Kinetic Modeling and Applications of Total-Body PET Technology

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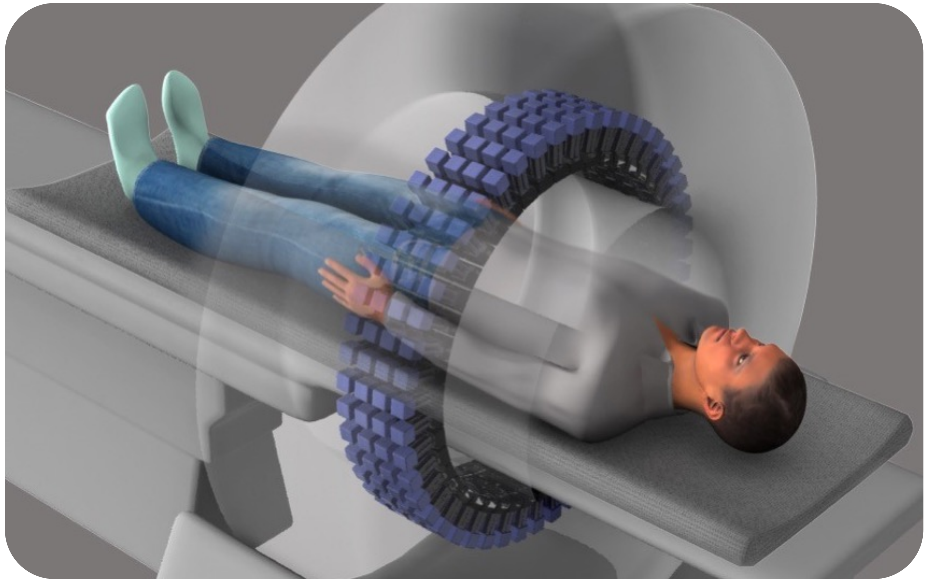
Disclosure

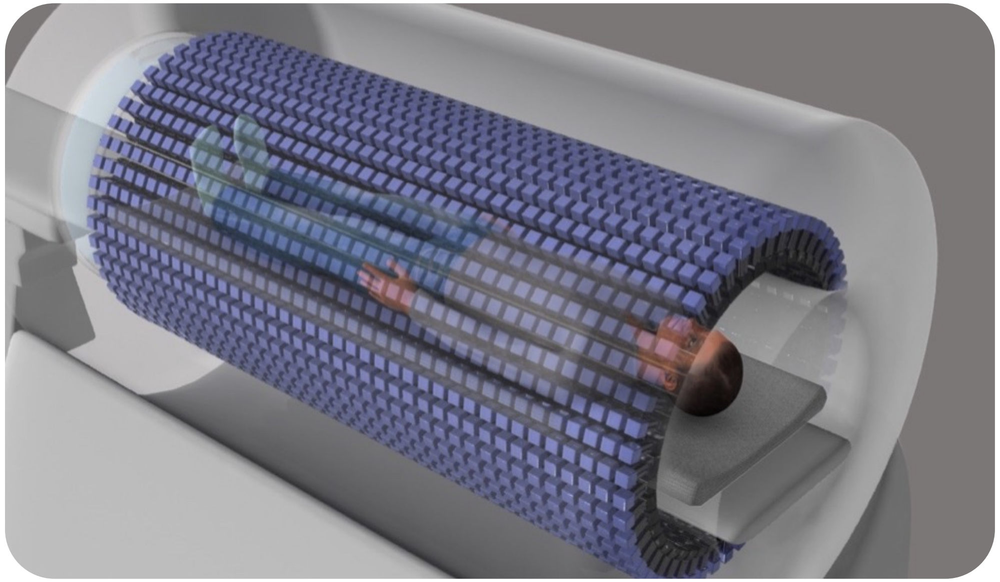
- University of California Davis has a revenue sharing agreement and a research agreement with United Imaging Healthcare (UIH)

Total-Body PET

(A) Conventional PET scanner
(Axial FOV: 15-30 cm)



(B) EXPLORER
(Axial FOV: 194 cm)



Total-body PET provides unprecedented photon detection sensitivity and enables simultaneous imaging of the entire body

