The Oncologist®

Symptom Management and Supportive Care

Sarcopenia Is Associated with Quality of Life and Depression in Patients with Advanced Cancer

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Key Words. Sarcopenia • Depression • Quality of life • Advanced cancer • Palliative care

Abstract

Background. Patients with advanced cancer often experience muscle wasting (sarcopenia), yet little is known about the characteristics associated with sarcopenia and the relationship between sarcopenia and patients' quality of life (QOL) and mood.

Materials and Methods. As part of a randomized trial, we assessed baseline QOL (Functional Assessment of Cancer Therapy-General [FACT-G]) and mood (Hospital Anxiety and Depression Scale [HADS]) in patients within 8 weeks of diagnosis of incurable lung or gastrointestinal cancer, and prior to randomization. Using computed tomography scans collected as part of routine clinical care, we assessed sarcopenia at the level of the third lumbar vertebra with validated sex-specific cutoffs. We used logistic regression to explore characteristics associated with presence of sarcopenia. To examine associations between sarcopenia, QOL and mood, we used linear regression, adjusted for patients' age, sex, marital status, education, and cancer type.

Results. Of 237 participants (mean age = 64.41 ± 10.93 years), the majority were male (54.0%) and married (70.5%) and had lung cancer (56.5%). Over half had sarcopenia (55.3%). Older age (odds ratio [OR] = 1.05, $p = .002$) and education beyond high school (OR = 1.95, $p = .047$) were associated with greater likelihood of having sarcopenia, while female sex (OR = 0.25, $p < .001$) and higher body mass index (OR = 0.79, $p < .001$) correlated with lower likelihood of sarcopenia. Sarcopenia was associated with worse QOL (FACT-G: B = −4.26, $p = .048$) and greater depression symptoms (HADS-depression: B = −1.56, $p = .005$).

Conclusion. Sarcopenia was highly prevalent among patients with newly diagnosed, incurable cancer. The associations of sarcopenia with worse QOL and depression symptoms highlight the need to address the issue of sarcopenia early in the course of illness. ***The Oncologist*** 2018;23:97–104

Implications for Practice: This study found that sarcopenia, assessed using computed tomography scans acquired as part of routine clinical care, is highly prevalent in patients with newly diagnosed, incurable cancer. Notably, patients with sarcopenia reported worse quality of life and greater depression symptoms than those without sarcopenia. These findings highlight the importance of addressing muscle loss early in the course of illness among patients with incurable cancer. In the future, investigators should expand upon these findings to develop strategies for assessing and treating sarcopenia while striving to enhance the quality of life and mood outcomes of patients with advanced cancer.

Introduction

Cancer cachexia, a syndrome of weight loss and low muscle mass (sarcopenia), occurs frequently in patients with advanced cancer and can negatively impact their outcomes, including treatment tolerance and survival [1–6]. Causes of cancer cachexia include reduced food intake, diminished physical activity, and abnormal metabolism [7–9]. Data suggest that patients

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with cancer cachexia experience poor treatment tolerance and worse morbidity and mortality compared with patients who maintain their weight and muscle mass [1–6]. In addition, cachexia has been linked to worse physical function and loss of functional independence [6, 10, 11]. Thus, cancer cachexia is a common and detrimental problem for patients with cancer, yet it often goes unaddressed and has been understudied among patients with advanced cancer [12].

Previous studies addressing cancer cachexia have been limited by the lack of a standard definition [13]. Cachexia, sarcopenia, and solitary muscle loss represent different aspects of the muscle wasting spectrum and can have different clinical presentations and prognoses [14, 15]. Simply measuring body weight to quantify cachexia is not adequate, as this fails to account for fluid accumulation, large tumor burden, and the slow rate of visceral organ atrophy present in some patients with cancer [16, 17]. Loss of muscle mass occurs frequently in patients with advanced cancer, though clinicians are often unaware of their patients' muscle mass by assessing body weight alone [6, 18]. Recently, an international consensus panel published a report clarifying the definition and classification of cancer cachexia [15]. This report highlighted the importance of assessing sarcopenia, defined by quantifying muscle mass using routinely collected computed tomography (CT), among patients with cancer. As a result, investigators studying cancer cachexia frequently use patients' CT scans to assess sarcopenia. However, we lack data regarding the relationship between these CT scan measurements of sarcopenia and important patient-reported outcomes, such as quality of life (QOL) and mood among patients with advanced cancer.

