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Prognostic value of the 7th edition of the AJCC staging system as a clinical staging system in patients with hepatocellular carcinoma

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ABSTRACT

Background/Aims: In 2009, the American Joint Committee on Cancer (AJCC) published the 7th edition of the hepatocellular carcinoma (HCC) staging system. We investigated the prognostic value of the 7th AJCC staging system as a clinical staging system in patients with HCC.

Methods: We retrospectively applied the 6th and 7th AJCC systems to 877 patients who were diagnosed with HCC between January 2004 and December 2006 using radiological findings and compared the performance of the AJCC systems to that of the Barcelona Clinic Liver Cancer (BCLC) system. The prognostic power was quantified using a linear trend χ^2 test and –2 log likelihood.

Results: The median age was 57 years and males predominated ($n = 701$, 79.9%). There was no significant difference in survival between adjoining advanced stages of the 6th and 7th AJCC systems ($\geqslant$stage IIIA in the 6th and $\geqslant$stage IIIB in the 7th; all $p > 0.05$), although a significant difference between adjoining early stages was identified. The 7th AJCC system had greater prognostic power than the 6th (linear trend χ^2 test, 168.195 versus 160.293; -2 log likelihood, 7366.347 versus 7396.380), but not greater than that of the BCLC system (linear trend χ^2 test = 207.013, -2 log likelihood = 7320.726).

Conclusions: The 7th AJCC staging system provided better prognostic power than the 6th for patients with HCC, but not better than that of the BCLC system. Thus, the 7th AJCC staging system should be applied cautiously in patients with advanced HCC because of its low prognostic power in advanced stages.

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1. Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide.[1] In South Korea, which is a highly endemic area of hepatitis B virus (HBV) infection, approximately 10,000 patients per year are diagnosed with HCC.[2] The relative frequency of HCC is 9.2% among all cancers, with an age-standardised incidence rate of 24.2 cases per 100,000 people,[3] making it the second leading cause of cancer-related deaths.[4]

Because of the heterogeneity in molecular and clinicopathological features of HCC, with diverse aetiologies[5,6] and varying treatment modalities among centres, no consensus exists as to which staging system is the best at predicting the survival of patients with HCC.[6–9] Consequently, various staging systems have been developed because a single staging system does not accurately demonstrate prognostic efficacy for all patients with HCC.[10]

Among several staging systems, the Tumour-Node-Metastasis (TNM) system is one of the most widely accepted.[7,11] The American Joint Committee on Cancer (AJCC) staging system for HCC adopted the TNM classification to stratify the prognosis of patients with HCC after surgical resection.[12] After introducing the 6th edition of the AJCC staging system in 2002,[13] the AJCC published the 7th edition in 2009.[12] The 7th edition separates the T3 stage into two subgroups, T3a and T3b. The T3a stage is defined as multiple tumours, any >5 cm, while the T3b stage is defined as tumours of any size involving a major portal or hepatic vein.

Originally, the AJCC staging system was based on postoperative pathological information.[11] However, because more than 80% of tumours are surgically unresectable at the time of diagnosis, due to advanced tumour stage or impaired liver function,[14] wide application of the AJCC staging system has been critically limited.[6,15] Currently, preoperative diagnosis of HCC can be more accurately performed, thanks to recent advances in imaging technology.[16] Thus, we tested the applicability of the 7th edition of the AJCC staging system for all patients with HCC, based on radiological information similar to the currently available clinical staging systems.[11] If the 7th AJCC staging system maintains its prognostic power even when we use clinical radiological information instead of postoperative pathological information,[14] then a wide range of patients with HCC may benefit from the AJCC staging system, regardless of operability.

Thus, based on radiological information, we compared the performance of the AJCC staging system to that of the Barcelona Clinic Liver Cancer (BCLC) staging system in patients with HCC. Additionally, we compared the postoperative performances of the 6th and 7th AJCC staging systems based on pathological findings in the subgroup of surgically treated patients.

