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Impact of muscle mass loss on outcomes in advanced or metastatic gastric cancer patients receiving a second-line treatment

V. ZURLO[1], F. ROSA[2,3], E. RINNINELLA[3,4], L. PONTOLILLO[5], V. BECCIA[5], M. MARATTA[5], G. TORTORA[3,5], S. ALFIERI[3,6], C. POZZO[5], A. STRIPPOLI[5]

[1]Division of Oncology, Vito Fazzi Hospital, Lecce, Italy
[2]Emergency and Trauma Surgery, Fondazione Policlinico Universitario A. Gemelli, IRCCS, Rome, Italy
[3]Università Cattolica del Sacro Cuore, Rome, Italy
[4]Department of Medical Sciences and Surgery, UOC di Nutrizione Clinica, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy
[5]Comprehensive Cancer Center, Fondazione Policlinico Universitario A. Gemelli, IRCCS, Rome, Italy
[6]Digestive Surgery, Fondazione Policlinico Universitario A. Gemelli, IRCCS, Rome, Italy

Abstract. – OBJECTIVE: Sarcopenia is a frequent disorder among cancer patients. It commonly leads to muscle mass wasting and poor clinical outcomes, even though it is rarely recognized and often undertreated. The relationship between skeletal muscle depletion and chemotherapy toxicity or postoperative complications is well known. The aim of the present study was to analyze the impact of sarcopenia on clinical outcomes of pretreated metastatic gastric cancer (GC) patients.

PATIENTS AND METHODS: 88 pretreated GC patients were retrospectively analyzed. Patients were divided into two groups according to their skeletal mass index (SMI): sarcopenic patients with low SMI (≤39 cm²/m² for women and ≤55 cm²/m² for men) and non-sarcopenic patients with normal/high SMI value. The two groups were compared according to outcomes and adverse events.

RESULTS: Progression-free survival (PFS) was significantly higher in patients with normal/high SMI than in those with low SMI (6 *vs.* 3.5 months, respectively; HR 0.52). Similarly, the overall response rate (ORR) was higher in the subgroup with normal/high SMI (41% *vs.* 20%; *p*=0.02). Overall survival (OS) was not significantly different, but multivariate analysis demonstrated that both SMI and performance status were associated with OS. In the sarcopenic group, the patients treated in the second line with paclitaxel and ramucirumab regimen showed a better outcome profile. Overall, adverse events (AEs) were more frequent in the group of patients with low SMI (*p*<0.0001).

CONCLUSIONS: Early recognition of sarcopenia may contribute to personalizing second or further lines of treatment in advanced GC and to weigh up the potential risk of serious toxicities.

Key Words:
Gastric Cancer, BMI, Sarcopenia, SMI, Malnutrition, Personalized therapy.

Introduction

Gastric cancer (GC) is the fifth most common cancer and the third leading cause of cancer death globally[1]. Despite some improvement, the prognosis remains poor[2,3]. Surgery represents the mainstay curative strategy; however, the disease is commonly diagnosed in an advanced stage with a median survival lower than 1 year[4,5].

Chemotherapy produces a moderate survival advantage in locally advanced and metastatic disease but only with a palliative intent[6].

Targeted treatments allow a moderate increase in the survival of selected patients with advanced disease. Trastuzumab, a humanized anti-HER2 monoclonal antibody, and ramucirumab, a humanized anti-VEGFR2 monoclonal antibody, are the only targeted therapies approved so far[7,8].

After first-line chemotherapy, the frequent worsening of symptoms and performance status reduce the expectations of further treatments. However, for patients with preserved performance status, a second-line chemotherapy treatment is appropriate, although no standard regimen has been established[9-11].

Loss of appetite, inactivity, and toxicity are common events in advanced GC, often leading to malnutrition and, consequently, a significant loss of muscle mass[12].

A loss of skeletal muscle mass due to cancer or other inflammatory diseases is named "secondary sarcopenia" (to distinguish it from the age-related "primary sarcopenia"[14]). In clinical settings, sarcopenia may be defined using an axial cross-sectional computerized tomography (CT) image of the psoas muscle at L3 level[12,13].

