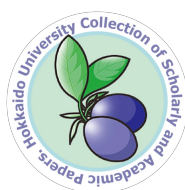




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Title	Clinicopathological Characteristics of Hepatocellular Carcinoma with Microscopic Portal Venous Invasion and the Role of Anatomical Liver Resection in These Cases
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Original article

Clinicopathological characteristics of hepatocellular carcinoma with microscopic portal venous invasion and the role of anatomical liver resection in these cases

Shingo Shimada, MD, PhD,¹ Toshiya Kamiyama, MD, PhD,¹ Hideki Yokoo, MD, PhD,¹

Tatsuya Orimo, MD, PhD,¹ Kenji Wakayama, MD, PhD,¹ Takahiro Einama, MD, PhD,¹

Tatsuhiko Kakisaka, MD, PhD,² Hirofumi Kamachi, MD, PhD,¹ and Akinobu Taketomi, MD, PhD,¹

The affiliation and address of the authors: ¹Department of Gastroenterological Surgery I, Hokkaido University Graduate School of Medicine, Sapporo, Japan

²Department of Surgery, Sapporo Kousei Hospital, Sapporo, Japan

Corresponding author: Shingo Shimada

Department of Gastroenterological Surgery I, Hokkaido University Graduate School of Medicine, Sapporo, Japan North15-West7, Kita-Ku, Sapporo, Hokkaido 060-8638, Japan

E-mail: shingoshimada1979@true.ocn.ne.jp

Tel: +81-11-7065927; Fax: +81-11-7177515.

Short title

Predictive factors for microscopic portal venous invasion and the place of anatomic liver resection.

Keywords

hepatocellular carcinoma, microscopic portal venous invasion, anatomic liver resection

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Competing interests

The authors declare no competing interests in relation to this study.

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Abstract

Background: The aims of this study were to investigate predictive factors for microscopic portal venous invasion (mPVI) in hepatocellular carcinoma (HCC) and whether anatomical liver resection (ALR) was useful in such cases.

Methods: We analyzed 852 patients with HCC without macroscopic portal venous invasion who were treated at our hospital between January 1990 and May 2014. These patients were stratified into a microscopic portal venous invasion group (mPVI group; n=153) and non-microscopic portal venous invasion group (NmPVI group; n=699).

Results: PIVKA-II ≥ 100 mAU/ml, a tumor size ≥ 5 cm, a confluent lesion, and poor differentiation were found to be independent risk factors for mPVI. Among the mPVI group who had single HCC under 5 cm, serum albumin level < 4.0 g/dl, PIVKA-II ≥ 100 mAU/ml, a positive surgical margin, and non-ALR (NALR) were independent unfavorable prognostic factors for overall survival (OS). PIVKA-II ≥ 100 mAU/ml, a positive surgical margin and NALR were independent unfavorable prognostic factors for relapse-free survival (RFS). ALR was significantly favorable factor for both OS and RFS of the mPVI group who had single HCC under 5 cm.

Conclusions: Even if no portal venous invasion is detectable in HCC patients preoperatively, a PIVKA-II ≥ 100 mAU/ml, tumor size ≥ 5 cm, and a confluent lesion indicate a high risk of mPVI. ALR should be considered for the patients with these characteristics because it is a favorable prognostic factor in these cases with mPVI.

Text

Background

Hepatocellular carcinoma (HCC) has a poor prognosis and accounts for 70-85% of primary liver cancers [1]. One of the reasons for this poor prognosis is the high incidence of recurrence after surgery [2]. Portal venous invasion is the most frequent type of vascular invasion in HCC [3] and is related to intrahepatic recurrence [2]. Hence, portal venous invasion is strongly related to survival and recurrence after surgery for HCC [2,3]. Portal venous invasion has two forms: 1) macroscopic portal venous invasion (MPVI) which is the presence of tumor thrombus in the second and first branches and trunk or opposite side branch of the portal vein, 2) microscopic portal venous invasion (mPVI) which is the presence of tumor thrombus in the distal to the third branches of the portal vein. MPVI often can be diagnosed preoperatively by computed tomography (CT) or other modalities. Magnetic resonance imaging (MRI) and ultrasonography (US) can detect MPVI in 81-95% of cases [4-6]. However, it is difficult to diagnose mPVI before surgery regardless of the modality. Both MPVI and mPVI are poor prognostic factors in terms of survival and recurrence in HCC [7-10]. It is widely known that the prognosis in MPVI cases is poorer than that of mPVI patients [7]. However, in a study by Fuks et al. involving an intention to treat analysis among 138 patients with hepatectomy first vs. 191 patients listed on a liver transplantation list, the independent predictive factors for recurrence beyond Milan criteria were reported to be microscopic vascular invasion, satellite nodules, tumor size >3 cm, poorly differentiated tumor, and liver cirrhosis [11]. These authors proposed that patients with three or more of these harmful factors should be considered for salvage transplantation