2. Patients and methods

2.1. Patients

Data were obtained for 877 patients who had been newly diagnosed with HCC and treated at Severance Hospital (Yonsei University, College of Medicine, Seoul, Korea) between January 2004 and December 2006. We retrospectively reviewed all patient medical records, which included demographical characteristics, laboratory results, tumour characteristics and stages, imaging study results and treatment modalities. We also reviewed postoperative pathological reports of patients who had undergone surgical treatment (resection or transplantation). Patients who had not been treated at our institute or visited only for a second opinion were excluded from the final analysis. The patients were followed until December 2009.

This study was approved by the institutional review board of Severance Hospital of Yonsei University Health System, Seoul, Korea (IRB No. 4-2010-0321).

2.2. Diagnosis of HCC

The diagnosis of HCC was made based on the guidelines proposed by the Korea Liver Cancer Study Group and the National Cancer Center.[17] According to these criteria, a patient is considered positive for HCC if the patient has one or more risk factors (HBV infection, hepatitis C virus infection or cirrhosis) and one of the following: a serum α-fetoprotein (AFP) level of >400 ng/mL and a positive finding with at least one of three typical imaging studies (spiral computed tomography (CT), contrast enhanced dynamic magnetic resonance imaging (MRI) or hepatic angiography), or a serum AFP level of <400 ng/mL and positive findings with at least two of the three imaging studies. A positive finding for typical HCC with dynamic CT or MRI is indicative of arterial enhancement, followed by venous washout in the delayed portal/venous phase.

2.3. Staging systems for HCC

All patients were retrospectively classified using the 6th and 7th AJCC staging systems based on imaging findings. The major change from the 6th AJCC staging system is that the T3 stage was separated into T3a (multiple tumours, any >5 cm) and T3b (major vascular invasion of portal or hepatic veins). In this study, we defined the AJCC staging system based on imaging findings as the clinical AJCC (cAJCC) staging system. We selected the BCLC staging system as a representative clinical staging system and classified patients according to the BCLC system.[6,18] To investigate the prognostic value of the cAJCC staging system as a clinical staging system, we compared it with that of the BCLC system.

For clinical assessment of the cAJCC staging system, vascular invasion was defined as tumour invasion of the portal or hepatic veins, which was confirmed by dynamic CT, MRI or angiography. Minor vascular invasion was defined as involvement of the lobar or segmental branches of the portal or hepatic veins,[19] whereas major vascular invasion was defined as invasion of the right or left main branches of the portal or hepatic veins.[12,19] Extrahepatic metastasis was assessed by bone scan, chest CT or positron emission tomography.

2.4. Subgroup analysis for patients who underwent surgery

To analyse the performance of the AJCC staging systems based on postoperative pathological information in the

subgroup of 110 surgically treated patients, we reviewed the postoperative pathological reports. We defined the AJCC staging system based on postoperative pathological information as the pathologic AJCC (pAJCC) staging system to differentiate from the cAJCC staging system. Evidence of tumour invasion into portal or hepatic veins was evaluated both macro- and microscopically.[8] Major vascular invasion was defined as gross invasion of the branches of the main portal vein or one of the main hepatic veins.[8]

2.5. Treatment modalities for HCC

Most patients (n = 866; 98.7%) received one of following initial treatment modalities: surgery (surgical resection or transplantation), radiofrequency thermal ablation (RFA), transarterial chemoembolization (TACE), intraarterial chemotherapy, concurrent chemoradiation therapy (CCRT), systemic chemotherapy or best supportive care. The initial treatment modalities were selected according to the guidelines proposed by the Korea Liver Cancer Study Group and the National Cancer Center.[17]

