

The Apparent Diffusion Coefficient of the Paraspinal and Psoas Muscles Are of Prognostic Relevance in Patients With Hepatocellular Carcinoma Undergoing Transarterial Radioembolization

CONSTANTIN EHRENGUT^{1*}, AARON SCHINDLER^{2*}, DANIEL SEEHOFER³, SEBASTIAN EBEL¹, KAREN STEINHOFF⁴, OSAMA SABRI⁴, THOMAS BERG², TIMM DENECKE¹, FLORIAN VAN BÖMMEL^{2*} and HANS-JONAS MEYER^{1*}

¹Department of Diagnostic and Interventional Radiology, University of Leipzig, Leipzig, Germany;

²Department of Hepatology, University of Leipzig, Leipzig, Germany;

³Department of Visceral, Transplant, Thoracic and Vascular Surgery, University of Leipzig, Leipzig, Germany;

⁴Department of Nuclear Medicine University of Leipzig, Leipzig, Germany

Abstract. *Background/Aim:* Transarterial radioembolization (TARE) is a treatment option for early or intermediate stage hepatocellular carcinoma (HCC). Sarcopenia is defined as loss of muscle strength and quality which can be estimated by imaging modalities and has been associated with prognosis and treatment response in HCC patients. Apparent diffusion coefficient (ADC) values derived from diffusion-weighted imaging (DWI) can reflect the tissue composition and might be better to determine muscle changes of sarcopenia than the standard method of computed tomography (CT). The present study sought to elucidate ADC values of the abdominal wall muscles as a prognostic factor in patients undergoing TARE. *Patients and Methods:* A retrospective analysis was performed between 2016 and 2020. Overall, 52 patients, 9 women

(17.3%) and 43 men (82.7%), with a mean age of 69±8.5 years were included into the analysis. In every case, the first pre-interventional magnetic resonance imaging (MRI) including DWI was used to measure the ADC values of paraspinal and psoas muscle. The 12-month survival after TARE was used as the primary study outcome. *Results:* Overall, 40 patients (76.9%) of the patient cohort died within the 12-month observation period. Mean overall survival was 10.9 months after TARE for all patients. Mean ADC values for all muscles were $1.31 \pm 0.13 \times 10^{-3} \text{ mm}^2/\text{s}$. The ADC values of the paraspinal muscles were statistically significantly higher compared to the ADC values of the psoas muscles ($p=0.0031$). A positive correlation was identified between mean ADC and the thrombocyte count ($r=0.37$, $p=0.005$) and serum bilirubin ($r=-0.30$, $p=0.03$). In the multivariate Cox regression analysis, the mean ADC values of all muscles were associated with the survival after 12 months ($HR=0.98$, 95% $CI=0.97-0.99$, $p=0.04$). *Conclusion:* ADC values of the abdominal wall muscles could be used as a prognostic biomarker in patients with HCC undergoing TARE. These preliminary results should be confirmed by further studies using external validation cohorts and other treatment modalities.

*These Authors contributed equally to this study.

Correspondence to: Hans-Jonas Meyer, Department of Diagnostic and Interventional Radiology, University of Leipzig, Liebigstraße 20, D-04103 Leipzig. Tel.: +49 341/9717400, e-mail: hans-jonas.meyer@medizin.uni-leipzig.de

Key Words: Hepatocellular carcinoma, transarterial radioembolization, diffusion-weighted imaging, apparent diffusion coefficient, magnetic resonance imaging.

©2024 International Institute of Anticancer Research
www.iiar-anticancer.org



This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY-NC-ND) 4.0 international license (<https://creativecommons.org/licenses/by-nc-nd/4.0>).

Hepatocellular carcinoma (HCC) is the most frequent malignant liver tumor accounting for about 90% of all liver cancers (1). It is a heterogeneous tumor entity classified according to the Barcelona-Clinic Liver Cancer (BCLC) classification into early HCC (stage 0 and A), intermediate (stage B) or advanced stage (stage C) and very poor life expectancy (stage D) (2, 3).

Transarterial radioembolization (TARE) is one transarterial treatment option for HCC patients (2-12). TARE can be performed using either glass (TheraSphere®, Boston

Scientific Corporation, Marlborough, MA, USA) or resin (SIR-Spheres®, Sirtex Medical Inc., Sydney, Australia) microspheres including the β -emitter Y-90 (5, 6). The potential clinical benefits of TARE have primarily been proven in advanced stage HCC (4). Prediction of the individual benefit of TARE is an important medical need, as alternative locoregional or systemic treatments become increasingly available (2, 4). Current approaches are mainly based on clinical and laboratory parameter scoring systems, such as MELD, ALBI or Child-Pugh score that are strongly influenced by liver function (2-4).

