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Clinical Significance of Serum Ornithine Carbamoyltransferase in Liver Diseases – Is the Ratio of OCT/ALT a New Tumor Marker?

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1. Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide and the third most common cause of cancer-related mortality (World Health Organization. Mortality database, 2010). According to the most recent nationwide Japanese registration data, primary liver cancer ranks fourth for men and sixth for women as cause of death from malignant neoplasm (Journal of Health and Welfare Statistics. Health and Welfare Statistics Association, 2009).

The leading major causes of HCC in Japan are viruses, hepatitis C accounting for 70% and hepatitis B for 16% of all cases of HCC. Recently, the incidence of HCC in cases of non-viral liver disease has gradually increased (Ikai et al., 2010). According to our hospital database, increasing numbers of HCC cases arising from non-alcoholic steatohepatitis (NASH) have been seen, with such cases accounting for 4% of all cases of HCC each year since 2000. Together with the recent increase the metabolic syndrome population in Japan, cases of NASH have increased dramatically, and it is logical that the incidence of HCC in these patients can be expected to increase as well (Tokushige et al., 2010).

Since evaluation of viable HCC is important for monitoring and deciding therapeutic strategies, the serum tumor markers alpha-fetoprotein (AFP) and des-gamma-carboxy prothrombin (DCP), the protein induced by vitamin K absence, as well as imaging provide useful information. However, a recent report demonstrated that AFP is not sensitive in NASH-related HCC (Hashimoto & Tokushige, 2011). Although DCP is highly specific for HCC, its sensitivity is reported to be no more than 50% in patients with HCC measuring 3cm or less in diameter (Okuda H et al., 2000). Moreover, DCP can be affected by some

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medicines such as warfarin, or by the condition of patients with severe liver failure or bile acid outflow obstruction. There are still some problems about tumor markers of HCC.

Histological analysis via liver biopsy is one of the most accurate methods for evaluating liver status, but the method is too invasive for frequent use. Especially, liver biopsy is only method for the diagnosis of NASH and the evaluation of progression. Hence, minimally invasive, impervious and reliable markers are still required for early diagnosis and optimal treatment. Ornithine carbamoyltransferase (OCT), a mitochondrion-derived protein, has been reported as a useful marker superior to cytosol-derived markers in the detection of liver injury in murine model (Maruyama et al., 2008). Murayama et al. also reported that OCT is highly liver-specific for the evaluation of hepatocellular damage, whereas alanine aminotransferase (AST) and aspartate aminotransferase (ALT) are useful but not liver-specific, existing in a variety of organs such as heart, muscle, and kidney. Since mitochondrial dysfunction is regarded as a pathogenesis of NASH, we thought that OCT might be a useful marker to detect the progression of NASH and NASH-caused HCC. In our previous study, we demonstrated that serum OCT levels and the ratios of OCT/ALT and OCT/AST were markedly increased in NASH with HCC. Importantly, the amount of serum OCT and the ratio of OCT/AST were significantly higher in patients with NASH-HCC than in those with NASH-liver cirrhosis (NASH-LC) (Tokushige et al., 2009). Therefore, in this study, we investigated the clinical significance of OCT in several chronic liver diseases, including HCC and OCT compared with the histological stage. To confirm whether OCT is a useful tumor marker for HCC, we measured serum OCT and OCT/ALT ratios before and after therapy, and then compared the results with other tumor markers such as AFP and DCP.

AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUC, area under the ROC curve; CH, chronic hepatitis; ELISA, enzyme-linked immunosorbent assay; HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; LC, liver cirrhosis; OCT, ornithine carbamoyltransferase; DCP, des-gamma-carboxy prothrombin

2. Patients and method

2.1 Patients

One hundred eighty-nine patients with biopsy-proven NASH (including 24 LC and 12 HCC), 27 patients with alcoholic liver diseases (ALD) according to the diagnostic criteria of ALD in Japan (Takada & Tsutsumi, 1995), and 70 patients with chronic liver diseases by hepatitis C virus (HCV) (including 16 LC and 14 HCC), at Tokyo Women's Medical University between 1995 and 2011 were evaluated along with 80 healthy subjects serving as controls (Table 1).

