Central tenet of cancer cachexia therapy: do patients with advanced cancer have exploitable anabolic potential?1–3

Carla M Prado, Michael B Sawyer, Sunita Ghosh, Jessica R Lieffers, Nina Esfandiari, Sami Antoun, and Vickie E Baracos

ABSTRACT

Background: Skeletal muscle wasting is considered the central feature of cachexia, but the potential for skeletal muscle anabolism in patients with advanced cancer is unproven.

Objective: We investigated the clinical course of skeletal muscle wasting in advanced cancer and the window of possible muscle anabolism.

Design: We conducted a quantitative analysis of computed tomography (CT) images for the loss and gain of muscle in population-based cohorts of advanced cancer patients (lung, colorectal, and pancreas cancer and cholangiocarcinoma) in a longitudinal observational study.

Results: Advanced-cancer patients (n = 368; median survival: 196 d) had a total of 1279 CT images over the course of their disease. With consideration of all time points, muscle loss occurred in 39% of intervals between any 2 scans. However, the overall frequency of muscle gain was 15.4%, and muscle was stable in 45.6% of intervals between any 2 scans, which made the maintenance or gain of muscle the predominant behavior. Multinomial logistic regression revealed that being within 90 d (compared with >90 d) from death was the principal risk factor for muscle loss (OR: 2.67; 95% CI: 1.45, 4.94; P = 0.002), and muscle gain was correspondingly less likely (OR: 0.37; 95% CI: 0.20, 0.69; P = 0.002) at this time. Sex, age, BMI, and tumor group were not significant predictors of muscle loss or gain.

Conclusions: A window of anabolic potential exists at defined early phases of the disease trajectory (>90 d survival), creating an opportunity for nutritional intervention to stop or reverse cachexia. Cancer patients within 90 d of death have a low likelihood of anabolic potential.


INTRODUCTION

Skeletal muscle loss is a defining feature of cancer cachexia and affects physiologic function, immunity, chemotherapy response, surgical outcomes, and survival (1–7). Wasting is hypothesized to be reversible, but to achieve this reversal, we must identify key molecules that signal muscle catabolism and clarify cancer patients’ potential for skeletal muscle anabolism. Although such potential is clearly presumed by proponents of cachexia therapy, it is an equally reasonable assumption that age, poor nutritional status, inactivity, and inflammation, which are characteristics of advanced cancer patients, may preclude the reversal of muscle wasting.

A few findings have a bearing on this important point. Deutz et al (8) measured the fractional rate of muscle protein synthesis (FSR)6 in cancer patients by using the tracer incorporation of L-[ring-13C(6)]-phenylalanine. They observed that the ingestion of 40 g casein and whey protein enriched with 10% free leucine increased the muscle-protein FSR from 0.073 ± 0.023%/h to 0.097 ± 0.033%/h (P = 0.072), whereas 24 g casein did not elicit an increase in the FSR. Winter et al (9) assessed whole-body [13C]leucine and [2H]glucose kinetics in lung cancer patients and healthy matched controls during the use of a euglycemic, hyperinsulinemic clamp. When the infusion was done under conditions of isoaminoacidemia, the nonoxidative rate of whole-body leucine disappearance was not stimulated in either healthy control subjects or lung cancer patients; however, there was a significant increase during hyperaminoacidemia in both groups (lung cancer patients: +26.3%; 2.59 ± 0.07 compared with 2.05 ± 0.07 μmol·kg lean body mass−1·min−1). Both studies were in agreement in their findings of some degree of anabolic potential under conditions of an adequate amino acid supply.

We have taken a different approach to this question [ie, a quantitative analysis of computed tomography (CT) images] (10, 11) and made preliminary observations of muscle gain. In Tan et al (10), muscle loss was the prevalent behavior, but 14% of patients with metastatic pancreatic cancer (considered the disease most highly associated with cachexia) exhibited a muscle gain of 7.9 ± 14.4%/100 d. In Lieffers et al (11), 14% of patients gained skeletal muscle during the year preceding death from colorectal cancer (+4.7 ± 5.4%/100 d). These observations led us to expand our study of this anabolic behavior to a population-based cohort of patients with advanced solid tumors treated with standard therapy in day-to-day clinical practice.

