**Cardiac structural and functional alterations in cancer cachexia**

by

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A thesis submitted in partial fulfillment of the requirements for the degree of

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## ABSTRACT

**Background:** Cancer cachexia is referred to as a wasting condition, with skeletal muscle and fat loss. Although heart atrophy is recognized as a notable component of experimental cancer cachexia models, it has not been characterized in human studies. The contribution of cardiac structural and functional impairment to worsening performance status, fatigue progression and dyspnea, is known in the context of heart failure; however, the pertinent clinical information in cancer cachexia has never been examined. Cancer cachexia still does not have an approved therapy; regulatory agencies claim functional measures such as stair climbing test improvement as a clinical benefit of experimental agents, however, the matter of heart function and structure at baseline and its alteration over time (as a potential source of functional variation) is ignored. In the absence of any clinical evidence for cardiac structure or function changes in cachexia context, two retrospective evaluations of cardiac function were conducted in pursuit of preliminary evidence of either: a) altered cardiac function over time in renal cell carcinoma patients or, b) evidence of concurrent cachexia and abnormally low cardiac mass in cirrhosis patients with or without hepatocellular carcinoma. My major hypothesis through a longitudinal work was that *heart is being atrophied and is dysfunctional in parallel to cancer cachexia progression.*

**Methods:** Three different clinical projects were considered for my PhD research (two retrospective/chart reviews and one longitudinal cohort study). In all these studies, standard of care computed tomography cross-sectional images were utilized to quantify skeletal muscle and fat. In the longitudinal study, we measured heart systolic [left ventricular ejection fraction (LVEF) and global longitudinal strain] and diastolic function in addition to left ventricular mass at baseline (before start of carboplatin-based therapy) and over time (4 months later) in patients with

metastatic non-small cell lung cancer (n=72). Standard questionnaires for assessment of performance status, fatigue and dyspnea also were applied.

For the first retrospective study, cirrhotic patients (n=100) with or without hepatocellular carcinoma were studied; values for left ventricular mass were abstracted from available echocardiography reports before liver transplant. For the second retrospective study in renal cell carcinoma patients (n=47), several multigated acquisition scans were gathered over one year of assessment to detect changes in LVEF.

**Results:** For the first time we demonstrated the occurrence of left ventricular mass atrophy in a group of patients with progressive cachexia and non-small cell lung cancer. Atrophy of left ventricular mass (median overall -8.9%, $p<0.001$) occurred during 112±6 days; this loss was equal or greater than the loss of skeletal muscle (overall -6.2%, $p<0.001$). Atrophy >8.9% of left ventricular mass associated with loss of skeletal muscle (OR, 95% CI) [4.5 (1.4-14.8) $p<0.01$] and total adipose tissue [10.0 (2.7-36.7) ($p<0.01$)]. While LVEF and diastolic function changes over time were not associated with left ventricular mass atrophy, left ventricular mass loss was associated with decreased global longitudinal strain [6.6 (1.9-22.7); $p<0.01$], worsening of fatigue [6.6 (1.9-22.7) ($p<0.01$)], aggravated performance status [4.8 (1.3-18.3); $p<0.05$] and deteriorated dyspnea [9.3 (2.4-35.8); $p<0.01$]. In non-small cell lung cancer patients, while their performance status at baseline was sufficient to receive chemotherapy, and these patients were potentially eligible for clinical trials, we found different types of cardiac disorders that may lead to confounded functional measures in clinical trials. For instance we found 9 patients (12.8%) to have clinically-relevant cardiac disorders [7 patients with (LVEF <50%)]. Ten (14.3%) other patients showed to have diastolic dysfunction with preserved LVEF.

In cirrhotic patients with most depleted left ventricular mass index (>1 SD below sex-specific mean value of left ventricular mass indexed by height$^2$) compared to the patients with average left ventricular mass index, sarcopenia was more prevalent (70.6% vs. 27.3%; 6.4 (1.9–20.7); p = 0.002). Fat loss also showed a trend to be more prevalent in group of patients with low left ventricular mass index.

In renal cell carcinoma patients multigated acquisition scan-defined cardio-toxicity appeared in 8/47 (17%) patients. This targeted therapy-induced cardio-toxicity was related to high fat mass at baseline [9.5 (1.1-86.0), p=0.04]; also the percentage of skeletal muscle loss over 1 year in patients with cardio-toxicity was greater than patients without cardiotoxicity [median loss -7.0% versus 0%, respectively; p=0.04].

**Conclusion:** Dynamic cardiac atrophy is reported for the first time in human patients with progressive cancer cachexia. Cardiac status in terms of structure and function should be recognized in further clinical trials.

## PREFACE

All of the projects that are presented in chapters 4, 5, 6, 7 and 8 were approved by relevant University of Alberta ethics committees. SMR Kazemi Bajestani was awarded several scholarships: **Faculty of Graduate Studies and Research** travel award**,** November 2016, 1492 $; **Queen Elizabeth II Graduate Scholarship-Doctoral**, October 2016-August 2017, 15,000$; **Dr Herbert Meltzer Family Scholarship**, October 2016-August 2017, 4400$; **Honorary Izaak Walton Killam Memorial Scholarship**, September 2014-September 2016, 10,000$; **Graduate Students' Association of the University of Alberta - Professional Development Award** [travel award]**,** December 2013, 500 $; **Alberta Innovates: Health Solutions scholarship** (Major support), October 2012-September 2016, 120,000 $; plus 8000 $ research allowance. Canadian Institutes of Health Research (CIHR) (held by V Baracos) partially supported my PhD projects.

*Chapters 2, 3, 6 and 7 were published:* **Chapter 2,** Kazemi-Bajestani SM, et al. *Semin Cell Dev Biol* 2016; 54:2-10. **Chapter 3,** Kazemi-Bajestani SM, et al. *J Cachexia Sarcopenia Muscle 2014*; 5:95-104. **Chapter 6,** Kazemi-Bajestani SM, et al. *J Cachexia Sarcopenia Muscle* 2016; 7: 97-9. **Chapter 7,** Kazemi-Bajestani SM, et al. *Clin Nutr* 2017; pii: S0261-5614(17)30117-6.

**Chapter 4** of this thesis has been submitted for peer review and **Chapter 5** will be submitted to a relevant journal after acceptance of chapter 4. Furthermore, three abstracts of my PhD projects were presented and cited in the journals/ proceedings:

- ✓ Kazemi-Bajestani SM, et al. Development of cancer cachexia-associated cardiac atrophy over time in advanced non-small cell lung cancer: First report in human patients. 8th International Conference of the Society on Sarcopenia, Cachexia and Wasting Disorders (SCWD), Paris, France, December 4-6$^{th}$ 2015. *J Cachexia Sarcopenia Muscle* 2015; 6: 462.

- ✓ Kazemi-Bajestani SM, et al. Cachexia evolution in renal cell carcinoma patients and its relation with cardiac ejection fraction evaluated by MUGA scan. 2nd cancer cachexia conference, Montreal, Canada, September 26-28th 2014. *J Cachexia, Sarcopenia and Muscle* 2015; 6 (1):4.
- ✓ Kazemi-Bajestani SM, et al. Skeletal muscle wasting and cardiac structural changes in cirrhotic patients with preserved left ventricular ejection fraction. 7th International Conference of the SCWD, Kobe, Japan, December 9-11th 2013. *J Cachexia, Sarcopenia and Muscle* 2013; 4: 303.

Authors of published, submitted and ready to submit manuscripts all agree with presentation of these work in my PhD thesis. Regarding the co-authors contributions: Dr Vickie Baracos (supervisor) wrote the CIHR-funding grant and actively worked on study design, research management, and mentorship in all steps of the research, data analysis/presentation and writing. Dr Harald Becher, mentored me in all cardiology aspects of my projects, also managed and analyzed the echocardiograms in the longitudinal cohort. Dr Quincy Chu, was the medical oncology lead of my longitudinal study and supported me in patient recruitment, data collection, data interpretation and writing the drafts. Drs Charles Butts, Naveen Basappa, Michael Smylie, Anil Joy, Randeep Sangha and Quincy Chu supported the longitudinal work and referred eligible lung cancer patients to my study. They were also supportive in all clinical steps of the study. Dr Aldo Montano-Loza provided the data base for cirrhotic patients and also commented on the manuscript. Drs Peter Venner and Scott North supported me for data collection and interpretation for the renal cell carcinoma study. Ms Andrea Gallivan assisted me in computed tomography image analysis. Dr Vera Mazurak supported me in systematic review article data collection and interpretation. Dr Sunita Ghosh helped me for statistical analysis in one of my retrospective papers. Dr Konrad Fassbender provided me some valuable data that used in one of my review articles. Dr Peter Kavsak mentored the biomarker section of my longitudinal project.

**DEDICATION**
**To**

**My beloved mother,** Mrs Hamideh Shah Heidari; my mother devoted herself to providing a peaceful life for me and my brother. She is a strong woman who sacrificed herself to make our family life a happy one. My mother is the kindest person I know, she poured her attention toward ensuring I received a successful education. Mom, you are my hero; many thanks "*madar jan*" for all you have done for me in my life; your encouragement and unconditional love has been my greatest support.

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| | |
|---|---|
| ♂ | male |
| ♀ | female |
| 5-FU | 5-Fluorouracil |
| ACE | angiotensin-converting enzyme |
| ActRIIB | activin receptor type IIB |
| Akt | protein kinase B |
| ARB | angiotensin II receptor blockers |
| BMI | body mass index |
| BNP | brain natriuretic peptide |
| BSA | body surface area |
| C26 | colon-26 |
| CMRI | cardiac magnetic resonance imaging |
| CRP | C-reactive protein |
| CT | computed tomography |
| CV | cardiovascular |
| DLBL | diffuse large B-cell lymphoma |
| DLT | dose limiting toxicity |
| ECG | electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| EF | ejection fraction |
| FACIT-F | Functional Assessment of Chronic Illness Therapy-Fatigue |
| FFM | fat free mass |
| FM | fat mass |
| FMI | fat mass indexed by height$^2$ |
| FoxO | forkhead box transcription factors O |
| FS | Fractional shortening |
| GLS | Global longitudinal strain |
| HAI | hepatic arterial infusion |
| HCC | hepatocellular carcinoma |
| HR | hazard ratio |
| Hs-TnI | high sensitivity troponin I |
| HU | Hounsfield Unit |
| ICD-9 | International Classification of Diseases-Ninth Revision |
| IMAT | inter-muscular adipose tissue |
| IL | interleukin |
| L3 | 3$^{rd}$ lumbar vertebrae |
| LOS | length of hospital stay |
| LV | left ventricular |
| LVEF | left ventricular ejection fraction |
| LVM | left ventricular mass |
| LVMI | left ventricular mass /height$^2$ |

| | |
|---|---|
| MA | muscle attenuation |
| MAFb | V-maf musculoaponeurotic fibrosarcoma oncogene homolog B |
| MRC | medical research council |
| MRI | magnetic resonance imaging |
| mTOR | mammalian target of rapamycin |
| MUGA | multi gated acquisition |
| N/A | not available |
| NAC | neoadjuvant chemotherapy |
| NBD | NEMO binding domain |
| NF-κB | nuclear factor kappa-light-chain-enhancer of activated B cells |
| MuRF1 | muscle RING-finger protein-1 |
| NSCLC | non-small-cell lung cancer |
| NT pro-BNP | N-terminal pro-B natriuretic peptide |
| OR | odds ratio |
| OS | overall survival |
| QRSD | QRS duration |
| QTc | QT corrected |
| PI3K | phosphoinositide 3 kinase |
| PFS | progression free survival |
| PRISMA | Preferred Reporting Items for Systematic Reviews and Meta-Analyses |
| PWT | posterior wall thickness |
| RCC | renal cell carcinoma |
| RCT | randomized clinical trials |
| RCHOP | rituximab,cyclophosphamide, doxorubicin, oncovin, prednisone |
| SAT | subcutaneous adipose tissue cross sectional area ($cm^2$) |
| SCC | squamous cell carcinoma |
| SD | Standard deviation |
| SM | skeletal muscle cross sectional area ($cm^2$) |
| SMI | skeletal muscle indexed by $height^2$ |
| TACE | transcatheter arterial chemoembolization |
| TAI | transcatheter arterial infusion |
| TAT | total adipose tissue cross sectional area ($cm^2$) |
| TATI | total adipose tissue cross sectional area ($cm^2$)/ $height^2$ |
| TDI | tissue Doppler imaging |
| TNF-α | tumor necrosis factor-α |
| VAT | visceral adipose tissue cross sectional area (cm2) |

**CHAPTER 1**:

# Introduction

## 1.1 Cardiac atrophy, the unilluminated side of cancer cachexia

An international consortium of clinical experts used a Delphi process (rigorous consensus process) in 2011 and provided a comprehensive description for cancer cachexia [1]. According to this consensus, cancer cachexia is a syndrome of wasting, featuring involuntary weight loss and characterized by continuing atrophy of two major conventionally considered tissues, skeletal muscle and fat [1]. Progressive functional impairment is the ultimate outcome of cancer cachexia [1].

Atrophy of the heart, in parallel to loss of skeletal muscle and fat, in rodent models of cancer cachexia, has grabbed a great deal of attention in recent decades [2, 3]; more than 45 articles so far have been published in this regard and most of these investigations explored underlying mechanisms as well as treatment for cardiac atrophy [2-49]. Traditionally vital organs such as heart were thought to be protected from cachexia because they are not considered energy or protein reserves. By contrast, skeletal muscle and fat are considered to be physiological reserves of protein and energy, for mobilization.

## 1.2 Cancer cachexia, an unmet clinical need: functional improvement requested by regulatory agencies as a clinical benefit of clinical trials

Currently there is no approved therapy against cancer cachexia [50]. Different classes of therapeutics have been considered in anti-cachexia clinical trials including appetite stimulants, immune modulators, anabolic compounds, anti-oxidant agents, nutritional support and exercise, as well as multimodality methods with various endpoints such as weight gain, skeletal muscle gain, appetite/ nutritional intake improvement. However, unresolved controversy surrounds clinical trial

endpoints and generally little agreement exists on *clinical benefits* of these therapies, as opposed to their ability to reverse muscle / fat loss. European and American regulatory agencies permitted two **objective physical functioning tests** as measures of clinical benefit in Phase III investigations of new cachexia therapeutics: improvement of hand grip and stair climbing test [50]. The main premise for requirement of aforementioned functional clinical benefit is the possible influence of anti-cachexia agents on increasing the amount of skeletal muscle as well as empowerment of its strength and work output. Several recent randomized phase III studies of cachexia therapy failed to show functional improvement in hand grip or stair climb tests [50], and while relevant tests of clinical benefit is still the top prerequisite of regulatory agencies, the clinical benefit for drug approval remains undefined [50].

**1.3 Conceptual model for the contribution of cachexia to functional impairment.**

Functional impairment as conceived and experienced by the patient is distinct from objective measures of physical performance described above. Patients experience fatigue and dyspnea and can rate their overall function in relation to how much time per day they spend in a bed or chair. Performance status refers to level of activity in a normal daily life. A range of performance status can extend from fully active person (i.e., normal) to a person that even cannot take care of his/her personal tasks and might be fully bed ridden [51]. This might be one class of metrics useful to describe the experience of cachexia and the efficacy of anti-cachexia therapies.

The majority of patients with advanced cancer including non-small cell lung cancer suffer from fatigue over their cancer trajectory [52, 53]. Several different descriptions of cancer fatigue are available, however, this is still a subject of debate. Cancer fatigue is traditionally defined as "*a persistent, subjective sense of tiredness related to cancer and cancer treatment that interferes with*

*usual functioning*" [54]. It has been suggested that cancer fatigue associates with a "clinically non-overt heart failure" [55], however, this has not been tested.

Cancer fatigue is a multi-factorial debilitating outcome in cancer patients with possible association with cancer cachexia (**Fig. 1-1 and Fig.1-2**).

Dyspnea is a prevalent symptom in patients with lung cancer, which at least partially impairs functional capabilities of patients. Dyspnea is proposed to be related to cachexia based on preclinical work suggesting diaphragm atrophy and subsequent ventilatory dysfunction in cancer cachexia [56]. Considering fatigue, dyspnea and performance status as isolated entities, is not sensible as there is always a certain degree of overlap between these entities. Accordingly consideration of concurrent occurrence of fatigue, declined performance status and dyspnea seems practical.

In cancer cachexia research, so far, skeletal muscle depletion has been recognized as the dimension of interest. Progressive compromise of daily functions could be theoretically owing to a combination of wasting of muscle and non-muscle tissues. In our novel research experience of cancer cachexia, we initiated a dialectic that cancer cachexia is a result of multi-organ involvement. Contribution of all components of cancer cachexia (skeletal muscle, fat and myocardium) to functional impairment can be conceptualized by understanding the role of these tissues (**Fig.1-3**). Skeletal muscle provides the work output of the body and it is known that skeletal muscle loss is strongly associated with loss of strength [57]; therefore, relatively rapid loss of skeletal muscle mass over a short period of time especially in metastatic stages of some certain cancers such as pancreas and non-small cell lung cancer can be a critical determinant of skeletal muscle dysfunction. Loss of skeletal muscle can have a direct relationship with the patient experience of fatigue, dyspnea and low performance status.

Elevated energy expenditure (i.e., hyper-metabolism) and reduced nutritional intake both associate with cancer cachexia [58]. This disproportionally increased resting energy expenditure in cancer cachexia results in a negative energy balance [59]. Augmented lipolysis and fat oxidation as well as diminished lipogenesis are the major phenomena that propagate fat loss [60]. Extreme weight loss (> 5%) (i.e., conventional description of cancer cachexia based on consensus [1]) also occurs in cancer patients with hyper-metabolism [59]. Energy "gap", the degree to which intake is insufficient relative to energy expenditure is potentially another determinant of aggravated functional capacity and fatigue.

Heart atrophy and associated cardiac dysfunction could further adversely impact on various aspects of function and symptoms. The impact of heart failure/dysfunction on functional class decline, dyspnea and fatigue progression has been appreciated traditionally for several years in the cardiology context [61-63]. However, vulnerability of the heart against cancer cachexia, and its functional/symptom consequences has not been elucidated. Possible alteration of heart function/structure as an impactful component of cancer cachexia is proposed [2]. One of the main premise indicating the existence of association between cachexia (skeletal muscle and fat loss) and a failed heart has been completely characterized in heart failure patients (i.e., in the cardiology context) [64, 65]. The catabolic/anabolic imbalance, wasting of skeletal muscle, functional decline and fatigue exist in heart failure patients (i.e., cardiac cachexia) [66].

The multi-organ involvement in cancer cachexia is made plain by animal studies, where muscle, fat and cardiac loss occur simultaneously, in association with impairment of physical functioning. In a rat hepatoma model of cancer cachexia, over 13 days heart mass decreased by 58% ($p<0.001$), gastrocnemius muscle weight decreased 26% ($p<0.01$) and white adipose tissue mass fell by 79% ($p<0.01$). Spontaneous movement of the rats was monitored by infrared system

over 24 h, and declined by 76% ($p<0.01$) [3]. The decline in activity is clearly greater than merely the decline in skeletal muscle mass, and there is no clear means of distinguishing to what degree cardiac, skeletal muscle or negative energy balance explain the decline in activity.

Underlying mechanism of cancer cachexia in human patients has not been understood thoroughly; however, this matter has been discussed extensively in rodent models of cancer cachexia. In this PhD thesis, this topic can be found in chapter 3 and discussion part of chapter 4.

### 1.4 A research track to investigate the possible occurrence of cardiac atrophy in clinical cancer cachexia

To start an innovative track of research with explicit insight of what alterations in heart function and structure occur in cancer cachexia- a well-designed prospective study is indispensable, utilizing sensitive tools for measurement of body composition (skeletal muscle and fat) and heart functional/structural properties. The selected cancer population should be susceptible to cancer cachexia, such as non-small cell lung cancer of advanced stage, for whom cachexia ensues in the majority of patients. Moreover, a homogenous group of patients in terms of stage disease and treatment seems to be ideal to limit confounding factors. However, due to tremendous lack of data in regard to the question of cardiac atrophy and dysfunction, new prospective studies and evidence potentially available in retrospective data sets could be considered, to assist further understanding of attributes and dimensions.

### 1.5 Rationale, objectives and hypothesis of each chapter

**CHAPTER 1:** *Introduction, an overview of the thesis concept*

**CHAPTER 2:** *A systematic review article of published articles to recapitulate the clinical outcomes of CT-defined cancer cachexia*

As a clinical cancer cachexia researcher, it is critical to have an inclusive understanding of current knowledge on skeletal muscle and fat loss. This systematic review summarized all published articles that used computed tomography cross sectional images [at 3rd lumbar vertebrae (L3)] for measurement of cancer cachexia.

Objectives: to systematically summarize all published articles using computed tomography cross sectional images (at L3) for measurement of cancer cachexia in cancer patients and its clinical outcomes.

Hypothesis: Computed tomography is a clinically useful tool to measure skeletal muscle and fat loss

**CHAPTER 3:** *A critical review article that summarized experimental evidence of cardiac atrophy in cancer cachexia and argued the clinical consequences of cancer cachexia-induced cardiac atrophy*

The main rationale of this review article was development of a conceptual framework that guides further clinical research on alteration of heart structure and function in cancer cachexia.

Objectives: to synthesize the existing evidence regarding underlying mechanisms of cancer cachexia-induced cardiac atrophy/ dysfunction.

Hypothesis: A bilateral vicious cycle between cancer cachexia induced atrophy of the heart, and heart failure exists

**CHAPTER 4:** *A novel longitudinal study of metastatic non-small cell lung cancer patients characterizing a rapid atrophy of heart mass in parallel to evolution of cancer cachexia*

Metastatic non-small cell lung cancer patients, with consistent therapy (first line carboplatin-based), were studied utilizing standard tools for measurement of skeletal muscle, fat and heart mass/function.

Objectives: To isolate the phenomenon of cardiac atrophy in clinical cancer cachexia; To elucidate the possible cardiac dysfunction subsequent to cardiac atrophy; To determine the association between cardiac atrophy and skeletal muscle and fat loss; To assess the relation between cardiac atrophy and aggravation of fatigue, performance status and dyspnea.

Hypothesis: Cardiac atrophy occurs during cancer cachexia progression, whilst this phenomenon is associated with skeletal muscle and fat loss. Cardiac atrophy, as a component of cancer cachexia complex, contributes to functional/ symptom aggravation.

**CHAPTER 5*:*** ***An investigation of baseline cardiovascular features of non-small cell lung cancer patients, potentially eligible for anti- cancer cachexia clinical trials***

Researchers and regulatory authorities deem physical functioning endpoints such as power and speed on a stair climbing test to be required for proof of clinical benefit of new therapeutics for cancer cachexia. Non-small cell lung cancer is the main tumor group studied in current cachexia randomized clinical trials. Cardiac function of non-small cell lung cancer patients is not well characterized and it is not known whether it is sufficient for patients to be able to complete functional tests.

Objectives: To provide a full cardiac assessment of metastatic non-small cell lung cancer patients candidates for carboplatin-based therapy

Hypothesis: Occult cardiovascular conditions exist in metastatic non-small cell lung cancer patients that may confound further functional measures.

**CHAPTER 6:** *A retrospective study of cirrhotic patients with or without liver cancer analyzed the relation between cardiac mass and cancer cachexia features*

Severe chronic liver disease (cirrhosis) with profound liver dysfunction is known to be related to severe muscle depletion [67, 68] (i.e., sarcopenia; please see chapter 2 for detailed description of sarcopenia). A group of cirrhotic patients with or without liver cancer waiting for liver transplant is suitable to assess the relation between depletion of skeletal muscle and left ventricular mass.

Objectives: To assess the concurrency of depletion of skeletal muscle, fat and left ventricular mass.

Hypothesis: Depleted left ventricular mass positively associates with sarcopenia in cirrhotic patients with or without hepatocellular carcinoma

**CHAPTER 7:** *A retrospective study of renal cell carcinoma patients characterizing the relation between skeletal muscle loss over duration of targeted therapy and development of cardio-toxicity*

Sarcopenia is a prominent feature of cancer cachexia and is known to be related to severe chemotherapy-toxicity [69]. Although this association has been proven previously, there is no study so far to investigate the possible association between features of cancer cachexia and development of *cardio-toxicity*.

Objectives: To investigate the relation between either baseline sarcopenia or over time loss of skeletal muscle and development of *cardio-toxicity* appeared by targeted therapy in patients with renal cell carcinoma. To determine the association between variations of fat at baseline and over time and occurrence of *cardio-toxicity*

Hypothesis: Development of targeted therapy-induced *cardio-toxicity* is associated with progression of cancer cachexia

**CHAPTER 8:** *Discussion and conclusion of all PhD studies*

**CHAPTER 9:** Appendix A, appendix for Chapter 4

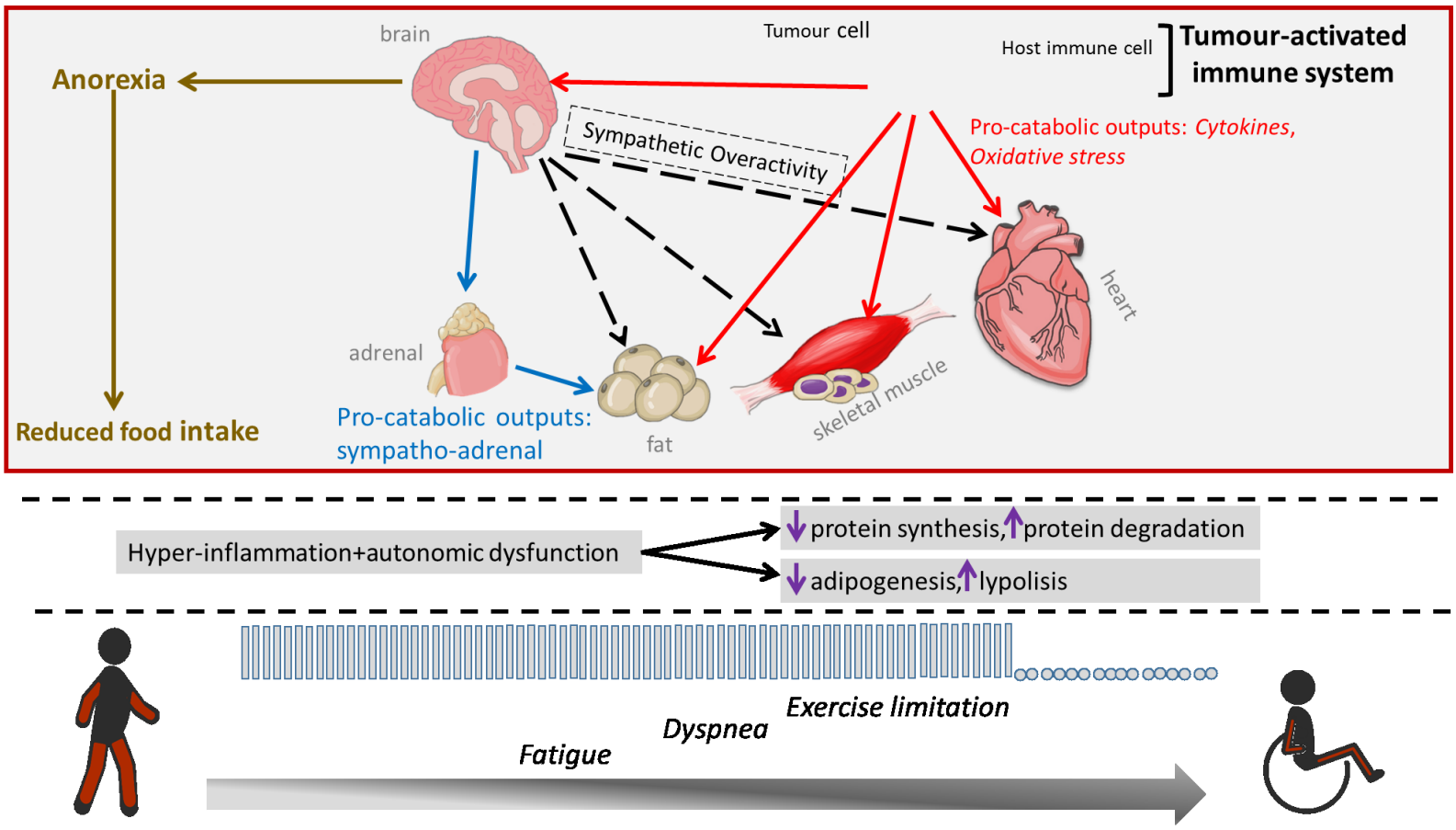


**Figure 1-1. Schematic upstream phenomena in cancer cachexia: contribution to functional/ symptom impairment.** Presence of tumour results in activated immune system and consequent hyper-inflammatory cytokines adversely impact on central nervous system (CNS) and tissues (skeletal muscle, heart muscle and fat). Autonomic dysfunction and reduced appetite, as two main consequences of CNS dysfunction, contributes to further tissue wasting. Impairment of CNS also associates with reduced appetite and declined food intake.

