Original Article

Critical appraisal of TNM versus HKU staging system for postoperative prognostic evaluation of hepatocellular carcinoma

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Background: The 8th edition of the American Joint Committee on Cancer tumor-node-metastasis staging system (AJCC 8th) has been launched with modifications in T staging. The University of Hong Kong liver cancer staging system (HKUSS) has been proven to better categorize hepatocellular carcinoma (HCC) into different T stages. This study aimed to compare the two systems' predictive ability for HCC recurrence after primary surgical resection.

Methods: Patients who had primary, curative resection for HCC between 1989 and 2017 were reviewed. The Kaplan-Meier plot was used to estimate disease-free survival (DFS), and the log-rank test was used for survival comparison between subgroups. The two systems' prediction of recurrence was evaluated by the Cox regression model.

Results: Totally 1,815 patients were included. With AJCC 8th, the 5-year DFS was 58.9% for T1a, 52.3% for T1b, 30% for T2, 16.9% for T3, and 14.4% for T4. No survival difference was demonstrated between T1a and T1b (P=0.668) or between T3 and T4 (P=0.562). With HKUSS, the 5-year DFS was 57.7% for T1, 43.4% for T2, 28.9% for T3, and 15.7% for T4. The T staging in HKUSS showed significant survival differences (T1 *vs.* T2, T2 *vs.* T3, and T3 *vs.* T4; P<0.001). Using receiver operating characteristic curves to show the recurrence status in the two systems, HKUSS had the largest area under curve (AUC) (HKUSS: AUC =0.655, SE 0.014, P<0.001, 95% CI, 0.628–0.681; AJCC 8th: AUC =0.652, SE 0.013, P<0.001, 95% CI, 0.625–0.677).

Conclusions: HKUSS showed better categorization of HCC. In the context of primary surgical resection, HKUSS may be more appropriate for stratification of patients with HCC with various T stages, and thus the choice of staging system when primary surgical resection is considered for patients of HCC.

Keywords: Hepatocellular carcinoma (HCC); HKU staging system; 8th AJCC TNM staging; Liver Cancer Study Group of Japan; disease-free survival (DFS)

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Introduction

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related deaths worldwide (1). Each year, 50,000 to 1,000,000 patients are newly diagnosed and approximately 600,000 patients die of it globally (2,3). Liver resection and liver transplantation are the best treatment options that attain long-term survival. However, even after potentially curative surgical extirpation, the 5-year survival rates are only 54.8% (4) and 70% respectively (5). Because of the scarcity of liver grafts, liver transplantation is not considered as the first-line treatment option. Liver resection remains as the gold standard but the long-term prognosis is often influenced by postoperative tumor recurrence (6). Staging systems categorize patients with cancer into cohorts based on the severity and extent of the disease and predict survival in each category. Hence, a proper tumor staging of the disease allows an accurate stratification of patients for suitable management, enabling the patients to have a realistic expectation about their disease.

Currently, there are two categories of staging system, clinical and pathological. A clinical system stages the disease with clinical parameters and radiological details, whereas a pathological system stages the disease with final pathological results obtained after surgery with curative intent. To date, there are two commonly used pathological staging systems: one was the consensus reached by the American Hepato-Pancreato-Biliary Association and the American Joint Committee on Cancer (AJCC) (7), and the Liver Cancer Study Group of Japan also developed its staging system (LCSGJ) (8). Both systems use TNM as parameters to stage the disease—T: tumor (tumor size, tumor number, and nearby invasion); N: node (regional lymph node involvement); M: metastasis (distant metastasis). The AJCC has released the 8th edition of its TNM staging system (AJCC 8th) (9) (*Table 1*). The major change is the subclassification of the T1 stage into T1a and T1b, depending on the size of the early small HCCs. There are also changes about T2 and T3, depending on tumor size, tumor number, and vascular invasion.

The University of Hong Kong liver cancer staging system (HKUSS) was based on the results of multivariable analysis of the clinical and pathological statuses of the patients. Microvascular invasion, tumor size and number, lobar distribution and symptomatic presentation impacted survival the most and formed the foundation of the HKUSS. The formulated HKUSS was validated with another group of HCC patients, which were not included in the initial test set. Results have shown that various T stages in HKUSS were statistically different from each other and that it is a better staging system, with a greater area under curve (AUC), suggestive of better predictability for disease recurrence as compared with other staging systems (10) (*Table 1*).

