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Sarcopenia in an Overweight or Obese Patient Is an Adverse Prognostic Factor in Pancreatic Cancer

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Abstract

Purpose: The average weight-losing pancreatic cancer patient undergoing palliative therapy is frequently overweight rather than underweight, and this can confound conventional measures used for risk stratification. The aim of this study was to evaluate if weight and body composition, specifically sarcopenia, assessed from diagnostic computed tomography (CT) scans, is of prognostic value in patients with pancreatic cancer. The nature and extent of tissue loss over subsequent months was also evaluated.

Experimental Design: A total of 111 patients entering a palliative therapy program, who had CT images and had undergone nutritional screening, were studied. In patients for whom follow-up scans were available ($n = 44$), longitudinal changes in body composition were studied at a mean of 230 ± 62 and 95 ± 60 days prior to demise.

Results: Sixty-two patients (55.9%) were sarcopenic, 44 (39.6%) were overweight/obese, and 18 (16.2%) were both. Age ≥59 years (hazard ratio, 1.71; 95% confidence interval, 1.10-2.66; $P = 0.018$), and overweight/obese sarcopenia (hazard ratio, 2.07; 95% confidence interval, 1.23-3.50; $P = 0.006$) were identified as independent predictors of survival on multivariate analysis. Longitudinal analysis revealed that total fat-free mass index decreased from 15.5 ± 2.5 kg/m^2 to 14.5 ± 2.0 kg/m^2 ($P = 0.002$), and total fat mass index decreased from 7.5 ± 2.0kg/m^2 to 6.0 ± 1.5kg/m^2 ($P < 0.0001$) over 135 days.

Conclusions: Sarcopenia in overweight/obese patients with advanced pancreatic cancer is an occult condition but can be identified using CT scans. This condition is an independent adverse prognostic indicator that should be considered for stratification of patients' entering clinical trials, systemic therapy, or support care programs. (Clin Cancer Res 2009;15(22):6973–9)

Pancreatic cancer is the fourth leading cause of cancer-related death in Western countries (1). At the time of diagnosis, tumor resection with curative intent is only possible in 10% to 15% of subjects (2, 3), leaving a large population with poor prognosis and limited therapeutic options. Overall, the 5-year survival rate is only about 4% (4).

One of the most distressing features of pancreatic cancer is marked and progressive weight loss. Cachexia occurs in up to 80% of deaths in patients with advanced pancreatic cancer (5). Cachexia has been shown to worsen prognosis and has also been associated with impairment of physical function, increased psychological distress, and low quality of life (6, 7). Patients with pancreatic cancer often report a decreased dietary intake and many symptoms such as anorexia, early satiety, anxiety, depression, pain, and nausea (8).

Due to the epidemic of obesity in Western society, a substantial proportion of oncology patients at the start of palliative therapy now have a body mass index (BMI) in the overweight range (9), and this can confound conventional measures used for risk stratification. Indeed recent studies have reported that obesity (i.e., BMI ≥30 kg/m^2) in the presence of sarcopenia is predictive of morbidity and mortality in both malignant and nonmalignant disease (10, 11). The development of novel methods of image analysis enabling routine derivation of body composition data from diagnostic computed tomography (CT) scans (and in particular the estimation of skeletal muscle mass) provides an opportunity to assess if measures of body composition have any prognostic value in patients with pancreatic cancer. The present study focused on sarcopenia specifically, both in the presence or absence of an elevated BMI.

When considering the significance of sarcopenia in a given population, it is important to know the likely longitudinal

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Translational Relevance

In the present study, patients had a mean body mass index of 23.9 with 40% of individuals being in the overweight/obese range. However, underneath this mantle of adipose tissue the previously noted tendency to muscle wasting continues. The use of computed tomography (CT) images in the present study identified that 56% of patients had sarcopenia at the time of presentation. This study also shows that sarcopenia in overweight or obese pancreatic cancer patients is an independent determinant of poor prognosis. Routine diagnostic CT scans are a good resource for detailed nutrition/metabolic assessment of patients and the identification of overweight/obese sarcopenia. The presence of overweight/obese sarcopenia should be considered in the stratification of patients' entering clinical trials, systemic therapy, or support care programs.

pattern of wasting and how this may be altered by concomitant systemic oncologic therapy. The nutritional and metabolic status of patients who respond to chemotherapy may improve spontaneously, and a substantial proportion of patients now receive antineoplastic therapy even in the last weeks of life. Another aim of the present study was to assess time course changes in regional body fat and lean tissue compartments by analyzing CT images in a subset of pancreatic cancer patients being managed within a regional palliative therapy program.

