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ORIGINAL ARTICLE

Angiographic evaluation of hepatic arterial damage after transarterial chemoembolization for hepatocellular carcinoma

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Abstract
Purpose. The aim of this study was to assess the incidence, degree, and predictors of hepatic arterial damage (HAD) after transarterial chemoembolization (TACE) for hepatocellular carcinoma (HCC).
Materials and methods. A total of 33 patients with unresectable HCC underwent TACE alone using a mixture of iodized oil, epirubicin, and gelatin sponge. A follow-up angiogram was available for 76 of 109 sessions, and HAD was evaluated at each subsegment of the hepatic artery using a three-grade scale (1, no or slight wall irregularity; 2, overt stenosis; 3, occlusion). Grades 2 and 3 were considered to indicate significant HAD. The predictors of HAD were analyzed by multivariate analysis.
Results. A total of 161 hepatic arteries were embolized from the lobar ($n = 43$), segmental ($n = 40$), subsegmental ($n = 72$), or more distal ($n = 6$) level. The follow-up period between the initial and last sessions ranged from 70 to 1505 days (median 497 days). Significant HAD occurred in 37 of 231 subsegmental hepatic arteries (16%) and in 16 of 33 patients (48%). The accumulated dose of epirubicin per artery ($P = 0.001$) and Child-Pugh score ($P < 0.001$) were significant predictors.
Conclusion. TACE is more likely to induce HAD in cirrhotic patients with impaired liver function and when a high dose of the chemotherapeutic agent was used.

Key words Hepatocellular carcinoma · Transarterial chemoembolization · Hepatic artery damage · Angiography

Introduction

Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide, with the largest concentration in Asia.[1] Treatment selection for HCC is variable compared with that for other cancers because patient prognosis depends on not only the tumor extent but also hepatic function reserve.[2–4] Eligibility for potentially curative treatments such as surgery and ablation are limited owing to tumor extent, multiplicity, or underlying cirrhosis. Thus, transcatheter arterial chemoembolization (TACE) is the mainstay for palliative treatment of unresectable HCC.[5] Patients with HCC often require repeated TACE for residual viable tumor or local recurrence. However, hepatic artery damage (HAD) associated with TACE may interfere with catheterization at the next session, compromising the treatment success and clinical outcome. Few reports have focused on the incidence and degree of HAD.[6] The purpose of this study was to analyze retrospectively the incidence, degree, and prognostic factors of HAD after TACE.

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Materials and methods

Patient background

Between January 2000 and March 2006, a total of 33 patients with unresectable HCC underwent TACE as the initial treatment, with a total of 109 sessions (mean 3.3 sessions) of TACE as the sole treatment modality in our hospital. The multidisciplinary HCC conference (which included radiologists, hepatologists, and surgeons) reached consensus that TACE was the appropriate treatment option in each session. All patients gave written informed consent to undergo TACE, and this retrospective study was approved by our institutional review board.

All patients who underwent other treatment(s) afterward, such as surgery, radiofrequency ablation (RFA), percutaneous ethanol injection (PEI), and/or hepatic arterial infusion chemotherapy were excluded from this study. There were 29 men and 4 women with an average age of 70 years (range 38–85 years). As causes for underlying cirrhosis, 19 (58%) patients had hepatitis C virus infection, 8 (24%) had hepatitis B virus infection, 1 (3%) had alcohol-induced hepatitis, and 5 (15%) had an unknown etiology. The Child-Pugh classification was class A in 26 (79%) patients and class B in 7 (21%) patients; none was class C. Okuda stage was stage I in 28 (85%) patients and stage II in 5 (15%) patients. Altogether, 19 patients had risk factors for arteriosclerosis, which included diabetes mellitus, hypertension, and angina pectoris (Table 1).

The clinical diagnosis of HCC was based on a combination of the imaging findings and an increased serum level of α-fetoprotein (AFP) and/or protein-induced vitamin K antagonist-II (PIVKA-II). The imaging studies included dynamic computed tomography (CT) or magnetic resonance imaging (MRI), CT during arterial portography (CTAP) or hepatic arteriography (CTHA), and digital subtraction angiography (DSA). At the time of initial TACE, 7 patients (21%) had a single main nodule, 2 (6%) had a single main nodule with satellite nodules, 5 (15%) had two distinct nodules, and 19 (58%) had multiple (more than two) distinct nodules.

