ABSTRACT
Background: The prominent clinical feature of cachexia has traditionally been understood to be weight loss; however, in recognition of the potential for divergent behavior of muscle and adipose tissue, cachexia was recently defined as loss of muscle with or without loss of fat mass. Detailed assessments are required to verify body composition in patients with cancer cachexia.
Design: We adopted a population-based approach to study body composition in patients with cancer, with the use of diagnostic computed tomography images acquired for cancer diagnosis and follow-up. A prospective cohort of 441 patients with non–small cell lung cancer, who were referred consecutively to a regional medical oncology service in Alberta, Canada, was evaluated.
Results: At referral (median time to death: 265 d), mean body mass index (BMI; in kg/m²) was 24.9, with 47.4% of patients being overweight or obese. Only 7.5% overall were underweight as conventionally understood (BMI < 18.5). Analysis of computed tomography images showed extremely high heterogeneity of muscle mass within all strata of BMI. The overall prevalence of severe muscle depletion (sarcopenia) was 46.8% and was present in patients in all BMI categories. A much higher proportion of men (61%) than women (31%) met the criteria for sarcopenia.
Conclusions: Wasting of skeletal muscle is a prominent feature of patients with lung cancer, despite normal or heavy body weights. The significance of muscle wasting in normal-weight, overweight, and obese patients as a nutritional risk factor, as a prognostic factor, and as a predictor of cancer treatment toxicity is discussed in this article. Am J Clin Nutr 2010;91(suppl):1133S–7S.

INTRODUCTION
Involuntary weight loss is considered a hallmark of advanced cancer. Weight loss varies in incidence and intensity, which results in large cumulative losses over time (1–3). This wasting is associated with poor quality of life, poor treatment response, and mortality (1–3). Weight loss varies with cancer stage, age, and sex (2–4), and the composition and trajectory of weight loss remain unclear. Studies of body composition in nonmalignant conditions identify skeletal muscle and adipose tissue as the physiologically important body compartments. Muscle loss is generally held to be a more serious concern; however, in the majority of investigations of body composition in patients with cancer, the methods used (ie, bioelectric impedance, whole-body K) do not distinguish skeletal muscles from other soft lean tissues (5–8).

A highly differentiated understanding of human body composition has evolved in tandem with image-based technologies such as magnetic resonance imaging and computed tomography (CT) (8–14). These approaches enjoy a high degree of specificity for individual discrimination of many organs and tissues. CT and magnetic resonance imaging have been used to evaluate body composition in elderly, obese, and diabetic populations (8, 12, 13, 15); these are the only analyses that permit separation of specific skeletal muscles and adipose tissue (ie, subcutaneous, visceral, intramuscular) (10–13). Skeletal muscle wasting is a phenomenon that may be obscured within the bulk of body weight and body weight change, and there is a new recognition of sarcopenia (severe muscle wasting) as a clinically important phenomenon. This term denotes a lower quantity of skeletal muscle >2 SDs below that typical of healthy adults (16). Sarcopenia has been associated with functional impairment and disability (16, 17), risk of fractures and falls (16), increased length of hospital stay (18), nosocomial infections (19), and decreased survival (20) in nonmalignant diseases. Sarcopenia is not unique to people who are underweight (21). The aging process is often paralleled by decreases in muscle and increases in fat mass, which may culminate in sarcopenic obesity (22, 23); this condition combines the health risks and functional losses of both conditions and is increasingly prevalent in westernized countries (24, 25).

Diagnostic images collected in most major cancer centers for staging and evaluation of tumor response are suitable for body-composition analyses. However, these images usually have not been used for body-composition research, despite their wide potential for divergent behavior of muscle and adipose tissue. These MAJOR studies have shown that the composition of body composition in patients with cancer, with the use of diagnostic computed tomography images acquired for cancer diagnosis and follow-up. A prospective cohort of 441 patients with non–small cell lung cancer, who were referred consecutively to a regional medical oncology service in Alberta, Canada, was evaluated. At referral (median time to death: 265 d), mean body mass index (BMI; in kg/m²) was 24.9, with 47.4% of patients being overweight or obese. Only 7.5% overall were underweight as conventionally understood (BMI < 18.5). Analysis of computed tomography images showed extremely high heterogeneity of muscle mass within all strata of BMI. The overall prevalence of severe muscle depletion (sarcopenia) was 46.8% and was present in patients in all BMI categories. A much higher proportion of men (61%) than women (31%) met the criteria for sarcopenia.