Table 1 Descriptions of the different T stages of primary liver cancer in HKUSS and AJCC 8th

HKUSS	
T1	Single tumor ≤5.0 cm, no microvascular invasion
T2	Single tumor >5.0 cm, no microvascular invasion
	Or single tumor ≤5.0 cm plus microvascular invasion
	Or unilobar multiple tumors, no microvascular invasion
T3	Single tumor >5.0 cm plus microvascular invasion
T4	Unilobar multiple tumors plus microvascular invasion
	Or bilobar tumors
	Or tumor invasion of a branch of the portal or hepatic vein
	Or tumor invasion of an adjacent organ except the gallbladder or rupture into the peritoneal cavity
AJCC 8th	
T1a	Solitary tumor ≤2 cm with/without vascular invasion
T1b	Solitary tumor >2 cm, no vascular invasion
T2	Solitary tumor >2 cm plus vascular invasion
	Or multiple tumors ≤5 cm
T3	Multiple tumors and >5 cm
T4	Tumor(s) involving a major branch of the portal or hepatic vein with direct invasion of adjacent organ(s) (including the diaphragm) other than the gallbladder or with perforation of visceral peritoneum

HKUSS, The University of Hong Kong liver cancer staging system; AJCC 8th, the 8th edition of the American Joint Committee on Cancer tumor-node-metastasis staging system. Adapted with permission from (10).

This study had two objectives in the context of primary surgical resection for HCC. The first one was to evaluate the prognostic value of AJCC 8th, using a population-based data set. The second one was to compare HKUSS with other staging systems in terms of prognostic ability.

Methods

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Institutional review board

approval was not obtained for this retrospective study, as according to local regulations, institutional review board approval is not required for retrospective studies analyzing anonymous data. All patients gave their written informed consent to collection and use of their data for research purposes. No individual patients can be identified with the anonymous data used in this study.

Clinicopathological data of all patients having primary, curative intent resection of HCC at our hospital from January 1989 to December 2017 were reviewed. Data were censored in December 2017. Patients who were intraoperatively found to have metastasis with metastasectomy performed (n=2), who had positive resection margins (n=98), and who died after the operation (n=57) were not included. The operative technique for hepatic resection was reported previously (4). Major resection was defined as resection of more than three liver segments.

AJCC 8th made a few changes to the T classification in the 7th edition (9,11). The staging of early HCC was changed in AJCC 8th, which divided T1 into T1a and T1b (9). Details of the T classification in AJCC 8th are shown in *Table 1*.

Major vascular invasion was defined as tumor invasion of the first branch of the portal vein or the first tributary of the hepatic vein. Microvascular invasion was defined as the existence of tumorous emboli in the tributaries of the hepatic or portal vein and only referred to the predominant tumor nodule. Tumor invasion of adjacent organs (other than the gallbladder) would be confirmed by visual inspection and examination and/or histological examination. Ruptured HCC was defined as the presence of peritumoral hematoma. Routine lymphadenectomy was not conducted since lymph node metastasis was not common in resectable HCC (12,13). The prognostic effect of lymph node metastasis could not be assessed because of a lack of sufficient data, so only T staging was evaluated.

In this study, HKUSS was used as validation and comparison, using the same cohort of patients included in the authors' center. Our proposed T staging was described previously (10). In HKUSS, solitary tumor ≤5.0 cm without microvascular invasion was classified as T1. As the 5-year survival rates were similar in patients with a solitary tumor ≤5.0 cm and microvascular invasion, those with a solitary tumor >5.0 cm and no microvascular invasion, and those with unilobar multiple tumors but no microvascular invasion, these conditions were all classified as T2. T3 disease was defined as solitary tumor >5.0 cm plus microvascular invasion, whereas unilobar multiple tumors plus microvascular invasion and bilobar tumors were classified as T4 disease. The following conditions were also classified as T4: ruptured tumor, invasion of adjacent organs, invasion of a branch of the portal vein or hepatic vein, and symptomatic presentation (10) (*Table 1*).

LCSGJ is another widely accepted pathological staging system for HCC (14,15). In short, the staging of T1–T4 tumors involves only 3 criteria: <2 or ≥2 cm, presence or absence of vascular invasion, and single or multiple tumors. Analysis of the cohort with LCSGJ was also used to compare its power of T stage stratification against AJCC 8th and HKUSS.

The follow-up protocol was previously described (10). Computed tomography or magnetic resonance imaging was performed at one month for confirmation of macroscopic tumor clearance and then every three months. Serum liver biochemistry check was done every month in the first year and every three months afterwards. Tumor recurrence was defined as new lesion found on computed tomography or magnetic resonance imaging. Biopsy was generally avoided. There were no patients lost to follow-up.

Statistical analysis was performed using SPSS, version 20.0 (IBM SPSS Statistics; IBM Corporation, Armonk, New York, USA). Continuous variables were shown as median with range. The Mann-Whitney U test was employed to compare continuous variable between groups. Fisher's exact test or χ^2 test was used to compare categorical variables. The Kaplan-Meier plot was adopted to estimate overall survival (OS) and disease-free survival (DFS). The log-rank test compared survival between subgroups. The primary endpoint was DFS, which was the length of time between operation and recurrence or death related to the disease/any complication of liver failure. OS was defined as the length of time between operation and death from any cause. Statistical significance was denoted by P value <0.05. Cox regression analysis was performed to evaluate the correlation between DFS and each staging system. Receiver operating characteristic (ROC) curves were constructed for various staging systems – HKUSS, LCSGJ, and the 5th, 6th, 7th and 8th editions of the AJCC system – in order to evaluate the AUC of the staging systems in predicting the risk of disease recurrence.

