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ORIGINAL REPORT

Cancer Cachexia in the Age of Obesity: Skeletal Muscle Depletion Is a Powerful Prognostic Factor, Independent of Body Mass Index

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ABSTRACT

Purpose
Emerging evidence suggests muscle depletion predicts survival of patients with cancer.

Patients and Methods
At a cancer center in Alberta, Canada, consecutive patients with cancer (lung or GI; N = 1,473) were assessed at presentation for weight loss history, lumbar skeletal muscle index, and mean muscle attenuation (Hounsfield units) by computed tomography (CT). Univariate and multivariate analyses were conducted. Concordance (c) statistics were used to test predictive accuracy of survival models.

Results
Body mass index (BMI) distribution was 17% obese, 35% overweight, 36% normal weight, and 12% underweight. Patients in all BMI categories varied widely in weight loss, muscle index, and muscle attenuation. Thresholds defining associations between these three variables and survival were determined using optimal stratification. High weight loss, low muscle index, and low muscle attenuation were independently prognostic of survival. A survival model containing conventional covariates (cancer diagnosis, stage, age, performance status) gave a c statistic of 0.73 (95% CI, 0.67 to 0.79), whereas a model ignoring conventional variables and including only BMI, weight loss, muscle index, and muscle attenuation gave a c statistic of 0.92 (95% CI, 0.88 to 0.95; $P < .001$). Patients who possessed all three of these poor prognostic variables survived 8.4 months (95% CI, 6.5 to 10.3), regardless of whether they presented as obese, overweight, normal weight, or underweight, in contrast to patients who had none of these features, who survived 28.4 months (95% CI, 24.2 to 32.6; $P < .001$).

Conclusion
CT images reveal otherwise occult muscle depletion. Patients with cancer who are cachexic by the conventional criterion (involuntary weight loss) and by two additional criteria (muscle depletion and low muscle attenuation) share a poor prognosis, regardless of overall body weight.

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INTRODUCTION

Involuntary weight loss has long been recognized as a hallmark of malignancy, and its culmination in emaciation still bears the ancient Greek name, cachexia. Unintentional weight loss > 5% was shown 30 years ago to predict reduced survival and increased treatment toxicity in multiple cancers,[1] and it continues to define grade 1 weight loss in the Common Criteria of Adverse Events.[2] Demographics of body weight have changed considerably since this benchmark was established. Overweight and obesity are now prevalent in Westernized countries,[3,4] and the marked shift in body weight renders the definition of clinically significant weight loss in patients with cancer increasingly unclear. There are inconsistencies as to what oncologists consider clinically important weight loss (varying from 5% to > 20%).[5,6] Levels of body mass index (BMI) associated with lower survival are also highly variable (across race/ethnicity, age, disease condition), as cited by various authorities and authors (ranges, < 18.5, < 20, and < 22 kg/m^2).[7,8]

Recent findings add new complexities to our ability to interpret human body weight. Obesity seems to confer a survival advantage in patients with diseases associated with wasting, including cancer, rather than a disadvantage, as understood from studies of all-cause mortality.[9] Also, body weight and weight loss vary considerably in their composition. Simultaneous loss of skeletal muscle and gain of adipose tissue can occur, culminating in the condition of sarcopenic obesity[10]; we recently found that sarcopenia (severe muscle depletion)

was independently prognostic of lower survival in obese patients with cancer in a model including conventional covariates.[11] Disparate behavior of skeletal muscle and adipose tissue has been acknowledged by an international consensus of experts on cancer cachexia, newly redefined as being characterized by loss of skeletal muscle, with or without loss of fat mass.[12] Muscle depletion is characterized by both a reduction in muscle size and increased proportion of inter- and intramuscular fat[13]; fat infiltration may be a further manifestation of the wasting process.

Bearing in mind these inconsistencies and evolving concepts, weight loss and body composition in underweight, normal weight, overweight, and obese patients with cancer seem due for a contemporary re-evaluation. We undertook to define the prognostic significance of weight loss and two aspects of muscle (lumbar skeletal muscle index [SMI] and muscle attenuation [MA]) determined by computed tomography (CT) imaging in a population-based cohort of patients with solid tumors.

PATIENTS AND METHODS

Population Cohort and Data Acquisition

This study was approved by the institutional research ethics board as a minimal-risk study (medical record review of standard clinical assessments). Some details of the study cohort have been described elsewhere.[11] Data were collected from January 2004 to January 2007 on adult patients with a diagnosis of GI or respiratory tract cancer referred to outpatient medical oncology clinics at the Cross Cancer Institute, a tertiary cancer treatment center serving northern Alberta (population approximately 1.8 million; Fig 1). Patients were assessed at their initial visit to medical oncology before receiving any cancer treatment; all data were collected at this time point. The cohort was observed prospectively thereafter.

Age, sex, dates of birth and death, cancer diagnosis, and cancer stage were obtained from the Alberta Cancer Registry, certified by the North American Association for Central Cancer Registries. Cancer stage was based on the American Joint Committee on Cancer (version 01.04.00) stage groupings I, II, III, and IV.

Anthropometric Measures

Height and weight histories over the 6 months preceding referral to our cancer center and performance status (PS) were collected using the patient-generated Subjective Global Assessment (PG-SGA), completed by patients at their initial visit to medical oncology (ie, before initiation of treatment). The PG-SGA includes a lay-language version of the Eastern Cooperative Oncology Group PS. The PG-SGA is accepted by the Oncology Nutrition Dietetic Practice Group of the Academy of Nutrition and Dietetics as the standard for nutrition assessment in patients with cancer.[14] Patient-reported variables have been validated.[15-17] BMI categories typically applied to older adults were selected a priori: $<$ 20.0, underweight; 20.0 to 24.9, normal weight; 25.0 to 29.9, overweight; and $\geq$ 30.0 kg/m^2, obese.

