論文内容の要旨

論文題目　Prognosis of Hepatocellular Carcinoma with Portal Vein Tumor Thrombus: Assessment Based on Clinical and Radiological Characteristics
（門脈腫瘍栓を合併した肝細胞癌の予後についての臨床放射線学的研究）

氏　名　　賈　立中

【Introduction】In recent years, the development of imaging techniques has facilitated the detection of hepatocellular carcinoma (HCC) at the early stages. The introduction of new therapeutic modalities has provided various options for the treatment of HCC, and has markedly improved the prognosis for this disease. Despite this marked progress in medical science, the prognosis of advanced HCC remains poor, particularly in patients with tumor thrombus in the portal vein (PV). Portal vein tumor thrombus (PVTT) is a crucial factor that can worsen the prognosis of HCC, the median survival time of patients with PVTT was 2.7 to 4 months if left untreated. Various treatments have been applied to improve the short-term prognosis of patients with PVTT of HCC, but the management of HCC with PVTT in the major branches is complicated and controversial. No standard treatment has been established for such patients. However, one previous study found that a substantial number of patients with PVTT had an extremely poor prognosis (several months), whereas some of these patients survived for several years or more. To improve outcomes in these patients, it is important to evaluate potential prognostic factors for the elucidation of treatment strategies. Diagnostic imaging is an important tool in the clinical setting to select the treatment and to evaluate the efficacy of the treatment once delivered. However, to our knowledge, few studies have evaluated the prognostic factors including diagnostic image factors for HCC with PVTT.

【Objective】In this retrospective study, prognostic factors were analyzed in patients of HCC with tumor thrombosis in the first branch or main trunk of the PV. Imaging characteristics that affected survival were evaluated, and the effects of the location and extent of PVTT were evaluated in association with long-term outcomes.

【Patients and Methods】During the 8-year period from January 2000 to September 2007, 3408 patients with HCC were admitted to the University of Tokyo Hospital in Japan. Of these, 107 (3%) patients were included in this study because they had gross PVTT in the first branch or/and the main trunk of the PV.

A series of imaging and clinical data were collected at the time of diagnosis of the presence of PVTT. Imaging characteristics of the tumor included the number of lesions, lobar distribution, diameter of the largest nodule, and presence of extrahepatic metastasis were evaluated. For HCC, 2 phases of data were recorded which included the initial period and the time PVTT was diagnosed. For the PVTT, recorded characteristics included location, type, maximal diameter of the PVTT, enhancement, A-P shunt, and the

presence of hepatic vein or bile duct invasion. The accumulation of Lipiodol was checked in patients who underwent transcatheter arterial chemoembolization (TACE). The effects of location, treatment for PVTT, and the initial HCC therapy were analyzed with regard to associations with patient survival.

Overall, cumulative survival rates were obtained using the Kaplan-Meier method. Each continuous variable was transformed into a binary variable divided by a median value. All possible prognostic factors for survival were analyzed by the log-rank test. Independent factors associated with the survival rate were assessed using Cox's proportional hazard regression model, where significant variables in a univariate analysis were included in a multivariate analysis.

【**Results**】The study population included a total of 107 patients (84 males and 23 females) with a mean age of 65.3 ± 10.4 years (range, 27–88 years). Median overall survival was 14 months following PVTT diagnosis. Survival rates at 6 months, 1 year, 2 years, and 3 years were 72.1%, 52.6%, 32.6%, and 29.6%, respectively. Possible associations between survival and the clinical and imaging variables were evaluated with univariate analysis using the log-rank test for all 107 patients. Fourteen factors were found to have a significant negative association with survival.

The biochemical and clinical variables (11 variables) were: age < 65 years, presence of ascites, presence of hepatic encephalopathy, AST < 54 IU/l, albumin ≥ 3.5 g/dl, total bilirubin < 2.0 mg/dl, platelet count ≥ 10×10^4/μl, Child-Pugh classification grades for the PVTT and initial HCC; HCC initial radical treatment, and PVTT treatment. The imaging variables (3 variables) were: HCC located in a single lobe, no invasion of HCC to hepatic vein or bile duct, and accumulation of Lipiodol in the PVTT after TACE. The remaining variables analyzed were not found to have predictive prognostic value in the univariate analyses:

To evaluate the prognostic factors for the survival of HCC patients with PVTT, we dichotomized the factors with a significant negative association with survival listed above and used Cox's proportional hazard model for multivariate analysis. The analysis revealed that the following variables were independent predictors for longer survival: patient age < 65 years, PVTT Child-Pugh classification grade A/B, PVTT treatment, accumulation of Lipiodol in PVTT after TACE, initial radical treatment for HCC, HCC located in a single lobe, and no invasion of the hepatic vein or bile duct.

