extrahepatic metastasis significantly reduces survival rates, as no effective systemic therapies are available to date [6, 7].

Recently, sorafenib, an oral multikinase inhibitor, has been approved as a new molecularly targeted therapy for advanced HCC. The magnitude of benefit obtained with sorafenib is similar to that with trastuzumab in breast cancer, bevacizumab in colon cancer, or erlotinib in lung cancer [8–10]. Sorafenib has been shown to suppress tumor growth and angiogenesis by inhibiting the Raf/MEK/ERK signaling pathway and receptor tyrosine kinases, such as vascular endothelial growth factor receptor (VEGFR) 1, VEGFR-2, VEGFR-3, and platelet-derived growth factor receptor beta [11].

The introduction of sorafenib has changed the standard systemic therapy for advanced HCC, as demonstrated by recent positive results from randomized controlled trials, and this new treatment was approved in Japan in May 2009 [12–14]. The strong evidence of sorafenib offering significant survival benefit in advanced HCC was derived from the SHARP (Sorafenib HCC Assessment Randomized Protocol) trial [12]. Another phase III clinical trial enrolling patients from the Asia-Pacific region concluded that sorafenib was a well-tolerated and effective treatment for advanced HCC [15].

Extrahepatic metastasis of HCC remains the leading cause of death from the disease [16]. To date, the prognostic factors for patients with extrahepatic metastasis remain unclear. Previous studies reported that these patients had a worse prognosis than those without extrahepatic metastasis [17]. The lungs are the most common organ for extrahepatic spread, but most pulmonary metastases are multifocal and often unsuitable for surgical resection [17]. Thus, the clinical outcome and prognosis of patients with extrahepatic metastasis treated with sorafenib require further investigation.

Therefore, in the present study, we prospectively assessed the efficacy and safety of sorafenib, identified the factors associated with improved survival in advanced HCC patients, and evaluated the prognostic impact of extrahepatic metastasis status.

Materials and Methods

Patients

Eligibility criteria for this study were similar to those of the SHARP trial. Briefly, all enrolled patients met the following requirements: (1) Eastern Cooperative Oncology Group performance status of 0–1, (2) measurable disease using the Response Evaluation Criteria in Solid Tumors (RECIST) [18], (3) Child-Pugh class A or B liver function, (4) leukocyte count of $\geq 2000/mm^3$, (5) platelet count of $\geq 50 \times 10^9/L$, (6) hemoglobin level of ≥8.5 g/dL, (7) serum creatinine level of <1.5 mg/dL, and (8) no ascites or encephalopathy. Between May 2009 and March 2014, 312 patients diagnosed with advanced HCC were enrolled in this study. HCC was either confirmed via histological studies or diagnosed using noninvasive criteria according to the European Association for the Study of Liver [19]. Enrolled patients were treated with sorafenib at one of the 13 experienced member institutions of the Kurume Liver Cancer Study Group of Japan: Asakura Medical Association Hospital, Chikugo City Hospital, Kurume General Hospital, Kurume University Medical Center, Kurume University School of Medicine, Kyushu Medical Center, Ōmuta City Hospital, Saga Social Insurance Hospital, Social Insurance Tagawa Hospital, St. Mary's Hospital, Tobata Kyouritsu Hospital, Yame General Hospital, and Yokokura Hospital. The primary outcome of this study was overall survival time, which was defined as the time from sorafenib treatment initiation to the date of death or the patient's last follow-up. Relevant data from all patients' clinical records, including medical history, laboratory results, radiologic findings, histologic results, and survival data, as well as the dosage and adverse events associated with sorafenib therapy, were prospectively collected. The study protocol was approved by the Ethics Committee of Kurume University (No. 10009) and University Hospital Medical Information Network (UMIN) Center (No. UMIN000007427), and conformed to the guidelines of the 1975 Declaration of Helsinki. Patients were given comprehensive information on the details of the clinical study, and they provided written informed consent prior to participation.

Diagnosis

Intrahepatic lesions and vascular invasion were diagnosed using a combination of contrast-enhanced computed tomography (CT), magnetic resonance imaging (MRI), ultrasonography (US), and digital subtraction angiography. In addition, alpha-fetoprotein (AFP), lens culinaris agglutinin-reactive fraction of AFP (AFP-L3), and des-gamma-carboxy prothrombin (DCP) serum levels were measured up to 1 month prior to treatment. Intra-abdominal metastases were detected via abdominal CT, MRI, and US, which were performed to evaluate intrahepatic lesions. Pulmonary lesions were detected on chest radiography or chest CT, which was routinely performed up to 1 month prior to treatment. Additional examinations, such as bone scintigraphy and brain CT or MRI, were indicated when symptoms attributable to extrahepatic metastasis appeared. These examinations were also conducted when AFP, AFP-L3, or DCP levels were elevated, and the elevation could not be explained by the status of the intrahepatic lesions [19]. Tumor stage was

determined according to the Barcelona Clinic Liver Cancer (BCLC) staging classification [20].

Sorafenib treatment

Performance status was used to determine the initial sorafenib dosage as per the chief physician's discretion. Discontinuation and dose reduction were allowed based on tolerance. Side effects of sorafenib treatment were documented according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. Treatments were discontinued upon development of CTCAE grade 3 or higher adverse events with the exception of a platelet count of $<25 \times 10^9$/L and a leukocyte count of $<1500/mm^3$.

Assessment of tumor response

Imaging studies were performed 4 weeks after the initiation of sorafenib treatment and every 4–6 weeks thereafter to assess tumor response. The assessment was conducted according to the RECIST, version 1.1 [18] as follows: complete response (CR), all measurable lesions disappeared for more than 4 weeks; partial response (PR), the sum of the diameters of the largest target lesions decreased by more than 30%, and there was no development of a new lesion for more than 4 weeks; progressive disease (PD), the sum of the largest diameters increased by more than 20%, or a new lesion appeared; and stable disease (SD), neither PR nor PD was observed [21]. Patients who died before their first radiographic assessment were classified as having PD. The time to radiologic progression was defined as the time from sorafenib treatment initiation to disease progression. Data from patients who died without tumor progression were censored. The disease control rate was defined, on the basis of independent radiologic review, as the percentage of patients whose best-response RECIST rating of CR, PR, or SD was maintained for at least 1 month after the first demonstration of such rating.

Statistical analysis

Baseline patient characteristics were analyzed using descriptive statistical methods. Survival curves were calculated using the Kaplan–Meier method. Univariate analysis of survival curves was performed using the log-rank test. A *P*-value of <0.05 was considered statistically significant. The Cox proportional hazards model was used to evaluate the interaction between baseline characteristics and the effect of sorafenib on overall survival. JMP software (SAS Institute, Inc., Cary, NC), version 11, was used for all analyses.

Results

Patient characteristics

The study cohort included 241 (77%) men and 71 (23%) women, with a mean age of 72 years (Table 1). Chronic hepatitis C virus infection was the predominant cause of HCC (n = 189; 62%), followed by chronic hepatitis B virus infection (n = 55; 23%). Of the enrolled patients, 165 (53%) had a Child-Pugh score of 5 and 100 (32%) had a Child-Pugh score of 6. Overall, 265 (85%) patients had Child-Pugh class A, whereas 47 (15%) had class B liver cirrhosis. According to the BCLC staging system, 100 (32%) patients had stage B disease, and 212 (68%) had stage C. Prior to sorafenib therapy, 277 (89%) patients had been treated with surgical, locoregional, or pharmacologic therapies. Of these, 176 received transcatheter arterial chemoembolization, 107 were treated with hepatic

Table 1. Characteristics of the total cohort (no. with % and median with range).

Variable	
Age, years [range]	72.0 [33–94]
Gender, *n* (%)	
Male	241 (77.2)
Female	71 (22.8)
Etiology, *n* (%)	
HBV	55 (17.6)
HCV	189 (60.6)
Both negative	68 (21.8)
Child-Pugh class, *n* (%)	
A	265 (84.9)
B	100 (32.1)
BCLC stage, *n* (%)	
B	100 (21.2)
C	212 (84.9)
Initial sorafenib dose, *n* (%)	
400 mg	209 (67.0)
800 mg	103 (33.0)
Extrahepatic metastasis, *n* (%)	178 (57.0)
Lung	105 (33.7)
Bone	40 (12.8)
Lymph node	38 (12.2)
Peritoneum	17 (5.4)
Adrenal gland	11 (3.5)
Macrovascular invasion, *n* (%)	
Presence	81 (26.0)
Absence	231 (74.0)
Albumin—median in g/L [range]	3.50 [2.39–4.70]
Total bilirubin—median in mg/dL [range]	0.78 [0.15–3.70]
Prothrombin time—median in % [range]	83.3 [10.8–136.0]
AFP—median in ng/mL [range]	105 [1–987,600]
DCP—median in mAU/mL [range]	738 [2–621,000]

HBV, hepatitis B virus; HCV, hepatitis C virus; BCLC, Barcelona Clinic Liver Cancer; AFP, alpha-fetoprotein; DCP, des-gamma-carboxy prothrombin.

arterial infusion chemotherapy, 92 underwent hepatic resection, and 76 had radiofrequency ablation.

