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ORIGINAL ARTICLE

Strong impact of sarcopenia as a risk factor of survival in resected gastric cancer patients: first Italian report of a Bicentric study

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Abstract

Gastric cancer (GC) accounts for 4% of all cancers in Europe. Sarcopenia is a complex syndrome characterized by a loss of muscle mass and function associated with age, often present in neoplastic patients. Recently, several studies have shown a significant association between sarcopenia and poor prognosis in various pathological conditions. The current observational retrospective study investigates the association between sarcopenia and overall survival (OS) and recurrence-free survival (RFS) in patients with GC undergoing up-front surgery with curative intent. Resected GC patients' clinical records and CT images were retrospectively assessed. The preoperative CT calculation of the skeletal muscle index (SMI) at L3 level allowed us to categorize patients as sarcopenic or not. Kaplan–Meyer and univariate and multivariate Cox regression analyses were performed to determine the difference in survival and presence of independent prognostic factors. Fifty-five patients, 28 male and 27 female, out of 298 studied for gastric cancer were enrolled in the current study from two cancer referral centers in Italy. The preoperative CT calculation of the SMI at L3 level allowed us to identify 39 patients with and 16 without sarcopenia. A statistically significant difference between the sarcopenic and non-sarcopenic groups was observed in both OS and RFS ($p < 0.023$; $p < 0.006$). Moreover, sarcopenia was strongly correlated to a higher risk of recurrence in univariate and multivariate analysis ($p < 0.02$). Sarcopenia can be considered a critical risk factor for survival in patients with resectable GC treated with up-front surgery. Identifying sarcopenic patients at the time of diagnosis would direct selection of patients who could benefit from early nutritional and/or physical treatments able to increase their muscle mass and possibly improve the prognosis. More extensive multicenter studies are needed to address this issue.

Keywords Sarcopenia · Gastric Cancer · Surgical oncology · Oncological Outcomes

Introduction

Gastric cancer (GC) accounts for 4% of all cancers in Europe, with an incidence rate of 13.7 per 100,000 and a mortality rate of 19.5 per 100,000. The incidence peaks in the seventh decade of age, with a 5-year survival rate of around 25% [1, 2]. Surgery is still the primary treatment modality for resectable advanced gastric cancer (AGC).

The European Working Group on Sarcopenia in Older People (EWGSOP) formulated the first definition of sarcopenia in 2009, considering it as loss of muscle mass and function associated with age. It is a complex syndrome related to

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both the isolated loss of muscle mass and the increase in fat mass. The causes are multifactorial and include functional disuse, endocrine function changes, chronic diseases, inflammation, insulin resistance, and nutritional deficiencies. Even if cachexia and sarcopenia could be related, they should not be considered the same condition [3]. In chronic pathologies, such as neoplasia, lean body mass is reduced, whereas fat mass remains stable or can even increase. This condition is called sarcopenic obesity, which is a decrease in muscle mass in an obese patient. Furthermore, obesity can worsen sarcopenia by increasing the fat infiltration into the muscle and reducing muscle function [4].

Computed tomography (CT) and magnetic resonance imaging (MRI) are considered the gold standard for non-invasive assessment of muscle mass [5]. In particular, CT provides an accurate measure of body composition, especially for cancer patients; cross-sectional CT images at the third lumbar vertebra (L3) level significantly correlated with total body muscle mass [6, 7]. At that level, the skeletal muscle area visible in the CT cross section includes the iliopsoasö muscles, the erectors of the spine muscles, the quadrates of loin muscles, the transverse abdominal muscles, the internal oblique muscles, the external oblique muscles, and the rectus abdominis muscles.

Recently, several studies have shown a significant association between sarcopenia and poor prognosis in various pathological conditions in recent years. In different types of cancer (colorectal, liver, pancreas), a low muscle mass index negatively impacts the outcome of patients suffering from the above-mentioned diseases. Sarcopenia is associated with an increase in hospital stay, post-operative complications, short-term mortality and chemotherapy toxicity, and a reduction in relapse-free survival (RFS) and overall survival (OS) [8–11].

Several clinical studies, mainly of Asian origin, have focused their attention on the relationship between sarcopenia and GC patients [12–15]; however, given the substantial diversity in the latter populations' physical and cancer characteristics, results are not easily comparable with Caucasians. According to the current literature, only a few clinical reports have been published in Europe.

The present observational retrospective study investigates whether the association between sarcopenia and GC impacts long-term outcomes in patients undergoing up-front surgery with curative intent.

Patients and methods

Data from patients with GC who underwent total gastrectomy (TG) or distal subtotal gastrectomy (DSG) with curative intent at the "Policlinico di Modena," and at "Morgagni-Pierantoni Hospital", two tertiary referral center in Northern Italy, between November 2008 and November 2018 were retrospectively analyzed.

