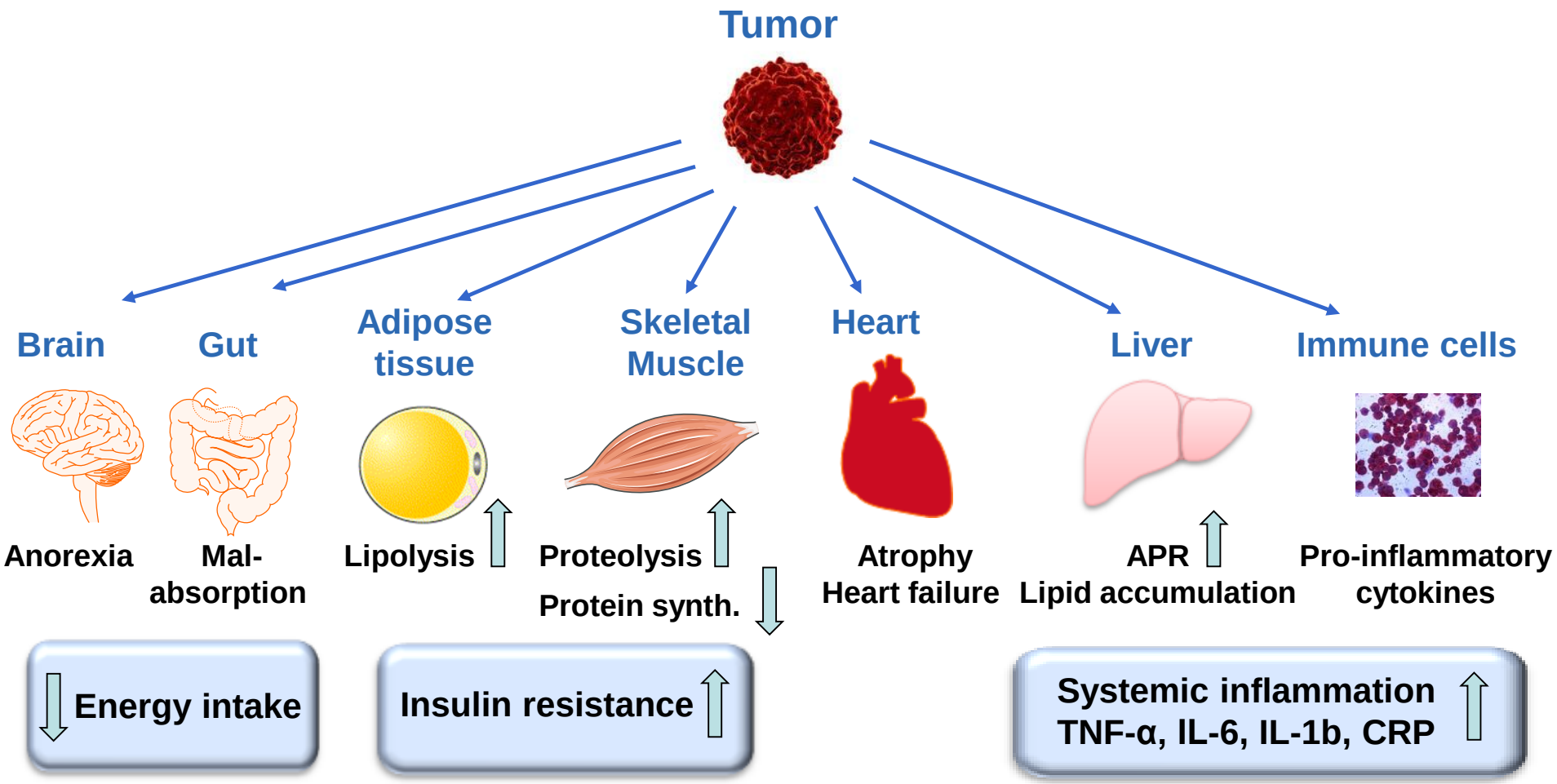
Project A9: Imaging and molecular characterization in cancer cachexia

Mauricio Berriel Diaz[1], Dimitrios Karampinos[2]

[1] Institute for Diabetes and Cancer, Helmholtz Zentrum München
[2] Department of Diagnostic and Interventional Radiology, TUM

A09: Dimitrios Karampinos, Mauricio Berriel Diaz, Stephan Herzig

Metabolic features of cancer cachexia

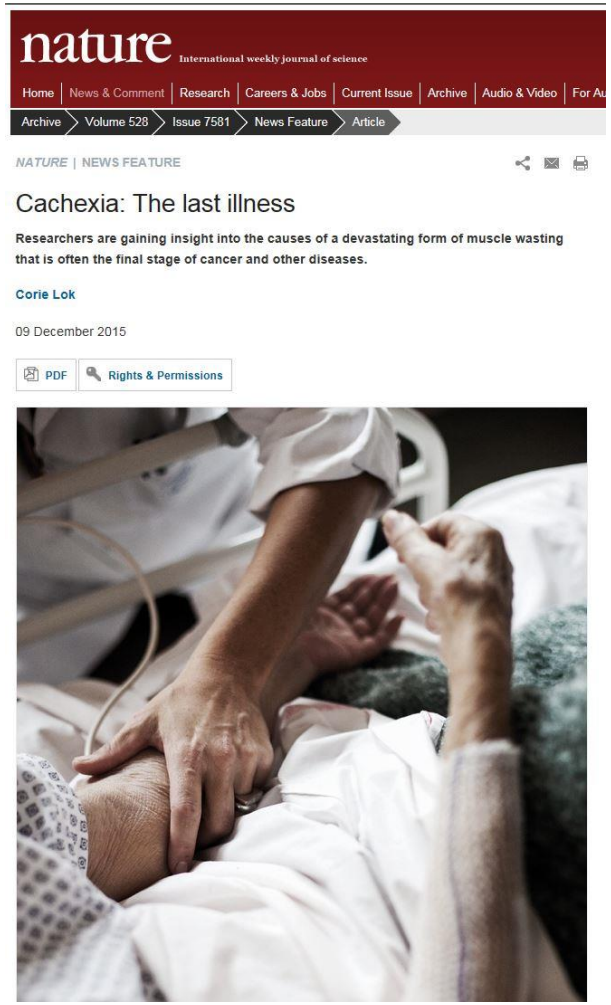


Cancer cachexia represents an unmet clinical need

CLINICAL RELEVANCE

Cancer cachexia…

- affects quality of life.
- results in reduced tolerance and efficacy of cancer therapy.
- is associated with a poor prognosis.
- accounts for 20-30% of cancer-related deaths.
- lack of stratification for cachexia risk and standardized therapies

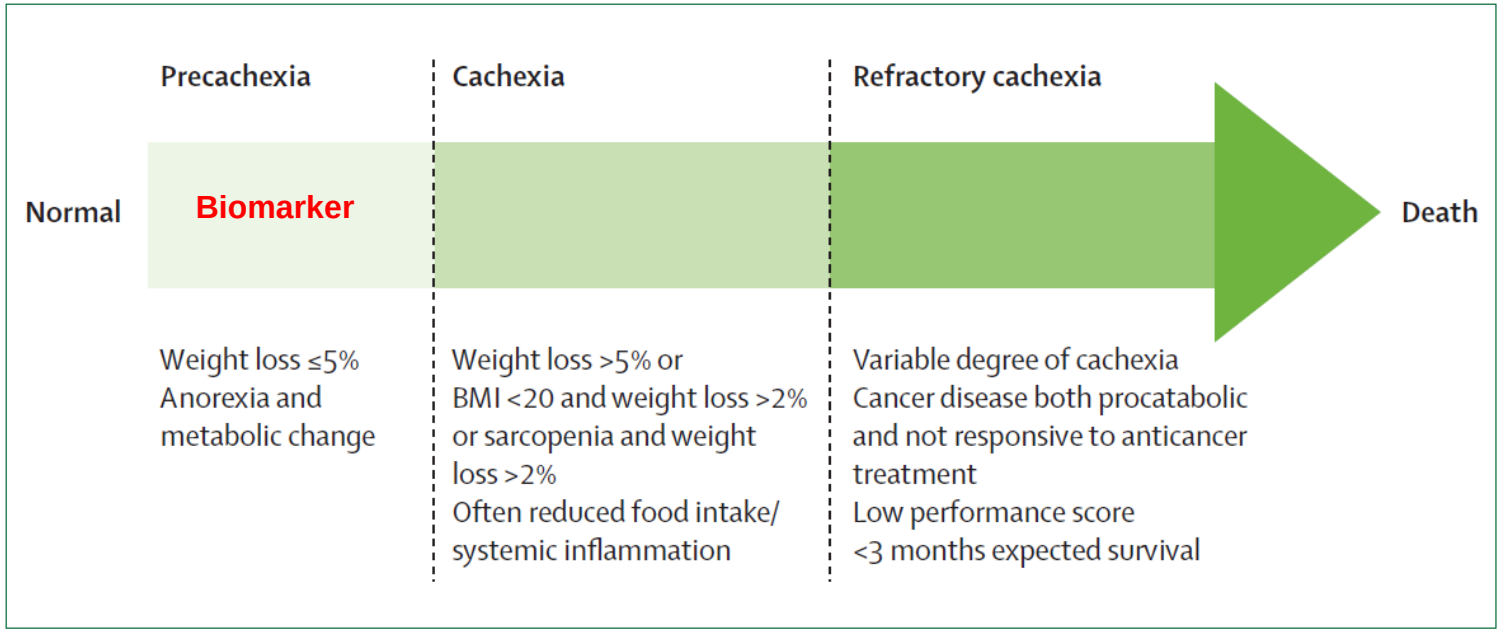


Fearon, K., et al., Lancet Oncol (2011); Tan, B.H., et al., Curr Opin Clin Nutr Metab Care (2008)

Successful treatment of cancer cachexia requires early recognition of the disease

- The efficacy of anti-cachexia therapies depend on early recognition and management of the disease, ideally at a pre-cachectic stage.
- Novel biomarkers could contribute to the detection of patients at risk and enable early initiation of multi-modal interventions to prevent progressive wasting.