1 From the Department of Nutrition, Food and Exercise Sciences, The Florida State University, Tallahassee, FL (CMP); the Department of Oncology, University of Alberta, Cross Cancer Institute, Edmonton, Canada (MBS, SG, NE, and VEB); the Division of Human Nutrition, University of Alberta, Edmonton, Canada (JRL); and the Department of Supportive Care, Institut Gustave Roussy, Villejuif, France (SA).
2 Supported by the Alberta Heritage Foundation for Medical Research and Alberta Health Services/Roche Fellowship in Translational Research (CMP) and by the Canadian Institutes of Health Research (VEB).
3 Address reprint requests and correspondence to VE Baracos, Division of Palliative Care Medicine, Department of Oncology, University of Alberta, Cross Cancer Institute, 11560 University Avenue, Edmonton, Alberta T6G 1Z2, Canada. E-mail: vickie.baracos@ualberta.ca.
4 Abbreviations used: CT, computed tomography; FSR, fractional rate of muscle protein synthesis; L3, third lumbar vertebra.

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An international consensus group suggested that within 3 mo of death, severe muscle wasting, ongoing cachexia, low performance status, and metastatic disease refractory to antineoplastic therapy characterize a cachexia stage that is refractory to treatment (12). This group proposed that the success of cachexia interventions at this late stage may be compromised, but conversely, there would be merit in defining the onset of cachexia so that interventions to reduce its effect can be implemented. The assessment of muscle loss and gain over the disease trajectory would assist in defining these key phases. In the current study, we set out to investigate the clinical course of skeletal muscle wasting. We hypothesized a progressive loss of potential for muscle anabolism becoming negligible within the last months preceding death.

SUBJECTS AND METHODS

Patient characteristics

This study was approved by the Alberta Cancer Board Research Ethics Board. Our site is the only cancer center serving Northern Alberta, Canada (population: 1,800,000). A database of all cancers (Alberta Cancer Registry) codes primary cancers by site, morphology, clinical, and demographic information. We are engaged in a large, prospective, longitudinal study of body composition in patients with advanced solid tumors (10, 11, 13). Patients had pancreatic, colorectal, lung cancer, or unresectable cholangiocarcinoma and were evaluated by using CT at 2 time points between the start of treatment and death. Sampling was obtained consecutively for all cancer types. For more-common cancer types such as lung cancer, sampling was obtained consecutively from patients diagnosed between 2006 and 2007. The sampling of colorectal cancer patients occurred between 2001 and 2004 and was discussed in detail in Lieffers et al (11). The sampling of rare cancers included a longer standard of time, which allowed us to capture a representative sample of these patients. With this method, patients diagnosed with cholangiocarcinoma between 1997 and 2007 and patients diagnosed with pancreatic cancers between 2004 and 2007 were included.

Specifics of metastatic colorectal (11) and pancreatic (10) cancer patients have been published. In addition, we selected non–small cell lung cancer [stages IIIb and IV (13)]. We planned to compare several cancers with a known propensity for cachexia in a common window of time (the year preceding death). All invasive cholangiocarcinoma cases in the Cancer Registry that met our search criteria were included (International Classification of Diseases-10 morphology codes: 8140/3, 8141/3, 8160/3, 8162/3, and 8180/3).

To set our results properly in context, we specified the local practices related to weight loss and malnutrition: Megestrol acetate and synthetic cannabinoids such as dronabinol for cancer cachexia-anorexia are not part of the standard of care in Alberta, Canada. Dronabinol does not have an indication (ie, it is not approved) for the treatment of cancer-associated cachexia and is not marketed in Canada. Megestrol acetate is not favored because of its associated risk of thrombosis and skeletal muscle wasting, and it is not covered by provincial drug plans. There are no existing guidelines that recommend either tube feeding or parenteral nutrition in patients in tumor groups that we have studied, and these methods are likewise not used. Our patients are referred to a registered dietitian on an ad hoc basis by their oncologist. Our patients do receive other forms of supportive care, and our medical oncologists make full use of analgesics, antiinasea medication, topical treatments for mucositis, and promotility agents.