Diagnosis of NASH was based on the following criteria: (1) detection of steatohepatitis on liver biospy, (2) intake of <100g of ethanol per week, and (3) approriate exclusion of other liver diseases (Brunt et al., 1999; Neuschwander-Tetri & Cadwell, 2003). All liver biopsy specimens were examined using hematoxylin-eosin, Mallory, and silver reticulin as stains. Fibrosis was scored using a 5-grade scale: F0, normal connective tissue; F1, foci of

perivenular fibrosis in zone 3; F2, perivenular or percicellular fibrosis confined to zone 3 and 2, with or without portal/periportal fibrosis; F3, bridging fibrosis or septal fibrosis; F4, cirrhosis. Patients in the HCV group were shown to be positive for HCV-RNA by a quantitative polymerase chain reaction assay.

We collected serum samples from 10 patients with HCC both pre-treatment and post-treatment, 4 patients with hepatitis C and 6 patients with non-virus diseases including NASH and ALD. Nine patients with HCC underwent transcatheter arterial chemoembolization (TACE). Partial hepatectomy was selected for 1 patient. Post-treatment samples were collected at 3 months after each therapy.

All patients underwent liver tests for measurement of the following laboratory parameters: AST, ALT, platelet count, hepatitis B serology (hepatitis B surface antigen, antibody to hepatitis B surface antigen, and antibody to hepatitis B core antigen), hepatitis C virus (HCV) serology (antibody to HCV and HCV-RNA polymerase chain reaction), and autoantibodies (antinuclear antibody (ANA), anti-smooth muscle antibody, and anti-mitochondrial antibody). Written informed consent was obtained from each patient, and the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by our institution's research committee.

2.2 Method

Serum OCT levels were measured by ELISA as reported previously (Murayama et al., 2006). Briefly, 50 µL of the HRP-conjugated F(ab') fraction of anti-OCT monoclonal IgG (secondary antibody, Mo5B11), and 50 µL of standard solution or sample diluted 10-fold with assay buffer (250 mmol/L glycine-buffer pH 9.4, containing 0.1% bovine serum albumin, 50 mmol/L NaCl and 0.1% ProClin950) were added to an antibody-coated dish (first antibody, Mo3B11). After mixing, the dish was incubated for 2 h and then washed with washing solution (10 mmol/L phosphate-buffer pH 7.4, containing 0.1% BSA, 150 mmol/L NaCl and 0.1% ProClin950). Then, a substrate solution (200 µg/mL 3, 3′, 5, 5′-teramethylbenzidine containing 0.001% H_2O_2) was added. After the coloring reaction (20 min) was terminated by adding a stop solution (0.5 mol/L H_2SO_4), absorbance at 450 nm was measured with a microplate reader.

The serum AFP levels were determined by enzyme-linked immunosorbent assay with a commercially available kit (ELISA-AFP, International Reagents, Kobe, Japan; cut-off level 10ng/ml). The serum DCP levels were determined by sensitive enzyme-linked immunoassay (Eitest PIVKA-II kit, Eisai Co., Tokyo, Japan; cut-off level 40 mAU/ml) according to the manufacturer's instructions.

2.3 Statistical analysis

Data were expressed as mean ± standard deviation (SD). Statistical comparison among the groups was conducted using Dunn's test, with $P < 0.05$ considered statistically significant. The comparison between pre-treatment and post-treatment of patients with HCC was performed by paired-t-test. The correlations between serum OCT levels and serum ALT and AST levels or platelet count were confirmed by Spearman's correlation test.

3. Results

3.1 Serum OCT levels and ratios of OCT/AST and OCT/ALT

Table 1 shows the mean serum AST, ALT, OCT levels, platelet counts, and the ratios of AST/ALT, OCT/AST and OCT/ALT in 153 NASH patients without HCC and LC, 24 NASH-LC patients, 12 NASH-HCC patients, 27 ALD patients, 40 chronic hepatitis with HCV<CH(C)> patients, 16 LC with HCV<LC(C)> patients without HCC, and 14 LC(C)-HCC patients. Significant associations between serum OCT levels and serum AST levels or ALT levels were noted (ALT, R=0.784 p<0.01; AST, r=0.853 p<0.01).

The AST and ALT levels of NASH-HCC were increased compared to those of NASH-LC. The ALT level of NASH-LC was slightly decreased compared to those of NASH. However, regarding AST and ALT, the differences between NASH and NASH-LC were not significant. In contrast, the serum OCT levels in NASH were higher than those of controls, and gradually increased with the development of liver disease from NASH to LC and HCC. In addition, the ratios of OCT/ALT and OCT/AST were significantly increased in parallel with the progression of NASH, LC and HCC. Especially, serum OCT levels and the ratios of OCT/ALT and OCT/AST were markedly increased in HCC.

