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**Retrospective Cohort Study**

Impact of sarcopenia on tumor response and survival outcomes in patients with hepatocellular carcinoma treated by trans-arterial (chemo)-embolization

Sarcopenia in HCC treated by TACE

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Abstract

BACKGROUND
At the diagnosis of hepatocellular carcinoma, more than 90% of HCC patients present a cirrhosis, a clinical condition often associated to a malnutrition. Sarcopenia is an indirect marker of malnutrition assessable on CT-scan.

AIM
This study aims to evaluate the prognostic value of sarcopenia in patients with hepatocellular carcinoma treated by trans-arterial (chemo)-embolization.

METHODS
Patients with hepatocellular carcinoma treated by a first session of trans-arterial (chemo)embolization and an available CT-scan before treatment were included. Sarcopenia was assessed using skeletal muscle index at baseline and at the first radiological assessment. Radiological response was recorded after the first session of treatment using mRECIST.

RESULTS
225 patients were treated by trans-arterial bland embolization (n = 71) or trans-arterial chemoembolization (n = 154) for hepatocellular carcinoma between 2007 and 2013. BCLC stage was A, B and C in respectively 27.5%, 55% and 16.8% of cases. Sarcopenia was present in 57.7% of the patients. Patients with sarcopenia presented a higher rate of progressive disease (19% vs 8%, p=0.0236), a shorter progression-free survival (8.3 vs 13.2 mo, p=0.0035) and a shorter median overall survival (19.4 mo vs 35.5 mo, p=0.0149) compared with non-sarcopenic patients. Finally, patients whose sarcopenia appeared after first transarterial treatment had the worst prognosis (p=0.0004).

CONCLUSION
Sarcopenia is associated with tumor progression and poor survival outcomes after trans-arterial (chemo)-embolization for hepatocellular carcinoma

**Key Words:** hepatocellular carcinoma; transarterial chemoembolization; bland embolization; sarcopenia; skeletal muscle index


**Core Tip:** This work evaluates the predictive value of sarcopenia on tumor response and survival outcomes in HCC patients treated by TACE or TAE. In this article, sarcopenia at imaging was observed in 57.7% of patients. It was associated with a higher rate of progressive disease and a decreased overall survival after adjustment with usual risk factors of death. Sarcopenia is an easy-to-assess radiological biomarker of poor prognosis that should be measured in order to assess prognosis and test a targeted intervention mixing nutritional support and physical activity.

**INTRODUCTION**

Liver cancer is the second cause of cancer-related deaths worldwide, mostly represented by hepatocellular carcinoma (HCC). At the diagnosis, 70% of HCC patients have only access to palliative treatments, and among intermediate HCC, classified as Barcelona Clinic of Liver Cancer (BCLC) B, transarterial chemoembolization (TACE) and transarterial embolization (TAE) are the best therapeutic options to offer. Nonetheless, despite a good level of tumor response, around 50-55%, these treatments suffer from a high level of relapse. It is well demonstrated that TACE presents the best results on patients with a good general status and a low level of liver
insufficiency [7], but we need additional reliable predictive markers to better define which patients will take full benefit of this procedure, and which ones present an increased risk of low efficacy and liver deterioration. At the diagnosis, more than 90% of HCC patients present a cirrhosis, a clinical condition often associated to a malnutrition with a sarcopenia. Indeed, sarcopenia, defined as the “progressive loss of muscle mass and strength with a risk of adverse outcomes such as disability, poor quality of life and death” [8], is a consequence of chronic inflammation, hypercatabolism and anorexia found in cirrhosis and advanced tumor stages. Sarcopenia has already been described as a poor prognostic factor in HCC patients undergoing a surgical resection or treated by systemic therapies [9-12]. Further studies are needed to clarify the predictive value of sarcopenia in other HCC treatment settings, such as TAE or TACE. Indeed, several studies with small numbers of patients showed interesting results on the predictive value of sarcopenia regarding survival outcomes of patients treated by TACE but without clear impact on tumor response [13]. This study aims to evaluate the predictive value of sarcopenia on tumor response and survival outcomes in a bicentric cohort of HCC patients treated by TACE or TAE.