Baracos, V.E., et al., Cancer-associated cachexia. Nat Rev Dis Primers, 2018. 4: p. 17105



[Fearon, K. et al. Definition and classification of cancer cachexia: an international consensus. Lancet Oncol 2011; 12: 489–95]

Development of biomarkers for cachexia monitoring and prediction

Preclinical arm
Molecular biomarkers

Time course with molecular characterization

Cancer cachexia

adipose tissue loss

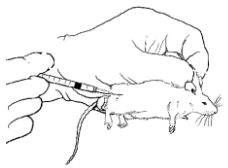
skeletal muscle loss

liver fat accumulation

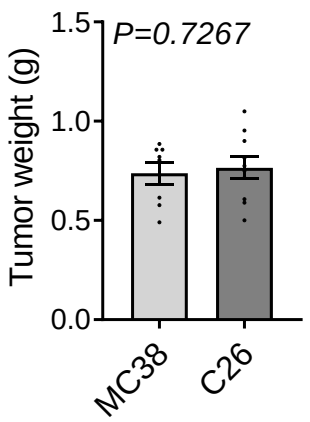
survival

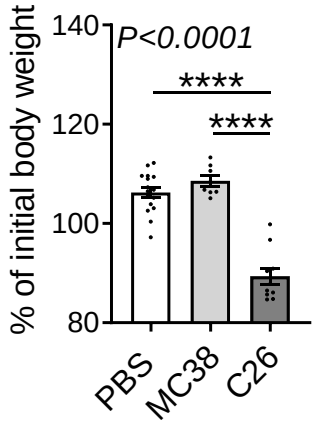
Time course with non-invasive imaging

Cachexia-inducing cancer cells are characterized by high Pla2g7 expression and secretion



subcutaneous implantation of C26 or MC38 cells





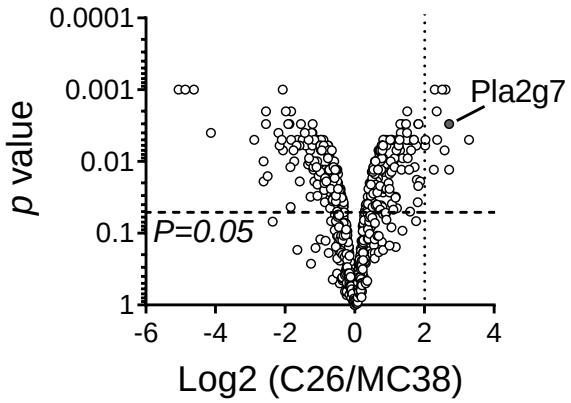
Non-cachexia-inducing cells **MC-38**

Cachexia-inducing cells **C-26**

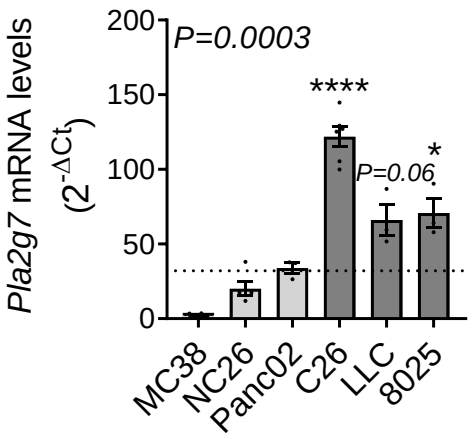
stabil isotope-labelled secreted proteins

LC-MS/MS

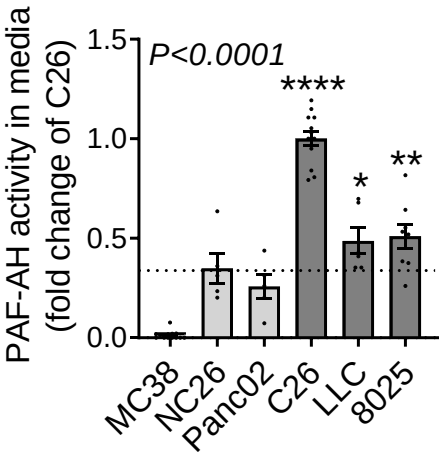
Differential secretome analysis C26 vs MC38



Pla2g7 mRNA levels



Pla2g7 enzymatic activity in cell-conditioned medium (CM)



Non-cachexia-inducing cell lines
Colon (MC38, NC26), pancreatic (Panc02) cancer

Cachexia-inducing cell lines
Colon (C26), lung (LLC), pancreatic (8025) cancer

Morigny et al., Journal of Cachexia, Sarcopenia and Muscle, 2021, accepted 06/2021

Phospholipase A2 Group VII (PLA2G7; PAF-AH; Lp-PLA2) activity could exert cachexia-inducing effects

↑PLA2G7 with cancer progression
↓survival

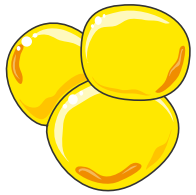
Xu et al., Cancer Res (2013)
Vaino et al., Oncotarget (2013)
Lehtinen et al., J of Pathol 2017

stable Pla2g7-KD

Tumor

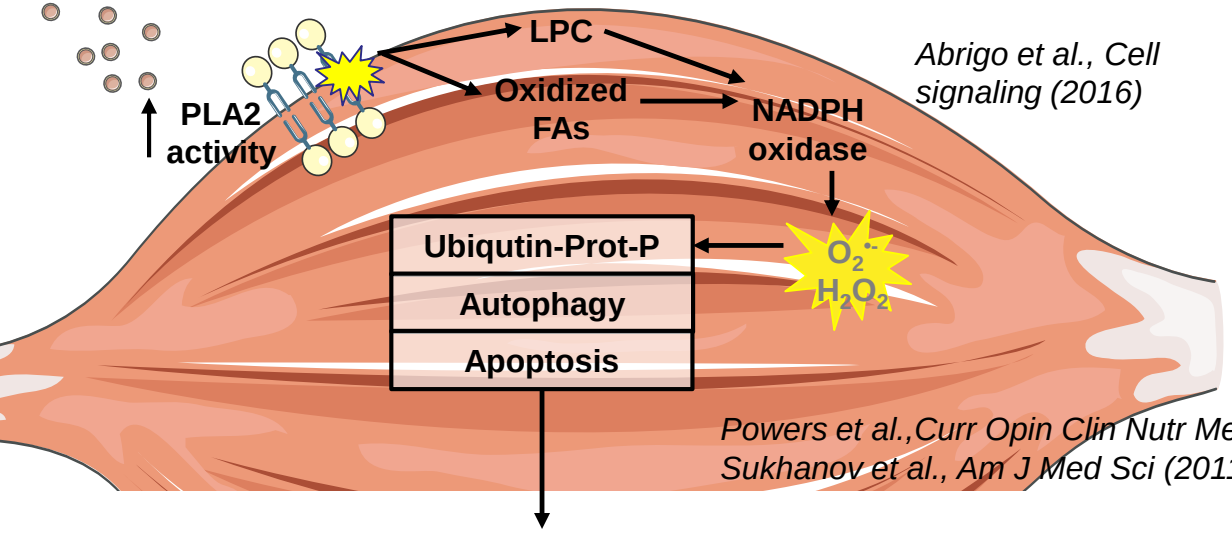
Darapladib

PLA2G7

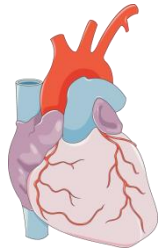


Adipose tissue wasting?

Systemic inflammation?