Concerning CH(C), serum OCT levels were increased, but the ratios of OCT/ALT and OCT/AST were not significantly different from those of NASH patients. The ratio of OCT/ALT was slightly increased in LC(C) patients, compared with CH(C). Furthermore, in HCC with LC(C), both the ratios of OCT/ALT and OCT/AST were significantly increased.

As for comparison with several liver diseases without LC and HCC, serum OCT levels, OCT/ALT and OCT/AST ratios in ALD were significantly higher than those of other liver diseases (Figure 1).

3.2 Association with fibrosis grade in NASH patients

Figure 2 shows the association between liver fibrosis grade and serum OCT levels and the ratios of OCT/AST and OCT/ALT in NASH patients on the basis of liver biopsies. Serum OCT levels and OCT/ALT ratios were significantly increased in parallel with fibrosis grade (mean OCT levels: 50.8 ng/mL in F0-1, 68.7 ng/mL in F2, 108.3 ng/mL in F3, 156.4 ng/mL in F4)(mean OCT/ALT ratio: 1.43 in F0-1, 1.05 in F2, 1.69 in F3, 2.58 in F4). Regarding the relationship between OCT or ratios and platelet counts, there was a significant association between the ratio of OCT/ALT and platelet counts (r=-0.285 p<0.01)(Figure 3).

3.3 OCT in NASH patients with a normal range of ALT

Among all NASH patients, 42 patients had a normal range of ALT, among these 42 patients, 13 (31%) had OCT over 43ng/mL (mean ± 1.96 SD in control=43.2ng/mL). Of these 13 patients, eight had F3 or F4 fibrosis (Figure 4).

3.4 Change of OCT and ratio of OCT/ALT after therapy

Serum level of OCT and OCT/ALT ratio were significantly decreased in HCC after a therapeutic procedure, TACE or surgery (p<0.05). Out of 10 patients received therapy,

serum OCT levels were decreased in 8 patients. The ratio of OCT/ALT was decreased in 7 patients (Figure 5). On the contrast, in 9 patients DCP was decreased, in 7 patients AFP was decreased. The tendencies were almost same among 4 tumor markers.

Disease	OCT (ng/mL)	AST (U/L)	ALT (U/L)	OCT /ALT	OCT /AST	AST /ALT	Plt (×10⁴/μL)
Control (n=80)	20.6 ± 12.6	18.4 ± 4.3	16.3 ± 7.0	1.30 ± 0.87	1.09 ± 0.62	1.22 ± 0.33	N.D.
NASH (n=153)	73.3 [a] ± 73.2	41.2 [a] ± 33.9	63.9 [a] ± 80.9	1.34 ± 0.95	1.68 [a,d] ± 0.84	0.8 [a] ± 0.27	21.7 ± 6.39
NASH-LC (n=24)	102.7 [a,b] ± 107.2	38.0 ± 16.2	35.5 ± 20.7	2.27 [a,b] ± 1.26	1.93 [a,b] ± 0.93	1.19 [b] ± 0.45	12.8 [b] ± 6.21
NASH-HCC (n=12)	375.9 [a,b,c] ± 574.9	80.25 [a,c] ± 38.4	88.3 [a,c] ± 101.2	4.95 [a,b,c] ± 4.73	3.74 [a,b,c] ± 0.153	1.27 [b] ± 0.9	12.9 [b] ± 4.1
ALD (n=27)	114.8 [a,b,d] ± 106.5	40.2 ± 26.0	35.6 ± 30.2	4.30 [a,b,d] ± 6.19	3.19 [a,b,d] ± 4.31	1.35 [b] ± 0.49	19.1 ± 8.65
CH(C) (n=40)	53.3 [a] ± 41.3	43.9 ± 23.3	49.9 ± 35.3	1.19 ± 0.98	1.14 ± 0.67	1.06 ± 0.43	17.8 ± 3.91
LC(C) (n=16)	51.7 [a] ±28.9	42.2 ± 22.2	33.1 ± 21.1	1.94 ± 1.25	1.29 ± 0.52	1.49 ± 0.73	4.95 [b,c,d] ± 1.87
LC(C)-HCC (n=14)	142.5 [a,d,e] ± 12.6	57.9 ± 18.0	51.6 ± 21.2	2.98 [d,e] ± 4.38	2.25 [d] ± 2.77	1.19 [d] ± 0.26	4.06 [b,c,d] ± 4.66