Treatment compliance

The initial dose of oral sorafenib administration was 400 mg daily in 209 patients and 800 mg daily in 103 patients. By the end of the follow-up period, 273 patients had discontinued treatment. The reasons for discontinuation were adverse events in 147 patients, radiologic and symptomatic progression in 90, and deterioration of performance status in 21.

Overall response and efficacy

The median duration of sorafenib treatment was 3.6 months (range: 0.1–49.5 months), and the median follow-up period was 8.6 months (range: 0.4–54.3 months). Of the enrolled patients, 245 (81%) received sorafenib treatment for more than 1 month. Sixty-seven patients who received sorafenib for less than a month were indeed treated with other therapeutic modalities, including transcatheter arterial chemoembolization, hepatic arterial infusion chemotherapy, systemic chemotherapy, or radiation therapy. In total, 228 (73%) died during the observation period and 84 (27%) were alive at the end of follow-up. At the first radiologic assessment, 18 (6%) patients showed PR, 127 (41%) had SD, and 134 (43%) experienced PD according to the RECIST, whereas follow-up radiologic evaluation was unavailable for 33 (10%) patients. Thus, the disease control rate was 47%.

Factors associated with survival outcomes

Cumulative survival curves of all patients are shown in Figures 1 and 2. The median survival time (MST) was 10.3 months (range: 0.4–54.3 months), with a 1 year survival rate of 44% (Fig. 1A). The median progression-free survival (PFS) time was 3.6 months (range: 0.1–31.3 months; Fig. 1B).

Cox proportional hazards regression analysis was performed to identify independent factors associated with survival (Table 2). The results of univariate analysis showed that gender (men, $P = 0.0042$), Child-Pugh class (B, $P = 0.0007$), serum DCP level at baseline (median level of ≥738 mAU/mL, $P = 0.0008$), and treatment duration (median duration of ≥3.6 months, $P < 0.0001$) were significant risk factors adversely affecting survival. Multivariate analysis confirmed that gender (men, $P = 0.022$, hazard ratio [HR] = 0.607, 95% confidence interval [CI] = 0.406–0.930), Child-Pugh class (B, $P = 0.001$, HR = 2.344, 95% CI = 1.435–3.680), serum DCP level at baseline (median level of ≥738 mAU/mL, $P = 0.003$, HR = 1.726, 95% CI = 1.203–2.495), and duration of treatment (median duration of ≥3.6 months, $P < 0.001$, HR = 0.254, 95% CI = 0.179–0.359) were independent factors for survival.

Adverse events

Hand–foot skin reaction (HFSR) was the most commonly observed adverse event in our series, occurring in 145 (46%) patients. Other frequent toxicities included diarrhea ($n = 53$; 17%), fatigue ($n = 39$; 13%), liver dysfunction ($n = 36$; 12%), alopecia ($n = 24$; 8%), and hypertension ($n = 24$; 8%). The most frequent adverse event leading to discontinuation of sorafenib treatment was liver dysfunction ($n = 43$, including 35 patients with Child-Pugh class A and 8 with class B; 14%), followed by HFSR ($n = 12$; 2%) and diarrhea ($n = 12$; 2%). Interstitial pneumonia ($n = 2$) and tumor lysis syndrome ($n = 1$) were serious adverse events. A case of interstitial pneumonia resulted in death.

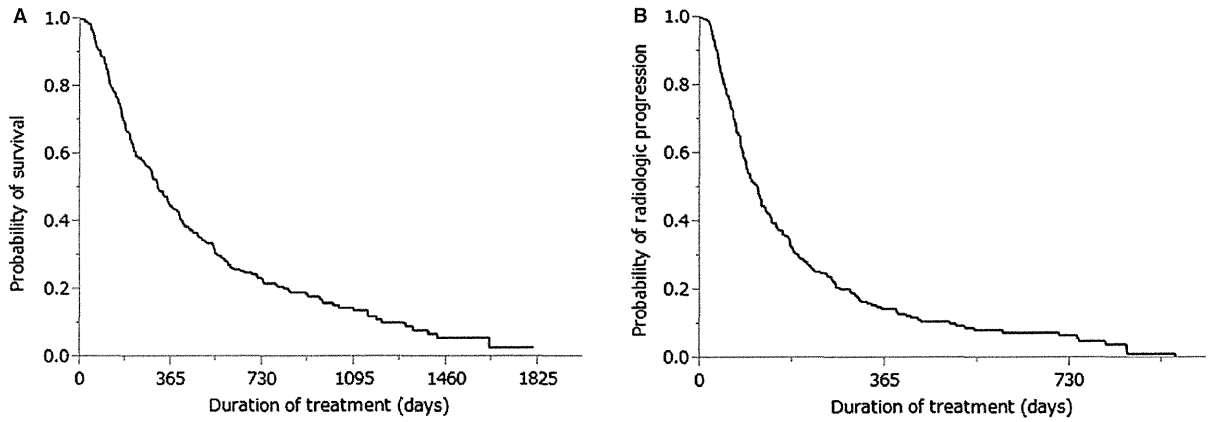

Figure 1. (A) Kaplan–Meier analysis of overall survival in all enrolled patients. Median survival time was 10.3 months and 1 year survival rate was 44%. (B) Kaplan–Meier analysis of radiologic progression-free survival in all enrolled patients. Median survival time was 3.6 months.

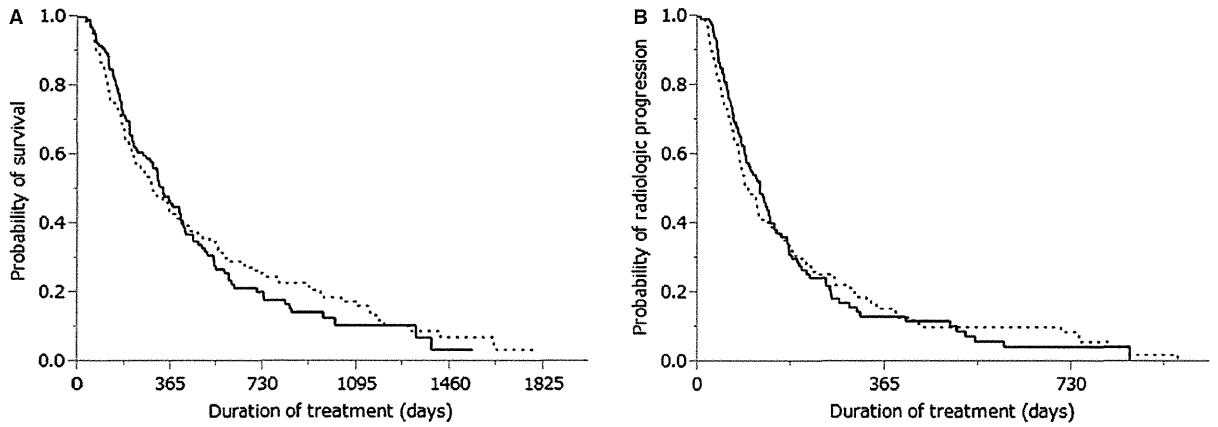

Figure 2. (A) Kaplan–Meier analysis of overall survival in patients with (dotted line) and without (solid line) extrahepatic metastasis (P = 0.7654). Median survival time was 11.0 months versus 9.6 months, respectively. (B) Kaplan–Meier analysis of radiologic progression-free survival in patients with (dotted line) and without (solid line) extrahepatic metastasis (P = 0.8658). Median survival time was 4.0 months versus 3.2 months, respectively.

Table 2. Univariate and multivariate analyses of overall survival in all patients.

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age (≥72 years)	1.213 (0.891–1.706)	0.2074		
Gender (male)	0.537 (0.360–0.818)	0.0042	0.634 (0.466–0.879)	0.0069
Child-Pugh class (B)	2.419 (1.479–3.817)	0.0007	2.236 (1.529–3.189)	<0.0001
Tumor stage (BCLC-C)	0.893 (0.634–1.277)	0.5272		
Initial dose (800 mg)	0.786 (0.547–1.112)	0.1851		
Daily average dosage (≥400 mg)	1.185 (0.821–1.717)	0.3644		
AFP (≥105 ng/mL)	1.116 (0.757–1.654)	0.5805		
AFP-L3 (≥22%)	1.233 (0.857–1.777)	0.2596		
DCP (≥738 mAU/mL)	1.791 (1.271–2.542)	0.0008	1.728 (1.321–2.266)	<0.0001
Duration of treatment (≥3.6 months)	0.374 (0.260–0.534)	<0.0001	0.370 (0.283–0.484)	<0.0001
Therapeutic effect (PD)	1.236 (0.879–1.737)	0.2221		

HR, hazard ratio; 95% CI, 95% confidence interval; BCLC, Barcelona Clinic Liver Cancer; AFP, alpha-fetoprotein; DCP, des-gamma-carboxy prothrombin; PD, progressive disease.

