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The Effects Of Curcumin On Body Composition Of Patients With Advanced Pancreatic Cancer

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THE EFFECTS OF CURCUMIN ON BODY COMPOSITION OF PATIENTS WITH ADVANCED PANCREATIC CANCER

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A

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DEDICATION

To my beloved wife Gaëlle, for her love, patience, continued support, and for being such a great example of dedication and persistence.

And to my son Dean, with thanks for his lively smile, unconditional love, and for always bringing happiness to our lives.

You both give me the strength (and the necessary pushing) to always keep going.

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ABSTRACT

Cachexia is very common among patients with advanced pancreatic cancer and is a marker of poor prognosis. Weight loss in cachexia is due to both adipose and muscle compartments, and sarcopenia (severe muscle depletion) is associated with worse outcomes. Curcumin has shown a myriad of biological effects, including anti-cancer and anti-inflammatory. The ability of curcumin to attenuate cachexia and muscle loss has been tested in animal models, with conflicting results so far. The hypothesis of this study was that patients with advanced pancreatic cancer treated with curcumin for two months have less fat and muscle loss as compared to matched controls not treated with this compound. A matched 1:2 case-control retrospective study was conducted with 22 patients with pancreatic cancer who were treated with curcumin on a previous protocol and 44 untreated controls with the same diagnosis matched by age, gender, time from advanced cancer, body mass index, and number of prior therapies. Data was collected regarding oncologic treatment, medication use, weights, heights, and survival. Body composition was determined by computerized tomography analyses at two timepoints separated by 60±20 days. For treated patients, the first image was at the beginning of treatment and for controls it was determined by the matching time from advanced cancer. The evolution of body composition over time was quantitatively analyzed comparing both groups. All patients lost weight both due to fat and muscle losses, and patients treated with curcumin presented greater losses both in lean adipose body mass. Use of medications, chemotherapy, age, time from advanced cancer, baseline albumin, performance status, and number of prior therapies were not independently correlated with changes in body composition variables. Patients treated with curcumin had borderline shorter survival when compared with untreated patients. Sarcopenic treated

patients had significantly shorter survival than non-sarcopenic counterparts, and sarcopenia status was not associated with survival among the controls. Treated patients with shorter survival showed a tendency to lose more lean and especially fat body mass as compared to untreated patients, maybe suggesting an effect of curcumin on shifting weight loss towards the end of life by impacting its mechanisms.

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ABBREVIATIONS

AgRP = agouti-related protein

ALT = alanine aminotransferase

AST = aspartate aminotransferase

BC = before Christ

BMI =body mass index

CART = cocaine-amphetamine-related transcript

CHF = congestive heart failure

CI = confidence interval

cm = centimeter

COPD = chronic obstructive pulmonary disease

CT = computerized tomography

DEXA = dual X-ray absortiometry

DICOM = digital imaging and communication in medicine

dL = deciliters

FM = fat mass

GABA = γ-aminobutyric acid

HU = Hounsfield units

IFNγ = interferon gamma

IL1 = interleukin 1

IL2 = interleukin 2

IL6 = interleukin 6

IQR = interquartile range

L3 = third lumbar vertebra

LBM = lean body mass

LMF = lipid mobilizing factor

m = meter

Malonyl-CoA = malonyl coenzyme A

MAPK = mitogen-activated protein kinase

MCH = melanin-concentrating hormone

MCR4 = melanocortin-4

mg = milligrams

mm = millimeters

mRNA = messenger ribonucleic acid

NF-κB = nuclear factor κB

NPY = neuropeptide Y

PACS = picture archiving and communication system

PD = progressive disease

PIF = proteolysis inducing factor

POMC = pro-opiomelanocortin

PPARγ = peroxisome proliferator-activated receptor γ

r = correlation coefficient

ROS = reactive oxygen species

SD = standard deviation

SE = side effect

SEM = standard error of the mean

STAT = signal transducer and activator of transcription

TNFα = tumor necrosis factor alpha

TRH = thyrotrophin-releasing hormone

ULN = upper limit of normality

ZAG = zinc-α_2-glycoprotein

βHCG = human corionic gonadotropin, fraction beta.

CHAPTER 1 – Introduction to cancer cachexia

Statement of importance

The whole spectrum of abnormalities in the amount of body fat and muscle (body composition) has been associated to cancer prevention, treatment outcomes, and survival. Increased body weight (overweight and obesity) has been associated with predisposition for several types of cancers such as endometrial, breast (in postmenopausal woman), colon, kidney, and esophagus (1-3). On the other hand, loss of body mass (both fat and lean contents), broadly termed "cancer cachexia" has been associated with worse outcomes such as decreased survival in patients with pancreatic cancer, loss of physical strength, and poorer response to therapy (4-7) . To date, there is no effective treatment for the loss of body mass in cancer cachexia. Finding strategies to fight this condition will allow for better patient care as it allows better outcomes of cancer treatment and increased quality of life.

Definition

The term cachexia comes from the Greek words *kakós* (bad) and *hexis* (condition, state) (8). In broad terms, cachexia is defined by an involuntary weight loss accompanied by various degrees of associated factors such as anorexia, decline in muscular strength, and inflammation (9). Recently, a specific definition of cancer cachexia has been suggested and states that it is "a multi-factorial syndrome defined by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment. The pathophysiology is characterized by a negative protein and energy balance driven by a variable combination of

reduced food intake and abnormal metabolism." (10). Clinically, a patient is considered to have cancer cachexia in the presence of weight loss greater than 5% in the past 6 months (if simple starvation can be excluded) or any weight loss greater than 2% if the patient has a BMI lower than 20 kg/m^2. Additionally, a patient can be diagnosed with cachexia if a weight loss greater than 2% is present combined with sarcopenia (defined as an appendicular skeletal muscle index lower than 7.26 kg/m^2 for males and 5.45 kg/m^2 for females) (10).

Epidemiology

Overall, half of all patients with cancer lose some weight in the course of their diseases (11). However, the prevalence of weight loss in patients with cancer is highly variable, and it is significantly more frequent among patients with solid tumors, in which up to 80% have weight loss of at least 5% of the premorbid body weight (5). In the last weeks of life, the prevalence of weight loss in patients with cancer has been described as 86% (12), and around 20% of all cancer deaths are directly related to cachexia (11).

In patients with pancreatic cancer, a 10% weight loss in comparison with premorbid weight is present in approximately 80% of all cases, and at least 25% of these cases presented cancer cachexia (6).

Pathophysiology

Cancer cachexia is multi-factorial and usually understood as having two major groups of causal factors. One group encompasses the effect of the tumor and the body's responses to its presence, and is usually referred to as "primary cachexia". The other group comprises a myriad of conditions that can co-occur and affect energy intake (such as nausea, stomatitis,

taste abnormalities, cognitive impairment, bowel obstruction, dental problems, for example), protein balance (ageing, concomitant corticosteroid use, ascitis/pleural effusion repeat drainage, for example), and induce catabolic states (such as infections, heart failure, hypothyroidism, for example) (Figure 1) (13). The pathophysiology of primary cachexia will be discussed here, and it is best understood by taking into account energy balance, muscle and fat metabolism, and the influence of inflammation on catabolism.

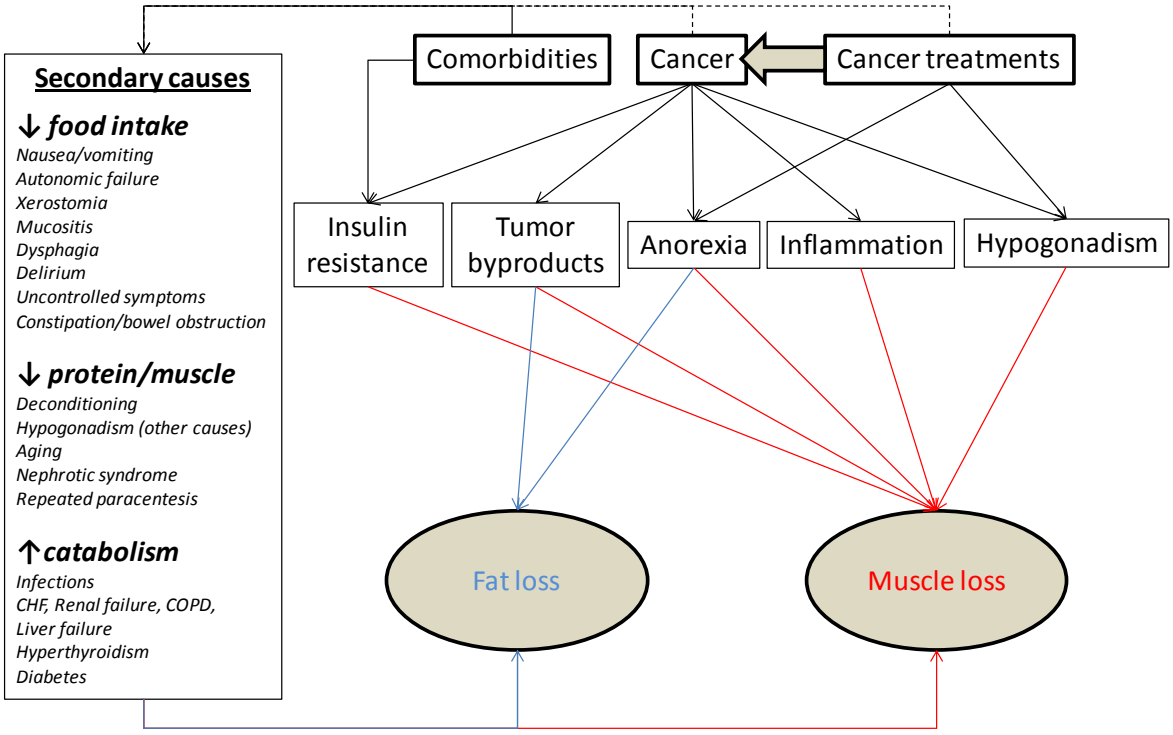

FIGURE 1 – Schematic representation of the mechanisms of cancer cachexia.

Energy balance and appetite regulation

Body weight is maintained relatively constant in healthy individuals when the energy balance is kept neutral. In other words, energy expenditure and energy intake are equivalent (14). In animal models, it has been proven that this equilibrium is tightly maintained by coordinated mechanisms: in times of low energy availability, oxygen consumption is

lowered, and when energy supply is abundant, basal metabolism and energy expenditure increase (15). Energy (food) intake is controlled by a hypothalamic system which integrates several afferent signals from organs such as the gastrointestinal tract, the liver, and adipose tissue (16).

The central hypothalamic integrative system is located adjacent to the third ventricle in the arcuate nucleus and is composed of two neuronal populations: the orexigenic pathway (which promotes food intake and reduces energy loss) and the anorexigenic pathway (which in turn inhibits food intake and promotes energy use) (16). The orexigenic pathway neurons express neuropeptide Y (NPY) and the agouti-related protein (AgRP) whereas the anorexigenic pathway neurons express pro-opiomelanocortin (POMC) and cocaine-amphetamine-related transcript (CART) (16). The message integrated in hypothalamus is relayed to several effector neuron populations, most importantly: (a) the melanin-concentrating hormone (MCH) and the orexin/hypocretin neurons, which have downstream orexigenic effect, ultimately leading to an increase in food intake (17-22); (b) neurons expressing thyrotrophin-releasing hormone (TRH), which ultimately exert an anorexigenic effect (23, 24); and (c) neurons secreting γ-aminobutyric acid (GABA), capable of modulation of both orexigenic and anorexigenic pathways (25, 26).

