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ORIGINAL SCIENTIFIC REPORT

The Predictors of Microscopic Vessel Invasion Differ Between Primary Hepatocellular Carcinoma and Hepatocellular Carcinoma with a Treatment History

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Abstract

Background and aim Previous studies have shown that microscopic vessel invasion (MVI) occurs in hepatocellular carcinoma (HCC) with a treatment history due to its poorer malignant behavior in comparison with primary HCC. The aim of the present study was to determine the predictors of MVI and overall survival in HCC patients with a treatment history.

Methods This retrospective study included 580 patients who underwent hepatectomy and whose preoperative imaging showed no evidence of macroscopic vessel invasion. The patients were classified into two groups: primary HCC (n = 425) and HCC with a treatment history (n = 155). MVI was defined as the presence of either microscopic portal vein invasion or venous invasion, which was invisible on preoperative imaging.

Results MVI was identified in 34 (21.9%) patients with a treatment history. A multivariate analysis showed that a high des-gamma-carboxy prothrombin (odds ratio [OR] 5.16, P = 0.002) and a large tumor diameter (OR 2.57, P = 0.030) were the significant predictor of MVI in HCC with a treatment history. Moreover, the presence of MVI (hazard ratio [HR] 2.27, P = 0.001) and tumor diameter >27 mm (HR 2.04, P = 0.006) remained significant predictors of the overall survival in HCC with a treatment history. The tumor diameter cutoff value for predicting MVI (27 mm) in HCC with a treatment history was smaller than in primary HCC (37 mm).

Conclusions The presence of MVI was a significant predictor in the HCC patients with a treatment history. The tumor diameter is an important factor that can be used to predict the presence of MVI, especially in HCC with a treatment history.

Introduction

Recent advances in diagnostic imaging technology have made possible to identify early-stage hepatocellular carcinoma (HCC), and multidisciplinary treatment has improved the survival rate in patients with the disease. However, HCC is still difficult to cure due to its high recurrence rate [1, 2]. Microscopic vessel invasion (MVI) is regarded as an independent predictor of early recurrence and poor overall survival after the surgical treatment of HCC [3–6]. However, in the absence of macrovascular invasion, MVI is difficult to detect on preoperative imagings [7, 8]. Thus, the diagnosis of MVI has limited impact on preoperative decision making.

HCC is characterized by an insidious onset at an early stage, followed by MVI with tumor growth [9–11]. Numerous studies have shown that the tumor diameter is a significant predictor of the presence of MVI [7, 11–15].

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However, no studies have shown the correlation between the tumor diameter and the presence of MVI while taking into account the difference of tumor behavior in primary HCC and HCC with a treatment history. Moreover, many recent studies have shown that the outcomes of repeat or salvage hepatectomy for recurrent HCC are acceptable and the procedure seems to be justified [16–24], while some have shown that the tumor behavior of HCC with a treatment history is worse than that of primary HCC [19–24]. These results suggest that predictors of MVI are likely to differ between the primary HCC and HCC with a treatment history, especially after therapeutic interventions therapy such as radiofrequency ablation (RFA) [19–24]. Based on the results of previous studies [12–24], we hypothesized that the predictors of MVI would differ in patients with a particular focus on simple factors such as the tumor diameter. If this hypothesis was correct, then it would become possible to determine appropriate treatment strategies for primary HCC and HCC with a treatment history based on the risk of the presence of MVI—which is invisible on the preoperative imaging. The aim of the present study was to determine the predictors of MVI and prognostic factors in patients with primary HCC and HCC with a treatment history.

Methods

Patients and methods

A total of 631 patients underwent hepatectomy with curative intent at the Division of Hepato-Biliary-Pancreatic Surgery, Shizuoka Cancer Center Hospital, in the period between September 2002 and December 2015. Based on the predictors of MVI in clinical setting, the patients were excluded from the analysis due to the presence of macroscopic vessel invasion on preoperative imaging.

All of the patients who were included in the study had undergone computed tomography (CT), abdominal ultrasonography and magnetic resonance imaging (MRI) before surgery. All preoperative imaging studies were reviewed by radiologists. Based on the radiologists' report, the presence of macroscopic vessel invasion was judged, and the diameter of tumor was generally measured by enhanced CT before surgery in the present study. In patients with multiple tumors, the diameter of the largest tumor was applied, and the differentiation between multicentric tumors and intrametastatic tumors was performed based on the pathological report in the present study. Subsequently, the patients were classified into two groups: the primary HCC group and HCC with a treatment history group.

All of the patients underwent preoperative viral serological testing, the measurement of tumor markers such as alpha-fetoprotein (AFP) and des-gamma-carboxy prothrombin (DCP), and a laboratory assessment of the liver function. The liver function was assessed according to the Child–Pugh classification [25]. HCC had been pathologically diagnosed in all cases. The tumor stage was assessed based on the seventh edition of the Union Internationale Contra le Cancer classification [26].

