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Original Article

New Staging Model for Radiation-based Hepatocellular Carcinoma Treatment: A National Multicenter Study

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Abstract

Background and Aims: The study aimed to create a new staging model for radiotherapy-based treatment for prognostic hepatocellular carcinoma (HCC) classification. ***Methods:*** The training cohort comprised 658 patients receiving stereotactic body radiotherapy and external validation cohort comprised 533 patients receiving three-dimensional conformal radiotherapy and intensity-modulated radiotherapy. We established a modified staging system as follows: stage I, solitary nodule without macrovascular invasion, or 2–3 nodules no more than 3.0 cm apart, and performance status (PS) 0–2 (Ia: ALBI-1 grade; Ib: ALBI-2 or 3 grade); stage II: 2–3 nodules with any one nodule more than 3.0-cm apart, or ≥4 nodules, and performance status 0–2 (IIa: ALBI-1 grade; IIb: ALBI-2 grade); stage III: macrovascular invasion, regional lymph node metastasis or distant metastasis, and performance status 0–2 (IIIa: ALBI-1 grade; IIIb: ALBI-2 grade); stage IV: performance status 3–4, or performance status 0–2 with ALBI-3 grade. We analyzed long-term overall survival based on different stages. ***Results:*** The staging model showed an excellent ability to discriminate patients according to four stages and seven substages with notably different curves in the training and validation cohort. The median survival decreased from stages I to IV with 63.0 months in stage I (not reached in Ia, and 53.0 months in Ib), 24.0 months in stage II (28.0 months in IIa, and 22.0 months in IIb), 11.0 months in stage III (18.0 months in IIIa, and 9.0 months in IIIb), and less than 9.0 months in stage IV in the training cohort. ***Conclusions:*** The modified staging model may provide an alternative for clinical radiation oncologists.

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Keywords: Hepatocellular carcinoma; Radiotherapy; Stereotactic body radiotherapy; Staging system; Overall survival.

Abbreviations: ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; CNLC, China Liver Cancer; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma; IMRT, intensity-modulated radiotherapy; OS, overall survival; PS, performance status; RT, radiotherapy; ROC, receiver operating characteristic; SBRT, stereotactic body radiotherapy.

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Introduction

Hepatocellular carcinoma (HCC) is the fourth most common cause of cancer-related deaths worldwide.[1] With the development of image guidance techniques, precision external beam radiation (RT) therapies, including intensity-modulated radiotherapy (IMRT) and stereotactic body radiotherapy (SBRT), are being increasingly used to treat HCC.[2,3] Radiotherapy has been used as a palliative to the radical treatment of HCC, depending on the tumor status, liver function, and patient's general state of health. Recently, increasing and encouraging prospective evidence has supported the clinical application of SBRT with a high local control rate and safety.[4–10] SBRT can provide better local control than radiofrequency ablation, with comparable toxicities.[11–13] SBRT, as an alternative to conventional bridging therapies, can be safely utilized as a bridge to liver transplantation in patients with HCC, with a similar dropout rate and long-term survival outcomes.[14] It is recommended as an alternative radical treatment for medically inoperable patients with HCC of some selected early stages.[15–18] In patients with small HCC (≤5 cm), SBRT can even achieve an effect similar to that of radical surgery.[19,20] In patients with advanced HCC, SBRT extended survival by 9.3 months compared with sorafenib.[21]

Several classifications of HCC have been proposed in clinical practice. The Barcelona Clinic Liver Cancer (BCLC) system, endorsed by the American Association for the Study of Liver Disease and the European Association for the Study of the Liver, is used worldwide.[22] The eighth edition of the TNM

American Joint Committee on Cancer (2017), based on only the tumor characteristics and extent of invasion without liver function, is also a commonly used staging system.[23] The China Liver Cancer (CNLC) staging system, including tumor status, number of nodules, liver function, and the Eastern Cooperative Oncology Group (ECOG) performance status score, are widely used in China.[2] However, radiotherapy is not recommended as a treatment option in the BCLC guidelines. To the best of our knowledge, there are no clinical staging models based on radiotherapy for HCC. In this study, we aimed to verify the predictive stratification ability of the existing staging systems with radiotherapy for HCC and to compare it with a new modified staging model for the prognostic classification of HCC with radiotherapy-based treatment by separating patients according to different stages and substages and analyzing their long-term overall survival (OS) and time-dependent receiver operating characteristic (ROC) curves.

Methods

Patients and study design

The demographic, clinical, and pathological data of consecutive patients with HCC were reviewed retrospectively. Overall, this multicenter cohort study involved 1,191 patients with HCC treated with radiotherapy. In addition, we divided patients receiving SBRT into a training cohort (Ruikang Hospital, The Fifth Medical Center of PLA General Hospital, Peking University Third Hospital, Changhai Hospital). Others on three-dimensional conformal radiotherapy and IMRT were divided into an external validation cohort (Guangxi Medical University Cancer Hospital, First Affiliated Hospital of Yangtze University, Yulin First People's Hospital). The study protocol conforms to the ethical guidelines of the Helsinki Declaration revised in 2013 as reflected in a priori approval by the ethics committees of Guangxi Medical University Cancer Hospital and the respective institutions (LW2021008). All subjects provided written informed consent in accordance with the Declaration of Helsinki. The STROBE guideline has been followed during the preparation of the manuscript.

Patients who met all of the following criteria were eligible to participate in this study:

1. HCC lesions are treated with radiotherapy or combination therapy;
2. Controllable liver function with or without cirrhosis;
3. ECOG scores 0–2;
4. Multiple adjacent lesions that a single RT target area could cover were allowed;
5. Patients with early-stage HCC that was inoperable or unsuitable for radiofrequency ablation.

Patients with the following were excluded:

1. Non-HCC confirmed by postoperative pathology or liver metastases;
2. Uncontrolled ascites and hepatic encephalopathy;
3. An active gastric or duodenal ulcer or other uncontrolled comorbidities;
4. A history of severe esophageal varices;
5. Double cancer;
6. A history of abdominal radiotherapy.

All included patients were re-evaluated 1 month after radiotherapy and every 3–6 months thereafter. All surviving patients were followed up regularly. Follow-up was performed via telephone calls at 3-month intervals or at outpatient. For patients who developed progressive or recurrent disease, multidisciplinary treatment was selected to treat recurrent HCC based on liver function, number of recurrence nodules, location of the tumor, and intra-, or extrahepatic metastases.