CT Image Analysis

CT scans completed with a spiral CT scanner for initial cancer staging and routine diagnostic purposes were used to quantify skeletal muscle area and attenuation.[11,18] Cross-sectional imaging using CT or magnetic resonance imaging is suggested as the preferred method for analyzing muscle mass in patients with cancer.[12] CT scans completed within 30 days of patients' initial visits were deemed to accurately represent muscle status at presentation. Two adjacent axial images within the same series, at the third lumbar vertebra, were selected for analysis of total muscle cross-sectional area (cm^2) and averaged for each patient.[11,18-20] CT image parameters included: contrast enhanced or unenhanced, 5-mm slice thickness, 120 kVp, and approximately 290 mA. Individuals (L.M., L.B., R.M.) were trained to correctly identify and quantify lumbar vertebrae and the following muscles: rectus abdominus, abdominal (lateral and oblique), psoas, and paraspinal (quadratus lumborum, erector spinae). An intraobserver coefficient of variation of 1.3% was required, which is consistent with other reports in the literature.[11,18,21] Observers were blinded to patients' survival status. Muscles were quantified within a Hounsfield unit (HU) range of -29 to 150 HU[19] using Slice-O-Matic software (v.4.3; Tomovision, Montreal, Quebec, Canada). Muscle area was normalized for height in meters squared (m^2) and reported as lumbar SMI (cm^2/m^2).[11,18] Mean MA (HU) is reported for the entire muscle area at the third lumbar vertebra.

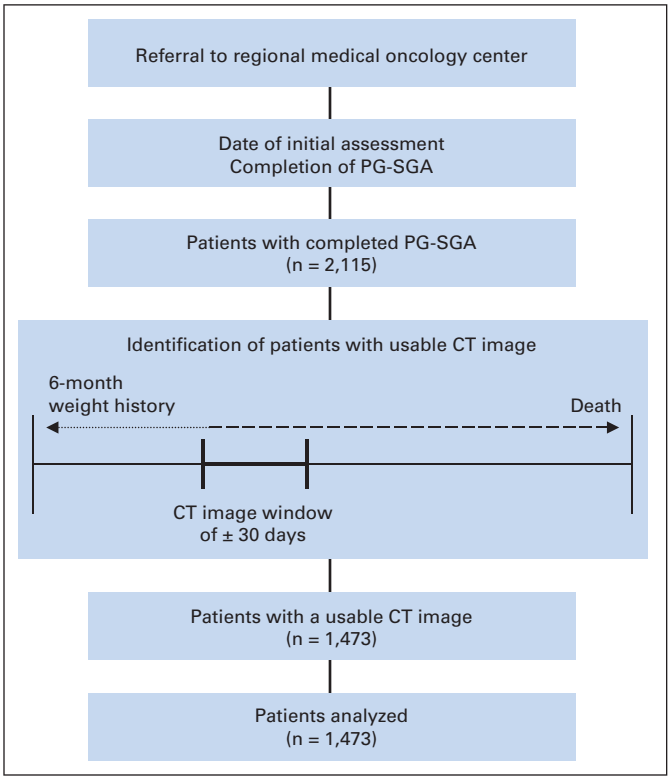

Fig 1. Patient flow diagram showing study timeline and patient selection. A total of 642 patients were excluded. A majority (64%) of patients' scans were excluded for technical reasons: 31% had computed tomography (CT) $>$ 30 days from initial assessment, 20% did not have lumbar region included in scan, and 13% had a portion of the analyzable area cut off from field of view. Thirty-six percent did not have a CT scan. PG-SGA, patient-generated Subjective Global Assessment.

Statistics

Differences between groups were analyzed using independent *t* (continuous variables) and Pearson's χ^2 tests (categorical variables) where appropriate. Correlations between continuous variables were assessed using Pearson correlation coefficients. The primary outcome was overall survival, defined as the number of days surviving after the

Table 1. Patient Clinical Characteristics by Sex at Initial Assessment

Characteristic	Men (n = 828)		Women (n = 645)		*P*
	No.	%	No.	%	
Age, years					.932
Mean		64.7		64.8	
SD		11.2		11.5	
Cancer site					.015
Colon/rectum	459	55	314	48	
Respiratory tract	229	28	211	12	
Pancreas	71	9	75	33	
Esophageal	17	2	7	1	
Stomach	33	4	18	3	
Other GI*	19	2	20	3	
Cancer stage					.258
I	35	4	35	5	
II	143	17	91	14	
III	233	28	176	27	
IV	417	50	343	53	
ECOG PS					.341
0	171	21	128	20	
1	399	48	289	45	
2	129	16	115	18	
3	121	15	101	16	
4	8	1	12	2	
Height, cm					< .001
Mean		175.5		161.1	
SD		6.9		6.9	
Weight, kg					< .001
Mean		80.1		65.3	
SD		16.2		15.7	
BMI, kg/m^2†					.003
Mean		26.0		25.1	
SD		4.9		5.8	
BMI category, kg/m^2†					< .001
< 20.0	67	8	114	18	
20.0 to 24.9	300	36	236	37	
25.0 to 29.9	328	40	183	28	
≥ 30.0	133	16	112	17	
Weight loss‡					.328
Mean		−7.5		−7.1	
SD		7.7		7.8	
CT image analysis					
Lumbar total muscle cross-sectional area, cm^2					< .001
Mean		158.3		107.1	
SD		28.0		18.3	
Skeletal muscle index, cm^2/m^2§					< .001
Mean		51.5		41.3	
SD		8.9		7.0	
Muscle attenuation, HU					.040
Mean		35.5		34.5	
SD		8.6		10.2	

NOTE. All measures were collected at time of initial patient assessment. CT scans for image analysis were collected within 30 days of initial assessment and are representative of patients' baseline condition.

Abbreviations: BMI, body mass index; CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; HU, Hounsfield unit; SD, standard deviation.

