European Radiology (2020) 30:3473–3485
https://doi.org/10.1007/s00330-019-06640-8

HEPATOBILIARY-PANCREAS

The presence of microvascular invasion guides treatment strategy in recurrent HBV-related HCC

Shu-Ling Chen[1] · Han Xiao[1] · Zong-Lin Xie[2] · Jing-Xian Shen[3] · Ze-Bin Chen[4] · Yuan-Qi Wang[5] · Bin Li[6] · Zhen-Wei Peng[6,7] · Ming Kuang[1,4] · Jia-Ming Lai[5] · Sui Peng[2,6]

Received: 14 September 2019 / Revised: 1 December 2019 / Accepted: 17 December 2019 / Published online: 11 February 2020

Abstract

Objectives We used the status of microvascular invasion (MVI) at primary resection to help treatment selection for hepatitis B virus–positive (HBV+) recurrent hepatocellular carcinoma (rHCC) patients in Barcelona Clinic Liver Cancer (BCLC) stage B-C.

Methods From 2009 to 2017, we enrolled 221 consecutive HBV+ rHCC patients at BCLC stage B-C who underwent re-resection (RR), radiofrequency ablation (RFA), or transarterial chemoembolization (TACE). Post recurrence survival (PRS) and overall survival (OS) were compared between RR/RFA and TACE according to MVI status. A one-to-one propensity score matching analysis was performed.

Results For MVI(−) patients, the median PRS was 62.3 months for the RR/RFA group and 21.1 months for the TACE group ($p = 0.039$). The corresponding OS was 71.4 months and 26.6 months, respectively ($p = 0.010$). For MVI(+) patients, the median PRS in the RR/RFA group and TACE group was 14.7 months and 10.1 months ($p = 0.115$). The corresponding OS was 23.4 months and 16.4 months, respectively ($p = 0.067$). After matching, the dominance of RR/RFA over TACE remained in MVI(−) patients for both PRS (62.3 months vs 15.3 months, $p = 0.019$) and OS (98.1 months vs 33.4 months, $p = 0.046$). No significant difference was found in MVI(+) patients for either PRS (14.7 months vs 11.8 months, $p = 0.593$) or OS (23.4 months vs 28.1 months, $p = 0.662$).

Conclusions MVI status definitely helps select treatment options in HBV+ rHCC patients. For MVI(−) patients, RR/RFA provided better survival than TACE while for MVI(+) patients, TACE shared similar survival outcomes.

Key Points

- *This study aimed at the determination of the optimal treatment options (ablation /resection vs TACE) in case of recurrent HBV-related HCC.*
- *It showed that MVI status, established at primary resection of HCC, was a powerful marker for selecting the best treatment option in these patients.*
- *In MVI(−) patients, RR/RFA achieved a better survival than TACE. In MVI(+) patients, TACE shared similar survival.*

Shu-Ling Chen and Han Xiao contributed equally to this work.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00330-019-06640-8) contains supplementary material, which is available to authorized users.

✉ Jia-Ming Lai
jmlai2000@aliyun.com

✉ Sui Peng
pengsui@vip.163.com

[1] Division of Interventional Ultrasound, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong, China

[2] Department of Gastroenterology, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong, China

[3] State Key Laboratory of Oncology in South China; Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center, Guangzhou, Guangdong, China

[4] Department of Liver Surgery, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong, China

[5] Department of Pancreatobiliary Surgery, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong, China

[6] Clinical Trials Unit, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong, China

[7] Department of Radiotherapy, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong, China

Keywords Carcinoma, hepatocellular · Recurrence · Chemoembolization, therapeutic · Hepatectomy · Radiofrequency ablation

Abbreviations

BCLC	Barcelona Clinic Liver Cancer
ECOG	Eastern Cooperative Oncology Group
HBV	Hepatitis B virus
HR	Hazard ratio
MVI	Microvascular invasion
OS	Overall survival
PRS	Post recurrence survival
RFA	Radiofrequency ablation
rHCC	Recurrent hepatocellular carcinoma
RR	Re-resection
TACE	Transarterial embolization

Introduction

More than 70% of patients with hepatocellular carcinoma (HCC) resection will recur within 5 years, raising the question of the optimal treatment strategy after recurrence.

Re-resection, radiofrequency ablation (RFA), and transarterial chemoembolization (TACE) have been performed in recurrent hepatocellular carcinoma (rHCC) at Barcelona Clinic Liver Cancer (BCLC) stage B-C, but the reported results are quite controversial [1–3]. A possible reason is the insufficient recognition of the biological variability of HCC when considering treatment selection for recurrence. Pathological characteristics of the primary tumor, including the presence or absence of microvascular invasion (MVI(+) and MVI(−)) respectively, are predictors of postsurgical recurrence [4–6]. MVI status has been used as a predictor for decision-making of additional treatment after initial resection [7]. Jin et al [8] compared TACE and surgery/RFA in rHCC patients within BCLC stage 0-A and found that TACE had a better survival over surgery for early recurrent MVI(+) patients. Conversely, Hou et al [9] indicated that a repeat hepatectomy had a better survival for rHCC patients if the primary tumor was MVI(+) and within the Milan criteria, not mentioning the stage of rHCC. MVI status is probably helpful in selecting the appropriate treatment for rHCC at an early stage. However, the relevance of MVI status in rHCC patients at intermediate-advanced stage is still lacking, while they represent almost half of all rHCC population [10, 11].

The aim of this retrospective study was to compare the benefit of different treatments in recurrent HBV-related HCC patients at BCLC stage B-C, according to the presence or absence of MVI. A propensity score matching (PSM) was also performed for a balanced baseline.

Methods

Study design

Comprehensive data of 2137 consecutive HCC patients who initially underwent liver resection at either the First Affiliated Hospital of Sun Yat-sen University or the Cancer Center of Sun Yat-sen University from June 2009 to June 2017 were collected. This study was conducted in accordance with the Declaration of Helsinki (1964) and approved by the ethical committees of these two centers. The inclusion criteria for the rHCC patients were (a) received curative resection for primary tumor without adjuvant therapy; (b) first recurrence after resection; (c) recurred tumor at BCLC stage of B/C [12]; (d) Child-Pugh grade A-B; (e) Eastern Cooperative Oncology Group (ECOG) performance status 0–1. The exclusion criteria included (a) missing data about MVI at primary resection; (b) receive other treatments for rHCC; (c) HBsAg-negative. At last, 221 rHCC patients were enrolled in this study.

HCC and recurrence were diagnosed mainly by the non-invasive criteria following the European Association for the Study of the Liver, European Organization for Research and Treatment of Cancer (EASL-EORTC) guideline [13, 14]. Patients were classified as BCLC stage B according to following criteria: multinodular tumors more than 3 or multinodular tumors larger than 3 cm and ECOG performance status 0. Patients were classified as BCLC stage C if with macrovascular invasion or extrahepatic metastasis or ECOG performance status 1. MVI status in the resected specimen of primary HCC was confirmed by two experienced pathologists in hepatology over 5 years. Evaluation of postsurgical recurrence was performed every 3 months for the first two years, 3–6 months thereafter. The contrast-enhanced ultrasound (US) and dynamic contrast-enhanced liver computed tomography (CT) were used for recurrence evaluation. Diagnosis criteria and the follow-up schedule of rHCC were referred to that of the primary HCC. The post recurrence survival (PRS) was defined as the time interval from the date of rHCC treatments to the date of death from any cause or to the date of the last follow-up visit. Overall survival (OS) in this study was defined as the interval between the first resection of HCC to the date of death from any cause or to the date of the last follow-up visit.