Impact of extrahepatic metastasis

Of the treated patients, 178 (57%) had extrahepatic metastasis and 134 (43%) did not. The most frequent organ sites of extrahepatic metastases were the lungs (n = 105), bone (n = 40), lymph nodes (n = 38), peritoneum (n = 17), and adrenal glands (n = 11). Cumulative survival curves of patients with (dotted line) and without (solid line) extrahepatic metastasis are shown in Figure 2A and B. The MST was 11.0 months for patients with extrahepatic metastasis and 9.6 months for those without (P = 0.7654, Fig. 2A), whereas the corresponding PFS time was 4.0 and 3.2 months, respectively (P = 0.8658, Fig. 2B). The therapeutic effect did not differ significantly between patients with and without extrahepatic metastasis (Table 3).

Cox proportional hazards regression analysis was performed to identify independent risk factors associated with overall survival in patients with extrahepatic metastasis (Table 4). The results of univariate analysis showed that gender (men, P = 0.0297), Child-Pugh class (B, P = 0.0182), serum DCP level at baseline (median level of ≥738 mAU/mL, P = 0.0032), and duration of treatment (median duration of ≥3.6 months, P < 0.0001) were significant risk factors adversely affecting overall survival in patients with extrahepatic metastasis. Multivariate analysis confirmed that gender (men, P = 0.0040, HR = 0.519, 95% CI = 0.344–0.805), Child-Pugh class (B, P = 0.0130, HR = 1.849, 95% CI = 1.145–2.875), serum DCP level at baseline (median level of ≥738 mAU/mL, P = 0.0010, HR = 1.816, 95% CI = 1.271–2.601), and duration of treatment (median duration of ≥3.6 months, P < 0.0001, HR = 0.285, 95% CI = 0.197–0.408) were independent risk factors for overall survival in patients with extrahepatic metastasis.

Table 3. Therapeutic effects in patients with and without extrahepatic metastasis; $P = 0.3061$ (via chi-square test).

Variable	With extrahepatic metastasis ($n = 178$)	Without extrahepatic metastasis ($n = 134$)
PR	8	10
SD	76	56
PD	83	56
Not evaluable	11	12

PR, partial response; SD, stable disease; PD, progressive disease.

Discussion

Sorafenib, an oral multikinase inhibitor and a new molecularly targeted therapy for advanced HCC, has been shown to offer significant survival benefit with good tolerance by two randomized phase III placebo-controlled trials [12, 15]. Thus, it has become the standard treatment for advanced HCC. The present study prospectively assessed the safety and efficacy of sorafenib and identified the factors associated with survival in advanced HCC patients. The MST and PFS of patients receiving sorafenib in this study were 10.6 and 3.8 months, respectively. This MST was longer than what was observed in the Asia-Pacific study (6.5 months) and comparable to the SHARP trial's result (10.7 months).

An exploratory multivariate analysis identified four baseline patient characteristics as prognostic indicators for overall survival, including gender, Child-Pugh class, serum DCP level at baseline, and duration of treatment. However, dosage and therapeutic effect of sorafenib were not significant risk factors adversely affecting survival in this study. It is noteworthy that men treated with sorafenib had higher survival rates than women. Although the reason for such a result is unclear, physical constitution might be a possible contributor. Moreover, the median treatment duration was 3.6 months in men and 3.0 months in women, suggesting that women might not be able to tolerate sorafenib treatment as well as men. Previous studies reported that in HCC patients, high serum DCP levels were associated with vascular invasion, metastasis, and tumor recurrence [22]. Furthermore, DCP was more useful as an HCC marker in larger tumors, which were more likely to be exposed to hypoxia during development. Thus, higher serum DCP levels might be indicative of a more advanced HCC state with reduced survival rates.

The overall disease control rate was 47% in this study, including 18 (6%) patients with PR and 127 (41%) with SD, whereas 134 (43%) patients had PD. Notably, the proportion of patients with PR in our study was higher than that of the SHARP trial (2%) and the Asia-Pacific study (3.3%). However, the reason for such a result is unclear. Previous studies suggested that there could be racial differences in terms of gene mutations that might affect sorafenib treatment [23]. Thus, Japanese patients with advanced HCC might be more sensitive to sorafenib than Western and other Asian patients. Further studies, with larger patient populations, are needed to investigate possible differences in the therapeutic effects of sorafenib.

Treatment-related adverse events are an important issue affecting the continuation of sorafenib treatment. In this study, although the overall incidence of treatment-related adverse events was high (86%), the observed events were primarily controlled with medical treatment and sorafenib dose reduction. Adverse events leading to discontinuation of treatment included liver dysfunction (14%), HFSR (2%), and diarrhea (2%), which are commonly associated with sorafenib [24, 25]. However, in the SHARP trial, the overall incidence of treatment-related adverse events was 80% in the sorafenib group, and the most frequent adverse events leading to discontinuation of sorafenib treatment were

Table 4. Univariate and multivariate analyses of overall survival in patients with extrahepatic metastasis.

	Univariate analysis		Multivariate analysis	
Variable	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age (≥72 years)	1.310 (0.836–2.057)	0.2379		
Gender (male)	0.533 (0.315–0.937)	0.0297	0.519 (0.344–0.805)	0.0040
Child-Pugh class (B)	2.242 (1.156–4.113)	0.0182	1.849 (1.145–2.875)	0.0130
Tumor stage (BCLC-C)	0.692 (0.197–4.406)	0.6419		
Initial dose (800 mg)	0.808 (0.493–1.302)	0.3857		
Daily average dosage (≥400 mg)	1.200 (0.762–1.909)	0.4322		
AFP (≥105 ng/mL)	0.969 (0.554–1.696)	0.9124		
AFP-L3 (≥22%)	0.931 (0.559–1.541)	0.7838		
DCP (≥738 mAU/mL)	1.966 (1.252–3.120)	0.0032	1.816 (1.271–2.601)	0.0010
Duration of treatment (≥3.6 months)	0.268 (0.162–0.439)	<0.0001	0.285 (0.197–0.408)	<0.0001
Therapeutic effect (PD)	1.105 (0.729–1.692)	0.6386		

HR, hazard ratio; 95% CI, 95% confidence interval; BCLC, Barcelona Clinic Liver Cancer; AFP, alpha-fetoprotein; DCP, des-gamma-carboxy prothrombin; PD, progressive disease.

gastrointestinal events (6%), fatigue (5%), and liver dysfunction (5%) [12]. HFSR is particularly well known as an early adverse event [26–28] associated with sorafenib therapy, and the severity of HFSR depends on treatment duration, dosage, and drug accumulation [29]. Further effort spent toward the effective control of adverse events and management of sorafenib dosing, with a priority given to facilitating long-term administration, will lead to the most effective therapy for HCC patients. Moreover, hepatic reserve is important for hepatic extraction and metabolism of sorafenib.

The prognosis of HCC patients with extrahepatic metastases is unsatisfactory [30, 31], but not well understood. In the present study, we assessed the prognosis of 312 consecutive HCC patients with or without extrahepatic metastases. We found that the most frequent metastatic sites were the lungs, bone, and lymph nodes. In addition, the overall survival and radiologic PFS time did not differ significantly between patients with and without extrahepatic metastasis. Multivariate analysis showed that independent risk factors for decreased overall survival in patients with extrahepatic metastasis were similar to those affecting all patients. Thus, the presence of extrahepatic metastasis might not affect the prognosis of advanced HCC patients treated with sorafenib. Moreover, previous studies reported that advanced HCC with extrahepatic metastasis often had poor prognosis. Therefore, these patients should be considered for sorafenib treatment.

In conclusion, our results indicated that the therapeutic effect of sorafenib was comparable in advanced HCC patients with or without extrahepatic metastasis. In addition, this study demonstrated that sorafenib should be administered for hepatic reserve and as long-term treatment for advanced HCC patients.

Conflict of Interest

None declared.

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Effect of pioglitazone on outcome following curative treatment for hepatocellular carcinoma in patients with hepatitis C virus infection: A prospective study

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Abstract. Pioglitazone is an insulin sensitizer used for the treatment of diabetes mellitus (DM). DM with insulin resistance is a risk factor for hepatocellular carcinoma (HCC) in patients with hepatitis C virus (HCV) infection. We aimed to investigate the effects of pioglitazone on HCC recurrence following treatment in HCV-infected patients. Between 2009 and 2011, 85 HCV-infected HCC patients who underwent curative treatment were enrolled in this prospective study. Among 45 patients with type 2 DM, 27 were administered pioglitazone (pioglitazone group) following treatment. The remaining 58 patients were assigned to the control group. The primary outcome was recurrence-free survival. Changes in insulin resistance and serum adiponectin levels resulting from pioglitazone treatment were also assessed. In the whole analysis (n=85), no significant difference in recurrence-free survival was observed between the pioglitazone and control groups. However, in a spline model analysis of DM patients, a decreased risk of HCC recurrence was associated with increased body weight in patients with a body mass index (BMI) ≥23; this association became significant at BMI ≥24 (hazard ratio=0.17; 95% confidence interval: 0.03-0.95). In addition, significantly decreased homeostasis model assessment for insulin resistance values (P=0.002) and significantly increased serum high-molecular-weight adiponectin levels (P<0.001) were observed following pioglitazone treatment. Although pioglitazone did not suppress HCC recurrence in the whole analysis, it inhibited HCC recurrence in overweight HCV-infected diabetic patients. Moreover, pioglitazone improved insulin resistance and adipocytokine levels. Thus, pioglitazone may suppress HCC recurrence, which is associated with glucose and fat metabolism disorders.