RT protocol

Contrast-enhanced computed tomography (CT) was performed with the patients in the supine position with both arms raised above the head and vacuum mold immobilization to restrain liver motion. Radical/combined/adjuvant/palliative radiotherapy was performed according to the tumor stage and previous treatment. The final RT dose was determined according to the tumor size, severity of liver dysfunction, and dose-volume constraints of the organ at risk. The general principle was using higher RT doses for patients with small tumors, in an early stage, and with better liver function, and lower doses for patients with larger tumors, in an advanced stage, or with worse liver function.

Three-dimensional (3D) RT and IMRT

The gross tumor volume (GTV) was defined as the primary lesion delineated using the CT simulation image and/or fused diagnostic MRI. The clinical target volume (CTV) was defined as GTV plus a 4–5-mm margin in all directions for intrahepatic tumors. The planning target volume (PTV) was established by adding an asymmetric 0.5–1-cm margin in the cranial-caudal direction and 5 mm axially to the CTV for uncertainties in treatment delivery. A median daily dose of 4.0 (range, 2–7) Gy at median fractions of 15 (range, 6–30) was administered to deliver a median total dose of 52 (range, 36–66) Gy.[24–26]

SBRT

SBRT was delivered using the CyberKnife system (Accuray, Sunnyvale, CA, USA) with tracking of liver motion using implanted fiducials. Three to four fiducials (diameter, 0.8 mm) were inserted into the tumor tissue or into the area surrounding the tumor under B-ultrasound or CT guidance, 1 week before the CT scan or MRI (slice thickness, 3 mm). The CTV coincided with the GTV. The PTV was defined as the GTV plus 5 mm to account for any setup error and was usually decreased manually when the dose-limiting organs overlapped. The median prescribed dose was 45 (range, 26–55) Gy, delivered with a median of three fractions (1–7 fractions) on consecutive days.[10,19,24,27]

New stage model

We designed a new staging model for radiotherapy-based treatment by incorporating tumor status and the bilirubin-albumin (ALBI) grade for the prognostic classification of HCC. The ALBI grade was calculated as follows: (log10 bilirubin × 0.66) + (albumin × −0.085). The cut points were as follows: ALBI grade 1: ≤−2.60, ALBI grade 2: more than −2.60 to ≤−1.39, and ALBI grade 3: more than −1.39; where bilirubin is in μmol/L and albumin is in g/L.[28] The new modified staging system was established as follows: stage I, solitary nodule without macrovascular invasion or 2–3 nodules no more than 3.0-cm apart, and performance status 0–2 (Ia: ALBI-1 grade; Ib: ALBI-2 or 3 grade); stage II: 2–3 nodules with any one more than 3.0-cm apart, or ≥4 nodules, and performance status 0–2 (IIa: ALBI-1 grade; IIb: ALBI-2 grade); stage III: macrovascular invasion, regional lymph node metastasis or distant metastasis, and

performance status 0–2 (IIIa: ALBI-1 grade; IIIb: ALBI-2 grade); stage IV: performance status 3–4 or performance status 0–2 with ALBI-3 grade.

Statistical analysis

Patients with HCC treated with RT were separated according to stages and substage. Cumulative OS was the primary endpoint and was compared using the log-rank test and calculated using the Kaplan-Meier method. OS was evaluated from the date of the first radiotherapy to the patient's death by any cause, the last date alive, or the last follow-up. Continuous variables were compared using Wilcoxon rank-sum test, whereas categorical variables were compared using Pearson's chi-squared test. In addition, time-dependent receiver operating characteristic (ROC) curve analysis was performed to compare the discriminatory ability of different staging systems.[29] The statistical analysis and data plotting were performed with R version 4.0.2 (2020-06-22). Results with p-values < 0.05 were considered statistically significant.

Results

Patient characteristics

Overall, this multicenter cohort study involved 1,191 patients with HCC after radiotherapy between January 1, 2000, and April 30, 2019. Table 1 shows the baseline characteristics. In addition, the training cohort comprised 658 patients and the external validation cohort comprised 533 patients. Among these patients, 362 (55.0%) in the training cohort died within a median follow-up time of 60.0 (range, 6–100) months, and 397 (77.5%) patients in the external validation cohort died within a median follow-up time of 58.0 (range, 6–120) months.

New staging model for the training cohort and external validation cohort

The new staging model showed an excellent ability to discriminate patients according to different stages with four notably different curves and substages with seven notably different curves (Fig. 1A, B). The median OS was 63.0 months in stage I (not reached in Ia and 53.0 months in Ib), 24 months in stage II (28.0 months in IIa and 22.0 months in IIb), 11 months in stage III (18.0 months in IIIa and 9.0 months in IIIb), and 9.0 months in stage IV.

The new staging model also showed an excellent ability to discriminate patients in the external validation cohort with four notably different curves and substages with six notably different curves (Fig. 2A, B). In addition, there was a crossover between stages IIa and IIb (Fig. 2C).

Discriminatory ability of the new staging model for the pretreatment or no-pretreatment cohort

Six hundred fifty-two patients received other treatments before radiotherapy and showed most recurrence and residue, and they were included in the pretreatment group. The remaining 539 patients were included in the no-pretreatment group who received radiotherapy as a first-line treatment. The new staging model also showed an excellent ability to discriminate patients in the pretreatment cohort with four notably different curves and substages with seven notably different curves (Supplementary Fig. 1A, B). The new staging model also showed an excellent ability to discriminate patients in the no-pretreatment cohort with four notably different curves and substages with seven curves with a crossover between stages IIIb and IV (Supplementary Fig. 1C, D).

Discriminatory ability of different staging models

The new staging model may supplement other staging systems, with a better area under the curve of time-dependent ROC than BCLC, TNM, and CNLC staging in the training cohort (Fig. 3A), external validation cohort (Fig. 3B), and the entire cohort (Fig. 3C). The Kaplan-Meier curves showed that existing BCLC, TNM, and CNLC staging system were not complete in differentiating survival outcomes among all stages. BCLC staging could not differentiate stages C to D in selected patients (Supplementary Fig. 2A). TNM staging could not completely distinguish stages IIIb to IV (Supplementary Fig. 2B). CNLC staging could not differentiate among stages IIIa, IIIb, and IV (Supplementary Fig. 2C). BCLC staging could not differentiate stages 0 to A in selected patients (Supplementary Fig. 2D). TNM staging could not completely distinguish stages Ia to Ib or IIIb to IV (Supplementary Fig. 2E). CNLC staging could not differentiate between stages Ia to Ib and IIIa, IIIb to IV (Supplementary Fig. 2F).

