

Impact of more detailed categorization of shrinkage or progression ratio at initial imaging response after sorafenib treatment in advanced hepatocellular carcinoma patients

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Background: Sorafenib therapy improves survival in unresectable hepatocellular carcinoma (HCC) patients without an objective response. The present study investigated whether the initial imaging response might be a prognostic indicator after administration of sorafenib therapy in HCC patients.

Patients and methods: This retrospective study reviewed unresectable HCC patients undergoing sorafenib therapy. Patients evaluated without complete response, partial response (PR), or progressive disease (PD) at the initial imaging response evaluation by modified Response Evaluation Criteria in Solid Tumors were divided into three groups according to more detailed categorization of the shrinkage/progression ratio in initial imaging response. A comparison of progression-free and overall survival among these groups was performed.

Results: Of the 43 non-PR non-PD patients with target lesions, ten (23.3%) exhibited mild response (MR; -30% to -5%), 14 (32.6%) exhibited no change (NC; -5% to $+5\%$), and 19 (44.2%) exhibited mild-PD (MPD; $+5\%$ to $+20\%$). There was no statistical difference in progression-free or overall survival between MR and NC patients. The median progression-free survivals in NC+MR and mild-PD patients were 15.0 and 5.3 months, respectively ($P < 0.01$), and the median survival times were 31.9 and 17.1 months, respectively ($P < 0.001$). In multivariate analysis, etiology (hepatitis C virus) and initial imaging response (MR+NC) was identified as an independently good prognostic factor.

Conclusion: More detailed categorization of shrinkage or progression at the initial imaging response evaluation may be a useful marker for predicting sorafenib treatment outcomes in HCC patients. If the initial imaging response is not progression but stability, sorafenib may have a survival benefit.

Keywords: sorafenib, hepatocellular carcinoma, liver, response, imaging, chemotherapy

Introduction

Hepatocellular carcinoma (HCC) is the third-most common cause of cancer mortality worldwide.^{1,2} HCC is often diagnosed at an advanced stage, or the patients have advanced liver cirrhosis at the time of diagnosis and are thus considered unsuitable for potentially curative approaches, such as resection, liver transplantation, or other locoregional therapies.³ Sorafenib is a molecularly targeted multikinase inhibitor that suppresses both signal transduction of tumor growth and angiogenesis by inhibiting Raf kinase and VEGF- and PDGF-receptor kinase.⁴ Two large-scale Phase III clinical studies – the SHARP⁵ and Asia-Pacific studies⁶ – demonstrated that sorafenib significantly prolonged time to progression and improved overall survival in patients

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with advanced HCC, and confirmed its efficacy in improving the prognosis in these patients as a systemic chemotherapeutic agent. Accordingly, sorafenib has been recognized as the only standard systemic chemotherapeutic agent for patients with advanced HCC for whom resection and local therapy are not indicated.⁵⁻⁷ Although treatment with sorafenib shows survival prolongation in advanced HCC patients, the antitumor effect of sorafenib is complete response (CR) or partial response (PR) in only 2.0%–3.3% of advanced HCC patients, and stable disease (SD) in 27.6%–54.0% of those.^{5,6} Sorafenib is a safe and effective treatment for patients with advanced HCC;^{5,6,8,9} however, details of its benefits for patients with SD remain to be determined. It also remains obscure which SD patients get a survival benefit from sorafenib.

Accordingly, the present study investigated whether the initial imaging response could be used as a prognostic indicator after administration of sorafenib therapy in HCC patients.

