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Sarcopenia: Pre-operative Assessment of Muscle Mass to Predict Surgical Complications and Prognosis in Patients with Endometrial Cancer

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Abstract

Background—Sarcopenia or loss of skeletal muscle mass is an objective measure of frailty that is associated with functional impairment and disability. We aim to examine the impact of sarcopenia on surgical complications and survival outcomes in patients with endometrial cancer.

Methods—We performed a retrospective review of endometrial cancer patients who underwent surgery between 2005 and 2009. Sarcopenia was assessed on pre-operative CT scan by measuring the lumbar psoas muscle cross-sectional area and defined as any value below the median ($< 4.33 \text{ cm}^2$). Sarcopenic obesity was defined as sarcopenia plus BMI $\geq 30 \text{ kg/m}^2$. Microsatellite instability (MSI) was analyzed using the NCI consensus markers and tumor from hysterectomy specimens.

Results—Of 122 patients, 27 (22%) met criteria for sarcopenic obesity. Compared to patients with normal muscle mass, sarcopenic patients were older (mean age 69.7 vs. 62.1 years, $p < 0.001$), had lower BMIs (31.1 kg/m^2 vs. 39.4 kg/m^2 , $p < 0.001$), and had more comorbidities ($p = 0.048$). Sarcopenia was not associated with tumor MSI, hospital stay, 90-day readmission rate, or early/late complications. Compared to non-sarcopenic patients, those with sarcopenia had a shorter recurrence-free survival (median 23.5 months vs. 32.1 months, log-rank $p = 0.02$), but there was no difference in overall survival (log-rank $p = 0.25$). After adjusting for race, BMI, lymphocyte count, and tumor histology, sarcopenia was associated with 4-fold shorter recurrence-free survival ($\text{HR}_{\text{adj}} = 3.99$, 95% CI 1.42, 11.3).

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Conclusions—Sarcopenia impacts recurrence-free survival, but does not appear to negatively impact surgical outcomes or overall survival in endometrial cancer patients who undergo pre-operative CT scan.

Keywords

Sarcopenia; Endometrial carcinoma; Surgical complications; Survival

BACKGROUND

The association of malnutrition with adverse clinical outcomes is well established in the literature and recognized as early as 1936 by Studley et al.¹ While validated screening tools exist to aid recognition of malnutrition,^{2,3} their clinical adoption has been underutilized and recognition of patients with or at high risk of malnutrition remains poor. Other markers of nutritional status such as serum protein concentrations and lymphocyte counts have also been investigated. However, there still remains no universally accepted index of nutritional status that predicts length of hospital stay and mortality.

More recently interest in studying the relationship between body composition and cancer incidence and outcomes has grown. Sarcopenia (*sarco* = muscle, *penia* = lack of) or loss of skeletal muscle mass is an objective measure of frailty that is associated with functional impairment and disability.⁴ Historically, sarcopenia was defined as muscle mass greater than 2 standard deviations below that of healthy adults.^{5,6} However, with more advanced methods of *in vivo* body composition using dual energy X-ray absorption (DEXA), magnetic resonance imaging (MRI), and computed tomography (CT) scans, the definition of sarcopenia has continuously evolved without much consensus. Nonetheless, the clinical implications of sarcopenia have been consistently associated with increased duration of hospital stay,^{7,8} higher costs of care, higher risk of nosocomial infections,⁹ and decreased survival in both nonmalignant^{4,10} and malignant conditions.^{11–17} Sarcopenia has also been shown to have a negative impact on patients undergoing surgery^{3,18,19} and a significant predictor of chemotherapy toxicity.²⁰ Despite this growing body of literature, the impact of sarcopenia in gynecologic oncology patients has yet to be elucidated.

The overall purpose of this study is to examine the impact of sarcopenia on surgical complications and overall morbidity/mortality in patients with endometrial cancer. Our specific study objectives are two-fold. First, we aim to assess the clinical implications of sarcopenia to predict the risk of surgical complications and overall prognosis in patients with endometrial cancer. Second, we hope to contribute novel data, not only by studying sarcopenia in this specific cancer population, but also by analyzing the relationship, if any, between specific molecular endometrial tumor markers [e.g., microsatellite instability (MSI)] and sarcopenia, to enhance perioperative counseling regarding clinical outcomes. We hypothesize that sarcopenia is associated with increased surgical morbidity and disease mortality in patients with endometrial cancer. We also postulate that patients with sarcopenia and MSI may have decreased survival rates compared to non-sarcopenic patients with microsatellite stability.

