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The radiological prognostic factors of transcatheter arterial chemoembolization to hepatocellular carcinoma

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Abstract

Transcatheter arterial chemoembolization (TACE) is the recommended treatment modality for intermediate stage hepatocellular carcinoma (HCC). The aim of this study was to determine the HCC radiological characteristics associated with prognosis of patients with intermediate stage HCC receiving TACE. Patients with HCC BCLC stage B from January 2005 to December 2009 were collected. According to mRECIST criteria, patients with complete response and partial response were assigned to the objective response (OR) group, while those with stable disease and progressive disease were assigned to the nonobjective response (non-OR) group. Among a total of 128 enrolled patients, there were 66 (51.6%) and 62 (48.4%) patients in the OR group and non-OR group, respectively. The clinical parameters in the two groups were similar, although HCC size was smaller in the OR group. Logistic analysis found combined radiological characteristics including complete lipiodol retention, tumor feeding artery blockage, and no residual tumor blush were significant correlated with achievement of OR (odds ratio 2.46, 95% CI 1.08–5.61, $P = .032$). However, no radiological characteristics had significant strength to predict overall survival. Patients with OR after TACE had significantly longer survival time than those with non-OR. Combined characteristics of complete lipiodol retention, tumor feeding artery blockage, and no residual tumor blush had a positive impact on OR in TACE. In patients receiving TACE, those who achieved OR had a better overall survival.

Abbreviations: CR = complete response, HCC = hepatocellular carcinoma, OR = objective response, PD = progressive disease, PR = partial response, SD = stable disease, TACE = Transcatheter arterial chemoembolization.

Keywords: Hepatocellular carcinoma, radiological characteristics, transcatheter arterial chemoembolization

1. Introduction

Hepatocellular carcinoma (HCC) is the most common cancer worldwide and predominantly develops in patients with liver cirrhosis.[1] The Barcelona Clinic Liver Cancer (BCLC) staging system integrates tumor characteristics and performance status with liver function and links them to evidence-based therapeutic options.[2] For BCLC stage B, or intermediate stage HCC, transcatheter arterial chemoembolization (TACE) is the recommended treatment modality.[3] The advantages of TACE include increasing the regional concentration of chemotherapeutic agents and depriving the blood supply to cancer tissue by means of embolic occlusion to maximize the killing of cancer cells while sparing healthy liver tissue and reducing systemic side effects.[4] TACE is, by far, the most common technique used to treat unresectable HCC.[1]

According to previous reports, TACE slows cancer progression and improves survival, compared to those treated with best supportive care, in patients with unresectable HCC.[5–7] However, the reported therapeutic outcomes among these patients are still variable.

The aim of our study was to determine the HCC radiological characteristics associated with the prognosis of patients with intermediate stage HCC receiving TACE as the primary treatment.

2. Methods

Newly diagnosed HCC patients, diagnosed in accordance with the AASLD guideline,[8] from January 2005 to December 2009 were retrospectively enrolled. The enrollment criteria were HCC BCLC stage B and TACE as the primary treatment. The

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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exclusion criteria were HCC BCLC stages A, C, and D, poor performance status, or loss to follow-up within the following day. The study project is approved by the Institutional Review Board of Taichung Veteran General Hospital (CE18315A).

The clinical parameters, including age, gender, liver function, such as total bilirubin, alanine aminotransferase, alpha-fetoprotein, presence of chronic HBV and HCV, cirrhotic Child-Pugh stage, and tumor size, as well as the numbers of enrolled subjects were collected. These patients were also subclassified as within or beyond the up-to-seven criteria,[9] defined as the sum of the diameter of the largest HCC and numbers of tumors.

2.1. TACE technique

TACE was performed after the patients provided written informed consent. A 5 or 6-French sheath was inserted into the common femoral artery. Digital subtraction angiography of the celiac and superior mesenteric arteries was performed to assess the portal vein patency, vascular anatomy, and tumor vascularity. All angiographic images were sent to a picture archiving and communication system. Following the initial arterial assessment, the catheter was advanced into the lobar or segmental hepatic artery supplying the tumor. If the initial 4 Fr or 5 Fr diagnostic catheter could be advanced into the optimal position, it was used for the TACE infusion and, in cases in which more selective catheterization was required, a 2.9 Fr microcatheter of Progreat (Terumo, Tokyo, Japan) was used. In general, the TACE infusion point was chosen to enable selective tumor embolization. However, if there were separate arterial feeders, or a discrete blood supply could not be identified, a right or left hepatic arterial infusion was performed. If concern regarding hepatic synthetic function was present, a selective approach was chosen. Once the lesion and its blood supply were identified, an emulsion of 10 to 50 mg epirubicin (Pfizer, New York) and 2 to 60 mL lipiodol (Guerbet, Aulnay sous Bois, France) was injected under fluoroscopic guidance into the arterial supply of the tumor. The administered doses of chemotherapy agents were adjusted in patients with liver or renal dysfunction, leukopenia, and thrombocytopenia. Administration of the emulsion was followed by embolization with a slurry of Spongostan (Ethicon, New Jersey) until stasis was achieved.

