

Evaluation of A New Prognostic Staging Model (Tokyo Score) for Hepatocellular Carcinoma Patients Undergoing Hepatic Resection

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The Tokyo score, a new prognostic staging system consisting of albumin, bilirubin, and size and number of tumor has recently been proposed. To evaluate its usefulness, we examined the survival of 213 patients of hepatocellular carcinoma who had undergone hepatectomy. Disease-free and overall survival rates were calculated and difference in these rates between patients with different Tokyo scores was tested for significance using log-rank test. Regarding disease-free survival, there was a significant difference in survival between patients with Tokyo score of 0 and 1 ($p < 0.05$); however, there was no significant difference among patients with Tokyo score of 1, 2, 3 and 4. Regarding overall survival, there were a significant difference between patients with Tokyo score 0 and 1 ($p < 0.01$); however, there was no significant difference among patients with Tokyo score of 1, 2, 3 and 4. The 3- and 5-year disease-free survival rates in patients with Tokyo score of 0 were 61% and 46%, respectively, and the 3- and 5-year overall survival rates in them were 97% and 81%, respectively. Survival in patients with Tokyo score of 0 was significantly better than in those with Tokyo score of 1. The Tokyo score, a simple staging system that combines tumor factors and hepatic function, might be a good predictor of prognosis for patients of early-stage hepatocellular carcinoma with hepatectomy.

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Introduction

The establishment of new staging systems for hepatocellular carcinoma (HCC) has recently been reported worldwide, with discussions on the strengths of each system.¹⁻⁶ In addition to tumor staging, the degree of hepatic function is also necessary to determine the prognosis for HCC patients.^{1,3,4} The effectiveness of combined staging systems has already been confirmed by the Cancer of the Liver Italian Program (CLIP),¹ Barcelona Clinic Liver Cancer (BCLC) staging,² the Japan Integrated Staging (JIS) score,³ the Construction of the Chinese University Prognostic Index (CUPI) score,⁴ the Groupe d'Etude et de Traitement du Carcinome Hepatocellulaire (GETCH) score,⁵ and the SLiDe score.⁶ The superiority of these staging systems is currently under discussion. Some staging systems require many factors to determine the score and a simpler system is necessary in the clinical practice. In 2005, Tateishi et al.⁷ reported a new prognostic model for HCC patients undergoing ablation therapy and hepatectomy, involving four simple clinical parameters such as

serum albumin, bilirubin, and the size and number of tumors. The predictive ability of this score is comparable to the CLIP score, and has an advantage that it can be clinically defined without special liver function tests such as the indocyanine green test (ICG).⁸ However, the usefulness of the Tokyo score has not been fully elucidated yet. For future comprehensive analysis using the various staging systems for HCC patients described above, the usefulness of the Tokyo score should be clarified by additional examination.

In this study, we evaluated the survival of 213 HCC patients who underwent hepatic resection at several cancer institutions in Nagasaki prefecture to determine the usefulness of the Tokyo score in this field.

Patients and Methods

Data were retrospectively collected from 213 HCC patients (180 males and 33 females) who underwent surgery at the Division of

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Surgical Oncology, Department of Translational Medical Sciences, Nagasaki University Graduate School of Biomedical Sciences (NUGSBS) and its associated hospitals between January 1994 and October 2004. Patients with tumor residues after hepatectomy were excluded from this study. Prior to surgery for HCC, 75 patients were treated with either chemoembolization (n=65), alcohol injection (n=3), radio frequency ablation (n=3) or a combination of chemoembolization and alcohol injection (n=4); however, tumors were not completely controlled in these patients. After surgery, 4 patients received adjuvant 5-fluorouracil chemotherapy by intra-arterial injection through a subcutaneously implanted reservoir to prevent tumor recurrence, although there were no definite indications of adjuvant treatments before and after hepatectomy in our patients at this stage. Of 134 patients (63%) who had tumor recurrence after hepatectomy (liver 126, bone 4, lung 2 and lymph node 2), 70 patients received chemoembolization, 29 alcohol injection, 5 re-resection, 7 ablation therapy, 5 intravenous chemotherapy as the second line treatment, and 18 received no adjuvant therapies.

The indication of operation was limited to Child A patients and some Child B patients.⁹ The volume of liver to be resected was estimated according to the indocyanine green retention rate at 15 min (ICG R15) using Takasaki's formula.⁸ The expected liver volume for resection, excluding the tumor (cm³) was measured by computed tomography (CT) volumetry.¹⁰ Operative procedures included lobectomy or extended lobectomy (n=59), segmentectomy or subsegmentectomy (n=67), and partial resection (n=87). Radical hepatectomy was performed to remove the hepatic tumor, leaving no residual tumor.