before recurrence [11]. This suggests therefore that not only MPVI but also mPVI should be investigated in detail.

Generally, anatomical liver resection (ALR) tends to be performed in patients diagnosed with HCC with MPVI before surgery. Moreover, ALR is a favorable factor for HCC with MPVI cases [12]. In contrast, the significance of ALR for HCC with mPVI is controversial. In our current study, we investigated the risk factors for mPVI and the place of ALR in these cases.

Patients and Methods

Between January 1990 and May 2014, 870 consecutive patients with HCC underwent primary liver resection at the Gastroenterological Surgery I unit of Hokkaido University Hospital in Sapporo, Japan. The cases who underwent R2 resection (n=18) were excluded from this study. We thus analyzed 852 patients who underwent R0 and R1 resections. When these resections were performed, the resection surfaces were found to be histologically or macroscopically free of HCC.

For stratification, we assigned patients as appropriate to a microscopic portal venous invasion group (mPVI group; n=153) and non-microscopic portal venous invasion group (NmPVI group; n=699).

Moreover, mPVI group was divided into two further sub-groups: an anatomical liver resection (ALR) group (n=121) or non-anatomical liver resection (NALR) group (n=32). ALR was defined as a resection in which the lesions were completely removed anatomically on the basis of Couinauds' classification (segmentectomy, sectionectomy, and hemihepatectomy or more). NALR denoted a partial liver resection. Postoperative morbidity was assessed using the validated classification system

by Clavien–Dindo [13]. Serious complications were categorized as grades III–V and defined as morbidity requiring surgical or radiological intervention. This study was approved by the Hokkaido University Hospital Voluntary Clinical Study Committee and was performed according to the Helsinki Declaration guidelines.

The indications for liver resection and the type of operative procedure to be used were usually based on the liver function reserve of the patient i.e., according to the results of the indocyanin green retention test at 15 min (ICGR15) [14]. ALR was performed on patients in whom the ICGR15 was lower than 25%. NALR was achieved in other cases.

Follow-up studies after liver resection were conducted at 3-month intervals, which included physical, serological, and radiological examinations.

Statistical analysis

The clinicopathological characteristics of the mPVI cases were compared with those of the NmPVI group. Univariate analyses were conducted using the χ^2 test. Multivariate analyses were performed using logistic regression model analyses. Overall survival (OS) and relapse-free survival (RFS) were determined via the Kaplan-Meier method and analyzed with the log-rank test. The Cox proportional hazards model was used for multivariate analyses. Moreover, we performed subgroup analyses about the place of ALR for HCC with mPVI which was single tumor <5cm. Statistical analyses were performed using JMP Pro 12.0.1 for Windows (SAS Institute, Cary, NC). Significance was defined as a *p*-value of <0.05.

Results

Clinical outcomes of this cohort

The five-year OS rate and median survival time (MST) of our 852 study patients were 69% and 122 months, respectively. The median RFS time of this cohort of patients was 23 months.

Median blood loss was 800 (20-10367) ml and median operative time was 345 (148-588) minutes. The 30-day and 90-day mortality were 0.4% (3/852), 1.3% (11/852), respectively. Morbidity was the followings; pleural effusion was 36 cases (4.2%), postoperative bleeding was 11 cases (1.3%), ascites was 11 cases (1.3%), bile leakage was 48 cases (5.6%), wound infection was 15 cases (1.8%).

The median follow-up period was 52 months (range, 0.2-289 months).