Materials and Methods

Patients. All patients referred to the regional cancer center in Edmonton, Alberta, Canada from January 2004 to October 2008 were considered for the study. Patients with a primary diagnosis of pancreatic cancer entering a palliative program who had an abdominal CT scan within 60 d of initial assessment were selected for the study (n = 111). Patients with ampullary carcinoma, cholangiocarcinoma, or neuroendocrine tumors were excluded. Coding of the primary cancer by its site and morphology, clinical information, and demographic information were obtained from the Alberta Cancer Registry for every patient in the cohort. The Alberta Cancer Registry is a computerized database of all cancer cases in the region (population 1.8 million). Patient-reported height, weight, and weight history were collected during this visit by use of the Patient-Generated Subjective Global Assessment (12). Height and weight data were subsequently used to compute a common anthropometric descriptor, BMI (kg/m^2). Height and weight recorded by hospital staff on the same date were used for verification where available, and classification of patients' BMI with the use of patient-reporting was found to be accurate. Patient-reported height, weight, and weight history have been shown to be reliable (13). Stage of disease was based on the American Joint Committee on Cancer stage groupings I, II, III, and IV.

From the initial cohort of 111 patients, 44 patients were further identified who: (*a*) had had at least one further follow-up CT scan, and (*b*) had a documented duration of survival for inclusion into the study of longitudinal changes of body composition.

CT image analysis. CT scans used for analysis were done solely for routine cancer care. Two consecutive transverse CT images extending from the third lumbar vertebrae (L3) in the inferior direction were assessed for each scan date and then averaged, the foremost image being the one in which both transverse processes were first clearly visible. Images were analyzed with SliceOmatic V4.3 software (Tomovision), which enables specific tissue demarcation using Hounsfield unit (HU) thresholds. Skeletal muscle was identified and quantified by HU thresholds of -29 to +150 (14). The muscles in the L3 region contain *psoas, erector spinae, quadratus lumborum, transversus abdominus,* external and internal obliques, and *rectus abdominus.* The following HU thresholds were used for adipose tissues: -190 to -30 for s.c. and i.m. adipose (15), and -150 to -50 for visceral adipose (16). Tissue boundaries were manually corrected as needed. Cross-sectional areas (cm^2) were computed automatically by summing tissue pixels and multiplying by pixel surface area. All CT images were analyzed by a single trained observer. Cross-sectional area for muscle and adipose tissue was normalized for stature (cm^2/m^2) and reported.

Routine diagnostic CT scans usually only evaluate the chest, abdomen, and pelvis, and therefore only partial images are available to determine skeletal muscle mass. Estimates of whole body stores were generated from the raw data (cm^2) using the following regression equations by

Table 1. Overall patient demographics, nutritional variables, and body composition at the time of assessment

	No. of patients (n = 111)
Age (y)*	64.4 ± 9.3
Sex	
Male	52 (46.8)
Female	59 (53.2)
Tumor site	
Head of pancreas	57 (61.3)†
Body of pancreas	18
Tail of pancreas	4
Pancreatic duct	1
Neck of pancreas	2
Overlapping lesion	11
Not recorded	18
Histology	
Adenocarcinoma	84 (75.7)
Unknown	27
Stage	
II	1
III	7
IV	103 (92.8)
BMI (kg/m^2)*	23.9 ± 4.9
Underweight (BMI <18.5 kg/m^2)	11 (9.9)
Normal (BMI 18.5-24.9 kg/m^2)	56 (50.5)
Overweight/obese (BMI ≥25 kg/m^2)	44 (39.6)
Percentage weight loss (in preceding 6 mo)*	12.14 ± 6.35
Lumbar total muscle cross-sectional area (cm^2)*	126.0 ± 30.7
Lumbar total adipose tissue cross-sectional area (cm^2)*	243.7 ± 162.3
Lumbar skeletal muscle index (cm^2/m^2)*	43.8 ± 7.9
Lumbar adipose tissue index (cm^2/m^2)*	86.1 ± 57.4
Estimated total fat-free mass (kg)*	43.9 ± 9.2
Estimated total fat mass (kg)*	21.2 ± 6.9
Sarcopenic	62 (55.9)
Overweight/obese and sarcopenic	18 (16.2)
Status	
Dead	101 (91.0)
Alive	10