*Other GI cancers: digestive tract and accessory organs.

†BMI calculated as patient weight (kg)/height (m)^2.

‡Weight loss in 6 months before initial assessment calculated with the following formula: [(current weight [kg] − weight 6 months ago [kg]) / weight 6 months ago (kg)] × 100%; negative values indicate weight loss.

§Skeletal muscle index calculated as lumbar total muscle cross-sectional area (cm^2)/height (m)^2.

initial visit by each patient. Patients were observed until their deaths or until August 26, 2010, at which time they were censored at the last date they were documented to have been alive.

Optimal stratification,[22] a statistical method similar to receiver operator curve analysis, was used to solve specific threshold values within three continuous covariates. Optimal stratification is based on log-rank statistics that best separate patients with respect to time to an event outcome (death). It is appropriate to determine survival-related threshold values empirically using statistical methods such as optimal stratification, where the relationship with survival for that covariate is not known (ie, MA). For some covariates, there may be published thresholds, but these may be values that were solved in dissimilar patient populations and/or in relation to outcomes other than survival. In our study, we defined threshold values related to overall survival for three continuous variables (percent weight loss, SMI, and MA); thresholds for these three variables were examined by sex and BMI. Throughout the text, we refer to weight loss, SMI, and MA as body composition variables.

The Kaplan-Meier method was used to establish effects of each variable on survival; log-rank tests were used to compare survival curves. Univariate and multivariate analyses for overall survival were conducted using the Cox proportional hazards model; hazard ratios (HRs) and corresponding 95% CIs were obtained. Analysis completed using SPSS version 18.0 (SPSS, Chicago, IL).

Concordance (c) statistics were used to assess the discrimination of a model to predict overall survival.[23] A c statistic of 0.5 indicates the model predicts the outcome as well as chance (ie, equal numbers of true and false positives), 0.7 to < 0.8 indicates acceptable discrimination, 0.8 to < 0.9 indicates excellent discrimination, 0.9 to 0.99 is outstanding discrimination, and 1.0 is perfect prediction.[24] The c statistic is applicable to all regression models, including survival models.[25] Overall c statistics and 95% CIs were estimated using a macro in SAS (version 9.1.3; SAS Institute, Cary, NC). Results were considered significant at the $P < .05$ level.

RESULTS

Population Cohort

Of 2,115 consecutive patients, 642 were excluded because they lacked a CT image that could be evaluated, as explained in Figure 1. Baseline data are presented for 1,473 included patients (Table 1). There were 966 deaths; median overall survival was 16.7 months (95% CI, 15.2 to 18.2); median follow-up for patients alive at censoring was 21.2 months (95% CI, 17.4 to 24.9).

Patients exhibited wide variation in body composition (Table 1). More than half of patients (52%) presented as overweight or obese. More men were overweight than women, and more women were underweight. Overall, the population was losing weight; weight loss occurred in all BMI categories. Wide variation in SMI and MA was recorded in men and women. SMI was significantly correlated to BMI in men ($r = 0.6$; $P < .001$) and women ($r = 0.6$; $P < .001$; Fig 2A). Figure $2B_{1\text{-}3}$ illustrates BMI variation for three women with an identical amount of skeletal muscle; notably, the morbidly obese (B_1) and overweight (B_2) women depicted have no more muscle than the completely cachexic woman (B_3), whose BMI was 15.0 kg/m^2. Figure $2B_{4\text{-}6}$ highlights skeletal muscle variation for three women with identical BMI (29.4 kg/m^2); these three women varied $>$ two-fold in their SMI. Low MA occurred in patients across all BMI categories, and this feature correlated weakly but significantly with BMI ($r = -0.4$; $P < .001$). Variation in MA across individuals with the same SMI and BMI is shown in Figure 2C. In this illustration, areas of low attenuation, spanning from -29 to 29 HU, appear in light gray.

Optimal Stratification

Threshold values associated with lower survival are listed in Table 2. Weight loss $> 8\%$ was associated with lower survival, independent of sex or BMI; 44% of patients presented with $> 8\%$ weight loss. SMI varied between men and women, as expected.[11,18] Threshold values demarcating significantly lower survival were defined as sarcopenia; we use this term hereafter. Using these thresholds, the prevalence of sarcopenia was 53% in women versus 31% in men ($P < .001$). MA varied with BMI, not with sex. The overall prevalence of MA below threshold values demarcating significantly reduced survival was 49%.

Survival

Variables examined by univariate analysis (Table 3) were: age (> 65 *v* < 65 years), sex, PS (1, 2, 3, or 4 *v* 0), cancer diagnosis (pancreatic, esophageal, stomach, respiratory tract, other GI *v* colorectal), cancer stage (II, III, or IV *v* I), BMI (25.0 to 29.9, 20.0 to 24.9, or < 20.0 *v* ≥ 30.0 kg/m^2), and threshold values (defined in Table 2) for weight loss, SMI, and MA.

Two multivariate analyses were conducted, and the c statistics of these models were compared (Table 3). Variables significant at the univariate level were entered into the multivariate models. A conventional multivariate model (model one) containing cancer diagnosis, stage, sex, age, and PS revealed expected values, with strong contributions of PS, cancer diagnosis, and stage. The c statistic for the conventional multivariate model was 0.73 (95% CI, 0.67 to 0.79; $P < .001$). Prior work established the independent prognostic value of BMI, weight loss,[1,9,12] and sarcopenia,[11] and model two was designed to test the prognostic value of these variables. In contrast to model one, the model including only four body composition variables gave a c statistic of 0.92 (95% CI, 0.88 to 0.95; $P < .001$), indicating excellent discrimination of overall survival.