1. Data are expressed as mean ± standard deviation (SD). [a] $P < 0.05$ versus control. [b] $P < 0.05$ versus NASH. [c] $P < 0.05$ versus NASH-LC. [d] $P < 0.05$ versus CH(C). [e] $P < 0.05$ versus LC(C).
2. NASH, non-alcoholic steatohepatitis; NASH-HCC, non-alcoholic steatohepatitis with hepatocellular carcinoma; NASH-LC, liver cirrhosis induced by NASH; ALD, alcoholic liver disease without liver cirrhosis and hepatocellular carcinoma; CH(C), chronic hepatitis C; LC(C), liver cirrhosis due to hepatitis C virus; LC(C)-HCC, liver cirrhosis due to hepatitis C virus with hepatocellular carcinoma;

Table 1. Serum levels of liver specific markers and their ratios in chronic liver disease
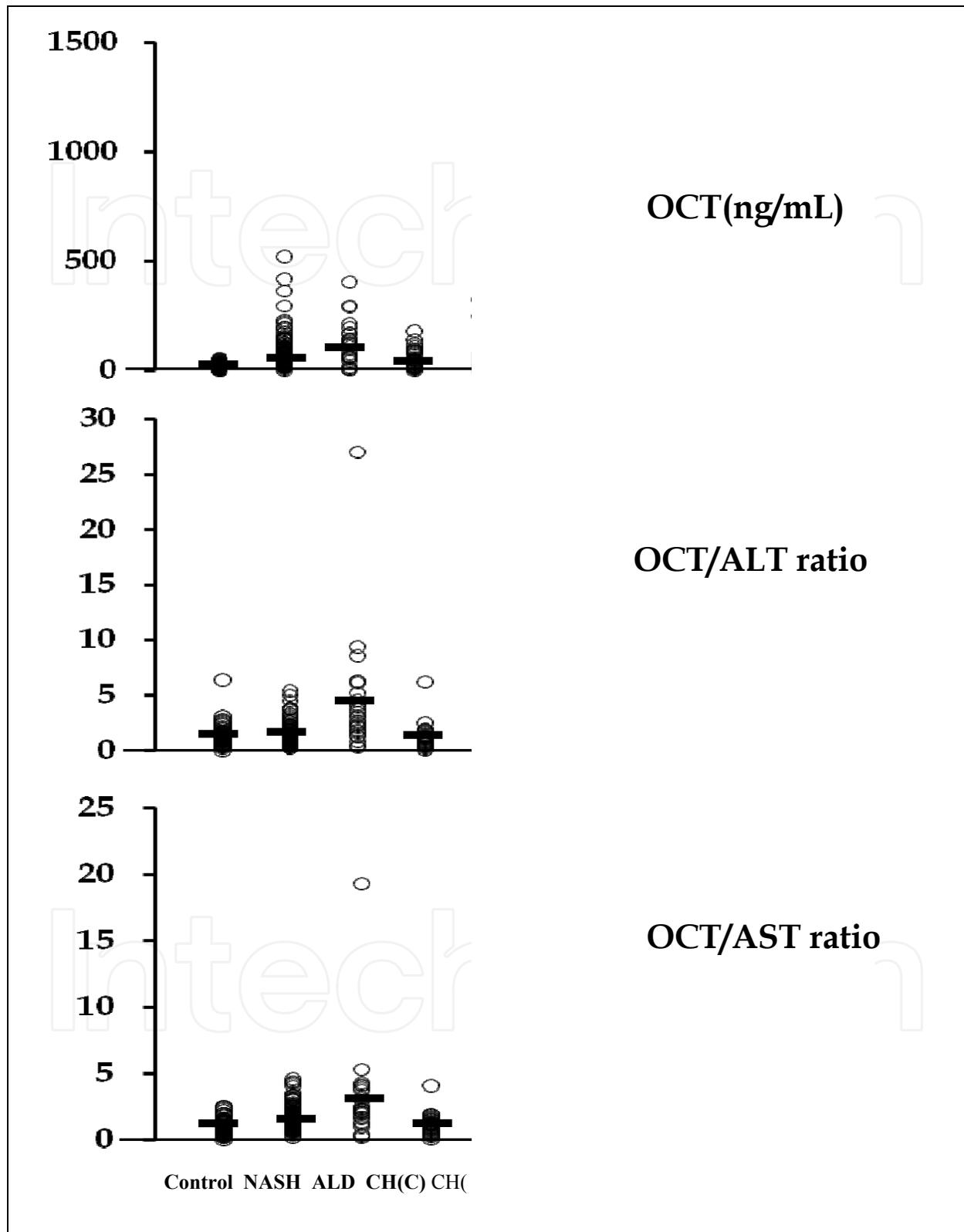
Fig. 1. Comparison of OCT and ratios of OCT/ALT, OCT/AST in various liver diseases without LC and HCC. Serum OCT levels, OCT/ALT and OCT/AST ratios in ALD were significantly higher.