Results

The study analyzed 1,815 patients (1,459 males and 356 females), with a median age of 58 years. Their demographic, operative and pathological details are shown in *Table 2*. Terminal malignancy (n=694, 73%), variceal bleeding (n=48, 5%) and liver failure (n=32, 3.4%) were

Table 2 Demographic, operative and pathological details of the 1,815 patients in different T stages in HKUSS

Details	Total		T1		T2		T3		T4		P value
	N	%	N	%	N	%	N	%	N	%	
Number	1,815	100	517	28.5	524	28.9	178	9.8	596	32.8	
Male:female		4:1		4:1		4:1		3:1		6:1	0.002
Male	1,459	80.4	406	78.5	416	79.4	131	73.6	506	84.9	
Female	356	19.6	111	21.5	108	20.6	47	26.4	90	15.1	
Age (years), median (range)	1,815	58 [18–89]	517	59 [19–84]	524	59.5 [18–86]	178	57 [28–83]	596	57 [19–89]	0.002
Body weight (kg), median (range)	1,808	62 (31.5–129.2)	516	63.65 (31.5–102.6)	522	64 [34–110]	175	60.5 (40–129.2)	595	60 (38–105.1)	<0.001
Body height (cm), median (range)	1,745	164 [136–190]	501	164 (141.5–183)	506	164.5 [140–187]	168	164 [137–182]	570	164.5 [136–190]	0.148
Diabetes mellitus	291	16	93	18	95	18.1	22	12.4	81	13.6	0.052
Hepatitis											
HBsAg (positive)	1,519	83.7	457	88.4	425	81.1	134	75.3	503	84.4	<0.001
HCV (positive)	74	4.1	28	5.4	22	4.2	5	2.8	19	3.2	0.232
Grouping											<0.001
HBV only	1,507	83	453	87.6	420	80.2	133	74.7	501	84.1	<0.001
HCV only	62	3.4	24	4.6	17	3.2	4	2.2	17	2.9	<0.001
Both HBV and HCV	12	0.7	4	0.8	5	1	1	0.6	2	0.3	0.307
Non-HBV, Non-HCV	234	12.9	36	7	82	15.6	40	22.5	76	12.8	<0.001
Liver status											
3 groups											<0.001
Non-cirrhotic	240	13.2	47	9.1	79	15.1	37	20.8	77	12.9	
Chronic hepatitis	505	27.8	118	22.8	140	26.7	61	34.3	186	31.2	
Cirrhosis	1,070	59	352	68.1	305	58.2	80	44.9	333	55.9	
2 groups											<0.001
Non-cirrhotic/chronic hepatitis	746	41.1	165	31.9	219	41.8	98	55.1	264	44.1	
Cirrhosis	1,071	58.9	352	68.1	305	58.2	80	44.9	334	55.9	
Child-Pugh class											0.066
Class A	1,751	96.4	505	97.7	508	96.9	171	96.1	567	94.8	
Class B	66	3.6	12	2.3	16	3.1	7	3.9	31	5.2	
ICG at 15 min (%), median (range)	1,653	10.7 (1.2–78)	459	10.6 (1.2–78)	463	10.6 (1.3–64.2)	171	10.8 (2.5–55.5)	560	10.7 (1.6–42.5)	0.707
AFP (ng/mL), median (range)	1,808	53.95 (1–1,335,900)	516	23 (2–32,843)	520	29.05 (1–835,700)	178	90 (2–1,043,700)	594	214.5 (1.8–1,335,900)	<0.001

Table 2 (*continued*)

Table 2 (*continued*)