The survival discrimination conferred by BMI, weight loss, sarcopenia, and low MA is summarized in Table 4. Overall survival was examined for the presence of zero, one or two, or all three prognostic body composition variables by BMI categories and by cancer site for overweight/obese patients. Overall, BMI was predictive of survival, with the heaviest patients showing the longest survival. Weight loss, sarcopenia, and low MA discriminated obese patients into disparate survival groups; obese patients with none of these variables had the longest survival (35.6 months; twice the overall median survival of 16.7 months) in contrast to obese patients with three poor prognostic variables, who survived only 8.5 months. Similar discrimination of survival was observed in overweight and obese patients (survival curves are presented in Appendix Fig A1, online only). For patients with BMI < 20.0 kg/m^2, there was less discrimination; survival was short regardless of the number of prognostic body composition features. The majority of these patients (92%) had weight loss, sarcopenia, and/or low MA. Even so, patients with BMI < 20.0 kg/m^2 and all three poor prognostic variables had lower survival ($P < .03$) than patients with none of them. Survival discrimination by three prognostic body composition variables was particularly strong in overweight/obese patients overall; this was true for the overweight/obese patients in the individual tumor groups of our sample (Table 4). Patients with

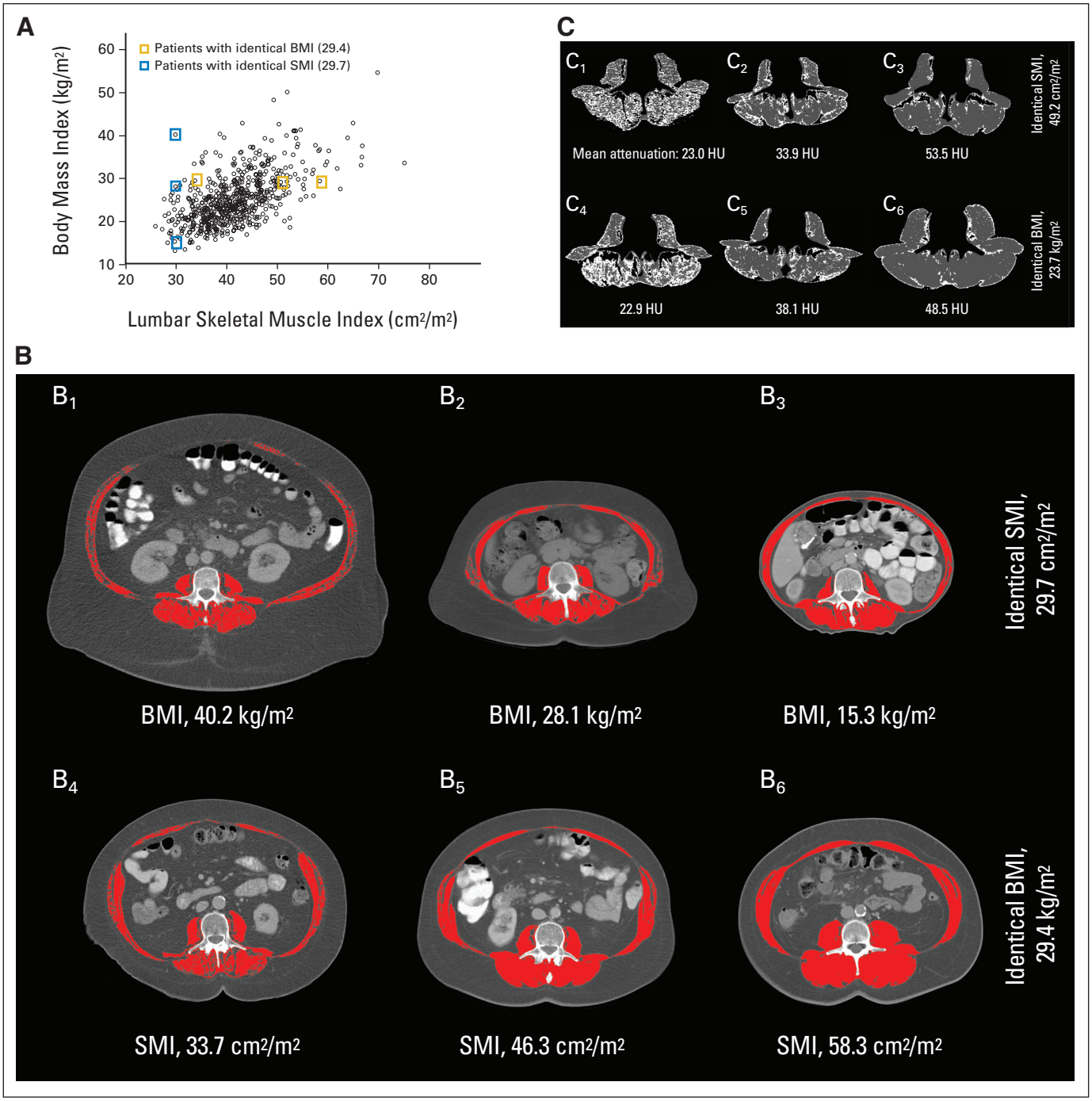

Fig 2. (A) Scatter plot highlights the relationship and variation between skeletal muscle index (SMI) and body mass index (BMI) for the female patient population (n = 645; Pearson $r = 0.6$; $P < .001$). Blue boxes highlight patients with identical SMI; gold boxes highlight patients with identical BMI. (B) Axial computed tomography (CT) images of the third lumbar vertebra region with skeletal muscle highlighted in red (−29 to 150 Hounsfield units [HU]). Panels B_{1-3} highlight variation in BMI for female patients with identical SMIs (29.7 cm^2/m^2) and different BMIs (points corresponding to these images are indicated in panel A with blue boxes). Panels B_{4-6} highlight variation in SMI for overweight female patients with identical BMIs (29.4 kg/m^2) and different SMIs (points corresponding to these images are indicated in panel A with gold boxes). (C) Axial CT image for muscle attenuation (MA) of paraspinal muscles only; light gray indicates MA from −29 to 29 HU; dark gray indicates MA from 30 to 150 HU. Panels C_{1-3} highlight variation in MA for three sarcopenic male patients with identical SMIs (49.2 cm^2/m^2). Panels C_{4-6} highlight variation in MA for three male patients with identical BMIs (23.7 kg/m^2).

colorectal cancer had a longer overall survival compared with poorer-prognosis diseases (ie, lung cancer; Table 4); however, the three prognostic variables resulted in similar discrimination of survival. The c statistics were 0.91 (95% CI, 0.84 to 0.96)) for colorectal and 0.93 (95% CI, 0.86 to 0.97) for lung cancers.