In contrast, imaging-based methods for individual outcome prediction for TARE have not yet been established. Diffusion-weighted imaging (DWI) is an imaging sequence of magnetic resonance imaging (MRI), which quantifies the random water movement in tissues (13-15). Thereby, it is able to reflect the microstructure of tissues, predominantly cellularity (16). DWI based techniques can also be used for quantification of muscle fiber architecture (17, 18). Indeed, those techniques have been shown to allow for estimation of muscle strength, training effect on muscles and muscle damage (19-22).

Several studies have reported that sarcopenia is associated with poor prognosis in cancer patients, including those with HCC (23-28). In previous studies, it was demonstrated that sarcopenia, defined by CT images as low-skeletal muscle area (LSMM) or low muscle density, is of prognostic relevance in patients with HCC undergoing transarterial chemoembolization (29, 30). However, to date the potential association of muscle status as measured by ADC with survival in HCC patients has not yet been investigated. We therefore aimed to evaluate the association of ADC values of the paraspinal and psoas muscles with survival outcomes in patients with HCC undergoing TARE.

Patients and Methods

Patient sample acquisition. For our retrospective single center study, we included all patients with HCC treated with TARE between 2016 and 2020. Inclusion criteria of the present analysis was TARE treatment in intermediate HCC stage, regardless of previous treatment, follow-up documentation for at least 12 months after TARE and availability of MRI within one month before TARE. In our center, TARE is considered for patients with large tumor burden, macrovascular invasion, and liver dominant disease.

Clinical and serological parameters. For every patient several clinical and serological parameters were retrieved from the clinical database. Regarding clinical parameters, the presence of cirrhosis, portal vein thrombosis and BCLC stage (2) were retrieved from the clinical records. The following routine laboratory parameters were retrieved: platelets, bilirubin, quick, INR, AST, ALT, albumin, alpha-fetoprotein, and MELD score (31).

TARE. TARE was performed with a standardized technique using 90Y resin microspheres (SIR-Spheres; Sirtex Medical Limited) or

90Y glass microspheres (TheraSphere, Boston Scientific Corp.) (5-7). Forty-two patients were treated with resin spheres (79.2%) and 10 patients (20.8%) with glass spheres. In all cases, the indication for TARE was given by a multidisciplinary tumor board.

In the first angiography setting, 99mTc-MAA was given from a microcatheter located in a hepatic artery to assess lung shunt fraction (32). For the glass microspheres, a lung dose fraction >30 Gy per treatment setting was set as a limit for the treatment. In cases of more TARE settings, a total of 50 Gy was defined as a dose limit. Regarding resin microspheres, 20% of lung shunt was set as a limit, and reduced activity was recommended for patients with 10-20% with lung shunt. The single photon emission/CT was not essential in dosimetry but could demonstrate the effect of the tumor response.

DWI and ADC measurement. In all patients, MRI of the liver was performed using one clinical 1.5 T scanner (Aera, Siemens Healthcare, Erlangen, Germany). The imaging protocol was comprised of a T2 weighted fat-suppressed short tau inversion recovery sequence, a half-Fourier acquisition single-shot turbo spin-echo T2 weighted sequence, and T1 weighted spin-echo (SE) images prior and after intravenous application of contrast medium with a dynamic acquisition.

In all cases, DWI was acquired with a multi-shot SE-echo planar sequence (repetition time: 7200 ms, echo time: 50 ms, slice thickness: 5 mm, matrix: 88×134, field of view: 450 mm). The sequences were obtained with the b-values of 50, 400 and 800 s/mm. The resulting apparent diffusion coefficient (ADC) maps were provided by the software. For ADC measurements four polygonal regions of interest (ROI) were drawn along the boundaries of the iliopsoas and paravertebral muscles on both sides. The ROIs were carefully placed to avoid large macroscopic fat areas and vessels. The reader was blinded to the clinical outcomes of the patients. The ADC values for iliopsoas and paravertebral muscles were calculated separately as a mean value of both sides. Moreover, a cumulative mean ADC value of the skeletal musculature was estimated out of the 4 ROIs, as described previously (33). Figure 1 displays a case patient for illustration purposes.

Clinical outcomes and assessments. The primary outcome of the present study was overall survival (OS) after 12 months, which was measured from the initial date of HCC diagnosis to the date of death from all causes. All survival data were obtained from the medical reports. The clinical efficacy of TARE was determined by follow-up contrast enhanced dynamic CT or MRI in every patient. Patients without residual viable tumor after TARE were monitored by contrast enhanced CT or MRI every 3 months.

Statistical analysis. The SPSS statistical software package (SPSS 29, SPSS Inc., Chicago IL, USA) was used for statistical analysis. Continuous variables are described by mean values, median and standard deviation. Categorical variables are provided with relative frequencies. ADC values between the tumor groups were compared using the Mann-Whitney *U*-test (two-group comparison). Multivariate survival analysis was conducted with the Cox regression model. Kaplan-Meier survival analysis and Log-rank test was further used for the 12-month survival analysis. Correlation analysis was performed with Spearman's correlation coefficient after testing for normal distribution. In all instances, *p*-values below 0.05 were considered statistically significant.

