0.027*
Sex	1.01(0.48-2.23)	0.976		
HCV	2.07(0.74-4.99)	0.153	2.09(0.55-7.65)	0.271
HBV	0.91(0.32-3.85)	0.882		
Alcohol	0.99(0.47-2.14)	0.975		
Location (within 10 mm from	0.66(0.31-1.47)	0.302	0.80(0.26-2.37)	0.687

the liver surface)

TACE, transcatheter arterial chemoembolization; 95% CI, 95% confidence interval; *, significant value. Other abbreviations are the same as described in Table 1.

Table 3　Risk factors for distant recurrence after TACE

Variables	Univariate		Multivariate	
	Risk ratio (95% CI)	P-value	Risk ratio (95% CI)	P-value
AFP (>10 ng/mL)	1.22(0.40-3.85)	0.721		
DCP (>28 mAU/mL)	1.19(0.37-3.83)	0.765	1.73(0.44-7.41)	0.425
Age (≥75 years)	2.07(0.67-7.67)	0.211	4.30(0.88-32.60)	0.073
Tumor number (≥2)	3.98(1.02-13.50)	0.047*	10.64(1.76-93.75)	0.010*
Child-Pugh score (≥7)	0.70(0.21-3.21)	0.611	0.71(0.16-4.21)	0.688
Tumor size (≥20 mm)	1.09(0.33-3.34)	0.879	1.50(0.33-7.08)	0.594
Lipiodol uptake (heterogeneous)	1.99(0.61-6.53)	0.250	1.32(0.08-15.76)	0.834
Sex	2.30(0.76-7.66)	0.138		
HCV	0.45(0.11-3.04)	0.360	0.64(0.08-7.19)	0.688
HBV	0.49(0.12-3.27)	0.405		
Alcohol	0.60(0.19-1.83)	0.365		
Location (within 10 mm from	0.54(0.17-1.84)	0.304	0.78(0.04-14.50)	0.864

the liver surface)

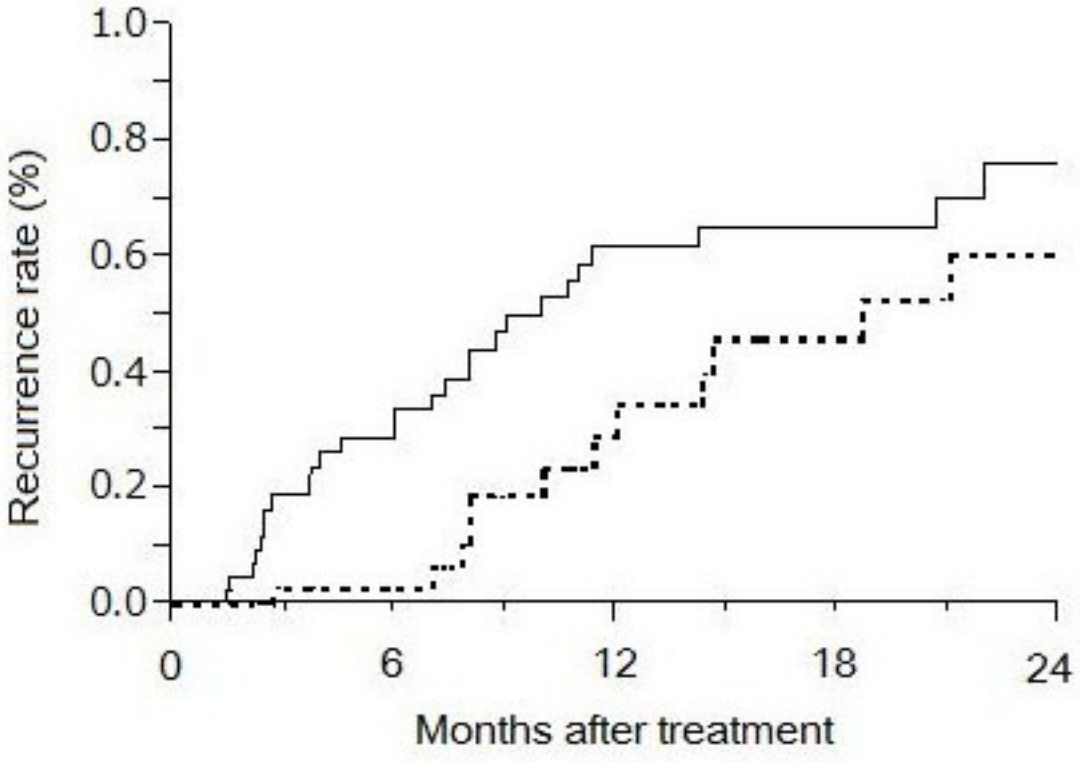
Abbreviations are the same as described in Table 2.

Figure legend

Fig. 1 Local and distant recurrence after transcatheter arterial chemoembolization.

The local recurrence rates (solid line) and intrahepatic distant recurrence rates (dotted line) at 3 months, 6 months, and 1 year were 18.6%, 33.4%, and 61.8%, and 2.8%, 2.8%, and 10.2%, respectively.

Fig.1


1.0
0.8
0.6
0.4
0.2
0.0
Recurrence rate (%)
0
6
12
18
24
Months after treatment

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