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No Deterioration in Clinical Outcomes of Carbon Ion Radiotherapy for Sarcopenia Patients with Hepatocellular Carcinoma

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Abstract. *Background/Aim: The relationship between sarcopenia and prognosis in carbon ion radiotherapy (C-ion RT) for hepatocellular carcinoma (HCC) has not yet been reported, therefore we analyzed the presence or absence of sarcopenia before C-ion RT as a prognostic factor for patients with HCC. Patients and Methods: Data were retrospectively collected for patients who had undergone C-ion RT for HCC between September 2010 and December 2016. For defining the presence or absence of sarcopenia, skeletal muscles in the third lumbar vertebrae level were measured. Clinical outcomes were compared in the sarcopenia and non-sarcopenia groups. Results: Of the 68 patients who were analyzed, 22 were classified into the sarcopenia and 46 into the non-sarcopenia groups. Median follow-up of patients was 33.5 months. The three-year overall survival (OS) rates in the sarcopenia and non-sarcopenia groups were 66% and 77%, respectively (p=0.51). Conclusion: Sarcopenia was not a prognostic factor for patients with HCC treated with C-ion RT, which was effective in HCC patients with sarcopenia without worsening the OS.*

The number of elderly patients with age-related loss of skeletal muscle mass (primary sarcopenia) has been on the rise in recent times. In addition, patients with cancer suffer from various metabolic disorders and malnutrition that may cause secondary sarcopenia, which is characterized by a loss of skeletal muscle mass in an early stage, unlike malnutrition which is caused by starvation. Several researchers reported that preoperative skeletal muscle mass is associated with the prognosis of cancers (1-4).

Bioelectrical impedance method is frequently used for assessing skeletal muscle mass. Recently, computed tomography (CT) and magnetic resonance imaging (MRI) have been well established for the measurement of skeletal muscle mass at the third lumbar vertebrae level because of objectivity and accuracy (5).

Hepatocellular carcinoma (HCC) is the sixth-most frequently occurring cancer type and the third major cause of cancer-related death worldwide (6). Numerous local treatment options can be employed for treating HCC, with particle therapy, such as proton beam therapy and carbon ion radiotherapy (C-ion RT), being one of the less-invasive options (7, 8). Most patients with HCC have a history of chronic liver disease resulting from alcohol abuse, or infection with hepatitis C or B virus, so that patients with HCC already are in a state of secondary sarcopenia caused by cirrhosis or chronic hepatitis. Harimoto *et al*. reported the clinical outcomes of surgery and noted a remarkable difference in overall survival (OS) because of the difference in preoperative skeletal muscle mass (2). However, the relationship between sarcopenia and prognosis in particle therapy for HCC has not yet been reported. In the present study, a retrospective analysis was conducted on the presence or absence of sarcopenia before C-ion RT as a prognostic factor for HCC.

Patients and Methods

Patients. This retrospective analysis was performed using the medical records of patients treated with C-ion RT for HCC at our hospital between September 2010 and December 2016. The diagnosis of all patients with HCC was confirmed histologically or by the presence of typical hallmarks of HCC using imaging

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techniques of four-phase multi-detector-row CT or dynamic contrast-enhanced MRI (hypervascular lesions in the arterial phase with washout in portal venous or delayed phases). Patients with single HCC and no direct infiltration of the gastrointestinal tract, any intrahepatic metastasis or distant metastasis, and who received C-ion RT as primary treatment were analyzed. Child-Pugh score was calculated for the evaluation of liver function in all patients and the disease stage was determined by CT, MRI, ultrasonography, and other variables in accordance with the Union for International Cancer Control (UICC) classification (seventh edition) (9). The present study complied with the standards of the Declaration of Helsinki and current ethical guidelines and was reviewed and approved by the institutional review board.