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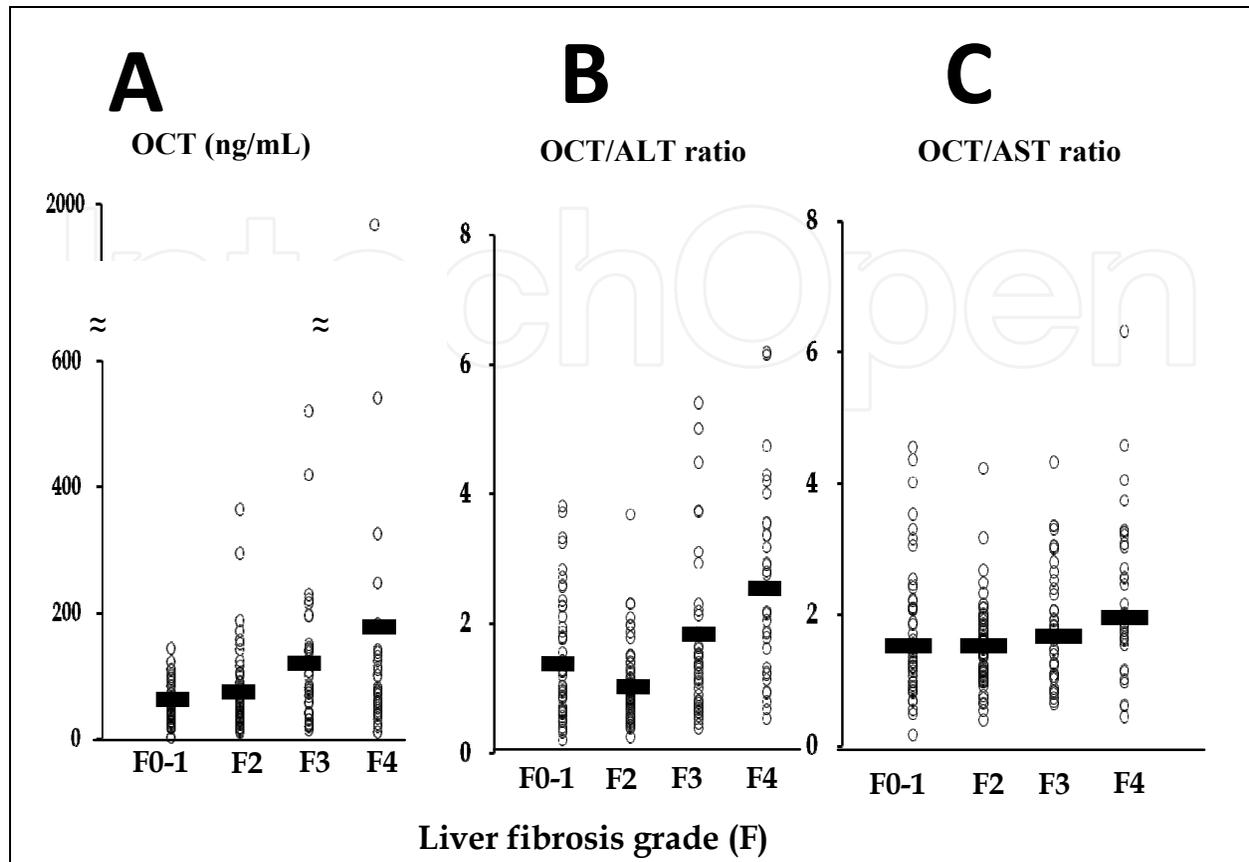
Fig. 2. The relationship between liver fibrosis grade (F) and OCT levels (A), OCT/ALT ratio (B), OCT/AST(C) ratio in NASH. The serum OCT levels and the ratio of OCT/ALT were increased in parallel with liver fibrosis.
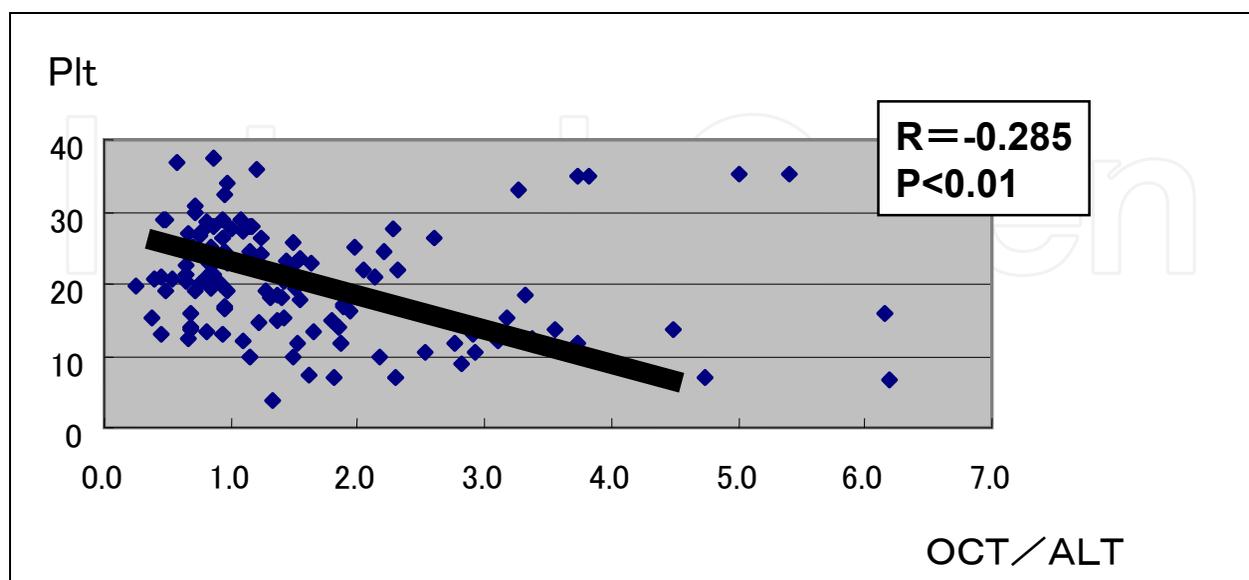