Discussion

The American Society for Radiation Oncology (ASTRO) Clinical Practice Guideline guides the definitive management of primary HCC with RT therapy, including standard, preoperative, adjuvant, salvage, and consolidative, and as a bridge to transplant, and palliative management for symptomatic cancers.[30] An HCC staging model based on RT data is urgently needed to guide treatment purposes effectively and expected survival. Consequently, incorporating tumor status and the bilirubin-albumin grade, we established a new staging model that divided patients into four-stage groups, with two substages each for stages I and II and III. Based on a multicenter, nationwide cohort involving a large sample set, the new staging system can distinguish the survival prognosis of each stage well when the median survival decreased from stages I to IV.

Pretreatment liver function is essential for patients with HCC receiving radiotherapy, as it is strongly associated with treatment toxicity, survival, and dose selection.[10,25,27,31–33] BCLC and CNLC staging systems utilize treatment algorithms based on baseline liver function quantified by the Child-Pugh score. The ALBI is purely quantitative, using only laboratory measures of albumin and bilirubin. Previous studies have shown that ALBI could discriminate liver function reserve and predict OS after radiotherapy more objectively than the Child-Pugh system in western and eastern countries.[27,34] Therefore, we established this new staging system by incorporating the liver function index (ALBI grade) for further substaging. The new staging model showed the ability to discriminate substages of HCC stages I, II, and III. It had a better area under the curve of time-dependent ROC than BCLC, TNM, and CNLC staging in the entire cohort.

Radiotherapy has also been used for the radical treatment of small or early-stage HCC. In Asian countries, a larger number of cases and expertise have led to more aggressive treatments, including radiotherapy. Notably, the CNLC guidelines in China provide the most liberal indica-

Table 1. Baseline characteristics of the study group

Baseline characteristic	ALL	Training cohort	Validation cohort	*p*-value
n	*1,191*	*658*	*533*	
Sex				0.006
female	145 (12.2%)	96 (14.6%)	49 (9.19%)	
male	1,046 (87.8%)	562 (85.4%)	484 (90.8%)	
Age in years	52.0 (12.0)	53.9 (12.3)	49.6 (11.1)	<0.001
Pretreatment				<0.001
no	539 (45.3%)	352 (53.5%)	187 (35.1%)	
yes	652 (54.7%)	306 (46.5%)	346 (64.9%)	
Hepatitis B surface antigen				<0.001
negative	173 (14.5%)	90 (13.7%)	83 (15.6%)	
positive	938 (78.8%)	488 (74.2%)	450 (84.4%)	
unknown	80 (6.72%)	80 (12.2%)	0 (0.00%)	
Alpha-fetoprotein in ng/mL				0.064
0–8	293 (24.6%)	170 (25.8%)	123 (23.1%)	
8–200	326 (27.4%)	192 (29.2%)	134 (25.1%)	
>200	572 (48.0%)	296 (45.0%)	276 (51.8%)	
Total bilirubin in μmol/L	19.3 (31.0)	19.7 (36.2)	18.9 (23.2)	0.643
Direct bilirubin in μmol/L	9.55 (21.0)	10.2 (23.7)	7.91 (10.8)	0.05
Albumin in g/L	37.2 (5.04)	37.2 (5.41)	37.1 (4.55)	0.633
ALT in U/L	45.5 (38.1)	45.9 (37.4)	44.6 (39.9)	0.66
AST in U/L	45.0 (44.9)	42.1 (43.3)	52.3 (48.3)	0.004
ALP in U/L	129 (189)	128 (246)	130 (71.7)	0.831
CHE in U/L	5,314 (2,071)	5,230 (2,201)	5,488 (1,762)	0.08
Urea in mmol/L	5.06 (5.31)	5.26 (6.19)	4.55 (1.27)	0.006
Creatinine in μmol/L	81.0 (40.8)	84.8 (46.6)	71.1 (14.6)	<0.001
PT in s	13.1 (1.70)	13.5 (1.79)	12.8 (1.51)	<0.001
Ascites				0.302
no	968 (81.3%)	530 (80.5%)	438 (82.2%)	
small	172 (14.4%)	103 (15.7%)	69 (12.9%)	
moderate	51 (4.28%)	25 (3.80%)	26 (4.88%)	
Child-Pugh				0.009
A	999 (83.9%)	540 (82.1%)	459 (86.1%)	
B	184 (15.4%)	110 (16.7%)	74 (13.9%)	
C	8 (0.67%)	8 (1.22%)	0 (0.00%)	
ALBI score	−2.39 (0.49)	−2.39 (0.53)	−2.38 (0.44)	0.599
ALBI grade				0.003
1	418 (35.1%)	254 (38.6%)	164 (30.8%)	
2	726 (61.0%)	373 (56.7%)	353 (66.2%)	
3	47 (3.95%)	31 (4.71%)	16 (3.00%)	
Tumor size in cm	6.82 (4.79)	6.11 (5.29)	7.69 (3.91)	<0.001
Total dose in Gy	47.7 (7.55)	43.2 (4.74)	53.2 (6.64)	<0.001
Fraction	9.32 (7.66)	3.69 (1.02)	16.3 (6.50)	<0.001

(continued)

