

Original paper

Evaluation of New Prognostic Staging Systems (SLiDe score) for Hepatocellular Carcinoma Patients who Underwent Hepatectomy

Atsushi Nanashima MD,¹ Katsuhisa Omagari MD,² Yoriyisa Sumida MD,¹

Takafumi Abo MD,¹ Hidetoshi Fukuoka MD,¹ Hiroaki Takeshita MD,¹

Shigekazu Hidaka MD,¹ Kenji Tanaka MD,¹ Terumitsu Sawai MD,¹

Toru Yasutake MD,¹ Takeshi Nagayasu MD,¹ Youhei Mizuta MD,²

Kazuo Ohba MD,² Ken Ohnita MD,² Yoshiko Kadokawa MD²

¹Division of Surgical Oncology and ²Second Department of Internal Medicine,
Department of Translational Medical Sciences, Nagasaki University Graduate School of
Biomedical Sciences, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan

Running Title: SLiDe score in HCC patients after hepatectomy

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Address correspondence to: Atsushi Nanashima, MD,

Division of Surgical Oncology, Department of Translational Medical Sciences,
Nagasaki University Graduate School of Biomedical Sciences, 1-7-1 Sakamoto,
Nagasaki 852-8501, JAPAN.

Tel.: +81-95-849-7304 Fax: +81-95-849-7306

E-mail: a-nanasm@net.nagasaki-u.ac.jp

ABSTRACT

Background/Aims: A new prognostic staging system, the SLiDe (S, stage; Li, liver damage; De, des-gamma-carboxy prothrombin) score was recently proposed. We examined 207 HCC patients following hepatic resection to determine the usefulness of this staging system for HCC patients after surgery.

Methodology: Disease-free and overall survival rates were calculated according to the Kaplan-Meier method, and differences between groups were tested for significance using the log-rank test.

Results: Regarding disease-free survival, there were no significant differences in survival between SLiDe score 0 *vs* 1, between score 2 *vs* 3, and between score 4 *vs* 5. There were significant differences between 0-1 *vs* 2-3 ($p < 0.01$) and between 2-3 *vs* 4-5 ($p < 0.01$). Regarding overall survival, there were no significant differences in survival between score 0 *vs* 1, between score 2 *vs* 3, and between score 4 *vs* 5. There were significant differences between 0-1 *vs* 2-3 ($p < 0.05$) and between 2-3 *vs* 4-5 ($p < 0.01$).

Conclusions: The SLiDe score, a staging system that combines tumor factors, a tumor marker and hepatic function, might be a better predictor of prognosis in HCC patients who have undergone hepatic resection.

KEY WORDS: Hepatocellular carcinoma; SLiDe score; Hepatectomy

ABBREVIATIONS: S, stage; Li, liver damage; De, des-gamma-carboxy prothrombin (SLiDe) score, Japan Integrated Staging System (JIS)

INTRODUCTION

The establishment of new staging systems for hepatocellular carcinoma (HCC) has been recently 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 of HCC patients (1, 3, 4). The effectiveness of combined staging systems has already been confirmed such as the Italian Cancer of the Liver 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 Tokyo score (6). In patients who underwent surgical resection, the appropriate staging of hepatic function instead of the Child-Pugh classification is expected because the majority of patients show good hepatic function. Sensitive tumor markers for HCC have been established. As the alpha fetoprotein (AFP) level does not always reflect malignancy, des-gamma-carboxy prothrombin (protein induced by vitamin K absence or the antagonist II; PIVKA-II) has been widely used to diagnose HCC in the last decade (7). Our group has proposed the effectiveness of the modified CLIP score using protein induced by vitamin K absence or antagonist II (PIVKA-II), instead of AFP concentration used in the original CLIP (8, 9). Omagari *et al.* recently proposed a new staging system called the SLiDe score, consisting of the Japanese TNM stage, Liver Damage grade and the serum level of des-gamma-carboxy prothrombin (DCP) based on a reasonable examination in HCC

patients using multivariate analysis (10). This staging system might well match the current status for evaluating HCC patients after hepatectomy.