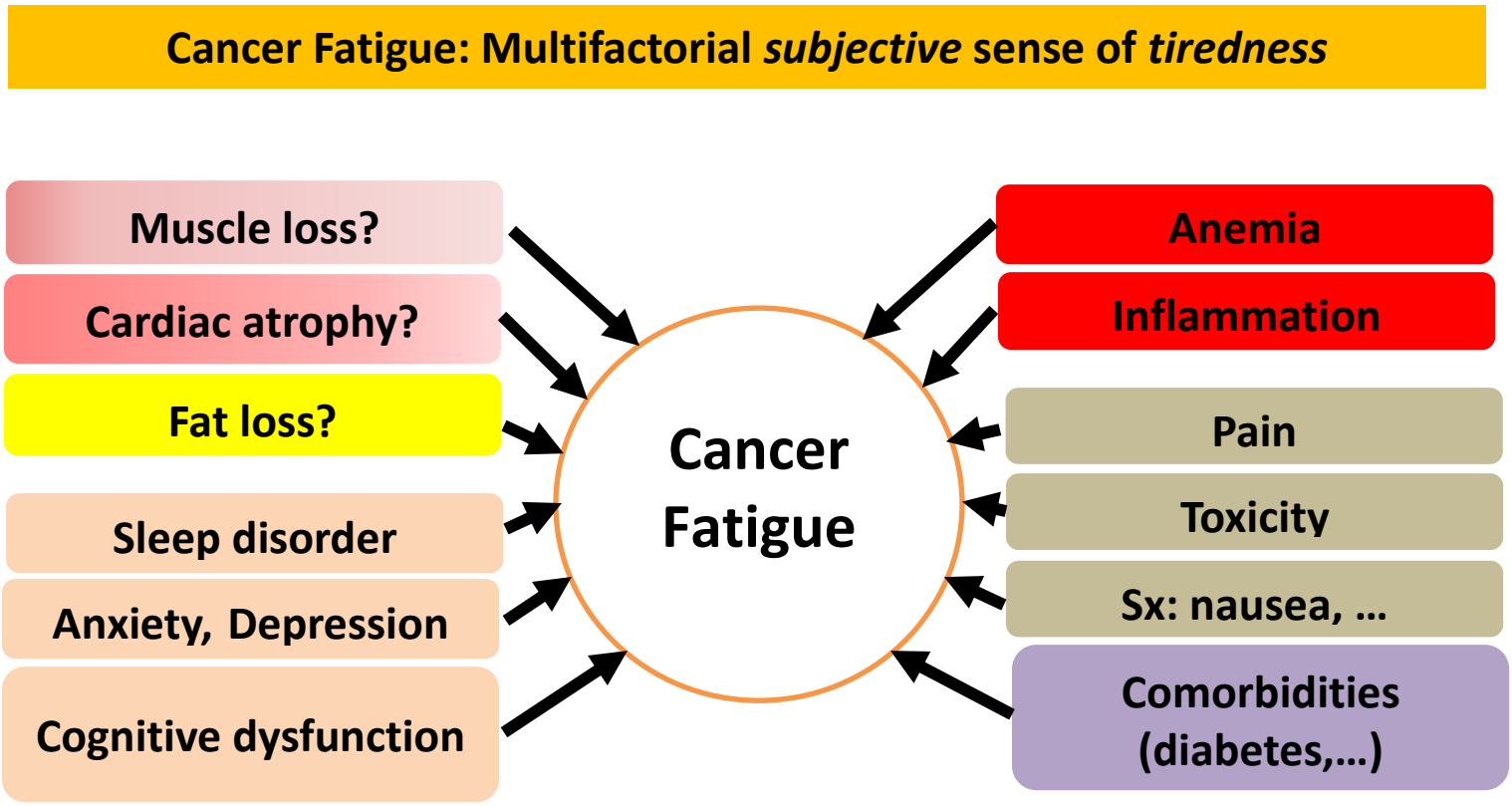


**Figure 1-2: Possible etiologies of cancer fatigue**

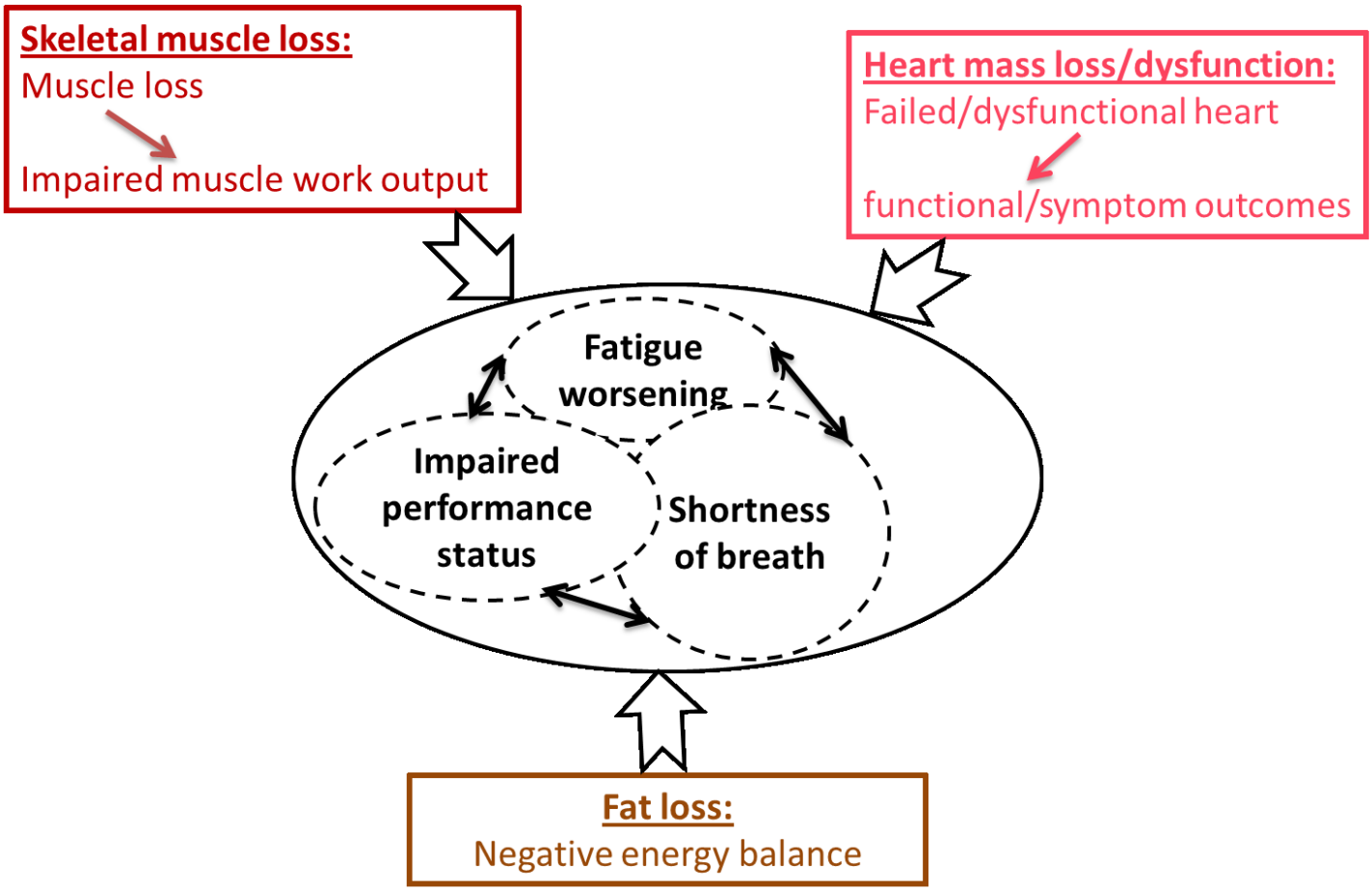


**Figure 1-3: Conceptual model of contribution of cancer cachexia to functional/ symptom outcomes**

**CHAPTER 2:**

This systematic review article was published in Semin Cell Dev Biol 2016; 54:2-10.

# Computed Tomography-defined Muscle and Fat Wasting are Associated with Cancer Clinical Outcomes

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## 2.1 Abstract:

Cancer cachexia (ie, skeletal muscle wasting with or without fat loss) relates to several adverse outcomes. Computed tomography cross-sectional images serve as an efficient biomarker for assessment of cachexia in cancer patients. We systematically reviewed literature reporting quantitative evaluation of the cross sectional area of the main tissues implicated in cancer cachexia, muscle and visceral, subcutaneous and inter-muscular fat in computed tomography scans at the 3rd lumbar vertebra. Our main goal was to summarize computed tomography -defined variation of muscle and fat and the relationship between these features and cancer outcomes such as chemotherapy toxicity, post-surgery complications and survival.

**Key words:** computed tomography, cancer, muscle, fat

## 2.2 Introduction

Cancer cachexia is a multifactorial syndrome that is a consequence of elevated inflammatory response combined with alterations in metabolism and reduced food intake [70]. Cachexia-induced impaired food intake and altered metabolism result in disordered protein and energy balance [70]. Cancer cachexia-associated skeletal muscle wasting with or without fat loss, has consequential association with survival and quality of life [70].

Severe muscle depletion (termed *sarcopenia*) was first described as part of the frailty syndrome found in older individuals and was later shown to be prevalent in patients with cancer, chronic obstructive pulmonary disease, heart and renal failure [57]. Measurements of muscle and fat are not in the standard repertoire of oncologic medicine, however since emerging data suggests that measures derived from computed tomography images provide prognostic information in cancer patient populations, such measurements may be given future consideration as an efficient biomarker in research and clinical evaluation [71].

CT and magnetic resonance imaging are ideal to quantify skeletal muscle as well as fat [visceral adipose tissue, subcutaneous adipose tissue, inter-muscular adipose tissue]. Precision of measures of tissue cross sectional areas with computed tomography is excellent (0.4–1.5%) [72-74] providing sensitivity to detect changes over time. Taking advantage of CT images acquired in standard care or clinical trials, body composition of cancer patients has begun to be described. This analysis has a low incremental cost and is feasible and precise [57].

Most researchers used consistent methods for computed tomography -defined cross sectional image analysis focusing on 3$^{rd}$ lumbar vertebra (L3) as a standard bony landmark (see **Tables 2-1, 2-2, 2-3**). Skeletal muscle [rectus abdominus, abdominal (transverse and oblique), psoas and paraspinal (quadratus lumborum, erector spinae)], inter-muscular adipose tissue, visceral adipose

tissue and subcutaneous adipose tissue appear at this level (**Fig. 2-1**). At *L3*, the cross sectional areas are linearly related to whole body mass of muscle ($r^2$=0.86) [75], visceral adipose tissue ($r^2$=0.89) [76], subcutaneous adipose tissue ($r^2$=0.92) [76] as well as total adipose tissue ($r^2$=0.93) [75]. Macroscopic IMAT within the fascial boundary of the muscle is quantified within the range of -190 to -30 Hounsfield Unit (HU) and is not included in the muscle cross sectional area. Muscle areas are typically quantified within a HU range of -29 to +150. HU ranges of –150 to -50 for visceral adipose tissue, and –190 to –30 for subcutaneous adipose tissue [77] (**Fig. 2-1**). Specific software [eg, Slice-O-Matic software (v.4.3, Tomovision, Montreal, Canada) or Image J software v1.42q (National Institutes of Health, http://rsb.info.nih.gov/ij)] are used to do this quantification

The purpose of this work is to summarize published findings on CT-defined variation of muscle and fat at *L3* and the relationship between these features and cancer outcomes.

**2.3 Materials and Methods:**

To capture the literature on computed tomography -derived body composition in cancer patients we used search terms for malignant disease [(cancer) or (neoplasm) or (carcinoma) or (tumor) or (tumour) or (malignant) or (metastasis)], computed tomography and body composition [(cachexia) or (wasting syndrome) or (weight loss) or (malnutrition) or (anorexia) or (skeletal muscle) or (skeletal muscle wasting) or (skeletal muscle loss) or (skeletal muscle depletion) or (sarcopenia) or (myopenia) or (lean body mass) or (adipose) or (adipose tissue) or (fat) or (fat loss) or (body composition) ]. The search was conducted on MEDLINE from January 1st 1990- January 15th 2015. Criteria for inclusion included human, adults (> 18 y/o), cancer patient populations, English language and assessment by *computed tomography scan* at *L3*. Articles were excluded if the quantification was done at a soft tissue landmark such as umbilicus or kidneys [78-80], or

exclusively the psoas muscle [81] as these are not comparable to the rest of the literature. Reference lists of the identified articles were screened to find additional relevant publications. There were no exclusion regarding number of patients and type of study (retrospective, prospective or cross sectional). Data were extracted from the result sections, tables and figures of each article. As we did not aggregate the data, we did not ask for any extra data from the investigators. All statistical methods for summarizing the measurements [e.g. odds ratio (OR)] were included in our review and we did not conduct any further statistical analysis (such as data synthesis or additional subgroup analysis) on individual findings. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [82] flow diagram of our search strategy is shown in Figure 2. All excluded articles were reviewed by SMRKB and VM to assure that they did not meet eligibility criteria.

## 2.4 Results

### *2.4.1 Overview*

Fifty-three studies met the selection criteria (**Fig. 2-2, Tables 2-1, 2-2, 2-3**), including a total of 9138 patients. Data included tissue cross sectional areas ($cm^2$) for skeletal muscle, visceral adipose tissue and / or subcutaneous adipose tissue, total adipose tissue and in 5/55 studies intermuscular adipose tissue area was given [83-87]. Tissue areas were also normalized for stature (i.e. divided by the height in $m^2$). Skeletal muscle index ($cm^2/m^2$, skeletal muscle index) is a representation of how muscular an individual is for their height. Mean skeletal muscle attenuation was reported in 5 articles [88, 89][90][91, 92], as some patients show greatly reduced attenuation values (**Fig. 2-1**), often with increased inter-muscular adipose tissue.

An early definition of sarcopenia was an absolute muscle mass > 2 standard deviations below mean values for healthy young adults [93]. Skeletal muscle index may be treated as a continuous

variable, but has also frequently been dichotomized (sarcopenic vs non-sarcopenic) with a statistical approach being used to identify threshold values below which low muscle mass associates with elevated risk of poor outcome (eg, overall or disease-free survival). On early study Prado *et al* identified such cut-points: L3 skeletal muscle index: ♂ < 52.4 $cm^2/m^2$; ♀ < 38.5 $cm^2/m^2$ that was associated with mortality of patients with solid tumours [89]; this cut points have been used in some publications afterwards [94-97] . Other authors used cut-points of ♂ 55.4 $cm^2/m^2$ and ♀ 38.9 $cm^2/m^2$ [98-102]. Two other work also used very close cut-points: ♂55.8 $cm^2/m^2$ and ♀38.9 $cm^2/m^2$ [103, 104].

Miyamoto *et al* established a dichotomous skeletal muscle index variable, defining the lowest quartile (Q4) as the sarcopenia group and combining Q1, Q2, and Q3 into the non-sarcopenia group in a Japanese study [105] . Skeletal muscle index associated with overall survival were defined as ♂43.75 $cm^2/m^2$ and ♀41.10 $cm^2/m^2$ in another Japanese population [106]. Moreover, other study of Japanese population even set very low cut-off points for sarcopenia as ♂36.0 $cm^2/m^2$ and ♀ 29.0 $cm^2/m^2$ [107]. Some quite large samples of cancer patients have been assembled (n=1473; lung or gastrointestinal diagnosis) with survival endpoint using different skeletal muscle index cut points for different categories of BMI [skeletal muscle index at L3 level: ♀≤41 $cm^2/m^2$ and ♂≤53 $cm^2/m^2$ with BMI ≥25 $kg/m^2$ and ♂ or♀ ≤43 $cm^2/m^2$ in patients with BMI< 25 $kg/m^2$] [92].

The endpoints evaluated in relation to the CT-defined muscle and fat included chemotherapy-induced toxicity (**Table 2-1**), infection and length of hospital stay (**Table 2-1**) and survival (**Table 2-2**). Longitudinal changes in muscle and fat over time are shown (**Table 2-3**).

*2.4.2 Chemotherapy-induced toxicity*

Fourteen studies related CT-based body composition to the prevalence of dose limiting toxicity [defined as treatment toxicity resulting in dose reduction or discontinuation of treatment] or different grades of toxicity (First part of **Table 2-1** and Yip et al [97]). These were mostly single site investigations with small numbers of patients. There was strong overall consistency in the finding that sarcopenia had a significant association with increased incidence of dose limiting toxicity or severe toxicity in 12/14 studies in which this was evaluated. This was true regardless of cancer site or type of systemic therapy, with the exception of the toxicity of localized hepatic arterial infusion which did not associate with sarcopenia [86]. The association between skeletal muscle index and dose limiting toxicity was evaluated using published cut-points for sarcopenia [86, 98-100, 108-110], using the median value within the population as a cut-point [111], using Receiver Operating Characteristic curve for most accurate prediction of toxicity [112] or using computed tomography-defined skeletal muscle area in $<25^{th}$ centile versus $>75^{th}$ centile of the population [113]. Few studies showed association between adipose tissue and dose limiting toxicity [97, 114]. Higher visceral adipose tissue correlated with greater incidence of grade 4 leukopenia (a characteristic toxicity of doxorubicin) in in both underweight and overweight patients with locally advanced or metastatic breast cancer [114]. Yip *et al* showed that baseline visceral adipose tissue, subcutaneous adipose tissue and fat free mass (estimated from computed tomography-defined muscle area) did not associate with chemotherapy dose reduction in the patients with oesophageal cancer who received neoadjuvant chemotherapy followed by oesophagectomy [97].

*2.4.3 Length of stay and post-operative complications after cancer surgery*

Nine articles concerned cancer patients hospitalized for surgery (Second part of **Table 2-1**). Sarcopenia at baseline appears to be a biomarker for prediction of post-operative infection [57, 115-117]. However, neither visceral adipose tissue, subcutaneous adipose tissue nor total adipose tissue were significantly related to postoperative infection [115]. Moreover, when sarcopenia occurred in older patients (≥ 65 y) the risk of post-surgery infection becomes prominent (OR=4.6, P=0.01) [115]. Lieffers *et al* reported that LOS was associated with sarcopenia [115], however, the study by Awad *et al* [94] and Lodewick *et al* [118] did not confirm this finding . Findings regarding adipose tissues and LOS seem to be contradictory [97, 119].

Postoperative complications within 30 days post-lymphadenectomy surgery in penile cancer patients including wound infection showed to be associated independently with baseline sarcopenia [116]. Death within 30 days was independently associated with sarcopenia in a relatively large sample of patients (n=310) who underwent oncologic colorectal surgery (OR=43.3; P = 0.007) [117] . Also, combination of sarcopenia, Groningen Frailty Index ≥ 5, and Short Nutritional Assessment Questionnaire≥ 3 were strongly associated with postoperative sepsis (OR=25.1; P=0.001) [117]. Lodewick *et al* did not confirm the effect of sarcopenia on post-operative complications for colorectal liver metastases; however sarcopenic obesity (obesity with depleted muscle mass) was significantly associated with higher readmission rate [118]. Voron *et al* showed no difference between sarcopenic and non-sarcopenic patients who underwent hepatectomy for hepatocellular carcinoma [96] in terms of mortality within 60 days and severe postoperative complications rates (including grades III, IV and V of the Dindo and Clavien classification).

*2.4.4 Survival/prognosis*

In 22 studies the main goal was to test for association between survival rate, overall survival, progression free survival, recurrence free survival and/or disease free survival and computed tomography-defined body composition (**Table 2-2**). Such survival outcomes were the secondary objectives in 14 additional studies [86, 94, 96, 97, 99, 100, 108, 109, 113, 116-120] (**Table 2-1 and 2-3**). Sarcopenia at baseline was uniformly a strong predictor of survival independent of age, sex, stage, disease site and performance status [89, 92, 96, 103, 105, 106, 108, 121-124]. Although this was noted in patients across the full range of body weight, sarcopenic obesity was particularly noted to have a strong association with poor survival when compared with non-sarcopenic obesity [87, 89, 102, 107]. Two studies did not confirm the influence of sarcopenic-obesity on mortality [91, 118]. Stene *et al* found that in advanced non-small cell lung cancer patients who received carboplatin-based therapy, skeletal muscle *wasting* over time, but not sarcopenia at baseline, independently predicted survival [125]. Reduced muscle attenuation associated with poorer prognosis [89, 92, 126]; however, it is notable that the description for low muscle attenuation and considered HU ranges are not consistent [92, 126]. Low fat mass was explored in elderly patients with diffuse large B-cell lymphoma by Camus *et al* [103] who showed that both sarcopenia and fat mass below median value associated with reduced overall survival (**Table 2-2**). The absolute gain in visceral adipose tissue associated with better overall survival (HR = 0.97; P = 0.001) in potentially respectable pancreatic cancer treated on a phase II trial of neoadjuvant chemotherapy and chemo-radiation [102].

*2.4.5 Quantification of change of fat and muscle over disease progression*

CT – derived body composition change over time was reported in 18 studies [Table 3 and 10 additional studies [83, 84, 87, 94, 95, 97, 102, 112, 125, 127] (**Table 2-1 and 2-2**)]. Skeletal muscle and total adipose tissue were lost over time during progression of advanced disease and these losses increased at an exponential rate [77, 128][22]. Computed tomography-defined fat or muscle gain did sometimes occur during the cancer trajectory, especially in association with tumour response to therapy [125]. Two chemotherapy agents [selumetinib,vandetanib] resulted in muscle gain in advanced cancer patients [112, 120]. Conversely, three other compounds, sorafenib [129], abiraterone [130] and MK-0646 (insulin-like growth factor 1 receptor) [83] provoked muscle wasting. Dietary fish oil supplementation associated with muscle gain in non-small-cell lung cancer patients in one study [88]. An adverse influence of skeletal muscle and/ or fat wasting (defined by over time CT measurements) on prognosis of cancer patients have been shown [84, 95, 102, 125, 127] (please see **Table 2-2**).

The influence of sex on muscle and fat changes over time was evaluated, however the results were inconsistent. A study of n=368 advanced cancer patients (pancreas, cholangiocarcinoma, lung, colorectal) concluded that sex did not relate to muscle wasting or gain *over time* [77] . Male pancreatic cancer patients lost more muscle and fat and at an accelerated rate compared with females [127]. Males usually have higher muscle and fat mass compared to females at time of diagnosis [92, 100, 126, 131] (see also **Table 2-4**). The small proportion of female patients in some studies is a limitation [87, 112].

## 2.5 Discussion

Cross-sectional imaging is increasingly used as a research tool for body composition analysis in cachexia, obesity, aging, critical care and endocrinology. This trend is reflected in oncology by the 53 articles on computed tomography-based measures of 9138 patients, summarized here. This work has a strong emphasis on sarcopenia. Statistical approaches have been used to define cut-points below which low computed tomography-defined L3 skeletal muscle index associates with significantly increased mortality, cancer treatment toxicity and complications following cancer surgery. Relating muscle characteristics (ie, skeletal muscle index, muscle attenuation) to specific health outcomes is parallel to a well-accepted paradigm: relating bone mineral density values to fracture risk. The papers reviewed here show the adoption of these methods in clinical research. These methods also hold promise for future studies in which the cellular and molecular mechanisms of cachexia are evaluated in biopsies of muscle and fat from patients whose tissue mass and rate of loss or gain has been precisely measured with computed tomography.

Some methodological points on tissue quantification as well as interpretation of the results are to be noted. Cross-sectional imaging (largely, but not exclusively L3) is usually done. We excluded publications reporting area/attenuation of the psoas muscle only, for the reason that this single muscle is unlikely to be representative of the musculature as a whole. Hounsfield unit ranges for specific tissues are standardized, but there exists some variation [132]. Reduced muscle attenuation values have been reported [89, 92, 126]; however, it is notable that the absolute values of "low" muscle attenuation are not consistent owing to the variation in the considered HU ranges [92, 126]. Population characteristics for the computed tomography-defined skeletal muscle, visceral adipose tissue, subcutaneous adipose tissue and muscle attenuation are just beginning to be described and these seem likely to have sex, age, race and disease-specific characteristics. Table

4 shows muscle, visceral adipose tissue and subcutaneous adipose tissue areas as well as muscle attenuation for the largest single sample analyzed to date for cancer patients (Canadian, Caucasian), stratified by sex and age [92]. Such data provide a point of reference however larger repositories of data are needed. A general agreement of cut- points for sarcopenia for different populations and outcomes is still a subject of debate. There is evidence that in general muscularity of Asians < Caucasians < African Americans [133-135] and therefore sarcopenia cut points in Asian cancer populations are lower than in Caucasians [89, 106]. Determination of specific cut-points for specific populations is of great importance in this field of research.

The most consistently studied endpoint was survival. Some authors suggested that the presence of sarcopenia be added to prognostic scores as well as to be used in the routine evaluation of elderly cancer patients in order to better assess their overall fitness to receive treatment and expected survival [71, 136]. A few relatively recent publications have suggested that reduced muscle attenuation associates independently with poorer prognosis in patients with melanoma, renal cell carcinoma, lung and gastrointestinal tumors [89, 92, 126]. The clinical relevance of muscle attenuation and its relation to muscle function and capacity has not been completely defined in the cancer context.

Sarcopenia [89, 92, 106, 108, 121] predicts survival regardless of body weight and low levels of muscle are not only seen in patients who appear thin or cachectic, but are also seen in individuals who are overweight or obese. Sarcopenic obesity is strongly related to reduced survival [87, 89, 137] and this adds another level of complexity to the importance of obesity in prognosis of patients with chronic diseases. On one hand, obesity at the time of diagnosis associates with a better prognosis [138]; on the other hand sarcopenic obesity implicates an important adverse effect on survival especially in cancer patients [89, 92]. These findings underscore the value of computed

tomography-defined quantification of muscle and fat, as oppose to overall body weight or BMI [89].

A major theme of the current literature on computed tomography-defined body composition in cancer patients is the relationship between sarcopenia and complications of cancer treatment. Severe chemotherapy toxicity is a major event which may be potentially life threatening or even fatal. A consistent finding was that sarcopenia had a significant association with increased incidence of dose limiting toxicity. Patients with sarcopenia are prone to development of chemotherapy toxicity, even though chemotherapy is scaled to body mass or surface area [86, 98, 139]. The association between sarcopenia and dose limiting toxicity may be explained by altered pharmacokinetics in sarcopenic patients including area under the time concentration curve [100, 136] and clearance [140]. Further investigations are expected to expand the observations to different populations and regimens, as well as to more fully characterize relationships between lean and fat tissue and drug metabolism and pharmacokinetics.

For the moment a small number of publications to date suggest that sarcopenia is an independent predictive risk factor for postoperative complications of cancer surgery (see Table 1). This is speculated to be due to association between muscle depletion and inability to respond appropriately to any form of stress, including infection [57, 141]. Further research needs to examine more closely the links between muscle and fat mass and inpatient complications postoperatively as well as during hospitalizations of cancer patients that are not connected with a surgical intervention.

Computed tomography-based evaluation of body composition over time in cancer patients is motivated, in part, by interest in cancer cachexia, which has been defined as being characterized by "*wasting of skeletal muscle, with or without loss of fat mass*"[70]. Computed tomography

provides a new window of appreciation of the specific wasting (and gains) in muscle and different adipose tissue depots. Recent studies highlighted the crucial role of muscle and fat wasting in prognosis [95, 102, 125] rather than baseline status of these tissues. Fat or muscle gain during the cancer trajectory, especially consequent to tumor response to therapy seems to be possible. There is still no clear conclusion regarding the associated clinical outcome and functionality/ quality of fat or muscle gain. Is gain of muscle or fat (and specifically total adipose tissue area or subcutaneous adipose tissue) beneficial? Some adipose tissue may associate with adverse effect. For example, a gain in inter-muscular adipose tissue has been associated with insulin resistance and poor function in patients with non-malignant disease [142, 143].

**2.6 Conclusion:**

Computed tomography studies at the L3 vertebra showed association between muscle depletion (ie, sarcopenia) and adverse outcomes including poor survival, postoperative infection, increased length of hospital stay and chemotherapy-induced dose limiting toxicity. Specific factors associated with muscle and fat gain have not been fully characterized. The association between computed tomography-defined body composition and cancer outcomes is developing, but suggests a future need for standardized radiologic reporting of relevant features to support continuing research in this area, and eventually clinical practice.

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**Table 2-1: Original articles discussed relation between CT-defined body composition at L3 level and outcomes of cancer treatment**

| Authors | (n) Patients/ Cancer type/Therapy | Major findings |
|---|---|---|
| **Chemotherapy – related toxicity** | | |
| Antoun [98] | 55/ metastatic RCC/ sorafenib | SMI was lower in patients with DLT compared to patients without DLT (P = 0.03); TAT not related to DLT (P>0.05). |
| Barret [110] | 51/ metastatic colorectal / fluoropyrimidine based therapy or irinotecan | Sarcopenia was independently associated with grade 3-4 toxicities (OR= 13.55; P = 0.043). |
| Cousins [111] | 93/various types cancer [stage: N/A]/ phase I trials | SMI was lower in patients with DLT compared to patients without DLT (P = 0.01). |
| Cushen [113] | 55/ metastatic RCC/ sunitinib | DLT was more prevalent in < 25th centile for SMI (< 44.8 cm2/m2) vs >75th centile for SMI (> 63.2 cm2/m2) (p=0.012). |
| Huillard [99] | 61/metastatic RCC/sunitinib | Combination of sarcopenia and BMI<25 kg/m2 independently predicted DLT (P=0.04). |
| Massicotte [112] | 33/advanced medullary thyroid /vandetanib (n=23) or placebo (n =10) | Patients with DLT had significantly lower SMI (37.2 vs 44.3 cm2/m2, P=.003) and a higher serum vandetanib level (1091 vs 739 ng/mL, P=0 .03) compared to patients without DLT. |
| Mir [100] | 40 /advanced HCC/ sorafenib | Sarcopenic patients experienced more DLTs compared to non-sarcopenic patients [82% vs 31%, (P = 0.005)]. |
| Parsons [86] | 48/advanced (different sites) and liver metastases / HAI oxaliplatin combined with 5-FU/leucovorin and bevacizumab | Grade 3-4 toxicity did not differ among patients with and without sarcopenia (P>0.05). |
| Prado [108] | 55/metastatic breast / capecitabine | DLT in sarcopenic vs non-sarcopenic patients: 50% vs 13% (P= 0.039). |
| Prado [144] | 62/ stage IIor III colon /5-FU and leucovorin | Mean of 5FU/kg estimated lean body mass (estimated from CT-defined SM) in patients with DLT versus patients without DLT: 17.9 versus 16.3 mg/kg (P=0.036) |
| Prado [140] | 24 / stage II or III breast / adjuvant FE100C | Estimated whole body skeletal muscle (estimated from CT-defined SM) in patients with DLT versus without DLT: 41.6 vs 56.2 kg (P = 0.002) |
| Tan [109] | 89/potentially curative oesophagogastric / NAC | Sarcopenia was independently associated with DLT (OR=2.95; p=0.015). |
| Wong [114] | 84/ advanced breast /doxorubicin or docetaxel | Doxorubicin area under the curve correlated with total abdominal fat volume (estimated from CT-defined TAT) (r2 = 0.262, P=0.001). |
| **Length of stay and postoperative complications after cancer surgery** | | |
| Awad [94] | 47/ locally advanced oesophagogastric / NAC | Patients with low estimated fat free mass (obtained from CT-defined SM) post- NAC did not have increased post-operative LOS (P=0.51), nor increased in-hospital mortality (P =0.60). |
| Lieffers [115] | 234/ stage II-IV colorectal / surgery | Sarcopenia independently predicted post-operative infections (OR= 4.6; P<0.01). Neither VAT nor TAT related to post-operative infection. |
| Lodewick [118] | 171 / colorectal with liver metastases/N/A | Major surgery related complications (P=0.235) and LOS (P=0.202) did not differ between sarcopenic and non-sarcopenic patients |
| Richards [145] | 174/ primary operable colorectal/surgery | Low SMI associated with an elevated systemic inflammatory response (P = 0.001) |

| | | |
|---|---|---|
| Reisinger [117] | 310/ (about 50% stage III-IV) colorectal /surgery | Sarcopenia independently predicted 30-day mortality and in-hospital mortality (OR=43.30, P=0.007) |
| Sharma [116] | 43/(about 67% stage II-III) penile SCC/lymphadenectomy | Sarcopenia independently predicted post-operative (within 30 days) complications (OR=4.79; P=0.038). |
| Torres [119] | 82/stage IIIC-IV ovarian/surgery | Median LOS in patients with SAT <77.2 cm2 versus SAT ≥77.2 cm2: 18 days, 8 days (P=0.02) |
| Voron *et al* [96] | 109 / resectable HCC/ hepatectomy | Severe post-operative complications rates (including grades III, IV and V of the Dindo and Clavien classification) in sarcopenic vs non-sarcopenic patients (20.3% versus 16%; P = 0.56) |
| Yip [97] | 35/ oesophageal / NAC followed by surgery | There was no significant association between TAT and LOS (P>0.05). |

5-FU, 5-Fluorouracil; BMI, body mass index; CT, computed tomography; DLT, dose limiting toxicity; FEC100C, 5FU 500 mg/$m^2$ , epirubicin 100 mg/$m^2$ , cyclophosphamide 500 mg/$m^2$; HAI, hepatic arterial infusion; HCC, hepatocellular carcinoma; LOS; length of hospital stay; N/A, not available; NAC, Neoadjuvant chemotherapy; OR, odds ratio; SM, skeletal muscle cross sectional area ($cm^2$); RCC, renal cell carcinoma; SMI, skeletal muscle cross-sectional area indexed by height in $m^2$; SAT, subcutaneous adipose tissue cross sectional area ($cm^2$); SCC, Squamous cell carcinoma; TAT, total adipose tissue cross sectional area ($cm^2$); VAT, visceral adipose tissue cross sectional area ($cm^2$).

