HotStart Taq Master Mix kit (Qiagen, Hilden, Germany) and primers that have been previously described [24]. Polymerase chain reaction (PCR) was initiated with a denaturation step at 95 °C for 15 min, followed by 45 cycles at 94 °C for 1 min, 45 °C for 1 min, and 72 °C for 3 min, and subsequent extension for 7 min. PCR products were resolved by agarose gel electrophoresis, purified using the QIA quick PCR purification kit (Qiagen), and directly sequenced using a Big Dye Terminator v3.1 Cycle Sequencing kit (Applied Biosystems, Tokyo, Japan). The sequences were determined using an ABI PRISM 310 Genetic Analyzer (Applied Biosystems).

As described previously, the double wild-type (DW-type) amino acid pattern was defined as the presence of arginine at residue 70 (wild-type) and leucine at residue 91 (wild-type) [19].

IFN treatment

Depending on whether IFN was administered, the patients were divided into the IFN (76%) and non-IFN groups (24%) (Fig. 1). Patients who received IFN monotherapy during follow-up were divided into two subgroups: the sustained virological response (SVR) group, including patients who tested negative for HCV RNA at 24 weeks after completion of therapy, and non-SVR group (Fig. 1). Of the 275 patients in the IFN group, 73 (26.5%) achieved SVR.

Follow-up and diagnosis of cirrhosis and HCC

Clinical assessments were performed at least once every month during IFN treatment and every 3–6 months after the treatment. During follow-up, abdominal US was performed every 3–6 months to determine whether HCC had developed (Fig. 1). If necessary, additional procedures like CT, MRI, abdominal angiography, and US-guided tumor biopsy were performed to confirm HCC development. We also evaluated whether cirrhosis had developed in non-cirrhotic patients (F0–F2 stage). Cirrhosis was diagnosed according to the criteria of cirrhosis as described previously [25,26]. The follow-up period was the duration from the initial liver biopsy to HCC diagnosis or the last follow-up visit. For non-cirrhotic patients, this was the duration from the start point to cirrhosis diagnosis.

Statistical analysis

The χ^2 test was used to compare categorical variables, and Student's t test to compare continuous variables related to background characteristics among groups. Continuous variables were expressed as mean ± standard deviation. The cumulative incidence of HCC and cirrhosis was calculated using the Kaplan–Meier method and evaluated using the Breslow–Gehan–Wilcoxon test. Multivariate analysis was performed using the Cox proportional-hazards model or multiple logistic regression analysis. The Cochran–Armitage trend test was used for analyzing the association between the prevalence of mutation and subject age. Statistical significance was defined as $p < 0.05$.

Results

Cumulative HCC incidence

During follow-up (median duration, 121 months; range, 8–257 months), 82 (22.7%) patients developed HCC [HCC group; 13 of 197 (6.6%) from F0–F1, 18 of 59 (30.5%) from F2, 23 of 52 (44.2%) from F3, and 28 of 53 (52.8%) from F4 stage at entry] and 279 (77.3%) did not (non-HCC group). The cumulative HCC incidence at 5, 10, and 15 years of follow-up was 9.5%, 22.9%, and 30.9%, respectively.

Core nucleotide sequences

The core nucleotide sequence was determined for 297 of 361 (82.3%) patients. In the entire patient group, the proportions of DW-type and non-DW-type patterns were 22% and 60%, respectively (Table 1).

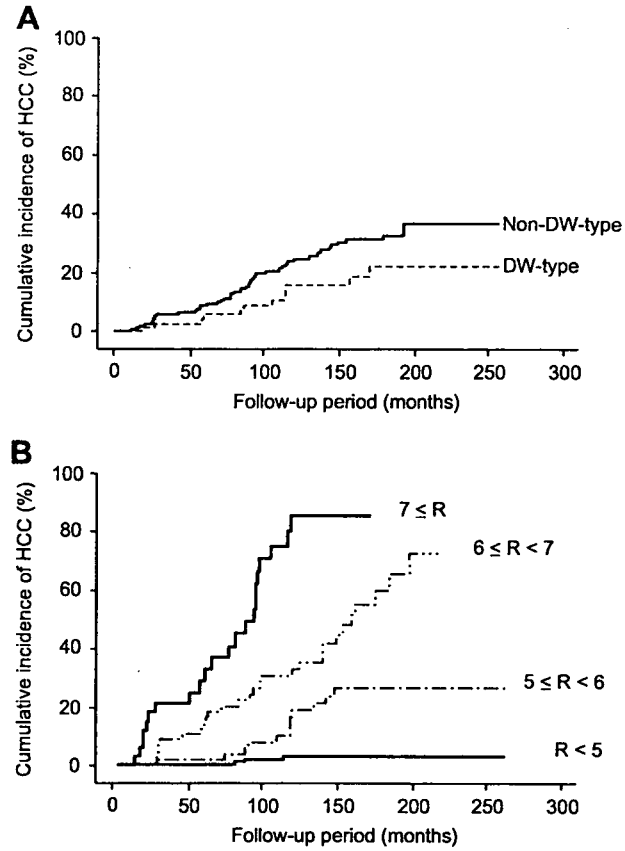

Fig. 2. Cumulative incidence of hepatocellular carcinoma (HCC) in hepatitis C genotype 1-infected patients. (A) Comparison between patients with double wild-type (DW-type: arginine, residue 70; leucine, residue 91) ($n = 81$) and non-DW-type ($n = 216$) amino acids in the core region ($p = 0.06$). (B) Comparison based on risk score (R) calculated using independent variables for HCC risk ($p < 0.0001$).

The core nucleotide sequence could not be determined for 64 patients because their samples showed significantly lower levels of the HCV core protein than those obtained from the 297 patients in whom the core sequence could be detected (119 vs. 217 pg/mL; $p = 0.0083$). There was no significant difference between the other variables shown in Table 1.

Cumulative HCC incidence according to core amino acid mutations

During follow-up, 12 of 81 (14.8%) patients with the DW-type pattern and 52 of 216 (24.1%) patients with the non-DW-type pattern developed HCC. Cumulative HCC incidence was 6.8% and 11% at 5 years, 19.1% and 27.7% at 10 years, and 26.6% and 38% at 15 years in the DW-type and non-DW-type groups, respectively. Cumulative HCC incidence in the DW-type group tended to be lower than that in the non-DW-type group ($p = 0.06$; Fig. 2A).

Predictive factors associated with HCC development

Potential predictive factors associated with HCC development are shown in Table 1. Univariate analysis revealed 10 parameters correlating with HCC development (Table 1). Multivariate analy-

Table 2. Factors associated with hepatocellular carcinoma development in hepatitis C genotype 1-infected patients, identified by multivariate analysis using the Cox proportional-hazards model.

Factor*	Category	Risk ratio (95% CI)	*p* value
Gender	Male	3.97 (2.05–7.63)	<0.0001
	Female	1.0	
Age (years)	⩾50	2.08 (1.01–4.33)	0.049
	<50	1.0	
Staging of fibrosis	⩾2	5.75 (2.68–12.35)	<0.0001
	<2	1.0	
IFN treatment and response	Absence of SVR	10.0 (2.29–43.48)	0.002
	SVR	1.0	
AST (IU/L)	>90	2.08 (1.20–3.62)	0.009
	⩽90	1.0	
AST/ALT	⩾0.8	2.21 (1.24–3.97)	0.007
	<0.8	1.0	
Amino acid pattern	Non-DW	1.96 (1.02–3.76)	0.04
	DW	1.0	

CI, confidence intervals; DW, double wild (arginine at residue 70 and leucine at residue 91 in the core region).
*Significant factors are shown.

sis with the Cox proportional-hazards model showed that the following seven independent parameters were significantly associated with HCC development: male gender ($p < 0.0001$), age ⩾ 50 years ($p = 0.049$), fibrosis ⩾ F2 ($p < 0.0001$), absence of SVR ($p = 0.002$), aspartate aminotransferase (AST) level > 90 IU/L ($p = 0.009$), AST/alanine aminotransferase (ALT) ratio ⩾ 0.8 ($p < 0.007$), and non-DW-type pattern in the core region ($p = 0.04$) (Table 2).

Prediction of HCC development based on risk score

Using the predictive variables from the previous step (Table 2), the risk score (R) for HCC development was calculated from the beta coefficients derived from the Cox proportional-hazards model as follows: $R = 0.671 \times$ (non-DW-type) $+ 2.307 \times$ (absence of SVR) $+ 0.733 \times$ (AST > 90 IU/L) $+ 0.733 \times$ (age ⩾ 50 years) $+ 1.752 \times$ (staging of fibrosis ⩾ 2) $+ 1.378 \times$ (male) $+ 0.795 \times$ (AST/ALT ⩾ 0.8) (each variable: yes = 1, no = 0). Fig. 2B shows the cumulative HCC incidence of four subgroups categorized by risk score, and the RR of each group is shown in Table 3. The cumulative HCC incidence increased with the risk score: from highest to lowest it was 84.7%, 35.1%, 18.5%, and 3.0% at 10 years.