Treatment selection

The decision of treatment option was initiated by a multidisciplinary team including surgeons, interventional radiologists,

and oncologists. The treatment-related issues such as possible efficacy, costs, and the risks of complication during and after different treatments were informed to the patient, who would make the final decision then.

Treatment protocol

Re-resection procedure

Re-resection was performed under general anesthesia by surgeons with 10–40 years of experience. Generally, the type of surgery was decided according to a routine preoperative discussion for each patient. Anatomic resection, defined as the complete removal of at least one Couinaud segment containing the tumor and the corresponding hepatic territory, was routinely performed if possible. Other types of surgery, such as wedge resection or tumor enucleation, were classified as non-anatomic resection. The surgical approach was chosen based on the liver remnant, tumor location, and preference of the operator. Intraoperative US was used to assist in operative evaluation.

RFA procedure

RFA was carried out by three doctors with over 10 years of ablation experience. RFA was performed under local anesthesia with LeVeen electrodes (Boston Scientific), Starburst XL electrodes (RITA Medical Systems), or Cool-tip electrodes (Valleylab). The electrode was percutaneously inserted under the real-time US guidance through the guiding needle. RFA was performed with the intent to completely eradicate the tumor with an ablative margin of at least 5 mm. Multiple overlapping ablations were performed for lesions larger than 3 cm. After RFA, the needle track was coagulated for reducing bleeding and tumor seeding.

TACE procedure

TACE was carried out by two radiologists with over 5 years of experience. A selective catheter was inserted into the tumor-feeding arteries after evaluating arterial blood supply of the liver and confirming patency of the portal vein by visceral angiography. Hepatic artery infusion chemotherapy was performed using carboplatin 300 mg (Bristol-Myers Squibb). Subsequently, chemolipiodolization was performed using epirubicin 50 mg (Pharmorubicin, Pfizer), and mitomycin C 8 mg (Zhejiang Hisun Pharmaceutical Co. Ltd.) mixed with 5 mL of lipiodol (Lipiodol Ultra- Fluide; Guerbet). Embolization was finally performed with absorbable gelatin sponge particles (Gelfoam; Hanzhou Alc Ltd., 1–2 mm in diameter) or polyvinyl alcohol particles (Alicon Pharm SCT&TEC CO., Ltd., 350–560 μm in diameter) until the blood flow was static for more than 10 successive heartbeats. After embolization, angiography was performed to determine the extent of vascular occlusion and to assess blood flow in other arterial vessels. Tumor response was evaluated 4 weeks after each treatment with TACE. Repeated TACE was performed if clinical necessary according to the follow-up images and the time interval was 6–8 weeks between 2 TACE procedures.

Statistical analysis

Normal distribution test was performed for continuous variables. Continuous variables which obey the normal distribution were presented as means ± standard deviation and others as median and quartile. Categorical variables were presented as numbers and percentages. Differences between the RR/RFA group and the TACE group were compared with the t test or the Mann–Whitney test for continuous variables and χ^2 test for categorical variables. Survival curves were generated by the Kaplan–Meier method and compared by the log-rank test. The potential survival predictors were analyzed by univariate and multivariate Cox proportional hazard regression models. A strong correlation between time to recurrence (TTR) and MVI at primary resection was observed; therefore, TTR was not included in the multivariate Cox regression models. Log-log plot of survival and the Schoenfeld residuals test were used to check the proportional hazards assumption.

Furthermore, PSM was performed to diminish the bias. Patients received RR/RFA and TACE in different MVI patterns were separately matched based on logistic regression model. Propensity scores were estimated according to significant variates in the cox model and the significantly different characteristics between the two treatment groups [15]. One-to-one matching without replacement was performed using a caliper width of 0.2 standard deviation of the logit of the propensity score [16].

Statistical significance was considered as a two-sided p value of less than 0.05. The above statistical analysis was performed with the STATA/MP 14.0.

Results

Baseline characteristics

The flow chart of patient selection was shown in Fig. 1. The baseline characteristics of rHCC patients at BCLC stage B-C are displayed in Table 1. Detailed baseline characteristics for primary tumor are shown in Supplementary Table 1–2. Patients were separated into two groups according to the MVI status at primary resection. Sixty-six rHCC patients were MVI-negative and 155 patients were MVI(+). MVI(+) rHCC patients at primary resection had a higher level of GGT, AST,

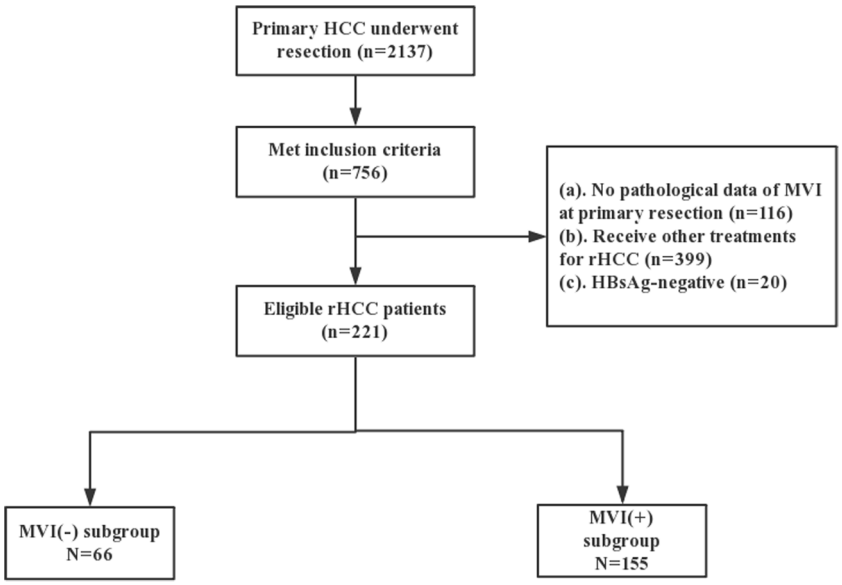

Fig. 1 Flow chart of patient selection

and AFP. Most of the MVI(+) patients (92.3%) recurred within 1 year, while the ratio was 71.2% for MVI(−) patients ($p < 0.001$). More patients received TACE than RR/RFA in both groups. The median time of TACE performed was once, with details listed in Supplementary Table 3. Distributions of treatment strategies were similar in the two groups.

Survival outcomes

Median PRS of all rHCC patients at BCLC stage B-C was 14.7 months. MVI(−) patients with had a significant longer PRS than MVI(+) patients (23.4 vs 11.1 months, $p < 0.001$) (Fig. 2a). Median OS was 22.7 months for all rHCC patients. Similar to the PRS, OS of patients with MVI(−) was longer than that of patients with MVI(+) (33.4 vs 16.8 months, $p < 0.001$) (Fig. 2b).