Body-composition measurements

Digitally stored CT images completed with a spiral CT scanner for initial staging and routine diagnostic purposes were analyzed by using Slice-O-Matic software (V4.2; Tomovision), which permitted specific tissue demarcation by using Hounsfield unit thresholds of –29 to +150 for skeletal muscles (14), –150 to –50 for visceral adipose tissue (15), and –190 to –30 for subcutaneous adipose tissue (14). Cross-sectional areas (cm²) were computed for each tissue by summing tissue pixels and multiplying by the pixel surface area. CT image variables were as follows: contrast enhanced or unenhanced, 5-mm slice thickness, 120 kVp, and ~290 mA. Cross-sectional imaging by using CT or MRI is suggested as the preferred method for analyzing mass in cancer patients (16, 17). The directly determined unit was centimeters squared of the total skeletal muscle and total adipose tissue at the third lumbar vertebra (L3), which is a vertebral landmark that has been previously validated (18) and used in studies of cancer patients (3, 4, 10, 11). Shen et al (18) detected that, in 5 different vertebral landmarks, the muscle area in a single image 5 cm above the junction of the fourth and fifth lumbar vertebrae (ie, L3) had the best correlation with whole-body muscle mass. Oncologic images almost never encompass the whole body, and the limbs are typically not included. Included muscles at L3 are the psoas, erector spinae, quadratus lumborum, transversus abdominis, external and internal obliques, and rectus abdominis; these trunk muscles are important for many types of physical activity.

Changes in muscle and adipose tissue over time were calculated as the absolute loss or gain of tissue area during each scan interval. The precision error of measurements was ~1.5% (19) with a minimum detectable change of ~3 cm². We attributed the change during each interval into the following categories: 1) muscle loss ≥6.0 cm², 2) stable muscle ±5.9 cm², or 3) muscle gain ≥6.0 cm². These cutoffs are equivalent to a loss or gain of ≥1 kg of skeletal muscle on a whole-body basis and are associated with alterations in muscle strength (18, 20). For adipose tissue, categories were based on the equivalence of 14.7 cm² total fat at L3 and 1 kg tissue on a whole-body basis (18); therefore, changes during each interval were categorized as 1) adipose tissue loss ≥14.7 cm², 2) stable adipose tissue ±14.6 cm², or 3) adipose tissue gain ≥14.7 cm².

Data analysis and statistics

Data are expressed as 1) means ± SDs for normally distributed variables, 2) medians and 95% CIs of the median for not normally distributed continuous variables, and 3) percentages for categorical variables. Comparisons for categorical variables were conducted by using the chi-square test and Fisher’s exact test, whereas Student’s t test was used for continuous variables. The median test (K samples) was used for nonnormal data. Multinomial logistic regression was used to determine factors associated with muscle/adipose loss and gain. Unpaired t tests were used to compare tumor groups for overall muscle and fat loss
at different time points. The statistical analysis was conducted with SPSS software (version 18.0; SPSS Inc). All P values were 2-sided, and the level of significance was considered at \( P < 0.05 \).

Advanced cancer and cachexia progress in tandem. We had previously shown that muscle and adipose tissue loss in colorectal cancer patients increased exponentially over the course of the year preceding death (11). With this effect taken into account, it would be essential to consider whether any 2 scans used to calculate a loss or gain of tissue took place close to death or at an earlier time. Thus, the date at the midpoint of each scan-scan interval was subtracted from the date of death to define the time to death for that interval.

RESULTS

Patients

CT scans were taken for the diagnosis, confirmation of stage, and follow-up of disease progression and treatment. With the understanding that cachexia evolves markedly in the end of life and to take advantage of repeated measures, we focused on patients with \( \geq 2 \) CT images (2–6 images) on record during the year preceding their deaths (\( n = 368 \)). A selection bias was not apparent in this sample; we showed that the sex distribution, age at death, survival time, primary tumor site, tumor morphology, and body-composition features (i.e., muscle and adipose tissues) in patients who had only a single scan were not different from those of the overall cohort at an equal time to death (\( P > 0.1 \)). Patients included in the analysis (\( n = 368 \)) were of advanced stage, and the median time to death of all groups was \(< 1 \) y. Details are provided in Table 1.