The surgical procedure and the extent of hepatectomy in each patient were decided in a weekly joint conference with surgeons, oncologists and radiologists. The details of the surgical strategy and procedure have been reported previously [27].

The patients underwent physical examinations and blood tests every 3 months after surgery. Serial CT or liver ultrasonography was performed for each patient every 3–6 months. When a recurrence of HCC was found, the most appropriate therapy (i.e., repeat hepatectomy, transcatheter arterial chemoembolization [TACE], RFA or sorafenib) was applied, after considering the patient's liver function and tumor factors. For the analysis of overall survival, the follow-up period ended at the time of all the death including any other reasons than HCC. The remaining patients were censored at the last follow-up visit. The study period ended in December 2016.

In the present study, MVI was defined as the presence of either microscopic portal vein invasion or venous invasion, which was difficult to recognize on preoperative imaging. The recurrence form was divided into two groups: local recurrence (residual tumor from the most recent treatment) and distant recurrence (new tumor different from the most recently treated tumor). This study was a retrospective study, and we got the Institutional Review Board of Shizuoka Cancer Center approval for the exception of patients' consent.

Statistical analyses

Continuous variables were presented as the median and range and were compared using the Mann–Whitney *U* test. Categorical variables were compared using the Chi-squared test or Fisher's exact test, as appropriate. All factors that were found to be significantly associated with the presence or absence of MVI ($P < 0.05$) in a univariate analysis were entered into a multivariate analysis. When converting continuous variables to categorical variables, a receiver operating characteristic (ROC) curve and Youden's index were used to determine the cutoff values. The cumulative recurrence-free and overall survival curves were analyzed using the Kaplan–Meier method. A Cox proportional hazards model was used for the univariate and multivariate analyses, and all factors found to be significant predictors of the recurrence-free and overall survival ($P < 0.05$) in the univariate analysis were entered into the

multivariate analysis. The multivariate analysis was performed using the logistic regression method with a backward stepwise selection model. All of the statistical analyses were performed using the SPSS 24.0 software package (SPSS, Inc., Chicago, IL). Two-tailed P values of <0.05 were considered to indicate statistical significance.

Results

Patient characteristics

Among 631 patients, 49 patients were excluded from the analysis due to the presence of macroscopic vessel invasion, while 2 patients were excluded because an exact pathological result was obtained. The remaining 580 patients with HCC were included in the analysis. The patient characteristics are shown in Table 1. There were 425 primary HCC patients and 155 HCC patients with a treatment history. The treatments that the 155 HCC patients with a treatment history had most recently undergone were as follows: surgical resection (n = 61), RFA (n = 29), TACE (n = 53) and the other treatments (n = 12). The rate of local recurrence was higher in the patients who underwent TACE and other treatments than in those who underwent surgical resection and RFA. The median period of follow-up was 42.2 months (range, 0.1–164.1 months). The 1-, 3- and 5-year overall survival rates were 93.9, 81.0 and 68.0%, respectively. The 1-, 3- and 5-year recurrence-free survival rates were 72.8, 40.5 and 30.7%, respectively. MVI was identified in 110 of the 580 patients (19.0%).

The preoperative factors of the primary HCC patients with and without MVI

MVI was identified in 76 of the 425 (17.9%) patients with primary HCC (Table 2). The cumulative overall survival rate in patients with MVI was significantly poorer than in patients without MVI (Fig. 1a, P = 0.034). The rate of poorly differentiated HCC of the patients with MVI was significantly higher than that of the patients without MVI (11.8 vs. 1.7%, $P < 0.001$). The tumor diameter of the patients with MVI was significantly larger than that of the patients without MVI (median diameter: 51 vs. 34 mm, $P < 0.001$). With regard to the preoperative blood examination results of the patients with and without MVI, significant differences were observed in five factors: the platelet count ($P < 0.001$), the prothrombin time (PT) (P = 0.002), the aspartate aminotransferase (AST) (P = 0.001), AFP ($P < 0.001$) and DCP ($P < 0.001$) levels.

