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Prognostic value of pretreatment sarcopenia in unresectable hepatocellular carcinoma treated with yttrium-90 radioembolization

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Abstract

Objective

Sarcopenia is a prognostic biomarker in hepatocellular carcinoma (HCC), but its impact after transarterial radioembolization (TARE) with yttrium-90 (^{90}Y) microspheres and its relationship with tumor absorbed dose remain unclear. We assessed the prognostic value of sarcopenia for local progression-free survival (LPFS), progression-free survival (PFS), and overall survival (OS) in patients with HCC treated with TARE.

Methods

We retrospectively analyzed 75 patients with HCC treated with 90Y glass or resin microspheres between June 2022 and December 2024. Skeletal muscle index (SMI) was derived from the CT component of [^{18}F]fluorodeoxyglucose positron emission tomography/computed tomography ([^{18}F]FDG PET/CT) at L3. Sarcopenia was defined using sex- and BMI-specific SMI cut-offs. Tumor absorbed dose was dichotomized at 485 Gy. Survival was assessed by Kaplan–Meier analysis, and prognostic factors were evaluated using Cox regression.

Results

Sarcopenia was present in 32 patients (42.7%). Compared with non-sarcopenic patients, sarcopenic patients had lower objective response (34.4% vs. 97.7%; $p < 0.001$) and disease control rates (62.5% vs. 100%; $p < 0.001$). Median LPFS, PFS, and OS were 6, 6, and 10 months in sarcopenic patients versus 21, 19 months, and not reached in non-sarcopenic patients (all $p < 0.001$). On multivariable analysis, sarcopenia independently predicted shorter LPFS (HR 4.0; 95% CI 2.1–7.7; $p < 0.001$), PFS (HR 2.8; 95% CI 1.6–5.2; $p < 0.001$), and OS (HR 5.5; 95% CI 2.5–12.0; $p < 0.001$). Tumor absorbed dose < 485 Gy independently predicted shorter LPFS (HR 1.9; 95% CI 1.1–3.6; $p = 0.034$), but not PFS (HR 1.7; 95% CI 0.94–3.0; $p = 0.078$) or OS (HR 1.7; 95% CI 0.81–3.6; $p = 0.161$).

Conclusion

Pretreatment sarcopenia is an independent predictor of LPFS, PFS, and OS after TARE for HCC. Tumor absorbed dose remains associated with local tumor control, but an adequate dose does not overcome the adverse prognosis associated with sarcopenia. Routine assessment of skeletal muscle mass may improve risk stratification and help identify patients requiring closer surveillance and earlier systemic therapy.

INTRODUCTION

Hepatocellular carcinoma (HCC) remains a leading cause of cancer-related mortality worldwide, and the majority of patients are diagnosed at a stage that precludes curative resection or transplantation (1, 2). In patients with unresectable disease, adequate hepatic reserve, and absent or limited macrovascular invasion, transarterial therapies have emerged as the standard treatment approach. Among these modalities, transarterial radioembolization (TARE) using yttrium-90 (^{90}Y) microspheres has gained increasing prominence due to its ability to individualize tumor absorbed dose, its applicability in patients with high tumor burden, and its feasibility in selected cases with portal vein invasion (3). Studies employing personalized dosimetry have demonstrated a significant association between tumor absorbed dose and both tumor response and survival outcomes (4).

Outcomes after TARE are influenced by both tumor-related factors, such as tumor size, tumor number, vascular invasion, and alpha-fetoprotein (AFP) level, and host-related factors, including Child–Pugh class, performance status, and albumin–bilirubin (ALBI) grade (5). In recent years, sarcopenia has emerged as an important prognostic biomarker and an additional determinant of clinical outcomes in patients with HCC (6). It is defined as the progressive loss of skeletal muscle mass and function and is highly prevalent in patients with cirrhosis and HCC owing to protein-energy malnutrition, systemic inflammation, hormonal derangements, and impaired hepatic synthetic function (7, 8). Computed tomography (CT)-based assessment of skeletal muscle mass at the level of the third lumbar vertebra (L3), expressed as the skeletal muscle index (SMI) by normalizing the cross-sectional muscle area to height squared, is a widely accepted, reproducible, and clinically relevant method for evaluating sarcopenia and body composition (9). In oncological imaging studies, including the present one, the term sarcopenia commonly denotes CT-defined low skeletal muscle mass.

Growing evidence suggests that sarcopenia is an important prognostic factor across a broad spectrum of therapeutic approaches for HCC. Previous studies have demonstrated that reduced skeletal muscle mass is associated with poorer postoperative outcomes following liver resection and with inferior treatment response and survival after transarterial chemoembolization (TACE) (10, 11). Furthermore, sarcopenia has also been associated with increased mortality after radiofrequency ablation and poorer outcomes in patients receiving systemic therapies such as sorafenib (12, 13). Overall, these findings indicate that sarcopenia reflects not only impaired nutritional and functional status but also an adverse biological phenotype that negatively influences treatment response and long-term prognosis in patients with HCC.

By contrast, evidence on the prognostic role of sarcopenia in patients undergoing TARE is comparatively limited (14). In HCC, MRI-derived fat-free muscle area and automated CT-based body-composition analysis have been associated with shorter OS after TARE (15, 16), but these studies did not evaluate local tumor control or tumor absorbed dose. Evidence simultaneously addressing local tumor control and the relationship between sarcopenia and tumor absorbed dose is therefore lacking. Whereas dosimetric studies have consistently demonstrated that higher tumor absorbed doses improve tumor response and local tumor control (4, 17), it remains unclear whether dose retains a prognostic role across all survival endpoints in patients with low muscle mass.

In this study, we evaluated the independent prognostic value of sarcopenia for local progression-free survival (LPFS), progression-free survival (PFS), and overall survival (OS), and compared its prognostic value with that of tumor absorbed dose, in a cohort of patients with unresectable HCC treated with TARE.

MATERIALS AND METHODS

Study design and patient selection

This retrospective, single-center cohort study included consecutive adult patients with unresectable HCC treated with TARE between June 2022 and December 2024. HCC was diagnosed according to histopathology or the non-invasive imaging criteria of the European Association for the Study of the Liver. Inclusion criteria were BCLC stage A, B, or C disease, Child–Pugh class A or B, ECOG performance status 0–2, and availability of pre-treatment [^{18}F]fluorodeoxyglucose positron emission tomography/computed tomography ([^{18}F]FDG PET/CT) suitable for skeletal muscle assessment at the L3 vertebral level. Exclusion criteria were active second primary malignancy, extensive extrahepatic disease, Child–Pugh class C, refractory ascites, ECOG performance status ≥ 3, excessive lung shunt fraction precluding TARE, follow-up of less than three months, and inability to assess skeletal muscle at the L3 vertebral level because of metal artifacts from lumbar spinal prostheses. Patients with BCLC stage A disease were treated with TARE when they were not candidates for resection or ablation. Each patient was included once, at the first TARE session. The protocol was approved by the institutional review board (Approval No: 485; September 2, 2026) and conducted in accordance with the Declaration of Helsinki. The requirement for informed consent was waived because of the retrospective design.