Understanding the association between sarcopenia and patients' QOL and mood is particularly important for patients with advanced cancer, as efforts to improve these outcomes are essential components of caring for this population. Notably, patients with advanced cancer are more likely to suffer the consequences of sarcopenia than those with curable disease, as they often experience a high symptom burden, including nausea, poor appetite, and fatigue [19, 20]. Additionally, sarcopenia can negatively affect patients' functional status and independence [6, 10, 11], which may influence both their physical and emotional well-being. Importantly, the manifestations of sarcopenia often appear gradually, as the disease worsens, and clinicians may only discover the profound muscle loss late in the disease trajectory, when efforts to intervene are less likely to provide much benefit. Thus, studies are needed to define the prevalence and understand the impact of sarcopenia earlier in the disease course, at a time when patients may experience the benefits of interventions focused on maintaining and improving their muscle mass.

Using baseline data from a randomized trial, we sought to explore the relationships among sarcopenia (using consensus definitions that recommend assessing muscle mass with CT scans [15]), QOL, and mood in patients with newly diagnosed, incurable cancer. We hypothesized that a substantial proportion of patients would meet criteria for sarcopenia on CT scans, even at an early point in the disease trajectory, and these patients would report worse QOL and mood symptoms compared with those without sarcopenia. By studying the relationship between sarcopenia and patients' QOL and mood, this study will inform future interventions seeking to address sarcopenia earlier in the disease course among patients with newly diagnosed, incurable cancer, ideally to improve their experience with the illness and health outcomes.

Materials and Methods

Study Design

As part of a randomized trial of early palliative care integrated with oncology care versus oncology care alone [21], we approached patients within 8 weeks of diagnosis with incurable cancer. For the current study, we utilized patient-reported data collected at baseline after informed consent, but prior to patient randomization and the start of the intervention. The Dana-Farber/Harvard Cancer Care Institutional Review Board approved the study protocol.

Patient Selection

The study sample was comprised of patients from Massachusetts General Hospital (MGH) Cancer Center with a confirmed diagnosis of incurable lung or noncolorectal gastrointestinal cancer within the previous 8 weeks and no prior therapy for metastatic disease. Other patient eligibility criteria included not receiving treatment with curative intent, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, age $\geq$18 years, plan to receive cancer care at MGH, and the ability to read and respond to questions in English or with minimal assistance from family or an interpreter. We did not enroll patients who were already receiving palliative care services, needed immediate referral for palliative care or hospice, or had significant psychiatric or other comorbid disease that would interfere with informed consent or study participation.

Study Measures

Sociodemographic and Clinical Factors

Participants completed a demographic questionnaire that included race, ethnicity, smoking history, religion, relationship status, education, and income. We reviewed participants' electronic medical records to obtain data on their age, sex, cancer diagnosis, ECOG performance status, and initial cancer treatment.

Quality of Life

We measured participants' QOL using the Functional Assessment of Cancer Therapy-General (FACT-G) [22]. The FACT-G contains 27 items with subscales assessing well-being across four domains (physical, functional, emotional, and social) during the past week. Higher scores indicate better QOL.

Depression and Anxiety

We measured patients' depression and anxiety symptoms using the Hospital Anxiety and Depression Scale (HADS) [23]. The 14-item HADS contains two 7-item subscales assessing depression and anxiety symptoms during the past week. Higher total and subscale scores indicate worse symptoms, and a score greater than 7 denotes clinically significant depression or anxiety.