Table 1 Clinicopathological characteristics of the patients

Characteristics	
Age (years)[a]	70 (30–87)
Gender (men/women)	470/110
Etiology of liver disease (viral/non-viral)	380/200
HBsAg positive (%)	113 (19.5)
Anti-HCV Ab positive (%)	264 (45.5)
Dual infection (%)	3 (0.5)
Treatment history of HCC (present)	155 (26.7)
Surgical resection	61
Recurrence form (local/distant)	1/60
RFA	29
Recurrence form (local/distant)	12/17
TACE	53
Recurrence form (local/distant)	41/12
The other	12
Recurrence form (local/distant)	7/5
Albumin (g/L)[a]	41 (23–56)
Total serum bilirubin (mg/dL)[a]	0.6 (0.1–2.3)
PT (%)[a]	87 (53–130)
AST (U/L)[a]	36 (15–211)
ALT (U/L)[a]	34 (5–281)
Platelet count ($\times 10^4$/μL)[a]	15.1 (4.8–79.0)
AFP (ng/mL)[a]	12.2 (1.1–239,119)
DCP (mAU/mL)[a]	120 (1–446,000)
Child–Pugh classification (A/B)	572/8
Cirrhosis (present)	176 (30.3)
Anatomical resection (present)	278 (47.9)
Maximum tumor diameter (mm)[a]	33 (3–180)
Tumor number (multiple)	152 (26.2)
Tumor differentiation (well/moderately/poorly)	100/452/28
Microscopic vessel invasion (present)	110 (19.0)
Tumor stage (I/II/III)	353/169/57

The values in parentheses are percentages unless otherwise indicated

HBsAg hepatitis B surface antigen, *HCV* hepatitis C virus, *Ab* antibody, *HCC* hepatocellular carcinoma, *RFA* radiofrequency ablation, *TACE* transcatheter arterial chemoembolization, *PT* prothrombin time, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *AFP* alpha-fetoprotein, *DCP* des-gamma-carboxy prothrombin

[a]The value indicates the median (range)

The univariate and multivariate analyses to identify the predictors of MVI in primary HCC patients

Seven preoperative factors were identified as the candidate predictors of the presence of MVI. After converting the continuous variables to categorical variables, an ROC curve analysis was performed to determine the cutoff values for the AST level (55 IU/L), the platelet count (15.1×10^4/μL), the PT (85%), the AFP (17.0 ng/mL) and

Table 2 The preoperative characteristics of the primary HCC patients with and without MVI

	With MVI $n = 76$	Without MVI $n = 349$	P
Age (years)[a]	69 (30–83)	70 (39–87)	0.289
Gender (men/women)	66/10	275/74	0.151
Etiology of liver disease (viral/non-viral)	45/31	212/135	0.651
Albumin (g/L)[a]	40 (23–56)	41 (29–51)	0.205
Total serum bilirubin (mg/dL)[a]	0.6 (0.3–1.3)	0.6 (0.2–2.3)	0.996
AST (IU/L)[a]	43 (15–211)	36 (16–135)	0.001
ALT (IU/L)[a]	39 (5–281)	35 (7–191)	0.259
Platelet count ($\times 10^4/\mu L$)[a]	18.5 (7.8–41.6)	15.0 (4.8–38.8)	<0.001
PT (%)[a]	82 (62–130)	89 (53–118)	0.002
AFP (ng/mL)[a]	34.7 (1.7–199,133)	10.6 (1.4–239,119)	<0.001
DCP (mAU/mL)[a]	946 (13–446,000)	121 (1–198,000)	<0.001
Cirrhosis (present)	15 (19.7)	104 (29.8)	0.069
Child–Pugh classification (B)	2 (2.6)	6 (1.7)	0.638
Tumor diameter (mm)[a]	51 (11–175)	34 (6–180)	<0.001
Tumor number (multiple)	21 (27.6)	79 (22.6)	0.372
Tumor differentiation (well/moderately/poorly)	9/59/9	62/280/6	<0.001
Tumor stage (I/II/III)	0/64/12	268/58/23	<0.001

The values in parentheses are percentages unless otherwise indicated

HCC hepatocellular carcinoma, *MVI* microscopic vessel invasion, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *PT* prothrombin time, *AFP* alpha-fetoprotein, *DCP* des-gamma-carboxy prothrombin

[a]The value indicates the median (range)

DCP (55 mAL/mL) levels and the tumor diameter (37 mm) (Fig. 2a). The odds ratios (ORs) for possible determinants of the presence of MVI, which were determined in the univariate logistic regression analyses, are shown in Table 3. In the multivariate analysis, the following factors remained as significant independent predictors of MVI in the primary HCC patients: DCP > 55 mAL/mL (OR 9.74, 95% confidence interval [CI] 3.40–27.9, $P < 0.001$), poorly tumor differentiation (OR 5.41, 95% CI 1.70–17.2, $P = 0.004$), AST > 55 IU/L (OR 2.62, 95% CI 1.44–4.78, $P = 0.002$), PT < 85% (OR 2.52, 95% CI 1.44–4.42, $P = 0.001$) and platelet count > $15.1 \times 10^4/\mu L$ (OR 2.42, 95% CI 1.33–4.41, $P = 0.004$) (Table 3).