Cherry *et al.* JNM 2018; Badawi *et al.* JNM 2019

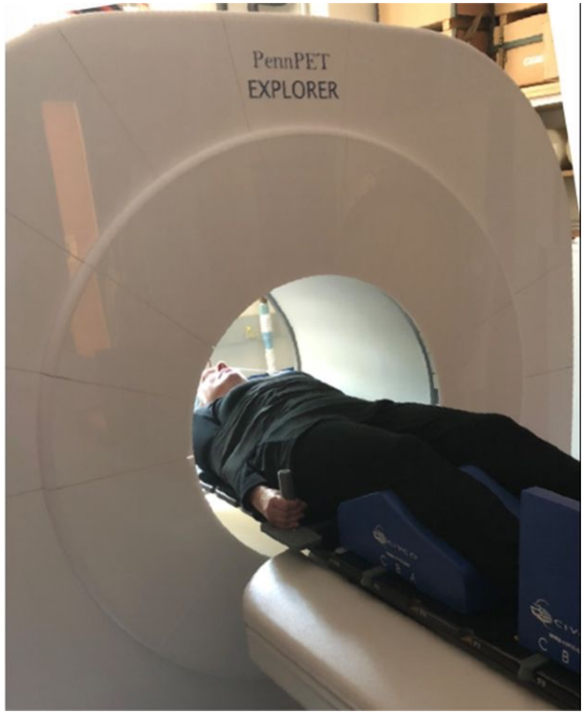
Long Axial FOV PET Scanners

UIH uEXPLORER (installed at UC Davis in 2019)

Axial FOV: 194 cm

Spencer *et al.* JNM 2021

PennPET EXPLORER



Axial FOV: 112 cm (extended)

