Original Article

Sarcopenia related to neoadjuvant chemotherapy and perioperative outcomes in resected gastric cancer: a multi-institutional analysis

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Background: This study's objective was to evaluate the change in sarcopenia score following neoadjuvant chemotherapy (NAC) and to correlate both sarcopenia and change in score with perioperative outcomes in patients with advanced resected gastric cancer.

Methods: Multi-institutional analysis of patients with gastric cancer who underwent NAC and resection from 2000–2015 was performed. Demographic and perioperative data were included. Sarcopenia score was defined as CT measurement of total psoas muscle at L3, stratified by height (m). Sarcopenia was defined as a score <385 mm^2/m^2 in women and <545 mm^2/m^2 in men.

Results: Of 36 patients, 19% were sarcopenic prior to NAC. Following NAC, 31% were sarcopenic, with 14% developing sarcopenia during NAC. One patient (3%) became non-sarcopenic. There were no significant differences in patient, disease, or surgery characteristics between patients who were sarcopenic *vs.* not. Patients with sarcopenia were more likely to have post-operative complications (P=0.05). There was no significant difference in hospital stay (P=0.7402) or survival (P=0.2317).

Conclusions: A significant number of patients with gastric cancer become sarcopenic during NAC. Although patients with sarcopenia were nearly twice as likely to develop post-operative complications, this did not appear to impact length of stay (LOS) or survival.

Keywords: Gastric cancer; sarcopenia; neoadjuvant chemotherapy (NAC)

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Introduction

Although gastric cancer is one of the most common cancers worldwide, it is not seen commonly in the U.S. Only approximately 22,000 patients are diagnosed with gastric cancer in the U.S. annually (1). Neoadjuvant chemotherapy (NAC) to improve survival has emerged as the standard of care in gastric cancer treatment in the U.S (2,3). However, some patients with gastric cancer present with frailty so severe, they may not tolerate NAC.

Biological age, as opposed to chronological age, has garnered increasing attention as a descriptor of functional status. Sarcopenia, defined as decreased skeletal muscle mass

and strength two standard deviations below that of healthy adults, has been used as a clinically significant marker of biological age, and has been found to be associated with functional impairment, perioperative complications, and decreased survival in patients with nonmalignant conditions (4-6). Changes in body composition on computed topography (CT) imaging occur after neoadjuvant treatment in many cancers, including esophageal and breast cancer (7-10).

This study sought to understand the impact of NAC on sarcopenia and to evaluate whether sarcopenia is correlated with perioperative outcomes in patients with advanced resected gastric cancer.

Methods

Patient selection

This was a multi-institutional, retrospective cohort study. Records of patients who underwent NAC and surgery for gastric adenocarcinoma at Penn State Hershey Medical Center and Moffitt Cancer Center from March 2000 to April 2015 were reviewed. Only patients who had both pre-NAC and post-NAC CT or positron emission tomography (PET-CT) scans, were included in final analysis.

Outcomes and covariates

Patient characteristics [including age, sex, body mass index (BMI), comorbidities, pre-operative weight], disease characteristics [American Joint Committee on Cancer (AJCC) T and N stage, tumor size, lymph nodes], and treatment characteristics (surgical approach, type of resection, NAC regimen, surgical margins) were retrospectively collected from the electronic medical record. Post-operative complications, hospital length of stay (LOS), and overall survival were the primary outcomes. Surgical complications were classified by the Clavien-Dindo Classification of Surgical Complications Scale, which grades complications based on deviation from the normal post-operative course and their requirement of therapeutic measures.

Imaging studies

Patients underwent contrast-enhanced abdominal/pelvic CT as part of routine preoperative work-up. All perioperative studies were collected. Only patients with CT imaging before and after neoadjuvant treatment were included. Imaging studies were analyzed using Advantage Workstation server 2.0 (GE Healthcare Waukesha, WI, USA) and Aquarius Intuition software, version 4.4.12, by Tera Recon Inc., Forest City, California, USA. Measurements of the psoas muscle surface area were performed on transverse axial slices at the caudal level of the third lumbar vertebra. Two consecutive slices were measured and averaged. Total cross-sectional area was calculated automatically and presented in square centimeters. Medically trained investigators independently carried out the image analysis at each institution. Cross sectional muscle measurements were corrected for patient height resulting in a sarcopenia score (mm^2/m^2). Sarcopenia was defined as less than 385 mm^2/m^2 in women and less than 545 mm^2/m^2 in men, as defined by an international consensus of experts on cancer cachexia (11).