Univariate and multivariate analyses of the prognostic factors for the overall survival in primary HCC patients

In the multivariate analysis, AFP > 17.0 ng/mL (hazard ratio [HR] 1.78, 95% CI 1.26–2.51, $P = 0.001$), tumor diameter > 37 mm (HR 1.75, 95% CI 1.25–2.44, $P = 0.001$), age ≥ 70 years (HR 1.58, 95% CI 1.13–2.44, $P = 0.008$), AST > 55 IU/L (HR 1.57, 95% CI 1.09–2.26, $P = 0.015$) and PT < 85% (HR 1.42, 95% CI 1.02–2.26, $P = 0.040$) remained significant independent predictors of the overall survival (Table 4).

The preoperative factors of HCC patients with a treatment history with and without MVI

MVI was identified in 34 of 155 (21.9%) HCC patients with a treatment history (Table 5). The cumulative overall survival rate in patients with MVI was significantly poorer than in patients without MVI (Fig. 1b, $P < 0.001$). Although there were no significant differences in the most recent treatments of the patients with and without MVI ($P = 0.177$), MVI was frequently identified in patients with local recurrence (31.1%). In contrast, MVI was identified in only 15 of 94 (16.0%) HCC patients with distant recurrence. Significant differences were observed in four factors: the recurrence form, time after the most recent treatment >24 months, the serum level of DCP and the tumor diameter ($P = 0.030$, $P = 0.049$, $P = 0.002$ and $P < 0.001$, respectively).

