



# Fat-free muscle area measured by magnetic resonance imaging predicts overall survival of patients undergoing radioembolization of colorectal cancer liver metastases

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## Abstract

**Objectives** To investigate the clinical potential of fat-free muscle area (FFMA) to predict outcome in patients with liver-predominant metastatic colorectal cancer (mCRC) undergoing radioembolization (RE) with <sup>90</sup>Yttrium microspheres.

**Methods** Patients with mCRC who underwent RE in our center were included in this retrospective study. All patients received liver magnetic resonance imaging including standard T2-weighted images. The total erector spinae muscle area and the intramuscular adipose tissue area were measured at the level of the origin of the superior mesenteric artery and subtracted to calculate FFMA. Cutoff values for definition of low FFMA were 3644 mm<sup>2</sup> in men and 2825 mm<sup>2</sup> in women. The main outcome was overall survival (OS). For survival analysis, the Kaplan-Meier method and Cox regressions comparing various clinic-oncological parameters which potentially may affect OS were performed.

**Results** Seventy-seven patients (28 female, mean age 60 ± 11 years) were analyzed. Mean time between MRI and the following RE was 17 ± 31 days. Median OS after RE was 178 days. Patients with low FFMA had significantly shortened OS compared to patients with high FFMA (median OS: 128 vs. 273 days, *p* = 0.017). On multivariate Cox regression analysis, OS was best predicted by FFMA (hazard ratio (HR) 2.652; *p* < 0.001). Baseline bilirubin (HR 1.875; *p* = 0.030), pattern of tumor manifestation (HR 1.679; *p* = 0.001), and model of endstage liver disease (MELD) score (HR 1.164; *p* < 0.001) were also significantly associated with OS.

**Conclusions** FFMA was associated with OS in patients receiving RE for treatment of mCRC and might be a new prognostic biomarker for survival prognosis.

## Key Points

- Fat-free muscle area (FFMA) as a measure of lean muscle area predicts survival in metastatic colorectal liver cancer following radioembolization.
- FFMA can easily be assessed from routine pre-interventional liver magnetic resonance imaging.
- FFMA might be a new promising biomarker for assessment of sarcopenia.

**Keywords** Sarcopenia · Colorectal cancer · Brachytherapy · Magnetic resonance imaging

## Abbreviations

ATA Adipose tissue area  
CRC Colorectal cancer

CT Computed tomography  
ECOG Eastern Cooperative Oncology Group performance status

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FFMA	Fat-free muscle area
mCRC	Liver-predominant metastatic colorectal cancer
MELD	Model of endstage liver disease
MRI	Magnetic resonance imaging
OS	Overall survival
PDFF	Proton density fat fraction
RE	Radioembolization
SMI	Skeletal muscle index
TIPS	Transjugular intrahepatic portosystemic shunt
TMA	Total muscle area
Y-90	<sup>90</sup> Yttrium microspheres

## Introduction

Colorectal cancer (CRC) is the third most common malignancy and a leading cause of death in the developed countries. In 2017, it was estimated that about 50,260 people died from CRC in the USA [1]. At time of diagnosis, one in five patients presents with distant metastatic disease, while during course of disease, distant metastases are observed in more than every second patient. The liver is the most frequently involved organ with hepatic failure causing the majority of deaths in these patients [2]. Surgical resection is the treatment of choice for CRC liver metastases [3, 4]. Unfortunately, potentially curative resection is possible only in about 10–20% of all patients [5]. Therefore, a growing need for treatment alternatives in patients with unresectable and chemorefractory disease exists. locoregional treatment approaches such as radioembolization (RE) evolved as promising therapeutic options. By accessing the tumor-supplying vessels with a catheter, a high radiation dose can be applied selectively to the tumor while reducing toxicity of healthy tissue and minimizing risk of systemic side effects [5]. RE can be utilized in terms of downstaging disease and consecutively allowing for secondary curative resection [2], leading to prolongation of survival. Furthermore, applying RE as an adjuvant to chemotherapy leads to a distinct improvement in progression-free survival in patients with CRC liver metastases [5].

Several biomarkers with prognostic value in predicting overall survival (OS) of patients undergoing RE for treatment of CRC liver metastases have been proposed in literature [2, 6]. However, these factors were shown not to be predictive when patients—in accordance with current guidelines—with a relatively advantageous clinical profile were treated [7]. It was puzzling that in a patient cohort which was very homogenous regarding baseline clinical characteristics, distinct differences in OS after RE were observed. Hence, for meticulous selection of patients likely to benefit from therapy and in order to improve clinical decision-making, additional reliable biomarkers that can provide further valuable information on outcome are strongly demanded [2, 3, 7].