Patients and methods

Patients

Data collected prospectively for a total of 78 patients with advanced HCC consecutively started on sorafenib (Nexavar; Bayer AG, Leverkusen, Germany) therapy at the Department of Hepato-Biliary-Pancreatic Surgery, National Hospital Organization Kyushu Medical Center between July 2009 and December 2011 were reviewed. Inclusion criteria for this study were as follows: HCC was diagnosed either by pathological examination or by the combination of typical radiological findings on dynamic multidetector-row computed tomography (MDCT) or magnetic resonance imaging (MRI) and elevated alpha-fetoprotein (AFP) serum levels or elevated des- γ -carboxy prothrombin serum levels, according to the American Association for the Study of Liver Diseases;⁷ patients were classified as having advanced HCC if they were not eligible for or had disease progression after surgical or locoregional therapies; Eastern Cooperative Oncology Group performance status score of 0–1; Child–Pugh liver function class A or B (<7); adequate hepatic function (albumin level >2.5 g/dL, total bilirubin level <3.0 mg/dL, and alanine and aspartate aminotransferase levels less than five times the upper limit of normal); dynamic MDCT was obtained at baseline and after 4–6 weeks of sorafenib treatment in order to assess the therapeutic effects. Of 78 patients, 13 discontinued sorafenib treatment before initial radiological response evaluation for adverse events excluded them. Sixty-five patients meeting the inclusion criteria were enrolled. This study was approved by the ethics committee of the National Hospital Organization Kyushu Medical Center and

performed in compliance with the Declaration of Helsinki. All patients provided informed consent.

Sorafenib therapy

The starting dosage of sorafenib was 800 mg/day orally. However, given the possibility of having to discontinue sorafenib treatment at an early stage due to adverse events, the initial dosage for patients with Child–Pugh B or comorbidities was reduced to 400 mg/day. Moreover, the initial dosage for patients aged ≥ 80 years, those with a body weight ≤ 40 kg, or a history of treatment for varices or ascites was set at 200–400 mg/day. Sorafenib therapy was continued until the occurrence of potentially fatal adverse events.

Image-based evaluation of antitumor effects

Dynamic MDCT images or dynamic MRI images were taken at baseline and after 4–6 weeks of sorafenib treatment. Tumor responses were defined as a time-point response 4–6 weeks after sorafenib administration, in accordance with the modified Response Evaluation Criteria in Solid Tumors (RECIST).¹⁰ A total of five target lesions were assessed in each patient, with a maximum of two lesions per organ. The criteria for determining objective tumor response for target lesions were as follows: CR, disappearance of all target lesions; PR, at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters; progressive disease (PD), at least a 20% increase in the sum of diameters of target lesions; and SD, neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. However, SD is defined by confirmation of stability at least 4 weeks after the first demonstration of stability. In this study, initial response assessment of neither CR nor PR nor PD was defined as non-PR non-PD. For initial imaging response evaluation, patients were initially divided into four groups according to tumor response: CR, PR, PD, and non-PR non-PD. In this study, the non-PR non-PD patients were further divided into patients with a mild response (MR; –30% to –5%), those with no change (NC; –5% to +5%), and those with mild-PD (MPD; +5% to +20%) as more detailed categorization. Prospectively maintained data of measured value of each tumor in the computed tomography (CT) scan or the MRI at baseline and the following evaluations was retrospectively reviewed.

Follow-up

All patients were followed at our outpatient clinic in a standardized manner, including tumor-marker tests every

1–2 months and CT or MRI every 6 weeks until the patient's death or last visit.

Statistics

Statistical analyses were performed using JMP version 11.0 software (SAS Institute Inc, Cary, NC, USA). Categorical variables were analyzed using the χ^2 test or Fisher's exact test, as appropriate. Continuous variables were analyzed using Student's *t*-test or the Mann–Whitney *U*-test, as appropriate. Progression-free survival and overall survival were analyzed using the Kaplan–Meier method, and comparisons between groups were performed using the log-rank test. Multivariate analysis was performed using a Cox proportional-hazard model and the backward-elimination procedure. A *P*-value <0.05 was taken to indicate a statistically significant difference.

Results

Patient characteristics at baseline

Table 1 shows the baseline characteristics of the 65 HCC patients enrolled in this study. The study cohort consisted of 48 males and 17 females, with a mean age of 68.5 years. For tumor condition, 32 (49.2%) HCC patients had extrahepatic spread, eleven (16.9%) had lymph-node metastases, 23 (35.4%) had distant metastasis, and ten (15.4%) had macrovascular invasion. A total of 23 (35.4%) were Barcelona Clinical Liver Cancer (BCLC)-B¹¹ and 42 (64.6%) were BCLC-C. All of BCLC-B patients had previously undergone transarterial chemoembolization and were refractory to. As for liver function, most were Child–Pugh A, and ten patients (15.4%) were Child–Pugh B. The starting dosage of sorafenib in this study was 800 mg/day in eleven patients, 400 mg/day in 48 patients, and 200 mg/day in five patients.

