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Can pancreatic cancer behavior be predicted based on computed tomography measurements of fat and muscle mass?

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Introduction: Many studies purport that obesity, and specifically visceral fat, impact survival after pancreaticoduodenectomy for pancreatic adenocarcinoma. However, these studies involve crude measures of obesity [eg, body mass index (BMI)] or visceral fat [eg, linear measurements on computed tomographic (CT) scans]. Some studies purport that weight loss and muscle wasting (ie, sarcopenia) presage poor survival in these patients. This study was undertaken to accurately measure and reexamine the impact of visceral fat, subcutaneous fat, and sarcopenia on pancreatic cancer.

Materials and methods: CT scans of 100 patients undergoing pancreaticoduodenectomy for pancreatic adenocarcinoma were reviewed using specialized software to precisely determine the cross-sectional area (CSA) of subcutaneous fat, visceral fat, and psoas muscles at the level of L5 vertebra. In addition, linear measurements of subcutaneous fat and visceral fat were undertaken. Measures of cancer progression included tumor (T) status, nodal (N) status, American Joint Committee on Cancer stage, and overall survival after resection. Regression analysis was utilized, with and without standardization of all measurements to body size. Median data are presented.

Results: The median patient age was 67 years, with a BMI of 24 kg/m^2. Cancer stage was IIB for 60% of patients. BMI, CSA of visceral fat, CSA for subcutaneous fat, CSA for psoas muscles, and linear measurements of visceral and subcutaneous fat were not significantly related to any measures of cancer progression or survival. Standardization to body size did not demonstrate any relationships with cancer progression or survival.

Conclusions: Precise and reproducible measures of visceral fat, subcutaneous fat, and muscle mass, even when standardized to body size, do not predict cancer progression or survival in patients undergoing pancreaticoduodenectomy for pancreatic adenocarcinoma. Pancreatic cancer biology and behavior is too complex to predict with a CT scanner. The main focus of pancreatic cancer research should continue to be at the molecular, genetic, and immunologic levels.

Keywords: Pancreaticoduodenectomy, Pancreatic adenocarcinoma, Computed tomography, Obesity, Sarcopenia

Introduction

Despite significant improvements in perioperative outcomes and surgical technique, long-term survival in pancreatic cancer patients has not improved in the modern era of surgery. Twenty percent of patients diagnosed with pancreatic cancer are deemed operable and ultimately undergo resection; nonetheless, even these patients have a dismal prognosis with a median survival of <2 years[1]. Modern cancer treatment paradigms focus on identifying genetically distinct subsets of patients with unique molecular alterations that may be targeted by specific therapies. Although this approach has shown promise with other malignancies[2–5], there have been no breakthrough advancements with regard to pancreatic cancer.

Given this limited and disappointing understanding of pancreatic cancer biology, there has been an increased focus on the theoretical ability to predict pancreatic tumor behavior and aggressiveness based on computed tomographic (CT) measurements of specific body tissues, for example, visceral fat and muscle mass. This paradigm is based upon numerous publications that have found potential relationships between obesity [increased body mass index (BMI) or visceral fat] or sarcopenia (decreased muscle mass) and oncologic outcome in some malignancies, such as colon and rectal cancer, liver cancer, and renal cell carcinoma[6–11]. One report hypothesized that this relation may be based on the known observation that visceral fat can increase levels of inflammatory cytokines and adipokines in human serum, thus increasing tumorogenesis[12]. However, this alleged relationship between visceral fat and cancer biology has been questioned in other reports[13,14]. Sarcopenia has also been associated with inferior outcomes following oncologic resection

