Original Article

Establishment of a prognosis-related predictive model for hepatocellular carcinoma patients with macrovascular invasion treated with transcatheter arterial chemoembolization combined with intensity modulated radiotherapy

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Background: So far, there are still few studies on the prognostic factors of hepatocellular carcinoma (HCC) patients with macrovascular invasion (MVI) treated with transcatheter arterial chemoembolization (TACE) combined with intensity modulated radiotherapy (IMRT), and no relevant model has been established to predict the prognosis of such patients. Thus, the purpose of this study was to determine the prognostic factors of HCC patients with MVI after treatment with TACE combined with IMRT, and to establish a nomogram model for forecasting 1-, 3-, 5-year overall survival (OS) of the patients.

Methods: HCC patients with MVI who were diagnosed and treated at Department of Gastroenterology, 3201 Hospital between January 2010 and December 2020 were enrolled in this study according to the inclusion and exclusion criteria. The risk factors linked to patient OS were determined by performing Cox regression analysis. The nomogram for predicting 1-, 3-, 5-year OS in HCC patients with MVI was stablished and validated based on the results of the Cox regression analysis.

Results: In total, 118 patients were included in the current study. The medium follow-up time was 46 months (range, 29–71 months). Univariate Cox regression analysis revealed that tumor diameter, treatment frequency of TACE, IMRT dose, Child-Pugh grade, liver cirrhosis and alpha fetoprotein (AFP) level were significantly related to the OS of the patients. Further multivariate Cox regression analysis showed that treatment frequency of TACE and Child-Pugh grade, liver cirrhosis and AFP level were the independent prognostic factors of the OS in patients who were treated with TACE combined with IMRT. The nomogram we constructed using the above independent risk factors exhibited good ability for predicting 1-, 3-, 5-year OS of the patients. The concordance-index of the nomogram was 0.727, indicating the nomogram had a good discrimination.

Conclusions: Treatment frequency of TACE and Child-Pugh grade, liver cirrhosis and AFP level were independent predictors of OS in HCC patients with MVI after TACE combined with IMRT treatment. The nomogram that we developed using these predictors provided a convenient tool to predict the survival probability in HCC patients with MVI.

Keywords: Hepatocellular carcinoma (HCC); macrovascular invasion (MVI); transcatheter arterial chemoembolization (TACE); intensity modulated radiotherapy (IMRT); nomogram

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Introduction

Liver cancer is one of the most common malignant tumors and the second leading cause of cancer death in the world (1). Hepatocellular carcinoma (HCC) accounts for about 90% of primary liver cancer, which shows a strong tendency of macrovascular invasion (MVI) and can invade the portal vein, hepatic vein or inferior vena cava and its branches (2). Due to the concealment of the early stage, most of the patients with HCC are in the late stage when they are diagnosed, thus missing the best opportunity for surgical treatment. The prognosis of patients with MVI is usually poor, which may be related to larger tumor, poor grade, poor liver function and high level of alpha fetoprotein (AFP). The prognosis of patients with advanced HCC complicated with MVI is particularly serious. Previous studies have shown that the median survival time of HCC patients with portal vein tumor thrombus (PVTT) is 2–3 months without treatment (3,4).

Transcatheter arterial chemoembolization (TACE) has become a consensus as the main treatment for inoperable HCC patients with MVI (5,6). The mechanism of TACE is to block the tumor blood vessels and cause necrosis caused by ischemia and hypoxia of liver cancer cells, so as to achieve the purpose of shrinking the tumor (7,8). However, the use of TACE alone is not effective for larger tumors, and patients will have liver function damage after treatment, which is disadvantageous to the prognosis of patients. Therefore, TACE combined with microwave ablation or intensity modulated radiotherapy (IMRT) is often used in clinic, which can better control the growth of tumor and obtain better therapeutic effect (9-11).