Cumulative HCC incidence according to IFN treatment and response

During follow-up, 4 (5.5%) patients in the SVR, 55 (27.2%) in the non-SVR, and 23 (26.7%) in the non-IFN groups developed HCC; cumulative HCC incidence was 0%, 11.3%, and 13.2%, respectively, at 5 years; 7.8%, 25.6%, and 27.3%, respectively, at 10 years; and 7.8%, 36.5%, and 35.5%, respectively, at 15 years. Moreover, cumulative HCC incidence was significantly lower in the SVR group than other groups ($p < 0.001$; Fig. 3).

Table 3. Relative risk of HCC development based on risk score, using the Cox proportional-hazards model.

Score (R)	Risk ratio (95% CI)	*p* value
$R < 5$	1	
$5 \leqslant R < 6$	9.22 (2.60–32.7)	0.0006
$6 \leqslant R < 7$	26.9 (8.15–89.0)	<0.0001
$7 \leqslant R$	88.3 (25.8–302)	<0.0001

CI, confidence intervals.

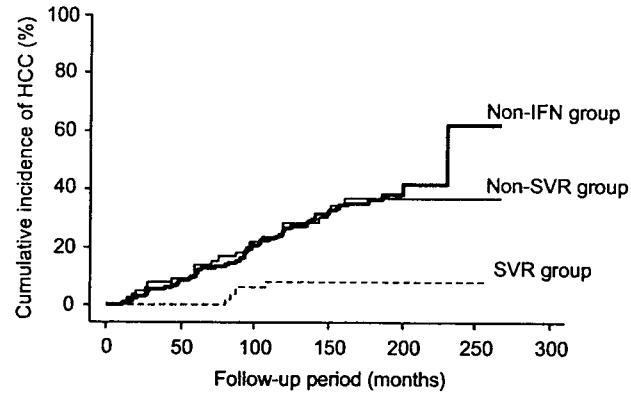

Fig. 3. Cumulative incidence of hepatocellular carcinoma (HCC). Comparison between the sustained virological response (SVR) ($n = 73$), non-SVR ($n = 202$), and non-interferon (IFN) ($n = 86$) groups ($p = 0.002$).

Analysis of SVR-associated factors

Compared to those in the non-IFN group, patients in the IFN group were younger (49 years vs. 54 years, $p = 0.003$), had higher aminotransferase levels (AST, 93 vs. 68 IU/L, $p = 0.001$; ALT, 137 vs. 87 IU/L, $p < 0.0001$) and lower core protein levels (183 vs. 263 pg/mL, $p = 0.01$). Table 4 shows baseline characteristics of patients according to interferon response. Univariate analysis revealed six SVR-associated parameters, whereas multiple logistic regression analysis revealed two independent significant predictors of SVR: AST/ALT ratio of <0.8 [$p = 0.005$; odds ratio (OR), 3.09; 95% confidence interval (CI), 1.40–6.82] and core protein level of <200 pg/mL [$p < 0.0001$; OR, 70.94; 95% CI, 9.56–526.2]. However, both univariate ($p = 0.64$) and multivariate analyses (data not shown) showed that the DW-type pattern in the core region was not associated with SVR.

Table 4. Baseline characteristics of patients according to interferon response.

Nature of the Regime	SVR $n = 73$	Non-SVR $n = 202$	*p* value
Gender (Male/Female)	47/26	126/76	0.76
Age (years)	46.6 ± 13.3	50.5 ± 11.5	0.02
BMI (kg/m^2)	22.7 ± 2.8	23.2 ± 3.0	0.24
Staging of fibrosis: (F0-1/F2/F3/F4)	45/12/9/7	104/34/34/30	0.42
Laboratory data			
AST (IU/L)	79 ± 56	97 ± 69	0.048
ALT (IU/L)	132 ± 92	139±100	0.60
AST/ALT	0.65 ± 0.22	0.75 ± 0.27	0.003
Platelets (10^4/mm^3)	18.6 ± 6.7	16.7 ± 6.1	0.03
Albumin (g/dL)	4.3 ± 0.3	4.2 ± 0.4	0.06
Total bilirubin (mg/dL)	0.7 ± 0.4	0.8 ± 0.4	0.02
Core protein (pg/mL)	31 ± 50	234 ± 226	<0.0001
Amino acid pattern			
70 Wild/Non-wild/ND	35/21/17	89/74/39	0.30
91 Wild/Non-wild/ND	24/32/17	76/87/39	0.62
DW/Non-DW/ND	14/42/17	46/117/39	0.64

BMI, body mass index; DW, double wild (arginine at residue 70 and leucine at residue 91 in the core region); ND, not detected.

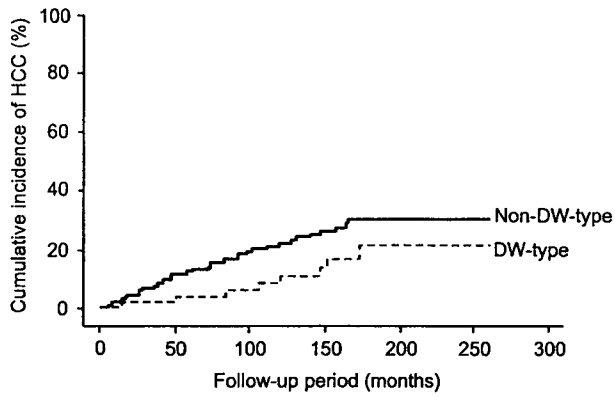

Fig. 4. Cumulative incidence of cirrhosis in non-cirrhotic patients (F0–F2). Comparison between patients with double wild-type (DW-type: arginine, residue 70; leucine, residue 91) ($n = 81$) and non-DW-type ($n = 216$) amino acids in the core region ($p = 0.051$).

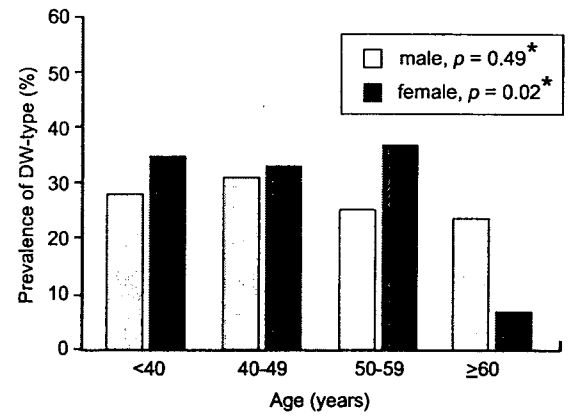

Fig. 5. Prevalence of double wild-type (DW-type: arginine, residue 70; leucine, residue 91) amino acids in the hepatitis C core region according to age and gender. *By the Cochran-Armitage trend test.

Cumulative cirrhosis incidence for non-cirrhotic patients (F0–F2)

Of the 256 non-cirrhotic patients (197 from F0–F1, 59 from F2), 50 (19.5%) developed cirrhosis (cirrhosis group) and 206 (80.5%) did not (non-cirrhosis group). The cumulative cirrhosis incidence at 5, 10, and 15 years of follow-up was 9.7%, 18.2%, and 26.4%, respectively. The HCC incidence was higher in the cirrhosis group [23/50 (46%)] than the non-cirrhosis group [8/206 (3.9%); $p < 0.0001$]. In the entire population, 71 of 82 (86.6%) patients who developed HCC had underlying cirrhosis and 11 (13.4%) did not, when HCC was detected ($p < 0.0001$).

Cumulative cirrhosis incidence according to the amino acid pattern in the core region for F0–F2 patients

The cumulative cirrhosis incidence tended to be higher in the non-DW-type group than the DW-type group (11.9% and 3.6% at 5 years, 21.5% and 10.4% at 10 years, and 29.7% and 20.7% at 15 years of follow-up, respectively; $p = 0.051$; Fig. 4).