Perhaps the most striking feature of this analysis was the uniformly short survival among patients exhibiting all three pre-existing conditions: weight loss, sarcopenia, and low MA (fifth column in Table 4). Independent of their BMI, these patients survived 8.4 months (95% CI, 6.5 to 10.3) compared with patients with none of

Table 2. Threshold Values* Significantly Associated With Low Survival

BMI Category (kg/m^2)	SMI (cm^2/m^2)†		Skeletal MA (HU)‡		Weight Loss (%)§	
	Men	Women	Men	Women	Men	Women
Underweight (< 20.0)	< 43	< 41	< 41	< 41	≥ 8	≥ 8
Normal weight (20.0 to 24.9)	< 43	< 41	< 41	< 41	≥ 8	≥ 8
Overweight (25.0 to 29.9)	< 53	< 41	< 33	< 33	≥ 8	≥ 8
Obese (≥ 30.0)	< 53	< 41	< 33	< 33	≥ 8	≥ 8

Abbreviations: BMI, body mass index; HU, Hounsfield unit; MA, muscle attenuation; SMI, skeletal muscle index.
*Threshold values defined using optimal stratification based on log-rank statistics to best separate patients with respect to time to death.
†Sarcopenia defined as SMI below these threshold values.
‡Low MA defined as skeletal MA below these threshold values.
§Period of weight loss was 6 months preceding patient's initial medical assessment at our cancer center.

these features, who survived 28.4 months (95% CI, 24.2 to 32.6; $P <$ .001). Survival of patients with weight loss, sarcopenia, and low MA was all but indistinguishable from the survival of patients who would be considered frankly cachexic by most people (underweight, with severe muscle depletion; 8.3 months; 95% CI, 5.6 to 10.9).

DISCUSSION

This exercise in prognostication was based on information typically found in the clinical record of patients with cancer: BMI, weight loss, and diagnostic images. The information content of clinical diagnostic images is often not exploited beyond assessment of tumor location, size, and response; here, we used these to derive information of potential clinical relevance. This population showed considerable variation in body weight, weight loss, and both the amount and radiation attenuation of skeletal muscle at the time of presentation, and these features predicted survival. Specifically, the following four factors were identified: BMI ≥ 25.0 kg/m^2 (overweight/obese), in both sexes, for increased survival; weight loss > 8%, in both sexes, for lower survival; sarcopenia, defined by sex- and BMI-specific threshold values, for lower survival; and low muscle attenuation, defined by BMI-specific threshold values, for lower survival.

The most common current definition of sarcopenia is appendicular SMI > two standard deviations below that typical of healthy adults (men, 7.26 kg/m^2; women, 5.45 kg/m^2). We did not use dual-energy x-ray absorptiometry and, consequently, did not report using these units of measure. The sex-specific cutoffs for lumbar SMI associated with mortality in this study are similar to values we previously reported for obese patients with cancer (men, 52.4 cm^2/m^2; women, 38.5 cm^2/m^2). We additionally demonstrate cutoffs specific to nonobese men and women.

In accordance with a conventional view of cancer cachexia, patients who appear thin or wasted frequently have a history of weight loss, depleted skeletal muscle mass, and a poor prognosis. Such conventionally cachexic patients with cancer were evident, if relatively rarely, in this population. Patients in our cohort were more commonly overweight or obese, but they often harbored occult, severe pre-existing muscle depletion. Diagnostic imaging provides additional important insight, especially for patients who are not thin or wasted in appearance and who may be normal weight, overweight, or obese. We feel this is of increasing importance as the world prevalence of overweight/obesity continues to climb; these patients have a survival no longer than patients who are frankly cachectic if they have simultaneous weight loss, sarcopenia, and low MA. The prognostic value of the latter three variables is striking, generating by themselves a c statistic of 0.92, for excellent discrimination of overall survival. Survival differences predicted by these variables, particularly in patients with heavier body weights, are also striking; this distinction was greatest in overweight/obese patients with three prognostic variables, and this was true for the overall sample and its specific tumor groups (Table 4). C statistics are valuable tools to evaluate the performance of survival models. The discrimination provided by the model based on weight loss, sarcopenia, and MA compares favorably with the conventional model and with c statistics of other cancer survival models reported in the literature (0.6 to 0.8).[17,26,27] A limitation to using the c statistic, and a factor that may explain the c statistics achieved here, is that a subset of patients included in this study with poor prognosis may have been discriminated by the features we measured.

The exact basis of these survival differences remains unknown. Some authors have suggested the survival advantage conferred by obesity relates to the relatively large energy store in a context where energy balance is likely to be negative, and the stores are drawn on.[9] Associations between weight loss and toxicity of chemotherapy have been known for a long time.[1] Sarcopenia was recently described to be associated with major chemotherapy toxicities resulting in dose reduction, dose delay, or definitive termination of therapy. This was true in patients treated with fluoropyrimidines, anthracyclines, and tyrosine kinase inhibitors, suggesting a generalized intolerance to therapy in sarcopenic patients.[28-30] The susceptibility of sarcopenic individuals to infections during hospitalization and in nursing homes has also been described,[31] and this also fits within a theme of generalized inability of individuals with severe muscle depletion to react appropriately to stress. Both premature termination of treatment and infection are possible contributors to shortened survival. We also speculate that pre-existing weight loss and changes in skeletal muscle may be driven by comorbid conditions, such as inflammation, which are numerous in advanced cancer populations, predict survival,[26,32] and require further study. Low MA has been associated with obesity, diabetes, detraining, and some forms of muscle atrophy[33] but has not previously been studied in relation to either cancer outcome or survival. Both the etiology and prognostic significance of low MA in patients with cancer remain matters for further study.

