Published in final edited form as:

Curr Opin Support Palliat Care. 2011 December ; 5(4): 327–333. doi:10.1097/SPC.0b013e32834c49ba.

Understanding cancer-induced cachexia: imaging the flame and its fuel

Marie-France Penet^a, Paul T. Winnard Jr^a, Michael A. Jacobs^{a,b}, and Zaver M. Bhujwala^{a,b}

^aJHU In Vivo Cellular and Molecular Imaging Center, The Russell H. Morgan Department of Radiology and Radiological Science, The Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

^bSidney Kimmel Comprehensive Cancer Center, The Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

Abstract

Purpose of review—One of the most under explored and yet devastating consequences of cancer is cachexia, a condition in which the body is consumed by deranged carbohydrate, lipid and protein metabolism that is induced by inflammatory cytokines. Cachexia is associated with poor treatment outcome, fatigue and poor quality of life. Because of its multifactorial characteristics, it has been difficult to understand the impact of the tumor on body organs and the sequence of events that leads to cachexia. Such insights are critically important in identifying therapeutic strategies.

Recent findings—The ability to understand the interaction between the tumor and normal tissues and to noninvasively image the development of this condition would be invaluable in identifying critical stages when cachexia becomes life-threatening. Current multimodality molecular and functional imaging capabilities provide unique opportunities to study cachexia holistically in preclinical models and clinically. In this review we have provided examples of how state-of-the-art imaging techniques in combination with molecular characterization can be used to understand cancer-induced cachexia.

Summary—Such studies will lead to clinically translatable indices for the early detection of this condition and will identify novel targets to inhibit the cachexia cascade.

Keywords

cachexia; clinical translation; metabolism; molecular and functional imaging

Introduction

The complexity of cancer dictates the necessity of studying this disease in the context of its microenvironment as well as in the context of interactions between the tumor and the body,

that is the ‘macro-environment’. Indeed the past decade has witnessed a major shift in viewing cancer from the perspective of oncogenes and tumor suppressor genes, to understanding the role of the tumor stroma and microenvironment in cancer progression and treatment. Investigating interactions between the tumor and the macroenvironment is, however, largely uncharted territory.

The main causes of mortality from cancer are metastasis-related organ function failure and cachexia [1]. The term cachexia derives from the Greek words ‘kakos’ and ‘hexis’ for ‘bad condition’ [2]. It is a progressive wasting condition that is encountered not only in cancer but also in other life-threatening diseases such as AIDS, rheumatoid arthritis, chronic obstructive pulmonary diseases, and organ failure [3–6]. Several randomized clinical trials have demonstrated that the condition cannot be reversed by nutritional supplementation [7–10]. Mortality from cachexia, and not tumor burden, accounts for 20–30% of cancer deaths [1]. The significant weight loss resulting from this condition causes impairment of immune function, poor outcome of chemotherapy, fatigue, and markedly reduced quality of life [11]. Since 2011 cachexia has been defined as a multifactorial syndrome characterized by an ongoing loss of skeletal muscle mass, with or without loss of fat mass, which cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment. Cachexia pathophysiology is characterized by a negative protein and energy balance driven by a variable combination of reduced food intake and abnormal metabolism [12*]. Currently there is no known cure for cachexia, as mechanisms underlying its manifestation are not defined clearly enough to identify and design effective therapeutic strategies. Several inflammatory cytokines such as tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), IL-1 β and interferon- γ (IFN- γ), glucocorticoids, tumor-derived proteolysis-inducing factor (PIF) and lipid-mobilizing factor (LMF) are reportedly functional components in this condition [13]. As outlined in Table 1, significant abnormalities in carbohydrate, lipid and protein metabolism are observed with cachexia, and are a major cause for the associated profound weight loss. In addition, cancer-induced anorexia due to disruption of leptin and neuropeptide Y regulation also contributes to weight loss [13,14].