Table 1. *(continued)*

Baseline characteristic	ALL	Training cohort	Validation cohort	*p*-value
Per dose in Gy	8.51 (4.89)	12.3 (2.87)	3.77 (1.59)	0
TNM-AJCC stage				<0.001
Ia	55 (4.62%)	44 (6.69%)	11 (2.06%)	
Ib	380 (31.9%)	225 (34.2%)	155 (29.1%)	
II	135 (11.3%)	88 (13.4%)	47 (8.82%)	
IIIa	134 (11.3%)	67 (10.2%)	67 (12.6%)	
IIIb	348 (29.2%)	161 (24.5%)	187 (35.1%)	
IVa	104 (8.73%)	38 (5.78%)	66 (12.4%)	
IVb	35 (2.94%)	35 (5.32%)	0 (0.00%)	
BCLC stage				.
0	51 (4.28%)	43 (6.53%)	8 (1.50%)	
A	352 (29.6%)	261 (39.7%)	91 (17.1%)	
B	255 (21.4%)	111 (16.9%)	144 (27.0%)	
C	525 (44.1%)	235 (35.7%)	290 (54.4%)	
D	8 (0.67%)	8 (1.22%)	0 (0.00%)	
CNLC stage				.
Ia	259 (21.7%)	181 (27.5%)	78 (14.6%)	
Ib	172 (14.4%)	128 (19.5%)	44 (8.26%)	
II	267 (22.4%)	112 (17.0%)	155 (29.1%)	
IIIa	349 (29.3%)	158 (24.0%)	191 (35.8%)	
IIIb	136 (11.4%)	71 (10.8%)	65 (12.2%)	
IV	8 (0.67%)	8 (1.22%)	0 (0.00%)	
New stage				<0.001
I	430 (36.1%)	309 (47.0%)	121 (22.7%)	
II	265 (22.3%)	112 (17.0%)	153 (28.7%)	
III	464 (39.0%)	214 (32.5%)	250 (46.9%)	
IV	32 (2.69%)	23 (3.50%)	9 (1.69%)	
New substage				<0.001
Ia	186 (15.6%)	153 (23.3%)	33 (6.19%)	
Ib	244 (20.5%)	156 (23.7%)	88 (16.5%)	
IIa	103 (8.65%)	44 (6.69%)	59 (11.1%)	
IIb	162 (13.6%)	68 (10.3%)	94 (17.6%)	
IIIa	136 (11.4%)	64 (9.73%)	72 (13.5%)	
IIIb	328 (27.5%)	150 (22.8%)	178 (33.4%)	
IV	32 (2.69%)	23 (3.50%)	9 (1.69%)	

AJCC, American Joint Committee on Cancer; ALBI, albumin-bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer; CNLC, China Liver Cancer; PT, prothrombin time.

tions for the use of radiotherapy. The BCLC system stratifies patients with HCC into five categories (0, A, B, C, and D).[35] The BCLC therapeutic flowchart is not applied routinely in radiotherapy management for HCC. SBRT recently provided better local control in medically inoperable early-stage HCC than transarterial chemoembolization (TACE)[15–18,36] or radiofrequency ablation.[11–13] Unlike radiofrequency ablation, which has the optimal outcomes for tumors less than 3 cm in a specific location,[37] radiotherapy is not limited by the tumor size or location.[38] Furthermore, irradiation is a potentially curative treatment option for small HCC (≤5 cm), achieving an effect similar to surgical resection.[19,20] In addition, SBRT can be safely utilized as a bridge to liver transplantation in patients with HCC.[14] Therefore, we refined HCC staging by merging the BCLC 0 (solitary nodule) and BCLC 0 (2–3 nodules ≤ 3.0 cm) groups into a single stage (stage I). After incorporating the ALBI grade, the new staging system showed a good discriminatory power in stratify-

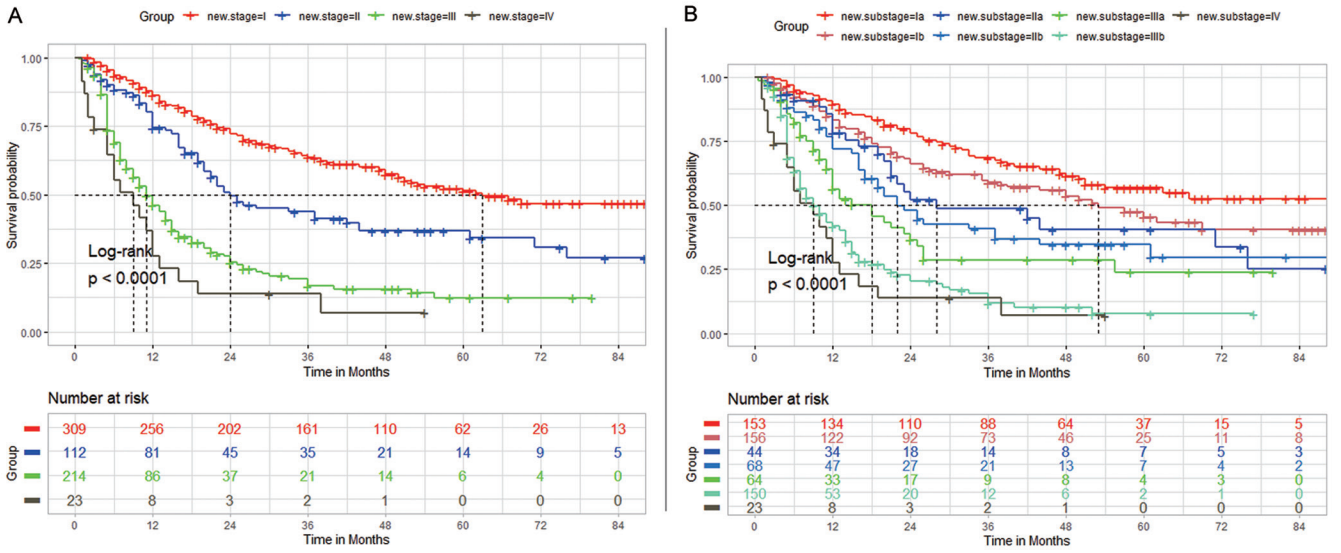

Fig. 1. (A) Four stages in the training cohort; (B) Seven substages in the training cohort.

ing early-stage patients into the Ia and Ib subgroups.

Multiple nodular lesions (2–3 nodules, more than 3.0 cm apart or with ≥ 4 nodules), classified as the new stage II/BCLC-B, exhibit considerable heterogeneity. TACE was recommended to the BCLC-B subpopulation, and the expected survival time was 20 months.[22] In real-world settings, curative treatments, including radiotherapy and its combinations, are widely applied, and they have shown promise in well-selected patients.[39] In particular, SBRT combined with TACE has been reported to have a synergistic effect with favorable outcomes and disease control.[40,41] In the current study, the median OS after SBRT was acceptable at 24 months in stage II (28.0 months in IIa and 22.0 months in IIb) in the selected patients with multiple nodular lesions. However, the selection of irradiation lesions and the optimal treatment strategies for combinations with TACE have to be explored further.