Surgical resection was planned as a first-line treatment for patients with one or two technically resectable tumours and favourable remnant liver function. Transplantation was tried for patients with solitary HCCs <5 cm or with up to three nodules smaller than 3 cm.[20] RFA was percutaneously performed under ultrasound guidance for patients with early-stage HCC who were not suitable for resection or for those who could not undergo liver transplantation due to the organ shortage. The indication for RFA was a single tumour ⩽5 cm or up to three nodules <3 cm.[21] Patients with more extensive tumours received TACE using a solution of 20–50 mg doxorubicin hydrochloride in 5–20 mL of a mixed solution of lipoidal and contrast agent.[22] Subsequently, embolisation was performed using gelatin sponge particles after TACE, except in cases with significant portal vein thrombosis (PVT).[14] Intraarterial chemotherapy was applied to advanced HCC patients who were not suitable for surgical resection or non-surgical interventions (such as RFA and TACE) because of multiple tumours involving both lobes of the liver or PVT. During intraarterial chemotherapy, patients received 5-fluorouracil (5-FU) 500 mg/m^2 for 5 h on Days 1–3, and cisplatin 60 mg/m^2 for 2 h on Day 2 through the hepatic artery every 4 weeks.[23,24] CCRT was performed for patients with locally advanced HCC with PVT and good liver function reserve. A total of 45 Gy was prescribed in 25 fractions of 1.8 Gy over 5 weeks, and during the first and fifth weeks of radiation therapy, concurrent continuous-infusion hepatic arterial 5-FU (at a dose of 500 mg/day) was delivered through a hepatic arterial catheter as previously described.[25] One month after CCRT, 3–12 cycles of intraarterial chemotherapy with 5-FU and cisplatin were administered every 4 weeks according to tumour response.[25] Systemic chemotherapy was indicated for patients with extrahepatic metastasis. Patients received 5-FU (1000 mg/m^2 for 24 h on Days 1–3) and cisplatin (80 mg/m^2 for 4 h on Day 2) or carboplatin (350–400 mg/m^2 for 4 h on Day 1) every 4 weeks[22] or sorafenib (400 mg orally, twice daily). Best supportive care involved symptomatic treatment and management of complications of liver cirrhosis.

2.6. Statistical analysis

To identify pretreatment predictors of overall survival, we used Cox's proportional hazard regression model. The prognostic values of staging systems were determined using survival times of patients, which were estimated from the date of HCC diagnosis. Cumulative survival rates were analysed using the Kaplan–Meier method, and the differences between curves were assessed by the log-rank test.

The performance of staging systems was assessed according to homogeneity (smaller differences in survival among patients in the same stage within each system) and discriminatory ability (greater differences in survival among patients in the different stages within each system).[26] To evaluate homogeneity within each staging system, –2 log likelihood was calculated using a Cox's proportional hazard regression model. The linear trend χ^2 method was used to measure the discriminatory ability of each staging system. Generally, more accurate stages showed lower –2 log likelihood and higher linear trend χ^2 values. A value of $p < 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS 12 for Windows (SPSS, Chicago, IL, USA).

3. Results

3.1. Baseline characteristics

Table 1 shows the baseline characteristics of all patients. The median age of the patients was 57 (range, 21–86) years and the male gender predominated (n = 701, 79.9%). The most common cause was HBV infection (n = 635, 72.4%), and most patients showed preserved liver function, of Child-Pugh A class (n = 669, 76.3%). A single tumour was identified in 400 patients (45.6%), and tumour sizes less than 2 cm were identified in 118 (13.5%). Major vascular invasion, which was detected by imaging studies, occurred in 257 (29.3%) patients. Surgical treatment was tried for 110 (12.5%) patients (surgical resection for 107 patients and transplantation for three patients) and RFA was performed for 15 (1.7%). Among non-curative treatment modalities, TACE was performed most often (n = 478, 54.5%). Five patients received systemic chemotherapy using 5-FU and cisplatin or carboplatin and two patients took sorafenib.

3.2. Pretreatment predictors of overall survival

In the univariate and subsequent multivariate analysis to identify independent pretreatment predictors of overall survival, Child-Pugh classification, major vascular invasion, tumour number, tumour size, lymph node metastasis, and distant metastasis were selected (all $p < 0.05$; Table 2).

3.3. Distribution of patients and overall survival according to each staging system

In total, 618 (70.5%) patients died during the study period. The overall median survival of the patients was 19.8 months, and the overall cumulative survival rates at 1, 3, and 5 years were 58.0%, 36.6%, and 23.0%, respectively (Fig. 1). The most common cause of death was tumour progression or hepatic fail-

Table 1 – Baseline characteristics (n = 877).