MATERIALS AND METHODS

Patient selection

Patients were retrospectively included from two institutions from December 1st 2007 to November 1st 2013 in Jean Verdier Hospital and from June 1st 2011 to December 1st 2014 in Grenoble-Alpes University Hospital. Inclusion criteria were as follow: age > 18 years, HCC diagnosed by histology or non-invasive criteria [7], first treatment using trans-arterial embolization or trans-arterial chemoembolization, available pre- and post-therapeutic CT scan. Transarterial procedures performed for an acute bleeding of HCC were excluded.

Transarterial procedures
Patients were treated with transarterial therapy following standard local protocol\cite{14}. Each indication of TACE or TAE was validated during multidisciplinary tumor board including a hepatologist, an interventional radiologist and a liver surgeon. In case of TACE, chemotherapy was either doxorubicin or idarubicin according to institutional standards of care, as previously described \cite{15}. The choice of chemotherapy was left to the investigator’s discretion. Every TACE or TAE was performed by an expert interventional radiologist.

As recommended by European guidelines, TACE could be repeated 2 mo after the first treatment in case of partial response on postoperative scan and preserved liver function after rediscussion in multidisciplinary tumor board \cite{6}.

**Ethical approval**

A written consent was obtained for every patient before transarterial procedures and the study protocol respects the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008). Study ethics was also approved by the independent French ethic committee CERIM (Comité d’éthique de la recherche en imagerie médicale)- number CRM-2004-084.

**Clinical and paraclinical data collection**

Clinical and biological data were recorded before the treatment: demographic data, body mass index, liver function, platelets, presence of cirrhosis, etiology of the underlying liver disease, alpha-fetoprotein (AFP) level, tumor size, numbers of nodule, tumor portal invasion and esophageal varices at the last upper endoscopy.

After the first treatment, all patients were prospectively followed up until death or the last recorded visit until June 30th 2018.

**Anthropometric measurements**

Anthropometric measurements were assessed on the pre therapeutic CT scan and the first follow-up CT scan realized 1-3 mo after the transarterial treatment by two
radiologists (OSu and YT) using the software Image J ®. Skeletal muscle and psoas muscle area were measured on a cross-sectional CT image at the level of the 3rd lumbar vertebra. Skeletal muscle index (SMI) was calculated using the total muscle area on the L3 CT slice divided by height² as previously described [16]. Sarcopenia was defined by skeletal muscle index < 50 cm²/m² in male and < 39 cm²/m² in female patients as defined by the North American expert statement on sarcopenia in liver transplantation [17]. Psoas muscle index (PMI) defined as the psoas muscle area on height ratio was also assessed as previously described [17].

The following data were recorded on imaging: liver volume, spleen volume, presence of ascites at imaging, presence of para-umbilical vein, presence of esophageal varices, presence of splenomegaly defined by a spleen’s cranio-caudal diameter superior to 12 cm.

Assessment of tumor response and survival outcomes

All imaging examinations were archived in a picture archiving and communication system (PACS) and blindly read by two radiologists (OSu and YT). Clinical and paraclinical parameters were extracted from the patient’s electronic medical records. Radiological response was assessed by two radiologists (OSu and YT) comparing the baseline imaging and the imaging available 1-3 mo after the first session of trans-arterial treatment as recommended [7]. Radiological response was classified in complete response, partial response, stable disease and progressive disease as defined by the modified RECIST criteria [7].

Progression-free survival was defined as the time between the date of the first treatment and the date of death, radiological progression or the last recorded visit. Patients were censored at the date of liver transplantation. Overall survival was defined as the time between the date of the first treatment and the date of death or the last recorded visit, with censure at the date of liver transplantation in transplanted patients.

Statistical analysis
Categorical variables were compared using the Fisher exact test for two groups and Chi squared test for three groups and more. Continuous variables were compared using the Mann-Whitney Test. Logistic regression was used to compare the association with radiological response and baseline variables. Survival outcomes as overall survival (OS) and progression free survival (PFS) were computed using the Kaplan-Meier method, and the Log-rank test was used to compare survival rates. The association between baseline variable and overall survival and progression free survival was assessed in univariate analysis using the Cox model. Variables with a p-value < 0.05 in univariate analysis were computed in multivariate analysis using the cox model. Statistical analysis was performed using Graph Pad (Prism) and the R software.