Sarcopenia Measured on CT Scans

We assessed for the presence of sarcopenia using CT scans collected as part of routine clinical care. We limited our study sample to only those patients with CT scans within 30 days before or after their baseline questionnaires and utilized only the CT scan closest to the date of the baseline questionnaire. We quantified skeletal muscle cross-sectional area (CSA) in cm^2 on a single axial image at the level of the third lumbar (L3)

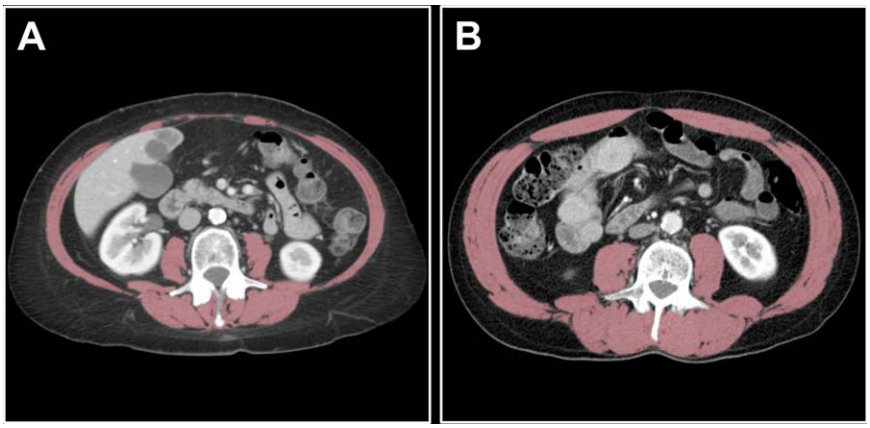

Figure 1. Computed tomography (CT) scans demonstrating patients with high (90th percentile) and low (10th percentile) muscle mass. Axial CT images of the third lumbar vertebra region, with skeletal muscle highlighted in red. **(A)**: Image of a 61-year-old female patient with skeletal muscle index of 34.2 cm^2/m^2. **(B)**: Image of a 53-year-old male patient with skeletal muscle index of 60.4 cm^2/m^2.

vertebral body with semi-automated threshold-based segmentation (OsiriX; Pixmeo, Bernex, Switzerland, http://www.osirix-viewer.com/). We used attenuation thresholds set at −29 and +150 Hounsfield units for skeletal muscle [24]. Figure 1 displays examples of patients with high and low muscle mass using our technique. We computed the lean muscle CSA in cm^2 by summing the given tissue's pixels and multiplying the sum by the absolute unit pixel surface area. A research assistant (G.F.) performed the measurement, and a board-certified radiologist (F.J.F.) with 8 years of experience verified each analysis. To assess inter- and intra-analyst agreement, we randomly selected 40 images and then had these images re-analyzed independently 9 months later by a second research assistant (J.M.) and by the primary analyst. We achieved excellent inter- and intra-analyst agreement with intraclass correlation coefficients of 0.9965 and 0.9996, respectively. We normalized skeletal muscle CSA for stature and reported this skeletal muscle index as cm^2/m^2. For the current study, we defined sarcopenia as an L3 skeletal muscle index of <55 cm^2/m^2 for men and <39 cm^2/m^2 for women, as proposed by the international consensus for cancer cachexia [15].

Statistical Analysis

We used descriptive statistics to analyze the frequencies, medians, means, and standard deviations (SDs) of the study variables for the overall study sample. We compared baseline characteristics of participants with and without sarcopenia using chi-square or Fisher's exact test for the categorical variables and independent-samples Student's *t* tests for the continuous variables. We used logistic regression, adjusted for variables with $p < .25$ on univariate analysis, to explore patient characteristics independently associated with the presence of sarcopenia. To examine the associations between sarcopenia (independent variable of interest) and patients' QOL and mood (dependent variables), we computed linear regression models adjusting for potential confounders, including age, sex, marital status, education, and cancer type [25, 26]. We performed our statistical analyses using SPSS version 17.0 (IBM, Armonk, NY, www.ibm.com).

