Sarcopenia is a Predictive Factor for Postoperative Morbidity and Mortality in Patients Having Radical Gastrectomy for Cancer

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Rezumat

Sarcopenia este un factor predictiv pentru morbiditate și mortalitate postoperatorie la pacienții cu gastrectomie radicală pentru cancer

Introducere: Pacienții cu cancer gastric prezintă deseori deficiențe ale statusului nutrițional, 30% până la 38% dintre aceștia pierzând mai mult de 10% din greutatea corporală în ultimele 6 luni de boală. Sarcopenia reprezintă o scădere a funcției și a masei musculare scheletale, de obicei fiind asociată cu procesul de îmbătrânire. Prevalența sarcopeniei raportată la pacienții cu cancer gastric ajunge până la 57.7%. Deși multe studii susțin impactul negativ al sarcopeniei la pacienții cu cancer gastric, există și rezultate contradictorii prezentate în literatură. Obiectivul acestui studiu este de a investiga dacă sarcopenia se corelează cu o morbiditate și o mortalitate crescută, la pacienții cu cancer gastric rezecat.

Metodă: Am analizat retrospectiv toți pacienții ce au suferit gastrectomie radicală pentru adenocarcinom gastric în Spitalul Clinic de Urgență București, în perioada Decembrie 2014 – Mai 2016. Am utilizat software-ul ImageJ pentru a măsura compoziția corporală a pacienților. Am identificat ca și punct de reper vertebra L3 și am extras o singură secțiune de tomografie computerizată (TC).

Rezultate: Am examinat 89 de pacienți care au avut gastrectomie radicală pentru cancer, însă 11 imagini TC nu au fost disponibile

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pentru analiză. Prin urmare, studiul a cuprins 78 de pacienți, dintre care 50 de bărbați (64.1%) și 28 de femei (35,9%). Vârsta medie a pacienților diagnosticați cu cancer gastric a fost 67.7 ani (între 22 și 92 de ani). Localizarea tumorii primare a fost în treimea medie gastrică la 45 de pacienți (57.7%), iar la 29 de pacienți (37.2%) localizarea tumorii primare a fost în treimea distală gastrică. Au fost 72 (92.3%) de pacienți externati în viață, iar 6 (7.7%) au decedat în spital. 72.2% dintre pacienți erau sarcopenici, iar 27.78% non-sarcopenici. Valoarea medie a sarcopenie a fost de 43.77. Cei mai mulți dintre pacienți au avut un index de masă musculară scheletală cuprins între 40.00 și 45.00. Al doilea cel mai mare grup de pacienți au avut acest index cuprins între 35.00 și 45.00. Indexul de masă musculară scheletală se corelează cu vârsta pacienților. Rata de complicații și rata de infecții de plagă se corelează deasemenea cu sarcopenia.

Concluzii: Sarcopenia prezintă o prevalență mare la pacienții operați pentru cancer gastric în România și se corelează cu o morbiditate postoperatorie crescută. Odată cu creșterea tendinței pentru terapia neoadjuvantă, echipa multidisciplinară trebuie să evalueze și să prevină sarcopenia.

Cuvinte cheie: sarcopenie, obezitate, gastrectomie, cancer gastric, morbiditate postoperatorie.

Abstract

Introduction: Patients with gastric cancer are frequently malnourished with 30% to 38% of them losing more than 10% of their weight in preceding six months. Sarcopenia represents a decrease in the skeletal muscle mass and function and is usually associated with the aging process. The prevalence of sarcopenia in patients with gastric cancer is reported to be as high as 57.7%. Although many studies support the negative impact of sarcopenia in patients with gastric cancer, contradictory results are also present in the literature. The objective of this study is to investigate if sarcopenia is correlated with increased morbidity and mortality, in patients with gastric adenocarcinoma.

Methods: We studied retrospectively all patients having radical resection for gastric adenocarcinoma managed in the Emergency Hospital of Bucharest between December 2014 and May 2016. ImageJ software was used to measure the patients' body composition. We identified the L3 landmark and extracted that corresponding single cross-sectional image contained within a CT study.