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Key words: pioglitazone, hepatocellular carcinoma, recurrence, obesity, diabetes mellitus, hepatitis C virus, insulin resistance

Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide. The incidence of HCC has increased in Eastern Asia and Africa over the last several decades and has also increased in the United States (1). In several countries, this trend is attributed to hepatitis C virus (HCV) infection and in Japan, >70% of HCC cases are associated with chronic liver disease with HCV infection (2). Recent advances in imaging procedures and surveillance programs for high-risk patients have led to increased detection of early-stage HCC, resulting in an increase in the identification of patients in whom curative treatments, such as hepatic resection and radiofrequency ablation, may be feasible (3). However, as HCC frequently recurs even following curative treatment, prevention of recurrence is required to prolong the survival of HCC patients with HCV infection. For the prevention of HCC recurrence following curative treatment, adjuvant interferon therapy is known to be highly effective and is generally used in patients with HCV infection (4,5). However, due to the high rate of non-response and severe adverse effects, interferon therapy is not universally used in HCV patients, particularly those who are older or who have a high viral load, genotype 1 and/or severe fibrosis (6,7). Therefore, it is crucial to investigate other adjuvant therapies for the prevention of HCC recurrence following curative treatment in patients with HCV infection.

In chronic liver disease with HCV infection, the prevalence of type 2 diabetes mellitus (DM) has been reported to be higher compared to that associated with other chronic liver diseases, including hepatitis B virus infection (8). To explain this strong association, in addition to obesity, hepatic inflammation and fibrosis, Kawaguchi *et al* (9) and Shintani *et al* (10) suggested that HCV directly causes hepatic insulin resistance and subsequent hyperinsulinemia. Moreover, DM with insulin resistance was found to be a potential risk factor for the development of HCC, as well as for the recurrence of HCC in patients with HCV infection (11,12). Thus, these findings led

us to hypothesize that the treatment of type 2 DM associated with insulin resistance significantly affects the development of HCC in patients with HCV infection.

Pioglitazone is a member of the thiazolidinedione family and is widely used for the treatment of type 2 DM. Pioglitazone reduces insulin resistance in the liver and peripheral tissues by stimulating the peroxisome proliferator-activated receptor (PPAR)-γ and improves macrovascular outcomes (13). Previous studies reported that pioglitazone improves insulin resistance in patients with HCV infection treated with peginterferon and ribavirin (14,15). In addition, pioglitazone itself was shown to exert anticarcinogenic activity through the inhibition of DNA synthesis and cell cycle progression in HCC cell lines and in an animal model of HCC (16,17). Moreover, pioglitazone was recently reported to suppress the onset of HCC in a hospital-based case-control study (18) and a population-based cohort study (19). Therefore, the aim of this study was to determine whether pioglitazone decreases the risk of HCC recurrence following curative treatment in patients with HCV infection. We also investigated the effect of pioglitazone on type 2 DM due to insulin resistance.

Patients and methods

Patients. This clinical trial was conducted at the Kurume University School of Medicine. A total of 85 patients who met the inclusion criteria were enrolled between 2009 and 2011. The diagnosis of HCC was histologically confirmed by needle biopsy or based on the findings of typical radiological characteristics on dynamic computed tomography (CT) and magnetic resonance imaging (MRI). Pretreatment hepatic function was evaluated using the Child-Pugh scoring system. The inclusion criteria were i) HCV infection, ii) diagnosis of HCC with ≤3 tumors, each ≤3 cm, by imaging studies and iii) HCC treated with curative treatment (radiofrequency ablation or resection). The exclusion criteria were i) severe gastrointestinal stasis, ii) severe renal injury (creatinine >2.0 mg/dl), iii) severe esophageal and/or gastric varices, iv) HCC with macroscopic vascular invasion or extrahepatic metastasis, v) poorly differentiated HCC, vi) heart failure, vii) liver cirrhosis of Child-Pugh grade C and viii) type 1 DM.

The study protocol was approved by the Ethics Committee of Kurume University and conformed to the guidelines of the 1975 Declaration of Helsinki. Written informed consent was obtained from each subject prior to enrolment. This study has been registered in the University Hospital Medical Information Network (UMIN) Clinical Trials Registry under the registration number UMIN000007344.

Study design and pioglitazone treatment protocol. Patients who met the inclusion criteria were prospectively enrolled and were first evaluated for the presence of type 2 DM. Patients who did not have type 2 DM were assigned to the control group (no treatment; n=40). For patients with type 2 DM, we additionally confirmed whether they wished to receive pioglitazone. Patients who declined administration of pioglitazone were assigned to the control group (n=18) and patients who consented to receiving pioglitazone were assigned to the pioglitazone treatment group (n=27). All the patients in the treatment group were administered pioglitazone at an initial dose of 30 mg/day following curative treatment. Treatment discontinuation and dose reduction were based on toxicity. In cases with symptomatic heart failure, pioglitazone was permanently discontinued without dose reduction, regardless of the severity. In cases with facial and/or lower limb edema with functional impairment or symptomatic ascites, the patients were first treated with diuretics, such as spironolactone and furosemide. If symptomatic edema or ascites did not improve despite the administration of diuretics, pioglitazone was reduced to a dose of 15 mg/day or interrupted until the symptoms disappeared. When weight gain ≥5% of baseline occurred, pioglitazone was reduced to a dose of 15 mg/day. To evaluate the tolerability to pioglitazone, all the adverse events were recorded.

Diagnosis of type 2 DM and use of antidiabetic agents. Type 2 DM was classified according to the 2010 American Diabetes Association criteria (20). Patients with fasting plasma glucose (FPG) ≥126 mg/dl, 2-h plasma glucose ≥200 mg/dl during an oral glucose tolerance test, or a random plasma glucose ≥200 mg/dl, were considered to have type 2 DM. Of the 85 patients included in this study, 45 were diagnosed with type 2 DM. Of the 45 patients with type 2 DM, no patients had been treated with pioglitazone prior to study enrolment and 24 patients were prescribed other antidiabetic agents, including biguanides (n=2), α-glucosidase inhibitors (n=11), sulfonylureas (n=13) and insulin injections (n=5).

Evaluation of type 2 DM control. In 27 of the 45 patients with type 2 DM, pioglitazone was administered following curative treatment. To evaluate the treatment effects of pioglitazone, body mass index (BMI), FPG, serum insulin level fasting immunoreactive insulin (FIRI), glycated hemoglobin (HbA1c) level and homeostasis model assessment for insulin resistance (HOMA-IR) values were measured at baseline and after 1-3 months. HOMA-IR values were calculated using the formula FPG (mg/dl) x FIRI (mU/l)/405. In addition, serum low-molecular-weight (LMW), middle-molecular-weight (MMW), high-molecular-weight (HMW) and total adiponectin levels were measured at baseline and after 1-3 months by enzyme-linked immunosorbent assay (ELISA) using the Human Adiponectin kit for Total and Multimers (Sekisui Medical Co., Ltd., Tokyo, Japan).

Follow-up and assessment of recurrence. Following curative treatment, each patient was closely followed up on a monthly basis. Serum biochemistry tests, α-fetoprotein (AFP) levels and des-γ-carboxy prothrombin (DCP) levels were measured and ultrasonography was performed monthly. Contrast-enhanced dynamic CT was performed every 3 months until 6 months post-treatment and every 6 months thereafter. MRI was performed as a supplemental examination. Recurrence was diagnosed based on the combined findings of these assessments (characteristic appearances typical of HCC). The primary endpoint was recurrence-free survival, which was defined as the time interval between study entry and the first recurrence of HCC. Patients who survived without HCC recurrence were censored at the closing date of this study, which was December, 2011. The median duration of follow-up was 521 days (range, 100-961 days).

Table I. Patient characteristics.

Characteristics	Pioglitazone group (n=27)	Control group (n=58)	P-value
Age, years (range)	72 (53-84)	70 (50-86)	0.832
Gender (male/female)	17/10	35/23	0.818
BMI (kg/m^2)	22.9 (20.1-30.7)	23.0 (15.2-29.3)	0.401
AST (U/l)	53 (23-137)	52 (17-118)	0.257
ALT (U/l)	44 (18-136)	45 (14-240)	0.781
Platelet count (x10^9/l)	107 (46-185)	111 (37-281)	0.431
Child-Pugh grade (A/B)	22/5	45/13	0.682
Type 2 diabetes mellitus (present/absent)	27/0	18/40	<0.001
FPG (mg/dl)	117 (89-200)	96 (76-185)	
FIRI (μU/ml)	11.4 (3.2-31.2)	10.6 (4.0-30.9)	
HOMA-IR	3.3 (1.1-10.1)	2.6 (0.9-7.7)	
HbA1c (%)	6.1 (4.7-8.0)	5.3 (4.5-8.6)	
AFP (ng/ml)	14.8 (2.3-282.1)	13.4 (2.4-710.4)	0.393
DCP (mAU/ml)	21 (11-8,220)	25 (8-486)	0.688
Tumor size (mm)	16 (12-26)	17 (10-29)	0.401
Tumor number (single/2-3)	20/7	37/21	0.348

Continuous variables are presented as median (range). BMI, body mass index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; FPG, fasting plasma glucose; FIRI, fasting immunoreactive insulin; HOMA-IR, homeostasis model assessment for insulin resistance; HbA1c, glycated hemoglobin; AFP, α-fetoprotein; DCP, des-γ-carboxy prothrombin.