Corresponding Author: Fausto Rosa, MD, Ph.D; e-mail: fausto.rosa@policlinicogemelli.it

The role of skeletal muscle mass as a prognostic marker of clinical outcomes in GC patients has been widely demonstrated[14-16]. A recent meta-analysis[17] showed that a low muscle mass at diagnosis is significantly associated with poorer OS, worse recurrence-free survival (RFS), and a higher risk of postoperative complications in GC patients undergoing gastrectomy.

Furthermore, cancer itself and chemotherapy could play a direct role in the loss of muscle mass and adipose tissue in neoplastic patients[18-21], especially in GC[22-27].

The aim of the present study was to analyze the impact of sarcopenia on clinical outcomes of pretreated metastatic GC patients.

Patients and Methods

Patients' Selection

Clinical and radiological data of patients with metastatic GC treated at the Medical Oncology Department of Fondazione Policlinico Universitario "A. Gemelli" IRCCS in Rome between January 2020 and June 2022 were retrospectively analyzed from a prospectively collected database.

All patients were treated at least with one line of platinum-containing therapy for metastatic GC.

Complete information regarding height, weight, treatment outcomes, and toxicities were collected. At the beginning of any treatment plan, all subjects signed an institutional consent form to collect their anonymized data for future clinical or translational research evaluation and scientific purpose publishing.

Anthropometric Measurements

Weight and height of the patients at diagnosis were collected.

Body mass index (BMI) was calculated according to the International System using the formula of weight/(height x height) (expressed as kilograms per square meter). The World Health Organization recommended categories were used: underweight, BMI<18.5; normal, 18.5≤BMI≤24.9; overweight, 25≤BMI≤29.9; obesity, BMI≥30.

Image Analysis

Muscle mass was measured by the analysis of electronically stored computer tomography (CT) images obtained during standard patients' assessment at the first-line disease progression before starting the second-line treatment. Axial images of the abdomen were exported and analyzed in a workstation using OSIRIX© V5.0 (Pixmeo, Sarl, Switzerland). The third lumbar vertebra (L3), at a level where both transverse processes were visible, was chosen as the standard landmark. Skeletal muscle mass was quantified based on Hounsfield Unit (HU) thresholds (−29 to +150). To evaluate sarcopenia, skeletal muscle index (SMI) normalized in relation to height (cm^2/m^2) was calculated according to a previously described protocol[28,29].

Progression-free survival (PFS) and overall response rate (ORR) to a second-line therapy were chosen as primary endpoints. Overall survival (OS) was considered as a secondary endpoint.

OS was defined as the time interval from diagnosis of metastatic disease to death or last follow-up visit. PFS was defined as the time interval from the beginning of second-line therapy to the date of clinical or radiological disease progression or treatment discontinuation.

Clinical response to treatment was defined according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1[30]. Complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) were classified using the imaging assessment by CT scan, which was performed from the first disease progression during front-line treatment at regular intervals based on clinical needs and in any case no longer than 3 months.

Adverse events (AEs) were defined according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0[31].

Ethical Approval Statement

The research was performed in compliance with the Helsinki Declaration and with the approval of the Institutional Ethics Committee of the Catholic University of Rome (No. PROT_OM 2016-I).

At the beginning of the therapeutic protocol, all patients signed an institutional consent form to collect their anonymized data for future clinical research and scientific purposes.

Statistical Analysis

Kaplan-Meier method and the log-rank test were used to estimate PFS and OS. A Multivariate Cox regression model was used to identify the predictive effect of different variables on PFS and OS. According to the retrospective nature of the study, descriptive statistics with the Exact Fisher's test and Chi-squared test were used to establish the significance of the association between the presence of sarcopenia

and other variables. All reported *p*-values are two-tailed, and a level of 0.05 or lower was considered statistically significant.

Data were analyzed using MedCal Statistical software (MedCalc version 20.115, European Customers, Ostend, Belgium; available at: https://www.medcalc.org; 2022).