Results: We reviewed 89 patients who had gastrectomy for cancer, but 11 Computed Tomography images were not available for analysis. Therefore, the study group consisted of 78 patients of which 50 were (64.1%) males and 28 (35.9%) females. The average age of patients diagnosed with gastric cancer was 67.7 years (range 22 to 92 years). The primary tumor location was the middle third of the stomach in 45 patients (57.7%), and the second in the lower third of the stomach in 29 patients (37.2%). There were 72 (92.3%) patients who were living on discharge, with mortality in 6 (7.7%) patients. 72.22% of patients are sarcopenic, and 27.78% were non-sarcopenic. The average sarcopenia value for both males and females is 43.77. The greatest number of patients had a skeletal muscle index between 40.00 and 45.00. The second greatest is between 35.00 and 40.00. The muscular skeletal index correlated with the age of the patients. The overall complications rate and the surgical site infection rate correlated with the sarcopenia.

Conclusions: Sarcopenia is highly prevalent in patients having surgery for gastric cancer in Romania and correlates with increased postoperative morbidity. Especially with the increased trend for neoadjuvant therapy, the multidisciplinary team should evaluate and address sarcopenia through the perioperative period.

Key words: sarcopenia, obesity, gastrectomy, gastric cancer, postoperative morbidity

Introduction

Although gastric cancer (GC) represents neoplasia with one of the most notable decreases in the age-standardized death rate between 2006 and 2016 (22.5%) (1), it is still the fifth most frequent cancer and third cancer-related cause of death worldwide (2). Surgical resection represents the cornerstone of curative treatment (3,4). Prognosis for , patients with non-resectable or metastatic disease is poor with the majority dying within 12 months even if they have palliative chemotherapy (5,6). Despite ongoing progresses in surgical technique and perioperative care, radical gastrectomy is still associated with significant postoperative mortality (1.8% – 14.4%) and morbidity (16.7% - 43%) (7–10).

Patients with gastric cancer are frequently malnourished, with 30% to 38% of them losing more than 10% of their weight in preceding six months (11). Ongoing evidence supports that physical pre-habilitation and nutritional support before major abdominal surgery

significantly improve the operative outcomes (12).

Sarcopenia represents a decrease in the skeletal muscle mass and function and is usually associated with the aging process (13). A decrease in the muscle mass is defined when a patient loses more than two standard deviations from the mean for healthy adults (14). Sarcopenia is correlated with a decrease in quality of life, injuries due to falls and increased mortality (15). The prevalence of sarcopenia in patients with gastric cancer was reported as high as 57.7% (16). In pathological conditions such as malignancies, the muscular body mass diminishes while the fatty tissue may remain the same or even increase. The sarcopenic obesity defines the loss of muscle mass associated with an increase in body fat; the current evidence supports an even worse impact on surgical outcomes in patients with gastric cancer (17). Although many studies support the negative impact of sarcopenia in patients with gastric cancer (18), contradictory results are also present in the literature (19) (see *Fig. 1*).

Figure 1. Text analysis of the titles and abstracts of the published literature (1793 papers), using in Web of Science all collections the following search strategy: TOPIC (gastrectomy) OR TOPIC: (gastric cancer) OR TOPIC: (stomach cancer) OR TOPIC: (gastric resection) OR TOPIC: (stomach resection) AND (sarcopenia) OR TOPIC: (muscle loss) OR TOPIC: (body composition). We can be observed the magnitude of relationships detailed in the medical literature between the surgical outcomes and nutritional parameters, in patients with gastrectomy.

The objective of this study is to investigate if sarcopenia is correlated with increased morbidity and mortality, in patients with gastric adenocarcinoma.

Methods

Patient Data

We studied retrospectively all patients who had radical resection for gastric adenocarcinoma managed in the Emergency Hospital of Bucharest between December 2014 and May 2016. The data were collected from the discharge forms of the patient charts using the hospital's computerized database.