The afferent signals to the hypothalamic integrative center come from several organs via different pathways. Ghrelin, for example, is mostly produced in the stomach in response to fasting, but also produced in smaller amounts by other organs (27), and exerts an orexigenic effect both by activating NPY/AgRP neurons and inhibiting POMC/CART neurons in the hypothalamic integrative center (27, 28). One group of specific afferent signals “inform” the hypothalamus about the adiposity status of the body. Leptin is an

important afferent adiposity signal arising from the adipocytes in response to the amount of energy stored (greater energy storage amounts are linked to increased leptin levels), with direct excitation of POMC/CART neurons and inhibition of NPY/AgRP neurons, decreasing food intake and increasing the metabolic rate (16, 29, 30). Another adipositiy-related signal is conveyed by insulin, which is secreted by the pancreas in response to adiposity and also has inhibitory action over NPY/AgRP neurons and excitatory action over POMC/CART neurons (31, 32).

The energy signals, another group of afferent signals, are responsible for "informing" the hypothalamus about the energy status of the organism. The most important of those signals is conveyed by the differential concentration of malonyl coenzyme A (malonyl-CoA) in the hypothalamus, which increases in the presence of abundant fatty acids (signaling to reduce appetite) and decreases when fatty acid concentration is low (signaling to increase appetite) (33). Another energy signal comes from specialized cells sitting mainly in the ileum and colon (L cells). Such cells respond to the presence of food and specifically its caloric content by proportionately secreting peptide YY which has inhibitory action on NPY/AgRP neurons, therefore with an anorexigenic effect (34, 35).

Pathogenesis of cancer anorexia

The pathogenesis of cancer anorexia is yet to be completely understood. Nevertheless, evidence both from cancer animal models and from clinical studies point to several derangements within the complex machinery that regulates energy intake. Several studies failed to show a direct involvement of leptin (36, 37) and ghrelin (38, 39) in the genesis of cancer anorexia, pointing towards a more central (hypothalamic) issue. There is evidence, for example, showing that in the tumor-bearing state, brain neurochemistry can be changed

in specific brain areas, including the hypothalamus (40). Another argument favoring the hypothesis of a hypothalamic derangement comes from research with NPY. It has been shown that in anorexic tumor-bearing rats there is a significant decrease in NPY imunorreactive neurons in the hypothalamus, suggesting that this might be part of the genesis of anorexia in those animals (41). There is also evidence pointing towards the impairment of the anorexigenic pathway in cancer anorexia. It has been shown that in anorexic tumor-bearing rats in which POMC/CART neurons were inactivated the food seeking behavior is restored (42, 43) and that in melanocortin-4 (MCR4) knock-out mice (in which the activation of the POMC/CART pathway is incomplete) tumor growth is not accompanied by anorexia as expected (42). It seems that cytokines play a major role in this hypothalamic derangement (44). For example, injections of mianserin (an antagonist of the IL1 receptor) directly to the hypothalamus of tumor-bearing anorexic rats were able to increase food intake (45). Also supporting this, it has been shown in an animal model of prostate adenocarcinoma that anorexia is associated with a detectable increase of IL1β mRNA (46).

The mechanisms through which cytokines directly affect the hypothalamic control of energy intake have been widely studied, and evidence now shows that cytokines act on the melanocortin system mostly through serotonin release in the hypothalamus (47). Fenfluramine, a serotonin agonist, has been shown to increase the concentration of serotonin in the hypothalamus, inducing anorexia by activating POMC/CART neurons (48). Also, it has been shown that in anorexic tumor-bearing rats the levels of hypothalamic serotonin are significantly higher than those of normal rats, and when the cancer is removed, the serotonin levels return to those of normal rats (49). In the clinical setting, the findings from animal

models were confirmed by quantification of tryptophan (serotonin precursor) in the cerebrospinal fluid of anorectic patients with cancer. These patients presented significantly higher levels of free tryptophan when compared to healthy volunteers or non-anorectic cancer patients (50). In addition, the same group was able to show that when the tumor is removed, the tryptophan levels return to premorbid levels (51).

Adipose tissue metabolism in cancer cachexia

Adipose tissue is the largest energy reservoir in the human body. In healthy individuals, adipose tissue stores triacylglicerol when energy balance is positive and releases non-sterified fatty acids when such balance is negative (52). Loss of adipose tissue is an important feature of cancer cachexia. It has been shown by evaluation of cancer patients' body composition by dual X-Ray absortiometry that the loss of adipose tissue precedes that of skeletal muscle, and this was confirmed by computerized tomography analyses in a different sample (53, 54). The major driver of lipid metabolism abnormalities in cancer cachexia is a reduction in lipoprotein lipase activity, reducing the catabolism of triglycerides and therefore impeding its accumulation in the adipocytes (55). This inhibition of lipoprotein lipase occurs mainly as a result of direct action of cytokines such as IL2 (56) and TNFα (57). The latter is also capable of increase lipolysis from the adipocytes themselves, by inhibiting the adipose tissue hormone-sensitive lipase (58).

Another important player in the changes in adipose tissue of cachectic individuals is the so-called Lipid Mobilizing Factor (LMF) which is a protein (zinc-α_2-glycoprotein, ZAG) identified in an animal model of cancer cachexia and found in the urine of cachectic patients. ZAG is an adipokine produced by the adipose tissue which locally regulates fat

mass and is overexpressed in several types of cancers (52). *In vitro* models show that ZAG induces lipolysis in cultured adipocytes (52) and studies in animals demonstrated that ZAG-induced weight loss is specifically due to adipose tissue loss (59). In humans, it has been shown that ZAG expression and concentration of mRNA is increased in the adipose tissue of cachectic patients (52).

Muscle metabolism in cancer cachexia - Sarcopenia

As it is for energy, muscle metabolism is also mostly based on the balance between protein synthesis and protein degradation (60). In the setting of cancer cachexia, both a reduction in protein synthesis (hypoanabolism) and an increase in its degradation (hypercatabolism) is observed (60, 61). To date, there is some debate on the importance of each alteration (62), but most studies are focused in the hypercatabolism aspect.

Three major proteolytic systems are usually described: the lysossomal, the calcium dependant, and the adenosine triphosphate- dependent ubiquitin-proteasome pathways (63). In cancer cachexia, there is evidence of a preponderance of the latter, since in tumor-bearing rats with increased proteolysis the inhibition of both lysossomal and calcium-dependant pathways did not lead to reduction in proteolysis. Additionally, ubiquitin levels in the atrophying muscles increased, therefore, the conclusion was that the ubiquitin-proteasome pathway was the driving force behind muscle atrophy in this model (64).

In patients with cancer, the increased activity of the proteasome is believed to be caused by several abnormalities such as increased oxidative stress, cytokines, and presence of the tumor-secreted proteolysis inducing factor. Increased oxidative stress has been proven to induce proteasome activity (65), and there is evidence that muscle wasting in animal models

is not only induced by oxidative stress but also can be prevented by antioxidants (66). It is believed that oxidative stress activates the expression of genes in the ubiquitin-proteasome pathway through TNFα and NFκB activity (67).

Cytokines such as IL1, IL6, IFNγ, and TNFα have been shown to be involved in the genesis of muscle atrophy in animal models of cachexia. TNFα administration caused an increase in protein degradation with increase in proteasome gene expression and ubiquitin levels (68). Innoculation of rats with cells that produce high levels of IFNγ caused severe cachexia and also led to increased levels of ubiquitin (69).

A proteolysis-inducing factor (PIF) has been described initially in animal models as a glycoprotein secreted by tumors (70) that increases protein degradation by increasing the activity of the ubiquitin-proteasome pathway (71). The true existence of a human PIF homologue has been debated. An independent group was unable to confirm its presence in cancer cell lines (72) and this was rebutted with possible methodological issues as the reason for the inability to detect PIF in such cases (73). Recently, a third independent detected PIF in a sample of non-small cell lung cancer patients and reported its association with survival and weight loss (74).

Trophic influence on skeletal muscle in cancer cachexia

Muscle hypoanabolism is tightly related to insulin resistance, hypogonadism, and physical inactivity, issues frequently present in patients with cancer. In healthy individuals, insulin exerts anabolic effects over the muscles. Muscle resistance to the anabolic effects of insulin has been shown in a tumor-bearing rat model (75, 76). Resistance to the anabolic effects of insulin has already been described in elderly, obese and diabetic adults. There is

no definitive proof that cancer causes insulin resistance, however, since these conditions frequently co-occur in patients with cancer, it is likely that insulin resistance plays a role in the genesis of muscle wasting in cancer patients (77).

Physical activity is an important trophic factor for skeletal muscle, while inactivity leads to muscle wasting. It has been shown in healthy elderly individuals that even a bed rest as short as 10 days lead to a significantly increased tendency to muscle loss (78, 79). It is likely that physical inactivity also plays a role in cancer cachexia, considering that cancer patients tend to spend a significant amount of time in the hospital in the last year of life (80).

Hypogonadism has been reported as frequent in a sample of 47 male patients with advanced cancer, with a prevalence of 81%. It impacts mood, fatigue, and more importantly, cachexia/anorexia symptoms (81). At the level of the hypothalamus, hypogonadism might be mediated by cytokines and drugs which lead to decreased gonadotrophin-releasing hormone production. At the testicular level, testosterone reduction may be caused, in cancer patients, by direct effect of chemotherapeutic drugs or by IL6. Opioid analgesics, megestrol acetate, and corticosteroids are frequently used in patients with advanced cancer and are concurrent causes of hypogonadism (77). Hypogonadism reduces an important anabolic stimulus to skeletal muscle, leading to muscle depletion.

Inflammation

From the mechanisms described above, it is clear that inflammation plays a major role in the genesis of primary cancer cachexia. Increase in inflammatory mediators can be brought about by several factors in the patient with cancer: the tumor cells can generate some amount of proinflammatory cytokines; the patient's immune reaction (recruitment of

immune cells to the tumor bed) brings up an increase in cytokine production; alterations in the gastrointestinal tract; production of cytokines in the muscles and adipose tissue themselves; and arise from secondary conditions such as infections (82).

The tumor environment is rich in inflammatory cytokines, some generated by the tumor itself, and most generated by the host reaction to the tumor presence by recruitment of macrophages to the tumor site. The presence of such cells in the tumor bed create a pool of cytokines, chemokines, angiogenesis-promoting factors, reactive oxygen species (ROS), matrix metalloproteinases, and prostanoids (83, 84) which only represent part of the greater inflammatory process in the whole tumor-bearing host.

In the course of cancer treatment, and as a result of several chemotherapy regimens (85, 86), alterations in the integrity of the gastrointestinal tract lead to impairment of its barrier function, allowing for the passage of bacterial endotoxins into the blood (87). The endotoxins transported to the blood are a very potent stimulus for cytokine liberation by mononuclear cells, and are considered to be a probable trigger for systemic inflammatory response which drives cachexia (77).

Inflammatory drive in patients with cancer can be triggered by the presence of concurrent chronic diseases. Patients with cancer usually are towards the 5^{th} decade of life or later, therefore at greater risk for chronic diseases such as cardiac failure, pulmonary diseases, arthritis, and renal disease. In addition, patients with cancer are at greater risk for infections. The presence of such comorbidities significantly increases the inflammatory burden in cancer patients, contributing to the genesis of cancer cachexia (77).

CHAPTER 2 – Curcumin

Origins and biochemistry

Curcumin is the phytochemical component responsible for the characteristic yellow-gold color of turmeric (also known as Indian Curry) a spice used mostly in Asia. Found in the root of the *Curcuma longa* plant, a member of the ginger family (Zingiberaceae), turmeric is used not only as a condiment but also to treat several medical issues since around 1900 BC both in the Ayurvedic and Traditional Chinese medicines (88).

