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Development of a Safety Index of Transarterial Chemoembolization for Hepatocellular Carcinoma to Prevent Acute Liver Damage

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Abstract. *Background: Transarterial chemoembolization (TACE) is the most effective palliative treatment for hepatocellular carcinoma (HCC), but may cause acute liver damage. Materials and Methods: One hundred and ninteen patients with unresectable HCCs, undergoing TACE, were studied prospectively. A safety index to prevent acute liver damage was developed by using logistic regression. Results: Acute liver damage by TACE was not related to the gender or age, but was mostly correlated to Child's classification (β=1.89, OR=6.6, CI: 2.07, 21.01) and the amount of Lipiodol (β=0.09, OR=1.09, CI: 1.02, 1.16) used for the TACE. Conclusion: In treatment of a Child's B/C patient by TACE, no more than 20ml Lipiodol should be used.*

Hepatocellular carcinoma (HCC) is the most common malignant hepatic tumor in the world and ranks fifth in incidence of malignant tumors. More than 372,000 new cases are reported annually, representing about 4.6% of all malignant tumors (1). Besides surgery and liver transplantation (2, 3), transarterial chemoembolization (TACE) is the most effective palliative treatment for HCC (4, 5), with an effective treatment rate of about 16-55%. Increasing the embolization dosage may increase the anti-tumor effect on HCC, but at the same time may cause more liver damage and may result in severe acute hepatic failure. A recent report stated that about 54% of HCC patients may suffer, at least once, from acute hepatic failure during TACE treatment (6). Our purpose was to develop a safety index for TACE treatment of HCC to prevent acute liver damage.

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Materials and Methods

From January 1997 to February 2004, a total of 119 patients with unresectable HCCs, undergoing TACE, were studied prospectively. Each patient gave informed consent. A local injection of 2% Lidocaine HCl was given in the inguinal area, a 4.1Fr catheter was inserted into the abdominal aorta by the Seldinger's method, and digital subtraction angiography (DSA) was performed using GE advantx LCA @DLX equipment. The Indocyanine green retention rate in 15 minutes (ICG-R15) was used to measure the pre- and post-TACE liver function. The acute liver damage caused by TACE was evaluated by the following factors and data: (a) The independent variables included age and gender. (b) Case-mix factors: the Child-Pugh's classification and Okuda staging were assessed by clinical data and imaging studies. (c) Clinical data: to obtain a well correlated pre-TACE hepatic function, the pre-TACE ICG-R15 and other biochemical laboratory tests such as GOT, GPT, bilirubin index, prothrombin time, alkaline phosphatase and albumin were performed two days before the TACE. Since the main purpose of our study was to evaluate acute hepatic damage, only the ICG-R15 test was used for post-TACE liver damage measurement and the post-TACE ICG-R15 was performed within a week. (d) Imaging data: tumor size, tumor number and portal vein patency were studied by ultrasound, CT, MRI or angiography. (e) Embolization factors: Epirubicin and Lipiodol were mixed into emulsion and injected transarterially into the tumor-supplying artery. Gelfoam cubes were then added to prevent any incoming fresh blood from washing-out the emulsion that had been injected into the tumor artery.

The relationships between clinical and other variables were examined using the Pearson's correlation. Those variables that were not normally distributed were rearranged. The highly correlated variables were not used together in the logistic regression model in order to avoid co-linearity. Univariate ($p<0.25$) and multivariate ($p<0.05$) analyses were used to select the vital factors (7, 8). A change between pre- and post-TACE ICG-R15 >5% was used as the cut-point for the logistic regression model. The odds ratio (OR)

Table I. *Characteristics of HCC patients.*

Categorical variables		Frequency	Percentage (%)
Sex	Female	22	18.49
	Male	97	81.51
Age (Years)		65.86[a]	12.26[b]
	Female	66.09[a]	8.32[b]
	Male	65.80[a]	13.03[b]
Child's	A	93	78.15
	B or C	26	21.85
Okuda staging	1	57	47.9
	2 or 3	62	52.1

[a]: Average; [b]: Standard deviation

Table II. *Bivariate association.*

	Albumin	PT	Epirubicin	Lipiodol	ICG-R15b	D
ICG-R15a	–0.52***	0.42***	–0.2*	–0.3***	0.89***	–0.2*
Albumin	1	–0.25**	–0.04	0.05	–0.55***	–0.1
Bilirubin	–0.07	0.19*	–0.24**	–0.13	0.32***	0.08
PT	–0.25**	1	–0.13	–0.18*	0.44***	0.06
Tumor size	0.02	–0.08	0.52***	0.64***	–0.09	0.24**

*: $p<0.05$; **:$p<0.01$; ***:$p<0.001$

PT: prothrombin time; ICG-R15a: pre-TACE ICG-R15; ICG-R15b: post-TACE ICG-R15; D: difference between pre- and post-TACE ICG-R15.