The ability to noninvasively detect this condition early on with noninvasive imaging, preferably before weight loss occurs, can significantly contribute to the design and optimization of therapeutic strategies, and to the detection of response to such treatments. Multimodality molecular and functional imaging techniques provide a panacea of capabilities to tackle key questions in cancer cachexia (Fig. 1) [15,16]. At the bench, transgenic mice and genetically engineered cancer cells can be used to image specific molecular pathways. When combined with functional imaging significant advances can be made in understanding the interaction between the tumor and the host in the cachexia cascade. As listed in Table 1, abnormalities in carbohydrate, lipid and protein metabolism can be detected and studied with noninvasive MRI and magnetic resonance spectroscopy (MRS) as well as with nuclear imaging methods such as positron emission tomography (PET). Both magnetic resonance and PET are noninvasive and therefore discoveries made at the bench can be clinically translated with relative ease [17*].

The multifaceted nature of this condition makes it imperative that a ‘holistic’ or macroenvironmental approach is used to understand the cachexic switch or cascade, and the

multiple interactive networks that most likely exist between a cachexia-inducing tumor and host organs and tissue, as well as the interaction between inflammatory cytokines and metabolism. Noninvasive imaging applied to study cachexia would enable the delineation of a sequence of progressive events and identify the most lethal aspects of the cascade. Once these critical single or multiple cachexic switches or cascades are identified, molecular-targeted approaches, such as multiple small interfering RNA (siRNA) targeting or pharmaceutical interventions, can be designed and developed to down-regulate or knockout effector molecules, pathways or enzymes that control the cascade. The focus of this review is to describe how state-of-the-art molecular and functional imaging capabilities in combination with novel molecular biology techniques can be used to understand the interactions between the tumor and normal tissues in the body in inducing cachexia.

Characterization of cachexia-inducing tumors and the feasibility of imaging these characteristics

Mechanisms involved in cancer cachexia have been comprehensively reviewed by Tisdale [18]. Cachectic patients are affected by an energy imbalance due to anorexia and increased resting energy expenditure. Changes in adipose tissue in cachexia are primarily due to increased lipolysis resulting in a loss of body fat. There is impairment not only of the lipid storage function of adipocytes but also of their differentiation. The cachectic tumor can affect adipose mass through the secretion of factors such as LMF, or protein zinc α_2 -glycoprotein (ZAG) that induce lipolysis by a cyclic adenosine monophosphate-mediated mechanism. TNF α can also induce lipolysis in adipocytes. Inflammatory pathways are also activated in cachexia. In addition to TNF α , other cytokines known to be involved are IL-1, IL-6 and IFN γ . Cachexia results in a loss of fat tissue as well as lean muscle tissue. Muscle atrophy in the syndrome results from a decrease in protein synthesis and an increase in protein degradation. Among the several pathways implicated in muscle atrophy, the ubiquitin-proteasome pathway has been shown to have a predominant function in the degradation of myofibrillar proteins. Synthesis of proteins is also affected by changes in the phosphorylation of protein synthesis initiation factors, such as protein kinase R and eIF2 α . PIF, glucocorticoids and TNF α are among the factors involved in the loss of muscle mass [18]. These mechanisms have mostly been explored *in vitro* and *ex vivo*.

Current state-of-the-art molecular and functional imaging can be applied to noninvasively characterized tumors that induce cachexia. This would enable the development of noninvasive biomarkers to identify tumors likely to induce cachexia, and to identify changes in normal tissues that are typical of the induction of cachexia. This ability to detect the onset or presence of cachexia noninvasively could be extended to detect response to treatment and to the development of new therapies. Clinically translatable ^{18}F FDG PET imaging can be used to characterize glycolysis. Both MRI and CT can be used to image the loss of lipids and the changes in muscle mass, and MRS and magnetic resonance spectroscopic imaging (MRSI) can detect alterations in carbohydrate, protein and lipid metabolism. Optical reporters could be used to image inflammatory pathways or proteasome activity involved in the cachexia cascade.