Conclusions: Wasting of skeletal muscle is a prominent feature of patients with lung cancer, despite normal or heavy body weights. The significance of muscle wasting in normal-weight, overweight, and obese patients as a nutritional risk factor, as a prognostic factor, and as a predictor of cancer treatment toxicity is discussed in this article.

Am J Clin Nutr 2010;91(suppl):1133S–7S. Printed in USA. © 2010 American Society for Nutrition

1 From the Department of Oncology, Division of Palliative Care Medicine, University of Alberta, Edmonton, Canada (VEB); the Department of Oncology, Dalhousie University, Saint John Regional Hospital, Saint John, Canada (TR); the Department of Kinesiology, Faculty of Applied Health Sciences, University of Waterloo, Waterloo, Canada (MM); the Department of Supportive Care, Institut Gustave Roussy, Villejuif, France (SA).
3 Supported by the Canadian Institutes of Health Research.
4 Address correspondence to VE Baracos, Department of Oncology, University of Alberta Cross Cancer Institute, 11560 University Avenue, Edmonton, AB T6G 1Z2, Canada. E-mail: vickie.baracos@ualberta.ca. First published online February 17, 2010; doi: 10.3945/ajcn.2010.28608C.
availability and the importance attributed to lean tissue loss in the cancer cachexia literature. We proposed the opportunistic use of oncologic images to describe details of body composition and its change over time in patients with cancer and to relate these to outcomes of cancer and cancer treatment (26–30). We produced the first extensive applications of CT image review in cancer cachexia, which included a longitudinal retrospective review of colorectal cancer patients (27) as well as a prospectively followed population cohort of 2115 patients with solid tumors of the lung or gastrointestinal tract referred to a regional medical oncology service. The article by Prado et al (28) was the first publication that resulted from a review of this cohort, and concerned the subset who had a body mass index (BMI; in kg/m²) > 30 at presentation. Obese patients had a wide range of muscle mass. Sex-specific cutoffs that defined a significant association between low muscle mass and mortality were ascertained by optimum stratification analysis. Sarcopenia was present in 15% of patients and was associated with poorer functional status compared with obese patients who did not have sarcopenia ($P < 0.01$), and was an independent predictor of survival (hazard ratio: 4.2; 95% CI: 2.4, 7.2; $P < 0.0001$). Sarcopenic obese patients’ median survival (10 mo) was half that of otherwise similar patients who did not have sarcopenia (21 mo).

Other recent efforts have also focused on the notion that cancer patients with sarcopenia may be prone to severe toxicity during systemic chemotherapy. Patients with stage II/III colon cancer treated with 5-fluorouracil were analyzed and the incidence of dose-limiting toxicity related to muscle tissue was measured by CT (29). Women in this study who had a low proportion of skeletal muscle in relation to their height and weight had a higher incidence of dose-limiting toxicity (odds ratio: 16.7; $P = 0.02$).

We went on to study patients with metastatic breast cancer who received capecitabine treatment (30). Approximately 25% of patients were classified as sarcopenic, and this feature was seen in normal-weight, overweight, and obese individuals. Toxicity was present in 50% of sarcopenic patients compared with only 20% of nonsarcopenic patients ($P = 0.03$).

We continue our series of investigations of body composition of patients with cancer in function of disease site, stage, comorbid conditions, and treatment regimens. Here, our objective was to characterize the demographics of weight and body composition in a contemporary cohort of patients with locally advanced or recurrent non–small cell lung cancer (NSCLC).

**SUBJECTS AND METHODS**

**Ethics approval and study cohort**

The study was approved by the research ethics board of the Alberta Cancer Board. A computerized database of all cancer cases in the province of Alberta (Cancer Registry) documents primary cancers by their site and morphology and provides corresponding biological, clinical, and demographic information. Our site is the only cancer treatment center that serves Northern Alberta (population: 1.8 million). The population included all new patients referred to medical oncology clinics for treatment of cancers of the respiratory tract. Patient-reported height, weight, weight history, and functional status were collected during the first clinic visit with the use of the Patient-Generated Subjective Global Assessment (31); height and weight recorded by hospital staff on the same date were used for verification where available.

