

Sarcopenia does not limit overall survival in patients with colorectal liver metastases undergoing interstitial brachytherapy

Sarkopenie beeinflusst nicht die Prognose von Patienten mit kolorektalen Lebermetastasen vor interstitieller Brachytherapie

Authors

Maximilian Thormann, Franziska Heitmann, Vanessa Wrobel, Felix Barajas Ordonez, Maciej Pech, Alexey Surov, Robert Damm, Jazan Omari

Affiliation

University Clinic for Radiology and Nuclear Medicine, University Hospital Magdeburg, Magdeburg, Germany

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Correspondence

Dr. med. Maximilian Thormann, M.A.
Clinic for Radiology and Nuclear Medicine
University Clinic Magdeburg, Leipziger Str. 44,
39120 Magdeburg, Germany
Tel.: +49/3 91/6 71 30 30
Maximilian.thormann@med.ovgu.de

ABSTRACT

Purpose Several studies report an association of sarcopenia with survival in oncologic patients. The aim of this study is to assess the influence of sarcopenia on overall survival (OS) in patients with colorectal liver metastases undergoing interstitial brachytherapy (iBT)

Methods We identified 144 patients with colorectal liver metastases from our database from 2014–2017. Computed tomography (CT) chest scans at the L3 level were retrospectively analyzed. Psoas muscle area (PMA), psoas muscle index (PMI), and skeletal muscle gauge (SMG) were measured on the CT scan before treatment. Parameters were associated with overall survival.

Results 116 patients were included. Median overall survival was 27 months. Median PMA was 13.79 cm², median PMI 4.51 cm²/m². Neither PMA (HR 1.036, 95 % CI 0.996–1.078,

p = 0.080), PMI (HR 1.068, 95 % CI 0.922–1.238, p = 0.382), nor SMG (HR 1.00, 95 % CI 0.998–1.003, p = 0.955) were significantly associated with overall survival.

Conclusion Sarcopenic patients undergoing iBT for colorectal liver metastases did not show decreased overall survival. If confirmed by comparative studies, sarcopenia may serve as a biomarker for treatment decision in patients with CRLM.

Key points: Sarcopenia is not a risk factor for survival in patients with CLRM undergoing iBT.

Citation Format

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ZUSAMMENFASSUNG

Ziel Mehrere Studien zeigen einen Einfluss von Sarkopenie auf das Überleben bei Krebspatienten. Ziel dieser Arbeit war die Untersuchung des Einflusses von Sarkopenie auf das Überleben bei Patienten mit kolorektalen Lebermetastasen vor interstitieller Brachytherapie (iBT).

Material und Methoden Retrospektiv wurden die Daten von 144 Patienten analysiert, die zwischen 2014 und 2017 eine interstitielle Brachytherapie bei kolorektalen Lebermetastasen in unserem Zentrum erhielten. Wir verwendeten die präinterventionelle Computertomografie (CT) auf Höhe L3 zur Bestimmung der psoas muscle area (PMA), des psoas muscle index (PMI) und des skeletal muscle gauge (SMG). Der Zusammenhang zwischen diesen Parametern und dem Überleben wurde untersucht.

Ergebnisse Insgesamt wurden 116 Patienten in die Analyse eingeschlossen. Das mediane Überleben betrug 27 Monate. Der mediane PMA war 13.79 cm², der mediane PMI 4.51 cm²/m². Weder PMA (HR 1.036, 95 % CI 0.996–1.078, p = 0.080) noch PMI (HR 1.068, 95 % CI 0.922–1.238, p = 0.382) oder SMG (HR 1.00, 95 % CI 0.998–1.003, p = 0.955) korrelierten signifikant mit dem Überleben.

Schlussfolgerung Bei Patienten mit kolorektalen Lebermetastasen vor iBT zeigte Sarkopenie keinen Einfluss auf das Überleben. Wenn dies durch vergleichende Studien bestätigt

wird, könnte die Sarkopenie als ein Biomarker für die Behandlungsentscheidung bei Patienten mit CRLM dienen.

Kernaussagen: Sarkopenie zeigt bei Patienten mit kolorektalen Lebermetastasen vor iBT keinen negativen Einfluss auf das Überleben.