Analysis of factors associated with cirrhosis development in F0–F2 patients

We analyzed the factors associated with cirrhosis development in patients with F0–F2 fibrosis at enrollment. Univariate analysis revealed nine parameters correlating with cirrhosis development: male gender ($p = 0.04$), older age ($p < 0.0001$), advanced fibrosis ($p < 0.0001$), absence of SVR ($p < 0.0001$), high AST level ($p < 0.0001$), high ALT level ($p = 0.01$), high AST/ALT ratio ($p = 0.001$), low platelet count ($p = 0.0009$), and high core protein level ($p = 0.02$). Multivariate analysis, including analysis of the amino acid pattern in the core region with the Cox proportional-hazards model, showed that the following three independent parameters were significantly associated with cirrhosis development: male gender ($p = 0.004$), fibrosis = F2 ($p = 0.004$), and absence of SVR ($p = 0.02$). Meanwhile, the presence of the non-DW-type pattern in the core region tended to lead to cirrhosis development (RR, 2.13; 95% CI, 0.93–4.91; $p = 0.07$).

Analysis of factors associated with mutations at core residues 70 and 91

Eighty-one patients with the DW-type pattern at core residues 70 and 91, who were at low risk for HCC, tended to be younger than the 216 patients with the non-DW-type pattern, who were at high risk for HCC (48.4 ± 11.8 years vs. 51.1 ± 11.8 years, respectively; $p = 0.08$). Separate analysis of men and women (Fig. 5) showed that the DW-type pattern was rare in women aged 60 years or above ($p = 0.02$).

Consistent with these results, HCC incidence was the same in men and women aged 60 or above (19% vs. 10% at 5 years and 32% vs. 38% at 10 years of follow-up, respectively; $p = 0.89$); however, in patients aged less than 60 years, HCC incidence was lower in women than in men (4% vs. 11% at 5 years and 15% vs. 22% at 10 years of follow-up, respectively; $p = 0.03$).

Discussion

Male gender, older age, advanced-stage fibrosis, and no IFN treatment are reported as important predictors of HCC development in chronic hepatitis C patients [4–7]. Viral factors associated with HCC development were also reported [27–29]. Several studies showed that mutations in the core protein are associated with HCC among HCV genotype 1b-infected patients, but the results varied between studies [18,30,31]. Consistent with a report by Akuta et al. [18], we showed that the presence of the non-DW-type pattern at core residues 70 and 91 is an independent risk factor for HCC development. Akuta et al. [18] studied 313 chronic hepatitis C patients who received IFN therapy (101 were excluded), and found that non-DW-type was an independent risk factor for HCC development (RR, 5.92; 95% CI, 1.58–22.2; $p = 0.008$) by using the Cox proportional-hazards model, and its correlation with HCC risk was stronger than that found in our study (RR, 1.96; 95% CI, 1.02–3.76; $p = 0.04$). We analyzed cirrhotic patients (14.7% of total population), most of whom developed HCC, and also non-cirrhotic patients, and found that the non-DW-type was still an independent risk factor for HCC development (RR, 2.90; 95% CI, 1.11–7.61; $p = 0.03$). Furthermore, we

found that the non-DW-type in patients with F0–F2 fibrosis was likely to lead to cirrhosis, diagnosed by US ($p = 0.051$). Moreover, the non-DW-type in patients with F0–F3 fibrosis was significantly associated with cirrhosis development ($p = 0.007$, data not shown). These results suggest that the non-DW-type may affect HCC development by accelerating cirrhosis development; however, prospective studies of histological findings are needed to confirm this.

It is unclear why the amino acids at residues 70 and 91 affect HCC development. The core protein cooperates with the Ras oncogene and transforms primary rat embryo fibroblasts into the tumorigenic phenotype [10]. The HCV core protein (residues 25–91) also interacts with the heterogeneous nuclear ribonucleoprotein K, which stimulates the c-myc promoter, downstream of the Wnt/beta-catenin signal [11]. Pavio et al. reported that the HCV core (residues 59–126, residues at 70 and 91 were non-wild-type) interacts with Smad3 and inhibits the TGF-beta pathway, important in apoptosis [12]. Mutations in the clustering variable regions (residues 39–76) are often seen in HCC patients [30], and mutations in the *N*-myristoylation sites (e.g., residue 91) in the core region, are associated with growth control and virus replication [31]. Delhem et al. have shown that the core protein with non-wild-type amino acids at residues 70 and 91 obtained from a HCC patient binds and activates PKR, which might cause carcinogenesis [13]. It was reported that the presence of a non-wild-type amino acid at residue 91 enhances internal initiation of HCV protein synthesis, leading to the expression of a core isoform, which may interact with viral and cellular components [32]. These results suggest that residues 70 and 91 themselves or via interactions with adjacent amino acids may be involved in HCC development; however, further studies are needed to evaluate the effect of core mutations on HCC development.

The presence of the DW-type pattern in the core region is also reportedly a predictor of the virological response to therapy with peginterferon and ribavirin [19]. With this therapy, an SVR of approximately 50% could be achieved by HCV genotype 1-infected patients having high viral load. We found the absence of an SVR and the non-DW-type pattern to be predictors of HCC development; however, the non-DW-type pattern was not a predictor of the absence of an SVR. This may be partly because we used IFN monotherapy without ribavirin, with which the SVR rate (26.5% in our study) was lower than that with peginterferon plus ribavirin [33,34]. Therefore, we believe that combination therapy, rather than IFN monotherapy, would more efficiently eradicate HCV with the DW-type pattern in the core region; however, further studies are required to test this hypothesis. Our current focus is on a prospective study to examine the association between core mutations and the outcome of combination treatment with peginterferon plus ribavirin.

Our study revealed that the DW-type pattern, associated with a low HCC risk, was rare in women aged 60 years or above. This may explain why HCC incidence in women was as high as that in men. The underlying mechanisms by which age or gender influence core-region mutations are unknown. In previous studies, a mutation at residue 70 was correlated with virological response to therapy with IFN plus ribavirin [17] and with AFP levels [35] in HCV genotype 1b-infected patients without HCC. Further follow-up studies must examine whether a mutation occurs in the wild-type amino acid.

We investigated two specific amino acid mutations in the HCV core region by direct sequencing. The HCV core sequence can be easily amplified using PCR because of its conservative nature and analysis of only two amino acid positions is timesaving; therefore, this method might be feasible for identifying predictive markers for HCC. A specific PCR method for detecting these mutations was reported [36]. Furthermore, we developed a rapid and sensitive real-time PCR method for quantitatively detecting these mutations [37]. We hope this method can be used to detect HCV sequences in case of a low viral load, and believe that it will be more useful for predicting HCC.

In conclusion, HCC risk could be predicted by studying mutations in the HCV core region, response to IFN, and host factors like age, gender, and liver fibrosis in HCV genotype 1-infected patients. These mutations might be involved in an oncogenic mechanism leading to HCC development in chronic HCV patients.

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ORIGINAL ARTICLE

Risk of Hepatocellular Carcinoma in Patients with Chronic Hepatitis B Virus Infection

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Abstract

Objective. To determine the risk factors for the occurrence of hepatocellular carcinoma (HCC) in patients with hepatitis B virus (HBV) infection. ***Material and methods.*** A total of 620 patients who tested positive for hepatitis B surface antigen and were referred to Chiba University Hospital between February 1985 and March 2008 were included in the study and the following characteristics were analyzed: age, gender, status of hepatitis B e antigen, alanine aminotransferase level, HBV DNA level, and number of platelets (PLTs). ***Results.*** HCC was detected in 30 cases during the follow-up period (5.4 ± 5.1 years). Multivariate analysis revealed that age >40 years [compared with patients aged <40 years; odds ratio (OR) = 4.28; 95% confidence interval (CI) = 1.68–10.9] and PLT level <206,000/μl (compared with patients with a higher PLT level; OR = 8.50; 95% CI = 1.98–36.2) were predictive factors for HCC occurrence. In patients aged >40 years, the HBV DNA level (compared with <5.0 log copies/ml; OR = 4.22, 95% CI = 1.13–15.8) and PLT level (compared with patients with >196,000/μl PLTs; OR = 15.6, 95% CI = 2.06–118.3) were predictive factors for HCC occurrence. ***Conclusions.*** Advanced age and low PLT level were risk factors for HCC occurrence in patients with HBV infection. In patients aged >40 years, viral load was also a risk factor for HCC.

Key Words: *Hepatitis B virus, hepatocellular carcinoma*

Introduction

The clinical course of patients with hepatitis B virus (HBV) infection varies considerably [1]. Therefore, long-term follow-up studies of patients with HBV infection are quite complex and difficult. In most of the patients, the disease is either non-progressive or shows a slow progression and is usually accompanied by the loss of serum HBV DNA after seroconversion of hepatitis B e antigen (HBeAg) [2]. Some patients show continuous elevation of the alanine aminotransferase (ALT) level, which leads to cirrhosis [3]. HBV infection is also associated with an increased risk of developing hepatocellular carcinoma (HCC), which is one of the most common human cancers and causes of death. Although previous studies have attempted to determine factors influencing the prognosis of patients with HBV infection, the key factors remain to be identified. Recent studies have indicated that the serum level of HBV DNA correlates with the progression of liver diseases [1,4–6]. However, viral load alone cannot predict the occurrence of HCC in the future [7]. In this study, multivariate analyses of the risk factors for HCC occurrence were performed for data obtained from 620 patients with HBV infection who were referred to a single institute in Japan.