Main inclusion criteria for the study population were:

- Histologically confirmed diagnosis of gastric or gastroesophageal junction adenocarcinoma;
- Resectable disease, for which endoscopic treatment was not indicated, in stages I, II, and III (T1b-T2-T3-T4 and/or with loco-regional metastatic lymph nodes N +);
- No clinical or instrumental evidence of distant metastases (M0);
- Surgical resection with curative intent (TG or DSG) with histopathologically free surgical margins (R0);
- No patients with combined resections were included in the final analysis;
- Availability in the PACS (Picture Archiving and Communication System) imaging archiving system of our institution of a staging thoraco-abdominal CT scan performed not more than 30 days before the surgery.

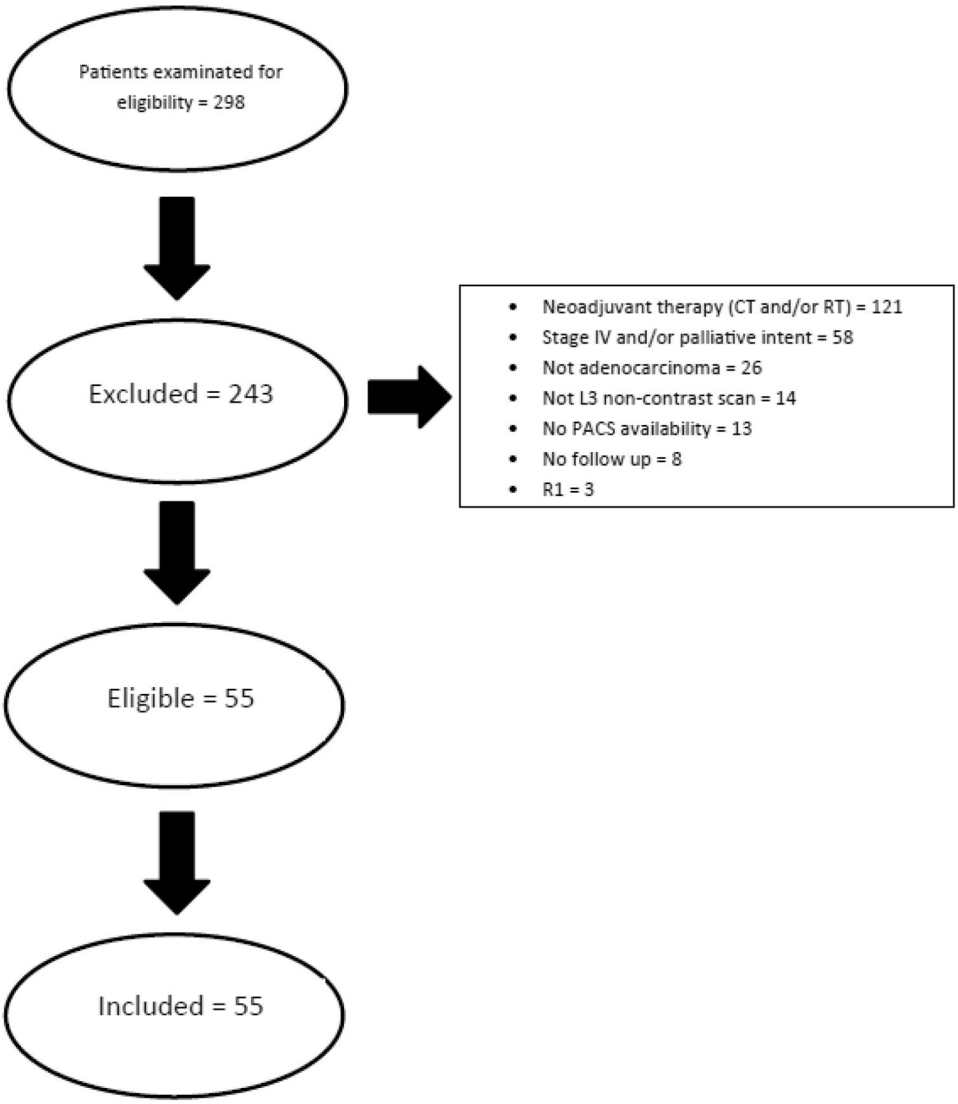
Patients with locally advanced un-resectable cancer who met the operability criteria after neoadjuvant treatment, patients who had undergone perioperative radiotherapy, and patients with preoperative CT exams in whom a non-contrast scan at the height of L3 was not performed were excluded from analysis (Fig. 1).

By reviewing the selected patients' medical records, we obtained a complete electronic database of demographic, clinical, and histopathological data. Then we collected anthropometric indexes (sex, weight, and height) at diagnosis, date of diagnosis, preoperative ECOG Performance Status (ECOG-PS), preoperative blood tests including complete blood count with leukocyte formula and tumor markers (CA 19.9 and CEA), date and type of surgery, histological features and TNM stage, any neoadjuvant and/or adjuvant chemotherapy protocols administered, survival outcomes (development of relapse, exitus, date of diagnosis of relapse, date of death or, for patients in life, date of last available follow-up).