Tumor response at initial imaging evaluation

Of the 65 patients, one (1.5%) exhibited PR, 46 (70.8%) exhibited non-PR non-PD, and 18 (27.7%) exhibited PD at the initial evaluation. The median survival time in the 65 patients was 15.6 months, and the time to progression was 5.7 months. The median survival time in BCLC-B and BCLC-C patients was 24.0 and 14.0 months, respectively (*P*=0.046). The median survival time in non-PR non-PD and PD patients was 17.2 and 7.2 months, respectively (*P*<0.01) (Figure 1), and the median time to progression in non-PR non-PD and PD patients was 8.1 and 1.8 months, respectively (*P*<0.001).

Table 1 Baseline clinical characteristics of the patients (n=65)

Age, years	
Average	68.5
Sex	
Male	48
Female	17
Etiology	
HBV	11
HCV	45
NBNC	9
Extrahepatic spread	
Yes	32
No	33
Distant metastasis	
Yes	23
No	42
Lymph-node metastasis	
Yes	11
No	54
Macroscopic vascular invasion	
Yes	10
No	55
BCLC stage	
B	23
C	42
Child–Pugh	
A	55
B	10
Initial dose of sorafenib (mg)	
800	11
400	48
200	11
AFP (ng/mL)	
≥200	14
<200	51
DCP (mAu/mL)	
≥1,000	21
<1,000	44

Abbreviations: AFP, alpha-fetoprotein; HBV, hepatitis B virus; HCV, hepatitis C virus; NBNC, non-HBV non-HCV; BCLC, Barcelona Clinical Liver Cancer; DCP, des- γ -carboxy prothrombin.

Minute tumor response (MR, NC, and MPD) at initial imaging evaluation in the non-PR non-PD patients

Patients exhibiting non-PR non-PD are generally assumed to be the most important group in terms of improving survival. To clarify which non-PR non-PD patients were endowed a survival benefit by sorafenib, the non-PR non-PD patients were further divided into three groups (MR, NC, and MPD) according to the shrinkage/progression ratio at the initial imaging response. Of the 46 non-PR non-PD patients, 43 had target lesions, while three did not. Among 43 non-PR non-PD patients, ten (23.3%) exhibited MR, 14 (32.6%) exhibited NC, and 19 (44.2%) exhibited MPD. Average shrinkage:progression ratios at initial imaging response among MR, NC, and MPD patients were $-12.8\% \pm 5.5\%$, $1.5\% \pm 2.9\%$, and $11.5\% \pm 3.8\%$,