Univariate and multivariate analysis

The results of univariate and multivariate analysis of PRS are shown in Table 2. GGT > 50 U/L (hazard ratio (HR) = 1.79, $p = 0.001$), AST > 40 U/L (HR = 1.93, $p < 0.001$), MVI(+) at primary resection (HR = 1.49, $p = 0.033$), macrovascular invasion at recurrence (HR = 1.58, $p = 0.026$), and receiving RR/RFA (HR = 0.65, $p = 0.045$) were independent prognostic factors of PRS. Analyses of OS were performed as well. AFP of primary tumor > 200 ng/mL (HR = 1.44, $p = 0.031$), size of primary tumor >5 cm (HR = 1.63, $p = 0.012$), MVI(+) at primary resection (HR = 1.72, $p = 0.004$), macrovascular invasion at recurrence (HR = 1.77, $p = 0.005$), and receiving RR/RFA for rHCC (HR = 0.54, $p = 0.004$) were independent prognostic factors of OS.

Subgroup analysis

MVI(–) group

Baseline characteristics of rHCC MVI(−) patients are shown in Table 3. Most patients (91.7%) in the TACE group were multifocal, compared with 66.7% in the curative treatment group ($p = 0.026$). As for the TTR, 81.3% of the patients in the TACE group were less than 1 year. The corresponding ratio was 44.4% in the RR/RFA group. PRS was significantly longer in the RR/RFA group (62.3 vs 21.1 months, $p = 0.039$) (Fig. 3a). Considering the uneven baseline, a PSM was performed for survival comparison. After PSM, all characteristics were balanced in the two treatment groups. The median PRS was 15.3 months for the TACE group and 62.3 months for the RR/RFA group ($p = 0.019$) (Fig. 3b). Median OS was significantly longer in the RR/RFA group (71.4 vs 26.6 months, $p = 0.010$). Median OS after PSM was 98.1 months for the RR/RFA group and 33.4 months for the TACE group ($p = 0.046$).

MVI(+) group

The same comparisons were done for MVI(+) patients. Baseline characteristics of MVI(+) rHCC patients were shown in Table 4. The ratio of multifocal tumors was larger in the TACE group compared to that in the RR/RFA group (87.8% vs 53.1%, $p < 0.001$). The unbalanced distribution of TTR in the MVI(−) patients disappeared in the MVI(+) subgroup. PRS was not significantly differed between the RR/RFA group and the TACE group (14.7 vs 10.1 months, $p = 0.115$) (Fig. 4a). After PSM, the median PRS was 11.8 months for the TACE group and 14.7 months for the RR/RFA group ($p = 0.593$) (Fig. 4b). Similar trends were observed in the analysis

Table 1 Baseline characteristics of HBV(+)-recurrent HCC patients at BCLC stage B-C

Variable	MVI(−) (n = 66)	MVI(+) (n = 155)	p value
Age (years)			0.345
≤ 60	51 (77.3)	129 (83.2)	
> 60	15 (22.7)	26 (16.8)	
Gender			0.090
Male	63 (92.8)	136 (87.7)	
Female	3 (7.2)	19 (12.3)	
Hemoglobin (g/L)			0.149
≤ 120	6 (9.1)	27 (17.4)	
> 120	60 (90.9)	128 (82.6)	
Albumin (g/L)			0.690
≤ 35	9 (13.6)	25 (16.1)	
> 35	57 (86.4)	130 (83.9)	
Total bilirubin (mmol/L)			0.556
≤ 34.2	66 (100.0)	152 (98.1)	
> 34.2	0 (0.0)	3 (1.9)	
ALT (U/L)			0.326
≤ 40	51 (77.3)	108 (69.7)	
> 40	15 (22.7)	47 (30.3)	
AST (U/L)			0.002
≤ 40	53 (80.3)	91 (58.7)	
> 40	13 (19.7)	64 (41.3)	
GGT (U/L)			0.012
≤ 50	41 (62.1)	67 (43.2)	
> 50	25 (37.9)	88 (56.8)	
PT (s)			0.474
≤ 14	61 (92.4)	137 (88.4)	
> 14	5 (7.6)	18 (11.6)	
Platelet (× 10^9/L)			0.460
≤ 100	15 (22.7)	28 (18.1)	
> 100	51 (77.3)	127 (81.9)	
AFP (μg/L)			0.013
≤ 200	52 (78.8)	95 (61.3)	
> 200	14 (21.2)	60 (38.7)	
Child-Pugh classification			0.109
Child-Pugh A	66 (100.0)	147 (94.8)	
Child-Pugh B	0 (0.0)	8 (5.2)	
Liver cirrhosis	24 (36.4)	51 (32.9)	0.643
Tumor size (cm)			0.569
≤ 5	51 (77.3)	128 (82.6)	
> 5	14 (21.2)	27 (17.4)	
Tumor number			0.246
1	8 (12.1)	30 (19.4)	
> 1	56 (84.8)	125 (80.6)	
Macrovascular invasion	9 (13.6)	34 (21.9)	0.194
TTR			< 0.001
< 1 year	47 (71.2)	143 (92.3)	
≥ 1 year	19 (28.8)	12 (7.7)	
BCLC stage of primary tumor			0.002
0-A	41 (62.1)	60 (38.7)	
B-C	25 (37.9)	95 (61.3)	
Edmonson stage of primary tumor			1.000
1–2	32 (50.8)	77 (51.0)	
3–4	31 (49.2)	74 (49.0)	
Capsule of primary tumor (yes)	50 (75.8)	115 (74.2)	0.280
Satellite nodules of primary tumor (yes)	10 (15.2)	62 (40.0)	< 0.001

HBV, hepatitis B virus; *HCC*, hepatocellular carcinoma; *BCLC*, Barcelona Clinic Liver Cancer; *MVI*, microvascular invasion; *ALT*, alanine transaminase; *AST*, aspartate aminotransferase; *GGT*, glutamyl transpeptidase; *PT*, prothrombin time; *AFP*, alpha fetal protein; *TTR*, time to recurrence

of OS. Median OS was 23.4 months for the RR/RFA group and 16.4 months for the TACE group ($p = 0.067$). The corresponding figures were 23.4 months and 28.1 months after PSM, respectively ($p = 0.662$).

Discussion

Our study found that for selected HBV-related rHCC patients at BCLC stage B-C, RR/RFA could provide better efficacy