Our findings provide evidence in support of the proposed international consensus definition of cancer cachexia as a multifactorial syndrome defined by an ongoing loss of skeletal muscle mass with or without loss of fat mass.[12] The key diagnostic criteria for cancer cachexia proposed by the cachexia consensus authors include weight

Table 3. Median Survival* and Univariate and Multivariate Analyses† for Predictors of Overall Survival

Characteristic	No. of Patients	No. of Deaths	Survival (months)		Univariate					Model One: Conventional					Model Two: Body Composition				
			Median	95% CI	Coefficient	SE	HR	95% CI	*P*	Coefficient	SE	HR	95% CI	*P*	Coefficient	SE	HR	95% CI	*P*
Sex																			
Female	645	417	15.9	13.8 to 17.9															
Male	828	549	17.0	14.9 to 19.1	0.10	0.06	1.01	0.89 to 1.15	.876	0.16	0.07	1.18	1.03 to 1.34	.014					
Age, years																			
< 65	674	413	18.0	15.5 to 20.5															
> 65	799	553	14.6	12.9 to 16.4	0.19	0.07	1.21	1.07 to 1.38	.003	0.18	0.07	1.20	1.06 to 1.37	.005					
Cancer diagnosis																			
Colorectal	773	369	31.5	27.9 to 35.1															
Pancreatic	146	128	5.2	3.7 to 6.8	1.42	0.10	4.15	3.39 to 5.09	< .001	1.22	0.11	3.38	2.74 to 4.17	< .001					
Esophageal	24	14	17.5	19.1 to 26.0	0.72	0.25	2.05	1.26 to 3.33	.004	0.51	0.25	1.66	1.02 to 2.71	.043					
Stomach	51	41	11.3	6.7 to 16.0	0.94	0.17	2.55	1.85 to 3.52	< .001	0.78	0.17	2.17	1.57 to 3.01	< .001					
Respiratory tract	440	386	9.4	7.7 to 11.1	1.08	0.07	2.94	2.54 to 3.39	< .001	1.00	0.08	2.72	2.34 to 3.17	< .001					
Other GI	39	25	19.9	7.6 to 32.3	0.54	0.21	1.71	1.14 to 2.57	.009	0.42	0.21	1.53	1.02 to 2.29	.041					
Cancer stage																			
I	70	21	37.2	22.2 to 52.3															
II	234	64	52.4	42.0 to 62.8	−0.30	0.25	0.74	0.45 to 1.22	.237	0.07	0.25	1.08	0.66 to 1.77	.771					
III	409	215	29.2	23.9 to 34.5	0.25	0.23	1.29	0.82 to 2.01	.272	0.42	0.23	1.52	0.97 to 2.38	.068					
IV	760	666	8.4	7.4 to 9.3	1.28	0.22	3.59	2.32 to 5.55	< .001	1.45	0.22	4.26	2.75 to 6.60	< .001					
ECOG PS																			
0	299	164	26.1	20.5 to 31.7															
1	688	414	21.6	18.7 to 24.4	0.14	0.09	1.16	0.96 to 1.38	.119	0.33	0.09	1.39	1.16 to 1.68	< .001					
2	244	182	9.3	6.8 to 11.8	0.79	0.11	2.21	1.79 to 2.73	< .001	0.78	0.11	2.19	1.76 to 2.71	< .001					
3	222	190	4.5	2.8 to 6.2	1.29	0.11	3.64	2.94 to 4.49	< .001	1.23	0.11	3.41	2.75 to 4.23	< .001					
4	20	16	1.0	0.0 to 4.5	1.18	0.26	3.27	1.96 to 5.46	< .001	1.40	0.26	4.07	2.42 to 6.83	< .001					
BMI, kg/m^2																			
≥ 30.0	245	152	20.1	15.8 to 23.4															
25.0 to 29.9	511	313	18.8	15.6 to 22.1	−0.20	0.10	0.98	0.81 to 1.19	.844						−0.40	0.10	0.96	0.79 to 1.17	.691
20.0 to 24.9	536	366	15.2	13.1 to 17.3	0.19	0.10	1.21	1.00 to 1.45	.045						0.08	0.10	1.08	0.89 to 1.32	.425
< 20.0	181	135	11.5	8.8 to 14.1	0.45	0.12	1.56	1.25 to 1.99	< .001						0.32	0.13	1.38	1.07 to 1.78	.014
Weight loss, %																			
< 8	821	509	19.9	17.9 to 21.6															
≥ 8	652	457	12.7	11.0 to 14.4	0.31	0.06	1.36	1.20 to 1.54	< .001						0.22	0.07	1.25	1.10 to 1.43	.001
SMI																			
Nonsarcopenic	870	539	20.1	17.9 to 22.3															
Sarcopenic	603	427	13.0	11.1 to 14.8	0.29	0.06	1.34	1.18 to 1.52	< .001						0.18	0.07	1.20	1.04 to 1.37	.010
Muscle attenuation																			
Above threshold	686	400	19.9	17.0 to 22.7															
Below threshold	787	566	13.4	11.6 to 15.1	0.34	0.07	1.40	1.24 to 1.60	< .001						0.31	0.07	1.36	1.19 to 1.55	< .001
C statistic‡												0.73					0.92		
95% CI												0.67 to 0.79					0.88 to 0.95		

Abbreviations: BMI, body mass index; C, concordance; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; SMI, skeletal muscle index.
*Median survival calculated with Kaplan-Meier method.
†Regression coefficient, HRs, and *P* values calculated with Cox proportional hazards model.
‡C statistic of 0.5 indicates the model predicts outcome as well as chance; 0.7 to < 0.8 indicates acceptable discrimination; 0.8 to < 0.9 indicates excellent discrimination; 0.9 to 0.99 is outstanding discrimination; 1.0 is perfect prediction.