Carbon ion radiotherapy. Immobilization devices, consisting of tailor-made fixation cushions and thermoplastic shells, were manufactured for patient fixation. Next, respiratory-gated CT, four-dimensional CT (4D-CT) images for treatment planning, and contrast-enhanced CT images were acquired. For the precise delineation of the gross tumor volume (GTV), treatment planning CT images and contrast-enhanced CT images were merged. The clinical target volume (CTV) was defined as a GTV plus 5 mm in all directions, including microscopic disease progression, and the internal margin (IM) was added as the extent of tumor motion displayed in 4D-CT images. The planning target volume (PTV) was defined as a summation of CTV, IM, and setup margin (8). Radiation dose measurements for the target volume and surrounding normal structures were expressed in Gy (relative biologic effectiveness [RBE]), which was defined as the physical dose multiplied by the RBE of carbon ions (10). XiO-N (version 4.47; collaborated product of Elekta AB, Stockholm, Sweden and Mitsubishi Electric, Tokyo, Japan) was used for treatment planning. Prescribed doses were as follows: 52.8 Gy (RBE) or 60.0 Gy (RBE) in four fractions with the planning aim for covering PTV with at least 90% of the prescribed dose. Dose constraints were as follows: (1) D_{1cc}<40 Gy (RBE) administered to the gastrointestinal tract and (2) V_{20}<35% administered to the liver. Dose to the portal vein and bile duct was reduced as much as was possible (8). Figure 1 shows a typical radiation field with dose distribution.

Patients received C-ion RT once daily for four days per week (from Tuesday to Friday). A fiducial gold marker was inserted in the liver for daily patient position matching. Patient positioning with the fiducial marker was confirmed using digital orthogonal X-ray and reference images, which were digitally reconstructed on the basis of CT images for treatment planning (11).

Evaluation during follow-up. Patients were followed up and examined one month after the completion of C-ion RT, and every three months thereafter at our hospital. The follow-up examinations consisted of interview, physical examination, routine blood cell counts, blood chemistry, and abdominal diagnostic imaging, such as four-phase multi-detector-row CT, dynamic contrast-enhanced MRI, or contrast-enhanced ultrasonography. Acute and late toxicities were classified using the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0 (12). Acute toxicity was evaluated as the highest toxicity within three months from the initiation of C-ion RT. Late toxicity was evaluated as the highest toxicity three months after the initiation of the treatments. Local recurrence was defined as tumor regrowth with the enhancement of the contrast effect on CT or MRI or ultrasonography in the irradiated field for the patients treated with C-ion RT.

Assessment of skeletal muscle index and definition of sarcopenia. Cross-sectional areas (cm^2) of skeletal muscles in the third lumbar vertebrae level were measured by manual outlining on the axial CT images by the radiation oncologist using MIM maestro (version 5.6; MIM Software, Cleveland, OH, USA; Figure 2). Next, cross-sectional areas of skeletal muscles were normalized for height (cm^2/m^2) for calculating skeletal muscle index (SMI). Sarcopenia was defined as SMI less than 43.75 cm^2/m^2 for men and less than 41.10 cm^2/m^2 for women (2, 13).

Data analysis. Prognostic factors were evaluated regarding OS and progression-free survival (PFS) on the basis of the following variables: sarcopenia (presence *versus* absence), age, sex, SMI, body mass index (BMI; calculated as weight [kg]/height [m^2]), performance status (PS) by Eastern Cooperative Oncology Group classification, serum albumin level, indocyanine green retention test at 15 min (ICGR15), Child-Pugh class, disease stage according to the UICC classification (seventh edition), and tumor size.