The Body Mass Index (BMI) at preoperative evaluation was calculated for all patients, and divided into four categories according to the classification adopted by the World Health Organization (WHO) for Caucasians, Hispanics, and Blacks [16], respectively: underweight (BMI < 18.5 kg/m^2); normal weight (BMI ≥ 18.5 and ≤ 24.9 kg/m^2); overweight (BMI ≥ 25 e ≤ 29.9 kg/m^2); obese (BMI ≥ 30 kg/m^2).

For each patient, the value of the lymph nodes ratio (LNR), which is the ratio between the number of metastatic lymph nodes on the number of total lymph nodes removed during surgery, was calculated and separated into four categories according to Marchet et al. [17], respectively: 0; ≤ 0.1; > 0.1 and ≤ 0.25; > 0.25.

Fig. 1 Study participants



An index of the Systemic Inflammatory Response, the neutrophil/lymphocyte ratio (NLR), was determined for all patients at the preoperative examination to verify significance as a risk factor.

Post-operative complications, graded according to Clavien–Dindo classification [18], were also retrieved to evidence any difference between groups.

For assessing body composition parameters, non-contrast scans of the staging CT examinations were used.

CT exams were performed using two 64-slice CT scanner (Lightspeed VCT, GE Healthcare, Milwaukee, WI; Optima, GE Healthcare, Milwaukee, WI). An advanced workstation (VolumeShare 7, GE Healthcare, Milwaukee, WI) was used to reconstruct and acquire anthropometric parameters. Dedicated software allows to selectively visualize specific tissues, such as muscle or adipose one, by setting density intervals representative of the tissues to be examined.

According to the current literature, muscle tissue was identified and quantified after selecting a range of density values between − 29 and + 150 Hounsfield Units (HU) [19]. More detailed segmentation of the skeletal muscle tissue at the level of L3 was then performed, at the height of a plane in which both transverse processes of the vertebra were clearly visible (Fig. 2A).

Regions of interest (ROI) corresponding to the total lumbar muscle area (TLA), including the psoas muscles, the para-spinal muscles, and the muscles of the abdominal wall, were drawn, and the area (cm^2) was automatically calculated by the software (Fig. 2B).

Therefore, for each patient, the Skeletal Muscle Index (SMI), a quantitative parameter obtained from the ratio between TLA and the square of the height (cm^2/m^2), was calculated. It represents a normalization index of skeletal muscle mass with respect to the patient's height. SMI assessed on staging CT was used to classify patients as sarcopenic

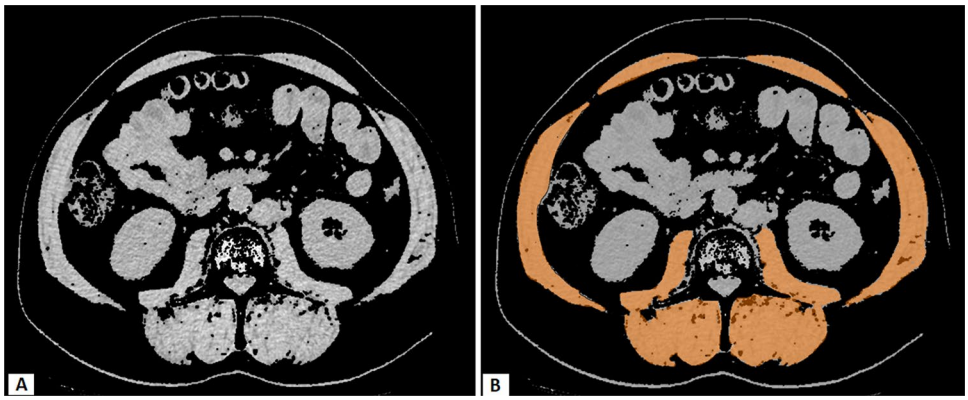


Fig. 2 **A** Once the appropriate density intervals were set (− 29 and + 150 HU), a selective view of the muscle compartment is obtained. **B** TLA at the level of L3 includes the psoas muscles, the para-spinal muscles, and the abdominal wall muscles

and not sarcopenic according to the cutoff values described by Prado et al. for the Caucasian population affected by solid tumors of the gastrointestinal and respiratory tract. Threshold values to define a low SMI, and therefore sarcopenia, were SMI < 52.4 cm^2/m^2 for men and SMI < 38.5 cm^2/m^2 for women [20].

The reconstructions and acquisitions of CT parameters were made consistently across the 2 centers by three radiologists, two of which from the Policlinico of Modena (one with decades of experience serving as team leader) and one from Morgagni-Pierantoni hospital of Forlì with proven experience. Each of them agreed and operated on the basis of a common schedule of operations.

The outcome of the current study was assessing the sarcopenia effect on RFS and OS in patients undergoing surgery with curative intent for GC.