Table 4. Median Overall Survival by BMI Category and Cancer Site for Overweight/Obese Patients

BMI Category (kg/m^2)	No. of Prognostic Variables													
	Overall				Zero			One or Two*				Three			Overall Comparisons Within BMI Categories[a,b,c] P†
	No. of Patients	No. of Deaths	Median Survival (months)	95% CI	No. of Patients	No. of Deaths	Median Survival (months)	95% CI	No. of Patients	No. of Deaths	Median Survival (months)	95% CI	No. of Patients	No. of Deaths	Median Survival (months)	95% CI	
Overall	1,473	966	16.7	15.2 to 18.2	292	147	28.4[a]	24.2 to 32.6[a]	995	671	16.0[b]	14.5 to 17.4[b]	186	148	8.4[c]	6.5 to 10.3[c]	< .001
< 20.0	181	135	11.5[d]	8.8 to 14.1[d]	14	10	13.3[a]	11.4 to 15.1[a]	129	92	13.2[a,b]	8.2 to 18.1[a,b]	38	33	8.3[b]	5.6 to 10.9[b]	.08
20.0 to 24.9	536	366	15.2[e]	13.1 to 17.3[e]	79	38	28.4[a]	23.7 to 33.2[a]	375	261	15.2[b]	12.9 to 17.4[b]	85	67	9.7[b]	5.3 to 14.1[b]	.001
25.0 to 29.9	511	313	18.8[e]	15.6 to 22.1[e]	131	63	27.0[a]	19.7 to 34.3[a]	331	213	17.2[b]	13.3 to 21.1[b]	49	37	9.4[c]	5.0 to 13.8[c]	< .001
≥ 30.0	245	152	20.1[f]	15.8 to 24.4[f]	68	36	35.6[a]	24.5 to 46.8[a]	163	105	17.3[b]	12.8 to 21.9[b]	14	11	8.5[c]	4.1 to 12.8[c]	< .001
Overall comparisons between BMI categories[d,e,f] P‡			< .001				.30				.017				.389		

Cancer Site (BMI ≥ 25.0 kg/m^2)	No. of Prognostic Variables																
	Overall				Zero				One or Two*				Three				Overall Comparisons Within Cancer Sites[a,b,c] P†
	No. of Patients	No. of Deaths	Median Survival (months)	95% CI	No. of Patients	No. of Deaths	Median Survival (months)	95% CI	No. of Patients	No. of Deaths	Median Survival (months)	95% CI	No. of Patients	No. of Deaths	Median Survival (months)	95% CI	
Overall	756	465	19.4	17.1 to 21.7	199	99	29.9[a]	23.4 to 36.3[a]	494	318	17.3[b]	14.6 to 20.1[b]	63	48	8.5[c]	5.1 to 11.8[c]	< .001
Colon/rectum	436	193	37.6[d]	32.7 to 42.5[d]	124	42	48.8[a]	30.8 to 66.8[a]	273	127	34.5b	27.0 to 42.1[b]	39	24	18.9[c]	3.5 to 34.4[c]	< .001
Respiratory tract	208	178	10.9[e]	8.2 to 13.6[e]	57	46	13.7[a]	9.0 to 18.4[a]	141	122	10.5a	7.9 to 13.2[a]	10	10	2.4[b]	0.0 to 8.3[b]	.006
Other GI§	112	94	8.8[e]	6.5 to 11.0[e]	18	11	18.8[a]	9.1 to 28.4[a]	80	69	8.9a	7.3 to 10.6[a]	14	14	1.8[b]	1.3 to 2.3[b]	< .001
Overall comparisons between cancer sites[d,e,f] P‡			< .001				< .001				< .001				< .001		

NOTE. Survival based on the presence of zero, one or two, or three of the following prognostic body composition variables: > 8% weight loss, sarcopenia, and low muscle attenuation.
Abbreviation: BMI, body mass index.
*There was no difference between survival curves for presence of one or two features; they were collapsed into one category.
†P values calculated using log-rank tests. P value represents overall comparisons for each BMI category or cancer site; superscript letters ([a,b,c]), read from left to right, represent differences ($P < .05$) between survival curves within a BMI category or cancer site for the overall cohort and with presence of zero, one or two, or three prognostic variables.
‡P values calculated using log-rank tests. P value represents overall comparisons between each BMI category or cancer site; superscript numbers ([d,e,f]), read from top to bottom, represent differences between survival curves for each BMI category or cancer site for the overall cohort and with presence of zero, one or two, or three prognostic variables.
§Other GI cancers include: digestive tract and accessory organs (pancreas, esophageal, stomach, liver, bile duct).

loss > 5% and sarcopenia. The results presented here using survival analysis can be used to further refine these diagnostic criteria to include weight loss and specific criteria for sarcopenia and low MA. We believe the label cachexia may be applied to all patients affected by the three factors of weight loss, sarcopenia, and low MA because these patients are unified by their equally poor prognosis.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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REFERENCES