Results

Patients' Characteristics

The clinical records of 210 patients with histologically proven diagnoses of GC treated in our center between January 2020 and June 2022 were retrospectively evaluated.

Eighty-eight patients were eligible according to the inclusion criteria. All these patients received second-line therapy after the progression of one of the following chemotherapy regimens: 5-fluoruracil, folinic acid, oxaliplatin (FOLFOX-6), 5-fluorouracil, folinic acid, irinotecan (FOLFIRI), docetaxel single agent or paclitaxel and ramucirumab combination. The treatment was continued until disease progression, unacceptable toxicity, or patient's withdrawal. Most patients were male (67%). The median age at diagnosis was 57 years (range 30-78); 10% of patients were ≥70 years old and were classified as "elderly"; 11% of patients were considered malnourished according to BMI, whereas 28% were overweight or obese.

Patients were divided into two groups according to their SMI: 53 sarcopenic patients with low SMI (≤39 cm^2/m^2 for women and ≤55 cm^2/m^2 for men) and 35 non-sarcopenic with normal/high SMI values. 50% of overweight patients (BMI >25 and <30) had sarcopenia, suggesting that sarcopenia was highly prevalent, even in overweight and obese patients (Figure 1).

The baseline clinical and body composition characteristics of patients are detailed in Table I.

At a median follow-up of 42 months, 66 death events (75%) occurred in the study population, 24 in the non-sarcopenic and 42 in the sarcopenic group, respectively.

No significant relationship between SMI value and sex, age, or BMI was found (Table I).

Response and Survival

Thirty-five (40%) patients were treated with FOLFIRI, 14 (16%) with FOLFOX-6, 18 (21%) with docetaxel, and 21 (23%) with paclitaxel and ramucirumab. In the whole cohort of patients, the median PFS and the median OS were 6 and 15 months, respectively (Figure 2). PFS was significantly longer in the non-sarcopenic population than in the sarcopenic group (8 *vs.* 3 months; HR 0.52; 95% CI 0.20-0.96; p=0.01) (Figure 3). No CRs were observed. Fifteen out of 35 non-sarcopenic patients (43%) experienced a PR in comparison to 12 out of 53 sarcopenic patients (22%), with a statistically significant difference (p=0.02). OS was 20 months in the normal/high and 15 months in the low SMI group, respectively; however, the difference was not significant (HR 0.82; 95% CI 0.41-1.63; p=0.55) (Figure 3).

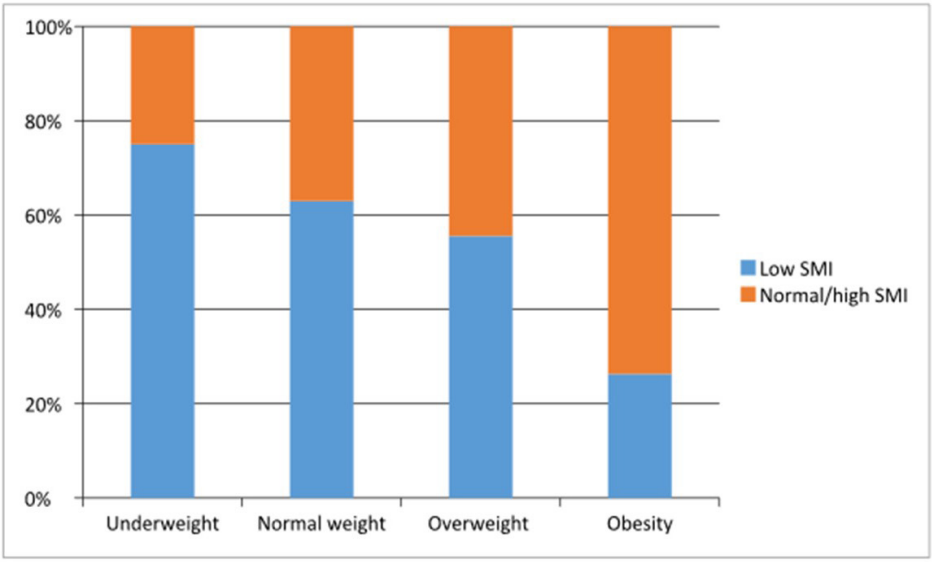

Figure 1. Distribution of Sarcopenia (Low SMI) according to BMI.