TABLE 1
Patient characteristics

<table>
<thead>
<tr>
<th>Population cohort</th>
<th>Lung</th>
<th>Colorectal</th>
<th>Pancreatic</th>
<th>Cholangiocarcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (( n ))</td>
<td>242</td>
<td>35</td>
<td>61</td>
<td>30</td>
</tr>
<tr>
<td>Sex (M) (%)</td>
<td>62.0</td>
<td>65.7</td>
<td>42.6</td>
<td>56.7</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>51% stage III; 49% stage IV</td>
<td>100% stage IV</td>
<td>100% stage IV</td>
<td>100% stage IV</td>
<td></td>
</tr>
<tr>
<td>Time to death (d)</td>
<td>215 (182, 234)</td>
<td>178 (163, 212)</td>
<td>118 (87, 168)</td>
<td>174.5 (106, 319)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>61 ± 9.4</td>
<td>59.9 ± 8.2</td>
<td>64.3 ± 8.9</td>
<td>58.6 ± 12.2</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.6 ± 4.6</td>
<td>25.0 ± 6.5</td>
<td>23.8 ± 4.4</td>
<td>25.9 ± 5.0</td>
</tr>
<tr>
<td>Total no. of scan intervals(^{3})</td>
<td>548</td>
<td>125</td>
<td>84</td>
<td>88</td>
</tr>
<tr>
<td>No. of scan intervals/patient</td>
<td>2.3 ± 1.5</td>
<td>4.0 ± 0.8</td>
<td>1.0 ± 0.5</td>
<td>3.0 ± 1.7</td>
</tr>
</tbody>
</table>

Evolution of body composition over time to death

The population of patients (\( n = 368 \)) had a total of 1279 CT scans in their clinical records. The progression over time of each patient was followed by the merit of these multiple scans per patient. A scan interval was defined in the current study as the time between any 2 scans (21). The median duration of a scan interval was 83 d, which was consistent with the follow-up of treatment in clinical practice and clinical trials.

\(^{1}\)Calculated from deceased patients; \( n = 342 \).
\(^{2}\)Median; 95% CI in parentheses (all such values).
\(^{3}\)Mean ± SD (all such values).
\(^{4}\)BMI was available for the following numbers of patients: lung, \( n = 229 \); colorectal, \( n = 23 \); pancreatic, \( n = 61 \); and cholangiocarcinoma, \( n = 15 \).
\(^{5}\)A scan interval was defined as the time between any 2 scans.
\(^{6}\)No. of observed intervals.
\(^{7}\)P values were calculated by using the median test (K samples).
\(^{8}\)Comparisons of tumor groups; medians with the same alphabetical superscript in the same row are not different, \( P > 0.05 \).
\(^{9}\)Estimated kilograms were calculated from Shen et al (18).
The analysis of 783 scan intervals on 342 patients who had died by the time of analysis is shown (Figure 1). On average, the population showed a simultaneous loss of muscle and adipose tissue, and they became progressively more catabolic over time from >9–6, 3, and 1 mo before death (Figure 1A). The mean overall changes of muscle and adipose tissue over time to death are shown in Figure 1B. The mean overall muscle loss showed no significant variation by age, sex, or tumor group (not significant, unpaired t test; Figure 1C). Men and women did not differ significantly for either the absolute loss or muscle area (cm²) (Figure 1C) or when data were expressed as the percentage of loss (not shown). Muscle loss did not differ in patients above compared with below the median age (61 y).