Radioembolization procedure

Treatment decisions were made by a multidisciplinary tumor board. Complete blood count and hepatic and renal function tests were evaluated before treatment. Patients underwent mapping angiography with [^{99m}Tc]macroaggregated albumin ([^{99m}Tc]MAA) injection prior to treatment. After 150–200 MBq (4–5 mCi) of [^{99m}Tc]MAA had been injected into the tumor-feeding (target) hepatic artery, the distribution within the target volume (tumor and non-tumoral liver), extrahepatic deposition, and the lung shunt fraction were evaluated with whole-body planar and single photon emission computed tomography/computed tomography (SPECT/CT) imaging. Treatment planning dosimetry was performed on pre-treatment [^{99m}Tc]MAA SPECT/CT images using Simplicit90Y™ software (Mirada Medical, Denver, CO, USA) based on the partition model. Treatment was performed 1–2 weeks after mapping angiography using either glass microspheres (TheraSphere®, Boston Scientific, Marlborough, MA, USA) or resin microspheres (SIR-Spheres®, Sirtex Medical, Sydney, Australia). Extrahepatic (aberrant) vessels were coil-embolized when necessary to prevent non-target deposition. Post-treatment ^{90}Y PET/CT was performed within 24 hours of the procedure to confirm target deposition and to quantify the tumor absorbed dose.

Imaging procedures

SPECT/CT imaging was performed within 1 hour after injection using a GE Discovery NM/CT 860 hybrid system (GE HealthCare, Chicago, IL, USA). SPECT acquisition was performed with a 128×128 matrix, LEHR collimator, and 140 keV ± 15% energy window over a 360° rotation. Attenuation and scatter correction were applied using low-dose CT data.

All patients underwent pre-treatment staging with [^{18}F]FDG PET/CT using a Philips Ingenuity TF PET/CT system (Philips Healthcare, Cleveland, OH, USA). Patients fasted for at least 6 hours before imaging, and blood glucose levels were confirmed to be < 200 mg/dL before intravenous administration of 3–4 MBq/kg (0.08–0.11 mCi/kg) of [^{18}F]FDG. PET/CT acquisition was performed approximately 60 minutes after tracer administration with an acquisition time of 2 minutes per bed position.

For post-treatment quantitative assessment, ^{90}Y PET/CT was performed within 24 hours after radioembolization using the same PET/CT system. Acquisition time was approximately 20 minutes per bed position (one or two bed positions depending on treatment extent). Images were reconstructed using a TOF-enabled OSEM algorithm with a 512 × 512 matrix. The quality control assessments were consistently implemented as recommended by the European Association of Nuclear Medicine (EANM) guideline (18). Low-dose CT (120 kV, automated mA modulation) was acquired for attenuation correction and anatomical image fusion.

Magnetic resonance imaging (MRI) examinations were performed on a 3-T scanner using gadoxetate disodium (Gd-EOB-DTPA; Eovist/Primovist, Bayer Healthcare) as the contrast agent. The standardized liver MRI protocol comprised T1-weighted in-phase and out-of-phase, T2-weighted, diffusion-weighted imaging (DWI) with b-values of 50, 400, and 800 s/mm² and apparent diffusion coefficient (ADC) mapping, and dynamic post-contrast acquisitions in the late arterial, portal venous, transitional, and hepatobiliary phases (20 min post-injection).

Skeletal muscle quantification and definition of sarcopenia

On the CT component of the pre-treatment [^{18}F]FDG PET/CT, a single axial image at the L3, where both transverse processes were clearly visible, was selected for skeletal muscle analysis. Total skeletal muscle area at L3 (bilateral psoas, erector spinae, quadratus lumborum, transversus abdominis, internal and external oblique, and rectus abdominis muscles) was measured using Hounsfield unit thresholds of − 29 to + 150 (19). The SMI (cm²/m²) was calculated by normalizing the total skeletal muscle cross-sectional area to height squared (m²). Sarcopenia was defined as an SMI < 43 cm²/m² for men with a body mass index (BMI) < 25 kg/m², < 53 cm²/m² for men with a BMI ≥ 25 kg/m², and < 41 cm²/m² for women, according to the Martin criteria (20).

Response evaluation and survival endpoints

Tumor response was initially assessed 4–8 weeks after treatment using multiphasic contrast-enhanced MRI according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST) by an experienced radiologist who was blinded to the patients' sarcopenia status. Follow-up MRI examinations were subsequently performed every 3 months or earlier if clinically indicated, according to the same surveillance schedule for sarcopenic and non-sarcopenic patients. Complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) were defined according to mRECIST. Objective response (OR) was defined as CR plus PR, whereas disease control (DC) comprised CR, PR, and SD. The best overall response during follow-up was recorded for each patient.

LPFS was defined as the interval from the date of treatment to the first documented progression within the treated lesion(s) or treated liver segment, or death from any cause. PFS was defined as the interval from treatment to the date of first progression (local, intrahepatic out-of-field, or extrahepatic) or death from any cause. OS was defined as the interval from treatment to the date of death or last follow-up.

Statistical analysis

Continuous variables were summarized as mean ± standard deviation (SD) or median with interquartile range (IQR), as appropriate; categorical variables were reported as n (%). Between-group comparisons used Student's t-test, the Mann–Whitney U test, the chi-square test, or Fisher's exact test, where indicated. Survival curves were estimated with the Kaplan–Meier method and compared with the log-rank test; curves were constructed according to sarcopenia status, according to tumor absorbed dose, and according to the combination of both. Receiver operating characteristic (ROC) curve analysis was performed to assess the ability of tumor absorbed dose to discriminate patients with and without subsequent local progression. The optimal cut-off value was determined using the Youden index. Univariable and multivariable Cox proportional hazards regression analyses were used to evaluate predictors of LPFS, PFS, and OS. Hazard ratios (HRs) with 95% confidence intervals (CIs) were reported. Because of the relatively limited number of events, multivariable models were restricted to sarcopenia and tumor absorbed dose to ensure model stability and reduce the risk of overfitting. A two-sided p-value < 0.05 was considered statistically significant. Analyses were performed with SPSS version 26.0 (IBM Corp., Armonk, NY).

RESULTS

Patient characteristics

The study cohort consisted of 75 patients with a mean age of 65.4 ± 8.6 years; 56 (74.7%) were male. Hepatitis B virus infection was the most common etiology of HCC, occurring in 40 patients (53.3%), followed by metabolic dysfunction–associated steatotic liver disease (MASLD) in 24 (32.0%). Underlying cirrhosis was present in 51 patients (68.0%). According to the Barcelona Clinic Liver Cancer (BCLC) staging system, 25 patients (33.3%) had stage A disease, 27 (36.0%) had stage B, and 23 (30.7%) had stage C. Child–Pugh class A liver function was observed in 65 patients (86.7%), while 56 (74.7%) had an

Eastern Cooperative Oncology Group (ECOG) performance status of 0. Glass and resin microspheres were used in 51 (68.0%) and 24 (32.0%) patients, respectively. The median tumor absorbed dose was 500 Gy (IQR, 350–720 Gy), and sarcopenia was identified in 32 patients (42.7%). Detailed baseline characteristics are summarized in Table 1.

Table 1
Baseline characteristics of the study population (n = 75)

Variables	Number (%)
Age	
Mean ± SD	65.4 ± 8.6
Sex	
Male	56 (74.7)
Female	19 (25.3)
Etiology of HCC	
HBV	40 (53.3)
MASLD	24 (32)
HCV	6 (8)
Other	5 (6.7)
Underlying cirrhosis	
Yes	51 (68)
No	24 (32)
ECOG performance status	
0	56 (74.7)
1	14 (18.6)
2	5 (6.7)
3 or more	0
Child-Pugh class	
A	65 (86.7)
B	10 (13.3)
BCLC	
A	25 (33.3)

Variables are expressed as median (interquartile range [IQR]; range), mean ± standard deviation (SD), or n (%). AFP, alpha-fetoprotein; ALBI, albumin–bilirubin; BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group performance status; GBq, gigabecquerel; Gy, gray; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; MELD, model for end-stage liver disease; MASLD, metabolic dysfunction–associated steatotic liver disease; WBC, white blood cell count.