Evidence to support the reliability of self-reported height, weight, and weight history is presented elsewhere (28, 32). Height and weight were used to compute common anthropometric descriptors, BMI, and body surface area (BSA) (33):

\[
\text{BSA (m}^2\text{)} = \left(\frac{\text{height (cm)} \times \text{weight (kg)}}{3600}\right)^{1/2}
\]

Weight was assessed before the initiation of treatments, so chemotherapy-associated weight changes did not confound our assessments. Each patient’s record was reviewed for recent CT images taken within 30 d of BMI assessment. Data were collected prospectively and patients were followed until death. Stage of disease was based on American Joint Committee on Cancer stage groupings, I, II, III, and IV, which, in turn, were based on the tumor-node-metastasis staging system. Patients included in the current analysis ($n = 441$) had a histologically confirmed diagnosis of NSCLC and were evaluated by CT scan in the abdominal region in the course of routine evaluation.

**Image analysis**

A lumbar vertebral landmark (L3) was selected because skeletal muscle and adipose tissue area in this region correspond to whole-body tissue quantities in nonmalignant populations (10, 11, 14, 15); this landmark was validated (26) and used (26–30) for patients with cancer. This field of view contains visceral and subcutaneous adipose tissue and the psoas and paraspinal muscles (erector spinae, quadratus lumborum), as well as the transversus abdominis, external and internal oblique abdominals, and rectus abdominus. Two consecutive CT images that extended from L3 in the inferior direction were assessed. Images were analyzed with the use of Slice-O-Matic software V4.2 (Tomovision, Montreal, Canada). To calculate tissue cross-sectional area (cm²), the surfaces of the respective tissues in each slice were computed automatically by summing the given tissue’s pixels and multiplying by the pixel surface area. CT Hounsfield unit ranges used for specific tissues included –29 to –150 for skeletal muscle, –190 to –30 for subcutaneous and intermuscular adipose tissue, and –150 to –50 for visceral adipose tissue. Boundaries were corrected manually as necessary.

The directly determined unit in the CT image analysis was area (cm²); ie, of total L3 skeletal muscle. This value is linearly related to whole-body muscle mass (14) and was thus normalized for stature, as is conventional for BMI and body composition components; the unit of expression of L3 skeletal muscle index is thus cm²/m².

Estimates of whole-body tissue mass were generated from the raw data of muscle area (cm²) with the use of the regression equation of Mourtzakis et al (26):

\[
\text{Whole-body fat-free mass determined by dual-energy}
\]

\[
\text{X-ray absorptiometry (kg)} = \left[0.3 \times \text{skeletal muscle at L3 (cm²)}\right] + 6.06 (r = 0.94)
\]

The mean absolute residual error of these estimates was 2.94 kg, which allowed an estimation of lean body mass ± 3 kg.

**Calculations and statistics**

Data are expressed as means ± SDs. Sarcopenia was defined as described (28) in patients with cancer with the use of optimal
stratification to define the cutoffs associated with mortality. The sex-specific cutoffs for L3 muscle index associated with mortality determined by optimal stratification were 55.4 cm²/m² for men and 38.9 cm²/m² for women (28); patients below these values were designated sarcopenic. Student’s t test was used for comparisons between men and women and statistical significance was determined at \( P < 0.05 \). Statistical analysis was completed with the use of SPSS for Windows (version 16.0; SPSS, Chicago, IL).

RESULTS

Demographic and anthropometric features of the patient population are given in Table 1. A history of weight loss during the 6 mo that preceded the referral was common, with an average loss of 6.0 ± 7.1%. The population quartiles of 6 mo weight loss were −16.5%, −6.6%, −4.4%, and +2.4%. However, because of the generally heavy body weights, many patients remained obese or overweight despite considerable weight loss. Analysis of BMI showed an average BMI of 24.9, with 50% of patients overweight or obese at referral, and with only 7.9% who presented as underweight (BMI < 18.5). Overall, 13% were obese at presentation, and, based on the weight history, 19.7% had been obese during the 6 mo that preceded the referral. Despite sometimes considerable weight loss, the classic image of cachexia, emaciation (ie, severely underweight, BMI < 16), was relatively rare.