Variables	Value
Age (years)	57 (21–86)
Male	701 (79.9)
Aetiology	
HBV/HCV/alcohol/others[a]	635 (72.4)/102 (11.6)/ 22 (2.5)/118 (13.5)
Child-Pugh classification	
A/B/C	669 (76.3)/177 (20.2)/ 31 (3.5)
Alanine aminotransferase (IU/L)	44 (2–1320)
Alpha-fetoprotein (ng/mL)	106.8 (0.8–83,000)
Tumour number	
Single/multiple	400 (45.6)/477 (54.4)
Tumour size (cm)	
<2/2–5/⩾5	118 (13.5)/319 (36.4)/ 440 (50.1)
Major portal vein or hepatic vein invasion	
No/yes	620 (70.7)/257 (29.3)
Lymph node metastasis	
No/yes	790 (90.1)/87 (9.9)
Distant metastasis	
No/yes	813 (92.7)/64 (7.3)
Treatment modalities	
Surgery including transplantation	110 (12.5)
Radiofrequency ablation	15 (1.7)
Transarterial chemoembolisation	478 (54.5)
Intraarterial chemotherapy	103 (11.7)
Concurrent chemoradiation therapy	32 (3.6)
Systemic chemotherapy	7 (0.8)
Best supportive care	121 (13.8)
Combination therapy	11 (1.4)

Variables are expressed as median (range) or n (%).
HBV, hepatitis B virus and HCV, hepatitis C virus.
[a] Others include mixed or unknown etiologies.

ure (n = 530, 85.8%), followed by infection (n = 12, 1.9%), hypovolemic shock (n = 12, 1.9%), treatment-related (n = 2, 0.4%), and unknown (n = 62, 10.0%).

Table 3 lists the patient distribution, median survival and survival rates according to the 6th and 7th cAJCC staging systems and the BCLC system. Although the cAJCC staging system was updated from the 6th to the 7th edition, patients in stages I and II were unchanged. In total, 265 patients in stage IIIA of the 6th cAJCC staging system were separated into stage IIIA (n = 89, 33.6%) and stage IIIB (n = 176, 66.4%) according to the 7th cAJCC staging system. All patients in stages IIIB, IIIC and IV of the 6th cAJCC staging system were categorised as stages IIIC, IVA and IVB, respectively, according to the 7th cAJCC staging system.

Fig. 2(a) and (b) illustrate the Kaplan–Meier survival curves based on the 6th and 7th cAJCC staging systems. Although there was a significant difference between relatively early adjoining stages of the 6th and 7th cAJCC staging systems (stages I versus II and stages II versus IIIA in the 6th and stages I versus II, stages II versus IIIA, and stages IIIA versus IIIB in the 7th cAJCC staging system; all $p < 0.05$), no significant difference in survival was identified between relatively advanced adjoining stages (⩾stage IIIA in the 6th and ⩾stage IIIB in the 7th cAJCC staging system; all $p > 0.05$). In particular, a significant difference in survival was noted between stages IIIA (T3a, N0, and M0) and IIIB (T3b, N0, and M0), which were separated by the 7th cAJCC staging system ($p < 0.001$).

Additionally, we stratified survival of the patients according to the BCLC system for comparison. According to the BCLC system, a significant difference between all adjoining stages was identified (all $p < 0.05$; Fig. 2(c)).

3.4. *Prognostic performance of each staging system*

Although the 7th cAJCC staging system had higher prognostic power than the 6th in terms of homogeneity and discriminatory ability, as shown in Table 4 (linear trend χ^2 test, 168.195 versus 160.293; –2 log likelihood, 7366.347 versus 7396.38; $p < 0.001$), the BCLC system had the highest prognostic power among the three staging systems (linear trend χ^2 test, 207.013; –2 log likelihood, 7320.726).