Details	Total		T1		T2		T3		T4		P value
	N	%	N	%	N	%	N	%	N	%	
INR, median (range)	1,786	1.1 (0.8–1.8)	512	1.1 (0.9–1.6)	519	1.1 (0.8–1.5)	170	1 (0.8–1.3)	585	1.1 (0.8–1.8)	0.138
Creatinine (μmol/L), median (range)	1,815	84 (31–948)	517	86 (35–839)	524	85 (38–948)	178	83 (52–198)	596	83 (31–168)	0.063
Total bilirubin (μmol/L), median (range)	1,815	11 [2–70]	517	11 [2–58]	524	11 [2–57]	178	10.5 [2–58]	596	11 [2–70]	0.078
Albumin (g/L), median (range)	1,815	41 [17–56]	517	42 [23–53]	524	41 [23–54]	178	40 [27–53]	596	40 [17–56]	<0.001
SGOT (μ/L), median (range)	1,815	44 (12–1,324)	517	36 (13–204)	524	41 (15–393)	178	60.5 (19–440)	596	55 (12–1,324)	<0.001
SGPT (μ/L), median (range)	1,815	42 (7–450)	517	37 (8–450)	524	40 (7–418)	178	47 (10–344)	596	47 (7–420)	<0.001
Tumor size (cm), median (range)	1,815	5 (0.5–28)	517	3 (0.5–5)	524	5 (0.8–25)	178	10 (5.2–28)	596	8.9 (1.3–27)	<0.001
≤2 cm	230	12.7	156	30.2	61	11.6	0	0	13	2.2	<0.001
>2 cm ≤5 cm	720	39.7	361	69.8	216	41.2	0	0	143	24	
>5 cm or diffuse	865	47.7	0	0	247	47.1	178	100	440	73.8	
Number of tumor, median (range)	1,815	1 (1–multiple)	517	1 (1–1)	524	1 (1–multiple)	178	1 (1–1)	596	2 (1–multiple)	<0.001
Solitary	1,359	74.9	517	100	419	80	178	100	245	41.1	<0.001
Multiple	456	25.1	0	0	105	20	0	0	351	58.9	
2	187	10.3	0	0	56	10.7	0	0	131	22	<0.001
3	60	3.3	0	0	22	4.2	0	0	38	6.4	
4	18	1	0	0	4	0.8	0	0	14	2.3	
≥5 or diffuse	191	10.5	0	0	23	4.4	0	0	168	28.2	
Margin involvement	0	0	0	0	0	0	0	0	0	0	-
Tumor differentiation											<0.001
Well	334	18.4	152	29.4	108	20.6	17	9.6	57	9.6	
Moderate	1,077	59.3	289	55.9	319	60.9	106	59.6	363	60.9	
Poor	355	19.6	60	11.6	87	16.6	53	29.8	155	26	
Undifferentiated	7	0.4	0	0	1	0.2	1	0.6	5	0.8	
Necrosis	5	0.3	2	0.4	1	0.2	0	0	2	0.3	
Unknown	13	0.7	5	1	2	0.4	1	0.6	5	0.8	
Microvascular invasion	846	46.6	0	0	220	42	178	100	448	75.2	<0.001
Macrovascular invasion	139	7.7	0	0	0	0	0	0	139	23.3	<0.001
Tumor rupture	108	6	0	0	0	0	0	0	108	18.1	<0.001
Regional lymph nodes involved	10	0.6	0	0	2	0.4	0	0	8	1.3	0.005

Table 2 (*continued*)

Table 2 (*continued*)

Details	Total		T1		T2		T3		T4		P value
	N	%	N	%	N	%	N	%	N	%	
Distant metastasis	0	0	0	0	0	0	0	0	0	0	-
Resection type											
Minor	816	45	379	73.3	272	51.9	32	18	133	22.3	<0.001
Major	999	55	138	26.7	252	48.1	146	82	463	77.7	
Right hepatectomy	516	28.4	82	15.9	167	31.9	86	48.3	181	30.4	<0.001
Left hepatectomy	111	6.1	23	4.4	31	5.9	16	9	41	6.9	
Extensive resection	370	20.4	32	6.2	53	10.1	44	24.7	241	40.4	
Operative blood transfusion	341	18.8	44	8.5	82	15.6	42	23.6	173	29	<0.001
Operative blood transfusion (L), median (range)	1,814	0 (0–16)	516	0 (0–9)	524	0 (0–6.02)	178	0 (0–5.16)	596	0 (0–16)	<0.001
Blood loss (L), median (range)	1,806	0.7 (0.01–30)	513	0.5 (0.01–14)	521	0.6 (0.01–15)	177	0.9 (0.1–11.56)	595	1 (0.01–30)	<0.001
Overall complication rate	402	22.1	86	16.6	110	21	46	25.8	160	26.8	<0.001
Hospital stay (d), median (range)	1,812	9 [2–198]	515	7 [2–113]	523	8 [2–86]	178	10 [3–130]	596	10 [2–198]	<0.001
Mortality rate	0	0	0	0	0	0	0	0	0	0	-
Recurrence											<0.001
No recurrence	658	36.3	269	52	211	40.3	56	31.5	122	20.5	
Intrahepatic recurrence	558	30.7	174	33.7	170	32.4	42	23.6	172	28.9	
Extrahepatic recurrence	155	8.5	13	2.5	32	6.1	34	19.1	76	12.8	
Intrahepatic + Extrahepatic	444	24.5	61	11.8	111	21.2	46	25.8	226	37.9	

HKUSS, The University of Hong Kong liver cancer staging system; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HBV, hepatitis B virus; ICG, indocyanine green; AFP, α-fetoprotein; INR, international normalized ratio; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; N, number.

the commonest causes of mortality. *Table 3* shows the distribution of the 1,815 patients in different T stages in AJCC 8th and LCSGJ.

