



NOVEL MANAGEMENT SCORE OF SYSTEMIC THERAPY FOR HEPATOCELLULAR CARCINOMA PATIENTS

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INTRODUCTION

The combination therapy of atezolizumab with bevacizumab is positioned as a first-line therapy for unresectable hepatocellular carcinoma (HCC), and previous first-line and second-line molecular targeted agents (MTAs) shift to second- and third-line therapies, respectively⁽¹⁾. Thus, the choice of MTAs after failure of this combination therapy is critical. We have reported that skeletal muscle volume was an independent predictor of survival after sorafenib failure for HCC⁽²⁾. As overall survival (OS) is associated with post-progression survival (PPS), post-progression therapy after sorafenib failure can be an important factor for prolonging OS.

AIM

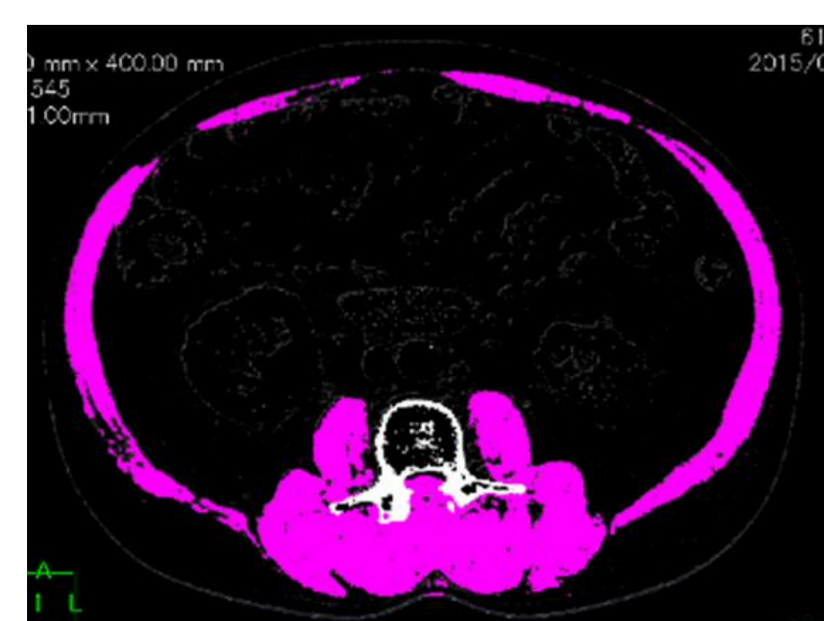
This study aimed to develop a novel management score of sorafenib based on the prognostic factors in HCC patients receiving sorafenib.

METHOD

We retrospectively enrolled 356 HCC patients at three hospitals in Japan. Various clinical parameters including skeletal muscle index (SMI), disease control with sorafenib, and post-sorafenib therapy were analyzed as prognostic factors of OS⁽¹⁾. According to the results of prognostic factors, a management of sorafenib score (MS score) was developed.

	Total (N = 356)	
Age	69.5 (63.0 – 75.0)	
Sex (male/female)	287/69	
Etiology (HCV/HBC/HBV+HCV/NBNC)	175(49%)/80/2/99	
Body mass index [kg/m ²]	22.9 (20.8 – 24.9)	
ECOG-PS (0/1/2/3)	314/37/3/2	
Child-Pugh class (A/B)	310(87%)/46	
Barcelona Clinic Liver Cancer stage (B/C)	78/278(78%)	
Tumor number	8 (2 - 8)	
Tumor size [mm]	35.0 (18.3 – 65.0)	
Macrovascular invasion (-/+)	258/98(28%)	
Extrahepatic spread (-/+)	167/189(53%)	
Response according to RECIST ver. 1.1 (CR / PR / SD / PD)	0/16(4%)/197(55%)/143	
Skeletal mass index	male	45.3 (41.2 – 50.4)
	female	38.3 (34.0 – 42.9)
Muscle volume (high/low)	181/175	