Table III. *Multivariate logistic regression model for prediction of difference between pre- and post-TACE ICG-R15>5%.*

Variables	β	S.E.	Wald χ^2	Pr > χ^2	O.R.	95% CI
Intercept	-3.20	0.60	28.85	<0.0001		
Child's class[Ψ]	1.89	0.59	10.19	0.0014	6.60	(2.07, 21.01)
Lipiodol dosage	0.09	0.03	7.16	0.0075	1.09	(1.02, 1.16)

Ψ: Two groups of Child's class: Group A and Group B/C.

was counted. The interactions between the above factors were also considered. A final model of logistic regression was built and the Receiver Operating Characteristic (ROC) curve was calculated for acute liver damage by TACE. Sensitivity was defined as the true changing rate of ICG-R15 after TACE (true-positive rate) and the specificity was defined as the change of ICG-R15 after TACE was within the prediction (true-negative rate). The area under the ROC curve (area under curve, AUC) represented accuracy. Statistical evaluation employed SAS (edition 8.0).

All patients in this study, had liver biopsies, αFP higher than 400 ng/ml, or at least higher than 20 ng/ml for more than three months of close observation and had proved to have liver tumor by image modalities. For simplicity, patients with other malignancies, diabetes, allergies or a bleeding tendency were excluded from this study. Cases where the main purpose of the TACE was for emergency treatment of ruptured HCC were also excluded from this study.

Results

Ninety-three Child's A patients and 26 Child's B/C patients were included. Their socioeconomic characteristics are presented in Table I. The ICG-R15 between the pre- and post-TACE were highly correlated (0.89, $p<0.001$). The bivariate association is presented in Table II. Only the Child's classification (β=1.89, OR=6.6, CI: 2.07, 21.01) and the Lipiodol dosage (β=0.09, OR=1.09, CI: 1.02, 1.16) were left in the final model ($p<0.05$, Table III). No interaction between these two variables was found. The Lipiodol dosage *versus* the probability of prediction of difference of ICG-R15 higher than 5% in multivariate logistic regression model is presented in Figure 1 and the ROC curve is presented in Figure 2.

Discussion

Indocyanine green (ICG) is a non-ionic dye of low toxicity, presented by Caesar *et al.* in 1961 for liver function testing. No toxicity case has been ever been reported. ICG is absorbed by hepatocytes and is excreted together with bile. ICG is not excreted by the kidneys, making it very suitable to use the ICG percentage retention to evaluate the absorption and transportation function of the liver (9, 10). In this study, we showed that patients with poorer liver function or advanced stage of liver cirrhosis will suffer more liver damage after TACE treatment. We also found that the use of embolizers might create a higher risk of liver failure. In deciding on how to treat inoperable HCC patients, we were faced with the same dilemma as the surgeon, *i.e.* to treat the patient anyway regardless of the severity of the illness. Within the factors of our study framework, age and gender were less related to the liver damage. Since the severity of illness is a more important factor than TACE factors, the pre-TACE ICG-R15, the prothrombin time and the Child's classification are the most important indices to predict the liver damage of a patient after TACE. Among the three drugs that we use in TACE, Lipiodol is the main variable to predict the post-TACE hepatic function, as well as the degree of acute liver damage. More than 40% of our study patients had acute liver damage after TACE, 16% of patients even showing more than a 5% increase in ICG-R15.