Preclinical studies

There has been interest in identifying ‘metabolic signatures’ that might be indicative of a cachexia-inducing tumor. ^1H MRS has been applied to identify cachexia biomarkers in the sera of C26 adenocarcinoma-bearing mice [19]. Increased amounts of very-low-density and low-density lipoproteins were detected along with decreased glucose levels [19]. Constantinou *et al.* [20**] applied ^{31}P MRS *in vivo* to detect changes in the muscle energy metabolism of cachectic mice inoculated with Lewis lung carcinoma cells. ^{31}P spectra revealed a reduction in the ATP synthesis rate in tumor-bearing mice compared with the control mice, which was attributed to mitochondrial dysfunction [20**]. The results were supported by genomic analysis that showed atypical expression levels of skeletal muscle regulatory genes such as peroxisomal proliferator activator receptor- γ -coactivator-1 β (PGC-1 β), which is a major regulator of mitochondrial biogenesis, and the mitochondrial uncoupling protein 3 (UCP3). These results showed that the hallmarks of skeletal muscle wasting could be detected noninvasively by *in vivo* using ^{31}P MRS, which could be translated to the clinic [20**].

Progressive cancer cachexia was also associated with depletion of energy stores in the liver and skeletal muscle as detected by steady-state assessment of hepatic and skeletal muscle bioenergetic status using ^{31}P MRS [21]. Rats were inoculated with methylcholanthrene-induced sarcoma to assess the effects of cancer on the visceral energy stores *in vivo*. An increased hepatic inorganic phosphate (Pi)/ATP ratio was detected by ^{31}P MRS and occurred early in the disease process [21]. Using the same model of cachexia, Gehman *et al.* [22] detected, using ^{31}P MRS, an increase in Pi generation and a more rapid removal of phosphomonoester (PME) in cachectic rat liver.

Magnetic resonance was recently applied to analyze the contribution of lipase to cancer-related cachexia [23]. Inhibition of lipolysis by targeting adipose triglyceride lipase and hormone-sensitive lipase reduced certain features of cachexia, such as myocyte apoptosis, proteasomal muscle degradation and loss of white adipose tissue. Magnetic resonance was used to assess the total body fat content demonstrating that the technique can be used to explore the effect of anticachexia treatment on lipid mass [23].

Clinical studies

Few imaging studies have been performed on patients who suffer from cachexia. Most of these have explored muscle mass. In the clinic, the order of preference for muscle mass assessment was listed as cross-sectional imaging [computed tomography (CT) or MRI], dual energy X-ray imaging (DEXA), anthropometry (mid-arm muscle area), and bioimpedance analysis [12*]. CT imaging provides an accurate assessment of muscle mass and body composition in patients with cancer [24–26]. CT scans acquired on pancreatic cancer patients with and without cachexia revealed that in the lower part of the abdomen, there was no significant difference between these groups in any of the examined muscle tissue thicknesses (Fig. 2) [27]. However, fat tissue thickness was significantly reduced in cachectic patients (Fig. 2). Although no significant difference between the two groups was observed in muscle thicknesses, lung function in cachectic patients was significantly decreased, demonstrating that in the early stages of the cachectic syndrome the muscle is

preserved but its function is impaired. CT scans revealed a significant influence of cachexia on fat metabolism, underlining the systemic effects of cachexia in patients with pancreatic cancer [27]. These studies demonstrated the advantages of using CT imaging in the assessment of the effect of cachexia on muscle and fat tissues. CT measurement of body composition was also shown to have potential in predicting prognosis and possibly chemotherapy toxicity [24,25]. CT imaging can also be used in clinical intervention trials to assess treatment efficacy on fat-free mass and specific muscles [28*].

Other imaging techniques have been applied to explore the effect of cachexia on normal tissues in cancer patients. To assess the impact of cachexia on skeletal muscle morphology, metabolism, and microcirculation, Weber *et al.* [29] acquired MRI, MRS and contrast-enhanced ultrasonography (CEUS) in cachectic patients and compared the results with measurements acquired in matched healthy volunteers (Fig. 3). As shown in Fig. 3, it is possible to quantify the muscle cross-sectional area, in this instance of the right quadriceps femoris, in magnetic resonance images. The cross-sectional area in a cachectic patient and a volunteer were 51.3 and 85.9 cm², respectively. Skeletal muscle microcirculation was quantified by CEUS, a technique that analyzes the replenishment kinetics after destruction of intravenously injected microbubbles by ultrasonographic pulses [29]. This study showed that morphologic parameters, body mass index, cross-sectional area and total fiber size were lower in cachectic patients than in volunteers. Capillary density, determined on histology sections, as well as microcirculation, measured *in vivo* by CEUS, and concentrations of muscular energy metabolites, pH, and trimethyl-ammonium-containing compounds, analyzed *in vivo* with MRS were comparable in both groups [29]. In this study, cancer cachexia was associated with a loss of muscle volume but not of muscular functionality.