Prevalence of tissue loss, gain, and no change

An additional analysis revealed a variation of both the magnitude and direction of tissue change. Although the overall skeletal muscle was lost, mean values (Figure 1B) obscured the fact that, in some instances, tissue did not change or was gained (Table 1). Muscle was indeed stable in 44.8% of all intervals, loss occurred in 39.8% of intervals, and gain occurred in 15.4% of intervals. Adipose tissue was stable in 27.1% of intervals, loss occurred in 48.1% of intervals, and gain occurred in 24.8% of intervals. These behaviors (stable, loss, and gain) are illustrated by tissue and time to death (Figure 2, A and B) and by tissue and cancer type (Figure 2, C and D). The percentage of patients who lost muscle and adipose tissue increased, and the percentage of patients who gained these tissues decreased as death approached. The magnitude and frequency of muscle loss also increased over time and were $-13.6 \pm 5.5$ cm² in intervals >9 mo to death and $-20.4 \pm 13.4$ cm² at 1 mo to death ($P < 0.003$; t test). Conversely, the majority (84.3%) of instances of muscle Gain and 86.9% of instances of adipose gain occurred >3 mo before death ($P = 0.0001$; chi-square test).

The 3 behaviors (stable, loss, and gain) were analyzed by using multinomial logistic regression (Table 2). In this analysis, one scan-scan interval per patient was included in the analysis ($n = 368$), which was either the last interval for patients who had multiple intervals or the only interval in patients who has just one interval. Risk factors in the multivariate analysis included the median age (±61 compared with >61 y), BMI, tumor group (cholangiocarcinoma, colorectal, or pancreas compared with lung), sex, and time to death (±90 compared with >90 d). The 90-d cutoff was chosen in consideration of the large incremental increase in muscle and fat loss in this period (Figure 1A). An international consensus group also suggested that 3 mo to death characterize a cachexia stage that is characterized by intense catabolism that may be refractory to treatment (12). The major risk factor was a time to death <90 d for muscle (OR: 2.67; $P < 0.002$) and adipose tissue loss (OR: 2.74; $P < 0.001$; Table 2), and muscle gain was correspondingly less likely (OR: 0.37; 95% CI: 0.20, 0.69; $P = 0.002$) at this time. There were no differences by sex, age, BMI, or tumor group except that adipose tissue loss was more likely in pancreatic cancer patients (OR: 2.95; $P = 0.003$; Table 2). In comparison with the reference category, muscle gain, men were less likely (OR: 0.42; 95% CI: 0.25, 0.69; $P = 0.001$), and patients with pancreatic cancer were less likely to show stable muscle overtime (OR: 0.44; 95% CI 0.21, 0.91; $P = 0.027$). Age, BMI, time to death, and tumor types other than of the pancreas were not significantly related to stable muscle behavior (data not shown). Compared with the reference category adipose tissue gain, no significant relations were shown for patients who showed no change in adipose tissue (stable category).

Characteristics of patients with large gain or loss of skeletal muscle

To gain insight into possible causes of muscle gain, a review of medical charts was conducted in individuals in the top 5% (with the quantitatively largest muscle gains) ($n = 43$ of 845 scan intervals) (Table 3). Reports from an oncologic consultation made reference to stable disease ($n = 38$) or a partial response to therapy ($n = 2$) in patients who gained muscle, and 23 of these reports included remarks about improvements in pain and symptom control, the ability to eat, and/or physical function. Three patients had received oral nutrition supplements; none of these patients had artificial enteral or parenteral feeding. By contrast, dominant features of patients with the largest magnitude of muscle loss were progressive disease and proximity to death (median ± SE time to death: 105 ± 17.5 d).

**DISCUSSION**

We characterized the natural history of cancer cachexia through an analysis of 1279 CT images representing the clinical course of 368 patients with advanced cancer. Overall, muscle and adipose...
tissue loss occurred continuously, with an exponentially increasing course, but cachexia is not necessarily an immutable phenomenon. Skeletal muscle gain occurred well within the year preceding death in some individuals. Muscle gain was more likely to occur further away from death. Results of a chart review suggested muscle gain occurred during time periods characterized by stable disease.

