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Preoperative sarcopenia predicts survival after hepatectomy for colorectal metastases: a prospective observational study

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Abstract. – OBJECTIVE: The surgical approach to colorectal liver metastases has highly improved the survival rates in metastatic colorectal cancer patients. Since sarcopenia estimates the physiologic reserve of an individual patient, it is considered a surrogate marker of patient frailty, and the selection of appropriate candidates for LR could be crucial to maximize the benefits derived from surgery. The present study investigated the impact of sarcopenia as a prognostic factor after LR from CRLM.

PATIENTS AND METHODS: The study retrospectively analyzed 74 patients. Skeletal Muscle Mass at the third lumbar vertebra in the inferior direction was quantified using enhanced computed tomography scans. The patients were divided into two subgroups, with and without sarcopenia, based on median Skeletal Muscle Index.

RESULTS: The study included 48 Sarcopenic patients and 26 Non Sarcopenic patients. The median follow-up considered for the patients was 32 months. Median SMI was 39.3 and 52.7 cm^2/m^2, respectively. The OS rate was significantly different between the two groups. Preoperative sarcopenia resulted in worse OS up to 48 months.

CONCLUSIONS: Sarcopenia represents a negative prognostic factor as it is associated with poor postoperative OS. Future programs focused on remediating to the preoperative sarcopenic status of colorectal liver metastatic patients should be implemented.

Key Words:
Sarcopenia, Liver metastases, Metastatic colorectal cancer, Liver resection.

Introduction

Colorectal liver metastases (CRLM), followed by metastasis from GEP-NET, are the primary cause of hepatic secondary reactions. Surgery offers a substantial benefit in the treatment of CRLM, while its role, in the treatment of metastases from breast or gastric cancer, is still doubted and it has not yet been validated[1,2].

The intuition that surgical approach to metastatic patients could have increased their survival rates dates back to the 1970s. The first scientific evidence that patients who had undergone liver resections obtained a survival benefit was published in 1984[3].

Nowadays, the study by Fong et al[4] assessed a 40% overall survival (OS) at 3 years from liver surgery, compared to lower survival rates in patients treated with chemotherapy or regional treatment.

Some studies[5,6] tried to identify markers of post-operative outcomes in order to better select the patients fit for surgery, ending up focusing on sarcopenia as a risk factor of post-operative complications after major hepatectomy, especially in the elderly[7].

Sarcopenia has been defined by "The European Working Group on Sarcopenia in Older People" as a "progressive loss of skeletal muscle mass associated with a downward spiral that may lead to decreased strength and functionality".

Sarcopenia has been shown to be an independent risk factor for poor overall survival (OS) and disease-free survival (DFS) rates with several kind of diseases, especially cancer. Evidence showed sarcopenic patients to be particularly vulnerable in the setting of major physiologic stressors such as major surgery or surgical complications[8,9].

Selecting appropriate candidates for liver resection is, therefore, crucial to implement the surgery benefits, since hepatectomy is considered

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a high-risk operation. Consequently, the present study aims to assess sarcopenia as a possible prognostic factor of OS and DFS after major hepatectomy for CRLM.

Patients and Methods

Between January 2015 and November 2019, a total of 74 consecutive patients who underwent liver resection for colorectal liver metastasis in a single center (Department of Hepato-Bilio-Pancreatic surgery, San Salvatore Hospital, L'Aquila, Italy) were prospectively identified. The data were recorded in collaboration with the Department of Surgery of the University of L'Aquila.

Patients with known extra-hepatic diseases were excluded from the study. Each patient received chemotherapy before liver resection. All patients enrolled in the study presented eligible criteria for liver resection, according to ESMO guidelines[10]. Patients who undergone first-time hepatic resections and whose preoperative computed tomography (CT) images were available, were included in the study. Patients' clinical and pathological data were retrospectively obtained from each patient medical record. All patients were staged with an abdomen and chest CT. The treatment plan was decided by a multidisciplinary team conference. Postoperative complications were scored according to Clavien-Dindo classification[11]. The primary endpoint was to establish OS and DFS.

Skeletal Muscle Measurement

Patient skeletal muscle mass was prospectively assessed using measurements of muscle area on existing diagnostic CT scans. The cross-sectional skeletal muscle area was manually traced and automatically calculated on a single transversal image of the abdomen at the level of the transverse process of the third lumbar vertebra (L3). Muscle attenuation was not taken into account. The calculated area was then normalized for body length, presenting as skeletal muscle index (cm^2/m^2) (SMI). L3 skeletal muscle area had previously been shown to correlate with whole-body muscle mass[12].