It is difficult to simultaneously evaluate HCC patients who have undergone various modalities such as hepatectomy, local ablation therapy or chemoembolization. Therefore, in this study, we applied the SLiDe score to evaluate patient survival in 207 HCC patients who underwent hepatic resection at several cancer institutions in Nagasaki prefecture, to determine its usefulness in this field.

METHODOLOGY

Patients

Data from 207 HCC patients (175 males, 32 females) who underwent surgery at the Division of Surgical Oncology, Department of Translational Medical Sciences, Nagasaki University Graduate School of Biomedical Sciences (NUGSBS) and its associated hospitals between January 1994 and December 2004 were retrospectively collected. Patients with tumor residues after hepatectomy were excluded from this study. Prior to surgery for HCC, 72 patients were treated with either chemoembolization (n=65), alcohol injection (n=3) or a combination of these two modalities (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; however, there were no definite indications of adjuvant treatments before and after hepatectomy in our patients at this stage. Of 132 patients (64%) with tumor recurrence

after hepatectomy (liver [n=124], bone [n=4], lung [n=2] and lymph node [n=2]), 68 patients received chemoembolization, 29 alcohol injection, 5 re-resection, 7 ablation therapy, 5 received intravenous chemotherapy as the second line treatment and 18 patients received no adjuvant therapies.

The indication of operation was limited to Child A patients and some Child B patients (11). The volume of liver to be resected was estimated according to the results of the indocyanine green retention rate at 15 min (ICG R15) using Takasaki's formula (12). The expected liver volume for resection, excluding the tumor (cm³) was measured by computed tomography (CT) volumetry (13). Operative procedures included lobectomy or extended lobectomy (n=57), segmentectomy or subsegmentectomy (n=65), and partial resection (n=85). Radical hepatectomy was performed to remove the hepatic tumor without leaving any residual tumor.

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

Measurement of tumor marker

A peripheral blood sample (4 mL) for tumor marker measurement was collected from each patient and centrifuged at 3,000 rpm (1,000 × g) for 10 minutes. DCP was assayed by an enzyme-linked immunoassay using *Eitest*® *PIVKA-II* (Sanko Junyaku Co., Tokyo, Japan). Up to 1996, the minimum measured value of DCP was 100 mAU/mL. After 1997, the normal value was determined as <40 mAU/mL.

Staging criteria

We used the pathological tumor-node-metastasis (pTNM) classification system of the Liver Cancer Study Group of Japan in 2000 (**Table 1**) (14). The Liver Damage Grade by the Liver Cancer Study Group of Japan was used for hepatic function staging (**Table 2**) (14). The sum of the score in each parameter (TNM stage, Liver damage grade and DCP) was counted in the SLiDe scoring system (**Table 3**) (15).

Statistical analysis

Disease-free and overall survival rates were calculated according to the Kaplan-Meier method, and differences between groups were tested for significance using the log-rank test. A two-tailed *P* value of < 0.05 was considered significant in this study.

Statistical analyses were performed using SAS software (Statistical Analysis System Inc., Cary, NC).

RESULTS

Patient characteristics

The mean age of the patients at the time of surgery was 63 ± 9 years (range, 28-81 years). Background liver abnormalities included chronic viral hepatitis in 113 patients (55%), cirrhosis in 85 (41%), hepatic fibrosis in 4 (2%) and normal liver in 5 (2%), associated with hepatitis virus B (n=68), hepatitis virus C (n=116), both hepatitis B and C (n=5), or non-B non-C hepatitis (n=18). Concerning the PIVKA-II level, 85 patients

showed a value ≥ 400 mAU/ml (41%). According to the Liver Damage grade, 159 patients were classified as A (77%) and 48 (23%) as B.