Results

Participant Sample

From May 2011 to July 2015, we enrolled 350 of 480 (72.9%) eligible patients, and for the current study we included 237 participants who had evaluable baseline CT scans. We compared participant characteristics between those with and without evaluable CT scans and found that these groups only differed across religion and not any other characteristic (supplemental online Table 1). Sample characteristics are presented in Table 1. Participants (mean age, 64.41 ± SD 10.93 years) were primarily white (93.2%), and the majority were male (54.0%) and married (70.5%) and had a lung cancer diagnosis (56.5%).

Sarcopenia

Over half (55.3%) of patients had sarcopenia (supplemental online Fig. 1). Patients with sarcopenia were older (66.66 years vs. 61.63 years, $p < .001$) and more likely to be male (65.6% vs. 39.6%, $p < .001$), of non-Hispanic ethnicity (0.0% vs. 6.6%, $p = .003$), and educated beyond high school (67.9% vs. 50.9%, $p = .011$). Multivariable logistic regression analyses showed that older age (odds ratio [OR] = 1.05, $p = .002$), white race (OR = 5.03, $p = .02$), and education beyond high school (OR = 1.95, $p = .047$) were associated with higher likelihood of sarcopenia, whereas female sex (OR = 0.25, $p < .001$) and higher body mass index (BMI; OR = 0.79, $p < .001$) were associated with lower likelihood of sarcopenia (Table 2).

Associations Between Sarcopenia and Patient-Reported Measures

Using linear regression adjusting for patients' age, sex, marital status, education, and cancer type, we found that sarcopenia was associated with worse QOL (Table 3). Specifically, sarcopenia was associated with lower FACT-G scores (unstandardized coefficient [B] = −4.26, standard error [SE] = 2.15, 95% confidence interval [CI] = −8.49 to −0.03, $p = .048$).

We also found an association between sarcopenia and HADS-depression (Fig. 2). Patients with sarcopenia had higher rates of clinically significant depression symptoms (29.0% vs. 16.0%, $p = .021$). On multivariable linear regression, we found that sarcopenia was associated with higher HADS-depression

Table 1. Baseline characteristics of study participants

Characteristic	Overall ($n = 237$), *n* (%)	Sarcopenic ($n = 131$), *n* (%)	Not Sarcopenic ($n = 106$), *n* (%)	*p* value
Age – mean (SD)	64.41 (10.93)	66.66 (9.52)	61.63 (11.92)	<.001
Sex				
Male	128 (54.0)	86 (65.6)	42 (39.6)	<.001
Female	109 (46.0)	45 (34.4)	64 (60.4)	
Race				
White	221 (93.2)	126 (96.2)	95 (89.6)	.050
African American	6 (2.5)	1 (0.8)	5 (4.7)	
Asian	4 (1.7)	3 (2.3)	1 (0.9)	
American Indian or Alaskan Native	2 (0.8)	1 (0.8)	1 (0.9)	
Other	4 (1.7)	0 (0.0)	4 (3.8)	
Hispanic ethnicity	7 (3.0)	0 (0.0)	7 (6.6)	.003
Cancer type				
Lung	134 (56.5)	72 (55.0)	62 (58.5)	.601
Gastrointestinal	103 (43.5)	59 (45.0)	44 (41.5)	
Smoking history				.658
Never or <10 pack years	88 (37.1)	46 (35.1)	42 (39.6)	
Greater than or equal to 10 pack years	135 (57.0)	76 (58.0)	59 (55.7)	
Unknown	14 (5.9)	9 (6.9)	5 (4.7)	
Charlson Comorbidity Index - mean (SD)	6.87 (1.35)	6.84 (1.27)	6.91 (1.44)	.712
BMI (date of consent) – mean (SD)	27.64 (6.03)	25.13 (4.50)	30.74 (6.30)	<.001
ECOG				
0	66 (27.8)	34 (26.0)	32 (30.2)	.644
1	152 (64.1)	85 (64.9)	67 (63.2)	
2	19 (8.0)	12 (9.2)	7 (6.6)	
Initial treatment[a]				
Chemotherapy	187 (78.9)	101 (77.1)	86 (81.1)	.862
Radiation	46 (19.4)	28 (21.4)	18 (17.0)	
Chemotherapy and radiation	2 (0.8)	1 (0.8)	1 (0.9)	
No treatment	2 (0.8)	1 (0.8)	1 (0.9)	
Religion				
Catholic	150 (63.3)	85 (65.4)	65 (61.3)	.525
Protestant	37 (15.6)	20 (15.4)	17 (16.0)	
Jewish	12 (5.1)	8 (6.2)	4 (3.8)	
Muslim	1 (0.4)	0 (0.0)	1 (0.9)	
None	22 (9.3)	12 (9.2)	10 (9.4)	
Other	14 (5.9)	5 (3.8)	9 (8.5)	
Unknown	1 (0.4)			
Relationship status				.055[b]
Married	167 (70.5)	99 (75.6)	68 (64.2)	
Single	26 (11.0)	13 (9.9)	13 (12.3)	
Divorced	22 (9.3)	10 (7.6)	12 (11.3)	
Widowed	22 (9.3)	9 (6.9)	13 (12.3)	
Education				
High school or less	94 (39.7)	42 (32.1)	52 (49.1)	.011
Beyond high school	143 (60.3)	89 (67.9)	54 (50.9)	
Income				
$50,000 or less	93 (39.2)	47 (38.5)	46 (45.1)	.343
More than $50,000	131 (55.3)	75 (61.5)	56 (54.9)	
Unknown	13 (5.5)			