Using HKUSS, the 1-, 3- and 5-year rates of DFS were 86.6%, 66.8% and 57.7% respectively in patients with T1 tumors, 72.5%, 54.8% and 43.4% respectively in patients with T2 tumors, 52.5%, 34.4% and 28.9% respectively in patients with T3 tumors, and 36.3%, 19.4% and 15.7%, respectively in patients with T4 tumor (P<0.001). The 1-, 3- and 5-year rates of OS were 98.4%, 91% and 83.9% respectively in patients with T1 tumors, 94.6%, 79.5% and 68.0% respectively in patients with T2 tumors, 89.8%, 62.3% and 45.5% respectively in patients with T3 tumors, and 75.7%, 46.4% and 31.5% respectively in patients with T4 tumors (P<0.001). DFS survival (P<0.001) and overall survival (P<0.001) were significantly different among groups (*Table 4*) (*Figure 1A*,*B*).

Using AJCC 8th, the 1-, 3- and 5-year rates of DFS were 84.8%, 69.7% and 58.9% respectively in patients with T1a tumors, 83.0%, 62.3% and 52.3% respectively in patients with T1b tumors, 58.3%, 38.1% and 30.0% respectively in patients with T2 tumors, 32.8%, 20.7% and 16.9%

Table 3 Distribution of the 1,815 patients in different T stages in AJCC 8th and LCSGJ

Staging systems	Total		T1a		T1b		T2		T3		T4	
	N	%	N	%	N	%	N	%	N	%	N	%
AJCC 8th	1,815	100	211	11.6	604	33.3	520	28.7	193	10.6	287	15.8
LCSGJ	1,815	100	119		6.6		720	39.7	688	37.9	288	15.9

AJCC 8th, the 8th edition of the American Joint Committee on Cancer tumor-node-metastasis staging system; LCSGJ, the Liver Cancer Study Group of Japan staging system; N, number.

Table 4 The study cohort's survival difference with different T stages in HKUSS, AJCC 8th, and LCSGJ

Survival	Stages	Number	Deaths	Median survival (months)	Standard error	95% confidence interval		P value
HKUSS								
Overall survival	T1	517	169	195.09	13.72	168.2	221.98	
	T2	523	257	102.01	10.17	82.09	121.94	
	T3	178	110	51.81	6.31	39.44	64.18	
	T4	596	419	31.93	2.07	27.88	35.99	
	Overall	1,814	955	79.74	5.1	69.74	89.73	<0.001
Disease-free survival	T1	516	275	81.68	6.65	68.65	94.71	
	T2	524	339	45.34	4.61	36.31	54.37	T1 *vs.* T2 <0.001
	T3	178	128	14.06	2.66	8.85	19.27	T2 *vs.* T3 <0.001
	T4	596	500	6.64	0.507	5.64	7.63	T3 *vs.* T4 <0.001
	Overall	1,814	1,242	26.02	2.07	21.97	30.07	<0.001
AJCC 8th								
Overall survival	T1a	211	68	189.44	41.98	107.16	271.72	
	T1b	604	235	168.31	16.17	136.61	200.01	
	T2	519	297	62.85	5.17	52.71	72.99	
	T3	193	146	31.93	4.29	23.54	40.33	
	T4	287	209	24.54	2.68	19.29	29.79	
	Overall	1,814	955	79.74	5.1	69.74	89.73	<0.001
Disease-free survival	T1a	210	113	75.66	7.48	60.99	90.33	
	T1b	604	347	74.15	8.33	57.83	90.47	T1a *vs.* T1b 0.668
	T2	520	370	16.46	2.03	12.48	20.44	T1a *vs.* T2 <0.001
								T1b *vs.* T2 <0.001
	T3	193	169	6.67	0.67	5.36	7.98	T2 *vs.* T3 <0.001
	T4	287	243	5.32	0.59	4.17	6.47	T2 *vs.* T4 <0.001
								T3 *vs.* T4 0.562
	Overall	1,814	1,242	26.02	2.07	21.97	30.07	<0.001

Table 4 (*continued*)

Table 4 (*continued*)

Survival	Stages	Number	Deaths	Median survival (months)	Standard error	95% confidence interval		P value
LCSGJ								
Overall survival	T1	119	33	>324.30	–	–	–	
	T2	720	290	160.89	14.09	133.27	188.51	
	T3	687	409	59.2	4.63	50.13	68.28	
	T4	288	223	26.09	2.03	22.12	30.06	
	Overall	1,814	955	79.74	5.1	69.74	89.73	<0.001
Disease-free survival	T1	118	55	83.68	27.53	29.72	137.64	
	T2	720	420	67.88	6.54	55.06	80.7	T1 *vs.* T2 0.053
	T3	688	509	14.69	1.31	12.12	17.26	T1 *vs.* T3 <0.001 T2 *vs.* T3 <0.001
	T4	288	258	4.8	0.4	4.02	5.58	T3 *vs.* T4 <0.001
	Overall	1,814	1,242	26.02	2.07	21.97	30.07	<0.001

HKUSS, The University of Hong Kong liver cancer staging system; AJCC 8th, the 8th edition of the American Joint Committee on Cancer tumor-node-metastasis staging system; LCSGJ, the Liver Cancer Study Group of Japan staging system.

