Original Article

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Indication for surgical resection in patients with hepatocellular carcinoma with major vascular invasion

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Summary **Major portal vein invasion (MVI) by hepatocellular carcinoma (HCC) carries an extremely poor prognosis. Our aim was to clarify the indications of hepatic resection in the presence of MVI by HCC. Between 2001 and 2015, 1,306 patients undergoing primary treatment for HCC were analyzed (866 hepatic resections and 440 transarterial therapies). Significant prognostic factors were identified by retrospectively analyzing tumor status, liver function and treatment. Overall survival was compared in terms of the degree of vascular invasion and treatment. The 5-year survival rates according to the degree of vascular invasion (Vp) were Vp0: 51.9%, Vp1: 33.0%, Vp2: 16.7%, Vp3: 21.8%, and Vp4: 0%, respectively. Overall survival (OS) did not differ significantly between patients with Vp3 and Vp4 MVI ($p = 0.153$). Median survival following hepatic resection of Vp3 cases was significantly better than that for Vp4 cases (1,913 *vs.* 258 days, $p = 0.014$), while OS following transarterial therapy was not significantly different (164 *vs.* 254 days in Vp3 *vs.* Vp4, $p = 0.137$). Multivariate analysis revealed hepatic resection (Odds: 2.335 [95%CI: 1.236-4.718], $p = 0.008$) and multiple tumors (1.698 [1.029-2.826], $p = 0.038$) as independent predictors of survival. Hepatic resection in HCC patients with MVI should be indicate in patients with Vp3 invasion.**

Keywords: Hepatocellular carcinoma, vascular invasion, survival, liver resection

1. Introduction

Major portal vein invasion (MVI) in patients with hepatocellular carcinoma (HCC), in which tumor thrombi extend to the main or first order branches of the portal trunk, is known to be associated with a poor prognosis. MVI is detected in 30-62% of advanced HCC cases (*1-6*). The median survival time of untreated patients with MVI is reportedly 2.7 to 4 months (*6-8*). Although hepatic resection is the only potentially curative treatment in patients with MVI, most patients rapidly develop recurrence in the remnant liver (*1-4,5,8*). Therefore, MVI is a contraindication for hepatic resection according to the American Association for the Study of Liver Disease (AASLD) and Barcelona Clinic for Liver Cancer (BCLC) guidelines, which instead recommend treatment with intra-arterial/portal chemotherapy or sorafenib (*9-11*).

However, recent advances in surgical techniques allow hepatic resection to be performed safely even for more severe cancers (*3,5,12,13*). Some studies showed that hepatic resection for MVI may be advantageous in terms of avoiding liver failure secondary to tumor thrombus (*13-17*). However, the indications for hepatic resection and transarterial therapy in HCC cases with MVI differ among institutions (*2,3,12,18-20*). Thus, the treatment for MVI is still controversial and few reports have documented the limits and clinical benefits of hepatic resection and other therapies.

This study aimed to identify categories of HCC patients with MVI who are likely to obtain survival benefits from hepatic resection. We retrospectively analyzed a large number of HCC patients at a single institution who were treated using uniform treatment criteria.

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2. Patients and Methods

2.1. *Patients*

Between April 2001 and December 2015, a total of 2,299 patients were treated for HCC at our hospital (1,459 patients underwent hepatic resection and 840 patients underwent transarterial therapy) (Figure 1). Among hepatic resection cases, 593 patients were excluded (407 patients who underwent repeat resection and 186 patients in whom pathology revealed that the tumor was not HCC) from this study. Four hundred of the transarterial therapy patients were excluded (319 patients with repeat transarterial therapy and 81 patients' whose tumor did not seem to be classical type HCC). Thus, the data from the remaining 1,306 HCC cases who underwent primary treatment of HCC at our hospital were analyzed.

