

Underlying histological activity of hepatitis Plays an Important Role for Tumor Recurrence After Curative Resection of Hepatocellular Carcinoma

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Background: Hepatocellular carcinoma (HCC) commonly develops in patients with chronic hepatitis. This situation is one of the reasons why intrahepatic recurrence frequently occurs even after curative resection. There are two different components of such recurrences, which occurs within 12 months (the early recurrence group) and at more than 12 months after resection (the late recurrence group). The present study was conducted to clarify the factors contributing to these different types of HCC recurrence.

Methods: Ninety seven patients who underwent curative resection for HCCs were followed for initial recurrence, and predictive factors of recurrence were examined.

Results: Early and late intrahepatic recurrences developed in 30 and 42 patients, respectively. In the former group, univariate analyses showed the serum AFP level (>100ng/ml, $P=0.045$), higher inflammatory activity (Grading) ($p=0.048$) and status of fibrosis (Staging) ($p=0.027$) in non-cancerous liver tissues to be significant risk factors, while the serum AFP level (>100ng/ml) was the only independent risk factor based on a multivariate analysis (RR: 2.78). In the latter group, only the presence of hyperplastic foci (HPF) was found to be a significant risk factor ($p=0.005$). Higher Grading tended to be linked to shorter disease-free survival time, although not significant. In the non-cancerous liver tissues with HPF, the level of Grading, Staging, and PCNA labeling index was significantly higher ($p=0.033$, 0.003 , 0.040 , respectively). **Conclusion:** Not only the tumor factors but also the underlying hepatic status including HPF, Grading, and Staging were significant risk factors for intrahepatic recurrence after curative resection for HCC.

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Keywords: Hepatocellular carcinoma; Early and late recurrence; HPF; Grading; Staging

Introduction

Hepatocellular carcinoma (HCC) is one of the common causes of cancer death in Asia. Hepatic resection has been established as a curative treatment for hepatocellular carcinoma. Nevertheless, the prognosis remains poor because postoperative recurrences frequently occur (50 - 60%).¹⁻³ Such recurrences could originate from the intrahepatic metastases of the primary HCC^{4,5} and the multicentric occurrence of new tumors in the postoperative liver remnant.⁶⁻⁸ These unique features might be due to underlying liver diseases such as chronic active hepatitis with hepatitis B and C viral infection. There were several reports that HCC development

was significantly linked to underlying liver diseases.^{6,9,10} Shuto et al.¹¹ suggested that hyperplastic foci (HPF), which are defined as a focal hepatic parenchymal lesion where the hepatocytes have dense and small nuclei as well as eosinophilic cytoplasm, was an important predictor of recurrence of HCC after hepatic resection. Therefore, not only HCC tumor factors but also the underlying liver status should be carefully examined in order to select the optimal treatments and also better predict tumor recurrence after curative resection.

The present study was conducted to clarify the risk factors associated with intrahepatic recurrences in HCC patients who underwent curative hepatic resection by investigating tumor factors, op-

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erative factors, and patient characterization giving special attention to the underlying status of non-cancerous liver tissues.

Patients and methods

Patients and follow up

Ninety-seven patients underwent curative resection for HCC was closely followed up for more than 12 months after resection at Department of Transplant and Digestive Surgery, Nagasaki University Graduate School of Biomedical Sciences. They included 81 males and 16 females, with a mean age of 61 years old (range: 20-80). Twenty-four patients (24.7%) were positive for hepatitis B virus surface antigen (HBV) only, 48 (49.5%) for hepatitis C virus anti body (HCV) only, 4 for both (4.1%), and 21 were negative for both. The serum chemistry and the serum levels of alpha-fetoprotein (AFP) were measured monthly, and ultrasonography as well as computed tomography scan were performed at a 3-month interval. Magnetic resonance imaging, angiography and liver biopsies were also performed to make a definitive diagnosis of recurrence, if needed.