Data from the CT image analysis showed sex differences in skeletal muscle area and skeletal muscle index. Both of these values had a large SD. A very high proportion of men met the criteria for sarcopenia (L3 muscle index < 55.4 cm²/m²; 61% of men) compared with women (L3 muscle index < 38.9 cm²/m²; 31% of women). Total lumbar fat area was larger in men, but when this value was normalized for stature, the sexes were not different. Fat area exhibited a high degree of variation in both sexes.

The variation in body composition of the lung cancer population is shown in Figures 1 and 2. Individual patients are classified by BMI and by muscularity (L3 muscle cross-sectional area) in Figure 1. The large variability in muscle area within any given stratum of BMI is evident for both sexes, with only 35% of the variation in muscle area explained by BMI. The 22 men whose BMI fell into a 1-unit range of BMI 25.0–25.99 make a striking example; these men had a lumbar muscle area that ranged from 114 to 205 cm² and a lumbar skeletal muscle index that ranged from 37.4 to 72.4 cm²/m². Of these patients with BMI classifiable as overweight, 13/22 (59%) met the criteria for sarcopenia.

Patients were classified by BSA, which is the usual basis of normalization for stature and weight for the administration of many chemotherapy agents, and by estimated lean body mass, as shown in Figure 2. As we have shown previously for obese patients with cancer (28), muscle area and hence estimated lean body mass were not strongly related to BMI (corrected for fluid retention) . . . “ (p 793). The prominent clinical feature of cachexia is characterized by loss of muscle with or without loss of fat mass (see text added). The prominent clinical feature of cachexia is weight loss in adults (corrected for fluid retention) . . . “ (p 793). There is also a developing understanding that it is possible not merely to lose muscle while fat is maintained, but to lose muscle and gain adipose tissue concurrently, with departure of these tissues in opposite directions, which culminates in sarcopenic

**TABLE 1**

| Age (y) | 67.0 ± 10.0 | 65.0 ± 10.7 | 0.035 |
| Stage III (%) | 51 | 42 | 0.24 |
| Stage IV (%) | 49 | 58 | — |
| Height (cm) | 175 ± 7.1 | 168 ± 9.8 | <0.001 |
| Weight (kg) | 77.0 ± 13.7 | 64.0 ± 16 | <0.001 |
| BMI (kg/m²) | 25.2 ± 4.1 | 24.6 ± 5.9 | 0.26 |
| BMI <18.5% (%) | 2.6 | 12.3 | — |
| BMI 18.5–24.99% (%) | 46.7 | 43.4 | — |
| BMI 25.0–29.99% (%) | 35.8 | 28.8 | — |
| BMI ≥30% (%) | 14.9 | 15.6 | — |
| Weight loss in preceding 6 mo (%) | −6.39 ± 7.76 | −5.58 ± 8.06 | 0.3 |
| Lumbar skeletal muscle area (cm²) | 154 ± 25.9 | 109 ± 19.4 | <0.001 |
| Lumbar total adipose area (cm²) | 310 ± 162 | 257 ± 170 | <0.001 |
| Lumbar skeletal muscle index (cm²/m²) | 50.6 ± 8.5 | 42.1 ± 7.6 | <0.001 |
| Lumbar total adipose index (cm²/m²) | 101 ± 53 | 99 ± 65 | 0.67 |
| Sarcopenic (%) | 61.1 | 31.3 | <0.001 |
| Estimated fat-free mass (kg) | 52.4 ± 7.8 | 38.8 ± 5.8 | <0.001 |
| Estimated fat mass (kg) | 24.2 ± 6.8 | 22.0 ± 7.1 | <0.001 |
| Vital status (% deceased) | 83.8 | 78.7 | 0.16 |
| Median time to death (d) | 244 | 320 | 0.22 |

1 Mean ± SD (all such values).
BMI (in kg/m²) was in a 1-unit range of 25.0–25.99 make a striking example; 35% of the variation in muscle area explained by BMI. The 22 men whose BSA. up to a 2-fold variation in the size of the lean body mass in a given range of skeletal muscle index ranging from 37.4 to 72.4 cm²/m². They had a lumbar muscle area ranging from 114 to 205 cm² and a lumbar skeletal muscle index ranging from 37.4 to 72.4 cm²/m².