Statistical analysis

All statistical analyses were performed with STATA software (version 12.1, StataCorp, College Station, TX, USA). Univariate statistical tests were used to compare baseline patient, disease, and surgery characteristics between patients with and without sarcopenia, using chi-square and *t*-tests where appropriate. Post-operative complications, LOS, and survival were compared using chi-square and *t*-tests where appropriate. Survival was modeled using Kaplan-Meier analyses.

Results

Patient characteristics

Of 41 patients who underwent NAC for advanced gastric adenocarcinoma, 36 had evaluable sarcopenia scores from both before and after NAC. Median follow-up from diagnosis was 17.8 months. This cohort was predominantly female (n=23, 64%), with median age of 64.5 years. There were no significant differences in sex, age, BMI classifications, or co-morbidities, between patients who were never sarcopenic (n=24, 66%) and those who were ever sarcopenic (n=12, 33%) (*Table 1*). Of the patients who were sarcopenic, 50% (n=6) were overweight, and 17% (n=2) met definition for class I obesity.

The majority of patients were Caucasian (n=24, 66%), had some history of tobacco use (n=19, 53%), 2 or more comorbidities (n=27, 75%), and an ASA class of 3 (n=23, 64%).

Table 1 Patient demographics

Variable	Never sarcopenic (N=24) (%)	Ever sarcopenic (N=12) (%)	P value
Sex			0.4860
Male	33.3	38.5	
Female	50.0	61.5	
Age, mean	61.7	67.58	0.1027
≤50	10.0	7.7	
51–60	26.7	7.7	
61–70	30.0	46.2	
71+	33.3	38.5	
BMI, mean	29.61	25.43	0.0845
Underweight	6.7	7.7	
Normal	0.0	0.0	
Overweight	16.7	53.8	
Class I obesity	16.7	15.4	
Class II obesity	13.3	0.0	
Class III obesity	26.7	0.0	
Comorbidities			
GERD	56.0	38.5	0.5530
Hypertension	60.0	69.2	0.2620
Hyperlipidemia	48.0	38.5	0.5630
Atrial fibrillation	24.0	15.4	0.4760
DM	48.0	7.7	0.1090
CAD	24.0	23.1	0.2770
Asthma	24.0	0.0	0.3130
Hypothyroid	28.0	0.0	0.2240
Arthritis	20.0	7.7	0.5270
Other	40.0	38.5	0.4250

BMI, body mass index.

Most patients underwent total gastrectomy (n=26, 72%), while the remainder of the cohort underwent subtotal gastrectomy (n=10, 28%). All patients had confirmed diagnosis of adenocarcinoma, with the majority (n=28, 78%) having poorly differentiated disease (n=28, 78%); the mean tumor size was 5.6 cm, with a median of 2.5 cm. The majority of tumors were located in the body (n=18, 50%). The average lymph node harvest was 24, with a median of 22 and range of 4–45. The average number of positive lymph nodes was 5.4, with a median of 1, and a range of 0–33. The majority of the cohort had negative surgical margins (n=30, 83%). Most patients received epirubicin-based NAC (n=24, 67%), with the most common regimen consisting of epirubicin, cisplatin and 5-fluorouracil (n=19, 53%).

Prior to NAC, 7 patients (19.4%) were sarcopenic (*Figure 1*). Five patients (14%) became sarcopenic during NAC and one (3%) became non-sarcopenic. One third of the total study population (n=12) was sarcopenic after NAC, prior to surgical resection. There were no significant differences in patient, disease, or surgery characteristics between patients who were never sarcopenic and those who were ever sarcopenic.

Between patients who were never sarcopenic and those who were ever sarcopenic, there were no significant differences in type of surgical resection, surgical approach, or surgical margins (P>0.05). There was no significant difference in type of NAC administered (P=0.948). Additionally, there were no differences in tumor size, pre- and post-treatment AJCC T or N stage, number of positive lymph nodes, perineural invasion, and lymphovascular invasion (P>0.05). There were also no differences in pre- or post-operative weight, or weight change (P>0.05).

Of the 23 female patients, 5 (21.7%) were sarcopenic prior to NAC, and 8 (34.8%) were sarcopenic after NAC (*Figure 2*). Of the 13 male patients, 2 (15.4%) were sarcopenic prior to NAC, and 4 (30.8%) were sarcopenic after NAC.

Peri-operative outcomes

Twelve (33%) patients developed post-operative complications, of which few (n=3, 25%) were Clavien-Dindo grade 3 (*Table 2*). There were no grade 4 or 5 complications. In total, 50% (n=3) of the sarcopenic patients who developed post-operative complications were overweight, and 17% (n=1) had class I obesity. Those who were sarcopenic prior to resection were more likely to develop post-operative complications than those who were never sarcopenic (58.3% *vs.* 25.0%, P=0.050). Patients with sarcopenic obesity (defined here as meeting our definition of sarcopenia with a BMI ≥30), were just as likely to develop a post-operative complication as patients who were sarcopenic but not obese (50.0% *vs.* 50.0%, P=1.000).