Pathological examination

Resected liver specimens were fixed in 10% formaldehyde solution. After a macroscopic examination, a slice containing the maximum tumor diameter and other slices of lesions suspicious for metastases or venous invasion were embedded in paraffin. Tissue sections were stained with hematoxylin and eosin (H & E). According to the classification of Primary Liver Cancer by the

Liver Cancer Study Group of Japan¹², the histological findings of each tumor were examined regarding the histological stage, the degrees of portal venous invasion and hepatic venous invasion as well as the presence of intrahepatic metastases.

Inflammatory activity (Grading), fibrotic status (Staging) and hyperplastic foci (HPF) in non-cancerous liver tissues

To classify the degree of hepatic inflammation (hepatitic activity), we used the Histological Activity Index (HAI) score as described by Knodell et al.¹³ Based on their criteria, the H & E stained specimens of the non-cancerous liver tissues were examined and classified into four categories according to Desmet's method¹⁴; G0 (normal, or minimal chronic hepatitis), G1 (mild chronic hepatitis), G2 (moderate chronic hepatitis), and G3 (severe chronic hepatitis). To classify fibrosis, Scheuer's method¹⁵ were used. The stage of fibrosis was categorized as F0 (non-fibrosis), F1 (enlarged, fibrotic portal tracts), F2 (fibrosis in periportal or portal-portal septa, but an intact architecture), F3 (fibrosis with architectural distortion, but not obvious cirrhosis) and F4 (probable or definite cirrhosis). Figure 1 shows a liver with inflammatory and fibrotic change (G2 and F3).

Hyperplastic foci (HPF) were defined as a focal hepatic parenchymal lesion where the hepatocytes have dense and small nuclei as well as eosinophilic cytoplasm^{11,16} (Figure 2). The presence of HPF was examined in H&E-stained specimens of non-cancerous liver tissues. The liver tissue with at least one lesion of hyperplastic cells was defined as positive for HPF. The pathological findings were independently judged by two pathologists (K.K. and S.O.).

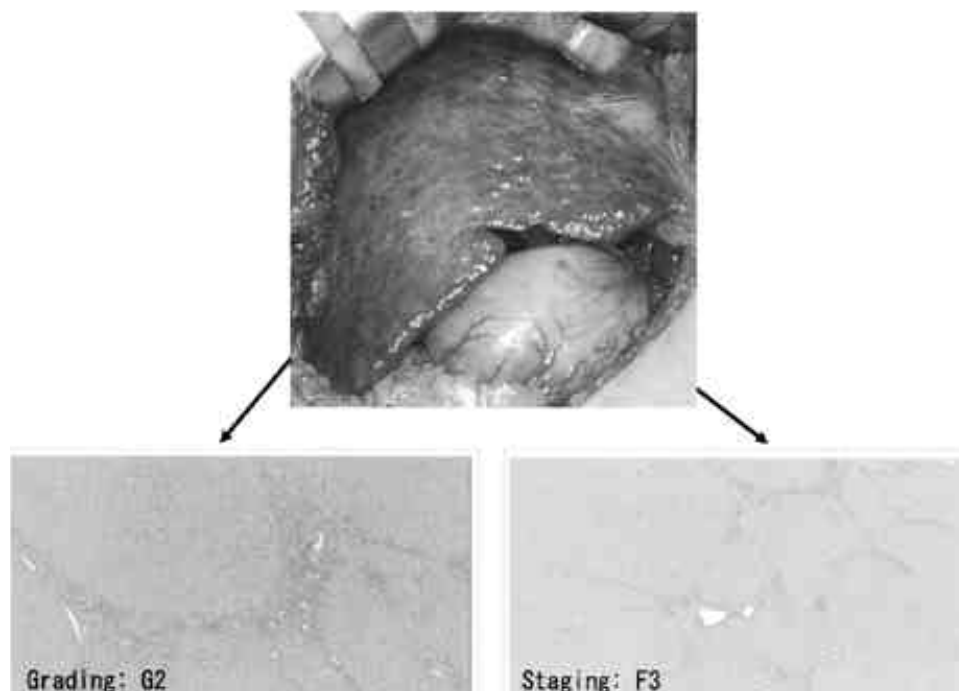


Figure 1. The liver with inflammatory and fibrotic change (G2 and F3).