NOTE: Values are number of patients with percentages in parentheses unless indicated otherwise.
*Values are mean ± SD.
†Unknown tumor site was excluded from calculation of overall percentage.

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Mourtzakis et al. (17), which show a close correlation between muscle and fat areas in CT images at the third lumbar vertebrae and whole body compartments of fat-free mass (FFM) and fat mass (FM) respectively.

Total body fat-free mass (FFM) (kg) = 0.3 × [skeletal muscle at L3 (cm^2)] + 6.06 (r = 0.94)

Total body fat mass (FM) (kg) = 0.042 × [total adipose tissue at L3 (cm^2)] + 11.2 (r = 0.88)

The respective indexes for FFM and FM (kg/m^2) were also reported.

CT dates were expressed in terms of the number of days to death. Any change in tissue area was expressed as either an absolute change (cm^2) or as a percentage change per 100 days. This provided a standardized unit and allowed for comparison across different intervals.

Cutoffs for sarcopenia were based on a CT-based sarcopenic obesity study of cancer patients by Prado et al. (i.e., L3 skeletal muscle index: ≤38.5 cm^2/m^2 for women and ≤52.4 cm^2/m^2 for men; ref. 10).

Statistical analysis. Data are presented as mean ± SD unless otherwise stated. Survival was determined from the time of initial assessment until death or until the censor date of January 5, 2009.

Univariate and multivariate survival analyses and calculation of hazard ratios were done using a Cox regression model. Owing to the large number of covariates examined, only those that were significant on univariate analysis were included in multivariate analysis. Receiver-operator characteristic curves were used to select cutoff values for continuous variables. Values with the best combination of sensitivity and specificity were chosen. A backward stepwise procedure was done to derive a final model of the variables that had a significant relationship with survival. To remove a variable from the model, the corresponding *P* value had to be >0.05.

Comparisons between groups of patients were assessed using one-way ANOVA or Pearson's χ^2 test. Survival curves were constructed using the Kaplain-Meier technique. Log-rank test was used to compare survival between groups of patients. Comparison of data at different time points for body composition analysis was done using the paired *t*-test. *P* values <0.05 were regarded as statistically significant. Statistical analysis was done using SPSS 15.0 statistical package (SPSS Inc.).

Results

Details of the 111 pancreatic cancer patients identified at the time of referral to the cancer center are shown (Table 1). About two thirds of the patients had tumors at the head of the pancreas. Approximately 75% of patients had biopsy-proven adenocarcinoma. At the time of censoring, 101 patients (91.0%) had died. Overall median survival was 130 days [interquartile (IQ) range, 71-302 days]. Percentage weight loss in the preceding six months was 12 ± 6%, with 89 patients (80.2%) losing >5% of their normal body weight. BMI at the time of assessment was 23.9 ± 4.9 kg/m^2, and 44 patients (39.6%) were overweight or frankly obese (BMI ≥25 kg/m^2). Body composition parameters of patients are also reported in Table 1. Sixty-two patients (55.9%) were sarcopenic at this point; 18 patients were overweight/obese (BMI ≥25 kg/m^2) and sarcopenic. The prevalence of sarcopenia within the various BMI categories is presented in Fig. 1.