We extracted the following data: patients demographic data (age, gender, body mass index), clinical characteristics (reasons for admission, emergency presentation, type of complication, preexisting co-morbidities, American Society of Anesthesiologist class), blood samples (hemoglobin, albumin, total proteins, triglycerides, total cholesterol), radiological data (CT axial image

on L3 vertebra), operative data (operation time, type of gastric resection, lymphadenectomy and reconstruction), pathology report (TNM staging, grading of differentiation), postoperative course (enteral and parenteral nutrition, length of stay, hospital mortality), and postoperative complications (20).

Evaluation of the Body Composition and Sarcopenia

To measure the patients' body composition, we used the Image J software. We identified the L3 landmark and extracted that corresponding single cross-sectional image contained within a CT study. In the L3 level CT axial-section, we distinguished the spinal vertebrae, small bowel loops, liver, kidney, visceral and subcutaneous adipose tissue, and seven muscle groups (the psoas, erector spinae, quadratus lumborum, external and internal obliques, transversus abdominis and rectus abdominis). We traced the abdominal perimeter to measure the waist circumference (see *Fig. 2*).

Figure 2. Measurement of the body composition: A – measurement of the abdominal circumference; B – measurement of the abdominal muscles external perimeter; C – measurement of the abdominal muscles internal perimeter; D – measurement of the L3 vertebral body perimeter.

After that, we measured the outer and inner musculature perimeters. These measurements were then compiled in a Microsoft Excel spreadsheet and the final calculations made (21). We used as sarcopenia definition a skeletal muscle index lower than $52.4 \text{ cm}^2/\text{m}^2$ in male and lower than $38.5 \text{ cm}^2/\text{m}^2$ in females.

Statistical Analysis

We reported all continuous variables with a normal distribution as mean and standard deviation. We used Kolmogorov-Smirnov test to verify the normal distribution of the data. For categorical data, we presented number and percentage. For univariate analysis, we used the independent T-test or Mann-Whitney U test, and Chi-square test or Fisher's exact test as appropriate.

For statistical analysis, we used SPSS version 24 for Mac. A two-tailed P of less than 0.05 was used to declare statistical significance.

Results

We reviewed 89 patients who had gastrectomy for cancer, but 11 Computed Tomography images were not available for analysis. Therefore, the study group consisted of 78 patients of which 50 were (64.1%) males and 28 (35.9%) females. The ratio between males and females was 1.78:1. The average age of patients diagnosed with gastric cancer was 67.7 ± 12.7 years (see *Table 1*).

The primary tumor location felled into the

middle third category of the stomach which includes 45 patients (57.7%), and the second in the lower third of the stomach 29 patients (37.2%).

There were 47 (66.2%) out of 78 patients with a history of cardiovascular disease. The second most common comorbidity was anemia with 35 (49.3%) patients, and the third most common was gastrointestinal pathology with 34 (47.9%) patients. Type 2 diabetes mellitus was present in 19 (26.8%) patients.

The main complaint on admission was accelerated weight loss in 56 (78.9%) and abdominal pain in 53 (74.6 %) of the patients. Vomiting was present in 45 (63.4%) of patients and nausea in 43 (60.6%) of patients. Loss of appetite was also widespread with 41 (57.7%) of patients noting this phenomenon associated with their weight loss. Bleeding was noted in 27 (38%) of patients, and there were 11 (15.5%) patients who complained of asthenia.

The lowest albumin and total protein value during hospitalization were 2.930.65 g/dl and 5.281.91 g/dl, respectively. The lowest cholesterol and triglycerides values were 137.9751.08 mg/dl and 92.2237.26 mg/dl, respectively.

The type of resection was subtotal distal and total gastrectomy in 39 (50%) and 37 (47.4%) of patients, respectively. The most common reconstruction procedure was Roux-en-Y gastro- or eso-jejunosomy in 49 (62.82%) of patients. The lymphadenectomy performed was a D1 and D1+ in 44 (56.42%) patients and spleen and pancreas preserving D2 in 34 (43.58 %) cases.