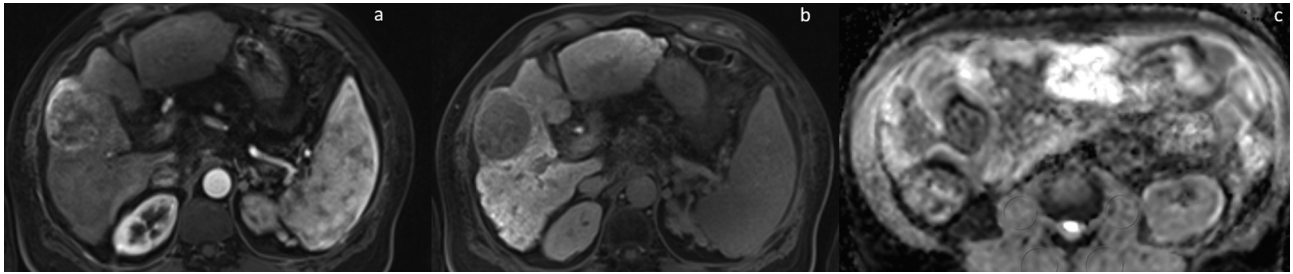


Figure 1. A representative patient case. The arterial phase (a) shows a heterogenous hypervascularization. In the hepatobiliary phase (b), there is a corresponding hypointense signal intensity. (c) In the apparent diffusion coefficient-map, one can appreciate the region of interest-measurement in both sides of the psoas and paraspinal muscles.

Table I. Overview of the investigated hepatocellular carcinoma patients.

Characteristics n=52	Mean±SD
Sex (male)	43 (81.1%)
Mean age	69±8.5
BMI	27.8±5.1
Platelets (unit/l)	161±77
Quick (%)	85±13
Albumin (g/l)	39.7±4.6
Bilirubin (μmol/l)	14.2±8.3
AFP (IU/ml)	8,943±17,012
Cirrhosis present	39 (75%)
BCLC pre-TARE	
A	2 (3.8%)
B	28 (52.8%)
C	22 (41.5%)
Macrovascular infiltration	11 (20.8%)
Child-Pugh stage	
A	38 (73.1%)
B	3 (5.8%)
Liver cirrhosis etiology	
Alcoholic steatohepatitis	16 (30.8%)
Non-alcoholic steatohepatitis	10 (19.2%)
Cryptogenic	19 (36.5%)
Hepatitis-C virus	5 (9.6%)
Hepatitis-B virus	1 (1.9%)
Hemochromatosis	1 (1.9%)
Non-cirrhosis	13 (25%)

SD: Standard deviation; BMI: body mass index; AFP: alpha-fetoprotein; BCLC: Barcelona Clinic Liver-Cancer.

Results

Patients and treatment outcomes. A total of 52 patients were enrolled into the study (patient characteristics are shown in Table I). Most patients were staged as BCLC B and C [28 (52.8%) and 22 (41.5%) cases, respectively]. Thirty-nine patients (75%) had liver cirrhosis. Overall, 40 patients (76.9%) of the patient cohort died within the 12-month observation period after TARE. The mean OS after TARE

Table II. Patient treatments before transarterial radioembolization (TARE).

Previous treatment	n (%)
None	25 (48.1%)
TACE	21 (40.4%)
Surgical resection	10 (19.2%)
Systemic chemotherapy	7 (13.5%)
RFA/MWA	2 (3.8%)
Brachytherapy	2 (3.8%)

TACE: Transarterial-chemo-embolization; RFA/MWA: radio-frequency-ablation/microwave-ablation.

was 10.9±10.5 (range=1-53) months. Table II provides data regarding previous patient treatments. Almost half of the patients were treatment naïve (n=25, 48.1%), followed by patients with previous transarterial chemoembolization (n=21, 40.4%).

ADC values before TARE. The ADC values before TARE were $1.27 \pm 0.17 \times 10^{-3} \text{ mm}^2/\text{s}$ (range=0.69-1.56×10⁻³ mm²/s) for psoas muscles, $1.37 \pm 0.13 \times 10^{-3} \text{ mm}^2/\text{s}$ (range=1.07-1.63×10⁻³ mm²/s) for the paraspinal muscles and $1.31 \pm 0.13 \times 10^{-3} \text{ mm}^2/\text{s}$ (range=0.93-1.60×10⁻³ mm²/s) for all muscles. The ADC values of the paraspinal muscles were statistically significantly higher ($p=0.0031$). There were no differences in regard to the mean ADC values of all muscles ($p=0.76$), psoas muscles ($p=0.63$), or paraspinal muscles ($p=0.19$) between survivors and non-survivors within 12 weeks after TARE.