Sarcopenia, defined as depletion of skeletal muscle mass and function, was identified as an independent risk factor for adverse outcomes in various severe diseases, including liver cancer [8–11]. In a clinical setting, sarcopenia can be determined by evaluation of muscle mass via cross-sectional imaging [12]. The majority of muscle measurements proposed in literature were acquired via computed tomography (CT) scans [9, 13–18]. However, since CT has several drawbacks such as nephrotoxicity of iodinated contrast, magnetic resonance imaging (MRI) can serve as a reasonable imaging alternative. Moreover, MRI allows for determination of several prognostic markers beyond volumetric measurements, such as assessment of myosteatosis [10].

The impact of sarcopenia on OS in patients undergoing locoregional intraarterial therapies for treatment of secondary liver cancer has not been investigated before. We therefore aimed to study the prognostic value of fat-free muscle area (FFMA), alongside with established prognostic criteria, as a marker for predicting OS in patients undergoing RE for treatment of unresectable CRC liver metastases.

## Material and methods

### Study population

Ethics commission approval was obtained for this retrospective study, and the requirement to obtain written informed consent was waived. This study included 77 patients undergoing primary RE with <sup>90</sup>Yttrium microspheres (Y-90) for treatment of liver-predominant metastatic CRC at our institution between June 2008 and September 2014. Muscle area was measured from pre-interventional MRI examinations. In three patients, pre-interventional MRI was not available. In these cases, first follow-up MRI after the procedure was used for analysis (1–4 months after therapy). Clinical data (e.g., laboratory results) were retrieved with the help of the clinical information management system of the relevant institution.

### Radioembolization procedure

Treatment with Y-90 RE was indicated by an interdisciplinary tumor review board on the basis of published indications for RE and general clinical condition of the treatment candidates [3]. Prior to RE, diagnostic catheter angiography with intraarterial injection of <sup>99m</sup>Tc-labeled macroaggregated albumin (99mTc-MAA), followed by both planar and single photon emission computed tomography (SPECT/CT) was performed to determine vascular supply of the tumor, extrahepatic perfusion, and pulmonary shunting. Extrahepatic vascular supply originating from the hepatic artery was coil embolized prior to the main procedure. For treatment, either SIR-spheres® (Sirtex Medical) or TheraSpheres™ (BTG

Interventional Medicine) was used. Intended administered activity was calculated for resin and glass hemispheres based on body surface area and the MIRD (Committee on Medical Internal Radiation Dose) method as recommended by the manufacturer, respectively. Target embolization was confirmed via postinterventional Bremsstrahlung SPECT/CT. After RE, all patients were admitted to a protected ward for two days post treatment in accordance with the guidelines of the Federal Office for Radiation Protection in Germany (BfS).

### Image acquisition and analysis

All patients underwent standardized liver MRI on clinical 1.5 Tesla (T) (Intera 1.5 T or Ingenia 1.5 T, Philips Healthcare) or 3.0 T whole-body scanner (Ingenia 3.0 T, Philips Healthcare) including axial T2-weighted turbo spin echo sequences (T2-TSE). Exemplary sequence parameters for 1.5 T were repetition time (TR) = 1500 ms; echo time (TE) = 80 ms; flip angle (FA): 90°; acquisition matrix: 560 × 560. Amount of skeletal muscle mass was estimated using T2-TSE images as previously described [10]. For assessment of skeletal muscle mass, cross-section images at the level of the radix of the superior mesenteric artery were exported from the institutional picture archiving and communication system (IMPAX EE, Agfa Healthcare). Image analysis was performed using freely available software (Image J, National Institutes of Health). For assessment of muscle area, a contour was manually and carefully drawn around both of the erector spinae muscles by an experienced radiologist. The total area of the erector spinae muscles was then measured bilaterally and total muscle area (TMA) was assessed. Differences in signal intensity between striated muscle and macroscopic adipose tissue allowed for an additional semiautomatic quantification and therefore assessment of pure muscle area. Hence, images were binarized based on signal intensity. Macroscopic adipose tissue area (ATA) was calculated by adding up the corresponding pixels and multiplication with pixel surface area. FFMA was subsequently obtained, subtracting ATA from TMA.