MRI can be used to not only measure muscle cross-sectional area and volume, but also to distinguish between different tissue types, such as muscle and subcutaneous fat, as shown in Fig. 4. Fatty infiltration within the quadriceps muscle can be observed in these magnetic resonance images. Gray *et al.* [30*] have developed a noninvasive optimization technique to separately quantify the contractile and the noncontractile compartments within the muscle on magnetic resonance images. The k-means technique allows a noninvasive estimation of the proportion of fatty infiltration in the muscle. Women with upper gastrointestinal cancer who have a predilection for cachexia presented with 48% less muscle with significantly higher fatty infiltration than healthy young women, indicating that the muscles of patients are not only smaller but also less homogeneous [30*].

Conclusion

Cancer-induced cachexia is an under explored problem that has devastating consequences. There are no known cures for this condition, and its multifaceted nature makes it difficult to investigate. Current state-of-the-art multimodality molecular and functional imaging approaches are ideally suited to identifying and characterizing this problem but to date they have not been extensively pursued. Studying and solving this problem would have a significant impact on improving the quality of life for patients, treatment outcome, and increasing the life expectancy of cancer patients.

Molecular and functional imaging of preclinical models of cachexia can be used to answer critical questions such as the sequence of changes in metabolism and whether these occur simultaneously or subsequent to inflammation. The sequence of changes in carbohydrate, protein and lipid metabolism in organs during the onset of cachexia can also be identified, together with the earliest and most life-threatening processes associated with cachexia. The tumor microenvironment is characterized by inflammation-inducing environments such as hypoxia and an acidic extracellular pH. One critical question that can be identified with molecular and functional imaging is whether these abnormal and inflammation-inducing physiological environments make a significant contribution to the cachexic response. Using preclinical tumor models and noninvasive imaging of hypoxia [31] and extracellular pH [32] we can study the interaction between cachexia-inducing and noncachexia-inducing tumors and the role of the tumor micro-environment in inducing cachexia. A significant alteration in choline metabolism, detected by MRS, and by molecular characterization of enzymes in the choline pathway are hallmarks of highly aggressive tumors, and this is currently being exploited for potential new therapies [33]. Increased total choline is also found to occur with inflammation [34]. The relationship between NF- κ B activity, choline metabolism and cachexia is entirely unexplored and should be a key focus of future investigations in order to identify early markers of cancer cachexia and to uncover new targets for its treatment. Once key organs or cancer-specific metabolic pathways and enzymes involved in the cascade are revealed, image-guided delivery of siRNA to target-specific enzymes using liposomes decorated with imaging reporters can be used as target-specific therapeutics against essential enzymes to reverse the condition.

Acknowledgments

Support from P50 CA103175, P30 CA006973, R01 CA73850, R01 CA82337, R01 CA136576, R01 CA138515, R01 CA138264, U01CA140204 and R21 CA133600 is gratefully acknowledged.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
 - of outstanding interest
- Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 366).
1. Loberg RD, Bradley DA, Tomlins SA, et al. The lethal phenotype of cancer: the molecular basis of death due to malignancy. *CA Cancer J Clin.* 2007; 57:225–241. [PubMed: 17626119]
 2. Inui A. Cancer anorexia-cachexia syndrome: current issues in research and management. *CA Cancer J Clin.* 2002; 52:72–91. [PubMed: 11929007]
 3. Berry J, Baum C. Reversal of COPD-associated weight loss. *Drugs.* 2004; 64:1041–1052. [PubMed: 15139785]
 4. Mak RHCW, Cone RD, Marks DL. Orexigenic and anorexigenic mechanisms in the control of nutrition in chronic kidney disease. *Pediatr Nephrol.* 2005; 20:427–431. [PubMed: 15662537]
 5. Ferrigno D, Bucchieri G. Anthropometric measurements in nonsmall cell lung cancer. *Supp Care Cancer.* 2001; 9:522–527.
 6. Tan BHFK. Cachexia: prevalence and impact in medicine. *Curr Opin Clin Nutr Metab Care.* 2008; 11:400–407. [PubMed: 18541999]