First isolated in 1815, curcumin had its structure determined as diferuloylmethane [1,7-bis(4-hydroxy-3methoxyphenyl)-1,6-heptadiene-3,5-dione] in 1910. It is now known that in addition to curcumin, two other curcumin analogues are found in turmeric: demethoxycurcumin and bisdemethoxycurcumin. Even though there is evidence pointing towards curcumin as the most effective among the three (89, 90), there is also some evidence that bisdemethoxycurcumin might be most effective (91) and even that the combination of the three analogues is what actually exerts the best action (92-94). Most commercially available preparations have around three-fourths diferuloylmethane, one-fifth demethoxycurcumin, and 5% bisdemethoxycurcumin.

Following oral administration, curcumin is metabolized into curcumin glucuronide and curcumin sulfonate, while when administered intravenously, it is converted into tetrahydrocurcumin, hexahydrocurcumin, and hexahydrocurcuminol. Curcumin is highly hydrophobic and has very poor bioavailability because of its very low serum and tissue levels, rapid metabolism, and rapid elimination (95). Efforts are underway to overcome this issue, such as the development of a liposomal curcumin (96), the use of nanoparticles for

curcumin delivery (97), the concomitant administration of adjuvants such as piperine (98), insert structural modifications into the molecule (99), and the use of bioconjugates (100).

Actions and molecular targets

Several actions have been ascribed for curcumin: anti-inflammatory, antioxidant, antiprotozoal, nematocidal, antibacterial, and anticancer, among others (101). Probably the most widely studied action of this compound is the anti-inflammatory, which makes it an interesting drug to be studied for the treatment of cancer cachexia.

Curcumin interacts with multiple molecular targets of interest for cancer cachexia treatment. With regards to transcription factors, it has been shown that curcumin is capable of inhibiting the activation of nuclear factor κB (NF-κB), peroxisome proliferator-activated receptor γ (PPARγ), signal transducer and activator of transcription proteins (STAT), and β catenin. Additionally, it also acts inhibiting the mitogen-activated protein kinase (MAPK) pathway, paramount for inflammatory cascades (102).

In the oncology setting, curcumin has been widely studied for both treatment and prevention of several types of cancers, because of is proven ability to inhibit cell proliferation and invasion, to block angiogenesis, and to impair the progression of metastasis (103). Of interest to this work, our group conducted a Phase II clinical trial in which a total of 48 advanced pancreatic cancer patients received 8g of oral curcumin daily for the investigation of its safety and antitumor activity. Objective responses were seen in two patients: one had a short-lived marked tumor reduction of 73% followed by increases in tumor size in subsequent re-evaluations and one had prolonged stable disease (greater than 8 months at publication which happened when accrual reached 25 patients) (104). Of note,

curcumin was overwhelmingly very well tolerated, and no toxicities were observed by the time of publication. In the treated patients, NF-κB, cyclooxygenase-2, and phosphorylated signal transducer and activator of transcription 3 (STAT-3), which were higher than healthy individuals at baseline, were reduced after treatment with curcumin, showing a potential effect of the drug on these targets (104).

Curcumin and cachexia

The effects of curcumin in cachexia (specifically in muscle loss) have been studied by several groups in animal models, yielding conflicting results. Busquets et al. studied the antitumor and anticachectic effects of curcumin in a Wistar rat model innoculated with the cachexia inducing Yoshida ascites hepatoma cells. Even though the investigators were able to show a significant tumor reduction effect, no anticachectic effect was identified (105). Another group, studying the effects of resveratrol and curcumin single-agent in a mice model with implanted MAC16 colon tumor cells was able to observe attenuation in total protein degradation with both drugs. In this model, however, curcumin was not able to prevent weight loss and muscle protein degradation, and this was ascribed to its low bioavailability (106). A third group studied the effects of curcumin on proteolysis and muscle wasting both *in vitro* and *in vivo* (in a mice model with MAC16 colon tumor), and was able to show a clear effect of weight loss reversal in mice treated with curcumin (107). Other groups were able to show anticatabolic effects of curcumin in animal models of sepsis, injury, and endotoxemia (108-110). To date, the effects of curcumin in cancer cachexia were not studied in humans.

CHAPTER 3 – RATIONALE, HYPOTHESIS, AND AIMS

Rationale

Cachexia is related to shorter survival and worse quality of life in patients with advanced cancer. It is a multifactorial syndrome, in which loss of body weight (both fat and muscle losses) is always present. Even though several mechanisms have been implicated in its genesis, with inflammation playing a crucial role, there are very few evidence-based strategies to date to face this problem. Curcumin has very potent anti-inflammatory properties and therefore its impact on body composition is being studied in the current work.

Hypothesis

Patients with advanced pancreatic cancer treated with curcumin for two months have less fat and muscle loss as compared to matched controls not treated with this compound.

Specific Aims

1. To determine the evolution of body tissue composition in patients with pancreatic cancer treated with curcumin.
2. To determine whether there is a difference in body tissue composition over time between patients with pancreatic cancer treated with curcumin and matched untreated patients.

CHAPTER 4 – METHODOLOGY

Patient population

The patient population for this retrospective observational study is composed of two groups. The first group (treatment group) was obtained from a sample of patients with advanced pancreatic cancer who participated on a clinical trial conducted at the Investigational Cancer Therapeutics department at the University of Texas MD Anderson Cancer Center between December/2004 and February/2006 (Protocol ID03-0009, Principal Investigator Professor Razelle Kurzrock MD). These patients ingested daily eight one-gram capsules containing 900mg of curcumin (90%), 80mg of desmethoxycurcumin (8%), and 20mg of bisdesmethoxycurcumin (2%) supplied by Sabinsa Corporation. The concentrations of each of the curcuminoids contained in the capsules were confirmed by mass spectrometry before the beginning of the trial (104). Forty-nine patients were treated on the clinical trial and were considered for inclusion in the current study. The second group (control group) is composed of patients with advanced pancreatic cancer treated at The University of Texas MD Anderson Cancer Center between December/2004 and February/2006 who did not receive curcumin.

The eligibility criteria for this study were expanded from the original clinical trial (inclusion a-g and exclusion)(111) and were as follows:

Inclusion criteria

a. "The patient had pathologically confirmed adenocarcinoma of the pancreas that was not amenable to curative surgical resection (includes locally advanced, metastatic, or recurrent disease).

b. The patient had a Karnofsky Performance Status of ≥ 60 at study entry.

c. The patient had ≥ 18 years of age.

d. The patient had adequate hematologic function as defined by an absolute neutrophil count $\geq 1{,}500/mm^2$, platelet count $\geq 100{,}000/mm^3$.

e. The patient had adequate hepatic function as defined by a total bilirubin ≤ 2 X ULN, alkaline phosphatase, ALT and/or AST ≤ 5 X ULN, and creatinine $\leq$ 2.0 mg/dL.

f. The patient had measurable disease.

g. The patient agreed to use effective contraception if procreative potential exists (for enrollment on the original clinical trial)" (111)

h. The patient in the treatment group had one abdominal CT image including the L3 vertebra level 28±7 days before the first day of treatment (baseline image) and one similar image within 60±20 days after the first day of treatment (follow up image).

i. The patient in the control group had two abdominal CT images including the L3 vertebra level separated by a range of 60±20 days. The number of days between the first image and the diagnosis of advanced pancreatic cancer must be within 30 days of the same difference for the matched treatment group patient.

Exclusion criteria

a. "The patient had a history of treated or active brain metastases, carcinomatous meningitis, an uncontrolled seizure disorder, or active neurological disease.

b. The patient had received prior radiation. Patients with measurable disease outside the radiation port or documented disease progression of previously irradiated measurable disease were eligible. Patient must be ≥ 4 weeks post-therapy and have recovered from all toxicities.
c. The patient had an unstable medical condition according to the investigator, including uncontrolled diabetes mellitus or hypertension; active infections requiring systemic antibiotics, antivirals, or antifungals, unstable CHF, uncontrolled arrhythmias, or unstable coagulation disorders.
d. The patient was pregnant or breast feeding.
e. The patient had received an investigational agent(s) within four weeks of study entry." (111)

Control matching procedure

Subjects in the control group were matched to those in the treatment group on a 1:2 matching ratio according to gender, age (within a range of ± 5 years), body mass index (± 5 kg/m^2), Karnofsky performance status (± 20), number of prior therapies (± 2), and time between first CT and advanced cancer diagnosis (± 3 months). Charts of all potential controls were reviewed and data collected regarding the matching variables. All charts received then a computer-generated random study accession number and the list of charts was ascendantly sorted. The list was then searched from lowest to highest accession number to find the first two adequate controls for each patient in the treatment group. This was done by sequentially identifying matching gender, age, time from advanced cancer to baseline image, body mass index, number of prior therapies, and performance status. On a first

round, all controls who matched all variables were identified. Then, for patients with no perfect matches available, variables were excluded from the matching procedure one by one in reverse order to allow an even distribution of mismatches across the matching variables. For example: the first variable not to be considered in the second matching round was "performance status". Therefore, remaining potential controls are searched for matches with regards to the other five variables and the selected control is the one with the lowest accession number that has performance status closest to the matching range. Once one treated patient is matched to a control in this round, the match search for another patient starts by excluding the variable "number of prior therapies" from the procedure and matching all other five variables. Whenever another treated patient is matched to the control with lowest accession number and closest "number of prior therapies" in this fashion, the match search for a third patient starts, now excluding the variable "body mass index" and so on.

Data collection

Basic demographic data, date of advanced pancreatic cancer diagnosis (defined as locally advanced, recurrent, or metastatic), laboratory results, presence of ascitis and/or edema, height, and weights were collected by chart review. Anticancer treatment history, use of corticosteroids, progestins, androgens, and cannabinoids were also obtained from the electronic charts.

Body mass indices (BMI) were calculated by dividing the weight (in kilograms) by the height (in meters) squared (112). Patients were considered to be overweight or obese if they had BMI $\geq$ 25.0 kg/m^2 (113).

Eligible abdominal CT images were identified by chart review and downloaded from the institutional PACS (Picture Archiving and Communication System) network. In addition to the baseline and follow up images described under "eligibility criteria", one additional image, 60±20 days before the baseline image, was downloaded for patients in whom it was available (pre-baseline image).

Body composition determination by CT image analyses

The gold standard for determination of body composition is the dual X-Ray absortiometry (DEXA), in which the different compartments of the body are determined by the detection of the amount of radiation that is able to pass through different tissues (114). However, it is not regularly clinically used in the population of patients with cancer. Indeed, none of the patients treated with curcumin in the previous study had performed this evaluation and therefore it was impossible to use this method for the purpose of this work. Conversely, CT images are frequently obtained in the course of standard cancer care, and provide direct view of the body fat and muscle compartments. In fact, it has been shown that CT images are appropriate for body composition analyses in healthy populations (115, 116). Mourtzakis et al have shown in cancer patients that quantification of the fat and muscle contents found on a single abdominal CT slice at the level of the third lumbar vertebra (L3) provide very adequate correlation with DEXA results ($r = 0.82$ and $r = 0.89$, for fat and fat-free masses, respectively, with $p<0.001$ for both correlations) (117).