Variables	Number (%)
B	27 (36)
C	23 (30.7)
Portal vein invasion	
Yes	9 (12)
No	66 (88)
Tumor	
Solitary	33 (44)
Multiple	42 (56)
Maximum tumor diameter (cm)	
Median (IQR; Range)	5 (3.9–7.9; 1.6–15)
AFP ng/ml	
Median (IQR; Range)	25.4 (4.1–1701; 1.2–45951)
WBC 10^9/L	
Median (IQR; Range)	5.8 (4.8–7.3; 2.9–12.4)
MELD score	
Median (IQR; Range)	6 (6–7; 6–13)
ALBI grade	
Grade 1	54 (72)
Grade 2	19 (25.3)
Grade 3	2 (2.7)
Body mass index (kg/m²)	
Median (IQR; Range)	27.5 (24.2–29.9; 17.6–39.9)
Skletal muscle index(cm²/m²)	
Median (IQR; Range)	47 (2.8–54.5; 32.9–75.6)

Variables are expressed as median (interquartile range [IQR]; range), mean ± standard deviation (SD), or n (%). AFP, alpha-fetoprotein; ALBI, albumin–bilirubin; BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group performance status; GBq, gigabecquerel; Gy, gray; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; MELD, model for end-stage liver disease; MASLD, metabolic dysfunction–associated steatotic liver disease; WBC, white blood cell count.

Variables	Number (%)
Sarcopenia	
Yes	32 (42.7)
No	43 (57.3)
Types of microspheres	
Glass	51 (68)
Resin	24 (32)
Lung shunt fraction (%)	
Median (IQR; Range)	2.7 (1.6–5.1; 0.5–15)
Lung absorbed dose (Gy)	
Median (IQR; Range)	3 (1.4–8.4; 0.1–29)
Activity administered (GBq)	
Median (IQR; Range)	1.8 (1.2– 4; 0.4–11.4)
Tumor absorbed dose (Gy)	
Median (IQR; Range)	500 (350–720; 120–1461)

Variables are expressed as median (interquartile range [IQR]; range), mean ± standard deviation (SD), or n (%). AFP, alpha-fetoprotein; ALBI, albumin–bilirubin; BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group performance status; GBq, gigabecquerel; Gy, gray; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; MELD, model for end-stage liver disease; MASLD, metabolic dysfunction–associated steatotic liver disease; WBC, white blood cell count.

Comparison of sarcopenic and non-sarcopenic patients

Compared with non-sarcopenic patients (n = 43), sarcopenic patients (n = 32) were significantly older (68.0 ± 9.1 vs. 63.5 ± 7.8 years; p = 0.025) and more frequently had impaired performance status (ECOG > 0: 50.0% vs. 7.0%; p < 0.001). The BCLC stage distribution differed between the groups (p = 0.007), with stage C disease in 50.0% of sarcopenic versus 16.3% of non-sarcopenic patients, and the maximum tumor diameter was larger in the sarcopenic group (median 6.0 vs. 4.7 cm; p = 0.034). As expected, SMI was markedly lower in the sarcopenic group (median 42.8 vs. 54.1 cm^2/m^2; p < 0.001). No significant differences were observed in sex, etiology, Child–Pugh class, ALBI grade, body mass index, AFP, and MELD score. Lung absorbed dose was higher in the sarcopenic group (median 4.4 vs. 2.1 Gy; p = 0.036), whereas tumor absorbed dose did not differ significantly between groups (median 400 vs. 597 Gy; p = 0.11).

Across the entire cohort, the CR, PR, SD, and PD rates were 26.7%, 44.0%, 13.3%, and 16.0%, respectively. The OR and DC rate were 70.7% and 84.0%, respectively. During follow-up, local tumor progression

occurred in 43 patients (57.3%), whereas disease progression at any site was observed in 49 patients (65.3%). Best overall response was markedly poorer in sarcopenic patients: OR was achieved in 34.4% versus 97.7% of non-sarcopenic patients ($p < 0.001$), and DC in 62.5% versus 100% ($p < 0.001$). PD as best response occurred in 37.5% of sarcopenic patients versus 0% of non-sarcopenic patients. During follow-up, local tumor progression occurred in 78.1% of sarcopenic versus 41.9% of non-sarcopenic patients ($p = 0.002$); any disease progression occurred in 81.3% versus 53.5%, respectively ($p = 0.012$). Representative examples of a sarcopenic and a non-sarcopenic patient, including their skeletal muscle measurements and clinical outcomes, are shown in Fig. 1.

Subsequent treatments after radioembolization included systemic therapy in 23 patients (30.7%), repeat radioembolization in 17 (22.7%), external-beam radiotherapy in 8 (10.7%), radiofrequency or microwave ablation in 7 (9.3%), surgical resection in 7 (9.3%), and TACE in 2 (2.7%). The distribution of these subsequent therapies did not differ significantly between sarcopenic and non-sarcopenic patients (all $p > 0.05$).

Median follow-up was 16 months (IQR 9–25), during which 32 patients (42.7%) died. Kaplan–Meier analysis demonstrated significantly worse outcomes in sarcopenic patients across all three endpoints: median LPFS was 6 versus 21 months (log-rank $p < 0.001$), median PFS 6 versus 19 months ($p < 0.001$), and median OS 10 months versus not reached ($p < 0.001$) (Fig. 2). Group comparisons are summarized in Table 2.

Table 2
Comparison of Patient Characteristics According to Sarcopenia.

Variables	Non Sarcopenic (n = 43)	Sarcopenic (n = 32)	P value
Age	63.5 ± 7.8	68.0 ± 9.1	**0.025**
Sex			0.55
Male	31 (72.1)	25 (78.1)	
Female	12 (27.9)	7 (21.9)	
Etiology of HCC			0.14
HBV	21 (48.8)	19 (59.4)	
MASLD	14 (32.6)	10 (31.3)	
HCV	6 (14)	0	
Other etiology	2 (4.6)	3 (9.3)	
Underlying cirrhosis			0.26
Yes	27 (62.8)	24 (75)	
No	16 (37.2)	8 (25)	
ECOG status			**< 0.001**
0	40 (93)	16 (50)	
1	2 (4.7)	12 (37.5)	
2	1 (2.3)	4 (12.5)	
Child-Pugh class			0.174
A	35 (81.4)	30 (93.8)	
B	8 (18.6)	2 (6.3)	

* P values for survival outcomes are from the log-rank test.

Variables are expressed as median (interquartile range [IQR]), mean ± standard deviation (SD), or n (%). AFP, alpha-fetoprotein; ALBI, albumin–bilirubin; BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group performance status; GBq, gigabecquerel; HCC, hepatocellular carcinoma; mRECIST, modified Response Evaluation Criteria in Solid Tumors; EBRT, external-beam radiotherapy; Gy, gray; HBV, hepatitis B virus; HCV, hepatitis C virus; IQR, interquartile range; LPFS, local progression-free survival; MELD, model for end-stage liver disease; mo., months; MWA, microwave ablation; NR, not reached; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; OR, objective response; DC, disease control; OS, overall survival; PFS, progression-free survival; RE, radioembolization; RFA, radiofrequency ablation; SLD, steatotic liver disease; TACE, transarterial chemoembolization; WBC, white blood cell count; NR, not reach.