Statistical analysis. Continuous variables are expressed as median (range) values. Comparisons between the two groups were performed using the Mann-Whitney U test for continuous variables and the Chi-square or Fisher's exact tests for discrete variables. Pioglitazone-induced metabolic changes were examined by the Wilcoxon's signed-rank test. Recurrence-free survival was measured by the Kaplan-Meier method and differences between subgroups were compared with log-rank tests. To investigate treatment efficacy in preventing HCC recurrence in the 45 patients with type 2 DM, we applied the Cox proportional hazards model, including not only the main terms BMI and group (pioglitazone or control) and their interaction term, but also knot terms for BMI that serve as inflection points. The Akaike information criterion (AIC) was used to evaluate these alternate models (21). The location of knots was determined objectively, with the minimum AIC among their prespecified candidates, which were whole-number BMI values from 15 to 30. This model is referred to as a spline model, which we have previously described in detail (22,23). Briefly, if the interaction term is selected, the hazard ratio (HR) between the pioglitazone and control groups has a functional form of BMI as the output of this model. All the P-values were two-tailed and P<0.05 was considered to indicate a statistically significant difference. Statistical analysis was performed using SPSS software, version 20 (IBM Corp., Somers, NY, USA) and the R package version 3.0.1 (http://www.r-project.org/index.html).

Results

Patient characteristics. Patient characteristics are shown in Table I. The baseline characteristics of the two groups, including age, gender, BMI, aspartate aminotransferase level, alanine aminotransferase level, platelet count and Child-Pugh grade, were comparable, with no significant differences between groups. In addition, no significant differences in tumor characteristics, including AFP level, DCP level, tumor size, or tumor number, were observed. All the patients in the pioglitazone group and 18 (32.0%) patients in the control group had type 2 DM (P<0.001).

Effect of pioglitazone on prevention of recurrence

Whole analysis. The recurrence-free survival curves of the 85 patients (whole analysis) are shown in Fig. 1A. The recurrence-free survival rates at 1 and 2 years were 84.6 and 44.2% respectively, in the pioglitazone group and 71.9 and 59.1% respectively, in the control group; none of these differences were statistically significant (P=0.9089).

Subanalysis of patients with type 2 DM

Log-rank test. The 45 patients with type 2 DM were evaluated in a subanalysis. The recurrence-free survival curves of these patients are shown in Fig. 1B. The recurrence-free survival rates at 1 and 2 years were 84.6 and 44.2%, respectively, in the pioglitazone group and 61.1 and 36.5%, respectively, in the control group; none of these differences were statistically significant (P=0.3735).

Spline model analysis. The efficacy of pioglitazone in preventing HCC recurrence was evaluated by a spline model. Fig. 2 shows the association between BMI and HRs with 95% confidence intervals (CIs) for HCC recurrence in the 45 patients with type 2 DM. In the Cox proportional hazards model, BMI=23 was selected as the knot location (i.e., interaction term with group) and indicated a significant dependence of the HR between the pioglitazone and control groups for BMI ≥23. A significantly decreased risk of HCC recurrence

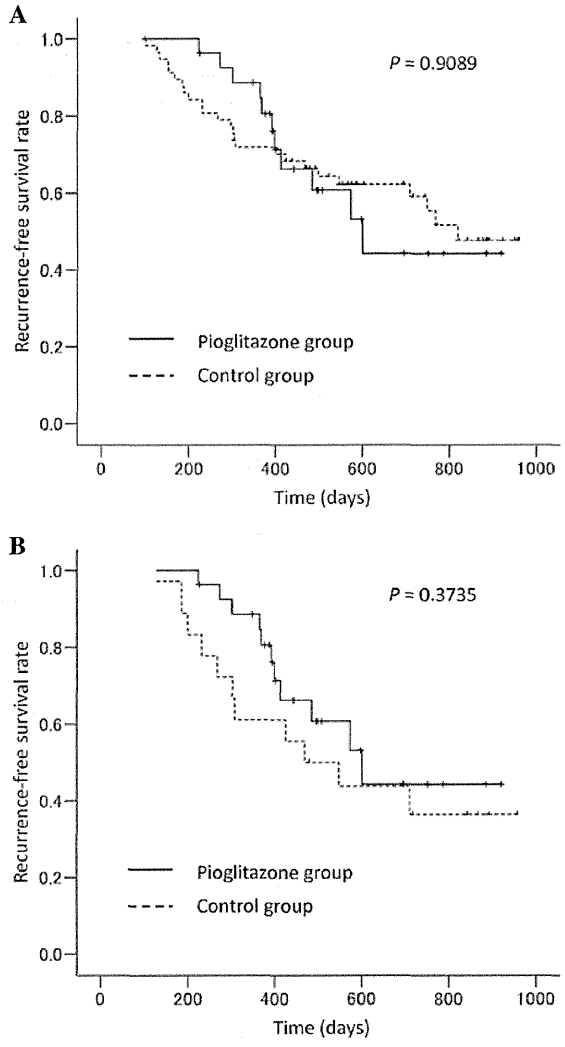

Figure 1. Recurrence-free survival curves of hepatocellular carcinoma patients with hepatitis C virus infection who underwent curative treatment. (A) Whole analysis of all 85 patients. (B) Subanalysis of 45 patients with type 2 diabetes mellitus.

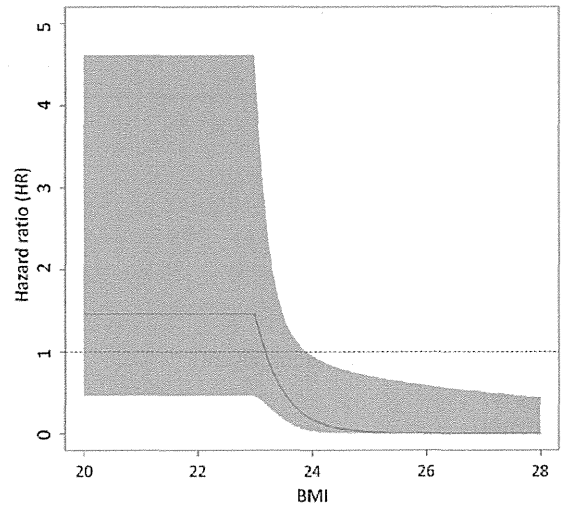

Figure 2. Association between body mass index (BMI) and hazard ratios (HRs) with 95% confidence intervals (CIs) for hepatocellular carcinoma (HCC) recurrence in the 45 patients with type 2 diabetes mellitus. A solid line and the gray area showed HRs and 95% CIs, respectively. A significantly decreased risk of HCC recurrence in the pioglitazone group is observed for patients with a BMI ≥24.

was observed in the pioglitazone group for patients with a BMI ≥24 (HR=0.17; 95% CI: 0.03-0.95).

Effect of pioglitazone on glucose metabolism and adiponectin levels. The changes in the metabolic variables in the 27 patients treated with pioglitazone are listed in Table II. BMI was significantly increased following pioglitazone treatment. By contrast, a significant improvement was observed in the glycemic variables, including FPG, FIRI, HOMA-IR and HbA1c. In addition, serum total, LMW, MMW and HMW adiponectin levels were significantly increased following pioglitazone treatment.

Adverse events. Of the 27 patients treated with pioglitazone, 18 (66.7%) experienced ≥1 adverse event. The most common adverse events were edema and subsequent weight gain, which occurred in 14 (51.8%) and 8 (29.6%) patients, respectively. These events were largely controlled by dose reduction of pioglitazone and diuretic treatment; however, 6 patients discontinued pioglitazone due to uncontrollable edema which inerfere with the activities of daily living. The median serum albumin levels in patients with and without edema were 3.4 and 3.9 mg/dl, respectively (P<0.016). Moreover, the serum albumin level in all patients with edema was <4.0 mg/dl. Other mild adverse events included increased appetite and ascites in 3 (11.1%) and 2 (7.4%) patients, respectively. Two patients developed hypoglycemia, possibly caused by combination of insulin injections; this was controlled by reducing the insulin injections. Severe adverse events included acute heart failure in 1 patient, who discontinued pioglitazone ~6 months after treatment initiation. No patients developed liver dysfunction or gastrointestinal symptoms.