Table I. Patients' characteristics.

	No. patients	Low SMI	Normal/high SMI	*p*-value
Sex (Male)	59/88 (67%)	46/53 (88%)	13/35 (38%)	0.14
Median age (years)	57 (30-78)	58 (30-78)	54 (36-77)	0.57
Age (>70)	9/88 (10%)	6/53 (12%)	2/35 (6%)	0.61
BMI				
Underweight (<18.5)	8/88 (9%)	6/53 (12%)	2/35 (6%)	0.69
Normal weight (18.5-24.9)	55/88 (63%)	34/53 (65%)	20/35 (59%)	
Overweight (25-29)	18/88 (21%)	10/53 (19%)	8/35 (23%)	
Obesity (>30)	6/88 (7%)	2/53 (4%)	4/35 (12%)	

SMI: skeletal mass index. BMI: body mass index.

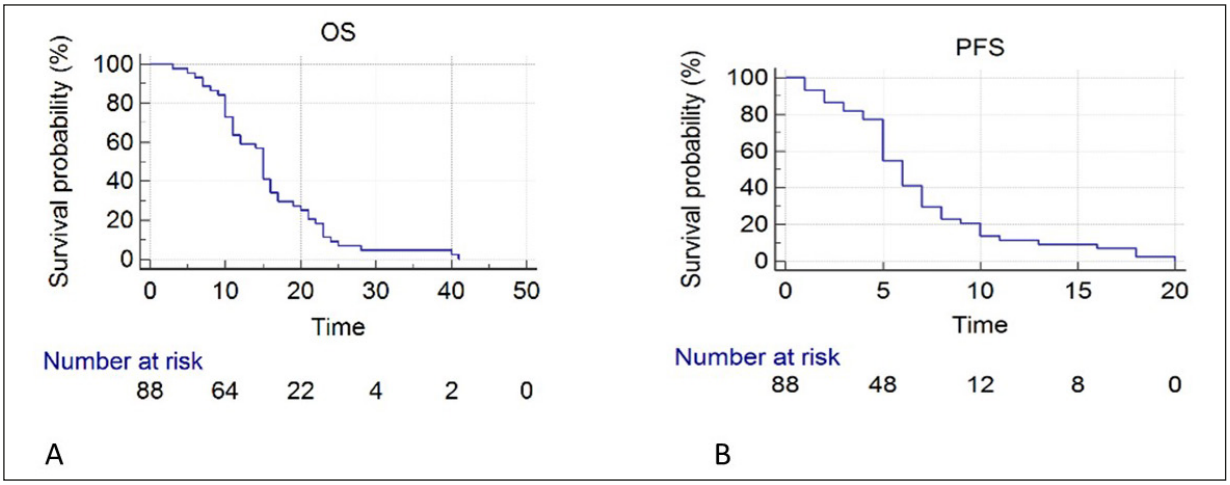

Figure 2. Kaplan-Maier curves for PFS (**A**) and OS (**B**).