2.2. Radiological characteristics

The radiological findings, such as intratumoral necrosis, which was defined as a non-enhancing low-attenuating region with ill-defined margins, and intratumoral hemorrhage, which was defined as non-enhancing high-attenuating regions with well-defined margins, were recorded. For superselective TACE, the tip of the catheter was placed into the hepatic arterial branch afferent to the segment or subsegment sites where the tumor was located. In nonselective TACE, a lobar technique was carried out in the case of a nodule fed by multiple arteries. On the post-TACE angiogram, tumor-feeding artery blockage was defined according to whether or not tumor-supplying arteries could be visualized. Presence of residual tumor blush was defined as either unchanged tumor stain or a reduction in intensity or size compared with the pre-TACE image. According to post-TACE CT images, depending on the pattern of tumor covered by lipiodol, complete lipiodol retention was defined as more than 90% lipiodol retention and no peripheral filling defects..

2.3. Assessment of responses following TACE

Patients were assessed every 2 months by dynamic imaging study until the endpoints were reached, including death, disease progression, or treatment failure after TACE. The assessment of the best tumor response was done according to the modified RECIST (mRECIST) criteria[10] with four response categories: complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). The patients with CR or PR were categorized into the objective response (OR) group and those with SD or PD were categorized into the nonobjective response (non-OR) group.

2.4. Statistical analysis

Data are expressed as standard deviation of the mean for each of the measured parameters. The positive rates of each stratified group are both expressed as a percentage of the total patient number. Statistical comparisons were made using Pearson's chi-square test in order to compare the effects of the positive rate of each stratified group. Independent *t* test was used to analyze continuous variables. A *P* value below .05 was considered statistically significant. Logistic regression with multivariate analysis was applied to determine the radiological patterns affecting patients' therapeutic responses, as shown by the odds ratio (OR) with a 95% confidence interval (CI). The multivariate Cox's regression was carried out to examine the strength of association between the radiological variables and the survival outcomes following TACE, as shown by the hazard ratios (HR) with a 95% CI.

2.5. Results

A total of 128 patients were enrolled, and the characteristics of these cases are shown in Table 1. The median age was 70.0 years, and male predominance (76.6%) was noted. Fifty-six patients (43.8%) and 41 patients (32.0%) had chronic HBV and HCV infection. Ninety-three cases (72.7%) and 35 cases (27.3%) belonged to Child-Pugh stages A and B, respectively. The median tumor nodules number was 4.2, and the median tumor diameter was 7.9 cm.

The outcomes of the enrolled patients after TACE are recorded. The numbers of cases with CR, PR, SD, and PD were 24 (18.8%), 42 (32.8%), 30 (23.4%), and 32 (25.0%) respectively. Overall, among patients who received TACE, there were 66 patients (51.6%) in the OR group and 62 (48.4%) patients in the non-OR group. The average number of TACE sessions required to achieve OR was 1.4 times (range 1–6). The overall survival of the enrolled patients was 20.6 ± 13.2 months, and the 1-year and 2-year survival rates were 66.4% and 44.5%, respectively.

The characteristics of the OR group and the non-OR group are also displayed in Table 1. Age, gender, ratio of chronic viral hepatitis infection, Child-Pugh stage, and laboratory parameters, including total bilirubin, alanine aminotransferase, and alpha-fetoprotein in the two groups were similar. However, the patients in the OR group had a significantly smaller size of HCC than those of the non-OR group (mean tumor size, 6.5 vs 9.5 cm, $P = .001$). The rate of the within up-to-seven criteria was 22.7% in the OR group and 6.5% in the non-OR group. The difference was significant ($P = .006$).

A comparison of the positive rates of radiological characteristics in the OR group and the non-OR group is also assessed. The OR group had a significantly lower rate of intratumoral necrosis (36.4% vs 54.8%, $P = .036$), a significant higher rate of tumor-feeding artery blockage (83.3% vs 64.5%, $P = .015$) and no residual tumor blush (83.3% vs 61.3%, $P = .005$), compared with the non-OR group.