Karp *et al.* JNM 2020

Siemens Biograph Vision Quadra

Axial FOV: 106 cm

Alberts *et al.* EJNMMI 2021

Use of Total-Body PET for Static Imaging

- Image better

  ~ 6-fold gain in SNR

- Image faster

  up to 1/40th time

- Image longer/later

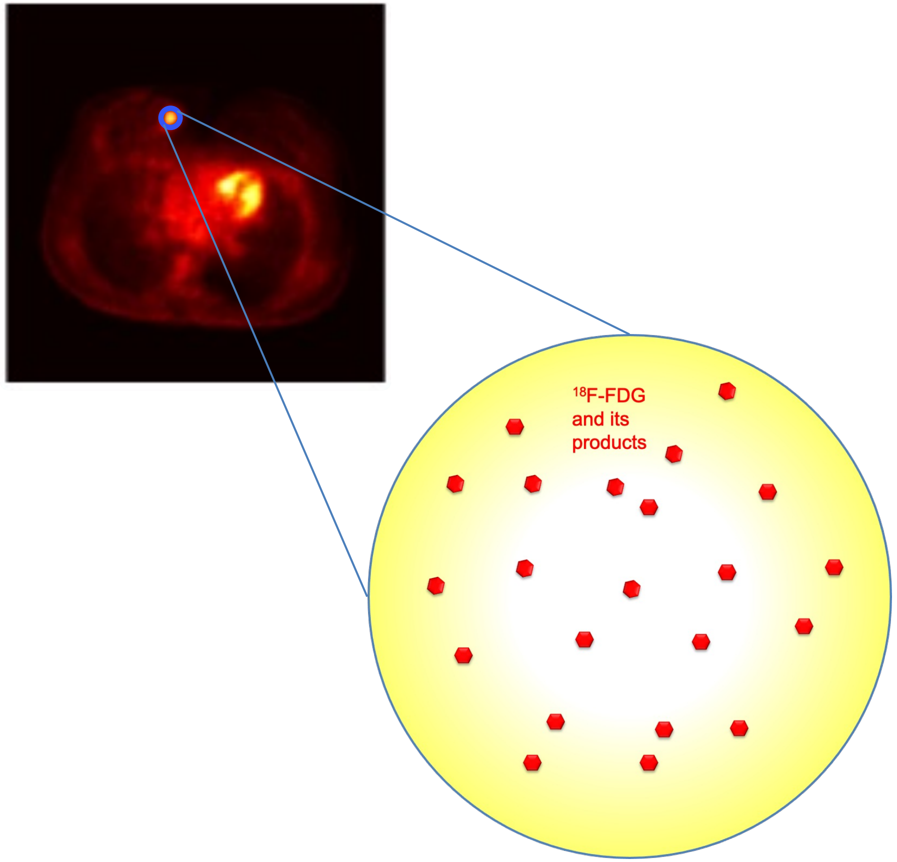
  ~ 5 more half-lives

- Image with low dose

  up to 1/40th dose

Courtesy of Ramsey D. Badawi

Limitation of Static Imaging

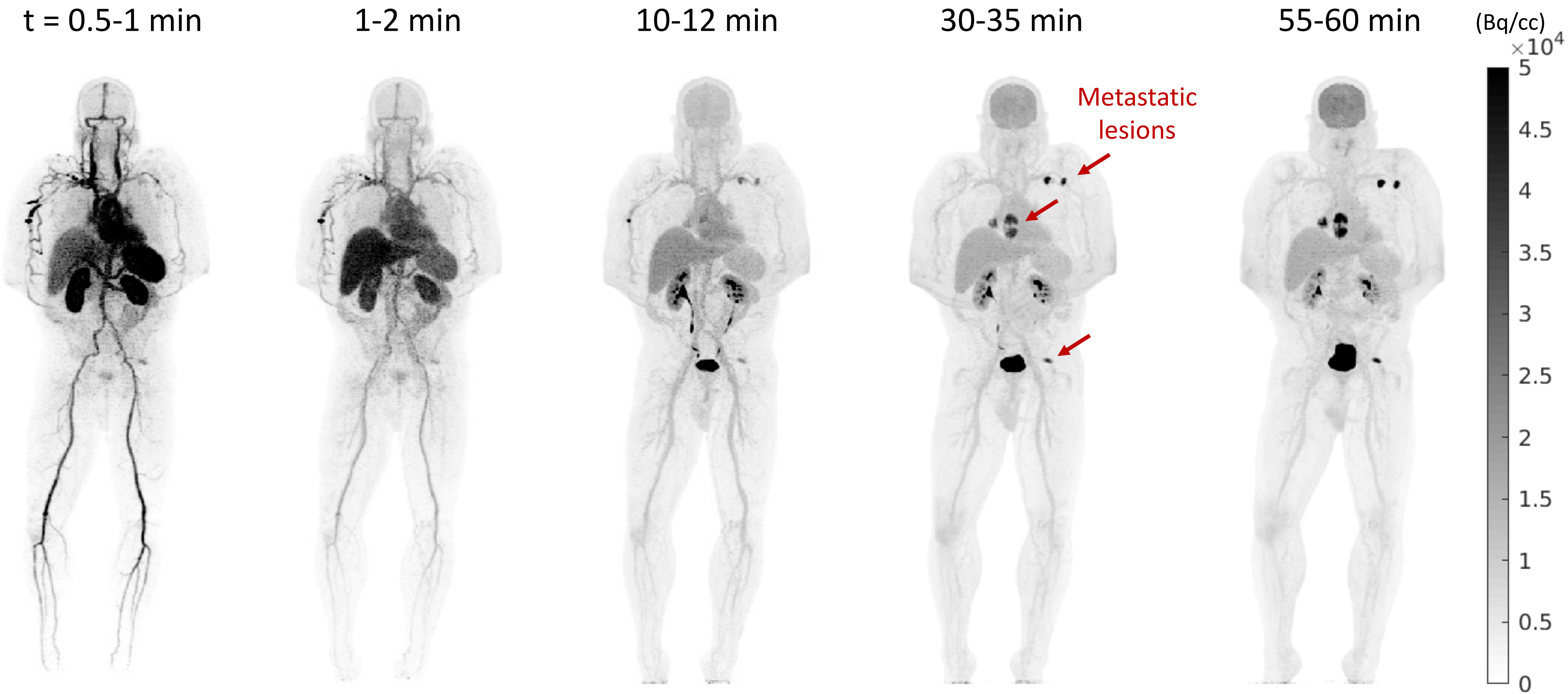


- Semi-quantification using standardized uptake value (SUV)

$$SUV = \frac{\text{Radiotracer Concentration}}{\text{Injected Dose / Body Weight}}$$