There was no significant difference in hospital LOS between those who were sarcopenic prior to resection

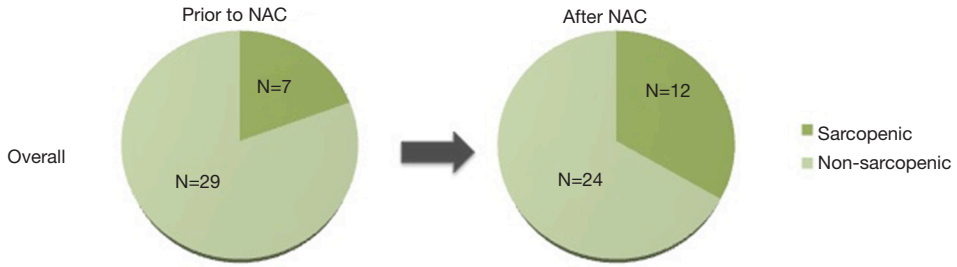

Figure 1 Sarcopenia.

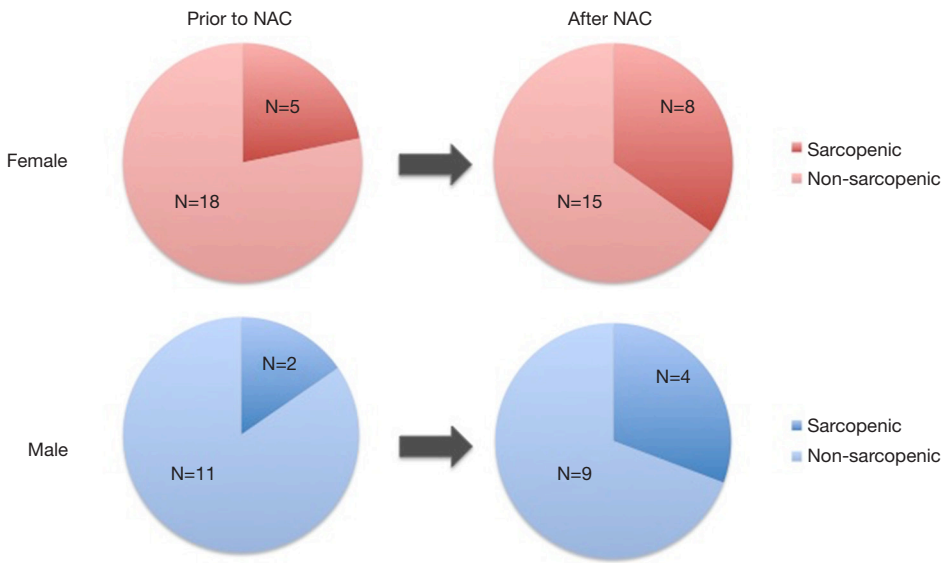

Figure 2 Sarcopenia by gender.

and those who were never sarcopenic (9.3 *vs.* 9.0 days, P=0.125). There was no significant difference in post-operative complications or hospital LOS amongst those who were sarcopenic prior to NAC, after NAC, and sarcopenic both before and after NAC (P=0.100, P=0.385, respectively) (*Table 3*).

Survival

There was no significant difference in survival in patients who were ever sarcopenic and those who were never sarcopenic (P=0.232) (*Figure 3*).

Discussion

Weight loss, early satiety, anorexia and dysphagia are some of the most common presenting symptoms of gastric cancer (12). Preoperative frailty and sub-optimal nutritional status are of particular concern in this patient population (13). In the US, it is possible to have patients who are simultaneously obese but also sarcopenic (14). The aim of this study was to investigate if sarcopenia impacted outcomes.

One third of our patient population was found to be sarcopenic prior to surgery, which is within the range of sarcopenia in gastric cancer patients reported in the literature (12.5–57.7%) (15-17). There is some controversy surrounding the association between sarcopenia and postoperative complications. In a study of 152 patients, sarcopenia was not associated with post-operative morbidity or mortality (17). In a large-scale Asian cohort of 937 patients, Zhuang *et al.* reported sarcopenia as an independent predictor of severe postoperative complications in patients who underwent radical gastrectomy for gastric