Logistic analysis of radiological characteristics, after adjustment for age, gender, Child-Pugh stage, tumor numbers, and size, in the OR group is shown in Table 2. Pre-TACE characteristics, including intratumoral necrosis (OR 0.86, 95% CI: 0.34–2.18, $P = .751$), intratumoral hemorrhage (OR 0.98, 95% CI: 0.25–3.83,

Table 1

The general data and radiological characteristics of all patients and the subgroups.

	All (N=128)		OR (N = 66, 51.6%)		Non-OR (N = 62, 48.4%)		*P* value
Variables	**M ± SD**	**N %**	**M ± SD**	**N %**	**M ± SD**	**N %**	
	70.0 ± 13.0		70.4 ± 13.8		69.5 ± 12.2		.681a
Age (yr)		98 (76.6%)		49 (74.2%)		49 (79.0%)	.523b
Gender (male)							.132b
Viral hepatitis		56 (43.8%)		26 (39.4%)		30 (48.4%)	
HBV		41 (32.0%)		27 (40.9%)		14 (22.6%)	
HCV		4 (3.1%)		1 (1.5%)		3 (4.8%)	
HBV/HCV		27 (21.1%)		12 (18.2%)		15 (24.2%)	
nil							
Cirrhosis, Child-Pugh							.985b
A		93 (72.7%)		48 (72.7%)		45 (72.6%)	
B		35 (27.3%)		18 (27.3%)		17 (27.4%)	
Total bilirubin (mg/dL)	B ± 0.9		1.1 ± 0.7		1.3 ± 1.2		.326a
ALT (u/L)	64.3 ± 67.6		57.9 ± 43.0		71.2 ± 86.3		.275a
AFP ($\times 10^3$ ng/mL)	3.4 ± 8.8		2.5 ± 7.8		4.4 ± 6.8		.434a
HCC numbers	4.2 ± 3.2		3.7 ± 2.8		4.7 ± 3.5		.070a
HCC size (cm)	7.9 ± 4.0		6.5 ± 2.9		9.5 ± 4.4		.001a
Within up-to-seven criteria				15 (22.7%)		4 (6.5%)	.006b
Radiological characteristics							
Intratumoral necrosis		58 (45.3%)		24 (36.4%)		34 (54.8%)	.036b
Intratumoral hemorrhage		13 (10.1%)		5 (7.6%)		8 (12.9%)	.319b
Superselective TACE		14 (10.9%)		7 (10.6%)		7 (11.3%)	.901b
Complete lipiodol retention		95 (74.2%)		52 (78.8%)		43 (69.4%)	.223b
Tumor feeding artery blockage		95 (74.2%)		55 (83.3%)		40 (64.5%)	.015b
No residual tumor blush		93 (72.6%)		55 (83.3%)		38 (61.3%)	.005b

a*P* values were analyzed with independent *t* test;

bPearson's Chi-square test

AFP = alpha-fetoprotein, ALT = alanine aminotransferase, HBV = hepatitis B, HCC = hepatocellular carcinoma, HCV = hepatitis C, M = mean, N = number of patients, SD = standard derivation, TACE = transcatheter arterial chemoembolization.

Table 2

The strength of association between radiological characteristics and objective tumor response.

Variables	N	OR	(95% CI)	*P* value
		1.00	(Reference)	
Intratumoral necrosis	58	0.86	(0.34–2.18)	.751
Intratumoral hemorrhage	13	0.98	(0.25–3.83)	.977
Superselective TACE	14	0.64	(0.19–2.18)	.482
Complete lipiodol retention (A)	95	1.65	(0.67–4.10)	.279
Tumor feeding artery blockage (B)	95	1.72	(0.61–4.86)	.304
No residual tumor blush (C)	93	2.21	(0.81–6.01)	.118
(A) + (B)	50	1.72	(0.69–4.31)	.246
(A) + (C)	56	0.81	(0.27–2.41)	.707
(B) + (C)	60	1.72	(0.61–4.86)	.304
(A) + (B) + (C)	29	2.46	(1.08–5.61)	.032

Analyzed with Logistic regression adjusted with age, gender, cirrhotic Child-Pugh stage, HCC numbers and size.

CI = confidence interval, N = number of patients, OR = odds ratio, TACE = transcatheter arterial chemoembolization.

Table 3

The strength of association between radiological characteristics and overall survival.