TACE procedures

All TACE procedures consisted of arterial injection of a mixture of chemotherapeutic agent and iodized oil (Lipiodol Ultra-Fluid; Andre Guerbert, Aulnay-sous-Bois, France) (Lipiodol mixture) followed by gelatin sponge particles using a microcatheter in a selective manner. The mixture was prepared by mixing the solution of epirubicin hydrochloride (Farmorubicin; Kyowa Hakko, Tokyo, Japan) dissolved in 300 mg I/ml nonionic contrast medium at concentration of 10 mg/ml with iodized oil in a 1 : 1–1.5 ratio (epirubicin solution/iodized oil). The maximum dose of epirubicin was 50 mg per session, and the total dose of Lipiodol (milliliters) was almost equal to sum of the target tumor diameter (centimeters).

Gelatin sponge particles were prepared by cutting a sponge sheet (Spongel; Astellas, Tokyo, Japan) with scalpel and scissors into small cubes approximately 1 mm in diameter; the particles were then suspended in nonionic contrast medium. Gelatin sponge particles were not immersed in the solution of antichemotherapeutic agent.

The endpoint of embolization was blood flow cessation of the tumor-feeding artery. During each session, the dominant tumor-bearing region was mainly treated, and the remaining tumors were embolized with gelatin sponge particles alone as needed.

Assessment and statistical analysis

Among the total 109 TACE sessions, follow-up hepatic arteriograms were available to evaluate HAD for 76

Table 1. Patient background

No. of patients	33
Age (years)	38–85 (mean 69.6 ± 11.0)
Sex (M/F)	29/4
Child-Pugh class (A/B)	26/7
Child-Pugh score (5/6/7/8)	13/13/4/3
No. of sessions per patient to be evaluated	1–7 (mean 2.3 ± 1.5)
Risk factors for arteriosclerosis (yes/no)	19/14
Level of embolization (lobar/segmental/subsegmental/more distal)	43/40/72/6
No. of arteries treated in all patients	169
Accumulated dose of epirubicin per artery (mg)	0–72.5 (mean 14.5 ± 12.7)
Follow-up period (days)	70–1505 (mean 497 ± 443)

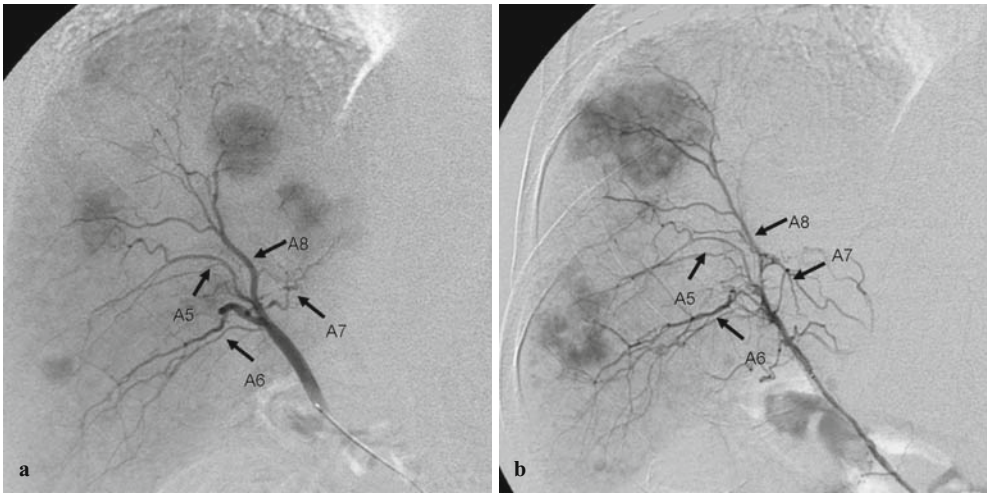

Fig. 1. A 71 year-old man underwent three sessions of transcatheter arterial chemoembolization (TACE) from the right hepatic artery and A4 during the follow-up period. Right hepatic arteriograms obtained at the initial session (**a**) and the last session (**b**) are shown. At the last session, overt stenosis of the right hepatic artery at each of *A5–A8* was observed. Therefore, hepatic arterial disease (HAD) was regarded as grade 2 for *A5–A8*

sessions. HAD of each subsegmental hepatic artery was assessed on the last hepatic arteriogram using a three-grade scale: 1, no or slight wall irregularity; 2, overt stenosis; 3, occlusion (Figs. 1, 2).