The tumor stage was T3 in 28 (35.9%), T4a

Table 1. Patients' demographic data

	Non-sarcopenic (22 patients)	Sarcopenic (56 patients)	Statistical significance
Age	61.7	70.05	P = 0.034
Sex (M/F)	1.83	1.76	P = 0.409
TNM stage I	4	2	P = 0.015
II	12	16	
III	13	28	
IV	4	9	
Total / Distal gastrectomy ratio	0.81	0.99	P = 0.028

in 14 (17.9%), T4b in 11 (14.1%), T2a in 11 (14.1%), T2b in 8 (10.3%), T1a in 3 (3.8%) and T1b in 3 (3.8%) patients. The stage of lymph node involvement was N2 in 27 (34.6%), N1 in 16 (20.5%), N0 in 12 (15.4%) and N3 in 8 (10.3%) patients. 65 (83.3%) did not have any metastasis present. Poorly, moderately differentiated and well differentiated tumors were present in 48 (61.5%), 24 (30.8%) and 6 (7.7%) of patients, respectively.

There were 72 (92.3%) patients who were living on discharge, with mortality in 6 (7.7%) patients. 72.22% of patients are sarcopenic, and 27.78% were non-sarcopenic. The average sarcopenia value for both males and females is 43.77. The greatest number of patients had a skeletal muscle index between 40.00 and 45.00. The second greatest is between 35.00 and 40.00. The muscular skeletal index correlated with the age of the patients (see Fig. 3). The overall complications rate and the surgical site infection rate correlated with the sarcopenia (see Table 2).

Discussions

We observed that sarcopenia correlates with increased overall complication and infection rate in patients with radical gastrectomy for cancer.

A prospective study of 158 patients with total gastrectomy and D2 lymphadenectomy

Figure 3. Correlation between skeletal muscular index and patients' age

showed a 30-day complication rate of 27.2% (22). On multivariable analysis the sarcopenia (OR = 3.084, P = 0.005) and tumor location at the cardia (OR = 2.347, P = 0.026) were independent predictors for postoperative complications (22). A study coming from China, which included 255 patients with gastrectomy showed that sarcopenia was present in 12.5% of cases (23). In multivariable analysis, the postoperative complications were correlated with sarcopenia (P < 0.001) and diabetes (P = 0.006) (23).

Shen et al. systematically reviewed the existing evidence about the impact of frailty

Table 2. Postoperative morbidities according to the skeletal muscular index.

Outcomes		Gender			
		Male (skeletal muscle index, cm ² /m ² ; mean ± standard deviation)		Female (skeletal muscle index, cm ² /m ² ; mean ± standard deviation)	
Overall complications (P = 0.002)	No	55.90	7.61	41.72	4.47
	Yes	48.43	8.16	35.72	4.14
Surgical site infections (P = 0.048)	No	48.17	7.68	38.27	4.56
	Yes	41.00	5.73	36.00	6.98
Thromboembolic events (P = 0.978)	No	48.05	7.74	38.19	4.49
	Yes	47.01	3.45	38.01	9.04
Pulmonary complications (P = 0.689)	No	47.78	7.68	38.55	4.46
	Yes	54.05	5.66	33.50	0.71
Cardiovascular complications (P = 0.329)	No	48.05	7.90	38.37	4.46
	Yes	47.67	2.08	33.00	-

and sarcopenia in patients with gastrectomy older than 60 years (24). The authors found that sarcopenia was an independent risk factor for major postoperative complications (OR = 3.12, 95% CI 2.23 to 4.37) (24). 28.8% of 240 elderly patients with gastrectomy were sarcopenic, and had a significantly increased rate of postoperative complications (49.3% versus 24.6%, $P < 0.001$) (25). Sato et al. found that low handgrip strength is a significant risk factor for increased morbidity after gastrectomy (26). Fukuda et al. revealed that sarcopenic patients had operatively a lower intake of calories and proteins (23.9 versus 27.9 kcal per kg ideal weight / day, and 0.86 versus 1.04 g per kg of ideal weight / day), and presented a higher rate of severe postoperative complications (57.1% versus 35.9%, $P = 0.02$) (27).