Our study had the following 2 methodologic strengths, which to our knowledge, were not shown in previous investigations: its population-based sampling of consecutive patients and the specific detection of tissue losses and gains by using CT-image analysis. CT-image–based methods are precise and allow for the critical discrimination of muscle and adipose tissue changes (16) and can easily be incorporated in a study design as outcome measures. With the use of these approaches, we showed that patients with advanced cancer may have a potential for muscle anabolism under specific conditions. In the last few months preceding death, in the face of progressive disease, losses of muscle and adipose tissue were the norm and were of large magnitude. Some of our findings were quite unexpected given the prevailing view of cachexia as an unrelenting and progressive condition. Indeed, muscle mass was stable (the expected condition for healthy adults) 45% of the time. Another expected behavior of healthy adults is to regain weight after weight loss. We suggest that the prevalence of muscle gain (15.4% overall) and adipose tissue gain (24.8%) may have constituted such a response. Large cumulative losses of muscle and adipose tissue clearly do occur, but the progression is punctuated by periods of stability and reversal.

FIGURE 2. Percentages of intervals exhibiting tissue loss, gain, or no change. Computed tomography images falling within the indicated time frames of months before death (A and B) and different cancers (C and D) were coded as a loss or gain if $\geq 5.9 \text{ cm}^2$ of total lumbar skeletal or $\geq 14.7 \text{ cm}^2$ of total lumbar adipose tissue was lost or gained. Values within these margins ($\leq 5.9 \text{ cm}^2$ muscle tissue; $\leq 14.6 \text{ cm}^2$ adipose tissue) were coded as no change (stable). Muscle (A) and adipose (B) tissue, $n = 108, 181, 161$, and 333 scan intervals at 1, 3, 6, and 9 mo before death, respectively. Muscle (C) and adipose (D) tissue by tumor group. Statistical analysis by using logistic regression is shown in Table 2.
At this time, we may only speculate as to the causes of the loss and gain behaviors. Progressive disease appears to be associated with intense catabolism, and in the colorectal cancer patients, we previously documented a rapid increase in tumor burden concurrently with the most rapid rates of muscle and fat loss (11). Conversely, one probable cause of tissue gain may well be successful cancer therapy and good overall standards of pain and symptom management. Megace, dronabinol, tube feeding, or intravenous nutrition were excluded as potential causes of tissue gain because they were not used in this population. In this study, as in most cancer-treatment settings, there was no clinical record of referral to dietitians, many patients never have a consultation, and if they had a consultation, it would be impossible to confirm compliance to dietetic recommendations. We inferred that patients with robust fat and muscle gains must have been in positive energy balance and must have had sufficient dietary inputs to support muscle gain. A new prospective study is required to determine in what degree nutrient deficiencies drive tissue catabolism and in what extent catabolism can be attenuated or reversed by active supplementation. Harkening to the studies of Deutz et al (8) and Winter et al (9), eg, the dose, timing, and amino acid composition of protein would be worthy of additional investigation. It remains to be determined by which approaches muscle gains may be maximized, and whether muscle gain may be induced in individuals with stable muscle mass or muscle loss.

Cachexia is treated by using nutrition therapy (eg, branched chain amino acids, leucine, and EPA) and drug therapy (eg, selective androgen receptor modulators, antagonists to cytokines, or myostatin). Randomized phase III clinical trials of cachexia therapy generally include patients with documented weight loss of a specific magnitude (ie, >5% weight loss). Given that, on average, there is loss of both muscle and adipose tissue at all times during the year preceding death, it would seem rational to provide therapy for patients even without weight loss because of the reasonable expectation that all patients will begin to experience losses in the immediate short term. This thinking would require an adjustment of inclusion criteria for cachexia trials. An international consensus group (12) suggested that cachexia may become clinically refractory in the presence of rapidly progressive cancer that is unresponsive to anticancer therapy. The current findings were consistent with this notion because patients in the last 3 mo of life experienced muscle and adipose tissue loss of a large magnitude and were highly unlikely to gain either tissue. A prediction of survival with the aid of prognostic algorithms or the input of a specialist palliative consultant physician may aid in the identification of this phase of disease progression. To date, most clinical trials that included both nutrition therapy (22, 23) and drug therapy (24–26) were conducted in patients who survived ≥3 mo with progressive disease. Indeed, these studies often had negative findings (22, 24–26) that undermined an enthusiasm for investigations of cachexia therapeutics.