### Statistical analysis

For data analysis, commercially available statistical software (IBM SPSS, version 23; IBM Analytics) was used. Plots were created using Prism (version 7; GraphPad). OS was defined as time from first RE procedure to documented date of death from any cause. All patients died within the observed time period. Unless otherwise specified, continuous and categorical data were given as means with standard deviations and frequencies, respectively. To date, consented cutoff values for determination of sarcopenia in MRI have not been proposed in literature [10, 19]. Therefore, the study population was dichotomized based on the median according to gender-specific FFMA values. Patients lying below the median were

further defined to have low FFMA, while patients lying above the median were considered to have high FFMA. For comparison of continuous clinical variables between the two groups, the Mann-Whitney *U* test was used. Dichotomous data were analyzed using either  $\chi^2$  test (for a cell count > 5) or Fisher's exact test (for a cell count ≤ 5). The impact of FFMA on OS was studied using the Kaplan-Meier method with the log-rank test. Univariate risk factor analysis was performed for all applicable variables, comparing OS of the patient cohort using Cox regression. All variables that were considered statistically significant on univariate analysis, were further stratified with stepwise forward multivariate risk analysis calculating Cox regression hazards models. Correlation analysis was performed using Spearman's rank correlation coefficient. Intra-rater reliability for FFMA assessment was studied using Pearson's correlation coefficient. Statistical significance was determined by a *p* value of < 0.05.

## Results

### General characteristics

Seventy-seven consecutive patients (28 female, 49 male) with a mean age of 60 ± 11 years (range 40–87 years) were included into the analysis. 72/77 (94%) patients had prior chemotherapy and 26/77 (34%) patients received prior liver resection. 51/77 (66%) patients had an estimated liver tumor burden of > 25% and in 67/77 (87%) patients both hepatic lobes were involved. Baseline bilirubin was 0.68 ± 0.48 mg/dL. 12/77 (16%) patients and 13/77 (17%) patients presented with ascites and cholestasis. Eastern Cooperative Oncology Group (ECOG) performance status was ≥ 1 in 34/77 (44%) patients. Mean and median overall survival after first RE was 282 ± 270 days (range 25–1665 days) and 178 days. Table 1 details clinical patient characteristics.

### Assessment of skeletal muscle mass

Mean time between MRI and RE was 17 ± 31 days. Mean TMA was 3600 ± 825 mm<sup>2</sup>, with mean TMA of 3905 ± 768 mm<sup>2</sup> and mean TMA of 3066 ± 636 mm<sup>2</sup> for men and women, respectively. Bilateral ATA was 195 ± 139 mm<sup>2</sup>, with mean ATA of 199 ± 149 mm<sup>2</sup> in male patients and mean ATA of 187 ± 123 mm<sup>2</sup> in female patients. Resulting FFMA was 3405 ± 823 mm<sup>2</sup>, with mean FFMA values of 3706 ± 779 mm<sup>2</sup> for men and 2879 ± 613 mm<sup>2</sup> for women. Intra-rater reliability for FFMA assessment was very high (*r* = 0.96; confidence interval 0.82–0.99; *p* < 0.0001). Patients were dichotomized according to gender-specific median FFMA, with FFMA < 3644 mm<sup>2</sup> and < 2825 mm<sup>2</sup> defined as low FFMA for men and women, respectively (see Fig. 1). We also assessed muscle area

**Table 1** Clinical characteristics of the whole study population of patients undergoing radioembolization for treatment of liver-predominant metastatic colorectal cancer ( $N=77$ ). Values are given as mean with standard deviation or whole numbers

Variable		Value
Age (years)		60 ± 11
Gender (female)		28 (36%)
Height (cm)		174 ± 10
Weight (kg)		79 ± 17
BMI (kg/m <sup>2</sup> )		25.9 ± 4
TMA (cm <sup>2</sup> )		3600 ± 825
FFMA (cm <sup>2</sup> )	All	3405 ± 823
	Male ( $N=49$ )	3706 ± 779
	Female ( $N=28$ )	2879 ± 613
Pattern of tumor manifestation	Solitary	6
	Oligofocal (2–5)	12
	Multifocal (>5)	42
	Diffuse	17
Estimated liver burden	<25%	26
	25–50%	39
	>50%	12
Extrahepatic metastases	–	51
Baseline bilirubin (mg/dL)	–	0.68 ± 0.48
ECOG score	<1	29
	≥1	34
MELD score	–	8 ± 2
Child-Pugh score	A	66
	B	1
	C	0
Prior chemotherapy	–	72
Ascites	–	12
Cholestasis	–	13
Mean administered activity (GBq)	–	1.6 ± 0.7
Overall survival (days)	–	282 ± 270