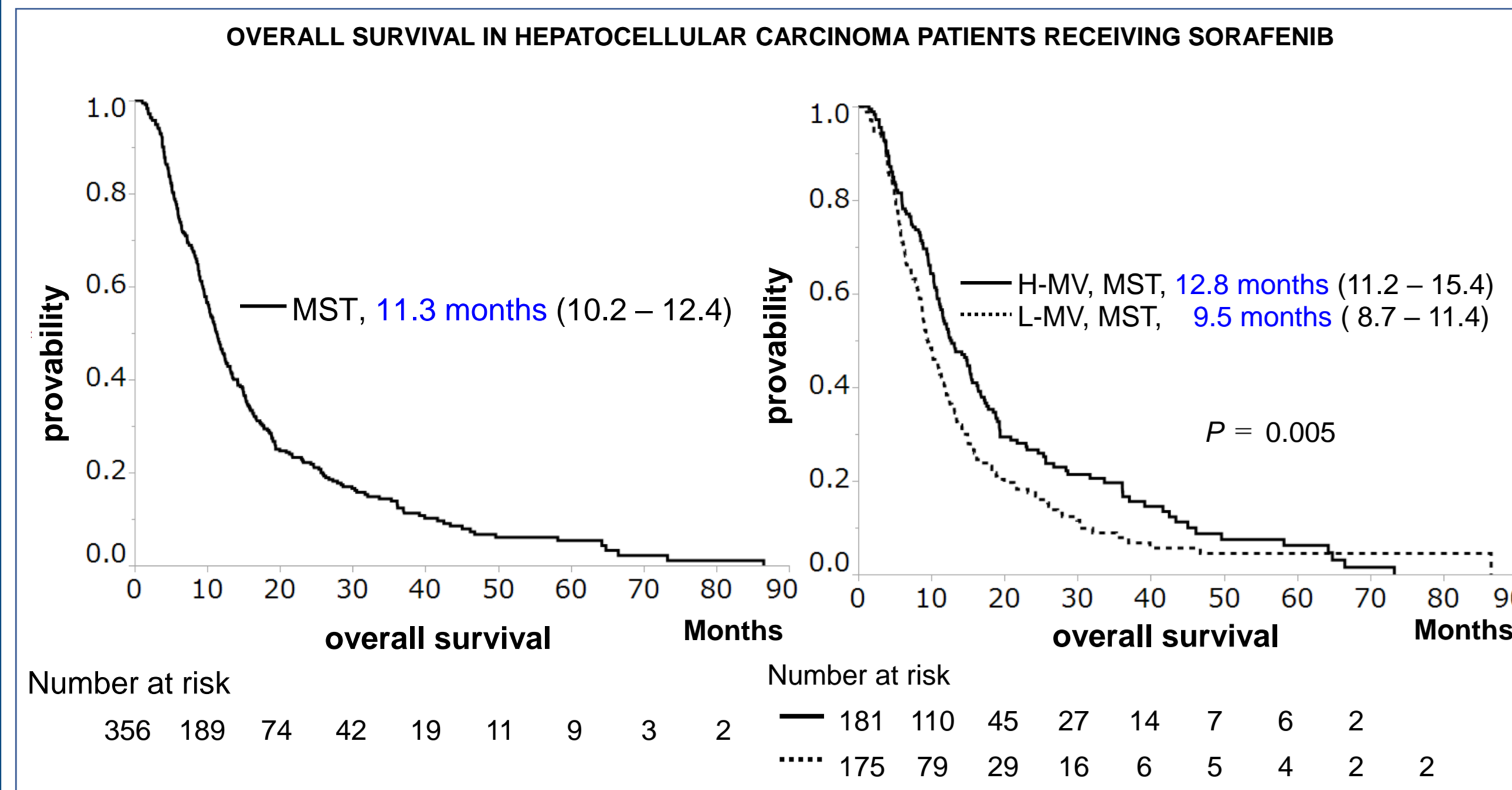
HCV, Hepatitis C virus; HBV, Hepatitis B virus; NBNC, NonBnonC; ECOG-PS, Eastern Cooperative Oncology Group performance status; CR, Complete response; PR, Partial response, SD, Stable disease; PD, Progressive disease



Cutoff value of muscle depletion
M : high-MV ≥ 45cm²/m², low-MV < 45cm²/m²
F : high-MV ≥ 38cm²/m², low-MV < 38cm²/m²

Skeletal muscle
-29 to +150 HU
AZE 3D workstation
(AZE Virtual Place Rajini; AZE Ltd., Tokyo, Japan)

RESULTS



The OS rates at 1, 2, and 3 years are 46.5%, 22.2%, and 13.9%, respectively, with a median survival time (MST) of 11.3 months. Patients with high muscle volume (H-MV) showed significantly longer survival than those with low muscle volume (L-MV) (MST: 12.8 vs. 9.5 months, p = 0.005).

(2) Saeki I, et al. Cancers (Basel). 2021 May 7;13(9):2247.