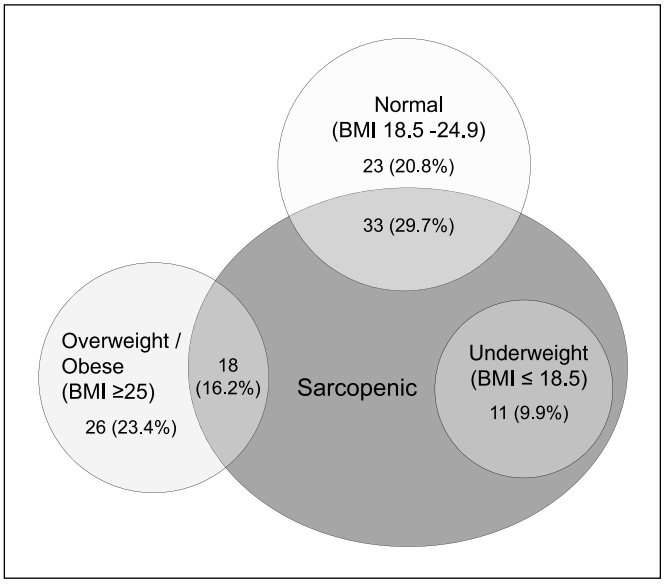

Fig. 1. Venn diagram of BMI classes and sarcopenic patients.

Patients were then divided into four groups: neither sarcopenic nor overweight/obese, overweight/obese, sarcopenic, and both sarcopenic and overweight/obese (Table 2). There were no significant differences in age, sex, tumor site, histology, stage of disease, and weight loss among the groups.

On univariate analysis, age and overweight/obese sarcopenia were associated with outcome for the patient group. Overweight/obesity (BMI ≥25 kg/m^2) alone as well as sarcopenia on its own failed to reach statistical significance for patient outcome (Table 3). In contrast, median survival for patients who were both overweight/obese and sarcopenic was 55 days (IQ range, 43-207 days) compared with 148 days (IQ range, 80-369 days) for the rest of the patient cohort without overweight/obese sarcopenia (log-rank test, *P* = 0.003; Fig. 2). Using receiver-operator characteristic curves, the cutoff value with the best discriminatory value for age was ≥59 years.

On multivariate analysis, age ≥59 years (hazard ratio, 1.71; 95% confidence interval, 1.10-2.66; *P* = 0.018) and overweight/obese sarcopenia (hazard ratio, 2.07; 95% confidence interval, 1.23-3.50; *P* = 0.006) retained independent prognostic value (Table 3).

Longitudinal analysis of body composition. A subset of 44 patients underwent repeated CT scans as part of their medical management and was therefore available for study of longitudinal changes in body composition. This cohort of patients had a significantly longer survival compared with the entire group (median survival, 189 days versus 130 days; *P* = 0.019, log-rank test). Seventy-one percent of patients with follow-up CT scans received active treatment compared with just 28% of patients who had no follow-up CT scans (*P* < 0.0001, χ^2 test). Patients had their first CT scan at a mean of 230 ± 62 days before death. The second CT scan was done at a mean of 95 ± 60 days before death.

The changes in cross-sectional area of skeletal muscle and adipose tissue between the two scans are presented in Table 4. Patients displayed a significant loss of both skeletal muscle and adipose tissue. Overall, 32 patients (72.7%) lost skeletal muscle and all but one patient (97.6%) lost adipose tissue. The measurements for cross-sectional area were used to estimate whole body FFM and whole body FM using regression equations and then normalized for height (kg/m^2; Table 4).

Twenty patients (45.5%) were sarcopenic at the time of the first CT, with an estimated FFM index of 15.5 ± 2.5 kg/m^2. By the time of the second CT, 27 patients (61.4%) were sarcopenic and FFM had decreased to 14.5 ± 2.0kg/m^2. Estimated FM index decreased from 7.5 ± 2.0 kg/m^2 (1st CT) to 6.0 ± 1.5 kg/m^2 (2nd CT).

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Table 2. Comparison of demographic characteristics and body composition of patients who were neither overweight nor sarcopenic, sarcopenic alone, overweight alone, and both overweight and sarcopenic