BMI body mass index, TMA total muscle area, FFMA fat-free muscle area, ECOG Eastern Cooperative Oncology Group performance status, MELD model of endstage liver disease

at L3 in all patients of our cohort in which this level was captured during liver imaging ( $n=46$ ). Mean TMA and FFMA obtained at L3 in these patients were 4631.9 mm<sup>2</sup> and 4083.2 mm<sup>2</sup>, respectively. There was a high correlation between FFMA obtained at the superior mesenteric artery level and the L3 level ( $r=0.85$ ;  $p<0.001$ ).

### Impact of skeletal muscle mass on clinical variables

Patients with low FFMA had a significantly lower body weight compared to patients with high FFMA ( $74 \pm 13$  kg vs.  $85 \pm 19$  kg;  $p=0.004$ ). No significant differences between the two groups were observed with regard to age

( $59 \pm 10$  years vs.  $61 \pm 11$  years;  $p=0.433$ ), body height ( $172 \pm 10$  cm vs.  $177 \pm 10$  cm;  $p=0.066$ ), and body mass index ( $25 \pm 4$  kg/m<sup>2</sup> vs.  $27 \pm 4$  kg/m<sup>2</sup>;  $p=0.103$ ). Statistical analysis revealed no significant differences between the two groups with regard to estimated liver tumor burden, pattern of tumor manifestation, presence of cholestasis or ascites, MELD score, and baseline bilirubin. Mean administered activity during RE procedure did not differ significantly between the two groups (see Table 2).