Abrigo et al., Cell signaling (2016)

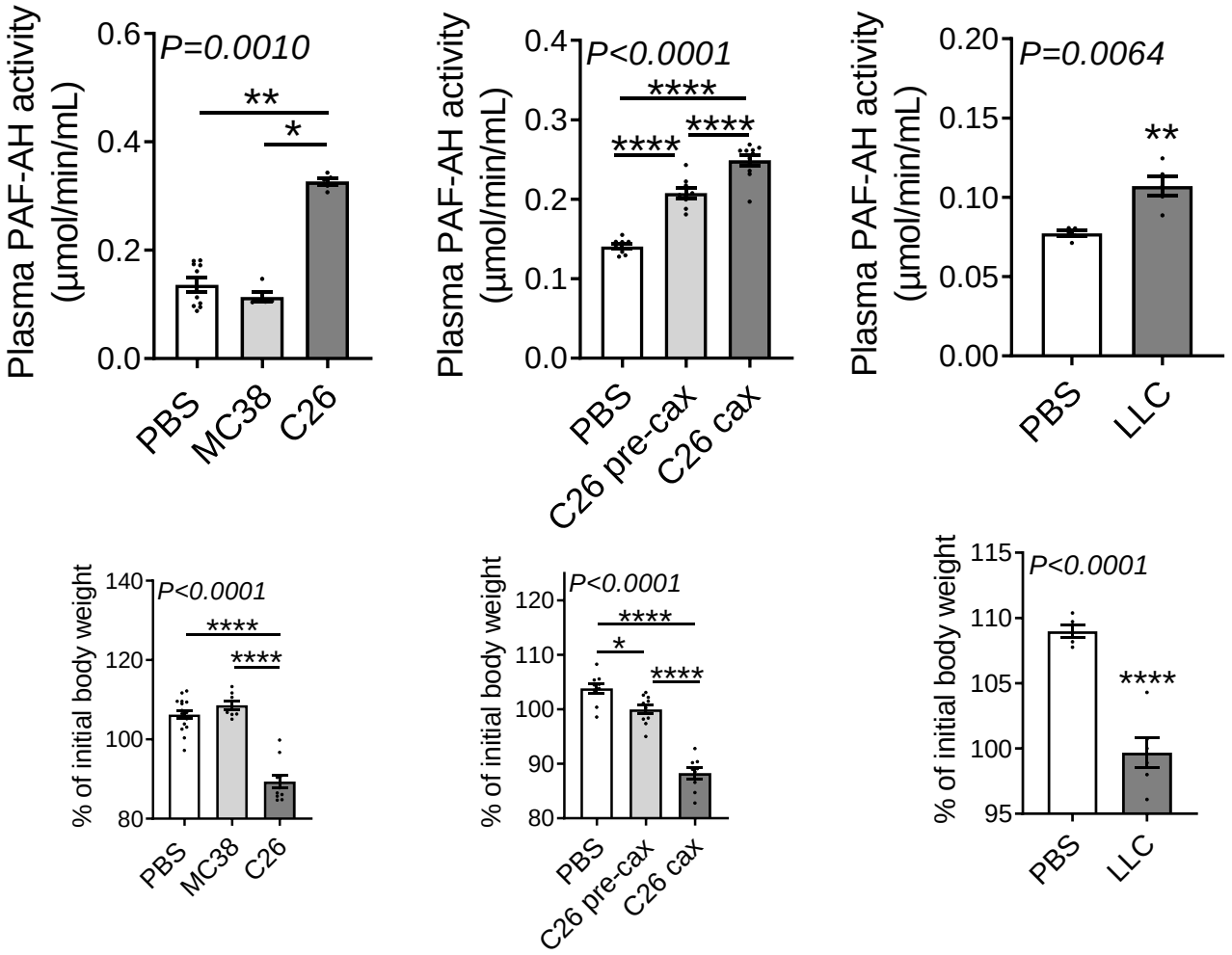


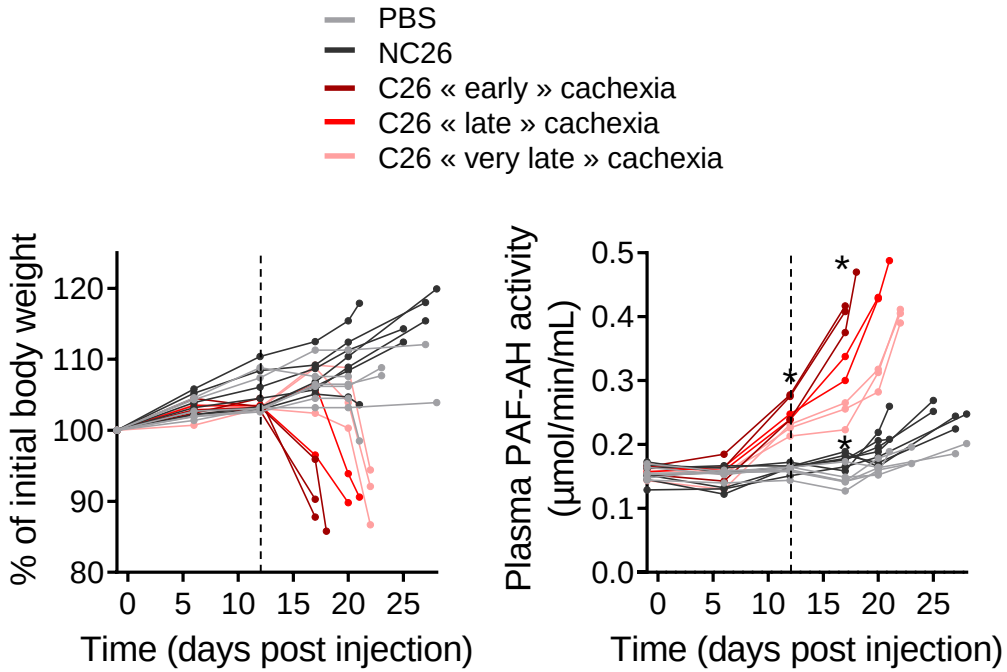
Heart atrophy?

Powers et al.,Curr Opin Clin Nutr Metab Care (2012)
Sukhanov et al., Am J Med Sci (2011)

Circulating PLA2G7 activity is induced in different mouse models of cancer cachexia

Pla2g7 enzymatic activity in plasma

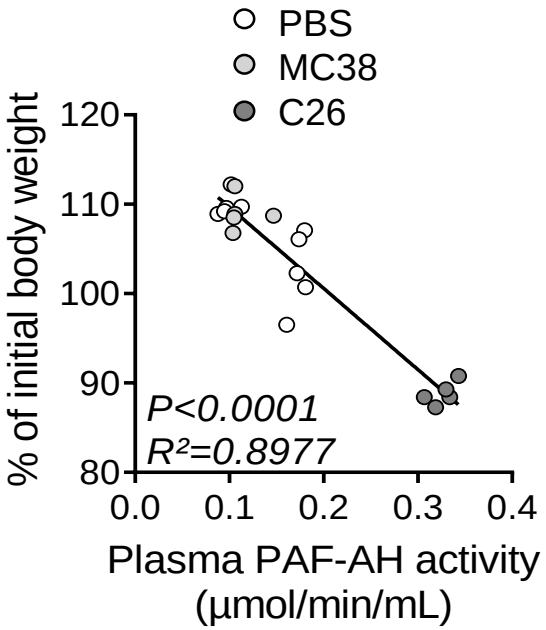


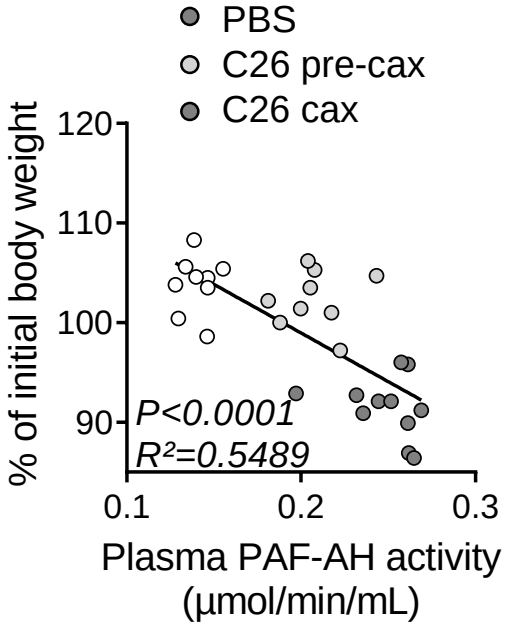


Morigny et al., Journal of Cachexia, Sarcopenia and Muscle, 2021, accepted 06/2021

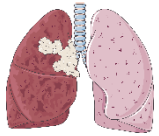
Circulating PLA2G7 activity levels correlate with the degree of weight loss in different mouse models of cancer cachexia