Statistical analysis. Survival was measured from the date of initiation of C-ion RT to the date of death or the most recent follow-up. PFS was measured from the date of initiation of C-ion RT to the date of the first tumor progression. Probabilities regarding OS, local control (LC), and PFS rates were calculated using the Kaplan-Meier method, and the log-rank test was used for comparing the two survival curves for univariate analyses. For determining the implications of potential prognostic factors, univariate and multivariate analyses of OS and PFS were performed using Cox proportional hazards models and the results have been presented as hazard ratios with 95% confidence interval. Statistical significance in the Cox models was determined using Wald's test. The statistical tests were two-sided, and $p<0.05$ was considered to be statistically significant. Factors with $p<0.1$ in univariate analyses were included in the multivariate analyses. Mann–Whitney's *U*-test was used for the statistical analysis of differences in patient characteristics noted between the sarcopenia and non-sarcopenia groups. Wilcoxon signed ranks test was used for statistical analyses for the difference in Child-Pugh score between before C-ion RT and within three months and after three months from the initiation of C-ion RT. All statistical analyses were performed using JMP Pro 12.2.0 software (SAS Institute, Inc., Cary, NC, USA).

Results

Patient characteristics. A total of 68 patients (22 in the sarcopenia and 46 in the non-sarcopenia groups) were treated with C-ion RT, and all patients completed C-ion RT as per schedule. Patient characteristics of the two groups are summarized in Table I.

Median follow-up for all patients was 33.5 months (range=3.9-83.1 months). Prior treatment for the target region of C-ion RT was surgery in three patients, percutaneous radiofrequency ablation (RFA) in six, RFA with transarterial chemoembolization (TACE) in one, and TACE with surgery in one. No patient received systemic therapy prior to C-ion RT. Dose fractionation schedule was 52.8 Gy (RBE)/4 fractions in 37 patients and 60 Gy (RBE)/4 fractions in 31 patients.