Statistical analysis

In this study, descriptive statistics are reported as proportions or medians with inter-quartile range. Statistical comparisons between subjects with and without sarcopenia were performed using Pearson's χ^2 test for categorical variables. In contrast, continuous variables were analyzed with *t* test or Mann–Whitney *U* test as appropriate. Survivals were estimated using the Kaplan–Meier method, and differences in survival between groups were compared using the log-rank test. OS was defined as the time elapsed between the date of surgery and date of exitus or last follow-up visit, whichever first. RFS was defined as the time elapsed between the date of surgery and date of tumor recurrence or last follow-up visit, whichever first. Risk factors associated with RFS and OS were identified by univariate and multivariate Cox proportional hazard regression models with hazard ratio (HR) and 95% confidence intervals. A value of $p < 0.05$ indicated a significance level. The statistical analyses were conducted using SPSS (Statistical Package for the Social Sciences) version 25.0 software (SPSS Inc., Chicago, IL, USA).

Results

Fifty-five patients out of the initially 298 presenting with a diagnosis of "gastric cancer" met the inclusion criteria, 28 male and 27 female, and were included in the current retrospective study. The mean age was 69.89 ± 11.1 years. The preoperative CT calculation of the SMI at the height of L3 in all patients allowed to identify 39 sarcopenic (70%, 22 men and 17 women, mean age 69.94 ± 11.04 years) and 16 not sarcopenic subjects (30%, 6 men and ten women, mean age 69.17 ± 11.55). The stratification of patients based on the presence or absence of sarcopenia showed that only age ($p < 0.01$), weight ($p < 0.02$), LNR ($p < 0.001$), and SMI ($p < 0.01$) were statistically different between the two groups. There were no statistically significant differences in terms of gender, BMI, and ECOG-PS. Mean BMI was 23.9 ± 4.2 kg/m^2, higher in the non-sarcopenic population than in the sarcopenic counterpart (26 ± 4.8 kg/m^2 vs. 22.9 ± 3.6 kg/m^2), although not statistically significant. No statistically significant differences were also found in terms of tumor profile, such as stage, grading, vascular and peri-neural invasion, common tumor markers (CEA and CA 19), or immune-inflammatory markers (NLR). Postoperative complications analyzed according to Clavien–Dindo classification did not show any difference between sarcopenic and non-sarcopenic patients. A statistically significant difference between the sarcopenic and non-sarcopenic groups was observed in terms of mean OS (30.15 ± 24.9 months vs. 48.94 ± 31.15 months, $p < 0.026$) and mean RFS (24.62 ± 24.4 months vs. 43.81 ± 31.9 months, $p < 0.023$).

Results of demographic, clinical, and pathological characteristics analyzed were summarized in Table 1. Kaplan–Meier OS and RFS curves for the patients with and without sarcopenia were developed and are shown in Figs. 3 and 4, respectively. Log-rank tests also confirmed a statistically significant difference between the sarcopenic and non-sarcopenic groups, both as regards OS ($p < 0.023$) and RFS ($p < 0.006$).

Table 1 Patient demographic, clinical and pathological characteristics

Characteristics	Patients ($n=55$)	Sarcopenic ($n=39$)	Not sarcopenic ($n=16$)	P
Age (years)	73 (15.0)	74 (14)	62 (16)	<0.01
Sex				
Male	28 (50.9%)	22 (78%)	6 (22%)	NS
Female	27 (49.1%)	17 (62%)	10 (38%)	
Weight (Kg)	64 (17.0)	62 (17)	71 (21)	<0.02
BMI (Kg/m^2)	23.45 (5.0)	23.33 (5.47)	25.86 (8.05)	NS
I (<18.5)	10 (18.1%)	8 (80%)	2 (20%)	
II ($\geq 18,5$ e $\leq 24,9$)	26 (47.2%)	21 (80%)	5 (20%)	
III (≥ 25 e $\leq 29,9$)	12 (21.9%)	7 (58%)	5 (42%)	
IV (≥ 30)	7 (12.8%)	3 (43%)	4 (67%)	
SMI (cm^2/m^2)	39.9 (11.73)	38.19 (9.83)	48.88 (12.61)	<0.01
ECOG-PS				
0	20 (36.3%)	13 (65%)	7 (35%)	NS
1	29 (52.7%)	23 (79%)	6 (21%)	
2	5 (9%)	2 (40%)	3 (60%)	
3	1 (2%)	1 (100%)	0 (0%)	
Stage				
IA	8 (14.5%)	7 (87%)	1 (13%)	NS
IB	6 (11%)	5 (83%)	1 (17%)	
IIA	4 (7.3%)	2 (50%)	2 (50%)	
IIB	8 (14.5%)	7 (87%)	1 (13%)	
IIIA	11 (20%)	5 (45%)	6 (55%)	
IIIB	10 (18.2%)	6 (60%)	4 (40%)	
IIIC	8 (14.5%)	7 (87%)	1 (13%)	
Lauren histology				
Intestinal	29 (52.7%)	15 (51.7%)	14 (48.3%)	NS
Diffuse	21 (38.1%)	10 (47.6%)	11 (52.4%)	
Mixed	5 (9%)	2 (40%)	3 (60%)	
Site oftumor				
Upper third	18 (32.7%)	8 (44.4%)	10 (55.6%)	NS
Central third	16 (29%)	9 (56.2%)	7 (43.8%)	
Distal third	21 (38.3%)	12 (57.1%)	9 (42.9%)	
Grading				
I	3 (6%)	1 (33%)	2 (66%)	NS
II	15 (27%)	11 (73%)	4 (27%)	
III	37 (67%)	25 (67%)	12 (33%)	
Vascular invasion				
Yes	23 (41%)	16 (69%)	7 (31%)	NS
No	32 (59%)	23 (71%)	9 (29%)	
Peri-neural invasion				
Yes	17 (31%)	12 (70%)	5 (30%)	NS
No	38 (69%)	27 (71%)	11 (29%)	
Type of resection				
Total gastrectomy	31 (53.6%)	17 (54.8%)	14 (45.3%)	NS
Distal subtotal gastrectomy	24 (46.4%)	14 (58.3%)	10 (41.7%)	
LNR				
I (0)	13 (23.6%)	12 (92%)	1 (8%)	<0.01
II (≤ 0.1)	9 (16.3%)	6 (66%)	3 (34%)	
III (>0.1 e ≤ 0.25)	17 (31%)	9 (53%)	8 (47%)	
IV (>0.25)	16 (29.1%)	12 (75%)	4 (25%)	