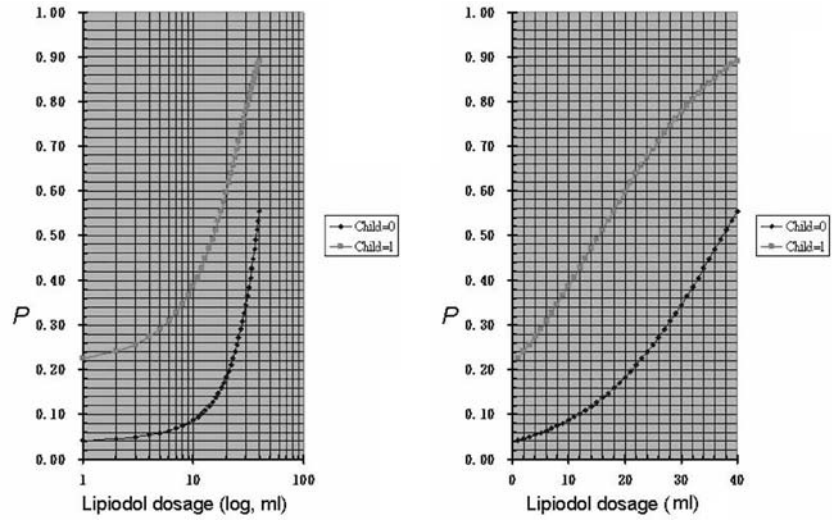

Figure 1. *Lipiodol dosage vs. the probability of prediction of difference of ICG-R15>5% in multivariate logistic regression model.*

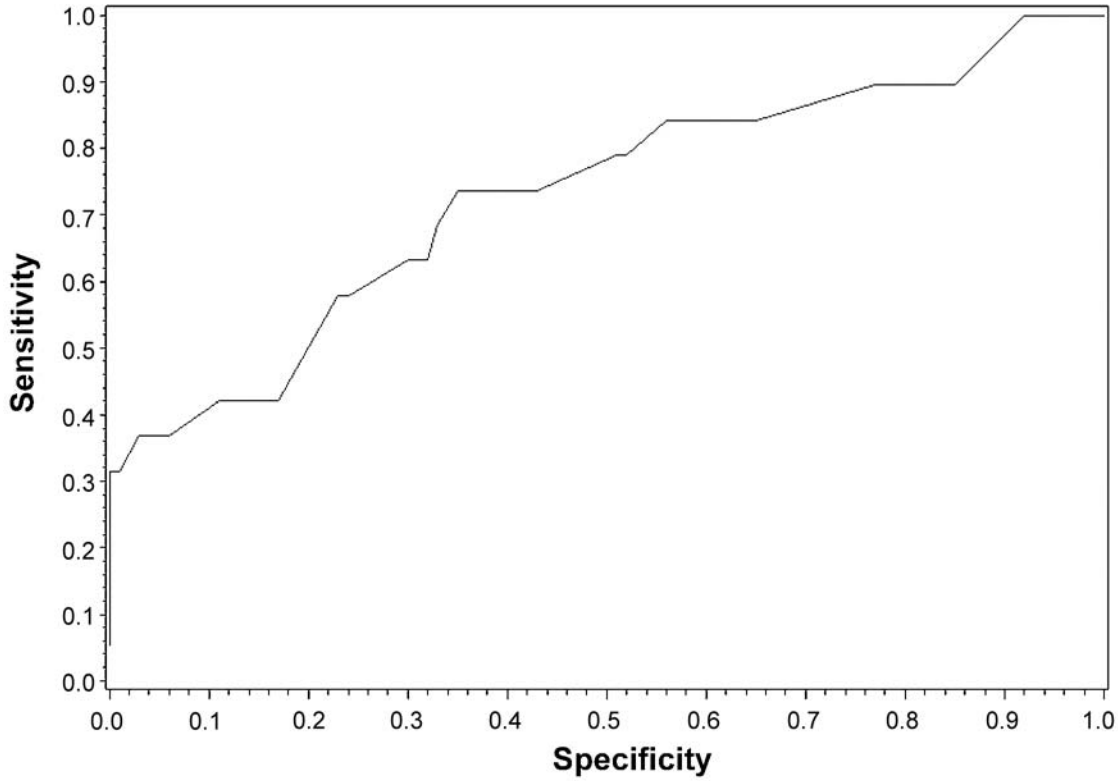

Figure 2. *ROC curve in a predictive model for difference of ICG-R15>5% in multivariable logistic recurrent model (AUC=71.3%).*

This proved that TACE had a marked adverse effect on the liver, emphasizing the need to make a more careful selection before we plan to treat a HCC patient. In case of treating a HCC patient, then the most important factors to cause acute liver damage after TACE is the dosage of Lipiodol. If 5 ml of Lipiodol or more is used, the risk of causing liver damage is more than 3 times the control group (use less than 5 ml of Lipiodol). So, for the treatment of a large tumor with hypervascularity, 5-20 ml Lipiodol is recommended for Child's A patients or patients with pre-TACE ICG-R15 less

than 30%. However, no more than 20 ml Lipiodol in TACE should be used for a Child's B/C patient or patient with pre-TACE ICG-R15 equal to or higher than 20%. We conclude that the acute liver damage by TACE was not related to the gender or age, but was correlated to the Child's classification and the amount of Lipiodol that was used.

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