The HCC-associated macrovascular invasion has been considered the bottleneck in HCC treatment. If untreated, a median survival time of 2.7 to 4.0 months has been reported.[42,43] In our previous study, radiotherapy-based treatment could extend the median survival to 10.0–15.0 months.[24,44] Neither the TNM nor the CNLC classification scheme satisfactorily discriminated OS between macrovascular invasion and extrahepatic metastasis disease, suggesting that they are prognostically similar. TNM staging classified HCC-associated macrovascular invasion as T4 and stage IIIb, but could not completely distinguish stages IIIb and IV. CNLC staging classified HCC-associated macrovascular invasion as stage IIIb, but could not differentiate stages IIIa, IIIb, and IV. Therefore, despite the heterogeneity, the proposed staging system classified HCC-associated macrovascular invasion and extrahepatic metastasis as stage III, incorporating the ALBI grade for substages IIIa and IIIb. This refined staging of HCC also had good discriminatory power in stratifying advanced-stage patients into subgroups. All these advantages may be important considerations in the clinical setting.

Here, we defined patients with stage IV as those with ECOG PS 0–2 combined with ALBI-3 or ECOG PS 3–4. Only then, staging can accommodate all patient types. The median OS was based on patients with ECOG 0–2 with median survival of 9 months. Palliative radiotherapy is still available for some cases of increased ECOG score due to metastasis, such as brain metastasis and bone metastasis.[45] Therefore, we empirically included patients with ECOG 3–4 in stage IV with expected survival of less than 9 months. For stage IV patients, the survival time is short, and we recommend careful selection of radiotherapy after fully weighing the potential benefits and risks of radiotherapy. Not all patients are suitable for radiotherapy, and the best supportive treatment is recommended for patients with end-stage in most HCC guides.

Some limitations of our study need to be acknowledged. First, this was a retrospective study with inherent defects; further prospective validation of this new model in patients with HCC is recommended. Second, we did not examine treatment-related mortalities, adverse effects, and morbidities. Third, radiotherapy technology (3D-RT, IMRT, or SBRT), radiotherapy equipment, and radiotherapy experience varied in different centers at different times. Following completion of the total dose of radiotherapy, the subsequent treatment choice of the tumor may further influence the patient's prognosis, which may further affect the accuracy of the model. Finally, no high-level evidence-based evidence strongly supports radiotherapy as a first-line treatment for HCC. Notably, the new staging model is not intended to replace or challenge existing staging but may supplement other staging systems. We encourage the new staging model to be validated with other treatments.

In conclusion, this new modified staging model has an excellent ability to discriminate patients according to different stages and substages after radiotherapy and may provide an alternative for clinical radiologists.

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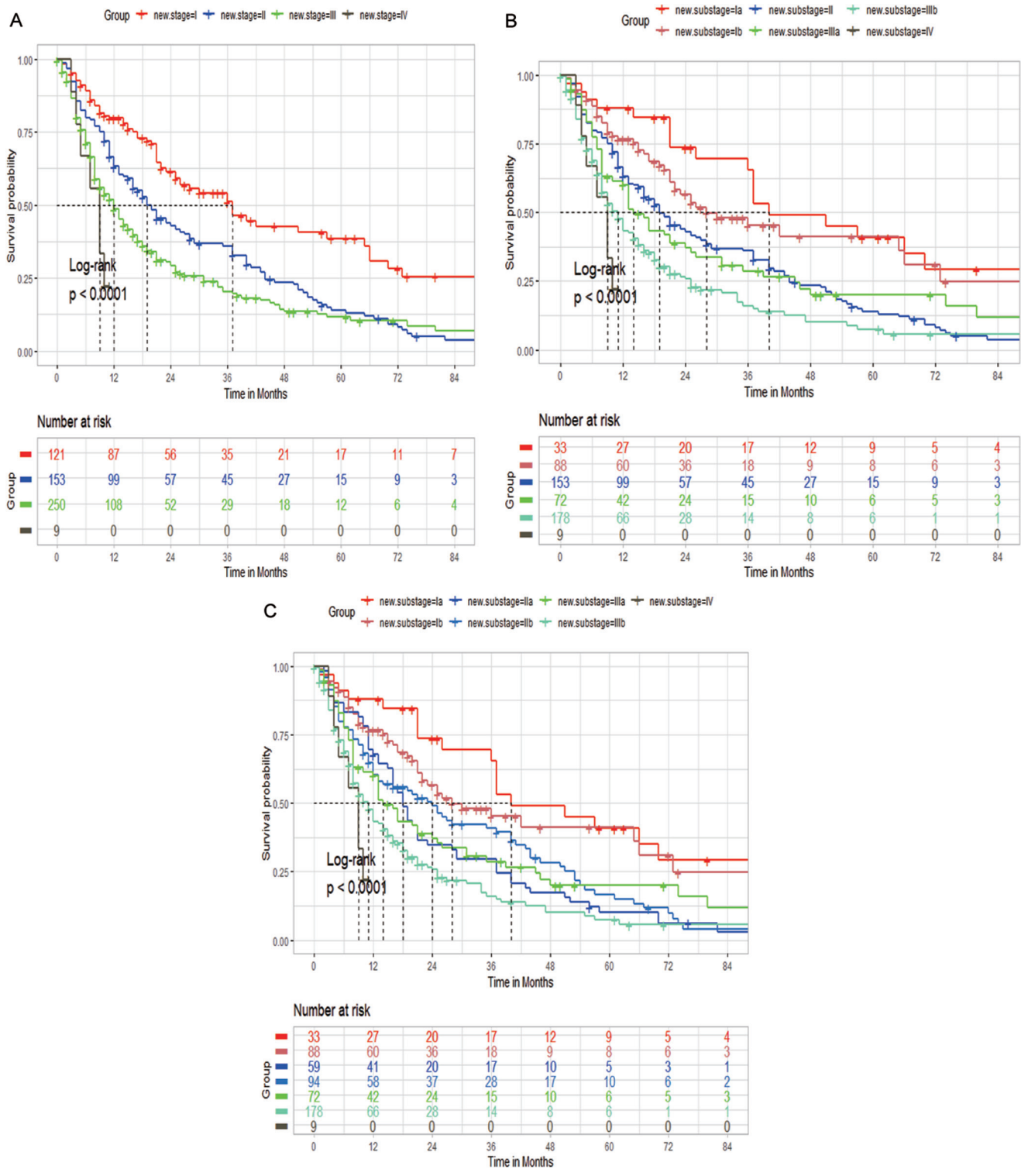

Fig. 2. (A) Four stages in the external validation cohort; (B) Six substages in the external validation cohort; (C) Seven substages in the external validation cohort.