The seven subsegments of the hepatic artery, from A2 to A8, were evaluated. The caudate lobe branch A1 was excluded because of the variable origin and multiplicity. Grades 2 and 3 were considered to indicate significant HAD. The highest HAD grade among the seven arteries was defined as the HAD grade for that patient. The HAD grades for a total of 231 subsegmental hepatic arteries in 33 cases were interpreted independently in a blinded fashion by two radiologists. Discrepancies were resolved by consensus.

To identify predictors of HAD, multivariate analysis was performed among the treated arteries for the following factors: age, sex, level of embolization, accumulated dose of epirubicin per artery, Child-Pugh score, number of sessions per artery, risk factors for arteriosclerosis, and the follow-up period. Poisson regression analysis with generalized estimating equations was used to revise the data clustering and dependency. When the Lipiodol mixture was injected from the segmental or more proximal level, the dose of epirubicin per subsegmental hepatic artery was determined by the average dose (i.e., total dose divided by the number of subsegments included in the treated area). For example, when 40 mg of epirubicin were used from the right hepatic artery, each dose of epirubicin per subsegmental hepatic artery (A5–A8) was recorded as 10 mg. For this estimation, the link function was set at identity link, and an exchangeable working correction matrix was used.

The survival period for all patients was calculated from the date of initial TACE, and the survival rate was analyzed at the end of March 2006. Patients lost to follow-up or alive at the time of analysis were censored.

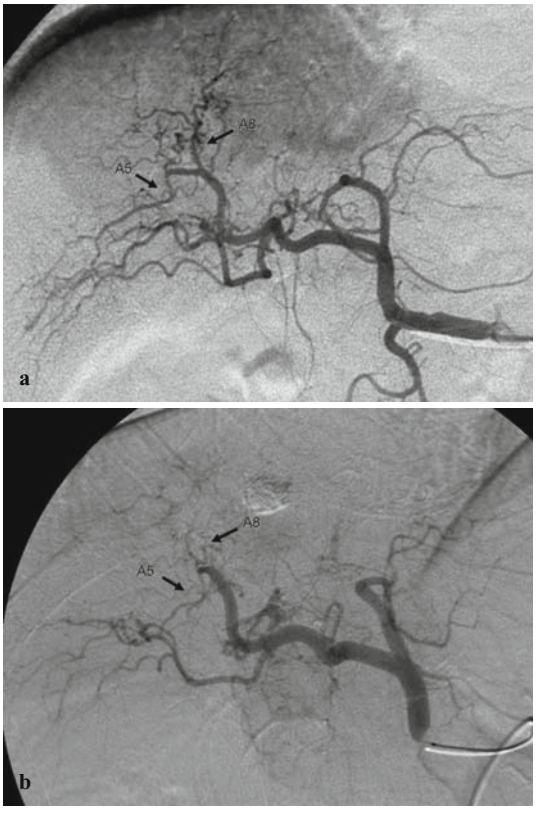

Fig. 2. A 77 year-old man underwent four sessions of TACE at A1, A4, A8, the right anterior hepatic artery, and the right inferior phrenic artery during the follow-up period. Control common or proper hepatic arteriograms obtained at the initial (**a**) and last (**b**) sessions are shown. At the last session, occlusion of *A8* and overt stenosis of *A5* were observed. Therefore, HAD was regarded as grade 3 for *A8* and as grade 2 for *A5*

The cumulative survival rates were estimated using the Kaplan-Meier method. The survival rates were compared between the groups with and without significant HAD using the log-rank test comparison. Statisti-