Discussion

In the whole analysis of this study, no significant differences in HCC recurrence-free survival rates were observed between the control and pioglitazone groups. However, a spline model analysis revealed that pioglitazone significantly decreased the risk of HCC recurrence in HCV-infected diabetic patients with a BMI ≥24. Moreover, pioglitazone treatment decreased HOMA-IR values and increased serum multimeric adiponectin levels in HCV-infected diabetic patients. Thus, pioglitazone may inhibit HCC recurrence through the regulation of insulin resistance and adipocytokine levels in HCV-infected diabetic patients who are overweight.

Pioglitazone, a PPAR-γ agonist, inhibits DNA synthesis and cell cycle progression, resulting in anticarcinogenic activity in HCC cell lines and in an animal model of HCC (16,17). Pioglitazone was recently reported to suppress the onset of HCC in a hospital-based case-control study (18) and a population-based cohort study (19). These findings suggest that pioglitazone may also exert inhibitory effects on HCC recurrence. However, the present results revealed no significant differences in HCC recurrence-free survival rates

Table II. Changes in metabolic variables in 27 patients treated with pioglitazone.

Variables	Pioglitazone treatment		P-value
	Before	After	
Body weight (kg)	59.8 (39.6-83.1)	60.3 (41.3-86.2)	0.012
FPG (mg/dl)	117.5 (89.0-200.0)	110.0 (80.0-159.0)	0.007
FIRI (μU/ml)	11.3 (3.2-31.2)	9.3 (1.8-27.7)	0.006
HOMA-IR	3.3 (1.1-10.0)	2.6 (0.6-7.1)	0.002
HbA1c (%)	6.1 (4.7-8.0)	5.6 (4.4-7.1)	0.002
Total adiponectin (μg/ml)	8.8 (1.5-49.3)	26.8 (3.1-60.7)	<0.001
HMW adiponectin (μg/ml)	4.3 (0.2-32.4)	17.3 (0.9-39.1)	<0.001
MMW adiponectin (μg/ml)	1.6 (0.4-9.1)	4.1 (0.9-12.6)	<0.001
LMW adiponectin (μg/ml)	3.7 (0.9-7.8)	5.6 (1.4-13.0)	<0.001

Continuous variables are presented as median (range). FPG, fasting plasma glucose; FIRI, fasting immunoreactive insulin; HOMA-IR, homeostasis model assessment for insulin resistance; HbA1c, glycated hemoglobin; HMW, high-molecular-weight; MMW, middle-molecular-weight; LMW, low-molecular-weight.

between the control and pioglitazone groups in the whole analysis. Although the reason for the discrepancy between previous studies and the present findings remains unclear, the proportions of patients with HCV infection may be responsible for the differences between these results. All the patients included in our study were HCV-positive, whereas the majority of patients in the previous studies were not infected with HCV. HCC frequently recurs due to various factors, including hepatic inflammation, hepatic fibrosis, HCV proteins, aging and therapeutic procedures in patients with HCV infection (24). Thus, pioglitazone may not have been sufficiently effective to universally suppress HCC recurrence in the present study.

We also performed a subanalysis of patients with type 2 DM. A log-rank test revealed no significant difference in HCC recurrence-free survival rates between the control and pioglitazone groups. However, the use of a Cox proportional hazards model, referred to as a spline model (22,23), revealed that the HR decreased exponentially in association with increased body weight starting at BMI=23 and this association became statistically significant at BMI ≥24. These findings revealed that being overweight is a key factor for pioglitazone-induced suppression of HCC recurrence. The overweight state causes insulin resistance and subsequent hyperinsulinemia (25). Since insulin is a growth-promoting hormone for HCC (26), we hypothesize that pioglitazone suppresses HCC recurrence through improvement of insulin resistance. In support of this hypothesis, we also demonstrated that pioglitazone significantly decreased HOMA-IR values, as well as serum insulin levels. An increased HOMA-IR value is a known risk factor for HCC recurrence (12), as is the use of antidiabetic agents that cause hyperinsulinemia, such as exogenous insulin and second-generation sulfonylurea agents (27), which further supports our hypothesis. Another mechanism underlying the development of HCC in overweight patients may be that overweight individuals exhibit increased expression of the pro-inflammatory cytokines tumor necrosis factor-α and interleukin-6 in adipose tissue, thereby causing hepatic inflammation and subsequent development of HCC (28). These cytokines have also been demonstrated to be positively associated with the development of HCC in patients with HCV infection (29). Consequently, pioglitazone treatment may also suppress HCC recurrence through the downregulation of these cytokines in adipose tissue.

In this study, we also demonstrated that pioglitazone significantly increased multimeric adiponectin levels in HCV-infected diabetic patients. Adiponectin is an adipocytokine that is inversely correlated with the amount of visceral fat accumulation, another important risk factor for HCC (30). Adiponectin not only increases insulin sensitivity, but was also shown to increase the levels of the tumor suppressor tuberous sclerosis, resulting in a significant reduction of liver tumorigenesis in an animal HCC model (31). We previously demonstrated that low serum adiponectin levels are associated with the development of HCC (32). Taken together, these findings suggest that the pioglitazone-induced upregulation of adiponectin may have contributed to the suppression of hepatocarcinogenesis observed in the present study. Moreover, lower adiponectin levels were recently reported to be associated with the malignant potential of HCC and poor prognosis in HCC patients (31,33). Further studies should focus on the effects of pioglitazone on the overall survival of HCC patients.

The most common adverse events in this study were edema and subsequent weight gain. In particular, severe lower limb edema may compromise the quality of life of the patients. Thiazolidinedione-induced edema has been shown to occur through enhanced sodium-coupled bicarbonate absorption from the renal proximal tubules via PPAR-γ-dependent non-genomic signaling (34). In this study, patients with low serum albumin levels frequently experienced edema. Thus, physicians must be on the lookout for the development of pioglitazone-induced edema in patients with advanced liver disease. Although no patients in this study developed severe liver dysfunction, troglitazone, a first-generation thiazolidinedione, is known to cause severe liver failure (35). Troglitazone-induced changes in the hepatic molecular profiles differ from those caused by pioglitazone (36). However, thiazolidinedione-induced liver

injury may occur through an idiosyncratic mechanism (37). In fact, fatal liver failure associated with pioglitazone has been previously reported (38). Therefore, we should also be aware of pioglitazone-induced liver injury in chronic liver disease with HCV infection.

In conclusion, the results of the present study demonstrated that pioglitazone did not suppress HCC recurrence in all patients. However, a spline model analysis revealed that pioglitazone significantly decreased the risk of HCC recurrence in HCV-infected diabetic patients with a BMI ≥24. Moreover, pioglitazone decreased HOMA-IR values and increased serum multimeric adiponectin levels in HCV-infected diabetic patients. Thus, although pioglitazone does not appear to suppress HCC recurrence universally, it may exert an inhibitory effect on HCC recurrence in overweight HCV-infected diabetic patients, possibly through the regulation of insulin resistance and adipocytokine levels.

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肝癌の疫学—国際比較—

Worldwide epidemiology of hepatocellular carcinoma

鳥村拓司

Key words：肝細胞癌，サーベイランス，B型肝炎ウイルス，C型肝炎ウイルス

はじめに

全世界における肝癌の発生数，死亡数に関して，GLOBOCANの2008年のデータでは全原発性肝癌の年間の患者発生数は748,000人で，すべての癌種のうち6番目に多い．このうち，男性では年間約522,000人が発症し，5番目に多い悪性腫瘍であり，女性では226,000人が発症するといわれており，7番目に多い癌種である[1]．2002年のデータでは年間の患者発生数は626,000人であり，世界的にみると肝癌の発生数は増加傾向にある．一方，死亡患者数は3番目に多く（男性：2番目，女性：5番目），年間696,000人が死亡している[2]．肝細胞癌のうち約85％は発展途上国において発生している．

肝細胞癌の約75％は肝炎ウイルス由来の肝障害を背景に発症するといわれている．B型肝炎患者は全世界で推定3億6千万人存在すると考えられており，世界中では肝細胞癌の50–55％がB型肝炎由来であり，B型肝炎ウイルスの高浸淫地域に限るとB型肝炎由来の肝細胞癌は89％を占める．一方，C型肝炎患者は全世界で推定1億7千万人存在し，C型肝炎由来の肝細胞癌は全肝細胞癌の25–30％を占めるといわれている．地域別にみると，中国，台湾，韓国など日本を除く極東もしくはアジア・太平洋地域ではB型肝炎由来の肝細胞癌患者が多く，サハラ砂漠以南のアフリカ諸国ではB型肝炎とアフラトキシンの曝露が主たる原因となっている．一方，日本および西洋諸国ではC型肝炎由来の肝細胞癌患者が主体となる．肝細胞癌の発症年齢，性差，人種差などは各地域におけるB型やC型肝炎の有病率や感染が広がった時期により異なっているといわれている．

肝細胞癌ハイリスクグループとしては，B型もしくはC型肝炎ウイルス感染者，男性，高齢者，肝硬変の合併，肥満，糖尿病患者，地域によってはアフラトキシンBの曝露などが挙げられる．