	BMI <25 kg/m²		BMI ≥25 kg/m²		*P*
	Not overweight, not sarcopenic (*n* = 23; 21%)	Not overweight, sarcopenic (*n* = 42; 38%)	Overweight/Obese (*n* = 28; 25%)	Overweight/Obese and sarcopenic (*n* = 18; 16%)	
Age (y)					
Mean ± SD	60.7 ± 7.5	65.8 ± 10.2	64.3 ± 9.0	66.0 ± 9.3	0.169*
Sex, *n* (%)					
Male	8 (34.8)	20 (47.6)	11 (39.3)	13 (72.2)	0.084†
Female	15 (65.2)	22 (52.4)	17 (60.7)	5 (27.8)	
Tumor site, *n* (%)					
Head	8 (34.8)	26 (61.9)	14 (50.0)	9 (50.0)	0.088†
Body	9 (39.1)	3 (7.1)	4 (14.3)	2 (11.1)	
Overlapping lesion	3 (13.0)	3 (7.1)	2 (7.1)	3 (16.7)	
Histology, *n* (%)					
Adenocarcinoma	18 (78.3)	28 (66.7)	22 (78.6)	16 (88.9)	0.287†
Stage, *n* (%)					
IV	20 (87.0)	37 (88.1)	28 (100)	18 (100)	0.149†
BMI (kg/m²)					
Mean ± SD	22.2 ± 1.9	20.5 ± 2.8	27.6 ± 2.7	28.5 ± 6.3	<0.0001*
% Weight loss					
Mean ± SD	12.83 ± 5.80	13.08 ± 6.45	11.36 ± 6.72	10.45 ± 6.24	0.435*
Lumbar total muscle cross-sectional area (cm²)					
Mean ± SD	129.5 ± 31.8	115.0 ± 29.2	138.5 ± 29.6	128.0 ± 27.6	0.014*
Lumbar total adipose tissue cross-sectional area (cm²)					
Mean ± SD	185.0 ± 137.7	168.8 ± 130.6	344.2 ± 148.0	348.6 ± 155.1	<0.0001*
Lumbar skeletal muscle index (cm²/m²)					
Mean ± SD	46.2 ± 7.1	39.3 ± 6.2	49.4 ± 7.3	42.7 ± 6.6	<0.0001*
Lumbar adipose tissue index (cm²/m²)					
Mean ± SD	68.4 ± 52.3	57.6 ± 42.0	125.6 ± 55.7	117.1 ± 50.7	<0.0001*
Estimated total fat-free mass (kg)					
Mean ± SD	44.9 ± 9.5	40.6 ± 8.8	47.6 ± 8.9	44.5 ± 8.3	0.014*
Estimated total fat mass (kg)					
Mean ± SD	19.0 ± 5.8	18.3 ± 5.5	25.7 ± 6.2	24.2 ± 7.7	<0.0001*

*One-way ANOVA.
†Pearson's χ^2 test.

A distinct distribution for muscle and adipose tissue changes over time is more clearly revealed by analysis of population tertiles (Fig. 3). The overall change of skeletal muscle was -3.1 ± 12.0%/100 days. However, the 1st tertile gained a small amount of muscle tissue (7.9 ± 14.4%/100 days) whereas the 3rd tertile lost muscle at a rate of -12.7 ± 5.2%/100 days. In comparison, adipose tissue was lost across all three tertiles and the overall change of adipose tissue was -40.4 ± 25.4%/100 days (*P* <

Table 3. Hazard ratio for risk of death associated with clinical variables and body composition in pancreatic cancer patients (*n* = 111)

	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	*P**	Hazard ratio	95% CI	*P*†
Age	1.025	1.002-1.048	0.03			
≥59 y				1.708	1.097-2.660	0.018
Sex	0.793	0.534-1.178	0.25			
Tumor site	1.031	0.977-1.087	0.268			
Histology	0.791	0.499-1.254	0.32			
Stage	1.829	0.910-3.677	0.09			
Overweight/obese vs. normal/under weight	1.454	0.969-2.181	0.071			
Percentage weight loss	0.991	0.959-1.025	0.599			
Lumbar skeletal muscle index (cm²/m²)	1.001	0.976-1.026	0.964			
Lumbar adipose tissue index (cm²/m²)	1.003	0.999-1.007	0.153			
Sarcopenia vs. no sarcopenia	1.284	0.863-1.910	0.217			
Sarcopenia plus overweight/obese vs. other patients	2.177	1.292-3.670	0.003	2.071	1.227-3.496	0.006

Abbreviations: 95% CI, 95% confidence interval.
*Cox univariate analysis.
†Backward conditional method of Cox proportional hazards model.