3.5. *Subgroup analysis for patients who underwent surgery*

We analysed 110 (12.5%) patients who were treated by surgical resection (n = 107) or transplantation (n = 3) based on pathological findings of liver explants. Postoperatively, 74 (67.3%) patients were in stage I, 27 (24.5%) in II, 8 (7.3%) in IIIA, and 1 (0.9%) in IIIB according to the 6th pAJCC staging system. According to the 7th pAJCC staging system, eight patients who were staged as IIIA according to the 6th pAJCC staging

Table 2 – Pretreatment predictors of overall survival.

Variables	Univariate	Multivariate		
	p Value	Hazard ratio	95% Confidence interval	p Value
Age	0.567	–	–	–
Male	0.087	–	–	–
Alanine aminotransferase	<0.001	1.000	0.999–1.001	0.676
Child-Pugh classification	<0.001	1.859	1.610–2.148	<0.001
Major vascular invasion	<0.001	1.812	1.477–2.223	<0.001
Tumour number	<0.001	1.347	1.254–1.448	<0.001
Tumour size	<0.001	1.291	1.195–1.394	<0.001
Lymph node metastasis	<0.001	1.647	1.281–2.118	<0.001
Distant metastasis	<0.001	1.403	1.057–1.861	0.019

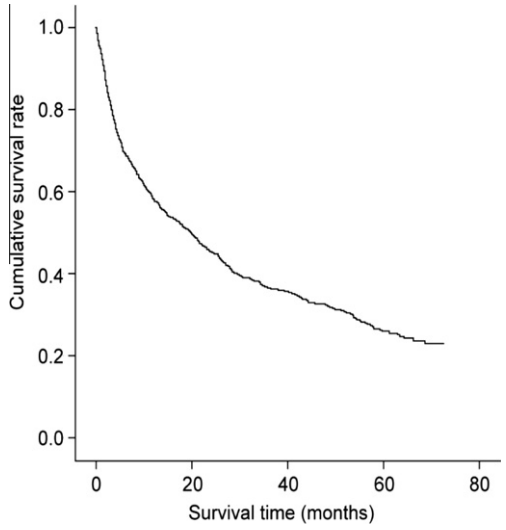

Fig. 1 – Kaplan–Meier estimated overall survival curves of all patients. Overall cumulative survival rates at 1, 3 and 5 years were 58.0%, 36.6%, and 23.0%, respectively.

system were determined to be in stages IIIA ($n = 4$, 3.6%) and IIIB ($n = 4$, 3.6%). Compared with preoperative stages, 22 (20.0%) patients were upstaged when using the 6th pAJCC staging system (19 with one level higher stage and three with more than two levels higher stage), and 23 (20.9%) (20 with one level higher stage and three with more than two levels higher stage) using the 7th pAJCC staging system. One patient who was upstaged according to the 7th pAJCC staging system (from stage IIIA to IIIB) due to major vessel invasion remained as stage IIIA according to the 6th pAJCC staging system.

Similar to the survival curves based on the cAJCC staging systems, significantly different survival was identified between relatively early adjoining stages of the 6th and 7th pAJCC staging systems (stages I versus II and stages II versus IIIA; all $p < 0.05$). There was no significant difference in survival between relatively advanced adjoining stages of the 6th and 7th pAJCC staging systems ($\geqslant$stage IIIA; all $p > 0.05$). In this subgroup analysis, the 6th pAJCC staging system showed higher prognostic power than did the 7th (linear trend χ^2 test, 17.848 versus 14.560; –2 log likelihood, 239.778 versus 243.999; all $p < 0.001$).