Based on the degree of portal vein invasion (Vp), these patients were divided into 5 groups according to the classification of the Liver Cancer Study Group of Japan (*21*), as Vp0 (no tumor thrombus), Vp1 (tumor thrombus in the third or lower order portal vein branch), Vp2 (tumor thrombus in the second order branch), Vp3 (tumor thrombus in the first order portal vein branch), and Vp4 (tumor thrombus extending to the main portal trunk or counter side of portal branch of tumor thrombus). We defined Vp1 and Vp2 as minor vascular invasion, and Vp3 and Vp4 as MVI.

2.2. *Indications*

The indication for hepatic resection was less than 3 HCCs with adequate liver functional reserve (*21*). The location and number of tumors were confirmed using three different imaging modalities (abdominal ultrasonography, enhanced CT and magnetic resonance imaging). The upper limit of liver volume to be resected was defined on the basis of Makuuchi's criteria, which are based on assessment of the indocyanine green retention rate at 15 minutes (*22*).

The first-line treatment for transarterial therapy is chemoembolization with cisplatin (CDDP), 50-100 mg/body, or epirubicin, 30-50 mg/body, in a gel form. Total bilirubin levels exceeding 3 mg/dL and Vp4 are contraindications to embolization, and performed transarterial chemotherapy alone (CDDP, 5-fluorouracil (5FU), 500 mg/body/5days or CDDP, 50-100 mg/body) performed to avoid hepatic failure. This study included only typical HCC cases, as assessed using radiological examinations.

2.3. *Surgical procedures*

Hepatic parenchymal transection was performed using the clamp-crushing method with the inflow blood occlusion technique (*23-25*). Anatomic resection of Couinaud's segment was the first-line operative procedure for HCC in patients with Child-Pugh class A liver function (*21*). Intraoperative ultrasonography was routinely performed to check for minor vascular invasion (*25*). When the tumor thrombus was found by intraoperative ultrasonography, extended hepatic resection was performed to remove the entire tumor thrombus as far as possible. In case of Vp3 and Vp4 MVI, entire tumor thrombectomy was performed using the peel off technique under inflow occlusion (*2,15*).

