

Staging Systems for Hepatocellular Carcinoma

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Received: May 5, 2013 Revised: June 28, 2013

Accepted: June 30, 2013

Published online: September 18, 2013

Zhang H, Yang T. Staging Systems for Hepatocellular Carcinoma. *Journal of tumor* 2013; 1(4): 20-23 Available from: URL: <http://www.ghrnet.org/index.php/jt>

INTRODUCTION

Hepatocellular carcinoma is the most common primary malignancy of the liver and a major cause of mortality. In the last few decades, the management of HCC has changed significantly due to an improved diagnostic capacity, the development of evidence-based staging systems, and the availability of effective treatment. A precise staging before making therapeutic decisions is helpful to estimate prognosis and satisfactory treatment with greatest survival advantage. To date, at least 8 staging systems have been proposed from independent study groups to predict the outcome of patients with HCC^[1]. Several staging systems are most widely adopted, such as Tumor-Node-Metastasis system by American Joint Committee on Cancer, Okuda staging, CLIP (Cancer of Liver Italian Program) staging, BCLC (Barcelona Clinic Liver Cancer) staging, CUPI (Chinese University Prognostic Index) staging, and JIS (Japanese Integrated System) staging^[2].

Different staging systems have different predictive power for HCC patient in different area of the world. That could be from the difference in tumour biology, the aetiology of liver cirrhosis and also the difference of treatment modality strategies. In Eastern countries, studies from China, Korea, and Taiwan demonstrated that either TNM^[3-5] or CLIP^[6,7] had better predictive power than others, while many studies from Japan favored JIS as the best staging system^[7-9]. In contrary, most studies from Western countries suggested that either BCLC^[8-10] or CLIP^[11] had superior discriminatory power.

THE TNM CLASSIFICATION

The TNM staging system is widely used by physicians in several fields. It has been proposed also as the best classification to assess the outcome of HCC patients undergoing resection or orthotopic liver transplantation. However, the TNM staging system only consists of variables regarding tumor morphology and pathology, while prognosis of HCC patients relies heavily on aspects related to liver cirrhosis as well. Although the TNM staging system may be useful to stratify series of patients at different stages, a couple of recent studies have shown that this classification lacks prognostic value for early HCC patients treated with resection or transplantation^[12,13].

ABSTRACT

Clinical staging systems for cancer provide guidelines for patient assessments and treatments. A proper staging is essential for objective comparison between the outcomes of different treatments. While the prognosis of most solid tumors is generally dependent on tumor stage at presentation, prediction of prognosis in hepatocellular carcinoma (HCC) patients is somewhat more complicated due to various aspects affecting patient survival including cirrhosis and underlying liver function. Up to date, at least eight staging systems have been proposed for HCC, but the optimal staging system for HCC is still under intense debate. Each existing staging system, characterized by the patient population based on which it was constructed, may have different predictive power for HCC patient in different area of the world, roughly the East and the West. The lack of a consensus on HCC staging systems is mostly in part related to the heterogeneity in treatment modalities at diagnosis. Therefore, we hereby propose a novel staging system for HCC, named as the Eastern staging, based on the authors' previous study with a large cohort of Chinese patients undergoing surgical resection. Compared with the six existing staging systems, including CLIP, TNM, JIS, BCLC, CUPI and Okuda, the Eastern staging appears to have the best predictive ability for mortality at 1, 3, and 5 years. Thus, we believe the Eastern staging to be a simple and practical system for prognostic factor evaluation, risk level determination, and prognosis assessment after surgical resection in patients with HCC.

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Key words: Hepatocellular carcinoma, Staging and Surgical resection

THE CLIP STAGING SYSTEM

The CLIP criteria combine the Child–Pugh classification with tumor characteristics including morphology (uninodular, multinodular or massive), portal vein thrombosis, and high serum levels of alpha fetoprotein (AFP, 400 ng/mL). The above factors have been described as adverse prognostic characteristics in patients with HCC. Inclusion of tumor-specific prognostic factors has improved the prognostic accuracy of the CLIP scores. The CLIP scores can adequately separate patients with no adverse tumor progression factors (CLIP 0), who have the best prognosis, from those with even one adverse prognostic factor, whose prognosis is significantly reduced.

THE JIS SCORE

The JIS score consists of the Child–Pugh classification and the TNM stage^[14], thus taking account of both liver function and tumor characteristics. The JIS score has been compared with the BCLC and CLIP in a Japanese study^[15] of 1679 patients, and found to be superior in prognostic determination. However, the JIS score was developed based solely on Japanese HCC patients, further prospective studies are required among distinct patients groups, countries, and racial groups.