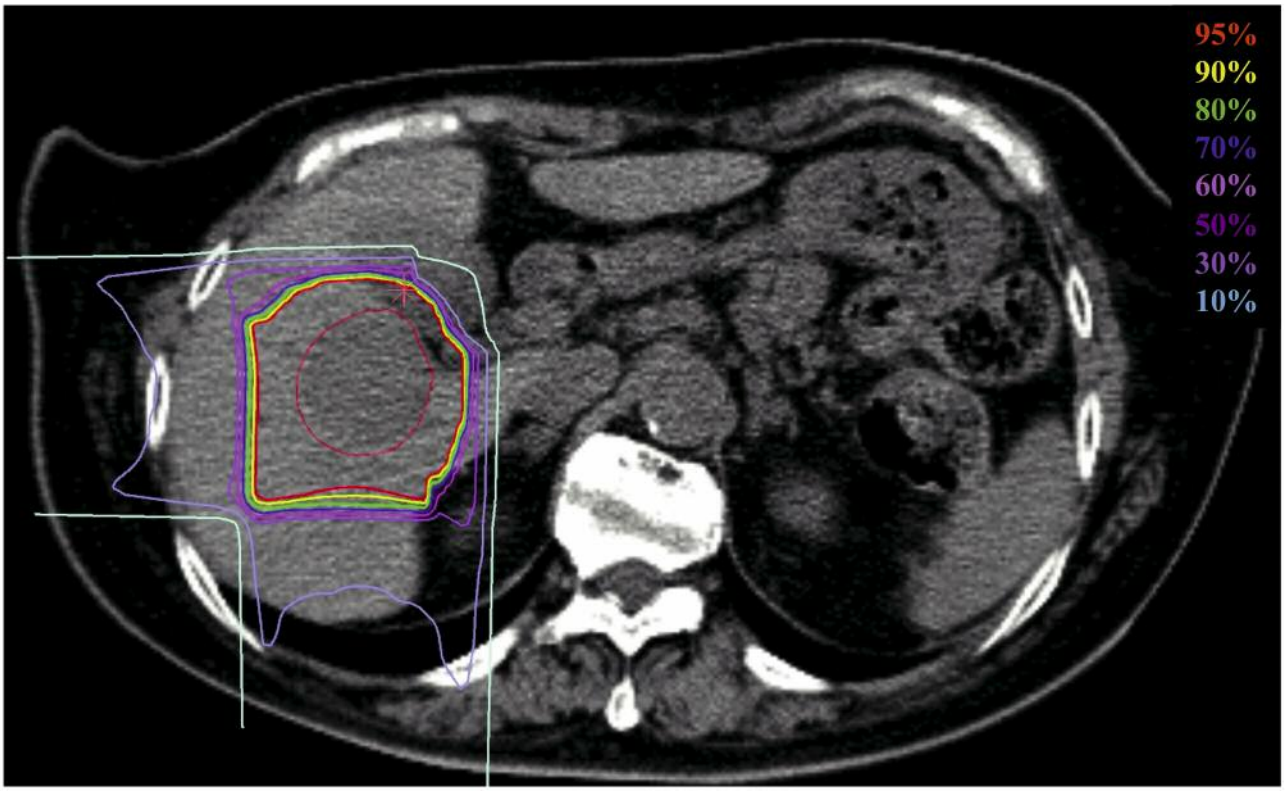

Figure 1. *Dose distribution of C-ion RT for HCC. Isodose curves of C-ion RT are superimposed on an axial CT image for the total irradiation plan. The area within the red outline is GTV. Highlighted are), 95% (red), 90% (yellow), 80% (green), 70% (blue), 60% (pink), 50% (purple), 30% (light purple), and 10% (light blue) isodose curves (100% was 52.8 Gy [RBE]).*

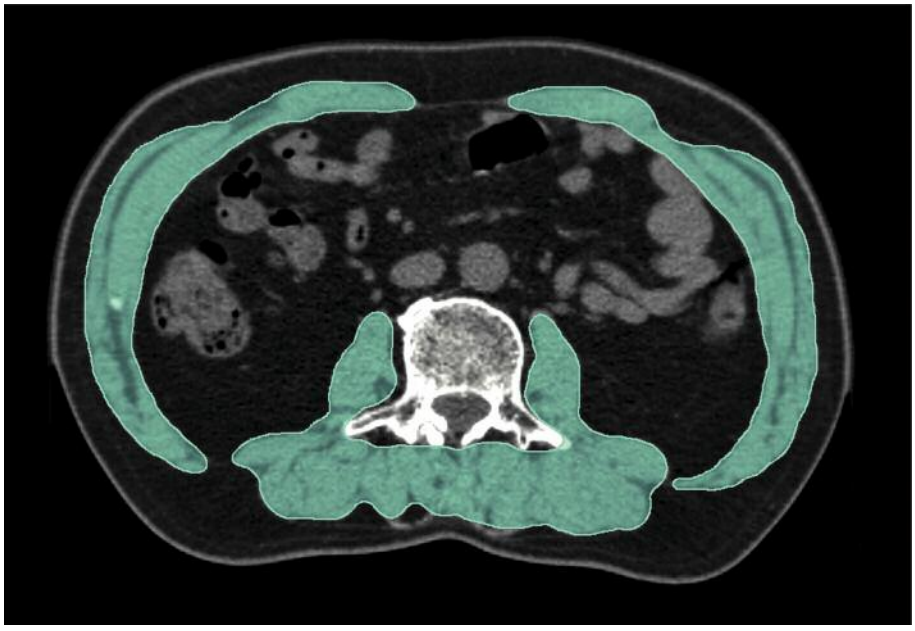

Figure 2. *Cross-sectional areas of skeletal muscles in the third lumbar vertebrae level are measured by manual outlining on an axial CT image (highlighted in cyan) for assessing the presence or absence of sarcopenia.*