Variables	Non Sarcopenic (n = 43)	Sarcopenic (n = 32)	P value
BCLC			**0.007**
A	17 (39.5)	8 (25)	
B	19 (44.2)	8 (25)	
C	7 (16.3)	16 (50)	
Portal vein invasion			0.32
Yes	4 (9.3)	5 (15.6)	
No	39 (90.7)	27 (84.4)	
Tumor number			0.33
Solitary	21 (48.8)	12 (37.5)	
Multiple	22 (51.2)	20 (62.5)	
Maximum tumor diameter (cm)	4.7 (3.9–6.7)	6 (4.5–9.4)	**0.034**
AFP ng/ml	17 (3.9–1061)	73 (4.7– 3237)	0.28
WBC 10^9/L	5.7 (4.5–7.3)	5.8 (4.9–7.3)	0.37
MELD score	6 (6–7)	6 (6–7)	0.41
ALBI grade			0.28
Grade 1	34 (79.1)	20 (62.5)	
Grade 2	8 (18.6)	11 (34.4)	
Grade 3	1 (2.3)	1 (3.1)	
Body mass index (kg/m²)	28.1 (24.2–30.6)	27.1 (24.8–28.7)	0.25
Skeletal muscle index(cm²/m²)	54.1 (45.4–56.6)	42.8 (38.8–49.2)	**< 0.001**
Lung shunt fraction (%)	2.7 (1.2–4.6)	2.9 (1.8–6.1)	0.19

* P values for survival outcomes are from the log-rank test.

Variables are expressed as median (interquartile range [IQR]), mean ± standard deviation (SD), or n (%). AFP, alpha-fetoprotein; ALBI, albumin–bilirubin; BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group performance status; GBq, gigabecquerel; HCC, hepatocellular carcinoma; mRECIST, modified Response Evaluation Criteria in Solid Tumors; EBRT, external-beam radiotherapy; Gy, gray; HBV, hepatitis B virus; HCV, hepatitis C virus; IQR, interquartile range; LPFS, local progression-free survival; MELD, model for end-stage liver disease; mo., months; MWA, microwave ablation; NR, not reached; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; OR, objective response; DC, disease control; OS, overall survival; PFS, progression-free survival; RE, radioembolization; RFA, radiofrequency ablation; SLD, steatotic liver disease; TACE, transarterial chemoembolization; WBC, white blood cell count; NR, not reach.

Variables	Non Sarcopenic (n = 43)	Sarcopenic (n = 32)	P value
Lung absorbed dose (Gy)	2.1 (1.1–6.5)	4.4 (2.6–15.7)	**0.036**
Activity administered (GBq)	1.6 (1.2–3.2)	2 (1.3–4.3)	0.28
Tumor absorbed dose (Gy)	597 (400–800)	400 (291–700)	0.11
Best radiological response by mRECIST			**< 0.001**
CR	15 (34.9)	5 (15.6)	
PR	27 (62.8)	6 (18.8)	
SD	1 (2.3)	9 (28.1)	
PD	0	12 (37.5)	
OR	42 (97.7)	11 (34.4)	**< 0.001**
DC	43 (100)	20 (62.5)	**< 0.001**
Progression during follow up time			
Local tumor progression	18 (41.9)	25 (78.1)	**0.002**
Any Disease Progression	23 (53.5)	26 (81.3)	**0.012**
Alive at last follow-up			**< 0.001**
Yes	34 (79.1)	9 (28.1)	
No	9 (20.9)	23 (71.9)	
Treatment After TARE			
Systemic Therapy	14 (32.6)	9 (28.1)	0.68
TACE	2 (4.7)	0	0.50
RFA or MWA	5 (11.6)	2 (6.3)	0.69

* P values for survival outcomes are from the log-rank test.

Variables are expressed as median (interquartile range [IQR]), mean ± standard deviation (SD), or n (%). AFP, alpha-fetoprotein; ALBI, albumin–bilirubin; BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group performance status; GBq, gigabecquerel; HCC, hepatocellular carcinoma; mRECIST, modified Response Evaluation Criteria in Solid Tumors; EBRT, external-beam radiotherapy; Gy, gray; HBV, hepatitis B virus; HCV, hepatitis C virus; IQR, interquartile range; LPFS, local progression-free survival; MELD, model for end-stage liver disease; mo., months; MWA, microwave ablation; NR, not reached; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; OR, objective response; DC, disease control; OS, overall survival; PFS, progression-free survival; RE, radioembolization; RFA, radiofrequency ablation; SLD, steatotic liver disease; TACE, transarterial chemoembolization; WBC, white blood cell count; NR, not reach.

Variables	Non Sarcopenic (n = 43)	Sarcopenic (n = 32)	P value
Surgical Resection	5 (11.6)	2 (6.3)	0.69
Repeat TARE	12 (27.9)	5 (15.6)	0.21
EBRT	4 (9.3)	4 (12.5)	0.72
Survival Outcomes			
LPFS			**< 0.001***
Median survival (mo.)	21	6	
PFS			**< 0.001***
Median survival (mo.)	19	6	
OS			**< 0.001***
Median survival (mo.)	NR	10	
* P values for survival outcomes are from the log-rank test.			
Variables are expressed as median (interquartile range [IQR]), mean ± standard deviation (SD), or n (%). AFP, alpha-fetoprotein; ALBI, albumin–bilirubin; BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group performance status; GBq, gigabecquerel; HCC, hepatocellular carcinoma; mRECIST, modified Response Evaluation Criteria in Solid Tumors; EBRT, external-beam radiotherapy; Gy, gray; HBV, hepatitis B virus; HCV, hepatitis C virus; IQR, interquartile range; LPFS, local progression-free survival; MELD, model for end-stage liver disease; mo., months; MWA, microwave ablation; NR, not reached; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; OR, objective response; DC, disease control; OS, overall survival; PFS, progression-free survival; RE, radioembolization; RFA, radiofrequency ablation; SLD, steatotic liver disease; TACE, transarterial chemoembolization; WBC, white blood cell count; NR, not reach.			

Predictors of survival

Using the occurrence of subsequent local progression as a binary outcome, ROC analysis identified a tumor absorbed dose cut-off of 485 Gy based on the Youden index, with a sensitivity of 63%, specificity of 75%, and an AUC of 0.75 (95% CI, 0.62–0.85; p < 0.001) (Supplementary Figure S1). A tumor absorbed dose ≥ 485 Gy was associated with significantly longer local progression-free survival (20 vs. 10 months; HR 2.13, 95% CI 1.15–3.97; p = 0.012), progression-free survival (17 vs. 8 months; HR 1.81, 95% CI 1.02–3.21; p = 0.031), and overall survival (not reached vs. 21 months; HR 2.19, 95% CI 1.05–4.57; p = 0.029) compared with doses < 485 Gy (Fig. 3).

On univariable analysis, sarcopenia (HR 4.2; 95% CI 2.2–7.8; $p < 0.001$), tumor absorbed dose < 485 Gy (HR 2.1; 95% CI 1.2–3.9; $p = 0.017$), ECOG performance status > 0 (HR 2.6; 95% CI 1.4–4.9; $p = 0.005$), BCLC stage C (HR 2.5; 95% CI 1.3–4.6; $p = 0.004$), portal vein invasion (HR 3.3; 95% CI 1.5–7.2; $p = 0.003$), maximum tumor diameter > 5 cm (HR 2.7; 95% CI 1.4–5.0; $p = 0.002$), and ALBI grade > 1 (HR 2.8; 95% CI 1.5–5.2; $p = 0.001$) were significantly associated with shorter LPFS. Given the limited number of

events, the multivariable model was restricted to the two variables of primary interest. Both sarcopenia (HR 4.0; 95% CI 2.1–7.7; $p < 0.001$) and tumor absorbed dose < 485 Gy (HR 1.9; 95% CI 1.1–3.6; $p = 0.034$) remained independent predictors of shorter LPFS (Table 3).