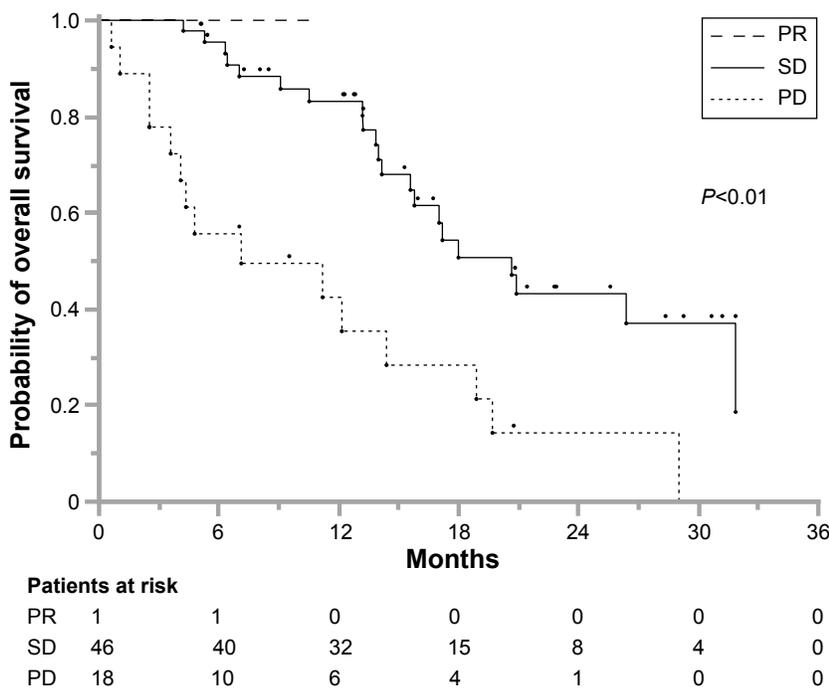


Figure 1 Kaplan–Meier curve of overall survival in all patients.
Abbreviations: PR, partial response; SD, stable disease; PD, progressive disease.

respectively ($P < 0.001$) (Figure 2). Characteristics of the three groups at baseline are shown in Table 2.

Cumulative overall survival and time to progression in the non-PR non-PD patients

As shown in Figure 3, the median survival time of NC patients of 31.9 months was superior to that of MPD patients

of 17.1 months ($P = 0.001$). The time to progression of NC patients of 14.8 months was superior to that of MPD of 5.3 months ($P < 0.001$) (Figure 4). There was no statistical difference in overall survival or progression-free survival between MR and NC patients. These findings indicate that the clinical meaning of MR is similar to that of no change.

Therefore, the NC+MR patients were compared with the MPD patients. In patient characteristics between these two

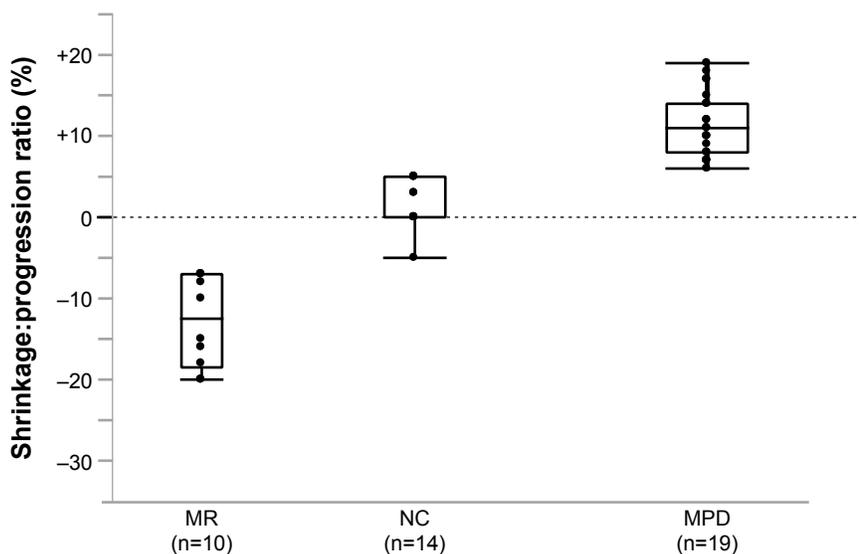


Figure 2 Shrinkage:progression ratio at initial imaging response among MR, NC, and MPD patients.
Abbreviations: MR, mild response; NC, no change; MPD, mild progressive disease.

Table 2 Characteristics at baseline of MR, NC, and MPD in non-PR non-PD patients

Variable	MR (n=10)	NC (n=14)	MPD (n=19)
Age			
Average	68.7	67.0	67.7
Sex			
Male	6	11	15
Female	4	3	4
Etiology			
HBV	2	2	3
HCV	6	11	13
NBNC	2	1	3
Extrahepatic spread			
Yes	7	4	11
No	3	10	8
Distant metastasis			
Yes	5	2	11
No	5	12	8
Distant metastasis			
Yes	2	2	4
No	8	12	15
Macroscopic vascular invasion			
Yes	0	2	3
No	10	12	16
BCLC stage			
B	3	8	7
C	7	6	12
Child–Pugh			
A	10	12	15
B	0	2	4
Initial dose of sorafenib (mg)			
800	3	3	4
400	6	11	11
200	1	0	4
AFP (ng/mL)			
≥200	1	3	1
<200	9	16	13
DCP (mAu/mL)			
≥1,000	1	7	1
<1,000	9	12	13
Interval for the initial radiological assessment (weeks)			
Average range	5.8 (4–6)	5.9 (5–6)	5.7 (5–6)