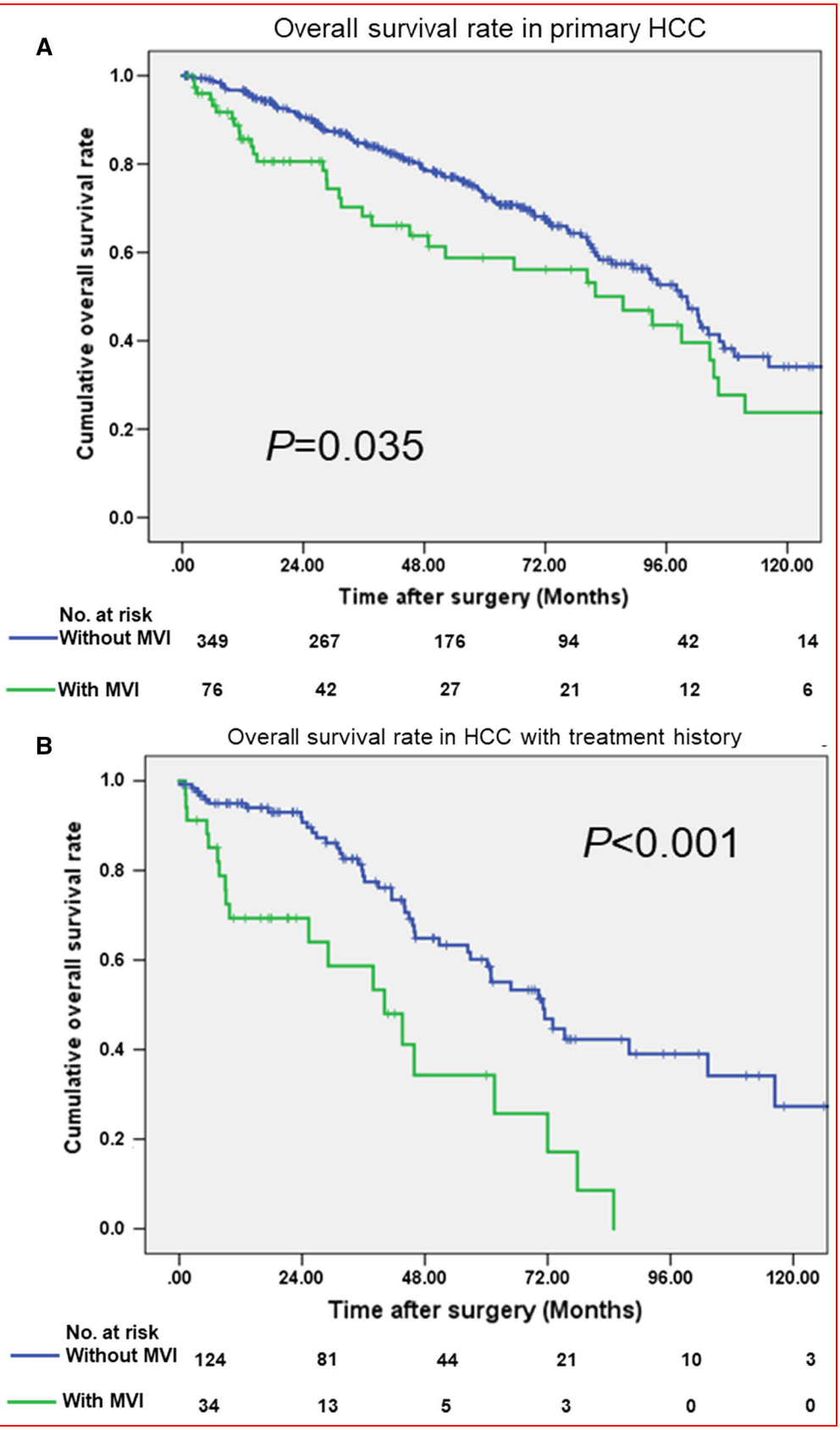

Fig. 1 Survival curves of patients who underwent hepatectomy using the Kaplan–Meier method. **a** Overall survival curve classified by the presence of MVI in primary HCC patients. **b** Overall survival curve classified by the presence of MVI in HCC patients with a treatment history

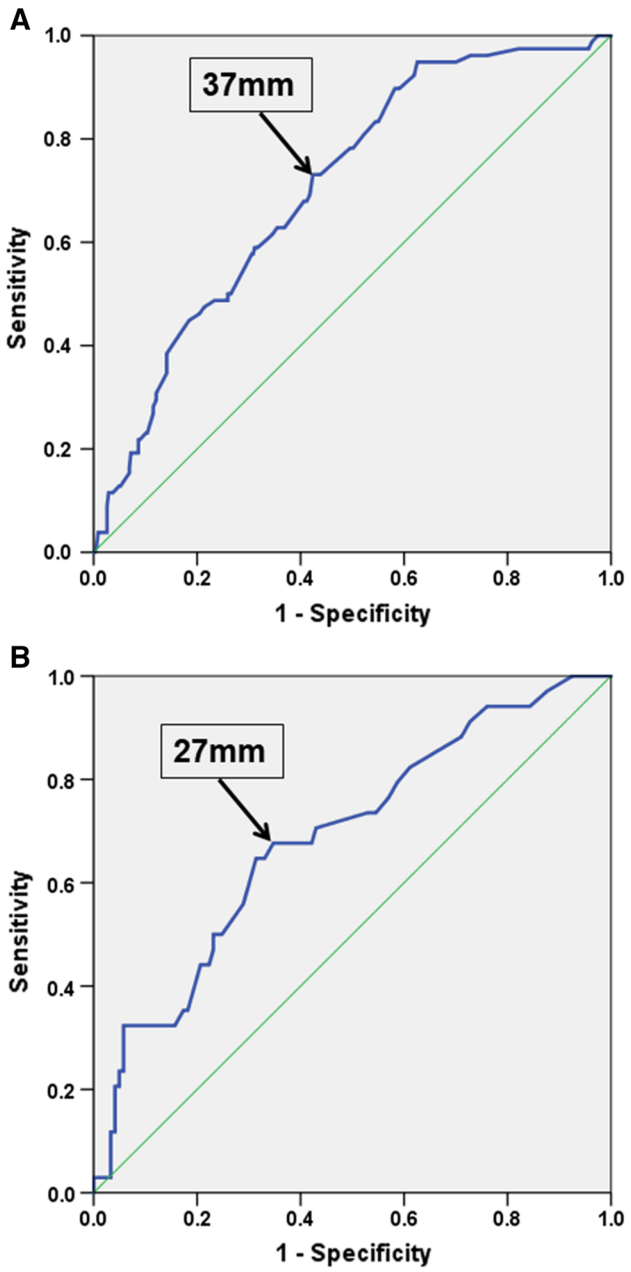

Fig. 2 The receiver operating characteristic (ROC) curves for determining the cutoff values of the possible predictors of MVI in patients with primary HCC and HCC with a treatment history. **a** The ROC curves for primary HCC. **b** The ROC curves for HCC with a treatment history

The univariate and multivariate analyses to identify the predictor of MVI in HCC patients with a treatment history

After converting the continuous variables to categorical variables, an ROC analysis was performed to determine the cutoff values for DCP (48 mAL/mL) and the tumor diameter (27 mm) (Fig. 2b). The results of the univariate logistic regression analyses, which were performed to calculate the ORs for possible determinants of MVI, are shown in Table 6. In the multivariate analysis, DCP > 48 mAL/mL (OR 5.16, 95% CI 1.80–14.8, $P = 0.002$) and tumor diameter >27 mm (OR 2.57, 95% CI 1.10–6.04, $P = 0.030$) were the significant independent predictor of the presence of MVI in the HCC patients with a treatment history (Table 6).

The preoperative DCP level and tumor diameter on imaging, which could be easily evaluated prior to hepatectomy, were selected as the independent predictors for MVI to establish the preoperative scoring system. Scoring was performed considering with each risk factor taken as 1 point. There were 57, 52 and 46 patients with scores of 0, 1 and 2, respectively. The rate of MVI in the patients with a score of 0 was 5.3%, whereas that in patients with a score of 2 was 43.5% (Fig. 3).