METHODS

We performed a single institution, retrospective review of 122 women diagnosed with endometrial cancer between 2005 and 2009, who had a pre-operative CT scan. Prior to initiation of the study all procedures were reviewed and approved by Washington University's Human Research Protection Office (HRPO# 201204131). Data extracted from patient's charts and electronic medical records included demographic information, physical exam findings, laboratory results, radiographic imaging, operative reports, pathology, and tumor markers. We excluded patients with recurrent disease and those who did not have a pre-operative CT scan within 60 days prior to surgery. We confirmed all diagnoses by documented histology on pathology reports.

Sarcopenia was defined as muscle mass below the median ($< 4.33 \text{ cm}^2$) on pre-operative CT scan. Muscle mass was assessed by psoas muscle density (PMD) and total psoas area (TPA). The third lumbar vertebra (L3) was chosen as the standard landmark^{21,22} and an average of left and right side was calculated. The psoas muscle was manually outlined and the cross-sectional area for muscle and adipose tissue was reported (cm^2) and normalized for stature (cm^2/m^2). All images were analyzed by a single trained observer (MM) within the Department of Radiology at Washington University School of Medicine in St. Louis. Estimates of whole body stores were generated using the following regression equations by Mourtzakis et al.²¹ which showed a close correlation (r value) between muscle and fat areas in CT images at the third lumbar vertebrae and whole body compartments of fat-free mass (FFM) and fat mass (FM) respectively.

$$\text{Total body fat-free mass (kg)} = 0.3 \times [\text{skeletal muscle at L3 (cm}^2\text{)}] + 6.06 \text{ (r=0.94)}$$

$$\text{Total body fat mass (kg)} = 0.042 \times [\text{total adipose tissue at L3 (cm}^2\text{)}] + 11.2 \text{ (r=0.33)}$$

Patients were classified as obese [body mass index (BMI) greater than or equal to 30 kg/m^2] or non-obese based on measurements taken on the date of their appointment at the Center for Pre-operative Assessment and Planning or day of surgery. Pre-operative factors included the following: age, race, weight, BMI, complete blood count (CBC), American Society of Anesthesiologists (ASA) score, and Adult Comorbidity Evaluation (ACE) score from the Cancer Center Registry at Washington University School of Medicine in St. Louis.

Post-operatively, we collected data on tumor histology from pathology reports and tumor markers from an IRB-approved database within the Division of Gynecologic Oncology at Washington University School of Medicine in St. Louis. We also accessed patient operative reports to determine type of surgery performed. Other outcome variables evaluated included post-operative complications, length of hospital stay, 90-day readmission for surgical complication, recurrence-free (RFS) and overall survival (OS).

Pre-operative characteristics, disease characteristics, radiographic features and clinical outcomes were compared using the Fisher's exact test, Student's t-test or the Wilcoxon rank sum test depending on the type of variable and its distribution. Time to recurrence was defined as the time from date of surgery to physical or radiographic evidence of disease

recurrence. RFS was the time from surgery to physical or radiographic evidence of disease recurrence or date of last contact if no recurrence occurred. Patients alive without disease recurrence were censored at the date of last contact. OS was defined as the time between date of surgery and the date of death or the date at last follow-up. The Kaplan-Meier method was used to estimate survival times and distributions were compared using the log-rank test. Multivariable survival analyses considered the following variables as potential confounders: age, race, BMI, lymphocyte count, ASA score, ACE score, all histologic types (eg, endometrioid, papillary serous, clear cell and mixed), stage of disease and MSI markers. However, only 4 of these variables (race, BMI, lymphocyte count, and histology) resulted in a greater than 10% change in the estimate of effect for sarcopenia, and were therefore, adjusted for in the multivariable models. Unadjusted and adjusted Cox proportional hazards models were estimated for RFS and OS separately. Alpha for all analyses was set at 0.05

RESULTS

Our study included 122 endometrial cancer patients with a mean age of 65.9 ± 10.4 years and BMI of 35.3 ± 10.2 kg/m² (Table 1). The majority of patients had grade 3 (40%), stages I-II (72%) disease with corresponding histology confirmed as endometrioid (72%), followed by mixed (18%), papillary serous (8%) and clear cell (2%). The mean lumbar total muscle cross-sectional area was 4.5 cm² and the total body fat-free mass was 7.4 kg. Given our predefined criteria of sarcopenia as psoas muscle mass below the median (< 4.33 cm²), 61 patients (50%) were sarcopenic based on their lumbar cross sectional area and 27 patients (22%) met criteria for sarcopenic obesity.