respectively in patients with T3 tumors, and 31.7%, 17.1% and 14.4% respectively in patients with T4 tumor (P<0.001). The 1-, 3- and 5-year rates of OS were 98.1%, 90.4% and 82.9% respectively in patients with T1a tumors, 97.2%, 87.3% and 78.6% respectively in patients with T1b tumors, 89.7%, 68.4% and 51.0% respectively in patients with T2 tumors, 86.9%, 47.6% and 34.3% respectively in patients with T3 tumors, and 65.4%, 38.1% and 26.7% respectively in patients with T4 tumors (P<0.001). There were significant survival differences between the T1a and T2 groups, between the T1b and T2 groups, between the T2 and T3 groups, and between the T2 and T4 groups. However, the survival difference between the T1a and T1b groups (P=0.668) and that between the T3 and T4 groups (P=0.562) were not statistically significant (*Table 4*) (*Figure 1C,D*).

Using LCSGJ, the 1-, 3- and 5-year rates of DFS were 86.4%, 71.9% and 61.9% respectively in patients with T1 tumors, 81.0%, 61.1% and 51.5% respectively in patients with T2 tumors, 55.2%, 35.7% and 28.9% respectively in patients with T3 tumors, and 25.6%, 14.1% and 9.8% respectively in patients with T4 tumors (P<0.001). The 1-, 3- and 5-year rates of OS were 99.2%, 91.7% and 87.3% respectively in patients with T1 tumors, 95.8%, 85% and 75.9% respectively in patients with T2 tumors, 87.5%, 64.7% and 49.4% respectively in patients with T3 tumors, and 71.7%, 38% and 24.3% respectively in patients with T4 tumors (P<0.001). There were significant survival differences between the T1 and T3 groups, between the T2 and T3 groups, and between the T3 and T4 groups. Nevertheless, the survival difference was not significant between the T1 and T2 groups (P=0.053) (*Table 4*) (*Figure 1E,F*).

Using ROC curves to compare the T classifications in predicting the risk of recurrence, all the staging systems showed an AUC of >0.648, P<0.001. Nonetheless, HKUSS showed the largest AUC of 0.655, with a standard error of 0.014, 95% CI, 0.628–0.681, P<0.001 (*Figure 2*).

Discussion

The AJCC staging system was formulated on the basis of survival analysis of post-resection patients. An optimal staging system would allow accurate categorization of patients based on tumor biology, tumor status, and the extent of disease. Different stages should allow stratifying different disease statuses into different disease categories, hence giving patients a realistic expectation of DFS, or, if possible, OS. Unfortunately, to date, current staging systems mainly focus on pathological staging only, and thus the disease can only be staged after surgery. The TNM staging system developed by the AJCC has been updated