Correlation of ADC values with outcomes after TARE. In the comparison analysis between survivors and non-survivors, there were no differences in regard to ADCmean of all muscles ($p=0.76$), psoas muscles ($p=0.63$) or paraspinal muscles ($p=0.19$). In the multivariate Cox regression analysis adjusted for age, BCLC stage, grading, and presence

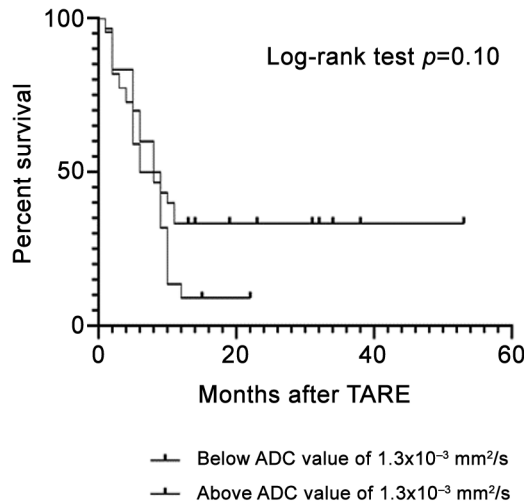


Figure 2. Kaplan-Meier curves for the 12-month survival after transarterial radioembolization (TARE), divided according to patients with apparent diffusion coefficient values below and above the median value of $1.3 \times 10^{-3} \text{ mm}^2/\text{s}$. The log rank test shows a statistical trend with a p -value of 0.10.

of liver cirrhosis, only the ADCmean of all muscles was associated with survival after 12 months (HR=0.98, 95% CI=0.97-0.99, $p=0.04$).

In the Kaplan-Meier curve, a statistical trend for better survival after 12 months can be seen for patients with an ADC value above the median of $1.3 \times 10^{-3} \text{ mm}^2/\text{s}$ (Figure 2).

Correlation of ADC values with other outcome markers after TARE. There were only weak correlations between ADC values and currently used markers for outcomes of TARE in HCC patients. There was an intermediate positive correlation between ADCmean and platelet count before ($r=0.37$, $p=0.005$) and after TARE treatment ($r=0.35$, $p=0.01$), while there was a negative correlation with serum bilirubin before ($r=-0.30$, $p=0.03$) and after treatment ($r=-0.44$, $p=0.03$) (Figure 3). There was no correlation of ADC values with MELD score ($r=0.08$, $p=0.55$), ALBI score ($r=-0.09$, $p=0.50$) or with Child-Pugh stage ($r=0.05$, $p=0.71$) before TARE.

Discussion

Many studies providing evidence of the efficacy of TARE have been published over the last years (5-9). The reported overall survival (OS) ranges widely for unresectable HCC patients undergoing TARE from 7 to 30 months (9-11). This is exceptionally wide, due to the heterogeneity of unresectable HCC, which includes disparate disease burdens, ranging from solitary lesions to multifocal or metastatic disease (9-12). As a direct consequence, there is a definite need for appropriate patient selection, which can also be

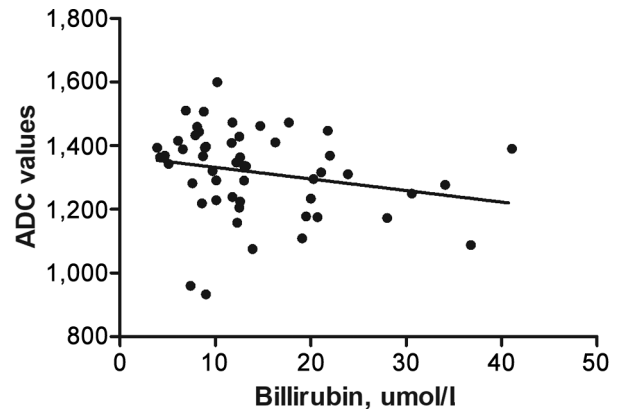


Figure 3. Correlation analysis between the apparent diffusion coefficient values and the bilirubin serum levels. The resulting Spearman's $r=-0.44$, $p=0.03$.

considered to be key in improving the clinical outcomes of this combined treatment.

Established prognosis factors for patients undergoing TARE are portal venous tumor thrombus extension, tumor bulk and bilirubin levels. They have an independent influence on long-term outcomes (12). A recent score system incorporated four parameters comprising maximal tumor size, tumor number, albumin, and portal vein tumor thrombosis to develop the SNAP-HCC score (8). In our study, we have for the first time used ADC values of the paraspinal and psoas muscles to test for association with 12 months outcomes in patients with intermediate stage HCC undergoing TARE. We found that in our patient population pre-treatment ADC values were associated with 12-month survival. Of note, only the ADC values of all muscles combined reached statistical significance, whereas the ADC value of the paraspinal and psoas muscles independently were not significantly associated with survival.