Statistical Analysis

Cumulative overall survival was evaluated by the Kaplan-Meier estimator which is a non-parametric statistic used to estimate the survival rate. The log-rank test was used as a non-parametric test. *p*-value was considered significant when < 0.05.

The disease-free survival data were compared using a two-way ANOVA. Sida's multiple comparison was used to evaluate the statistical significance with CI computed for 95%. All analyses were performed using Graph-Pad Prism 8.3.0.

Results

Seventy-four patients met inclusion criteria for the study. All enrolled patients received chemotherapy before surgery. The type of chemotherapy regimen was chosen by the medical oncologist after individual assessment and oxaliplatin-based chemotherapy was normally considered as the first choice of treatment. As reported in the study of Martin et al[13], who defined sarcopenia as SMI lower than 52.4 cm^2/m^2 for men and lower than 38.5 cm^2/m^2 for women, we adopted the same cut-offs. According to this definition, we identified 48 sarcopenic patients and 26 non sarcopenic patients. The patients'

Table I. Characteristics of the patients enrolled in the study and divided in a Sarcopenic (S) and a NonSarcopenic (NS) group.

Characteristics of the patients	Sarcopenic (S) *vs.* (n° = 48)	Non Sarcopeic (NS) (n° = 26)
BMI (Kg/cm^2)	24.2	27.6
Weight (Kg)	74.2	76.5
Albumin levels (mg/dL)	3.2	3.8
Nodes positive primary	19	18
Number of lesions	2 (1-4)	2 (1-5)
Largest nodules (mm)	18 (8-90)	27.5 (11-68)
Major vs Minor resection	24:24	15:11
Major complications Sec. Clavien-Dindo > 3	6	3
Lenght of stay (day)	10.8	11.2

characteristics are shown in Table I. Several parameters, such as nutritional status, tumor progression and surgical treatment received by each patient were considered, as long as postoperative complications and length of hospitalization. The parameters evaluated in both groups were normally distributed, thus the two samples were considered for further analysis. The median follow-up considered for the patients was 32 months (3-59 months). We evaluated two groups: preoperative sarcopenic and non-sarcopenic patients, and we measured the overall survival up to 48 months. OS is shown by the Kaplan-Meier survival analysis, which indicate that preoperative sarcopenia resulted in worse OS (Figure 1). The OS rate was significantly different between the two groups based on the Log-rank (Mantel-Cox) test (p-value = 0.0297). Comparing the survival data between the two groups, this result indicated that sarcopenia might be a useful preoperative prognostic factor for patients with CRLM. Subsequently, we evaluated whether also the DFS was dependent on the presence or absence of preoperative sarcopenia. However, no significant differences were found in the disease-free survival rates between the sarcopenic and non-sarcopenic patients (Figure 2). The statistical comparison of the two groups was evaluated with the Sidak's multiple comparison test (CI = -9.884 to 25.91).

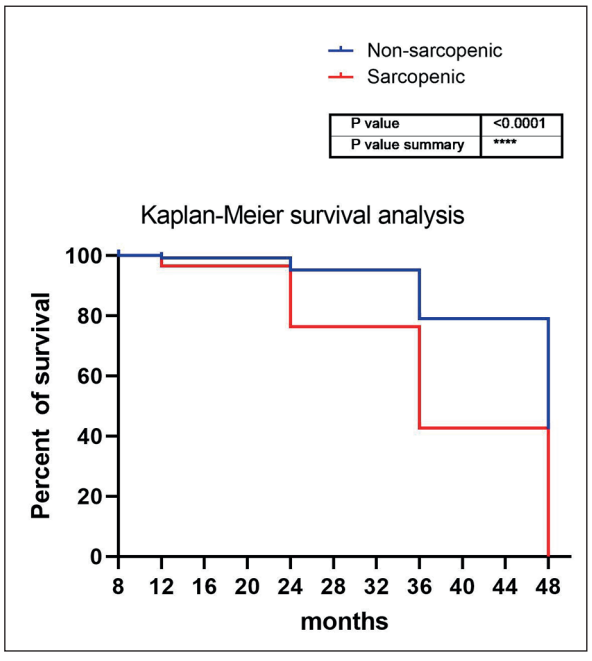

Figure 1. OS Kaplan-Meier survival analysis.