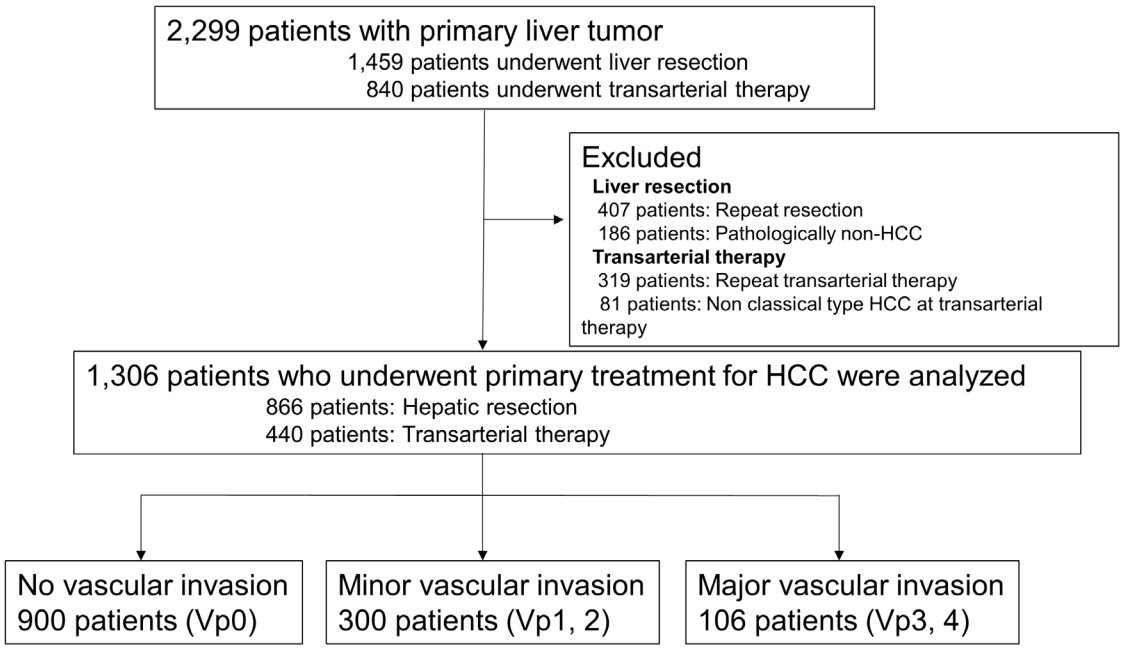

Figure 1. Flow chart of patient inclusion in the study.

Table 1. Patients' characteristics according to the degree of vascular invasion

Degree of vasclar invasion	vp0 (*n* = 900)	vp1 (*n* = 241)	vp2 (*n* = 59)	vp3 (*n* = 72)	vp4 (*n* = 34)	Total (*n* = 1306)
Treatment (Hepatic resection)	660 (73.3%)	161 (66.8%)	21(35.6%)	19 (26.4%)	8 (23.5%)	869 (66.5%)
Gender (male)	645 (71.7%)	192 (79.7%)	44 (74.6%)	65 (90.3%)	29 (85.3%)	975 (74.7%)
Age (year)	70 (32-87)	69 (31-86)	70 (47-86)	72(52-88)	69(44-82)	69 (44-88)
Tumor diameter (cm)	2.5 (1.8-3.7)	4.5 (1.4-17.0)	6.5 (2.0-20.0)	10.0 (4.0-23.0)	8.0 (2.4-20.0)	2.7 (1.84-23.0)
Mulltiple tumors (%)	250 (27.8%)	102 (42.3%)	29 (49.2%)	34 (47.2%)	19 (55.9%)	434 (33.2%)
Hepatitis virus infection (%)	613 (68.1%)	157 (65.1%)	36 (61.0%)	53 (73.6%)	27 (79.4%)	886 (67.8%)
Platelet count (mm^4/dL)	13.6 (3.7-41.2)	15.3 (4.0-51.0)	15.9 (9.5-68.6)	15.5 (3.9-49.8)	17.5 (8.1-45.5)	14.0 (3.9-49.8)
Albumin (g/dL)	3.8 (2.1-4.8)	3.8 (1.8-5.0)	3.5 (2.1-4.6)	3.5 (1.6-4.8)	3.6 (2.4-4.9)	3.8 (1.6-4.9)
Bilirubin (mg/dL)	0.65 (0.19-2.87)	0.66 (0.26-3.32)	0.69 (0.24-2.71)	0.79 (0.24-8.3)	0.82 (0.44-2.7)	0.63 (0.24-2.70)
Prothrombin activity (%)	96 (43-100)	98 (36-100)	95 (57-100)	93 (48-100)	93 (60-100)	96 (36-100)
IGCR15* (%)	12.9 (8.9-19.4)	12.2 (8.2-17.5)	11.1 (9.3-14.2)	11.3 (9.3-13.7)	17.0 (11.9-22.1)	12.7 (8.8-22.1)
AFP (ng/mL)	13.1 (0.8-10,618)	33.2 (0.6-145,900)	207.1 (2.1-425,700)	991.5 (1.0-365,400)	640.0 (1.4-235,099)	15.4 (0.6-425,700)
PIVKA-II (mAU/mL)	63 (1.0-75,000)	287 (4.3-75,000)	1633 (17.0-114,100)	4582 (15.0-75,000)	4297 (15.0-89,380)	127.0 (1.0-114,100)

*: Only operated cases, AFP, alpha-fetoprotein; PIVKA-II, protein induced by Vitamin K absence/antagonists-II.