**Table 2-2: Original articles discussed CT-defined body composition at L3 level and prognostication/survival**

| Authors | (n) Patients/Cancer type/Therapy | Major findings |
|---|---|---|
| Antoun [126] | 149/metastatic RCC/ sorafenib, sunitinib, everolimus, placebo | Median OS in patients with low MA (<median) vs with high MA (>median): 14 months vs 29 months (P<0.001). |
| Camus [103] | 80/DLBL /R-CHOP or R-miniCHOP | 2-yr OS in the sarcopenic patients versus non-sarcopenic patients: 46% versus 84% (HR = 3.12: P = 0.0004). |
| Cooper [102] | 89/ potentially resectable pancreatic / Phase II NAC-chemo radiation therapy | Lesser wasting of SM (absolute difference pre and post treatment) associated with improved DFS (HR = 0.89; P = 0.04) ; Lesser wasting of VAT associated with better OS (HR = 0.97; P = 0.001) and PFS (HR = 0.98; p = 0.01). |
| Dalal [95] | 41/ advanced pancreatic / bevacizumab in combination with capecitabine and RT | Accelerated VAT loss (% VAT loss > or < median) independently predicted poorer OS (HR =2.06; P = 0.03). |
| Di Sebastiano [127] | 50/ stage IIB-IVpancreatic; N/A | Patients losing VAT at >-0.40 kg/100 d had poorer OS versus patients with <-0.10 kg/100 d (P=0·02) |
| Fogelman [83] | 53/ pancreatic /anti- IGF-1 drug | SM preservation at 2 months (wasting of < 6cm2) associates with better OS (HR= 0.51, P=0.03). |
| Harimoto [106] | 186/ stage I-IV HCC/ partial hepatectomy | SM independently predicted OS (HR=0.90; P=0.002) |
| Iritani [107] | 217/ stage I-IV HCC/ surgery, ablation, TACE, TAI or sorafenib | OS of sarcopenic patients was poorer vs non-sarcopenic (P=0.0043). |
| Lanic [104] | 82/ DLBL /R-CHOP or R-miniCHOP | 2 year OS in sarcopenic vs non-sarcopenic: 46% vs 84% (HR = 3.22; P=0.0002) |
| Martin [92] | 1473/ stage I-IV (78% III or IV) lung or gasterointestinal / N/A | Patients with all weight loss, low SMI, and low MA survived 8.4 months (P<0.001), vs patients with none of these features (28.months , P=0.001). |
| Meza-Junco [123] | 116/ stage I-IV (80% I or II) HCC/ ablation, TACE, TAI or combined | Median OS survival for sarcopenic vs non-sarcopenic patients: 16±6 months vs 28±3 months (P=0.003). |
| Mir [101] | 18/ advanced HCC/ gemcitabine plus oxaliplatin | OS in sarcopenic versus non-sarcopenic patients: 3.0 months vs 10.0 months (P<0.001). |
| Murphy [84] | 108/ locally advanced or metastatic colorectal and lung/N/A | Median survival for patients with TAT rate of change above specific cut-points (-29.2%/100 days ) compared to patients below: 88 versus 46 days (P=0.001) |
| Miyamoto [105] | 220/ stage I-III colorectal / surgery | Sarcopenia was independently associated with shorter RFS (HR=2.176, P=0.010) and OS (HR=2.27;P=0.019) |
| Parsons [85] | 104/advanced (different sites)/N/A | Median survival of patients with BMI≥25 kg/m$^2$ without sarcopenia vs BMI<25 kg/m$^2$ and sarcopenia: 501 vs 215 days (P=0.013). |

| | | |
|---|---|---|
| Prado [89] | 250/ stage I-IV (68% III or IV) lung, colorectal, gastrointestinal/ N/A | Sarcopenic obesity (BMI≥ 30 kg/m2) independently predicted reduced OS (HR= 4.2, P=0.001) compared with obese non-sarcopenic. |
| Psutka [91] | 262/bladder (about 90% metastatic) /radical cystectomy | 5-year survival among sarcopenic patients, with or without obesity (male: FMI>9 kg/$m^2$, female: FMI>13 kg/$m^2$)(40% vs. 37.4%, p=0.72) |
| Psutka [124] | 205/bladder/ radical cystectomy | Sarcopenia independently associated with increased risk of both cancer-specific survival (HR=2.14; P=0.007) and all-cause mortality (HR, 1.93; P=0.004). |
| Stene [125] | 35/advanced NSCLC/ carboplatin- vinorelbine or carboplatin- gemcitabine | SM change (ie, > 2% wasting) (p = 0.040), but not sarcopenia at baseline, independently predicted survival |
| Tan [87] | 111/stage II-IV (92.8% IV) pancreatic/N/A | Overweight/obese (BMI ≥25 kg/m2) sarcopenia independently predicted OS (HR= 2.07; P = 0.006) |
| Veasey Rodrigues [121] | 306 / advanced cancer (different sites)/ N/A | SMI (continuous variable) independently predicted OS (HR: 0.982, P=0.04) |
| van Vledder [122] | 196/colorectal / NAC | Sarcopenia independently predicted reduced PFS (HR=1·88, P = 0·002) & OS (HR= 2·53; P< 0·001). |

BMI, body mass index; CT, computed tomography; DFS, disease-free survival; DLBL, diffuse large B-cell lymphoma; FMI, fat mass indexed by height in $m^2$; HCC, hepatocellular carcinoma; HR, hazard ratio; MA, muscle attenuation (HU); N/A; not available; NAC, neoadjuvant chemotherapy; NSCLC, non-small-cell lung cancer; OS, overall survival; PFS, progression free survival; RCHOP, rituximab,cyclophosphamide, doxorubicin, oncovin, prednisone; RFS, recurrence free survival; SAT, subcutaneous adipose tissue cross sectional area ($cm^2$); SM, skeletal muscle cross-sectional area ($cm^2$); SMI, skeletal muscle cross-sectional area indexed by height in $m^2$; TACE, transcatheter arterial chemoembolization; TAI, transcatheter arterial infusion; TAT, total adipose tissue area ($cm^2$);

**Table 2-3: Original articles discussed CT-defined muscle and fat change over time at L3 level**

| Authors | (n) Patients/Cancer type/Therapy | Major findings |
|---|---|---|
| Antoun [129] | 80/ metastatic RCC /sorafenib vs placebo | SM wasting at 6 months (sorafenib vs placebo): -7.4 ± 1.7 vs -3.1 ± 1.3 cm2 (P =0.02) |
| Lieffers [128] | 34/ metastatic colorectal /N/A | SM, 10.7 vs 1.2 months to death: 151 ± 38 versus 127±36 cm2 (P<0.001) |
| Murphy [88] | 40/ stage III-IV NSCLC (16 eicosapentaenoic acid group versus 24 standard of care group)/platinum-based doublet chemotherapy | SM rate of change (%/ 100 days )( eicosapentaenoic acid versus standard of care patients):-6.8±2.6 vs 0.1±1.6 $cm^2$ (P<0.05)<br>TAT rate of change (%/ 100 days) )( eicosapentaenoic acid vs standard of care patients): -3.9±5.0 vs -5.0±6.5 $cm^2$ (P>0.05) |
| Esfandiari [22] | 1719/ stage I-IV, different sites /N/A | Change in MA over time associated with TAT area (P<0.001) and time to death ≤92 days (P=0.03) |
| Pezaro [130] | 55/ metatstatic prostate / abiraterone followed by abiraterone and dexamethasone | Abiraterone consumption (median of 7.5 months) contributes to SM wasting, with wasting greatest in patients with BMI> 30 $kg/m^2$: -4.3% ; BMI<25 $kg/m^2$:-2.9%' BMI 25-30 $kg/m^2$: -2.8% |
| Poterucha [146] | 57/ metastatic colorectal / bevacizumab | SM at baseline vs at 3 months: 148 $cm^2$ to 145 $cm^2$ (P = 0.02). |
| Prado [77] | 386/ advanced cancer (different sites)/ N/A | Being within 90 days (compared with>90 days) from death was the independent risk factor for SM wasting (OR: 2.67; P = 0.002) |
| Prado [120] | 20/ advanced cholangiocarcinoma/ selumetinib therapy vs standard of care | Selumetnib therapy resulted in 13.6 $cm^2$/100 days (~2.3 kg/ 100 days) muscle gain vs -7.3 $cm^2$/100 days (~1.2 kg/ 100 days) muscle wasting for standard of care group. |

BMI, body mass index; CT, computed tomography; MA, muscle attenuation; N/A, not available; NSCLC, non-small-cell lung cancer; OR, odds ratio; SM, skeletal muscle cross-sectional area ($cm^2$); SMI, skeletal muscle cross-sectional area indexed by height in $m^2$ TAT, total adipose tissue cross sectional area ($cm^2$)

One article by Baracos et al [10] which showed prevalence of sarcopenia in lung cancer patients with different BMIs is not included in the tables.

**Table 2-4: Variation of CT-defined body composition at L3 level in patients with solid tumors, by sex and age; Further analysis of cancer patients from Martin *et al*. [92].**

| | Age stratum (year) | N | Muscle area ($cm^2$) | Muscle index ($cm^2/m^2$) | Muscle attenuation (HU) | Visceral adipose tissue area ($cm^2$) | Subcutaneous adipose tissue ($cm^2$)* | Total adipose tissue area ($cm^2$) |
|---|---|---|---|---|---|---|---|---|
| **Male** | <50 | 82 | 173.0±30.0 | 55.0±9.5 | 43.4±7.7 | 119.2±110.5 | 154.4±98.4 | 264.1±167.4 |
| | 50-60 | 178 | 164.4±25.6 | 52.6±8.4 | 38.8±7.2 | 149.2±110.5 | 163.1±96.3 | 305.6±179.4 |
| | 60-70 | 260 | 161.6±29.7 | 52.6±9.6 | 35.4±8.2 | 198.2±119.5 | 156.8±78.7 | 347.5±170.5 |
| | 70-80 | 248 | 151.0±23.1 | 49.5±7.5 | 31.8±7.7 | 185.0±113.4 | 155.0±73.9 | 337.8±165.7 |
| | >80 | 60 | 135.6±21.8 | 46.2±7.6 | 30.5±8.1 | 164.6±107.1 | 137.4±77.4 | 302.2±159.9 |
| **Female** | <50 | 71 | 112.3±17.5 | 43.2±6.4 | 43.9±6.9 | 66.1±95.7 | 189.9±128.8 | 246.0±179.2 |
| | 50-60 | 135 | 110.4±19.1 | 41.9±6.6 | 37.8±10.9 | 87.1±87.5 | 189.1±122.4 | 274.9±199.2 |
| | 60-70 | 200 | 109.4±19.6 | 41.9±7.3 | 34.4±9.5 | 104.4±102.3 | 196.3±119.1 | 294.4±189.3 |
| | 70-80 | 175 | 103.6±15.9 | 40.5±6.9 | 30.8±8.0 | 105.6±80.8 | 185.0±104.5 | 288.6±166.6 |
| | >80 | 64 | 97.3±14.3 | 39±7.4 | 27.2±8.8 | 83.1±57.6 | 157.5±89.5 | 237.1±131.1 |
| **Total Male** | | 828 | 158.3±28.0 | 51.5±8.9 | 35.5±8.6 | 173.5±116.6 | 156.0±83.5 | 324.0±171.6 |
| **Total Female** | | 645 | 107.1±18.3 | 41.3±7.0 | 34.5±10.2 | 94.8±89.9 | 187.1±114.7 | 277.8±180.0 |
| **Overall** | | 1473 | 135.9±35.1 | 47.0±9.6 | 35.0±9.3 | 139.0±112.7 | 169.6±99.5 | 303.8±176.7 |

Values are expressed as mean±SD. HU, Hounsfield unit; L3, 3rd lumbar vertebra; * These authors included inter-muscular adipose tissue in the total value of reported SAT.

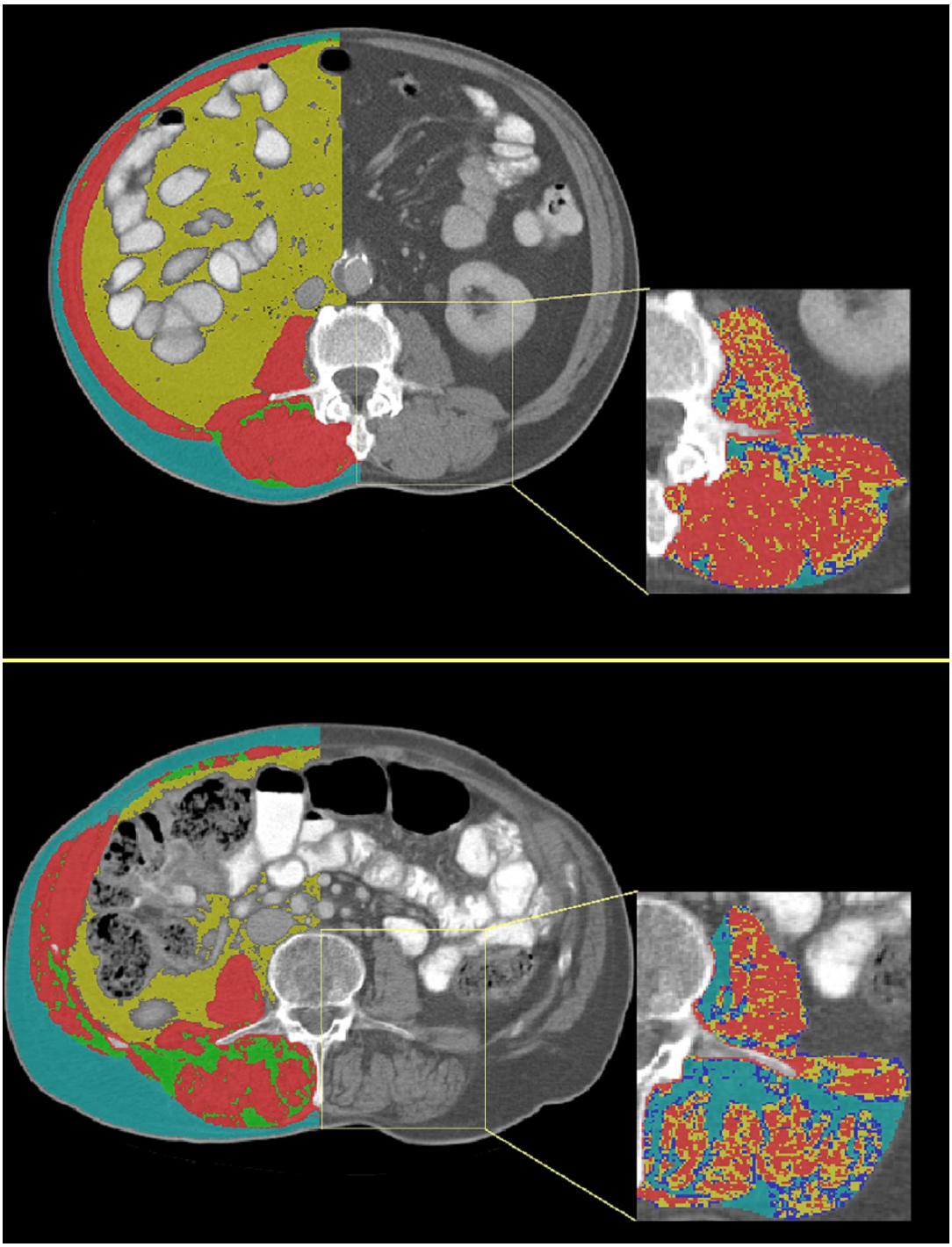

**Figure 2-1: Two cancer patients with different mean muscle attenuation and inter-muscular adipose tissue**

**Main panels**: Total lumbar CT images (at 3rd lumbar vertebra level); attenuation ranges used for skeletal muscle (SM), -29 to +150 Hounsfield Units (HU) ; visceral adipose tissue, VAT, -150 to -50 HU ; subcutaneous adipose tissue, SAT, -190 to -30 HU; inter-muscular adipose tissue, IMAT, -190 to -30 HU.

**Insets:** Psoas and paraspinal muscles: attenuation ranges used for normal attenuation SM, +30 to +150 HU; and abnormal (reduced) attenuation muscle in two range [132]:[ -29 to 0 HU; +1 to +29 HU] and IMAT, -190 to -30 HU.

Patient in upper panel represents a typical (median) individual: male, BMI 22.5 kg/$m^2$, aged 69 y with sigmoid colon adenocarcinoma stage III. Overall SM=164.9 $cm^2$ with mean attenuation 34.9 HU; VAT=319.7 $cm^2$; SAT=78.0 $cm^2$and IMAT=8.2 $cm^2$. Psoas and paraspinal normal muscle (inset) 65% of area is between +30 and +150 HU. Patient in lower panel has extensive fatty infiltration and extensive areas of abnormal attenuation: male, BMI 22.5 kg/$m^2$, aged 69 y with metastatic gastroadenocarcinoma. Overall: SM=129.5 $cm^2$ with mean attenuation 23.3 HU; VAT=58.7 $cm^2$; SAT=114.0 $cm^2$; IMAT=38.9 $cm^2$. Psoas and paraspinal normal muscle (inset) 34% of area is between +30 and +150 HU and remaining area is in abnormally low attenuation ranges between -29 and +29 HU. Neither patient had a history of diabetes or neuromuscular diseases.

**Figure 2-2. Flow chart of search.**

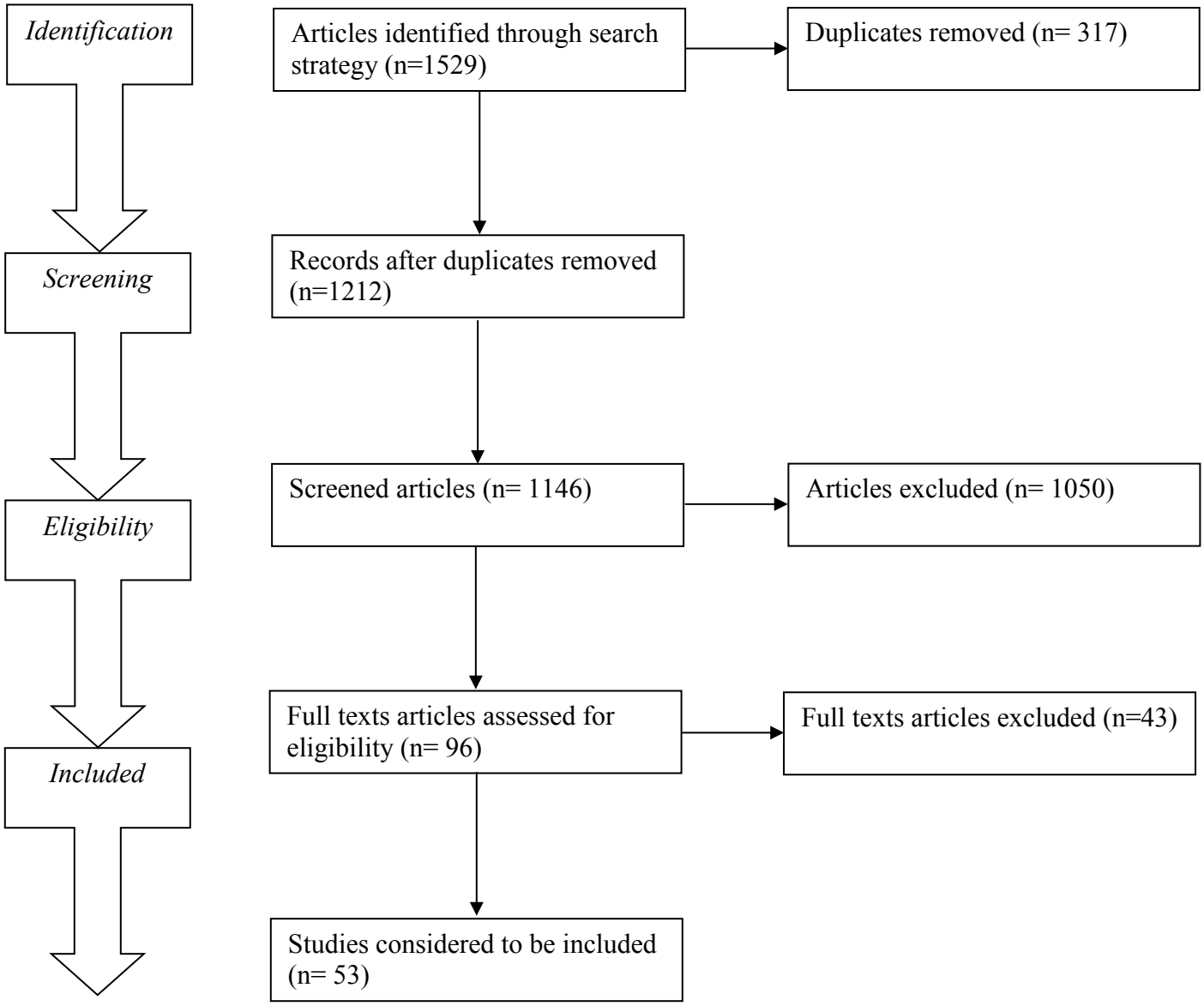


**Figure 2-2 Caption:**

PRISMA diagram for the identification, screening, eligibility and inclusion of papers (January 1st 1990 to January 15th 2015) from MEDLINE. All the included articles investigated body composition in cancer patients using CT scan at 3rd lumbar vertebra level (L3) level. Excluded records: case studies, review articles, studies used other land marks than L3, studies used other methods of body composition measurements such as dual-energy X-ray absorptiometry. All papers used English language and included adult patients.

**CHAPTER 3:**

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## Concurrent Evolution of Cancer Cachexia and Heart Failure: Bilateral Effects Exist

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## 3.1 Abstract

Cancer cachexia is defined as a multi-factorial syndrome of involuntary weight loss characterized by an ongoing loss of skeletal muscle mass and progressive functional impairment. It is postulated that cardiac dysfunction/ atrophy parallels skeletal muscle atrophy in cancer cachexia. Cardiotoxic chemotherapy may additionally result in cardiac dysfunction and heart failure in some cancer patients. Heart failure thus may be a consequence of either ongoing cachexia or chemotherapy-induced cardiotoxicity; at the same time heart failure can result in cachexia, especially muscle wasting. Therefore, the subsequent heart failure and cardiac cachexia can exacerbate the existing cancer-induced cachexia. We discuss these bilateral effects between cancer cachexia and heart failure in cancer patients.

Since cachectic patients are more susceptible to chemotherapy-induced toxicity overall, this may also include increased cardio-toxicity of antineoplastic agents. Patients with cachexia could thus be doubly unfortunate, with cachexia-related cardiac dysfunction/ heart failure and increased susceptibility to [cardio] toxicity during treatment.

Cardiovascular risk factors as well as pre-existing heart failure seem to exacerbate cardiac susceptibility against cachexia and also increase the rate of cardiac cachexia. Hence, chemotherapy-induced cardiotoxicity, cardiovascular risk factors and pre-existing heart failure may accelerate the vicious cycle of cachexia-heart failure.

The impact of cancer cachexia on cardiac dysfunction/ heart failure in cancer patients has not been thoroughly studied. A combination of serial echocardiography for detection of cachexia-induced cardiac remodeling and computed tomography image analysis for detection of skeletal muscle wasting would appear a practical and non- invasive approach to develop an understanding of cardiac structural/ functional alterations that are directly related to cachexia.

### 3.2 Introduction:

Cancer cachexia is a multi-factorial syndrome of involuntary weight loss defined by an ongoing loss of skeletal muscle, fat mass and progressive functional impairment [1, 147, 148]. Cachexia is a major cause of morbidity and mortality, occurring in up to 80% of patients with progressive cancer, and suggested to be responsible for death in up to 20% of the patients [149]. Cachexia-associated clinical manifestations include skeletal muscle wasting, anemia, anorexia, and altered immune function which contribute to fatigue, impaired quality of life, and reduced survival [150] . Patients with severe features of cachexia/ skeletal muscle wasting are generally unable to react appropriately to stress, and have increased susceptibility to infections, complications during hospitalization and chemotherapy toxicity [98, 115].

Cachexia can be found in several pathological conditions in humans such as heart failure, chronic obstructive pulmonary disease, acquired immunodeficiency syndrome, cancer and renal failure and the presence of cachexia is associated with poor prognosis [151].

Weight loss in cachexia involves muscle and fat mass as well as multiple organs including liver, kidney, spleen and lung [152]. A new finding in animal studies is that cardiac dysfunction and atrophy parallels skeletal muscle atrophy in cancer cachexia [5, 7]. Effects of cancer-induced cachexia on cardiac function and structure have not been widely studied in human. Wilens et al. [153] performed necropsies on unselected men (n=1375) and suggested that weight loss due to disseminated cancer was the most common cause of cardiac atrophy. Wilens appears to have first used the term *cardiac atrophy* in cancer patients. Burch et al. [154] reported that cancer patients have smaller hearts and cardiac dysfunction based on electrocardiogram and x-ray imaging.

Heart failure is by itself and in the absence of any other disease associated with *cardiac cachexia*. Cardiac cachexia is characterized by involuntary weight loss, reduced anthropometric

indices of muscle mass and disturbed homeostasis of several body systems [155]. Since HF is an independent cause of cachexia, cancer cachexia-induced cardiac atrophy and HF may appear as an additional contributing factor to cachexia that consequently exacerbates wasting in the cancer patient.

The purpose of this paper is to review findings which suggest that patients with cancer cachexia may develop a vicious cycle of progressive heart failure and cachexia (**Fig. 3-1**).

### 3.3 Underlying mechanism of cancer muscle wasting/ cachexia

Cachexia is caused by complex interactions between pro-inflammatory cytokines, hypermetabolism, catabolism of muscle protein, neuro-hormonal changes, and proteolytic and lipolytic factors produced by host and tumor [1, 147, 148]. Cancer cachexia is also associated with a decrease in protein synthesis that might be a consequence of , at least in part, alteration in the activation of the 5' AMP-activated protein kinase, protein kinase B (Akt) and mammalian target of rapamycin (mTOR) signaling pathways [156, 157].

Activation of the ubiquitin-proteasome system seems to be crucially important in cachexia induced muscle wasting, resulting in degradation of intracellular proteins including myofibrillar proteins [158]. Several studies showed the importance of pro-inflammatory cytokines (interleukin [IL]-1β, IL-6 and tumor necrosis factor-α [TNF- α]), which activate their receptors on muscle and subsequently activate the transcription factor nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB). NF-κB activation up-regulates the ubiquitin-dependent degradation of the myofibrillar proteins [159-161] . Furthermore, increased oxidative stress and reduced activity of antioxidant enzyme contribute to anorexia and cachexia [162, 163].

It is believed that insulin resistance may play a potential role in pathogenesis of cancer cachexia through multiple mechanisms [164, 165]. Overlap exists between insulin signaling and ubiquitin–proteasome pathways in both insulin sensitive and insulin resistant states. Due to the resistance against binding of insulin to its receptor, phosphoinositide 3-kinase activity is decreased, leading to decreased phosphorylation of Akt. Lower levels of pAkt release the inhibition of forkhead box transcription factors O (FoxO) and caspase-3, resulting in increased proteolytic activity [165]. Cancer cachexia substantially impacts on fast twitch skeletal fibers. FoxO and NF-κB affect fast, glycolytic fibers more than slow, oxidative fibers [166].

### 3.4 Cancer cachexia and cardiac alterations: animal models

Mechanisms by which cancer cachexia causes cardiac dysfunction or heart failure are becoming clearer (Figure 2). Sjöström et al. [17] investigated a sarcoma model of cachexia in mice and showed significant cardiac atrophy [almost 9% reduction in heart dry weight ($p<0.01$)] and a reduced amount of myofibrillar, collagen and soluble proteins 11 days after tumor implantation, compared to control animals. Tian et al. [12, 13] investigated the effects of colon-26 (C26) tumor-induced cachexia on cardiac function and structure. They showed echocardiography-defined evidence of functional impairment [(decreased heartbeat per minute: 528±8 in control mice vs 418±13 in tumor bearing mice; $p<0.05$) and (decreased fractional shortening: 33% difference; $p<0.05$)] and decreased posterior wall thickness (30% difference at systole) which is a feature of cardiac atrophy. Gene expression analysis also indicated increased brain natriuretic peptide and c-fos, reduced peroxisome proliferator-activated receptor α and its responsive gene muscle-type carnitine palmitoyltransferase 1 β. A decreased amount of cardiac myofibrillar proteins and

troponin I and increased protein ubiquitination were also consistent with cardiac atrophy and impaired cardiac contractility in cachectic mice. Tian et al. suggested that disturbance in p44/42 mitogen-activated protein kinase plays an important role in initiation and progression of cancer-associated cardiac atrophy in [12, 13]. Xu et al. [5] in a similar study reported the significant adverse effect of C26 tumor on systolic function/ contractility (decreased % fractional shortening: $28.4 \pm 4.18$ vs. $41.2 \pm 5.01$ in controls, $p < 0.01$). They also showed significant decrease of diastolic PWT in tumor bearing mice ($0.5997 \pm 0.090$ mm vs. $0.7575 \pm 0.1147$ mm in controls, $p<0.05$) as evidence of atrophy.

Cosper et al. [7] claimed that cardiac atrophy caused by C-26 adenocarcinoma in mice is more prominent in males due to lack of the protective effects of estrogen. Unlike Xu et al. [5], Cosper et al. [7] did not find any significant change in ejection fraction (EF) or % fractional shortening. Preserved EF along with increased rate of cardiac fibrosis as reported by Cosper et al. [7] perhaps suggests an association between cancer cachexia and diastolic heart failure with preserved EF. There is no evidence regarding diastolic cardiac function in Cosper et al's study. Cosper et al. [7] also indicated that cardiac atrophy is due to a decrease in myocyte size and not an increase in cell death which was again more prominent in male mice. Based on Cosper et al. [7] findings, autophagy especially after a long period of cachexia is the main underlying mechanism of cardiac atrophy in tumor bearing mice [7]. Manne et al. [167] also confirmed increased autophagy, not protein ubiquitination or cardiomyocyte apoptosis, in cachectic ApcMin/+ mice atrophic hearts .

Muhlfeld et al. [9] studied Lewis lung carcinoma in mice and did not find any significant functional and structural changes in echocardiographic parameters. This inconsistency with other results [12] may be due to different type of tumor (i.e. Lewis lung carcinoma *vs* C26). However, in this study only a few parameters of systolic function were reported and diastolic function was

not reported. They showed robust metabolic changes of cardiomyocytes in tumor bearing animals: decreased myofibrillar volume ($p= 0.06$), increased sarcoplasmic volume ($p<0.01$) and increased volume of lipid droplets ($p<0.01$). Muhlfeld et al. [9] showed increased lipid content of cardiomyocytes in tumor bearing mice (triglycerides per unit myocardium (mg/mg): 12.12±3.75 vs 19.5±7.91; $p< 0.05$), but markers of lipid peroxidation and apoptosis was not different in tumor bearing vs control mice. Interestingly, they found a reduction in expression of various innervation-related targets such as neuropeptide Y and nerve growth factor as well as reduced length of axons, in tumor bearing mice. This hypo-innervation is suggested to contribute to cardiac atrophy in tumor bearing mice [9].

There are a variety of potential sources of variation which could contribute to differences in the magnitude of heart structure and functional changes. Skeletal muscle atrophy in rodent cancer models is affected by tumor primary type, degree of tumor burden, tumor-associated metabolic changes, host animal type and sex, and it seems likewise plausible that these factors influence the heart as well. The specific measures which were made on the hearts in rodent models of cancer have also been somewhat heterogeneous. Finally, it is also noteworthy that the animal models lack the distinctive profiles of comorbidity, including cardiac comorbidity of human cancer patients (see below).

### 3.5 Modulation of cancer-induced cardiac alterations

Wysong et al. [14] confirmed the cardiac atrophy in C-26 adenocarcinoma model of cachexia in mice and were able to block it using systemic administration of compounds that can specifically inhibit NF-κB (Compound A and NEMO binding domain (NBD) peptide). Furthermore, Shadfar

et al. [11] proved protective effects of resveratrol against C-26-induced cardiac atrophy in mice through NF-κB inhibition.

Palus et al. [10] reported overall cardiac atrophy in rats with cancer cachexia, induced by Yoshida AH1-30 hepatoma cells, which was seen in the heart weight (752±9 mg versus 496±15 mg) as well as a reduction of the end-diastolic diameter compared to sham. They showed that treatment with simvastatin somewhat can improve the cardiac function in cancer rats (cardiac output in untreated sham: 78.9mL/min vs tumour-bearing rats: 42.4mL/min and improved by 1, 10 or 20mg/kg/d simvastatin: 62.2, 59.0 and 57.0mL/min, respectively, all $p<0.05$ vs. placebo). Partial normalization of cardiac atrophy due to simvastatin treatment is another interesting finding of Palus et al. [10].

Zhou et al. [6] showed that in both the cachectic C26 tumor-bearing mice and cachectic inhibin-deficient mice heart weights were decreased by 20%–29% compared to the normal controls (ie, cardiac atrophy), and a considerable reduction in ventricular wall thickness. They found that treating the mice with ActRIIB antagonist can completely block the cardiac atrophy in both C26 mice and inhibin-deficient mice.

Springer et al. [168] showed that the xanthine oxidase inhibitor, oxypurinol, partially recovered left ventricular (LV) mass ($p<0.05$) and LVEF ($p<0.05$) in Yoshida AH-130 hepatoma cachexia rat model.

These findings in rodents further support the idea that cancer cachexia results in atrophy of the myocardium by mechanisms similar to those described for skeletal muscle wasting. However, whether cardiac atrophy occurs in humans with cancer cachexia is still a subject of debate. We cannot conclude any relation between the rate of cachexia and severity of cardiac remodeling in

rodent studies. It is postulated that based on the rate of cachexia, a range of heart failure severity can be resulted from diastolic heart failure with preserved EF to pure systolic heart failure.

Further research should be performed to investigate the effects of cachexia on the ability of the heart to respond appropriately to physiologic and pathologic stressors. For instance, cachexia effects on a rodent model of pressure-overload (transverse aortic constriction) may uncover the interaction between transverse aortic constriction model, which results in cardiac hypertrophy, and atrophy which might be the consequence of cachexia.

### 3.6 Heart failure and cachexia development: Cardiac Cachexia

Cardiac cachexia is a frequent finding in classical heart failure patients with impaired systolic function [155]. Piepoli et al. [169] found cachexia features/ marked muscle mass wasting in heart failure patients compared with matched healthy controls using dual energy x ray. Significant computed tomography (CT)-defined reduction of muscle cross-sectional area of the thigh as well as impaired maximal quadriceps muscle strength were noticeable signs of cachexia in heart failure patients compared with age-matched healthy controls [170].