Procedure

The evaluation of body composition by CT analysis is based on the fact that different body tissues absorb different amounts of radiation, allowing their identification and

quantification (118). The amount of radiation absorbed by a tissue is measured in Hounsfield units (HU), in which the amount of X-ray energy absorbed by water is defined as 0 HU and then the percent absorption coefficient for bone is equivalent to 100 HU, and for air is equivalent to -100 HU (119). It is known that skeletal muscle is characterized by a range of -29 to 150 HU, subcutaneous and intramuscular adipose tissues by a range of -190 to -30 HU (120), and visceral adipose tissue by a range of -50 to -150 HU (121).

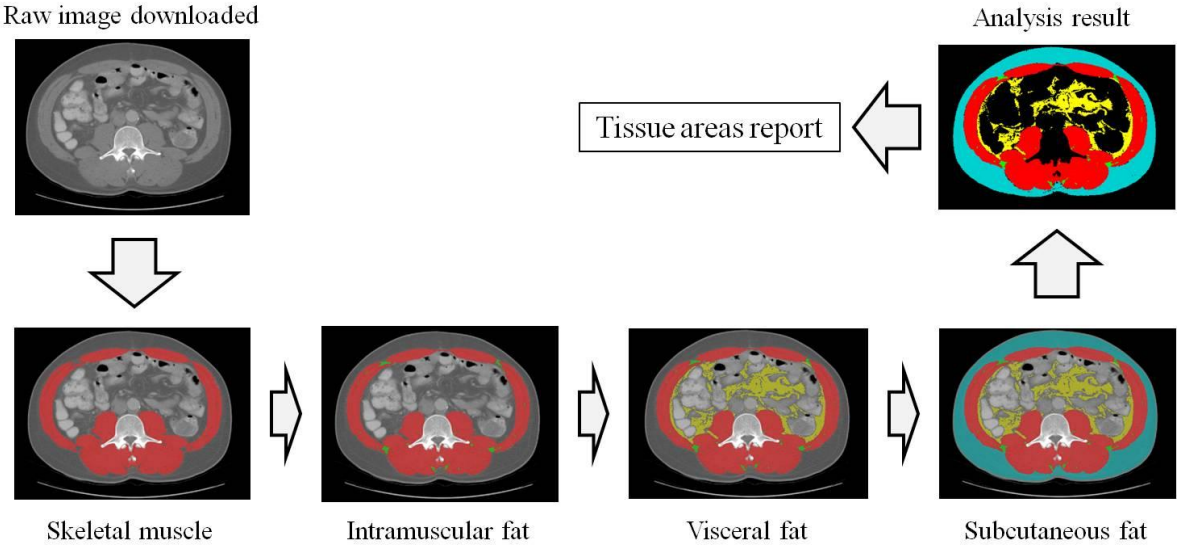

FIGURE 2 – CT image body composition determination procedure.

CT images are generated in a data format in which it is possible to determine the amount of Hounsfield units per pixel (118). For this study, this determination was performed by using Tomovision SliceOMatic computer software (Tomovision, Montreal, QC, Canada). Abdominal CT images at L3 level were identified for all study subjects by chart review and downloaded. Their identifiers were removed and the images were randomized for blinded analysis. Each raw image was then loaded with the SliceOMatic software and the different compartments (skeletal muscle and visceral, subcutaneous, and intramuscular adipose) were

manually identified and marked according to their anatomical distribution and following the described X-ray absorption coefficients (Figure 2). After completion of the identification of the specified areas, the software calculates the area of each compartment, by multiplying the number of pixels marked for each of them by the known area of each pixel.

A height-normalized muscle index is calculated by dividing the area of skeletal muscle at L3 in centimeters squared by the height (in meters) squared (122). Patients were classified as having sarcopenia (reduced muscularity) according to muscle index cutoffs previously described of 52.4 cm^2/m^2 for men and 38.5 cm^2/m^2 for women (123).

The areas of skeletal muscle and fat were used to estimate the total body fat and lean masses, according to the following formulae described by Mourtzakis et al (115): $LBM(kg) = 0.30 \times skeletal\ muscle\ at\ L3(cm^2) + 6.06$ and $FM(kg) = 0.042 \times fat\ tissue\ at\ L3\ (cm^2) + 11.2)$, which have good correlation with DEXA measurements ($r=0.94$, $p<0.0001$ and $r=0.88$, $p<0.0001$, respectively) (117).

Statistical analyses

Descriptive statistics were used to summarize the data. Continuous variables were tested for normality using the Kolmogorov-Smirnov test. Means and standard errors of the means were used for summarizing continuous variables with normal distribution, while medians and ranges were used for summarizing continuous variables which did not follow a normal distribution pattern. For consistency when presenting comparisons between variables in which normality could not be assumed for all groups, medians and ranges were used to summarize the data. Categorical variables were summarized by frequency. Differences in categorical variables were tested for statistical significance by using the chi-squared or

Fisher exact tests, where appropriate. Differences in paired continuous variables were tested by paired t-tests when the underlying distribution was normal and by the Wilcoxon rank-sum test when not normally distributed. Statistical significance for differences between independent continuous variables was evaluated by t-tests and Mann-Whitney tests depending if normality was respectively assumed or not. Correlations were evaluated by Pearson or Spearman coefficients, whenever appropriate also according with normality. Survival analyses were conducted using Kaplan Meier plots with log-rank analyses. Patients for whom date of death was not found were censored at the time of last follow up. Differences were deemed to be statistically significant when the p values were less than or equal to 0.05. All analyses were performed using SPSS v. 16 (SPSS Inc, Chicago, IL). Selected graphs were composed using GraphPad Prism v. 5.04 (GraphPad Software, Inc., La Jolla, CA).

CHAPTER 5 – RESULTS

Study sample

Forty-nine patients were treated on protocol and were therefore considered for the treatment group. Baseline images were available for all patients. However, 20/49 patients (41%) were excluded because they did not have a follow up image. The reasons for lack of images were: (a) patients died before restaging was performed (n=6/20, 30%), (b) patients taken off study because of disease progression or clinical worsening (n=7/20, 35%), (c) patients transferred to other services or lost to follow up (n=5/20, 25%), and (d) patients were prematurely taken off study because of drug intolerance (n=2/20, 10%). Three additional patients were excluded from the study sample because they had no suitable images, and for four patients it was not possible to identify suitable controls. Reasons for exclusion are summarized in Figure 3. As a result, 22 patients had two images meeting the inclusion criteria and available controls, being included in the study group.

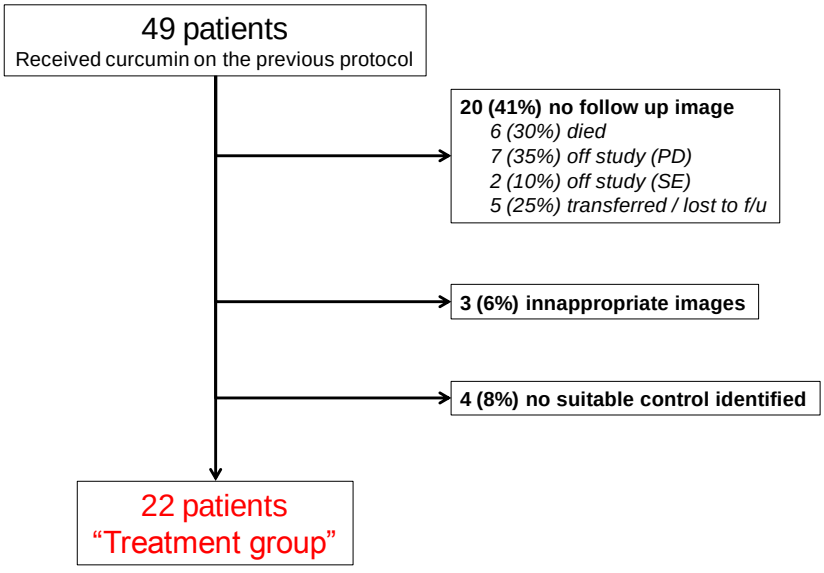

FIGURE 3 – Study population flowchart (PD=Progressive disease, SE=Side effects).

The treatment group was composed by 10 women (45.5%) and 12 men (54.5%), with median age 65.5 years (range 40-77). The median number of prior systemic therapies for this group was 2 (range 0-6), and the median Karnofsky performance status was 80% (range 60%-100%).

Potential patients for the control group were pooled from all patients with pancreatic cancer registered at the institution (excluded the 49 patients treated on the curcumin clinical trial) who were seen between January/2005 and February/2006 (n=948). Of those, 399 (42%) patients were excluded because they have had only one abdominal CT performed within the timeframe, being ineligible for the study. Of the remaining 549 patients, 309 (56%) had at least two images separated by 60±20 days, being selected to compose the pool of patients potentially eligible for the control group. The two best matches for each patient were selected to compose the control group, and the overall matched patient characteristics are shown in Table 1. Median (IQR) time between baseline and follow up images was 63 (52-67.5) and 66 (59.75-75.25) days for patients in the treatment and control groups, respectively (p=0.04).

	Treatment (N=22)		**Control** (N=44)		**p value**
Female Gender (n, %)	10	(45.5%)	20	(54.5%)	1.000
Age (years) (mean, SEM)	63.8	(2.2)	63.2	(1.3)	0.823
Body Mass Index (mean, SEM)	23.8	(0.6)	24.1	(0.4)	0.707
Number of prior therapies (median, IQR)	2	(1-3)	2	(1-2)	0.237
Time between advanced cancer and baseline image (months) (median, IQR)	7	(2-13.5)	6	(3-13.75)	0.749

TABLE 1 – Results of the matching process (SEM = standard error of the mean, IQR = interquartile range).

Body weight

Body weight and body mass index (BMI) data for patients without ascitis and/or edema is summarized in Table 2 [ascitis and/or edema were present in 4/22 (18%) patients in the treatment group and in 10/44 (23%) patients in the control group (p=0.759)]. The majority of patients lost weight between baseline and follow up in both study groups, with a greater frequency of weight losers in the treatment group [15/18 (83%) and 19/34 (56%) in the treatment and control groups, respectively, p=0.07]. The absolute average weight loss in this timeframe was somewhat greater in the treatment group [2.4 kg (SEM 0.8)] in comparison with the control group [1.1 kg (SEM 0.6)], not reaching statistical significance (p=0.174). The average percent weight loss was of 3.3% of the baseline weight for the treatment group and 1.3% of the baseline weight for the control group, also not reaching statistical significance (p=0.130) (Figure 4). Weight change was not different according to gender in any of the groups.

		Weight (kg)			**BMI** (kg/m^2)		
		n	**(SEM)**	**P**	**n**	**(SEM)**	**p**
Treatment	Baseline	69.4	(2.4)	0.007	23.9	(0.5)	0.006
	Follow up	67.0	(2.2)		23.1	(0.5)	
	Variation	*-2.4*	*(0.8)*	-.-	*-0.8*	*(0.3)*	-.-
Control	Baseline	69.0	(2.2)	0.05	24.0	(0.5)	0.05
	Follow up	67.9	(2.0)		23.6	(0.4)	
	Variation	*-1.1*	*(0.6)*	*0.175**	*-0.4*	*(0.2)*	*0.160**

* p values for the comparison between the variations in the Treatment and Control groups.

TABLE 2 – Weight and BMI values for patients in both study groups at the 2 time points.