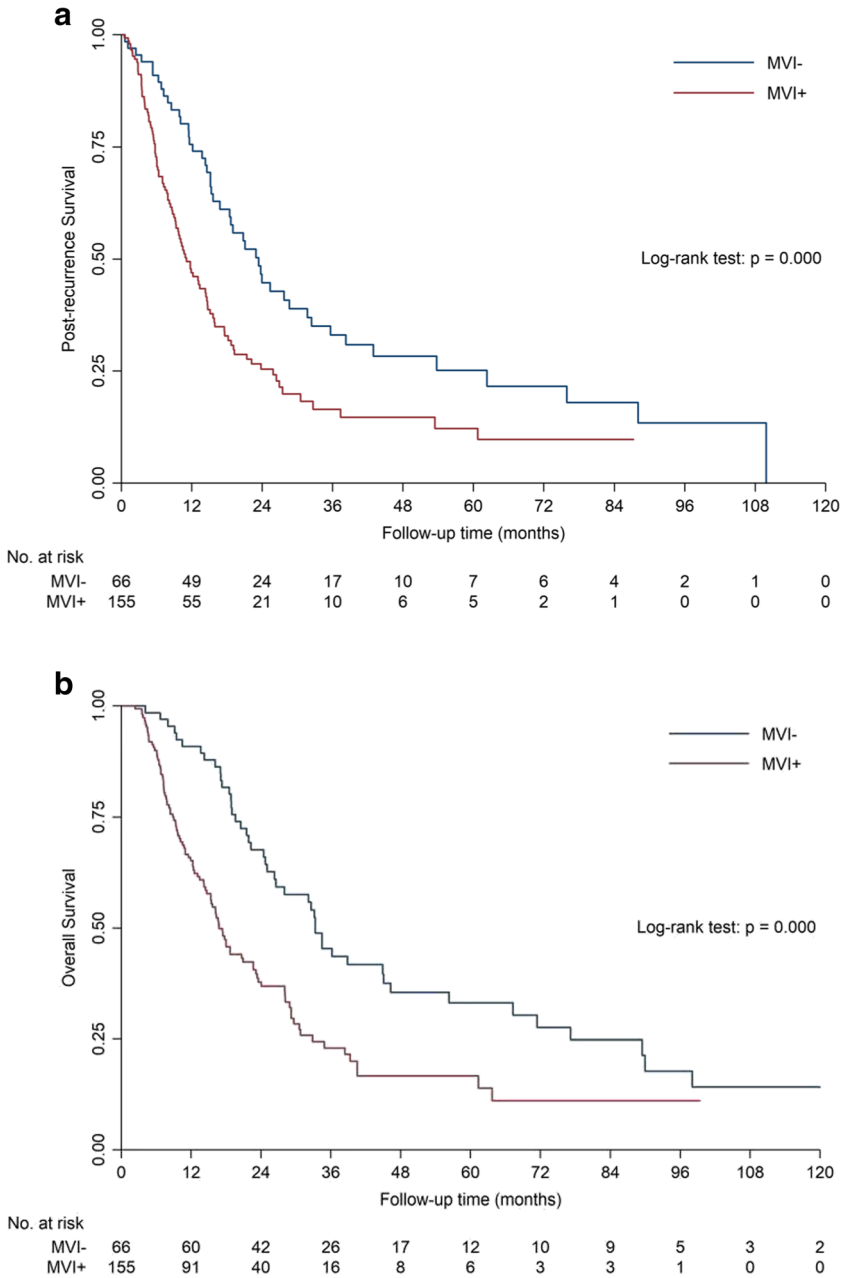

Fig. 2 Kaplan–Meier survival curves of the PRS (**a**) and the OS (**b**) for groups stratified by the MVI status at primary resection

than TACE in MVI(−) patients, while TACE shared a similar efficacy with RR/RFA if the patients were MVI(+).

Previous studies have emphasized the prognostic importance of pathological profile at primary resection for rHCC patients, especially the existence of MVI. Yet the role of MVI status in the treatment selection was rarely discussed. This article first showed the possibility to use MVI status as a predictor for treatment selection in selected rHCC patients within BCLC stage B-C. According to our results, RR/RFA provided a better survival than TACE for rHCC patients at BCLC stage B-C if the patients were MVI(−). The comparison of surgery, RFA, and TACE in primary HCC has been widely discussed, especially in BCLC stage B-C. Surgery and RFA had a survival advantage in the majority of these studies [17–22]. The limited remnant liver volume might cause difficulty in performing aggressive treatments. Yet early studies showed that re-resection could be safely performed even for patients who received major resection as the first treatment, and by applying approaches like laparoscopic resection, similar perioperative outcomes to primary resection

Table 2 Variables associated with post recurrence survival according to the Cox proportional hazard model

Variable	Univariable analysis			Multivariable analysis		
	HR	95%CI	*p* value	HR	95%CI	*p* value
Age (> 60 years)	0.94	0.62, 1.42	0.758			
Gender (female)	0.59	0.32, 1.10	0.095			
Hemoglobin (> 120 g/L)	0.70	0.45, 1.10	0.123			
Albumin (> 35 g/L)	0.60	0.39, 0.91	0.018			
Total bilirubin (> 34.2 mmol/L)	1.61	0.40, 6.54	0.503			
ALT (> 40 U/L)	1.66	1.18, 2.35	0.004			
AST (> 40 U/L)	2.41	1.73, 3.35	< 0.001	1.93	1.37, 2.72	< 0.001
GGT (> 50 U/L)	2.18	1.57, 3.03	< 0.001	1.79	1.28, 2.52	0.001
PT (> 14 s)	1.20	0.73, 2.00	0.473			
BCLC stage of primary tumor (B-C)	1.25	0.90, 1.73	0.178			
Edmondson stage of primary tumor (3–4)	1.03	0.74, 1.42	0.882			
Capsule of primary tumor (yes)	0.90	0.56, 1.43	0.651			
Satellite nodules of primary tumor (yes)	1.28	0.90, 1.83	0.163			
Liver cirrhosis	1.09	0.78, 1.53	0.616			
Macrovascular invasion	2.06	1.39, 3.06	< 0.001	1.58	1.06, 2.36	0.026
Treatment for rHCC			0.011			0.045
TACE	1.00			1.00		
RR/RFA	0.58	0.38, 0.88		0.65	0.42, 0.99	
Platelet (> 100 × 10^9/L)	0.82	0.55, 1.21	0.312			
AFP (> 200 μg/L)	1.71	1.22, 2.38	0.002			
Child-Pugh classification B	1.85	0.86, 3.96	0.113			
Tumor size (> 5 cm)	1.27	0.84, 1.92	0.251			
Tumor number (> 1)	0.87	0.56, 1.34	0.520			
TTR (> 1 year)	0.39	0.22, 0.68	0.001			
MVI-positive at first resection	1.89	1.32, 2.70	< 0.001	1.49	1.03, 2.16	0.033

ALT, alanine transaminase; *AST*, aspartate aminotransferase; *GGT*, glutamyl transpeptidase; *PT*, prothrombin time; *HBV*, hepatitis B virus; *AFP*, alpha fetal protein; *TTR*, time to recurrence; *MVI*, microvascular invasion

could be achieved [23, 24]. Therefore, we recommend RR/RFA as the first-line treatment for MVI(−) patients at BCLC stage B-C. Survival was not significantly different in patients with MVI(+) whatever the treatment option. There might be two explanations for this difference. Firstly, MVI(+) patients' recurrent tumor might be more aggressive. According to our results, the level of AFP was significantly higher in the MVI(+) group. The correlation of high serum AFP level and MVI in primary HCC has been proved in early studies [25, 26]. Elevated AFP translates a more aggressive tumor behavior and a higher degree of tumor cell proliferation [27–29]. The aggressive tumor behavior might hamper the theoretical benefit of curative over palliative treatments. Secondly, as previous studies, our MVI(+) patients were more likely to recur within 1 year. This may indicate that rHCC in these patients is a dissemination of the original tumor via the vascular circulation before primary resection rather than de novo [4]. The behavior of these disseminated tumors is likely similar to that of the primary tumor, prompting recurrence even after curative-intend treatments. However, repeatable TACE could provide a sustained devascularization for rHCC and might prevent potential hematogenous metastasis. This might be one explanation for the similar efficacy of TACE vs RR/RFA in these patients. Therefore, TACE should be considered as the first choice for rHCC MVI(+) patients at BCLC stage B-C.