Fig. 3. The relationship between OCT / ALT ratio and platelet counts. There was a significant association between the ratio of OCT/ALT and platelet counts
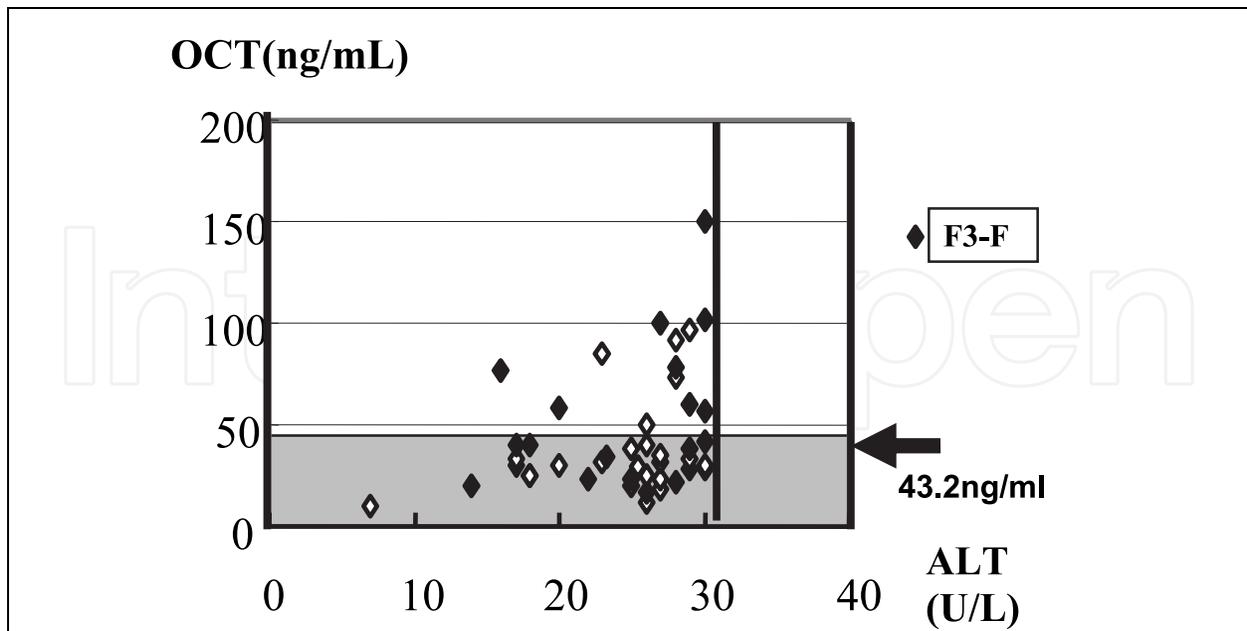
Fig. 4. OCT in NASH patients with a normal range of ALT. Forty-two patients had a normal rage of ALT, among these 42 patients, 