Univariate and multivariate analyses of the prognostic factors for overall survival in HCC patients with a treatment history

In the multivariate analysis, the presence of MVI (HR 2.27, 95% CI 1.30–3.97, $P = 0.001$) and tumor diameter >27 mm (HR 2.04, 95% CI 1.22–3.40, $P = 0.006$) remained significant independent predictors of the overall survival (Table 7).

Discussion

The present study showed that the predictors of MVI were different in primary HCC and HCC with a treatment history and that the tumor diameter cutoff value for predicting MVI in HCC with a treatment history was smaller in comparison with that in primary HCC.

The present study reveals some interesting results. First, the present study is the first report to show the predictors of MVI in HCC with a treatment history though several studies have shown the predictors of MVI in patients with primary HCC alone or in populations that included patients with primary and treatment history. We found that a tumor diameter of >27 mm was the significant predictor in this subgroup of patients. Many studies have shown the frequency of MVI after repeat hepatectomy or salvage hepatectomy after RFA [16–18, 23, 24]. The results of the present study suggest that MVI is likely to occur in HCC with a treatment history even if the tumors are still small—as previous studies have reported [19–22]. In local recurrence cases in particular, MVI tended to occur at a high rate, whereas the rate of MVI in distant recurrence cases was almost the same as that of primary HCC. This suggests

Table 3 The predictor of MVI in the patients with primary HCC

Variables	Univariate		Multivariate	
	Odds ratio (95% confidence interval)	*P*	Odds ratio (95% confidence interval)	*P*
AST (>55 IU/L)	2.37 (1.40–4.04)	0.001	2.62 (1.44–4.78)	0.002
Platelet count (>15.1 × 10^4/μL)	2.37 (1.39–4.04)	0.001	2.42 (1.33–4.41)	0.004
PT (<85%)	2.58 (1.55–4.30)	<0.001	2.52 (1.44–4.42)	0.001
AFP (>17.0 ng/mL)	2.25 (1.35–3.75)	0.002		
DCP (>55 mAL/mL)	12.2 (4.37–34.2)	<0.001	9.74 (3.40–27.9)	<0.001
Tumor diameter (>37 mm)	3.52 (2.04–6.07)	<0.001		
Tumor differentiation (poorly)	7.68 (2.65–22.3)	<0.001	5.41 (1.70–17.2)	0.004

MVI microscopic vessel invasion, *HCC* hepatocellular carcinoma, *AST* aspartate aminotransferase, *PT* prothrombin time, *AFP* alpha-fetoprotein, *DCP* des-gamma-carboxy prothrombin

Table 4 Prognostic factors for the overall survival in primary HCC patients by univariate and multivariate analyses

Variables	Univariate		Multivariate	
	Hazard ratio (95% confidence interval)	*P*	Hazard ratio (95% confidence interval)	*P*
Age (≥70 years)	1.48 (1.06–2.07)	0.020	1.58 (1.13–2.44)	0.008
Gender (male)	1.05 (0.69–1.60)	0.823		
Etiology of liver disease (viral)	1.06 (0.75–1.49)	0.748		
Albumin (<40 g/L)	1.36 (0.77–2.42)	0.290		
PT (<85%)	1.46 (1.05–2.03)	0.025	1.42 (1.02–1.99)	0.040
AST (>55 IU/L)	1.74 (1.23–2.42)	0.002	1.57 (1.09–2.26)	0.015
Platelet count (>15.1 × 10^4/μL)	1.02 (0.73–1.41)	0.928		
AFP (>17.0 ng/mL)	1.90 (1.36–2.65)	<0.001	1.78 (1.26–2.51)	0.001
DCP (≥55 mAL/mL)	1.74 (1.20–2.51)	0.003		
Child–Pugh classification (B)	2.15 (1.01–4.60)	0.049		
Cirrhosis (present)	1.26 (0.88–1.79)	0.207		
Anatomical resection (present)	1.04 (0.75–1.45)	0.797		
Tumor diameter (>37 mm)	1.61 (1.16–2.25)	0.004	1.75 (1.25–2.44)	0.001
Tumor number (multiple)	1.46 (1.02–2.10)	0.041		
Tumor differentiation (poorly)	2.45 (1.08–5.57)	0.032		
Microscopic vessel invasion (present)	1.52 (1.03–2.25)	0.036		

HCC hepatocellular carcinoma, *AFP* alpha-fetoprotein, *DCP* des-gamma-carboxy prothrombin

that most distant recurrence cases were considered as multicentric recurrence in the present study, and such tumors may need to be handled in the same way as primary HCC.