Elucidating novel prognostic biomarkers is crucial for modern treatment planning. This is especially important for HCC patients, who are treated in a multimodal manner and for whom decision making across an increasing number of treatment options is warranted in clinical practice (1-4). In our study, we could show that ADC values have the potential to be such a tool.

Sarcopenia is a key factor for survival in patients with liver cirrhosis or HCC (23, 29, 30, 34). Another study investigated sarcopenia assessed by CT images and could demonstrate that sarcopenia was more commonly observed in HCC patients with disease progression after TARE (38.6% vs. 11.9%; $p=0.006$) (29). In another study using the skeletal muscle index, sarcopenia was considered an emerging prognostic factor in patients with HCC undergoing bland TAE therapy as it was associated with increased mortality

(30). In comparison to CT based approaches to quantify sarcopenia, ADC values have the advantage that they can be derived from MRI which is the standard imaging method for many primary liver cancers (1-3). The development of ADC as a clinical tool could fill a gap for the large number of HCC patients for whom only MRI and no CT images are available. Moreover, it could provide more insight into the microstructure of the muscles compared to conventional CT images. It is still unknown how the ADC values of the muscles are directly associated with the conventional sarcopenia-defining skeletal muscle index derived from CT images. In another recent study, a German group elucidated the prognostic value of T2-weighted images to reflect the muscle infiltration as a muscle quality surrogate parameter derived from MRI with promising results (35). The authors derived an imaging marker, called fat-free muscle area, which was associated with tumor burden and even overall survival (35). It would be very interesting to combine the morphological information of the T2-weighted images with the functional characteristics of the DWI sequence to better characterize the muscle quality by MRI.

Other approaches are currently investigated for their potential in predicting outcomes of transarterial treatments in HCC patients. Thus, in a recent study by Nam *et al.*, four independent risk factors were associated with OS, including maximal tumor size, tumor number, serum albumin, and portal vein tumor thrombosis, which were used to develop the SNAP-HCC score (8). This score and other scoring systems that were included into our analysis as MELD, ALBI, and Child-Pugh scores, largely reflect liver function and they therefore may be subject to wide fluctuations that may limit their accuracy. Besides our study, ADC values were to date only validated in another study investigating 114 patients with liver cirrhosis listed for transplantation (33). It has been shown that ADC values are intermediately correlated with MELD-score ($r=0.47$, $p=0.0001$) and that ADC values of patients with liver cirrhosis are significantly higher compared to healthy controls (33). Established prognosis factors for patients undergoing TARE are portal venous tumor thrombus extension, tumor bulk and bilirubin level, all of which are independently associated with long-term outcomes (12). As validated by imaging findings, quantitative tumor assessment by RECIST, mRECIST, EASL and qEASL are independent response biomarkers that predict OS after TARE (36). Our findings suggest that ADC may represent another promising and easy to apply tool for estimating individual survival chances and for tailoring personalized treatment concepts. Indeed, ADC value quantification of the paraspinal muscle could be easily translated into clinical routine, as DWI is a standard sequence within the liver MRI protocol (37). As such, the ADC value of the paraspinal muscle would be a by-product with no additional time or cost. Beyond that, in recent years,

the systemic treatment options have been expanded and have been incorporated into earlier BCLC stages (38).

The present analysis has some limitations to address. Firstly, it is a retrospective study with a known inherent bias. However, the calculation of the ADC values was performed blinded to the clinical results and was standardized to reduce possible bias. Secondly, the results are based on a single center, which limits possibly external validity. There is a definite need to confirm the present results in different patients. Thirdly, resin as well as glass spheres were used in the present analysis, which could be a possible confounder. However, this reflects the clinical routine better than only one kind of sphere. Fourthly, the patient group was a heterogeneous HCC group with a low 12-month survival rate, which highlights the advanced stage of the included patients. These results might not be transferable to patients with less extensive HCC burden. Fifthly, different TARE indications, according to local preferences, could lead to earlier or later start of systemic treatment.

Conclusion

ADC values of the abdominal wall muscles could be used as a prognostic biomarker in patients with HCC undergoing TARE. ADC values of the muscles could be used as a novel surrogate parameter for sarcopenia assessment. Our results need to be validated in further studies using external validation cohorts and other treatments for HCC.

Conflicts of Interest

The Authors declare that they have no conflicts of interest related to the contents of this article.

Authors' Contributions

A.S., C.E., E.B., K.S., O.S., D.S. performed imaging and data analyses; T.D., T.B., F.B. supplied resources and supervised the study; C.E. and HJ.M. conceived the study; HJ.M. drafted the manuscript; all the Authors contributed to the discussion and review of the final manuscript and approved the final manuscript.