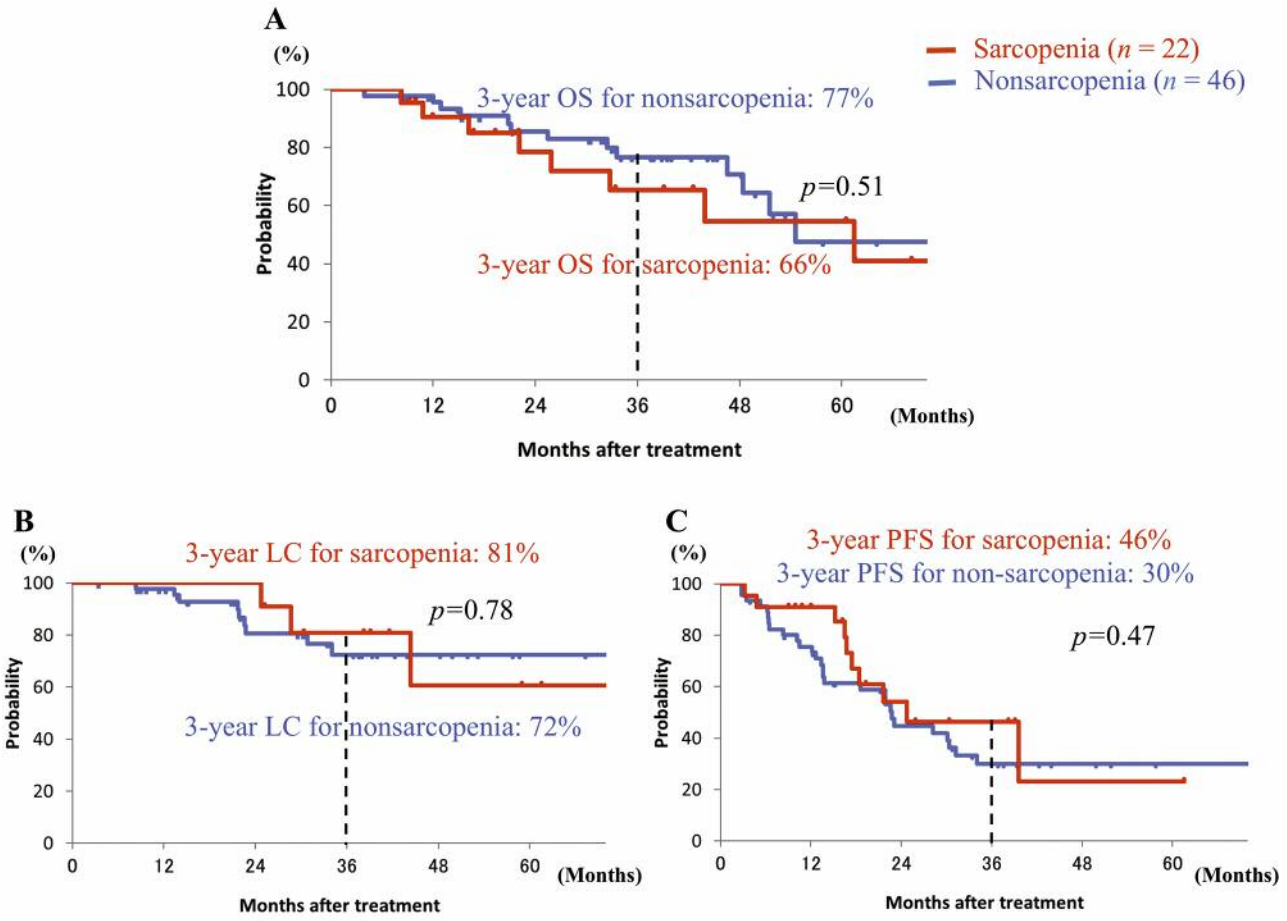

Figure 3. *Survival curves of the sarcopenia and non-sarcopenia groups. (A) The overall survival curves of the sarcopenia (red) and non-sarcopenia (blue) groups. (B) The local control curves of the sarcopenia (red) and non-sarcopenia (blue) groups. (C) The PFS curves of the sarcopenia (red) and non-sarcopenia (blue) groups.*

OS, LC, and PFS. The OS, LC, and PFS curves of the sarcopenia and non-sarcopenia groups are presented in Figure 3. The three-year estimated OS, LC, and PFS rates were 66%, 81%, and 46%, respectively, in the sarcopenia group and 77%, 72%, and 30%, respectively, in the non-sarcopenia group (p=0.51, 0.78, 0.47, respectively; Figure 3). At the time of analysis, four patients in the sarcopenia group and eight in the non-sarcopenia group died with HCC as the cause of death, while one and four, respectively, died of intercurrent diseases (pulmonary embolism in the sarcopenia group, and cholangiocarcinoma, renal failure, myocardial infarction, and senility in the non-sarcopenia group).