The possible mechanism of cachexia development in heart failure includes increased energy requirements, decreased nutrient absorption, decreased energy intake, increased inflammatory cytokines, neurohormonal activation and impairment of skeletal muscle growth hormones [171, 172] , similar to mechanisms proposed for cancer cachexia.

Although baseline echocardiographic and cardiac magnetic resonance imaging (MRI) measurements did not show any different in left ventricular mass between the patients with and without cardiac cachexia, overtime assessments after 6 months (echocardiography) and mean of

15 months (MRI) showed a significant reduction [173, 174]. Both of these studies showed that cardiac atrophy developed as cachexia progressed [173, 174].

### 3.7 Bilateral effects of cachexia and heart failure

Heart failure clearly results in cachexia in humans and if, as suggested by animal studies, cancer cachexia leads to heart failure, then it is possible to hypothesize that there may exist bilateral effects of the two conditions (Figure 1). The suggestion that cancer cachexia may lead to the development of heart failure requires new investigations. Some individuals with cancer lose skeletal muscle very intensely (i.e. >5 kg of muscle mass in 90 days) [175] and these would be obvious candidates for developing concurrent cardiac atrophy with development of cardiac dysfunction.

A simple model (Fig 1) would have a primary interaction between the development of cachexia and heart failure in cancer patients. There are two additional factors which would serve to exacerbate the primary interaction, the use of cardiotoxic chemotherapy and cardiovascular morbidity that pre-existed the development of the malignancy.

### 3.8 Chemotherapy-induced cardiotoxicity: Postulated association with cachexia

Different classes of chemotherapy, targeted therapy drugs and chemoprevention regimens showed cardiotoxic side-effects in a subgroup of patients [176]. Cardiac toxicities are thought to be under-reported [177]. Since cachectic patients are more susceptible to anti-cancer agent-induced toxicity [98], this may also include increased cardio-toxicity of antineoplastic agents. A wide range of cardiac disorders such as acute coronary syndrome and dysrhythmia have been

associated with chemotherapy-induced cardiotoxicity [178]. Anthracyclines and tyrosine kinase inhibitors are two major examples.

New concerns arise regarding the unexpected cardiac events following tyrosine kinase inhibitors, in particular sunitinib therapy. Di Lorenzo et al. [179] conducted a multicenter study and showed 6.9% incidence of heart failure following sunitinib therapy. Apart from LVEF reduction and heart failure, other cardiac abnormalities are also observed subsequent to sunitinib therapy. Acute coronary syndrome, atrial fibrillation [180], decreased heart rate and dose dependent QT interval changes [181] has also been associated with sunitinib therapy. Cho et al. [182] evaluated the cardiac events of 23 patients with renal cell carcinoma who received salvage IL -2 therapy and reported severe cardiac events in 6 patients who all had the prior use of tyrosine kinase inhibitors (sorafenib or sunitinib).

Anthracyclines such as doxorubicin can also lead to cardiomyocyte injury. Roughly 10% of patients treated with doxorubicin or its derivatives will present with cardiac side-effects up to 10 years after the cessation of chemotherapy [164]. Several underlying mechanisms have been proposed for doxorubicin cardiotoxicity, however no clinically proven treatment has been found for doxorubicin cardiomyopathy [183].

Generally cardiotoxicity of any kind and its severity due to anticancer therapy is multifactorial in nature, determined by the interaction between genetic and environmental factors [176]. Individual genetic background is known to be important in anthracycline cardiotoxicity [184]. Several predisposing factors have been mentioned to be related to chemotherapy-induced cardiotoxicity. For instance, a history of hypertension [179], coronary artery disease [179, 185] and heart failure [185] seem to be associated with sunitinib-induced cardiotoxicity. Cochet et al. [186] reported that impaired LV diastolic function before treatment is an independent predictor of

trastuzumab-induced cardiotoxicity after adjuvant anthracycline therapy in the patients with breast cancer while Serrano et al. [187] confirmed that age, history of cardiac disease and/or diabetes are risk factors for trastuzumab-related cardiotoxicity in breast cancer patients.

Severe muscle wasting is suggested to predispose patients to dose-limiting toxicity characteristic of different chemotherapies and regimens. Antoun et al. [98] reported a significant association between low body mass index and skeletal muscle wasting and sorafenib dose limiting toxicity in patients with renal cell carcinoma. Similar associations were found for fluoropyrimidines in metastatic breast and colorectal cancer, adjuvant multidrug regimens in breast cancer and sorafenib in hepatocellular carcinoma settings [139]. One question that needs to be asked, however, is whether any relation exists between cancer cachexia and cardiotoxicity specifically. No study so far specifically investigated the impact of cachexia on the degree and progression of cardiac dysfunction/ cardiotoxicity following potentially cardiotoxic chemotherapy agents. More extensive research in regard to chemotherapy-induced cardiotoxicity is required, including its potential interaction with cachexia.

Generally a wide range of chemotherapy-induced heart failure has been reported: Acute heart failure, chronic heart failure with impaired systolic function and diastolic heart failure with preserved EF.

Currently there is no robust evidence of any association between diastolic heart failure with preserved EF and cancer cachexia. Cardiac follow up for the cancer patients undergoing chemotherapy should definitely include the techniques which can elucidate diastolic function (eg, tissue Doppler imaging). Tissue Doppler imaging to complement conventional echocardiography has been shown to be beneficial in recent studies regarding chemotherapy-induced cardiotoxicity follow up [188, 189]. Furthermore adding strain and strain-rate measurements are highly sensitive

in early precise detection of diastolic heart failure with preserved EF [190] . Strain imaging is highly sensitive for early detection of chemotherapy-induced cardiotoxicity [191, 192].

In conclusion, patients with cachexia could thus be doubly unfortunate, with both cachexia-related heart failure and increased susceptibility to cardio-toxicity during treatment.

**3.9 Cachexia and pre-existing cardiovascular risk**

A preliminary report suggests that cancer and heart failure patients both have clinical manifestation of tachycardia and reduced LVEF, dyspnea, fatigue and reduced exercise capacity [193]. Indeed it has been suggested that cancer fatigue syndrome may reflect a presentation of non-overt heart failure [55]. However beyond studies looking specifically at cardiotoxic chemotherapy, there is a lack of detailed assessment of cardiac function in cancer patients. Von Haehling et al. [194] reported that patients with cancer tend to have higher values for blood pressure, stroke volume, cardiac output, and dP/dtmax at rest which may represent a higher cardiovascular risk in cancer patients compared to control subjects. A recent cross-sectional analysis of data from of 93,663 patients (Gourin et al.) who had head and neck cancer surgery showed that after controlling for all other variables, patients with weight loss (ie, evidence of cachexia) had an increased risk of acute cardiac events compared with patients without weight loss (relative risk ratio=1.32, p=0.016) [22].

Heart disease is one of many categories of comorbidity that affect cancer patients. Table 3-1 shows the prevalence of cardiac disorders in a population of 16,500 patients who died of cancer in Alberta, Canada, 1993-2000. These disorders were noted in administrative health data (hospital discharge abstracts) encompassing all hospitalizations occurring in the 365 days preceding the death of each patient. This time encompasses the part of the disease trajectory when cachexia is the most prominent [175]. Overall a diagnosis of heart failure was noted in 7.5% of patients;

however this was especially prevalent in certain subsets (14.4% in multiple myeloma, 10.4% in leukemia, 9.7% in lymphoma, 8.9% in male genital in urinary system cancers, 8.5% in lung cancer and 7.6% in female breast cancer). By contrast relatively few (1.5 - 3 %) patients with cancers of the brain, endocrine system, oral cavity, pharynx and skin had a diagnosis of heart failure. Smoking and cardiovascular atherosclerotic diseases in some cancer types may exacerbate consequent cardiac complications. This variation in cardiac comorbidity as well as the inherent individual and tumor –specific variation in the evolution of cachexia will contribute to variation in the cachexia – cardiac interactions.

Although the association between heart failure and cancer has been established, there has been little discussion about the effects of cachexia on cardiac alterations in the presence of cardiovascular risk factors and morbidity. In other words, the effects of cachexia on the heart of the patients with either pre-existing risk factors or heart failure need to be studied in the near future. Likewise, in non – malignant disease, researchers are beginning to probe the complex interactions among heart failure, cachexia and comorbid conditions [195].

### 3.10 An argument for more detailed assessments in cardio-oncology research and practice

A global guideline of assessments (imaging or biomarkers) for the early detection, management and prevention of cancer-induced cardiac disorders does not currently exist. Cardiac management may have been ignored in part owing to the poor prognosis of some patients. However with improvement in the management of cardiac comorbidity and tolerance of cancer therapy, research in cardio-oncology is needed.

In animal studies, development of cardiac atrophy subsequent to cancer cachexia is clearly proven [5-7, 9-14, 17, 167]. Prospective studies are needed to uncover the possibility of association

between cachexia and heart failure in human patients. It may be somewhat complicated to separately evaluate the effects of cardio-toxicity and the effects of cancer cachexia on cardiac function and structure. Also co-existence of cardiovascular morbidities (e.g. hypertension) makes the interpretation problematic.

Further investigations should be undertaken to clarify the association between cancer cachexia and cardiac structural and functional alterations in human patients. Application of cardiac imaging techniques combined with skeletal computed tomography scan in longitudinal studies may elucidate the parallel wasting of skeletal and cardiac muscle. Computed tomography is extensively used for routine oncology-related clinical assessments and these images can be efficiently used to detect skeletal muscle wasting/ cachexia as well as other features of clinical importance (accumulation of visceral adipose tissue, pathological accumulation of lipids in tissues) [72, 131, 196]. A detailed treatment of methods can be found elsewhere [85-87, 89, 128, 131, 196]. For assessment of cardiac functional and structural alterations, advanced echocardiographic methods appear to be suitable. Magnetic resonance imaging offers better image quality in some patients and would also provide additional structural information of the myocardium. But the limited availability and the relatively high costs would not allow serial measurements in larger cohorts of patients.

It will be of interest to evaluate plasma biomarkers in detection of cardiac alterations in cancer patients. The utility of brain natriuretic peptide (BNP) and pro-BNP in detection of heart failure patients has been proven [197]. Promising evidence exists in regard to high sensitivity troponin I (hs-Tn I) and BNP in detection of chemotherapy-induced cardiotoxicity [198, 199]. Some inflammatory biomarkers including C-reactive protein, TNF-α and IL-6 seem to be acceptable predictors of cancer cachexia/ muscle wasting [200, 201] as well as heart failure progression in

cardiac (ie, non-cancer) patients [202, 203]. Hs-TNI and BNP suggested to be tested in further longitudinal cancer studies with both cardiotoxic and non-cardiotoxic agents.

We are proposing that there is a group of cancer patients who have elevated risk of cardiac impairments that reduce their fitness to tolerate treatment, reduce their quality of life and potentially limit their survival. This group of patients is not currently receiving cardiac investigations as part of standard care and thus their cardiac problems could be underestimated. Oncologists have existing indications for cardiac investigation and follow up; however these are restricted to investigational new drugs and drugs in current use that are cardiotoxic (**Fig. 3-3**). Regulatory agencies require electrocardiogram in all cancer patients in all clinical trials, and multi gated acquisition scan and echocardiography are used in trials of new drugs with potential cardiotoxicity. For doxorubicin and epirubicin, which have established cardiotoxicity, cardiac evaluation is part of clinical practice guidelines [204]. Multigated acquisition scan is standard of care for patients receiving these agents at specified doses. Aside of these specific instances, there is no mandated cardiac investigation in cancer patients and no basis to make recommendations without new evidence. Collaboration between medical oncologists and cardiologists is essential to develop this area [176]. We must develop a clearer idea of which cancer patients could benefit from cardiac therapies. The new clinical investigations should be focused in patients with multiple risk factors as discussed here (comorbidity, sarcopenia, cachexia risk factors, cardiovascular risk factors, presenting with severe fatigue / exercise intolerance) but whose quality and quantity of life over the disease trajectory is likely to be significantly compromised if their heart condition remained untreated. The deployment of interventions is at this time entirely speculative, but it is of interest in rodent studies heart failure medications such as statins, beta blockers and aldosterone

antagonists could attenuate both skeletal and heart muscle wasting in cancer cachexia-models [3, 10].

## Conclusion

It is postulated that over time during development of cancer cachexia, significant cardiac dysfunction and also progressive cardiac muscle wasting may occur. Also, developed heart failure as a consequence of cachexia itself or pre-existing cardiovascular disease and/or anti-cancer drug cardiotoxicity may play a role as a further source of cachexia. Possible bilateral effects between cancer-induced cachexia and subsequent heart failure require investigation in human studies. Although a large and growing body of literature has investigated the cardiotoxic effects of several types of chemotherapy agents, whether cachexia aggravates chemotherapy-induced cardiotoxicity requires investigation. Moving forward, identification of skeletal muscle loss in cancer patients with regular CT scan as well as parallel cardiac assessments with feasible tools (i.e. echocardiography) will contribute to development of novel knowledge in human patients.

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**Table 3-1: The prevalence of cardiac disorders in a population of 16,500 patients who died of cancer in Alberta, Canada.**

| *Cardiac Disorder* | ICD-9 | Most Responsible diagnosis for the hospital stay | % | Any diagnosis of cardiac disorder | % |
|---|---|---|---|---|---|
| **Ischemic heart disease** | 410.x–414.x | 228 | 0.7 | 3914 | 12.2 |
| **Cardiomyopathy** | 425.x | 8 | 0.0 | 169 | 0.5 |
| **Conduction disorders** | 426.x | 18 | 0.1 | 652 | 2.0 |
| **Cardiac disrhythmia** | 427.x | 129 | 0.4 | 3127 | 9.7 |
| **Heart failure** | 428.x | 262 | 0.8 | 2428 | 7.5 |
| **Total** | | 645 | 2.0 | 10290 | 32.0 |

ICD-9, International Classification of Diseases-Ninth Revision

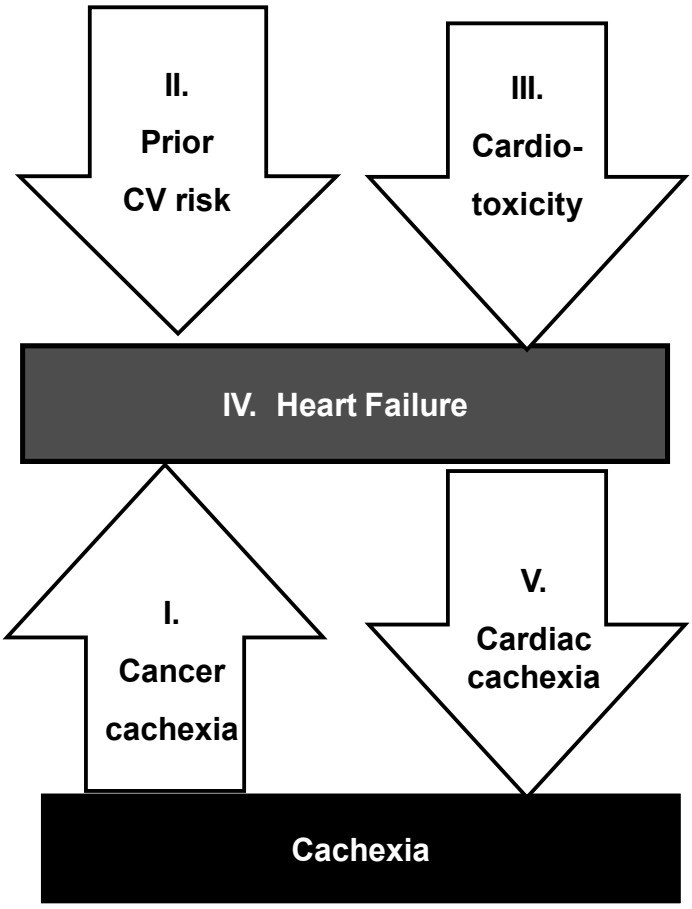


**Figure 3-1:** Bilateral effects of cachexia and heart failure in the cancer context.
I) Cancer cachexia is postulated to result in cardiac atrophy/ heart failure leading to loss of cardiac function.
II & III) Pre-existing cardiovascular risk / morbidity as well as cardiotoxic chemotherapy are additional factors that contribute to heart failure in some cancer patients.
IV) Heart Failure can be initialized/ exacerbated by both of cancer cachexia and cardiotoxic chemotherapy.
V) Developed heart failure by itself is demonstrated to result in cachexia (cardiac cachexia), augments the severity of the existing cancer cachexia and potentially increases the susceptibility to chemotherapy-induced cardiotoxicity.
These effects could sequentially worsen with cachexia driving heart failure and heart failure contributing to augmented cachexia.
CV, cardiovascular

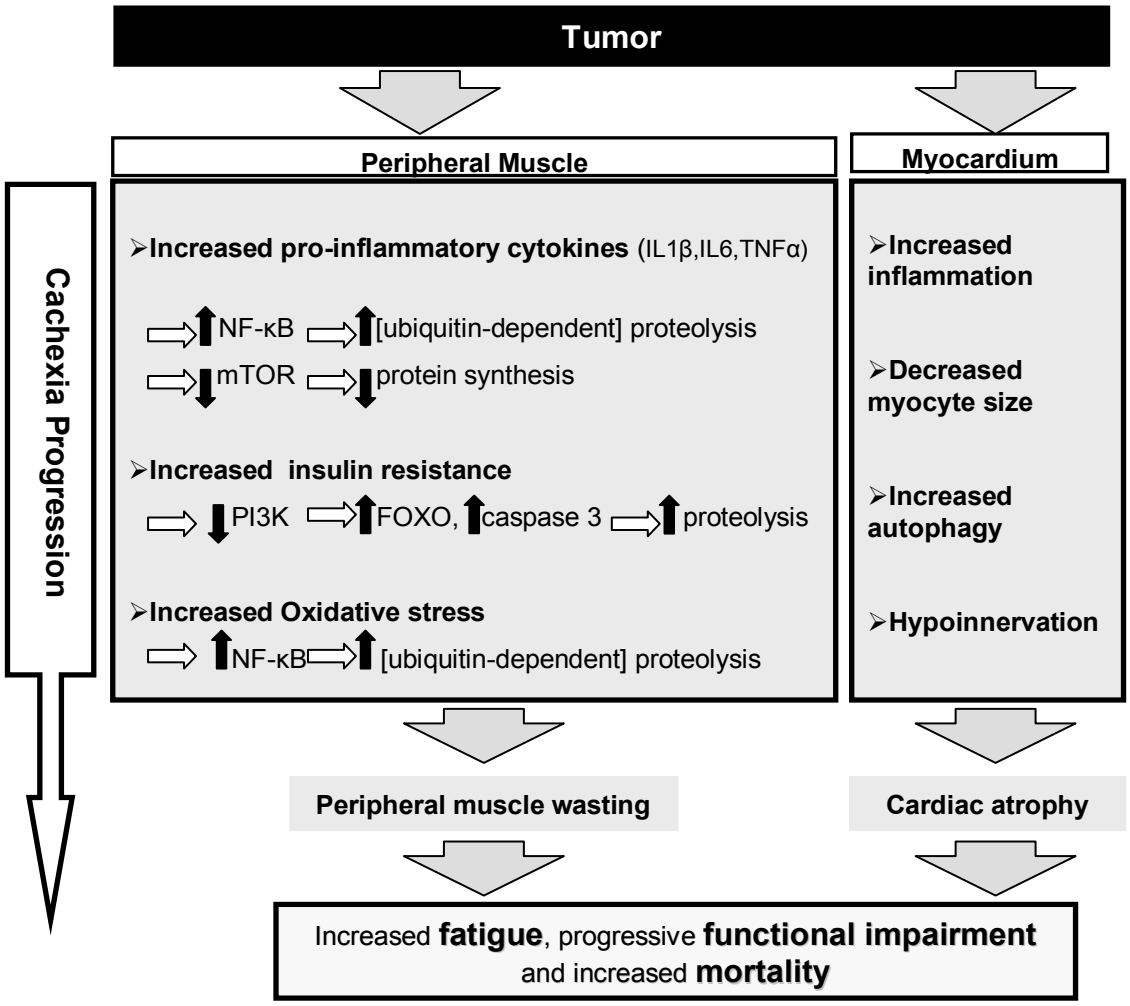


**Figure 3-2:** Cardiac atrophy parallels skeletal muscle wasting occurs in cancer cachexia. Gray arrow, shows the effects of tumor on peripheral muscle and myocardium which results in peripheral muscle wasting as well as myocardial atrophy; White arrow, biochemical pathways; Black arrows, up-regulation and down-regulation. FOXO, forkhead box O3; IL, interleukin; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; PI3K, phosphoinositide 3 kinase; TNFα, tumor necrosis factor α.

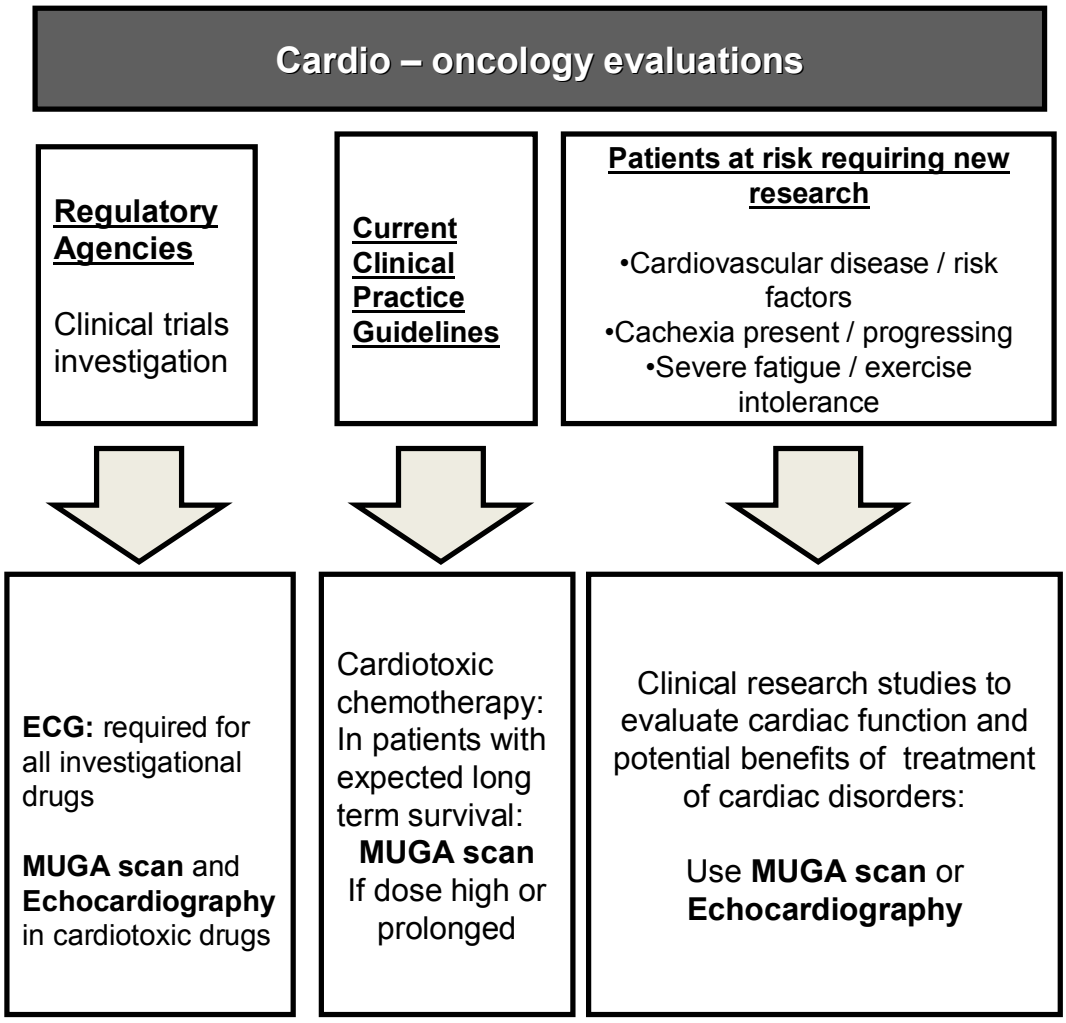


**Figure 3-3:** Suggested cardio-oncology evaluations for cancer patients undergoing cardiotoxic treatment or are at high risk of cardiac disorder development. ECG, electrocardiogram; MUGA, multi gated acquisition scan.

**CHAPTER 4:**

*This article was submitted for peer review*

**Rapid atrophy of cardiac left ventricular mass in humans with cancer cachexia**

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## 4.1 Abstract

### Background

Mechanical unloading is the only context in which cardiac atrophy in humans has been documented. Cancer cachexia is a systemic catabolic condition affecting skeletal muscle and fat; we aimed to determine whether echocardiography-defined left ventricular mass atrophy also occurs.

### Methods

Fifty treatment-naïve metastatic non-small cell lung cancer patients [64.8±7.8 y; 24 (48%) male] were treated with carboplatin-based chemotherapy. Assessments were conducted prior to and 4 months after commencement of chemotherapy and included echocardiography for left ventricular mass and LV function [LV ejection fraction (LVEF), global longitudinal strain and diastolic function]; computed tomography to quantify skeletal muscle and adipose tissue and questionnaires to assess dyspnea, performance status and fatigue.

### Results

Overall median loss of left ventricular mass was -8.9% (95%CI: -10.8, -4.8; p<0.001) during 112±6 days between assessments; this loss was greater than the median loss of skeletal muscle of -6.2% (95%CI: -8.7, -4.2; p<0.001). Quartiles of left ventricular mass loss were: -20.1%, -12.9%, -4.8%, +5.5%. Atrophy >8.9% of left ventricular mass associated with a risk for loss of skeletal muscle [OR=4.5 (95%CI: 1.4, 14.8); p=0.01] and of total adipose tissue [OR=10.0 (2.7-36.7); p<0.001]. While there were minimal systolic (LVEF) and diastolic left ventricular function changes over time; left ventricular mass loss associated with decreased global longitudinal strain [OR=6.6 (1.9, 22.7); p=0.003], worsening of fatigue [OR=6.6 (1.9, 22.7); p=0.003], worse

performance status [OR=4.8 (1.3, 18.3); p=0.02] and increased dyspnea [OR=9.3 (2.4, 35.8); p=0.001].

**Conclusions**

Intense left ventricular mass atrophy is a prominent and integral component of cachexia in metastatic lung cancer and is associated with deterioration of heart function, cardiopulmonary symptoms and functional status.

## 4.2 Introduction:

Skeletal muscle is a highly plastic tissue which exhibits a broad capacity for hypertrophy and atrophy in response to sustained mechanical, endocrine and metabolic stimuli. Anabolic and catabolic processes in skeletal muscles are well understood and have been intensively studied in relation to a variety of muscle pathologies. While respiratory and cardiac muscles are suggested to have considerable adaptive capacity, the physiology of atrophy and hypertrophy of these organs is less well-understood. Mechanical unloading induces atrophy of skeletal muscles [205], respiratory muscles during mechanical ventilation [206], as well as cardiac muscle during space flight, bed rest [207] and use of ventricular assist devices [208]. Aside from the latter instances, ***cardiac atrophy*** is a virtually unknown clinical entity. By contrast, it is cardiac hypertrophy, a prevalent pathology associated with hypertension and obesity, which dominates our current base of knowledge [209].

Cancer cachexia is a systemic catabolic condition associated with involuntary losses of skeletal muscle and adipose tissue[7]. Rodent models of cancer cachexia suggested that atrophy of cardiac muscles occurs to a similar degree to skeletal muscles, by pathways, involving inflammation, proteolysis, apoptosis and autophagy[2]. Rodent studies also demonstrated progressive decline in heart systolic [impaired left ventricular ejection fraction (LVEF)] and diastolic function in atrophied hearts[2, 3]. There have been no studies to determine whether human cancer cachexia is associated with cardiac atrophy over time.

Clinically, cancer cachexia is associated with progressive functional impairment: reduced capacity for physical work and strength, low performance status and symptoms such as fatigue and dyspnea, the latter being prominent in patients with non-small cell lung cancer. These issues are among the most important detriments to the quality of life of patients with advanced malignant

disease and are outcome measures in clinical trials of cachexia therapy. There is some understanding of how cachexia relates to these symptoms. Dietary intake of cancer patients is typically insufficient to meet even basal metabolic demands, and fatigue is a well-characterized outcome of chronic malnutrition. Skeletal muscle is directly implicated in all forms of physical functioning including respiration, which makes muscle loss a likely driver of functional impairment. If indeed cardiac atrophy develops over the course of cancer cachexia, fatigue, dyspnea and reduced physical functioning experienced by cancer patients as a consequence could be in part associated with cardiac atrophy as these symptoms are well known consequences of primary cardiac dysfunction.

We aimed to determine whether echocardiography-defined left ventricular mass atrophy occurs in a population of patients with a known propensity for cancer cachexia, metastatic non-small cell lung cancer [210].

## 4.3 Material and Methods:

### *4.3.1 Population and study design*

This was a longitudinal investigation of the alterations of left ventricular mass (as a measure of heart mass) in non-small cell lung cancer patients. The study was approved by the Health Research Ethics Board of Alberta.

To reduce the impact of extraneous factors causing variance in the study outcomes, inclusion was restricted to stage IV non-small cell lung cancer patients who were eligible for 1$^{st}$ line carboplatin-based therapy. Treatments included non-cardiotoxic agents, for a maximum of 4 cycles. All patients met eligibility criteria for carboplatin-based treatments (Eastern Cooperative Oncology Group (ECOG) [51] performance status $\leq 2$, with adequate hematologic and organ function). Patients with any other active malignancy in the last 5 years, known dilated, or diabetic cardiomyopathy; acute coronary syndrome and cerebrovascular disease within 3 months prior to enrollment were excluded.

Evaluations were conducted before the start of chemotherapy and 2-4 weeks after the last planned (4$^{th}$) cycle of chemotherapy (~3.5-4 months after enrollment). Echocardiography-defined change of left ventricular mass over time was the primary endpoint.

### *4.3.2. Cardiac measures*

Echocardiography was performed using an Epiq® scanner (Philips Medical systems, Bothell, WA, USA) according the 2015 European Association of Cardiovascular Imaging and the American Society of Echocardiography Recommendations for Chamber Quantification and 2016 Recommendations for Evaluation of Diastolic Function by Echocardiography [211] . LVEF was calculated using the biplane Simpson-method. Left ventricular mass was calculated by 2D

echocardiography; Global longitudinal strain measurements were made in the three standard apical views. Average global longitudinal strain from the three views was reported. LV diastolic function was graded normal, mild (grade 1), moderate (grade 2) and severe (grade 3) depending on the measurements of pulsed-wave Doppler of mitral inflow, tissue Doppler of mitral annulus movement, left atrium volume measurement and CW-Doppler of the tricuspid regurgitation if present [211].

Echocardiographic measurements were acquired by two experienced sonographers and all recordings were analyzed by an echocardiographer with 33 years' experience in clinical echocardiography. Both the sonographers and echocardiographer were blinded to the results of other assessments.

Twelve-lead Electrocardiography (ECG) was performed and major parameters including heart rate, PR interval, QRS duration (QRSD), heart rate corrected QT interval (QTc) were abstracted.

*4.3.3. Clinical assessments and Functional measures*

Performance status was evaluated according to ECOG [51]. Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scale was used for fatigue assessment [212]. Medical Research Council (MRC) Breathlessness Scale [213] was used to score the level of dyspnea (**Supp items 9-1, 2, 3**). Medication history of patients up to 1 month prior to enrollment and tumour response by RECIST 1.1 criteria [214] were collected.

Axial computed tomography images at the 3$^{rd}$ lumbar vertebra were used to assess skeletal muscle and total adipose tissue by validated methods [75] [69]. A single expert in anatomic radiology assessed all images and was blinded to other study findings.

Venous blood for cardiac high sensitivity troponins (hs-cTnT) and (hs-cTnI), galectin-3, N-terminal pro-B natriuretic peptide (NT pro-BNP) and C-reactive protein (CRP) were collected (**Supp item 9-4**).

*4.3.4. Statistical analysis*

We used SPSS software version 24 (Chicago, IL, USA) for statistical evaluations. Normally and non-normally distributed quantitative variables were tested using ANOVA and Mann-Whitney U tests respectively. Chi-square and bivariate logistic regression were considered for categorical variables. For over time comparisons paired t-test and Wilcoxon tests were used.

No human data on cardiac atrophy was available for sample size calculation. In animal models atrophy of cardiac and skeletal muscle had a similar effect sizes and variances [3]. CT-defined skeletal muscle loss in cancer patients on chemotherapy was -4.2% to -6.3% (SD 7.8) [128, 215]; we used the lower of these values (-4.2%), $\alpha$ of 0.01 and a power of 90%, yielding a sample size of n=50 in a paired t-test to detect cardiac atrophy.