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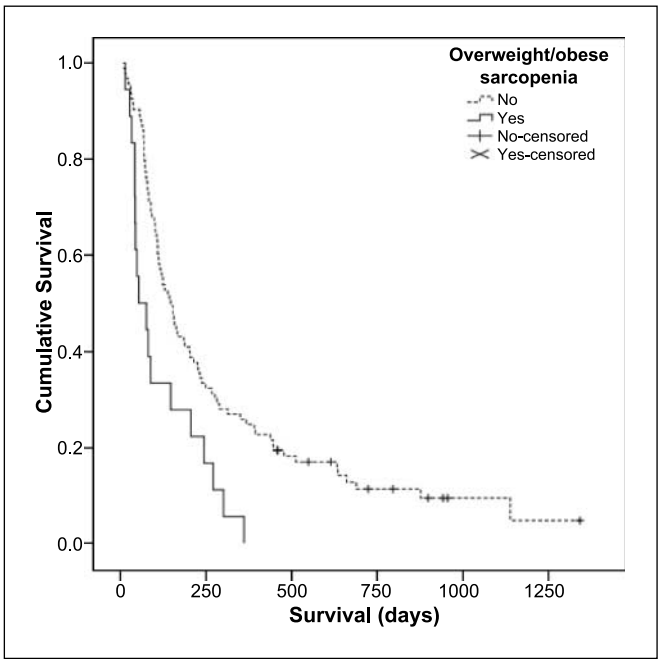

Fig. 2. Survival curves of patients with overweight/obese sarcopenia and patients without overweight/obese sarcopenia.

0.0001, paired *t*-test). The proportion of patients receiving chemotherapy was not significantly different across all three tertiles of muscle ($P = 0.372$, χ^2 test) or adipose tissue loss ($P = 0.804$, χ^2 test). Moreover, the changes in muscle ($P = 0.113$, Student's *t*-test) and fat mass ($P = 0.862$, Student's *t*-test) were not significantly different between those who did or did not receive chemotherapy. There was also no significant difference in survival across all three tertiles for both muscle loss ($P = 0.142$, log-rank test) and adipose tissue loss ($P = 0.542$, log-rank test).

Discussion

Patients with pancreatic cancer have long been associated with the most severe forms of cachexia. In a similar study undertaken more than 10 years ago, the present authors documented median BMI at diagnosis to be 20.7, and this fell to 17.7 near to the time of death (18). Average weight loss over this time increased from 15% to 25%. Loss of muscle and fat to levels consistent with significant undernutrition increased from 30% to 70% and from 65% to 90%, respectively. This was consistent with the conventional view of cancer cachexia (i.e., marked weight loss, severe muscle wasting and gross loss of s.c. fat; ref. 19). In the present study, patients had a mean BMI of 23.9 with 40% of individuals being in the overweight/obese range. Thus, the average physiognomy seems to have changed with patients showing large energy reserves (fat) at the time of presentation with advanced disease. However, underneath this mantle of adipose tissue the previously noted tendency to muscle wasting continued. The use of CT images in the present study identified that 56% of patients had sarcopenia at the time of presentation (Table 1) and the tendency to muscle loss continued in at least a proportion of patients (Fig. 3).

A BMI <18.5kg/m^2 is considered by many authorities to represent an individual at serious risk of undernutrition (20). In the present study, only 10% of individuals at baseline fulfilled this criterion. Given the prevalence of overweight/obesity (40%) it would seem unlikely that even in the presence of ongoing weight loss, the majority would reach this boundary at or near the time of death. However, BMI has clear limitations, and more detailed evaluation of body composition clearly revealed wasting of the lean tissues, with a majority of patients below or well below benchmark levels of muscularity known to be associated with mortality and functional disability (21). The estimated lean body mass of patients classified as sarcopenic was within the range described for a variety of wasted/emaciated patient populations with and without malignant disease (10, 22). In the current literature it is becoming increasingly evident that concurrent sarcopenia and high fat mass is a worst case scenario (10, 11, 23, 24), and this was clearly apparent in our study group (albeit small), in which sarcopenic overweight/obese patients had the worst prognosis overall, even compared with patients who were sarcopenic and had a lower body weight.