Furthermore, the present study revealed that the tumor diameter cutoff value for predicting the presence of MVI in HCC with a treatment history (27 mm) was smaller than that in the primary HCC (37 mm). Although the multivariate analysis did not show that the tumor diameter was a predictor of MVI in patients with primary HCC, previous studies have reported the tumor diameter to be an important factor for predicting MVI [7, 11–15]. In terms of primary HCC patients, Zhong et al. [11] reviewed the frequency of MVI in the literature series and found that the frequency of MVI in patients with a tumor diameter of >5 cm (64.1%) was markedly increased in comparison with patients with a tumor diameter of ≤5 cm. Several other studies have reported a tumor diameter cutoff value of 5 cm [13, 15]. In contrast, the rate of MVI was high in the patients with a high DCP level, even in those with primary HCC ≤2 cm [28], results that were partially consistent with our own; DCP was a significant independent predictor of the presence of MVI in both primary HCC and HCC patients with a treatment history.

Table 5 The preoperative characteristics of the HCC patients with a treatment history with and without MVI

	With MVI $n = 34$	Without MVI $n = 121$	P
Age (years)[a]	69 (53–83)	69 (38–84)	0.856
Gender (men/women)	30/4	99/22	0.447
Etiology of liver disease (viral/non-viral)	27/7	94/27	0.950
Recurrence form (local/distant)	19/15	42/79	0.030
The most recent treatment of HCC			0.177
Surgery	11 (32.3)	50 (41.3)	
RFA	5 (14.7)	24 (19.8)	
TACE	14 (41.2)	39 (32.2)	
The other	4 (11.8)	8 (6.6)	
Time after the most recent treatment (months)[a]	11.8 (0.3–73.2)	18.9 (0.7–186.1)	0.080
Time after the most recent treatment (>6 months)	23 (67.6)	92 (76.0)	0.376
Time after the most recent treatment (>12 months)	17 (50.0)	78 (64.5)	0.163
Time after the most recent treatment (>24 months)	9 (26.5)	57 (47.1)	0.049
Albumin (g/L)[a]	42 (27–49)	41 (29–49)	0.958
Total serum bilirubin (mg/dL)[a]	0.6 (0.3–1.0)	0.6 (0.1–1.6)	0.576
AST (IU/L)[a]	35 (19–152)	34 (16–169)	0.296
ALT (IU/L)[a]	36 (11–133)	29 (9–191)	0.259
Platelet count ($\times 10^4/\mu L$)[a]	15.0 (5.7–79.0)	14.2 (6.2–72.9)	0.106
PT (%)[a]	83 (53–102)	86 (60–117)	0.088
AFP (ng/mL)[a]	24.6 (1.8–107,890)	9.7 (1.111213)	0.138
DCP (mAU/mL)[a]	123 (12–91,200)	37 (1–89,200)	0.002
Cirrhosis (present)	11 (32.4)	46 (38.0)	0.688
Child–Pugh classification (B)	0	0	
Tumor diameter (mm)[a]	32 (10–150)	20 (3–140)	0.001
Tumor number (multiple)	16 (47.1)	36 (29.8)	0.461
Tumor differentiation (well/moderately/poorly)	4/25/5	25/88/8	0.202
Tumor stage (I/II/III)	0/24/10	82/27/12	<0.001

The values in parentheses are percentages unless otherwise indicated

HCC hepatocellular carcinoma, *MVI* microvessel invasion, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *PT* prothrombin time, *AFP* alpha-fetoprotein, *DCP* des-gamma-carboxy prothrombin

[a]The value indicates the median (range)

Table 6 The predictor of MVI in the HCC patients with a treatment history

Variables	Univariate		Multivariate	
	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P
Recurrence form (local)	2.38 (1.10–5.16)	0.028		
Time after most recent treatment (>24 months)	0.40 (0.17–0.94)	0.049		
DCP (>48 mAL/mL)	6.96 (2.52–19.2)	<0.001	5.16 (1.80–14.8)	0.002
Tumor diameter (>27 mm)	4.00 (1.80–8.92)	0.001	2.57 (1.10–6.04)	0.030

HCC hepatocellular carcinoma, *MVI* microvessel invasion, *DCP* des-gamma-carboxy prothrombin

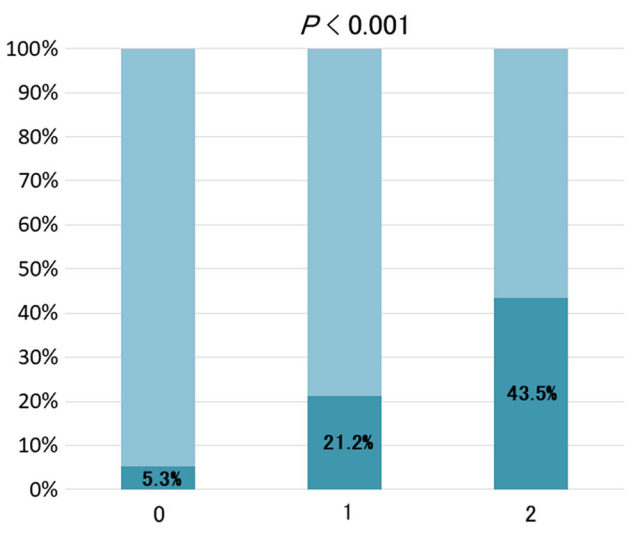

Fig. 3 The incidence of MVI significantly increased as the score of scoring system increased ($P < 0.001$)