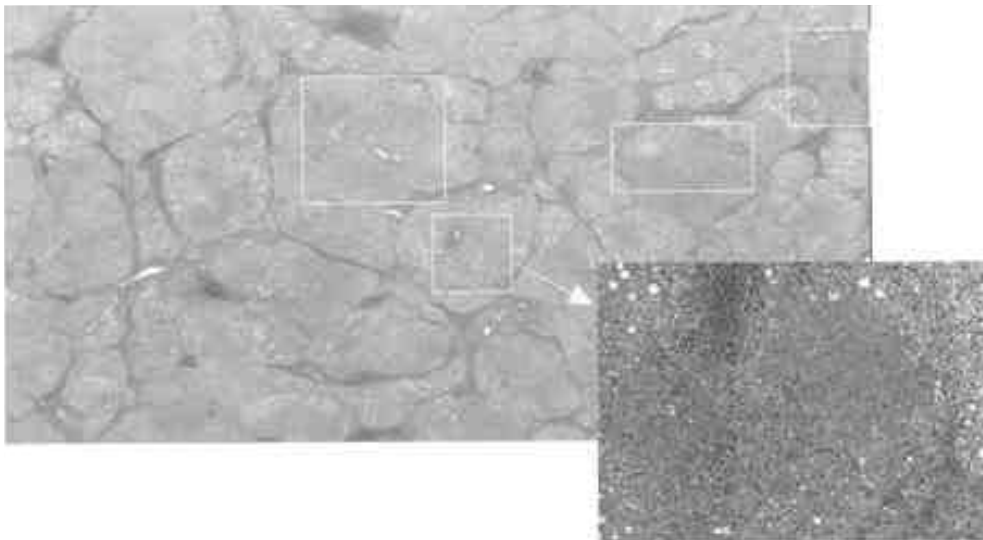


Figure 2. Hyperplastic foci is defined as a focal hepatic parenchymal lesion where the hepatocytes have dense and small nuclei as well as eosinophilic cytoplasm (in boxes) (x200, x400)

Proliferating cell nuclear antigen labeling index (PCNA L.I.)

The labeling index of PCNA was examined according to a method described in a previous report¹⁷, which was determined by the ratio of PCNA-positive hepatocytes per 1000 hepatocytes.

Statistical analyses

Possible risk factors for early recurrence were compared using the chi-square test with Yates' correction (or Fisher's exact test where appropriate) for nominal variables and/or unpaired Student *t* test for continuous variables. Risk factors in either the chi-square or Student *t* test for early recurrence were consecutively analyzed based on multivariate logistic regression models. Possible risk factors for late recurrence were entered into Cox's multivariate proportional hazard model. The cumulative recurrence-free survival curves were analyzed using the Kaplan-Meier method and then were compared with the log rank test. A *p* value of less than 0.05 was considered to be statistically significant.

Results

Figure 3 shows the cumulative recurrence-free survival curve among 97 patients in the present study. Seventy-two of them (74.2 %) developed intrahepatic recurrence while the remaining 25 had no recurrence during the follow-up period. Two different components were observed in the recurrence-free survival curve. The first component was rapidly decreased within 12 months after curative hepatectomy, and these patients were classified as the early recurrence group. The second component was slowly decreased thereafter, and this group was classified as the late recurrence group.