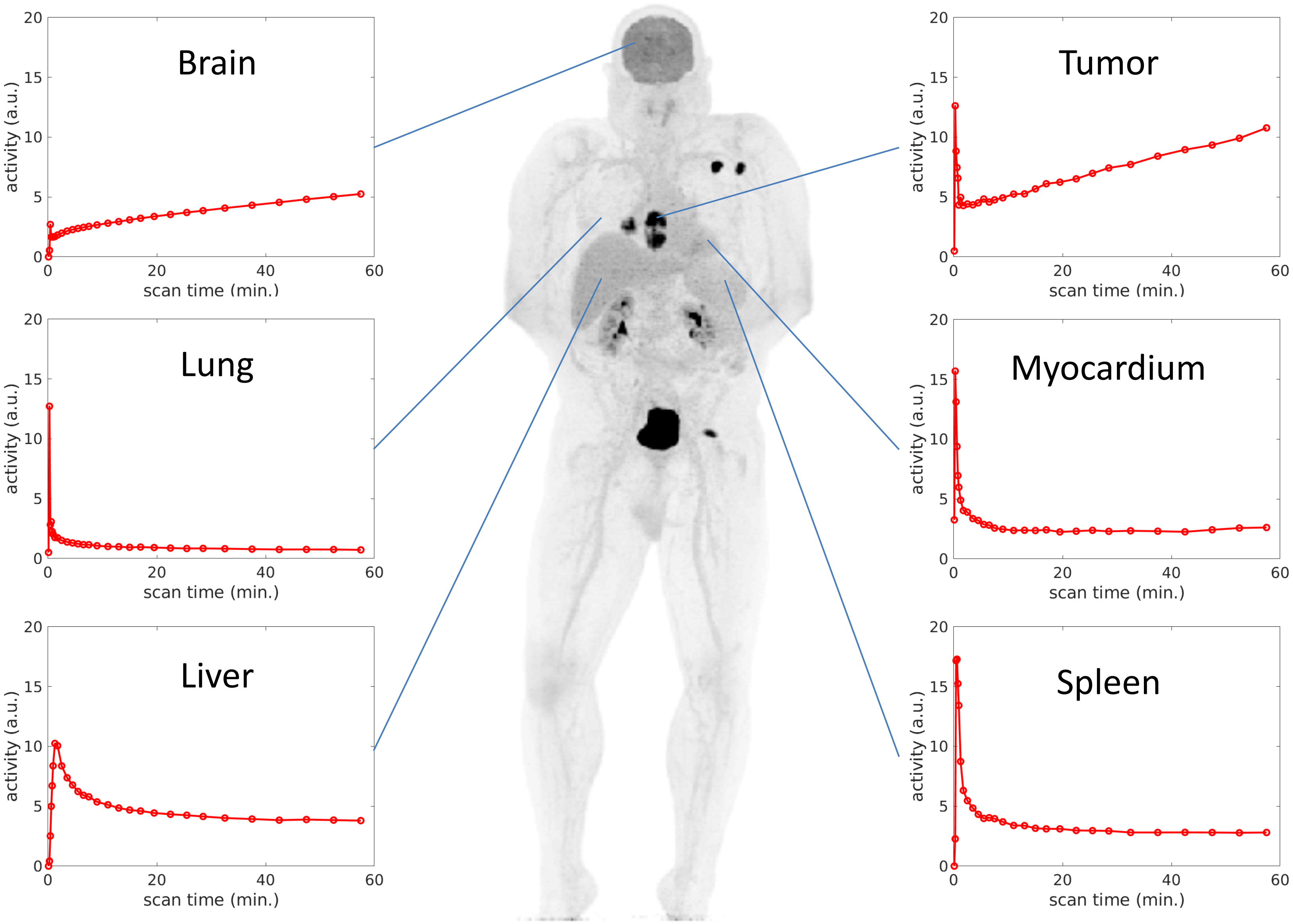
- Being specific to a time point
- Affected by body habitus and dietary preparation
- Mixing signal in vascular space and cellular space