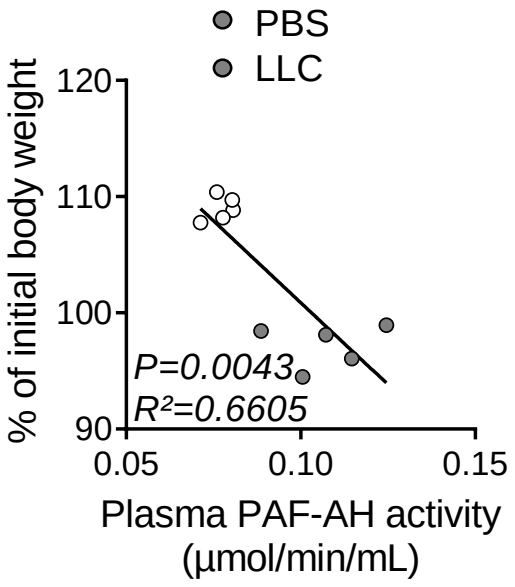
Colon cancer



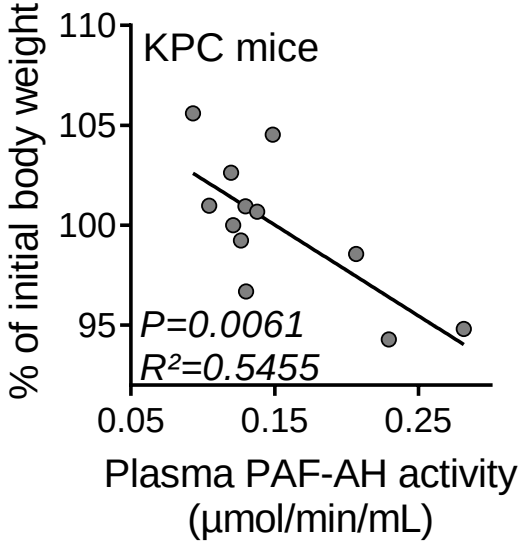


Lung cancer





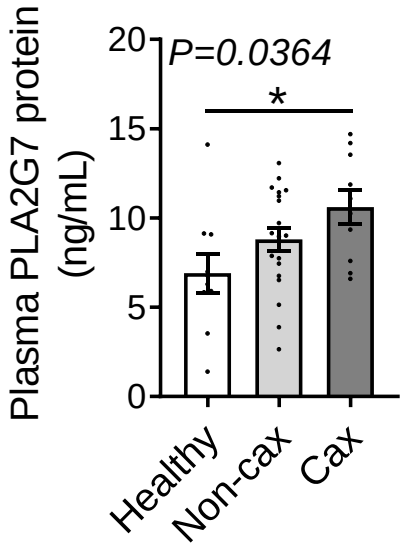
Pancreatic cancer



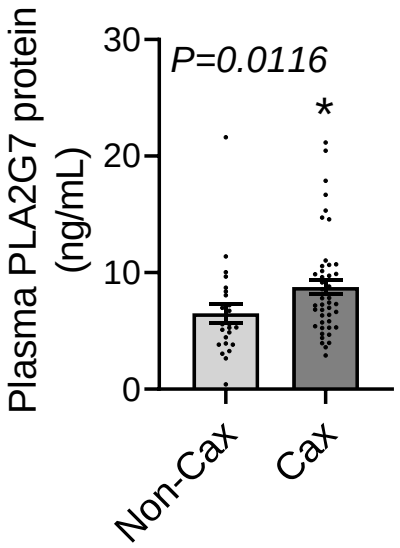
Morigny et al., Journal of Cachexia, Sarcopenia and Muscle, 2021, accepted 06/2021

Circulating PLA2G7 levels are increased in cachectic cancer patients

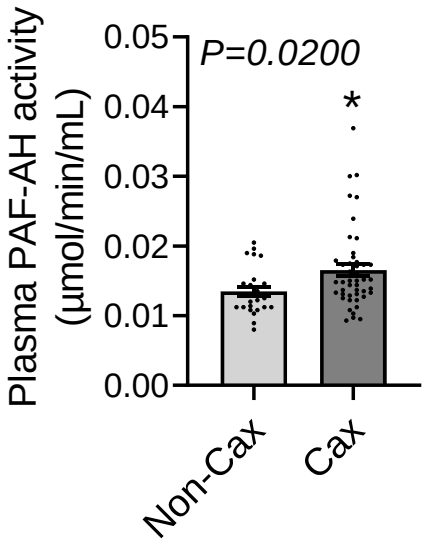
Cohort 1
Colon cancer
PDAC

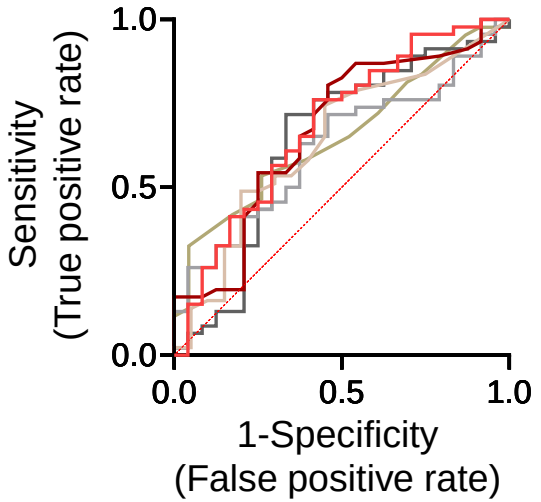


Cohort 2
PDAC



Cohort 2
PDAC

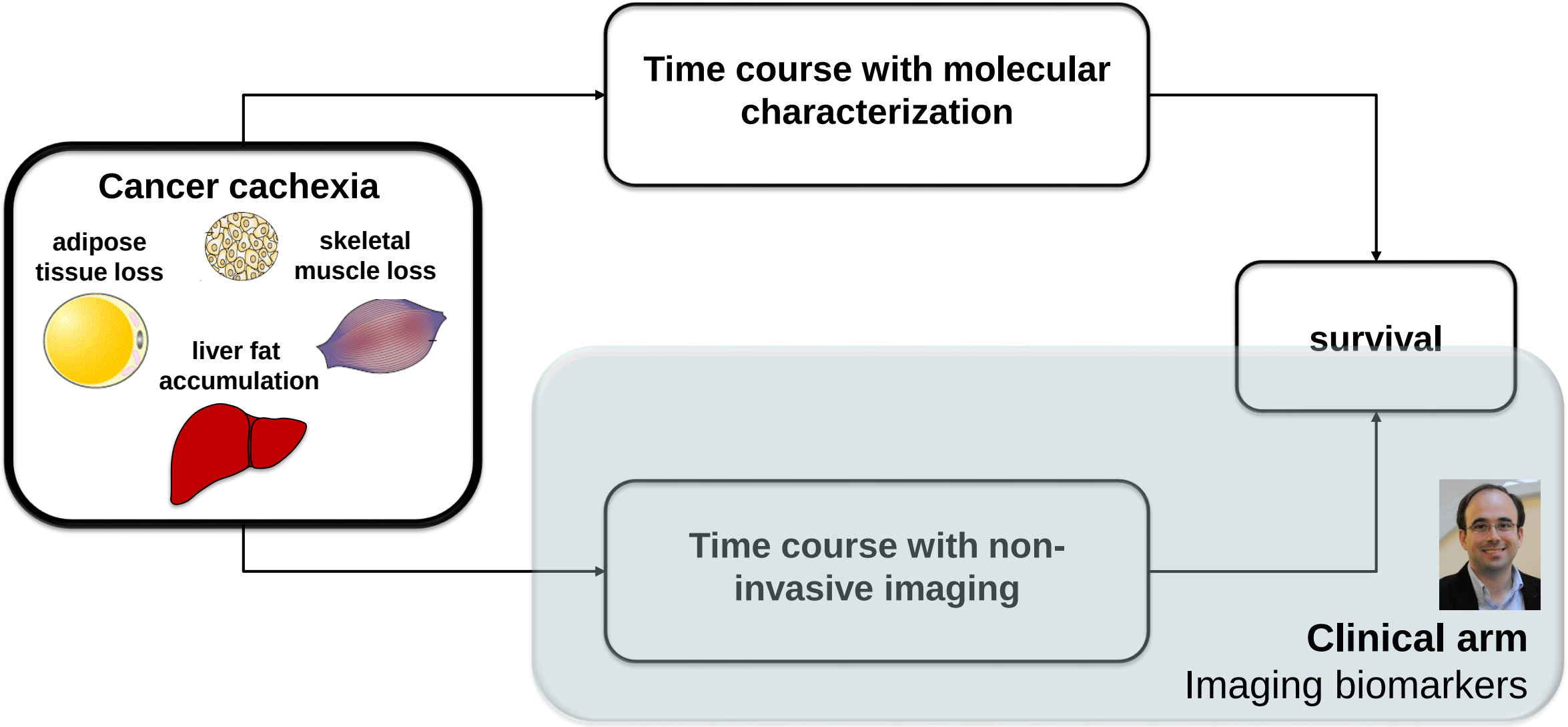




- **PLA2G7**: AUROC = 0.683 ± 0.069, *P=0.0124*
- **PAF-AH activity**: AUROC = 0.669 ± 0.070, *P=0.0207*
- **GDF-15**: AUROC = 0.639 ± 0.075, *P=0.0583*
- **IL-6**: AUROC = 0.621 ± 0.068, *P=0.0998*
- **CRP**: AUROC = 0.6372 ± 0.076, *P=0.0814*
- **Albumin**: AUROC = 0.6517 ± 0.068, *P=0.0435*

Morigny et al., Journal of Cachexia, Sarcopenia and Muscle, 2021, accepted 06/2021

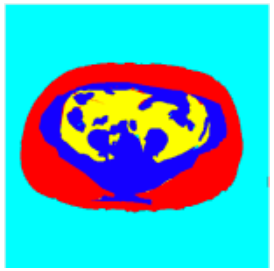
Development of biomarkers for cachexia monitoring and prediction



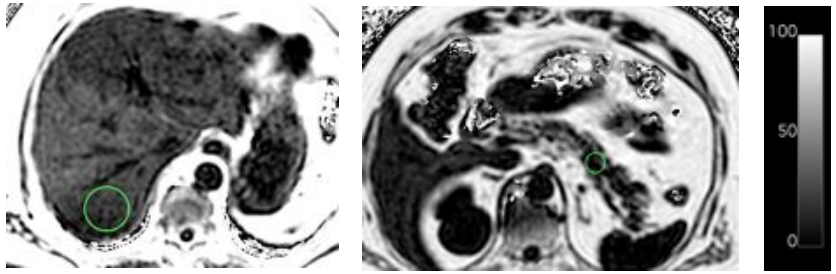
MR imaging markers for tracking cachexia