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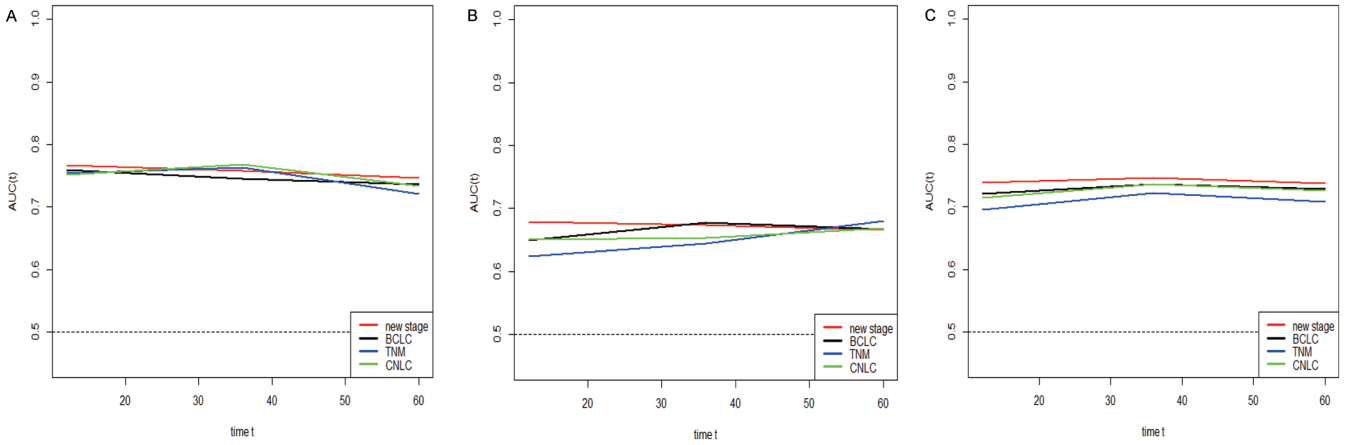

Fig. 3. Time-dependent (months) receiver operating characteristic curves: (A) in the training cohort; (B) in the external validation cohort; (C) in the entire cohort.

Conflict of interest

The authors have no conflicts of interest related to this publication.

Author contributions

Study conception and design, and data analysis (TSS), writing of the first draft of the manuscript (LQL, TSS), material preparation and data collection (all authors), providing commentary on previous versions of the manuscript and reading and giving approval to the final manuscript (all authors).

Ethical statement

The study protocol conforms to the ethical guidelines of the Helsinki Declaration revised in 2013 as reflected in a priori approval by the ethics committees of Guangxi Medical University Cancer Hospital and the respective institutions (LW2021008). All subjects provided written informed consent in accordance with the Declaration of Helsinki.

Data sharing statement

The datasets generated during the current study are not publicly available due to hospital confidentiality policy, but they are available from the corresponding author (Su, sutingshi@163.com) on reasonable request.