**4.4. Results:**

From October 2013 to May 2016, 91 patients were approached, 72 consented and had baseline measurements, and 50 reached the 2$^{nd}$ time point at 112±6 days later (**Supp Fig 9-1**). Baseline patient features are shown in **Table 4-1**. All patients were treated with carboplatin-based therapy and 48 (96%) had ECOG- performance status of 0 or 1.

*4.4.1 Left ventricular mass atrophy is a prominent and integral component of non-small cell lung cancer cachexia*

Echocardiography-defined left ventricular mass showed active atrophy over time: ($p<0.001$) (**Table 4-2**). The median overall change in left ventricular mass was -8.9% (95%CI: -10.8, -4.8; $p<0.001$). Left ventricular mass loss quartiles: -20.1%, -12.9%, -4.8%, +5.5% are illustrated (**Fig. 9- 1.A1**).The 4$^{th}$ quartile did not lose left ventricular mass, while the 1$^{st}$ quartile lost -20.1% of left ventricular mass within our short window of observation. The maximum left ventricular mass loss was -24.5%. Left ventricular mass loss was of similar magnitude in males and females: -8.5±10.6% versus -7.2±10.1% respectively ($p=0.71$). Left ventricular mass expressed as a proportion of body surface area fell by 7.6% ($p<0.001$) (**Table 4-2**).

The overall median loss of left ventricular mass (-8.9%) was equal or greater than that of skeletal muscle (-6.2%), total adipose tissue (-4.8%) and BMI (-3.0%) (**Fig. 4-1.A1-A4**). The relatively small % loss of BMI overall is explained by the fact that some of the patients gained fat mass, which could obscure other manifestations of cachexia.

Losses of left ventricular mass, skeletal muscle and fat mass were often concurrent within individual patients. Patients whose left ventricular mass loss was above the median value (%) were at a higher risk of also being above median value for skeletal muscle loss [**OR 4.5** (95% CI 1.4-14.8); $p=0.01$] and total adipose tissue loss [**OR 10.0** (95% CI 2.7-36.7); $p<0.001$] (**Table 4-3.A**). A Venn diagram (**Fig. 4-1B**), illustrates the considerable overlap of left ventricular mass, skeletal muscle and total adipose tissue loss: 17 of 25 patients with above median left ventricular mass loss also had above median skeletal muscle loss and 19 of 25 had above median total adipose tissue loss. A small number of patients had isolated fat loss (n=6) or isolated skeletal muscle loss

(n=8). Eleven of 50 patients had concurrent high values of all three tissues loss, left ventricular mass, skeletal muscle and adipose tissue.

A prior history of > 5% weight loss in 3-6 months before start of chemotherapy was the major baseline characteristic associated with development of left ventricular mass loss over time, **OR 11.2** (95% CI 2.9-43.5; p<0.001) (**SuppTable 9-1**). Percent BMI loss correlated with percent left ventricular mass loss (r=0.6; p<0.001). Baseline cardiovascular characteristics did not relate to left ventricular mass loss (**SuppTable 9-1**).

Plasma CRP, an inflammatory biomarker associated with cachexia, increased over time (p=0.008) (**Table 4-1**). Baseline CRP value > 10 mg/L was a predictor of left ventricular mass loss over time **OR 3.9** (95% CI 1.2-12.6; p=0.02) (**SuppTable 9-1**). Patients with radiologically-defined tumour progression at the 2nd time point had higher risk of development left ventricular mass loss, **OR 18.8** (95% CI 2.2-162.0; p=0.007) (**Supp Table 9-2**).

*4.4.2 Cardiac function and biomarkers in non-small cell lung cancer cachexia*

Overall changes in systolic and diastolic function were limited. There was no change in the proportion of patients with normal diastolic function over time (76% versus 72%, p=0.20) (**Table 2**). There was a small overall decline of LVEF (58.2±8.0% to 56.8±7.5%; p=0.006). Notable cardiac changes included an overall decline in global longitudinal strain, which decreased by a median of 8.1% (IQR -15.0; 4.1, p=0.001). QTc increased from 443.7±26.6 ms to 448.7±29.4 ms. Plasma levels of the cardiac biomarkers hs-cTnT (p=0.03) and galectin-3 (p=0.02) increased. Plasma levels of NT-pro BNP and hs-cTnI did not change over time (**Table 4-2**).

We endeavored to determine how left ventricular mass atrophy might be associated with other outcomes. Above median left ventricular mass loss was associated with decline of global

longitudinal strain (**OR 6.6,** 95% CI 1.9-22.7; p=0.003) and with decreased QRSD, (**OR 4.5**, 95% CI 1.4-14.8; p=0.01) (**Table 4**); however, it was not related to loss of LVEF and other echocardiographic and ECG parameters. None of the cardiac biomarkers associated with left ventricular mass loss (**Table 4-4**).

Some of the patients in the study cohort were on cardiovascular medications at baseline (**Supp Table 9-1**). Although usage of anti-heart failure drugs was not related to left ventricular mass loss (**Supp Table 9-1**), β -blocker usage associated with less left ventricular mass wasting (p=0.05) (**Supp Table 9-3**).

*4.4.3 Functional impairments in patients with cachexia and cardiac atrophy*

Overall, patients experienced deterioration of ECOG-performance status (p<0.001), exacerbation of fatigue (p=0.001) and MRC-dyspnea score (p<0.001) (**Table 4-2**). Development of poor performance status, severe dyspnea and fatigue significantly associated with active left ventricular mass atrophy (**Table 4-3.B**). However, quantifying the specific contribution of cardiac atrophy to patients' burden of symptoms and clinical signs is difficult because muscle and/or fat loss were also simultaneously present (**Fig. 4-1.B**). The greater the number of tissues implicated in the cachexia (loss of skeletal muscle, adipose tissue and left ventricular mass), the more likely that a patient would experience simultaneous aggravation of performance status and symptoms (p=0.02; **Fig. 4-1.B**). Tumour response to chemotherapy was less likely in patients who lost multiple tissues compared with patients with limited or no tissue

loss (p<0.001; **Fig. 4-1.C**). Concurrent loss of all three tissues was associated with elevated plasma levels of CRP (p=0.04) and hs-cTnT (p=0.04) at 4 months (**Supp Table 9-4**).

**4.5 Discussion:**

Rapid cardiac atrophy occurs in patients with non-small cell lung cancer and is an integral part of cancer cachexia. Consistent with the well-known variability in the incidence and severity of cancer cachexia, individual patients appeared on a spectrum ranging from no loss of left ventricular mass to a maximum loss of 24.5% in a period of 112 days. Given our observations were taken over a short window within the longer patient journey with cancer cachexia, we may have observed only a small part of the total left ventricular mass loss. It seems plausible that patients in our sample had prior catabolic losses of cardiac tissue, since many had weight loss during the 6 months prior to study participation and weight loss was a strong predictor of cardiac atrophy. Further losses of left ventricular mass were likely to have occurred during disease progression subsequent to our observation period, as catabolic losses of skeletal muscle and fat accelerate with an exponential rate during 12 months preceding cancer death [77, 128]. A new longer term study would be required to fully evaluate cardiac atrophy across the cancer trajectory and its impact. Generalizability of results must be further evaluated in other cachexia-prone tumor groups.

Cardiac atrophy is an integral part of non-small cell lung cancer cachexia which cannot be specifically isolated from concurrent losses of skeletal muscle and adipose tissue. An international consensus definition describes cancer cachexia as "…*loss of skeletal muscle mass with or without loss of adipose tissue…associated with progressive functional impairment"[1]*. Cachexia may be associated with a larger constellation of body composition changes also including loss of left ventricular mass. A high rate of left ventricular mass loss as compared to other tissues resulted in a disproportionally lower ratio of left ventricular mass to body surface area by the 2$^{nd}$ study time point. Our data suggest that concurrent left ventricular mass, muscle and fat losses predict the

development of fatigue, dyspnea and reduced performance status. These could be considered as components of potential composite functional endpoints for future clinical studies of cachexia.

Echocardiography showed the functional consequences of cardiac atrophy. The main index of systolic function, LVEF, was slightly lower at the 2nd study time point. Diastolic function was not altered over time. These results are consistent with rodent studies in which at least 20% loss of left ventricular mass and of overall body weight were required [3], before significant impairments occurred in LVEF and diastolic parameters [3]. We observed two sub-clinical and possibly early changes associated with left ventricular mass atrophy, decreased ECG-defined QRSD and echocardiography-defined global longitudinal strain. There are some published data to suggest a positive relation between increased QRSD and left ventricular mass [216]. Likewise, in some conditions it has been suggested that a large fall in global longitudinal strain may be a prelude to decreased LVEF [217].

Cardiac atrophy appears to be a tumor-, rather than treatment-driven part of cancer cachexia, as we saw no association of left ventricular mass loss with prior chest irradiation nor with specific chemotherapy drugs used in combination with carboplatin. In the 2016 ESC position paper [218] on cancer treatment and cardiovascular toxicity carboplatin was not listed as a cause of LV dysfunction. Therefore it is more likely that the reduction in global longitudinal strain is related to a loss in cardiac mass.

Mechanisms involved in cardiac atrophy in non-small cell lung cancer remain to be fully elucidated. We did not observe association of cardiac atrophy with the cancer treatment or baseline clinical characteristics, except history of weight loss and elevated CRP prior to chemotherapy. In some degree, loss of skeletal and cardiac muscle mass may be due to deconditioning. Detailed studies of morphological, cellular and biochemical aspects of cardiac atrophy would require heart

biopsy, which was out of the scope of our investigation. The literature on cardiac atrophy in rodent models of cancer cachexia is informative with respect to tissue level changes; however, the extrapolation of these findings into human patients remains speculative. Hyper-inflammation in cancer upregulates NFκB leading to activation of ubiquitin ligases (MuRF-1 and atrogin-1/MAFb), which finally forms ubiquitin proteasome system-related catabolism [2, 219]. Furthermore, dysregulation of protein kinase B and subsequent impairment in mammalian target of rapamycin regulatory actions contributes to reduction in anabolic pathways [3, 219]. Beta-blockers restored skeletal muscle, fat and cardiac atrophy in the cancer cachexia models [3]. Beta-blocker consumption in patients with classic heart failure was protective against fat loss [220]. Here, patients who used beta-blockers had a reduced rate of left ventricular mass and fat loss; however, this requires further verification.

Cardiac biomarkers, such as troponin I and T for cardiomyocyte injury and BNP for cardiomyocyte stress, have long been studied in heart failure [221]. Some cachexia-induced cardiac atrophy rodent models showed increased plasma cTn-T [3], and gene expression of BNP in heart tissue [12]. In our study, cardiac specific biomarker (hs-cTnT) increased over time and was associated with concurrent loss of left ventricular mass, skeletal muscle and fat. Galectin-3 increased over time in our study, but was not related to left ventricular mass loss. Circulating galecin-3 has been related to either heart failure [222] or cancer progression [223].

## 4.6 **Conclusion**

Echocardiography-defined left ventricular mass atrophy and its consequent cardiac dysfunction was characterized for the first time in metastatic non-small cell lung cancer patients. Left

ventricular mass atrophy arises in conjunction with losses of fat, skeletal muscle and associates with clinically meaningful declines of performance status, worsening of fatigue and dyspnea.

**Table 4-1: Baseline characteristics of patients with metastatic NSCLC (N=50).**

| | | |
|---|---|---|
| **Demographic data** | Age (y) | 64.8±7.8 |
| | Male n (%) | 24 (48) |
| | Caucasian n (%) | 49 (98) |
| **Tumour Histology** | Adenocarcinoma | 36 (72) |
| | Squamous cell carcinoma | 11 (22) |
| | Others | 3 (6) |
| **Chemotherapy added to carboplatin** | Vinorelbine n (%) | 15 (30) |
| | Gemcitabine n (%) | 8 (16) |
| | Paclitaxel n (%) | 1 (2) |
| | Pemetrexed n (%) | 26 (52) |
| **Prior chest radiotherapy** | | 23 (46) |
| **Biochemical parameters** | White blood cell (X109/L) | 8.3±3.9 |
| | Hemoglobin (g/L) | 129.7±15.8 |
| | Platelet (g/L) | 329.7±107.1 |
| | Creatinine (μmol/L) | 73.9±24.7 |
| | Na (mmol/L) | 139.8±3.5 |
| | K (mmol/L) | 4.5±0.4 |
| **Cardiovascular risk factors** | Hypertension n (%) | 16 (32) |
| | Diabetes mellitus n (%) | 8 (16) |
| | Smoking n (%) | 41 (82) |
| | [#]Prior myocardial infarction n (%) | 5 (10) |
| **Drug history one month before start of chemotherapy** | ACE inhibitor n (%) | 9 (18) |
| | Angiotensin receptor blocker n (%) | 5 (10) |
| | Beta-blocker n (%) | 13 (26) |
| | Statin n (%) | 14 (28) |
| **Weight loss history** | >5% weight loss in recent 6 months n (%) | 21 (42) |

Values are expressed as mean ± SD. ACE, angiotensin converting enzyme.
[#] Recent myocardial infarction (3 month before inclusion) was an exclusion criterion.

**Table 4-2: Body composition, cardiac parameters and functional indices at baseline and at study endpoint (n=50)**

| | | Time course | | P-value |
|---|---|---|---|---|
| | | **Baseline; Day 0** | **Post treatment; Day 112±6** | |
| **Weight and body composition** | Body mass index (kg/m$^2$) | 26.5±5.8 | **25.5±5.4** | **0.001** |
| | Skeletal muscle (cm$^2$) | 130.5±36.0 | **120.9±29.7** | **<0.001** |
| | Muscle radiation attenuation (HU) | 29.4±8.7 | **27.7±8.5** | **0.03** |
| | Total adipose tissue (cm$^2$) | 317.9±204.2 | **290.6±180.5** | **0.02** |
| **Echocardiography parameters** | LV mass (grams) | 161.9±53.3 | **148.3±49.6g** | **<0.001** |
| | LVM/body surface area (grams/m$^2$) | 86.9 ±22.6 | **80.3±20.8** | **<0.001** |
| | LV posterior wall thickness-diastole (cm) | 0.96±0.17 | **0.89±0.16** | **0.01** |
| | Inter ventricular septum-diastole (cm) | 1.1±0.18 | **0.92±0.16** | **0.003** |
| | Left ventricular ejection fraction (%) | 58.2±8.0 | **56.8±7.5** | **0.006** |
| | Global longitudinal strain (%) | 18.6±3.1 | **17.3±3.6** | **0.001** |
| | Normal diastolic function n (%) | 38 (76) | 36 (72) | 0.20 |
| **ECG parameters** | Heart rate (beats/min) | 78.9±14.9 | 80.5±15.2 | 0.39 |
| | PR (ms) | 166.6±25.8 | 195.6±134.5 | 0.12 |
| | QRS duration (ms) | 94.4±19.3 | 96.2±22.7 | 0.21 |
| | QTc (ms) | 443.7±26.6 | 448.7±29.4 | 0.05 |
| **Plasma Biomarkers[#]** | CRP (mg/L) | 7.9 (3.4;22.7) | **12.3(3.9;35.1)** | **0.008** |
| | hs-cTroponin T (ng/L) | 6.1 (3.8;12.5) | **7.6 (4.9;15.4)** | **0.03** |
| | hs-cTroponin I (ng/L) | 1.5 (0.6-3.0) | 2.0 (0.1;4.0) | 0.86 |
| | NT pro-BNP (ng/L) | 123.5(60.0;292.6) | 145.5 (71;433.0) | 0.44 |
| | Galectin-3 (ng/mL) | 17.7±7.3 | **19.9±7.0** | **0.03** |
| **Functional parameters** | FACIT-F fatigue score [0 (worst) -52] | 32.4±11.1 | **28.4±12.6** | **0.001** |
| | ECOG (0-1) n (%) [0-5 (worst)] | 48 (96) | **20 (40)** | **<0.001** |
| | MRC-dyspnea score (1-2) n (%) [1-5 (worst)] | 44 (88) | **20 (40)** | **<0.001** |

Values are expressed as mean±SD or median (interquartile ranges).; CRP, C reactive protein; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; GLS, global longitudinal strain; MRC, medical research council; hs-cTroponin T, high sensitivity cardiac troponin T; hs-cTroponin I, high sensitivity cardiac troponin I; NT pro-BNP, N-terminal pro-B natriuretic peptide; LV, left ventricular.

**Table 4-3: Univariate association between LVM loss and other clinical features over time**

| | Clinical features Stable vs deteriorating | Patients with LVM loss > median overall value (-8.9%) N (%) | Unadjusted Odds Ratio | P-value |
|---|---|---|---|---|
| **A. Skeletal muscle and fat** | Skeletal muscle loss[@] (n=25) | 17 (68%) | **4.5 (1.4-14.8)** | **0.01** |
| | Skeletal muscle stable (n=25) | 8(32%) | | |
| | Total adipose tissue loss[$] (n=25) | 19 (76%) | **10.0 (2.7-36.7)** | **<0.001** |
| | Total adipose tissue stable (n=25) | 6 (24%) | | |
| **B. Performance status, fatigue and dyspnea** | Fatigue worsening[&] (n=25) | 18 (72%) | **6.6 (1.9-22.7)** | **0.003** |
| | Fatigue stable (n=25) | 7 (28%) | | |
| | Dyspnea worsening[#] (n=30) | 21 (70.0%) | **9.3 (2.4-35.8)** | **0.001** |
| | Stable dyspnea (n=20) | 4 (25.0%) | | |
| | Performance status worsening[$] (n=16) | 12 (75%) | **4.8 (1.3-18.3)** | **0.02** |
| | Stable performance status (n=34) | 13 (38.2%) | | |

[@]CT-defined skeletal muscle loss> median overall value (-6.2%). [$] CT-defined total adipose tissue (fat) loss> median overall value (-4.6%).[&] Loss of FACIT-F defined score> median value (-12.5%) ;[#]Patients whose dyspnea scores increased over time and were within the clinically meaningful worsened status (MRC≥3). [#]Patients whose performance status increased over time and reached the clinically meaningful worsened performance status (ECOG≥3); LVM, left ventricular mass.

**Table 4-4: Univariate association between LVM loss and cardiac functional parameters over time.**

| Cardiac functional parameter Stable versus deteriorating | Patients with LVM loss > median overall value (-8.9%) N (%) | Unadjusted Odds Ratio | P-value |
|---|---|---|---|
| **Global longitudinal strain loss**[+] (n=25) | 18 (72%) | **6.6 (1.9-22.7)** | **0.003** |
| **Global longitudinal strain stable** (n=25) | 7 (28%) | | |
| **Left ventricular ejection fraction loss** (n=25) | 12 (48%) | 0.85 (0.3-2.5) | 0.78 |
| **Left ventricular ejection fraction stable** (n=25) | 13 (52%) | | |
| **Impaired diastolic function**[&] (N=14) | 8 (57.1%) | 1.5 (0.43-5.2) | 0.53 |
| **Normal diastolic function** (N=36) | 17 (47.2%) | | |
| **Increased heart rate**[#] (n=25) | 14 (56%) | 1.6 (0.5-4.9) | 0.39 |
| **Stable heart rate** (n=25) | 11 (44%) | | |
| **Decreased QRS duration**[α] (n=25) | 17 (68%) | **4.5 (1.4-14.8)** | **0.01** |
| **Stable QRS duration** (n=25) | 8 (32%) | | |
| **Increased PR interval**[@] (n=25) | 13 (52%) | 1.17 (0.4-3.6) | 0.78 |
| **Stable PR interval** (n=25) | 12 (48%) | | |
| **Increased QTc** (n=25) | 15 (60%) | 2.3 (0.73-7.0) | 0.16 |
| **Stable QTc** (n=25) | 10 (40%) | | |
| **Increased hs-cTroponin I**[!] (n=20) | 11 (55%) | 1.4 (0.45-4.4) | 0.56 |
| **Stable hs-cTroponin I** (n=30) | 14 (46.7%) | | |
| **Increased hs-cTroponin T**[α] (n=25) | 13 (52%) | 1.17 (0.4-3.6) | 0.78 |
| **Stable hs-cTroponin T** (n=25) | 12 (48%) | | |
| **Increased NT pro-BNP**[β] (n=21) | 12 (57.1%) | 1.5 (0.42-5.2) | 0.54 |
| **Stable NT pro-BNP** (n=19) | 9 (47.4%) | | |

[+] Global longitudinal strain loss > median overall value (-8.1%). [&]Impaired or normal diastolic function at follow up. [#] Increased heart rate > median overall value (1.64%). [α] Decreased QRS duration< median overall value (0%). [@]Increased PR interval > median overall value (0%). [!] Increased hs-cTroponin I > median overall value (0%). [α]Increased hs-cTroponin T> median overall value (15.5%). [β] increased NT pro-BNP> median overall value (0.6%) (BNP values available for n=40 patients). hs-cTroponin, high sensitivity troponin; NT pro-BNP, N-terminal pro-B natriuretic peptide; QTc, heart rate corrected QT interval

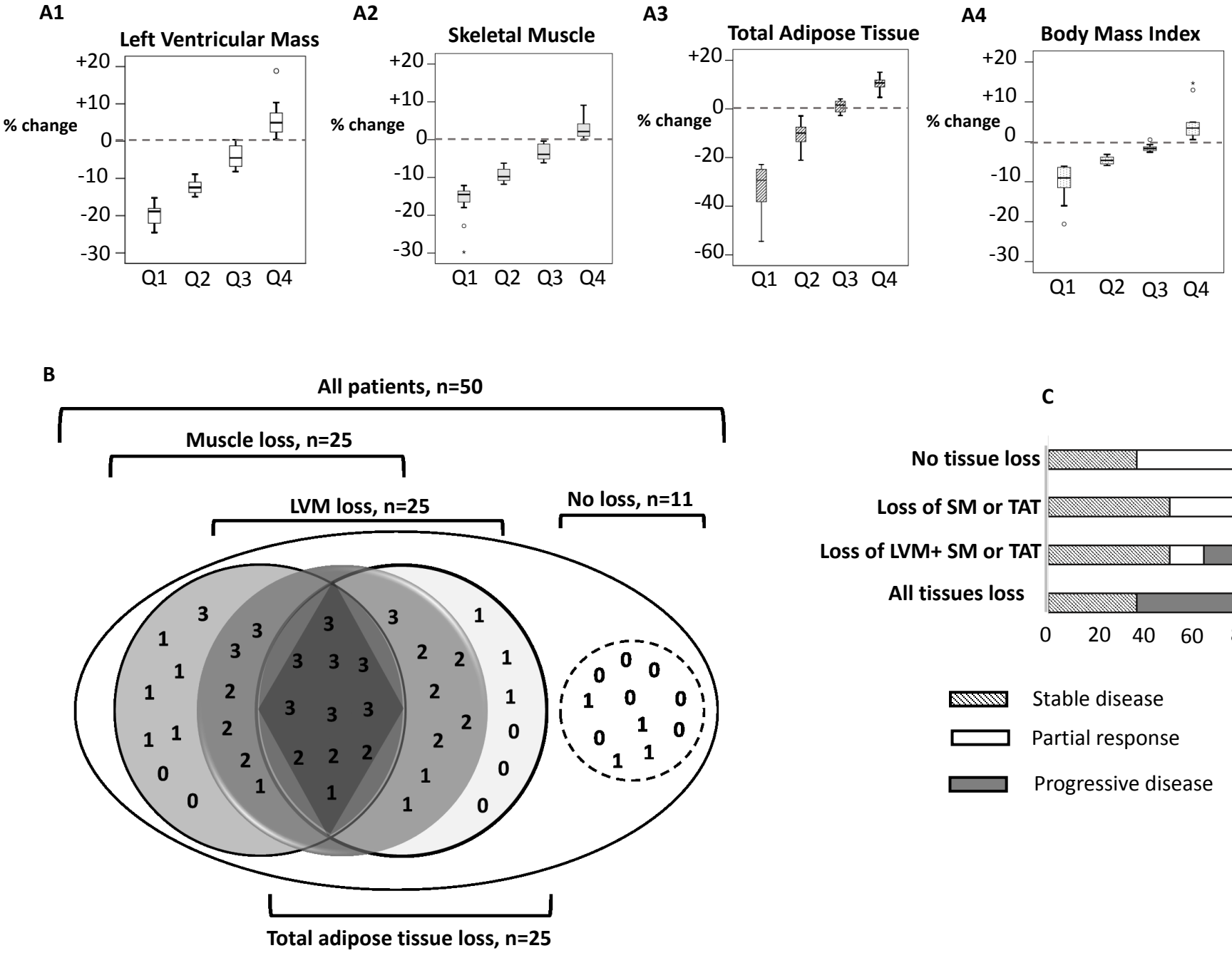
A1
Left Ventricular Mass
% change
+20
+10
0
-10
-20
-30
Q1 Q2 Q3 Q4
A2
Skeletal Muscle
% change
+20
+10
0
-10
-20
-30
Q1 Q2 Q3 Q4
A3
Total Adipose Tissue
% change
+20
0
-20
-40
-60
Q1 Q2 Q3 Q4
A4
Body Mass Index
% change
+20
+10
0
-10
-20
-30
Q1 Q2 Q3 Q4
B
All patients, n=50
Muscle loss, n=25
LVM loss, n=25
No loss, n=11
Total adipose tissue loss, n=25
C
No tissue loss
Loss of SM or TAT
Loss of LVM+ SM or TAT
All tissues loss
0 20 40 60 80 100
Stable disease
Partial response
Progressive disease

**Fig 4-1. Variation of cancer cachexia components; association with function/symptoms and tumour response.**

**A)** Population quartiles (Q) of tissue loss over time, left ventricular mass (LVM) (A1), skeletal muscle (SM) (A2), total adipose tissue (TAT) (A3) and body mass index (BMI) (A4).

**B)** Association between loss of LVM, SM and TAT. Venn diagram elements includes patients with tissue loss > median overall values for each tissue. N=11 (22%) of patients showed concurrent LVM, SM and TAT loss (patients in rhombus). N=11 (22%) patients showed no tissue loss (dotted circle).

**0,1,2,3** Each number represents an individual patient
**3:** Patients experienced worsening of all three of performance status (ECOG- performance status), dyspnea (MRC) and fatigue (FACIT-F) over time (n=11)
**2:** Patients who experienced 2 out of 3 aforementioned items (n=11)
**1:** Patients who experienced 1 out of 3 aforementioned items (n=16)
**0:** Patients who did not experience any of the aforementioned items (n=12)

**C)** Association between tumour response to therapy and loss of different tissues ($p<0.001$). 7/11 (63.6%) from no tissue loss group showed partial response; 7/14 (50%) of patients with isolated loss of SM or TAT group showed partial response; 7/14 (50%) of patients with loss of LVM+ SM or TAT had stable disease and 7/11 (63.6%) of patients with all tissues loss had progressive disease.

**CHAPTER 5:**

*This manuscript is ready to submit to a relevant journal*

**Occult deficits in baseline cardiac function in non-small cell lung cancer patients eligible for carboplatin- based therapy: implications for anti-cachexia clinical trials**

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## 5.1 Abstract


### Background

Currently an approved therapy against cancer cachexia does not exist. According to European and American regulatory agencies, physical function improvements (e.g. stair climbing test) would be approvable (co) primary endpoints of new anti-cachexia medications. We aimed to explore the cardiac status of a group of patients meeting current criteria for inclusion in anti-cachexia clinical trial.

### Methods:

Seventy patients with metastatic non-small cell lung cancer [36 (51.4%) male; 96% ECOG 0-1; eligible for carboplatin-based therapy] were referred by medical oncologists to our study before start of 1$^{st}$ line chemotherapy. All of the patients were evaluated by echocardiography, electrocardiography, fatigue and dyspnea scales. Computed tomography cross sectional images were utilized for body composition analysis.

### Results:

In 9 patients (12.8%) echocardiography allow discovery of clinically-relevant cardiac disorders [7 patients with left ventricular ejection fraction (LVEF) 32%-47%; one patient with severe right ventricular dilation and severe pulmonary hypertension and one patient with severe pericardial effusion warranted hospitalization and drainage]. Ten (14.3%) additional patients had diastolic dysfunction with preserved LVEF. The cardiac conditions were associated with worsened fatigue ($p<0.05$), dyspnea ($p<0.05$) and anemia ($p=0.06$). Five out of 7 patients with LVEF<50% were sarcopenic and one was borderline sarcopenic.

**Conclusion:**

Baseline cardiac status of the metastatic non-small cell lung cancer patients adds potential heterogeneity for anti-cachexia clinical trials. Detailed cardiac screening data might be useful for inclusion/exclusion criteria, randomization and *post hoc* analysis. These investigations may also be useful in clinical practice.

## 5.2 Introduction:

Cancer cachexia is defined as skeletal muscle and fat wasting and is highly prevalent in patients with advanced diseases. Cancer cachexia contributes to poor prognosis, worsening of performance status, impaired quality of life, increased rate of chemotherapy toxicity, post-surgery complications (e.g. infection) and increased length of hospital stay [69].

Cancer cachexia therapy is an unmet clinical need; an approved therapeutic product does not currently exist. Several recent Phase III clinical trials (POWER trials: NCT01355484 and NCT01355497; ROMANA trials: NCT01387269 and NCT01387282; MENAC trial: NCT02330926) have been performed so far to reverse/treat cancer cachexia. These aforementioned trials currently focus on non-small cell lung cancer; collectively, these three phase III investigations will have included up to 1700 non-small cell lung cancer patients: 1) POWER studies: Two randomized, double-blind, placebo-controlled, used Enobosarm, a nonsteroidal selective androgen receptor modulator; co-primary efficacy endpoints: physical function, tested by *stair climb power*, and dual-energy X-ray absorptiometry-defined lean body mass [224]. 2) ROMANA studies: Two randomized, double-blind, placebo-controlled, used a ghrelin-receptor agonist, anamorelin. Co-primary efficacy endpoints: the median change in lean body mass and handgrip strength [210]. 3) MENAC study (currently accruing patients, NCT02330926): A randomised, open-label trial; used multimodal intervention (resistance and aerobic exercise, nutrition and ibuprofen) plus standard care versus standard care alone; primary outcome: body weight change. Also, functional endpoints such as actigraphy, 6-minute walk and hand grip will be evaluated in MENAC. Home-based self-assisted exercise program is the interventional exercise for MENAC study.

There has been little agreement on approaches/endpoints in anti-cachexia clinical trials [50]. The clinical benefits of proposed therapies for cancer cachexia are controversial [50]. According to the European and American regulatory agencies, one of the major expected clinical benefits is described as improvement of physical function tests (stair climbing test, handgrip as co-primary endpoint) [50, 225]. Various secondary endpoints are also functional measures. As in the MENAC study, exercise is both an intervention and an endpoint. Although physical function improvement as a major endpoint has been requested by regulatory agencies; cardiac status, as one of the major sources of physical function fluctuations has not been thoroughly considered. Most cachexia clinical trials include patients who are candidates for standard chemotherapy, and therefore have acceptable performance status [usually The Eastern Cooperative Oncology Group (ECOG)] score 0-1. Specific indicators of intact cardiovascular function are not part of cachexia trial inclusion criteria; however, patients with a prior history of severe heart failure are excluded. Considering locally advanced or metastatic non-small cell lung cancer, a patient population which is currently a focus for cachexia clinical trials, these are exposed to common non-modifiable (e.g., age) and modifiable (e.g, smoking) cardiovascular risk factors and common comorbidities include ischemic heart disease, cardiac dysrhythmia and heart failure [2]. Therefore, the presence of overt and non-overt cardiac disorders in non-small cell lung cancer patients is plausible. We hypothesized that cardiac screening of metastatic non-small cell lung cancer patients who are potentially eligible candidates of cachexia clinical trials, might reveal cardiac abnormalities that could impose functional limitation.

## 5.3 Material and Methods:

*5.3.1 Patient population/Eligibility and exclusion criteria*

This study was approved by the Health Research Ethics Board of Alberta. From October 2013 till May 2016, 91 patients were referred by medical oncologists and were approached for consent form; finally 70 patients were enrolled in the study (**Supp Fig. 9-1**). Patients had metastatic non-small cell lung cancer and were eligible for 1$^{st}$ line carboplatin-based therapy. In addition to the general eligibility of carboplatin-based therapy (ECOG ≤2), we excluded the patients who had any other active malignancy, except for adequately treated carcinoma in situ, basal cell carcinoma and squamous cell carcinoma of the skin, as well as curative malignancy with no recurrence for more than 5 years. Known dilated, hypertrophic, or diabetic cardiomyopathy; within 3 months having acute coronary syndrome (including unstable angina, or myocardial infarction), ischemic or hemorrhagic cerebrovascular disease, or peripheral vascular disease requiring revascularization, or coronary artery bypass graft or percutaneous coronary angioplasty and baseline blood pressure >180/110 mmHg were other exclusion criteria of our study. Patients with either *uncontrolled* hypertension or *uncontrolled* diabetes mellitus were not included. Full cardiac evaluation [echocardiography and electrocardiography (ECG)] were performed for 70 patients (**Table 5-1**).