Another interesting finding was that results showed that 92.3% of MVI+ patients recurred within the year following surgery. This leads to a further emphasis on the necessity of assessing MVI status for naïve HCC patients. Lately published articles showed promising predictive performance of

Table 3 Baseline characteristics of recurrent HCC patients with MVI(−) at first resection

Variable	Before PSM			After PSM		
	RR/RFA (n = 18)	TACE (n = 48)	p value	RR/RFA (n = 11)	TACE (n = 11)	p value
Age (years)			1.000			1.000
≤ 60	14 (77.8)	37 (77.1)		8 (72.7)	7 (68.4)	
> 60	4 (22.2)	11 (22.9)		3 (27.3)	4 (31.6)	
Gender			0.178			1.000
Male	16 (88.9)	47 (97.9)		10 (90.9)	11 (100.0)	
Female	2 (11.1)	1 (2.1)		1 (9.1)	0 (0.0)	
Hemoglobin (g/L)			0.661			1.000
≤ 120	2 (11.1)	4 (8.3)		1 (9.1)	1 (9.1)	
> 120	16 (88.9)	44 (91.7)		10 (90.9)	10 (90.9)	
Albumin (g/L)			0.696			1.000
≤ 35	3 (16.7)	6 (12.5)		2 (18.2)	1 (9.1)	
> 35	15 (83.3)	42 (87.5)		9 (81.8)	10 (90.9)	
Total bilirubin (mmol/L)			1.000			1.000
≤ 34.2	18 (100.0)	48 (100.0)		11 (100.0)	11 (100.0)	
ALT (U/L)			1.000			1.000
≤ 40	14 (77.8)	37 (77.1)		9 (81.8)	9 (81.8)	
> 40	4 (22.2)	11 (22.9)		2 (18.2)	2 (18.2)	
AST (U/L)			0.488			0.586
≤ 40	16 (88.9)	37 (77.1)		10 (90.9)	8 (72.7)	
> 40	2 (11.1)	11 (22.9)		1 (9.1)	3 (27.3)	
GGT (U/L)			0.574			1.000
≤ 50	10 (55.6)	31 (64.6)		6 (54.5)	6 (54.5)	
> 50	8 (44.4)	17 (35.4)		5 (45.5)	5 (45.5)	
PT (s)			1.000			1.000
≤ 14	17 (94.4)	44 (91.7)		10 (90.9)	10 (90.9)	
> 14	1 (5.6)	4 (8.3)		1 (9.1)	1 (9.1)	
Platelet ($\times 10^9$/L)			0.322			0.586
≤ 100	6 (33.3)	9 (18.8)		3 (27.3)	1 (9.1)	
> 100	12 (66.7)	39 (81.3)		8 (72.7)	10 (90.9)	
AFP (μg/L)			0.503			1.000
≤ 200	13 (72.2)	39 (81.3)		7 (63.6)	7 (63.6)	
> 200	5 (27.8)	9 (18.8)		4 (36.4)	4 (36.4)	
Child-Pugh classification			1.000			1.000
Child-Pugh A	18 (100.0)	48 (100.0)		11 (100.0)	11 (100.0)	
Tumor size (cm)			0.006			1.000
≤ 5	9 (50.0)	42 (87.5)		9 (81.8)	8 (72.7)	
> 5	8 (44.4)	6 (12.5)		2 (18.2)	3 (27.3)	
Tumor number			0.026			0.476
1	5 (27.8)	3 (6.3)		2 (18.2)	0 (0.0)	
> 1	12 (66.7)	44 (91.7)		9 (81.8)	11 (100.0)	
Liver cirrhosis	5 (27.8)	19 (39.6)	0.566	3 (27.3)	3 (27.3)	1.000
Macrovascular invasion	3 (16.7)	6 (12.5)	0.696	1 (9.1)	0 (0.0)	1.000
TTR			0.006			1.000
< 1 year	8 (44.4)	39 (81.3)		7 (63.6)	7 (63.6)	
≥ 1 year	10 (55.6)	9 (18.8)		4 (36.4)	4 (36.4)	
BCLC stage of primary tumor			1.000			0.659
0-A	11 (61.1)	30 (62.5)		8 (72.7)	6 (54.5)	
B-C	7 (38.9)	18 (37.5)		3 (27.3)	5 (45.5)	
Edmonson stage of primary tumor			0.782			1.000
1–2	10 (55.6)	22 (48.9)		5 (45.5)	4 (36.4)	
3–4	8 (44.4)	23 (51.1)		6 (55.5)	7 (63.6)	
Capsule of primary tumor (yes)	16 (88.9)	34 (70.8)	1.000	10 (90.9)	9 (81.8)	1.000
Satellite nodules of primary tumor (yes)	3 (16.7)	7 (14.6)	1.000	1 (9.1)	1 (9.1)	1.000

HCC, hepatocellular carcinoma; *PSM*, propensity score matching; *ALT*, alanine transaminase; *AST*, aspartate aminotransferase; *GGT*, glutamyl transpeptidase; *PT*, prothrombin time; *HBV*, hepatitis B virus; *AFP*, alpha fetal protein; *TTR*, time to recurrence