Table 1 (continued)

Characteristics	Patients ($n=55$)	Sarcopenic ($n=39$)	Not sarcopenic ($n=16$)	P
Adjuvant chemotherapy				
Yes	32 (58%)	20 (62%)	12 (38%)	NS
No	23 (42%)	19 (82%)	4 (18%)	
NLR	2.13 (1.50)	1.94 (1.62)	2.43 (1.10)	NS
CA 19.9	10.2 (13.3)	10.8 (15.7)	6.5 (7.68)	NS
CEA	1.7 (1.8)	1.8 (1.7)	1.5 (2.02)	NS
RFS (months)	19 (43)	12 (37)	50 (46)	<0.02
OS (months)	32 (49)	25 (45)	51 (46)	<0.02
Post-Op. complications				
Yes	17 (31%)	9 (53%)	8 (47%)	NS
No	38 (69%)	16 (42%)	22 (58%)	

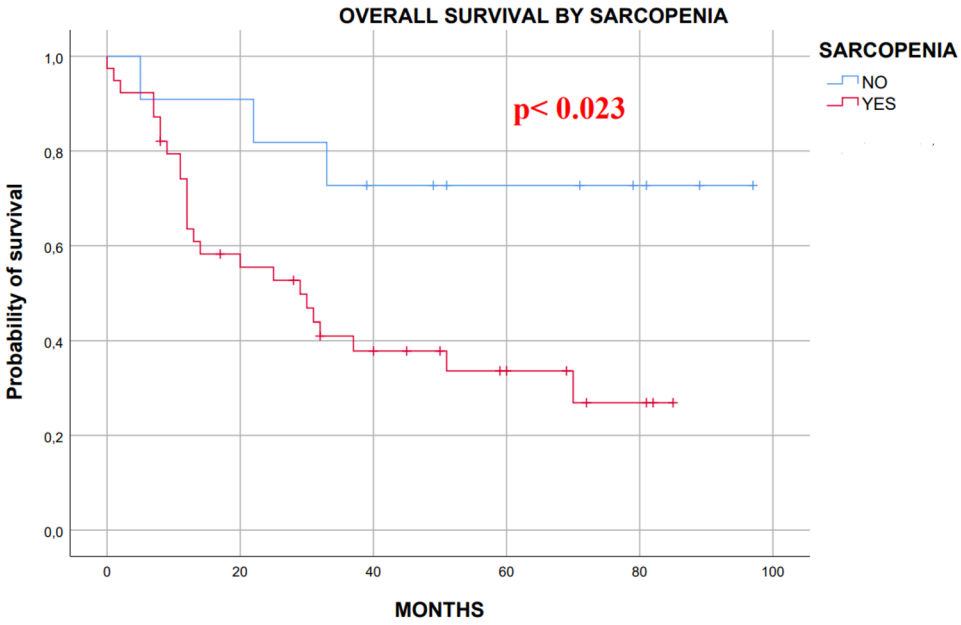


Fig. 3 Kaplan–Meier analysis for the OS comparison in patients with and without sarcopenia

Cox univariate and multivariate regression analyses of several examined characteristics, other than sarcopenia, were analyzed to weigh impact as independent risk factors for OS and RFS.