Table 3
Univariate and Multivariable Predictors of LPFS

Variable	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age > 65	1.08 (0.59–1.9)	0.79		
Male sex	1.47 (0.7–3.1)	0.31		
HBV etiology	1.34 (0.73–2.5)	0.35		
Underlying cirrhosis	1.28 (0.66–2.5)	0.47		
ECOG > 0	2.6 (1.4–4.9)	**0.005**		
Child-Pugh class B	1.4 (0.64–3.3)	0.38		
BCLC C	2.5 (1.3–4.6)	**0.004**		
Portal vein invasion	3.3 (1.5–7.2)	**0.003**		
Multiple tumors	1.1 (0.59–1.9)	0.83		
Max. tumor diameter > 5 cm	2.7 (1.4–5)	**0.002**		
Sarcopenia	4.2 (2.2–7.8)	**< 0.001**	4 (2.1–7.7)	**< 0.001**
AFP > 200 ng/ml	1.8 (0.98–3.3)	0.058		
WBC > 6.5 10^9/L	1.2 (0.66–2.3)	0.515		
MELD score > 6	1.3 (0.72–2.5)	0.366		
ALBI grade > 1	2.8 (1.5–5.2)	**0.001**		
Glass microspheres	0.99 (0.53–1.9)	0.98		
Tumor absorbed dose < 485 Gy	2.1 (1.2–3.9)	**0.017**	1.9 (1.1–3.6)	**0.034**

Cox proportional hazards regression analyses. AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; Gy, gray; HBV, hepatitis B virus; HR, hazard ratio; LPFS, local progression-free survival; MELD, model for end-stage liver disease; WBC, white blood cell count.

Similarly, univariable analysis showed that sarcopenia (HR 3.0; 95% CI 1.7–5.3; $p < 0.001$), tumor absorbed dose < 485 Gy (HR 1.8; 95% CI 1.02–3.2; $p = 0.041$), ECOG performance status > 0 (HR 2.2; 95% CI 1.2–4.1; $p = 0.015$), BCLC stage C (HR 1.9; 95% CI 1.1–3.5; $p = 0.026$), portal vein invasion (HR 2.3; 95% CI 1.04–4.9; $p = 0.038$), maximum tumor diameter > 5 cm (HR 2.0; 95% CI 1.2–3.6; $p = 0.017$), AFP >

200 ng/mL (HR 1.9; 95% CI 1.1–3.4; $p = 0.021$), and ALBI grade > 1 (HR 2.5; 95% CI 1.4–4.6; $p = 0.003$) were significantly associated with poorer PFS. In multivariable analysis, sarcopenia remained an independent predictor of poorer PFS (HR 2.8; 95% CI 1.6–5.2; $p < 0.001$), whereas the association of tumor absorbed dose < 485 Gy with PFS was not statistically significant (HR 1.7; 95% CI 0.94–3.0; $p = 0.078$) (Table 4).

Table 4
Univariate and Multivariable Predictors of PFS

Variable	**Univariate Analysis**		**Multivariate Analysis**	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**
Age > 65	0.75 (0.42–1.3)	0.31		
Male sex	1.37 (0.69–2.7)	0.36		
HBV etiology	1.11 (0.63–1.9)	0.73		
Underlying cirrhosis	1.14 (0.62–2.1)	0.67		
ECOG > 0	2.2 (1.2–4.1)	**0.015**		
Child-Pugh class B	1.45 (0.68–3.2)	0.34		
BCLC C	1.9 (1.1–3.5)	**0.026**		
Portal vein invasion	2.3 (1.04–4.9)	**0.038**		
Multiple tumors	1.46 (0.82–2.6)	0.20		
Max. tumor diameter > 5 cm	2 (1.2–3.6)	**0.017**		
Sarcopenia	3.0 (1.7–5.3)	**< 0.001**	2.8 (1.6–5.2)	**< 0.001**
AFP > 200 ng/ml	1.9 (1.1–3.4)	**0.021**		
WBC > 6.5 10^9/L	1.1 (0.62–1.9)	0.73		
MELD score > 6	1.3 (0.71–2.3)	0.42		
ALBI grade > 1	2.5 (1.4–4.6)	**0.003**		
Glass microspheres	0.97 (0.54–1.8)	0.92		
Tumor absorbed dose < 485 Gy	1.8 (1.02–3.2)	**0.041**	1.7 (0.94–3.0)	0.076

Cox proportional hazards regression analyses. AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; Gy, gray; HBV, hepatitis B virus; HR, hazard ratio; PFS, progression-free survival; MELD, model for end-stage liver disease; WBC, white blood cell count.

Likewise, univariable analysis showed that sarcopenia (HR 5.9; 95% CI 2.7–13.0; $p < 0.001$), tumor absorbed dose < 485 Gy (HR 2.2; 95% CI 1.1–4.6; $p = 0.036$), ECOG performance status > 0 (HR 4.2; 95% CI 2.0–8.7; $p < 0.001$), Child–Pugh class B (HR 2.6; 95% CI 1.1–6.0; $p = 0.030$), BCLC stage C (HR 4.4;

95% CI 2.1–9.0; $p < 0.001$), portal vein invasion (HR 4.7; 95% CI 2.0–10.7; $p < 0.001$), maximum tumor diameter > 5 cm (HR 2.4; 95% CI 1.2–4.9; $p = 0.019$), AFP > 200 ng/mL (HR 3.0; 95% CI 1.4–6.4; $p = 0.004$), MELD score > 6 (HR 2.4; 95% CI 1.2–4.9; $p = 0.017$), and ALBI grade > 1 (HR 2.7; 95% CI 1.4–5.5; $p = 0.005$) were significantly associated with poorer OS. In multivariable analysis, sarcopenia remained an independent predictor of poorer OS (HR 5.5; 95% CI 2.5–12.0; $p < 0.001$), whereas the association of tumor absorbed dose < 485 Gy with OS was not statistically significant (HR 1.7; 95% CI 0.81–3.6; $p = 0.161$) (Table 5).

Table 5
Univariate and Multivariable Predictors of OS

Variable	**Univariate Analysis**		**Multivariate Analysis**	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**
Age > 65	1.2 (0.6–2.4)	0.61		
Male sex	2.1 (0.79–5.3)	0.14		
HBV etiology	1.8 (0.88–3.7)	0.11		
Underlying cirrhosis	1.7 (0.72–3.8)	0.24		
ECOG > 0	4.2 (2–8.7)	**< 0.001**		
Child-Pugh class B	2.6 (1.1–6)	**0.03**		
BCLC C	4.4 (2.1–9)	**< 0.001**		
Portal vein invasion	4.7 (2–10.7)	**< 0.001**		
Multiple tumors	1.1 (0.54–2.2)	0.79		
Max. tumor diameter > 5 cm	2.4 (1.2–4.9)	**0.019**		
Sarcopenia	5.9 (2.7–13.0)	**< 0.001**	5.5 (2.5–12)	**< 0.001**
AFP > 200 ng/ml	3 (1.4–6.4)	**0.004**		
WBC > 6.5 10^9/L	1.1 (0.53–2.2)	0.84		
MELD score > 6	2.4 (1.2–4.9)	**0.017**		
ALBI grade > 1	2.7 (1.4–5.5)	**0.005**		
Glass microspheres	1.1 (0.51–2.2)	0.87		
Tumor absorbed dose < 485 Gy	2.2 (1.1–4.6)	**0.036**	1.7 (0.81–3.6)	0.161

Cox proportional hazards regression analyses. AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; Gy, gray; HBV, hepatitis B virus; HR, hazard ratio; OS, overall survival; MELD, model for end-stage liver disease; WBC, white blood cell count.