References

[1] Yang JD, Hainaut P, Gores GJ, Amadou A, Plymoth A, Roberts LR. A global view of hepatocellular carcinoma: trends, risk, prevention and management. Nat Rev Gastroenterol Hepatol 2019;16(10):589–604. doi:10.1038/s41575-019-0186-y, PMID:31439937.
[2] Zhou J, Sun H, Wang Z, Cong W, Wang J, Zeng M, *et al*. Guidelines for the Diagnosis and Treatment of Hepatocellular Carcinoma (2019 Edition). Liver Cancer 2020;9(6):682–720. doi:10.1159/000509424, PMID:33442540.
[3] Korean Liver Cancer Association (KLCA) and National Cancer Center (NCC), Goyang, Korea. 2018 Korean Liver Cancer Association-National Cancer Center Korea Practice Guidelines for the Management of Hepatocellular Carcinoma. Korean J Radiol 2019;20(7):1042–1113. doi:10.3348/kjr.2019.0140, PMID:31270974.
[4] Bujold A, Massey CA, Kim JJ, Brierley J, Cho C, Wong RK, *et al*. Sequential phase I and II trials of stereotactic body radiotherapy for locally advanced hepatocellular carcinoma. J Clin Oncol 2013;31(13):1631–1639. doi:10.1200/JCO.2012.44.1659, PMID:23547075.
[5] Takeda A, Sanuki N, Tsurugai Y, Iwabuchi S, Matsunaga K, Ebinuma H, *et al*. Phase 2 study of stereotactic body radiotherapy and optional transarterial chemoembolization for solitary hepatocellular carcinoma not amenable to resection and radiofrequency ablation. Cancer 2016;122(13):2041–2049. doi:10.1002/cncr.30008, PMID:27062278.
[6] Durand-Labrunie J, Baumann AS, Ayav A, Laurent V, Boleslawski E, Cattan S, *et al*. Curative Irradiation Treatment of Hepatocellular Carcinoma: A Multicenter Phase 2 Trial. Int J Radiat Oncol Biol Phys 2020;107(1):116–125. doi:10.1016/j.ijrobp.2019.12.004, PMID:32001057.
[7] Kimura T, Takeda A, Sanuki N, Ariyoshi K, Yamaguchi T, Imagumbai T, *et al*. Multicenter prospective study of stereotactic body radiotherapy for previously untreated solitary primary hepatocellular carcinoma: The STRSPH study. Hepatol Res 2021;51(4):461–471. doi:10.1111/hepr.13595, PMID:33217113.
[8] Yoon SM, Kim SY, Lim YS, Kim KM, Shim JH, Lee D, *et al*. Stereotactic body radiation therapy for small (≤5 cm) hepatocellular carcinoma not amenable to curative treatment: Results of a single-arm, phase II clinical trial. Clin Mol Hepatol 2020;26(4):506–515. doi:10.3350/cmh.2020.0038, PMID:32646200.
[9] Jang WI, Bae SH, Kim MS, Han CJ, Park SC, Kim SB, *et al*. A phase 2 multicenter study of stereotactic body radiotherapy for hepatocellular carcinoma: Safety and efficacy. Cancer 2020;126(2):363–372. doi:10.1002/cncr.32502, PMID:31747476.
[10] Su TS, Luo R, Liang P, Cheng T, Zhou Y, Huang Y. A prospective cohort study of hepatic toxicity after stereotactic body radiation therapy for hepatocellular carcinoma. Radiother Oncol 2018;129(1):136–142. doi:10.1016/j.radonc.2018.02.031, PMID:29548558.
[11] Kim N, Cheng J, Jung I, Liang J, Shih YL, Huang WY, *et al*. Stereotactic body radiation therapy vs. radiofrequency ablation in Asian patients with hepatocellular carcinoma. J Hepatol 2020;73(1):121–129. doi:10.1016/j.jhep.2020.03.005, PMID:32165253.
[12] Wahl DR, Stenmark MH, Tao Y, Pollom EL, Caoili EM, Lawrence TS, *et al*. Outcomes After Stereotactic Body Radiotherapy or Radiofrequency Ablation for Hepatocellular Carcinoma. J Clin Oncol 2016;34(5):452–459. doi:10.1200/JCO.2015.61.4925, PMID:26628466.
[13] Kim N, Kim HJ, Won JY, Kim DY, Han KH, Jung I, *et al*. Retrospective analysis of stereotactic body radiation therapy efficacy over radiofrequency ablation for hepatocellular carcinoma. Radiother Oncol 2019;131:81–87. doi:10.1016/j.radonc.2018.12.013, PMID:30773192.
[14] Sapisochin G, Barry A, Doherty M, Fischer S, Goldaracena N, Rosales R, *et al*. Stereotactic body radiotherapy vs. TACE or RFA as a bridge to transplant in patients with hepatocellular carcinoma. An intention-to-treat analysis. J Hepatol 2017;67(1):92–99. doi:10.1016/j.jhep.2017.02.022, PMID:28257902.
[15] Su TS, Liang P, Zhou Y, Huang Y, Cheng T, Qu S, *et al*. Stereotactic Body Radiation Therapy vs. Transarterial Chemoembolization in Inoperable Barcelona Clinic Liver Cancer Stage a Hepatocellular Carcinoma: A Retrospective, Propensity-Matched Analysis. Front Oncol 2020;10:347. doi:10.3389/fonc.2020.00347, PMID:32266136.
[16] Sapir E, Tao Y, Schipper MJ, Bazzi L, Novelli PM, Devlin P, *et al*. Stereotactic Body Radiation Therapy as an Alternative to Transarterial Chemoembolization for Hepatocellular Carcinoma. Int J Radiat Oncol Biol Phys 2018;100(1):122–130. doi:10.1016/j.ijrobp.2017.09.001, PMID:29066120.
[17] Shen PC, Chang WC, Lo CH, Yang JF, Lee MS, Dai YH, *et al*. Comparison of Stereotactic Body Radiation Therapy and Transarterial Chemoembolization for Unresectable Medium-Sized Hepatocellular Carcinoma. Int J Radiat Oncol Biol Phys 2019;105(2):307–318. doi:10.1016/j.ijrobp.2019.05.066, PMID:31175903.
[18] Yuan Z, Tian L, Wang P, Song Y, Dong Y, Zhuang H. Comparative research