Abbreviations: AFP, alpha-fetoprotein; MR, mild response; NC, no change; MPD, mild progressive disease; PR, partial response; PD, progressive disease; HBV, hepatitis B virus; HCV, hepatitis C virus; NBNC, non-HBV non-HCV; BCLC, Barcelona Clinical Liver Cancer; DCP, des-γ-carboxy prothrombin.

groups, des-γ-carboxy prothrombin ($\geq 1,000$ mAu/mL) was significantly different ($P=0.02$) (Table 3). The median survival time in the former group of 31.9 months was superior to that in MPD patients of 17.1 months ($P<0.001$) (Figure 5). The time to progression in the MR+NC patients of 15.0 months was superior to that in MPD patients of 5.3 months ($P<0.01$) (Figure 6). These findings indicate that MR and NC effects implied long survival and a long SD effect at the initial radiological evaluation in SD patients.

Prediction of survival in the SD patients

In univariate analysis of prognostic factors by multivariate Cox's proportional-hazard modeling of overall survival,

etiology, the Child–Pugh status, and initial imaging response were significant indicators. In multivariate analysis, etiology (hepatitis C virus) (hazard ratio 0.122, 95% confidence interval 0.029–1.478; $P<0.01$) and initial imaging response (MR+NC) (hazard ratio 0.354, 95% confidence interval 0.117–0.987; $P=0.047$) were identified as an independent prognostic factor (Table 4).

Discussion

The present study sought to clarify which patients showed a longer-term SD effect among the advanced HCC patients exhibiting non-PR non-PD by sorafenib treatment. Comparison of progression-free survival or overall survival

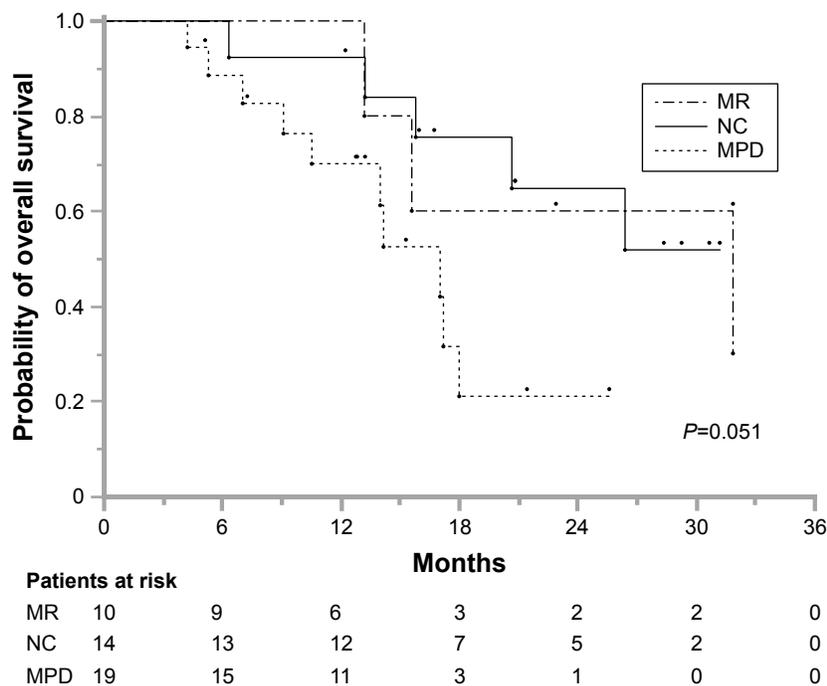


Figure 3 Kaplan–Meier curve of overall survival in MR, NC, and MPD patients.
Abbreviations: MR, mild response; NC, no change; MPD, mild progressive disease.

in groups with mildly different initial imaging results revealed that more detailed categorization of the progression or shrinkage ratio at the initial imaging response evaluation may be a useful marker for predicting sorafenib-treatment outcomes in HCC patients.