Regarding the HCC with a treatment history, the studies related to third or more repeat hepatectomy from Japan showed that the median tumor diameter was <2 cm in cases treated with repeat hepatectomy [17, 18]. Yamashita et al. [17] reported that, despite the small tumor diameter, the frequency of MVI was very high (>60%). In contrast, Mise et al. [18] reported that the frequency of MVI was relatively low, and concluded that third or more repeat hepatectomy offers favorable survival that is similar to second hepatectomy, in spite of the low rate of anatomical resection (the procedure that they recommended for HCC) [29]. Our established scoring system is useful for deciding on the operative procedure (anatomical resection or non-anatomical resection) following the prediction of the presence of MVI which is invisible on preoperative imaging because the two factors constituting the scoring system can be easily evaluated prior to hepatectomy. In particular, the preoperative DCP level reflects the biological behavior of HCC more strongly than does the tumor diameter, as the DCP level was found to be an independent predictor of the presence of MVI in both primary HCC and HCC patients with a treatment history. Given the results of these studies, a favorable prognosis might be achieved by not performing anatomical resection for HCC patients with a treatment history with a score of 0.

With regard to the image findings, MRI findings, non-smooth tumor margins, peritumoral enhancement [30], a macroscopic appearance on CT [12] and intraoperative ultrasound findings [31], have recently been reported as predictors of MVI. The image findings are important, especially in primary HCC patients. In contrast, objective predictors such as tumor diameter are desirable for HCC with a treatment history because macroscopic appearance after treatment is strongly affected by recent treatment and is difficult to recognize based on imaging features. Although it is not denied that the tumor diameter is also affected by recent treatment, the results of the present study were reliable in terms of showing the association between the tumor diameter on preoperative images and the presence of MVI.

Table 7 Prognostic factors for the overall survival in HCC patients with a treatment history by univariate and multivariate analyses

Variables	Univariate		Multivariate	
	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*
Age (≥70 years)	1.29 (0.76–2.17)	0.347		
Gender (male)	2.41 (0.87–6.66)	0.090		
Etiology of liver disease (viral)	1.04 (0.56–1.92)	0.913		
Treatment history of HCC (surgical resection)	0.77 (0.46–1.31)	0.338		
Recurrence form (local)	1.83 (1.12–3.00)	0.016		
Albumin (<40 g/L)	1.09 (0.50–2.37)	0.837		
AFP (≥20 ng/mL)	1.53 (0.91–2.59)	0.112		
DCP (≥48 mAL/mL)	1.08 (0.65–1.79)	0.781		
Cirrhosis (present)	1.32 (0.78–2.24)	0.304		
Systemic resection (present)	1.11 (0.64–1.90)	0.716		
Tumor diameter (>27 mm)	2.63 (1.54–4.50)	<0.001	2.04 (1.22–3.40)	0.006
Tumor number (multiple)	1.46 (0.86–2.46)	0.158		
Tumor differentiation (poorly)	2.60 (1.30–5.21)	0.007		
Microscopic vessel invasion (present)	3.17 (1.75–5.72)	<0.001	2.27 (1.30–3.97)	0.004

HCC hepatocellular carcinoma, *AFP* alpha-fetoprotein, *DCP* des-gamma-carboxy prothrombin

The present study is associated with several limitations. First, this study was retrospective in nature and was performed at a single center; thus, the influence of a selection bias cannot be ruled out. Further prospective multi-institutional studies are therefore needed to objectively validate the results of the present study. However, the results of the present study, which were based on a relatively large study population (>500 patients) and a long follow-up period (median, 42.2 months), were reliable. Second, the rate of MVI in the present study (19.0%) was relatively low in comparison with other studies [12–14]. However, the prevalence of MVI in the review article varied widely (15.0–57.1%) [6]. Patients with macroscopic invasion were initially excluded from the present study. If these patients had been included, the rate of MVI would increase to 25.6%.

In conclusion, the predictors of MVI differ between primary HCC and HCC with a treatment history and the tumor diameter should be considered when predicting MVI—especially in HCC with a treatment history. This is especially important for determining the treatment strategy because primary HCC and HCC with a treatment history show different levels of malignant potential.

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