on the efficacy of CyberKnife(R) and surgical excision for Stage I hepatocellular carcinoma. Onco Targets Ther 2013;6:1527–1532. doi:10.2147/OTT.S51452, PMID:24194645.
[19] Su TS, Liang P, Liang J, Lu HZ, Jiang HY, Cheng T, *et al*. Long-Term Survival Analysis of Stereotactic Ablative Radiotherapy Versus Liver Resection for Small Hepatocellular Carcinoma. Int J Radiat Oncol Biol Phys 2017;98(3):639–646. doi:10.1016/j.ijrobp.2017.02.095, PMID:28581406.
[20] Sun J, Wang Q, Hong ZX, Li WG, He WP, Zhang T, *et al*. Stereotactic body radiotherapy versus hepatic resection for hepatocellular carcinoma (</= 5 cm): a propensity score analysis. Hepatol Int 2020;14(5):788–797. doi:10.1007/s12072-020-10088-0, PMID:32886334.
[21] Bettinger D, Pinato DJ, Schultheiss M, Sharma R, Rimassa L, Pressiani T, *et al*. Stereotactic Body Radiation Therapy as an Alternative Treatment for Patients with Hepatocellular Carcinoma Compared to Sorafenib: A Propensity Score Analysis. Liver Cancer 2019;8(4):281–294. doi:10.1159/000490260, PMID:31602371.
[22] European Association for the Study of the Liver; European Organisation for Research and Treatment of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2012;56(4):908–943. doi:10.1016/j.jhep.2011.12.001, PMID:22424438.
[23] Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol 2010;17(6):1471–1474. doi:10.1245/s10434-010-0985-4, PMID:20180029.
[24] Li LQ, Zhou Y, Huang Y, Liang P, Liang SX, Su TS. Stereotactic body radiotherapy versus intensity-modulated radiotherapy for hepatocellular carcinoma with portal vein tumor thrombosis. Hepatol Int 2021;15(3):630–641. doi:10.1007/s12072-021-10173-y, PMID:33818714.
[25] Liang SX, Zhu XD, Lu HJ, Pan CY, Li FX, Huang QF, *et al*. Hypofractionated three-dimensional conformal radiation therapy for primary liver carcinoma. Cancer 2005;103(10):2181–2188. doi:10.1002/cncr.21012, PMID:15812834.
[26] Su TS, Li LQ, Liang SX, Xiang BD, Li JX, Ye JZ, *et al*. A Prospective Study of Liver Regeneration After Radiotherapy Based on a New (Su'S) Target Area Delineation. Front Oncol 2021;11:680303. doi:10.3389/fonc.2021.680303, PMID:34513671.
[27] Su TS, Yang HM, Zhou Y, Huang Y, Liang P, Cheng T, *et al*. Albumin - bilirubin (ALBI) versus Child-Turcotte-Pugh (CTP) in prognosis of HCC after stereotactic body radiation therapy. Radiat Oncol 2019;14(1):50. doi:10.1186/s13014-019-1251-y, PMID:30917853.
[28] Johnson PJ, Berhane S, Kagebayashi C, Satomura S, Teng M, Reeves HL, *et al*. Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach-the ALBI grade. J Clin Oncol 2015;33(6):550–558. doi:10.1200/JCO.2014.57.9151, PMID:25512453.
[29] Bansal A, Heagerty PJ. A comparison of landmark methods and time-dependent ROC methods to evaluate the time-varying performance of prognostic markers for survival outcomes. Diagn Progn Res 2019;3:14. doi:10.1186/s41512-019-0057-6, PMID:31367681.
[30] Apisarnthanarax S, Barry A, Cao M, Czito B, DeMatteo R, Drinane M, *et al*. External Beam Radiation Therapy for Primary Liver Cancers: An ASTRO Clinical Practice Guideline. Pract Radiat Oncol 2022;12(1):28–51. doi:10.1016/j.prro.2021.09.004, PMID:34688956.
[31] Su TS, Liu QH, Zhu XF, Liang P, Liang SX, Lai L, *et al*. Optimal stereotactic body radiotherapy dosage for hepatocellular carcinoma: a multicenter study. Radiat Oncol 2021;16(1):79. doi:10.1186/s13014-021-01778-6, PMID:33882972.
[32] Su TS, Liang P, Lu HZ, Liang J, Gao YC, Zhou Y, *et al*. Stereotactic body radiation therapy for small primary or recurrent hepatocellular carcinoma in 132 Chinese patients. J Surg Oncol 2016;113(2):181–187. doi:10.1002/jso.24128, PMID:26799260.
[33] Liang SX, Zhu XD, Xu ZY, Zhu J, Zhao JD, Lu HJ, *et al*. Radiation-induced liver disease in three-dimensional conformal radiation therapy for primary liver carcinoma: the risk factors and hepatic radiation tolerance. Int J Radiat Oncol Biol Phys 2006;65(2):426–434. doi:10.1016/j.ijrobp.2005.12.031, PMID:16690430.
[34] Murray LJ, Sykes J, Brierley J, Kim JJ, Wong RKS, Ringash J, *et al*. Baseline Albumin-Bilirubin (ALBI) Score in Western Patients With Hepatocellular Carcinoma Treated With Stereotactic Body Radiation Therapy (SBRT). Int J Radiat Oncol Biol Phys 2018;101(4):900–909. doi:10.1016/j.ijrobp.2018.04.011, PMID:29976502.
[35] Llovet JM, Brú C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis 1999;19(3):329–338. doi:10.1055/s-2007-1007122, PMID:10518312.
[36] Chen YX, Zhuang Y, Yang P, Fan J, Zhou J, Hu Y, *et al*. Helical IMRT-Based Stereotactic Body Radiation Therapy Using an Abdominal Compression Technique and Modified Fractionation Regimen for Small Hepatocellular Carcinoma. Technol Cancer Res Treat 2020;19:1533033820937002. doi:10.1177/1533033820937002, PMID:32613904.
[37] Xu Q, Kobayashi S, Ye X, Meng X. Comparison of hepatic resection and radiofrequency ablation for small hepatocellular carcinoma: a meta-analysis of 16,103 patients. Sci Rep 2014;4:7252. doi:10.1038/srep07252, PMID:25429732.
[38] Hara K, Takeda A, Tsurugai Y, Saigusa Y, Sanuki N, Eriguchi T, *et al*. Radiotherapy for Hepatocellular Carcinoma Results in Comparable Survival to Radiofrequency Ablation: A Propensity Score Analysis. Hepatology 2019;69(6):2533–2545. doi:10.1002/hep.30591, PMID:30805950.
[39] Byun HK, Kim N, Seong J. Optimal Timing of Radiotherapy after Incomplete Transarterial Chemoembolization for Barcelona Clinic Liver Cancer Stage B Hepatocellular Carcinoma. Yonsei Med J 2021;62(5):409–416. doi:10.3349/ymj.2021.62.5.409, PMID:33908211.
[40] Wong TC, Chiang CL, Lee AS, Lee VH, Yeung CS, Ho CH, *et al*. Better survival after stereotactic body radiation therapy following transarterial chemoembolization in nonresectable hepatocellular carcinoma: A propensity score matched analysis. Surg Oncol 2019;28:228–235. doi:10.1016/j.suronc.2019.01.006, PMID:30851906.
[41] Jun BG, Kim SG, Kim YD, Cheon GJ, Han KH, Yoo JJ, *et al*. Combined therapy of transarterial chemoembolization and stereotactic body radiation therapy versus transarterial chemoembolization for ≤5cm hepatocellular carcinoma: Propensity score matching analysis. PLoS One 2018;13(10):e0206381. doi:10.1371/journal.pone.0206381, PMID:30379885.
[42] Bruix J, Raoul JL, Sherman M, Mazzaferro V, Bolondi L, Craxi A, *et al*. Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma: subanalyses of a phase III trial. J Hepatol 2012;57(4):821–829. doi:10.1016/j.jhep.2012.06.014, PMID:22727733.
[43] Cheng AL, Guan Z, Chen Z, Tsao CJ, Qin S, Kim JS, *et al*. Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma according to baseline status: subset analyses of the phase III Sorafenib Asia-Pacific trial. Eur J Cancer 2012;48(10):1452–1465. doi:10.1016/j.ejca.2011.12.006, PMID:22240282.
[44] Su TS, Li LQ, Meng WW, Wang YD, Chen YT, Li JX, *et al*. Long-Term Survival Analysis of Transarterial Chemoembolization Plus Radiotherapy vs. Radiotherapy for Hepatocellular Carcinoma With Macroscopic Vascular Invasion. Front Oncol 2020;10:1205. doi:10.3389/fonc.2020.01205, PMID:32850352.
[45] He J, Zeng ZC, Tang ZY, Fan J, Zhou J, Zeng MS, *et al*. Clinical features and prognostic factors in patients with bone metastases from hepatocellular carcinoma receiving external beam radiotherapy. Cancer 2009;115(12):2710–2720. doi:10.1002/cncr.24300, PMID:19382203.