References

- 1 Villanueva A: Hepatocellular carcinoma. *N Engl J Med* 380(15): 1450-1462, 2019. DOI: 10.1056/NEJMra1713263
- 2 Reig M, Forner A, Rimola J, Ferrer-Fàbrega J, Burrel M, Garcia-Criado Á, Kelley RK, Galle PR, Mazzaferro V, Salem R, Sangro B, Singal AG, Vogel A, Fuster J, Ayuso C, Bruix J: BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update. *J Hepatol* 76(3): 681-693, 2022. DOI: 10.1016/j.jhep.2021.11.018
- 3 Bruix J, Reig M, Sherman M: Evidence-based diagnosis, staging, and treatment of patients with hepatocellular carcinoma. *Gastroenterology* 150(4): 835-853, 2016. DOI: 10.1053/j.gastro.2015.12.041

- 4 Guiu B, Garin E, Allimant C, Edeline J, Salem R: TARE in hepatocellular carcinoma: from the right to the left of BCLC. *Cardiovasc Intervent Radiol* 45(11): 1599-1607, 2022. DOI: 10.1007/s00270-022-03072-8
- 5 Miller FH, Lopes Vendrami C, Gabr A, Horowitz JM, Kelahan LC, Riaz A, Salem R, Lewandowski RJ: Evolution of radioembolization in treatment of hepatocellular carcinoma: a pictorial review. *Radiographics* 41(6): 1802-1818, 2021. DOI: 10.1148/rg.2021210014
- 6 Alrfooh A, Patel A, Laroia S: Transarterial radioembolization agents: a review of the radionuclide agents and the carriers. *Nucl Med Mol Imaging* 55(4): 162-172, 2021. DOI: 10.1007/s13139-021-00709-3
- 7 Kallini JR, Gabr A, Salem R, Lewandowski RJ: Transarterial radioembolization with Yttrium-90 for the treatment of hepatocellular carcinoma. *Adv Ther* 33(5): 699-714, 2016. DOI: 10.1007/s12325-016-0324-7
- 8 Nam JY, Lee YB, Lee JH, Yu SJ, Kim HC, Chung JW, Yoon JH, Kim YJ: A prognostic prediction model of transarterial radioembolization in hepatocellular carcinoma: SNAP-HCC. *Dig Dis Sci* 67(1): 329-336, 2022. DOI: 10.1007/s10620-021-06843-4
- 9 Sangro B, Carpanese L, Cianni R, Golfieri R, Gasparini D, Ezziddin S, Paprottka PM, Fiore F, Van Buskirk M, Bilbao JI, Ettorre GM, Salvatori R, Giampalma E, Geatti O, Wilhelm K, Hoffmann RT, Izzo F, Iñárraigui M, Maini CL, Urigo C, Cappelli A, Vit A, Ahmadzadehfah H, Jakobs TF, Lastoria S; European Network on Radioembolization with Yttrium-90 Resin Microspheres (ENRY): Survival after yttrium-90 resin microsphere radioembolization of hepatocellular carcinoma across Barcelona clinic liver cancer stages: A European evaluation. *Hepatology* 54(3): 868-878, 2011. DOI: 10.1002/hep.24451
- 10 Dhondt E, Lambert B, Hermie L, Huyck L, Vanlangenhove P, Geerts A, Verhelst X, Aerts M, Vanlander A, Berrevoet F, Troisi RI, Van Vlierberghe H, Defreyne L: ⁹⁰Y radioembolization versus drug-eluting bead chemoembolization for unresectable hepatocellular carcinoma: results from the TRACE phase II randomized controlled trial. *Radiology* 303(3): 699-710, 2022. DOI: 10.1148/radiol.211806
- 11 Kolligs F, Arnold D, Golfieri R, Pech M, Peynircioglu B, Pfammatter T, Ronot M, Sangro B, Schaefer N, Maleux G, Munneke G, Pereira H, Zeka B, de Jong N, Helmlinger T, CIRT Principle Investigators: Factors impacting survival after transarterial radioembolization in patients with hepatocellular carcinoma: Results from the prospective CIRT study. *JHEP Rep* 5(2): 100633, 2022. DOI: 10.1016/j.jhepr.2022.100633
- 12 Spreafico C, Sposito C, Vaiani M, Cascella T, Bhoori S, Morosi C, Lanocita R, Romito R, Chiesa C, Maccauro M, Marchianò A, Mazzaferro V: Development of a prognostic score to predict response to Yttrium-90 radioembolization for hepatocellular carcinoma with portal vein invasion. *J Hepatol* 68(4): 724-732, 2018. DOI: 10.1016/j.jhep.2017.12.026
- 13 Mannelli L, Nougaret S, Vargas HA, Do RK: Advances in diffusion-weighted imaging. *Radiol Clin North Am* 53(3): 569-581, 2015. DOI: 10.1016/j.rcl.2015.01.002