Nutrition therapy would be more successful if applied during the initial phase of the disease, when the window to anabolism is more likely to be open. Antithetical to current practice, we propose that candidates for cancer nutrition therapy who are most likely to

### TABLE 3

Demographics and clinical features of patients at extremes of muscle loss and gain

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>5% of individuals with the greatest muscle gain</th>
<th>5% of individuals with the greatest muscle loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle gain/loss (cm²)</td>
<td>14 (12.9, 15.3)</td>
<td>−32 (−28.6, −39.7)</td>
</tr>
<tr>
<td>Estimated kg²</td>
<td>2.3</td>
<td>−5.3</td>
</tr>
<tr>
<td>Range, kg</td>
<td>1.8–7.2</td>
<td>−11.3 to −4.1</td>
</tr>
<tr>
<td>Total n</td>
<td>43</td>
<td>43</td>
</tr>
<tr>
<td>Solid tumors (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>21</td>
<td>19</td>
</tr>
<tr>
<td>Colorectal</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Sex (M/%) (n)</td>
<td>76</td>
<td>88</td>
</tr>
<tr>
<td>Age (y)</td>
<td>60.6 ± 9.0</td>
<td>60.2 ± 8.2</td>
</tr>
<tr>
<td>Time to death (d)</td>
<td>246 (179, 281)</td>
<td>105 (57, 126)</td>
</tr>
<tr>
<td>Chart review: potential causes of loss/gain (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial response</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Stable disease</td>
<td>15</td>
<td>4</td>
</tr>
<tr>
<td>Stable disease, noted improvement in symptoms, nutrition, and functional status</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>1</td>
<td>38</td>
</tr>
<tr>
<td>Disease status unclear</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Nutrition intervention</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

1 Median; 95% CI in parentheses (all such values).
2 Estimated kilograms was calculated from Shen et al (18) as follows: whole-body skeletal muscle mass (kg) = 0.166 × [skeletal muscle >5 cm above L4–L5 (cm²)] + 2.142; $R^2 = 0.855$.
3 All values are means ± SDs.
4 Defined as a diet consult followed by a prescription of an oral nutritional supplement.
respond are patients with stable disease with >3 mo life expectancy, who may not necessarily be losing weight at that time. Rather than attempting to stem catastrophic losses in final stages of disease, the objective of early intervention would be to replenish losses and bank reserves against future losses. Multimodal therapy encompassing anti-inflammatory, anabolic, nutritional support, and physical activity may optimize such responses (27, 28).

Our population-based findings provide a backdrop for interpreting a variety of clinical trial results. The prevalence of tissue loss-stable-gain at different times in the disease trajectory provides an idea of the distribution of these features in the absence of any purposeful intervention (ie, in a placebo arm). Both anticachexia drugs and antineoplastic drugs have an obligate passage through phase I/II clinical trials, in which potential benefits and toxicities begin to be clarified. If any such therapies show a rate of net muscle gain well in excess of 15% of patients (the base value seen in our population-based cohort) (ie, as did selumetinib in a phase II trial) (21), they can be subjected to additional study as potential anabolic treatment. Conversely, drugs such as sorafenib (29) that exhibit a potent catabolic effect on muscle can be identified early, and patients who receive this type of agent may eventually receive a nutrition therapy designed to limit the degree of this unintended side effect.

In conclusion, our work provides a promising line of evidence to support the notion that advanced cancer patients have exploitable anabolic potential, which we hope will spur the development of new trials. Notwithstanding multiple factors that conspire to result in a relentless progression of cachexia, a capacity to gain physiologically meaningful amounts of muscle and adipose tissue is revealed. In individuals who gained muscle, the median quantity was estimated to be 1.3–1.9 kg and was >3 kg in some individuals. To what degree this gain translates to physical function or another clinical benefit including survival remains a matter for speculation. Future studies require outcome measures that may reveal possible functional benefits of muscle gain.

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REFERENCES