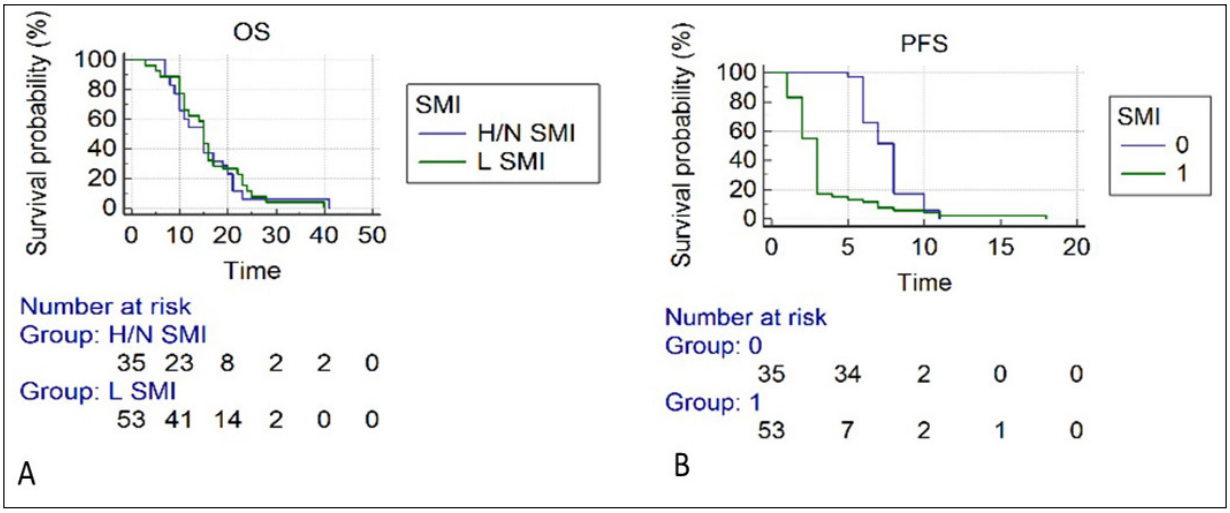

Figure 3. Kaplan-Maier curves for PFS (**A**) and OS (**B**) in sarcopenic group

In a multivariate analysis including SMI, BMI, age (≥70 yrs. old), and performance status, both lower SMI values (95% CI 0.56-2.47; p=0.04) and poor performance status (95% CI 1.07-5.02; p<0.0001) were independently associated with shorter OS. None of the variables considered resulted in an association with a shorter PFS (Table II).

There were no differences in PFS and OS in relation to the chemotherapy regimen. In subgroup analysis, the sarcopenic group seems to

have a slight PFS advantage from the treatment with paclitaxel and ramucirumab (4 months) in comparison to other chemotherapy regimens (1 month) (HR 0.96; 95% CI 5.98-9.76 p=0.02). The same effect was not observed in non-sarcopenic patients (Figure 4).

QoL and Tolerability

During second-line treatment, no patient had an improvement in performance status independently on SMI. Thirty-two out of 53 patients (61%) in the low SMI group experienced AEs of any grade during the treatment. On the contrary, no adverse event occurred in the normal/high SMI group. The most common AEs in sarcopenic patients were neutropenia and diarrhea in 30% and 20% of cases, respectively. Only 3 patients had grade 3-4 AEs. There was no treatment-related death in either group. In patients of the low SMI group treated with FOLFIRI, more gastrointestinal AEs occurred (30%), whereas, in the sarcopenic population treated with docetaxel, neutropenia was more common (30%). Twelve patients in the SMI group needed a dose reduction or a dose delay for neutropenia, but there was no treatment interruption due to serious AEs (Table III).

Patients were divided into two groups, according to their SMI: 53 sarcopenic patients with low SMI (≤39 cm^2/m^2 for women and ≤55 cm^2/m^2 for men) and 35 non-sarcopenic patients with normal/high SMI values. 50% of overweight patients (BMI >25 and <30) had sarcopenia, suggesting that it was highly prevalent, even in overweight and obese patients. In our study, sarcopenia was highly prevalent even in overweight and obese patients, suggesting that BMI and weight are not a suitable parameter for evaluating individual body composition.

In the whole cohort of patients, the median PFS and the median OS were 5 and 15 months, respectively.

PFS was significantly higher in the non-sarcopenic population than in the sarcopenic group (6 *vs.* 3.5 months; HR 0.52; 95% CI 0.20-0.96; p=0.04). OS was 20 months in the normal/high

Table II. Multivariable Cox regression analysis of PFS and OS for prognostic factors.