Five patients (5.2 %) developed extra-hepatic recurrence, 7 (7.2

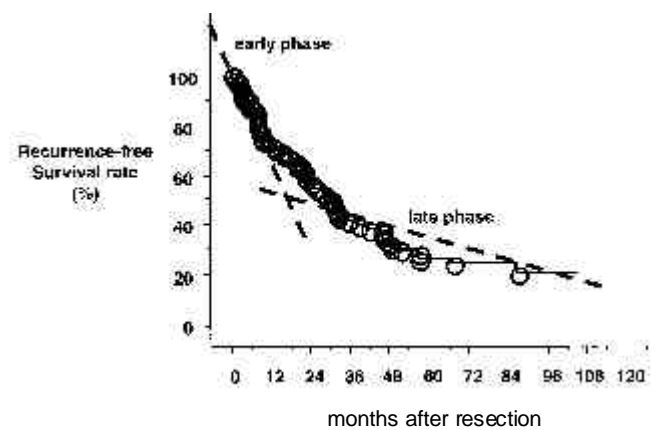


Figure 3. The cumulative recurrence-free survival curve after curative resection of HCC. There were two different components as follows; 1) rapid decrease within 12 months and 2) slow decrease more than 12 months.

%) underwent a re-resection, and 27 (27.8 %) received chemolipiodolization. The 1-, 3-, and 5-year recurrence-free survival rates were 69 %, 38 % and 23 %, respectively. The median recurrence-free survival time was 30.7 months (range: 4.5 - 106.5 months). Preoperative patient characterization, tumor factors, and operative factors associated with HCC recurrences are shown in Table 1. The early and late recurrences developed in 30 and 42 patients, respectively.

Risk factors for early intrahepatic recurrence (Tables 1-3)

Thirty of 72 patients with recurrent HCCs (41.7 %) developed early intrahepatic recurrence within 12 months after a curative resection. The median recurrence-free survival time in the early phase was 5.9 months. Higher Grading (G2+G3; *p*=0.048), Staging

(F3+F4; $p=0.027$), and serum AFP levels ($>100\text{ng/ml}$; $p=0.045$) were significant risk factors based on a univariate analysis, whereas no operative factors were found to be significant. Eleven of 30 patients suffered from the early recurrence had HPF in the

non-cancerous liver tissues. The presence of HPF was not significantly related to the early recurrence. A multivariate analysis demonstrated only the serum AFP levels to be independently significant (RR: 2.78).

Table 1. Differences between early, late, or no recurrence

Characteristics	Categorization	Early recurrence (n=30)	Late recurrence (n=42)	No recurrence (n=25)
<i>(Host factors)</i>				
Gender	M	26	34	21
	F	4	8	4
Age (yrs)	62	19	19	12
	> 62	11	23	13
Virus	B	8	9	7
	B+C	1	2	1
	C	15	22	11
	None	6	9	6
ICGR15 (%)	10.0	10	11	10
	> 10.0	20	30	15
PT (%)	91.0	18	21	11
	> 91.0	12	20	13
Alb (g/dl)	3.5	23	34	22
	> 3.5	7	7	3
T.Bil (mg/dl)	1.0	24	35	21
	> 1.0	6	7	4
ALT (IU/L)	80.0	23	34	22
	> 80.0	7	8	3
Plt ($\times 10^9/\text{ml}$)	10.0	9	10	6
	> 10.0	21	32	19
staging	F0+1+2	10	23	17
grading	F3+4	20	19	8
	G0+1	10	20	18
HPF	G2+3	20	22	7
	(-)	19	21	20
	(+)	11	21	5
<i>(Tumor factors)</i>				
Tumor differentiation	well	4	3	3
	moderate	20	32	20
	poorly	2	4	1
	necrosis	4	3	1
Tumor diameter (cm)	3.0	11	18	9
	> 3.0	19	24	16
venous invasion or satellite lesion	(-)	13	23	19
	(+)	17	19	6
AFP (ng/dl)	100	18	33	21
	> 100	12	9	4
<i>(Operative factors)</i>				
Type of resection	subsegmentectomy or less	16	13	11
	segmentectomy	4	14	9
	lobectomy or more	10	15	5
surgical margin (cm)	1.0	14	25	6
	> 1.0	16	17	19
intraoperative blood loss (g)	1300	12	20	18
	> 1300	18	22	7