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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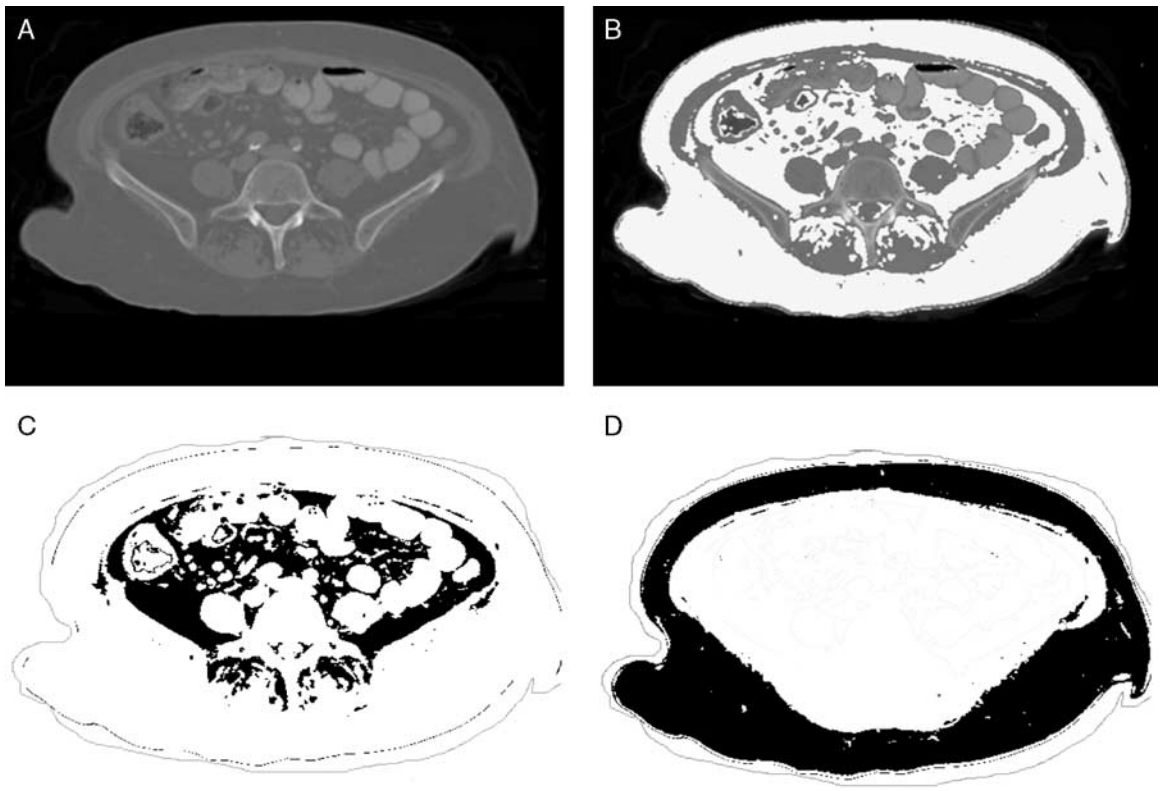

Figure 1. A, Original DICOM image. B, The white highlighted area represents visceral and subcutaneous fat set to a threshold value of – 30 to – 190 HU. C, The black highlighted area represent visceral fat. D, The black highlighted area represents subcutaneous fat, respectively.

of colon cancer[15], hepatocellular carcinoma[16], and esophageal cancer.[17] Interestingly, sarcopenia has recently been linked to poor outcomes following pancreaticoduodenectomy for pancreatic cancer[18].

Nonetheless, when thoroughly examining the studies describing a relationship between pancreatic cancer and the aforementioned CT measurements, we can see that these studies generally lack standardization in regard to measurement techniques and definitions of obesity and sarcopenia. These differences in methodology may have led to different conclusions. For example, in comparing 2 published papers, one suggested that patients with pancreatic cancer who are in the lower quartile of muscle mass have worse survival, whereas the other paper suggested worse survival in association with obesity and concomitant sarcopenia[18,19]. Since these groups are different, as were the methodology and definitions, it is hard to draw any practical conclusions. Other studies, including some of ours, looking at the impact of visceral fat and BMI on pancreatic cancer outcomes came to totally different, and sometimes conflicting, conclusions[20–24].

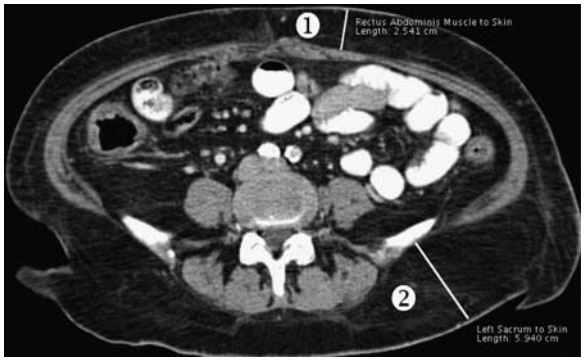

Figure 2. Abdominal wall fat thickness (1): paramedian vertical distance between the left rectus abdominus fascia and the skin at the level of the umbilicus. Hip girdle fat thickness (2): distance between the iliac plate and skin at the level of the posterior superior iliac spine.