13 (31%) had OCT over 43.2ng/mL. Of these 13 patients, eight had F3 or F4 fibrosis
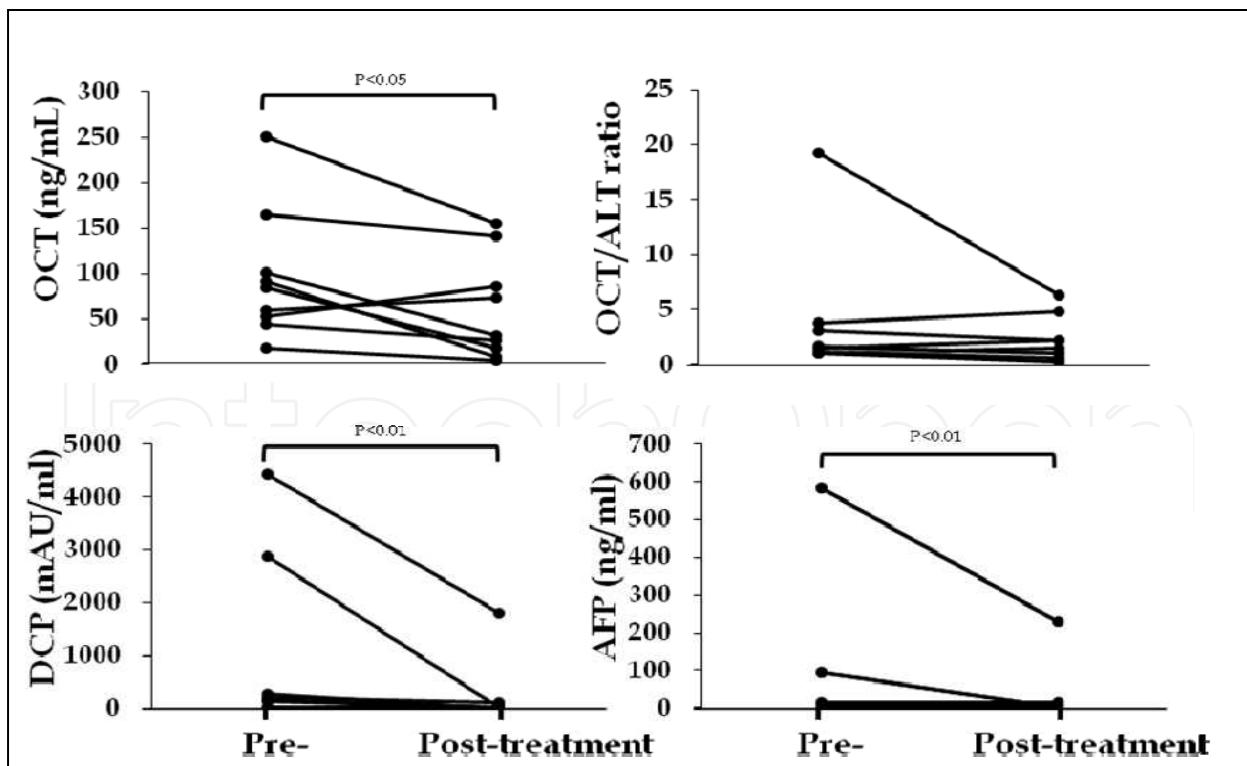
Fig. 5. Variations between the serum levels of OCT, OCT/ALT, DCP, and AFP in patients with HCC pre- and post-treatment. Serum level of OCT and OCT/ALT ratio were significantly decreased in HCC after a therapy