RESULTS

Description of the population
A total of 225 patients were included in the analysis including 93 from Jean Verdier Hospital and 132 from Grenoble-Alpes University Hospital (Figure 1). Patients were mainly male (88.8%) with a median age of 65 years old (58-75). The underlying liver diseases were mainly related to chronic alcohol intake (61%), hepatitis C (28%) and Non-alcoholic steatohepatitis (29%) with 81.6% of patients classified as Child Pugh A. HCCs were classified as BCLC A in 27.5%, BCLC B in 55.5% and BCLC C due to segmental portal vein thrombosis in 16.8% of patients. 154 patients (68.4%) of the patients were treated by TACE (127 with doxorubicin and 27 by idarubicin; including 87 by lipiodol TACE and 40 by TACE using drug eluting beads). 71 patients (31.5%) were treated by TAE using lipiodol with gelatin sponge. Patients' characteristics are detailed in Table 1.

Anthropometric and portal hypertension assessment at imaging
Anthropometric measurements including the value of total muscle area in L3 and psoas area in L3 were detailed in Table 1. Ascites was identified in 23.5% of the cases at
imaging as well as splenomegaly in 57% of the cases, umbilical vein repermeabilization in 36.4% of the cases, and esophageal varices in 71.1% of the cases. 57.7% of patients ($n = 130$) had sarcopenia based on the SMI. The value of Psoas/height (cm$^2$/m$^2$) was significantly positively associated with BMI, liver volume, albumin, alcohol intake, male, NASH and negatively associated with age and hepatitis C virus (Figure 2A). Sarcopenia at imaging (defined by Skeletal muscle index < 50 cm$^2$/m$^2$ in male and < 39 cm$^2$/m$^2$ in female patients) was observed in 130 patients (57.7%).

Sarcopenic patients were significantly older (67.5 years old vs 62.5 years old; $p=0.0338$), with a lower body mass index (24.3 vs 28.7 $p<0.0001$) and a higher median serum AFP level (11.5 vs 7.7ng/mL $p=0.0152$) compared to non-sarcopenic patients at imaging (Table 1 and Figure 2B). Sarcopenia was also associated with a higher tumor burden (sum of the size of the 2 main tumors), a lower BMI, ALAT level and spleen volume and was less frequent in alcohol-related cirrhosis and in NASH patients (Figure 2B). At the first radiological assessment, 28.7% of the patients with sarcopenia harbored an increase in Child Pugh Class (A to B/C or B to C) compared to 24.53% of patients without sarcopenia ($p=0.6862$, Fisher exact test). Patients’ baseline features as well as treatments following TACE or TAE, according to the presence or not of sarcopenia, are detailed in Table 1.

**Relationship between sarcopenia and radiological response**

At the first radiological evaluation after TACE or TAE, 23% ($n = 52$) of patients harbored a complete response, 39% a partial response ($n = 88$), 23% a stable disease ($n = 52$) and 15% ($n = 33$) a progressive disease using mRECIST criteria. Presence of portal hypertension signs on endoscopy or imaging were not encountered as predictive markers of radiological response. Presence of sarcopenia had a significant impact on progression proportions after to TACE ($p=0.0084$, Chi square test Figure 3A). Whereas, objective tumor response (complete and partial radiological response) was not statistically different in sarcopenic (64%) compared to non-sarcopenic patients (67%, $p=0.66$, Fisher exact test), a higher rate of progressive disease was observed in
patients with sarcopenia compared to patients without sarcopenia (19% vs 8%, \( p = 0.0236 \), Fisher exact Test, Figure 3B). In univariate analysis, sarcopenia (OR=2.59 CI95%: 1.16-6.40, \( p = 0.0274 \), serum AFP level (OR=1.00029 CI95%:1.00008-1.0006, \( p = 0.0226 \)) and BCLC C staging (OR=2.22 CI95%:1.25-4.05, \( p = 0.00758 \)) were related to progressive disease at imaging. In multivariate analysis, only BCLC C staging (OR=1.98 CI95%:1.038-3.88, \( p = 0.0416 \)) remains independently associated with a higher rate of progressive disease.

**Relationship between sarcopenia before TACE and survival**

The median progression-free survival was 9.4 mo. Patients with sarcopenia had a lower median PFS compared to patients without sarcopenia (8.3 vs 13.2 mo, \( p = 0.0035 \), log rank test, Figure 4A). In univariate analysis, sarcopenia, tumor portal vein thrombosis, size of the largest nodule, serum AFP level and platelets level were significantly associated with a lower PFS (Table 2). In multivariate analysis, sarcopenia (HR=1.62 CI95%: 1.15-2.28), tumor portal vein thrombosis (HR=1.77 CI95%: 1.11-2.83), size of the largest nodules (HR=1.008, CI95%: 1.002-1.013), and platelets level (HR=1.002, CI95%: 1.002, CI95%: 1.0001-1.005) remain independently associated with lower PFS (Table 2).