Table 2. Multivariate analysis for the treated hepatic arteries

Parameter	Estimated β	Standard error	*P*
Age	–0.004	0.002	0.107
Sex	–0.076	0.094	0.420
Child-Pugh score	0.229	0.055	<0.001
No. of sessions per artery	0.018	0.060	0.765
Level of embolization	0.017	0.043	0.693
Accumulated dose of epirubicin	0.018	0.006	0.001
Follow-up period	0.000	0.000	0.666

Hepatic arterial damage (HAD) grade was significantly correlated with the Child-Pugh score and the accumulated dose of epirubicin

cal significance was defined as $P < 0.05$. All analyses were performed using a statistical software package (SPSS 11.0 for Windows; SPSS Japan, Tokyo, Japan) and a macro program (GEE95, version 1.01; courtesy of Methodology and Statistics Group, Oregon Research Institute, Eugene, OR, USA).[7]

Results

At the 76 sessions evaluated, embolization was performed at 161 sites of the hepatic artery from the lobar ($n = 43$), segmental ($n = 40$), subsegmental ($n = 72$), or more distal ($n = 6$) level according to the tumor extension. In seven patients, embolization with gelatin sponge particles alone was adjunctively performed at 16 sites of the hepatic artery from the lobar ($n = 5$), segmental ($n = 4$), subsegmental ($n = 5$), or more distal ($n = 2$) level. Altogether, 74 subsegmental hepatic arteries did not receive any treatment during the course. There were no technical failures during hepatic angiography or TACE. The follow-up period between the initial TACE and the last control hepatic arteriogram ranged from 70 to 1505 days (median 497 days). The accumulated dose of epirubicin per subsegmental hepatic artery ranged from 0 to 72.5 mg (average 16.1 mg) (Fig. 3).

Hepatic arterial disease was interpreted as grade 1, grade 2, and grade 3 in 194 (84%), 31 (13%), and 6 (3%) arteries, respectively. HAD grade per patient was grade 1, 2, or 3 in 17 (52%), 11 (33%), and 5 (15%) patients, respectively. Therefore, the incidence of significant HAD was 16% per artery and 48% per patient. A total of 16 subsegmental hepatic arteries underwent embolization with gelatin sponge particles alone; and HAD was all interpreted as grade 1 in all of these arteries.

In one patient, two arteries (A5, A8) showed grade 2 HAD, although these arteries received neither Lipiodol mixture nor gelatin sponge. In this case, the neighboring arteries (A6, A7) were treated and showed grade 2 HAD.

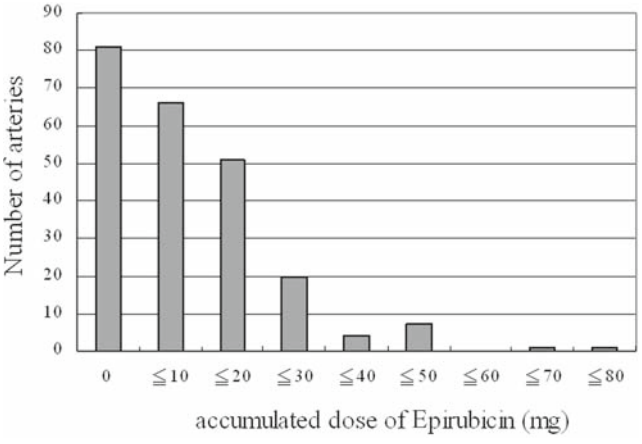

Fig. 3. Distribution of the accumulated dose of epirubicin per artery used at all sessions

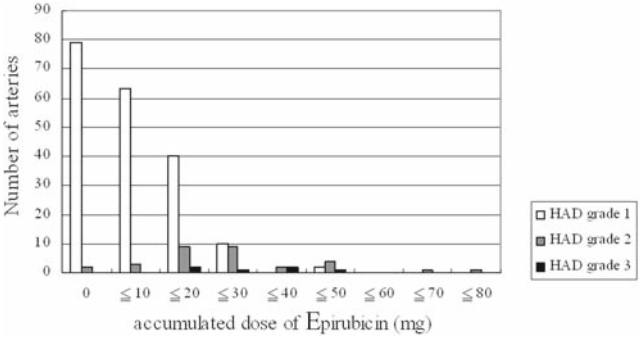

Fig. 4. Distribution of the HAD grade. The number of arteries with HAD grades 1, 2, and 3 were 194 (84%), 31 (13%), and 6 (3%), respectively

The results of the multivariate analysis are shown in Table 2. HAD grade was significantly correlated with the Child-Pugh score and the accumulated dose of epirubicin per artery (Table 2) (Fig. 4).