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Material and methods

Patients

This was a retrospective analysis. The study was approved by the ethical committee of Chiba University and written informed consent was obtained from all the patients. Of the hepatitis B surface antigen (HBsAg)-positive carriers ($n = 676$) who were referred to Chiba University Hospital between February 1985 and March 2008, those who tested positive for hepatitis C virus (HCV) antibody (anti-HCV) or had autoimmune liver disease and those who had another potential cause of chronic liver disease were excluded. The characteristics of the excluded HBsAg-positive carriers were as follows: anti-HCV positivity in 12, autoimmune liver disease in four and primary biliary cirrhosis in one. Five patients who had previously received lamivudine treatment were also excluded. Thirty-nine patients consulted a physician only once and were excluded from further analysis. Thus, a total of 620 patients were further analyzed. Serum samples were collected during diagnosis and stored at –20°C until analysis.

Serologic markers, HBV DNA quantitative assay, and genotyping

HBsAg, HBeAg, and anti-HBe levels were determined by enzyme-linked immunosorbent assay (ELISA; Abbott Laboratories, Chicago, IL) and anti-HCV was also measured by ELISA (Ortho Diagnostics, Tokyo, Japan). Serum HBV DNA levels were quantified by polymerase chain reaction (PCR) assay (Amplicor HBV Monitor; Roche Diagnostics, Basle, Switzerland); the linear range of this assay was 2.6–7.6 log copies (LC)/ml. The six major genotypes of HBV (A–F) were determined by EIA (HBV Genotype EIA; Institute of Immunology Co., Ltd., Tokyo, Japan). Aspartate aminotransferase (AST), ALT, and the number of platelets were determined and the aminotransferase to platelet ratio index (APRI) was calculated [8].

Statistical analysis

The baseline data are presented as mean ± SD. The difference in the values of clinical parameters between the two groups was analyzed by unpaired t-test, Welch's t-test, and chi-square test. The Cox proportional hazards model was used to identify factors predictive of HCC occurrence using the SPSS version 16.1 software package (SPSS Inc., Chicago, IL).

Results

Demographic characteristics of HCC and control patients

None of the study participants had HCC at entry. In total, 30 incident HCC cases (HCC group) occurred during the follow-up period. During the follow-up period, most of the patients were re-evaluated at least once a year for liver function and detection of HCC. Screening for detection of HCC was performed on the basis of typical findings of abdominal ultrasonography, dynamic CT, angiography, and/or MRI. For all patients suspected of having HCC by imaging analysis, the diagnosis of HCC was confirmed by pathological analysis. If the patient had HCC or was being treated with an antiviral drug (lamivudine or entecavir), we terminated the follow-up. At baseline, significant differences were observed in age, gender, status of HBeAg, ALT and HBV DNA levels, number of platelets (PLTs), and APRI between the HCC ($n = 30$) and control ($n = 590$) groups (Table I). The 590 patients in whom HCC was not detected during the follow-up period constituted the control group. The average follow-up period was 5.1 ± 4.1 and 5.4 ± 5.2 years in the HCC and control groups, respectively, and this difference was not significant.

Patients with HBV

The differences in age, sex, PLT and ALT levels, status of HBeAg, and HBV DNA level between the HCC and control groups were investigated. We defined threshold levels as age 40 years, HBV DNA 5.3 LC/ml, ALT 72.9 IU/l, and PLTs 206,000/μl according to the average data of all patients. Univariate analysis revealed that age, number of PLTs, and HBV DNA level at baseline were predictive factors for HCC occurrence. Multivariate analysis revealed that age >40 years [compared with patients aged <40 years; odds ratio (OR) = 4.28; 95% confidence interval (CI) = 1.68–10.9] and PLT level <206,000/μl (compared with patients with a higher PLT level; OR = 8.50, 95% CI = 1.98–36.2) were predictive factors for HCC occurrence (Table II). Thus, these analyses revealed that age and PLT level were the most important factors influencing future occurrence of HCC. Kaplan–Meier curves were constructed for age ($P < 0.0001$; log-rank test; Figure 1a), PLT level ($P < 0.0001$; log-rank test; Figure 1b), and HBV DNA (P = NS; log-rank test; Figure 1c). Next, we categorized the HBV patients into two subgroups according to the thresholds of age and PLT level based on the average data, and performed further analysis. Because there was only one HCC patient aged <40 years and

Table I. Characteristics of study subjects and their association with HCC.

Parameter	Group			*P*
	Total	HCC	Controls	
No. of patients	620	30	590	
Gender; *n* (%)				<0.001[a]
Male	364 (59)	20 (67)	344 (58)	
Female	256 (41)	10 (33)	246 (42)	
Age (years); mean ± SD	40.0 ± 14.2	50.0 ± 11.6	40.0 ± 14.2	<0.001[b]
HBeAg status; *n* (%)				<0.001[a]
Positive	269 (43)	17 (57)	252 (43)	
Negative	351 (57)	13 (43)	338 (57)	
HBV DNA (LC/mL); mean ± SD	5.3 ± 2.0	6.4 ± 1.3	5.3 ± 2.0	0.002[b]
ALT (IU/l); mean ± SD	72.9 ± 89.3	105.0 ± 129.3	71.0 ± 86.6	0.041[c]
PLTs (/μl); mean ± SD	206,000 ± 66,000	130,000 ± 51,160	210,000 ± 64,410	<0.001[c]
APRI > 0.5; *n* (%)	294 (47.4)	27 (90)	267 (45.3)	<0.001[a]
Interval between two consecutive visits (years); mean ± SD	5.4 ± 5.1	5.1 ± 4.1	5.4 ± 5.2	NS[c]
Genotype A/B/C/D/not determined; *n*	7/38/333/0/242	1/0/24/0/5	6/38/309/0/237	NS[a]

[a]Chi-square test.
[b]Welch's *t*-test.
[c]Unpaired *t*-test.

only two cases had a PLT level > 206,000/μl, we did not analyze these groups.

Analysis of the subgroup of HBV patients aged > 40 years

HCC was detected in 29 patients in the group aged > 40 years (n = 372). Significant differences were observed in the status of HBeAg, HBV DNA, and PLT levels at baseline between the HCC (n = 29) and control groups (n = 343). The average follow-up period was 5.1 ± 4.1 and 5.0 ± 4.7 years in the HCC and control groups, respectively, and this difference was not significant. We defined thresholds as age 49 years, HBV DNA 5.0 LC/ml, ALT 66.0 IU/l, and PLTs 196,000/μl, according to the average data for the patients aged > 40 years. The risk factors for HCC occurrence in patients aged > 40 years were analyzed by Cox regression analysis. Univariate analysis revealed that ALT, PLT, and HBV DNA levels at baseline were predictive factors for HCC occurrence. Multivariate analysis revealed that the HBV DNA

Table II. Multivariate analysis of risk factors associated with HCC in patients with HBV infection.

Risk factor	All patients[a]		Patients aged > 40 years[b]		Patients with PLTs < 206,000 /μl[c]	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Age	4.28 (1.68–10.9)	0.002	2.16 (0.88–5.29)	NS	1.75 (0.71–4.34)	NS
Male gender	1.48 (0.67–3.26)	NS	2.25 (0.86–5.90)	NS	1.43 (0.61–3.35)	NS
HBeAg-positive	1.34 (0.59–3.06)	NS	0.98 (0.41–2.33)	NS	1.06 (0.45–2.51)	NS
HBV-DNA	1.59 (0.62–4.13)	NS	4.22 (1.13–15.8)	0.032	1.20 (0.49–2.94)	NS
ALT	0.86 (0.40–1.87)	NS	1.44 (0.61–3.44)	NS	0.923 (0.40–2.11)	NS
PLTs	8.50 (1.98–36.2)	0.004	15.6 (2.06–118.3)	0.008	4.49 (1.62–12.5)	0.004

[a]The thresholds of age, HBV-DNA, ALT, and PLTs were defined as 40 years, 5.3 LC/ml, 72.9 IU/l, and 206,000 /μl, respectively.
[b]The thresholds of age, HBV-DNA, ALT, and PLTs were defined as 49 years, 5.0 LC /ml, 66.0 IU/l, and 196,000 /μl, respectively.
[c]The thresholds of age, HBV-DNA, ALT, and PLTs were defined as 42 years, 5.8 LC /ml, 84 IU/l, and 159,000 /μl, respectively.
HR = hazard ratio.