4. Discussion

An ideal biomarker should be simple, accurate, specific, inexpensive and readily available.

In this study, both the ratios of OCT/ALT and OCT/AST were increased in LC induced by NASH or HCV. Further, the significant association with fibrosis grade in NASH was confirmed. These data suggested that even without liver biopsy, we are able to speculate about the progression of various liver diseases by routine laboratory examinations. Concerning to the relationship between aminotransferase and the progression of liver diseases, serum AST and ALT levels do not necessarily reflect the activity and progression of NASH. It was reported that more than half of NASH patients with persistently normal ALT have a potentially progressive liver disease   (Fracanzani et al., 2008). In our study, about 30% of NASH patients with a normal range of ALT show the elevation of OCT. In addition, the majority of these patients had severe fibrosis. It was reported that serum ALT levels in severe fibrosis of NASH were decreased (Hashimoto et al., 2009). Taken together, in NASH patients with normal range of ALT and severe fibrosis, OCT might be a normal useful marker. It is unclear why OCT is frequently elevated in NASH patients with a normal range of ALT and severe fibrosis.

In addition, serum OCT and both ratios were increased in HCC compared to LC. In the previous study, we reported that the ratios were increased in HCC with NASH (Tokushige et al., 2009). In the present study, the increase in the ratios was confirmed in HCC on chronic liver dieases infected by HCV. These data suggested that the ratios were common tumor markers in HCC based on various liver diseases. In addition, we confirmed that OCT and OCT/ALT ratio were decreased after therapy. These data suggested that OCT and OCT/ALT ratio might be useful for monitoring HCC during follow-up. Especially, in HCC with NASH, the positive percentage of DPC was higher than that of AFP. However, DCP can be affected by certain medications such as warfarin, or by the condition of the patients with severe liver failure or with bile acid outflow obstruction. As some of the NASH patients were complicated with cardiovascular diseases, they required warfarinization. Also, in about 25% of HCC patients, AFP and DCP were negative (Okuda et al.,, 2001). In these cases, OCT and OCT/ALT ratio might be useful as new HCC tumor markers for diagnosis and monitoring. We need to compare the sensitivity and specificity of these ratios and AFP or DCP in much greater numbers of samples. Recently, the association of DCP with tumor invasion and pathological grading was reported (Sakon et al., 1992; Koike et al., 2001). In the future, we need to investigate the association between OCT, OCT/ALT ratio and pathological grading or the condition of HCC.

The reason why the ratio of OCT/ALT was increased in HCC is still unclear. This increase could not be explained by the distribution of OCT and ALT, since both are located in the periportal region. One possibility is that cancer cells, expressing Fas-Ligand, might have induced apoptosis of hepatocytes (Shiraki et al., 1997). Then, in apoptotic cell death, mitochondoria-related proteins were released. Another possibility is that the expression of enzymes might change in HCC.

As for comparison with several liver diseases, serum OCT levels, OCT/ALT and OCT/AST ratios in ALD were significantly higher than those of other liver diseases. ALD

is reported to be associated with mitochondrial dysfunction (Dey & Cederbaum, 2006). Therefore, it is reasonable that serum OCT levels are increased in ALD. In the future, we need to compare the sensitivity and specificity of serum OCT levels with those of serum γ-GTP levels in ALD.

5. Conclusion

Serum OCT levels and the ratios of OCT/ALT and OCT/AST are useful for monitoring the progression of liver diseases. Moreover, the possibility was suggested that serum OCT level and the OCT/ALT ratio might represent a new tumor marker of HCC and be a potent indicator for evaluation of the post-treatment HCC status. To confirm this possibility, we need validation study in much greater numbers of HCC samples.

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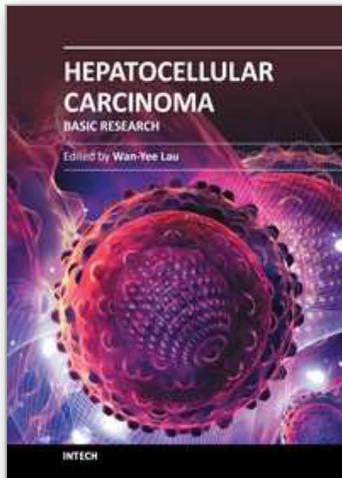
Hepatocellular Carcinoma - Basic Research

Edited by Dr. Joseph W.Y. Lau

Hepatocellular Carcinoma represents a leading cause of cancer death and a major health problem in developing countries where hepatitis B infection is prevalent. It has also become increasingly important with the increase in hepatitis C infection in developed countries. Knowledge of hepatocellular carcinoma has progressed rapidly. This book is a compendium of papers written by experts to present the most up-to-date knowledge on hepatocellular carcinoma. This book deals mainly with the basic research aspect of hepatocellular carcinoma. The book is divided into three sections: (I) Biomarkers / Therapeutic Target; (II) Carcinogenesis / Invasion / Metastasis; and (III) Detection / Prevention / Prevalence. There are 18 chapters in this book. This book is an important contribution to the basic research of hepatocellular carcinoma. The intended readers of this book are scientists and clinicians who are interested in research on hepatocellular carcinoma. Epidemiologists, pathologists, hospital administrators and drug manufacturers will also find this book useful.

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