Table 2 Disease and surgery characteristics

Variable	Never sarcopenic (N=24) (%)	Ever sarcopenic (N=12) (%)	P value
Surgical resection			0.565
Subtotal gastrectomy	26.7	23.1	
Total gastrectomy	56.7	76.9	
Surgical approach			0.728
Robotic	20.0	15.4	
Tumor			
Tumor size	5.75	7.56	0.540
Pre-treatment AJCC T	2.61	2.78	0.484
Post-treatment AJCC T	2.60	2.69	0.853
Change in AJCC T	–0.13	–0.11	0.972
Lymph nodes			
Number of positive LN	4.88	5.92	0.705
Pre-treatment AJCC N	1.00	1.46	0.193
Post-treatment AJCC N	1.32	1.23	0.843
Perineural invasion	40.0	36.4	0.842
Lymphovascular invasion	62.5	41.7	0.236
Surgical margins			0.068
Positive	6.7	30.8	
Negative	76.7	69.2	
Post-operative complication	25.0	58.3	0.050
Weight (kg)			
Pre-operative	86.26	72.93	0.168
Post-operative	77.95	70.42	0.316
Weight change	–8.49	–2.51	0.139
Neoadjuvant chemotherapy			0.948
DCF	3.3	7.7	
ECX	10.0	15.4	
ECF	43.3	58.9	
Other	23.3	23.1	

AJCC, American Joint Committee on Cancer.

cancer (16). Moreover, in another Asian study of 255 patients, Wang *et al.* reported sarcopenic patients were associated with a higher risk of postoperative complications, longer postoperative hospital stays and greater hospital costs (15). In our study, patients with sarcopenia were nearly twice as likely to experience post-operative complications.

There is evidence that sarcopenic obesity is a unique combination with compound burdens on outcomes, but there are conflicting reports regarding the association between sarcopenic obesity and postoperative outcomes (14). Peng *et al.* reported an increase in severe post-operative complications in patients with colorectal cancer with sarcopenic obesity who underwent hepatic resection (18). However, Lodewick *et al.* reported that sarcopenia and sarcopenic obesity did not impact complication rates in a similar study population (19). A meta-analysis of 14 studies linking sarcopenic obesity to clinical outcomes in cancer patients concluded that sarcopenic obesity was associated with increased surgical complications (14). This study found similar rates of complications between patients with sarcopenia and sarcopenic obesity, which was higher than non-sarcopenic patients.

Reports in the literature are varied regarding the impact of sarcopenia on mortality in patients with gastric cancer, however, there is a paucity of data from Western populations (16,17). In this small cohort, there was no significant difference in survival in patients who were never sarcopenic and those who were sarcopenic. This current study attempts to focus on determining the number of patients who become sarcopenic during NAC and determine whether sarcopenia has an impact on perioperative morbidity and mortality.

There are several limitations in this study that should be acknowledged. Our conclusions are limited by small sample size and the retrospective nature of this investigation. Regarding sarcopenia calculations, there is inherent variability in measuring skeletal muscle area on CT. A validation study with large sample size is necessary to further characterize the impact of preoperative sarcopenia on perioperative outcomes and survival.

Conclusions

During NAC, a significant number of patients with gastric cancer become sarcopenic, adding to a sizeable percentage of already sarcopenic patients presenting for surgery. In this small cohort, patients with sarcopenia were nearly twice as

Table 3 Perioperative outcomes

Outcomes	Sarcopenic				P value
	Never sarcopenic (N=24)	Prior to NAC (N=1)	After NAC (N=5)	Both before and after NAC (N=6)	
Post-operative complication	26.1%	0.0%	20.0%	83.3%	0.054
Length of stay (days)	9.2	5	9.4	9.2	0.753

NAC, neoadjuvant chemotherapy.

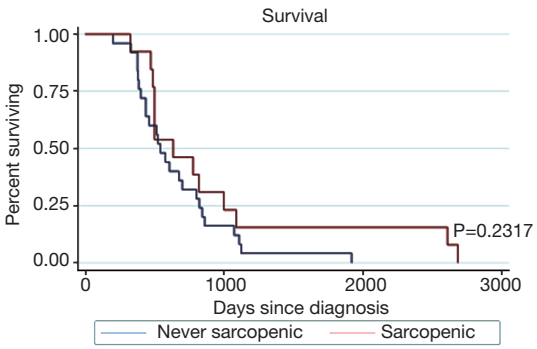

Figure 3 Kaplan Meier survival.

likely to develop post-operative complications; however, this did not appear to impact LOS or survival. Further study with a larger population is warranted to assess the impact of sarcopenia on gastric cancer outcomes in a Western population.

Acknowledgements

None.

Footnote

Conflicts of Interest: SSAT Digestive Disease Week, Poster of Distinction, San Diego, CA, May 21–24, 2016.

Ethical Statement: The study was approved by the Institutional Scientific Review Committee of Penn State Hershey Cancer Institute (PSHCI 15-036).

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