There is ongoing controversy as to what the best definition for sarcopenia is. Mourtzakis et al. have previously shown that CT cross-sectional area at L3 is strongly related to appendicular skeletal mass, measured by dual-energy X-ray densitometry, used commonly in the definition of sarcopenia (17). Subsequent derived cutoffs for sarcopenia, based on CT, used in this study are in fact close to that described by Baumgartner et al.

Table 4. Change in body composition over time in pancreatic cancer patients ($n = 44$)

	First CT scan	Second CT scan	Δ	*P**
Time to death (d)	230 ± 62	95 ± 60	135 ± 57	
Skeletal muscle (cm^2)	126.5 ± 31.1	119.6 ± 28.6	-7.0 ± 13.6	0.002
Adipose tissue (cm^2)				
Visceral adipose tissue	91.2 ± 69.9	45.4 ± 47.0	-45.8 ± 47.5	<0.0001
Intramuscular and subcutaneous adipose tissue	148.5 ± 85.8	87.0 ± 66.4	-61.5 ± 53.9	<0.0001
Total	236.6 ± 145.5	128.6 ± 102.6	-108.0 ± 89.1	<0.0001
Estimated whole body FFM (kg)	44.0 ± 9.3	41.9 ± 8.6	-2.1 ± 4.1	0.002
Estimated whole body adipose tissue (FM) (kg)	21.1 ± 6.1	16.6 ± 4.3	-4.5 ± 3.7	<0.0001
Estimated FFM index (kg/m^2)	15.5 ± 2.5	14.5 ± 2.0	-1.0 ± 1.5	0.002
Estimated FM index (kg/m^2)	7.5 ± 2.0	6.0 ± 1.5	-1.5 ± 1.5	<0.0001

NOTE: Values are mean ± SD.
*Paired *t*-test.

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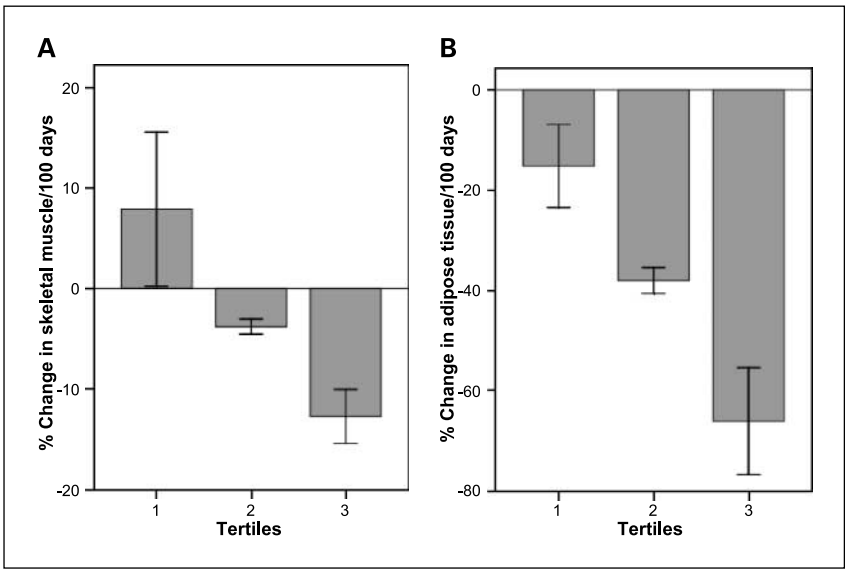

Fig. 3. Intensity of changes in body composition presented by tertiles. *A,* skeletal muscle. *B,* adipose tissue.

(ref. 22; i.e., appendicular skeletal mass >2 SDs below a young healthy adult population). Equally, the optimal regression for conversion of CT image data to conventional units of whole-body composition measures has yet to be resolved in large population studies. In the present study, previously reported regression equations determined from a heterogeneous group of cancer patients were used (17).