- 14 Padhani AR, Liu G, Koh DM, Chenevert TL, Thoeny HC, Takahara T, Dzik-Jurasz A, Ross BD, Van Cauteren M, Collins D, Hammoud DA, Rustin GJ, Taouli B, Choyke PL: Diffusion-weighted magnetic resonance imaging as a cancer biomarker: consensus and recommendations. *Neoplasia* 11(2): 102-125, 2009. DOI: 10.1593/neo.81328
- 15 Messina C, Bignone R, Bruno A, Bruno A, Bruno F, Calandri M, Caruso D, Coppolino P, Robertis R, Gentili F, Grazzini I, Natella R, Scalise P, Barile A, Grassi R, Albano D: Diffusion-weighted imaging in oncology: an update. *Cancers (Basel)* 12(6): 1493, 2020. DOI: 10.3390/cancers12061493
- 16 Surov A, Meyer HJ, Wienke A: Correlation between apparent diffusion coefficient (ADC) and cellularity is different in several tumors: a meta-analysis. *Oncotarget* 8(35): 59492-59499, 2017. DOI: 10.18632/oncotarget.17752
- 17 Meyer HJ, Schneider I, Emmer A, Kornhuber M, Surov A: Associations between apparent diffusion coefficient values and histopathological tissue alterations in myopathies. *Brain Behav* 10(11): e01809, 2020. DOI: 10.1002/brb3.1809
- 18 Meyer HJ, Emmer A, Kornhuber M, Surov A: Histogram analysis derived from apparent diffusion coefficient (ADC) is more sensitive to reflect serological parameters in myositis than conventional ADC analysis. *Br J Radiol* 91(1085): 20170900, 2018. DOI: 10.1259/bjr.20170900
- 19 Okamoto Y, Kemp GJ, Isobe T, Sato E, Hirano Y, Shoda J, Minami M: Changes in diffusion tensor imaging (DTI) eigenvalues of skeletal muscle due to hybrid exercise training. *Magn Reson Imaging* 32(10): 1297-1300, 2014. DOI: 10.1016/j.mri.2014.07.002
- 20 Takao S, Kaneda M, Sasahara M, Takayama S, Matsumura Y, Okahisa T, Goto T, Sato N, Katoh S, Harada M, Ueno J: Diffusion tensor imaging (DTI) of human lower leg muscles: correlation between DTI parameters and muscle power with different ankle positions. *Jpn J Radiol* 40(9): 939-948, 2022. DOI: 10.1007/s11604-022-01274-1
- 21 Keller S, Yamamura J, Sedlacik J, Wang ZJ, Gebert P, Starekova J, Tahir E: Diffusion tensor imaging combined with T2 mapping to quantify changes in the skeletal muscle associated with training and endurance exercise in competitive triathletes. *Eur Radiol* 30(5): 2830-2842, 2020. DOI: 10.1007/s00330-019-06576-z
- 22 Stavres J, Wang J, Sica CT, Blaha C, Herr M, Pai S, Cauffman A, Vesek J, Yang QX, Sinoway LI: Diffusion tensor imaging indices of acute muscle damage are augmented after exercise in peripheral arterial disease. *Eur J Appl Physiol* 121(9): 2595-2606, 2021. DOI: 10.1007/s00421-021-04711-7
- 23 Tantai X, Liu Y, Yeo YH, Praktikno J, Mauro E, Hamaguchi Y, Engelmann C, Zhang P, Jeong JY, Van Vugt JLA, Xiao H, Deng H, Gao X, Ye Q, Zhang J, Yang L, Cai Y, Liu Y, Liu N, Li Z, Han T, Kaido T, Sohn JH, Strassburg C, Berg T, Trebicka J, Hsu Y, Ijzermans JNM, Wang J, Su GL, Ji F, Nguyen MH: Effect of sarcopenia on survival in patients with cirrhosis: A meta-analysis. *J Hepatol* 76(3): 588-599, 2022. DOI: 10.1016/j.jhep.2021.11.006
- 24 Feliciano EMC, Kroenke CH, Meyerhardt JA, Prado CM, Bradshaw PT, Kwan ML, Xiao J, Alexeeff S, Corley D, Weltzien E, Castillo AL, Caan BJ: Association of systemic inflammation and sarcopenia with survival in nonmetastatic colorectal cancer: results from the C SCANS study. *JAMA Oncol* 3(12): e172319, 2017. DOI: 10.1001/jamaoncol.2017.2319
- 25 Caan BJ, Cespedes Feliciano EM, Prado CM, Alexeeff S, Kroenke CH, Bradshaw P, Quesenberry CP, Weltzien EK, Castillo AL, Olobatuyi TA, Chen WY: Association of muscle and adiposity measured by computed tomography with survival in patients with nonmetastatic breast cancer. *JAMA Oncol* 4(6): 798-804, 2018. DOI: 10.1001/jamaoncol.2018.0137
- 26 Chang KV, Chen JD, Wu WT, Huang KC, Hsu CT, Han DS: Association between loss of skeletal muscle mass and mortality