Simultaneous Dynamic Imaging of the Entire Body

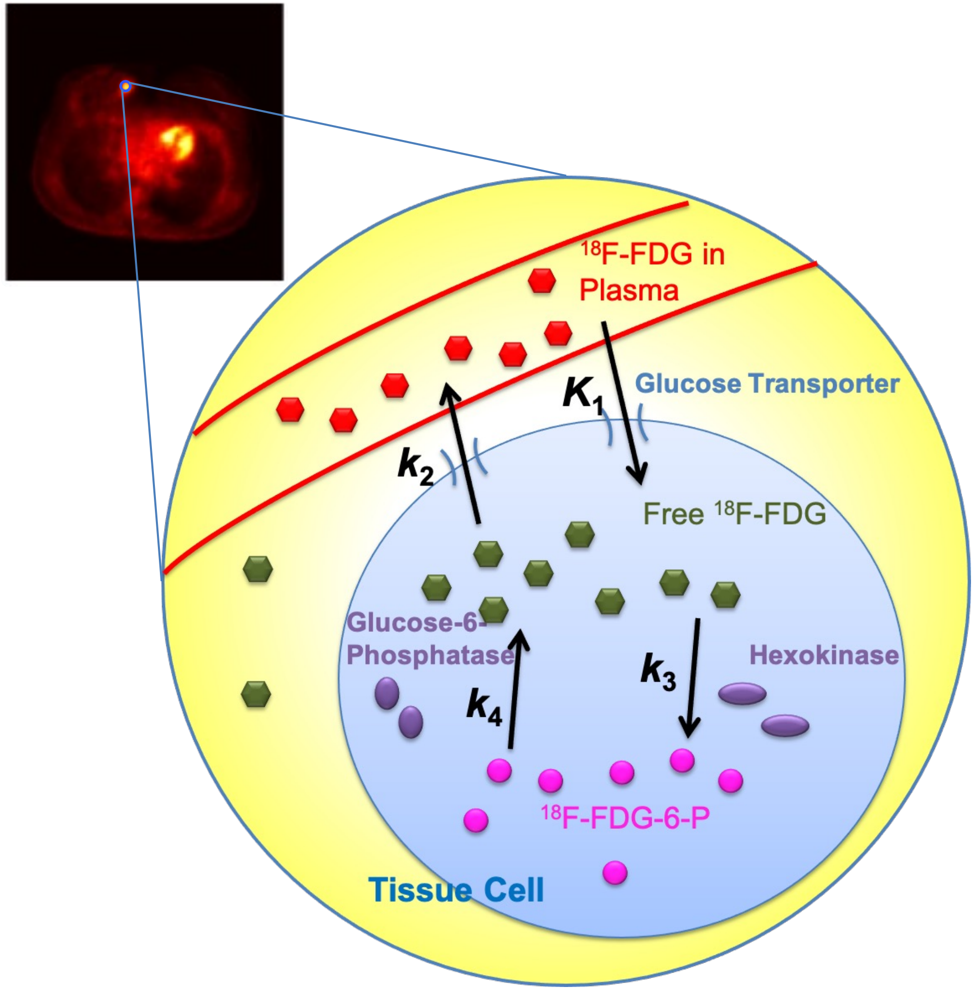


Shown are MIP (maximum intensity projection) images.

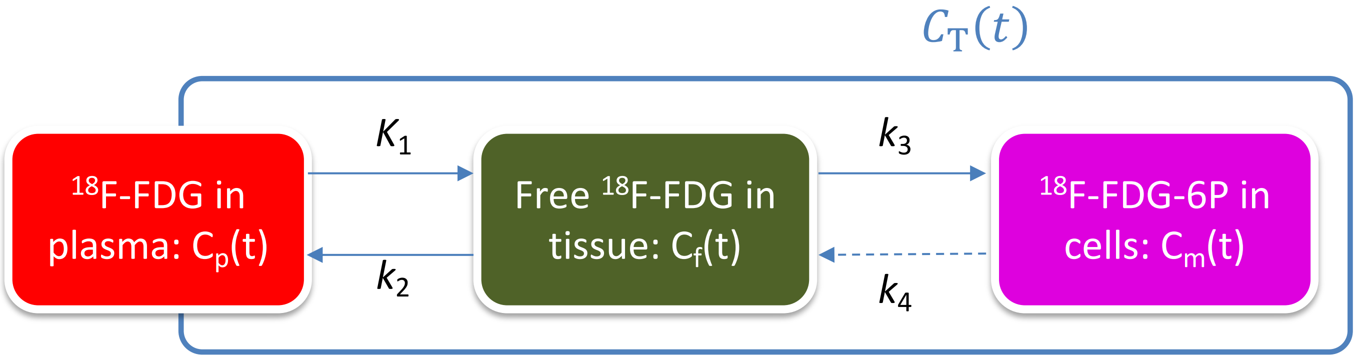
Capturing the Full Time Course of Tracer Activity in All Organs



Quantification Using Tracer Kinetic Modeling



- Compartmental model



- Differential equations

$$\frac{\mathrm{d}}{\mathrm{d}t}\begin{bmatrix} C_\mathrm{f}(t) \\ C_\mathrm{m}(t) \end{bmatrix} = \begin{bmatrix} -(k_2+k_3) & k_4 \\ k_3 & -k_4 \end{bmatrix}\begin{bmatrix} C_\mathrm{f}(t) \\ C_\mathrm{m}(t) \end{bmatrix} + \begin{bmatrix} K_1 \\ 0 \end{bmatrix} C_\mathrm{p}(t)$$

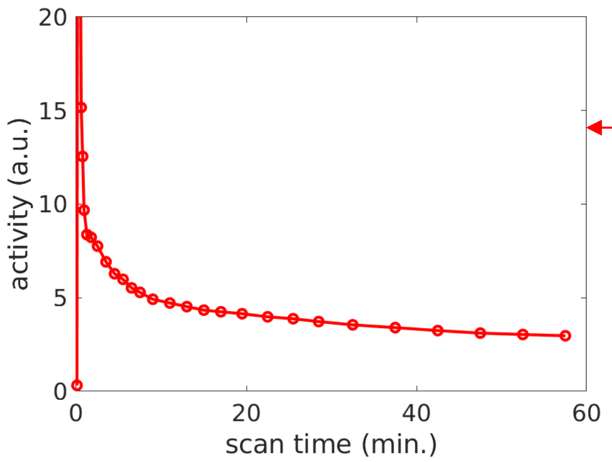
- Total activity that is measured by PET is

$$C_\mathrm{T}(t) = (1-v_\mathrm{b})[C_\mathrm{f}(t)+C_\mathrm{m}(t)] + v_\mathrm{b}\, C_\mathrm{b}(t)$$