4. Discussion

The AJCC staging system for HCC was developed in 1977 and has been modified several times. The major change from the 6th to the 7th AJCC staging system is that the new system imposes heavier prognostic weight on major vascular invasion as a potential predictive factor for poor prognosis. The 7th AJCC staging system divided stage T3 into T3a (multiple tumours, any >5 cm) and T3b (major vascular invasion of portal or hepatic veins). In this study, 265 patients in stage T3 according to the 6th cAJCC staging system were separated into two heterogeneous subgroups, 89 (33.6%) in T3a and 176 (66.4%) in T3b, using the 7th cAJCC staging system. Accordingly, the median survival of 5.7 months in stage T3 of the 6th cAJCC staging system was also significantly separated into 13.7 months in T3a and 4.0 months in T3b in the 7th cAJCC staging system ($p < 0.001$). Similar to our results, Poon and Fan[5] identified significantly poorer survival rates in T3b patients compared with T3a (5-year survival rate 6.2% versus 8.4%; $p < 0.001$). Moreover, Minagawa et al.[27] stressed the prognostic role of portal vein invasion by show-

Table 3 – Distribution of patients and survival according to each staging system.

Staging system		*n* (%)	Median survival (months)	Deaths (%)	Survival rate (%)		
					1 year	3 years	5 years
6th cAJCC system							
I	T1N0M0	326 (37.2)	64.2	143 (43.9)	85.6	65.6	50.6
II	T2N0M0	157 (17.9)	27.3	110 (70.1)	76.4	44.6	23.9
IIIA	T3N0M0	265 (30.2)	5.7	240 (90.6)	34.3	11.3	9.2
IIIB	T4N0M0	4 (0.5)	4.5	4 (100)	25.0	0	0
IIIC	T1-4N1M0	62 (7.1)	4.1	59 (95.2)	16.1	4.8	0
IV	T1-4N0-1M1	63 (7.2)	3.4	62 (98.4)	12.7	6.4	0
7th cAJCC system							
I	T1N0M0	326 (37.2)	64.2	143 (43.9)	85.6	65.6	50.6
II	T2N0M0	157 (17.9)	27.3	110 (70.1)	76.4	44.6	23.9
IIIA	T3aN0M0	89 (10.1)	13.7	75 (84.3)	55.1	16.9	8.4
IIIB	T3bN0M0	176 (20.1)	4.0	165 (93.8)	23.9	8.5	6.2
IIIC	T4N0M0	4 (0.5)	4.5	4 (100)	25.0	0	0
IVA	T1-4N1M0	62 (7.1)	4.1	59 (95.2)	16.1	4.8	0
IVB	T1-4N0-1M1	63 (7.2)	3.4	62 (98.4)	12.7	6.4	0
BCLC system							
A		324 (36.9)	66.2	138 (42.6)	89.5	67.9	51.8
B		198 (22.6)	21.6	144 (72.7)	68.2	35.9	23.0
C		315 (35.9)	4.4	299 (94.9)	23.8	8.3	4.4
D		40 (4.6)	1.7	37 (92.5)	22.5	10.0	0

