Body composition impact on survival and toxicity of treatment in pancreatic cancer: cross-sectional pilot study

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ABSTRACT – **Background** – Weight loss and body composition changes are common in patients with pancreatic cancer. Computed tomography (CT) images are helpful to investigate body composition and its changes and to discriminate the different kinds of body tissues. Patients with pancreatic cancer routinely undergo CT scans. **Objective** – To verify the association of muscle mass and visceral fat measured by CT with toxicity and survival of patients with pancreatic cancer. **Methods** – We evaluated the imaging of the abdomen of all consecutive adult patients with pancreatic cancer treated between October 2007 and September 2015 in our service, to assess skeletal muscle mass and fat, intramuscular fat and visceral fat. We graded treatment toxicity symptoms according to the Common Toxicity Criteria of the United States National Cancer Institute (version 2.0). **Results** – The study involved 17 patients, with a mean age of 63 ($\pm$10) years (range: 51–73 years). Eleven (65%) were male. The mean initial body mass index (BMI) was 26 kg/m^2 ($\pm$3) and 23 kg/m^2 ($\pm$3) after treatment. The mean weight loss was 10.0 kg ($\pm$6.8; 13%). Sarcopenia was present in 47% of patients, and it was not associated with significant differences in muscle mass, visceral fat, toxicity or survival. The mean skeletal muscle attenuation was 36 Hounsfield units, not associated with survival or treatment toxicity. Mean muscle mass was not associated with toxicity either. However, there was a significant inverse association between toxicity and visceral fat. **Conclusion** – Muscle mass had no impact on the survival or on treatment toxicity among the patients with pancreatic cancer. However, the visceral fat exerted a protective effect against the treatment toxicity. We stress the importance of further studies on visceral fat associated with prognosis and toxicity in cancer patients.

HEADINGS – Body composition. Pancreatic neoplasms. Nutritional assessment.

INTRODUCTION

Pancreatic cancer is a highly lethal malignancy, with a survival rate at 5 years ranging from 0.4% to 4%[1-4]. In Brazil, the disease is responsible for about 2% of all diagnosed cases of cancer and 4% of all deaths[5]. Weight loss is common in patients with pancreatic cancer at diagnosis (5%–10%) and before death (≤24%), which contributes to a worse prognosis. Associated with weight loss, the individual may show changes in body composition (lean and adipose tissue compartments), resulting from the decrease in food intake and metabolic disorders, and the disease may also lead to cachexia and/or sarcopenia[6-9].

Nutritional assessment using body mass index (BMI) solely does not reveal changes in body composition. With the advancement of new technologies, different methods to assess body composition (lean and adipose tissue) have been developed and validated for research, focused on aging and chronic diseases, and have emerged as important predictors of oncology outcomes[7,9-11]. Computerized tomography (CT) images are helpful to investigate body composition and its changes throughout the disease evolution and to discriminate the different kinds of body tissues[9-11]. However, there are limitations in this method such as high-dose radiation exposure, high cost, and low accessibility[9,10]. Still, because cancer patients routinely undergo routine CT scans, there would be no increment in the risk of exposure to radiation nor difficult access to this technology[12,13].

We performed a retrospective cross-sectional study designed to evaluate the association of muscle mass and visceral fat with toxicity and survival in patients with pancreatic cancer.

METHODS

Patients and study

This is a cross-sectional study carried out at one private hospital (in São Paulo, Brazil), from October 2007 to September 2015, based on the review of medical records. The Institutional Review Board approved the study (protocol 2098-14), and the anonymity of the patients was guaranteed. Informed consent was waived by the ethics committee since the study is based on medical records review.

Initially, we evaluated all patients with pancreatic cancer undergoing antineoplastic treatment (surgery, chemotherapy and/or radiotherapy) for inclusion in this study. The inclusion criteria for this study were: adult (≥18 years), pancreatic cancer patients who had undergone surgery and chemotherapy and routine CT scans

for disease staging, containing images at L3. Exclusion criteria: patients who did not have tomographic staging images available, chronic renal failure, congestive heart failure or liver cirrhosis cases. We also excluded patients who had undergone radiotherapy or chemotherapy alone.