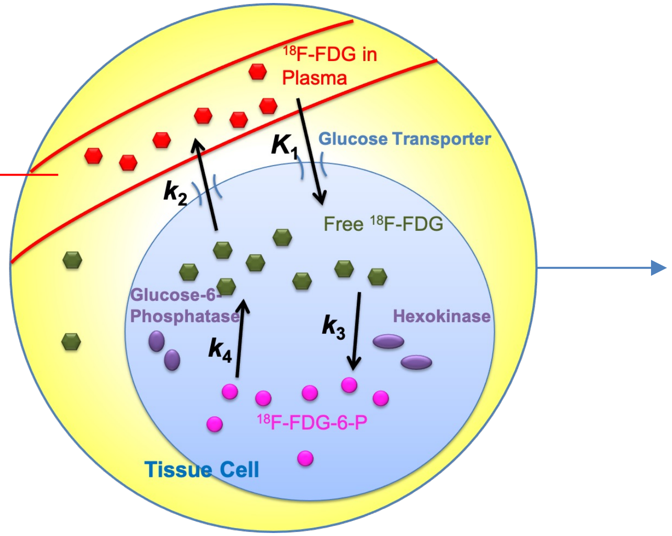
Sokoloff *et al.* 1977; Phelps *et al.* 1979; Huang *et al.* 1980. Online book chapter: Morris *et al.* 2004; Carson 2005

Kinetic Parametric Estimation by Time Activity Curve (TAC) Fitting

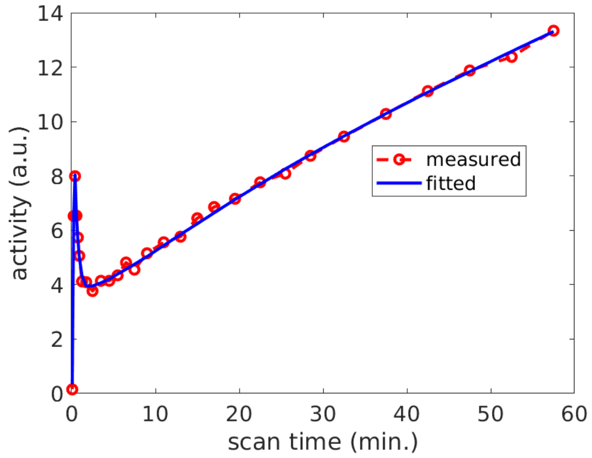
Blood Input



Kinetic Model $C_{\mathrm{T}}(t)$



Total Tissue Output



- Macro kinetic parameters can be calculated, e.g., for FDG:

$$\text{Net influx rate } K_{\mathrm{i}} = \frac{K_1 k_3}{k_2 + k_3};\ \ \text{Initial volume of distribution } V_0 = \frac{K_1 k_2}{(k_2 + k_3)^2}$$

- Voxel-wise implementation provides parametric imaging

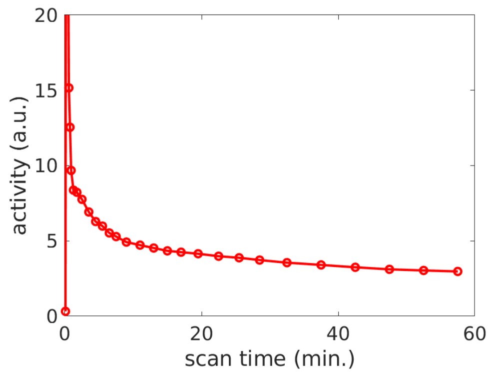
Benefits of Total-Body PET for Kinetic Modeling

- Improved sensitivity
  - makes it more robust to estimate kinetic parameters ⟹ Clinical reliability
  - enables dynamic PET imaging with higher temporal resolution (Badawi *et al* JNM 2019; Zhang *et al* PNAS 2021) ⟹ Probing physiology
- Total-body coverage
  - covers both major blood pools and all organs simultaneously ⟹ Good image-derived input function
  - allows full compartmental modeling for all organs (and metastases) ⟹ Total-body quantification of micro kinetic parameters