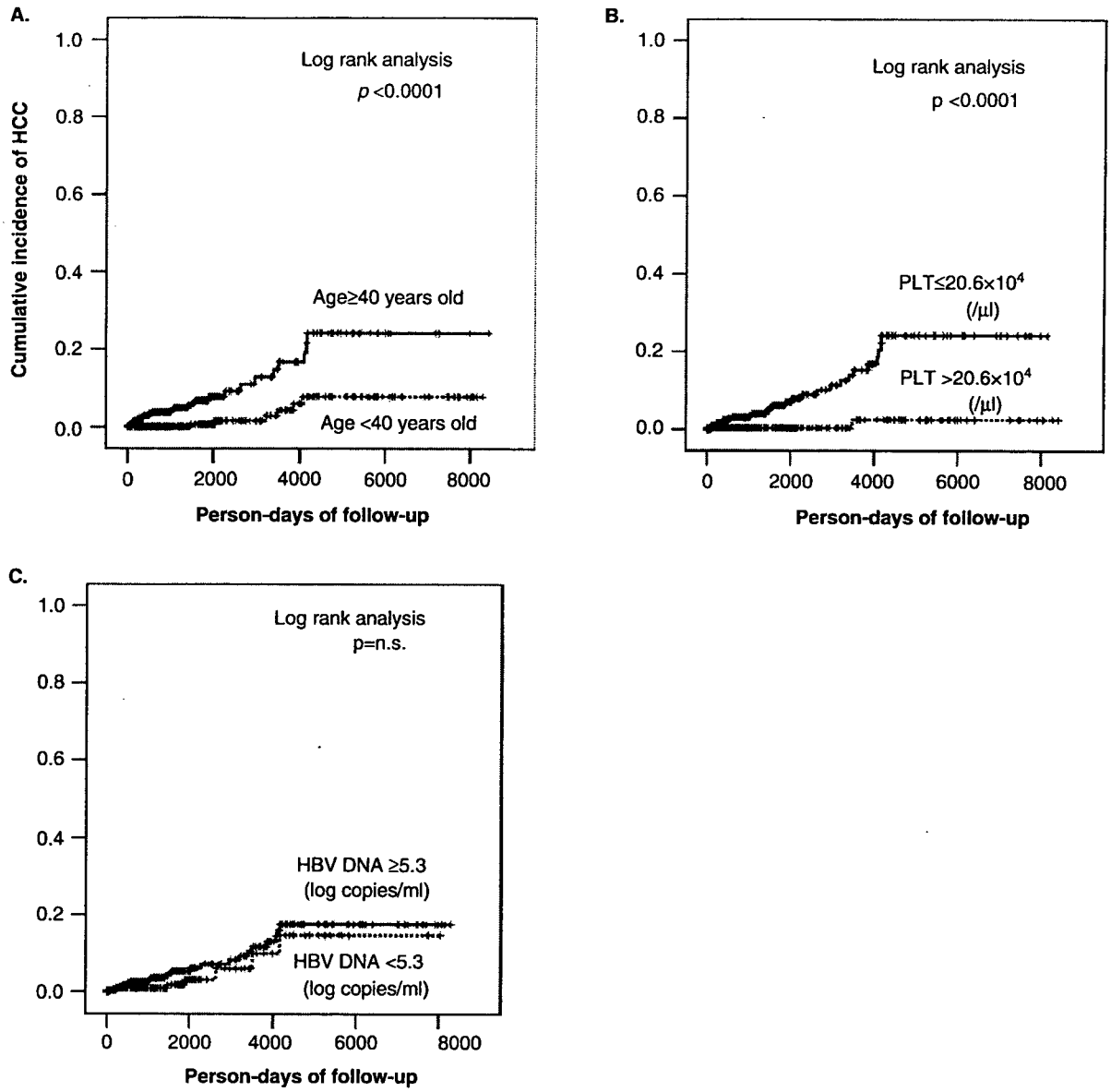

Figure 1. Cumulative occurrence of HCC based on (a) number of PLTs, (b) age, and (c) HBV DNA level. Thresholds for age, number of PLTs, and HBV DNA level were defined according to the average data for all patients. Dotted lines indicate the control group (high number of PLTs, younger age, and low HBV DNA level).

level (compared with <5.0 LC/ml; OR = 4.22; 95% CI = 1.13–15.8) and PLT level (compared with >196,000/μl; OR = 15.6; 95% CI = 2.06–118.3) were predictive factors for HCC occurrence (Table II). Kaplan–Meier curves were constructed for HBV DNA ($P = 0.001$; log-rank test; Figure 2).

Analysis of the subgroup of HBV patients with PLTs <206,000/μl

HCC was detected in 28 patients in the group with PLTs <206,000/μl ($n = 329$). The risk factors for HCC occurrence in the group with <206,000/μl PLTs were analyzed by Cox regression analysis. Univariate analysis revealed that age and PLT level at baseline were predictive factors for HCC occurrence. Multivariate analysis revealed that PLT level (compared with patients with >159,000/μl; OR = 4.49; 95% CI = 1.62–12.5) was the only predictive factor for HCC occurrence (Table II).

Discussion

In Japan, HBV infection is one of the most important factors determining HCC occurrence [9]. Moreover, HCC is one of the most important determinants for

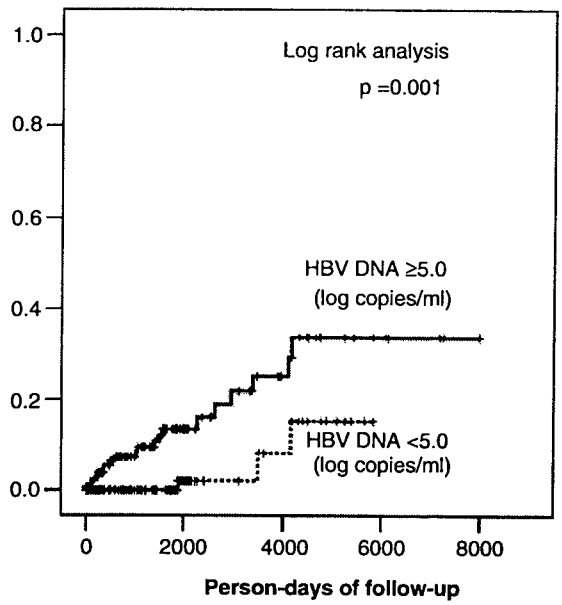

Figure 2. Cumulative occurrence of HCC based on the HBV DNA level in patients aged >40 years. The threshold for the HBV DNA level was defined according to the average data for the patients aged >40 years. A significant difference was observed by log-rank test. The dotted line indicates the control group (low HBV DNA level).

the prognosis of patients with HBV infection. In previous studies, factors associated with an increased risk of HCC among people with chronic HBV infection included demographic characteristics, lifestyle, and environmental, viral and clinical factors. Among these, male gender, older age, HBV genotype, cirrhosis, elevated ALT, and high viral load were found to be factors associated with HCC [6,10–19]. We focused on clinical factors which may be tested easily and for which tests are available all over the world. This report clarifies the relative risk for HCC in all patients with HBV who were referred to a single institute in Japan and provides important information for physicians.

In this study, the relative risk of HCC was found to be increased to 4.28 (95% CI 1.68–10.9) times higher for patients aged >40 years compared with those aged <40 years. In addition, a low PLT level, which indicates advanced fibrosis in the liver, including cirrhosis, was a risk factor for HCC: the relative risk was found to be increased to 8.50 (95% CI 1.98–36.2) times higher for patients with a PLT level <206,000/μl compared with higher levels. The HBV DNA level was not selected as a risk factor for HCC occurrence in all patients with HBV infection by multivariate analysis. Previous follow-up studies have shown that viral load is an important and independent factor for HCC occurrence [4,5,20]. However, in the present study, although various thresholds of HBV DNA level were used for analysis, none of the thresholds showed statistical significance in multivariate analysis (data not shown). In contrast, the analysis intended for patients aged >40 years revealed that high HBV viral load was added as a risk factor for HCC. By changing the threshold of HBV DNA from 4.5 to 5.3 LC/ml in 0.1-log increments, 5.0 or 5.1 LC/ml were found to be the best (data not shown); therefore we designated the threshold of HBV DNA level as >5.0 LC/ml. In our study, HBV carriers aged >40 years with HBV DNA levels >5.0 LC/ml had a 4.22-times higher risk of HCC compared to HBV carriers with lower viral loads. In previous studies in Japan regarding predictive factors for HCC, Ohata et al. [5] reported that age, HBV DNA, and staging of fibrosis were the important factors, while Murata et al. [21] reported that the number of PLTs was the only factor after HBeAg seroconversion. On the other hand, in an analysis of patients with liver cirrhosis in Japan, levels of HBV DNA and/or ALT were the predictive factors for HCC [12,19]. Taken together with the present study, these reports suggest that the HBV DNA level may not be an absolute factor for predicting HCC in the analysis, irrespective of the age of the patients and the number of PLTs, but that in patients with advanced age or low numbers of PLTs, indicating advanced fibrosis of the liver, HBV DNA could be a predictive factor for the occurrence of HCC. The PLT level negatively reflects the extent of liver fibrosis [22], therefore it is very difficult to achieve an improvement in liver fibrosis and to recover the PLT level concomitantly, but a high viral load can be lowered by antiviral drug treatment. Therefore, in patients aged >40 years, lowering the viral load using an antiviral drug might be an important way to avoid the occurrence of HCC but, in younger patients, lowering the HBV DNA level may not result in direct inhibition of HCC occurrence, although the activity of hepatitis could be suppressed.