THE BCLC STAGING SYSTEM

The BCLC staging has emerged during recent years as the standard classification that is used for trial design and clinical management of patients with HCC. This classification has been approved by European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD) and has subsequently been corroborated in clinical studies. However, it seems that BCLC is suboptimal to predict prognosis of HCC patients undergoing surgical resection. Many factors contribute to interpret this finding. First, BCLC mainly included a small number of HCC patients undergoing surgery in their original studies, so they include prognostic variables that theoretically have less predictive power in the subgroup undergoing surgical resection. Secondly, there is considerable conflict in surgical indications for HCC in different centers. In the BCLC staging treatment strategy, surgical resection is only recommended for BCLC A stage. However, many selected patients with intermediate even advanced HCC still underwent surgical resection in many centers, especially from Eastern countries. In 2011, the authors reported a consecutive series of 511 selected patients from China with advanced HCC (BCLC stage C) who underwent surgical resection in the authors' unit from 2001 to 2007^[16], which was obviously distinctive from therapeutic principles by the BCLC constitutors. Finally, the BCLC system seems to have overemphasized the prognostic effect of performance status, which leads to relatively poor performance in patient survival prediction in other settings of patient demographic characteristics.

THE EASTERN STAGING—BETTER PROGNOSIS PREDICTION FOR SURGICALLY TREATED PATIENTS

Treatment modality is a significant confounding effect on the prognosis of HCC. The lack of a consensus on HCC staging systems is mostly in part related to the heterogeneity in treatment modalities at diagnosis. Therefore, it is necessary to establish specific HCC staging systems to assess prognosis, directed toward different treatment modalities, so as to own more powerful discriminatory ability.

Therefore, the authors used a large cohort of surgically treated Chinese patients, and identified independent risk factors of poor survival by univariate and multivariate analyses. A total of 958 patients with 857 males and 101 females, the median age was 50 years (range, 10–83 years). The HBsAg positive rate was 91.8%, while the anti-hepatitis C virus (HCV) positive rate was 2.5%. Although 73.6% of patients had histologic evidence of cirrhosis in the resected specimens, the majority of patients presented with well-preserved hepatic function; 88.2% of patients had biochemical profiles consistent with Child–Pugh A, and 11.8% with Child–Pugh B. The tumor was larger than 5 cm in 52.3% in these patients. Macroscopic vascular invasion was present in 152 patients (15.9%), mainly including portal vein thrombosis (PVT) in 133 patients. On the basis of this cohort of patients, a new staging system named the Eastern staging with five stages was proposed (Table 1).

Table 1 The Eastern Staging System for resectable hepatocellular carcinoma in a Chinese cohort.

Variable	Score	
	0	1
Macroscopic vascular invasion	No	Yes
Tumor number	Solitary	Multiple
Performance status	0	1–2
Microscopic vascular invasion	No	Yes
Extrahepatic spread	No	Yes
Maximum tumor size	≤5 cm	>5 cm
Albumin	≥35 g/L	<35 g/L
AST ¹	≤40 U/L	>40 U/L
Total bilirubin	≤17 μmol/L	>17 μmol/L
Presence of cirrhosis	No	Yes
Cumulative score		
Stage 1		
Stage 2	0–1	
Stage 3	2–3	
Stage 4	4–5	
Stage 5	6–7	

¹: AST aspartate aminotransferase.

The Eastern staging was compared with six existing staging systems (Figure 1). It appears to have the best predictive ability for mortality at 1, 3, and 5 years. The prognostic results presented as comparison of 5-year survival of different stages among five staging systems was shown in table 2. However, it is by no means a universal staging system for HCC. It focuses predominantly on those patients subject to scheduled surgical resection. The majority of patients in this Chinese cohort had chronic HBV infection, which is common situation in many Eastern countries, thus the results may not be applicable readily to patients in the United States or other Western countries. In addition, approximately 15–50% of patients in the cohort were in relatively advanced stage by different staging systems, and this might limit the generalizability of this study. In brief, from the Eastern staging, it is easy to determine the patient's risk level and assess prognosis after surgical resection. So we consider this a novel staging designed for resectable HCC exclusively, and it will provide adequate prognostic information to patients, when surgical resection is adopted, especially in Chinese and other Eastern countries.

Table 2 5-year survival of different stages among five staging systems.