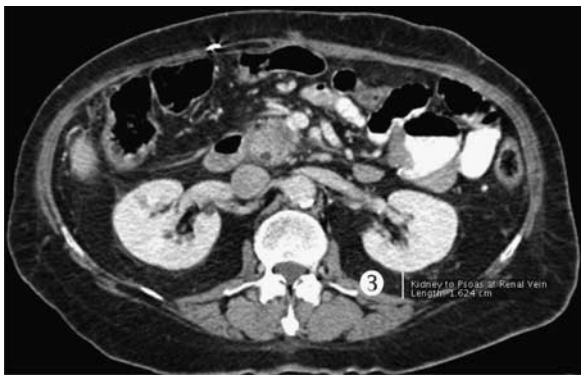

Figure 3. PNF thickness (3): vertical distance between the left posterior renal capsule and the junction of the abdominal wall and paraspinal musculature at the level of the left renal vein.

Table 1

Baseline characteristics of patients undergoing pancreaticoduodenectomy.

	All patients	Men	Women	*P*
No. patients	100	58	42	
Age (y)	66 (67 ± 10.2)	67 (66 ± 10.6)	66 (68 ± 9.4)	0.567
Length of stay (d)	12 (17 ± 12.3)	12 (17 ± 13.6)	15 (16 ± 10.2)	0.529
BMI (kg/m^2)	25 (26 ± 5.1)	27 (27 ± 5.1)	24 (25 ± 4.9)	0.093
Tumor size (cm)	4 (3 ± 1.5)	4 (4 ± 1.5)	3 (3 ± 1.3)	0.050
Survival (mo)	17 (19 ± 16.5)	18 (19 ± 15.3)	16 (19 ± 18.2)	0.990

Median (mean ± SD).
BMI indicates body mass index.

Therefore, in designing this study, we aimed to obtain accurate, objective, and reproducible volumetric measurements of visceral fat and muscle mass, using technologically advanced and dedicated CT software. After performing these precise measurements, we aimed to examine the impact of visceral fat and muscle mass on the behavior and progression of pancreatic cancer, and thus to determine whether prognosis can be predicted based on these measurements. This can have important clinical implications in the long and generally frustrating management of this disease.

Materials and methods

With Institutional Review Board approval, CT scans of 100 patients undergoing pancreaticoduodenectomy for pancreatic adenocarcinoma were reviewed. OsiriX (32-bit software version 3.8.1; Pixmeo, Geneva, Switzerland) medical imaging software was utilized to measure 3 cross-sectional areas (CSA): subcutaneous fat area, visceral fat area (VFA), and total psoas muscle area at the L5 vertebral level (**Fig. 1**). In addition, to further define the implications of fat mass assessment, linear measurements of subcutaneous and visceral fat were obtained; for subcutaneous fat, the sum of the abdominal wall fat thickness and hip girdle fat thickness was determined (**Fig. 2**), and for visceral fat, the perinephric visceral fat thickness was measured (**Fig. 3**).

All patients were determined preoperatively to be free of metastases (M0) based on imaging. The progression of pancreatic cancer in each patient was determined by the tumor (T) status, nodal (N) status, overall American Joint Committee on Cancer (AJCC) stage, and overall patient survival after pancreaticoduodenectomy.

Data management and analysis

Patient data were stored in an institutional pancreatic cancer database. Statistical analysis utilized Graphpad Instat version 3.06 and Graphpad Prism 5 (Graphpad Software Inc., San Diego, CA). Significant relationships were determined using linear regression.

χ^2 analysis or *t* tests were also used, where appropriate, and significance was accepted with 95% probability. Log-rank and Wilcoxon tests on the Kaplan-Meier survival curves were used. For illustrative purposes, data are reported as median (mean ± SD). Survival data are presented as median predicted survival with 95% confidence intervals.