7. Bosaeus I, Daneryd P, Svanberg E, Lundholm K. Dietary intake and resting energy expenditure in relation to weight loss in unselected cancer patients. *Int J Cancer*. 2001; 93:380–383. [PubMed: 11433403]
8. Evans WK, Makuch R, Clamon GH, et al. Limited impact of total parenteral nutrition on nutritional status during treatment for small cell lung cancer. *Cancer Res*. 1985; 45:3347–3353. [PubMed: 2988769]
9. Lowell BB, Ruderman NB, Goodman MN. Evidence that lysosomes are not involved in the degradation of myofibrillar proteins in rat skeletal muscle. *Biochem J*. 1986; 234:237–240. [PubMed: 3707546]
10. Simons JP, Schols AM, Hoefnagels JM, et al. Effects of medroxyprogesterone acetate on food intake, body composition, and resting energy expenditure in patients with advanced, non hormone sensitive cancer. *Cancer Res*. 1998; 82:553–560.
11. Rowland KM Jr, Loprinzi CL, Shaw EG, et al. Randomised double-blind placebo-controlled trial of cisplatin and etoposide plus megestrol acetate/placebo in extensive-stage small-cell lung cancer: a North Central Cancer Treatment Group Study. *J Clin Oncol*. 1996; 14:135–141. [PubMed: 8558188]
12. Fearon K, Strasser F, Anker SD, et al. Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol*. 2011; 12:489–495. This review summarizes the most recent definition, diagnostic criteria, and classification of cancer cachexia to improve clinical management, trial design, education and policy. [PubMed: 21296615]
13. Tisdale MJ. Molecular pathways leading to cancer cachexia. *Physiology (Bethesda)*. 2005; 20:340–348. [PubMed: 16174873]
14. Esper DH, Harb WA. The cancer cachexia syndrome: a review of metabolic and clinical manifestations. *Nutr Clin Pract*. 2005; 20:369–376. [PubMed: 16207677]
15. Couch M, Lai V, Cannon T, et al. Cancer cachexia syndrome in head and neck cancer patients. Part I: Diagnosis, impact on quality of life and survival, and treatment. *Head Neck*. 2007; 29:401–411. [PubMed: 17285641]
16. Glunde K, Pathak AP, Bhujwalla ZM. Molecular-functional imaging of cancer: to image and imagine. *Trends Mol Med*. 2007; 13:287–297. [PubMed: 17544849]
17. Jacobs MA, Ouwerkerk R, Wolff AC, et al. Monitoring of neoadjuvant chemotherapy using multiparametric, (23)Na sodium MR, and multimodality (PET/CT/MRI) imaging in locally advanced breast cancer. *Breast Cancer Res Treat*. 2011; 128:119–126. This clinical study provides examples of multimodal imaging techniques applied to breast cancer that can, in the future, be applied to better understand cachexia. [PubMed: 21455671]
18. Tisdale MJ. Mechanisms of cancer cachexia. *Physiol Rev*. 2009; 89:381–410. [PubMed: 19342610]
19. O'Connell TM, Ardeshipour F, Asher SA, et al. Metabolomic analysis of cancer cachexia reveals distinct lipid and glucose alterations. *Metabolomics*. 2008; 4:216–225.
20. Constantinou C, Fontes de Oliveira CC, Mintzopoulos D, et al. Nuclear magnetic resonance in conjunction with functional genomics suggests mitochondrial dysfunction in a murine model of cancer cachexia. *Int J Mol Med*. 2011; 27:15–24. In these preclinical studies *in vivo* ³¹P MRS combined with genome transcriptome analysis revealed the implication of mitochondrial dysfunction in cachexia, showing the importance of combining multiple techniques to better characterize the syndrome. [PubMed: 21069263]
21. Schneeberger AL, Thompson RT, Driedger AA, et al. Effect of cancer on the *in vivo* energy state of rat liver and skeletal muscle. *Cancer Res*. 1989; 49:1160–1164. [PubMed: 2917347]
22. Gehman KE, Incullet RI, Brauer M, et al. Early detection of cancer cachexia in the rat using ³¹P magnetic resonance spectroscopy of the liver and a fructose stress test. *NMR Biomed*. 1996; 9:271–275. [PubMed: 9073305]
23. Das SK, Eder S, Schauer S, et al. Adipose triglyceride lipase contributes to cancer-associated cachexia. *Science*. 2011; 833:233–238. [PubMed: 21680814]
24. Tan BH, Birdsell LA, Martin L, et al. Sarcopenia in an overweight or obese patient is an adverse prognostic factor in pancreatic cancer. *Clin Cancer Res*. 2009; 15:6973–6979. [PubMed: 19887488]