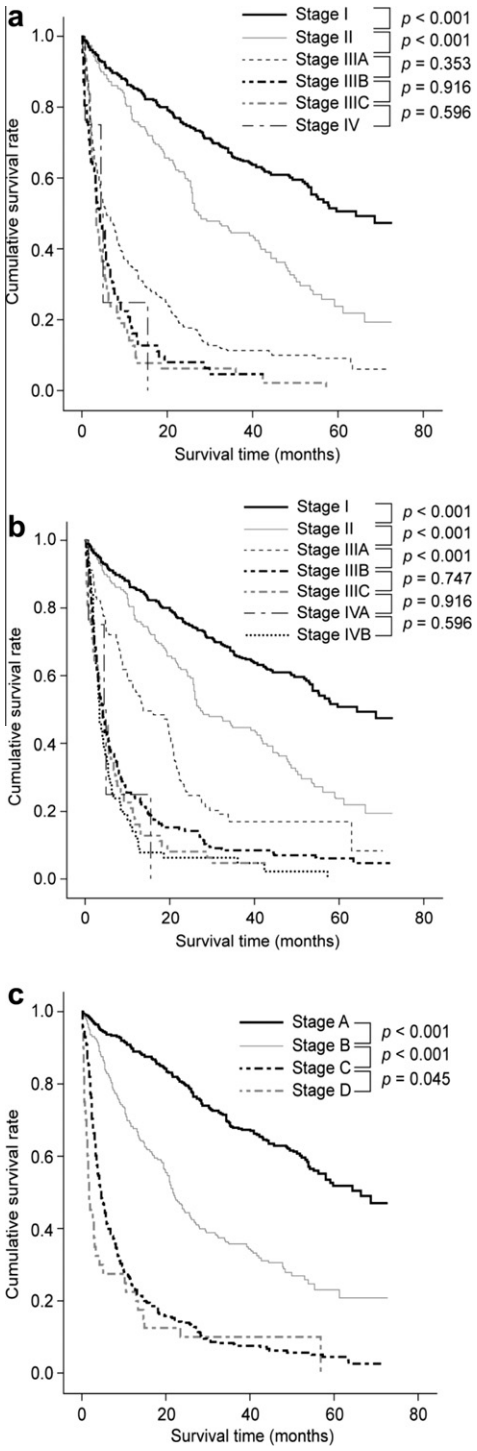

Fig. 2 – Kaplan–Meier estimated survival curves of the 6th edition of the clinical AJCC (cAJCC) staging system (a), the 7th edition of the cAJCC staging system (b), and the Barcelona Clinic Liver Cancer (BCLC) system (c). (a) The 6th edition; stages I versus II, $p < 0.001$; stages II versus IIIA, $p < 0.001$; stages IIIA versus IIIB, $p = 0.353$; stages IIIB versus IIIC, $p = 0.916$; stages IIIC versus IV, $p = 0.596$. (b) The 7th edition; stages I versus II, $p < 0.001$; stages II versus IIIA, $p < 0.001$; stages IIIA versus IIIB, $p < 0.001$; stages IIIB versus IIIC, $p = 0.747$; stages IIIC versus IVA, $p = 0.916$; stages IVA versus IVB, $p = 0.596$. (c) BCLC; stages A versus B, $p < 0.001$; stages B versus C, $p < 0.001$; stages C versus D, $p = 0.045$.

Table 4 – Prognostic performance of each staging system.

Staging system	Linear trend χ^2 test	–2 log likelihood (p value)
6th cAJCC system	160.293	7396.638 (<0.001)
7th cAJCC system	168.195	7366.347 (<0.001)
BCLC system	207.013	7320.726 (<0.001)

cAJCC, clinical American Joint Committee on Cancer and BCLC, Barcelona Clinic Liver Cancer.

ing a poorer prognosis in patients with first branch or trunk invasion of portal veins than those with second or third branch invasion or without portal vein invasion. All of this evidence, including our results, support the rationale of the separation of T3 into T3a and T3b in the new 7th AJCC staging system.

Most studies validating the AJCC staging system have analysed only patients who received surgical resection.[5,8,19,27,28] Thus, the clinical usefulness of the AJCC staging system for a wide spectrum of patients with HCC has been limited because HCC is generally found to be unresectable in the majority of cases at the time of diagnosis.[14,15] To overcome this drawback of the AJCC staging system, several studies tested the applicability of the AJCC staging system for all patients with HCC based on preoperative imaging findings. Kee *et al.*[15] demonstrated that the 6th AJCC staging system showed better prognostic performance than did the 5th AJCC staging system based on imaging findings, and proposed a potential role of the modified 6th AJCC staging system as a clinical staging system for all patients with HCC. However, Seo et al.[14] suggested that the 6th AJCC staging system should not be applied to patients receiving non-surgical treatment because their survival was not significantly different according to the 6th AJCC staging system. Hence, the prognostic value of the cAJCC staging system as a clinical staging system based on imaging findings still remains to be further clarified.