IMRT is a precise radiotherapy technique developed on the basis of three-dimensional conformal radiotherapy in recent years, which has been widely used in the treatment of head and neck tumors and other malignant tumors (12,13). The advantage of IMRT dosimetry distribution is that the dose conformability and uniformity of tumor target are better, and the dose of endangering organs and normal tissue is smaller, which is beneficial to the control of tumor tissue and the protection of normal tissue (12,13). Studies have shown that TACE combined with IMRT shows obvious advantages in both short-term and long-term efficacy (9,11,14). In addition, some studies have explored the influencing factors of TACE combined with IMRT on the therapeutic effect of HCC (15,16). It is suggested that Child-Pugh grade, vascular thrombus, Karnofsky performance status (KPS), radiotherapy dose, ascites, combination therapy, and pattern of progression were related to the survival of patients (15). It is also reported that IMRT, sorafenib, tumor size, and Child-Pugh grade were independent prognostic factors for HCC patients with intrahepatic vessel invasion (16). In clinical practice, it will be very convenient for clinicians to predict the survival of patients based on these prognostic factors if there is a simple and clear prognostic model. Indeed, there have been many reports on the construction of prognostic models for HCC patients, which provide a convenient tool for predicting the prognosis of HCC patients (17-20). However, up to now, there are still few studies to analyze the prognostic factors of HCC patients with MVI who have received TACE combined with IMRT, and no relevant prognostic models have been established to predict the prognosis of these patients.

Therefore, the purpose of this study was to analyze the factors affecting the overall survival (OS) of HCC patients with MVI treated with TACE combined with IMRT, and to establish a nomogram model to predict the 1-, 3-, 5-year OS of these patients. We present this article in accordance with the TRIPOD reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-1226/rc).

Highlight box

Key findings

- Treatment frequency of transcatheter arterial chemoembolization (TACE), Child-Pugh grade, liver cirrhosis and alpha fetoprotein (AFP) level were independent predictors for overall survival (OS) in hepatocellular carcinoma (HCC) patients with macrovascular invasion (MVI) The nomogram constructed based the above factors showed a good discrimination and accuracy in predicting 1-, 3-, 5-year OS of the patients who received transcatheter arterial chemoembolization (TACE) combined with intensity modulated radiotherapy (IMRT).

What is known and what is new?

- There are still few studies to analyze the prognostic factors of HCC patients with MVI who have received TACE combined with IMRT, and no relevant prognostic models have been established to predict the prognosis of these patients.
- We determined that treatment frequency of TACE and Child-Pugh grade, liver cirrhosis and AFP level were the independent prognostic factors of the OS in patients who were treated with TACE combined with IMRT. And we constructed a nomogram model for forecasting the OS of the patients.

What is the implication, and what should change now?

- The nomogram constructed in this study provided a convenient tool to predict the survival probability in HCC patients with MVI.

Methods

Study population

This study is a single-center retrospective study. There were 118 HCC patients with MVI enrolled in this study, who were diagnosed and treated in Department of Gastroenterology, 3201 Hospital between January 2010 and December 2020. The inclusion criteria were as follows: (I) HCC with MVI was diagnosed; (II) Eastern Cooperative Oncology Group (ECOG) score ≤2; (III) normal renal function; (IV) no anti-tumor treatment has been received before; (V) normal liver volume can tolerate radiotherapy; (VI) complete clinicopathological data. The exclusion criteria were as follows: (I) ECOG score >2; (II) serious heart, lung, kidney and other organ diseases; (III) incomplete clinicopathological data. We used outpatient follow-up or telephone follow-up to acquire the patient's survival status and time. OS is defined as the time from pathological diagnosis to death. This study adhered to the Declaration of Helsinki (as revised in 2013), and was approved and supervised by the Ethics Committee of 3201 Hospital (No. 817). Informed consent was waived due to the retrospective nature of the design.