	PFS		OS	
	HR (95% CI) for progression	*p*-value	HR (95% CI) for mortality	*p*-value
BMI <18.5	0.49 (0.13-1.90)	0.30	0.70 (0.20-2.38)	0.57
Age ≥70	1.57 (0.39-6.19)	0.52	0.81 (0.21-3.11)	0.76
PS ECOG 1	1.78 (0.77-4.09)	0.17	1.78 (1.07-5.02)	<0.0001
Low SMI	2.39 (1.08-5.26)	0.07	1.18 (0.56-2.47)	0.04

PFS: progression-free survival. OS: overall survival. HR: hazard ratio. BMI: body mass index. PS ECOG: Performance status Eastern Cooperative Oncology Group.

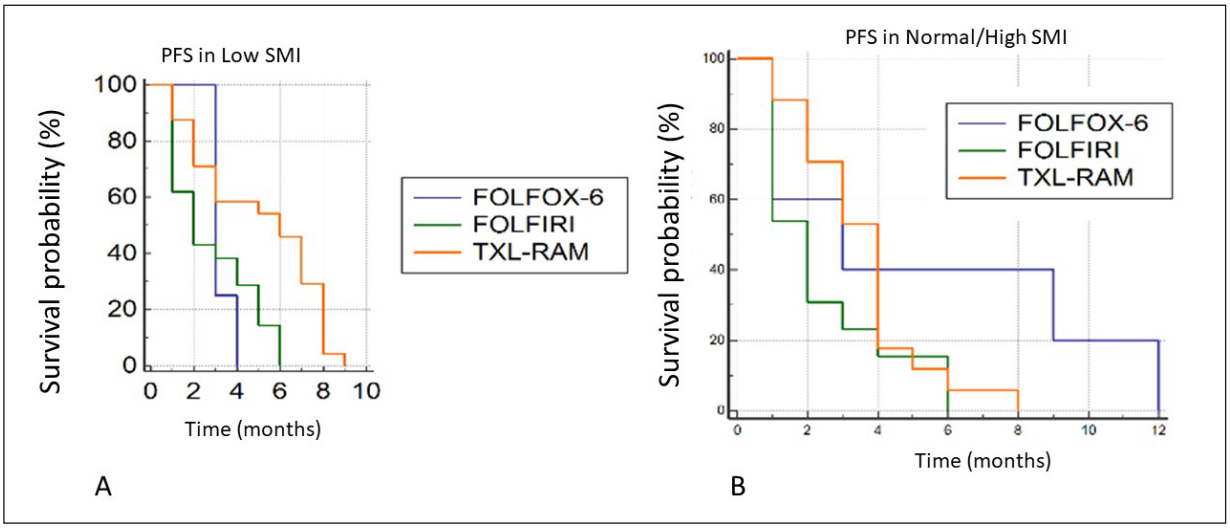

Figure 4. Kaplan-Maier curves for PFS in sarcopenic (**A**) and non-sarcopenic group (**B**).

Table III. Toxicity profile in low SMI group according to Common Terminology Criteria for Adverse Events (CTCAE) v. 4.0.

Event	Grade 1	Grade 2	Grade 3	Grade 4
Hematological				
Anemia	4	0	0	0
Thrombocytopenia	1	0	0	0
Neutropenia	6	0	0	1
Non hematological				
Peripheral neuropathy	10	6	1	0
Stomatitis	1	1	0	0
Hypertransaminasemia	0	0	1	0
Diarrhea	2	2	0	0
Asthenia	5	2	1	0

SMI: skeletal mass index.

and 15 months in the low SMI group, respectively; the difference was not significant (HR 0.82; 95% CI 0.41-1.63; p=0.55).

In the subgroup analysis, the sarcopenic group seemed to have a PFS advantage from treatment with paclitaxel and ramucirumab (10 months) in comparison to other chemotherapy regimens (HR 0.96; 95% CI 5.98-9.76 p=0.02). The same effect was not observed in non-sarcopenic patients.