[a]One person who received transarterial chemoembolization (TACE) as their initial cancer therapy is included within the radiation category.
[b]*p*-value for married versus not married.
Abbreviations: BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; SD, standard deviation.

Table 2. Associations between patient characteristics and sarcopenia

	Multivariable associations with sarcopenia[a]		
Variables	**OR (SE)**	**95% CI**	***p* value**
Age	1.053 (0.016)	1.020 to 1.087	.002
Female sex	0.249 (0.360)	0.123 to 0.504	<.001
White race	5.034 (0.695)	1.290 to 19.648	.020
BMI	0.793 (0.037)	0.738 to 0.853	<.001
Married	1.116 (0.380)	0.529 to 2.352	.774
Education beyond high school	1.954 (0.338)	1.007 to 3.790	.047

[a]Included variables with $p < .25$ on univariate analysis.
Abbreviations: BMI, body mass index; CI, confidence interval; OR, odds ratio; SE, standard error.

Table 3. Associations between sarcopenia and patient-reported outcomes

	Multivariable associations between sarcopenia and patient-reported outcomes[a]		
Patient-reported outcomes	**B (SE)**	**95% CI**	***p* value**
Sarcopenia associated with FACT-G	−4.261 (2.147)	−8.492 to −0.031	.048
Sarcopenia associated with HADS-Depression	1.558 (0.553)	0.468 to 2.647	.005
Sarcopenia associated with HADS-Anxiety	−0.039 (0.549)	−1.120 to 1.042	.943

[a]Adjusted for age, sex, marital status, education, and cancer type.
Abbreviations: B, unstandardized coefficient; CI, confidence interval; FACT-G, Functional Assessment of Cancer Therapy-General; HADS, Hospital Anxiety and Depression Scale; SE, standard error.