The decrease in the number of PLTs in patients with liver disease reflects advanced fibrosis of the liver, which is strongly related to HCC occurrence. In fact, the patients in the HCC group of our study were suggested to show advanced fibrosis because they had higher values of APRI than the controls. In addition to being a marker of liver fibrosis, the influence of PLTs on cytotoxic T lymphocytes (CTLs) has been studied with keen interest. Chronic HBV infection is characterized by an inefficient CTL response, which often results in continuous destruction of hepatocytes. A recent study indicated that PLTs are required for virus-specific CTLs to accumulate within the liver and perform pathogenetic and/or antiviral roles [23]. In our study, low PLT number was a strong risk factor for HCC in all the HBV carriers, irrespective of age or PLT number at baseline. Especially in the HBV

carriers aged >40 years, low PLT number has the strongest association with HCC occurrence. Therefore, older HBV carriers with low PLT levels should be followed closely because of a high possibility of HCC occurrence, as for HCV carriers with low PLT levels [24].

The presence of HBeAg is often associated with active liver disease, whereas HBeAg seroconversion often coincides with loss of HBV DNA in serum, normalization of the ALT level, and clinical remission [25]. Spontaneous HBeAg seroconversion confers a good long-term outcome on most patients. In this study, the status of HBeAg at baseline differed significantly between the HCC and control groups; however, the status of HBeAg was not identified by univariate analysis as a predictive factor for HCC occurrence. From these results, we speculated that the HBe protein was not the direct precursor of HCC, although the HBe antigen status often reflects the replication of HBV DNA.

In this study, we evaluated parameters for predicting HCC only at first admission. A previous study reported that changes in ALT or HBV DNA levels during the follow-up period were important for predicting advanced liver disease and HCC [26]. We need to evaluate the importance of following changes in these parameters.

There was only one HCC patient aged <40 years. This patient was male and was followed up from the age of 27 years; his ALT, HBV DNA, and PLT levels and the status of HBeAg at baseline were 34 IU/l, 7.7 LC/ml, 203,000/μl, and positive, respectively. It was difficult to predict the occurrence of HCC in this case only on the basis of the risk factors for HCC indicated in this study. Hence, we need to find an adequate risk factor to predict HCC in such a case.

In conclusion, advanced age and low PLT level were the risk factors for HCC in patients with HBV infection, irrespective of the PLT level at baseline. In patients aged >40 years, viral load was added as a risk factor for HCC.

Declaration of interests: The authors indicated no potential conflict of interest.

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特集 増え続ける大腸癌ー基礎から臨床までー

術後サーベイランスは予後の改善に寄与するか

Effect of the surveillance on prognosis after surgery for colorectal cancers

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ISHIGURO Megumi KOBAYASHI Hirotoshi
杉原 健一**
SUGIHARA Kenichi

本邦の大腸癌症例の5年生存率は約70%と世界でも高い水準を示しているが，一方で約30%に再発をきたす現状がある．大腸癌の予後の改善においては，再発を切除可能な状態で発見することが重要であり，術後サーベイランスの目的はその点にある．再発巣を治癒切除がすれば約40%の5年生存率が期待できる．術後サーベイランスは再発巣の治癒切除率を向上させることによって大腸癌の予後の改善に寄与し，本邦の良好な治療成績の一端を担っている．

I. 大腸癌治療における術後サーベイランスの位置づけ

近年，本邦における大腸癌罹患数は増加の一途であり，2005年の悪性腫瘍関連死亡のうち，大腸癌の死亡率は，男性では肺癌，胃癌，肝癌についで4位，女性では1位である．このように大腸癌が“ふつうの病気”となった現在，その治療成績の向上が求められるのは当然のことである．

大腸癌研究会の大腸癌全国登録1991年～1994年度症例における，本邦の大腸癌の5年生存率は約70%であり[1]，大腸癌の地域がん登録の5年生存率を国別に示したColemanらの報告[2]によれば，本邦は男性では1位，女性では6位と，世界でも高い水準を示している．

このような他国に比較して良好な治療成績は，本邦における精度の高い内視鏡診断技術と高度な内視鏡治療技術や，D3郭清や側方郭清が標準的に行われているという高い手術技術によるところが大きいと思われるが，加えて，治療後のサーベイランスが綿密に行われ，再発の早期発見・早期治療が行われていることも寄与していると考える．

大腸癌患者の予後を向上させる要素としては，
①早期発見，
②病巣の完全切除，
③再発後の生存期間の延長，
があげられる(図1)．本邦においては，「大腸癌治療ガイドライン」に沿ったリンパ節郭清を伴

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Key words：大腸癌／サーベイランス／再発／治癒切除／ガイドライン

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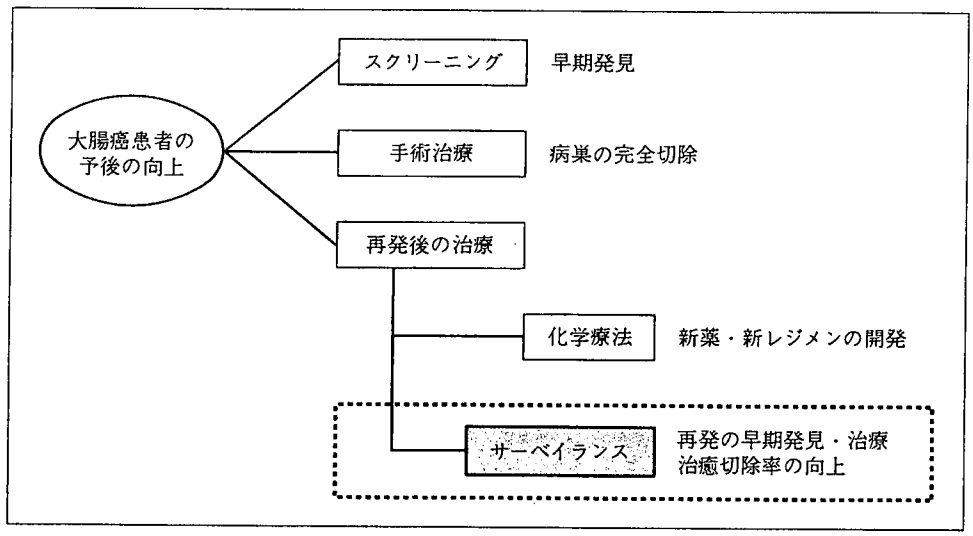

図1 大腸癌治療における術後サーベイランスの位置づけ

う手術が標準治療としてひろく普及しており，そのため，一般に治癒切除可能であるStage 0～Stage IIIの大腸癌においては，今後は手術手技そのものによる治療成績の大きな改善はないものと予想される．一方で，高度な手術技術や診断技術をもってしても，残念ながら一定の割合で再発を伴うことは避けられず，本邦における大腸癌治癒切除後の再発率は約30%である．したがって，今後の大腸癌患者の生存期間を延長させる主なポイントのひとつは，これらに対する「再発後の治療」であろう．

新規抗がん剤や分子標的治療薬の登場と，それに伴う新しい多剤併用レジメンの開発により，切除不能進行・再発大腸癌の生存期間中央値は20ヵ月を超える時代に突入している．しかし，化学療法を主とした非手術治療のみでは，根治にいたる症例はいまなお非常にまれである．

つまり，再発大腸癌を治癒させるためには，再発を切除可能な時期に発見することが重要であり，術後サーベイランスの目的は，まさにその点にある．術後サーベイランスは，再発大腸癌の治療，ひいては患者の予後を大きく左右する，非常に重要な要素であることを認識する必要がある．