Patient survival

Figure 1 shows the disease-free and overall survival associated with the SLiDe score. With respect to disease-free survival, there were no significant differences in survival, between score 0 vs 1, between score 2 vs 3, and between score 4 vs 5. There were significant differences between 0, 1 vs 2, 3 ($p < 0.01$) and between 2, 3 vs 4, 5 ($p < 0.01$). With respect to overall survival, there were no significant differences in survival, between score 0 vs 1, between score 2 vs 3, and between score 4 vs 5. There were significant differences between 0, 1 vs 2, 3 ($p < 0.05$) and between 2, 3 vs 4, 5 ($p < 0.01$).

DISCUSSION

European and Asian institutes have recently proposed new staging systems with potentially superior capability for predicting survival in HCC patients compared to the TNM system (1-7, 15, 16); however, the superiority of these staging systems has not been fully demonstrated with reliable statistical analysis as evidence of their applicability.

Kudo *et al.* have reported the usefulness of JIS staging, which has superior prognostic capabilities for the survival of HCC patients when compared to the CLIP score (3, 17). The JIS score consists of the Japanese TNM stage and Child-Pugh classification although the majority of patients had Child-Pugh A disease and even

patients with Child-Pugh B had no encephalopathy, ascites or significant hyperbilirubinemia in HCC patients undergoing surgical resection in this series. Therefore, HCC patients who underwent surgery might be classified using other classifications of hepatic function. The liver damage grade based on the value of the indocyanine green retention rate at 15 minutes (ICG R15) was appropriate to individualize the population of HCC patients compared to using the Child-Pugh classification. ICGR15 is an estimation of indocyanine green clearance; this parameter has been widely used in the field of surgery in Japan as a useful marker of hepatic function (12, 13). ICGR15 is a significant prognostic factor in HCC patients with or without cirrhosis (18). In the SLiDe score (10), the TNM stage and liver damage grade were included. Furthermore, the DCP level was also applied in this staging system. This parameter was thought to be useful for predicting poor patient survival. In our preliminary study, a higher PIVKA-II level after treatment might also reflect poor survival compared to the AFP level in HCC patients undergoing hepatectomy (in-press, HBP). The SLiDe score consisting of these 3 powerful parameters was thought to be more reliable compared to other combined staging systems. Omagari et al. reported that the SLiDe classification showed a lower AIC score compared with the JIS and CLIP score in HCC patients treated with other modalities, indicating that it was the most appropriate system (10).

This study revealed that the discrimination of disease-free and overall survival between scores is good; however, discrimination between 0 vs 1, 2 vs 3, and 4 vs 5 was not significant, respectively. Therefore, these populations could be divided into 3

subgroups (score 0-1, 2-3, and 4-5). Omagari et al. also reported in their original manuscript that SLiDe 0 and 1, or SLiDe 4, 5 and 6 needed to be joined, respectively. Our future goal is to clarify the superiority of this staging system by comparing with other reliable staging systems in a larger number of HCC patients using multivariate analysis for patient survival (10).

In conclusion, we conducted a retrospective analysis of prognosis using a new staging system called the SLiDe score in 207 Japanese HCC patients who underwent hepatic resection. The discrimination ability of disease-free and overall survival between SLiDe 0-1 and 2-3 and 4-5 was statistically significant, respectively. The staging systems, combined with tumor-related factors, sensitive tumor markers and hepatic function are useful predictors of HCC prognosis.

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TABLE 1 Definition of Tumor Node Metastasis Classification

T factor defined by 3 criteria: Single, <2 cm in diameter, or no vascular involvement

T1	Agree with all 3 criteria
T2	Agree with 2 of 3 criteria
T3	Agree with 1 of 3 criteria
T4	Agree with no criteria
N0	No metastasis to lymph nodes
N1	Metastasis to lymph nodes
M0	No distant metastasis
M1	Distant metastasis

Stage I	T1N0M0
Stage II	T2N0M0
Stage III	T3N0M0
Stage IVA	T4N0M0 or any T N1M0
Stage IVB	Any T N0-1 M1

TABLE 2 Definition of Liver Damage Grade

	A	B	C
Ascites	None	Responsive	Unresponsive
Serum bilirubin (mg/dL)	<2.0	2.0-3.0	>3.0
Serum albumin (g/dL)	>3.5	3.0-3.5	<3.0
ICG R15 (%)	<15	15-40	>40
Prothrombin activity (%)	>80	50-80	<50