2.4. *Measurements*

Patient status (age, gender, presence of hepatic viral infection and liver functional reserve), tumor status (tumor diameter, number, and tumor marker levels) and patient survival were compared in terms of the degree of vascular invasion. Postoperatively, the specimens were separately checked by a pathologist without access to the clinical information, and the degree of vascular invasion was estimated.

2.5. *Measurements*

Student's *t*-test, χ^2 test, Mann-Whitney *U* test, and Fisher's exact test were used for univariate analysis, as required. The Cox hazard model was used to calculate survival rates, Kaplan-Meier method was used to obtain survival curves, and all comparisons were made using the log-rank test. *P* values < 0.05 were considered to indicate statistical significance. All the analyses were performed using a statistical software package (JMP version 10.0, SAS Institute Inc., CA).

3. Results

3.1. *Survival in cases with major vascular invasion*

There were 900 patients with no vascular invasion (Vp0), 241 patients with Vp1, 59 patients with Vp2, 72 patients with Vp3 and 34 patients with Vp4 invasion (Table 1). The 1-, 3-, and 5-year survival rates according to the degree of vascular invasion were Vp0: 91.5%, 72.6% and 51.9%, Vp1: 78.8%, 46.7% and 33.0%, Vp2: 54.8%, 30.0% and 16.7%, Vp3: 36.4%, 21.8% and 21.8%, and Vp4: 35.3%, 15.4% and 0%, respectively ($p < 0.001$) (Figure 2A). The 1-, 3-, and 5-year survival rates in patients with major Vp were significantly worse than in those with minor Vp (37.1%, 21.8% and 12.4% *vs*. 74.6%, 43.4% and 31.3%, respectively, $p < 0.001$) (Figure 2B).

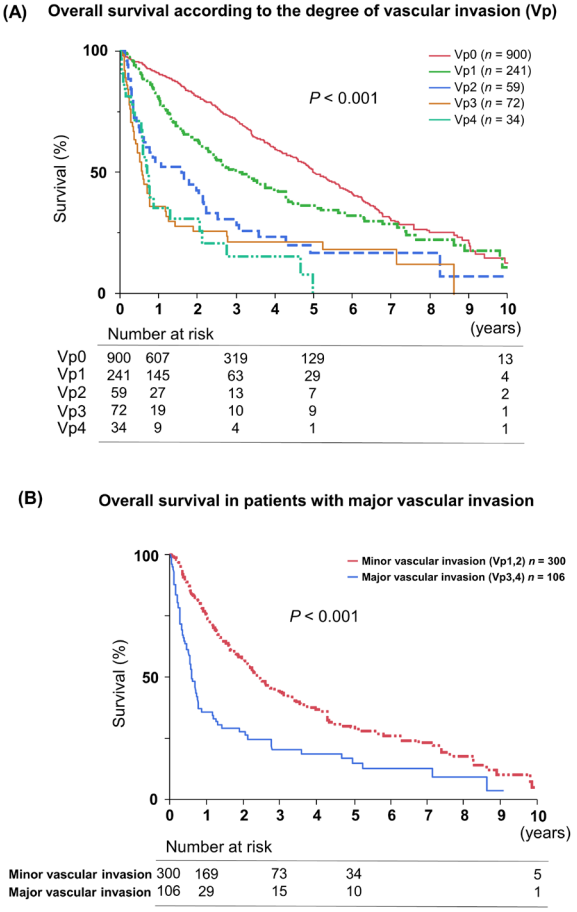

Figure 2. Cumulative survival rates based on the degree of vascular invasion. The 1-, 3-, and 5-year survival rates according to the degree of vascular invasion were distinct among the five groups **(A)**. The 1-, 3-, and 5-year survival rates with major vascular invasion were significantly worse than those with minor vascular invasion **(B)**.