The cumulative survival rates were 93.5%, 85.2%, and 77.4% at 1, 2, and 3 years, respectively (Fig. 5). The

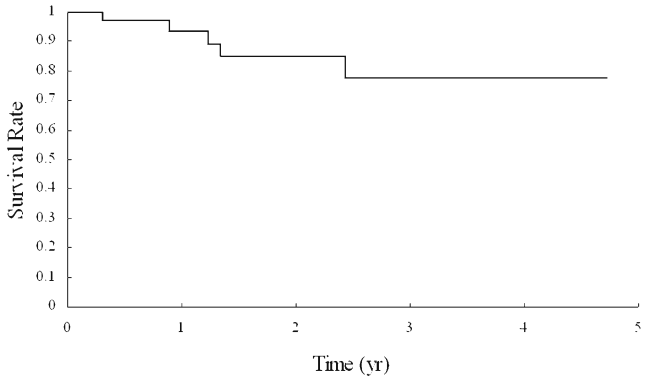

Fig. 5. Cumulative survival rates for all 33 patients. The 1-, 2-, and 3-year survival rates were 93.5%, 85.2%, and 77.4%, respectively

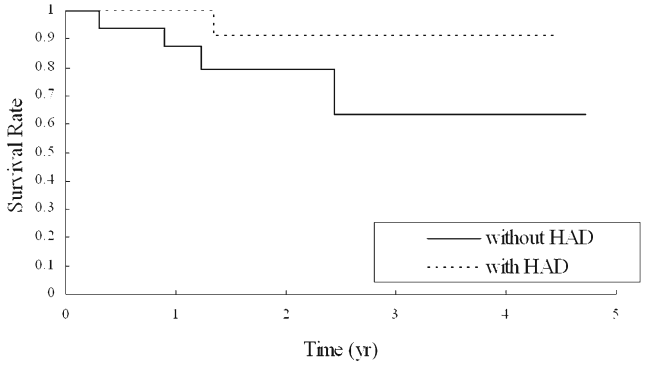

Fig. 6. Cumulative survival rates with or without significant HAD. The 1-, 2-, and 3- year survival rates with HAD were 100%, 90.9%, and 90.9%, respectively; and those without HAD were 87.4%, 79.5%, and 63.6%, respectively. No significant difference was seen between the two groups

survival rates for the patients with significant HAD were 100%, 90.9%, and 90.9%; and for those without HAD they were 87.4%, 79.5%, and 63.6% at 1, 2, and 3 years, respectively (Fig. 6). There was no significant difference in survival rates between the two groups ($P = 0.159$).

Discussion

Transcatheter arterial chemoembolization is the most widely performed treatment for patients with HCC who are not eligible for curative surgery or ablation, and the efficacy of TACE has been described in numerous reports.[8–11] The survival benefit of TACE has been also confirmed by recent randomized controlled trials and meta-analysis.[12–15] Thus, TACE is a favorable treatment option for patients with unresectable HCC. The mixture of iodized oil and chemotherapeutic agents as a water-in-oil emulsion is commonly infused prior to injection of gelatin sponge particles.[5,11,13,16–19] Segmental or subsegmental TACE using a microcatheter has been developed,[16,17] and targeted TACE with assistance of CTAP and/or CTHA is the current technique used to maximize local therapeutic effects and minimize nontumor tissue damage.[18] Even with these refined techniques, the local tumor control effect of TACE is limited, and the reported local recurrence rates generally exceeded 30% within 3 years after TACE for HCCs < 5 cm in diameter.[17,18] In addition, cirrhosis related to chronic infection with the hepatitis C virus, the dominant etiology in the current study, is more likely to have de novo recurrence in a multicentric manner.[20] Therefore, patients with HCC often require repeated TACE sessions to treat local or de novo recurrence.