overweight and sarcopenic obesity (22–25, 28). It is becoming increasingly recognized that a unit of human body weight, or of body weight change, does not have a constant composition. Our results obtained in a population cohort of patients with lung cancer provide evidence to support these concepts. At presentation, patients with lung cancer were, in the vast majority (>92%), within the BMI ranges considered normal weight, overweight, and obese. We also observed skeletal muscle wasting in all of the BMI categories, with nearly half of patients below or well below the benchmark levels of muscularity known to be associated with mortality and functional disability (28). The overall prevalence of sarcopenia of nearly 50% is as high or higher than that described in the literature for healthy elderly well into or beyond their ninth decade of life (16). Because muscle depletion is an occult condition in patients with larger body weight and fat mass, valid approaches for the determination of muscularity are required to evaluate this feature. In patients with cancer, the secondary analysis of CT images is an accessible means of making this evaluation (26–30). Adoption of this approach provides a high methodologic standard and presents an important advance in our ability to diagnose, classify, and evaluate treatment of cancer cachexia.

The features of this patient population also suggest some limitations in the conventional notions of nutritional risk centered on BMI and weight loss. A BMI <18.5 is considered by many authorities to represent a serious risk of undernutrition (35), and 3% of men and 12% of women here had this feature. Weight loss is also considered a primary nutritional risk factor in patients with cancer, and here 25% presented with weight loss >10% during the 6 mo that preceded referral. A far higher proportion (46.8%) were sarcopenic and the estimated lean body mass of patients classified as sarcopenic in our study was within the range described in patient populations described as emaciated or cachectic, both with and without malignant disease (5–7, 16, 36). With a mean estimated fat mass of 23 kg overall, the energy reserves of these patients could be described as substantial, and thus the nutritional risk for these individuals may be more highly related to their lean body mass.

Variation in body composition has potential implications in antineoplastic therapy. BSA is used as a conventional basis for administration of cytotoxic chemotherapy and this measure, like BMI, is derived from height and weight. We reported previously that patients with colorectal cancer might have a low fat-free mass relative to their BSA (29). Later, in the larger, population-based data set (28) on obese cancer patients (n = 250) with solid tumors, we showed that the relation between estimated total body fat-free mass and BSA was poor (r² = 0.37), even though both are related to height. The present study is the first large cohort (n = 441) that encompasses the entire BMI range in which we have analyzed this relation, and here again a relatively weak relation (r² = 0.55) was evident, with up to 2-fold variation in estimated lean body mass in any narrow range of BSA. One consequence of low fat-free mass would be a low volume of distribution of cytotoxic chemotherapy drugs, and our earlier study suggested that higher doses of 5-fluorouracil/kg fat-free mass were associated with a higher incidence of overall toxicity (29). We showed additional evidence of this concept in patients with breast cancer treated with capecitabine (30). This concept remains to be established for typical regimens used in the treatment of NSCLC but seems worthy of investigation in light of our prior results and given the great heterogeneity of these features in patients with lung cancer. If some of the currently unexplained variation in toxicity may be explained partially by features of body composition, it becomes important to identify
clinical measures of body composition for a more refined delivery of chemotherapy dose.

Finally, the current findings have some implications for nutritional support of cancer patients. Given the widespread nature of sarcopenia, a strong focus on nutritional therapy for the maintenance or gain of skeletal muscle tissue would appear justified. However, it seems likely that prescribed energy intakes must be framed separately for sarcopenic underweight patients for whom overall weight gain is an objective, and for sarcopenic obese or overweight patients for whom weight stability or even loss of fat is a concurrent target.

The authors' responsibilities were as follows—VEB and TR: study design; MM and TR: data collection and analysis; IG and SA: data interpretation and discussion; VEB: draft of the manuscript; and all authors: contribution to the development of the final manuscript. No conflicts of interest were reported.

REFERENCES

24. Bouchard DR, Dionne IJ, Brochu M. Sarcopenic Obesity and Physical Capacity in Older Men and Women: Data From the Nutrition as a Determinant of Successful Aging (NuAge)-the Quebec Longitudinal Study. Obesity (Silver Spring) 2009;17:2082–8.