### Predictors of overall survival

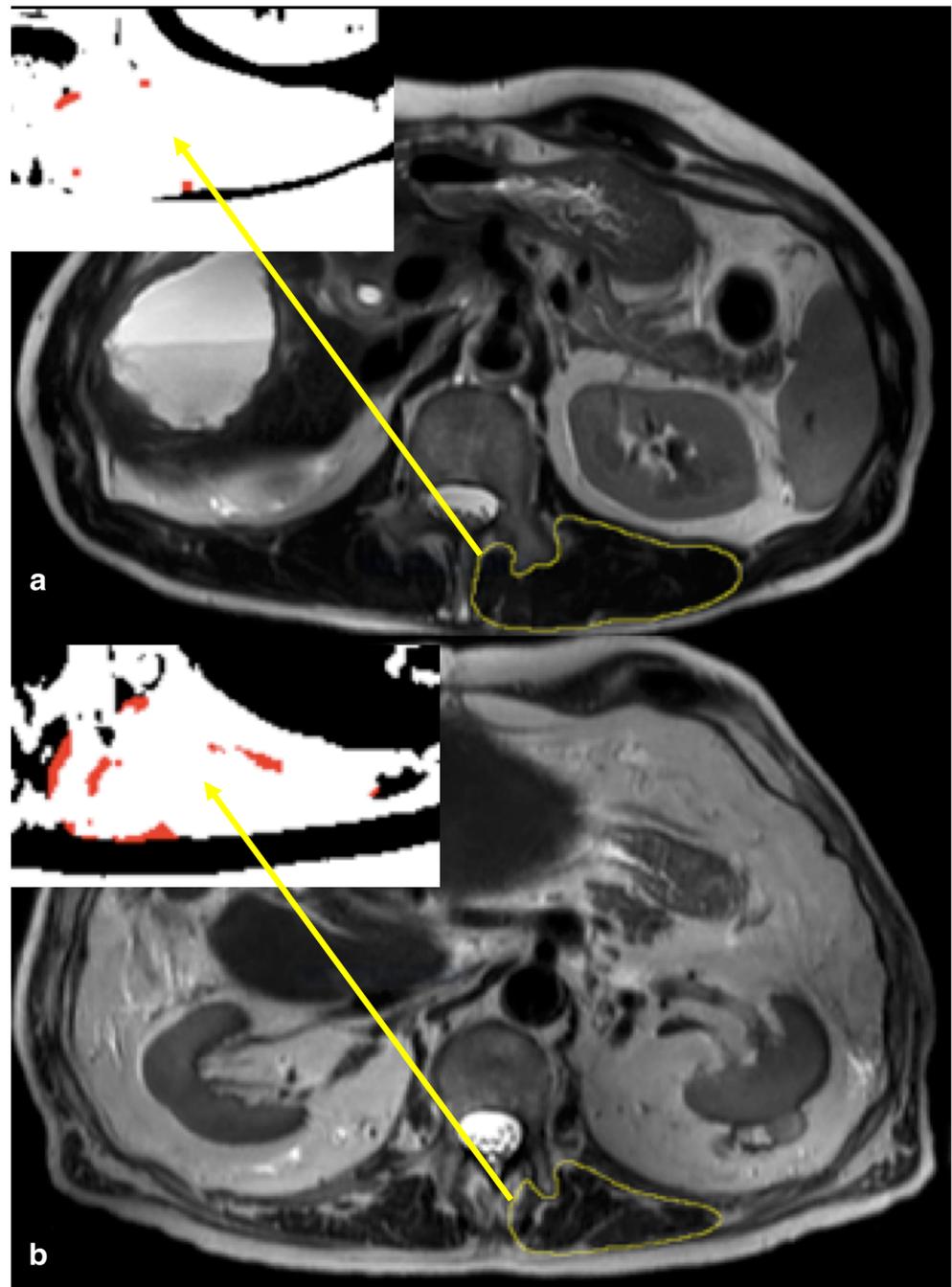
Kaplan-Meier analysis indicated a significantly increased OS for patients with high FFMA compared to patients with low FFMA (median OS: 273 days vs. 128 days;  $p=0.017$ ; see Fig. 2). On univariate Cox regression analysis, FFMA ( $p=0.019$ ), pattern of tumor manifestation ( $p=0.009$ ), liver tumor burden ( $p=0.035$ ), baseline bilirubin ( $p=0.002$ ), mean administered activity ( $p=0.038$ ), MELD score ( $p=0.011$ ), and gender ( $p=0.030$ ) were predictive of OS. In the multivariate model, only FFMA (hazard ratio, 2.652 [95% CI 1.555–4.523];  $p<0.001$ ), baseline bilirubin (hazard ratio, 1.875 [95% CI 1.062–3.309];  $p=0.030$ ), pattern of tumor manifestation (hazard ratio, 1.679 [95% CI 1.233–2.288];  $p=0.001$ ), and MELD score (hazard ratio, 1.164 [95% CI 1.082–1.252];  $p<0.001$ ) were associated with OS (see Table 3). To preclude that differences in time intervals between MRI and RE in our cohort might have affected the results, a similar analysis was conducted defining overall survival as time from MRI to documented death from any cause. In this analysis, similar results were achieved with FFMA being the strongest predictor of OS on multivariate analysis (hazard ratio, 2.669 [95% CI 1.568–4.644];  $p<0.001$ ).

### Discussion

We aimed to investigate the prognostic value of FFMA as a marker for outcome prediction in patients undergoing RE for treatment of CRC liver metastases. As the main finding of our study, patients with low FFMA had a significantly shortened OS compared to patients with high FFMA.

The results of our study suggest that MRI-based assessment of pure skeletal muscle mass yields significant prognostic information about duration of survival in patients undergoing locoregional intraarterial treatment of CRC liver metastases. We studied the impact of FFMA on OS alongside with baseline clinical characteristics and several clinico-oncological parameters. For some of these, such as baseline bilirubin, liver tumor burden, or ECOG performance status, prognostic value in terms of outcome prediction in patients undergoing RE has been described in literature before [2, 6, 20]. For others, such as MELD score, prognostic value in this

**Fig. 1** Clinical cross-sectional images (standard liver-MRI, T2-weighted turbo spin echo sequences) with erector spinae muscles on the level of radix of the superior mesenteric artery. Exemplary patients with (a) high fat-free muscle area (FFMA, 4819 mm<sup>2</sup>), male, 59 years, overall survival 384 days and (b) low fat-free muscle area (FFMA, 2631 mm<sup>2</sup>), male, 72 years, overall survival 79 days



setting has not been determined so far. It is worth mentioning that among all assessed parameters in our study OS was best predicted by FFMA. For baseline bilirubin, which is considered a valuable prognostic criterion in patients with secondary liver cancer [2, 20], a less strong association with OS was observed. Other factors with previously described negative prognostic impact on OS, such as ECOG performance status or liver tumor burden [20], did not show a significant association with OS in our study. We did not observe a significant association of total muscle area with OS in our cohort. This

finding does not invalidate our results; in accordance with literature more probably, it may suggest that in terms of outcome prediction the amount of pure muscle tissue—which in our cohort was characterized by FFMA—might be of greater relevance than the total muscle mass itself [10, 21].