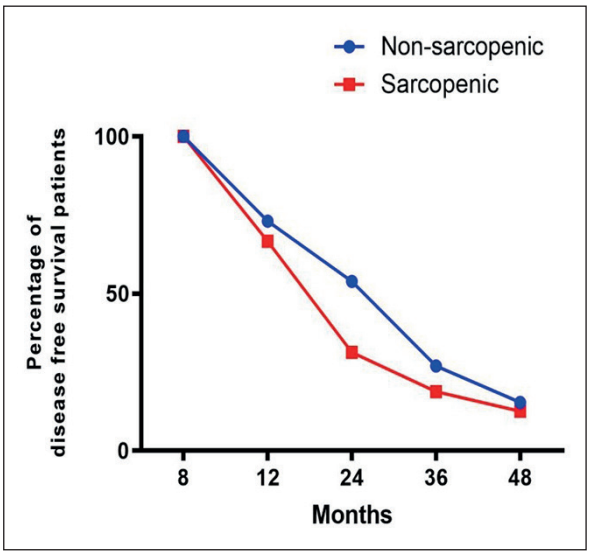

Figure 2. Disease Free Survival rates.

Discussion

Prognostic factors, to predict recurrences or overall survival, could be identified as oncological and non-oncological factors.

Oncological Prognostic Risk Factors

Fong et al[4] identified prognostic factors for colorectal cancer in patients with liver metastasis after hepatic resection. According to FONG Clinical Risk Score[14], the site of the primitive tumor, such as right or left site, advanced grading (G2 *vs.* G3), CEA values >200 ng/dL and synchronous metastasis represent unfavorable prognostic factors. Patients with Fong Score 0-2 are considered "low risk" and may proceed with surgical intervention. They are usually associated with a good prognosis. On the contrary, patients with Fong Score 3-5 are considered "high risk" and are associated with a bad prognosis. In fact, 5 year-OS in patients with Fong score 0 is approximately 60%, while in patients with score 5 it decreases to 14%.

Negative predictive factors are: positive nodal status (N+) at the time of diagnosis, size of the larger tumor greater than 5 cm and multiple metastases[15].

Furthermore, new evidence focused on the role of the mutational status of the primitive cancer. Mutated KRAS and BRAF do represent independent prognostic factors. The mutation of KRAS is associated with a high rate of extrahepatic spread, short disease-free interval and

poor prognosis despite resection. BRAF mutated patients have a reduced OS if compared to wilde type, and liver resections do not increase long-term survival[16-18].

Non-Oncological Prognostic Risk Factors

Several studies[19,20] showed that malnutrition, which is found in 21% of oncological patients, 17% to 46% of patients undergoing general surgery and up to 70% of the patients in the waiting list for liver transplantation, significantly increases morbidity and mortality after surgery for cancer[21].

Commonly used methods to detect malnutrition, as anthropometric measurements (e.g., involuntary weight loss and BMI), are not sensitive and a normal or high BMI might mask malnutrition[22].

Furthermore, the biochemical assessment of nutritional status, using serum albumin or transthyretine, is not suitable in cirrhosis, as these are synthesized by the liver and, therefore their serum levels are influenced by liver diseases[23]. Consequently, they are not correlated with anthropometric measures in patients with liver disease. These findings support a new strategy for the screening of malnutrition, in which body composition evaluation takes a greater role.

Emerging evidence[24] suggests that severe muscle depletion is independently associated with poor prognosis in many cancers, with or without the loss of fat mass associated, and linked with functional status and chemotherapy toxicity.

Sarcopenia has been shown to be an independent risk factor for poor overall and disease-free survival rates with several kind of diseases, especially cancer. Malignancies can result in an hypercatabolic state caused by tumors metabolism, systemic inflammation, and other tumor-mediated effects[25]. This disequilibrium in the homeostasis, together with other cancer-mediated effects such as anorexia, fatigue, decreased functional status, and immobility, leads to a reduction of skeletal muscle and the development of sarcopenia.

The literature evidence showed that in patients treated with chemotherapeutic agents, it has been shown to forecast drug toxicity, time to tumor progression, and mortality. Muscle loss itself is also intensified by the administration of cytotoxic chemotherapy[26].