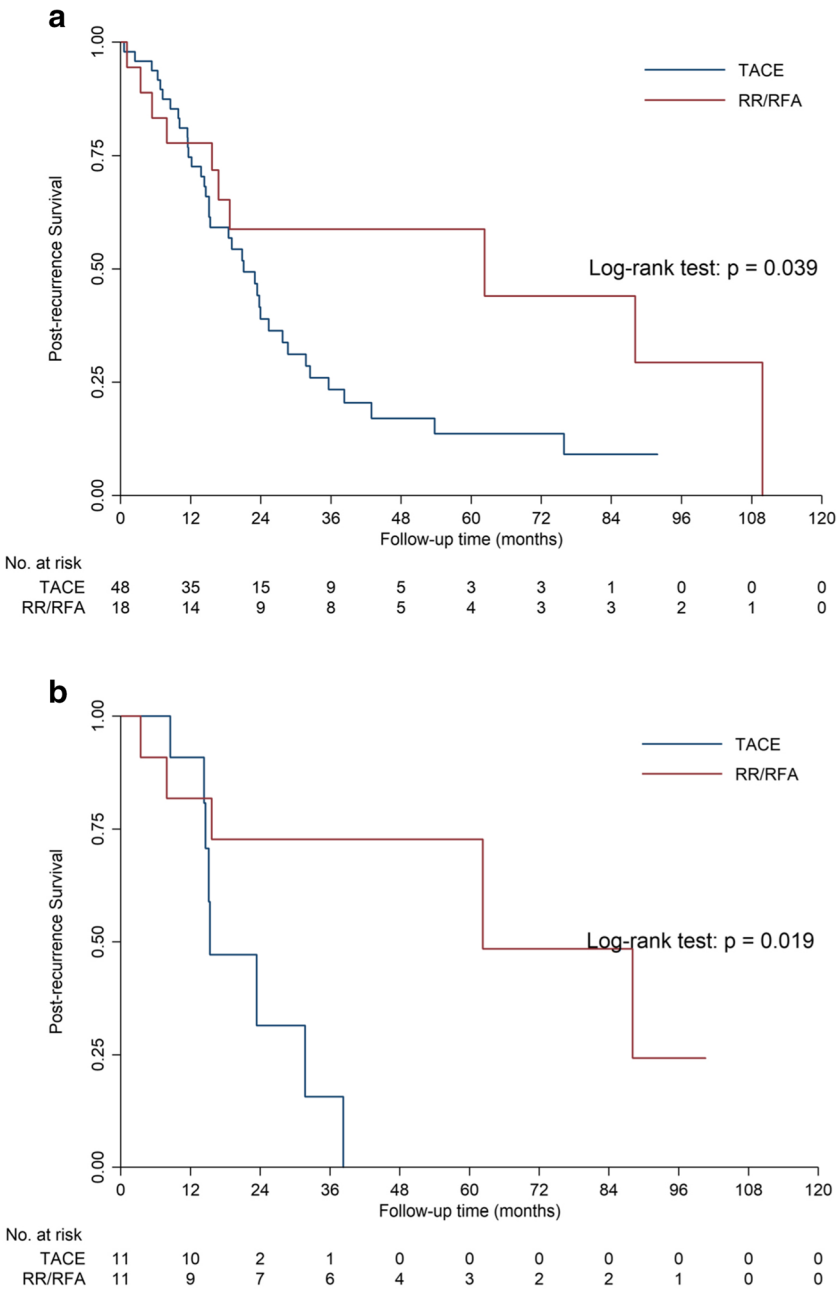

Fig. 3 Kaplan–Meier survival curves of the PRS for patients with MVI(−) at primary resection. PRS of the RR/RFA group was significantly longer than that of the TACE group both before (**a**) and after (**b**) PSM

MVI scoring systems [30, 31]. Predicting model based on radiomics also showed satisfactory accuracy [32–34]. However, clinical use of these predicting systems is limited due to the lack of multiregional validation. Further studies are still needed.

There are some study limitations. First, we did not make a comparison of treatments mentioned in this study with sorafenib, which is the standard treatment for advanced HCC patients. This is because the proportion of patients receiving sorafenib is quite low due to the limited cost-effectiveness, making the retrospective data of sorafenib treatment very finite. Second, despite the fact that TTR was reported to be a prognostic factor of rHCC, we did no subgroup analysis by TTR. Over 90% of patients in the MVI(+) group and about 70% of patients in the MVI(−) group recurred within 1 year, making the subgroup comparison hard to perform.

In conclusion, we found that MVI at primary resection could be used as a marker to guide the treatment selection of HBV+ rHCC at BCLC stage B-C. For patients with MVI(−) at primary resection, curative treatments are recommended, while for MVI(+) patients, TACE, RR, and RFA shared similar survival benefits.

Table 4 Baseline characteristics of recurrent HCC patients with MVI(+) at first resection

Variable	Before PSM			After PSM		
	RR/RFA (n = 32)	TACE (n = 123)	p value	RR/RFA (n = 32)	TACE (n = 32)	p value
Age (years)			0.427			1.000
≤ 60	25 (78.1)	104 (84.6)		25 (78.1)	26 (81.2)	
> 60	7 (21.9)	19 (15.4)		7 (21.9)	6 (18.8)	
Gender			0.074			0.774
Male	25 (78.1)	111 (90.2)		25 (78.1)	23 (71.9)	
Female	7 (21.9)	12 (9.8)		7 (21.9)	9 (28.1)	
Hemoglobin (g/L)			1.000			0.750
≤ 120	5 (15.6)	22 (17.9)		5 (15.6)	7 (21.9)	
> 120	27 (84.4)	101 (82.1)		27 (84.4)	25 (78.1)	
Albumin (g/L)			0.293			0.708
≤ 35	3 (9.4)	22 (17.9)		3 (9.4)	5 (15.6)	
> 35	29 (90.6)	101 (82.1)		29 (90.6)	27 (84.4)	
Total bilirubin (mmol/L)			0.503			1.000
≤ 34.2	31 (96.9)	121 (98.4)		31 (96.9)	32 (100.0)	
> 34.2	1 (3.1)	2 (1.6)		1 (3.1)	0 (0.0)	
ALT (U/L)			0.524			1.000
≤ 40	24 (75.0)	84 (68.3)		24 (75.0)	25 (78.1)	
> 40	8 (25.0)	39 (31.7)		8 (25.0)	7 (21.9)	
AST (U/L)			0.230			1.000
≤ 40	22 (68.8)	69 (56.1)		22 (68.8)	23 (71.9)	
> 40	10 (31.3)	54 (43.9)		10 (31.3)	9 (28.1)	
GGT (U/L)			0.233			1.000
≤ 50	17 (53.1)	50 (40.7)		17 (53.1)	16 (50.0)	
> 50	15 (46.9)	73 (59.3)		15 (46.9)	16 (50.0)	
PT (s)			0.124			1.000
≤ 14	31 (96.9)	106 (86.2)		31 (96.9)	30 (93.8)	
> 14	1 (3.1)	17(13.8)		1 (3.1)	2 (6.3)	
Platelet ($\times 10^9$/L)			0.069			0.492
≤ 100	2 (6.3)	26 (21.1)		2 (6.3)	0 (0.0)	
> 100	30 (93.8)	97 (78.9)		30 (93.8)	32 (100.0)	
AFP (μg/L)			1.000			1.000
≤ 200	20 (62.5)	75 (61.0)		20 (62.5)	19 (59.4)	
> 200	12 (37.5)	48 (39.0)		12 (37.5)	13 (40.6)	
Child-Pugh classification			0.207			1.000
Child-Pugh A	32 (100.0)	115 (93.5)		32 (100.0)	32 (100.0)	
Child-Pugh B	0 (0.0)	8 (6.5)		0 (0.0)	0 (0.0)	
Tumor size (cm)			0.601			0.213
≤ 5	28 (87.5)	100 (81.3)		28 (87.5)	23 (71.9)	
> 5	4 (12.5)	23 (18.7)		4 (12.5)	9 (28.1)	
Tumor number			< 0.001			0.446
1	15 (46.9)	15 (12.2)		15 (46.9)	11 (34.4)	
> 1	17 (53.1)	108 (87.8)		17 (53.1)	21 (65.6)	
Liver cirrhosis	10 (31.3)	41 (33.3)	1.000	10 (31.3)	8 (25.0)	0.782
Macrovascular invasion	5 (15.6)	29 (23.6)	0.472	5 (15.6)	9 (28.1)	0.365
TTR			0.271			0.732
< 1 year	28 (87.5)	115 (93.5)		28 (87.5)	26 (81.2)	
≥ 1 year	4 (12.5)	8 (6.5)		4 (12.5)	6 (18.8)	
BCLC stage of primary tumor			0.313			0.801
0-A	15 (46.9)	45 (36.6)		15 (46.9)	13 (40.6)	
B-C	17 (53.1)	78 (63.4)		17 (53.1)	19 (59.4)	
Edmonson stage of primary tumor			0.841			1.000
1–2	15 (48.4)	62 (51.7)		15 (48.4)	16 (51.6)	
3–4	16 (51.6)	58 (48.3)		16 (51.6)	15 (48.4)	
Capsule of primary tumor (yes)	25 (78.1)	90 (73.2)	0.408	25 (78.1)	26 (81.3)	1.000
Satellite nodules of primary tumor (yes)	13 (40.6)	49 (39.8)	1.000	13 (40.6)	16 (50.0)	0.616