Results

One hundred randomly selected patients, 58% men, with a median age of 67 years (66 ± 10.6 y) underwent pancreaticoduodenectomy for pancreatic adenocarcinoma between 2004 and 2012. Baseline characteristics of these patients are displayed in **Table 1**. Seventy five percent of patients had an R0 margin status and 60% had an AJCC stage of IIB. Median survival for all patients was 17 months, (19 ± 16.5 mo). Median operative duration was 284 minutes (300 ± 84.6 min), and intraoperative blood loss was 400 mL (535 ± 423.4 mL).

Table 2 summarizes the results of the measurements of subcutaneous fat, visceral fat, and muscle mass.

Comprehensive linear regression analyses failed to demonstrate any significant correlations between cancer progression and any of the CSA measurements or linear measurements performed, or with BMI (**Fig. 4** and **Table 3**).

Nonetheless, in an effort to find some correlations, we did the following modification: because of the diversity in body build and size among patients, we used the CSA of the L5 vertebral body as an indicator of body size. We then standardized all CT measurements to the L5 vertebral body CSA. Now, we repeated all the linear regression analyses using these standardized measurements. Again, no correlation between cancer progression and any of the standardized CSA measurements or linear measurements was found. Standardization to patient height, as another indicator for body size, also did not yield any correlations between cancer progression and any of the standardized CSA measurements or linear measurements.

Discussion

The findings in this manuscript underscore the fact that pancreatic cancer behavior is complex and cannot be predicted using CT measurements of fat and muscle mass. We used very sophisticated and rigorous measurements, that included

Table 2

CT measures including cross-sectional areas of VFA, SFA, CSAPM, CSAL5, and linear measurements of retrorenal fat and AW and HG fat.

	Median			Mean			SD			
	All	Men	Women	All	Men	Women	All	Men	Women	Men vs. women (*P*)
VFA (mm^2)	15,620	18,137	12,672	17,133	19,237	14,228	10,384	10,888	8980	0.1800
SFA (mm^2)	25,911	24,788	26,921	26,988	25,728	28,727	12,442	11,330	13,783	0.7466
CSAPM (mm^2)	1874	2286	1383	1914	2220	1491	670	631	464	0.5743
Retrorenal fat thickness (mm)	15	21	11	16	19	11	10.5	11.4	6.7	0.6608
AW&HG fat thickness (mm)	74	68	84	71	64	80	31.2	30.7	30.0	0.1902
CSAL5 (mm^2)	1620	1768	1453	1700	1834	1515	443	429	397	0.6252

AW indicates abdominal wall; CSAPM, cross-sectional area psoas muscle; CSAL5, cross-sectional area L5 vertebral body; CT, computed tomography; HG, hip girdle; SFA, subcutaneous fat area; VFA, visceral fat area.