Patients were then divided into 2 groups: sarcopenia versus no sarcopenia (Table 1). Among the pre-operative factors analyzed, there were no significant differences between sarcopenic and non-sarcopenic patients with regards to race, height, ASA score, and lymphocyte count. However, compared to non-sarcopenic patients, those with sarcopenia were older ($p < 0.001$), had lower BMIs ($p < 0.001$), and more comorbidities, as represented by higher ACE scores ($p = 0.048$). Radiographic features including lumbar total muscle cross-sectional area ($p < 0.001$), lumbar skeletal muscle index ($p < 0.001$), estimated total fat-free mass ($p < 0.001$), and BSA ($p < 0.001$) were all significantly lower among those with sarcopenia. No tumor features (e.g., histologic type, grade, stage or MSI), or clinical/surgical outcomes (Table 2) differed between sarcopenic and non-sarcopenic women.

Kaplan-Meier analysis comparing sarcopenic and non-sarcopenic patients showed faster time to recurrence among endometrial cancer patients with sarcopenia (log rank p -value=0.02; Figure 1a), but no significant difference in OS (log-rank p -value=0.25; Figure 1b). We performed multivariable regression using Cox proportional hazards models adjusting for potential confounders (e.g., race, BMI, lymphocyte count, and tumor histology) that resulted in a greater than 10% change in the estimate of effect for sarcopenia. Sarcopenia was associated with quicker recurrence (hazard ratio (HR) = 2.92, 95% CI 1.12, 7.59) and remained significant even after adjustment for potential confounders (HR_{adj} = 3.99, 95% CI 1.42, 11.3). However, sarcopenia did not predict OS in the unadjusted or adjusted multivariable model (HR= 1.57, 95% CI 0.73, 3.42; HR_{adj} = 1.98, 95% CI 0.81, 4.86 respectively).

CONCLUSIONS

Our study is the first, to our knowledge, to investigate the role of sarcopenia within endometrial cancer patients and demonstrate a high prevalence of sarcopenic obesity (25%) in this population. The ability of cancer to induce muscular atrophy complicates the interplay between sarcopenia and obesity. However, endometrial cancer patients are a particularly interesting population to study given that obesity is a highly prevalent and well established risk factor for endometrioid carcinomas. Furthermore, the association we demonstrated between sarcopenia and increased number of medical comorbidities provides an area for improved perioperative counseling. Sarcopenia predicted decreased RFS, but OS was not significantly impacted on multivariate analysis. This may be due to the limitations of our small sample size and the number of deaths that occurred within our study period.

Sarcopenia is a phenomenon of ageing and within our population of endometrial cancer patients we confirmed that sarcopenic patients were older by 7.6 years. However, we did not adjust for age in the multivariable analysis because age did not result in a greater than 10% change in the estimate of effect for sarcopenia in the model for RFS or OS. Nonetheless we recognize age is a strong predictor of sarcopenia, and therefore ran a separate multivariate analysis including age (as a continuous variable) to assess whether the effect of sarcopenia on RFS and OS would diverge from the model without age. Essentially there were insignificant differences between models: RFS: HR=3.70 vs. HR_{adj} = 3.99 and OS: HR=1.79 vs. HR_{adj} = 1.98). This suggests age may not have a large confounder effect due to our narrow age range within our study population, giving us a rather homogenous population of older patients with endometrial cancer.

Although our paper is dedicated to studying the impact of sarcopenia on endometrial cancer patients, in general sarcopenia is becoming more prevalent and appropriately so, is being studied across medical disciplines. Unfortunately, published findings have currently inconsistent findings. Prado et al.²⁰ studied sarcopenia as a determinant of chemotherapy toxicity in patients with metastatic breast cancer receiving capecitabine. They showed that toxicity was present in 50% of sarcopenic patients versus 20% in patients with normal muscle mass (p = 0.03). Time to tumor progression was shorter in sarcopenic patients by 72 days, p=0.05. Contrary to these results, Awad et al.²³ demonstrated that there were no associations between sarcopenia and loss of fat-free mass, incomplete neoadjuvant chemotherapy, increased hospital stay or mortality in patients with esophagogastric cancer.

These inconsistencies may stem from the lack of a standardized definition of sarcopenia.²⁴ It was initially defined as a level of muscle mass 2 standard deviations below sex-specific norms for young adults.^{5,6} However, the majority of published studies use arbitrary criteria that are study-specific, some utilizing imaging modalities and other based on muscle strength due to the cost-effectiveness of the measurements.²⁴ Newer data within the realm of oncology suggest that CT cross-sectional area at L3 is strongly related to the appendicular skeletal mass,^{13,21} with reported precision error of about 1.4%.²² Given the inconsistency of definitions, we recognize this as a limitation, and chose to define sarcopenia as the mean L3 muscle mass that fell below the median (< 4.33 cm²).