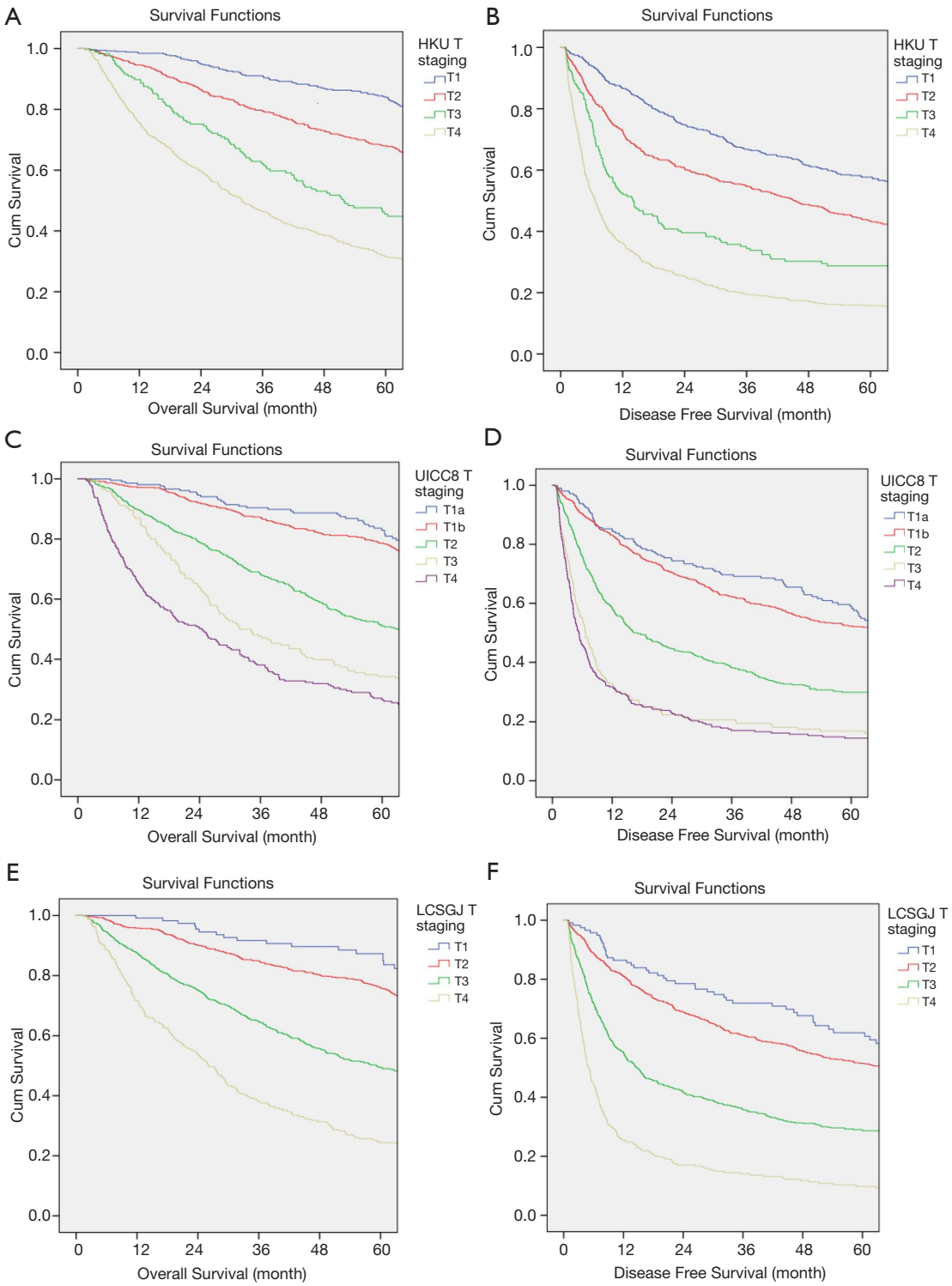

Figure 1 Overall survival and disease-free survival with various T stages in The University of Hong Kong liver cancer staging system (A,B), the 8th edition of the American Joint Committee on Cancer tumor-node-metastasis staging system (C,D), and the Liver Cancer Study Group of Japan staging system (E,F) (HKU, The University of Hong Kong liver cancer staging system; UICC8, the 8th edition of the American Joint Committee on Cancer tumor-node-metastasis staging system; LCSGJ, the Liver Cancer Study Group of Japan staging system).

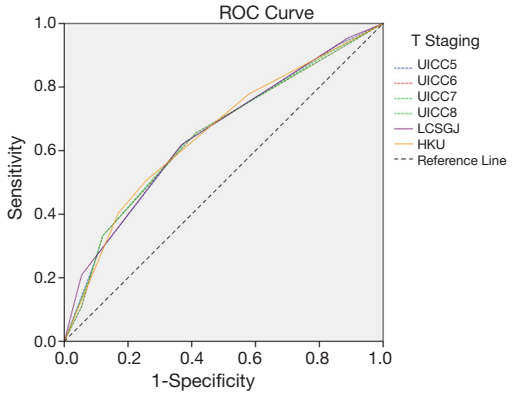

Figure 2 Receiver operating characteristic curves for various staging systems in predicting disease recurrence. (All T staging systems are significant with area under curve, while The University of Hong Kong liver cancer staging system and the Liver Cancer Study Group of Japan staging system are the two having the largest area under curve, followed by the 8th edition, the 5th edition, the 7th edition and the 6th edition of the American Joint Committee on Cancer tumor-node-metastasis staging system).

and validated regularly since its 1st edition (16). The system was meant to provide information best on pathological characteristics of resected specimens. The 8th edition was published in 2017. The major changes in this version included subcategorization of the T staging according to tumor size and presence/absence of vascular invasion (9). The present study evaluated the prognostic power of four editions of the AJCC staging system (the 5th, 6th, 7th and 8th editions) as well as LCSGJ. All of them failed to make adequate stratification of the patients into subgroups with distinct survival differences.

An ideal T staging system should have a good separation of T stages for different subsets of tumors. The inadequacy of the various staging systems has been briefly mentioned (10). In brief, the 7th edition shows improvement in prognosis when compared with the editions before, but it still lacks enough power for prognosis of advanced-stage HCC (17). T3 tumors are divided into T3a (multiple tumors, any of which can be >5.0 cm) and T3b (tumor invasion of a major branch of the portal vein or the hepatic vein), but such subclassification of T3 tumors was shown to be unjustified, as the survival curves for T3a, T3b and T4 tumors were close to each other, signifying that these subgroups had very little difference in survival (10). This means the 7th edition was unable to differentiate advanced disease, and thus specific adjuvant treatment targeting advanced stage disease would be lacking.

In AJCC 8th, early-stage T1 tumors were further subclassified into T1a and T1b, showing improvement of staging by shifting the focus of substratification to earlier HCC, which may allow patients with relatively common presentation of the disease to undergo more aggressive therapies. However, the survival curves for T1a and T1b approximated one another closely, signifying very slight survival differences in these two groups of patients without a definite need for subclassification. Therefore, the 2-cm cutoff with absence of microvascular invasion might require further definition. Furthermore, in this analysis, the accuracy in staging more advanced disease did not achieve better substratification, as shown by the overlapping of the DFS survival curves for T3 and T4 diseases. Better refinement on the earlier and advanced stages is therefore needed.