25. Prado CM, Baracos VE, McCargar LJ, et al. Sarcopenia as a determinant of chemotherapy toxicity and time to tumor progression in metastatic breast cancer patients receiving capecitabine treatment. *Clin Cancer Res.* 2009; 15:2920–2926. [PubMed: 19351764]
26. Del Fabbro E. More is better: a multimodality approach to cancer cachexia. *Oncologist.* 2010; 15:119–121. [PubMed: 20133501]
27. Bachmann J, Ketterer K, Marsch C, et al. Pancreatic cancer related cachexia: influence on metabolism and correlation to weight loss and pulmonary function. *BMC Cancer.* 2009; 9:255. [PubMed: 19635171]
- 28•. Mantovani G, Maccio A, Madeddu C, et al. Randomized phase III clinical trial of five different arms of treatment in 332 patients with cancer cachexia. *Oncologist.* 2010; 15:200–211. CT measurements, amongst other clinical parameters, were analyzed to assess the efficacy of different treatments in cachectic patients. [PubMed: 20156909]
29. Weber MA, Krakowski-Roosen H, Schroder L, et al. Morphology, metabolism, microcirculation, and strength of skeletal muscles in cancer-related cachexia. *Acta Oncol.* 2009; 48:116–124. [PubMed: 18607877]
- 30•. Gray C, MacGillivray TJ, Eeley C, et al. Magnetic resonance imaging with k-means clustering objectively measures whole muscle volume compartments in sarcopenia/cancer cachexia. *Clin Nutr.* 2011; 30:106–111. These clinical studies show the importance of using MRI techniques to assess how cachexia affects muscles not only by measuring their volume, but also by distinguishing between contractile and noncontractile components. [PubMed: 20727625]
31. Raman V, Artemov D, Pathak AP, et al. Characterizing vascular parameters in hypoxic regions: a combined magnetic resonance and optical imaging study of a human prostate cancer model. *Cancer Res.* 2006; 66:9929–9936. [PubMed: 17047055]
32. Bhujwalla ZM, Artemov D, Ballesteros P, et al. Combined vascular and extracellular pH imaging of solid tumors. *NMR Biomed.* 2002; 15:114–119. [PubMed: 11870907]
33. Glunde K, Raman V, Mori N, Bhujwalla ZM. RNA interference-mediated choline kinase suppression in breast cancer cells induces differentiation and reduces proliferation. *Cancer Res.* 2005; 65:11034–11043. [PubMed: 16322253]
34. Narayana PA. Magnetic resonance spectroscopy in the monitoring of multiple sclerosis. *J Neuroimaging.* 2005; 15 (4 Suppl):46S–57S. [PubMed: 16385018]

Key points

- The ability to noninvasively detect cachexia early on with noninvasive imaging could significantly improve the design of therapeutic strategies and treatment efficacy.
- The sequence of changes in carbohydrate, protein and lipid metabolism in organs during the onset of cachexia can be identified.
- Biomarkers of cachexia determined in preclinical studies noninvasively with imaging techniques can be translated to the clinic.
- Imaging studies of cachectic muscle have been performed in the clinic; however, studies have not as yet been performed on primary tumors inducing cachexia.