3.2. *Characteristics of patients with major vascular invasion*

In the MVI group, there were 72 patients with Vp3 and 34 patients with Vp4 invasion (Table 2). The number of tumors were significantly smaller in the hepatic

Table 2. Characteristics of patients stratified according to the degree of major vascular invasion (Vp) and the treatment received

Items	vp3 (n = 72)			vp4 (n = 34)		
	Hepatic resection (n = 19)	TATx (n = 53)	p-value	Hepatic resection (n = 8)	TATx (n = 26)	p-value
Gender (male)	19 (100%)	46 (86.8%)	0.033	8 (100%)	21 (80.8%)	0.179
Age (year)	63 (53-78)	73 (52-88)	0.001	64 (44-81)	70 (58-82)	0.132
Multiple tumors (%)	5 (26.3%)	29 (54.7%)	0.017	1 (12.5%)	18 (69.2%)	0.005
Tumor diameter (cm)	7.7 (1.7-18.0)	10.0 (5.7-23.0)	0.116	7.0 (1.0-12.0)	8.5 (1.5-20.0)	0.163
Hepatitis vuirus infection (%)	12 (63.2%)	41 (76.9%)	0.246	7 (87.5%)	20 (76.9%)	0.518
Albumin (g/dL)	4.0 (2.5-4.8)	3.4 (1.6-4.6)	0.004	3.9 (3.7-4.4)	3.5 (2.4-4.9)	0.012
Bilirubin (mg/dL)	0.62 (0.24-2.9)	0.81(0.39-10.7)	0.172	0.71 (0.5-1.1)	0.92 (0.44-2.7)	0.234
Prothrombin activity (%)	96 (69-100)	89 (48-100)	0.051	100 (88-100)	92 (60-100)	0.113
Platelet count (mm^4/dL)	19.1 (8.1-49.8)	15.1 (3.9-41.2)	0.052	12.9 (10.9-18.4)	17.8 (8.1-45.5)	0.139
AFP (ng/mL)	677 (1-100500)	1593 (3-365400)	0.256	26 (2.4-17541.1)	1114 (1.4-235099)	0.520
PIVKA-II (mAU/mL)	2905 (15-75000)	5776 (22-75000)	0.413	2848 (404-178000)	5007 (15-89380)	0.351

TATx, transarterial therapy; AFP, alfa fetoprotein; PIVKA-II, prothrombin induced by Vitamin K absence/antagonists-II.

resection than the transarterial therapy groups [Vp3: 5 (26.3%) *vs*. 29 (54.7%) patients, p = 0.017, and Vp4; 1 (12.5%) *vs*. 18 (69.2%) patients, respectively, p = 0.005]. Serum albumin levels were significantly higher in the hepatic resection than in the transarterial therapy group (Vp3: median 4.0 g/dL [range: 2.5-4.8g/dL] *vs*. 3.4 [1.6-4.6], p = 0.004, Vp4: 3.9 g/dL [3.7-4.4g/dL] *vs*. 3.5 [2.4-4.9], respectively, p = 0.012). There were no significant differences in serum bilirubin levels, prothrombin activity and platelet count between the two treatment groups. Also, median alfa fetoprotein (AFP) levels (p = 0.256 and p = 0.520) and median prothrombin induced by Vitamin K absence/antagonists-II (PIVKA-II) levels (p = 0.413 and p = 0.351) did not differ significantly between the two treatment groups for both Vp3 and Vp4 invasion.

3.3. *Survival in HCC patients with major vascular invasion stratified according to treatment*

Analysis of patients with MVI showed that there were no significant differences in survival rates between patients with Vp3 and Vp4 invasion (1-, 3- and 5-year survival rates: 36.4%, 21.8% and 21.8% *vs*. 35.3%, 15.4% and 0%, respectively, p = 0.153). Median survival did not differ significantly according t the degree of MVI (Vp3 *vs*. Vp4: 254 days *vs*. 206, p = 0.696) (Figure 3A). In contrast, median survival with Vp3 invasion was significantly better than that with Vp4 invasion among patients who underwent hepatic resection (1,913 days *vs*. 258, p = 0.014), while median survival did not differ significantly between patients with Vp3 and Vp4 invasion who underwent transarterial therapy (164 days *vs*. 254, p = 0.137) (Figures 3B, C). In patients with Vp4 invasion, seven out of 8 patients (87.5%) rapidly developed recurrence of tumor thrombus in the remnant liver within 1 year.