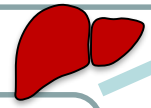
SAT/VAT volumes

SAT
VAT
NAT
Air



Hepatic & pancreatic fat fraction



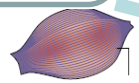


Ectopic fat deposition

Adipose tissue loss

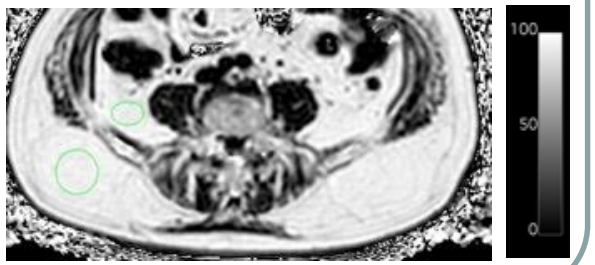
Adipose tissue composition changes

Chemical shift encoding-based water-fat separation



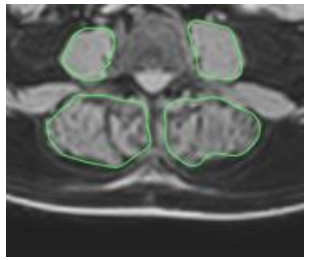
Skeletal muscle loss

Adipose tissue fat fraction

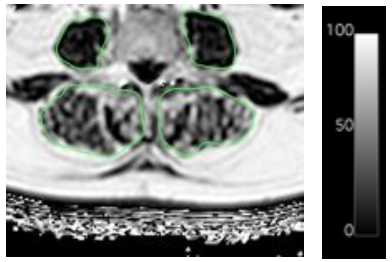


Paraspinal

muscle volume



intramuscular fat



Franz,…, ***Karampinos****, Roefo 2018*

Chemical shift encoding-based water-fat separation

Data acquisition

Time-interleaved multi-echo gradient echo pulse sequence

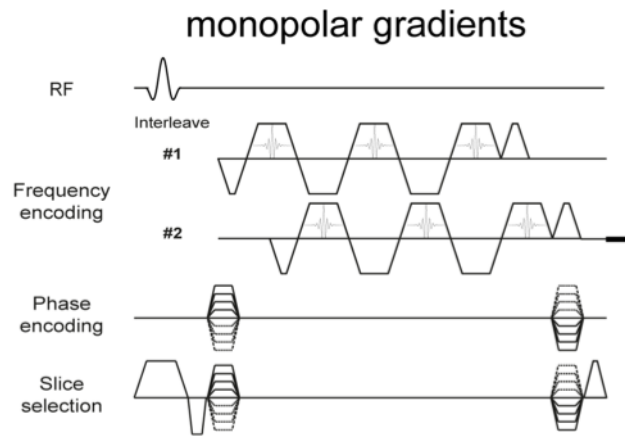
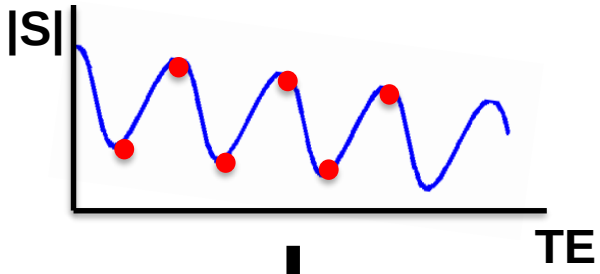


Image reconstruction

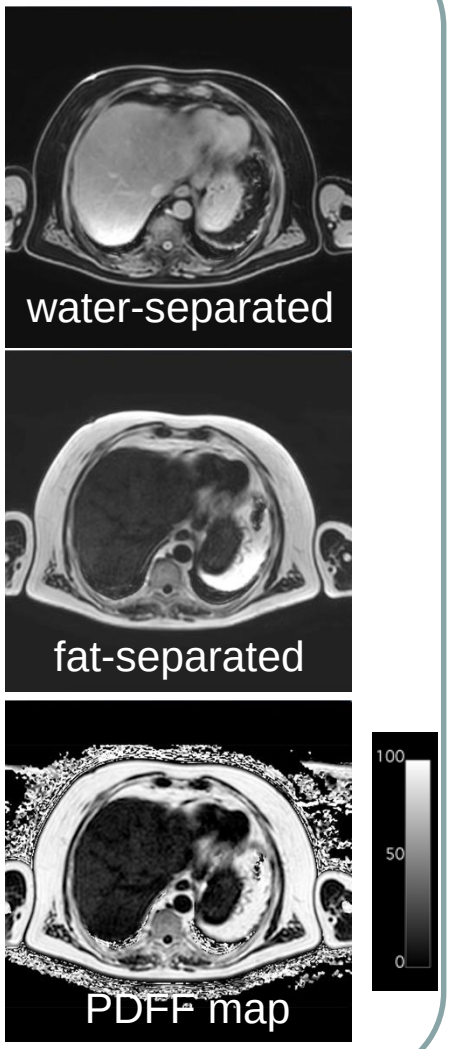


Water-fat signal model addressing

- multiple fat peaks
- T2* decay
- T1 bias
- phase errors

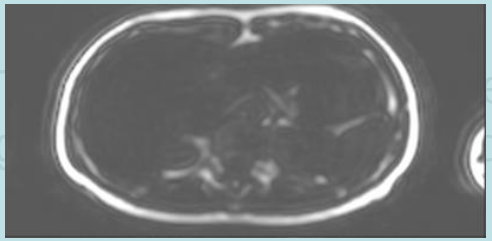
Proton density fat fraction (PDFF) quantification

Output



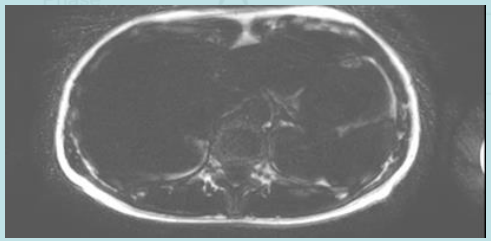
Ruschke, Magn Reson Med 2018

Chemical shift encoding-based water-fat separation



State-of-the-art fat quantification methodology
- **low resoltution**
- **uses breath-hold acquisitions**

Technical development

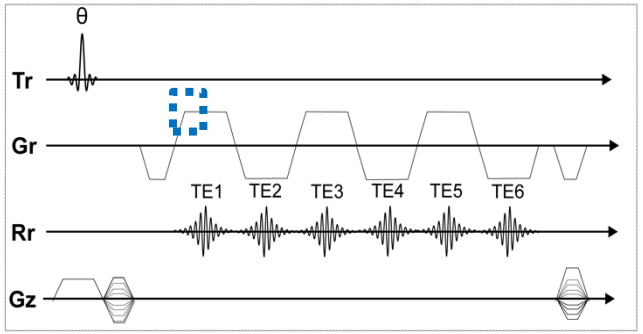


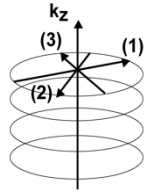
Fat quantification methodology in cancer cachexia
- **high resoltution**
- **free breathing**

Ruschke, Magn Reson Med 2018

Free-breathing high-resolution fat quantification

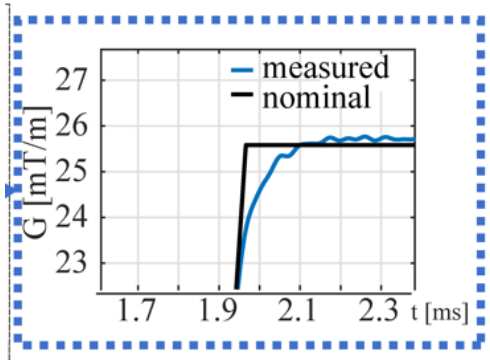
Radial stack-of-stars multi-echo gradient echo pulse sequence[1]