Introduction

Colorectal cancer (CRC) is among the most common malignancies and is the third most common cause of cancer-related death in Europe [1]. More than a third of patients present with metastases at the time of diagnosis and around 15–25% of patients develop liver metastases [2]. Resection of lung and liver metastases remains the primary treatment option for patients with oligometastatic disease. A curative approach exists for patients with metastases confined to a single organ, most commonly the liver [3]. However, not all metastases are eligible for surgical approaches and the contribution of surgery to overall survival in patients with extensive oligometastatic or multiple-site disease is contentious. For both patient groups, locally ablative approaches can be applied, with the goal of either R0 ablation or long-term disease control [3].

Thermal ablation methods such as microwave ablation (MWA) or radiofrequency ablation (RFA) are unsuitable for liver metastases located near critical structures [4]. Local tumor progression-free survival in RFA is reduced in lesions >3 cm [5]. Newer techniques such as irreversible electroporation (IRE) show promising results in lesions <5 cm [6]. Recent research has focused on the combination of chemotherapy and transarterial radioembolization as first line-treatments for CRLM [7]. Interstitial brachytherapy (iBT) has been adopted as a viable alternative to resection and thermal ablation methods. Performed under MRI or CT guidance, an iridium-92 source is placed in the lesion via a percutaneous catheter. iBT does not show technical limitation regarding tumor size or structures vulnerable to thermal damage and studies have shown a good local tumor control rates safety profile [8].

Sarcopenia is defined as the loss of muscle mass or low muscle mass, low muscle strength, and impaired muscle quality [9]. A commonly used indicator for sarcopenia is the psoas muscle index (PMI), which can be assessed on computed tomography (CT) scans. The PMI and the psoas muscle area (PMA) are indicators of sarcopenia and have been shown to be predictors of patient outcome [10]. It has also been reported that measurements of skeletal muscle mass in Hounsfield units (HU) can reflect lipid content and be an indicator of muscle quality [11]. The skeletal muscle gauge (SMG) uses a ratio of PMI and muscle density and has been associated with outcomes in cancer patients [12].

In oncologic diseases, sarcopenia has been found to be an essential marker of poor prognosis. It has been a predictor of worse overall survival (OS) in different malignancies [13–15]. Whether sarcopenia is a determinant of survival in patients undergoing iBT for colorectal liver metastases (CRLM) is yet unclear. For iBT, increasing tumor size and applied dose regimen are known to affect local recurrence rates, while older age and comorbidities do not [16, 17].

The aim of the present study is to assess the influence of pre-treatment sarcopenia on patients with metastatic CRC undergoing iBT.

Methods

Study design

We identified 144 patients with metastatic CRC from our database who underwent iBT at our institution from 2014–2017. The database contains retrospective data on individual patient characteristics, systemic treatment, tumor burden, disease spread, local tumor control, progression, and survival. All patients were seen at our department for follow-up visits every 3–6 months after therapy. Patients were followed up until 2020. For our purpose, we selected only patients for whom a CT scan of the abdomen was available within three months prior to treatment. The study was approved by the local ethics committee (145/21).

Inclusion criteria were:

- Confirmed colorectal cancer liver metastases.
- Available CT scan including the psoas muscle on the level of L3 before treatment
- Available clinical data regarding OS

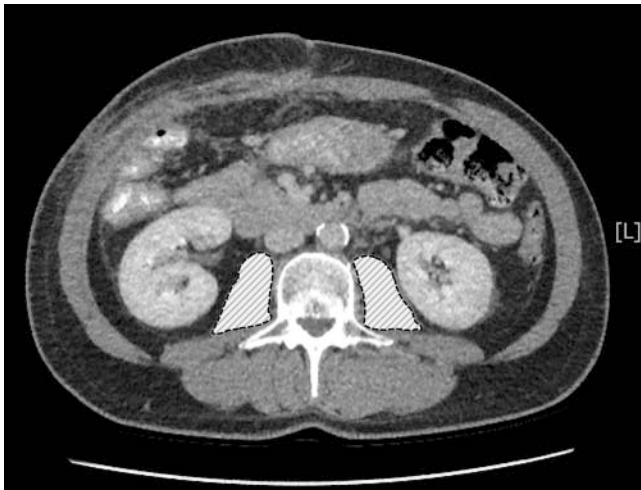
Exclusion criteria were:

- Missing pretreatment CT images
- Strong motion artifacts on CT scans
- Missing clinical data

Imaging analysis

All CT scans were performed using a Siemens Somatom Definition AS+ (Siemens Healthcare, Erlangen, Germany) or Canon Aquilion Prime (Canon, Otawara, Japan) multidetector CT scanner. Patients were placed in a supine position. The CT technique was as follows: acquisition slice thickness of 1 mm with reconstructions of 5 mm, tube voltage of 120 kV, automated tube current modulation, pitch factor of 1.2, and collimation of 0.6 mm.