Body composition measurements
Anthropometric measurements

We measured the initial and the final weight and height. We recorded weight with a medical balance beam scale and height with a stadiometer. We calculated body mass index (BMI) as weight (kg)/height (m²). For patients aged 18–60 years, we classified the results of BMI as recommended by the World Health Organization (WHO)[14]. For elderly patients (≥60 years), we used the SABE/OPAS classification (2003)[15].

Image analysis

We measured regional adipose tissue (visceral and subcutaneous) and muscle tissue in the CT images, in the period of ≤60 days before the start of treatment. We used the third lumbar vertebra (L3) as a reference point because it contains muscle tissue of the psoas, erector spinae, quadratus lumborum, transversus abdominus, external and internal obliques, rectus abdominus[16]. Taken together, they present excellent correlation to estimate total lean body mass[16]. We used pre-established thresholds of Hounsfield units (HU), and we identified the different tissues by CT, considering the following parameters: muscle mass varies between -29 and +150 HU, subcutaneous and intramuscular fat tissues vary from -190 to -30 HU, and visceral fat from -150 to -50 HU[16,17].

We assessed four consecutive slices, from L3 to the iliac crests, to measure the cross-sectional area of muscle and adipose tissue (visceral, subcutaneous and intramuscular), expressed as cm², and the skeletal muscle attenuation. We analyzed images using Slice-O-Matic software V4.3 (Tomovision). to quantify lean mass, intramuscular adipose tissue, subcutaneous adipose tissue, visceral fat, and total adipose tissue. We took these tissue areas in cm² and used them to calculate whole-body mass for each in kilograms (kg)[16-18]. We used the following equations to calculate it[16-18]:

– Lean mass tissue (kg) = 0.3 × [lean mass tissue at L3 (cm²)] + 6.06;

– Fat tissue (kg) = 0.042 × [fat tissue at L3 (cm²)] + 11.2.

We also calculated the skeletal muscle index (SMI) according to the equation:

SMI = skeletal muscle area of the L3 region (cm²)/height (m²)

We considered individuals as sarcopenic when showing SMI in the region of L3 of <38.5 cm²/m² for women and <52.4 cm²/m² for men[19].

Toxicity assessment

We graded cancer treatment toxicity (gastrointestinal events) according to the National Cancer Institute Common Toxicity Criteria, version 2.0. We obtained patient toxicity assessments from the medical records[20].

Statistical analysis

Data were expressed by mean ± standard deviations (SD) in the case of quantitative variables and absolute frequencies and percentages for the qualitative variables. The association of the body composition characteristics with toxicity was assessed with the Mann-Whitney test. Spearman correlations of the initial and final weight/BMI and measures body composition were calculated. The influence of anthropometric measurements and body composition in the survival of patients was evaluated with bivariate Cox regression. The estimate of survival was performed using the Kaplan-Meier function according to the presence of sarcopenia and compared using the log-rank test. The tests were performed at the 5% significance level. Statistical analysis was done using SPSS software.

RESULTS

We identified 60 eligible cases from the hospital's medical archives, of which 17 underwent surgery followed by chemotherapy and had CT scans available. The most commonly used chemotherapeutics were gemcitabine, cisplatinum, and oxaliplatin. FIGURE 1 shows the flowchart of patients' inclusion. The study consisted of 11 male patients (65%) and 6 women (35%), with a mean age of 63 years (±10) (51–73 years). The patients' demographics are described in TABLE 1.
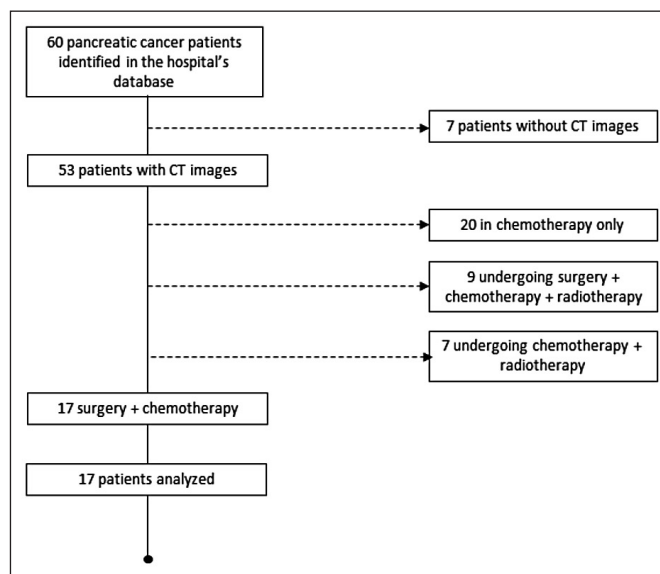