ICG R15; Indocyanine green retention rate at 15 minutes

TABLE 3 Classification of SLiDe Score

	0	1	2	3
Liver damage	A	B	C	
TNM stage	I	II	III	IVA-B
DCP (mAU/mL)	<400	≥400		

DCP, des- γ -carboxy prothrombin

FIGURE LEGENDS

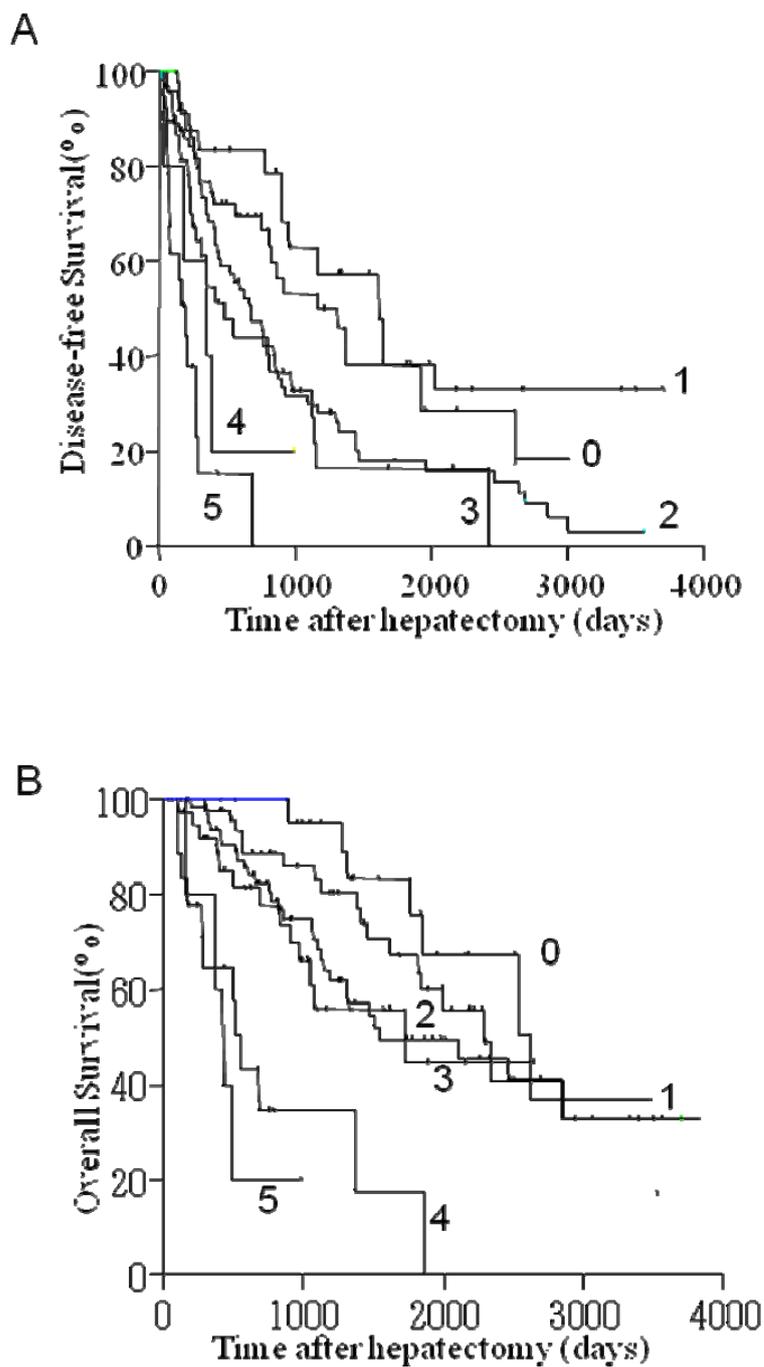


FIGURE 1 Kaplan-Meier disease-free (A) and overall survival (B) curves in patients

who underwent hepatectomy for HCC by SLiDe score.