We analyzed the most recent pre-treatment CT scan available within three months after iBT. All scans were evaluated in consensus by two experienced radiologists (MT and AS) with 3 and 16 years of radiological experience, respectively, who were blinded to the patients' clinical history. On a dedicated workstation, measurements were taken on axial pictures at the L3 level in the soft tissue window (window of 45 to 250 HU) (Infinit PACS, Version 3.0, Infinit Healthcare, Korea). To obtain the PMA, a line was drawn along the contours of the psoas muscles on both sides, and the bilateral areas as determined by the software were added (► Fig. 1). On all contrast scans, muscle density was evaluated on each side and the mean was computed. The PMI was attained by dividing the PMA by the square



► **Fig. 1** Exemplary measurements of bilateral psoas muscles at the L3 level. A line was drawn manually around the psoas muscle on both sides and the area was combined to calculate the psoas muscle area (PMA).

of the patient's body height in cm. The SMG was computed by multiplying the PMI by the mean muscle density, as previously published [18]. SMG units are $\text{cm}^2 \times \text{HU}/\text{m}^2$ and are given as arbitrary units (AU) for simplicity. Two extra variables were obtained: the mean density divided by the PMA and the mean density multiplied by the PMA. Patients were classified as sarcopenic if they had a PMI of $5.40 \text{ cm}^2/\text{m}^2$ for men and $3.56 \text{ cm}^2/\text{m}^2$ for women [18].

Statistical analysis

SPSS version 26 was used for statistical analysis. For continuous variables, the mean and standard deviation as well as the median and interquartile range (IQR) were computed. Box plots were used to illustrate the data. A univariate cox regression analysis was used to assess the impact of psoas muscle composition on survival. We included variables with a significance of $p < 0.1$ in a multivariate Cox regression with forward selection.

Results

Included patients and muscle mass analysis

A total of 116 patients were included in the analysis (76 males, 40 females). 28 patients were excluded due to missing CT scans. The median age was 65 years (range: 32–93 years). All patients had undergone surgical resection of the primary tumor. The ECOG status of all patients was 0 or 1. 46 patients had undergone resection of liver metastases and 40 patients had received other local ablative therapies before iBT. 106 patients had received systemic therapies. Patient characteristics are summarized in ► **Table 1**.

The median PMA was 13.79 cm^2 , and the median PMI was $4.51 \text{ cm}^2/\text{m}^2$. The median SMG was 234.9 AU. Based on the definition of the PMI, 72 patients (62.1%) were considered sarcopenic at the time of iBT.

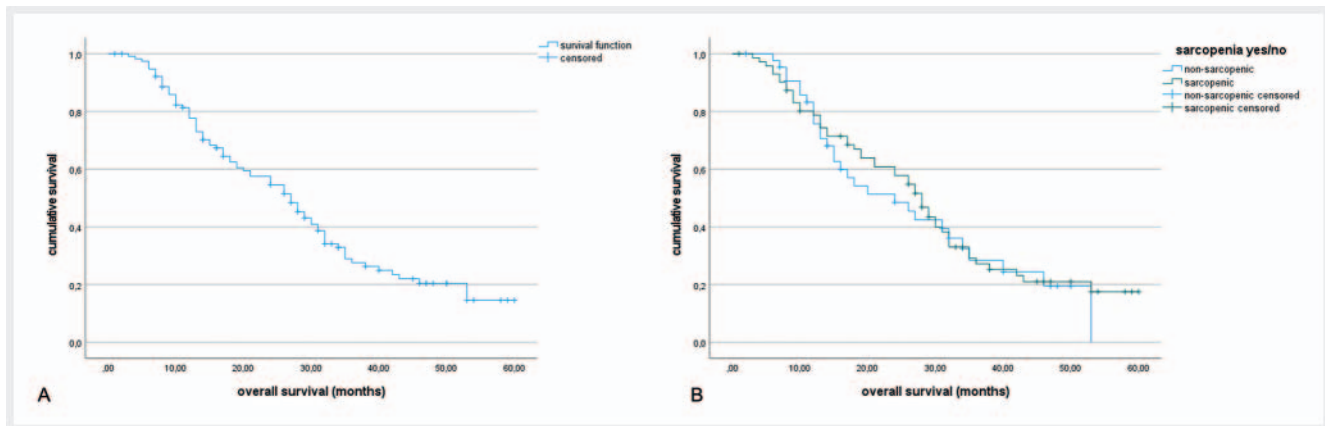
► **Table 1** Patient characteristics.