FIGURE 1. Flowchart of patients' inclusion in the study.

TABLE 1. Anthropometric data of patients with pancreatic cancer in means (standard deviation).

Variables	Patients (n=17)
Age (years)	63 (±10)
Initial weight (kg)	74 (±13)
Initial BMI (kg/m²)	26 (±3.0)
Final weight (kg)	65 (±14)
Final BMI (kg/m²)	23 (±3.0)
Weight loss (kg)	10 (±6.8)

BMI: body mass index.

Over half of the patients (65%) had localized tumors in the pancreas head, followed by 29% and 6% on the tail of the pancreas body. The main histological type was adenocarcinoma, stage II (76%), III (12%) and IV (12%). The adverse events most frequently reported by patients were nausea (76.5%), loss of appetite (59%),

vomiting (41%), diarrhea (35%), and constipation (12%). Only 2 (12%) patients reported no adverse events resulting from antineoplastic therapy. In our population, 10 (59%) patients died, over a period of 8 years. The median overall survival was 19 months (±14).

The initial mean BMI was 26 kg/m^2 (±3.2), and final BMI was 23 kg/m^2 (±3.0). At diagnosis, there was 1 (6.0%) malnourished patient, there were 8 (47.0%) eutrophic, 7 (41.0%) overweight and 1 (6.0%) obese patients. At the end of study, we observed 8 (47.0%) malnourished patients, 6 (35.0%) eutrophic, and 3 (18%) were overweight. The mean weight loss was 10 kg (±6.8) (13%) after the treatment. TABLE 2 shows the data of body composition (in cm^2), from which we estimated the amount of lean body mass and adipose tissue, described in TABLE 3.

A greater amount of visceral fat was significantly associated with the absence of symptoms of toxicity (Mann-Whitney test; P=0.003). However, there was no significant association of these symptoms with muscle mass (TABLE 4). Age was not significantly associated with initial body weight, BMI or adipose tissue. There was no association of muscular attenuation and survival or toxicity.

TABLE 2. Variables of body composition in patients with pancreatic cancer in means (standard deviation).

Variables	Values
Lean mass (cm^2)	127 (±31.3)
Intramuscular adipose tissue (cm^2)	11 (±8.1)
Visceral fat (cm^2)	148 (±79.1)
Subcutaneous adipose tissue (cm^2)	187 (±79.3)
Total adipose tissue (cm^2)	345 (±129.7)
Lean mass (kg)	44 (±9.4)
Visceral fat (kg)	18 (±5.5)
Total adipose tissue (kg)	28 (±5.5)
Muscle attenuation (HU)	36 (±8.9)

HU: Hounsfield units.

TABLE 3. Values of weight and body compartments according to age.

Variables	Patients <60 years (n=06)	Patients >60 years (n=11)	P
Initial weight (kg)	72.5 (±18.0)	75 (±11.0)	0.718
Final weight (kg)	58 (±14.0)	67 (±14.0)	0.265
Initial BMI (kg/m^2)	26 (±4.5)	26.5 (±2.5)	0.670
Final BMI (kg/m^2)	22 (±3.0)	23 (±2.8)	0.268
Lean mass (kg)	45 (±10.9)	44 (±9.0)	0.884
Visceral fat (kg)	17 (±3.0)	18 (±3.0)	0.149
Muscle attenuation (HU)	40 (±9)	34 (±8.4)	0.149

BMI: body mass index. HU: Hounsfield units.