Regarding OS, in univariate regression analysis, age ($p<0.01$, HR = 1.063), weight ($p<0.038$, HR = 0.963), sarcopenia ($p<0.038$, HR = 3.598), ECOG-PS ($p<0.01$, HR = 4.468), LNR ($p<0.017$, HR = 2.409), and adjuvant chemotherapy ($p<0.01$, HR = 0.183) showed statistical significance as prognostic factors for OS. Among these factors, only sarcopenia ($p<0.022$, HR = 4.434), ECOG-PS ($p<0.01$, HR = 5.364) and LNR ($p<0.01$, HR = 2.204) were independent predictors of poor OS in multivariate analysis (Table 2).

As about RFS, univariate regression analysis resulted slightly different, as age ($p<0.027$, HR = 1.056), weight ($p<0.01$, HR = 0.936), sarcopenia ($p<0.031$, HR = 10.038), ECOG-PS ($p<0.012$, HR = 2.841), LNR ($p<0.01$, HR = 18.570), stage of disease ($p<0.034$, HR = 1.610) and adjuvant chemotherapy ($p<0.01$, HR = 0.135) resulted significant prognostic factors for RFS. Sarcopenia ($p<0.029$, HR = 10.791), more than ECOG-PS ($p<0.01$, HR = 2.805) and LNR ($p<0.01$, HR = 2.550) showed the strongest hazard risk as independent predictor of poor RFS in multivariate analysis (Table 3).

Discussion

In the current study, the authors investigated the relevant effect of sarcopenia on RFS and OS in patients undergoing up-front surgery with curative intent for GC. Patients were selected from a consistent number of almost 300 patients coming from two Cancer centers. Several studies concerning

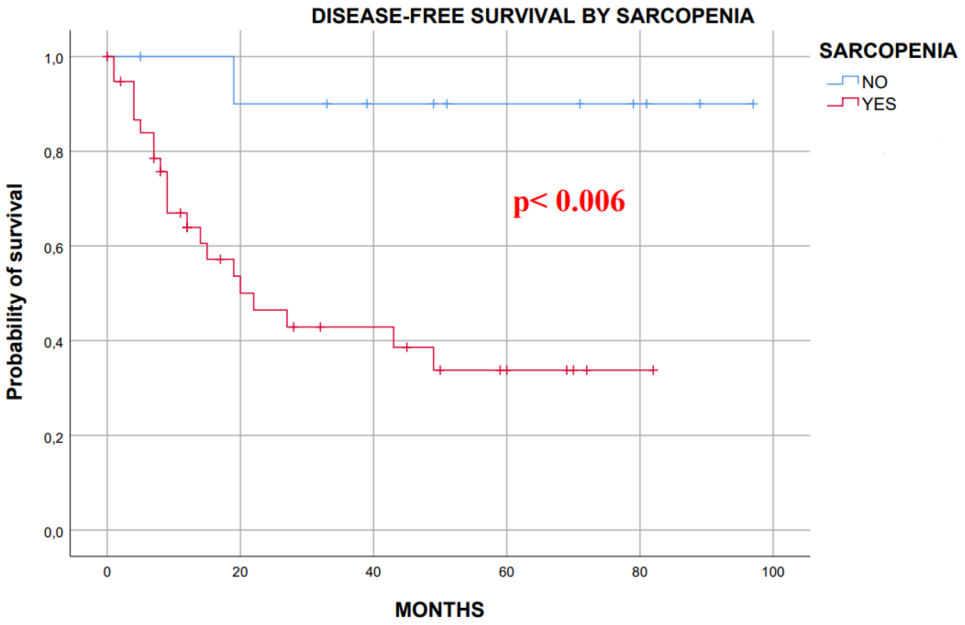


Fig. 4 Kaplan–Meier analysis for the RFS comparison in patients with and without sarcopenia

Table 2 Univariate and multivariate Cox regression analysis of clinical–pathological factors related to OS

Characteristics	HR	Univariate 95% CI	*p*	HR	Multivariate 95% CI	*p*
Age	1.063	1.019–1.108	< 0.01			
Sex	0.915	0.429–1.949	ns			
Weight	0.963	0.929–0.998	< 0.03			
BMI	0.93	0.839–1.030	ns			
Sarcopenia	3.598	1.072–12.071	< 0.03	4.434	1.242–15.829	< 0.02
ECOG-PS	4.468	2.272–8.787	< 0.01	5.364	2.694–10.679	< 0.01
LNR	2.409	1.172–4.953	< 0.01	2.204	1.212–4.008	< 0.01
Diff./mix vs intest	0.924	0.486–2.571	ns			
Cardia vs non-cardia	0.825	0.397–2.087	ns			
Total vs partial res	1.962	0.614–4.571	ns			
Stage	0.524					
IA	0.312	0.036–2.736	ns			
IB	0.406	0.078–2.119	ns			
IIA	0.117	0.013–1.025	< 0.05			
IIB	0.577	0.110–3.024	ns			
IIIA	0.692	0.193–2.485	ns			
IIIB	0.804	0.253–2.551	ns			
IIIC	0.37	0.097–1.416	ns			
Grading	0.96	0.436–2.115	ns			
Vascular invasion	0.865	0.363–2.064	ns			
Perineural invasion	1.662	0.682–4.051	ns			
NLR	1.363	0.765–2.429	ns			
CEA	1.034	0.937–1.141	ns			
CA 19.9	1.006	0.999–1.013	ns			
Adj. chemotherapy	0.183	0.060–0.562	< 0.01			