The study was approved by the Ethics Review Board of our department at NUGSBS. Mortality and morbidity data were collected from the NUGSBS database, and provided by collaborating associated hospitals.

The Tokyo score is defined by four simple parameters (Table 1).⁷ The Tokyo score is defined as the sum of the 4 scores assigned to respective parameters, and can take the values from 0 to 8.

Disease-free and overall survival rates were calculated according to the Kaplan-Meier method, and difference between groups was tested for significance using the log-rank test. Necessary calculations were performed using StatView J5.0 (Statistical Analysis System Inc., Cary, NC).

Table 1. Definition of Tokyo score^a

Item	Score		
	0	1	2
Serum albumin (g/dL)	>3.5	2.8-3.5	<2.8
Serum bilirubin (mg/dL)	<1	1-2	>2
Tumor size (cm)	<2	2-5	>5
Number of tumors	<3	3	>3

^a Tokyo score is defined as the sum of the respective scores assigned to each item.

Results

Patient characteristics

The age of patients at the time of surgery varied from 28 to 81 years with the mean (\pm standard deviation) of 61 ± 10 years. Background liver abnormalities included chronic viral hepatitis in 118 patients (56%), cirrhosis in 86 (40%), hepatic fibrosis in 4 (2%), normal liver in 5 (2%), and were associated with hepatitis virus B (n=72), hepatitis virus C (n=118), both hepatitis B and C (n=5), or non-B non-C hepatitis (n=18).

Patient survival

In the present series, the Tokyo score varied from 0 to 5; 0 in 25 patients, 1 in 53, 2 in 70, 3 in 41, 4 in 20 and 5 in 4. Figure 1 shows the disease-free and overall survivals by Tokyo score and Table 2 shows the 1-, 3- and 5-year survival rates by Tokyo score. With respect to the disease-free survival, difference between pa-

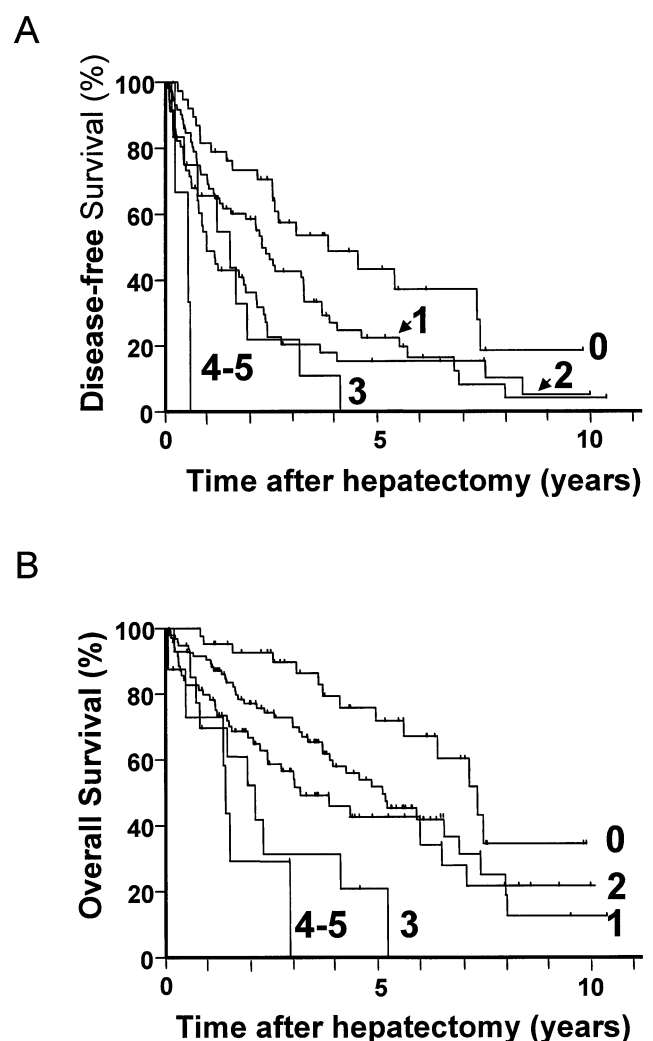


Figure 1. Kaplan-Meier disease-free (A) and overall survival (B) curves by Tokyo score in patients who underwent hepatectomy for HCC.