The incidence of patients with mPVI in our current study cohort was 18% (153/852). The five-year OS rate and MST of mPVI group were 47% and 57 months, whereas those of NmPVI group were 73% and 132 months, respectively. The median RFS time of the mPVI and NmPVI sub-groups were 10 months and 31 months, respectively. Both the OS and RFS were significantly more unfavorable in the mPVI group than the NmPVI group ($p<0.01$) (Fig.1).

Risk factors for mPVI

Table 1 presents the clinicopathological characteristics of mPVI and NmPVI group determined by univariate analyses. Univariate analyses showed that mPVI group had the following characteristics: age <60 years old, HBs-antigen (HBs-Ag)-positive, hepatitis C virus (HCV)-antibody

(HCV-Ab)-negative, ICGR15 <15 %, AFP $\geq$ 20 ng/ml, PIVKA-II $\geq$ 100 mAU/ml, multiple tumors, tumor size $\geq$ 5 cm, a confluent lesion, and poor differentiation. By multivariate analyses, the independent risk factors for mPVI were PIVKA-II $\geq$ 100 mAU/ml, tumor size $\geq$ 5 cm, a confluent lesion, and poor differentiation of the tumor (Table 2). These four factors were risk factors for mPVI. 852 patients were categorized into the following groups according to the number of these four risk factors: risk 0 if they had no risk factor (n=337); risk 1 if they had any one risk factor (n=235); risk 2 if they had any two risk factors (n=173); risk 3 if they had any three risk factors (n=91); risk 4 if they had all four risk factors (n=16). The positive rate of mPVI in the cases without these factors was 5.6% (19/337). Those in the cases with 1 factor, 2 factors, 3 factors, and all these 4 factors were 17.9% (42/235), 28.3% (49/173), 37.4% (34/91), and 43.8% (7/16), respectively (Table 3).

Factors related to the OS and RFS outcomes in patients with mPVI who had single tumor under 5 cm

The cases which had single tumor under 5 cm were 58 cases. Table 4 shows the factors that were found to influence the OS and RFS in the mPVI group. Univariate analyses revealed that the OS outcome was significantly related to HCV-Ab-positivity, platelets <100,000 /mm³, a serum albumin level <4.0 g/dl, ICGR15 $\geq$ 15 %, PIVKA-II $\geq$ 100 mAU/ml, NALR, and a positive surgical margin. These analyses also indicated that the RFS was significantly related to platelets <100,000 /mm³, serum albumin level <4.0 g/dl, ICGR15 $\geq$ 15 %, PIVKA-II $\geq$ 100 mAU/ml, NALR, and a positive surgical margin. Multivariate analyses indicated that serum albumin level <4.0 g/dl,

PIVKA-II ≥ 100 mAU/ml, NALR, and a positive surgical margin were independent unfavorable prognostic factors for OS, and that PIVKA-II ≥ 100 mAU/ml, NALR, and a positive surgical margin were independent unfavorable prognostic factors for RFS in the patients with mPVI.

Univariate and multivariate analyses showed that ALR was significantly favorable factor for both OS and RFS (Fig.2). While ALR was performed 40 cases (69%), NALR was performed 18 cases (31%). The 30-day and 90-day mortality of both ALR and NALR were 0% and 0%.

The patients who were performed ALR showed 2 pleural effusion (5%), 1 ascites (2.5%), 4 bile leakage (10%), and 1 wound infection (2.5%). Meanwhile, the patients who were performed NALR showed 1 pleural effusion (5.6%), 1 ascites (5.6%), 1 bile leakage (5.6%), and 2 wound infection (11.1%). Postoperative bleeding was nothing among the patients with or without ALR. No significant differences between ALR and NALR (Table 4). Median blood loss was 790 (36-2850) ml and median operative time was 360 (187-588) minutes in the patients with ALR. Those of the patients with NALR were 550 (50-4000) ml and 276 (171-445) minutes, respectively (Table 5).

Discussion

The results of our present study indicate that the risk factors for mPVI in HCC include PIVKA-II ≥ 100 mAU/ml, a maximum tumor size ≥ 5 cm, a confluent lesion, and poor differentiation of the lesions. The positive rate of mPVI in the cases with all these 4 factors was 43.8% (7/16). Among the patients with mPVI who had single tumor < 5 cm, multivariate analyses revealed that serum albumin level < 4.0 g/dl, PIVKA-II ≥ 100 mAU/ml, a positive surgical margin, and NALR were

independent unfavorable prognostic factors for OS and that PIVKA-II ≥ 100 mAU/ml, a positive surgical margin, and NALR were independent unfavorable prognostic factors for RFS in mPVI cases. ALR was significantly favorable factor for both OS and RFS. In these cases, mortality and morbidity rate were not significantly different between ALR and NALR.