Figure 1. Clinical manifestations of cancer cachexia

a.a., amino acid; APP, acute phase proteins; CRP, C-reactive protein; dec, decrease; inc, increase; IL-1β, interleukin 1β; IL-6, interleukin 6; LMF, lipid mobilizing factor; NPY, neuropeptide Y; PIF, proteolysis inducing factor; REE, resin energy expenditure; TNF, tumor necrosis factor α. Adapted from Couch *et al.* [15] and from Glunde *et al.* [16].

Figure 2. Computed tomography scans of pancreatic cancer patients with and without cachexia
 (a) Computed tomography (CT) slide of the renal pelvis demonstrating measurements of muscles. (1) Peri-renal fat: orthograft to renal capsule and to line 2. (2) Musculus erector spinae: thickness of the muscle in a parallel line to the dorsal process. (b) CT slide of iliac crest. (3a) Thickness of the musculus psoas in a parallel line to the dorsal process. (3b) Area of the psoas muscle. (4) Subcutaneous fat medial: parallel to the dorsal process. (5) Subcutaneous fat lateral: parallel to the dorsal process starting at the iliac spine posterior superior area of the psoas muscle. Adapted from [27].

Figure 3. Comparison of MRI, magnetic resonance spectroscopy and contrast-enhanced ultrasonography of cachectic patients and healthy individuals

Magnetic resonance T₁-weighted imaging of the right thigh in a 54-year-old man with cachexia due to pancreatic cancer (a) and the corresponding right thigh at the same level of a matched healthy volunteer (b). The corresponding ¹H magnetic resonance spectrum (c) from the right vastus lateralis muscle and the ³¹P magnetic resonance spectrum of the same region (d) of the patient with cachexia illustrate the metabolites that were quantified. Peak assignments in (c): Cr, (phospho-)creatine; TMA peak, trimethyl-ammonium-containing compounds including choline; IMCL, intramyocellular lipids; EMCL, extramyocellular lipids. Peak assignments in D): phosphocreatine (PCr), inorganic phosphate (Pi), phosphodiester (PDE), and the three resonances (α, β, γ) of adenosine 5'-triphosphate (ATP). Only the signals printed in bold in (c) and (d) were quantified. The corresponding transverse power Doppler images after bolus injection of 10 ml Levovist at a depth of 1.5 cm (focus area) show the initial increase (e) and maximum plateau (f) of microbubbles replenishment within the right vastus lateralis muscle of the patient with cachexia.

Microcirculation and concentration of lipid and energy metabolites *in vivo* were comparable in muscles of volunteers and cachectic patients at rest. Adapted from [29].

Figure 4. Magnetic resonance images showing fatty infiltration within the quadriceps muscle group

Magnetic resonance cross-sectional images at the mid-thigh level in healthy women aged 23 years (a) and 80 years (b) and a woman with upper gastrointestinal cancer who was 75 years old (c). Adapted from [30*].

Table 1

Abnormalities in carbohydrate, lipid and protein metabolism in cancer cachexia

Carbohydrate metabolism	Glucose intolerance	PET imaging of ^{18}F labeled deoxyglucose
	Increased hepatic gluconeogenesis	^{13}C MRSI of ^{13}C labeled substrates
	Increased Cori cycle activity	^1H MRSI of lactate
	Decreased skeletal muscle glucose uptake	^1H MRSI of extracellular pH
Lipid metabolism	Hyperlipidemia	^1H MRSI of whole body lipid triglyceride and total choline phospholipid signal
	Increased lipolysis	
	Abnormal lipoprotein metabolism	
	Decreased whole-body lipid stores	
Protein metabolism	Increased whole-body protein turnover	^1H MRI of magnetization transfer to detect proteins
	Increased hepatic protein synthesis, acute-phase proteins	^{31}P MRS of energy metabolism (ATP, phosphocreatine) in muscle
	Increased skeletal-muscle breakdown	^1H MRSI of total creatine in muscle

MRSI, magnetic resonance spectroscopic imaging. Adapted from [14], and the ability of imaging (column 3) to study these abnormalities.