*5.3.2 Echocardiography:*

Echocardiography measurements was carried out using an Epiq® scanner (Philips Medical systems, N.A., Bothell, WA, USA). Two systolic function parameters [LVEF and global longitudinal strain] were assessed as previously described [chapter 4]. Diastolic function evaluation performed by using a recent protocol and categorized as negative (i.e., normal), indeterminate, Grade I, Grade II, Grade III [211]. Detailed echocardiography measurement information can be seen in Kazemi-Bajestani *et al* [chapter 4].

*5.3.3 Electrocardiography:*

For all patients routine 12 lead ECG were performed and major parameters including heart rate, PR, QRS duration (QRSD), QT corrected (QTc) were abstracted.

*5.3.4 Performance status, shortness of breath, and fatigue assessment*

Performance status was assessed by using ECOG [51]. Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scale was used for fatigue assessment [212]. Medical Research Council (MRC) Breathlessness Scale [213] was applied for evaluation of dyspnea.

*5.3.5 Clinical assessment of patients*

Past medical history and drug history (within 1 month before referral to our study) were abstracted through medical charts.

*5.3.6 Body composition analysis*

Baseline computed tomography cross sectional images at the 3$^{rd}$ lumbar vertebrae (L3) was used to assess body composition of the patients. This method has been validated in several previous publications in cancer patients [69]. This analysis may help us to clarify the variation of body composition in patients with possible cardiac disorders.

*5.3.7 Statistical analysis*

We used SPSS software version 24 (Chicago, IL, USA) for data analysis. Kolomogorov-Smirnov test was considered to assess the normality of the variables. T-test and chi-square tests were applied for comparison of quantitative and qualitative variables respectively. A $p<0.05$ was considered statistically significant. Overall survival was defined as the number of days from the first day of carboplatin-based therapy until death. Patients were monitored until the actual date of death or March 1st 2017.

## 5.4 Results:

### *5.4.1 Overall features of the population*

The mean age of our patients was 65.1±8.0 y/o [N=70, 36 (51.4%) males, 68 (97.1%) were Caucasian]. All of the patients were candidates for carboplatin-based therapy at the time of referral [67 (95.7%) were within ECOG 0-1]. The FACIT-F fatigue score was 33.0 ±11.9 for all the patients [score 52 is the highest (i.e., normal) score] (**Table 5-1**). The results of biochemical parameters are shown in Table 5-1.

### *5.4.2 Cardiovascular history*

Twenty eight patients (40.0%) had a history of hypertension and 17 (24.3%) were diabetic. Eighty % of our patients were smokers and 6 (8.6%) patients had a history of myocardial infarction (MI) event (remote, not within 3 months of referral). Cardiovascular drug history of the patients is shown in Table 5-1. In terms of cardiovascular background and also medications, there were no difference between males and females ($p>0.05$) (**Table 5-1**).

### *5.4.3 Echocardiography and ECG findings*

The average of echocardiography-defined LVEF was 56.7%±7.5%. Overall 7 (10%) of our patients had LVEF <50% (32%-47%). Twenty five patients (35.7%) had abnormal global longitudinal strain (i.e., less than 18%). (**Table 5-1**). ECG-defined QRSD and QTc abnormalities were found in 10% and 40% of patients respectively (**Table 5-1**).

### *5.4.4 Body composition analysis*

The mean of body mass index (BMI) was 26.3±5.6 kg/m$^2$. Sixteen (22.9%) had BMI> 30 kg/m$^2$. BMI was not significantly different between males and females (26.7±5.5 versus 25.7±5.7;

p>0.05). Sarcopenia (i.e., skeletal muscle depletion based on previously described cut offs) [92] was found in 54% of patients (**Table 5-1).**

5.4.5 *Patient categorization*

Based on the cardiac evaluations we categorized patients into three groups: 1) *Critical Cardiac Findings*: Patients with classic finding of systolic heart failure (LVEF <50%) or any cardiac finding that warrants admission or major interventions 2) Patients with any degree of diastolic dysfunction [211] with preserved LVEF (>50%). 3) Patients with no major cardiac finding **(Table 5-2)**. Although this study is not powered for survival analysis, median overall survival in patients with critical cardiac findings was considerably shorter than other groups.

*5.4.6 Cardiac evaluation revealed patients with critical cardiac findings*

Cardiac findings for this group are presented in **Table 5-3**. Although all patients were candidates for 1$^{st}$ line carboplatin-based therapy [67 (96%) patients had ECOG 0-1], clinically-relevant cardiac disorders were discovered in 9 (12.9%) patients (**Table 5-2**). Patient study #53 was the only patient with a recent cardiac history (ischemic cardiomyopathy/heart failure). None of the other patients (8 out of 9) in this group had a current medical history of heart failure. Severe cardiac dysfunction of patient study# 17 (LVEF=32%; without any known cardiac history) resulted in treatment plan cancellation and initiation of maintenance therapy. However the treating oncologist initiated the treatment plan in all other patients in this category. Seven patients in this group had classic findings of systolic dysfunction highly probable due to pre-existing ischemic pathology (all had regional wall motion abnormality- wall motion index>1). Two other critical findings were reported. Patient study # 66, found to have massive pericardial effusion at echocardiography, and was very close to having cardiac tamponade. Patient was admitted immediately after

echocardiography and pericardiocentesis took place and patient discharged symptom-free. Patient study# 29, had severe right ventricular dilatation and severe pulmonary artery hypertension.

Additional findings in this group are gathered in Table 5-2 and Table 5-3. Among the 7 patients with impaired LVEF, 5 patients were sarcopenic, and one was borderline sarcopenic. Only one patient was in the normal skeletal muscle index range (**Table 5-3**). Two out of 9 patients had BMI> 30 kg/m$^2$. Patients with critical findings showed to have higher MRC score compared to patients without major cardiac findings (i.e., more dyspenic $p<0.01$).

*5.4.7 Patients with diastolic dysfunction and preserved ejection fraction*

Ten (14.3%) patients found to have different degrees of diastolic dysfunction with preserved LVEF. One of these patients had a history of MI 16 years previously (study# 43) and one other patient had an echocardiography-defined evidence of DDPEF 2 years previously. General characteristics of patients with diastolic dysfunction with preserved LVEF are shown in **Table 5-4**. Amongst patients with diastolic dysfunction with preserved LVEF, 3 patients had BMI> 30 kg/m$^2$. Patient #4, BMI=31.4 kg/m$^2$ and sarcopenic; Patient #13, BMI=39.8 kg/m$^2$ and Patients # 73, BMI=32.1 kg/m$^2$ and sarcopenic (**Table 5-3**). Patients with diastolic dysfunction with preserved LVEF found to be more fatigued compared to patients without major cardiac findings ($p<0.01$) (**Table 5-2**).

Patients with abnormal cardiac finding (either critical finding or diastolic dysfunction with preserved LVEF) were more dyspenic and more fatigued compared to patients without major cardiac findings (**Table 5-4**). Also anemia was considerably more prevalent in patients with cardiac conditions (**Table 5-4**).

### 5.5 Discussion

We focused our analysis on sample of non-small cell lung cancer patients in 1st line therapy who conformed to criteria of eligibility for recent randomized Phase III clinical trials of cancer cachexia therapy. A detailed evaluation of the cardiac function of this clinical trial – eligible population, reveals a disturbingly heterogeneous cardiac profile and symptom burden (fatigue, dyspnea, anemia, sarcopenia) that would plausibly have a significant impact on the ability of these patients to perform physical functions as trial endpoints or interventions. The presence of heart failure or impaired diastolic function was often concurrent with severe dyspnea, fatigue, sarcopenia and/or anemia, all of which are associated with functional limitation.

Our patients conformed to the cardiovascular inclusion/exclusion criteria of cachexia clinical trials (**Table 5-5**). When these criteria are applied to our non-small cell lung cancer population, individuals with critical cardiac findings, as well as those with diastolic dysfunction with preserved LVEF would be included, and would be eligible to be participants in the clinical trials. Only one out 70 patients (1.4%) had a known current diagnosis of heart failure (based on medical history) (**Table 5-5**); however echocardiographic examination revealed a 13% rate of heart failure / critical cardiac conditions. A further, 14.3% of the sample had diastolic dysfunction with preserved LVEF. Several major Phase III clinical trials focused on non-small cell lung cancer patients due to extremely progressive nature of cancer cachexia in this group of patients. So far several interventional studies have been conducted to tackle cancer cachexia; here we consider three major regulatory agency-authorized clinical trials (**Table 5-5**). Considering these clinical trial inclusion/exclusion criteria, it seems that cardiac screening has not been considered thoroughly in these trials (**Table 5-5**). Cardiac – related inclusion and exclusion criteria of these trials is not specific enough to identify the kinds of patients we saw with notable cardiac impairment (i.e.,

exclusion in the POWER studies of "concurrent illness based on investigator judgement", or exclusion in the MENAC study of "NYHA class III or IV cardiac dysfunction") (**Table 5-5**). On the other hand, a general exclusion of "[any] history of MI or cardiac intervention" (MENAC) (**Table 5-5**) may exclude several patients for whom these events were far in the past, without a clear reason. As we see in our study, 4 out of 6 patients with a history of myocardial infarction were within the normal cardiac function group.

It was not our intention to conduct functional measures such as stair climbing test or hand grip on our patients, but we speculate that their cardiac function would influence their ability to perform functional tests of different types. Classic heart failure [202] as well as diastolic dysfunction with preserved LVEF [226] both associate with depletion of skeletal muscle mass (i.e., cardiac cachexia) and strength and also functional parameters such as 6-minute walk test. In cardiology, heart failure is defined as an insufficient heart to response to demands of the tissue (mainly skeletal muscle), which contributes to fatigue and dyspnea. Accordingly reduced capacity for aerobic exercise is the hall mark of heart failure [227]. Moreover, bilateral relation between a failed heart and wasting skeletal muscle has been discussed [2, 221]. Therefore, it is highly probable that failed functional response of some of the patients to the anti-cachexia agents is owing to extra-confounding factor (i.e., cardiac disorders).

Exercise performance capacity as evaluated by peak oxygen consumption (peak $VO_2$) was reduced in colorectal cancer patients with skeletal muscle depletion compared to control subject and this maladaptation of the heart was independent of chemotherapy [228]. Decreased peak $VO_2$ indexed to lean body mass in noncancerous older patients with diastolic dysfunction with preserved LVEF (69±7 y/o, similar to our study population) compared to the age-matched control

subjects indicates impaired exercise intolerance in this cardiac condition [229]. In cardiology context, heart failure is also associated with reduced hand grip [202].

Cardio-toxic chemotherapy is the main focus of the discipline of cardio-oncology. However, heart function and structure could be affected by other factors. Some of the cancers such as lung cancer share similar risk factors with atherosclerotic cardiovascular diseases. Similar modifiable and non-modifiable risk factors including aging, smoking and hyper-inflammatory status can be found in both lung cancer and atherosclerosis process. Moreover, existence of prolonged chronic obstructive pulmonary diseases in cancer patients could generate backward pressure on the right side of the heart. Possibly, the heart also can be functionally and structurally damaged in wasting syndromes such as cancer which is due to independent influence of cancer cachexia [2, 230].

Our findings in a palliative setting would be important for cachexia trials, as well as fatigue trials (eg, NCT00866970, NCT00040885, NCT00829322) and exercise trials (eg, NCT01581346, NCT01136083) in advanced non-small cell lung cancer patients. Cancer fatigue is a multi-factorial parameter that is basically a subjective sense and may relate to several different factors including hyper-inflammatory status, anemia, treatment side effects, psychologic burden and potentially aggravation of cancer cachexia [231] with lack of specific therapy in palliative settings [232]. Patients with advanced non-small cell lung cancer suffer from progressive aggravation of symptoms such as fatigue and dyspnea, considering that fatigue and dyspnea are the most prevalent symptoms in this group of vulnerable patients [52, 233]. Both fatigue and cancer cachexia are outcomes of similar pathophysiologic pathways, mainly activated immune response as a consequence of tumour presence [234]. Dyspnea in lung cancer patients might be a consequence of tumour, treatments, comorbidities such as chronic obstructive pulmonary disease, cardiovascular diseases or progressive cachexia [235]. Anemia is a prevalent finding in both

cancer and heart failure settings; in our study anemia was prevalent in patients with either systolic and diastolic heart findings; anemia prevalence is high in either systolic or diastolic heart failure and is associated with reduced hand grip [236].

Although cardiovascular history of males versus females was similar, several cardiac and symptom conditions were worse in males compared to females including LVEF, global longitudinal strain, percentage of patients with diastolic dysfunction and score of fatigue all were worse in males compare to females. Also, 7 out of 9 patients with critical findings were male. Generally, male patients with advanced non-small cell lung cancer have poorer outcome versus females; however, higher rate of cardiac dysfunction in males is a new finding [237].

According to the drug history of the patients, 20% of the patients were under beta-blocker therapy, also other cardio-protective drugs were used in 13-21% of the patients. Our data collection showed that 33 (47%) of patients at least used one beta-blockers, angiotensin-converting-enzyme inhibitors, angiotensin receptor blockers or statins. This is also a notable point in cancer cachexia clinical trials and *post hoc* analysis should be considered based on consumption of these drugs. Recent animal studies confirmed the anti-cachectic effects of beta-blockers, angiotensin-converting-enzyme inhibitors [3] and statins [10]. Accordingly, cardiovascular medication usage may be effective in mitigation of tissue wasting.

The significance of some findings such as decreased global longitudinal strain, increased QRSD, abnormal QTc and prolonged PR in 36%, 10%, 40% and 13% of patients, respectively, remain unclear. The impact of these findings on further functional measurements needs further investigations.

### 5.6 Conclusion:

Comprehensive measurements/ data collection of cardiac status, symptoms (dyspnea and fatigue) and body composition entities will ascertain a more useful anti-cachexia clinical trial design.

**Table 5-1: Patients' characteristics, 70 metastatic NSCLC patient candidates for carboplatin-based therapy**

| | | Total (n=70) | Males (n=36) | Females (n=34) |
|---|---|---|---|---|
| **Demographic data** | Age (y) | 65.7±8.5 | 64.5±7.5 | 64.5±7.6 |
| | Caucasian n (%) | 68 (97.1) | 35 (97.2) | 33 (97.1) |
| **Tumour Histology** | Adenocarcinoma | 48 (68.6) | 21 (58.3) | 27 (79.4) |
| | Squamous cell carcinoma | 17 (24.3) | 11 (30.5) | 6 (17.6) |
| | Others | 5 (7.1) | 4 (11.1) | 1 (2.9) |
| **Cardiovascular risk factors/ background** | Hypertension n (%) | 28 (40.0) | 18 (50.0) | 10 (30.3) |
| | Diabetes mellitus n (%) | 10 (14.3) | 6 (16.6) | 4 (11.7) |
| | Smoking n (%) | 56 (80) | 29 (80.5) | 27 (79.4) |
| | Myocardial infarction n (%) | 6 (8.6) | 4 (11.1) | 2 (5.8) |
| **Biochemical parameters** | White blood cell ($X10^9$/L) | 9.2± 4.4 | 10.2±5.4$^{+}$ | 8.2±2.8 |
| | Hemoglobin (g/L) | 129.7± 15.4 | 134.1±16.1* | 125.5± 13.2 |
| | $^{\$}$Anemia | 32 (45.7) | 17 (47.2) | 15 (44.1) |
| | Platelet (g/L) | 341.1±117.4 | 320.2±109.6 | 364.0±123.0 |
| | Creatinine (μmol/L) | 75.2± 25.9 | 85.5± 30.5*** | 64.5± 14.0 |
| | Na (mmol/L) | 139.9± 3.2 | 140.2±3.5 | 139.7±3.0 |
| | K (mmol/L) | 4.6 ±0.48 | 4.6±0.5 | 4.5±0.45 |
| | aspartate aminotransferase (U/L) | 29.6±18.1 | 32.8± 21.5 | 26.1± 13.2 |
| | CRP <10 | 37 (52.9) | 21 (58.3) | 16 (47.1) |
| **Drug history within 1 month before start of chemotherapy** | ACE inhibitor n (%) | 11 (15.7) | 8 (22.2) | 3 (8.8) |
| | Angiotensin receptor blocker n (%) | 9 (12.8) | 5 (13.9) | 4 (11.8) |
| | Beta-blocker n (%) | 14 (20) | 9 (25.0) | 5 (14.7) |
| | Statins n (%) | 15 (21.4) | 9 (25.0) | 6 (17.6) |
| **Performance/ functional status** | ECOG (0-1) | 67 (95.7) | 33 (91.7) | 34 (100) |
| | MRC (1-2) | 61 (87.1) | 34 (94.4) | 27 (81.8) |
| | Fatigue-FACIT-F | 33.0±11.9 | 29.1±11.4 | 36.2±10.2** |
| **Echocardiography findings** | LVEF (%) | 58.5±7.5 | 56.7±8.2 | 60.4±6.3* |
| | LVEF <50% n (%) | 7 (10) | 5 (13.9) | 2 (5.8) |
| | GLS (%) | 18.4±3.1 | 17.6 ±3.3* | 19.3±2.6 |
| | GLS< 18% n (%) | 25 (35.7) | 17 (47.2) * | 8 (23.5) |
| | LVM/BSA ($g/m^2$) | 86.4±22.9 | 95.8 ±20.2*** | 75.4±20.5 |
| | Diastolic dysfunction | 18 (25.7) | 13 (36.1)* | 5 (14.7) |
| | Pericardial Effusion | 18 (25.7) | 9 (25) | 9 (26.5) |
| **Electro-cardiography findings** | Rate (beats/min) | 78.7±15.2 | 77.7±14.9 | 79.7±15.4 |
| | QRSD>120 ms n (%) | 7 (10) | 6 (16.7)* | 1 (2.9) |
| | $^{\#}$Abnormal QTc n (%) | 28 (40) | 7 (22.4) | 21 (61.8) ** |
| | PR>200ms n (%) | 9 (12.9) | 3 (8.3) | 6 (17.6) |
| **Anthropometric/ Body composition** | History of > 5% weight loss | 34 (48.6%) | 21 (58.3) | 13 (38.2) |
| | BMI ($kg/m^2$) | 26.3± 5.6 | 27.2±4.8 | 25.7±5.6 |
| | BMI> 30 $kg/m^2$ | 16 (22.9) | 8 (22.2) | 8 (23.5) |
| | CT-defined skeletal muscle area/height$^2$ ($cm^2/m^2$) | 46.2± 10.9 | 52.4±9.0*** | 39.5±8.6 |
| | CT-defined muscle attenuation (HU) | 29.3 ±9.0 | 28.4±8.4 | 30.3±9.6 |
| | CT-defined total adipose tissue area/ height$^2$($cm^2/m^2$) | 104.6± 63.5 | 106.4±57.1 | 102.6±71.3 |
| | Sarcopenia n(%) | 38 (54.2) | 20 (55.5) | 18 (52.9) |

ACE, angiotensin-converting-enzyme; BSA, Body Surface Area; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; GLS, global longitudinal strain; LVEF, left ventricular ejection fraction; LVM, left ventricular mass; #QTc> 440ms in men or > 460ms in women; $ anemia defined as hemoglobin < 135 g/L for males and < 120 g/L for females before start of chemotherapy. $^{+}$p=0.06; $^{\&}$p=0.08. * p<0.05; *** p<0.001

**Table 5-2: Characteristics of patients in different groups**

| | Patients with no major cardiac finding (n=51) | Patients with critical findings (n=9) | Patients with DDPEF (n=10) | Patients with heart problem (critical findings or DDPEF) (n=19) |
|---|---|---|---|---|
| **Age (y)** | 64.1±7.9 | 68.3±8.6 | 67.3±7.1 | 67.7±7.6 |
| **Male n (%)** | 24 (47.1) | 7 (77.8) | 6 (60.0) | 13 (68.4) |
| **ECOG (0-1) n (%)** | 58 (95.1) | 9 (100) | 10 (100) | 19 (100) |
| **Dyspnea-MRC score** | 1.7±0.5 | 2.4±0.5** | 1.8±0.6 | 2.1±0.6* |
| **Fatigue-FACIT** | 34.8±11.6 | 30.2±12.6 | 26.1±10.4* | 28.0±11.4* |
| **Sarcopenia n (%)** | 28 (54.9) | 6 (66.7)[@] | 4 (40) | 10 (52.6) |
| **BMI (kg/m$^2$)** | 26.2±5.8 | 24.9± 3.6 | 27.6±6.1 | 26.42.1±5.1 |
| **Obesity (BMI>30 kg/m$^2$)** | 11 (21.6) | 2 (22.2) | 3 (30) | 5 (26.3) |
| **High estimated fat mass index[$] (kg) n (%)** | 23 (45.1) | 4 (44.4) | 7 (70) | 11 (57.9) |
| **Anemia** | 19 (37.2) | 6 (66.7) | 7 (70)[#] | 13 (68.4) |
| **Hypertension n (%)** | 19 (37.2) | 4 (44.4) | 5 (50) | 9 (47.4) |
| **Diabetes mellitus n (%)** | 7 (13.7) | 2 (22.2) | 1 (10) | 3 (15.8) |
| **Median Overall survival (days)** | 221 | 159 | 238 | 207 |

[@] In the patients with critical cardiovascular findings (Table 2), among the first 7 patients with impaired LVEF and symptoms of classic heart failure, 5 patients were sarcopenic, and one patients was borderline sarcopenic (SMI=54 cm$^2$/m$^2$, zscore=0.2). Only one patient had non-depleted skeletal muscle index. DDPEF, diastolic dysfunction with preserved ejection fraction. [$] CT-defined estimated fat mass indexed by height$^2$ > sex specific median value (7.6 kg/m$^2$ for females and 7.8 kg/m$^2$for males). # p=0.06; *p<0.05, **p<0.01

**Table 5-3: Characteristics of patients◊ with critical cardiovascular findings**

| Study #, sex, Age, *BMI* | Risk Factors | Drug history | LVEF (%) | GLS (%) | Diastolic Dysfunction | ECG | Known cardiac disease | Known CHF in recent year | Overall Survival (days) | Others |
|---|---|---|---|---|---|---|---|---|---|---|
| 09, F, 56, *23* | Dyslipidemia, smoking | Statins | 40.9 | 13.0 | Grade I | Sinus tachy-cardia | No | No | 109 | Sarcopenic; FACIT-F=41; MRC=2 |
| 10, M, 61, *30.1* | HTN, DM II, smoking | Beta-blocker, spironolactone | 42.0 | 7.0 | Grade II | AF | AF | No | 159 | FACIT-F= 10; MRC=3 |
| 12, M, 79, *31.1* | DM II, smoking | Beta-blocker, ACEI | 47.0 | 15.6 | Grade I | RBBB | MI | No | 153 | Borderline sarcopenic (SMI=54, zscore=0.2); FACIT-F= 21; MRC=3 |
| 17, M, 67, *22.9* | Smoking | No | 32.2 | 11.6 | Grade I | IVCD | No | No | 156 | Main treatment plan cancelled Sarcopenic ; FACIT-F=31; MRC=2 |
| 53,M,68, *20.3* | Smoking | Beta-blocker, statins | 35.4 | 15.2 | Grade I | Ischemic pattern | MI, ICM | Yes | >365 | Sarcopenic; FACIT-F= 44; MRC=2 |
| 71, M, 84, *24.6* | HTN, smoking | Beta-blocker, ACEI, statins | 44.4 | 17.5 | Grade I | RBBB | MI | No | 253 | Sarcopenic; FACIT-F= 44; MRC=2 |
| 38, F, 64, *24.4* | Dyslipidemia, smoking | Statins | 46.7 | 18.8 | Grade I | Normal | No | No | >365 | Sarcopenic; FACIT-F= 33; MRC=2 |
| 66, M, 69, *25.7* | HTN, Dyslipidemia, smoking | ACEI, statins | 52.1 | N/A | Grade I | Normal | CAD | No | 207 | **PE**, admitted for drainage; FACIT-F= 14; MRC=3 |
| 29, M, 67, *23.6* | HTN, smoking | ARB | 55 | 18.1 | Negative | Ischemic pattern | No | No | 97 | **Severe PHTN**; Severe RVD; Sarcopenic; FACIT-F= 34; MRC=3 |

ACEI, angiotensin-converting-enzyme inhibitor; AF, atrial fibrillation; ARB, Angiotensin receptor blockers; DM II, diabetes mellitus type II; FACIT-F, The Functional Assessment of Chronic Illness Therapy-Fatigue scale [score]; HTN, hypertension; ICM, ischemic cardiomyopathy; MI, myocardial infarction; MRC, medical research council shortness of breath scale [score]; PE, pericardial effusion; RBBB, right bundle branch block; RV, right ventricular; SMI, skeletal muscle indexed by height $^2$. ◊ *All these patients ECOG 0-1*

**Table 5-4: Characteristics of 10 patients showing diastolic dysfunction with preserved ejection fraction**

| Study #, sex, Age, *BMI* | Risk Factors | Drug history | LVEF (%) | GLS (%) | Diastolic Dysfunction | ECG finding | Known cardiac disease | Overall Survival (days) | Others |
|---|---|---|---|---|---|---|---|---|---|
| 04, F,70, *31.4* | No | No | 59 | 22 | Grade II | Ischemic pattern | No | > 365 | Sarcopenic; FACIT-F= 48; MRC=1 |
| 5, M,71, *23.1* | Dyslipidemia, smoking | No | 61 | 17 | Grade II | Normal | No | 51 | FACIT-F= 13; MRC=2 |
| 11, F, 73, *20.0* | No | Beta-blocker, statins | 53 | 18 | Grade I | Ischemic pattern | MI | 290 | FACIT-F= 30; MRC=2 |
| 13, M, 56, *39.8* | Dyslipidemia, HTN, smoking | Beta-blocker, ACEI, statins | 60.3 | 16.9 | Grade I | LA abnormality | MI | 226 | FACIT-F= 28; MRC=3 |
| 24, F, 64, *27.5* | Dyslipidemia, HTN, smoking | Beta-blocker, statins | 58.8 | 21.5 | Grade II | APC | No | > 365 | FACIT-F= 29; MRC=2 |
| 43,M,65, *24.6* | Smoking | Statin, ARB | 52.4 | 15.4 | Grade I | Normal | MI | 251 | FACIT-F= 14; MRC=2 |
| 49, M, 71, *29.8* | HTN, smoking | ARB | 54.4 | 18.30 | Grade I | RBBB | DDPEF | 43 | Sarcopenic; FACIT-F= 32; MRC=2 |
| 51,M,55, *19.9* | Smoking | No | 51 | 15.8 | Grade I | Normal | No | 141 | Sarcopenic; FACIT-F= 19; MRC=2 |
| 58, M, 75, *28.1* | Dyslipidemia, HTN | Beta-blocker, ACEI, statins | 59 | | Grade I | Ischemic pattern | No | 175 | MRC=1 |
| 61, F, 73, *32.1* | Dyslipidemia, HTN, DM II, smoking | ACEI, statins | 63 | 20 | Grade II | Normal | No | 266 | Sarcopenic; MRC=1 |

ARB, Angiotensin receptor blockers; APC, atrial premature complexes; DDPEF, diastolic dysfunction with preserved ejection fraction; FACIT-F, The Functional Assessment of Chronic Illness Therapy-Fatigue scale [score]; HTN, hypertension; MI, myocardial infarction; RBBB, right bundle branch block; MRC, medical research council shortness of breath scale [score]

**Table 5-5: Major information about three discussed anti-cachexia clinical trials (Phase III)**

| | **POWER** | **ROMANA** | **MENAC** | **Our study** |
|---|---|---|---|---|
| **Included patients** | Stage III or IV NSCLC | Stage III or IV NSCLC | Stage III or IV NSCLC, pancreatic adenocarcinoma (stage III or IV) or non-operable cholangiocarcinoma | Stage IV NSCLC |
| **Excluded BMI** | BMI>32 kg/m$^2$ | BMI>30 kg/m$^2$ | BMI>30 kg/m$^2$ | None, 16 (22.9%)> 30 kg/m$^2$ ; 10 (14.3%) > 32 kg/m$^2$ |
| **Time of intervention** | Before start of 1$^{st}$ line chemotherapy | Before or after chemotherapy and/or radiation therapy | Before first or second line anticancer therapy | Before start of 1$^{st}$ line chemotherapy |
| **Performance status** | ECOG ≤1 | ECOG ≤2 | Karnofsky score>70 | ECOG ≤2; 67 (95.7%) ECOG 0-1 |
| **Cardiovascular considerations (exclusion criteria)** | Clinically concurrent illness that would interfere with protocol (investigator judgment); Uncontrolled hypertension, CHF, or angina; Baseline stair climb time ≥30 s (mean of two stair climb tests) | Uncontrolled diabetes mellitus; Other clinical diagnosis, ongoing or intercurrent illness that in the Investigator's opinion would prevent the patient's participation | Positive history of heart disease, i.e., severe (NYHA class III orIV) CHF, uncontrolled hypertension, history of previous MI, unstable angina, coronary revascularization, uncontrolled arrhythmia, and cerebrovascular accident | - |

BMI, body mass index; CHF, congestive heart failure; ECOG, Eastern Cooperative Oncology Group; MENAC, Multimodal Intervention for Cachexia in Advanced Cancer Patients Undergoing Chemotherapy; NYHA, New York Heart Association; NSCLC, non-small cell lung cancer; POWER, Clinical Development Program of Enobosarm, a Selective Androgen Receptor Modulator, for the Prevention and Treatment of Muscle Wasting in Cancer Patient; ROMANA, Anamorelin in patients with non-small cell lung cancer and cachexia.

**CHAPTER 6:**

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# Concurrent depletion of skeletal muscle, fat and left ventricular mass in patients with cirrhosis of the liver

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## 6.1 Letter to the editor

Dear Editor

Evidence for cardiac atrophy has now been demonstrated multiple times in animal models of cancer cachexia [2]; however, prospective clinical studies to detect an active process of cardiac atrophy in patients with cachexia have not yet been undertaken. Nevertheless if this were to occur, it would be expected that in patients with diseases associated with cachexia, a very low cardiac mass would coincide with the presence of severe skeletal muscle depletion (i.e., *sarcopenia*) as well as depletion of the fat mass. To test this conjecture, we evaluated left ventricular mass determined by echocardiography and body composition [skeletal muscle and total adipose tissue] by computed tomography cross sectional images at the level of the 3$^{rd}$ lumbar vertebra [68], in a population of patients with liver cirrhosis, 50% of whom had concurrent hepatocellular carcinoma [n=100]. These patients were candidates for liver transplantation, and had routine evaluations with echocardiography and computed tomography, from which left ventricular mass and body composition can be derived. Cirrhotic patients are at risk for weight loss and sarcopenia, which associate with mortality [67, 68]. Cross sectional areas of skeletal muscle and total adipose tissue were used to calculate estimated total body fat free mass and fat mass respectively [131]. All parameters (skeletal muscle, total adipose tissue, fat free mass, fat mass) were normalized for stature (divided by height in $m^2$). Patients were categorized based on left ventricular mass/height$^2$ (left ventricular mass index): **Low** left ventricular mass index [>1 standard deviation below sex-specific mean value, n=17], **Average** left ventricular mass index [within ±1 standard deviation of sex-specific mean value, n=66], and **High** left ventricular mass index [>1 standard deviation above sex-specific mean value, n=17] (**Table 6-1**).