Toxicity. All observed acute and late toxicities are listed in Table II. Regarding acute toxicities, no patient had Grade 2 or higher radiation dermatitis. One patient in each group experienced Grade 2 elevation of aspartate aminotransferase (AST). One patient in the sarcopenia group and none in the non-sarcopenia group experienced progression in Child-Pugh class from A to B within three months from the initiation of C-ion RT. There was no significant difference noted in the Child-Pugh score between before and within three months from initiation of C-ion RT in either group (p=0.42 and p=0.62).

Regarding late toxicities, two patients in each group experienced Grade 3 encephalopathy. Both patients in the sarcopenia group had progression of HCC and hepatic failure. One of the two patients in the non-sarcopenia group suffered from constipation, and encephalopathy improved with the improvement in constipation, while one experienced a progression of HCC and hepatic failure. Grade 2 ascites occurred in one patient in the sarcopenia group and in two patients in the non-sarcopenia group. Grade 2 elevation of AST occurred in two and one patients, respectively (the latter patient also had elevated alanine aminotransferase

Table I. *Characteristics of patients with sarcopenia and non-sarcopenia.*

	Sarcopenia (n=22)	Non-sarcopenia (n=46)	p-Value
Age, year, median (range)	77 (57-95)	74 (45-90)	0.28
Sex ratio (Male:Female)	11:11	30:16	0.23
SMI, cm^2/m^2, median (range)	36.6 (28.4-42.9)	48.9 (41.3-66.3)	<0.01
BMI	19.9 (15.7-23.9)	24.7 (18.7-32.0)	<0.01
PS (0:1:2)	12:10:0	33:11:2	0.22
Albumin	3.7 (2.5-4.2)	3.8 (2.8-4.6)	0.17
ICGR15	20.2 (3.2-44)	19.4 (2.3-62.2)	0.84
Child-Pugh class (A:B)	17:5	40:6	0.41
Stage (I:II:III)	18:2:2	39:5:2	0.55
Tumor size, mm, median (range)	30 (12-90)	36 (9-77)	0.19

BMI: Body mass index; ICGR15: indocyanine green retention test at 15 min; PS: performance status; SMI: skeletal muscle index.

levels). No patient had other late toxicities higher than Grade 2, such as dermatitis, pneumonitis, and rib fracture. Late toxicity progression in Child-Pugh class from A to B occurred in two and one patients. There was no significant difference noted in Child-Pugh score between before and three months after initiation of C-ion RT in either group (p=0.48 and p=0.64).

Data analysis. Serum albumin level and Child-Pugh class were identified as prognostic factors for OS after C-ion RT in univariate analysis (p<0.01 and p<0.01, respectively); however, sarcopenia was not noted to be a prognostic factor (p=0.51; Table III). In multivariate analysis, prognostic factors for OS were analyzed on the basis of clinical characteristics of PS, serum albumin level, ICGR15, and Child-Pugh class, and PS and serum albumin level were identified as poor prognostic factors (p<0.01 and p=0.04, respectively; Table III).

Serum albumin level, ICGR15, and Child-Pugh class were identified as prognostic factors for PFS after C-ion RT in univariate analysis (p=0.01, p<0.01, and p=0.03, respectively); however, sarcopenia was not noted to be a prognostic factor (p=0.47; Table IV). In multivariate analysis, prognostic factors for PFS were analyzed on the basis of clinical characteristics of BMI, serum albumin level, ICGR15, and Child-Pugh class, and Child-Pugh class was identified as a prognostic factor (p=0.04; Table IV).