Previous studies have reported an mPVI incidence ranging from 15-20% in resected HCC [8,15] which is consistent with our current finding of 18%. In terms of an underlying mechanism of PVI, Mitsunobu et al. have reported previously that the portal vein serves as an efferent vessel for HCC, whilst the hepatic artery is the feeding vessel. These authors also reported that the efferent vessels penetrating the capsule are the path of least resistance for tumor infiltration or expansion and that cancer cells invade efferent vessels by budding and expanding into the vascular cavity and then extending beyond the capsule to the portal vein branches [16].

It is reported that the risk factors for mPVI are larger tumors, a high PIVKA-II, and a macroscopic multinodular type of lesion [7,9,17]. We found in our current study that larger tumors (≥ 5 cm), a high PIVKA-II (≥ 100 mAU/ml), a confluent lesion, and poor differentiation were significantly predictive of mPVI. Shirabe *et al.* have reported that poor differentiation is a risk factor for mPVI by univariate analysis but not by multivariate analysis [18]. Adachi et al. reported that not only the size but also the histologic grades of HCC were the biggest risk factors for PVI [19]. Our current results are consistent with these previous reports. In general, the larger the tumor size the higher the histologic grade [20]. Meanwhile, HBs-Ag-positivity was found to be a significant risk factor for mPVI by univariate analysis in our current study. It has been shown that the tumor size

related HBV tends to be larger than that related to HCV [21, 22]. Therefore, both tumor differentiation and HBs-Ag are suggested to be associated with tumor size in HCC. Even if no portal venous invasion is detected by any image modality, it should be assumed that a HCC with these characteristics involves an mPVI.

One of the reason why the patients with HCC have unsatisfactory outcome is high incidence of intrahepatic recurrence [23], intrahepatic metastasis [24], and multicentric occurrence of a new tumor [25]. Intrahepatic recurrence occurs mainly in the early phase after liver resection, whereas multicentric occurrence occurs mainly in the later phase [26-28]. Previous reports showed that intrahepatic metastasis can occur via the portal venous system [29, 30]. The superiority of ALR for HCC is still controversial. Hasegawa et al. suggested that ALR improved both OS and RFS and also an independent favorable factor as well as the absence of microscopic vascular invasion in patients with HCC [31]. On the other hand, some reports suggested that there is no superiority of ALR to NALR relevant among the patients without MPVI [32, 33]. Kobayashi et al. suggested that ALR was superior to NALR for early intrahepatic recurrence by resecting tumor-bearing portal branches, but not for late recurrence [34]. Recently, Matsumoto et al showed ALR is significantly favorable factor for the patients of HCC with mPVI and MPVI compared with NALR [35]. The superiority of ALR for only the patients with mPVI is elusive.

Shirabe *et al.* reported that NALR is a significantly unfavorable prognostic factor in terms of disease free survival and tended to be a poor prognostic factor for cumulative survival in cases of HCC with mPVI [8]. With regard to other prognostic factors, a tumor size >3 cm and histologic

grade (Edmondson 3 or 4) [19], HCV Ab-positivity [9], and a high AFP [9] have been reported. In our current study, multivariate analyses showed that serum albumin level <4.0 g/dl, PIVKA-II ≥ 100 mAU/ml, a positive surgical margin, and NALR were independent unfavorable prognostic factors for OS in our patients with mPVI who had single tumor <5 cm. PIVKA-II ≥ 100 mAU/ml, a positive surgical margin, and NALR were found in our analysis to be independent unfavorable prognostic factors for RFS in our patients with mPVI who had single tumor <5 cm. Globally, the larger tumor is, the more frequent mPVI is. So, we investigated the factors related to OS and RFS in the patients with mPVI among the patients who had single and tumor size <5 cm. ALR was significantly favorable factor for both OS and RFS of the patients with mPVI. These results suggest that ALR possibly contributes to an improvement in prognosis in HCC patients who have the risk factors for mPVI with no detection of PVI by any image modality. Yamashita et al suggested that ALR for the patients with HCC who had PIVKA-II ≥ 100 mAU/ml or pathological vascular invasion and intrahepatic metastasis was significantly favorable for disease-free survival [36]. This is consistent with our report.