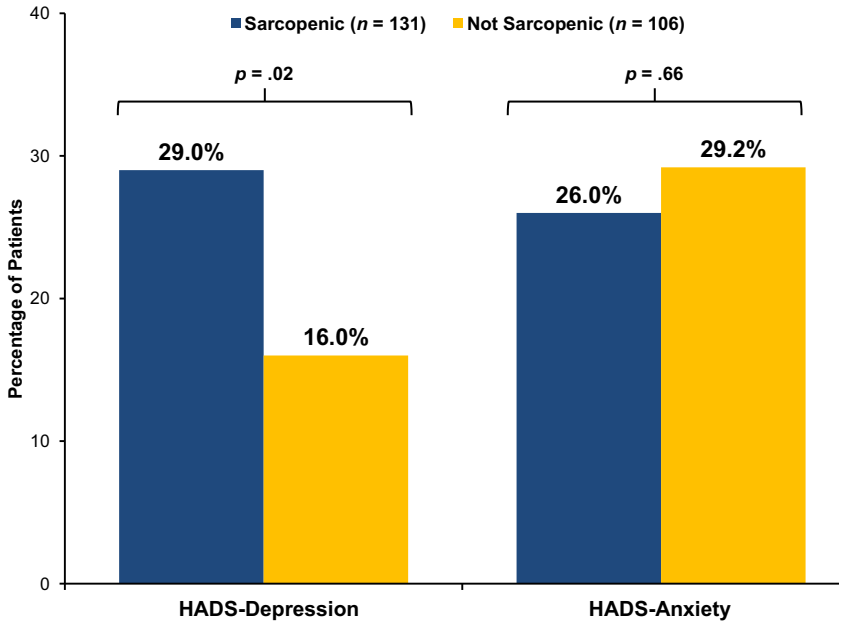

Figure 2. Depression and anxiety among sarcopenic and nonsarcopenic patients.
Abbreviations: HADS, Hospital Anxiety and Depression Scale.

scores (B = 1.56, SE = 0.55, 95% CI = 0.47 to 2.65, $p = .005$). We did not find a significant association between sarcopenia and HADS-anxiety (B = −0.04, SE = 0.55, 95% CI = −1.12 to 1.04, $p = .943$).

Discussion

In this exploratory analysis of patients with newly diagnosed, incurable lung and gastrointestinal cancer, we found that sarcopenia was associated with worse QOL and greater depression symptoms. Notably, patients in our sample were newly diagnosed, yet over half met criteria for sarcopenia on CT images acquired for routine clinical care. We also demonstrated a statistically significant relationship between the presence of sarcopenia and certain patient characteristics, such as age and sex. The remarkably high rates of sarcopenia in our sample, coupled with the negative impact of low muscle mass on patient outcomes in this population, underscore the critical need to address this issue early in the disease course for patients with advanced cancer.

Our work highlights the considerably high prevalence of sarcopenia among patients with newly diagnosed, incurable

cancer. Over half of patients met criteria for sarcopenia, which is higher than a prior study involving patients with lung and gastrointestinal cancer, and may be related to the fact that our study involved patients with advanced cancer, whereas the prior study included patients of all stages [27]. A more comprehensive understanding of the frequency and impact of sarcopenia in this population can be instrumental in (a) identifying patients at risk for experiencing sarcopenia, (b) understanding how sarcopenia can influence patient outcomes, and (c) providing additional services to meet the supportive care needs of these patients. Additionally, by demonstrating the negative association between sarcopenia and patients' QOL and mood soon after their cancer diagnosis, our work provides compelling evidence supporting the need for interventions, such as consultation with nutrition specialists or recommendations for exercise, to address sarcopenia and target patients earlier in their cancer course [28–31]. Thus, our study successfully identifies the highly prevalent and problematic issue of sarcopenia in patients with newly diagnosed, incurable cancer, which can enable us to better support this population, improve the quality of their care, and enhance patient outcomes.

To our knowledge, this is the first study to report that sarcopenia, assessed using CT scans collected as part of routine care, is associated with both QOL and depression symptoms in patients with newly diagnosed, incurable cancer. Researchers have postulated that the physical decline associated with sarcopenia reduces patients' functional ability, which can adversely impact the QOL of patients with cancer [32, 33]. Similarly, the relationship between depressive symptoms and patients' lack of appetite and diminished physical activity may provide a mechanism linking sarcopenia and depression among patients with cancer [33–36]. Importantly, our findings will inform future efforts to address sarcopenia earlier in the cancer trajectory in order to improve outcomes for this highly symptomatic population [19, 37–39]. By evaluating patients with advanced cancer for the presence of sarcopenia at the time of diagnosis using routinely performed CT scans, we can identify those at higher risk for poor physical and emotional well-being and begin to implement strategies to better meet the needs of these individuals.