Discussion

We analyzed whether the presence or absence of sarcopenia before C-ion RT was a prognostic factor for HCC. The findings of this study indicate that the presence of sarcopenia was not a prognostic factor for OS and PFS in patients with HCC treated with C-ion RT. In other words, C-ion RT showed the same efficacy in patients in both groups.

Table II. *Acute and late toxicities by CTCAE, version 4.0.*

Acute toxicities in sarcopenia patients (n=22)

Organs involved	G0	G1	G2	G3	G4
Dermatitis	3	19	0	0	0
Encephalopathy	22	0	0	0	0
Ascites	22	0	0	0	0
Elevation of AST and/or ALT	17	4	1	0	0

Late toxicities sarcopenia patients (n=22)

Organs involved	G0	G1	G2	G3	G4
Dermatitis	11	11	0	0	0
Encephalopathy	20	0	0	2	0
Ascites	17	4	1	0	0
Rib bone fracture	22	0	0	0	0
Elevation of AST and/or ALT	18	2	2	0	0

Acute toxicities in non-sarcopenia patients (n=46)

Organs involved	G0	G1	G2	G3	G4
Dermatitis	6	40	0	0	0
Encephalopathy	46	0	0	0	0
Ascites	46	0	0	0	0
Elevation of AST and/or ALT	44	1	1	0	0

Late toxicities in non-sarcopenia patients (n=46)

Organs involved	G0	G1	G2	G3	G4
Dermatitis	11	35	0	0	0
Encephalopathy	44	0	0	2	0
Ascites	38	6	2	0	0
Rib bone fracture	46	0	0	0	0
Elevation of AST and/or ALT	44	1	1	0	0

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CTCAE: National Cancer Institute's Common Terminology Criteria for Adverse Events.

Table III. *Univariate and multivariate analyses of clinical factors and overall survival.*

	Univariate analysis		Multivariate analysis	
	Hazard ratio	*p*-Value	Hazard ratio	*p*-Value
Sarcopenia (presence *versus* absence)	1.35 (0.53-3.22)	0.51		
Age	1.02 (0.98-1.08)	0.24		
Gender	0.91 (0.38-2.20)	0.83		
SMI	0.96 (0.91-1.01)	0.12		
BMI	0.91 (0.79-1.04)	0.18		
PS	2.18 (0.91-5.19)	0.08	3.26 (1.05-11.39)	<0.01
Albumin	0.10 (0.04-0.27)	<0.01	0.15 (0.04-0.55)	0.04
ICGR15	1.03 (0.99-1.05)	0.06	1.01 (0.99-1.04)	0.33
Child-Pugh class	3.99 (1.50-9.64)	<0.01	2.39 (0.59-10.29)	0.22
Stage	1.45 (0.58-2.83)	0.34		
Tumor size	1.01 (0.98-1.04)	0.36		

BMI; Body mass index; ICGR15; indocyanine green retention test at 15 min; PS; performance status; SMI; skeletal muscle index.

Table IV. *Univariate and multivariate analyses of clinical factors and progression-free survival.*

	Univariate analysis		Multivariate analysis	
	Hazard ratio	*p*-Value	Hazard ratio	*p*-Value
Sarcopenia (presence *versus* absence)	0.77 (0.35-1.53)	0.47		
Age	1.00 (0.97-1.04)	0.95		
Gender	1.05 (0.56-2.07)	0.87		
SMI	1.01 (0.97-1.04)	0.74		
BMI	1.08 (0.99-1.19)	0.09	1.05 (0.95-1.16)	0.37
PS	1.11 (0.54-2.15)	0.77		
Albumin	0.39 (0.19-0.82)	0.01	0.69 (0.29-1.64)	0.40
ICGR15	1.02 (1.00-1.04)	0.04	1.01 (0.99-1.03)	0.41
Child-Pugh class	4.42 (1.78-10.11)	<0.01	2.86 (1.01-7.89)	0.04
Stage	1.23 (0.65-2.02)	0.47		
Tumor size	0.98 (0.97-1.01)	0.19		

BMI: Body mass index; ICGR15: indocyanine green retention test at 15 min; PS: performance status; SMI: skeletal muscle index.