Non-PR non-PD refers to a relatively wide range – from a 30% decrease to a 20% increase – in the sum of diameters of target lesions. As for sorafenib treatment for advanced HCC patients, although only a few patients exhibit CR or PR and 48%–71% patients exhibit SD,^{5,6,12} sorafenib

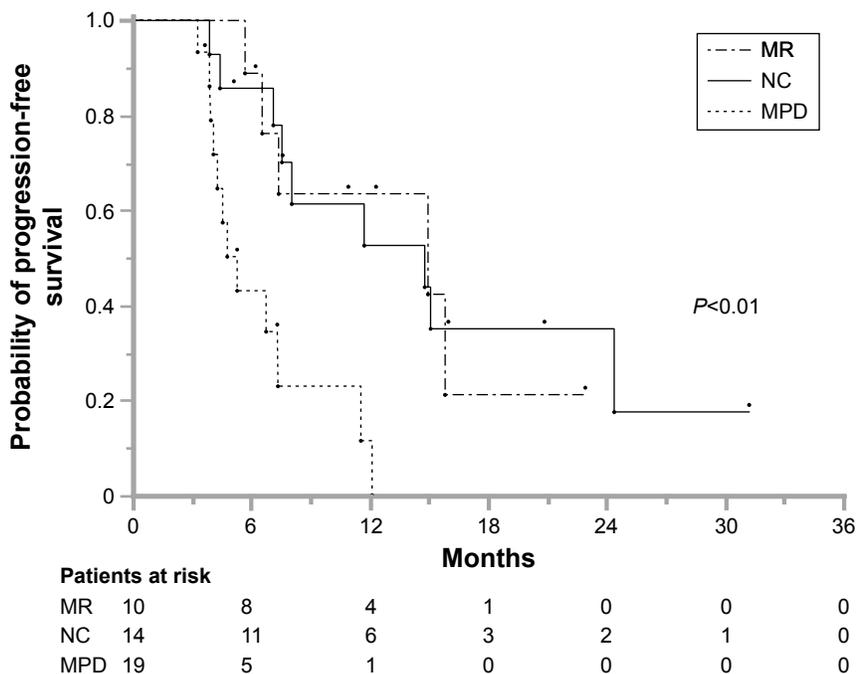


Figure 4 Kaplan–Meier curve of progression-free survival in MR, NC, and MPD patients.
Abbreviations: MR, mild response; NC, no change; MPD, mild progressive disease.

Table 3 Patients characteristics at baseline of MR+NC and MPD patients in non-PR non-PD patients

Variable	MR+NC (n=24)	MPD (n=19)	P-value
Age, years			
Average	67.7	67.7	0.99
Sex			
Male	14	15	0.54
Female	7	4	
Etiology			
HBV	4	3	0.95
HCV	17	13	
NBNC	3	3	
Extrahepatic spread			
Yes	11	11	0.43
No	13	8	
Distant metastasis			
Yes	7	8	0.38
No	17	11	
Lymph-node metastasis			
Yes	4	4	0.74
No	20	15	
Macroscopic vascular invasion			
Yes	2	3	0.41
No	22	16	
BCLC stage			
B	11	7	0.55
C	13	12	
Child–Pugh			
A	22	15	0.23
B	2	4	
Initial dose of sorafenib (mg)			
800	6	4	0.26
400	17	11	
200	1	4	
AFP (ng/mL)			
≥200	2	3	0.45
<200	22	16	
DCP (mAu/mL)			
≥1,000	2	7	0.02
<1,000	22	12	

Abbreviations: AFP, alpha-fetoprotein; MR, mild response; NC, no change; MPD, mild progressive disease; PR, partial response; HBV, hepatitis B virus; HCV, hepatitis C virus; NBNC, non-HBV non-HCV; BCLC, Barcelona Clinical Liver Cancer; DCP, des-γ-carboxy prothrombin.

treatment prolonged the survival of advanced HCC patients. This suggests that successful sorafenib treatment was characterized by a long-SD effect. The present study revealed that 46 patients (70.6%) exhibited non-PR non-SD at the initial radiological evaluation of tumor response and that the median survival time of 17.2 months in non-PR non-PD patients was significantly superior to that of 7.2 months in PD patients. These findings agreed with those of previous reports. The previous results raised the question of which among the non-PR non-PD patients showed a longer-SD effect; however, that question was not pursued. To clarify

which non-PR non-PD patients showed a long-SD effect, the present study focused on tumor shrinkage or progression ratios at the initial radiological evaluation of tumor response in non-PR non-PD patients.