When patients were stratified by both sarcopenia and tumor absorbed dose (Fig. 4), sarcopenic patients had the poorest outcomes in both dose groups: median OS was 19 months in sarcopenic patients receiving ≥ 485 Gy and 9 months in those receiving < 485 Gy, whereas it was not reached in non-sarcopenic patients irrespective of dose group (overall log-rank $p < 0.001$ for LPFS, PFS, and OS).

DISCUSSION

TARE with ^{90}Y microspheres has become an effective treatment option for unresectable HCC, achieving high rates of local control through personalized tumor absorbed dose (3, 4). In this single-center cohort of 75 patients, we demonstrate that sarcopenia is strongly and independently associated with worse outcomes across all three survival endpoints—LPFS, PFS, and OS. A second observation is that tumor absorbed dose < 485 Gy retained independent prognostic significance for LPFS but not for PFS or OS in the multivariable analysis, although the confidence intervals for the latter were wide. Taken together, these findings suggest that an adequate tumor absorbed dose is necessary for local tumor control but does not offset the adverse prognosis conferred by sarcopenia.

The prevalence of sarcopenia in our cohort (42.7%) is comparable to that reported in previous studies of intermediate-to-advanced HCC, ranging from 39% in patients treated with TACE to 57% in patients receiving sorafenib for advanced-stage disease (13, 21). Sarcopenic patients in our series were older, had poorer performance status, larger tumors, and more frequently presented with BCLC-C disease, suggesting that sarcopenia reflects both advanced tumor burden and impaired physiologic reserve rather than simply reduced skeletal muscle mass. This interpretation is consistent with previous studies demonstrating that sarcopenia is associated with increased mortality in patients with cirrhosis and with both poorer survival and higher tumor recurrence rates in HCC (8, 22). Accordingly, sarcopenia should be regarded not merely as a measure of skeletal muscle depletion, but as a composite biomarker of impaired physiologic reserve, reflecting the complex interplay of malnutrition, systemic inflammation, metabolic disturbances, and reduced hepatic functional reserve that characterizes advanced liver disease (23).

The substantially lower OR rate (34.4% vs. 97.7%) and DC rate (62.5% vs. 100%) observed in sarcopenic patients are consistent with previous studies demonstrating inferior treatment outcomes in patients with pre-sarcopenia undergoing TACE and poorer survival among patients receiving sorafenib for advanced HCC (13, 21). Although Roth et al. did not identify sarcopenia as an independent predictor of radiological response, our findings suggest that sarcopenia is associated with a markedly poorer early treatment response (24). The very high response rate among non-sarcopenic patients should, however, be interpreted in the light of their smaller tumors and higher tumor absorbed doses and of the use of the best overall response during follow-up. In TARE specifically, the available studies—using MRI-derived fat-free muscle area or automated CT-based body-composition analysis—have consistently linked low muscle mass with shorter OS (14–16), but none evaluated local tumor control or tumor absorbed dose. Differences in sarcopenia definitions, imaging modality, patient selection, BCLC stage distribution, and treatment strategies limit direct comparison between studies (25).

A key finding of our study concerns the relative prognostic weight of tumor absorbed dose and pretreatment sarcopenia. Tumor absorbed dose remained an independent predictor of LPFS, consistent with the dose–response relationship demonstrated in DOSISPHERE-01 and in the SARAH dosimetric analyses, reinforcing the concept that an adequate tumor absorbed dose is essential for durable local tumor control (4, 17). For PFS and OS, the association of tumor absorbed dose was attenuated and did not reach statistical significance in the multivariable models; however, the confidence intervals were wide, and with 32 deaths our study was not powered to exclude an effect of dose on survival. The stratified curves (Fig. 4) illustrate this point: sarcopenic patients had the poorest outcomes in both dose groups, and although those receiving ≥ 485 Gy had a longer median OS than those receiving < 485 Gy (19 vs. 9 months), their survival remained far shorter than that of non-sarcopenic patients, in whom the median OS was not reached irrespective of dose group. Taken together, these findings suggest that an adequate tumor absorbed dose is necessary for local tumor control but does not offset the adverse prognosis conferred by sarcopenia, which reflects impaired physiologic reserve, systemic inflammation, and diminished hepatic functional reserve (23, 26) and may favour disease progression outside the treated field. Notably, the 485 Gy threshold identified in this cohort is considerably higher than the thresholds reported in DOSISPHERE-01 (≥ 205 Gy for glass microspheres) and SARAH (≥ 100 Gy for resin microspheres), reflecting differences in dosimetric approach and the pooling of glass and resin microspheres in our series; the threshold should therefore be regarded as cohort-specific.

Several clinical implications emerge from these findings. First, achieving an adequate tumor absorbed dose remains essential for durable local tumor control but, by itself, may be insufficient to improve long-term outcomes in patients with sarcopenia. Second, patients with sarcopenia may benefit from closer imaging surveillance after TARE to facilitate earlier detection of new intrahepatic or extrahepatic disease. Third, early multidisciplinary reassessment may be warranted when recurrent or progressive disease is identified, allowing timely consideration of additional locoregional or systemic treatment strategies. Fourth, the consistently poor PFS and OS observed in patients with sarcopenia suggest that earlier integration of effective systemic therapy warrants prospective evaluation, bearing in mind that sarcopenia also predicts poorer outcomes under systemic therapy (13). Whether initiating contemporary first-line regimens, such as atezolizumab plus bevacizumab or lenvatinib, at an earlier stage can improve outcomes in this high-risk subgroup remains to be determined in prospective studies (27, 28). Finally, prehabilitation strategies combining nutritional support and exercise may help preserve skeletal muscle mass and improve outcomes in patients with sarcopenia (29).

Compared with the extensive literature evaluating sarcopenia in patients undergoing TACE or systemic therapy, evidence regarding its prognostic significance in TARE remains limited (14–16, 30). Our study addresses this knowledge gap by simultaneously evaluating the impact of pretreatment sarcopenia on LPFS, PFS, and OS, while directly comparing its prognostic value with that of tumor absorbed dose. Notably, currently available prognostic models for locoregional therapy, including the HAP score, six-and-twelve score, ALBI-TAE, and FAIL-T, do not incorporate skeletal muscle assessment (31, 32). Our findings provide a rationale for incorporating sarcopenia into TARE-specific prognostic models to improve risk stratification and facilitate more individualized treatment planning.

Our study has several limitations. First, its retrospective, single-center design may have introduced selection bias. Second, the relatively limited sample size and number of outcome events—particularly the 32 deaths—constrained the complexity of the multivariable analyses and limited the power to exclude an effect of tumor absorbed dose on PFS and OS. To minimize the risk of overfitting, we restricted the multivariable models to the two variables of primary interest: pretreatment sarcopenia and tumor absorbed dose. Consequently, the independent prognostic value of other variables identified in the univariable analyses, including BCLC stage, portal vein invasion, ALBI grade, ECOG performance status, and AFP level, could not be assessed simultaneously in the multivariable models, and residual confounding cannot be excluded. Third, the 485 Gy tumor absorbed dose threshold was derived from the present cohort using ROC analysis and should therefore be considered exploratory, requiring validation in independent cohorts; moreover, it was applied to both glass and resin microspheres, which have different dose–response relationships, and the number of patients treated with resin microspheres was small. Fourth, tumor response was assessed by a single reader as the best overall response during follow-up, and patients with less than three months of follow-up were excluded, which may have favoured survival estimates. Finally, changes in dosimetric strategies and microsphere selection during the study period may have introduced treatment heterogeneity. Our findings should be validated in larger, prospective multicenter cohorts.