Moreover, sarcopenia is independently associated with postoperative outcomes due to the resection of malignancy in colorectal cancer, colorectal liver metastasis, esophageal carcinoma, hepatocellular carcinoma, melanoma, pancreatic adenocarcinoma, and bladder cancer (8). Sarcopenia has also been recently identified as a significant prognostic factor of mortality before and after liver transplantation[27].

Hence, several studies ended up focusing on sarcopenia with the aim to identify a further prognostic risk factor of post-operative outcomes, in order to better select patients, fit for surgery.

Selecting appropriate candidates for liver resection is crucial to implement the surgery benefits since hepatectomy is still a high-risk operation in elderly patients. Sarcopenia may therefore be useful for identifying patients with low physical activity for whom major hepatectomy might be unbearable.

In addition, it was found to be a strong and independent prognostic factor for mortality after hepatectomy for HCC in European patients and could be used to evaluate eligibility of patients with HCC before surgery[28].

Hamaguchi et al[29] demonstrated that not only preoperative low muscularity but also visceral adiposity was a significant risk factor for mortality (hazard ratio [HR] = 1.566, $p < 0.001$) and HCC recurrence (HR = 1.329, $p = 0.020$) after hepatectomy. Visceral adiposity was calculated as the visceral-to-subcutaneous adipose tissue area ratio (VSR), and a high VSR has been reported to be a useful predictor of poor prognosis in various kinds of disease, including several cancers. On the other hand, there are evidence[30] showing that sarcopenia, but not visceral fat amount, is a risk factor of post-operative complications after major hepatectomy, since the BMI, used as indirect index for visceral fat amount, cannot directly reflect differences in the fat distribution. A high BMI is not a significant risk factor for postoperative death or HCC recurrence since it could be present in both sarcopenic and non-sarcopenic patients.

Valero et al[30] attempted to determine the impact of sarcopenia on outcomes following resection or transplantation of patients with primary liver tumors. Specifically, the objective of the study was to define the incidence of sarcopenia and to characterize the effect of sarcopenia on both short- and long-term morbidity and mortality among patients undergoing surgery for HCC or ICC. In the current study, sarcopenia was crucial to spot short-term morbidity following hepatic resection or transplantation for HCC and ICC. They found that patients with sarcopenia had an increased risk of a postoperative complications.

In addition, all patients who presented a major complication had underlying sarcopenia[30]. Peng et al[31] demonstrate how sarcopenia impact on short term OS in patients undergoing hepatectomy for CRLM.

Since a strong association between sarcopenia and surgical outcomes, following liver malignancies resection has been proved, we can identify sarcopenia as a powerful predictor of postoperative complications, including morbidity, liver-related morbidity, and mortality following major hepatectomy. Furthermore, it is associated with increased length of hospital stay and requirements for prolonged rehabilitation. Considering that sarcopenia is a surrogate marker of patient frailty because it estimates the physiologic reserve of an individual patient, selecting appropriate candidates for liver resection is crucial to maximize the benefits derived from surgery. Sarcopenia may therefore be useful to identify patients with low physical activity who are unable to tolerate major hepatectomy. The association between sarcopenia and surgical outcomes provides the surgeon an important useful tool to evaluate the possibility of surgery.

In our study, sarcopenic patients had a reduced OS compared to the non-sarcopenic ones, but the groups did not show any significant difference in terms of DFS. This result indicates that recurrence of malignancy was not related to the presence of sarcopenia itself but to the natural history of the primary disease.

Conclusions

The evaluation of the surgical risk in patients with CRLM who need liver resection remains one of the greatest challenges for surgeons. Side by side with the common negative prognostic factors mainly related to the oncological disease, non-oncological risk factors should be evaluated. According to the results of our study and to the evidence proposed by the literature, it is mandatory to consider the patient's nutritional status in stratifying the surgical risk. Each patient nutritional status can be easily evaluated as SMI on preoperative CT scans. Sarcopenia represents a negative prognostic factor as it is associated with poor postoperative overall survival above all. Future programs focused on remediating to the sarcopenic status of cancer patients are desirable.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Ethics Approval and Consent to Participate

This is an observational clinical study, so ethics approval is not required. Informed consent was obtained from all individual participants included in the study.

Authors' Contribution

M.S. and F.C. provided study conception and design. S.L and V.V. have acquired the data. B.P., L.R. and A.G. drafted the manuscript. All authors revised, read and approved the final manuscript.

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