Variables	N	HR	(95% CI)	*P* value
		1.00	(Reference)	
Objective response	66	1.60	(1.03–2.47)	.035
Intratumoral necrosis	58	0.91	(0.57–1.46)	.694
Intratumoral hemorrhage	13	0.60	(0.33–1.11)	.105
Superselective for TACE	14	0.67	(0.36–1.28)	.227
Complete lipiodol retention (A)	95	1.02	(0.64–1.64)	.910
Tumor feeding artery blockage (B)	95	1.19	(0.67–2.13)	.537
No residual tumor blush (C)	93	1.20	(0.69–2.08)	.510
(A) + (B)	50	1.01	(0.63–1.64)	.957
(A) + (C)	56	1.07	(0.62–1.87)	.802
(B) + (C)	60	1.19	(0.67–2.12)	.537
(A) + (B) + (C)	29	1.17	(0.76–1.80)	.484

Analyzed with Logistic regression adjusted with age, gender, cirrhotic Child-Pugh stage, HCC numbers and size.

CI = confidence interval, HR = hazard ratio, N = number of patients, TACE = transcatheter arterial chemoembolization.

Absence of Bias in NSQIP Benchmarking

P = .977), and super-selection for TACE (OR 0.64, 95% CI: 0.19–2.18, *P* = .482), had a negative impact on achievement of OR after TACE, but the strength of these associations was non-significant. In contrast, post-TACE image findings, such as complete lipiodol retention (OR 1.65, 95% CI: 0.67–4.10, *P* = .279), tumor-feeding artery blockage (OR 1.72, 95% CI: 0.61–4.86, *P* = .304), and no residual tumor blush (OR 2.21, 95% CI: 0.81–6.01, *P* = .118), had a positive impact on OR after TACE, although the correlation strength still lacked significance. However, for subjects whose findings for complete lipiodol retention, tumor feeding artery blockage, and no residual tumor blush were all positive had a significantly greater tendency to achieve OR after TACE than those without (OR 2.46, 95% CI: 1.08–5.61, *P* = .032).

Logistic analysis of radiological characteristics, after adjustment for age, gender, Child-Pugh stage, tumor numbers, and size, and their effects on overall survival of the enrolled patients are listed in Table 3. The achievement of OR had a significant beneficial impact on overall survival (HR 1.60, 95% CI: 1.03–2.47, *P* = .035). As shown in Figure 1, The average survival time of the OR group was 25.8 ± 12.1 months compared with 15.1 ± 12.1 months in the non-OR group. However, other radiological characteristics did not have sufficient statistical strength to predict the overall survival of the enrolled patients in our study.

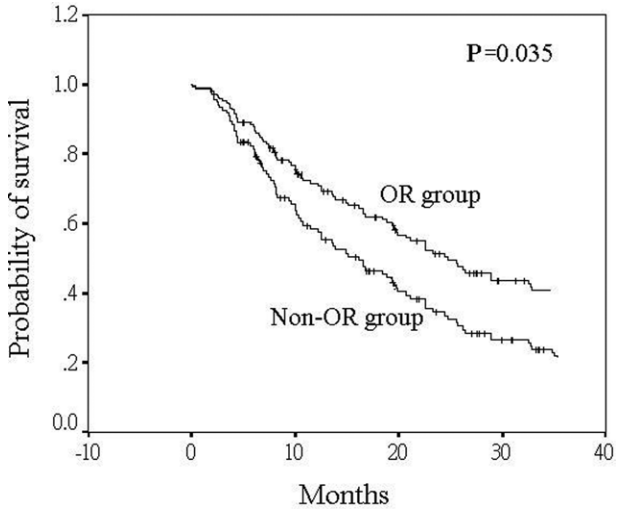

Figure 1. Comparison of overall survival between the OR group and non-OR group. OR = objective response.

3. Discussion

HCC is a common type of primary liver malignancy worldwide. However, only 30% to 40% of patients are diagnosed at an early stage, which means that most cases can not benefit from curative therapies.[11] Recommended treatment modalities for unresectable HCC include locoregional therapy, including TACE, and systemic therapy, including sorafenib. According to the BCLC staging system, TACE is the standard treatment for BCLC stage B HCC, while sorafenib is the recommended care for BCLC stage C HCC.[2]

However, since the characteristics of the patients with BCLC stage B HCC are heterogeneous, the therapeutic outcomes of TACE in these subjects are also variable. For example, a study conducted in Asia and a randomized control study in Europe reported a 3-year survival rate of only 26% to 29%,[7,12] but in another Asian cohort study 3-year survival was as high as 55%.[13] In our enrolled patients, most cases belonged to Child-Pugh stage A (72.2%), and the 1-year and 2-year survival rates were 66.4% and 44.5%, respectively.