4. *Prognostic factors in patients with major vascular invasion*

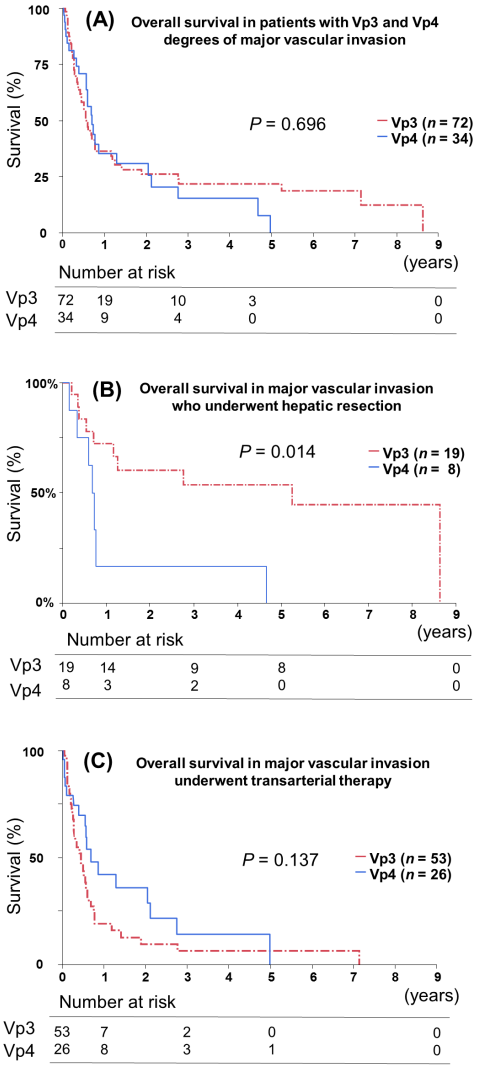

Figure 3. Cumulative survival rates in patients with major vascular invasion based on the treatment given. The 1-, 3- and 5-year survival rates did not differ significantly between Vp3 *vs*. Vp4 invasion, (36.4%, 21.8% and 12.5% *vs*. 35.3%, 15.4% and 0%, respectively, p = 0.696) **(A)**. Median survival among patients who underwent hepatic resection was significantly higher in those with Vp3 versus Vp4 invasion (1,913 *vs*. 258 days, p = 0.014) **(B)**, while median survival did not differ significantly in patients with Vp3 and Vp4 invasion who underwent transarterial therapy (164 *vs*. 254 days, p = 0.137) **(C)**.

Table. 3 Uni- and multivariate analysis of prognostic factors in patients with hepatocellular carcinoma with major vascular invasion

Variables	Univariate analysis			Multivariate analysis		
	Odds	95% CI (Low-High)	*p*-value	Odds	95% CI (Low-High)	*p*-value
Treatment (surgery)	2.641	1.535 - 4.823	< 0.001	2.335	1.236 - 4.718	0.008
Gender (male)	0.555	0.310 - 1.083	0.815			
Age (> 70 yr.)	0.983	0.627 - 1.543	0.940			
Multiple tumors	1.984	1.239 - 3.197	0.004	1.698	1.029 - 2.826	0.038
Tumor diameter (> 50 mm)	1.834	1.004 - 3.692	0.049			
Hepatitis virus infection	1.149	0.732 - 1.821	0.548			
Platelet count (mm^4/dL)	1.049	0.431 - 2.171	0.907			
Albumin (< 3.0 g)	1.793	1.105 - 3.014	0.046	1.060	0.484 - 2.112	0.877
Bilirubin (> 2 mg/dL)	2.848	1.178 - 5.867	0.023	1.910	0.622 - 5.593	0.250
Child Pugh class (B)	2.480	0.950 - 5.353	0.062			
AFP (> 400 ng/mL)	1.408	0.896 - 2.215	0.137			
PIVKA-II (>1000 mAU/mL)	1.361	0.747 - 2.732	0.330			

AFP, alpha-fetoprotein; PIVKA-II, protein induced by Vitamin K absence/antagonists-II.