CONCLUSION

In patients with unresectable HCC treated with TARE, CT-defined sarcopenia was a strong, independent predictor of LPFS, PFS, and OS. Tumor absorbed dose remained associated with local tumor control, but an adequate dose did not overcome the adverse prognostic impact of sarcopenia. Routine measurement of the skeletal muscle index on pretreatment imaging may improve risk stratification and help to identify patients who require closer surveillance, nutritional and functional support, and timely consideration of systemic therapy.

Declarations

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Competing Interests

The authors declare no competing interests.

Author Contributions

Study concept and overall design were developed by Fuad Aghazada. Data collection was performed by Fuad Aghazada, Enes Mustafa Kaya, and Halil Burak Kapucu. Data analysis was performed by Enes Mustafa Kaya and Fuad Aghazada. The manuscript was drafted by Fuad Aghazada. All authors read and contributed to previous drafts of the manuscript, and all authors read and approved the final manuscript.

Ethics Approval

This retrospective study was approved by the local institutional ethics committee and was conducted in accordance with the Declaration of Helsinki (Approval No: 485; Date: September 2, 2026).

Consent to Participate

Written informed consent was obtained from all individual participants included in the study.

Consent to Publish

Additional written informed consent was obtained from the patients whose de-identified clinical image is presented in Figures 1.

Data Availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Figures

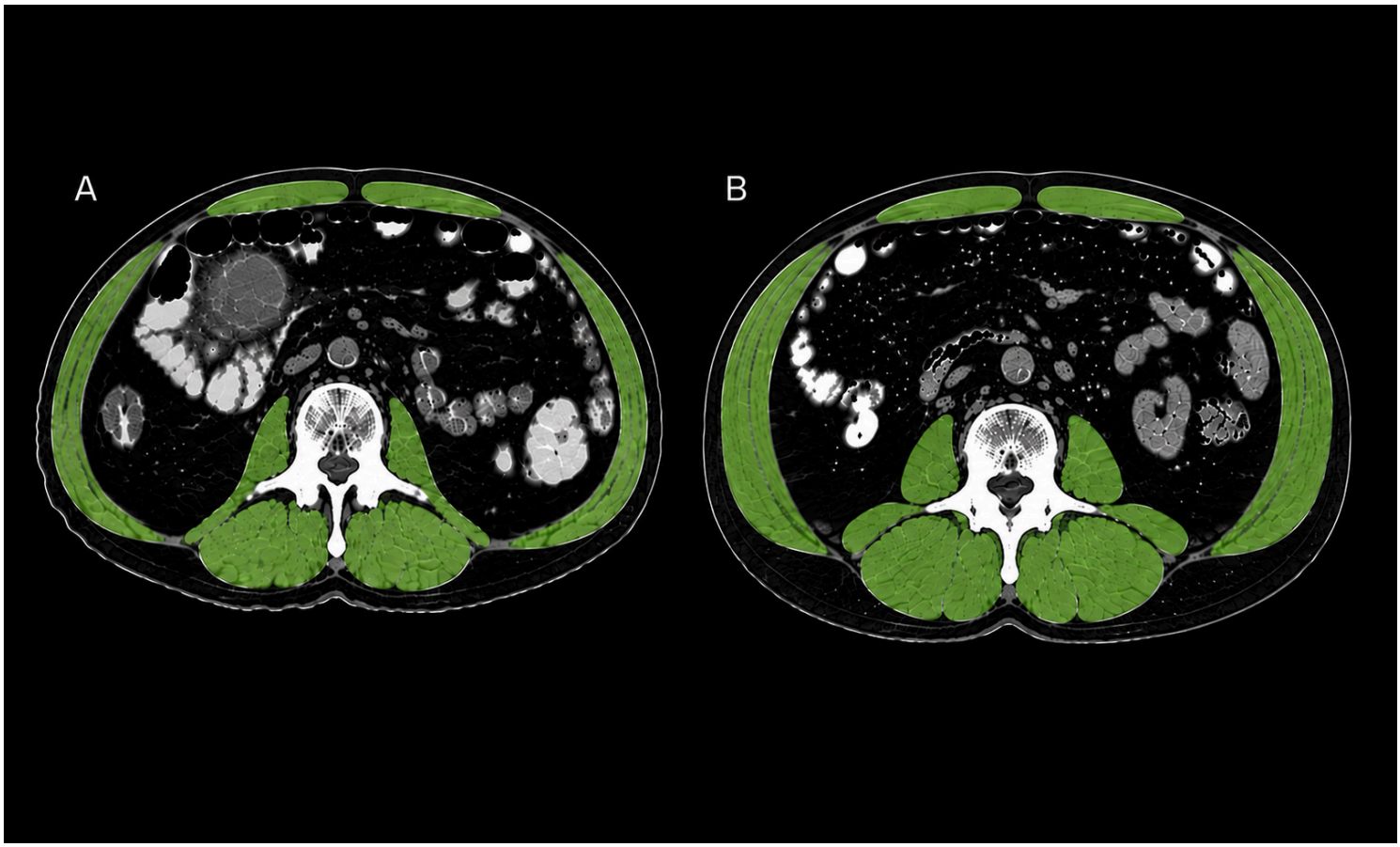


Figure 1

Representative axial CT images at the L3 vertebral level illustrating differences in skeletal muscle mass and clinical outcomes in patients with HCC treated with TARE. (A) A 62-year-old male patient with sarcopenia (SMI, 32 cm²/m²) and a 44×38 mm HCC lesion received a tumor absorbed dose of 650 Gy. Stable disease was observed after treatment; however, PFS and OS were 3 and 8 months, respectively. (B) A 71-year-old male patient without sarcopenia (SMI, 49 cm²/m²) and a 62×45 mm HCC lesion received a tumor absorbed dose of 510 Gy. Complete response was achieved, with no progression or death observed during 26 months of follow-up. The skeletal muscle areas used for SMI calculation, including the bilateral psoas, erector spinae, quadratus lumborum, transversus abdominis, internal and external oblique, and rectus abdominis muscles, are highlighted in green.