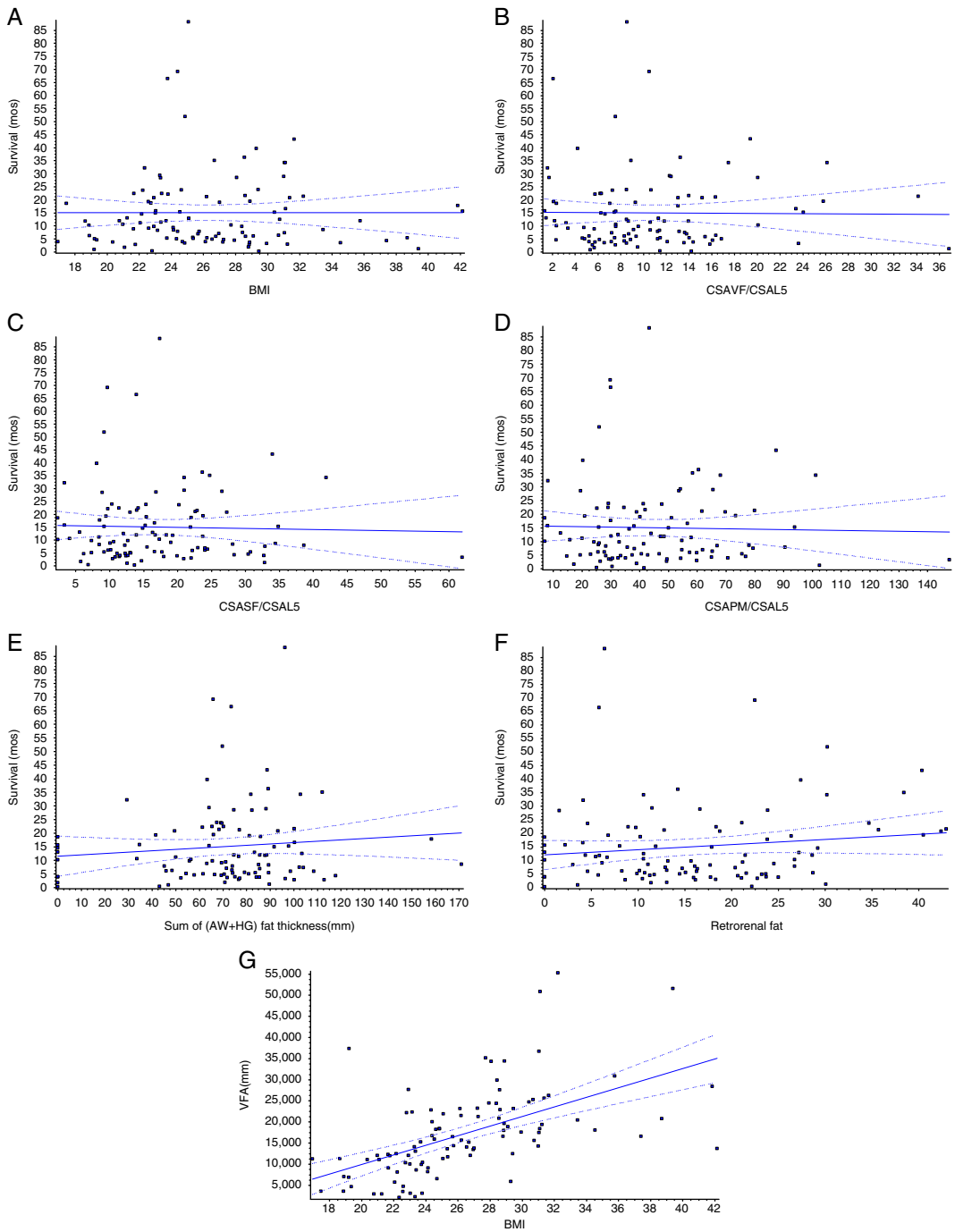

Figure 4. Summary of regression analyses comparing computed tomography–measured variables and body mass index (BMI) with survival. A, BMI versus survival ($P = 0.9984$). B, CSAVF/CSAL5 versus survival ($P = 0.9214$). C, Cross-sectional area of subcutaneous fat (CSASF)/CSAL5 versus survival ($P = 0.7894$); *CSASF standardized to cross-sectional area at the fifth lumbar vertebrate (CSAL5). D, CSAPM/CSAL5 versus survival ($P = 0.8066$). E, Abdominal wall (AW) + hip girdle (HG) fat thickness (mm) versus survival ($P = 0.3010$). F, Retrorenal fat thickness (mm) versus survival ($P = 0.1856$). G, BMI versus visceral fat area (VFA) ($P < 0.0001$).

3 cross-sectional and 2 linear measurements that were also normalized to body size, as well as BMI. However, these precise and comprehensive analyses failed to demonstrate any correlation between the progression of pancreatic cancer, including survival, and visceral fat mass, subcutaneous fat mass, muscle mass, or BMI.