本稿では，我が国における肝細胞癌の疫学的特徴や治療成績をより理解していただくために，世界各地における肝細胞癌の疫学的特徴を紹介したいと思う．

1 世界各地における肝細胞癌の発生状況

肝癌の80％以上はサハラ砂漠以南のアフリカ諸国と東アジアで発生している．なかでも，GLOBOCANの2002年における調査によると，発生患者数は中国が最も多かった[2]．年齢補正した人口10万人あたり肝癌の発生率は韓国，朝鮮民主主義人民共和国では男性が47.1人，女性が11.4人と最も高く，ついでタイ，中国の

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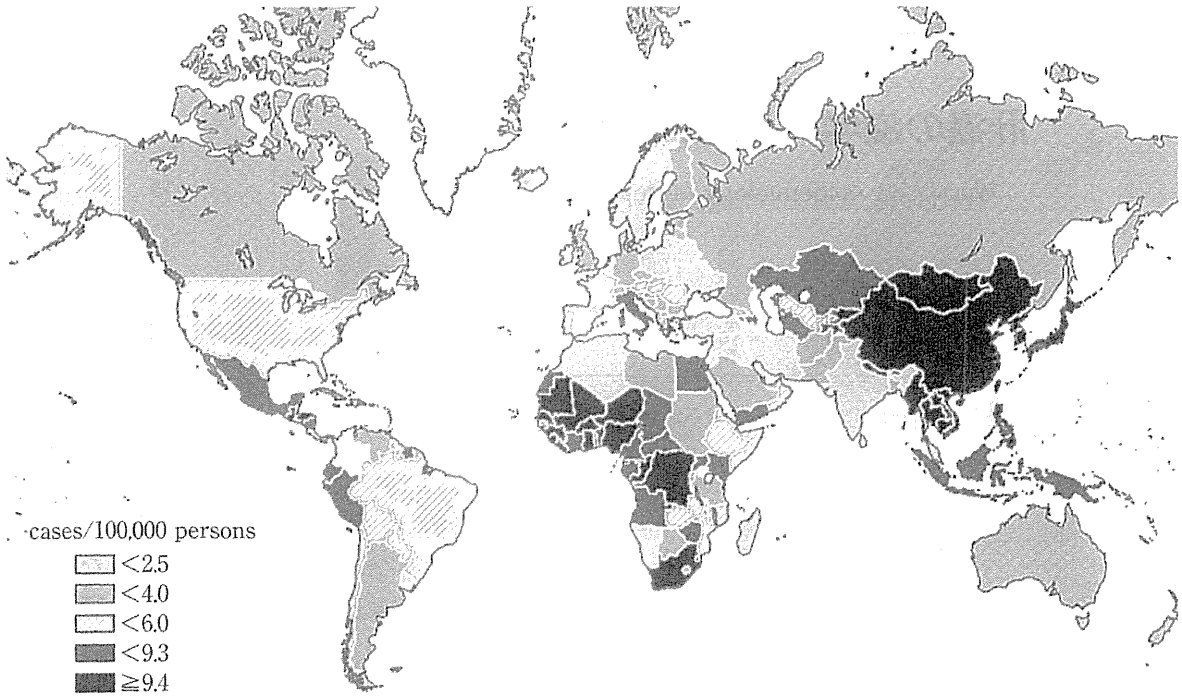

図1　世界各地域での肝癌発生状況
（Hashem B, et al: N Engl J Med 365: 1118–1127, 2011. より引用）

順であり，発生頻度の高い地域は東アジア，中央アフリカ，東アフリカ，東南アジアなどであった．反対に発生頻度の最も低い国は，イランついでトルコであり，発生頻度の低い地域は南中央アジア，北部ヨーロッパ，オセアニア，南北アメリカ，北アフリカ，西アジア，ついで東，西ヨーロッパ，南アフリカ，カリブ海諸国などであり，総じて先進国では肝癌の発生頻度は低い傾向にあった（**図1**）．

男女比はイランを除くすべての国々で男性の方が女性に比べて多く，全体での男女比は2.4：1であったが，肝癌の発生頻度が高い国ほど男性の占める割合が多い傾向にあった．

2　地域別の肝細胞癌の特徴

1）アジア・太平洋地域

a. 中　　国

中国においては，推定1億3千万人存在するといわれているB型肝炎ウイルス持続感染者が最も重要な危険因子である．また，C型肝炎ウイルス感染者も，1,300万人存在するといわれており，中国全体での肝細胞癌の発症は全世界の55％を占めている．肝細胞癌の平均発症年齢は55–59歳であった[3]．

b. 韓　　国

韓国でもB型肝炎ウイルス持続感染者が最も重要な危険因子である．40歳以上の国民のうち男性では4.8％，女性では3.6％，全体では4.1％がB型肝炎ウイルス持続感染者といわれている[4]．

c. 台　　湾

台湾もB型肝炎ウイルス持続感染者が最も重要な危険因子である．しかし，1984年から開始されたワクチン治療により40歳以下の肝細胞癌発生率は同年齢のB型肝炎ウイルス持続感染者の減少とともに低下傾向にある．さらに，B型肝炎ウイルス高浸淫地区における腹部超音波検査によるスクリーニングにより45–69歳の肝細胞癌による死亡率が31％減少したとの報告がある[5]．

d. マレーシア，タイ，オーストラリア

マレーシアにおける肝細胞癌患者のうち57.6％はB型肝炎ウイルス持続感染者であり，わず

か2.4％がC型肝炎ウイルス由来であった．平均発症年齢は55歳と若く，男女比は3.7：1であった．肝細胞癌発見時に51.9％の症例で多発腫瘍が認められ，82.9％は治療が行えなかった．このため発見からの生存期間の中央値はわずか1.9カ月であった．タイにおいても同様で，B型肝炎ウイルス由来の肝細胞癌が49.6％で，C型肝炎ウイルス由来は19.2％であった．男性患者は全体の79.2％を占め，平均発症年齢は57.4歳であった．発見からの生存期間はマレーシアよりは良好で10.5カ月であった．オーストラリアにおいてはアジア・太平洋地域からの移民の増加によりB型肝炎由来の肝細胞癌が急増してきており，1960年に比べ2005年は実に140倍の患者数となっている[6]．

2）アフリカ

a．エジプト

エジプトはアフリカ諸国の一つでありながら，世界の中でもC型肝炎ウイルス高浸淫地域の一つである．このため，C型肝炎ウイルス由来の肝細胞癌が増加し91.3％を占めている．一方，B型肝炎由来の肝細胞癌はわずか2.5％にとどまっている．発症年齢は50–60歳が最も多い[7]．

b．サハラ砂漠以南のアフリカ諸国

肝細胞癌に対する正確な疫学的データは乏しいが，B型肝炎ウイルス感染とアフラトキシンの曝露が肝細胞癌の主たる原因となっている．同地域では毎年46,000例の新規患者が診断されており，人口10万人あたり41.2人が発症している．最も肝発癌率が高いのはモザンビークである．診断された患者のうち93％は1年以内に死亡する[8]．

3）ヨーロッパ

a．イタリア

イタリアは2000年初頭までヨーロッパの中でも肝細胞癌による死亡が最も多かった．しかし，その後徐々に減少傾向にある．C型肝炎ウイルス由来の肝細胞癌が肝細胞癌全体に占める割合は63％で，こちらも近年減少傾向にある．発癌の平均年齢は徐々に高齢化し2006年から2010年の調査では70.8歳であった．近年，サーベイランスシステムが発達したためC型肝炎ウイルス由来の肝細胞癌の発見時の平均腫瘍径は，1986年から1990年までの調査では4.2 cmであったが2006年から2010年の調査では3.2 cmと縮小し，これに伴い平均生存期間も24カ月から37カ月へ改善した[9]．

b．スペイン

スペインにおける肝細胞癌のうち42％はC型肝炎ウイルス由来であり，30％はアルコール由来であった．肝細胞癌患者のうち47％はスクリーニングにより発見された．78％は男性患者であり，平均年齢は65歳であった．初回治療では46.4％に対して肝動脈化学塞栓術が選択された[10]．

c．フランス

フランスではアルコール性肝硬変が肝細胞癌の背景因子として最も多い．ついで近年では非アルコール性脂肪性肝硬変が増加してきている．腹部超音波検査によるサーベイランスシステムが不十分なため，わずか20％の患者がサーベイランスにて検出されるにすぎない．また，肝細胞癌患者の25％が外科的切除，肝移植，ラジオ波焼灼療法など根治的治療の適応となるにすぎず，約1/3の症例は積極的な治療が行えない状態で発見される[11]．

d．ロシア

ロシアにおける人口10万人あたりのB型肝炎ウイルス，C型肝炎ウイルスの感染者は各々7.6人，5.4人である．B型肝炎ウイルス由来の肝細胞癌は全体の39.9％，C型肝炎ウイルス由来は17.4％であった．B型肝炎ウイルス由来の肝細胞癌患者，C型肝炎ウイルス由来の肝細胞癌患者の生存期間の中央値はともに3カ月であった[12]．