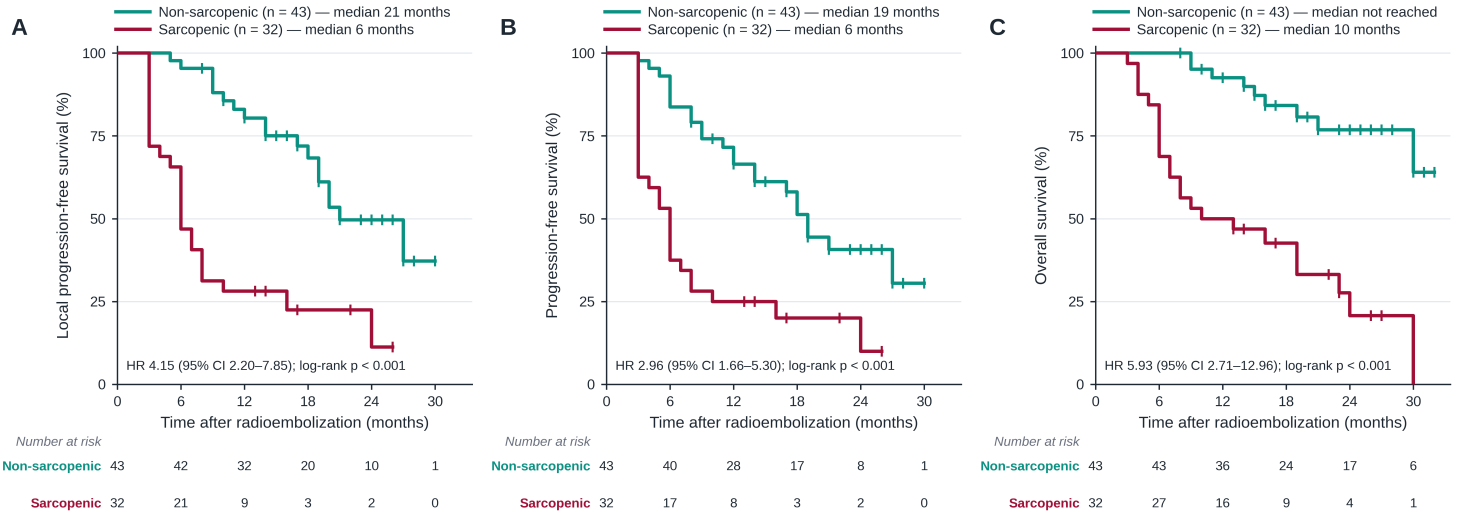


Figure 2

Kaplan–Meier estimates of (A) local progression-free survival (LPFS), (B) progression-free survival (PFS), and (C) overall survival (OS) according to pretreatment sarcopenia (n=75).

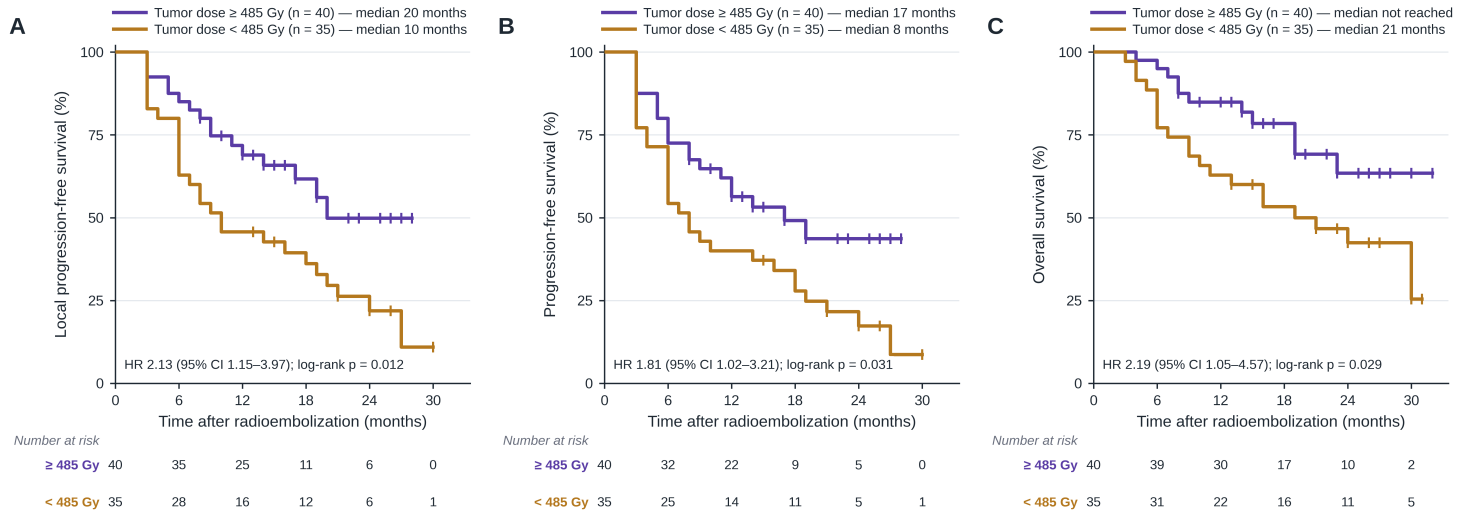


Figure 3

Kaplan–Meier estimates of (A) LPFS, (B) PFS, and (C) OS according to tumor absorbed dose (≥485 Gy vs. <485 Gy; cut-off derived by ROC analysis).

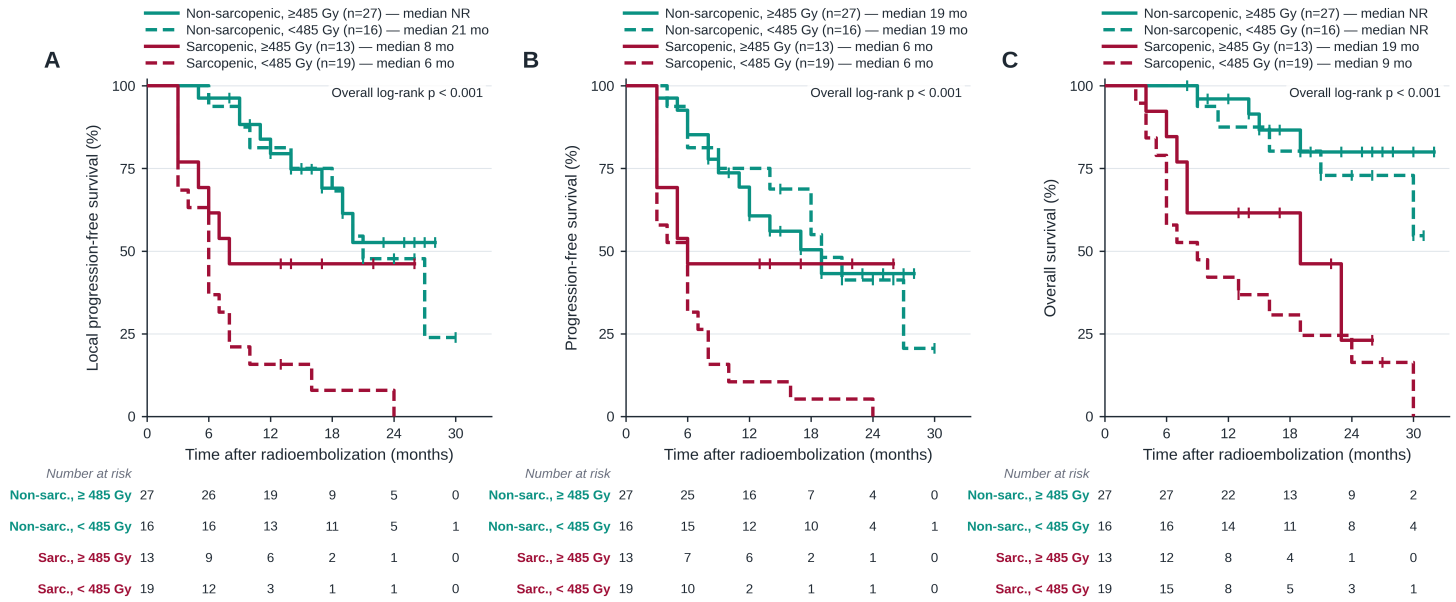


Figure 4

Kaplan–Meier estimates of (A) LPFS, (B) PFS, and (C) OS in the four groups defined by pretreatment sarcopenia (colour) and tumor absorbed dose ≥485 Gy (solid lines) or <485 Gy (dashed lines). p-values are from the log-rank test across the four groups. NR, not reached.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryFigureS1.png