However, the number of patients with mPVI in this study was only 153 patients. This is the limitation in this study. Large studies such as multicenter study are necessary to establish the confirmative role of ALR for HCC with mPVI.

In conclusion, even if no portal venous invasion is detectable in HCC patients preoperatively, a PIVKA-II ≥ 100 mAU/ml, tumor size ≥ 5 cm, and a confluent lesion indicate a high risk of mPVI. ALR should be considered for the patients with these characteristics because it is a favorable

prognostic factor in these cases with mPVI.

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Figure captions

Fig.1

- (a) Overall survival curves for the study patients with or without microscopic portal vein invasion.
- (b) Relapse-free survival curves for the study patients with or without microscopic portal vein invasion.

Fig.2

- (a) Overall survival curves for patients with or without ALR for single HCC with mPVI under 5 cm
- (b) Relapse-free survival curves for patients with or without ALR for single HCC with mPVI under 5 cm

Table 1 Clinicopathological characteristics and risk factors for mPVI, clinicopathological characteristics by univariate analyses

Table 2 Clinicopathological characteristics and risk factors for mPVI, risk factors for mPVI by multivariate analyses

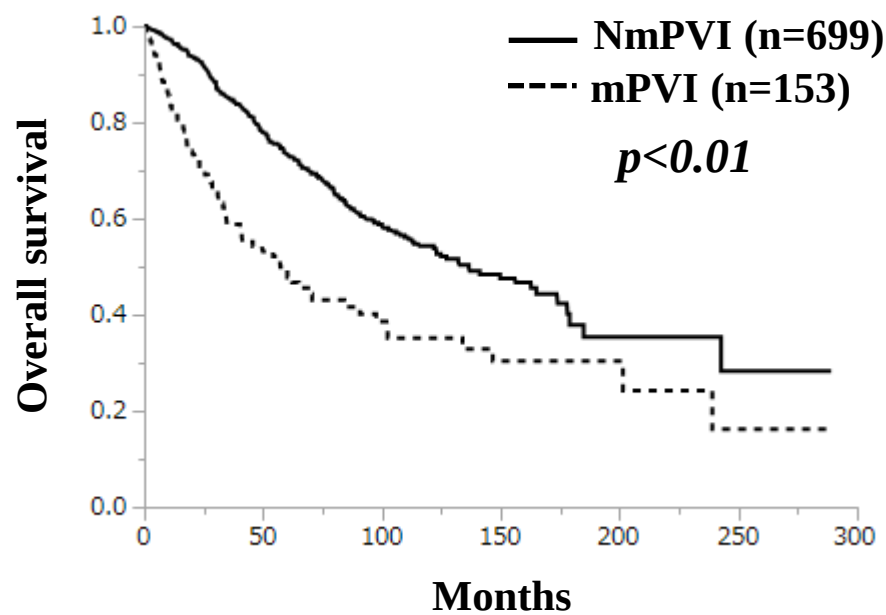
Table 3 Risk score and mPVI rates

**Table 4 Prognostic factors for survival and recurrence among the mPVI patients with a
single HCC which tumor size <5 cm**

Table 5 Surgical outcome of ALR and NALR

Fig. 1

(a)



(b)