Discussion

Our study showed a prevalence of 60% of sarcopenic status in a cohort of metastatic GC patients. At the multivariate analysis, both lower SMI values (95% CI 0.56-2.47; p=0.04) and poor performance status (95% CI 1.07-5.02; p<0.0001) were independently associated with shorter OS. To the best of our knowledge, our study represents the first experience investigating the prognostic role of SMI in a cohort of pretreated patients with advanced or metastatic GC, potentially candidates for a further line of treatment. Our results suggest that, at least at this stage of GC, sarcopenia might have a prognostic role and should be considered in the treatment planning.

PFS and ORR in the sarcopenic group were higher in patients with paclitaxel and ramucirumab in comparison to other regimens. Despite the small sample size, this observation seems reasonable because of the good tolerability profile of weekly paclitaxel and ramucirumab, prompting the hypothesis that the choice of treatment in these frail patients may be tailored, allowing benefits similar to those achieved in non-sarcopenic patients.

We can argue that low SMI and a poor performance status are strictly related.

Indeed, sarcopenia is properly defined as both low muscle mass and muscle strength, and severe sarcopenia is identified when poor physical performance is present[12].

The prevalence of sarcopenia in GC patients is high and it may vary.

In our recent experience enrolling patients with locally advanced GC undergoing preoperative FLOT therapy, sarcopenia was present in 19 out of 26 (73%) patients[32]. In a cohort of 118 Japanese patients affected by metastatic GC, 89% had baseline sarcopenia and 31% developed muscle loss during chemotherapy[16].

More than half of GC patients are malnourished at diagnosis[33]. Disease-related malnutrition (DRM) is a frequent disorder among cancer patients and even more in GC ones.

According to the European Society for Clinical Nutrition and Metabolism (ESPEN), malnutrition results "from the activation of systemic inflammation causing anorexia and tissue breakdown leading to alterations in body composition"[34]. The recently released Criteria of the Global Leadership Initiative on Malnutrition (GLIM) highlighted the role of sarcopenia as one of the phenotypic criteria for the diagnosis of malnutrition[35].

In a multicenter, observational cohort study[33] including 877 hospitalized GC patients, Li et al[33] observed a shorter median survival time in patients diagnosed with severe malnutrition based on different muscle mass indices.

Malnutrition and sarcopenia represent two sides of the same coin. Both represent independent prognostic risk factors of poor survival and toxicity in GC patients[17,33].

However, even if malnutrition assessment is complex and multifaceted, sarcopenia is simply obtained by the use of L3-CT-scan images, already obtained for diagnosis and follow-up of GC patients.

Sarcopenia has also been associated with more toxicity, resulting in dose reduction and delay or definitive termination of chemotherapy in both metastatic and neoadjuvant or adjuvant treatment[26,36-38]. The mechanism by which sarcopenia increases treatment toxicity is still little known.

As a matter of fact, chemotherapy dosing based on the body surface area (BSA) does not take into account interindividual variations in body composition. The relative amount of skeletal muscle mass (SMM) and adipose tissue may vary in patients with identical weights and similar BMI because a decrease in SMM could be masked by excess adipose tissue[39]. The simultaneous presence of sarcopenia and obesity/overweight is associated with a poor prognosis. Different proportions of lean and adipose tissue compartments influence drug distribution, disposition, metabolism, and clearance, causing higher serum concentration and an excess of toxicity[40]. In turn, fat tissue promotes an environment characterized by the production of inflammatory cytokines that play an important role in insulin resistance, resulting in muscle protein loss.

In our study, muscle mass loss was found to be highly prevalent even in overweight and obese patients, suggesting that BMI and weight are not suitable parameters for evaluating individual body composition (Figure 1). Moreover, the muscle mass loss condition was not restricted to older patients, and it is independent of sex, BMI, and performance status (Table I).