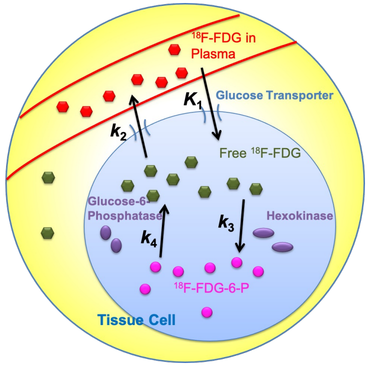
Challenges of Total-Body Kinetic Modeling and Parametric Imaging

Key Components

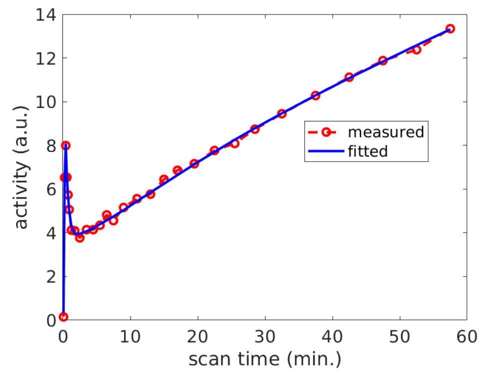
Blood Input Function



Kinetic Model



Tissue TACs and Fitting



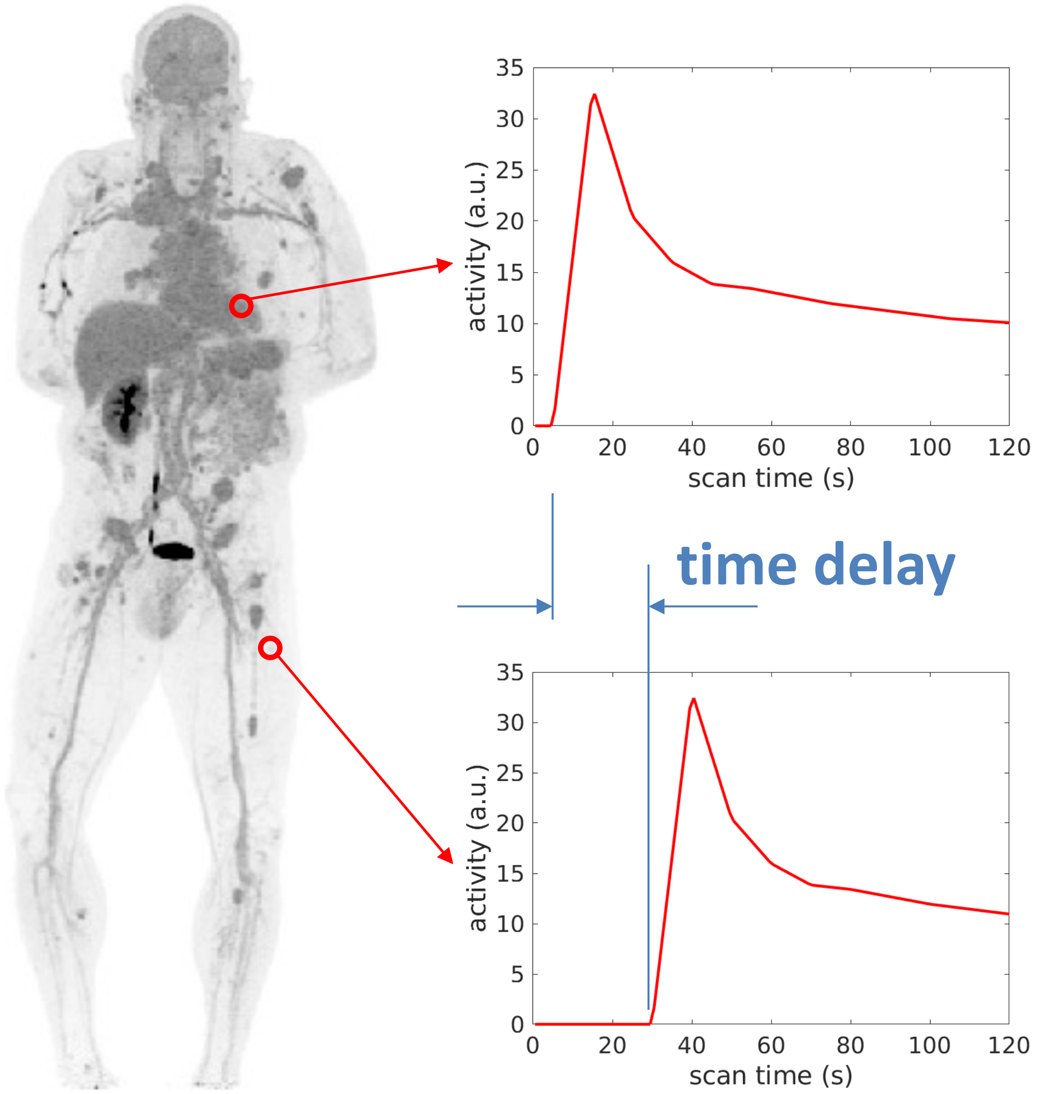
Challenges

- Time delay and dispersion correction
- Modeling of dual blood supplies (in liver, lung)
- Parent fraction correction
- Metabolite correction