different types of solid tumors (colorectal, liver, pancreas) have shown that a low SMI represents an independent prognostic factor for adverse events and poor survival [8–12]. Sarcopenia is associated with increased hospital stay length and post-operative complications, an increase in mortality, and a decrease in survival both as RFS and OS [21–23].

Table 3 Univariate and multivariate Cox regression analysis of clinical–pathological factors related to RFS

Characteristics	HR	Univariate 95% CI	*p*	HR	Multivariate 95% CI	*p*
Age	1.056	1.006–1.107	<0.02			
Sex	0.594	0.244–1.451	ns			
Weight	0.936	0.891–0.984	<0.01			
BMI	0.828	0.553–1.241	ns			
Sarcopenia	10.03	1.232–81.762	<0.03	10.791	1.273–91.435	<0.02
ECOG-PS	2.841	1.253–6.443	<0.01	2.805	1.387–5.673	<0.01
LNR	18.57	4.207–81.972	<0.01	2.55	1.557–4.177	<0.01
Diff/mix vs Intest	1.118	0.871–1.647	ns			
Cardia vs non-cardia	0.59	0.292–0.691	ns			
Total vs partial res	1.07	0.824–1.468	ns			
Stage	0.237					
IA	0	0	ns			
IB	0	0	ns			
IIA	0.77	0.009–0.654	<0.01			
IIB	0.317	0.061–1.641	ns			
IIIA	0.314	0.086–1.150	ns			
IIIB	0.187	0.046–0.769	<0.02			
IIIC	0.356	0.106–1.204	ns			
Grading	1.265	0.479–3.338	ns			
Vascular invasion	1.254	0.484–3.249	ns			
Peri-neural invasion	2.39	0.950–6.010	ns			
NLR	1.695	0.907–3.169	ns			
CEA	1.032	0.943–1.129	ns			
CA 19.9	1.007	0.994–1.020	ns			
Adj. chemotherapy	0.135	0.040–0.457	<0.01			

The cut-off values used to discriminate whether a patient is sarcopenic or not vary between studies. The SMI values measured in CT at the L3 level define sarcopenia in GC range from 36 to 53 cm^2/m^2 in men and 29 to 41 cm^2/m^2 in women [12, 22, 24–27]. The EWGSOP recommends using data from a healthy young adult population with cut-off values at two standard deviations below the mean reference value [28]. However, the definition of sarcopenia can vary according to the reference population's characteristics, such as age, race, and geographical origin. The SMI values, according to Prado et al. and adopted in this study, are frequently used for the identification of sarcopenia; they derive from a cohort of patients suffering from different types of neoplastic pathologies of the respiratory and gastrointestinal tract [20].

For the first time in Italy, we show that sarcopenia is commonly present in our GC patients, even in 70% of subjects in our series. In previous studies regarding the role of sarcopenia in operated GC, mostly of Asian race or geographical origin, the prevalence of preoperative sarcopenia ranged from 12.5 to 57.7% [12–15, 22, 24–26, 29].

Moreover, the prevalence of sarcopenia in the current series was almost equally distributed between men and women (22 vs. 17), in line with several epidemiological studies that analyzed the prevalence of sarcopenia in the western population older than 60 years. In these studies, the prevalence of sarcopenia in men and women was 25.7% vs. 23.1% in Germany and 26.8% vs. 22.6% in America [30, 31]. Conversely, in Eastern populations, this prevalence appears to be significantly reduced in the elderly population and clearly biased toward males, as evidenced by a Korean study (12.4% vs. 0.1%) [32].

Sarcopenia is often not associated with loss of fat mass, thus not necessarily reflecting changes in BMI; this was also observed in our series, where within the sarcopenic group, only 8 out of 39 patients (20.5%) were underweight (BMI < 18.5). Furthermore, we did not observe a statistically significant difference in BMI between the two groups. BMI was not associated with a worse prognosis in terms of RFS and OS in the multivariate analysis. This observation was also confirmed in one of the few western works that studied the role of sarcopenia in the outcome of patients undergoing gastrectomy for GC. In their study, O'Brien et al. did not find a modification in prognosis related to BMI. However, there was a statistically significant difference in the BMI value between the sarcopenic and non-sarcopenic group [21]. Similar results were also reported in a series of patients with hepatocellular carcinoma [10]. However, another recent

study investigating the effects of sarcopenia in GC patients undergoing surgery failed to demonstrate its relationship with survival [27]. The substantial difference between this study and the current one is that 30.6% of patients included by the authors underwent palliative surgery, and 37.1% had stage IV disease. On the contrary, in our study, only patients addressed to surgery with curative intent and not undergoing neoadjuvant chemotherapy have been included.