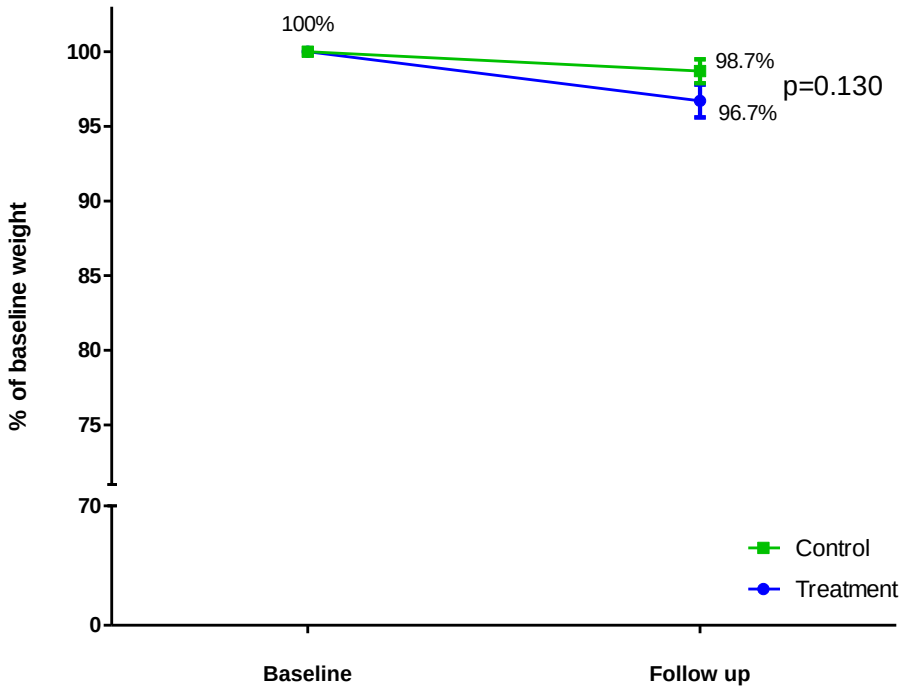

FIGURE 4 – Percent weight change in the study groups. (Whiskers represent the SEM)

According to usual BMI cutoffs, 6/18 (33%) treated patients and 12/34 (35%) controls were considered to be overweight or obese at baseline (p=1.000) and 4/18 (22%) and 11/34 (32%) were classified as overweight or obese at follow up (p=0.532).

Body composition

All body composition parameters decreased in both groups between baseline and follow up. The evolution of body composition variables is summarized in Table 3. No significant differences were found with regards to such variables between patients in the treatment and control groups at baseline. At follow up, the treatment group showed a trend towards lower subcutaneous fat area at L3, total adipose area at L3 and total estimated body fat.

	Baseline					Follow up				
	Treatment N=22		Controls N=44		p	Treatment N=22		Controls N=44		p
	Median	(IQR)	Median	(IQR)		Median	(IQR)	Median	(IQR)	
Skeletal muscle area at L3 (cm^2)	119.7	(104-145.7)	125.1	(108-146.7)	0.661	112.5**	(95.6-137.5)	122.6	(102-149)	0.202
Muscle index (cm^2/m^2)	42.3	(37-46.7)	42.3	(37.6-47.4)	0.747	40.2**	(35.6-45.4)	41.6	(37.5-46.8)	0.115
Intramuscular adipose area at L3 (cm^2)	7.5	(3.4-12)	7.9	(5.4-11)	0.833	7.7	(2.5-10.5)	7.0	(4.9-13)	0.430
Visceral adipose area at L3 (cm^2)	57.3	(36.4-133.2)	73.4	(44.7-116.6)	0.668	42.3*	(26.2-101)	68.5*	(35.7-104)	0.286
Subcutaneous adipose area at L3 (cm^2)	95	(65.7-191.9)	120	(101.6-172.7)	0.331	72.7**	(59.9-160.5)	116.7*	(84.6-149.2)	0.054
Total adipose area at L3 (cm^2)	208.9	(119-317.5)	228.4	(147.3-294.8)	0.732	137.8**	(85.8-266.8)	217.8*	(154.2-282.9)	0.07
Estimated total lean body mass (kg)	42	(37.3-49.8)	43.6	(38.5-50.1)	0.661	39.8**	(34.7-47.3)	42.8	(36.7-50.8)	0.202
Estimated total fat body mass (kg)	20	(16.2-24.5)	20.8	(18.5-23.6)	0.732	17**	(14.8-22.4)	20.4*	(17.7-23.1)	0.07

* statistically significant differences between baseline and follow up time points within study groups. (* $p < 0.05$; ** $p<0.001$)

TABLE 3 –Body composition variables in both groups at baseline and follow up. (IQR = interquartile range).

Percent variation in body composition variables according to study groups are shown in Figure 5. Patients in the treatment group showed greater percent reduction in all parameters when compared to those in the control group. Significantly different reductions were observed for skeletal muscle area at L3, intramuscular adipose area at L3, total adipose area at L3, estimated total adipose body mass, and estimated total lean body mass. The median percent change in estimated total lean body mass and total adipose body mass was significantly greater for treated [-4.8% (IQR -9.1 to -0.1) and -6.8% (IQR -15 to -0.6), respectively] than for untreated patients [-0.05% (IQR -4.2 to 2.6) and -4.0% (IQR -7.6 to 1.3), respectively] ($p<0.001$ and $p=0.04$ for lean and fat body mass changes, respectively). The difference in percent changes for estimated total lean and adipose body masses was not statistically different among curcumin treated patients, but was significantly different among the controls, with the fat loss being greater ($p=0.03$).

Sarcopenia was present in 15/22 (68%) treated patients and 27/44 (61%) controls at baseline ($p=0.787$). At follow up, sarcopenia was present in 18/22 (82%) treated patients and 29/44 (66%) controls ($p=0.252$). Sarcopenia combined with overweight or obesity (BMI $\geq$ 25kg/m^2) occurred in 3/18 (17%) and 5/34 (15%) treated and untreated patients at baseline, respectively ($p=0.574$) and in 3/18 (17%) and 3/34 (9%) treated and untreated patients at follow up, respectively ($p=0.339$). Male patients in the treatment group had a significantly greater frequency of sarcopenia as compared to female patients in the same group [11/12(92%) versus 4/10(40%) at baseline and 12/12 (100%) versus 6/10 (60%) at follow up ($p=0.020$ and 0.029, respectively)]. In the control group, the frequency of sarcopenia in males was also greater, however did not attain statistical significance in any of the timepoints. No baseline sarcopenic patients reversed their low muscularity status at follow

up. However, five patients developed sarcopenia at follow up (2 women and 1 man in the treatment group and 2 women in the control group).

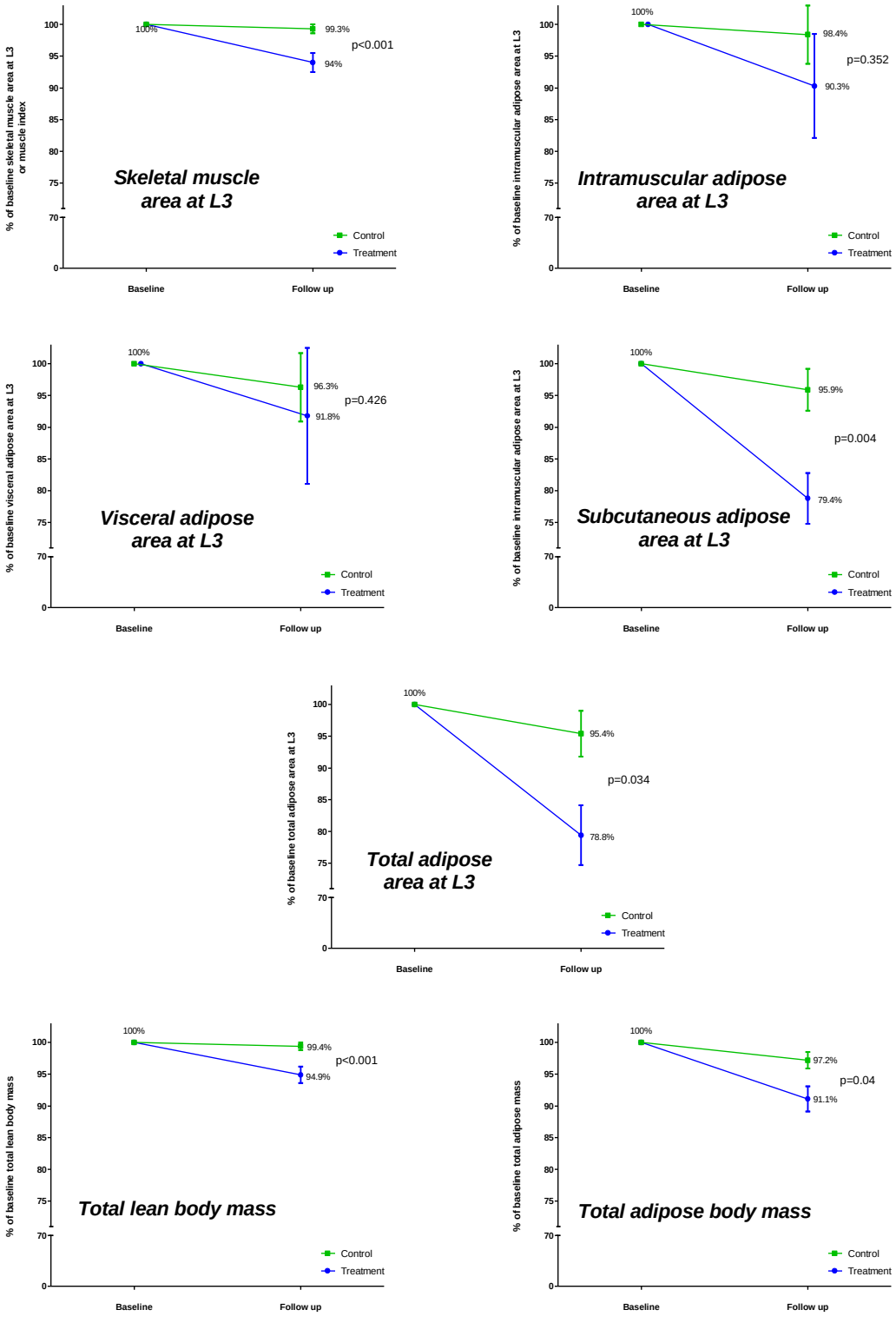

FIGURE 5 – Percent change in body composition variables between baseline and follow up. (Whiskers represent the SEM)

With regards to the use of medications that can impact body composition (especially affecting muscularity), 4/22 (18%) of the treated patients used such drugs in the study period (progestin in three cases and testosterone in one), while 2/44 (4.5%) controls were receiving those medications (one progestin and one testosterone) (p=0.09). No patients were found to be under treatment with cannabinoids or corticosteroids in the study period. Among the treated patients, no difference was found between subjects who received such drugs and those who did not receive them with regards to total lean body mass [-6.4% (SEM 3.5) vs. -4.8 (SEM 1.4), respectively, p=0.523] and total body fat [-9.9% (SEM 4.2) vs. -8.7 (SEM 2.3), respectively, p=0.58]. Statistical significance was not tested for the control patients due to the small number of subjects who received the drugs.

A proportion of patients in the control group received oncologic treatment in the study period (26/44, 59%). Gemcitabine, cisplatin, and oxaliplatin were the most common chemotherapeutics used. The percent change in total lean body mass was not statistically different between controls who received and did not receive oncologic treatment [-0.7% (SEM 0.8) vs. -0.5% (SEM 1.0), respectively, p=0.828]. Similarly, the percent change in total adipose body mass was not significantly different between controls according to oncologic treatment during the study period [-4.3% (SEM 1.5) vs. -0.7% (SEM 2.3), respectively, p=0.179].

The correlations between other potential confounders and variations in body composition were also analyzed by determining correlations (Table 4). No statistically significant correlations were observed.