TABLE 4. Association between adverse effects of treatment and variables of body composition and anthropometry.

Variables	Adverse effects		P
	Yes (n=15)	No (n=2)	
Lean mass (kg)	48 (±21.5)	44 (±8.0)	0.941
Visceral fat (kg)	22 (±0.2)	17 (±3.1)	0.029
Skeletal mass index (cm^2/m^2)	44 (±7.5)	46.5 (±11)	0.721
Initial BMI (kg/m^2)	26 (±3.4)	28 (±0.1)	0.721
Final BMI (kg/m^2)	23 (±3.0)	20 (±0.1)	0.500
Muscle attenuation (HU)	37 (±6.8)	32 (±24.3)	>0.999

BMI: body mass index. HU: Hounsfield units.

According to the tomographic images, we classified 8 (47%) patients as sarcopenic. Although more than 50% of patients meet these criteria, we found no significant differences concerning death, toxicity, and BMI (initial and final) between sarcopenic and not sarcopenic patients. The average estimate of survival by Kaplan-Meier can be seen in FIGURE 2.
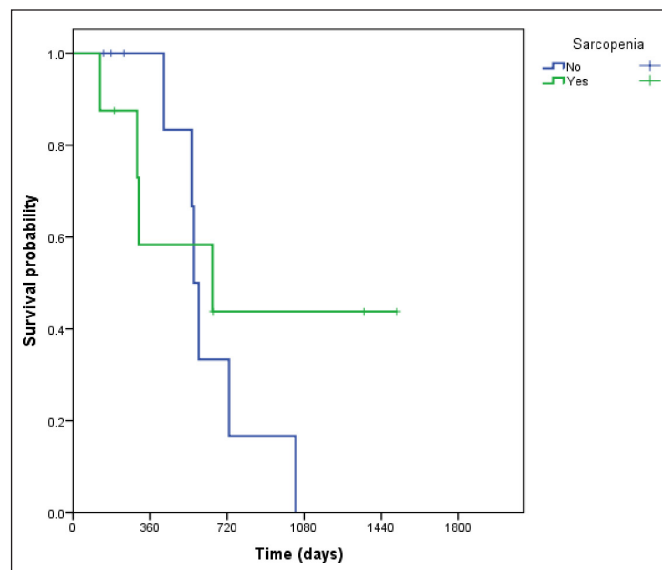

FIGURE 2. Survival and correlation with sarcopenia in patients with pancreatic cancer.

DISCUSSION

In our study, the majority of patients (47%) were overweight initially (6% were obese and 41% overweight). In fact, it is well demonstrated in the literature that the prevalence of overweight is high among pancreas cancer patients[12,21]. We found no significant correlation between BMI and survival in our study, and this could be explained by the sample size and the severity of pancreatic cancer (59% of deaths).

We observed a mean weight loss of 10 kg (13%) compared to the weight at diagnosis, which was higher compared to other studies[2,22]. However, the weight loss found in our study was not correlated with survival[2,3,22]. Studies have shown weight loss from 17% to 25% and association with lower survival rates[2,23]. It is known that pancreatic cancer leads to nutritional depletion, with considerable losses of the body compartments, evidenced anthropometric and body composition evaluations[24].

Regarding the toxicity of the chemotherapeutic treatment, unlike other studies, we found a significant and inverse correlation between the amount of visceral fat and adverse events[25-26]. The findings of this study show that visceral fat promoted a protective impact in relation to toxicity. In a systematic review by Vrieling et al., visceral fat showed a positive association with recurrence of the disease, however, its relation with toxicity was not mentioned[27]. Cushen et al. found, in a study with patients undergoing docetaxel chemotherapy, a relationship between higher visceral fat and lower survival, but also without mentioning anything on toxicity[28]. A study by Wong et al. showed a positive association between hematologic toxicity and increased visceral fat reserves in breast cancer patients[29]. Perhaps the specific treatment is less

toxic and there may be a greater relapse as the medication is stored in the visceral fat. Therefore, it is important to carry out new studies on visceral fat associated with prognosis and toxicity in cancer patients, as well as in patients with pancreatic cancer, to elucidate these issues.