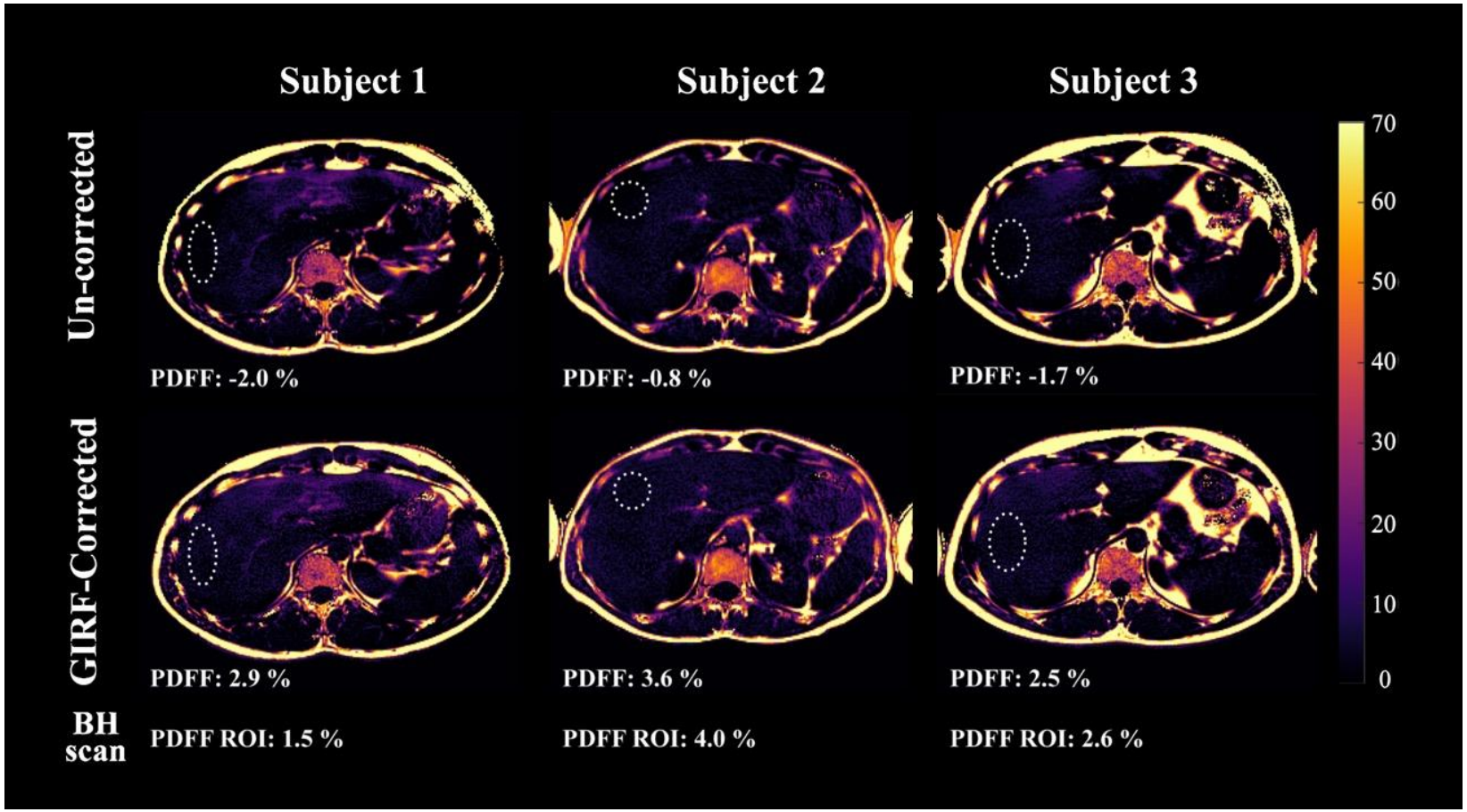




Stack-of-stars golden angle ordering

Trajectory correction using the gradient impulse response function (GIRF)[2]





[1]Zoellner,…, **Karampinos**, Proc ISMRM 2020, p. 517 [Magna Cum Laude Award]
[2]Kronthaler,…, **Karampinos**, Magn Reson Med 2021 [Magn Reson Med Editor Pick]

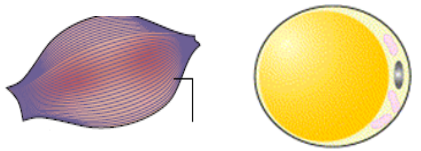
Clinical study in cancer patients

- 58 patients newly diagnosed with cancer with different tumor entities (21 female, 37 male)

- MRI of abdomen/pelvis
  - 89 study scans
  - 32 longitudinal scans completed on 22 patients

- Anthropometric measurements: body weight & height (→ BMI), waist circumference, thigh circumference

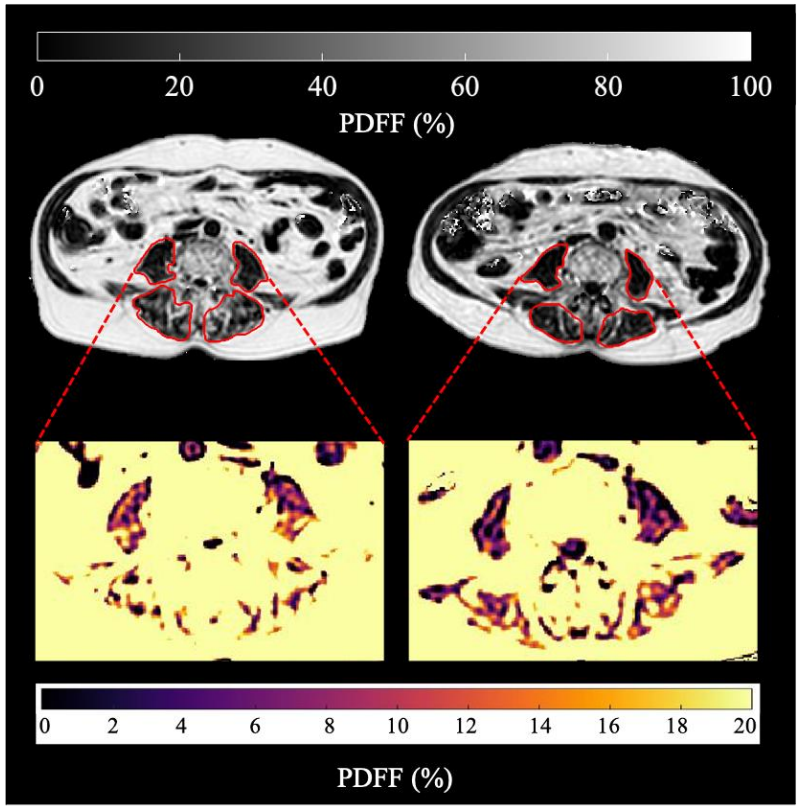
- MRI biomarkers
  - paraspinal muscle, contractile tissue and fat volume & muscle PDFF
  - SAT, VAT volume and PDFF