	Treatment group				Control group			
	Total lean body mass variation		Total body fat mass variation		Total lean body mass variation		Total body fat mass variation	
	R	p	R	p	R	p	R	p
Age	0.27	0.232	-0.41	0.062	-0.29	0.79	-0.14	0.372
Time between advanced cancer to baseline	0.04	0.871	0.19	0.405	-0.05	0.748	0.12	0.423
Baseline albumin	-0.29	0.195	0.2	0.372	0.14	0.539	-0.21	0.353
Performance status	-0.19	0.398	0.21	0.345	0.13	0.398	-0.19	0.214
Number of prior therapies	0.21	0.343	0.23	0.306	-0.04	0.79	0.09	0.554

TABLE 4 – Correlations between body composition variation and confounding variables.

Survival analyses

Overall median survival from baseline (95% CI) was of 189 (142-236) days for the patients treated with curcumin and 299 (240-357) days for the patients in the control group (log rank p=0.065) (Figure 6). Survival was not significantly different between sarcopenic and non-sarcopenic patients overall [254 (216-291) vs. 293 (143-443) days, p=0.588]. However, when analyzed separately, the 15 sarcopenic patients in the treatment group showed significantly shorter survival [169 (115-223) days] in comparison with the 27 sarcopenic patients in the control group [299 (229-369) days, p=0.024], whereas no difference was found between the survival of the seven non-sarcopenic patients in the treatment group [254 (216-291)] and the 17 non-sarcopenic control patients [304 (184-423), p=0.910] (Figure 7).

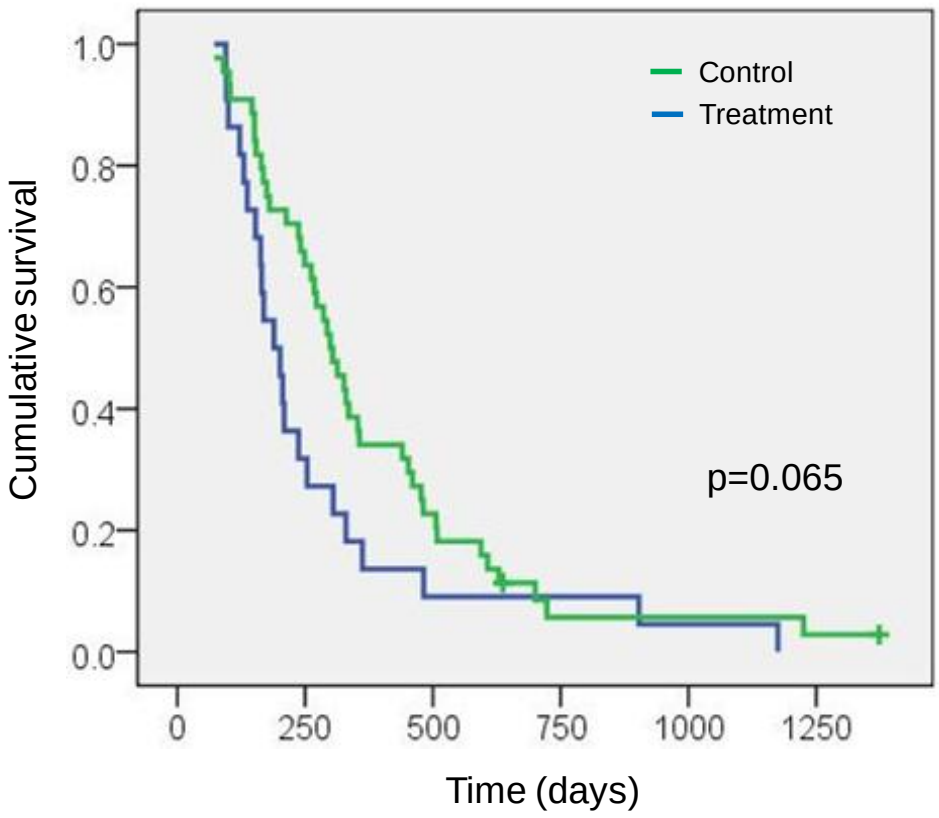

FIGURE 6 – Kaplan-Meier plot: survival from baseline of patients in the treatment (n=22) and control (n=44) groups.

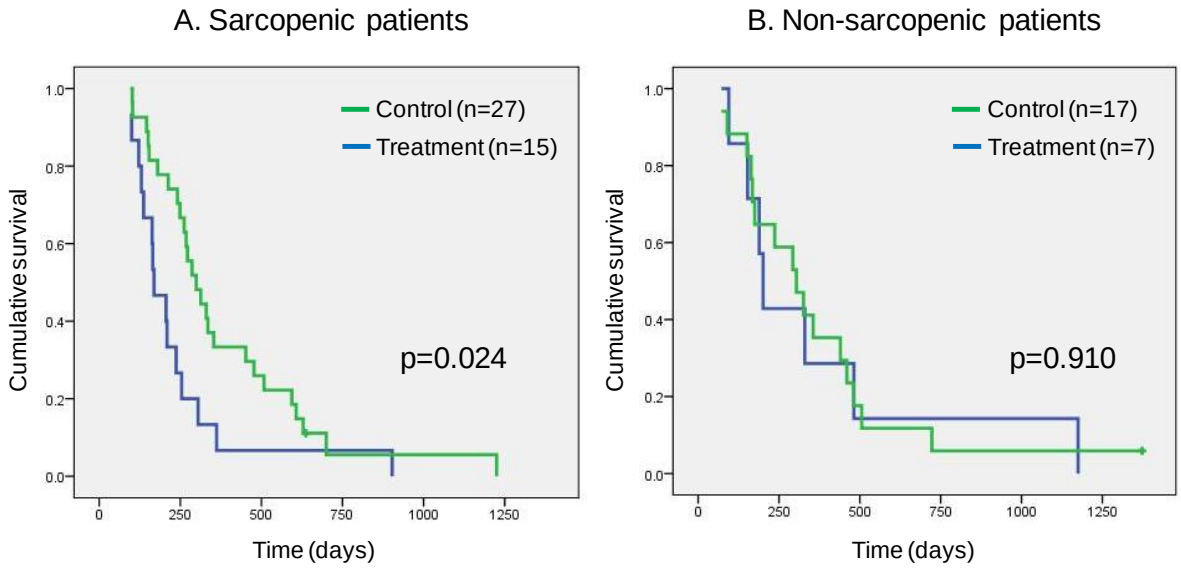

FIGURE 7 –Kaplan-Meier plots: survival of sarcopenic and non sarcopenic patients.

Survival was plotted against changes in body composition between baseline and follow up for patients in the treatment and control groups whose death was confimed (22/22 and 42/44, respectively) (Figures 8 and 9). The correlation between the variation of total lean body mass and survival yielded coefficients of 0.283 and -0.035 ($p=0.202$ and 0.824) for cases and controls, respectively, whereas the correlation between survival and variation in total fat body mass yielded coefficients of 0.367 and 0.058 ($p=0.09$ and 0.713) for cases and controls, respectively. Even though not statistically significant, shorter survival appeared to be correlated with greater reductions in body composition parameters only in the group of patients treated with curcumin.

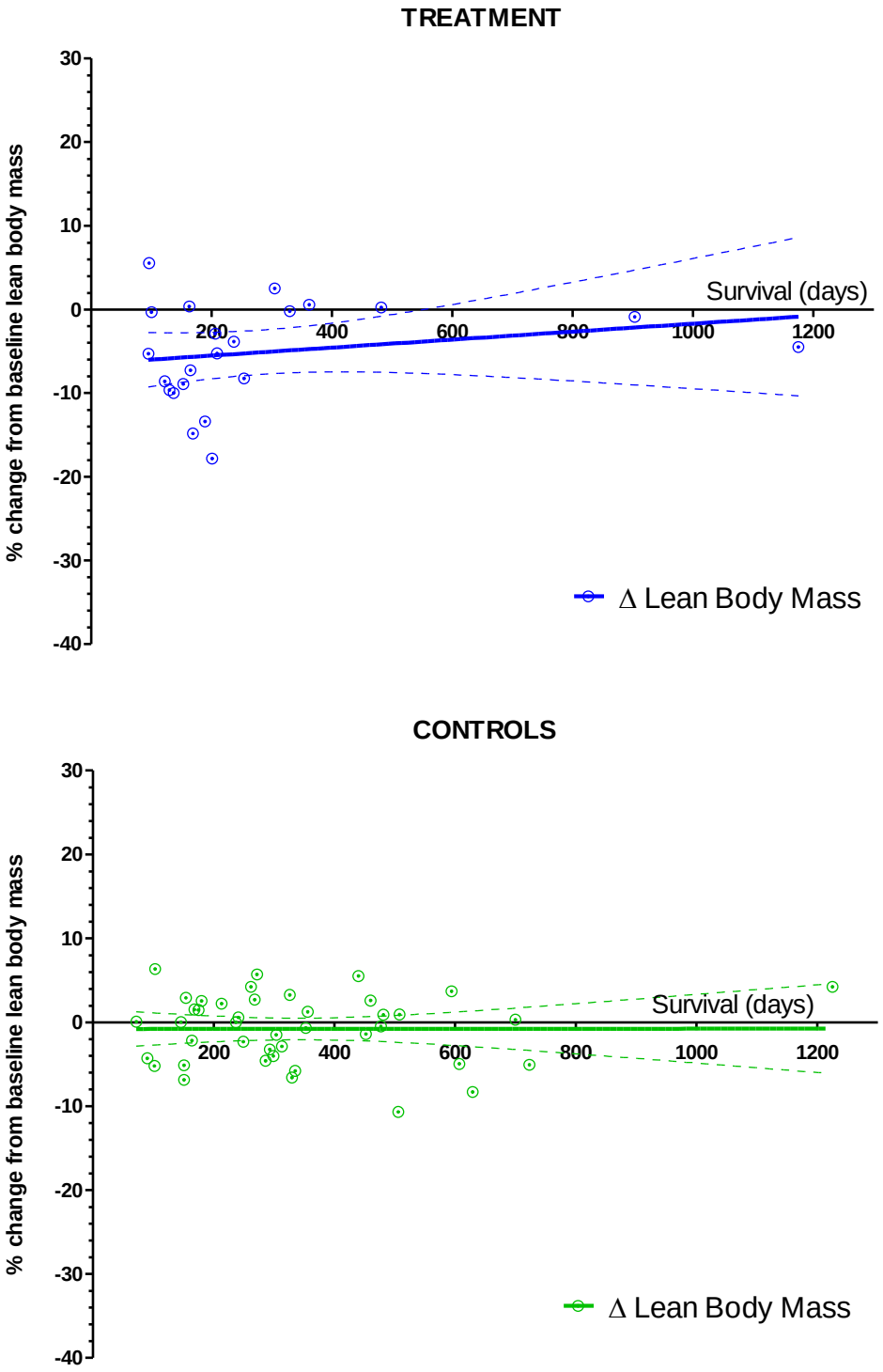

FIGURE 8 – Percent change in lean body mass according to survival from baseline. Circles represent individual patients, solid line the regression line fitted, and dashed lines the 95%CI band.