With the same cohort of patients, the DFS curves for T1–T4 diseases in HKUSS showed distinct and even separation of stages. This suggests that the survival difference in HKUSS for all stages represented a more realistic estimation of the DFS, making HKUSS a better T staging system. In addition, the OS curves were also well separated. The distinct and even curve separations indicate better categorization of patients into the various groups based on tumor pathology.

For LCSGJ, despite the insignificant difference in DFS between T1 and T2 diseases, both the DFS and OS curves showed good separation of various T stages. LCSGJ had been proven to be able to make accurate stratification (18). Our result echoed the previous study and suggested that LCSGJ was also able to predict individual patient's prognosis. The use of LCSGHJ in this study was to further compare the T staging in different systems. Using T staging alone allowed better understanding of the treatment effect of surgery on specific tumor conditions. As seen from the ROC curves, LCSGJ performed almost as good as HKUSS.

Unfortunately, tumor burden, which is assessed radiologically only, is a poor surrogate of HCC's biological aggressiveness. Apart from pathological features such as poor differentiation and presence of microvascular or macrovascular invasion, behavior of a tumor may also be revealed by the serum proteins it produces. α-fetoprotein has been used as a surrogate of tumor burden, which is also considered to be the tumor marker to monitor disease progression and treatment response (19). Des-y-carboxyprothrombin, an abnormal form of prothrombin, is mainly produced by HCC cells (20), and an increase of des-y-carboxyprothrombin has been shown to indicate a

more aggressive tumor phenotype (21), the presence of microvascular invasion (22), and accelerated proliferation (23). It has been proposed that inflammatory markers such as neutrophil-to-lymphocyte ratio (24), platelet-to-lymphocyte ratio (25) and lymphocyte-to-monocyte ratio (26) be used to predict post-transplant HCC recurrence, OS, and waitlist dropouts. The Lens culinaris agglutinin fraction of α-fetoprotein is a variant of α-fetoprotein observed mainly in malignant cells (27) and it correlates with tumor size (28). Furthermore, dual-tracer (11C-acetate and 18F-fludeoxyglucose) positron emission tomography can increase sensitivity in HCC detection and predict the presence of microvascular invasion (29). These markers can be obtained preoperatively and are potentially useful for better stratification of patients in risk analyses, thereby offering better treatment options.

The current HKUSS was first proposed in 2012 (10). It has been shown to prognosticate DFS and OS more accurately. When HKUSS was formulated, only patients who had undergone surgery without preoperative evidence of metastasis and had been followed for more than 60 months were included. This reflected the genuine status of the T staging, and allowed sufficient time to monitor tumor behavior in each T stage after surgery. The experience of surgical management of patients with HCC at a single center allowed standardization of operative techniques and perioperative management, and therefore surgical outcomes (4). However, one might argue that generalization of the results might not be possible since variations in operative approaches might make a difference in long-term survival (30). To increase its generalizability, it would be most ideal to have the system externally validated by other centers. Anyway, additional patients recruited in the recent years had made the cohort larger, and hence the results of HKUSS more refined and thus more accurate. In this study, DFS was selected as the determinant of the performance of the staging systems, as DFS is more representative of underlying tumor characteristics and treatment outcomes from surgery itself, without the treatment effects from other therapies that would otherwise confound the analysis. On the other hand, if OS was set as the primary endpoint, survival comparison between different centers/places could hardly be fair and equal, since there would be a lack of standardization of treatment algorithms for postoperative tumor recurrence, and different forms of treatment (alone or combined) deployed for management of recurrent disease could have variable impact on OS, making it a confounding factor. In this study, it was seen that with surgery as the treatment, HKUSS gave better prediction. HKUSS has continued to show a clear stratification of patients in both DFS and OS, which indicates that it is a clinically practicable staging system for HCC.

There are several pitfalls in this study. First, our patient population was predominantly affected by hepatitis B. Whether HKUSS is applicable to HCC with other etiologies needs further evaluation. By the same principle, HKUSS was derived solely from patients with preserved liver function who received liver resection. As a result, this system might not be applicable to non-surgical patients or patients with impaired liver function.

Conclusions

HKUSS showed better categorization of HCC. In the context of primary surgical resection, HKUSS may be more appropriate for stratification of patients with HCC with various T stages, and thus the choice of staging system when primary surgical resection is considered for HCC patients.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-20-7611). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work (including full data access, integrity of the data and the accuracy of the data analysis) in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Institutional review board approval was not obtained for this retrospective study, as according to local regulations, institutional review board approval is not required for retrospective studies analyzing

anonymous data. All patients gave their written informed consent to collection and use of their data for research purposes. No individual patients can be identified with the anonymous data used in this study.

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