Staging System	Stage 1	Stage 2	Stage 3	Stage 4	Stage 5
TNM	75.6%	64.4%	15.0%	11.3%	
CLIP	81.3%	62.1%	37.7%	19.8%	10.6%
JIS	90.5%	72.2%	31.0%	11.1%	
BCLC	A: 81.7%	B: 66.0%	C: 31.2%		11.5%
Eastern staging	93.3%	76.0%	43.2%	11.5%	0%

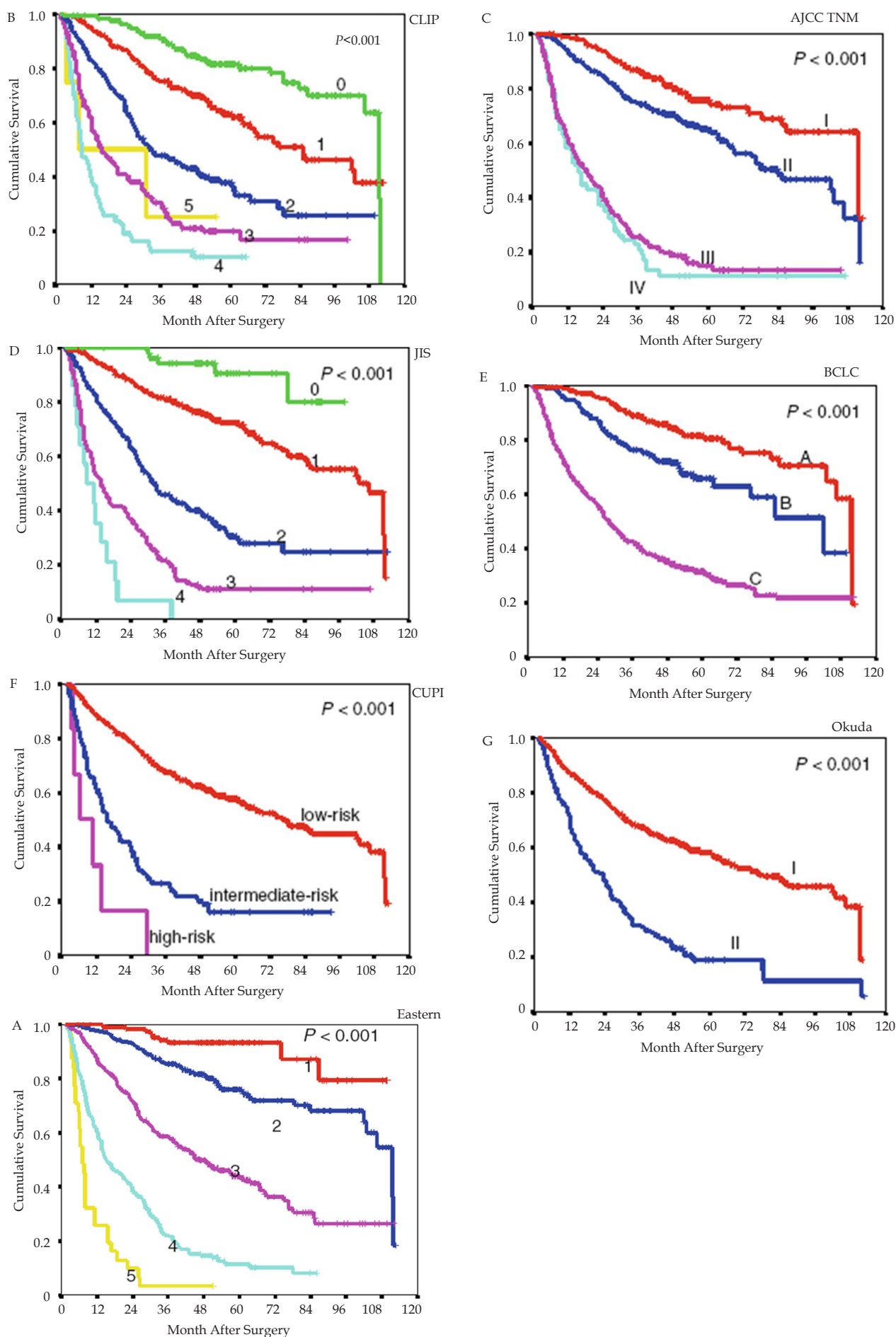


Figure1 Comparison of overall survival between the Eastern staging and six existing staging systems.

CONCLUSION

More than 10 staging systems have been proposed for HCC. The optimal staging for HCC is still under intense debate. The Eastern staging appears to be a simple and practical system for prognostic factor evaluation, risk level determination, and prognosis assessment after surgical resection in patients with HCC.