► **Tab. 1** Patientencharakteristika.

Patient characteristics		
Female, n	n = 40	34.5 %
Male, n	n = 76	65.5 %
Age, median (range)	65 (32–93)	
BMI, kg/m^2 , median	26.40	
Pretreatment characteristics		
Prior local therapies	40	34.5 %
Prior hepatic resection	46	39.7 %
Systemic therapy	106	91.4 %
Extrahepatic metastases	49	42.2 %
Tumor characteristics		
Size		
0–3 cm, n	66	
3–5 cm, n	32	
> 5 cm, n	18	
Treatment characteristics		
Number of catheters, n, median	1	
Radiation dose, gray, median	24.2	
Radiation time, seconds, median	1688.5	
Body composition parameters		
PMA, cm^2 , median	13.79	
PMI, cm^2/m^2 , median	4.51	
Density, HU, median	53.74	
Density * PMA, $\text{HU} * \text{cm}^2$, median	664.0	
Density/PMA, HU/cm^2 , median	3.77	
SMG, median, AU	234.93	
Sarcopenia, n	72	

Overall survival

The median overall survival was 27 months (► **Fig. 2a**). Sarcopenic patients showed a median OS of 28 months, while non-sarcopenic patients had a median OS of 24 months (log-rank test 0.673, ► **Fig. 2b**). In a univariate cox regression, the PMA (HR 1.036, 95% CI 0.996–1.078, $p = 0.080$) and PMI (HR 1.068, 95% CI 0.922–1.238, $p = 0.382$) were not significantly associated with survival. Other parameters of muscle quality, average density (HR 0.972, 95% CI 0.944–1.001, $p = 0.056$), average density multiplied by PMA (HR 1.00, 95% CI 0.999–1.001, $p = 0.837$), average density divided by PMA (HR 0.880, 95% CI 0.778–0.996, $p = 0.043$) and SMG (HR 1.00, 95% CI 0.998–1.003, $p = 0.955$), did not have a significant effect on survival. When using sarcopenia as a binary variable, sarcopenia did not have a significant influence on survival (HR 1.058, 95% CI 0.668–1.675, $p = 0.810$). Clinical variables such as sex, radiation dose, chemotherapy, previous local ablation, or lesion size > 5 cm were not associated with OS



► **Fig. 2** Kaplan-Meier curves on overall survival of the entire cohort of 116 patients **A** and on sarcopenic vs. non-sarcopenic patients **B**. The log-rank test did not show a significant difference between the two groups ($p = 0.673$).

► **Table 2** Regression analysis. Results in the univariate analysis ($p < 0.1$) were included in a multivariate Cox regression with forward selection.

► **Tab. 2** Regressionsanalyse. Ergebnisse mit $p < 0.1$ in der univariaten Analyse wurden in eine multivariate Cox-Regressionsanalyse mit forward selection eingeschlossen.