RECIST criteria (version 1.1)¹³ or the modified RECIST assessment¹⁰ defines the category of SD (non-PR non-PD) as a relatively wide range: between 30% shrinkage and 20% progression. The present study investigated the correlation between more detailed categories of initial radiological response and survival. The non-PR non-PD patients were further divided into three groups (MR, NC, and MPD) as more detailed categorization of the tumor shrinkage/progression ratio. Comparing the times to progression among these groups, that of NC patients was similar to that of MR patients; however, that of MPD patients (5.3 months) were significantly inferior to that of NC patients (14.8 months) ($P=0.001$). The same result was found for overall survival. The median survival time of MPD patients (17.1 months) was significantly inferior to that of NC patients (31.9 months) ($P<0.001$). These results suggested that radiological progression, even if only slightly progressed, led to poorer prognosis. On the other hand, the median survival time of NC patients was similar to that of MR patients. These results are supported by previous reports^{5,6,14,15} that the significant feature of sorafenib was inhibition of tumor progression. The present study distinctly proved that sorafenib treatment showed disease stabilization for a long period.^{5,6,14,15}

It is quite difficult to predict associated factors for prognosis or tumor response of sorafenib before administration of sorafenib. No molecular biomarker has been found for sorafenib. However, several retrospective studies have reported that a reaction in the early period of administration, such as the appearance of an adverse event^{16–18} or variation of a tumor marker,^{12,19,20} may be associated with prognosis or response. It has been reported that a severe adverse event was associated with a good prognosis.²¹

There are several limitations to this study. The first limitation concerns the administration dose of sorafenib. In this study, only 17% of patients underwent sorafenib treatment at the recommended dose of 800 mg/day. Nonetheless, a sorafenib dose of 400 mg/day has previously been shown to have similar efficacy,²² and the issue of the administration dose of sorafenib is controversial. In this study, patients with poor liver-reserve function, comorbidities, old age, low body weight, or deterioration of liver function were initiated with a reduced sorafenib dose of 200–400 mg/day, and the sorafenib dose was escalated by tolerability. This method can improve patient tolerance and long-term treatment.

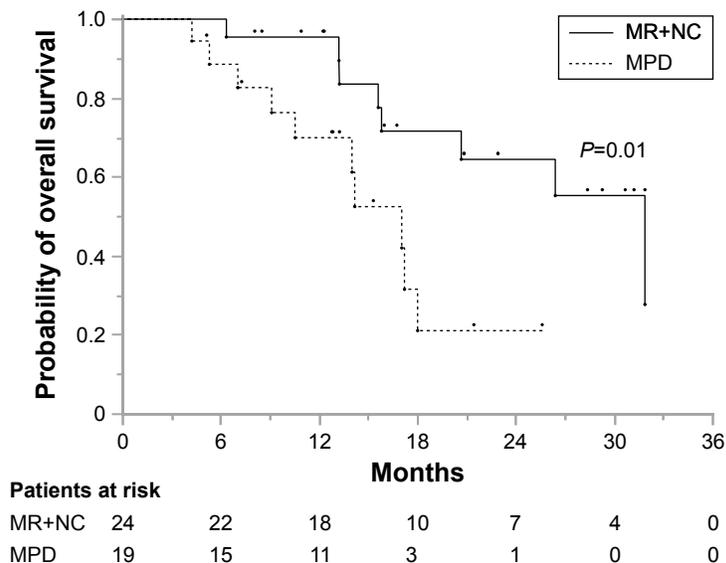


Figure 5 Kaplan–Meier curve of overall survival in MR+NC and MPD patients.
Abbreviations: MR, mild response; NC, no change; MPD, mild progressive disease.