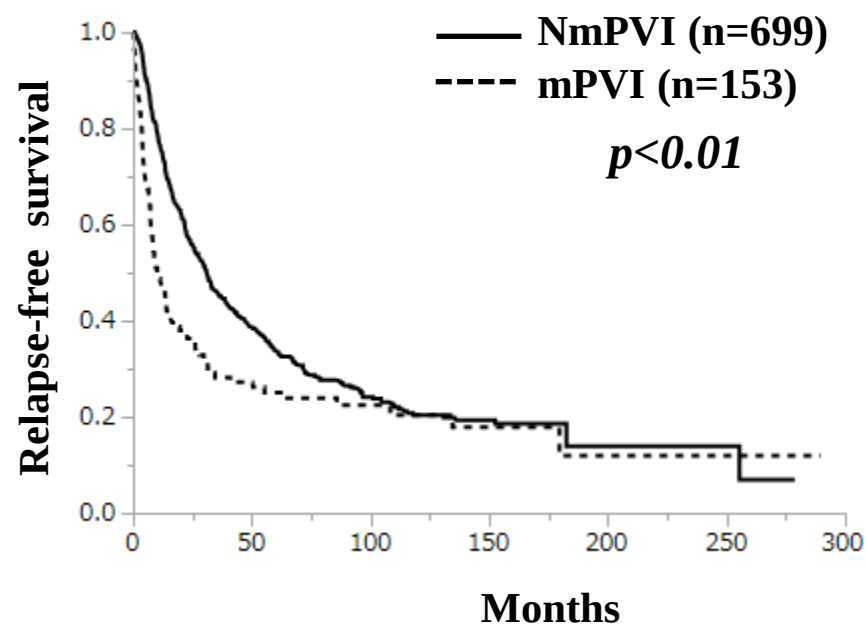
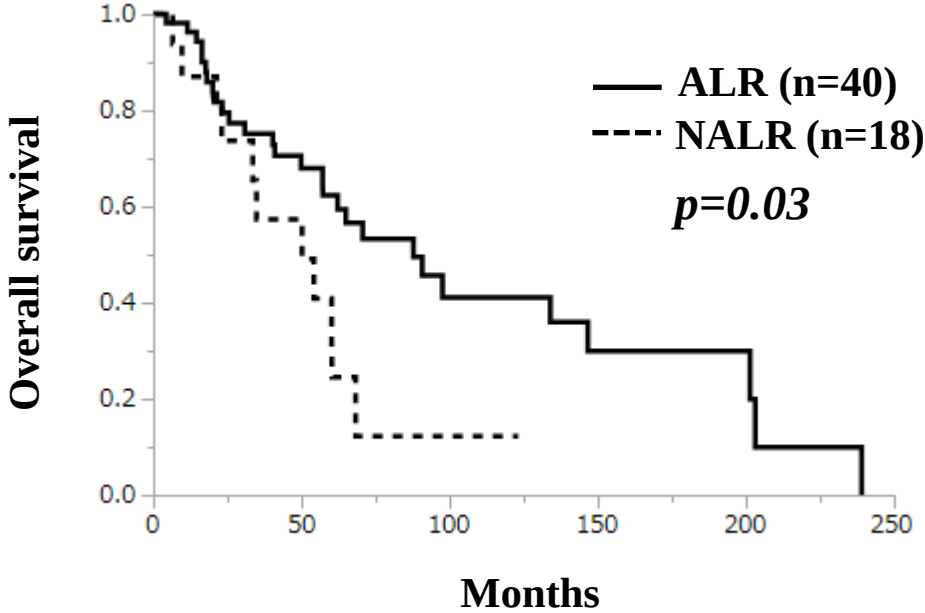


Fig.2

(a)



(b)

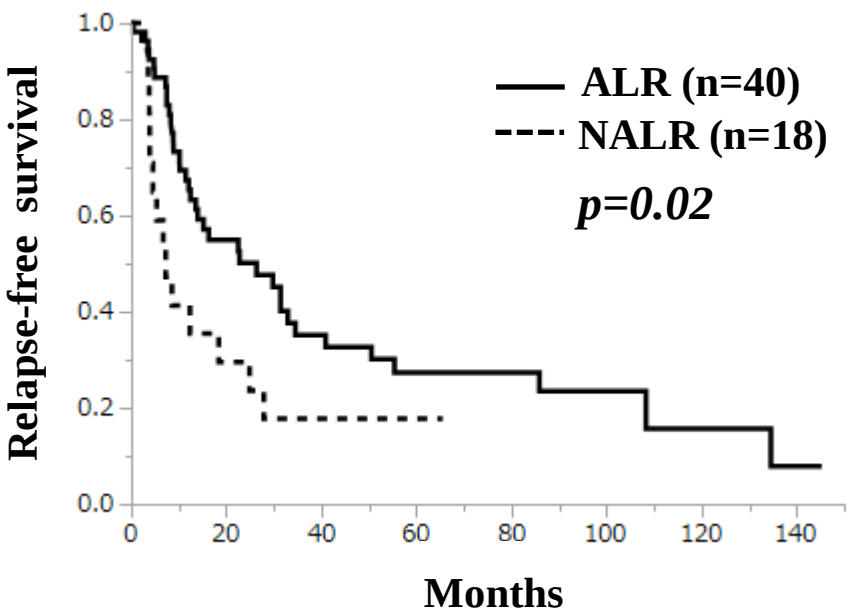


Table 1 Clinicopathological characteristics and risk factors for mPVI, clinicopathological characteristics by univariate analyses