Table 2. Univariate analysis for early recurrence

Characteristics	Categorization	Chi-square	p-value
<i>(Host factors)</i>			
Gender	M / F	0.315	0.7691
Age (yrs)	62 / > 62	2.416	0.1311
Virus	HCV / Others	0.005	0.9999
ICGR15 (%)	10.0 / > 10.0	0.022	0.9999
PT (%)	91.0 / >91.0	0.955	0.3809
Alb (g/dl)	3.5 / > 3.5	0.429	0.5569
T.Bil (mg/dl)	1.0 / > 1.0	0.184	0.7738
ALT (IU/L)	80.0 / >80.0	0.656	0.4130
Plt (x10 ⁴)	10.0 / > 10.0	0.406	0.6169
Staging*	F0+1+2 / F3+4	5.768	0.0271
Grading*	G0+1 / G2+3	4.532	0.0476
HPF	Negative / Positive	0.040	0.9999
<i>(Tumor factors)</i>			
Tumor differentiation	well+moderate / poorly	0.0020	0.9999
Tumor diameter (cm)	3.0 / > 3.0	0.115	0.8237
venous invasion	Negative / Positive	3.161	0.0822
AFP* (ng/ml)	100 / > 100	4.595	0.0445
<i>(Operative factors)</i>			
Type of resection	less than segmentectomy / lobectomy or more	0.118	0.8133
surgical margin (cm)	1.0 / > 1.0	0.001	0.9999
intraoperative blood loss (g)	1300 / > 1300	2.318	0.1869

* significant factor

Table 3. Multivariate analysis for early recurrence

variables	Risk ratio	95% confidence interval	p-value
AFP* (ng/ml)	2.779	1.016-7.600	0.0464
Grading	0.472	0.166-1.338	0.1579
Staging	0.51	0.183-1.426	0.1995

* significant factor

Risk factors for late intrahepatic recurrence

Forty-two of 72 patients with recurrent HCCs (58.3 %) developed late intrahepatic recurrence and the median recurrence-free survival time was 46.1 months. Regarding the cumulative recurrence-free survival, patients with higher grading (G2+G3) tended to have a shorter recurrence-free survival time, although the difference was not statistically significant (Figure 4). On the other hand, Staging in non-cancerous liver tissues did not affect the late recur-

rence (Figure 4). Twenty-one of 42 patients suffered from the late recurrence had HPF in the non-cancerous liver tissues. The presence of HPF was a significant risk factor for the late recurrence (Table 4, Figure 4), while neither operative factors nor tumor factors were not significant risk factors for the late recurrence (Table 4). In addition, HPF-positive livers demonstrated not only higher Grading and Staging but also higher score of PCNA L.I. than those in HPF-negative livers (Figure 5).