Other limitations of our study are inherent to any retrospective design. We included consecutive patients who met eligibility criteria and as such, the study was not powered to detect differences in clinical outcomes. Furthermore, despite having a reasonable representation across histologic types, our study population was not evenly distributed across all stages. It would have been advantageous to have a greater representation of advanced stage tumors, as these are the patients that are most likely to benefit from nutritional assessment prior to surgery in anticipation for extensive tumor burden, prolonged operative time, higher risk for complications, and ultimate need for adjuvant therapy.

Despite recent interest in clinical implications of sarcopenia in the setting of cancer, the scope of available data is still limited by the type malignancy and clinical outcomes studied. We selectively studied a high-risk population by including only those patients with pre-operative CT scans. However, sarcopenic obesity may have more clinical implications in a population study which includes both low- and high-risk endometrial cancer patients and warrants further investigation. Other future prospective studies may benefit from further investigating the relationship between other tumor markers associated with Type I endometrial cancers and sarcopenia in order to better counsel patients of their perioperative risks and overall disease prognosis. Evidence suggests PTEN (60–80%), K-ras, and MSI mutations often coexist with each other²⁵ and are more prevalent among endometrioid histology.²⁶ Risinger et al.²⁷ specifically studied clinical implications of PTEN mutations on endometrial cancer and showed correlations between this tumor suppressor gene and early stage, non-metastatic disease. Such data provide more avenues of investigation to further study the relationship between sarcopenia and these common tumor markers and their impact on surgical and survival outcomes.

Extrapolating from the current body of literature, sarcopenia and sarcopenic obesity may have more clinical implications in gynecologic oncology, beyond endometrial cancer patients, and warrants further investigation. We hope our results serve as a platform for future studies, especially given the increasing prevalence of sarcopenia among older patients and the growing trend of obesity in the United States. It is a potential modifiable risk factor that should be addressed during pre-operative counseling so that patients are well informed and may choose to adjust their lifestyle to optimize their health prior to undergoing treatment(s).

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Synopsis

Among endometrial cancer patients who undergo pre-operative CT scan, sarcopenia is associated with shorter recurrence-free survival. Sarcopenia does not appear to negatively impact surgical complications or overall survival.

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Figure 1.

Time to recurrence and death by Kaplan-Meier analysis between patients with sarcopenia versus no sarcopenia.

Kaplan-Meier survival curves comparing endometrial cancer patients with sarcopenia versus no sarcopenia. **(A)** Time to recurrence, log rank $p = 0.02$; **(B)** Overall survival, log rank $p = 0.25$.

Table 1

Patient demographics and clinical characteristics, N=122

	All women N=122 N (col %)	No sarcopenia N=61 N (row %)	Sarcopenia N=61 N (row %)	P-value
Pre-operative characteristics				
Age in years, mean(SD)	65.9 (10.4)	62.1 (9.1)	69.7 (10.2)	<0.001
35–49	8 (7)	7 (88)	1 (13)	
50–64	52 (43)	30 (58)	22 (42)	
65 and older	62 (51)	24 (39)	38 (61)	
Race				0.558
White	104 (85)	50 (48)	54 (52)	
Black	14 (11)	9 (64)	5 (36)	
Other	4 (3)	2 (50)	2 (50)	
Body mass index (kg/m ²), mean(SD)	35.3 (10.2)	39.4 (9.8)	31.1 (8.9)	<0.001
Underweight, <18.5	1 (1)	0 (0)	1 (100)	
Normal weight, 18.5–24.9	15 (12)	0 (0)	15 (100)	
Overweight, 25–29.9	27 (22)	9 (33)	18 (67)	
Obese, 30+	79 (65)	52 (66)	27 (34)	
American society of anesthesiologists (ASA) score				0.267
1	3 (2)	0 (0)	3 (100)	
2	59 (48)	28 (47)	31 (53)	
3	56 (46)	30 (54)	26 (46)	
4	4 (3)	3 (75)	1 (25)	
Adult comorbidity evaluation (ACE) Score				0.048
0	26 (21)	8 (31)	18 (69)	
1	53 (43)	26 (49)	27 (51)	
2	29 (24)	20 (69)	9 (31)	
3	14 (11)	7 (50)	7 (50)	
Lymphocytes				0.839
< 1.5	34 (30)	18 (53)	16 (47)	
1.5	80 (70)	40 (50)	40 (50)	
Disease characteristics				
Histology				0.630
Endometrioid	88 (72)	44 (50)	44 (50)	
Papillary Serous	10 (8)	4 (40)	6 (60)	
Clear cell	2 (2)	2 (100)	0 (0)	
Mixed	22 (18)	11 (50)	11 (50)	