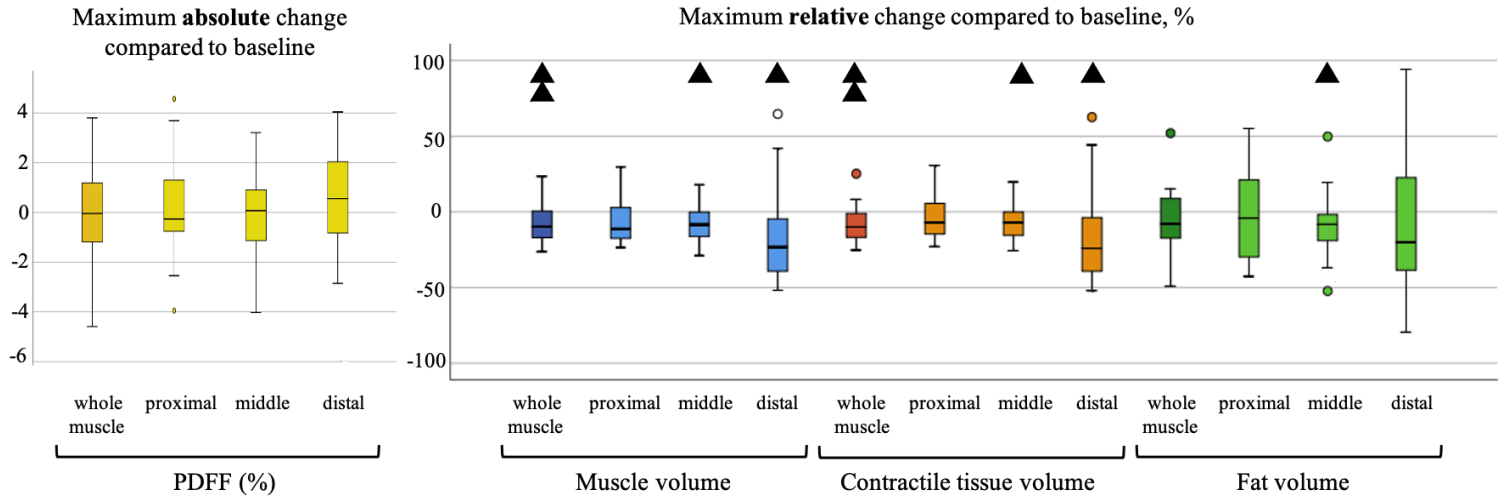
Longitudinal skeletal muscle changes

▲ p < 0.05 * p < 0.05
▲▲ p < 0.01 ** p < 0.01

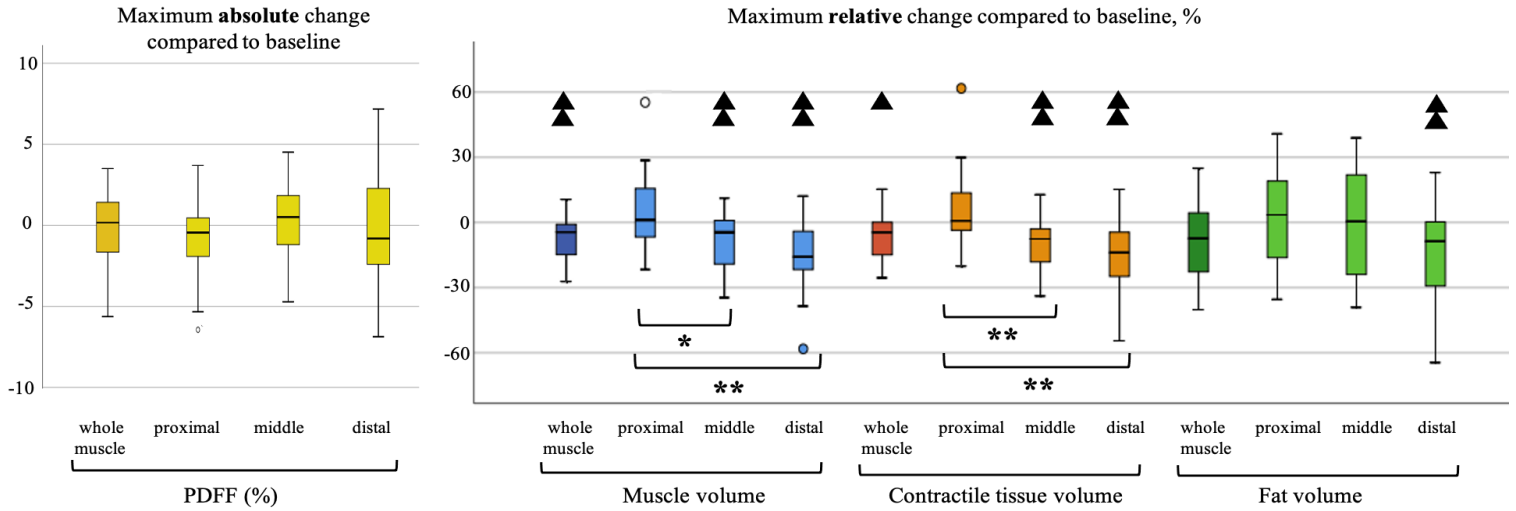
baseline follow-up



Psoas muscles

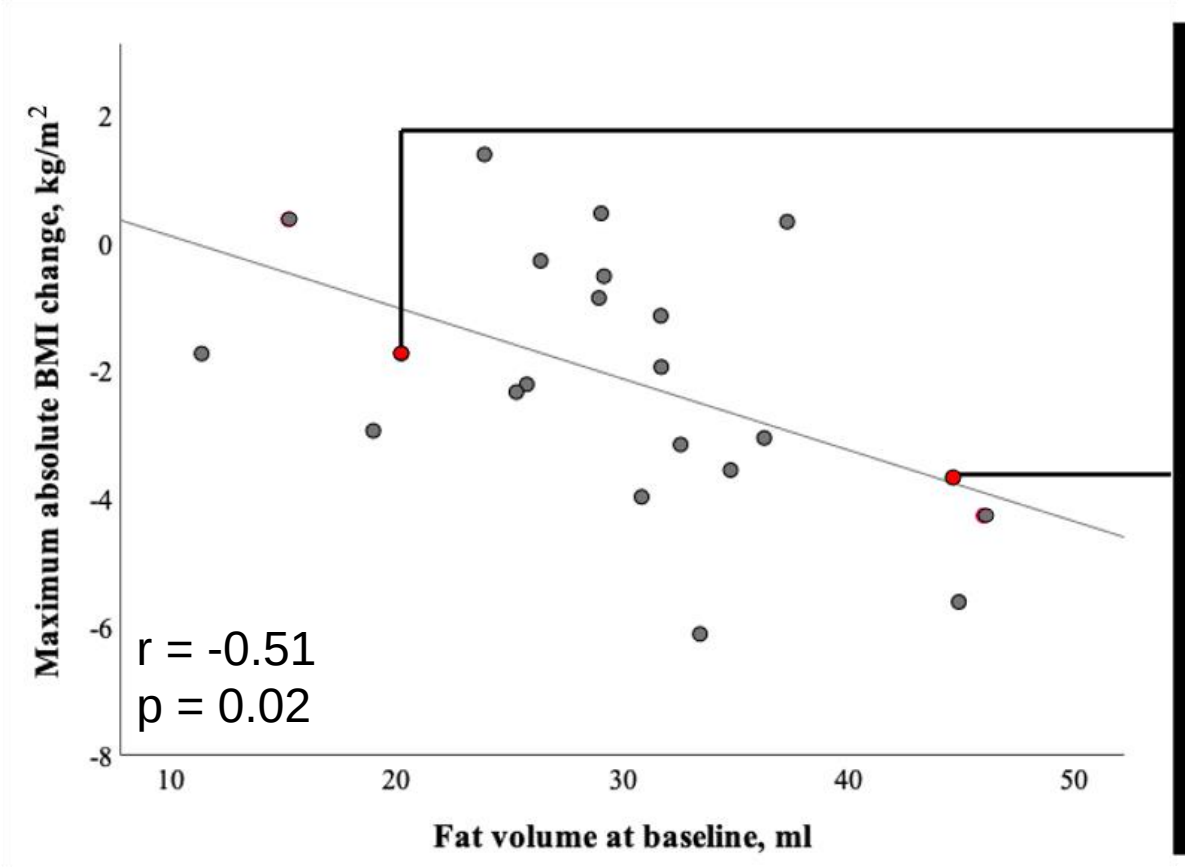


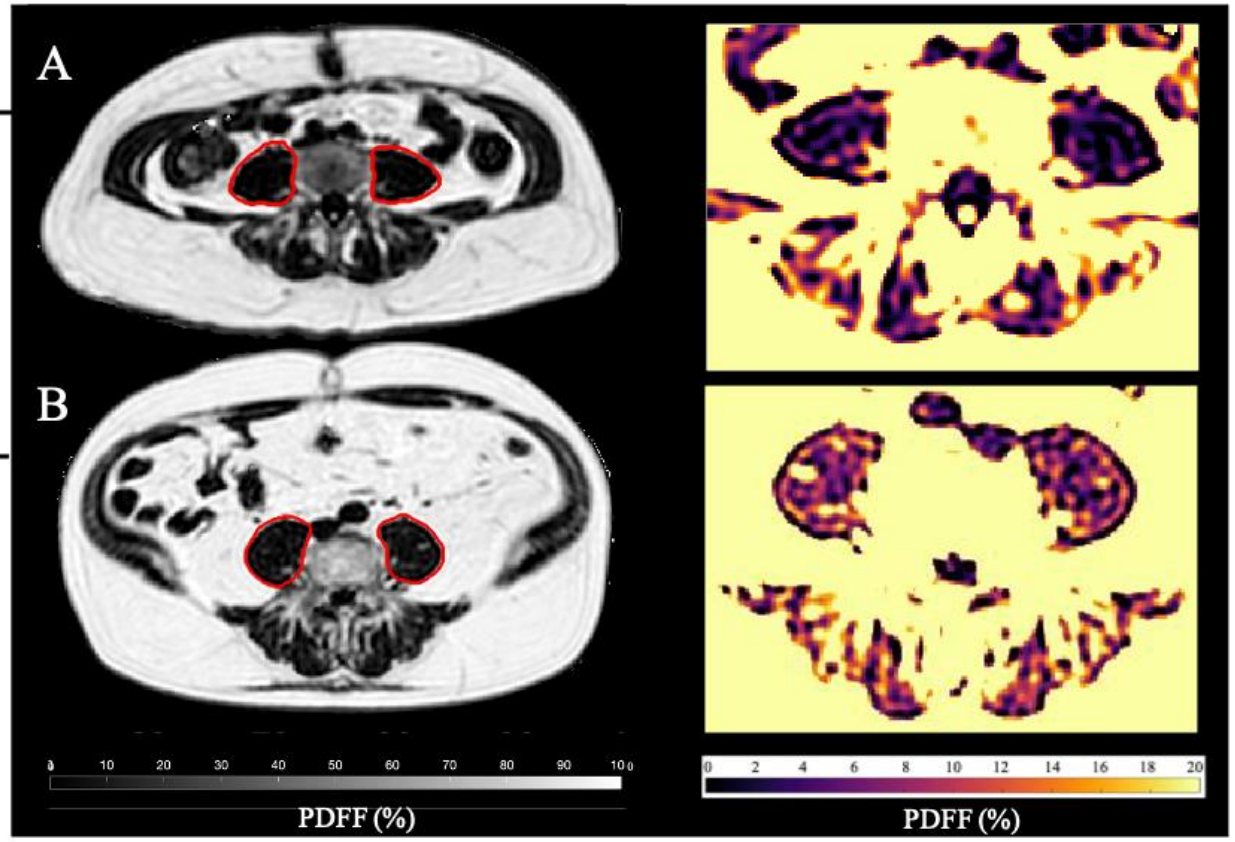
Erector spinae muscles



Patzelt, …, Herzig, Berriel Diaz, Karampinos, under review

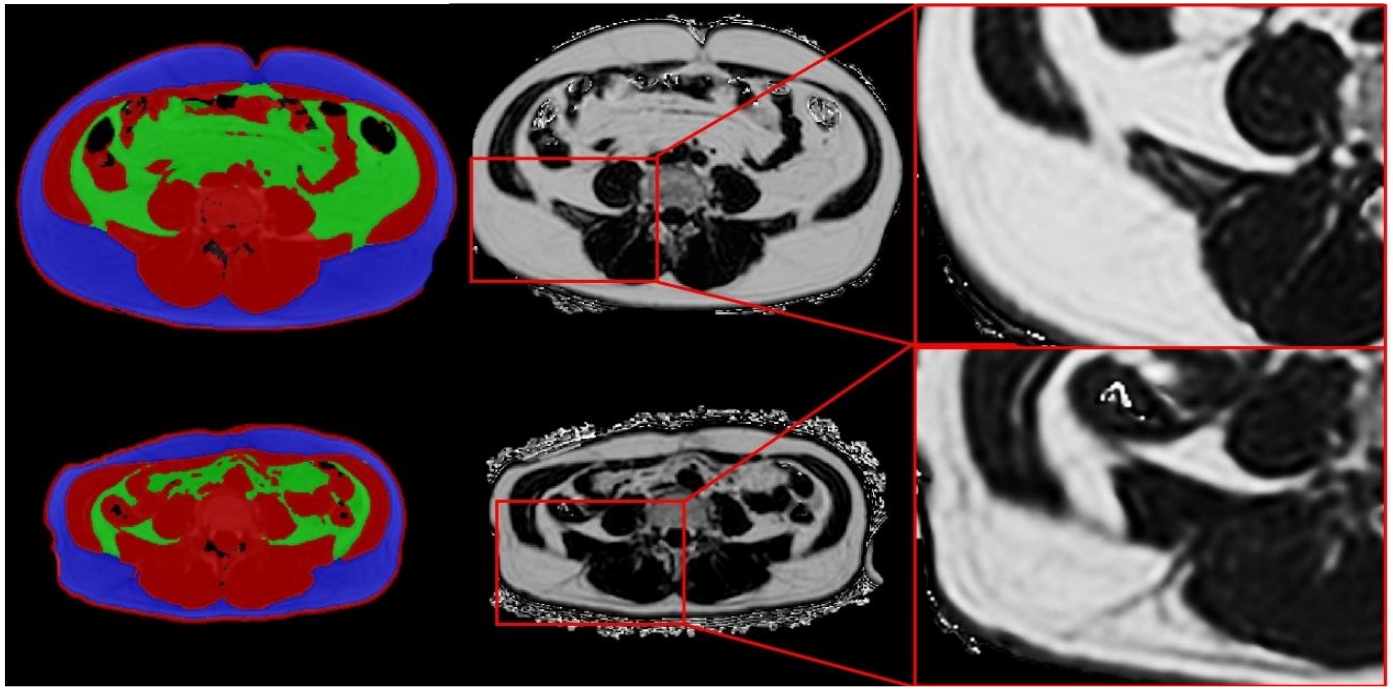
Psoas fat infiltration as predictor for cachexia progression