Survival rates of our patients were comparable to those reported previously [7, 22]. Several studies have already suggested that muscle depletion is associated with worsened prognosis in patients with various malignancies, including colorectal cancer in different stages of disease [9, 11, 13, 16,

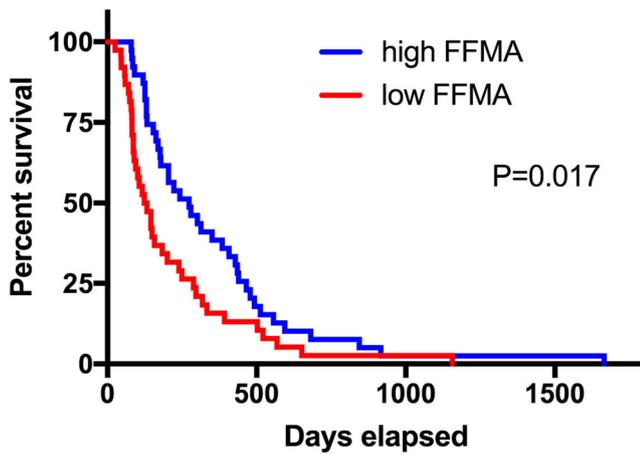
**Table 2** Clinical baseline characteristics of patients with low versus high FFMA. Values are given as total count or mean with standard deviation. Continuous variables were compared using Mann-Whitney *U* test. For comparison of dichotomous variables, either  $\chi^2$  test (for a cell count > 5) or Fisher's exact test (for a cell count  $\leq$  5) were used

Variable		Low FFMA ( <i>N</i> = 38) Value	High FFMA ( <i>N</i> = 39) Value	<i>p</i> value
Age (years)	–	59 ± 10	61 ± 11	0.433
Gender	Male ( <i>N</i> = 49)	24 (63%)	25 (64%)	0.931
	Female ( <i>N</i> = 28)	14 (37%)	14 (36%)	0.931
Height (cm)	–	172 ± 10	177 ± 10	0.066
Weight (kg)	–	74 ± 13	85 ± 19	0.004
BMI (kg/m <sup>2</sup> )	–	25 ± 4	27 ± 4	0.103
TMA (cm <sup>2</sup> )	–	3025 ± 556	4161 ± 638	< 0.0001
FFMA (cm <sup>2</sup> )	All	2838 ± 535	3958 ± 663	< 0.0001
	Male ( <i>N</i> = 49)	3104 ± 467	4284 ± 541	< 0.0001
	Female ( <i>N</i> = 28)	2383 ± 278	3374 ± 416	< 0.0001
Pattern of tumor manifestation	Solitary	4 (11%)	2 (5%)	0.431
	Oligofocal (2–5)	6 (16%)	6 (15%)	0.961
	Multifocal (> 5)	23 (61%)	19 (49%)	0.298
	Diffuse	5 (13%)	12 (31%)	0.098
Estimated liver burden	< 25%	12 (32%)	14 (36%)	0.689
	25–50%	17 (45%)	22 (56%)	0.306
	> 50%	9 (24%)	3 (8%)	0.065
Extrahepatic metastases	–	27 (71%)	24 (62%)	0.377
Baseline bilirubin (mg/dL)	–	0.71 ± 0.54	0.65 ± 0.42	0.617
ECOG score	< 1	16 (50%)	13 (42%)	0.521
	≥ 1	16 (50%)	18 (58%)	0.521
MELD score	–	8 ± 2	8 ± 4	0.620
Child-Pugh score	A	32 (100%)	34 (97%)	> 0.999
	B	0 (0%)	1 (3%)	> 0.999
	C	0 (0%)	0 (0%)	> 0.999
Prior chemotherapy	–	36 (95%)	36 (92%)	> 0.999
Ascites	–	7 (18%)	5 (13%)	0.545
Cholestasis	–	6 (16%)	7 (18%)	0.800
Mean administered activity (GBq)	–	1.6 ± 0.7	1.6 ± 0.7	0.931

*BMI* body mass index, *TMA* total muscle area, *FFMA* fat-free muscle area, *ECOG* Eastern Cooperative Oncology Group performance status, *MELD* model of endstage liver disease, *GBq* Gigabecquerel