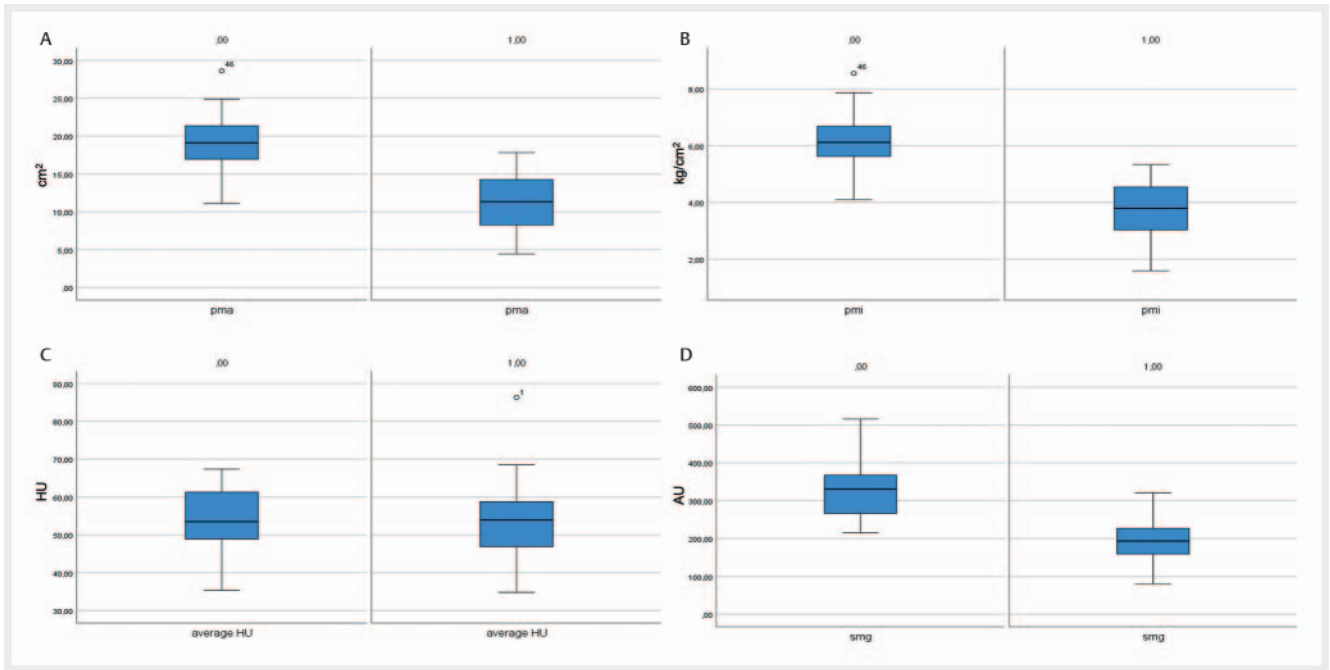
Cox regression	Hazard	(95 % CI)	Univariate P	Multivariate P
PMA	1.036	(0.996–1.078)	0.080	0.483
PMI	1.068	(0.922–1.238)	0.382	
Density	0.972	(0.944–1.001)	0.056	0.085
SMG	1.00	(0.998–1.003)	0.955	
Density * PMA	1.00	(0.999–1.001)	0.837	
Density/PMA	0.880	(0.778–0.996)	0.043	0.506
Sarcopenia	1.058	(0.668–1.675)	0.810	
Sex	0.668	(0.430–1.018)	0.060	0.140
Tumor size > 5 cm	1.379	(0.805–2.361)	0.242	
BMI	1.009	(0.967–1.053)	0.681	
Radiation dose	0.978	(0.916–1.044)	0.510	
Previous chemotherapy	1.311	(0.569–3.019)	0.525	
Previous liver resection	0.872	(0.552–1.377)	0.556	
Previous local therapies	1.231	(0.785–1.932)	0.365	
Extrahepatic metastases	1.277	(0.822–1.984)	0.278	
Histology	0.972	(0.906–1.043)	0.432	

(► **Table 2**). Explorative box plot analyses for selected variables are given in ► **Fig. 3**.

When including all variables showing $p < 0.1$ into a multivariate cox regression, PMA, density divided by PMI, and average density did not have a significant influence on OS. Cox regression results are summarized in ► **Table 2**.

Discussion

Our study evaluated the impact of sarcopenia on the overall survival of patients with colorectal liver metastases undergoing iBT. We applied multiple parameters as a proxy for sarcopenia and muscle quality, including PMA, PMI, SMG and ratios of measured parameters. To the best of our knowledge, this is the first study investigating the impact of sarcopenia in patients undergoing iBT for CRC metastases. We were not able to find an influence of sarcopenia on overall survival in our cohort.



► **Fig. 3** Box whisker plot comparing values of PMA (A), PMI (B), average density (C), and SMG (D) values for sarcopenic and non-sarcopenic patients. Each plot shows the 25th and 75th percentile, with median values indicated by the lines within the boxes. The bars extending above and below the box indicate the 90th and 10th percentiles. Values for SMG are given in arbitrary units (AU) for simplicity.

Oncologic diseases are often associated with loss of muscle mass and weight. Body composition is an important patient-related factor and may influence treatment outcomes. Skeletal muscle plays an important role in homeostasis, showing endocrine and paracrine function [19]. Cancer treatments may cause muscle depletion, leading to increased therapy associated toxicity and therapy limitations [20]. Studies have shown that sarcopenia is associated with multiple negative outcomes in cancer patients. It has been associated with elevated intracellular inflammation, oxidative stress, and high protein consumption [9]. In pancreatic and lung cancer, sarcopenic patients showed worse overall survival [15, 21].