1. Dewys WD, Begg C, Lavin PT, et al: Prognostic effect of weight loss prior to chemotherapy in cancer patients: Eastern Cooperative Oncology Group. Am J Med 69:491-497, 1980
2. National Institutes of Health, National Cancer Institute: Common Terminology Criteria for Adverse Eventsversion4.0(CTCAE).http://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf
3. Tjepkema M: Measured obesity: Adult obesity in Canada—Measured height and weight. http://www.aboutmen.ca/application/www.aboutmen.ca/asset/upload/tiny_mce/page/link/Adult-Obesity-in-Canada.pdf
4. Flegal KM, Carroll MD, Ogden CL, et al: Prevalence and trends in obesity among US adults, 1999-2008. JAMA 303:235-241, 2010
5. Blum D, Omlin A, Baracos VE, et al: Cancer cachexia: A systematic literature review of items and domains associated with involuntary weight loss in cancer. Crit Rev Oncol Hematol 80:114-144, 2011
6. Spiro A, Baldwin C, Patterson A, et al: The views and practice of oncologists towards nutritional support in patients receiving chemotherapy. Br J Cancer 95:431-434, 2006
7. Bouillanne O, Morineau G, Dupont C, et al: Geriatric Nutritional Risk Index: A new index for evaluating at-risk elderly medical patients. Am J Clin Nutr 82:777-783, 2005
8. Guigoz Y, Vellas B, Garry PJ: Assessing the nutritional status of the elderly: The Mini Nutritional Assessment as part of the geriatric evaluation. Nutr Rev 54:S59-S65, 1996
9. Kalantar-Zadeh K, Horwich TB, Oreopoulos A, et al: Risk factor paradox in wasting diseases. Curr Opin Clin Nutr Metab Care 10:433-442, 2007
10. Baumgartner RN: Body composition in healthy aging. Ann N Y Acad Sci 904:437-448, 2000
11. Prado CM, Lieffers JR, McCargar LJ, et al: Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: A population-based study. Lancet Oncol 9:629-635, 2008
12. Fearon K, Strasser F, Anker SD, et al: Definition and classification of cancer cachexia: An international consensus framework. Lancet Oncol 12:489-495, 2010
13. Delmonico MJ, Harris TB, Lee JS, et al: Alternative definitions of sarcopenia, lower extremity performance, and functional impairment with aging in older men and women. J Am Geriatr Soc 55:769-774, 2007
14. McCalllum PD: Patient-generated subjective global assessment, in McCallum PD, Polisena C (eds): The Clinical Guide to Oncology Nutrition. Chicago, IL, American Dietetic Association, 2000, pp 11-23
15. Perry GS, Byers TE, Mokdad AH, et al: The validity of self-reports of past body weights by U.S. adults. Epidemiology 6:61-66, 1995
16. Payette H, Kergoat MJ, Shatenstein B, et al: Validity of self-reported height and weight estimates in cognitively-intact and impaired elderly individuals. J Nutr Health Aging 4:223-228, 2000
17. Martin L, Watanabe S, Fainsinger R, et al: Prognostic factors in patients with advanced cancer: Use of the patient-generated subjective global assessment in survival prediction. J Clin Oncol 28:4376-4383, 2010
18. Mourtzakis M, Prado CM, Lieffers JR, et al: A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. Appl Physiol Nutr Metab 33:997-1006, 2008
19. Mitsiopoulos N, Baumgartner RN, Heymsfield SB, et al: Cadaver validation of skeletal muscle measurement by magnetic resonance imaging and computerized tomography. J Appl Physiol 85:115-122, 1998
20. Shen W, Punyanitya M, Wang Z, et al: Total body skeletal muscle and adipose tissue volumes: Estimation from a single abdominal cross-sectional image. J Appl Physiol 97:2333-2338, 2004
21. Irving BA, Weltman JY, Brock DW, et al: NIH image and Slice-O-Matic computed tomography imaging software to quantify soft tissue. Obesity (Silver Spring) 15:370-376, 2007
22. Williams BA, Mandrekar JA, Mandrekar SJ, et al: Finding optimal cutpoints for continuous covariates with binary and time-to-event outcomes. Rochester, MN, Mayo Foundation, Technical Report Series 79, 2006
23. Harrell FE Jr, Lee KL, Mark DB: Multivariable prognostic models: Issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 15:361-387, 1996
24. Hosmer DW, Lemeshow S: Applied Logistic Regression (ed 2). New York, NY, John Wiley and Sons, 2000
25. Pencina MJ, D'Agostino RB: Overall C as a measure of discrimination in survival analysis: Model specific population value and confidence interval estimation. Stat Med 23:2109-2123, 2004
26. Lieffers JR, Baracos VE, Winget M, et al: A comparison of charlson and elixhauser comorbidity measures to predict colorectal cancer survival using administrative health data. Cancer 117:1957-1965, 2011
27. Quinten C, Coens C, Mauer M, et al: Baseline quality of life as a prognostic indicator of survival: A meta-analysis of individual patient data from EORTC clinical trials. Lancet Oncol 10:865-871, 2009
28. Prado CM, Baracos VE, McCargar LJ, et al: Body composition as an independent determinant of 5-fluorouracil-based chemotherapy toxicity. Clin Cancer Res 13:3264-3268, 2007
29. Prado CM, Baracos VE, McCargar LJ, et al: Sarcopenia as a determinant of chemotherapy toxicity and time to tumor progression in metastatic breast cancer patients receiving capecitabine treatment. Clin Cancer Res 15:2920-2926, 2009
30. Antoun S, Baracos VE, Birdsell L, et al: Low body mass index and sarcopenia associated with dose-limiting toxicity of sorafenib in patients with renal cell carcinoma. Ann Oncol 21:1594-1598, 2010
31. Cosquéric G, Sebag A, Ducolombier C, et al: Sarcopenia is predictive of nosocomial infection in care of the elderly. Br J Nutr 96:895-901, 2006
32. McMillan DC: Systemic inflammation, nutritional status and survival in patients with cancer. Curr Opin Clin Nutr Metab Care 12:223-226, 2009
33. Miljkovic I, Zmuda JM: Epidemiology of myosteatosis. Curr Opin Clin Nutr Metab Care 13:260-264, 2010