Huang et al. evaluated the impact of different stages of the sarcopenia on the postoperative outcomes after radical gastrectomy (26). From a total of 470 patients, 20.6%, 10%, and 6.8% had presarcopenia, sarcopenia, and severe sarcopenia, respectively. Although all the three stages sarcopenia correlated with medical complications, only the severe stage was associated with an increased rate of surgical complications (26). In this study the 1-year mortality was 13.9% (26). After the inclusion of sarcopenia, the predictive power of the area under the receiver operating characteristic curve for 1-year mortality increased from 0.835 to 0.868 (26). The current evidence supports that sarcopenia is not only associated with the perioperative outcomes, but also with poorer overall and disease-free survival in patients with stage II and III gastric cancer (18).

Contrary to the above mentioned evidence, an analysis of 152 patients from the Netherlands showed that 57.7% were sarcopenic, but this was not associated with increased in-hospital mortality ($P = 0.52$), severe complications ($P = 1.00$), and six-month mortality ($P = 0.069$) (26).

Carneiro et al. reviewed 14 studies regarding the clinical consequences of sarcopenic obesity in cancer (28). The prevalence of sarcopenic obesity was 1 – 29% in populations of all body mass index categories, and 15 – 36% when only obese

patients were included. The sarcopenic obesity was associated with higher surgical complication rate, physical disability and shorter survival (28). Analysis of 206 overweight or obese patients showed that 14 were sarcopenic (29). The sarcopenia was associated with higher postoperative complications, hospital costs, and 30-day readmissions (29). Takeuchi et al. demonstrated that high visceral fat area is more useful than body mass index in predicting post-gastrectomy complications (26). A high visceral fat area was a predictor of anastomotic leakage (hazard ratio of 4.62, 95% CI 1.02 to 21.02, $P = 0.048$) and incisional surgical site infections (hazard ratio 4.32, 95%CI 1.18 to 15.8, $P = 0.02$) (26).

Neoadjuvant chemotherapy (NAC) is recommended by NCCN guidelines in patients with locally advanced gastric cancer, being associated with better overall survival, disease-free survival, and R0 resection rates (30–33). Mirkin et al. evaluated the change in sarcopenia score after NAC in 36 patients with surgical resection for advanced gastric cancer (34). 19% of patients were sarcopenic before neoadjuvant treatment, and an additional 14% developed sarcopenia during NAC. Sarcopenia was associated with increased postoperative complications ($P = 0.05$) but not with higher mortality ($P = 0.23$) or hospital stay ($P = 0.74$) (34). Tan et al. analyzed 89 patients with resections for esophago-gastric cancers, and found that sarcopenia (OR = 2.95, $P = 0.015$) is associated with toxicity in patients under neoadjuvant chemotherapy (35). The sarcopenic patients presented a significant lower median survival (569 versus 1013 days, $P = 0.04$) (35).

The current evidence reveals two mechanisms through which cancer induces significant loss of muscle mass: a) cachexia, present in 50 – 80% of patients, secondary to muscle and adipose tissue degradation by systemic cytokines; b) sarcopenia, characterized by a decrease in muscle mass secondary advancing age, and present in 20 – 70% of patients (36,37). However, it seems that preoperative prehabilitation is associated with better postoperative outcomes after major abdominal surgery (12, 38–42).

A Cochrane systematic review which evaluates the effects of nutritional supplements administered preoperatively, found that immune-enhancing nutrition reduces the postoperative complication rate with a risk ratio (RR) of 0.67 (95%CI 0.53 – 0.4) and that parenteral nutrition reduced the complication rate with a RR of 0.67 (95%CI 0.53 – 0.84) (36).

The results of the present study should be regarded with caution due to its limitations. First, there are inherent biases related to the retrospective nature of the collected data. Second, we reported a single-center, relatively small cohort of patients. Our hospital has an increased experience in managing patients with gastric cancer, and the results may not apply to other centers. Third, we evaluated the sarcopenia only through CT image analysis, without considering the muscle strength and performance.

Conclusions

Sarcopenia is highly prevalent in patients having surgery for gastric cancer in Romania and correlates with increased postoperative morbidity. Especially with the increased trend for neoadjuvant therapy, the multidisciplinary team should evaluate and address sarcopenia through the perioperative period. The preoperative prehabilitation, including nutritional and physical interventions, seems to be associated with better postoperative outcomes.

Conflicts of Interest

Nothing to declare.

Authors' Contributions

All authors had equal contributed to this scientific paper.

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