4）南北アメリカ

a．アメリカ合衆国

米国における肝細胞癌の発生頻度は1980年代に比べ約3倍に増加している．アジア系が最も発生頻度が高いが，近年ヒスパニックや黒人および白人の患者が増加してきている．男女比は3：1で男性に多い．肝細胞癌患者において10–15％はB型肝炎ウイルス感染者，50–60％はC型肝炎ウイルス感染者，20–25％はアルコ

ール性肝障害を合併し，20-30％はメタボリックシンドロームを合併していた．人種別にみてみると，肥満や糖尿病は白人やヒスパニックの肝細胞癌患者に多く，アジア系や黒人ではC型肝炎ウイルス感染者が多かった．年齢に関しては45-60歳で最も増加する傾向にあった．地域別では，テキサス，ルイジアナやミシシッピを含む南部地域に多発していた[13]．

b. ブラジル

ブラジルにおける肝細胞癌患者のうち65.3％はC型肝炎由来であり，56.9％が男性で平均発症年齢は57歳であった．79.2％の患者はミラノ基準内で診断されており，平均生存期間は52.3カ月であった[14]．

3 肝細胞癌発症の危険因子

1）B型肝炎ウイルス感染

全世界において人口の約5％がB型肝炎ウイルスの持続感染者と考えられており，このうち75％の感染者はアジア地域に存在している．西欧諸国での感染率は0.3-1.5％と比較的低い．日本を除くアジア地域，サハラ以南のアフリカではB型肝炎ウイルスの持続感染は肝細胞癌発症の強い危険因子となっている．世界全体では肝細胞癌の50-80％はB型肝炎ウイルス由来と考えられている．特に，小児期における肝細胞癌の発症には，ほぼ100％B型肝炎ウイルスが関与しているといわれている．

B型肝炎ウイルスのジェノタイプのうちBとCの多いアジアにおける検討では，ジェノタイプCの方がジェノタイプBよりも肝障害の進展が速く肝発癌の頻度も高かったと報告されている．しかし，台湾における検討では，ジェノタイプBは50歳以下の若年者や小児における肝細胞癌の発症に強く関わっていることが明らかにされた．一方，ジェノタイプAやDの頻度の多い西ヨーロッパや北アメリカでの検討では，ジェノタイプDの方がAに比べて肝障害の進展が速く肝発癌の頻度も高かったと報告されている．

アフラトキシンはB型肝炎ウイルスとともにアジアやサハラ以南のアフリカにおける肝細胞癌発症の要因の一つである．中国における検討では，アフラトキシンはB型肝炎ウイルス感染者においては肝発癌の危険性を相乗的に高めることが示唆された．

2）C型肝炎ウイルス感染

全世界におけるC型肝炎ウイルスの感染率はおよそ1-3％といわれている．C型肝炎ウイルスに感染した患者からの肝細胞癌の発症頻度は感染していない人々に比べて15-20倍高いといわれている．一般的に，C型肝炎ウイルスに由来する発癌の場合，進行した肝線維化や肝硬変を背景にして起こってくるといわれている．C型肝炎ウイルスによる肝硬変症の場合，年間の発癌率は我が国では約8％といわれているが，全世界ではやや低く1-4％となる．

4 肝細胞癌発症に関わるそのほかの因子

1）性　差

男性は女性に比べて肝細胞癌発症の頻度が高い．その原因として考えられているのが男性ホルモンの関与である．台湾と中国における検討では，B型肝炎ウイルスに感染した男性において血中のテストステロンの濃度の高い人の方が肝細胞癌発症の頻度が高かった．

2）B型肝炎ウイルスとC型肝炎ウイルスの二重感染

スペイン，台湾，アメリカ，日本など8カ国からの報告をまとめた検討では，肝炎ウイルス未感染者に比べてB型肝炎ウイルス感染者の発癌は23倍，C型肝炎ウイルス感染者の発癌は17倍であるのに対し，二重感染者のそれは165倍であった．中国における検討でもB型肝炎ウイルス感染者の発癌は14.1倍，C型肝炎ウイルス感染者の発癌は4.6倍であるのに対し，二重感染者のそれは35.7倍であり，二重感染はB型肝炎ウイルスもしくはC型肝炎ウイルスの単独感染に比べて肝細胞癌の発症を促進するようである．

3) アルコール摂取

アルコールの過剰摂取はそれ単独でも発癌の危険因子であるが，B型肝炎ウイルスやC型肝炎ウイルス感染者においては相乗的に発癌の危険性が増す．このうち，C型肝炎ウイルス感染者の方がB型肝炎ウイルス感染者よりもアルコールの過剰摂取による発癌への関与が強いといわれている．

4) 喫　煙

喫煙と肝発癌に関する報告は今までに60以上あるが，喫煙単独で肝発癌を促進するか否かは結果が分かれており結論は出ていない．しかし，B型肝炎ウイルスやC型肝炎ウイルス感染者においては，フランスからの報告では喫煙はB型肝炎ウイルス感染者においては相加的に肝発癌を促進し，C型肝炎ウイルス感染者では相乗的に発癌を促進するとされている．

5) メタボリックシンドローム

台湾における検討では，BMIが30以上の高度肥満は肝細胞癌発症の独立した危険因子であり，B型やC型肝炎ウイルスに感染していなくても約2倍に発癌の危険性が増すが，C型肝炎ウイルス感染者では約4倍に発癌の危険性が増すことが明らかとなった．肥満に合併しやすい非アルコール性脂肪性肝炎を含めた脂肪性肝疾患(NAFLD)からの発癌が近年先進国を中心に増加している．さらに，C型肝炎ウイルス感染やアルコール性肝疾患などにNAFLDが加わることで相乗的に発癌の危険性が増すといわれている．糖尿病もまた肝発癌の独立した危険因子であり，約2.3倍発癌の危険性が増すといわれている[15]．さらに，糖尿病の治療薬であるスルホニルウレア製剤やインスリンの長期使用は発癌を助長するといわれている．

おわりに

今後，世界全体では肝細胞癌の発生はしばらくの間は増加し，2015-20年には平衡状態に達し，その後徐々に減少することが予想されている．地域別に現状をみると，我が国ではサーベイランスシステムの確立により肝細胞癌の約70％は根治的治療が可能な状態で発見され予後も比較的良好であるが，その他の国々ではサーベイランスシステムが確立されておらず，十分な治療がなされていないのが現状である．特に東南アジア諸国，サハラ以南のアフリカ諸国，ロシアにおいては予後が著しく不良である．今後，これらの地域でのサーベイランスシステムの確立が急務と考えられた．

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VI 特　　論

ウイルス性肝炎患者拾い上げの問題

Issues of picking up hepatitis virus carriers

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Key words：住民健診，職域健診，無料肝炎ウイルス検査，マルチメディア，地域肝炎治療コーディネーター

はじめに

本邦には，300万-370万人もの肝炎ウイルス持続感染者(キャリア)が存在すると推計されている．肝炎ウイルスの持続感染は，肝硬変や肝がんへ進行することが問題である．現在，年間3.2万人が肝がんによって死亡しており，その約8割がHCVやHBVの持続感染が原因となっている．近年，飛躍的に肝炎ウイルス感染の治療法が進歩し，高い確率でウイルス排除が可能となってきた．そのため，今後ますます，肝炎ウイルスキャリアを早期発見・早期治療する重要性が高まってこよう．

現在，肝炎ウイルス感染の検査は，住民健診，人間ドック，職域健診などと併せて行われる肝炎検診(HCV抗体検査，HBs抗原検査)や，保健所やその提携医療機関での無料の肝炎検診にて行われている．これら肝炎検診の受検率が，肝炎ウイルスキャリアに対して低いことが，いまだ肝炎ウイルス感染による肝がん死亡率が高い一因となっている．そのため，できるだけ多くの肝炎ウイルスキャリアを拾い上げるために，肝炎検査の受検率を向上させる様々な対策が各地域で施されている．各対策において，一定の成果が得られている一方，問題点も浮き彫りとなっている．

1 住民健診における拾い上げ対策と問題点

平成14-18年度に老人保健事業に基づいて，住民基本健診(一般住民健診)と併せて，40歳から5歳ごとに70歳までの方を対象に5年間の肝炎節目検診が実施された．その結果，特にHCV感染率は年齢が高くなるのに伴って上昇し，高齢者(特に男性)に多くの感染者が存在することが明らかとなった[1]．一方で，この肝炎節目検診事業の対象から外れた当時の40歳未満者の中にも，肝炎ウイルスキャリアが多く存在している可能性がある．この年齢層における肝炎ウイルスキャリアを拾い上げる対策として，現在，多くの自治体において，40歳時点での肝炎節目検診が行われている．

茨城県の各自治体にて，平成21-23年度に実施された40歳節目検診では，受検数6,128人中(受検率5.41％)，HCV陽性者は16人であった(陽性率0.26％)[2]．同期間中に，同じ自治体で41歳以上が受検した肝炎ウイルス検査では，265人の陽性者が検出された(国勢調査による住民数から算出した受検率2.76％，陽性率0.60

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