II. 再発巣の切除による予後の改善

「大腸癌治療ガイドライン」[1]では，再発大腸癌に対する治療方針として，再発巣の完全切除が可能であり，かつ残存臓器機能が保たれること，患者が耐術可能であること等の条件を満たせば，積極的に手術(再発巣の切除)を行うよう推奨している．

では，再発巣の切除によって得られる予後改善効果はどの程度なのであろうか？

大腸癌研究会では，2003年7月に「大腸癌術後再発に関するフォローアップに関する研究プロジェクト」(表1)を発足し，14施設から1991年～1996年の大腸癌治癒切除症例5,230例を集積し，検討した[2]．再発例906例(再発率：17.3%)のうち，初回再発巣に対して治癒切除を施行した379例(再発巣治癒切除率：41.8%)の初回再発後5年生存率は42.2%，生存期間中央値は1,293日であり，非治癒切除例(手術非施行例を含む)の生存期間中央値381日に比し，有意に良好であった(図2)．

加えて注目すべきは，初回再発診断時期別の予後の検討において，再発巣治癒切除後の予後は，初回再発の診断時期による差はなく，いずれも5年生存率が約40%と比較的良好であった点である

表1　大腸癌研究会「大腸癌術後再発に関するフォローアップに関する研究プロジェクト」参加施設

施設名	施設代表者	施設名	施設代表者
防衛医科大学校　外科	望月　英隆	癌研究会附属有明病院　外科	大矢　雅敏
弘前大学　第二外科	森田　隆幸	自衛隊中央病院　外科	長谷　和生
栃木県立がんセンター　外科	固武健二郎	国立国際医療センター　大腸肛門外科	斉藤　幸夫
東京医科歯科大学　腫瘍外科	杉原　健一	愛知県がんセンター中央病院　消化器外科	平井　孝
東京女子医科大学　第二外科	亀岡　信悟	藤田保健衛生大学　外科	前田耕太郎
都立駒込病院　外科	高橋　慶一	大阪府立成人病センター　第一外科	亀山　雅雄
東邦大学　消化器外科	寺本　龍生	久留米大学　外科	白水　和雄

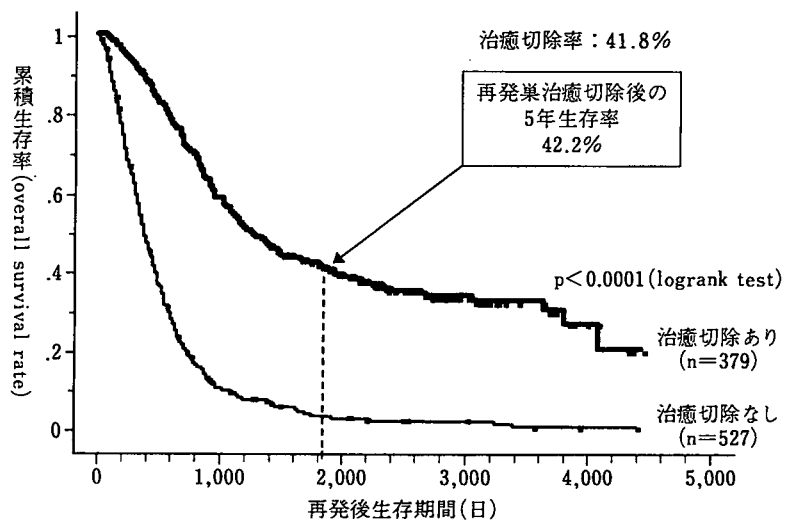

図2　大腸癌初回再発後の生存曲線

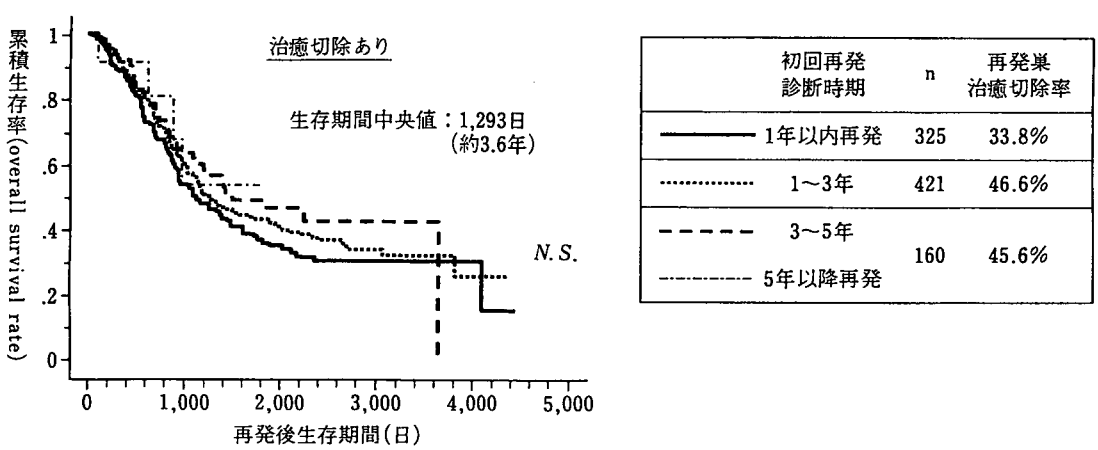

図3　初回再発診断時期別の再発巣治癒切除率と再発後生存曲線

表2 大腸癌術後サーベイランスに関するメタアナリシス
intensive サーベイランス群と less-intensive 群の比較

報告者	報告年	検討 RCT 数	症例数	再発率	再発発見時期	再発巣 治癒切除率※	全生存率※
Renehan[4]	2002	5	1,342	32%：33% (NS)	−8.5ヵ月 [−9.4〜−7.6]	−	0.81 [0.70〜0.94]
Figueredo[5]	2003	6	1,679	(NS)	−	−	0.8 [0.70〜0.91]
Renehan[6]	2005	6	1,679	31%：40% (NS)	−	2.12 [1.43〜3.15]	0.76 [0.67〜0.86]
Jeffery[7]	2007	8	2,141	−	−6.75ヵ月 [−11.6〜−2.44]	2.41 [1.63〜3.54]	0.73 [0.59〜0.91]
Tjandra[8]	2007	8	2,923	29%：28.8% (NS)	−5.91ヵ月 [−8.74〜−3.09]	2.81 [1.65〜4.79]	0.74 [0.59〜0.93]

※オッズ比([ ]：95%信頼区間)

(図3)．術後1年以内の再発例では，再発巣治癒切除率が低いため，再発例全体としての予後は術後1年以降の再発例に比し不良であるが，再発時期にかかわらず，再発巣に対し治癒切除を行うことができれば，約40%の5年生存が期待できることが明らかになった．

III. 術後サーベイランスは予後の改善に寄与するか？

では，術後サーベイランスは再発巣の治癒切除率の向上に貢献し，予後を改善することができるのであろうか？

前述のごとく，本邦の標準的な術後サーベイランスのもとで，再発巣治癒切除率が41.8%，再発巣治癒切除後の5年生存率が42.2%であったが，この結果が術後サーベイランスによってもたらされたものかどうかは証明できない．本邦においては，大腸癌術後の再発サーベイランス法に関する比較試験は行われておらず，今後もその施行は困難と考える．

一方，海外からは，1990年代後半から行われた大腸癌術後サーベイランスに関する代表的なランダム化比較試験(RCT)の結果を解析したメタアナリシス[4)-8)]が2000年以降に発表されており，定期的な血清 CEA 値測定や肝画像検査を含む intensive なサーベイランスが再発巣の治癒切除率を高め，生存率を有意に改善するという結果が示された(表2)．

元来欧米における大腸癌の術後サーベイランスでは，定期的な画像検査は行われてこなかった．しかし，これらのメタアナリシスの結果をふまえ，定期的な腹部超音波検査や CT を含む intensive なサーベイランスの有用性が認識されるようになり，欧米の各種ガイドラインの内容も，本邦に近い intensive なサーベイランスを推奨するように変化した[9)-11)](表3)．

これらの動きから，現在では，“適切な術後サーベイランスを行うことによって再発の早期発見および再発巣治癒切除率の向上がもたらされ，予後が改善する”との国際的コンセンサスが得られている状況であると考える．

IV. 大腸癌術後サーベイランスのポイント

当然ではあるが，頻回なサーベイランス(検査)を行えば，再発をごく早期に発見することは可能である．しかし，非常に小さな段階の再発巣を発見しても，必ずしも即座に治療の対象となるわけではなく，一定の観察期間を設けることもしばしばある．また，頻回な検査は患者の身体的・経済的負担を伴うと同時に，昨今は社会的にも医療費