HCC, hepatocellular carcinoma; *PSM*, propensity score matching; *ALT*, alanine transaminase; *AST*, aspartate aminotransferase; *GGT*, glutamyl transpeptidase; *PT*, prothrombin time; *HBV*, hepatitis B virus; *AFP*, alpha fetal protein; *TTR*, time to recurrence

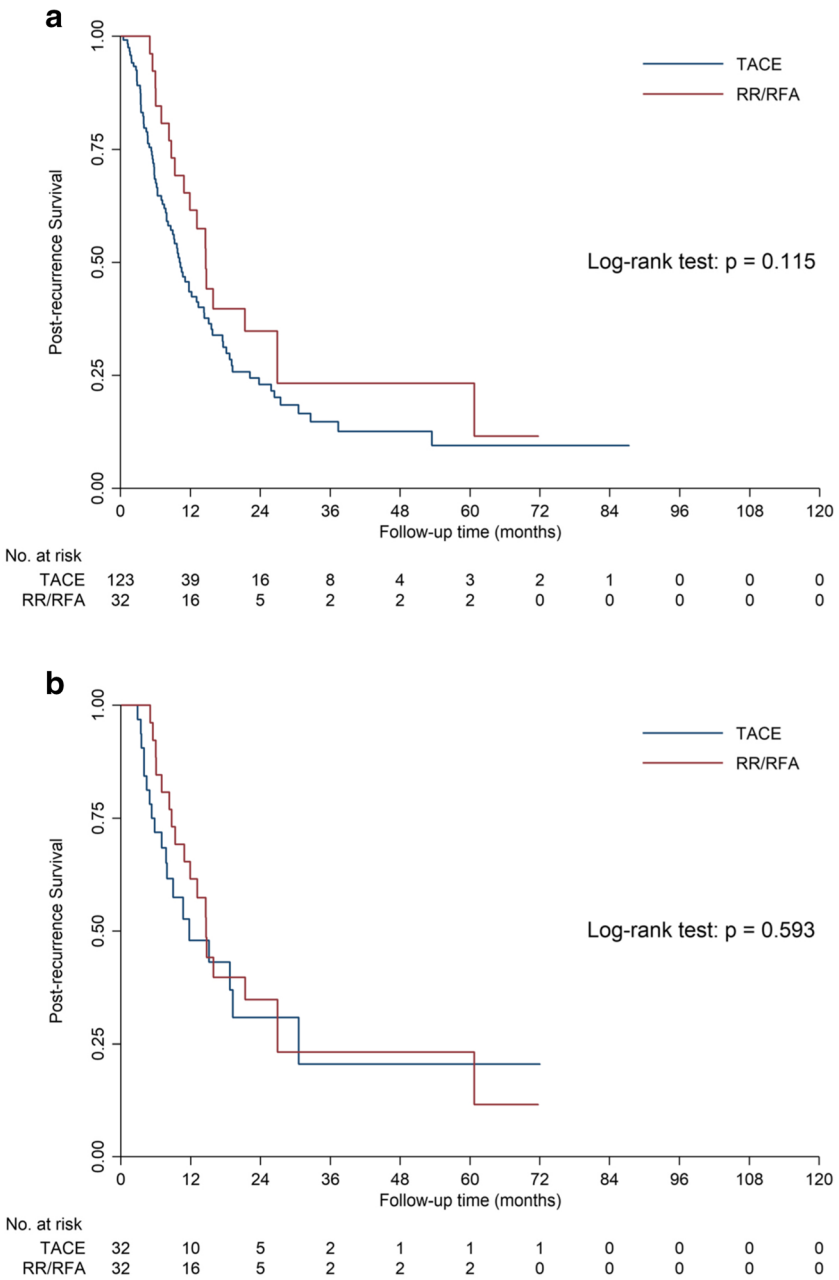

Fig. 4 Kaplan–Meier survival curves of the PRS for patients with MVI(+) at primary resection. No significant difference was found between RR/RFA and TACE group before (**a**) or after (**b**) PSM

Acknowledgments We thank the kind statistical help provided by the clinical trials unit.

Funding information This work is supported by grants from the National Natural Science Foundation of China (NSFC, Nos. 81770608 and 81801703), the National Science Fund for Distinguished Young Scholars (No. 81825013), the Natural Science Foundation of Guangdong Province (No. 2018A030310282), and the National high level talents special support plan—"Ten thousand plan"—Young top-notch talent support program and the Kelin Outstanding Young Scientist of the First Affiliated Hospital of Sun Yet-sen University (2017), Guangdong Medical Science and Technology Foundation (A2017191), Science and Technology Program of Guangzhou, China (No. 201704020215).

Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Sui Peng.

Conflict of interest The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

Statistics and biometry One of the authors (Bin Li) has significant statistical expertise.

Informed consent Written informed consent was waived by the Institutional Review Board.

Ethical approval Institutional Review Board approval was obtained.

Study subjects or cohorts overlap Some study subjects or cohorts have been previously reported in the *American Journal of Translational Research*. The former article focused on characteristics of patients with MVI(+). To explore the role of MVI in guidance of treatments for HBV+ recurrent intermediate-advanced HCC, we limited the population to HBV+ patients and further added data of patients with MVI(−) at primary resection. Therefore, the role of MVI in treatment selection for HBV+ rHCC patients could only be evaluated in this study.