UNIVARIATE AND MULTIVARIATE ANALYSES FOR PROGNOSTIC FACTORS OF OVERALL SURVIVAL IN PATIENTS WITH PROGRESSION

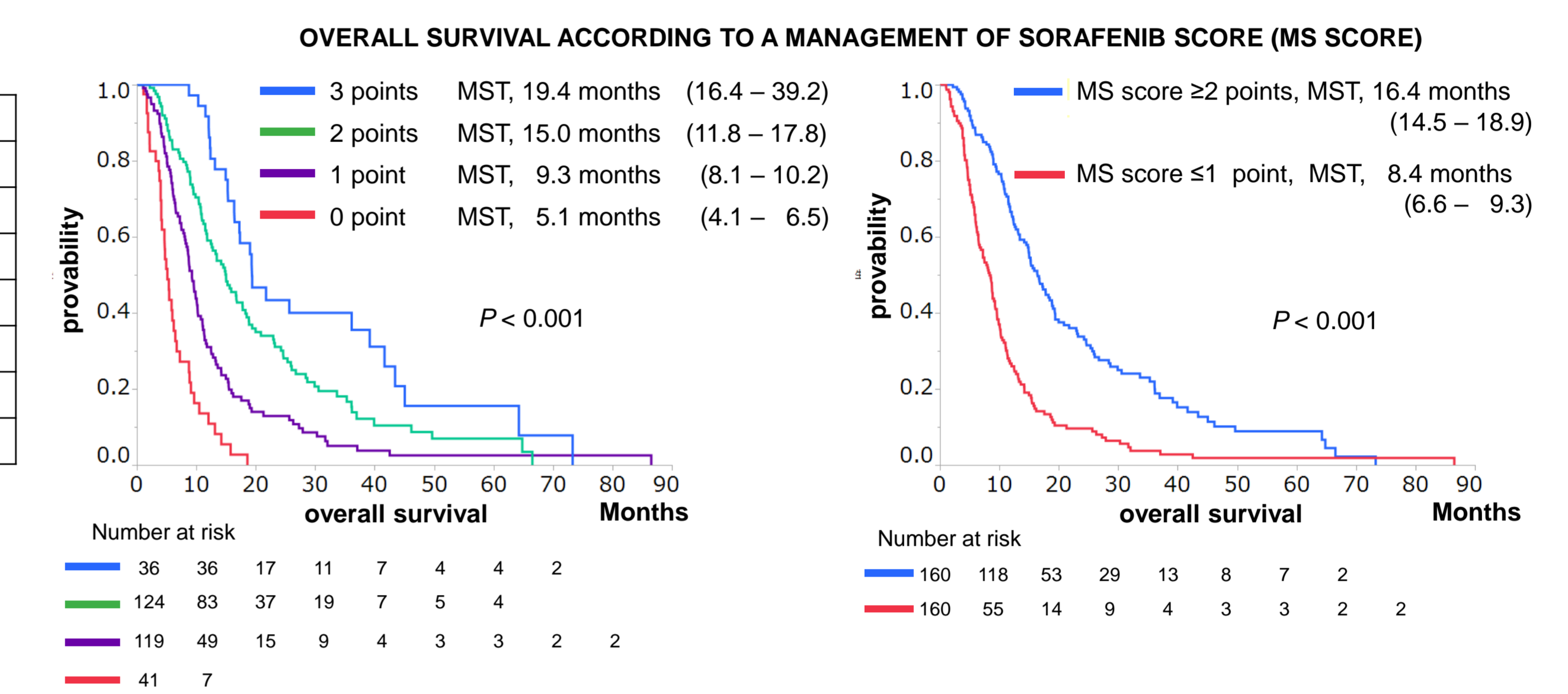
Factors	Univariate analysis			Multivariate analysis		
	HR	95%CI	P value	HR	95%CI	P value
Age (<70/≥70)	1.092	0.860 – 1.385	0.471	0.996	0.774 – 1.282	0.975
Sex (male/female)	0.718	0.531 – 0.972	0.032	0.717	0.524 – 0.980	0.037
Body mass index [kg/m ²] (≥22/<22)	0.913	0.716 – 1.164	0.463	1.193	0.871 – 1.635	0.271
ECOG-PS (1/2-)	0.572	0.235 – 1.390	0.217	0.570	0.229 – 1.421	0.228
Child-Pugh class (A/B)	0.691	0.484 – 0.986	0.041	0.685	0.469 – 1.002	0.051
Tumor number (<8/≥8)	0.673	0.528 – 0.858	0.001	0.615	0.476 – 0.793	<0.001
Tumor size [mm] (<35/≥35)	0.774	0.609 – 0.984	0.037	0.807	0.612 – 1.063	0.127
Macrovascular invasion (-/+)	0.585	0.446 – 0.766	<0.001	0.858	0.621 – 1.185	0.352
Extrahepatic spread (-/+)	0.799	0.627 – 1.017	0.068	0.684	0.527 – 0.887	0.004
Muscle volume (high/low)	0.704	0.555 – 0.894	0.004	0.545	0.393 – 0.755	<0.001
Disease control (yes/no)	0.431	0.336 – 0.552	<0.001	0.398	0.307 – 0.516	<0.001
Post-sorafenib therapy (yes/no)	0.575	0.449 – 0.736	<0.001	0.610	0.472 – 0.789	<0.001