Sarcopenia has been reported as a prognostic factor for HCC patients treated with hepatic resection with curative intent as the initial treatment (2, 4, 14). These results were obtained from patient characteristics in which median age was 62-69 years and the frequency of Child-Pugh class A was 94-100%. Regarding patient characteristics, if the patient's condition in our study was better than that in surgical studies, it may indicate good prognosis in patients with sarcopenia. However, patient characteristics in our study, such as age or Child-Pugh class, were higher compared with those in the surgical studies. In this study, median age was 76 years and frequency of Child-Pugh class A was 84%. In general, higher age or Child-Pugh class was strongly correlated with poor prognosis (15). Thus, patient characteristics in our study did not contribute to good results in patients with sarcopenia.

The invasiveness of cancer treatment was considered a possible reason for the difference noted between our study and surgical studies in the prognosis of sarcopenia. First, the frequency of severe toxicities may have affected the results. Regarding acute toxicities, no patient had Grade 3 or higher acute toxicities in our study. In contrast, 18% of the patients in a surgical study had Grade 3 or higher acute toxicities (4). Second, fasting duration during treatment may have been associated with the results showing the same efficacy in the sarcopenia as in the non-sarcopenia groups. Patients who underwent surgery had 2.8 days of postoperative fasting (16). In contrast, patients who underwent C-ion RT had no fasting

duration, and there was no deterioration of nutritional condition. Longer fasting duration was thus considered to worsen nutrition in patients with sarcopenia and to affect prognosis after surgery. Third, liver functional reserve after cancer treatment may have affected the results of this study. Liver functional reserve is reportedly one of the crucial factors determining survival (15). C-ion RT has an excellent dose distribution property and enables the delivery of a high dose to tumors while minimizing damage to normal tissue (7) so that normal liver suffered less damage. In this study, only two patients (9%) in the sarcopenia group experienced the progression of Child-Pugh class from A to B as late toxicity. This result suggested that C-ion RT could be a safe treatment for patients with sarcopenia with similar survival as for patients with non-sarcopenia.

Previous report indicate that the improvement of malnutrition by the intervention of a nutrition support team and early physical therapy intervention aimed at improving skeletal muscle mass are considered to improve the survival of patients with sarcopenia (17-19). There are no fasting duration and postoperative activity restrictions in C-ion RT; thus, nutrition and physical therapy interventions could be initiated from the commencement of treatment without any interruption during C-ion RT.

Numerous local treatment options are present for treating HCC. We compared survival in this study to that of other studies using other cancer treatments, such as surgery, TACE, and RFA. The clinical outcomes of hepatectomy (11, 20, 21) TACE (22), and RFA (20, 22, 23) have been previously reported, with three-year OS rates of 82%, 57%, and 81%, respectively. The above-mentioned results of other modalities were obtained from patients regardless of the presence or absence of sarcopenia. In this study, the three-year OS rates were 66% and 77% in the sarcopenia and non-sarcopenia groups, respectively. Even though the number of patients in this study was small, our results supported the continued evaluation of efficacy compared to surgery, TACE, and RFA.

This study had a few limitations. First, this is a single institutional analysis with a limited number of patients and insufficient statistical power. Second, the retrospective nature makes this study vulnerable to potential biases. Third, we analyzed only Japanese patients, so the results of this study may not be directly applicable to various ethnic populations. However, to our knowledge, this is the first study to demonstrate that sarcopenia is not a prognostic factor for clinical outcomes of patients with HCC treated with C-ion RT.

In conclusion, sarcopenia was not a prognostic factor for patients with HCC treated with C-ion RT. C-ion RT for patients with HCC and sarcopenia was effective with minimal toxicities without worsening survival. This result suggested that C-ion RT may become an alternative treatment option for patients with HCC and sarcopenia for whom other treatment, such as surgery, was not a viable choice.

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