Characteristics		mPVI (n=153)	Non-mPVI (n=699)	<i>p</i>
Epidemiology				
Age	<60	75 (49 %)	242 (35 %)	<0.01
	60 ≤	78 (51 %)	457 (65 %)	
Sex	male	121 (79 %)	570 (82 %)	0.48
	Female	32 (21 %)	129 (18 %)	
HBs-Ag	positive	83 (54 %)	237 (34 %)	<0.01
	Negative	70 (46 %)	462 (66 %)	
HCV-Ab	positive	41 (27 %)	288 (41 %)	<0.01
	Negative	112 (73 %)	411 (59 %)	
NBNC	yes	34 (22 %)	183 (26 %)	0.30
	No	119 (78 %)	516 (74 %)	
Biochemical Factors				
Platelets	< 100,000 /mm³	22 (14 %)	133 (19 %)	0.17
	100,000 /mm³ ≤	131 (86 %)	566 (81 %)	
Albumin	< 4.0 g/dl	76 (50 %)	307 (44 %)	0.19
	4.0 g/dl ≤	77 (50 %)	392 (56 %)	
Total bilirubin	1.5 mg/dl ≤	8 (5 %)	43 (6 %)	0.66
	< 1.5 mg/dl	145 (95 %)	656 (94 %)	
PT	< 70%	7 (5 %)	38 (5 %)	0.66
	70% ≤	146 (95 %)	661 (95 %)	
ICGR15	15% ≤	52 (34 %)	339 (48 %)	<0.01
	< 15%	101 (66 %)	360 (52 %)	
AFP	20 ng/ml ≤	95 (62 %)	315 (45 %)	<0.01
	< 20 ng/ml	58 (38 %)	384 (55 %)	
PIVKA-II	100 mAU/ml ≤	110 (72 %)	295 (42 %)	<0.01
	< 100 mAU/ml	43 (28 %)	404 (58 %)	
Tumor Factors				
Tumor number	multiple	63 (41 %)	198 (28 %)	<0.01
	Solitary	90 (59 %)	501 (72 %)	
Tumor size	5cm≤	86 (56 %)	217 (31 %)	<0.01
	<5cm	67 (44 %)	482 (69 %)	
Macroscopic classification				

	confluent type	37 (24 %)	90 (13 %)	<i><0.01</i>
	except confluent type	116 (76 %)	609 (87 %)	
Histological Factors				
Differentiation	poor	60 (39 %)	169 (24 %)	<i><0.01</i>
	well/moderate/others	93 (61 %)	530 (76 %)	
Cirrhosis	LF or LC	74 (48 %)	349 (50 %)	<i>0.72</i>
	CH or NL	79 (52 %)	350 (50 %)	

mPVI, microscopic portal venous invasion; HBs-Ag, HBs-antigen; HCV-Ab, HCV-antibody; NBNC, without HBV and HCV; PT, prothrombin time; ICGR15, indocyanin green retention rate at 15 min; AFP, alpha-fetoprotein; PIVKA-II, protein induced by vitamin K absence-II; LF, liver fibrosis; LC, liver cirrhosis; CH, chronic hepatitis; NL, normal liver; NS, non-significant.