ECOG-PS, Eastern Cooperative Oncology Group performance status; HR, Hazard ratio; CI, Confidence interval

Favorable prognostic factors : male, tumor number <8, extrahepatic spread, high-muscle volume, disease control(+), post-sorafenib therapy(+)

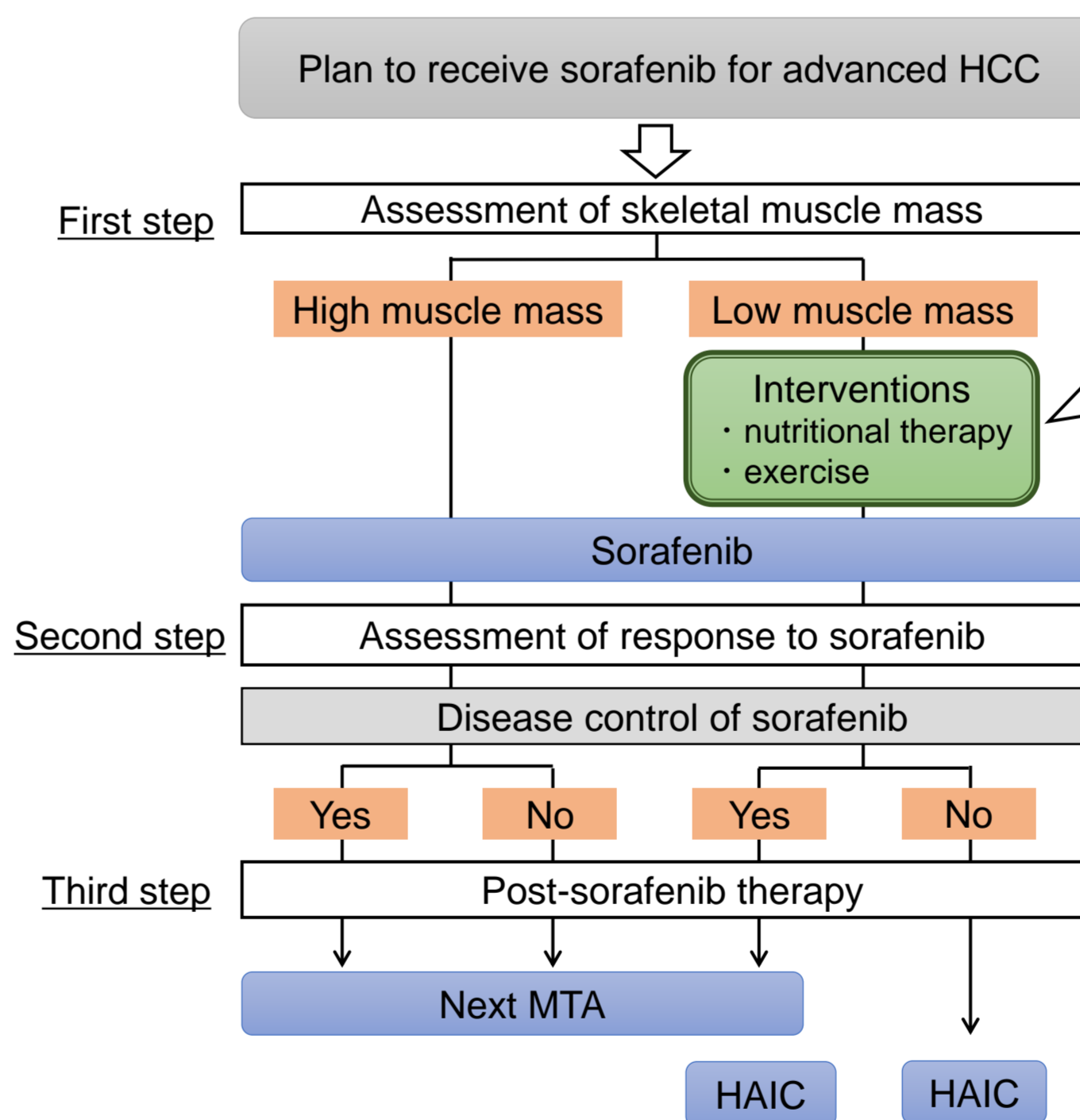
A MANAGEMENT OF SORAFENIB SCORE (MS SCORE)