As patients were candidates for a major surgery (liver transplantation), all of them presented with normal left ventricular ejection fraction (>50%) and none showed any echocardiographic evidence of myocardial infarction or severe valvular disease. Mean age, sex distribution, diastolic dysfunction, main etiology of cirrhosis, serum creatinine, albumin and bilirubin and prevalence of hepatocellular carcinoma were not different among the three groups (**Low, Average & High** left ventricular mass index ) (**Table 6-1**). **Low** left ventricular mass index group included individuals with absolute left ventricular mass ranging from 57-124 g (♂) and 88-112 g (♀). Overall *sarcopenia* [68] was more prevalent in patients with **Low** left ventricular mass index compared to the patients with **Average** left ventricular mass index [70.6% versus 27.3%; OR=6.4; 95% CI, 1.9-20.7; p=0.002]. Five (29%) patients in the **Low** left ventricular mass index group were extremely sarcopenic (skeletal muscle index <39 $cm^2/m^2$ ♂ and skeletal muscle index <34 $cm^2/m^2$ ♀, while only two (3%) of patients with **Average** left ventricular mass index group were extremely sarcopenic (p=0.003, Fisher's Exact Test). Fat depletion (total adipose tissue index <sex-specific median value) tended to be more prevalent in patients with **Low** left ventricular mass index (70.6%) versus the **Average** left ventricular mass index (43.9%) (p=0.08). Collectively, these data suggest concurrent depletion of skeletal muscle, total adipose tissue and left ventricular mass.

The **High** left ventricular mass index group deserves separate consideration. As expected for a group of polymorbid elderly patients, this population with cirrhosis includes some individuals with evidence of cardiac hypertrophy. The **High** left ventricular mass index group appeared to show some manifestations of cardiac cachexia. Overall sarcopenia was more prevalent in patients with **High** left ventricular mass index versus **Average** left ventricular mass index [52.9% versus 27.3%; OR=3.0; 95% CI, 1.1-8.9; p=0.04]. Four (23.5%) patients in the **High** left ventricular mass index group were extremely sarcopenic (skeletal muscle index <39 $cm^2/m^2$ ♂ and skeletal muscle

index <34 $cm^2/m^2$ ♀). Over the entire population there was a weak correlation between left ventricular mass and computed tomography-defined skeletal muscle area (r=0.37; p<0.001), and this was not surprising given that patients with the largest hearts could be of high or average muscularity, sarcopenic or indeed extremely sarcopenic. Also, total adipose tissue correlated weakly with left ventricular mass (r=0.26; p=0.009). Both these relationships were weaker than those reported in the general population (r=0.5 for lean body mass and r=0.6 for fat) [238, 239] perhaps because chronic catabolic disease results in additional variation in organ mass not present in healthy individuals. We recently discussed that in human patients with chronic hypercatabolic diseases both atrophied and hypertrophied hearts could be significantly associated with severe muscle depletion [2]. The association between muscle and fat depletion and both extreme ends of cardiac remodeling (atrophy and hypertrophy) in diseases associated with cachexia need to be tested in larger scale studies with specific focus on related underlying mechanisms.

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**Conflict of interest statement**

SMRKB, HB, SG, AML and VEB declare that they have no conflict of interest.

**Table 6-1: Distribution of Left Ventricular Mass Index and Cachexia Characteristics**

| | Left Ventricular Mass Indexed by height$^2$ | | |
|---|---|---|---|
| | **Low LVMI$^{\#}$ (n=17)** | **Average LVMI$^{\$}$ (n=66)** | **High LVMI$^{@}$ (n=17)** |
| **Age (y) (95% CI)** | 57.5±8.5; (53.1-61.8) | 58.0±9.0; (55.7-60.2) | 56.7±6.5; (53.4-60.0) |
| **Male (%)** | 10 (58.8) | 43 (65.2) | 12 (70.6) |
| **BMI (kg/m$^2$) (95% CI)** | 24.2±5.2; (21.6-26.9) | 27.0±5.4; (25.7-28.4) | 25.7±7.1; (22.1-29.4) |
| **LVM (g) (95% CI)** | 95.8±16.5*** (87.3-104.3) | 164.9±25.8 (158.6-171.3) | 221.7±36.0××× (203.3-240.2) |
| **LVMI (g/m$^2$) (95% CI)** | 33.4±7.2*** (29.7-37.1) | 57.7±7.3 (55.8-59.5) | 77.7±10.7××× (72.2-83.2) |
| **LVM indexed by BSA (g/m$^2$) (95% CI)** | 52.3±11.7*** (46.3-58.3) | 87.3±11.7 (84.4-90.1) | 119.8±13.1××× (113.1-126.5) |
| **Normal diastolic function n (%)** | 8 (47.1) | 35 (53.0) | 9 (52.9) |
| **Hypertension (%)** | 1 (5.9) | 8 (12.3) | 2 (11.8) |
| **Diabetes Mellitus (%)** | 3 (17.6) | 11 (16.7) | 2 (11.8) |
| **CT-defined SMI (cm$^2$/m$^2$); (95% CI)**<br>**Men**<br>**Women** | 42.7±7.5*** ; (38.9-46.6)<br>♂44.7 ±5.5***<br>♀39.9± 9.3*** | 51.5±8.2; (49.5-53.5)<br>♂54.2±7.1<br>♀46.4±7.7 | 49.3±10.7; (43.9-54.9)<br>♂51.3 ±8.8<br>♀44.8 ±14.4 |
| **CT-defined TATI (cm$^2$/m$^2$) (95% CI)** | 69.5±61.1 (38.1-100.9) | 107.8± 70.1 (90.5-125.0) | 113.9±71.8 (77.0-150.8) |
| **Estimated FFMI (kg/m$^2$) (95% CI)** | 14.8±2.3*** (13.6-16) | 17.5±2.4 (16.9-18.1) | 16.8±3.2 (15.2-18.5) |
| **Estimated FMI (kg/m$^2$); (95% CI)** | 6.4±2.7 (4.9-7.7) | 8.1±3.0; (7.3-8.7) | 8.3±3.0; (6.7-9.8) |
| **Sarcopenia $^{£}$ (%)** | 12 (70.6)** | 18 (27.3) | 9 (52.9) × |
| **Fat depletion$^{€}$ (%)** | 12 (70.6) | 29 (43.9) | 8 (47.1) |
| **Creatinine (µmol/L) (95% CI)** | 138.4±155.1 (55.7-221.0) | 85.2±36.4 (76.3-94.2) | 91.1±38.4 (71.3-110.8) |
| **Bilirubin (µmol/L) (95% CI)** | 152.0±233.4 (27.5-276.3) | 118.8±223.3 (63.9-173.7) | 134.3±154.5 (54.9-213.8) |
| **Albumin (g/L); (95% CI)** | 35.1±6.0; (31.9-38.2) | 34.2±5.7; (32.8-35.6) | 35.2±9.4; (30.3-40.0) |
| **Hepatocellular carcinoma n (%)** | 9 (52.5) | 31 (47.0) | 10 (58.8) |
| **Hepatitis C virus (etiology) n (%)** | 7 (41.2) | 36 (54.5) | 8 (47.1) |

$^{\#}$Low LVMI; > 1 SD below of sex-specific mean value of LVMI; $^{\$}$ Average LVMI; within ±1 SD of sex- specific mean value of LVMI ; $^{@}$High LVMI; > 1 SD above sex-specific mean value of LVMI.

$^{£}$ Sarcopenia, skeletal muscle depletion based on CT findings as described previously [68] $^{€}$ Fat depletion, TATI< sex-specific median value of TATI. BMI, body mass index; BSA, body surface area; CT, computed tomography; FFMI, fat free mass indexed by height$^2$; FMI, fat mass indexed by height$^2$; LVMI, left ventricular mass indexed by height$^2$; SMI, skeletal muscle indexed by height$^2$; TATI, total adipose tissue indexed by height$^2$. Values (quantitative and qualitative) of Low LVMI group versus Average LVMI group: *** p<0.001; **p<0.01 Values of High LVMI group versus Average LVMI group: ××× p<0.001; ×p<0.05

**CHAPTER 7:**

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# High fat mass associates with occurrence of targeted therapy-induced left ventricular ejection fraction reduction in patients with renal cell carcinoma

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## 7.1 Abstract


**Background & Aims:**

Recent research suggests that variations of skeletal muscle and fat predict the severity of chemotherapy-induced toxicities in patients with renal cell carcinoma. *Cardio-toxicity* has not been evaluated in this context.

**Methods:**

In this study we considered 47 renal cell carcinoma patients who participated in randomized clinical trials of sorafenib or sunitinib (i.e., targeted therapy). To capture *cardio-toxicity,* multi gated acquisition scan-defined left ventricular ejection fraction (LVEF) tests (at least 3 tests over 1 year of treatment) were abstracted. Computed tomography cross-sectional images were analyzed before start of targeted therapy and at 1 year to define skeletal muscle and fat at baseline and changes over time concurrent with multigated acquisition scan-defined LVEF measurement.

**Results:**

Multigated acquisition scan-defined *cardio-toxicity* (usually fall in LVEF >10% to an absolute LVEF<55%) occurred in 8/47 (17%) patients over 1 year of targeted therapy (all were male). Percentage of patients with high fat mass (baseline computed tomography-defined total adipose tissue/ indexed by height$^2$ greater than the sex-specific median value) was higher among patients with *cardio-toxicity* versus patients without *cardio-toxicity* [7 (87.5%) versus 16 (41.0%); p=0.02]. The percentage of skeletal muscle loss in patients with *cardio-toxicity* was higher than the patients without *cardio-toxicity* [median of loss (%) -7 versus 0 respectively; p=0.04].

**Conclusion:**

C*ardio-toxicity* in renal cell carcinoma patients might be associated with high fat mass. This finding is distinct from prior observations that low body weight and sarcopenia associated with non-cardiac toxicities of targeted therapies. Concurrence of skeletal muscle loss over time and development of *cardio-toxicity* is reported for the first time.

**Key words:** body composition, cardio-toxicity, skeletal muscle, fat

## 7.2 Introduction

In renal cell carcinoma patients undergoing targeted therapy with oral multi-targeted receptor tyrosine kinase inhibitors (sorafenib or sunitinib) a sub-population with increased susceptibility to dose-limiting treatment toxicity was identified. This group was typified by concurrent low body mass index (BMI) and sarcopenia [98, 99] and had more gastrointestinal, cutaneous and haematological dose limiting toxicity. *Cardio-toxicity* was not specifically assessed in these investigations however this would be of interest because targeted therapies are potentially *cardio-toxic* agents. We therefore undertook to evaluate renal cell carcinoma patients under targeted therapy for body composition using computed tomography and left ventricular ejection fraction (LVEF) [240] by Multi Gated Acquisition scan.

## 7.3 Methods:

This review was approved by the Health Research Ethics Board of Alberta. Subjects were Alberta residents who participated in prospectively conducted randomized clinical trials [NCT00326898, NCT00903175, NCT00720941, NCT00083889] of renal cell carcinoma therapy. Patients on study arms treated with either sorafenib or sunitinib with either metastatic (N=24) or localized renal cell carcinoma (N=23) were included. All randomized clinical trials excluded patients with any prior systemic anti-cancer therapy, major recent cardiovascular events and poorly controlled hypertension. Determination of LVEF by multigated acquisition scan and CT imaging were mandated within the RCT protocols. All analyzed patients had at least 3 multigated acquisition scan over 1 year of study (~90% had ≥4 multigated acquisition scans). *Cardio-toxicity* was defined as a fall in LVEF >10% to an absolute LVEF<55% [240]. Skeletal muscle and total adipose tissue cross sectional area were quantified in axial computed tomography images, as

described [69, 129]. Estimated whole body free fat mass and fat mass based on computed tomography-defined cross sectional area were calculated [131]. Previously recognized criteria for sarcopenia in cancer patients were used [computed tomography-defined skeletal muscle area (at 3rd lumbar vertebra level) indexed by height$^2$: <52.4 cm$^2$/m$^2$ for males and < 38.5 cm$^2$/m$^2$ for females] [89].

We used SPSS version 24 (SPSS Inc, Chicago, IL, USA) for statistical analysis. Data were evaluated for normality (Kolomogorov-Smirnov test). For normally distributed data mean and standard deviation and for non-normally distributed data median and interquartile ranges are provided. In our comparisons, t-tests and chi-square tests were used for quantitative and qualitative variables. Univariate and multivariate binary logistic analysis was used to determine the odds ratio (OR) of development of *cardio-toxicity*.

**7.4 Results:**

A total of 59 participants in RCTs of targeted therapy were identified. A group (n=12) were excluded because they did not complete 12 months of treatment (non-compliance, death) and were missing multigated acquisition scan and/or computed tomography scans. Included patients (n=47) (**Table 7-1)** completed 12 months of treatment and had ≥ 3 multigated acquisition scan over that time in addition CT at baseline and 12 months. Included patients did not encounter major grade 3 or 4 toxicity, drug discontinuation or death.

*Cardio-toxicity* appeared in 8/47 (17%) patients, all of these were male (**Table 7-2)** (n=2 had localized renal cell carcinoma and n=6 had metastatic renal cell carcinoma). Baseline sarcopenia % was not different in patients with and without *cardio-toxicity*. High fat mass (defined as total adipose tissue /height$^2$ greater than the sex-specific median value) was a feature of 7 / 8 (87.5%)

of patients who experienced *cardio- toxicity*, while 16 / 39 (41.0%) of patients without *cardio-toxicity* (p=0.02) (unadjusted OR 10.1 (95% CI 1.12 to 89.9), p=0.03) (**Table 7-2, Fig.7-1**). Hypertension, diabetes mellitus, prior history of coronary artery disease, and current use of cardiovascular medications were not related to *cardio-toxicity* (**Table 7-2**). In multivariate analysis *cardio-toxicity* was independently related to high fat mass (adjusted for age (> 61 y/o)) [OR 9.5 (1.1 to 86.0), p=0.04]); this was also true when further adjusted for sex (OR= 9.3 (1.1 to 86.6), p=0.04) and when adjusted for use of statin therapy [OR 9.8 (1.3 to 93.4), p=0.047]. A model with high fat mass/age/sex and baseline sarcopenia showed a trend for high fat mass as a predictor of *cardio-toxicity* [OR 8.7 (0.92 to 81.8), p=0.06].

From baseline to 1 year of treatment the rate of muscle loss in patients with *cardio-toxicity* was higher than the patients without *cardio-toxicity* [median loss -7.0% versus 0%, respectively; p=0.04]. In patients whose muscle loss over 12 months was <10 $cm^2$ (~1.5 kg muscle on a whole body basis) the rate of *cardio-toxicity* was 5.7%, however if the muscle loss was >10 $cm^2$ the rate of *cardio-toxicity* was 50% (p=0.0002). Computed tomography-defined total adipose tissue cross sectional area was stable over time (baseline: 225.8±33.3 $cm^2$ versus 1 year later: 226.9±33.5 $cm^2$ p=0.10) and *cardio-toxicity* did not associate with changes in fat area (p=0.71).

**7.5 Discussion**

High fat mass at the initiation of targeted therapy might be associated with the development of *cardio-toxicity* in our study. Renal cell carcinoma is a cancer associated with obesity and the mean BMI (30.5±6.4 $kg/m^2$) and mean estimated fat mass (29.5±9.5 kg) of the included patients was high. *Cardio-toxicity* associated with high fat mass and the patients who experienced this symptom had a mean estimated fat mass of 37.8±3.5 kg. The following speculations may be made concerning these results. The main influence of high fat mass on the heart is hypertrophic

remodeling and the presence of this pathology preceding cancer treatment may sensitize the heart to the toxic effects of antineoplastic therapy. While other studies did not measure fat mass, obesity (higher BMI) was related to trastuzumab -induced *cardio-toxicity* (LVEF measured by echocardiography or multigated acquisition scan) in breast cancer patients [241, 242].

The association between high fat mass, development of *cardio-toxicity* and muscle loss cannot currently be explained based on available data, and requires newly designed prospective studies. One possible connector is inflammation which has documented associations with obesity, with *cardio-toxicity* and with muscle loss. Augmented inflammatory status in obesity and also *cardio-toxicity* has been discussed in cardiology context. Association between *cardio-toxicity* and muscle loss (i.e., cancer cachexia) has been speculated [2].

These findings should be repeated / validated in larger longitudinal studies. Small sample size and type 2 error is possibly a limitation of this study. The development of *cardio-toxicity* was seen only in male patients, and a larger sample of women would help to resolve whether this occurs in both sexes. Temporal LVEF measurements were performed in the context of clinical trials, which allowed for the collection of these data. It is not currently the standard of care to monitor the LVEF during treatment of renal cell carcinoma.

### 7.6 Conclusion

Specific body composition features associate with targeted therapy-related *cardio-toxicity* in renal cell carcinoma patients. High fat mass at baseline was possibly associated with development of reduced LVEF during 1 year of anticancer therapy. Concurrent development of *cardio-toxicity* and muscle loss over time was reported for the first time in this work.

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**Statement of Authorship**

SMRKB performed data collection and data analysis; HB, PV and SN provided advice for study design and data analysis; VB mentored all aspects of the study

**Conflict of Interest Statement**

The authors declare that there are no conflicts of interest

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**Table 7-1: Baseline patient information**

| | **All patients (N=47)** |
|---|---|
| **Age (y)** | 61.3±9.2 |
| **Sex (male) n (%)** | 36 (76.6) |
| **Hypertension n (%)** | 6 (12.8) |
| **Diabetes Mellitus n (%)** | 2 (4.3) |
| **Coronary artery disease[@] n (%)** | 3 (6.3) |
| **Current ACE inhibitors or ARBs n (%)** | 6 (12.8) |
| **Current Beta blockers n (%)** | 7 (14.9) |
| **Current Statins n (%)** | 9 (19.1) |
| **Body mass index (kg/m$^2$)**<br>Male<br>Female | 30.5±6.4<br>30.5±5.5<br>30.8±9.1 |
| **CT – defined Skeletal Muscle Area (cm$^2$)**<br>Male<br>Female | 157.3±34.3<br>169.1±28.4<br>118.6±20.6 |
| **Estimated total body fat free mass (kg)***<br>Male<br>Female | 53.2±10.3<br>56.8±8.5<br>41.6±6.2 |
| **Sarcopenia* n (%)**<br>Male n (%)<br>Female n (%) | 16 (34.0)<br>14 (38.9)<br>2 (18.2) |
| **CT- defined Total Adipose Tissue Area (cm$^2$)**<br>Male<br>Female | 431.6 (291.2-563.5)<br>442.9±211.5<br>419.4±277.2 |
| **Estimated total body fat mass (kg) ****<br>Male<br>Female | 29.5±9.5<br>29.8±8.9<br>28.8±11.6 |

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blockers [@] One person had myocardial infarction, one had coronary angioplasty and one had coronary artery bypass graft (all three events were non-recent). * Using sex-specific cut points as defined by Prado et al. [89] **Estimated according to Mourtzakis et al. [131].

**Table 7- 2: Patient features associated with cardio-toxicity**

| | | Cardio-toxicity n=8 (17.0%) | Non-cardio-toxicity N=39 (83%) | p-value | Unadjusted ORs (95% CI) | p-value | Adjusted ORs (95% CI) | p-value |
|---|---|---|---|---|---|---|---|---|
| **Age (y)** | | 62.8±9.6 | 60.9±9.2 | 0.59 | - | - | - | - |
| **Age > 61 y**[@] | | 5 (62.5) | 18 (46.2) | 0.46 | 1.9 (0. 4 to 9.2) | 0.41 | 1.6 (0.3 to 8.2) | 0.60 |
| **Female n (%)** | | 0(0) | 11 (28.2) | 0.17 | 0 (0 to undetermined) | 1.0 | - | - |
| **Body mass index (kg/m$^2$)** | | 32.6±3.6 | 30.1±6.8 | 0.32 | - | | - | - |
| **Cardiovascular comorbidities** | **Diabetes Mellitus n (%)** | 0 (0) | 2 (5.1) | 1.0 | 0 (0 to undetermined ) | 1.0 | - | - |
| | **Hypertension n (%)** | 1 (12.5) | 5 (12.8) | 1.0 | 0.97 (0.1 to 0.96) | 0.97 | - | - |
| | **Coronary artery disease n (%)** | 0 (0) | 3 (7.7) | 1.0 | 0 (0 to undetermined) | 1.0 | - | - |
| **Cardiovascular medications** | **ACE inhibitors or ARBs n (%)** | 1 (12.5) | 5 (12.8) | 1.0 | 0.97 (0.1 to 0.96) | 0.97 | - | - |
| | **Beta blockers n (%)** | 1 (12.5) | 6 (15.4) | 1.0 | 0.79 (0.1 to 7.6) | 0.84 | - | - |
| | **Statins n (%)** | 2 (25) | 7 (17.9) | 0.64 | 1.5 (0.25 to 9.2) | 0.65 | - | - |
| High fat mass* n=23 | | 7(87.5%) | 16 (41.0%) | 0.02 | 10.1 (1.12 to 89.9) | 0.03 | 9.5 (1.1 to 86.0) | 0.04 |
| **Mean estimated fat mass (kg)** | | 37.8±3.5 | 37.1±7.3 | 0.58 | - | | - | - |
| **Low fat mass* n=24** | | 1 (12.5%) | 23 (59.0%) | - | - | | - | - |
| **Mean estimated fat mass (kg)** | | 18.9 | 25.1±8.7 | - | - | | - | - |
| **Total n= 47 (100%)** | | 8 (100%) | 39 (100%) | - | - | | - | -- |
| **Sarcopenic**n=16 (34.0%)** | | 2 (25%) | 14 (35.9%) | 0.69 | 0.6 (0.11 to 3.4) | 0.56 | - | - |
| **Non-Sarcopenic n=31 (66.0%)** | | 6 (75%) | 25 (64.1%) | 0.60 | - | - | - | - |
| **Total n= 47 (100%)** | | 8 (100%) | 39 (100%) | | - | - | - | - |

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blockers. [@] median of age=61 y; *High and Low fat mass categories were split at the sex-specific median values of total adipose tissue indexed by height$^2$: Males:>153.2 cm$^2$/m$^2$; Females: >128.0 cm$^2$/m$^2$
** Sex-specific cut points as defined by Prado et al. [89]

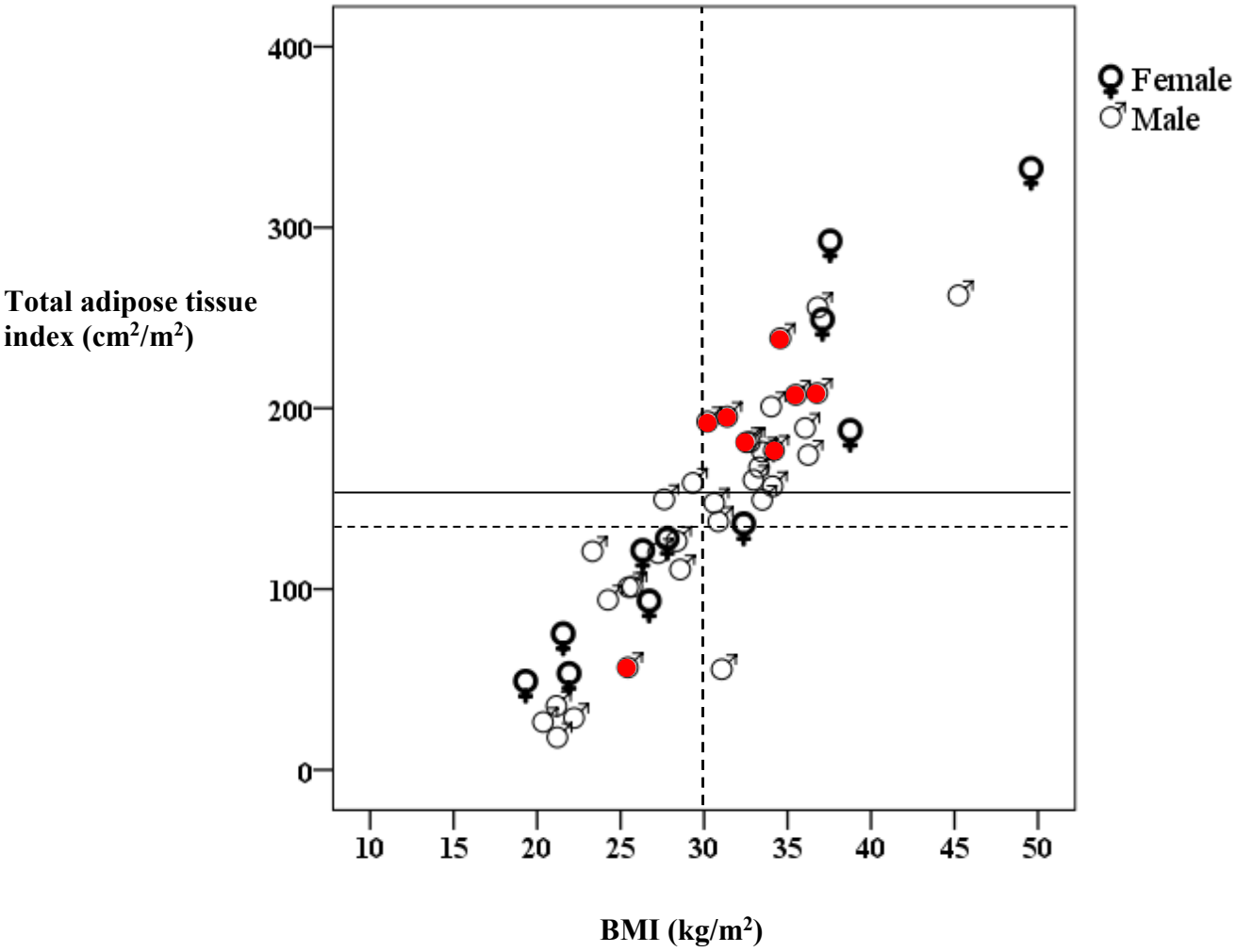


**Figure 7-1**. Distribution of Total Adipose Tissue Index versus BMI for males and females. Vertical dotted line, body mass index >30 kg/m$^2$; horizontal dotted line, represents TAT index 128.0 cm$^2$/m$^2$ (median of total adipose tissue index for females); horizontal solid line, represents TAT index 153.2 cm$^2$/m$^2$ (median of total adipose tissue index for males). Red color shows the patients with cardio-toxicity .

**CHAPTER 8:**

# Discussion and Conclusion

## 8.1 Future work- confirming cardiac atrophy

As our major longitudinal work was a first time demonstration of cancer-cachexia associated cardiac atrophy in clinical context, it is necessary that our findings to be confirmed and further evaluated in the future investigations. To confirm the quantitative findings, cardiac magnetic resonance imaging (CMRI) is a proper choice. Application of echocardiography versus CMRI in outcome studies, for measurement and follow up of left ventricular mass in hypertrophic or dilated cardiomyopathy, has been encouraged due to its feasibility and low cost [243]; however, precision of CMRI (two times more than echocardiography) [243] and its inter-study reproducibility [244] were superior to echocardiography in assessment of left ventricular mass in aforementioned cardiac disorders. Cardiac MRI is known to be a gold standard tool for measurement of cardiac volumes, wall thickness and function in the *heart failure* setting [245]. Cardiac magnetic resonance imaging has been used for cardiac atrophy portraying through bed rest and space flight research studies [207, 246], however, CMRI in detection of cancer cachexia-induced left ventricular mass atrophy has never been used. Moreover, superiority of CMRI to echocardiography is unknown in this context.

Our successful endeavor of a single center clinical study, as well as available experience of study design would be a reasonable basis for initiation of a CMRI-based project. Currently we cannot generalize our findings to all cancer types and this research question should be tested in each cancer separately. In this track of research we should be confident that the standard of care chemotherapy agent is not cardio-toxic which enables us to isolate the relation between cancer

cachexia and cardiac atrophy. Also, the possible effects of standard of care chemotherapy agent on cachexia should be known, as some of these drugs are pro-muscle wasting *per se* [69, 247, 248].

Furthermore, continuation of imaging (echocardiography or CMRI) until the latest days of cancer trajectory may clarify more dimensions of cardiac atrophy progression in cancer cachexia. Obviously, identification of loss *over time* is the solely available approach at this time as clear cut off values of cardiac atrophy, to be exploited in single time measurement studies, does not exist at this time. We witnessed only a slight decrease of LVEF in about 4 months; however, continuation of measurements approaching death may clarify if there is any further significant decline in LVEF. Animal models of cancer cachexia also proved that LVEF is spared until the end days of cancer trajectory [3].

Additionally, the relation between baseline occult findings (refer to chapter 5) and atrophic consequences of the heart (refer to chapter 4) and actual functional tests such as stair climbing test and hand grip should be evaluated in future.

## 8.2 Major concerns in clinical trials design

### *8.2.1 Notable heterogeneity, possible confounding factors!*

In the present paradigm of conduction of clinical trials, functional endpoints have consistently failed [50]. We discovered a group of unnoticed possible confounder variables (heart failure, dyspnea, fatigue and anemia) in metastatic non-small cell lung cancer patients, a group of patients that are currently of major focus in anti-cachexia clinical trials. If functional endpoints continue to be required by regulatory agencies for approval, we should consider further clinical longitudinal cohorts to test the relation between these function-related confounders and variability in response to anti-cachexia therapeutics. If these important parameters were considered previously, *post-hoc* analysis would have clarified the relation between these confounders and failed response to

functional endpoints. ROMANA studies (used anamorelin in non-small cell lung cancer patients, see chapter 5) performed a substantial post-hoc analysis and found the effects of sex, age, history of weight loss, and ECOG (0-1 versus 2) on improvement of lean body mass [210]; however, heart failure status was not assessed in this study [210]. Association between heart failure and impaired hand grip (endpoint in ROMANA studies) was previously shown in cardiology context [202]. We found heterogeneity in a group of patients who were infinitely more homogenous than all recent Phase III anti-cachexia trials (see chapter 5): Our study was single center; all baseline measurements occurred before first line therapy; patients had one type of tumour, all were metastatic and underwent one type of therapy; also they showed consistent limited ECOG scores.

Another important understanding from our cohort was the matter of missing data in cancer cachexia trials. In cancer therapeutic trials, mortality is an outcome; however, in cancer cachexia trials, death-related missing data results in scientific bias and increased cost. Prognostic models have been extensively argued in cancer patients; high CRP is known to be an important prognostic factor for non-small cell lung cancer patients [249]. CRP, as a feasible prognostication factor of different advanced cancers has been discussed comprehensively, moreover it is associated with cancer cachexia progression [58, 250, 251]. Prognostication algorithms using some other factors such as albumin [252] or combined CRP and albumin levels (Glasgow Prognostic Score) showed to be useful [253]. We recommend to use these algorithms in anti-cachexia clinical trial designs to exclude the patients with a high probability of short term survival. In our study, 20 patients could not attend the second time point of measurements (3.5-4 months after baseline) due to death or poor conditions (completely bed ridden at home or remote hospitals). Sixteen (80%) out of these 20 patients baseline CRP was > 10 mg/L; however, only 21/50 (42%) patients who reached the second time point had CRP> 10 mg/L ($p=0.007$; median 34.3 mg/L versus 7.9 mg/L respectively,

p=0.003) (data not shown). Also, baseline CRP> 10 mg/L was associated with overall survival (p<0.001) (data not shown).

*8.2.2. Ambiguous points in clinical trials*

a) There is no definite evidence that power and speed of a stairclimbing test is the best functional endpoint. We should consider different methodologies/ functionality measures such as 6-minute walk and sit-to-stand to find the most appropriate functional test with sufficient sensitivity to be useful as an endpoint.

b) Regarding the influence of anti-cachexia experimental agents, we should be able to provide a clear answer to this questions: Should our intervention result in improvement or at least preservation of the tissues? Furthermore, the utility of cachexia therapy to alter treatment toxicity, tumour response and survival remains unproven.

c) A successful anti-cachexia therapy should provide a meaningful change for the patients. Therefore, assessment of patients' experience through quality of life, symptom and functional scales/ questionnaires are reasonable. No accepted standard exists to assess quality of life in relation to cachexia, especially from the perspective of the cachectic patients. Although several subjects of debate and uncertainty currently exist, but we still keep our hope alive [50].

*8.2.3 Suggestions: reconsideration of initiation of new phase III clinical trials*

Considering this long list of heterogeneity, and unanswered questions, we suggest to reconsider initiation of new phase III clinical trials. Instead of that, we should make attempts to conduct more longitudinal clinical observational studies to increase our knowledge regarding these critical points. For the first step, an inexpensive package of baseline CRP, echocardiography, fatigue and dyspnea assessment and some further conventional biochemical assessments such as hemoglobin

will be informative at least in metastatic non-small cell lung cancer anti-cancer cachexia studies (**Fig. 8-1**).

## 8.3 Treatment suggestions-targeting the concurrent loss of the tissues (heart, skeletal muscle and fat)

Rodent studies used different agents to target concurrent wasting of heart, skeletal muscle and fat: sActRIIB [6] (activin receptor type IIB antagonist), compound A [14] [NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) inhibitor], resveretrol [11] (NF-κB inhibitor), baicalin [21] (a Chinese herbal medicine with anti-inflammatory, anti-oxidant and anti-cancer property), tandospirone [8] [5-HT1A (hydroxytryptamine ) agonist], oxypurinol [4] [xanthine oxidase inhibitor], febuxostat [254] (second-generation xanthine oxidase inhibitor), formetrol [23] ($\beta_2$-selective agonist) and rosiglitazone [15] [peroxisome proliferator-activated receptor gamma (PPARγ) activator)] are some major examples.