All three staging systems in our study showed a significant progressive decrease in overall survival from the earliest to the most advanced stages (log-rank test, all $p < 0.001$). However, the cAJCC staging systems did not show significant survival differences in advanced stages ($\geqslant$stage IIIA in the 6th and $\geqslant$stage IIIB in the 7th cAJCC staging system), and only the BCLC system showed significant differences between all adjoining stages. The reason why overall survival in advanced stages in the cAJCC staging systems did not show significant differences may be explained by the difficulties in identifying the T4 stage (especially perforation of the visceral peritoneum) using only imaging studies. Another explanation may be the relatively small number of patients in advanced stages due to more detailed stratification of the AJCC staging system, which led to a potential type II statistical error. When we simplified the 6th and 7th cAJCC staging systems as four stages from I to IV, a significant difference in survival was observed between all adjoining stages of the 6th and 7th cAJCC staging systems (all $p < 0.05$). However, the performance of these four-staged 6th and 7th cAJCC staging systems was still inferior to that of the BCLC staging system (data not shown).

When we analysed whether the 7th cAJCC staging system, based on imaging findings, could be applied to all patients

with HCC, the 7th cAJCC staging system showed better prognostic power than the 6th cAJCC staging system. The 7th AJCC staging system might be more homogeneous and discriminatory than the previous edition because it imposes heavier prognostic weight on major vascular invasion, and current imaging techniques are sufficient to detect such invasion. However, the 7th cAJCC staging system showed poorer predictable performance than did the BCLC system, which we selected as the representative clinical staging system for comparison.[9,14,29] This phenomenon can be explained by the major weakness of the AJCC staging system. Because the AJCC staging system was originally derived from patients with good liver function reserve who could tolerate surgical resection, it was not necessary to consider underlying liver function. Thus, the AJCC staging system is composed only of tumour factors, regardless of background liver function.[27] However, because the prognosis of HCC is affected by underlying function of the organ itself, unlike that of other malignancies,[8] application of the cAJCC staging system to HCC patients who cannot undergo surgical resection due to poor liver function may be limited, which resulted in the poorer performance of the cAJCC staging system in our study. On the other hand, the BCLC system includes variables related to liver function and physical status as well as tumour factors[9,18,29,30] and, not surprisingly, it was selected as the best clinical staging system for all patients with diverse baseline liver function and treatment modalities in our study. Indeed, underlying liver function, reflected by Child-Pugh classification, was selected as an independent pretreatment predictor of overall survival in our study. Taken as a whole, the BCLC system showed the best prognostic power in terms of stratifying patients according to homogeneity, discriminatory ability and survival. Finally, we may say that the use of the cAJCC staging system cannot be extended to all patients with HCC.

Unexpectedly, in subgroup analysis of patients who underwent surgery, the 6th pAJCC system was superior to the 7th when pathologically assessed. Although the reason is unclear, the inferiority of the 7th pAJCC staging system might be explained by the relatively small number of surgically treated patients. Moreover, the number was quite small because surgical resection could not be applied to the patients in advanced stages. These statistical problems might have been raised by spectrum bias, leading to this confusing result. Thus, a large-scale prospective study is needed to validate the superiority of the 7th pAJCC staging system, based on pathological findings.

Although we reviewed a large number of patients with uniformity in the diagnostic and treatment strategies according to the guidelines,[17] which could be a strength of our study, we are aware of several limitations. First, because our data were retrospectively reviewed, future prospective studies are needed for validation. Second, because this is a single tertiary centre study with potential referral bias due to a high prevalence of advanced HCC, the results should be cautiously interpreted. Third, *N* factor (node) might have been underestimated because lymph node dissection during surgical resection for HCC was not routinely performed. Fourth, although patients with a single tumour or smaller tumours less than 5 cm comprised more than 40% of the study population, the number of surgically treated patients was low. Patients who were not surgically treated included those who were initially indicated for surgical treatment but refused, and those who were too old or whose reserve liver function was too poor to undergo surgery. This might have influenced the prognosis of the study population. Finally, it is uncertain whether the data of this study are also applicable to Western patients, because factors determining the outcomes of Asian patients might not be identical to those of Western patients.

In conclusion, the new 7th cAJCC staging system provided better prognostic power than the 6th for patients with HCC. However, because the prognostic power of the 7th cAJCC staging system was poorer than that of the BCLC system, especially in advanced stages, the 7th cAJCC staging system should be applied cautiously in patients with advanced HCC.

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Conflict of interest statement

None declared.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejca.2011.07.002.

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