表3 欧米の主なガイドラインにおける大腸癌術後サーベイランス

	ASCO 2005年[9]	ESMO 2009年(結腸癌)[10]	NCCN 2008年(結腸癌)[11]
診察	術後3年間は3～6ヵ月ごと 術後4～5年は6ヵ月ごと	術後3年間は3～6ヵ月ごと 術後4～5年は6～12ヵ月ごと	術後2年間は3～6ヵ月ごと その後術後5年までは6ヵ月ごと
腫瘍マーカー(CEA)	術後3年以上は3ヵ月ごと (Stage II・III症例)	術後3年間は3～6ヵ月ごと 術後4～5年は6～12ヵ月ごと	術後2年間は3～6ヵ月ごと その後術後5年までは6ヵ月ごと (T2以上症例)
CT	高リスク群：術後3年間は年1回の胸部・腹部CT 骨盤CT：放射線未照射の直腸癌術後	高リスク群では術後3年間は6ヵ月ごとの胸部・腹部CTを考慮	高リスク群では術後3年間は12ヵ月ごとの胸部・腹部・骨盤CTを考慮
大腸内視鏡検査	術後3年目 正常ならその後5年ごと すべての大腸癌患者は術前にクリーンコロンであることを確認すべきである	術後1年目 その後3年ごと	術後1年目 異常があれば1年以内に再検．腺腫があれば3年以内に再検，その後5年ごと

ASCO：American Society of Clinical Oncology
ESMO：European Society of Medical Oncology
NCCN：National Comprehensive Cancer Network

増大が問題であり，その妥当性は十分検討する必要がある．

術後サーベイランスの目的は生存率の向上であり，安全かつ完全に切除ができる状態で再発を発見できれば，その目的は果たされる．それに加え，患者の身体的負担や医療経済性を考慮した，より“効率的”なサーベイランス法を確立することが重要である．そのためには，再発の特徴(再発の起こりやすい時期，起こりやすい臓器)を認識しておくことがポイントとなる．

前述のプロジェクト研究では，集積した5,230例のうち，906例の再発症例を詳細に検討し，その結果が「大腸癌治療ガイドライン」[1]に記載されている．初回再発部位のうち，最も多いのは肝再発(373例，7.1%)であり，ついで肺再発(251例，4.8%)，局所再発(206例，4.0%)の順であった．直腸癌では結腸癌に比し，有意に再発率が高率であった(それぞれ24.3%，14.1%，$p<0.001$)．再発部位では，結腸癌では初回再発の約半数(252例，7.0%)が肝再発であるのに比し，直腸癌では肝再発(121例，7.3%)，肺再発(124例，7.5%)，局所再発(145例，8.8%)がほぼ同数であった(図4)．これより，直腸癌の術後サーベイランスでは，結腸癌に比し，肺再発・局所再発にも留意すべきである．また，再発の80%以上が術後3年以内に，95%以上が術後5年以内に診断されていた(図5)．術後5年を超えて診断された再発は，全5,230例のわずか0.6%(33例)のみであった．これより，

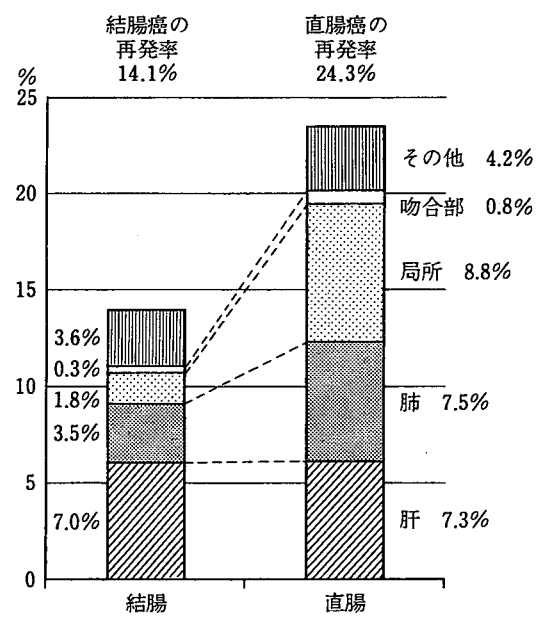

図4 結腸癌・直腸癌における初回再発部位の比較
RSは結腸として集計

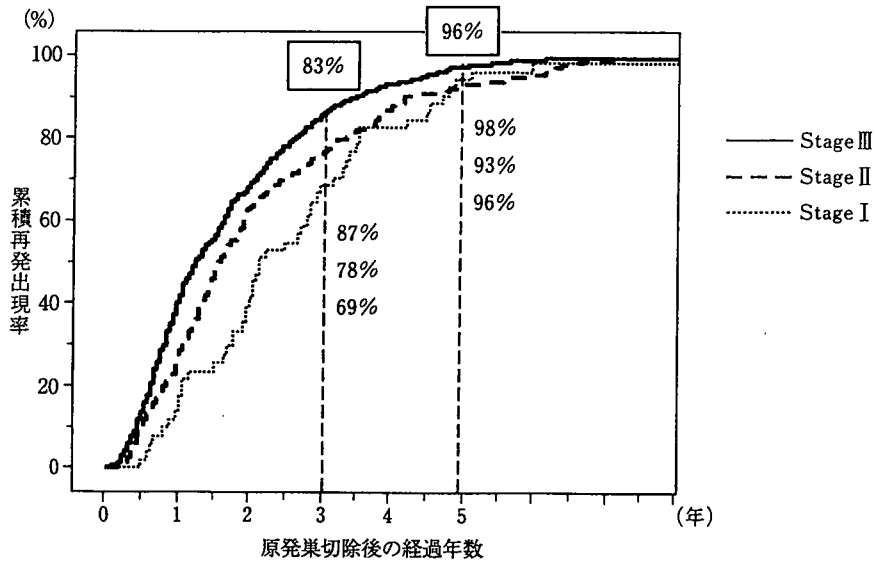

図5 Stage 別累積再発出現率
注：Stage 分類は大腸癌取扱い規約(第6版)による.

術後3年までのサーベイランスはintansive に行い，また，少なくとも術後5年間は，再発の可能性を念頭に置き，サーベイランスを継続すべきである.

また，Stage のほかに再発リスク因子を加えるなどして再発リスクを層別化することでサーベイランスの効率化をはかるなどの試みも，今後の方向性として検討すべきと考える.

ま と め

再発大腸癌の治療成績の向上には，再発を治癒切除可能な状態で発見することが重要であり，この点において術後サーベイランスは，患者の予後を左右する重要な要素であるとともに，本邦の良好な治療成績の一端を担っている．大腸癌術後の再発の特徴をよく把握し，大腸癌治療ガイドラインに準じて適切なサーベイランスを行うとともに，今後はサーベイランスの効率化を目指して新しいデータを集積・検討し，臨床にフィードバックしていく必要がある.

(謝辞)

症例の集積・検討に多大なご尽力をいただきました「大腸癌術後再発に関するフォローアップに関する研究プロジェクト」参加各施設の先生方に深謝いたします.

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＜大腸がんの術後補助化学療法＞

大腸がんの術後補助化学療法、今後の展望

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☞ *Point*

- ●①適切な対象に、②適切な薬剤・レジメンを、③適切な期間投与することを追求した、適切な治療の選別―「治療の個別化」が今後の課題である。
- ●より効率的かつ可能な限り簡便な方法で「ハイリスクStage Ⅱ」症例を抽出して補助化学療法の対象に含め、予後の向上を目指すことが早急な課題である。
- ●再々発予防のための、転移・再発巣切除後の補助化学療法が考慮されるが、その有用性はいまだ確立されておらず、検証が待たれる。
- ●対象に見合ったレジメンを選択する手法として、再発リスクによる治療intensityの個別化とバイオマーカーによる薬剤の個別化がある。
- ●補助化学療法としての経口抗がん剤の投与期間に関しては、いまだ明確なエビデンスはない。患者のQOLおよび経済的負担に直結する重要な問題であり、検証の結果が待たれる。
- ●適切な「治療の個別化」により、有効性・安全性の向上のみならず、治療の効率化による患者QOL・医療経済性の向上も期待できる。わが国の治療成績に基づいた、わが国独自のエビデンスを発信することが強く望まれる。

大腸癌研究会の大腸癌全国登録1991～1994年度症例における5年生存率は約70％であり、大腸がんの地域がん登録の5年生存率を国別に示したColemanらの報告[1]によれば、わが国は男性では1位、女性では6位と、

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