Studies have shown that muscle mass plays an important role in clinical outcomes and that sarcopenia indicates worse prognosis and lower survival rates[24,30]. In a study by Tan et al., the authors verified 56% of pancreas cancer patients with sarcopenia when evaluating body composition by CT[25]. In our study, although the rates of sarcopenia (47%) were similar to those of other studies addressing gastrointestinal, pancreatic and pulmonary tumors (15%–56%)[19,31,32], there was no influence of sarcopenia on survival. It should be considered that this is a retrospective study based on medical records and that data on muscle strength and functionality could be obtained only in prospective studies[33].

Muscle attenuation indices, which theoretically could represent muscle quality, did not reveal associations with survival or toxicity of the treatment in this study. According to Aubrey et al., it is necessary to standardize the cutoff parameters, that is, the establishment of criteria for muscle attenuation is necessary for better analysis of the results[11].

CONCLUSION

We conclude that CT is a useful method to evaluate body composition, especially in cancer patients, since they already undergo these assessments throughout their oncological treatment (for staging, and prognosis evaluation). Sarcopenia is prevalent in the population of patients with pancreatic cancer, and may promote unfavorable outcomes, such as increased toxicity and shorter survival. However, we found no association between survival and muscle mass in our sample. We did find an inverse relationship between visceral fat and toxicity. There is a need to better elucidate the role of adipose tissue in severe diseases, such as pancreatic cancer, especially with regard to toxicity and survival.

Authors' contribution

Barrère APN: study conception and design, data acquisition and analysis, manuscript drafting and final approval. Piovacari SMF, Usón Junior PLS, Gansl RC: data interpretation, manuscript reviewing and final approval. Pereira AZ: study conception and design, data collection and interpretation, manuscript reviewing and final approval. Hamerschlak N: study conception and design, data interpretation, manuscript reviewing and final approval. All authors agree to be accountable for all aspects of the work.

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RESUMO – **Contexto** – Perda de peso e mudanças na composição corpórea são frequentes em pacientes com câncer do pâncreas. Imagens de tomografia computadorizada são úteis na investigação da composição corporal e suas mudanças e para discriminar diferentes tipos de tecidos corporais. Pacientes com câncer pancreático são submetidos à tomografia computadorizada rotineiramente. **Objetivo** – Verificar a associação entre massa muscular e gordura visceral medida por tomografia computadorizada e a toxicidade do tratamento e a sobrevida de pacientes com câncer de pâncreas. **Métodos** – Avaliamos imagens tomográficas abdominais de todos os pacientes adultos com câncer pancreático consecutivamente tratados entre outubro de 2007 e setembro de 2015 no serviço, para estimativa da massa muscular esquelética e gordura, tecido adiposo intramuscular e visceral. Classificamos a toxicidade do tratamento conforme os Critérios Comuns de Toxicidade do Instituto Nacional do Câncer dos Estados Unidos (versão 2.0). **Resultados** – O estudo envolveu 17 pacientes, com idade média de 63 (±10) anos (51–73 anos); 11 (65%) homens. O índice de massa corporal médio inicial foi de 26 kg/m^2 (±3); 23 kg/m^2 (±3) após o tratamento. A perda de peso média foi de 10,0 kg (±6,8; 13%). Observamos sarcopenia em 47% dos pacientes, não associada a diferenças significativas na massa muscular, tecido adiposo visceral, toxicidade ou sobrevivência. A atenuação média do músculo esquelético foi de 36 unidades Hounsfield, não associada à sobrevivência ou toxicidade. A massa muscular média também não foi associada à toxicidade. No entanto, observamos associação inversa significativa entre toxicidade e gordura visceral. **Conclusão** – A massa muscular não teve impacto na sobrevida ou na toxicidade do tratamento dos pacientes com câncer pancreático. No entanto, a gordura visceral exerceu efeito protetor contra a toxicidade. Ressaltamos a importância de mais estudos sobre a gordura visceral associada ao prognóstico e à toxicidade em pacientes com câncer.

DESCRITORES – Composição corporal. Neoplasias pancreáticas. Avaliação nutricional.

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