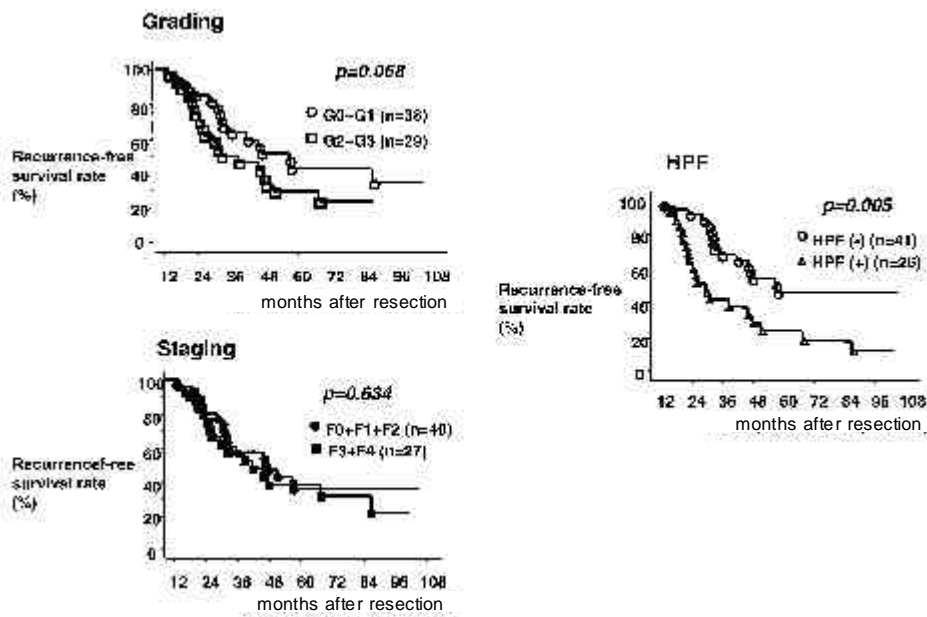


Figure 4. Relationship of recurrence-free survival time with Grading, Staging, and HPF. The presence of HPF was significantly related to shorter recurrence-free survival time. Higher Grading (G2+G3) tended to be associated with shorter recurrence-free survival time, whereas Staging was not associated.

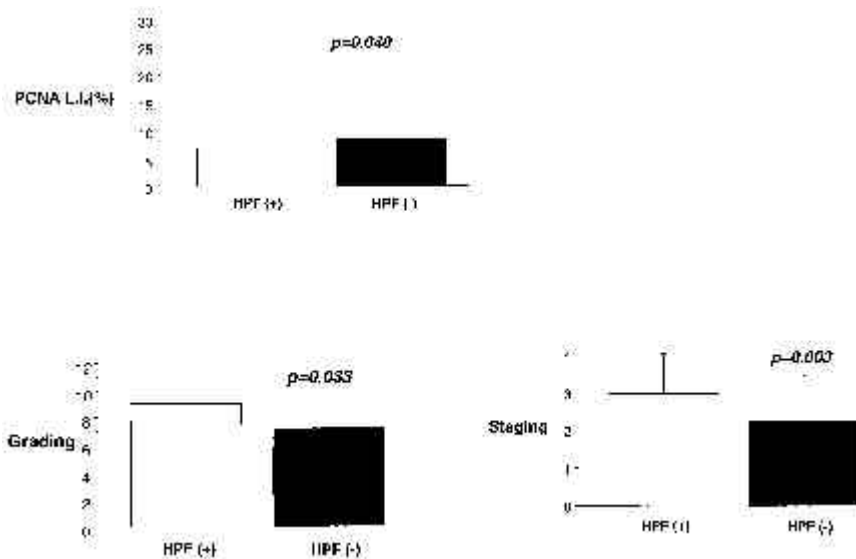


Figure 5. Relationship between HPF and Grading, Staging, PCNA L.I. HPF is significantly associated with higher Grading, Staging and PCNA L.I.

Table 4. Analysis for late recurrence by Cox's proportional hazard model

Characteristics	categorization	Hazrd ratio	95% confidence interval	p-value
<i>(Host factors)</i>				
Gender	M / F	1.000	0.438-2.285	0.9970
Age (yrs)	62 / > 62	1.090	0.566-2.100	0.7973
Virus	C / others	1.656	0.699-3.923	0.2520
Staging	F0+1+2 / F3+4	0.852	0.441-1.467	0.6346
Grading	G0+1 / G2+3	0.611	0.316-1.180	0.1425
HPF*	(-) / (+)	2.611	1.346-5.067	0.0045
ICGR15 (%)	10.0 / > 10.0	1.507	0.721-3.147	0.2753
PT (%)	91.0 / > 91.0	0.633	0.320-1.251	0.1885
Alb (g/dl)	3.5/ > 3.5	0.629	0.240-1.647	0.3449
T.Bil (mg/dl)	1.0 / > 1.0	1.288	0.534-3.109	0.5733
ALT (IU/l)	80.0 / > 80.0	1.365	0.595-3.130	0.4620
Plt (x10 ⁴ / μl)	10.0 / > 10.0	0.694	0.322-1.494	0.3501
<i>(Tumor factors)</i>				
Tumor differentiation	well+moderately / poorly	0.4430	0.097-2.021	0.2929
Tumor diameter (cm)	3.0 / > 3.0	1.162	0.603-2.238	0.6531
fc	(-) / (+)	0.683	0.282-1.655	0.3981
fc-inf	(-) / (+)	1.019	0.466-2.226	0.9629
venous invasion	(-) / (+)	1.650	0.852-3.195	0.1373
AFP (ng/ml)	100 / > 100	0.955	0.417-2.189	0.9141
<i>(Operative factors)</i>				
Type of operation ^{a)}	A+B/C	1.657	0.737-3.727	0.2219
surgical margin (cm)	(-) / (+)	1.845	0.949-3.587	0.0708
Intraoperative blood loss (g)	1300 / > 1300	1.831	0.944-3.552	0.0735