Data collection and processing

The clinicopathological data and treatment-related data of the patients, including age, gender, body mass index (BMI), smoking status, drinking status, family history of cancer, American Joint Committee on Cancer (AJCC) stage, tumor diameter, ascites, Child-Pugh grade, hepatitis, liver cirrhosis, portal hypertension, vessel invasion, treatment frequency of TACE, IMRT dose, alanine aminotransferase (ALT), aspartate aminotransferase (AST) and AFP, were collected for further analysis. Data processing was carried out by using Microsoft Excel and SPSS 26.0 software. Following this, the continuous variables were transformed into categorical variables based on the normal value range of the index. The normal value ranges of BMI, ALT, AST, AST/ALT and AFP are 18.5–24.0 kg/m^2, 0–40 U/L, 0–40 U/L, 0.8–1.15 and 0–25 μg/L, respectively.

Construction and validation of the nomogram prediction model

Cox regression analysis was utilized to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for the variables. According to the results of univariate Cox regression analysis, factors with P<0.05 in the were selected for further multivariate Cox regression analysis to identify independent factors related to the OS of patients. According to the results of multivariate Cox regression analysis, a nomogram for predicting 1-, 3-, 5-year OS of HCC patients with MVI was constructed by using R software. Further, concordance-index (C-index) and Bootstrap calibration curve were conducted to assess the discrimination and calibration of the nomogram. The C-index value greater than 0.7 indicated that the model had good prediction accuracy.

Statistical analysis

SPSS 26.0 software was used for data analysis. The factors related to the OS of the patients were determined by Cox regression analysis. Development and validation of the nomogram for forecasting 1-, 3-, 5-year OS were conducted by RStudio software. Bilateral P<0.05 was considered to be statistically significant.

Results

Characteristics of HCC patients with MVI who were treated with TACE combined with IMRT

A total of 118 patients were enrolled in this study according to the inclusion and exclusion criteria. The medium follow-up time was 46 months (range, 29–71 months). The median age of the patients was 55 years old (range, 20–84 years old). Among these patients, 105 (88.98%) were male, while 13 (11.02%) were female. The number of patients with AJCC stage III and IV was 51 (43.22%) and 67 (56.78%), respectively. In this study, 21 (17.80%) HCC patients had hepatic vein invasion, while 97 (82.20%) patients had portal vein invasion. Other clinical characteristics of the patients can be found in *Table 1*.

Cox regression analysis for identifying the factors related to the OS of HCC patients with MVI who were treated with TACE combined with IMRT

To determine the factor that might affect patient OS after treatment of TACE combined with IMRT, we conducted univariate Cox regression analysis. The results showed that tumor diameter (HR: 2.194, 95% CI: 1.219–0.3.950, P=0.009), treatment frequency of TACE (HR: 0.590, 95%

Table 1 Characteristics of HCC patients with MVI who were treated with TACE combined with IMRT

Characteristic	All patients (n=118)
Age (years), median [range]	55 [20–84]
Gender, n (%)	
Male	105 (88.98)
Female	13 (11.02)
BMI (kg/m^2), median [range]	22.48 [16.33–28.73]
Smoking, n (%)	
Yes	52 (44.07)
No	66 (55.93)
Drinking, n (%)	
Yes	32 (27.12)
No	86 (72.88)
Family history of cancer, n (%)	
Yes	10 (8.47)
No	108 (91.53)
AJCC stage, n (%)	
III	51 (43.22)
IV	67 (56.78)
Tumor diameter (cm), median [range]	5.0 [1.0–12.0]
Ascites, n (%)	
Yes	53 (44.92)
No	65 (55.08)
Child-Pugh, n (%)	
A	89 (75.42)
B	24 (20.34)
C	54 (45.76)
Hepatitis, n (%)	
No	58 (49.15)
HBV	58 (49.15)
HCV	2 (1.69)
Portal hypertension, n (%)	
Yes	40 (33.90)
No	78 (66.10)
Vessel invasion, n (%)	
Hepatic vein	21 (17.80)
Portal vein I	30 (25.42)
Portal vein II	57 (48.31)
Portal vein III	10 (8.47)
Treatment frequency of TACE, n (%)	
<2	71 (60.17)
≥2	47 (39.83)
IMRT dose (Gy), n (%)	
<50	69 (58.47)
≥50	49 (41.53)

HCC, hepatocellular carcinoma; MVI, macrovascular invasion; TACE, transcatheter arterial chemoembolization; IMRT, intensity modulated radiotherapy; BMI, body mass index; AJCC, American Joint Committee on Cancer; HBV, viral hepatitis type B; HCV, viral hepatitis type C.