The effect of the extent of the PVTT on survival was evaluated in terms of association with the curative strategy for PVTT and the initial treatment for HCC. The evaluation showed a non-significant negative association with invasion of the major branches of the portal trunk. Treatment for PVTT was associated with better survival than supportive care alone. Especially, surgical resection was seen to be associated with better outcomes. Concerning HCC initial treatments and prognosis, radical therapies were better than conservative treatment, hepatectomy was better than TACE/ transcatheter arterial infusion (TAI), and TACE/ TAI was better than supportive care.

【**Discussion**】In this study, Age <65 years was the only significant prognostic factor in the patient background category in this study. The risk of HCC is known to be age dependent, but the influence of

age on prognosis is controversial. Age was not found to be a prognostic factor in some previous studies performed on HCC patients with PVTT. However, the present data may conform to the generally accepted theory that younger patients need to be treated in order to gain longer survival, and that these patients should be treated with a positive, radical approach if possible.

Among measurements of liver function, factors significantly associated with prognosis were AST, albumin, and total bilirubin. The presence of ascites and hepatic encephalopathy were also associated with significant differences in survival by univariate analysis. Except for the level of AST, other parameters are used in the Child-Pugh classification system. Child-Pugh grading was an independent factor with a significant influence on overall survival based on both univariate and multivariate analyses. Poor overall survival rates in the present study were strongly associated with liver function.

Applied treatment was another major factor predictive of survival. Both univariate and Cox's multivariate analyses showed that the strategy of treatment for HCC and PVTT were positive prognostic factors. Curative initial treatment for HCC was an independent prognostic factor. The cumulative survival rate for locoregional curative treatments for HCC were better than conservative treatments. The present cases also had large differences in survival between the treated and untreated groups (with supportive care alone). The median survival time was 16 months for the treatment group, whereas the median survival time for the supportive care group was 4 months. Among the treatment strategies, surgical resection was the most effective therapy. Therefore, surgical resection may be regarded as the only potentially curative treatment for HCC with PVTT. However, hepatic resection is usually not suitable for patients who have HCC with a tumor thrombus in the main trunk or major branches of the PV. In the present study only a few (13%, 14/107) patients received resection surgery. The survival rate at 3 years was 58.7%.

Several nonsurgical modalities can be used for patients who have HCC with PVTT, such as TACE, TAI (including continuous hepatic arterial infusion chemotherapy, CHAIC), and radiotherapy (RT). TACE is usually contraindicated in patients with portal obstruction because of the high risk of hepatic insufficiency. Recently, it reported that TACE can be safe for patients who have HCC with PVTT if sufficient collateral circulation around the portal trunk were established. In the present retrospective series, 59 patients received TACE, and the accumulation of iodized oil (Lipiodol) not only in HCC nodules but also in PVTT was seen in the vast majority of patients. There was a significantly difference of survival rates according to whether accumulated Lipiodol in PVTT after underwent TACE. It seems reasonable to suppose that TACE can impair the rapid growth of PVTT.

In recent years, RT has been reported to be used for HCC patients with major PV invasion. In the present study, 18 patients received three-dimensional conformal RT; the response rate was 83%.

With regard to imaging characteristics, the tumor size, number, and extent are well known to be prognostic factors after treatment in patients with HCC. Of those factors, only the extent of HCC was seen to be a significant and independent determinant of survival. The present study had many patients with multiple HCC. There were significant differences in survival between patients with HCC in both

lobes compared with patients with HCC in only 1 lobe (p = 0.0004). For advanced HCC, prognosis should be even worse if the HCC has spread to both lobes.

HCC often involves the intrahepatic portal vein, but sometimes hepatic venous or bile duct invasion is present. According to the present data, other vascular invasion along with portal vein invasion, including hepatic vein, inferior vena cava, and bile duct invasion was 20.6% (22/107 patients) overall. There was a significant difference in the median survival time between patients with and without other vascular invasion (p = 0.001), 7.5 months and 17.5 months, respectively. Other vascular invasion along with portal vein invasion was an independent prognostic factor and therefore should receive full attention during diagnostic imaging.

【Conclusion】 In conclusion, prognostic factors were analyzed for HCC patients with tumor thrombosis in the major portal vein. Survival was associated with variables reflecting liver function, as assessed by Child-Pugh classification, by treatments for HCC and PVTT, and also by tumor extension. All treatments influenced patient outcomes, although only in the advanced stages. The results of treatments for patients with this disease remain unsatisfactory. Further prevention, early diagnosis, and development of new treatment strategies are required for such patients.