Radiological response assessment plays a central role in the evaluation of treatment success following TACE. The modified RECIST retains the concept of measuring the viable part of residual tumor tissue, but recommends the uni-dimensional assessment of the longest viable tumor diameter and the numeric definitions of response according to RECIST.[10] Determination of objective treatment response following TACE by measuring residual viable tumor tissue, defined as CR or PR, has been proven to be a surrogate marker of overall survival.[15,16] A previous study enrolled 332 Koreans with intermediate stage HCC who underwent TACE and found a clear prognostic difference among CR (HR 1), PR (HR 2.75, $P < .001$), SD (HR 6.32, $P < .001$), and PD (HR 16.06, $P < .001$).[15]

Moreover, the number and size of HCC are significantly correlated with the radiological response after TACE. For example, radiological CR rates of up to 77% were achieved in tumors less than 2 cm in size, but rates of only 25% were attained in tumors with diameters greater than 5 cm after the first TACE.[16,17] Our results found the radiological responses including CR, PR, SD, and PD were 18.8%, 32.8%, 23.4%, and 25.0%, respectively. A total of 66 patients (51.6%) achieved OR following TACE. Furthermore, the patients in the OR group had a smaller tumor size and fewer HCC tumors. The subjects who met the up-to-seven criteria more readily achieved radiological OR following TACE (22.7% vs 6.5%, $P = .006$).

The goals of chemoembolization are to deliver a highly concentrated dose of chemotherapy to tumor cells, to prolong the contact time between the chemotherapeutic agents and the cancer cells, and to minimize systemic toxicity. Intratumoral necrosis of HCC on a dynamic image could be caused by rapid cell proliferation in the tumor center, which increases the interstitial pressure and leads to compressive closure of tumor capillaries and regression of neovascularization. This phenomenon is often observed in poorly differentiated and larger HCC with diminished arterial blood flow.[18]

The characteristics of lipiodol retention by tumor tissue has been associated with tumor response and could also be considered a prognostic marker.[19] A heterogeneous and incomplete lipiodol pattern was correlated with a higher risk of recurrence,[20,21] and the presence of lipiodol in at least 75% of the lesion was a predictor of improved patient survival.[22] Incomplete lipiodol deposition appearance may be due to incomplete catheterization and treatment injection in all tumor feeders, resulting in lipiodol particles being unable to penetrate the smallest tumor capillary vessels.

Superselective TACE is advocated by all guidelines as the method of choice to minimize liver damage, but the term seems to be poorly defined and its application is difficult to monitor. The issue of selective catheter placement (lobar vs segmental) during chemoembolization remains somewhat controversial. Previous data suggest that injectable volumes of chemotherapy and long-term arterial patency were improved by embolizing the tumor-feeding vessels only after the entire dose of chemotherapy had been delivered. These results may have a positive effect on the success of chemoembolization because delayed embolization allows multiple TACE sessions through maintained arterial patency.[23]

Logistic analysis of our results found that a combination of all three radiological characteristics, that is, complete lipiodol retention, tumor-feeding artery blockage, and no residual tumor blush, significantly improved the rate of OR after TACE (HR 2.46, 95% CI: 1.08–5.61, $P = .032$), but the effect on overall survival was non-significant (HR 1.17, 95% CI: 0.76–1.80, $P = .484$). The reason that the aforementioned radiological characteristics did not significantly improve overall survival might be due to the application of alternative cancer therapies, such as sorafenib, radiotherapy, or conventional chemotherapy, in subjects with poor initial response to TACE.

An objective tumor response after treatment has been identified as an independent prognostic factor.[26,27] In the literature, the best overall survival was often observed in patients with objective tumor response, and was better than that in patients who showed persistent non-response. Our results were similar. The achievement of OR, compared with persistent non-OR, significantly improved the overall survival (HR 1.60, 95% CI: 1.03–2.47, $P = .035$).

Our study had a few limitations. First, this study design was retrospective, and selection or reporting bias may have existed. Second, epirubicin and lipiodol dosage of TACE were not recorded, and the dose-tumor response relationship was not assessed. Third, patient tolerability to TACE and the operator-dependent endpoints were variable. Fourth, combined or subsequent alternative tumor therapy, including sorafenib, radiotherapy or chemotherapy, were not taken into consideration. Further prospective studies that include a higher number of cases and more variables is necessary.

4. Conclusion

A combination of radiological characteristics, complete lipiodol retention, tumor-feeding artery blockage, and no residual tumor blu sh, had a positive impact on the radiological objective tumor response after TACE. Objective tumor response significantly improved the overall survival of these patients.

Author contributions

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Writing – review & editing: Sheng Shun Yang, Teng-Yu Lee.

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