CI: 0.365–0.954, P=0.03), IMRT dose (HR: 0.583, 95% CI: 0.349–0.976, P=0.04), Child-Pugh grade (HR: 1.905, 95% CI: 1.330–2.729, P<0.001), liver cirrhosis (HR: 2.306, 95% CI: 1.443–3.683, P<0.001), and AFP level (HR: 1.691, 95% CI: 1.214–2.354, P=0.002) were significantly related to the OS of the patients (*Table 2*). Therefore, the above factors were enrolled in further multivariate Cox regression analysis. We observed that treatment frequency of TACE (HR: 0.526, 95% CI: 0.311–0.889, P=0.02) and Child-Pugh grade (HR: 1.712, 95% CI: 1.125–2.604, P=0.01), liver cirrhosis (HR: 1.701, 95% CI: 1.004–2.881, P=0.048) and AFP level (HR: 1.989, 95% CI: 1.275–3.103, P=0.002) were the independent factors affecting the OS of the patients who were treated with TACE combined with IMRT (*Table 3*).

Construction and validation of the nomogram for predicting the OS of HCC patients with MVI received TACE combined with IMRT

Based on treatment frequency of TACE, Child-Pugh grade, liver cirrhosis and AFP level, we developed a nomogram for predicting 1-, 3-, 5-year OS (*Figure 1*). The C-index of the

Table 2 Univariate Cox regression analysis of prognostic factors in HCC patients with MVI who were treated with TACE combined with IMRT

Factors	Univariate analysis			
	HR	95% CI		P
		Lower	Upper	
Age (years) (<18 *vs.* 18–45 *vs.* 46–59 *vs.* 60–74 *vs.* ≥75)	1.046	0.781	1.400	0.76
Gender (male *vs.* female)	1.062	0.520	2.170	0.87
BMI (kg/m^2) (<18.5 *vs.* 18.5–24 *vs.* >24)	0.879	0.563	1.371	0.57
Smoking (no *vs.* yes)	1.072	0.847	1.356	0.56
Drinking (no *vs.* yes)	0.999	0.774	1.288	0.99
Family history of cancer (no *vs.* yes)	0.897	0.589	1.367	0.61
Tumor diameter (cm) (<5 *vs.* ≥5)	2.194	1.219	3.950	0.009
Ascites (no *vs.* yes)	1.062	0.667	1.691	0.80
Treatment frequency of TACE (<2 *vs.* ≥2)	0.590	0.365	0.954	0.03
IMRT dose (Gy) (<50 *vs.* ≥50)	0.583	0.349	0.976	0.04
AJCC stage (III *vs.* IV)	1.160	0.727	1.850	0.53
Child-Pugh (A *vs.* B *vs.* C)	1.905	1.330	2.729	<0.001
Hepatitis (no *vs.* HBV *vs.* HCV)	1.330	0.887	1.994	0.17
Liver cirrhosis (no *vs.* yes)	2.306	1.443	3.683	<0.001
Portal hypertension (no *vs.* yes)	1.324	0.823	2.130	0.25
Vessel invasion (hepatic vein *vs.* portal vein I *vs.* portal vein II *vs.* portal vein III)	1.143	0.874	1.494	0.33
ALT (U/L) (≤40 *vs.* >40)	0.923	0.514	1.657	0.79
AST (U/L) (≤40 *vs.* >40)	0.983	0.590	1.637	0.95
AST/ALT (<0.8 *vs.* 0.8–1.15 *vs.* >1.15)	1.070	0.664	1.724	0.78
AFP (μg/L) (<25 *vs.* 25–400 *vs.* >400)	1.691	1.214	2.354	0.002