The median overall survival was 24.3 mo. OS was shorter in patients with sarcopenia compared to patients without sarcopenia (19.4 vs 35.5 mo, \( p = 0.0149 \), log rank test, Figure 4B). Sarcopenia, ascites at imaging, size of the largest nodule, serum AFP level, Child-Pugh Score and body mass index were associated with OS at univariate analysis (Table 3). At multivariate analysis, sarcopenia (HR=1.68 CI95%: 1.04-2.72), the AFP level (HR=1.0001 CI95%: 1.00001-1.002) and size of the largest nodules (HR=1.007, CI95%: 1.0015-1.013) were independently associated with a higher risk of death (Table 3).

**Evolution of sarcopenia after TACE and its impact on overall survival**

Post-TACE SMI was assessed by CT-scan at the first radiological assessment in 218 patients in order to assess the evolution of sarcopenia after treatment. Among the
patients without sarcopenia at baseline, 71 patients were still non sarcopenic, and 22 patients became sarcopenic. Among the 22 patients who became sarcopenic, 19 of them have a progressive disease at the first radiological assessment.

Patients with post-TACE sarcopenia presented a shorter median OS ($n = 147, 18.15$ mo) compared with non-sarcopenic patients ($n = 71, 35.7$ mo, $p=0.0019$) (Figure 4C).

In non-sarcopenic patients at baseline, emergence of a post-TACE sarcopenia was associated with a significant shorter median OS of $17$ mo when compared with already sarcopenic patients before TACE ($19.3$ mo) and patients who stayed non sarcopenic along TACE procedure ($36.43$ mo, $p=0.0004$) (Figure 4D).

**DISCUSSION**

**Discussion**

This study is the largest multicentric cohort study exploring the impact of sarcopenia on tumor response and survival outcomes in patients with HCC treated by TACE or TAE. Sarcopenia represents a major challenge in chronic diseases and especially in the treatment of cancers where the general status is classically altered, and aggressive treatments with poor tolerance profiles are frequent. Sarcopenia in cirrhosis has already been described as impacting survival confirming the need of a global approach with a close nutritional support of these patients. Sarcopenia measures were assessed on the open-access software Image J®, which has been proved as equivalently efficient as other commercial programs, meaning that radiological assessment of sarcopenia is accessible to every center [18]. The use of skeletal muscle index was preferred to methods only based on the measurement of the psoas muscle index or the transverse psoas muscle thickness. Even though the two latter are simple to assess and showed interesting results in term of survival in HCC patients treated by TACE in previous studies, the SMI seems to offer a more robust and complete measurement of the muscle mass in cirrhotic patients. Besides, the PMI may identify less patients at risk of an increased mortality and presents a higher inter-observer variability. To finish, the SMI is easy-to-use to and recommended by the North American Expert Opinion Statement on
Sarcopenia in Liver Transplantation [17, 19, 20]. In this study, measures were performed by only one radiologist per center which limits bias induced by potential interobserver variability. This also constitutes a limit as interobserver variability should be studied to improve results exportability and better evaluate their reproducibility.

In this study, a high prevalence of sarcopenia (57%) in patients with HCC treated by transarterial treatment was observed despite the predominance of Child Pugh A patients and intermediate stage tumors (BCLC B). This is consistent with recent HCC cohorts studying the impact of sarcopenia on survival in patients treated by hepatectomy where 54% of patients were sarcopenic, as well as published data in liver transplantation [17]. Even if patients with sarcopenia have a lower BMI than patients without sarcopenia, most of patients with sarcopenia harbored a normal BMI (median value of 24). Moreover, with the increase of overweight and obesity which represents 15-20% of the worldwide population [21], BMI is even less sensitive to detect malnutrition in patients with chronic diseases and especially liver diseases. These elements suggest that sarcopenia measured by performant radiological methods reflect more precisely the nutritional state and the protein catabolism of these patients. Nonetheless, other markers that could impact the outcomes after trans-arterial (chemo)embolization such as patient’s daily activities and diet are not collected in this study due to its retrospective character. As well, this study lacks of otherfrailty parameters such as grip strength or walking speed. It constitutes another limit that cannot be adressed due to the retrospective character of the study.