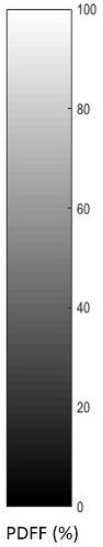


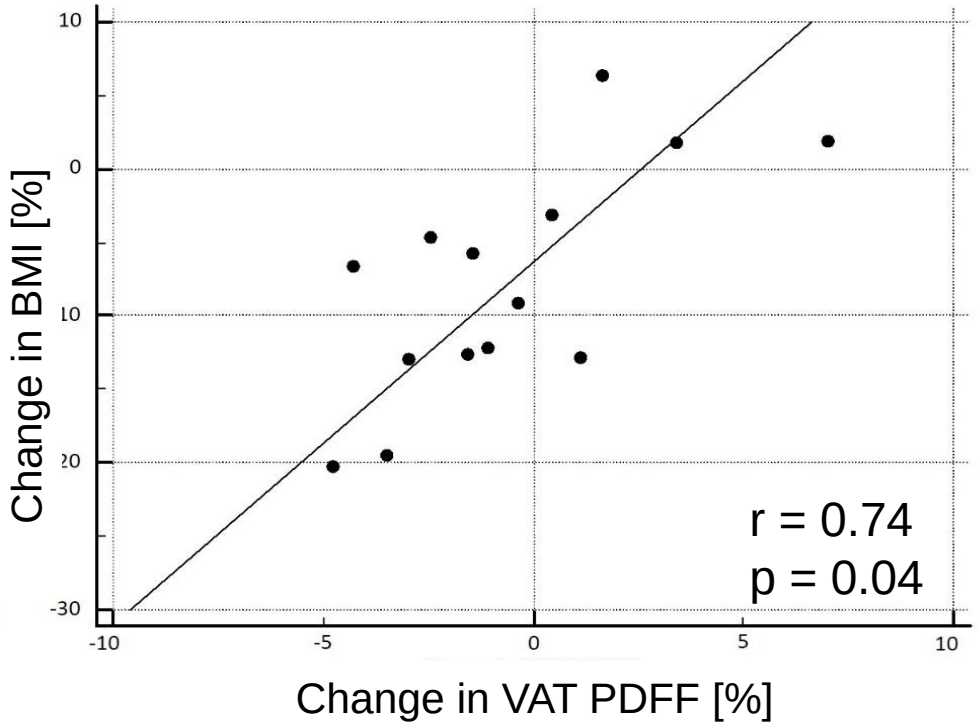


Patzelt, …, Herzig, Berriel Diaz, Karampinos, under review

Longitudinal adipose tissue changes







Franz, Proc ISMRM 2019, p. 1941

Summary

Preclinical Part:

- Circulating PLA2G7 activity is induced in different mouse models of cancer cachexia and the levels correlate with the degree of weight loss.
- Circulating PLA2G7 levels are increased in cachectic cancer patients (CRC & PDAC).
- PLA2G7 protein levels and activity could distinguish between cachectic and non-cachectic patients, suggesting a potential biomarker function.

Clinical Part:

- High-resolution PDFF mapping is technically feasible using non-cartesian imaging techniques.
- Paraspinal muscle, contractile tissue and fat volume decrease in cancer cachexia-induced weight loss.
- A regional variation of intramuscular fat changes is observed in the paraspinal muscles.
- Baseline psoas muscle PDFF and fat volume correlated with weight loss and could serve as MRI-determined biomarkers for early cachexia risk stratification.

Selected published publications

D. Franz, J. Syvaeri, D. Weidlich, T. Baum,, E. J. Rummeny, **D. C Karampinos**, Magnetic resonance imaging of adipose tissue in metabolic dysfunction, Roefo, 190:1121, 2018 [review article]

D. C Karampinos, D. Weidlich, M. Wu, H. Hu, D. Franz, Techniques and applications of Magnetic Resonance Imaging for studying brown adipose tissue morphometry and function, Handbook of Experimental Pharmacology, Brown Adipose Tissue, 299, 2019 [review article]

M. Wu, D. Junker, R. T. Branca, **D. C. Karampinos**, Magnetic resonance imaging techniques for brown adipose tissue detection, Frontiers in Endocrinology, 11:421, 2020 [review article]

Schmidt SF, Rohm M, **Herzig S, Berriel Diaz M**. Cancer Cachexia: More Than Skeletal Muscle Wasting. Trends in Cancer, 2018 Dec;4(12):849-860 [review article]

F. K. Lohöfer, G. A. Kaissis, C. Müller-Leisse, D. Franz, C. Katemann, A. Hock, J. M. Peeters, E. J. Rummeny, **D. C. Karampinos**, R. F. Braren, Acceleration of chemical shift encoding-based water fat MRI for liver proton density fat fraction and T2* mapping using compressed sensing, PLos One, 14(11): e0224988, 2019

Publications in preparation, under review or in press

L. Patzelt, D. Junker, J. Syväri, E. Burian, M. Wu, O. Prokopchuk, U. Nitsche, M.R. Makowski, **S. Herzig**, **M. Berriel Diaz**, **D.C. Karampinos**, Psoas muscle fat infiltration correlates with severity of weight loss during cancer cachexia, submitted to Journal of Cachexia, Sarcopenia

D.Junker, L.Patzelt, J. Syväri, E. Burian, M. Wu, O. Prokopchuk, U. Nitsche, M.R. Makowski, **S. Herzig**, **M. Berriel Diaz**, **D.C. Karampinos**, Proton density fat fraction mapping for tracking adipose tissue changes under weight loss in cancer cachexia, in preparation

C. Zöllner, S. Kronthaler, S. Ruschke, J. Rahmer, J. M. Peeters, H. Eggers, P. Börnert, R. F. Braren, **D. C. Karampinos**, Trajectory correction in high-resolution gated golden-angle radial Dixon imaging using the gradient impulse response function, in preparation

C. Zöllner, S. Kronthaler, S. Ruschke, H. Eggers, J. Rahmer, P. Börnert, R. F. Braren, D. Franz, **D. C. Karampinos**, Correcting gradient chain-induced fat quantification errors in multi-echo SoS acquisition using the gradient impulse response function, in preparation

P. Morigny, D. Kaltenecker, J. Zuber, J. Machado, L. Mehr,…, A. Krüger, J. Krijgsveld, O. Prokopchuk, S. Fisker Schmidt, M. Rohm, **S. Herzig**, **M. Berriel Diaz**, Association of circulating PLA2G7 levels with cancer cachexia and assessment of darapladib as a therapy, **accepted for publication in Journal of Cachexia, Sarcopenia and Muscle 06/15/2021**

J. Machado, D. Kaltenecker, C.-E. Molocea, J. Zuber, P. Morigny, ,…, **D. C. Karampinos**, A. Krüger, M. Seelaender, M. Rohm, **S. Herzig, M. Berriel Diaz**, Tumor-derived FactorX is a mediator of tissue wasting during cancer associated-cachexia, in preparation

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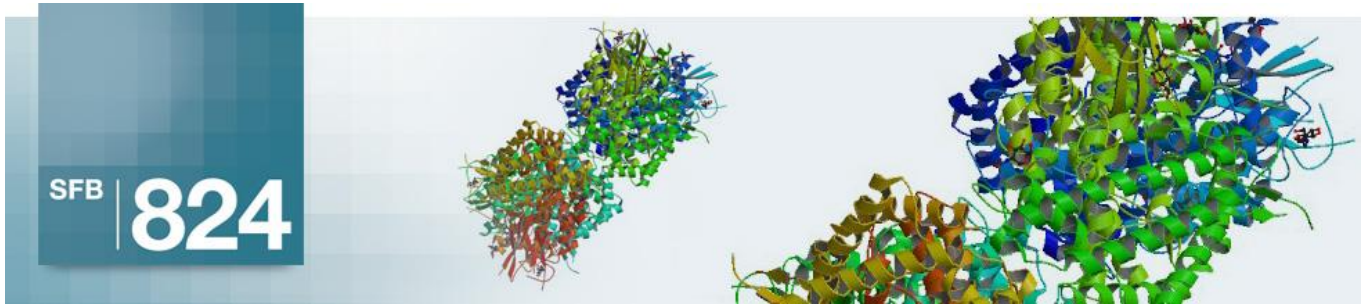

DFG Deutsche Forschungsgemeinschaft
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HELMHOLTZ RESEARCH FOR GRAND CHALLENGES

DZD Deutsches Zentrum für Diabetesforschung