17, 23]. For instance, a reduced OS has been reported for patients with gastrointestinal cancer and cachexia [9]. In another report, muscle depletion was identified as an independent predictor of shortened OS in patients undergoing chemotherapy of colorectal liver cancer [16]. Our data is in line with these previous findings and beyond that indicates that even in patients with a very advanced stage of disease the amount of skeletal muscle mass seems to be of strong prognostic value in predicting OS. In previous studies, muscle mass was determined by measurement of skeletal muscle index (SMI) using CT scans. For calculation of SMI, the total cross-sectional muscle area at the level of the third lumbar vertebra was measured and then was adjusted to body height [9]. However, in

our liver MRI cohort, the third lumbar vertebra was captured only in 46 out of 77 patients. We tried to overcome this issue by assessment of skeletal muscle area from the superior mesenteric artery level, which is constantly captured during routine liver imaging, easy-to-identify from the axial plane, and for which evidence in patients with liver disease has been provided in literature before [10]. In an additional analysis, we obtained FFMA at the third lumbar vertebra in those patients, in which this level was captured during imaging. FFMA measurements at L3 were highly correlated with measurements obtained at the offspring of the superior mesenteric artery. Therefore, the superior mesenteric artery seems to be a reliable landmark for assessment of muscle mass.



**Fig. 2** Kaplan-Meier curves demonstrating overall survival (OS) of patients with low Fat-free muscle are (FFMA) versus patients with high FFMA. For statistical analysis, the log-rank test was used. Median OS was 128 days and 273 days, respectively

Furthermore, FFMA measured at the level of the origin of the superior mesenteric artery has been recently demonstrated to predict adverse outcomes in patients with decompensated

liver cirrhosis treated by transjugular intrahepatic portosystemic shunt (TIPS) therapy [10].

In our study, patients with high and low FFMA did not differ significantly with regard to body mass index. However, patients with high FFMA had a significantly higher body weight. Possibly, this finding can be attributed to the survival paradox observed in wasting diseases [24]. Overnutrition, which usually is considered an unfavorable condition increasing for example metabolic or cardiovascular risk, seems to confer a survival advantage in several severe diseases. Most likely, this phenomenon termed “reverse epidemiology” is explained by the time discrepancy of two conflictive risk factors. In patients with a reduced life expectancy, the long-term disadvantages of obesity seem to be less critical than the short-term effects of malnutrition and cachexia. Adipose tissue is considered an endocrine organ with several potentially protective effects such as elimination of circulating inflammatory cytokines and endotoxins. Moreover, skeletal muscle tissue is protective for example due to its oxidative capacity. Loss of muscle mass consecutively reduces oxidative capacity of the organism, leading to impaired

**Table 3** Predictors of overall survival in patients undergoing radioembolization of liver metastatic colorectal cancer. Predictors were determined by using Cox regression. Significant univariate predictors

were entered into the multivariate model with stepwise forward selection. Hazard ratios are given with 95% confidence interval for all variables that were included to the multivariate model

Variable	Univariate analysis		Multivariate analysis	
	Hazard ratio	p value	Hazard ratio	p value
Age	0.997 (0.977–1.018)	0.799	–	–
Gender	1.723 (1.054–2.816)	0.030	NA	0.365
Weight	0.998 (0.986–1.010)	0.720	–	–
Height	2.248 (0.381–13.268)	0.371	–	–
BMI	0.967 (0.916–1.020)	0.218	–	–
ECOG score	1.217 (0.884–1.675)	0.229	–	–
MELD score	1.080 (1.018–1.145)	0.011	1.164 (1.082–1.252)	< 0.001
Child-Pugh score	2.216 (0.300–16.395)	0.436	–	–
Pattern of tumor manifestation (unifocal, oligofocal, multifocal, diffuse)	1.413 (1.092–1.829)	0.009	1.679 (1.233–2.288)	0.001
Estimated liver tumor burden (< 25% vs. 25–50% vs. > 50%)	1.396 (1.025–1.901)	0.035	NA	0.826
Extrahepatic metastases	1.530 (0.937–2.499)	0.089	–	–
Baseline bilirubin (mg/dL)	2.445 (1.370–4.365)	0.002	1.875 (1.062–3.309)	0.030
Ascites (yes vs. no)	1.646 (0.963–2.183)	0.069	–	–
Cholestasis (yes vs. no)	1.125 (0.669–1.892)	0.658	–	–
Mean administered activity (GBq)	1.452 (1.021–2.064)	0.038	NA	0.759
Prior chemotherapy	1.051 (0.255–4.324)	0.945	–	–
FFMA (low FFMA vs. high FFMA)	1.721 (1.094–2.709)	0.019	2.652 (1.555–4.523)	< 0.001
TMA (low TMA vs. high TMA)	1.529 (0.973–2.405)	0.066	–	–