	All women N=122 N (col %)	No sarcopenia N=61 N (row %)	Sarcopenia N=61 N (row %)	P-value
Grade				
1	35 (29)	19 (54)	16 (46)	0.476
2	37 (30)	20 (54)	17 (46)	
3	49 (40)	21 (43)	28 (57)	
Undifferentiated	1 (1)	1 (100)	0 (0)	
Stage				
I–II	88 (72)	43 (49)	45 (51)	0.420
III–IV	34 (28)	18 (53)	16 (47)	
Tumor markers				
Microsatellite stability	81 (66)	44 (54)	37 (46)	0.250
Microsatellite instability-low	1 (1)	0 (0)	1 (100)	
Microsatellite instability-high	40 (33)	17 (43)	23 (58)	
Radiographic features on pre-operative CT scan				
Lumbar total muscle cross-sectional area (cm ²)	4.51 (1.4)	5.6 (1.2)	3.4 (0.6)	<0.001
Lumbar skeletal muscle index (cm ² /m ²)	1.7 (0.5)	2.1 (0.4)	1.3 (0.3)	<0.001
Estimated total fat-free mass (kg)	7.4 (0.4)	7.7 (0.3)	7.1 (0.2)	<0.001
Body-surface area (m ²)	1.9 (0.3)	2.0 (0.3)	1.8 (0.3)	<0.001
Operative procedure				
Surgery type [†]				
Open	117 (96)	59 (97)	58 (95)	1.000
Minimally invasive	5 (4)	2 (3)	3 (5)	
Lymphadenectomy				
Yes	106 (87)	50 (82)	56 (92)	0.179
No	16 (13)	11 (18)	5 (8)	

[†] Open procedure includes total abdominal hysterectomy +/- bilateral salpingo-oophorectomy (BSO); minimally invasive surgery includes robotic-assisted total laparoscopic hysterectomy (TLH), TLH, and laparoscopic-assisted vaginal hysterectomy +/- BSO.

* All P-values estimated from Fisher's exact test.

Table 2

Clinical outcomes by presence of sarcopenia, N=122

	All women N=122 N (col %)	No Sarcopenia N=61 N (row%)	Sarcopenia N=61 N (row%)	P-value
Hospital stay (days), mean (SD)	5.6 (3.8)	5.7 (4.3)	5.5 (3.2)	0.772
Early complications, n (%) [†]	42 (35)	23 (55)	19 (45)	0.566
Abscess		1 (33)	2 (67)	
Blood transfusion		13 (48)	14 (52)	
Ileus/small bowel obstruction		4 (57)	3 (43)	
Interventional radiology procedure		1 (33)	2 (67)	
Return to the operating room		1 (100)	0 (0)	
Thromboembolism		3 (43)	4 (57)	
Wound infection		8 (67)	4 (33)	
Late complications, n (%) [†]	12 (10)	8 (67)	4 (33)	0.362
Blood transfusion		0 (0)	1 (100)	
Ileus/small bowel obstruction		2 (100)	0 (0)	
Interventional radiology procedure		3 (75)	1 (25)	
Thromboembolism		1 (50)	1 (50)	
Wound infection		4 (80)	1 (20)	
Readmission, n (%)	7 (6)	4 (57)	3 (43)	1.000
Treatment, n (%)				
None	51 (42)	27 (53)	24 (47)	0.365
Radiation	18 (15)	8 (44)	10 (56)	
Chemotherapy	27 (22)	14 (52)	13 (48)	
Chemotherapy/Radiation	19 (16)	11 (58)	8 (42)	
Unknown	7 (6)	1 (14)	6 (86)	
Recurrence, n (%)				
No	102 (83)	55 (54)	47 (46)	0.085
Yes	20 (17)	6 (30)	14 (70)	
Site of recurrence, N=20				
Vagina	5 (5)	1 (20)	4 (80)	0.193
Pelvis	4 (4)	2 (50)	2 (50)	1.000
Distant	11 (10)	3 (27)	8 (73)	0.121
Time to recurrence (months), median *	22.0	19.1	22.5	0.626
Recurrence-free survival (months), median *	30.0	32.1	23.5	0.046
Overall survival (months), median *	32.8	33.9	29.4	0.587

[†]n represents number of patients who experienced a complication. Subcategories of specific complications are not mutually exclusive, as patients may have had more than one complication.

* P-value from Wilcoxon rank sum test of difference in medians.

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