MS score	Score point	
Skeletal muscle volume	High	1
	Low	0
Disease control	Yes	1
	No	0
Post-sorafenib therapy	Yes	1
	No	0



Low-muscle volume was defined as a median SMI of <45 cm²/m² in males and <38 cm²/m² in females. On multivariate analysis, the following six factors were found to be independent prognostic factors of OS: male sex (HR 0.717, P = 0.037), tumor number <8 (HR 0.615, P < 0.001), absence of extrahepatic spread (HR 0.684, P = 0.004), high-muscle volume (HR 0.545, P < 0.001), disease control: yes (HR 0.398, P < 0.001), and post-sorafenib therapy: yes (HR 0.610, P < 0.001). We developed the MS score, which was calculated as the top three following parameters having favorable HRs: skeletal muscle volume (high = 1, low = 0), disease control (yes = 1, no = 0), and post-sorafenib therapy (yes = 1, no = 0), with ranging from 0 to 3. The MSTs of 0 (n = 41), 1 (n = 119), 2 (n = 123), and 3 (n = 36) points were 5.1, 9.3, 15.0, and 19.4 months, respectively (P < 0.001). Furthermore, when the cutoff value of MS score was set as 2 points, the patients with scores ≥2 (n = 160) showed significantly longer survival than those with scores ≤1 (n = 160) (median survival time: 16.4 vs. 8.4 months, P < 0.001).

A DRAFT PROPOSAL OF THE TREATMENT STRATEGY FOR ADVANCED HEPATOCELLULAR CARCINOMA PATIENTS WHO PLAN TO RECEIVE SORAFENIB THERAPY, BASED ON THE MANAGEMENT OF SORAFENIB SCORE (MS SCORE).



Interventions can improve low muscle mass. These therapies might improve patient survival.

Based on the MS score, we present a draft proposal of a treatment strategy for advanced HCC patients who plan to receive sorafenib therapy. This strategy consists of three steps.

First step: skeletal muscle mass is assessed and divided into two groups, high muscle mass or low muscle mass. Thereafter, sorafenib is administered. Interventions, which are nutritional therapies, including branched-chain amino acid (BCAA) supplementation and L-carnitine, and exercise (cancer rehabilitation), are introduced to patients with low muscle mass, because interventions can improve low muscle mass even during MTA therapy. When these interventions improve sarcopenia in HCC patients receiving sorafenib, patient survival might be improved.

Second step: the assessment of the response to sorafenib is performed.

Third step: post-sorafenib therapy is considered. For patients with low muscle mass without disease control, HAIC may be considered because there is no association between OS and low muscle mass⁽³⁾, while the next MTA is considered for patients with high muscle mass without disease control. For patients with disease control, the next MTA is considered when sorafenib is discontinued. For patients with disease control who have low muscle mass, Hepatic arterial infusion chemotherapy (HAIC) may also be considered. In addition, HAIC might be considered as a front-line treatment choice in patients with macrovascular invasion without EHS or with Child-Pugh class B, regardless of skeletal muscle mass⁽⁴⁾.

CONCLUSIONS

HCC patients receiving sorafenib need to at least two positive MS score parameters to prolong OS, and this MS score may be a useful tool to choose the next MTA after the combination therapy of atezolizumab with bevacizumab.

REFERENCES

- (1) Llovet JM, et al. Trial design and endpoints in hepatocellular carcinoma: AASLD consensus conference. *Hepatology*. 2021 Jan;73:Suppl 1:158–91.
- (2) Saeki I, et al. Skeletal muscle volume is an independent predictor of survival after sorafenib treatment failure for hepatocellular carcinoma. *Cancers (Basel)*. 2021 May 7;13(9):2247.
- (3) Saeki I, et al. Effect of body composition on survival benefit of hepatic arterial infusion chemotherapy for advanced hepatocellular carcinoma: A comparison with sorafenib therapy. *PLOS ONE*. 2019 Jun 13;14(6):e0218136.
- (4) Yamasaki T, Saeki I, et al. Clinical benefits of hepatic arterial infusion chemotherapy for advanced hepatocellular carcinoma. *Appl Sci (Basel)*. 2021 Feb 20;11(4):1882.

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