BMI body mass index, ECOG Eastern Cooperative Oncology Group performance status, FFMA fat-free muscle area, MELD model of endstage liver disease, NA not available, TMA total muscle area

antioxidant defense [25]. Another interesting finding of our study was that in our cohort MELD score was found to be of prognostic value regarding OS. This finding is in line with a recent study where MELD score was found to predict mortality following hepatectomy for metastatic liver disease [26]. Originally, the score was developed to predict short-term mortality of patients with liver cirrhosis undergoing TIPS procedure for treatment of portal hypertension and enables for evaluation of severity of liver disease. However, its prognostic role in patients undergoing RE has not been determined so far. Due to its prognostic value in patients undergoing radiation therapy of primary and secondary liver cancer, we also evaluated the potential impact of the Child-Pugh score on OS in our patients [27]. This scoring system is usually applied to patients with liver cirrhosis. However, some of the included laboratory parameters were shown to predict OS in patients undergoing radioembolization of colorectal liver cancer [28]. Of note, we did not observe a significant association with OS in our cohort. Therefore, the findings regarding MELD and Child-Pugh score must be treated with caution and require further validation. We studied an easy-applicable method for determination of pure muscle tissue from routine liver MR imaging. The potentially outstanding prognostic value of FFMA is underlined by the fact that we observed distinct differences in OS in a patient cohort, which apart from FFMA and body weight was very homogenous regarding baseline clinical characteristics. The clinical significance of our results is stressed by the fact that compared to several other clinico-oncological markers of known prognostic value, FFMA was the strongest predictor of OS in our cohort. FFMA does not duplicate accessible prognostic information since it was identified as an independent prognosticator of OS. Of note, against our expectations, several parameters with previously described prognostic value, such as liver tumor burden or ECOG performance status, were not linked to OS in our dataset. Most probably, this is due to the composition of our cohort. In this context, further validation in larger cohorts might be necessary.

We acknowledge that our study has several limitations. Due to the retrospective single-center character of the study, reproducibility cannot be ascertained and therefore any conclusions have to be drawn with caution. The salvage character of the studied therapy made only a limited number of patients available for evaluation. Since a complex statistical method was applied, this study can only be considered as an exploratory analysis. However, in this study, we respond to the growing need for additional reliable biomarkers for stratification of survival in patients undergoing RE [7]. Despite the exploratory design, FFMA was the strongest predictor of OS, although we also included several other parameters with potential impact on OS. Therefore, the findings of this study warrant further investigations and further studies with larger cohorts and a more adequate sample size are necessary to substantiate and confirm its results. With the selected

approach simultaneous measurement of diffuse muscular fat infiltration was not possible. In MRI, analysis of proton density fat fraction (PDFF) via magnetic resonance spectroscopy or DIXON imaging allows for assessment of myosteatosis which in this study possibly could have revealed additional information regarding muscle quality [29]. Recently, PDFF measurements of the erector spinae muscles were shown to be associated with muscle strength [30]. Future studies should also include PDFF-based assessment of myosteatosis. We notice that currently it is unclear whether selective internal radiation therapy influences OS [31, 32]. However, our data indicate that when RE is applied, duration of survival is significantly affected by the amount of skeletal muscle mass. This finding may have meaningful implications for appropriate patient selection in the future.

To conclude, our study offers an easy-to-apply MRI-based measurement of FFMA as a marker of sarcopenia which can predict OS in patients receiving RE for treatment of liver-predominant metastatic CRC. FFMA might become a new prognostic imaging biomarker for survival prognosis in patients receiving local intraarterial treatment of CRC liver metastases.

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## Compliance with ethical standards

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**Statistics and biometry** One of the authors (R.F.) has significant statistical expertise.

**Informed consent** Written informed consent was waived by the Institutional Review Board.

**Ethical approval** Institutional Review Board approval was obtained.

## Methodology

- retrospective
- prognostic study
- performed at one institution

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