Table 2. Disease-free and overall survival rates by Tokyo score

Survival	Tokyo score	Survival rate (%)		
		1-year survival	3-year survival	5-year survival
Disease-free survival	0	83	61	46
	1	69	43	23
	2	49	20	15
	3	66	22	11
	4	0	0	0
Overall survival	0	100	97	81
	1	90	71	48
	2	81	51	42
	3	75	34	23
	4	73	0	0

tients with Tokyo score of 0 and 1 ($p=0.013$) was more remarkable compared to difference in survival between patients with Tokyo score of 1 and 2 ($p=0.085$), 2 and 3 ($p=0.683$), and 3 and 4-5 ($p=0.0698$). With respect to the overall survival, difference between patients with Tokyo score of 0 and 1 was also remarkable ($p=0.004$) compared to difference in survival between patients with Tokyo score of 1 and 2 ($p=0.413$), 2 and 3 ($p=0.160$), and 3 and 4-5 ($p=0.232$). Table 2 shows that the survival rates of disease-free and overall survival were remarkably better in patients with Tokyo score of 0 than in those with the score of 1.

Discussion

European and Asian institutes have recently proposed new staging systems with potentially superior to the TNM system for predicting survival in HCC patients.^{1-7,11,12} However, the superiority of these staging systems has not been fully demonstrated to confirm their applicability. To clarify the superiority of various staging models, comprehensive analysis is expected. Kudo et al.,^{3,13} Ueno et al.,¹⁴ and Omagari et al.⁶ examined the significance of staging systems in Japanese HCC patients; however, the treatment modalities of these studies varied. It is difficult to study such heterogeneous groups because the survival of patients in each modality is not comparable. Therefore, in this study we focused on HCC patients who had undergone hepatectomy.

The Tokyo score, involving four common parameters assessed by multivariate analysis of a large number of HCC patients, is thought to be a reliable system compared to the CLIP score or BCLC system.⁷ The present study revealed that the discrimination of disease-free and overall survival was more remarkable only between patients with score of 0 and 1, although the number of patients with Tokyo score of 0 was not large. Our previous results indicate that the survival curve in HCC patients with the earliest stage cannot be compared well with the TNM stage, CLIP score, JIS score or their modification.¹⁵⁻⁷ From Tateishi's report,⁷ the 5-year survival rate in

patients with Tokyo score of 0 was 78.7%, which was higher than the rate in those with Tokyo score of 1 (62.1%). Similarly, in the present study, which restricted the patients to those undergoing hepatic resection, the 5-year survival in patients with Tokyo score of 0 (81%) was highest. Therefore, with respect to the discrimination of the earliest-stage HCC, the Tokyo score was superior to the staging systems described above. However, the ability in the discrimination of patients with respective Tokyo scores of 1-4 was not significant in the present study. In particular, no difference was observed between patients with Tokyo score of 1 and 2. The smallness of patients with Tokyo score of 0, 4 and 5 compared to those with Tokyo score of 1, 2 and 3 might be due to that patients in the present study were restricted to those who underwent surgical resection. Previous reports showed that difference in survival by Tokyo score in the advanced stage was statistically significant in a similar population of HCC patients.^{15,17} Tateishi et al.⁷ also stated that the Tokyo score might not be predictive for advanced disease. From these results, the superiority of the Tokyo score to other staging models could not be confirmed. A comprehensive examination of these staging systems and reliable statistical analysis by multivariate analysis^{6,7,17} using Akaike's information criteria (AIC)¹⁸ is necessary in the next step. Although CLIP score, which might not be appropriate for discriminating early HCC,^{3,13} has been frequently used in the western countries,¹⁹⁻²¹ the Tokyo score could be applied in such countries as well because the parameters in Tokyo score were all simple. Besides, it is possible to detect small HCC less than 2 cm as the diagnostic ability may be improved in such countries nowadays.²²

To improve the discrimination capability of the Tokyo score retaining its advantages, inclusion of additional useful parameters is necessary. Vascular involvement in tumors, which is a strong predictor of malignant behavior in HCC, is not used in Tateishi's analysis.⁷ Sensitive tumor markers such as protein induced by vitamin K absence, the antagonist II (PIVKA-II) or a-feto protein L3 fraction may be candidates for additional predictors.^{15,17,18,23,24} It is important that parameters in the staging model are simple, and can be

used in general clinical practice without special laboratory examinations or images.

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