HCC, hepatocellular carcinoma; MVI, macrovascular invasion; TACE, transcatheter arterial chemoembolization; IMRT, intensity modulated radiotherapy; BMI, body mass index; AJCC, American Joint Committee on Cancer; HBV, viral hepatitis type B; HCV, viral hepatitis type C; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AFP, alpha fetoprotein; HR, hazard ratio; CI, confidence interval.

nomogram was 0.727, indicating the nomogram had a good discrimination. Besides, the Bootstrap calibration curve also indicated that the trend between true values and predicted values was consistent, suggesting that the nomogram had the accuracy for forecasting 1-, 3-, 5-year OS of HCC patients with MVI received TACE combined with IMRT (*Figure 2*).

Discussion

Clinically, the treatment of liver cancer includes surgery, hepatic artery ligation, TACE, chemotherapy and radiotherapy, among which TACE is the first-line treatment for patients with liver cancer who have lost the opportunity of surgical resection. TACE can effectively block the blood vessels supplied by the lesions and improve the clinical symptoms. Studies have shown that the average survival time of early HCC patients receiving TACE is 16–40 months, while that of mid-stage HCC patients is 15–27 months (7). In addition, after receiving TACE, the objective remission rate and disease control rate of HCC patients can reach 53.1% and 78.1%, respectively (8). However, due to the general condition of patients, liver function, tumor local blood supply, tumor size, number and tumor heterogeneity and other factors, TACE still cannot completely kill tumor cells, resulting in local recurrence of tumor, resulting in

Table 3 Multivariate Cox regression analysis of prognostic factors in HCC patients with MVI who were treated with TACE combined with IMRT

Factors	Multivariate analysis			
	HR	95% CI		P
		Lower	Upper	
Tumor diameter (cm) (<5 *vs.* ≥5)	1.005	0.507	1.989	0.99
Treatment frequency of TACE (<2 *vs.* ≥2)	0.526	0.311	0.889	0.02
IMRT dose (Gy) (<50 *vs.* ≥50)	1.059	0.582	1.927	0.85
Child-Pugh (A *vs.* B *vs.* C)	1.712	1.125	2.604	0.01
Liver cirrhosis (no *vs.* yes)	1.701	1.004	2.881	0.048
AFP (μg/L) (<25 *vs.* 25–400 *vs.* >400)	1.989	1.275	3.103	0.002

HCC, hepatocellular carcinoma; MVI, macrovascular invasion; TACE, transcatheter arterial chemoembolization; IMRT, intensity modulated radiotherapy; AFP, alpha fetoprotein; HR, hazard ratio; CI, confidence interval.