More specifically, we found that VFA did not correlate with tumor progression or overall survival, a finding that has been described inconsistently in the literature. Our data should end this debate. The theoretical principle behind this alleged correlation is that visceral fat functions as an endocrine organ, secreting adipokines and inflammatory cytokines such as IL-6 and TNF-α,

Table 3

***P*-values from regression analyses comparing quantitative CT measured variables to measures of pancreatic cancer progression.**

	VFA/CSAL5	SFA/CSAL5	CSAPM/CSAL5	Retrorenal fat thickness	Sum of AW&HG fat thickness	BMI
AJCC stage	0.4864	0.3822	0.6047	0.4381	0.8318	0.7765
Tumor grade	0.7572	0.2354	0.3794	0.6984	0.9493	0.7948
Nodal status	0.629	0.0917	0.1318	0.6004	0.9494	0.0685
Survival (mo)	0.9211	0.7893	0.8065	0.1856	0.301	0.9984

AW indicates abdominal wall; BMI, body mass index; CSAPM, cross-sectional area psoas muscle; CSAL5, cross-sectional area L5 vertebral body; CT, computed tomography; HG, hip girdle; SFA, subcutaneous fat area; VFA, visceral fat area.

which promote a milieu that could affect cancer behavior[8,12]. Epidemiologic studies have shown a link between visceral obesity, obesity (BMI > 30), and increased risk of pancreatic cancer[6,22,23,25]. In 2008, House and colleagues reported an increased rate of perioperative complications and pancreatic fistula in patients with increased visceral adiposity. Visceral fat was approximated by a retrorenal linear measurements. Although they did not study long-term outcomes, the concept was intriguing and inspired further investigation[20,26].

Our group and others have investigated the possibility that visceral adiposity could represent a surrogate for pancreatic steatosis (fatty infiltration of the pancreas)[24,26]. Pancreatic steatosis in pancreatic cancer patients has been demonstrated to correlate with increased angiolymphatic invasion, cancer infiltration of lymph nodes, and worse survival[27] Tranchart et al[26] found that on preoperative CT, a VFA of $> 84\ cm^2$ was the only predictor of both pancreatic steatosis and pancreatic fistula after pancraticoduodenectmy, thus adding to the evidence of a potential relationship between VFA, pancreatic steatosis, and outcome.

However, BMI and VFA have been inconsistently linked to oncologic surgical outcomes. Our results suggest there is no correlation between either BMI or VFA and pancreatic cancer progression. In 2012, a group at Memorial Sloan Kettering reported that neither BMI nor VFA (determined by linear measurements of retrorenal fat thickness) correlated with pancreatic tumor progression or with survival in patients undergoing pancreatic resection[21]. To add to the inconsistency of conclusions, a recent paper evaluated BMI and CT scans in 408 patients with pancreatic cancer and concluded that patients with low BMI had greater 90-day mortality. This paper also suggested that patients with increased subcutaneous fat had better survival and lower risk of complications[14]. Furthermore, Tsai et al[28] found that patients with BMI > 30 undergoing pancreaticoduodenectomy have improved long-term survival and lower rates of positive margins.

We did not find any significant association between measured muscle mass and tumor progression or survival. There is some recent literature to suggest that sarcopenia is associated with worse survival in patients with pancreatic adenocarcinoma. Peng et al[18] stratified patients into quartiles and separated them by sex, and were able to show sarcopenia was a predictor of inferior survival at 3 years. In another report, Pausch et al[14] concluded that patients at risk for lower survival are those with "sarcopenic obesity," or sacropenia plus obesity. It is not clear whether this "increased risk" resulted from obesity, sarcopenia, or the combination of both. These findings should be further investigated.

Many of the aforementioned studies used different and inconsistent measurements of fat and muscle mass. In most, calculations were based solely on single linear measurements of retrorenal fat thickness. We are the first investigators to use comprehensive and highly precise CT measures of visceral fat and muscle mass, including cross-sectional and volumetric measurements, in an attempt to elucidate relationships with pancreatic cancer. None of the multiple cross-sectional or linear measurements in this study correlated with tumor progression or survival, and neither did BMI. Standardization to patient body size did not change the picture. Despite some existing literature suggesting relationships may exist between pancreatic cancer and fat and muscle mass, we have shown herein that muscle and fat mass do not have meaningful contributions to our ability to predict pancreatic cancer behavior or outcome. It seems this rigorous investigation "closes the door" on this subset.

Apparently, pancreatic cancer biology and behavior are far too complex to predict with a CT scanner. The main focus of pancreatic cancer research should continue to be at the molecular, genetic and immunologic levels, in an attempt to reach a breakthrough knowledge that will improve the universal dismal prognosis associated with this disease.

Conflict of interest statement

The authors declare that they have no financial conflict of interest with regard to the content of this report.

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