Univariate analysis revealed five factors that affect the prognosis of HCC with MVI (Table 3): hepatic resection (Odds ratio: 2.641 [95%CI; 1.535-4.823], $p < 0.001$), multiple tumors (Odds ratio: 1.984 [1.239-3.197], $p = 0.004$), tumor diameter (Odds ratio: 1.834 [1.004-3.692], $p = 0.049$), albumin level (Odds ratio: 1.793 [1.105-3.014], $p = 0.046$) and bilirubin level (Odds ratio: 2.848 [1.178-5.862], $p = 0.023$.) Multivariate analysis revealed that only two factors contribute to survival in patients with MVI. Hepatic resection is the strongest predictor of survival (Odds ratio: 2.335 [1.236-4.718], $p = 0.008$), while the presence of multiple tumors is the second predictor (Odds ratio: 1.698 [1.029-2.826], $p = 0.038$).

4. Discussion

We found that the vascular invasion by HCC is an unfavorable factor for survival. In particular, in the MVI group, only patients with Vp3 invasion experience survival benefits with hepatic resection, while there is no clinical benefit of performing hepatic resection in patients with Vp4 invasion. Thus, patients with Vp4 invasion should be treat by transarterial therapy or other treatments.

Anatomic resection is the primary therapeutic strategy in patients with minor vascular invasion. This results in simultaneous treatment of potential intrahepatic metastasis *via* the portal vein (*25*). Thus, hepatic resection provides significant local tumor control in case of minor vascular invasion (*26,27*). In contrast, in patients with MVI, the risk of recurrence after liver resection remains disappointingly high despite hepatic resection (*1,28-30*). Therefore, the ideal treatment strategy for surgical control of vascular invasion in patients with MVI is still debatable.

Multivariate analysis in our study revealed that performing hepatic resection is the strongest predictor for survival in MVI. Hepatic resection significantly contributed to OS in patients with Vp3, while it had no prognostic benefit in patients with Vp4 invasion (*31-34*). In our study, seven out of 8 patients with Vp4 invasion (87.5%) developed rapid recurrence of tumor thrombus in the remnant liver within 1 year. We speculate that Vp4 invasion may result in occult intrahepatic metastasis prior to development of the visible thrombus, even though the tumor may be single or small. Hepatic resection for MVI itself may be one of the risk factors for intrahepatic metastasis *via* the portal vein. Therefore, hepatic resection alone does not improve the outcomes of HCC with Vp4 invasion. Thus, Vp3 is the only degree of invasion that has potential survival benefits following hepatic resection. Perioperative transarterial chemotherapy, including molecularly-targeted therapy, may be a possible treatment option for improving survival in patients with Vp4 invasion (*18,29-35*).

Our study is limited by its retrospective nature, which would probably have introduced a selection bias between patients who underwent hepatic resection and transarterial therapy. However, all treatment protocols were decided using uniform criteria, which is a merit of this being a single institution study.

In conclusion, the present study revealed that among HCC with MVI patients, only those with Vp3 invasion are likely to benefit from hepatic resection. Surgical resection in patients with Vp4 invasion should be strictly limited, even if the tumor seems completely removable by surgery, because of the high incidence of early intrahepatic recurrence in the remnant liver. Careful consideration of the indications for surgery in patients with major Vp contributes to the quality of life in patients with advanced HCC.

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