One of the main strengths of this study is the radiological reviewing of radiological response using mRECIST criteria. This analysis has revealed that sarcopenia was associated with a higher risk of progressive disease after trans-arterial treatment but without any difference on objective tumor response. Nevertheless, in multivariate analysis, only BCLC C (segmental portal thrombosis) was independently associated with progressive disease. Sarcopenia was also associated with a shorter progression free survival together with tumor size in multivariate analysis. These data suggest that a subgroup of patients with advanced tumor stage and sarcopenia have a more
aggressive disease which is more prone to resist to trans-arterial treatments. Indeed, sarcopenia may reflect the consequences of an intense hypercatabolism due to a particularly aggressive disease. In these patients, transarterial treatment may be deleterious in addition to be less effective as it could lead to liver failure and decrease the possibility of using systemic treatments after progression. Besides, the increased rate of radiological response obtained with the recent combination atezolizumab-bevacizumab forces us to better select the optimal treatment for patients between TACE and systemic treatments [22]. However, as sarcopenia has also been associated with poorer survival outcomes in patients under systemic therapies [10], it remains to be studied if sarcopenic patients with a high tumor burden benefit more from systemic treatments than trans-arterial procedures. In any case, sarcopenia needs to be detected as early as possible to initiate a medical intervention using nutritional support and physical activity to reverse sarcopenia and potentially improve survival. Indeed, muscle restoration before starting these treatments showed interesting results in terms of survival [10, 23], and this type of intervention should be tested in a randomized controlled trial as up to 60% of patients treated by TACE harbored sarcopenia.

Sarcopenia was also associated with a shorter overall survival independently of tumor burden suggesting that undernutrition and loss of muscle are key prognostic factors in patients with HCC treated by TACE or TAE. As sarcopenia is easily assessable using a CT scan in clinical practice, it could be useful to stratify patients in clinical trials. This study showed that sarcopenia assessed at the first radiological evaluation after TACE was also associated with shorter overall survival underlying the robustness of this association. Moreover, a subset of patients rapidly developed sarcopenia at the first radiological assessment which was particularly associated with a poor overall survival. Almost all these patients presented a progressive disease at the first evaluation, suggesting that they harbored an aggressive tumoral disease potentially responsible of the fast development of sarcopenia.
CONCLUSION
In conclusion, sarcopenia is associated with a higher rate of tumor progression and shorter survival in patients with HCC treated by TACE or TAE. Moreover, sarcopenia is an easy-to-assess radiological biomarker of poor prognosis that should be measured in order to assess prognosis and test a targeted intervention mixing nutritional support and physical activity.

ARTICLE HIGHLIGHTS

Research background
Research background: At the diagnosis of hepatocellular carcinoma, more than 90% of hepatocellular carcinoma (HCC) patients present a cirrhosis, a clinical condition often associated to a malnutrition. Sarcopenia has been associated with lower tumor response or poorer survival of patients undergoing various treatment such as surgery or systemic therapies. Transarterial chemoembolization (TACE) is the treatment of choice of intermediate HCC and is largely use worldwide but the impact of sarcopenia on its results was poorly studied.

Research motivation
Research motivation: Finding easy ways to detect sarcopenia within daily practice should benefit to patients by better characterizing their prognosis and taking their nutritional status into account in therapeutic decisions.

Research objectives
Research objectives: This study aims to evaluate the prognostic value of sarcopenia in patients with hepatocellular carcinoma treated by trans-arterial (chemo)-embolization based on baseline CT-scan findings and study its impact on objective tumor response and survival outcomes.
Research methods

Sarcopenia is easy to assess on CT scan by measuring the skeletal muscle index. A SMI < 50 cm²/m² in male and < 39 cm²/m² in female patients correspond to sarcopenia. A was observed in 57.7% of patients.

Research results

Research results: Based on SMI analysis measured on baseline imaging, a sarcopenia was observed in 57.7% of patients. After full review of radiological response using mRECIST criteria, sarcopenia was associated with a higher rate of progressive disease. It was also associated with a decrease overall survival even after adjustment with usual risk factors of death.

Research conclusions

Research conclusions: Sarcopenia is an easy-to-assess radiological biomarker of poor prognosis that should be measured in order to better assess prognosis of HCC patients.

Research perspectives

Research perspectives: Systematic detection of sarcopenia at baseline, should induce a targeted intervention mixing nutritional support and physical activity. Further studies are needed to assess the benefit of these strategies in HCC patients.
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