Increasing evidence suggests that body composition may be an essential biomarker in patients with CRC [22]. Murachi et al. demonstrated an association between sarcopenia and DLT in patients with metastatic colorectal cancer receiving regorafenib-therapy [23]. Other studies show that sarcopenia is associated with worse postoperative outcome and shorter overall survival in patients with metastatic colorectal cancer [24, 25]. However, in a study with 259 patients undergoing liver resection for CRLM, sarcopenia was not predictive of recurrence-free or overall survival [26]. Similarly, Lodewick et al. did not find an influence of sarcopenia on prognosis in 171 patients undergoing liver surgery for CRLM [27].

The role of sarcopenia for non-surgical ablative or locoregional treatments is insufficiently understood. Dodson et al. reported sarcopenia to be an independent predictor of mortality in 216 patients receiving intraarterial treatments (IAT), among them a small number with CRLM [28]. Data on patients undergoing TACE is inconclusive [29, 30]. In cohorts receiving RFA for HCC, sarcopenia

was associated with a lower OS [31–33]. To the best of our knowledge, to date there are no studies investigating the impact of sarcopenia on clinical outcomes in CRLM patients after locally ablative therapies like RFA or MWA.

Our results did not reveal sarcopenia to be a limiting factor for patients receiving iBT for hepatic CRC metastases. This means that baseline sarcopenia should not be regarded as a contraindication to iBT and that sarcopenia does not affect survival after iBT in patients with CRLM. The reason for this can only be speculated on for now. Hypothetically, liver function could have a higher impact on skeletal muscle than cancer stage, with iBT preserving liver function reserves. If sarcopenic patients do not show worse overall survival after iBT, this could be an important parameter in patient allocation and may be used for treatment decisions. Other factors such as adipose tissue measurements and loss of skeletal muscle mass over time may also be important biomarkers in iBT that will need to be addressed in the future.

Measuring skeletal muscle parameters can be easily included into clinical imaging routine. Early identification of sarcopenia may induce multimodal interventions and improve patient outcomes. With more data available, it may also be worth considering using sarcopenia as an additional criterion in the allocation of patients to specific treatment arms based on individual assessment. While our data show that sarcopenia is not associated with overall survival in patients with CRLM undergoing iBT, additional comparative studies with surgical and other locally ablative procedures will be needed to evaluate whether this translates into an actual survival benefit.

Our study has several limitations that need to be considered. It was a retrospective study at a single institution. Not all patients

received a CT scan within 3 months prior to therapy, leading to exclusions and potential bias. We applied the PMI as an indicator of sarcopenia, the effect of SMI or other measures of sarcopenia was not evaluated. The rate of sarcopenia was 62.1 %, which is higher than in many previously analyzed cohorts, potentially affecting results [22]. We did not associate our muscle indices with comorbidities. We did not perform a comparative analysis with patient groups undergoing RFA, MWA, or hepatic resection to assess differences in outcome according to body composition status. While we did not find an association between sarcopenia and OS, body composition may exert an influence on other variables not measured in the present study, such as quality of life. Further studies will need to address this. Nevertheless, to the best of our knowledge, this is the largest study investigating the impact of sarcopenia on survival in patients undergoing locally ablative therapies for colorectal liver metastases so far.

In conclusion, our retrospective analysis reveals that sarcopenic patients do not show decreased overall survival when undergoing iBT for colorectal liver metastases. Neither investigated parameter showed influence on survival time. Our findings suggest that iBT may be a reasonable treatment option for sarcopenic patients with CRLM. Further studies comparing iBT with other local treatment strategies in sarcopenic patients are warranted to find optimal treatment pathways for patients.

Clinical relevance

Sarcopenia does not influence overall survival in patients with CLRM treated with iBT and may be a potential biomarker for treatment decisions in patients eligible for non-surgical local therapy. Further comparative studies are warranted to confirm impact on patient outcome.

Compliance with Ethical Standards

Disclosure of potential conflicts of interest: The authors declare that they have no conflict of interest.

Funding: This study was not supported by any funding.

Ethical approval: For this type of study formal consent is not required.

Informed consent: This study has obtained IRB approval from the local ethics committee.

Conflict of Interest

The authors declare that they have no conflict of interest.

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ERRATUM

Erratum: Thormann M, Heitmann F, Wrobel V et al. Sarcopenia does not limit overall survival in patients with colorectal liver metastases undergoing interstitial brachytherapy. *Fortschr Röntgenstr* 2023; 195: 217–223.

We apologize for an error in the eFirst publication of this article. The last name of the author Felix Barajas Ordonez was misspelled.