Methodology
- retrospective
- observational
- multicenter study

References

1. Koh PS, Chan ACY, Cheung TT et al (2016) Efficacy of radiofrequency ablation compared with transarterial chemoembolization for the treatment of recurrent hepatocellular carcinoma: a comparative survival analysis. HPB (Oxford) 18:72–78. https://doi.org/10.1016/j.hpb.2015.07.005
2. Dai WC, Cheung TT (2016) Strategic overview on the best treatment option for intrahepaitc hepatocellular carcinoma recurrence. Expert Rev Anticancer Ther 16:1063–1072. https://doi.org/10.1080/14737140.2016.1226136
3. Joliat G-R, Allemann P, Labgaa I et al (2017) Treatment and outcomes of recurrent hepatocellular carcinomas. Langenbecks Arch Surg 402:1–8. https://doi.org/10.1007/s00423-017-1582-9
4. Imamura H, Matsuyama Y, Tanaka E et al (2003) Risk factors contributing to early and late phase intrahepatic recurrence of hepatocellular carcinoma after hepatectomy. J Hepatol 38:200–207
5. Tung-Ping Poon R, Fan ST, Wong J (2000) Risk factors, prevention, and management of postoperative recurrence after resection of hepatocellular carcinoma. Ann Surg 232:10–24. https://doi.org/10.1097/00000658-200007000-00003
6. Ali MA, Li W-F, Wang J-H et al (2016) Impact of pathological features of primary hepatocellular carcinoma on the outcomes of intrahepatic recurrence management: single center experience from Southern Taiwan. HPB (Oxford) 18:851–860. https://doi.org/10.1016/j.hpb.2016.07.004
7. Pinyol R, Montal R, Bassaganyas L et al (2019) Molecular predictors of prevention of recurrence in HCC with sorafenib as adjuvant treatment and prognostic factors in the phase 3 STORM trial. Gut 68:1065–1075. https://doi.org/10.1136/gutjnl-2018-316408
8. Jin Y-J, Lee J-W, Lee OH et al (2014) Transarterial chemoembolization versus surgery/radiofrequency ablation for recurrent hepatocellular carcinoma with or without microvascular invasion. J Gastroenterol Hepatol 29:1056–1064. https://doi.org/10.1111/jgh.12507
9. Hou Y-F, Li B, Wei Y-G et al (2015) Second hepatectomy improves survival in patients with microvascular invasive hepatocellular carcinoma meeting the Milan criteria. Medicine (Baltimore) 94:e2070–e2078. https://doi.org/10.1097/MD.0000000000002070
10. Tabrizian P, Jibara G, Shrager B et al (2015) Recurrence of hepatocellular cancer after resection: patterns, treatments, and prognosis. Ann Surg 261:947–955. https://doi.org/10.1097/SLA.0000000000000710
11. He W, Peng B, Tang Y et al (2018) Nomogram to predict survival of patients with recurrence of hepatocellular carcinoma after surgery. Clin Gastroenterol Hepatol 16:756–764.e10. https://doi.org/10.1016/j.cgh.2017.12.002
12. Bruix J, Reig M, Sherman M (2016) Evidence-based diagnosis, staging, and treatment of patients with hepatocellular carcinoma. Gastroenterology 150:835–853. https://doi.org/10.1053/j.gastro.2015.12.041
13. European Association for Study of Liver, European Organisation for Research and Treatment of Cancer (2012) EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. Eur J Cancer 48:599–641. https://doi.org/10.1016/j.ejca.2011.12.021
14. European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu, European Association For The Study Of The Liver (2018) EASL clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 69:182–236. https://doi.org/10.1016/j.jhep.2018.03.019
15. Brookhart MA, Schneeweiss S, Rothman KJ et al (2006) Variable selection for propensity score models. Am J Epidemiol 163:1149–1156. https://doi.org/10.1093/aje/kwj149
16. Austin PC (2008) The performance of different propensity-score methods for estimating relative risks. J Clin Epidemiol 61:537–545. https://doi.org/10.1016/j.jclinepi.2007.07.011
17. Roayaie S, Jibara G, Tabrizian P et al (2015) The role of hepatic resection in the treatment of hepatocellular cancer. Hepatology 62:440–451. https://doi.org/10.1002/hep.27745
18. Kokudo T, Hasegawa K, Matsuyama Y et al (2016) Survival benefit of liver resection for hepatocellular carcinoma associated with portal vein invasion. J Hepatol 65:938–943. https://doi.org/10.1016/j.jhep.2016.05.044
19. Zhong J-H, Ke Y, Gong W-F et al (2014) Hepatic resection associated with good survival for selected patients with intermediate and advanced-stage hepatocellular carcinoma. Ann Surg 260:329–340. https://doi.org/10.1097/SLA.0000000000000236
20. Kim H, Ahn SW, Hong SK et al (2017) Survival benefit of liver resection for Barcelona clinic liver cancer stage B hepatocellular carcinoma. Br J Surg 104:1045–1052. https://doi.org/10.1002/bjs.10541
21. Torzilli G, Belghiti J, Kokudo N et al (2013) A snapshot of the effective indications and results of surgery for hepatocellular carcinoma in tertiary referral centers: is it adherent to the EASL/AASLD recommendations?: an observational study of the HCC East-West study group. Ann Surg 257:929–937. https://doi.org/10.1097/SLA.0b013e31828329b8
22. Yuan B-H, Yuan W-P, Li R-H et al (2016) Propensity score-based comparison of hepatic resection and transarterial chemoembolization for patients with advanced hepatocellular carcinoma. Tumour Biol 37:2435–2441. https://doi.org/10.1007/s13277-015-4091-x
23. Minagawa M, Makuuchi M, Takayama T, Kokudo N (2003) Selection criteria for repeat hepatectomy in patients with recurrent hepatocellular carcinoma. Ann Surg 238:703–710. https://doi.org/10.1097/01.sla.0000094549.11754.e6
24. Goh BKP, Syn N, Teo JY et al (2018) Perioperative outcomes of laparoscopic repeat liver resection for recurrent HCC: comparison with open repeat liver resection for recurrent HCC and laparoscopic resection for primary HCC. World J Surg:1–8. https://doi.org/10.1007/s00268-018-4828-y
25. Lei Z, Li J, Wu D et al (2016) Nomogram for preoperative estimation of microvascular invasion risk in hepatitis B virus-related hepatocellular carcinoma within the Milan criteria. JAMA Surg 151:356–363. https://doi.org/10.1001/jamasurg.2015.4257
26. Rodríguez-Perálvarez M, Luong TV, Andreana L et al (2013) A systematic review of microvascular invasion in hepatocellular carcinoma: diagnostic and prognostic variability. Ann Surg Oncol 20:325–339. https://doi.org/10.1245/s10434-012-2513-1
27. Dudich E, Semenkova L, Gorbatova E et al (1998) Growth-regulative activity of human alpha-fetoprotein for different types of tumor and normal cells. Tumor Biol 19:30–40

28. Wang XW, Xu B (1998) Stimulation of tumor-cell growth by alpha-fetoprotein. Int J Cancer 75:596–599
29. Tajiri H, Takano T, Tanaka H et al (2016) Hepatocellular carcinoma in children and young patients with chronic HBV infection and the usefulness of alpha-fetoprotein assessment. Cancer Med 5:3102–3110. https://doi.org/10.1002/cam4.917
30. Zhang X-P, Wang K, Wei X-B, et al (2019) An eastern hepatobiliary surgery hospital microvascular invasion scoring system in predicting prognosis of patients with hepatocellular carcinoma and microvascular invasion after R0 liver resection: a large-scale, multicenter study. Oncologist 2018–0868. https://doi.org/10.1634/theoncologist.2018-0868
31. Lee S, Kang TW, Song KD et al (2019) Effect of microvascular invasion risk on early recurrence of hepatocellular carcinoma after surgery and radiofrequency ablation. Ann Surg:1–8. https://doi.org/10.1097/SLA.0000000000003268
32. Feng ST, Jia Y, Liao B et al (2019) Preoperative prediction of microvascular invasion in hepatocellular cancer: a radiomics model using Gd-EOB-DTPA-enhanced MRI. Eur Radiol 89:500–512. https://doi.org/10.1007/s00330-018-5935-8
33. Ma X, Wei J, Gu D et al (2019) Preoperative radiomics nomogram for microvascular invasion prediction in hepatocellular carcinoma using contrast-enhanced CT. Eur Radiol 136:1–11. https://doi.org/10.1007/s00330-018-5985-y
34. Xu X, Zhang H-L, Liu Q-P et al (2019) Radiomic analysis of contrast-enhanced CT predicts microvascular invasion and outcome in hepatocellular carcinoma. J Hepatol 70:1133–1144. https://doi.org/10.1016/j.jhep.2019.02.023