There are some possible explanations to define how sarcopenia worsens the prognosis in cancer patients. For example, tumors with more aggressive behavior tend to have increased metabolic activity, leading to sarcopenia [33]. Some studies suggest that myokines, hormones produced by skeletal muscle, may have an anti-inflammatory and anti-carcinogenic action; therefore, the reduction in myokines secretion due to muscle tissue loss could be linked to a possible tumor progression [34]. Furthermore, low tolerance to chemotherapy could explain the adverse effects of sarcopenia on survival [35]. In our study and others previously [36], we did not observe statistically significant differences in survival after adjuvant chemotherapy between the sarcopenic and non-sarcopenic populations in multivariate analyses. In a study that analyzed body composition changes after neoadjuvant chemotherapy in patients with esophago-gastric neoplasms, a statistically significant increase in the number of sarcopenic patients after chemotherapy was observed [37]. We chose not to analyze the role of neoadjuvant chemotherapy on sarcopenic patients as this was not within the scope of this report.

The C-SCANS study results suggest that systemic inflammation and sarcopenia at diagnosis are associated with an increased risk of mortality in patients with non-metastatic colorectal cancer [38]. We have tested this hypothesis, the negative prognostic role of the NLR on survival in our series with GC [39], although no statistical association was found.

To ascertain whether other risk factors were present besides sarcopenia in our series that could play a crucial role in both RFS and OS, we operated a multivariate analysis for both aspects. Only ECOG-PS and LNR did show a significant hazard ratio as independent risk factors for survival. Marchet et al. have previously established that LNR is one of the most significant prognostic factors in patients with GC undergoing surgery with curative intent, more than the absolute number of metastatic lymph nodes [17]. However, in Italy, no reports have been made thus far where sarcopenia retains a more substantial weight than LNR as a risk factor for both OS and RFS. Probably factors related to the tumor, as is the stage, do not seem to have statistical significance for survival in our series only because of the small size of the sample examined. Moreover sarcopenia, ECOG-PS and stage are complex indicators as they can be influenced by some patient-dependent factors, like metabolic state, aging, immune depression among the others; whereas LNR is a "simple", linear indicator. This complex array of interdependent factors should support the basis for novel studies with higher numbers of patients. However, it is undeniable that, despite the small sample size, from the analysis of our data, sarcopenia appears to be an important and not negligible element for survival in this type of patient.

The results of the present study have some limitations that need to be considered.

First, it is a retrospective analysis conducted on a small series of patients from two northern Italy cancer centers; however, to improve accuracy, we selected only patients operated with radical intervention with curative intent, whereas patients with metastases at diagnosis, patients undergoing palliative surgery, or neoadjuvant chemo-radiotherapy were excluded from this analysis to limit the confounding factors for survival results. This strong selection made necessary to widen the timespan of our series to a 10-year period.

Second, we have extensively discussed the role of sarcopenia in GC patients, although a possible role of muscle density in further studies, in our opinion, should be considered. Skeletal muscle density reflects the amount of lipids in the muscle: the higher the lipid content, the lower the muscle density, and the weaker the muscle strength. It decreases with age and in some pathological conditions, such as neoplastic diseases [40]. CT measures muscle density in a similar way to SMI; the cutoffs for determining low muscle density are < 33 HU in obese patients and < 41 HU in non-obese patients [41]. Some studies believe that low muscle density values may have a negative prognostic value in patients with metastatic chemo-treated GC [42] and in other forms of solid tumor [43, 44].

Conclusion

As a first report from two Italian cancer centers, we demonstrate that sarcopenia can be considered a critical risk factor for prognosis in patients with resectable GC undergoing up-front surgery, certainly more suitable than BMI, even more potent than LNR. We believe that the use of CT in identifying sarcopenia even in patients with normal BMI is currently not sufficiently exploited; reporting the value of SMI would represent a potential added value that radiologists could provide to clinicians and surgeons. Identifying sarcopenic patients at the time of diagnosis would direct selection of patients who could benefit from early nutritional and/or physical treatments to increase their muscle mass and possibly improve the prognosis. Moreover, it might be particularly desirable for those patients who require neoadjuvant chemotherapy.

More extensive multicenter studies are definitely needed to confirm the prognostic role of sarcopenia in patients

suffering from resectable gastric adenocarcinoma and clarify if acting against sarcopenia, together with surgical and/or pharmacological measures can have a great impact in determining a significant improvement in patients' long-term survival.

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Declarations

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

Ethical approval All procedures performed in the study were in accordance with ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent For this type of study formal consent is not required by local regulations.

Consent for publication All authors give their consent for publication.

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