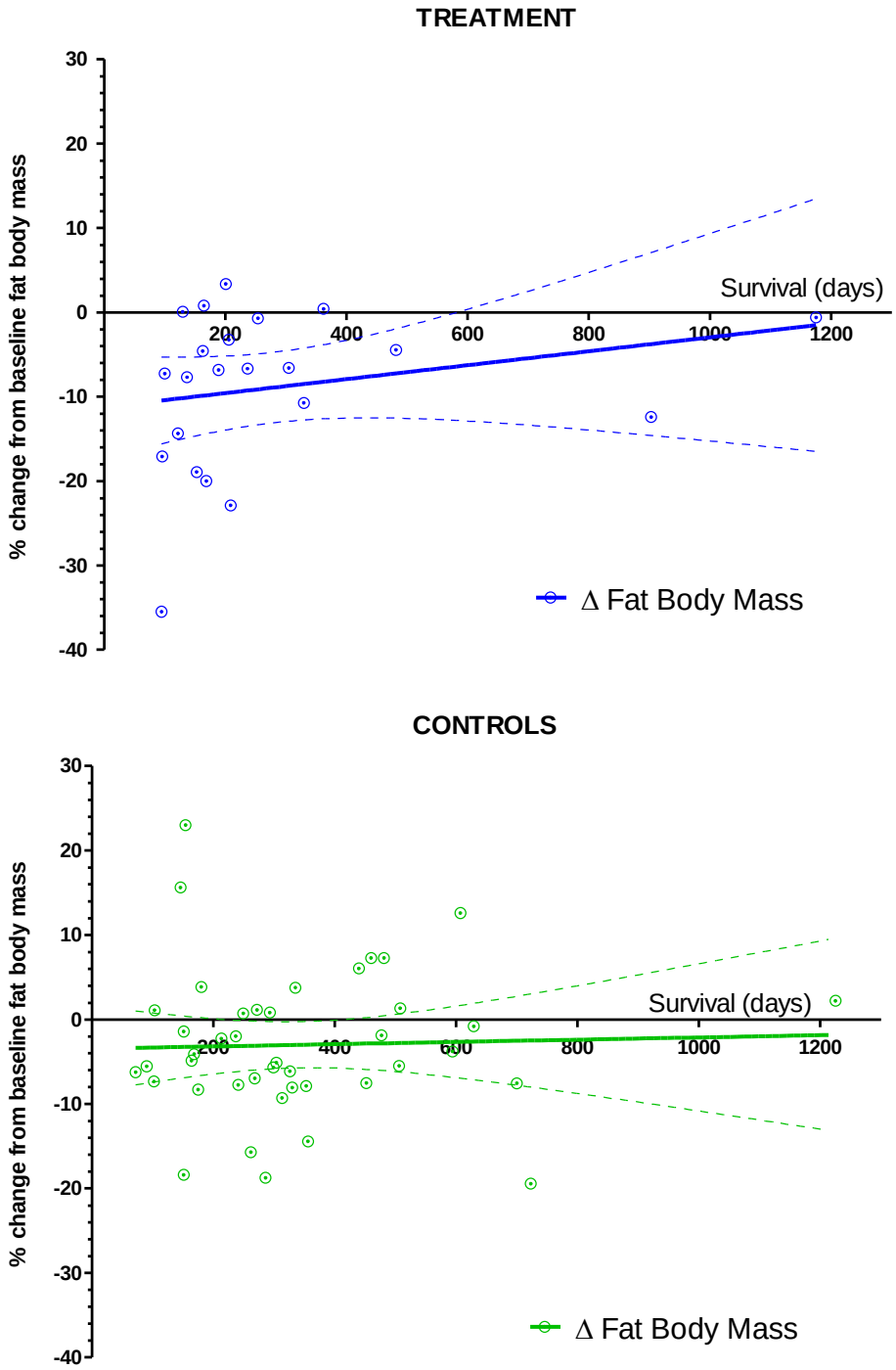

FIGURE 9 – Percent change in adipose body mass according to survival from baseline. Circles represent individual patients, solid line the regression line fitted, and dashed lines the 95%CI band.

Exploratory pre-baseline data analyses

Weight data was available for 10/22 (45%) patients in the treatment group and for 17/20 (85%) of their controls. Since one of the treated patients had no controls with prebaseline weights available, this triad was excluded from comparative prebaseline weight analysis. Similarly to what was found between baseline and follow up timepoints, the majority of patients also lost weight between pre-baseline and baseline, with 7/9 (78%) and 15/17 (88%) patients losing weight in the treatment and control groups, respectively. Figure 10 summarizes the evolution of the body weight (in percentage of the pre-baseline weight). The variation in percentage of the pre-baseline weight between pre-baseline and baseline time points was of -2.4% (SEM 1.5) and -1.9% (SEM 1.6) for the treatment and control groups, respectively (p=0.848) and between baseline and follow up time points it was of -3.1% (SEM 1.5) and -1.5 (SEM 1.1) of the prebaseline weight for the treatment and control groups, respectively (p=0.403).

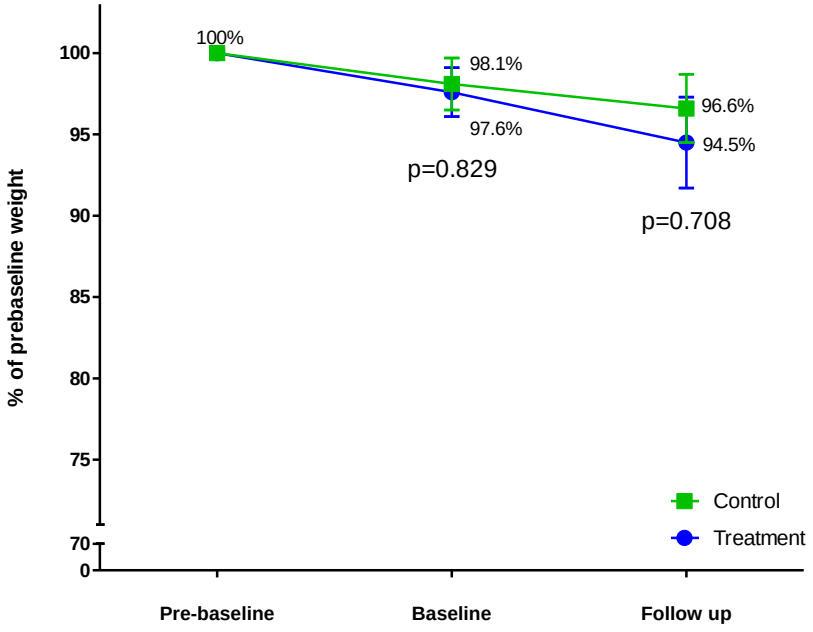

FIGURE 10 – Percent weight changes at three time points. (Whiskers represent the SEM)

Treatment responders exploratory analyses

Two patients had significant responses to the previous clinical trial. One of them had prolonged stable disease for more than 9 months and the other had a significant though short lived decrease in tumor size [decrease of 73% of the baseline tumor size by RECIST measurements (124)]. No information was available regarding pre-baseline weights on these patients. Data regarding weight and body composition for the baseline and follow up time points are summarized in Table 5. Weight loss in both patients was lower than the average weight loss for the overall treatment group (3.3%), and the slight increase in total body adipose mass was a departure from the average reduction of 8.9% in the treatment group. The patient with partial response had a decrease of total lean body mass greater than the average decrease of 5.1% in the treatment group, whereas the patient with prolonged stable disease had a slight increase in this variable.

	Partial response patient			**Stable disease patient**		
	Treated	**Control A**	**Control B**	**Treated**	**Control A**	**Control B**
% weight change from baseline	-1.4%	+1.2%	+4.0%	-0.6%	+3.2%	+4.6%
% lean body mass change from baseline	-7.3%	+3.7%	+5.5%	+0.6%	+5.7%	+5.5%
% adipose body mass from baseline	+0.8%	-3.8%	+6.0%	+0.4%	+1.1%	+6.0%

TABLE 5 – Body composition changes in the responder patients and their controls.

CHAPTER 6 – DISCUSSION

Curcumin did not seem to reverse nor attenuate body mass losses

The hypothesis for this study was that patients with advanced pancreatic cancer treated with curcumin for two months have less fat and muscle loss as compared to matched controls not treated with this compound. In order to evaluate this, the evolution of weight and body composition was observed in a group of 22 patients who received the drug and 44 controls who did not receive it, matched according to gender, age, time from advanced cancer diagnosis, body mass index, and number of prior therapies (refer to Table 1 for a summary of the matching variables).

This study showed that the sample of patients treated with curcumin for two months lost weight due to both fat and muscle losses, therefore the drug seem to not play a role in reversing body mass loss in those patients. The weight loss is in line with the previously described evolution of body composition in populations of patients with pancreatic cancer. Wigmore et al. showed in a prospective observational study of 20 advanced pancreatic cancer patients that absolute fat and muscle losses measured by bioelectrical impedance are significantly different between diagnosis and death (125). Using the same retrospective CT analysis technique as this study, Tan et al. also described that the majority of patients with advanced pancreatic cancer lost body mass from both fat and muscle compartments as the disease evolved (126).

Attenuation of weight loss by curcumin in the setting of pancreatic cancer was previously described in animal models only. One study in an animal model of cachexia (MAC16 colon tumor-bearing mice) showed that the administration of a 100mg/kg dose of a

curcumin complex (curcumin c3, composed of 72% curcumin, 22% desmethoxycurcumin, and 4% bisdesmethoxycurcumin) was able to attenuate weight loss in the animals (107). In addition to the fact that animal models frequently do not translate well to human clinical practice (127), it is of interest to note that the analogue composition of the drug used in the current study was somewhat different than the used in this animal study (87.2% curcumin, 10% desmethoxycurcumin, and 2.3% bisdesmethoxycurcumin) (104), which might also contribute for the different findings. Indeed, it appears that each curcumin analogue might have different activities and potencies, but this is still to be completely determined (128). Therefore, further research is needed to investigate if distinct curcumin analogues or combinations can differentially affect body weight. Two other groups, one studying the effects of curcumin on rats bearing the Yoshida AH-130 ascitis hepatoma cells (which is known to cause cachexia) (105), and another in mice bearing MAC16 tumor cells (106) did not show the weight loss attenuation found in the previously described animal study (107). Interestingly, the latter showed an attenuation of the PIF-induced proteasome expression in murine myotubes treated with curcumin *in vitro* (106).

In the present study, both treatment and control groups showed statistically significant absolute and percent weight losses, with greater losses in the curcumin treated group. The difference in absolute and percent weight loss was not statistically significant between the two groups after approximately 2 months. Therefore, our findings do not support the hypothesis of this study. Of note, the different compartments of body composition, while consistently decreased, did so in a different fashion between groups.

At baseline, the area of all body compartments measured at L3 (subcutaneous, intramuscular and visceral fat and skeletal muscle) were similar between groups, as

therefore were the estimated total lean and adipose body masses (Table 3). At follow up, significant differences were found when comparing the percent reduction in areas of skeletal muscle and subcutaneous fat between treated and untreated patients. As expected from these results, both estimated total lean body mass and total adipose body mass showed significantly greater reductions in the treatment group (Table 3 and Figure 5). In addition, patients in the control group lost significantly more adipose tissue than muscle whereas treated patients lost comparable percentages of muscle and fat.

Efforts are being made towards the creation of a classification of cancer cachexia. Recently, a preliminary classification of cancer cachexia in three severity degrees (precachexia, cachexia, and refractory cachexia) was proposed (10). Patients with refractory cachexia, as the name implies, do not respond to therapies aimed at reversing the process and invariably undergo a progressive worsening of body composition variables. It might be that the patients in this study were towards this end of the cachexia spectrum, therefore being not amenable to reversal of the cachexia process. It is not possible to definitively identify if the patients in the current study had refractory cachexia, due both to its retrospective nature and to the lack of a clear and validated definition of the cachexia severity degrees.