Notably, we identified patient characteristics associated with the presence of sarcopenia. We found that older patients were more likely to meet criteria for sarcopenia, a finding that aligns with the geriatric literature [6, 40, 41]. Research suggests that older patients frequently experience diminished skeletal muscle mass and changes in muscle quality, thought to be related to neurologic, metabolic, hormonal, nutritional, and physical-activity-related factors [41–43]. In turn, these changes in muscle mass and function can lead to disability, diminished mobility, functional dependence, and falls [11, 44, 45]. Clinically, our findings support the need for oncologists to screen for sarcopenia in older adults with advanced cancer and address their nutritional and functional status early in the course of their care. We also found that female patients were less likely to have sarcopenia than males, consistent with previous work [6, 46, 47]. A potential explanation is that the pattern of muscle loss may differ between male and female patients, as research has previously demonstrated [48–50]. Moreover, another explanation may relate to the different sex-specific cutoffs used to quantify sarcopenia, which although consistent with consensus guidelines, may differ in certain populations. In addition, we found that education beyond high school was associated with higher likelihood of sarcopenia. This finding is hypothesis-generating, and additional research should seek to confirm and expand upon this result. Collectively, our findings help identify individuals at higher risk for having sarcopenia soon after the diagnosis of advanced cancer and should help inform future efforts to target these patients with interventions tailored to their needs.

Several limitations of our study warrant consideration. First, we performed this study at a single academic cancer center in a patient sample with limited racial and ethnic diversity. Thus, our findings may not generalize to other, more heterogeneous populations, and additional research should seek to confirm our results in more diverse populations. Second, this study included patients who had enrolled in a randomized trial of early palliative care, and these patients may differ from those who choose not to participate in clinical trials. Also, by excluding patients already receiving palliative care services and those who needed immediate referral for palliative care or hospice, we may be underestimating the prevalence of sarcopenia, as these excluded patients may have had more advanced sarcopenia than those enrolled. Third, we did not collect information about whether patients utilized other services, such as physical and occupational therapy or dietary and nutrition services, which may affect patients' ability to maintain muscle mass [30, 51–53]. Notably, participants are unlikely to have extensively received these services, as we conducted the study early in patients' disease course. In addition, we lack information regarding weight loss for the participants in this study, and therefore cannot comment on how weight change influences sarcopenia and patient-reported outcomes. Furthermore, although prior research has shown differential effects of sarcopenia on patient outcomes depending on patient BMI, we do not have the sample size for BMI-specific subgroup analyses [6, 27]. Finally, the cross-sectional nature of our study allows us only to report associations between sarcopenia and patients' QOL and mood, and thus we cannot state the directionality of the relationships. In addition, without longitudinal data, our study does not provide information about how changes in muscle mass throughout the cancer trajectory may further influence patients' QOL and mood.

Conclusion

In summary, we demonstrated that patients with newly diagnosed, incurable cancer experience high rates of sarcopenia assessed using CT scans performed as part of routine clinical care. It is noteworthy that patients with sarcopenia report worse QOL and greater depression symptoms, as this highlights an important need for interventions to address muscle loss early in the course of illness among patients with incurable cancer. Future research should focus on determining the optimal timing and modality of efforts to assess and treat sarcopenia while working to improve the QOL and mood outcomes of patients with advanced cancer.

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Disclosures

The authors indicated no financial relationships.

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See http://www.TheOncologist.com for supplemental material available online.

For Further Reading:

Hánah N. Rier, Agnes Jager, Stefan Sleijfer et al. The Prevalence and Prognostic Value of Low Muscle Mass in Cancer Patients: A Review of the Literature. ***The Oncologist*** 2016;21:1396–1409.

Implications for Practice:

An increasing number of studies underline the clinical value of low muscle mass as a prognostic factor for adverse outcomes in cancer patients. However, studies show large heterogeneity because of the lack of a standardized approach to measure muscle mass and the lack of reference populations. As a result, the interpretation of data and further progress are severely hampered, hindering the implementation of muscle measurement in oncological care. This review summarizes the methods of diagnosing low muscle mass in cancer patients, the difference between underlying syndromes such as sarcopenia and cachexia, and the association with clinical outcomes described so far.