The adverse effects of TACE, such as postembolization syndrome, biliary damage, and impaired liver function have been often discussed.[19,21,22] Considering the fact that TACE is often repeated in most patients, longer patency of the hepatic artery is preferable for proper deploying the Lipiodol mixture and embolic agents into the tumor. However, few reports have focused on the incidence and degree of HAD after TACE as a prognostic factor.

In this study, the incidence of significant HAD was considerable: 16% per subsegmental hepatic artery and 48% per patient. According to the multivariate analysis, the Child-Pugh score and the accumulated dose of epirubicin were significant predictors of HAD, whereas the HAD grade was not correlated with the number of sessions or the level of embolization. Apparently, an increasing number of TACE sessions may incrementally increase the accumulated dose of chemotherapeutic agent and thus is more likely to induce HAD. However, this multivariate analysis revealed no correlation of HAD with the number of TACE sessions. This is probably because the number of sessions was variable even among the patients treated with the same total dose of epirubicin. In other words, one patient may receive a high dose of epirubicin at one session, but another may receive the same total dose at separate sessions. Although the cause of HAD in more cirrhotic liver is unclear, it may result from the biological factors responsible for impaired liver function or from a technical factor during irritable catheterization beyond the tortuous arteries. In one case, two arteries showed grade 2 HAD, although they did not receive the Lipiodol mixture. Overflow of Lipiodol mixture from the neighboring arteries may be the cause for HAD of these arteries.

In the current study, the overall survival rates were relatively high compared with previously reported results of TACE.[12,13] However, in our hospital, most patients who did not respond to repeated TACE

underwent hepatic arterial infusion chemotherapy afterward, and these patients were excluded from this study. Although there was no significant difference, the survival rates for the group with significant HAD tended to be higher than those without HAD, probably because more dose of Lipiodol mixture was used in these patients with HAD.

There are several limitations in the current study. First, this is a retrospective study with a small number of patients. Indeed, patients with unresectable HCC often underwent percutaneous tumor ablation following TACE as a combination therapy or hepatic arterial infusion chemotherapy as the next alternative option to repeated TACE. These patients were excluded from this study. Second, we assessed HAD only at the level of subsegments of the hepatic artery. Thus, HAD at more proximal or distal hepatic artery levels is unknown. Third, we did not assess the impact of HAD on the tumor response after embolization of the corresponding artery. In this study, only the patients who needed repeated TACE because of persistent viable tumor or newly recurrent tumors were enrolled. In addition, HAD was assessed only after the last session with various follow-up periods. Therefore, it was difficult to analyze the impact of HAD on the tumor response, and we instead evaluated the correlation with survival rates. Fourth, we assessed the dose only of epirubicin, not of Lipiodol. Because epirubicin and Lipiodol were injected together as a mixture, it is difficult to prove the impact of one of the two beyond that of the other.

Lastly, the results of this study might change if different chemotherapy protocols and embolic agents are used or if the manner in which they are delivered is not the same. In the current study, infusion of the intended dose of Lipiodol mixture adjusted to the tumor size and vascularity was followed by injection of gelatin sponge particles until the blood flow cessation. This technique is rather conventional but still the standard method in most Asian countries. Currently, calibrated microspheres have been commonly used in either bland embolization or TACE in Western countries.[23] They tend to penetrate more deeply into the tumor vessels to achieve longer-term vascular occlusion than is encountered with gelatin sponge particles. Drug-eluting beads are a newer form of microsphere that locally releases chemotherapy more slowly than does the Lipiodol mixture.[24] The incidence and degree of HAD may variably differ among these updated techniques.

Further investigation by larger prospective clinical trials is necessary to validate the predictors for HAD. In addition, improvement and optimization of TACE protocols or techniques are warranted to achieve longer patency of the hepatic arteries.

Conclusion

Transcatheter arterial chemoembolization is more likely to induce HAD in cirrhotic patients with impaired liver function and when high doses of chemotherapeutic agents are used. To protect the hepatic artery from HAD, which might preclude subsequent use of TACE, it is necessary to improve the TACE technique by employing it in a more selective manner and optimizing the dose of the chemotherapeutic agent.

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