### *8.3.1 A reasonable class of medications to mitigate cancer cachexia*

Remarkably, anti-heart failure medications also used in similar animal models. Conventional anti-heart failure agents such as angiotensin-converting-enzyme inhibitors (imidapril), aldosterone antagonists (spironolactone), beta-blockers (bisoprolol) [3] and statins (simvastatin) [10] were used. The efficacy of spironolactone and bisoprolol compared to placebo were most prominent (**Fig. 8-2**). Bisoprolol and spironolactone both showed relatively similar effects on preservation of skeletal muscle, fat and heart mass/function. Considering the limitations of spironolactone in cancer patients (eg, monitoring of potassium), beta-blockers can be a proper candidate for anti-cachexia clinical trials. The main premise of using beta-blockers in cancer cachexia is the high prevalence of autonomic dysfunction in cancer patients [255-257]. Autonomic dysfunction can

aggravate cancer cachexia through over-activation of immune system and progression of tumour growth [258, 259]. Isolated working rat heart studies demonstrated that 10% loss of heart mass is associated with impairment of contractile function in the presence of preserved pumping performance [16]. This is consistent with our human findings that mean of 9% loss of left ventricular mass was associated with preserved LVEF (represents pumping function of LV) and impaired global longitudinal strain (represents contractile function of LV). In the same isolated working model, tumour-bearing animal heart tissue had increased oxygen consumption in response to beta-adrenergic stimuli compared to control animals [39]. Accordingly, there is a suggestion that, heart in cancer cachexia process contributes to high energy expenditure [39], probably due to a higher adrenergic output in cancer cachexia and its effects on the heart.

Generally beta-blockers are safe in cancer cachexia; beta-blockers have limited contra-indication in cancer with great history and fast forward position. Different classes of beta-blockers have been proposed in > 70 clinical trials for two major endpoints: cardio-toxicity mitigation and improved overall survival. Several studies have tested the probable relation between history of beta-blocker medication and cancer development suggesting favorable or neutral effects of beta blocker usage against cancer development [260-265]. Several studies also showed positive effects of beta-blockers on cancer outcomes [266-269], with same positive effects in non-small cell lung cancer patients [270-272]. Using beta-blockers in patients with cardiac cachexia (cachexia relates to the failed heart), apart from its positive effects on the heart (improvement of LVEF, mitigation of heart failure progression and prolongation of survival) showed to be effective on weight and fat mass gain [220, 273]. Recently a phase II clinical trial (ACT-ONE trial) in patients with stage III/IV non-small cell lung cancer or colorectal cancer, used espindolol (a non-selective beta-blocker with partial beta-agonist effects) with successful weight gain and increase in lean body

mass [274]. Taken together, preclinical and clinical evidence suggests beta-blockers as a proper drug to target concurrent wasting of heart, skeletal muscle and fat. This approach-targeting the concurrent loss of skeletal muscle, fat and heart mass (i.e., composite endpoint) is entirely novel and comes from our achievements from my PhD thesis study.

### 8.4 Cardio-oncology research: *Not only the matter of cardio-toxic chemotherapy*

Cardio-oncology research, mainly focused on chemotherapy toxic effects on the heart in recent decades [275]. However, evolving data suggest consideration of similar genetic and traditional risk factors including insulin resistance, in cancer and cardiovascular diseases; the matter that may predispose the heart to further structural and functional impairment [275]. Continuation of research on occult cardiac disorders in cancer patients with high risk of cardiac diseases such as non-small cell lung cancer, is highly recommended.

Recently, analysis of cardiac function and structure in cancer cachexia has been encouraged [2, 276]. According to our findings, progressive cancer cachexia might be considered as a risk factor for cardiac disorders. This new chapter in cardio-oncology research still needs several research projects.

### 8.5 A multidisciplinary team in cancer cachexia research

Our longitudinal work during my PhD program is a true example of collaboration of key investigators from different disciplines: clinical cachexia researchers, cardiologists, medical oncologists and biomarker biochemists. Cooperation of medical oncologists in clinical cachexia research is crucial. Great support and involvement of medical oncologists in our longitudinal clinical cachexia study was one of the major reasons of our success. Our work also showed the close connection between a cardiology team and clinical cancer cachexia researchers. We had the

great privilege that Mazankowski Alberta Heart Institute staff supported our study. Furthermore, an expert cardiologist (Dr HB) guided our work.

**8.6 Argument of limitations of the studies**

As we discussed two retrospective studies were designed and conducted to gather more information regarding the alteration of cardiac function and structure in cancer cachexia. Basically sample selection bias and unrecognized effects of confounding factors are major limitations of retrospective studies. Despite of the limitations, we definitely encourage to continue two major concepts in larger sample sizes: firstly, further characterization of cardiac atrophy in cirrhotic patients with or without liver cancer. Secondly, association between cancer cachexia and cardio-toxicity in other potentially cardio-toxic agents such as doxorubicin.

In our longitudinal work, some limitations are identified. Food intake and energy expenditure could have been measured; however, fat loss measurement was recognized as a surrogate. Some certain pathophysiologic measures for sympathetic and/or adrenal outputs could have been considered to elucidate the influence of autonomic dysfunction on cardiac atrophy.

Although we had performance status evaluation as well as patient reported outcomes such as fatigue and dyspnea; actual functional measurements such as stair climbing test and 6-minute walk test could clarify the relation between cardiac alterations and exercise limitations. Hand grip test, a test that its sensitivity has been questioned recently, also may reveal the relation between skeletal muscle strength variation and progressive concurrent loss of tissues (heart, skeletal muscle and fat).

It should be appreciated that performing all different aforementioned tests in a palliative care setting in patients with poor prognosis and extremely poor health conditions is not practically possible. In our longitudinal work we were successful to have a 80% accrual rate which is

substantially a high rate according to our knowledge. Constant presence and follow up of the research coordinator and offering a beneficial test to the patients (echocardiography) were probably important positive factors. **Finally, the great support and commitment of Albertan patients to our study was the reason of our work success.**

### 8.7 Revisiting animal model of cancer cachexia

We propose redesign of animal models of cancer cachexia based on **realistic conditions of human cancer cachexia** such as percentage of tissue loss. The rate of loss in most of the models is relatively higher than clinical values; for instance C-26 mice model results in a tumour with 2% of total body weight and consequent 30% weight loss [277]. Most of the experimental models of cancer cachexia consider young rodents due to high cost of using older animals [278]. Most of the results of published animal models of cancer cachexia-induced cardiac atrophy cannot be extrapolated to human studies, as none of them added chemotherapy to their models. Furthermore, in animal models many of the major symptoms experienced by cancer patients cannot be quantitatively or objectively measured such as fatigue, pain and dyspnea [278].

In cancer cachexia animal models ectopic injection of tumour is usually considered (most often subcutaneous); however, orthotopic injection of the tumour is usually not a choice due to technical and time limitations [277]. This ectopic injection of the tumour associates with an accelerated progression of the tumour which is notably faster than cancer cachexia development and therefore cannot be efficiently used in cancer cachexia translational research [277].

Furthermore, there is no data regarding the exposure of cardiovascular models to cancer cachexia; exposure of rodent cardiovascular models such as transverse aortic constriction or obese

rodents to cancer cachexia may reveal the reaction of hearts with pre-existing hypertrophic heart failure to cachexic signals [2].

## 8.8 Conclusion

Overall, we realized that heart function and structure is altered in cancer cachexia. Cardiac atrophy as a main integral component of cancer cachexia, for the first time, demonstrated in human patients with metastatic non-small cell lung cancer. We also found some extra evidence of occurrence of cardiac mass loss in parallel to skeletal muscle and fat loss in a group of patients with cirrhosis. Moreover, the relation between ongoing cancer cachexia and presence of cardio-toxicity in renal cell carcinoma patients was found.

We understood that patients with metastatic non-small cell lung cancer, potentially eligible for current anti-cancer cachexia clinical trials, have some degree of cardiac disorders which might influence on their capacity for functional improvement (i.e., expected benefit of anti-cancer cachexia intervention). Cardiac assessment as well as symptom evaluation (fatigue, dyspnea) are suggested to be considered in anti-cachexia clinical trials. Further studies for probing cardiac atrophy phenomenon in different types of cancers is recommended. Underlying mechanisms remained speculative.

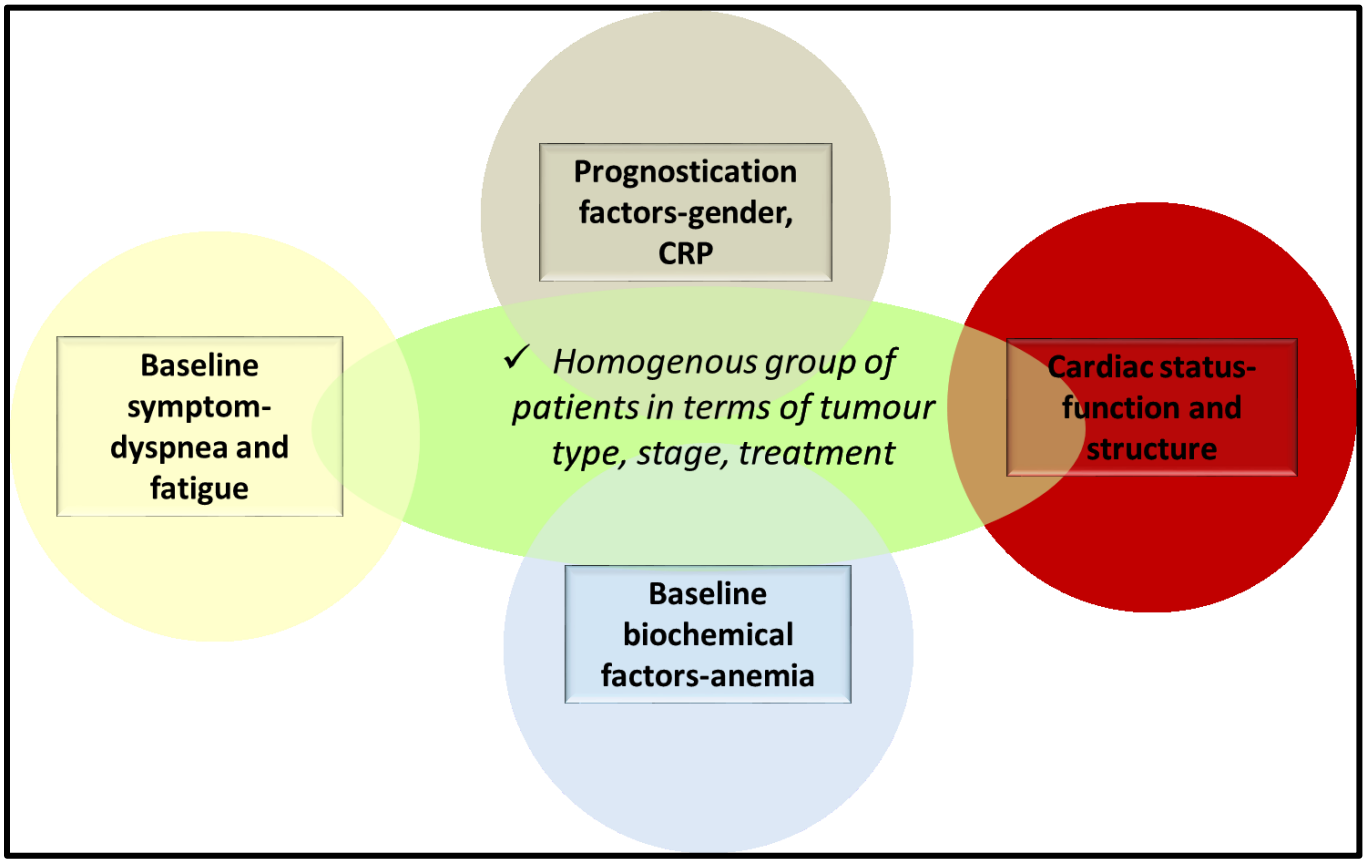


**Figure 8-1. Our proposed package of assessment in further anti-cachexia clinical studies**

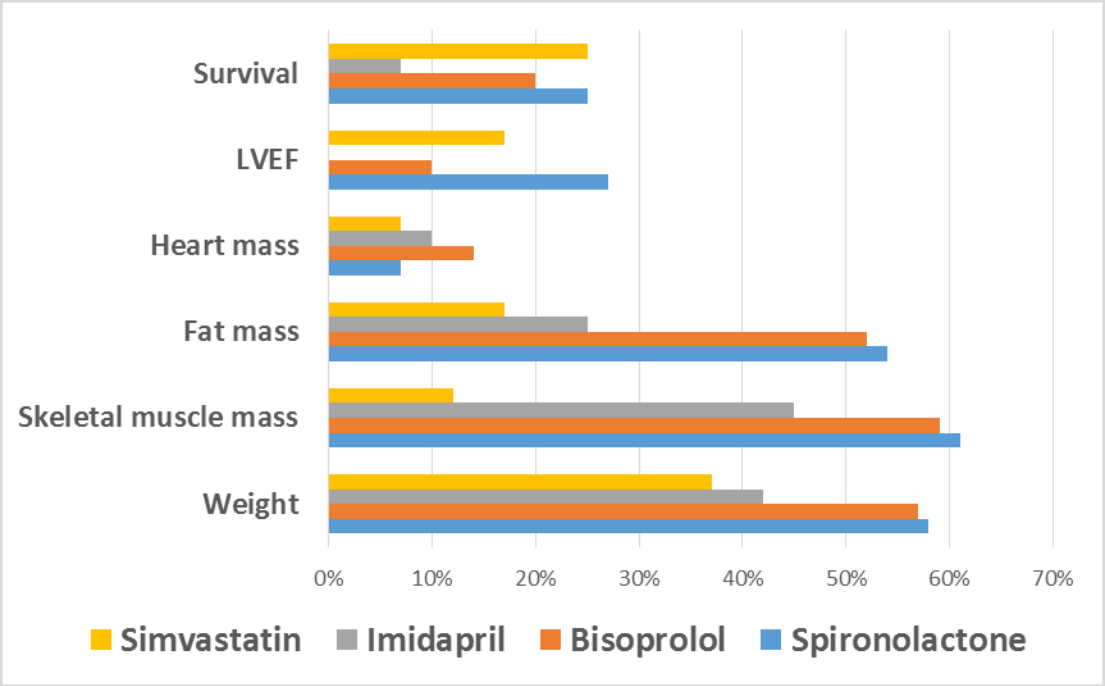


**Figure 8-2. Synthesized diagram showing the percentage of change in different variables in response to treatment compared to placebo in rat models of cancer cachexia.** Spironolactone, bisoprolol, imidapril [3] and simvastatin [10] used in cachexia models.

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**CHAPTER 9: Appendix A**

# Supplementary materials and results

**Rapid atrophy of cardiac left ventricular mass in humans with cancer cachexia**

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## Expanded Methods:

**Item 9-1. FACIT-F scale.**

Fatigue measurement using Functional Assessment of Chronic Illness Therapy (FACIT-F) consists of 13 questions concerning tiredness, level of activity and level of energy which applies to the past 7 days. FACIT-F is suitable to be used in patients with low level of education and can be completed in 5-10 minutes. FACIT-F has been used to measure fatigue in several cancer clinical trials [1, 2].

| | | Not At All | A Little Bit | Somewhat | Quite a Bit | Very Much |
|---|---|---|---|---|---|---|
| 1 | I feel fatigued | | | | | |
| 2 | I feel weak all over | | | | | |
| 3 | I feel listless ("washed out") | | | | | |
| 4 | I feel tired | | | | | |
| 5 | I have trouble starting things because I am tired | | | | | |
| 6 | I have trouble finishing things because I am tired | | | | | |
| 7 | I have energy | | | | | |
| 8 | I am able to do my usual activities | | | | | |
| 9 | I need to sleep during the day | | | | | |
| 10 | I am too tired to eat | | | | | |
| 11 | I need help doing my usual activities | | | | | |
| 12 | I am frustrated by being too tired to do the things I want to do | | | | | |
| 13 | I have to limit my social activity because I am tired | | | | | |

Each statement can be scored from 0 to 4; 4=Not At All; 3=A Little Bit; 2=Somewhat; 1=Quite A Bit; 0=Very Much, EXCEPT statements #7 and #8 which are reversed scored. Lowest score=0 (the worse level of fatigue) and highest score is 52 (normal or no fatigue) (for more information please visit https://consultgeri.org/try-this/general-assessment/issue-30.pdf and http://www.facit.org/).

**Item 9-2. Medical Research Council (MRC) dyspnea scale [3]**

This MRC questionnaire was used to grade the level of breathlessness. In this study the MRC scale was evaluated by the researchers.

| Grade | Level of Activity |
|---|---|
| **1** | None. Not troubled with breathlessness except with strenuous exercise |
| **2** | Slight. Troubled by shortness of breath when hurrying on the level or walking up a slight hill |
| **3** | Moderate. Walks slower than people of the same age on the level because of breathlessness or has to stop for breath when walking at own pace on the level |
| **4** | Severe. Stops for breath after walking about a 100 m or after a few minutes on the level |
| **5** | Very severe. Too breathless to leave the house or breathless when dressing or undressing |

**Item 9-3. Eastern Cooperative Oncology Group (ECOG) Performance Status Scale**

ECOG is a generally accepted tool to measure the performance status of cancer patients.

| | |
|---|---|
| **0** | Normal activity. Fully active, able to carry on all pre-disease performance without restriction. |
| **1** | Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work). |
| **2** | In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours. |
| **3** | In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. |
| **4** | 100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. |
| **5** | Dead. |

ECOG as published by Oken et al [4] in J. Clin.Oncol, 1982.

**Item 9-4. Plasma biomarker analysis**

Samples for high-sensitivity cardiac troponin T and I (hs-cTnT and hs-cTnI respectively), galectin 3 and N-terminal pro-B natriuretic peptide (NT pro-BNP) were drawn into BD Vacutainer® K2EDTA coated tubes. Samples for C-reactive protein (CRP) were drawn into lithium heparin BD Vacutainer® coated tubes. The samples were separated and frozen at -80°C before analyses to mitigate stability issues.

CRP was measured using the CRPH enzyme-linked immunosorbent assay (Synchron LX system, Beckman Coulter). Functional sensitivity defined as the lowest concentration that can be measured with CV=20% is ≤ 0.18 mg/L.

hs-cTnT was measured using an immunoassay analyzer (E-modularRoche Diagnostics). The limit of blank (LoB) and detection (LoD) for hs-cTnT were 3 ng/L and 5 ng/L respectively, and we considered the value of 2.99 ng/L for concentrations below the LoB. The upper reference limit (99th percentile) outside the United States of the assay is 14 ng/L (95% confidence interval 12.7-24.9 ng/L). The lowest stated concentration with a coefficient of variance (CV) ≤ 10% with the hs-TnT assay is 13 ng/L.

hs-cTnI was measured using a chemiluminescent microparticle immunoassay assay (ARCHITECT i1000 ; Abbott Diagnostics). The LoB and LoD for hs-cTnI measurement were <1 ng/L and 1.2 ng/L, and we considered value of 0.99 for values under 1 ng/L. The precision at 99th percentiles of 26.2 ng/L is 4.0%. The lowest concentration with a CV ≤ 10% with the hs-cTnT assay is 4.7 ng/L.

NT-proBNP was also measured an immunoassay analyzer (E-modular, Roche Diagnostics,). The LoD of this assay is 5 ng/L with measuring range of 5-35000 ng/L. The NT-proBNP concentrations for all patients at baseline and over time was > 5 ng/L.

Galectin-3 was measured using a chemiluminescent microparticle immunoassay assay (ARICHITECT i1000 ; Abbott Diagnostics). The stated LoB and LoD of this assay were 1 ng/mL and 1.1 ng/mL respectively. The assay has an imprecision (CV) ≤ 10% for measurements ranging from 4.0 to 114.0 ng/mL. The Galectin-3 values for all patients at baseline and over time was > 1 ng/mL.

**91** patients referred by medical oncologists

19 patients declined our request [11 (57.9%) males, 67.8±4.8 y/o; p=0.16 comparad to 72 included patients]

**72** patients consented with baseline measurements [38 (52.75) males, 65.2±8.1 y/o]

22 patients did not have over time measurements [14 (63.6%) males, 66.2±9.0 y/o; p=0.5 compared to final 50 patients:

**50** patients had baseline and over time measurements

*Description of 22 patients who did not have second time measurement:*
2 patients canceled their treatment
3 patients treatment plan changed to cisplatin therapy few days before start of chemotherapy
3 patients never started chemotherapy and continued with palliative care because of aggravation of patients conditions
10 patients started carboplatin-based therapy but died before 105 days after baseline echocardiogram [over time echocardiography considered between 105 till 120 days after baseline echocardiography (112±6 days)].
2 patients were bed ridden at home and could not attend the over time measurements
1 patient was admitted in the hospital with comatose condition
1 patient was admitted in a remote hospice

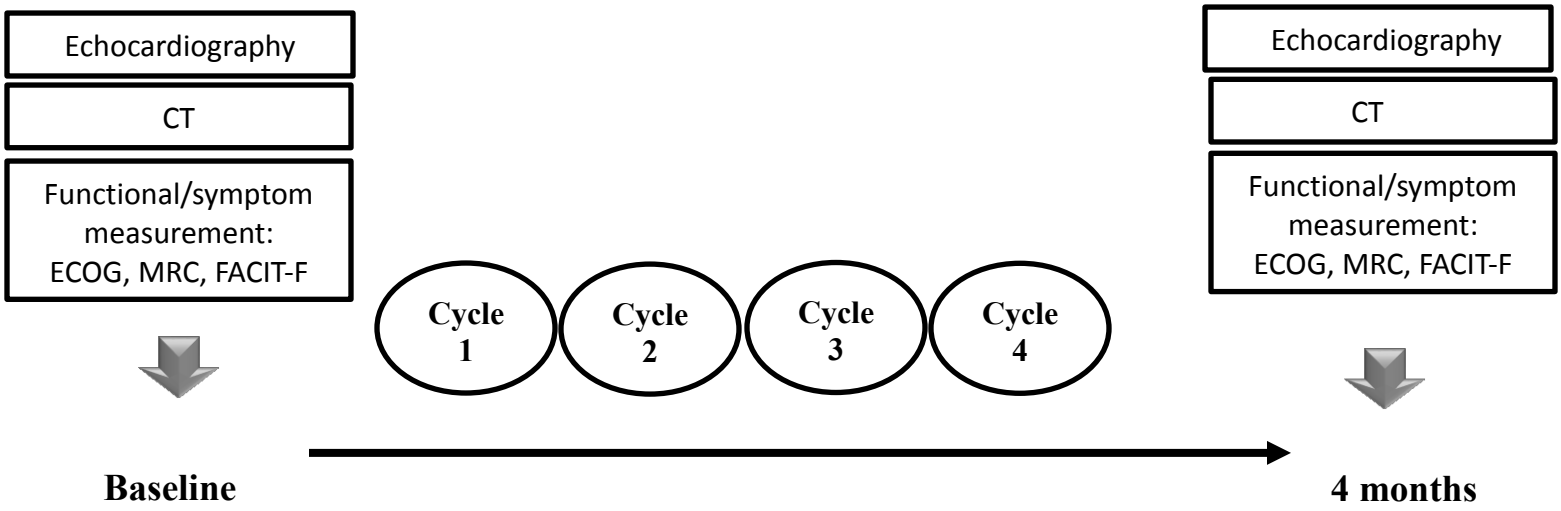


**Figure 9-1. Patient inclusion and study design.** CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; MRC,Medical Research Council; NSCLC, non-small cell lung cancer. This single centre study was conducted in Cross Cancer Institute (CCI), University of Alberta, Edmonton, Alberta, Canada. CCI is the cancer treatment centre for Northern Alberta.

**Supplementary Table 9-1: Predictive factors at baseline for development of LVM loss over time**

| Patient characteristics | Patients with LVM loss > median value (-8.9%) N (%) | Unadjusted Odds Ratio | P-value |
|---|---|---|---|
| **Male (n=24)** | 13 (54.2) | 1.4 (0.45-4.2) | 0.57 |
| **Female (n=26)** | 12 (46.2) | | |
| **Age > 65 y (n=27)** | 13 (48.1) | 0.71 (0.23-2.2) | 0.71 |
| **Age < 65 y (n=23)** | 12 (52.2) | | |
| **Normal left ventricular ejection fraction[@] (n=44)** | 24 (54.5%) | 6.0 (0.65-55.6) | 0.12 |
| **Impaired left ventricular ejection fraction (n=6)** | 1 (16.7%) | | |
| **Normal global longitudinal strain[#] (N=33)** | 17 (51.5%) | 1.1 (0.3-3.4) | 0.92 |
| **Impaired global longitudinal strain (N=17)** | 8 (44.5%) | | |
| **Previous myocardial infarction (n=5)** | 3 (60) | 1.6 (0.24-10.3) | 0.64 |
| **No myocardial infarction history (n=45)** | 22 (48.9) | | |
| **Normal diastolic function (n=38)** | 19 (50%) | 1.8 (0.5-7.0) | 0.40 |
| **Impaired diastolic function (n=12)** | 6 (50%) | | |
| **Non-hypertensive (n=34)** | 15 (44.2%) | 0.50 (0.14-1.6) | 0.23 |
| **Hypertensive (n=16)** | 10 (62.5%) | | |
| **Non-diabetic (n=42)** | 22 (52.4%) | 1.8 (0.39-8.6) | 0.45 |
| **Diabetic (n=8)** | 3 (37.5%) | | |
| **>5% weight loss[&] (n=21)** | 17 (81.0%) | 11.2 (2.9-43.5) | <0.001 |
| **<5% weight loss (n=29)** | 8 (27.5%) | | |
| **Fatigue score<30 (n=21)** | 14 (66.7%) | 3.3 (1.1-10.6) | 0.04 |
| **Fatigue score>30 (n=29)** | 11 (37.9%) | | |
| **ACEI or ARB (yes=14)** | 7 (50) | 0.71 (0.21-2.46) | 0.59 |
| **ACEI or ARB (No=36)** | 21 (58.3) | | |
| **Beta blocker (yes=13)** | 6 (46.2) | 0.81 (0.23-2.8) | 0.75 |
| **Beta blocker (No=37)** | 19 (51.4) | | |
| **Statins (yes=14)** | 7 (50) | 1.0 (0.3-3.6) | 1.0 |
| **Statins (No=36)** | 18 (50) | | |
| **Pemetrexed (n=26)** | 12 (46.2) | 0.72 (0.24-2.2) | 0.57 |
| **Other agents (n=24)** | 13 (54.2) | | |
| **Prior chest radiotherapy (n=23)** | 12 (52.2) | 1.17 (0.39-3.6) | 0.78 |
| **No chest radiotherapy (n=27)** | 13 (48.1) | | |

[@] LVEF≥ 50%; [#] GLS≥ 18%. [&] weight loss > 5% in 6 months preceding chemotherapy. ACEI, angiotensin-converting-enzyme inhibitor; ARB, Angiotensin receptor blocker

**Supplementary Table 9-1: Predictive factor at baseline for development of LVM loss (continued)**

| Patient characteristics | Patients with LVM loss > median value [-8.9%] N (%) | Unadjusted Odds Ratio | P-value |
|---|---|---|---|
| **CRP> 10 (mg/L) (n=22)** | 15 (68.2) | **3.9 (1.2-12.6)** | **0.02** |
| **CRP<10 (mg/L) (n=28)** | 10 (35.7) | | |
| **hs-cTroponin nT>6 (ng/L) (n=25)** | 13 (26) | 1.17 (0.4-3.6) | 0.78 |
| **hs-cTroponin nT<6(ng/L) (n=25)** | 12 (24) | | |
| **hs-cTroponin I>2 (ng/L) (n=16)** | 8 (50) | 1.0 (0.30-3.2) | 1.0 |
| **hs-cTroponin I<2(ng/L) (n=34)** | 17 (50) | | |
| **NT pro-BNP> 125 (ng/L) (n=23)** | 12 (57.2) | 1.1 (0.3-3.6) | 0.96 |
| **NT pro-BNP> 125 (ng/L) (n=17)** | 9 (52.6) | | |
| **Galectin-3 >15.1[@] (ng/mL) (n=20)** | 11 (55) | 1.2 (0.35 to 4.2) | 0.75 |
| **Galectin-3<15.1 (ng/mL) (n=20)** | 10 (50) | | |

hs-cTroponin T, high sensitivity cardiac troponin T; hs-cTroponin I, high sensitivity cardiac troponin I; NT pro-BNP, N-terminal pro-B natriuretic peptide For NT pro-BNP and Galectin measurements were available for 40 patients.

**Supplementary Table 9-2: Univariate association between Left Ventricular Mass (LVM) loss and tumour response**

| Tumour response at 4 month | Patients with LVM loss > median value (-8.9%) N (%) | Unadjusted Odds Ratio | P-value |
|---|---|---|---|
| **Progression (n=12)** | 11 (91.6%) | **18.8 (2.2-162.0)** | **0.007** |
| **Stable disease or partial response (n=38)** | 14 (36.8%) | | |

**Supplementary Table 9-3: Relation between tissue loss over time and use of cardiovascular medications**

| | | Body mass index | Skeletal muscle | Total adipose tissue | Left ventricular mass |
|---|---|---|---|---|---|
| **Beta-blockers** | Users (n=13) | 0.27±6.2 | -8.8±4.9 | **6.2±30.2** | **-2.5±9.4** |
| | Non-users (n=37) | -6.4±16.9 | -6.0±8.8 | **-8.0±22.2** | **-9.8±9.9** |
| | P-value | 0.10 | 0.47 | **0.09** | **0.05** |
| **ACEI or ARB** | Users (n=14) | -3.3±4.4 | -6.3±5.4 | -5.5±19.3 | -7.7±11.4 |
| | Non-users (n=36) | -5.4±17.8 | -6.5±8.9 | -3.8±27.4 | -7.7±9.8 |
| | P-value | 0.68 | 0.90 | 0.77 | 0.51 |
| **Statins** | Users (n=14) | -1.7±6.0 | -6.2±5.2 | -5.8±16.7 | -8.2±9.9 |
| | Non-users (n=36) | -6.0±17.3 | -6.6±8.9 | -3.7±27.8 | -7.5±10.4 |
| | P-value | 0.31 | 0.92 | 0.36 | 0.92 |

Values are percentage of gain or loss over time in each group. ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blockers.

**Supplementary Table 9-4: Biomarker values in patients associated with multiple tissue loss.**

| | Median at Baseline | | | | | Median at 4 months | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **Three tissue Loss[#] (n=11)** | **Two tissue loss[$] (n=14)** | **One tissue loss[&] (n=14)** | **No tissue loss[@] (n=11)** | **P-value** | **Three tissue Loss (n=11)** | **Two tissue loss (n=14)** | **One tissue loss (n=14)** | **No tissue loss (n=11)** | **P-value** |
| **CRP (mg/L)** | 19.8* | 6.4 | 7.8 | 5.2 | 0.03 | 43.8* | 13.2 | 13.5 | 4.5 | 0.04 |
| **hs-cTroponin T (ng/L)** | 7.1 | 4.4 | 6.5 | 6.2 | 0.17 | 11.7* | 5.3 | 8.4 | 6.5 | 0.04 |
| **hs-cTroponin I (ng/L)** | 3.0 | 1.0 | 1.5 | 2.0 | 0.39 | 2.5 | 1.0 | 3.5 | 1.5 | 0.45 |
| **NT pro-BNP (ng/L)** | 102.7 | 107.4 | 193.2 | 162.4 | 0.61 | 183.1 | 117.9 | 164.9 | 126.1 | 0.52 |
| **Galectin-3 (ng/mL)** | 14.4 | 14.5 | 17.7 | 15.3 | 0.66 | 17.9 | 16.5 | 21.6 | 17.7 | 0.48 |

[#] Patients who had concurrent loss of left ventricular mass, skeletal mass and total adipose tissue mass (n=11). [$]Patients who lost two of aforementioned tissues (n=14); [&]Patients who lost only one of the aforementioned tissues (n=14). [@] Patients who did not have any tissue loss (n=11). CRP, C reactive protein; hs-cTroponinT, high-sensitivity cardiac troponin T; hs-cTroponin I, high-sensitivity cardiac troponin I; NT pro-BNP, N-terminal pro-B natriuretic peptide.

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