- and tumor recurrence in hepatocellular carcinoma: a systematic review and meta-analysis. *Liver Cancer* 7(1): 90-103, 2018. DOI: 10.1159/000484950
- 27 Mir O, Coriat R, Blanchet B, Durand JP, Boudou-Rouquette P, Michels J, Ropert S, Vidal M, Pol S, Chaussade S, Goldwasser F: Sarcopenia predicts early dose-limiting toxicities and pharmacokinetics of sorafenib in patients with hepatocellular carcinoma. *PLoS One* 7(5): e37563, 2012. DOI: 10.1371/journal.pone.0037563
- 28 Omiya S, Komatsu S, Kido M, Kuramitsu K, Gon H, Fukushima K, Urade T, So S, Sofue K, Yano Y, Sakai Y, Yanagimoto H, Toyama H, Ajiki T, Fukumoto T: Impact of sarcopenia as a prognostic factor on reductive hepatectomy for advanced hepatocellular carcinoma. *Anticancer Res* 41(11): 5775-5783, 2021. DOI: 10.21873/anticancer.15394
- 29 Vallati GE, Trobiani C, Teodoli L, Lai Q, Cappelli F, Ungania S, Catalano C, Lucatelli P: Sarcopenia worsening one month after transarterial radioembolization predicts progressive disease in patients with advanced hepatocellular carcinoma. *Biology (Basel)* 10(8): 728, 2021. DOI: 10.3390/biology10080728
- 30 Lanza E, Masetti C, Messana G, Muglia R, Pugliese N, Ceriani R, Lleo de Nalda A, Rimassa L, Torzilli G, Poretti D, D'Antuono F, Politi LS, Pedicini V, Aghemo A, Humanitas HCC Multidisciplinary Group: Sarcopenia as a predictor of survival in patients undergoing bland transarterial embolization for unresectable hepatocellular carcinoma. *PLoS One* 15(6): e0232371, 2020. DOI: 10.1371/journal.pone.0232371
- 31 Ruf A, Dirchwolf M, Freeman RB: From Child-Pugh to MELD score and beyond: Taking a walk down memory lane. *Ann Hepatol* 27(1): 100535, 2022. DOI: 10.1016/j.aohp.2021.100535
- 32 Mirka H, Duras P, Baxa J, Korcakova E, Ferda J: Contribution of computed tomographic angiography to pretreatment planning of radio-embolization of liver tumors. *Anticancer Res* 38(7): 3825-3829, 2018. DOI: 10.21873/anticancer.12666
- 33 Surov A, Paul L, Meyer HJ, Schob S, Engelmann C, Wienke A: Apparent diffusion coefficient is a novel imaging biomarker of myopathic changes in liver cirrhosis. *J Clin Med* 7(10): 359, 2018. DOI: 10.3390/jcm7100359
- 34 Engelmann C, Schob S, Nonnenmacher I, Werlich L, Aehling N, Ullrich S, Kaiser T, Krohn S, Herber A, Sucher R, Bartels M, Surov A, Hasenclever D, Kahn T, Seehofer D, Moche M, Berg T: Loss of paraspinal muscle mass is a gender-specific consequence of cirrhosis that predicts complications and death. *Aliment Pharmacol Ther* 48(11-12): 1271-1281, 2018. DOI: 10.1111/apt.15026
- 35 Faron A, Sprinkart AM, Pieper CC, Kuetting DL, Fimmers R, Block W, Meyer C, Thomas D, Attenberger U, Luetkens JA: Yttrium-90 radioembolization for hepatocellular carcinoma: Outcome prediction with MRI derived fat-free muscle area. *Eur J Radiol* 125: 108889, 2020. DOI: 10.1016/j.ejrad.2020.108889
- 36 Ghosn M, Derbel H, Kharrat R, Oubaya N, Mulé S, Chalaye J, Regnault H, Amaddeo G, Itti E, Luciani A, Kobeiter H, Tacher V: Prediction of overall survival in patients with hepatocellular carcinoma treated with Y-90 radioembolization by imaging response criteria. *Diagn Interv Imaging* 102(1): 35-44, 2021. DOI: 10.1016/j.diii.2020.09.004
- 37 Kamal O, Sy E, Chernyak V, Gupta A, Yaghmai V, Fowler K, Karampinos D, Shanbhogue K, Miller FH, Kambadakone A, Fung A: Optional MRI sequences for LI-RADS: why, what, and how? *Abdom Radiol (NY)* 48(2): 519-531, 2022. DOI: 10.1007/s00261-022-03726-8
- 38 Stefanini B, Ielasi L, Chen R, Abbati C, Tonnini M, Tovoli F, Granito A: TKIs in combination with immunotherapy for hepatocellular carcinoma. *Expert Rev Anticancer Ther* 23(3): 279-291, 2023. DOI: 10.1080/14737140.2023.2181162

Received January 17, 2024

Revised February 19, 2024

Accepted February 26, 2024