a) A: subsegmentectomy or less; B: segmentectomy; C: lobectomy or more.

*significant factor

Discussion

In the present study, the recurrence-free survival curve after curative resection for HCC had different components including the early recurrence within 12 months after resection and late recurrence after more than 12 months. This finding was consistent with the report by Poon et al.⁴ In the early recurrence group, a multivariate analysis revealed that the significant risk factor was higher serum AFP level (>100ng/ml). This finding suggests that tumor factors such as malignant potential of HCC cells are one of the important risk factors for the early recurrence.¹⁸⁻²⁰ In addition, univariate analyses in the risk factors of early recurrence also showed higher Grading and Staging of non-cancerous liver tissues

to be significant risk factors, suggesting that higher hepatic activity also enhanced early intrahepatic recurrence.⁶ This finding also suggests that one of the mechanisms for early recurrence is due to metachronous occurrence of new tumors (multicentric origin, referred to as MO). However, the rate of intrahepatic recurrence due to MO is not so high (14 - 25%).^{17,21} Therefore, high incidence of early recurrence in the active hepatitis group (G2+G3, F3+F4) compared to the other group (G0+G1, F1+F2) could not be explained by the MO-mechanism alone. It was previously reported that the expression of vascular adhesion molecules including endothelial leukocyte adhesion molecule-1 (ELAM-1), intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 and CD-44 in the hepatocytes and/or hepatic sinusoidal lining cells

was up-regulated in chronic active hepatitis.^{22,23} These adhesion molecules, especially ELAM-1, were reported to mediate the adhesion of HepG2 cells and the serum ICAM-1 levels also increased after a hepatectomy.²³ The up-regulation of adhesion molecules and hepatic activity could enhance early intrahepatic metastasis from primary HCCs. Adachi et al.¹⁷ reported that hepatic resection especially in the active hepatitis group might give rise to various grades of impaired immunity. If HCC cells were spread in the remnant liver during and/or after resection, it would be easy for them to survive and proliferate in the liver of patients with such an impaired immunity. Taking together, early intrahepatic recurrence after curative resection of HCCs seems to be associated with not only primary tumor factors but also underlying hepatic activity.

On the other hand, the significant risk factor for late recurrence in the present study was only the underlying hepatic status such as the presence of HPF, but neither primary tumor factors nor operative factors. The livers with HPF had higher hepatic activity (higher Grading, and/or Staging) and higher scores of PCNA L.I. than HPF-negative ones. Hyperplastic foci are analogous to parts of adenomatous hyperplasias (AHs) or early HCCs.¹¹ Wakasa et al.²⁴ reported that the proliferative activity of HPF, as expressed according to the PCNA L.I., is almost the same as that of AHs and early HCCs. They also reported that HPF-positive livers had a higher hepatic activity and HPF lesions reflected the risk of multicentric hepato-carcinogenesis. Terao et al.⁹ and Koike et al.¹⁰ reported that HCC development was significantly linked to underlying liver diseases with a high degree of DNA synthesis, suggesting that inflammatory liver tissues has a potential to develop HCCs. Therefore, it is possible that HPF itself may be one of the precancerous lesions in multicentric carcinogenesis.

In conclusions, not only the tumor factors but also the underlying hepatic status including Grading, Staging, and the presence of HPF were significant risk factors for the intrahepatic recurrence after curative resection for HCC. To achieve better outcome in HCC patients after curative resection, anti-hepatitis treatments as well as anti-tumor treatments during pre- and post-operative phase should be established.

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