The correlation between body composition and chemotherapy-related toxicity was addressed by Kazemi-Bajestani et al[41], who reviewed single-center and small-sized trials including one on GC patients[41]. In colorectal cancer (CRC) Prado et al[42] reported a higher percentage of dose-limiting toxicities (DLT) in sarcopenic prospectively compared to non-sarcopenic patients treated with 5-Fluorouracil. Ali et al[43] showed that a small lean body mass is an independent determinant of dose-limiting toxicity (DLT) and neuropathy in patients with CRC treated with FOLFOX regimens[43]. In the low SMI group of our study, a clear trend toward more toxicity and dose reductions/delay has been observed, in particular in the docetaxel-treated group. Interestingly, no AE occurred in the normal/high SMI group.

In addition to survival and toxicity, sarcopenia also seems to influence response to treatment; early treatment interruption and patient frailty could potentially contribute to reducing survival[44]. Similarly to esophageal cancer, GC is at high risk for malnutrition and frailty, especially among elderly patients. The prevalence of frailty and sarcopenia among patients with GC has been reported to be as high as 30% and 38%, respectively[17,25-28,36-45]. Despite the high incidence, data on the association of frailty, sarcopenia, and outcomes after gastric surgery and chemotherapy are very little. Noteworthy, neoadjuvant therapy seems able to change the body composition in esophagogastric cancer, increasing the percentage of sarcopenic patients[45-47].

A recent study[46] showed that the global distribution of the incidence, mortality, and burden of stomach cancers varies across geographies. The mortality and burden of stomach cancer are related to the sociodemographic indicators of the countries. Although no correlation was found between the incidence of stomach cancer and sociodemographic indicators, the different distribution of sarcopenia in the global population could correlate with survival and toxicity in patients with metastatic gastric cancer[46-47].

However, the sarcopenia-inducing effect of chemotherapy might be inconstant and dependent on tumor, stage, and drug combination.

Limitations

This study has several limitations, mainly due to its retrospective nature, the small sample size, and the lack of complete radiologic records of all the 210 patients who underwent second-line therapy.

Nevertheless, the results seem sufficient to support the need for sarcopenia evaluation before selecting patients and combined therapy in second-line GC.

Conclusions

In conclusion, our study demonstrates the clinical impact of sarcopenia in GC patients and its strict relationship with PFS, RR, and AEs. The SMI could represent an objective method of estimating the degree of cancer cachexia in these patients and selecting those with worse prognosis as well as a major risk of drug-related adverse events. As a consequence, nutritional assessment and support should become an essential aid in the management of patients with advanced GC.

Ethics Approval

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. The Institutional Ethics Committee of the Catholic University of Rome approval was obtained (No. PROT_OM 2016-I).

Conflict of Interest
None of the authors has any conflict of interest or financial ties to disclose.

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Availability of Data and Materials
The dataset generated in the present study are available from the corresponding authors. Requests for material must be addressed to the corresponding authors with valid motivation and a declaration of purpose of use.

Authors' Contributions
Study concepts: Strippoli, Tortora, Pozzo. Study design: Strippoli, Zurlo, Maratta, Beccia. Data acquisition: Zurlo, Pontolillo, Beccia, Maratta. Quality control of data and algorithms: Strippoli, Rosa, Rinninella, Tortora, Pozzo. Data analysis and interpretation: Zurlo, Maratta, Pontolillo, Beccia. Statistical analysis: Zurlo, Beccia, Pontolillo, Maratta. Manuscript preparation: Rosa, Strippoli, Quero, Fiorillo. Manuscript editing: Rinninella, Rosa, Strippoli, Pozzo. Manuscript review: Rosa, Rinninella, Tortora, Pozzo.

ORCID ID
Valeria Zurlo: 0000-0002-8876-4691
Fausto Rosa: 0000-0002-7280-8354
Emanuele Rinninella: 0000-0002-9165-2367
Letizia Pontolillo: 0009-0006-3363-8512
Viria Beccia: 0009-0007-6892-0099
Mariagrazia Maratta: 0000-0002-8057-6629
Giampaolo Tortora: 0000-0002-1378-4962
Sergio Alfieri: 0000-0002-7813-4426
Carmelo Pozzo: 0000-0003-4004-9098
Antonia Strippoli: 0000-0003-4463-469X

Informed Consent
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