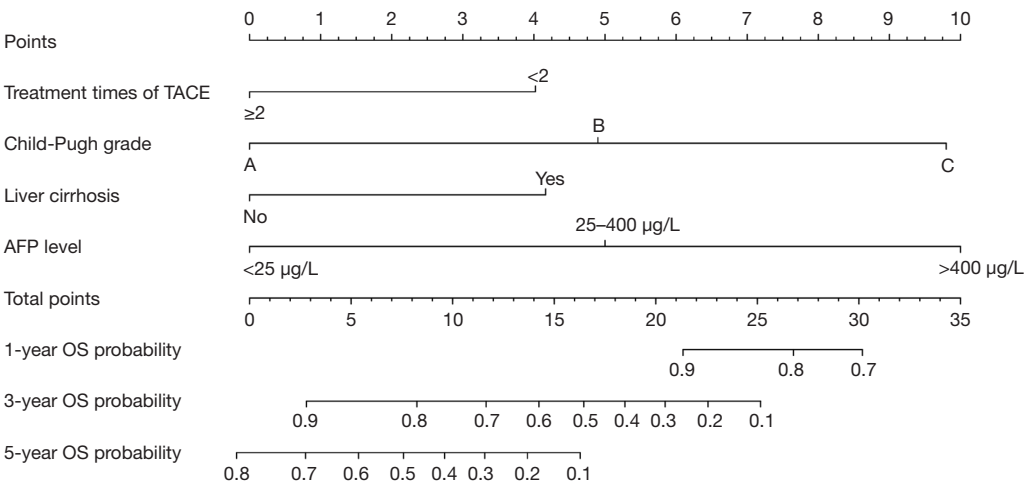

Figure 1 The nomogram for predicting 1-, 3-, 5-year OS of HCC patients with MVI after treatment TACE combined with IMRT. TACE, transcatheter arterial chemoembolization; AFP, alpha fetoprotein; OS, overall survival; HCC, hepatocellular carcinoma; MVI, macrovascular invasion; IMRT, intensity modulated radiotherapy.

treatment failure (21). Therefore, the comprehensive treatment based on TACE combined with other treatments has become the focus of clinical research on locally advanced HCC which cannot be operated.

Radiotherapy can kill tumor cells in the small branches of the portal vein, but the normal liver is more sensitive to radiation, and large area radiotherapy is easy to produce radioactive loss, so radiotherapy can only be used as a palliative treatment. In recent years, with the continuous development of computer technology, the clinical application of fine radiotherapy represented by IMRT is gradually increasing. With the application of IMRT, the shape of high dose area is highly consistent with that of clinical target area, which can effectively improve the dose relationship between normal tissues and organs in tumor target area, increase the dose of tumor target area, and greatly reduce the radiation dose of normal tissue (12,13). Studies have shown that TACE combined with IMRT can significantly improve the short-term efficacy and long-term survival rate of patients (9,11,14). For example, patients receiving TACE combined with IMRT had a median OS of 20.2 months (95% CI: 8.6–31.9 months) and a 3-year OS rate of 36.7% (9). In addition, the median OS and progression-free survival time of HCC patients with