The second limitation concerns the variety of tumor conditions. Responses vary according to the location or size of the tumor. However, the location of the tumor did not affect the response to sorafenib of patients in this study (data not shown). The third limitation regards the study design, since our results are based on a retrospectively selected patient analysis. However, the current study was based on prospectively collected data, and during the investigation period, patients were treated using a unified strategy at a single institution with extensive experience caring for HCC

patients. A further prospective study is needed to confirm the validity of our results.

Conclusion

This study revealed that more detailed categorization of the progression or shrinkage ratio at the initial imaging response evaluation could be a surrogate marker for the long-term outcome of sorafenib treatment in HCC patients. If the initial imaging response is not progression but stability, sorafenib may result in survival benefit.

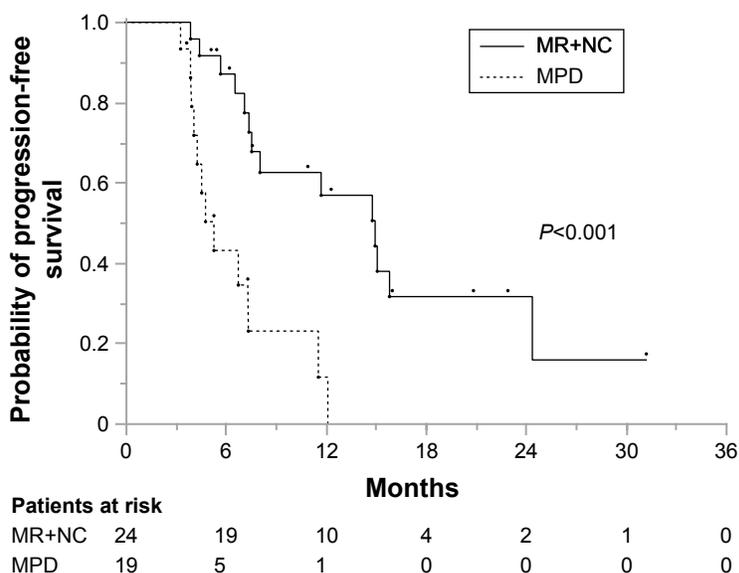


Figure 6 Kaplan–Meier curve of progression-free survival in MR+NC and MPD patients.
Abbreviations: MR, mild response; NC, no change; MPD, mild progressive disease.

Table 4 Prognostic factors in non-PR non-PD patients

Variable	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Age (<70 years)	2.591 (0.984–7.626)	0.054	1.154 (0.419–3.536)	0.79
Sex (male)	2.005 (0.652–8.718)	0.24	2.707 (0.773–12.976)	0.13
Etiology (HCV)	0.349 (0.131–0.992)	0.048	0.122 (0.029–0.478)	<0.01
Extrahepatic spread (yes)	1.290 (0.492–3.444)	0.60	–	–
Macroscopic vascular invasion (no)	1.810 (0.396–6.215)	0.40	–	–
BCLC (B)	0.667 (0.229–1.760)	0.42	–	–
Child–Pugh (B)	3.619 (0.976–11.194)	0.054	2.394 (0.634–7.581)	0.18
Initial dose of sorafenib (800 mg)	2.012 (0.714–5.442)	0.18	2.338 (0.738–7.416)	0.15
AFP (<200 ng/mL)	2.234 (0.455–40.332)	0.38	–	–
DCP (\geq 1,000 mAu/mL)	1.435 (0.400–4.134)	0.55	–	–
Initial imaging response (MR+NC)	0.299 (0.100–0.817)	0.019	0.354 (0.117–0.987)	0.047

Abbreviations: AFP, alpha-fetoprotein; PR, partial response; PD, progressive disease; CI, confidence interval; HCV, hepatitis C virus; BCLC, Barcelona Clinical Liver Cancer; DCP, des- γ -carboxy prothrombin; MR, mild response; NC, no change.

Disclosure

The authors report no conflicts of interest in this work.

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