REFERENCES

- Marrero JA, Fontana RJ, Barrat A, Askari F, Conjeevaram HS, Su GL, Lok AS. Prognosis of hepatocellular carcinoma: comparison of 7 staging systems in an American cohort. *Hepatology* 2005; **41**(4): 707-716
- Kudo M, Chung H, Haji S, Osaki Y, Oka H, Seki T, Kasugai H, Sasaki Y, Matsunaga T. Validation of a new prognostic staging system for hepatocellular carcinoma: the JIS score compared with the CLIP score. *Hepatology* 2004; **40**(6): 1396-1405
- Huang YH, Chen CH, Chang TT, Chen SC, Wang SY, Lee HS, Lin PW, Huang GT, Sheu JC, Tsai HM, Lee PC, Chau GY, Lui WY, Lee SD, Wu JC. Evaluation of predictive value of CLIP, Okuda, TNM and JIS staging systems for hepatocellular carcinoma patients undergoing surgery. *J Gastroenterol Hepatol* 2005; **20**(5): 765-771
- Seong J, Shim SJ, Lee IJ, Han KH, Chon CY, Ahn SH. Evaluation of the prognostic value of Okuda, Cancer of the Liver Italian Program, and Japan Integrated Staging systems for hepatocellular carcinoma patients undergoing radiotherapy. *Int J Radiat Oncol Biol Phys* 2007; **67**(4): 1037-1042
- Chen TW, Chu CM, Yu JC, Chen CJ, Chan DC, Liu YC, Hsieh CB. Comparison of clinical staging systems in predicting survival of hepatocellular carcinoma patients receiving major or minor hepatectomy. *Eur J Surg Oncol* 2007; **33**(4): 480-487
- Cho YK, Chung JW, Kim JK, Ahn YS, Kim MY, Park YO, Kim WT, Byun JH. Comparison of 7 staging systems for patients with hepatocellular carcinoma undergoing transarterial chemoembolization. *Cancer* 2008; **112**(2): 352-361
- Kondo K, Chijiwa K, Nagano M, Hiyoshi M, Kai M, Maebara N, Ohuchida J, Nakao H, Ohkuwa Y. Comparison of seven prognostic staging systems in patients who undergo hepatectomy for hepatocellular carcinoma. *Hepatology* 2007; **54**(7): 1534-1538
- Guglielmi A, Ruzzenente A, Pachera S, Valdegamberi A, Sandri M, D'Onofrio M, Iacono C. Comparison of seven staging systems in cirrhotic patients with hepatocellular carcinoma in a cohort of patients who underwent radiofrequency ablation with complete response. *Am J Gastroenterol* 2008; **103**(3): 597-604
- Cillo U, Vitale A, Grigoletto F, Farinati F, Brolese A, Zanusi G, Neri D, Boccagni P, Srsen N, D'Amico F, Ciarleglio FA, Bridda A, D'Amico DF. Prospective validation of the Barcelona Clinic Liver Cancer staging system. *J Hepatol* 2006; **44**(4): 723-731
- Collette S, Bonnetain F, Paoletti X, Doffoel M, Bouché O, Raoul JL, Rougier P, Masskouri F, Bedenne L, Barbare JC. Prognosis of advanced hepatocellular carcinoma: comparison of three staging systems in two French clinical trials. *Ann Oncol* 2008; **19**(6): 1117-1126
- Cammà C, Di Marco V, Cabibbo G, Latteri F, Sandonato L, Parisi P, Enea M, Attanasio M, Galia M, Alessi N, Licata A, Latteri MA, Craxi A. Survival of patients with hepatocellular carcinoma in cirrhosis: a comparison of BCLC, CLIP and GRETCH staging systems. *Aliment Pharmacol Ther* 2008; **28**(1): 62-75
- Marsh JW, Dvorchik I, Bonham CA, Iwatsuki S. Is the pathologic TNM staging system for patients with hepatoma predictive of outcome? *Cancer* 2000; **88**(3): 538-543
- Llovet JM, Bruix J, Fuster J, Castells A, Garcia-Valdecasas JC, Grande L, Franca A, Brú C, Navasa M, Ayuso MC, Solé M, Real MI, Vilana R, Rimola A, Visa J, Rodés J. Liver transplantation for small hepatocellular carcinoma: the tumor-node-metastasis classification does not have prognostic power. *Hepatology* 1998; **27**(6): 1572-1577
- The general rules for the clinical and pathological study of primary liver cancer. Liver Cancer Study Group of Japan. *Jpn J Surg* 1989; **19**(1): 98-129
- Toyoda H, Kumada T, Kiriya S, Sone Y, Tanikawa M, Hisanaga Y, Yamaguchi A, Isogai M, Kaneoka Y, Washizu J. Comparison of the usefulness of three staging systems for hepatocellular carcinoma (CLIP, BCLC, and JIS) in Japan. *Am J Gastroenterol* 2005; **100**(8): 1764-1771
- Yang T, Zhang J, Lu JH, Yang LQ, Yang GS, Wu MC, Yu WF. A new staging system for resectable hepatocellular carcinoma: comparison with six existing staging systems in a large Chinese cohort. *J Cancer Res Clin Oncol* 2011; **137**(5): 739-750

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