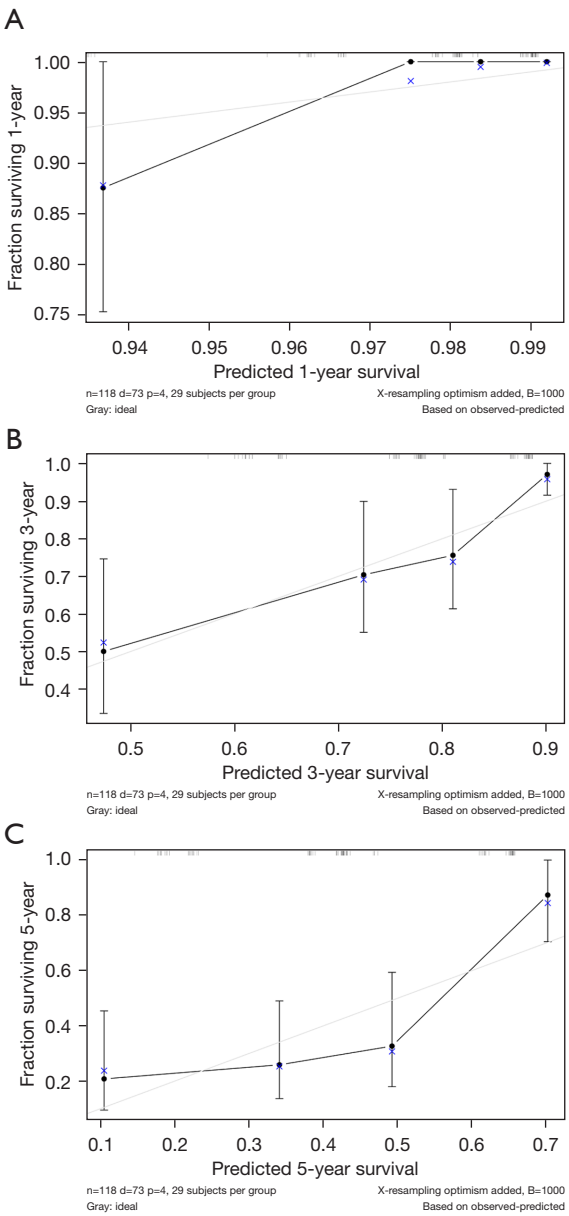

Figure 2 Bootstrap calibration curve of the nomogram for predicting 1-, 3-, 5-year OS of HCC patients with MVI after treatment TACE combined with IMRT. The X-axis represents the predicted probability, and the Y-axis represents the actual probability. The gray line represents the ideal value, and the black line represents the predicted value. It is showed that the trend of the predicted value is consistent with the true value, indicating the good calibration effect of the nomogram. OS, overall survival; HCC, hepatocellular carcinoma; MVI, macrovascular invasion; TACE, transcatheter arterial chemoembolization; IMRT, intensity modulated radiotherapy.

MVI after TACE combined with IMRT treatment were 15.2 months and 9.2 months, respectively (11).

Some previous studies have analyzed the risk factors affecting the prognosis of HCC patients treated with TACE combined with IMRT. For example, a study by Luo *et al.* (15) showed that vascular thrombus, combination therapy and pattern of failure were prognostic factors for disease-free survival in HCC patients with extrahepatic oligometastasis. However, Lo *et al.* (16) showed that IMRT, sorafenib and tumor size and Child-Pugh class were independent prognostic factors for HCC patients with intrahepatic vascular infiltration. In addition, Zhang *et al.* (22) found that tumor size, albumin-bilirubin grade and PVTT type were independent prognostic factors in HCC patients with MVI treated with TACE combined with Sorafenib. Based on these results, a nomogram model was established to predict the prognosis of HCC patients. However, so far, there are still few studies to analyze the prognostic factors of HCC patients with MVI who received TACE combined with IMRT, and no relevant prognostic models have been established to predict the prognosis of these patients. Therefore, we have explored this.

Similarly, univariate analysis showed that tumor diameter, treatment frequency of TACE, IMRT dose, Child-Pugh grade, liver cirrhosis, and AFP level could affect the prognosis of patients. Further multivariate analysis showed that the treatment frequency of TACE, Child-Pugh grade, liver cirrhosis, AFP level were independent prognostic factors for OS in HCC patients with MVI after receiving TACE combined with IMRT. Nomogram is a convenient tool for predicting results and is widely used to quantify the risk of various diseases (22). Therefore, based on the results of multivariate analysis, we established a nomogram to predict 1-, 3-, 5-year OS after TACE combined with IMRT treatment in HCC patients with MVI. The c-index and the Bootstrap calibration curve show that nomogram has a good discrimination and accuracy of predicting OS.

However, the limitations in this study cannot be ignored. First, as a single-center and retrospective research, the sample size was relatively small, and only internal validation of the nomogram was performed. Second, only some common clinicopathological indexes were analyzed in this study, the laboratory indicators and other potential predictors of the patients were not included for analyzing. Third, although the population of this study was controlled by inclusion and exclusion criteria, the impact of individual

factors on OS cannot be avoided. Therefore, further studies should be conducted using a prospective, multi-center approach with a larger sample size to verify the findings of the current study. Additionally, external validation of the nomogram should be performed based on a multi-center study.

Conclusions

Our study revealed that treatment frequency of TACE, Child-Pugh grade, liver cirrhosis and AFP level were independent predictors for OS in HCC patients with MVI. The nomogram constructed in this research showed good discrimination and accuracy in predicting 1-, 3-, 5-year OS of the patients who received TACE combined with IMRT. This provides a convenient tool to predict the survival probability in HCC patients with MVI.

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Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-1226/rc

Data Sharing Statement: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-1226/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-1226/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study adhered to the Declaration of Helsinki (as revised in 2013), and was approved and supervised by the Ethics Committee of 3201 Hospital (No. 817). Informed consent was waived due to the retrospective nature of the design.

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