Table 2 Clinicopathological characteristics and risk factors for mPVI, risk factors for mPVI by multivariate analyses

Risk factors	Odds ratio	95% CI	<i>p</i>
Age < 60	1.4619	0.9475-2.2556	0.08
HBs-Ag positive	1.5876	0.9753-2.5842	0.06
HCV-Ab negative	1.1342	0.6920-1.8589	0.61
ICGR15 < 15%	1.3943	0.9311-2.0879	0.10
AFP 20 ng/ml ≤	1.3085	0.8742-1.9588	0.19
PIVKA-II 100 mAU/ml ≤	2.7411	1.7755-4.2320	<0.01
Tumor number multiple	1.2245	0.8148-1.8402	0.32
Tumor size 5 cm ≤	1.6741	1.0797-2.5956	0.02
Confluent type	1.8537	1.1519-2.9831	0.01
Differentiation poor	1.5165	1.0016-2.2959	0.04

HBs-Ag, HBs-antigen; HCV-Ab, HCV-antibody; ICGR15, indocyanin green retention rate at 15 min; AFP, alpha-fetoprotein; PIVKA-II, protein induced by vitamin K absence-II; NS, non-significant.

Table 3 Risk score and mPVI rates

Risk factors	Risk score	mPVI rates
PIVKA-II ≥ 100 mAU/ml	0	5.6 %
Tumor size ≥ 5 cm	1	17.9 %
Confluent lesion	2	28.3 %
Poor differentiation	3	37.4 %
	4	43.8 %

Table 4 Prognostic factors for survival and recurrence among the mPVI patients with a single HCC which tumor size <5 cm

Characteristics	Overall Survival		Relapse-free survival	
	Univariate (<i>p</i>)	Multivariate (<i>p</i>) (hazard ratio) (95% CI)	Univariate (<i>p</i>)	Multivariate (<i>p</i>) (hazard ratio) (95% CI)
Epidemiology				
Age	0.67		0.42	
Sex	0.41		0.86	
HBs-Ag positive	0.35		0.70	
HCV-Ab positive	<0.01	0.74 (1.2277) (0.3548-4.2487)	0.91	
Biochemical Factors				
Platelets<100,000 /mm ³	0.03	0.62 (1.3525) (0.3971-4.6063)	0.03	0.91 (1.0528) (0.3919-7.8282)
Albumin <4.0 g/dl	<0.01	0.04 (3.6944) (1.0264-13.2980)	0.02	0.18 (1.6475) (0.7907-3.4323)
T-bil 1.5 mg/dl ≤	0.12		0.06	
PT <70 %	0.20		0.37	
ICGR15 15 %≤	0.04	0.97 (1.0214) (0.3337-3.1262)	0.03	0.54 (1.2656) (0.5912-2.7095)
AFP 20 ng/ml ≤	0.37		0.70	
PIVKA-II100mAU/ml ≤	<0.01	0.04 (5.0076) (1.0707-23.4216)	<0.01	0.04 (2.4640) (1.0102-6.0096)

Tumor Factors

Confluent lesion	0.07	0.63
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Surgical Factors

Non-anatomical resection	0.03	0.02
	(3.6199)	(3.0649)
	(1.1183-11.7178)	(1.1625-8.0809)

Histological Factors

Differentiation poor	0.73	0.73
Surgical margin positive	<0.01	<0.01
	(26.3310)	(3.9968)
	(5.4777-126.5724)	(1.3953-11.4492)
Cirrhosis (LF or LC)	0.24	0.86

HBs-Ag, HBs-antigen; HCV-Ab, HCV-antibody; T-bil, Total bilirubin; PT, prothrombin time; ICGR15, indocyanin green retention rate at 15 min; AFP, alpha-fetoprotein; PIVKA-II, protein induced by vitamin K absence-II; LF, liver fibrosis; LC, liver cirrhosis; NS, non-significant.

Table 5 Surgical outcome of ALR and NALR

	ALR (n=40)	NALR (n=18)	<i>p</i>
Median blood loss (range) ml	790 (36-2850)	550 (50-4000)	0.60
Median operative time (range) minutes	360 (187-588)	276 (171-445)	<0.01
Morbidity			
Pleural effusion	2 (5 %)	1 (5.6 %)	0.92
Ascites	1 (2.5 %)	1 (5.6 %)	0.55
Postoperative bleeding	0 (0 %)	0 (0 %)	1.00
Bile leakage	4 (10 %)	1 (5.6 %)	0.57
Wound infection	1 (2.5 %)	2 (11.1 %)	0.17
Mortality			
30-day	0 (0 %)	0 (0 %)	1.00
90-day	0 (0 %)	0 (0 %)	1.00

ALR, anatomical liver resection; NALR, Non-anatomical liver resection.