Mounting evidence exists on the potential effects of curcumin in the adipose tissue and more so in modulation of signal transduction pathways that are paramount for the genesis of obesity and several of its complications (129). The present study showed that patients with advanced pancreatic cancer treated with curcumin had significantly greater losses of fat as compared to matched untreated controls (Figure 5). This might indicate a direct effect of

curcumin on adiposity which is interesting to be explored in anti-obesity research. Further research is needed in larger samples of non-cancer patients and healthy individuals.

Sarcopenia (decreased muscle mass) was present at baseline in 68% of the patients who received curcumin and 61% of the controls, and these prevalences increased at follow up in both groups, to 82% and 66% for treated and untreated patients, respectively. These figures are greater than the 51% prevalence that we have shown for a sample of 104 patients with advanced cancer at our Phase I program (130). This is probably explained by the heterogeneous population in the previous study. In the setting of pancreatic cancer, the Tan et al. group reported in a set of 44 patients a proportion of 46% sarcopenic patients at baseline and of 61% around 135 days later (126). One might interpret that difference as caused by a selection of patients in a more advanced stage of disease in our study. Interestingly, however, is that the median overall survival after the baseline image in Tan's study is the same as for the patients treated with curcumin in our study (189 days), and shorter than the median survival for patients in the control group (299 days). Therefore, it is likely that other factors are in play and affecting the genesis of sarcopenia or survival in our patients.

Curcumin and survival

In the current study, patients treated with curcumin had median survival from baseline 189 days (95%CI 142-246), 110 days shorter than untreated patients (p=0.065). There are very few published clinical studies of curcumin in humans, and survival data is scarce. Epelbaum et al. studied the effects of curcumin combined with gemcitabine for the treatment of advanced pancreatic cancer in 17 patients and reported a comparable median overall

survival of 5 months, ranging from 1 to 24 months in the 11 patients who were considered evaluable (131).

In a retrospective analysis of 83 consecutive pancreatic cancer patients referred to our Phase I program, it has been shown that they had a median overall survival from referral of 5 months (95%CI 3.3-6.2 months) (132). This is shorter than the results reported here for both study groups from the baseline image [6.3 months (95%CI 4.7-7.9 months) for patients treated with curcumin and 10 months (95%CI 8-12 months) for the controls]. For the patients in the treatment group, the dates of referral to the Phase I program and baseline image are very similar so it is fair to state that patients who received curcumin had an overall survival around 1 month longer than the average of referred patients with the same diagnosis. Of note, patients in the control group had longer overall survival (5 months) than what was reported for patients with the same diagnosis seen at our Phase I program. This is of interest because might point out to an unforeseeable selection bias, caused by a systematic difference between patients referred to phase I and those who were not. It might be that, regardless of the matching efforts, patients in the control group had better health conditions at the inception point (time of first image), not being perceived by their physicians as candidates to the curcumin clinical trial and therefore not referred. This might be contributing to the difference in overall survival between patients in the treatment and control groups. In addition, it is important to mention that overall survival is subject to interference of all treatments undertaken after the inception point, and that more than 50% of the patients in the control group were receiving oncologic treatment at the time of study entry and some of the patients in the treatment group received further treatments after being taken off the curcumin trial. Therefore, it is not possible to ascribe differences in survival

only to the use of curcumin based solely on the data reported here. This is inherent to the retrospective design of the current study, despite all matching efforts.

It was also shown in this work that sarcopenic patients treated with curcumin had a median survival significantly shorter (130 days) than sarcopenic patients in the control group (Figure 7). Shorter survival in patients with sarcopenia has been previously described among overweight pancreatic cancer patients (126) and among obese patients with cancers of the gastrointestinal and respiratory tracts (123). Unfortunately, due to the small number of patients with combined sarcopenia and overweight/obesity in this study, it was impossible to conduct survival analyses to explore the influences of this combination of variables in this patient population. It is of interest that sarcopenic patients treated with curcumin had shorter survival as compared to untreated patients. Curcumin suffers with low bioavailability issues (95), and it might be that the differential distribution in the body tissues in sarcopenic patients had driven a particular action of curcumin in those patients. Further research is needed to confirm this finding and elucidate the mechanisms by which survival is significantly reduced when curcumin is used in patients with sarcopenia.

An interesting finding relates to Figures 8 e 9, is the apparent correlation between percent loss of total lean body mass and total adipose body mass with shorter survival in patients treated with curcumin. By observing the graphs, it is possible to note that patients who are closer to death and are receiving curcumin present a greater loss of both total lean and adipose body masses, while patients in the control group present an almost flat regression line, denoting that total lean and adipose body mass losses in these patients remain more stable, regardless of the proximity to death. It seems as if patients who receive curcumin undergo a metabolic shift towards a more lipolytic weight loss pattern when they

are towards the end of their lives. It is not possible to determine causality in this retrospective study, but it is plausible to hypothesize that maybe curcumin is having a direct effect on the cancer and activating the secretion of LMF (lipid mobilizing factor), for example. Further research is needed to prove this new hypothesis.

Potential confounders of body composition changes

Changes in body composition might be impacted by several factors. Age, for example, is well known for being frequently accompanied by fat and muscle loss (133). Performance status might impact body composition to the extent that it impacts physical conditioning (134). Considering the very small sample size of the current study, it was not possible to generate multivariate models to evaluate the participation of potential confounders of the total adipose and lean body mass variation variables. Therefore, the dyadic correlation between the potential confounders and each of the body composition percent change variables was performed to provide preliminary evidence of their independent association with body composition outcomes (Table 4). Interestingly, the correlation coefficients were very low and none was statistically significant, pointing towards a small or absent impact of those potential confounders, when taken independently, on the results of this study. However, further research in larger samples is needed to evaluate the importance of such variables in body composition changes in patients with advanced pancreatic cancer.

Medications such as corticosteroids, androgenic steroids, progestins, and cannabinoids more often than not have a role in the therapeutic arsenal of advanced cancer patients. These drugs can impact body composition and have to be considered as potential confounders. Corticosteroids, for example, when used for long periods of time can cause muscle wasting

(135). Androgenic steroids are capable of decreasing weight loss and/or increase muscle mass. Nandrolone has been studied in patients with non small cell lung cancer, for example, and showed lower frequency and intensity of weight loss in patients who received the drug as opposed to patients who did not receive it (136). In patients with COPD treated with nandrolone, an increase in fat free muscle mass was shown in comparison with patients treated with placebo (137). Progestins are the mainstay treatment for cancer cachexia and have a positive orexigenic effect with some gains in weight (138). In the current study, very few patients were under treatment with such drugs, and their use was not associated with differences in body composition.

Patients in the control group could be under oncologic treatments during the study period, and this is also a potential source of bias since it has been shown in several types of cancers that the oncologic treatment itself might have an effect on body composition. In patients with breast cancer, for example, an increase in weight mostly due to fat mass has been described after oncologic treatment (139). Similar results were described for patients receiving chemotherapy for Hodgkins lymphoma (140). In the current study, 59% of the control group was under active oncologic treatment with chemotherapeutic and biologic anti-cancer agents during the study period. In the control group, no differences were found with regards to changes in body composition over time when comparing patients according to presence of absence of oncologic treatment.

Exploratory analyses of the best responders

One important issue regarding the use of curcumin is its very low oral bioavailability in the currently available formulations (95). Two patients in particular presented interesting

clinical oncologic responses to the drug in the previous protocol: one had a prolonged stable disease (more than 9 months) and the other had a 73% tumor reduction that was short lived. It is plausible that one of the reasons for these patients to respond to the drug is that their organisms are specially equipped to absorb and adequately utilize curcumin (because of reasons that are yet to be discovered that might include mutant players in metabolic pathways, for example). Therefore, analyses of those particular responders were conducted separately, to evaluate if their body composition changes were particularly different than that of the majority of the patients on study (Table 5). It was found that both responder patients lost weight as their non-responder counterparts but on a smaller percent rate, whereas both gained small amounts of fat mass, a completely different result as compared to the overall fat loss of almost 9% in the non-responders. Considering this study's very small sample, it is impossible to draw definite conclusions about the body composition behavior of those two patients. In addition, it might be the case that the differences in body composition changes are reflecting the fact that the patient had an oncologic response and therefore is progressing differently than the other patients. Whether curcumin is itself having a different action directly on body composition or the changes in body composition are a consequence of curcumin action on the cancer is subject for future prospective studies with larger samples.

CHAPTER 7 – CONCLUSIONS AND FINAL CONSIDERATIONS

This study was not able to confirm the hypothesis that patients with advanced pancreatic cancer treated with curcumin for two months have less fat and muscle loss as compared to matched untreated controls. Both curcumin-treated and untreated patients lost weight due to a combination of fat and muscle depletion. Curcumin treated patients lost more weight and had greater losses in all body composition variables. Fat loss was the prominent feature in both groups, with different adipose compartments behaving differently: the significant fat loss occurred only in the subcutaneous area. Lean body mass loss also occurred and was significantly greater in the treated patients.

Overall, patients on curcumin had a borderline significant shorter survival as compared to their untreated controls, and patients on curcumin with sarcopenia had shorter survivals as compared to those who did not have sarcopenia.

Additionally, the current study allowed for the rising of some new research hypothesis such as the possible direct effect of curcumin in the tumor activating the secretion of LMF and shifting the weight loss from a predominantly proteolytic pattern to a more lipolytic one in patients towards the end of life.

Some limitations have to be cited for this study. The small sample size and its retrospective nature impair the ability of drawing definite conclusions. Additionally and also related to its retrospective characteristic, the study is subject to selection bias, even though several measures were taken to minimize this risk (1:2 matching by several characteristics, random selection of controls). However, it is still possible that some remaining systematic difference between patients treated with curcumin and controls persisted. For example, all

study subjects had the same diagnosis and were treated at M. D. Anderson Cancer Center at the same time period. Therefore, it is likely that all of them were treated by a consistent "pool" of physicians, who sometimes referred the patients to the curcumin clinical trial and sometimes did not. The choice for referral might have been influenced by several factors, including the subjective impression of the clinician about the patient's overall health state. It might very well be that patients who were considered in better condition were not referred to the curcumin trial because of the impression that those patients were doing well on current treatments or could be changed to other therapy lines. This is supported by the finding that patients in the control group showed an overall survival about five months longer than what was reported for a group of 83 consecutive patients with advanced pancreatic cancer referred to our Phase I program. Therefore, it is not impossible that patients in the control group were in better overall health state (even though not reflected in the matching variables) at the time of baseline imaging when compared to patients in the treatment group. Unfortunately the retrospective nature of this study makes it is impossible to precisely quantify the controls' overall health state at baseline beyond what was already performed by the stringent five-variable matching procedure.

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VITA

Henrique A. Parsons was born in São Paulo, Brazil, son of Harry Anthony and Maria Bernadete A. Parsons, received his MD from the Pontifícia Universidade Católica of São Paulo in 2002. He then went on to train in Internal Medicine and after that undertook a Preventive Medicine/Public Health residency in 2005. After that, worked as a practicing Internist and Palliative Care physician and moved to the USA in 2007 to pursue further training in Palliative/Supportive Oncology care staying 1.5 years in the Palliative Care and Rehabilitation Medicine Dept. and finally moving to the Investigational Cancer Therapeutics Department in 2009 when he enrolled into the Graduate School of Biomedical Sciences and started his work with body composition and cachexia research. Henrique is married to Gaëlle Parsons and they have a Texan son, Dean Parsons. A new addition to the clan is currently on the way and is anxiously expected for November 2011.