Sarcopenia alone had no discernable effect on mortality, yet being overweight/obese and sarcopenic was associated with decreased survival duration. However, a variable can only serve a predictive function where it varies in the relevant population. It should be noted that all patients with a BMI <18.5 were sarcopenic, and the majority were sarcopenic in the BMI range of 18.5-24.9. Thus, one explanation for the finding that sarcopenia was not predictive for the overall population, but was predictive for those with obesity, would lie in the differential frequency distribution of sarcopenia in the different BMI categories. Evaluation of this question in a much larger patient population would help resolve this issue. There has also been some evidence that body composition changes in advanced cancer may have different impacts on survival in males and females (25). However, the present study was not powered sufficiently to analyze the differences in gender due to the small sample sizes. It would be interesting to evaluate this in a larger population.

In the present study, patients entering the palliative phase of their pancreatic cancer management had a remarkably high prevalence of sarcopenia compared with reports in the literature for healthy elderly in a similar age bracket (22), thereby suggesting that substantial muscle wasting had occurred prior to initial evaluation of these patients. The pre-existing nature of this muscle loss makes it difficult to comment as to its mechanisms, except perhaps to suggest that it may be driven by the primary malignancy, by weight loss, and/or by comorbid conditions that include obesity, insulin resistance, various types of organ failure, and low levels of physical activity. The muscle loss that occurred thereafter, which was characterized during the 135-days scan-scan interval, may be driven by disease progression, increased metabolism, and inflammation (26, 27), and by negative energy balance that might be inferred from the loss of fat mass (i.e., 4.54 kg × ~9,000 kcal/kg = 40,840 kcal) in 135 days.

The mechanism that links sarcopenic overweight/obesity with accelerated demise is not known. Muscle wasting is a known complication associated with insulin resistance found commonly in obesity (28). Adipose tissue synthesizes and secretes circulating hormones and "adipokines" that act as systemic inflammatory mediators and signals of nutritional status (29). These adipocyte factors, such as tumor necrosis factor-α and interleukin-6, are thought to play a major role in the induction of insulin resistance in skeletal muscle leading to an increase in muscle protein loss. The main mediators thought to be involved in this process are inhibitor κB kinase and its downstream effector NF-κB (30). However, not all patients who are overweight/obese have sarcopenia. It may be that cancer-related factors stimulate the initial loss of muscle, and being overweight/obese perpetuates and/or enhances muscle loss/loss of muscle function leading to poorer survival. The observation that overweight/obesity may be associated with better survival in patients with weight-losing cardiac failure (31) may seem to contradict the present observations in cancer patients. However, the studies in patients with cardiac failure have not been stratified for body composition (specifically sarcopenia) and may represent a disease-specific phenomenon.

Current published results on body composition changes in cancer are varied. Some studies confirm a decline in lean body mass (32, 33), whereas others emphasize a loss of body fat (34, 35). There are also reports that suggest a proportional loss of lean tissue and fat leading to an unchanged body composition (36, 37). In the present study, roughly half of the patients were found to be already sarcopenic at the time of assessment. Subsequently, a much greater rate of fat loss was noted as compared with muscle loss (see longitudinal study). In fact, some patients were able to maintain or even gain muscle mass. The patients that gained muscle could have been positive responders to chemotherapy. However, in patients with pancreatic cancer, the use of CT scans to determine response to chemotherapy is complicated by factors such as peritumoral inflammation, therefore duration of survival was regarded as a more robust measure (accepting the small numbers involved in this study). In the present study the survival of patients was not significantly different across all three tertiles of loss of muscle

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mass. Thus, response to chemotherapy as the main reason for patients to gain muscle mass cannot be confirmed. An alternative hypothesis would be that a proportion of patients were able to activate compensatory mechanisms aimed at conserving muscle. There is increasing evidence that gene polymorphisms are related to cancer cachexia susceptibility (38, 39).

Systemic inflammation is known to be a key mediator in cachexia (40), and has been associated with poor prognosis in previous studies on pancreatic cancer (41, 42). The present study lacks measures of systemic inflammation such as C-reactive protein, which may be significant when assessing factors influencing survival in pancreatic cancer. Nevertheless, this study has shown that advanced pancreatic cancer patients who are both overweight/obese and sarcopenic can be identified using diagnostic CT scans. Due to the very short median survival of such patients (55 days) overweight/obese sarcopenia should be taken into consideration when planning whether systemic anticancer therapy is appropriate. Moreover, overweight/obese sarcopenia should be considered for stratification of patient's entering clinical trials.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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