- Model selection
- Identifiability
- …

- Huge dataset
- Motion
- Local minimum
- …

Time Delay of the Blood Input Function

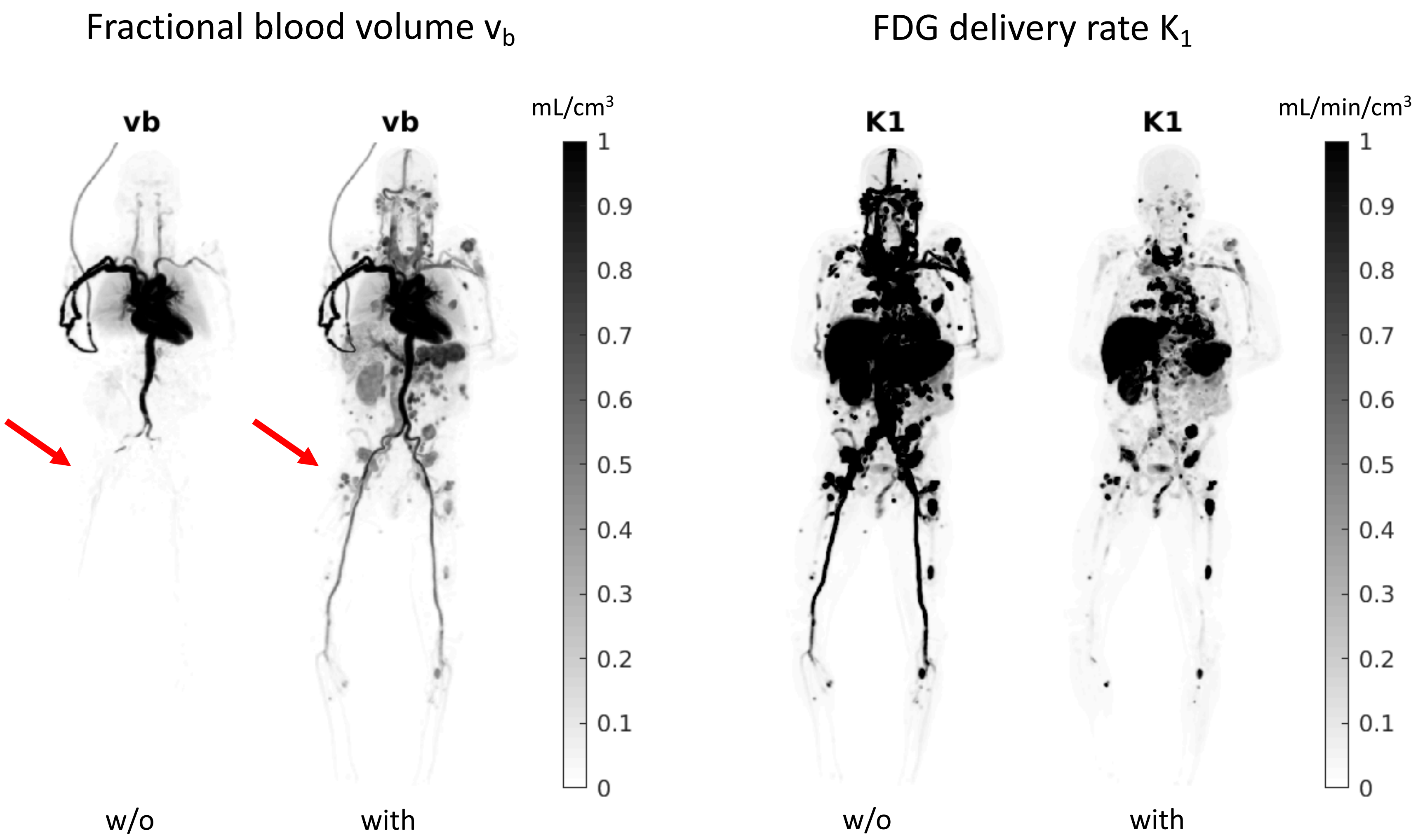


(A) IDIF extracted in left ventricle

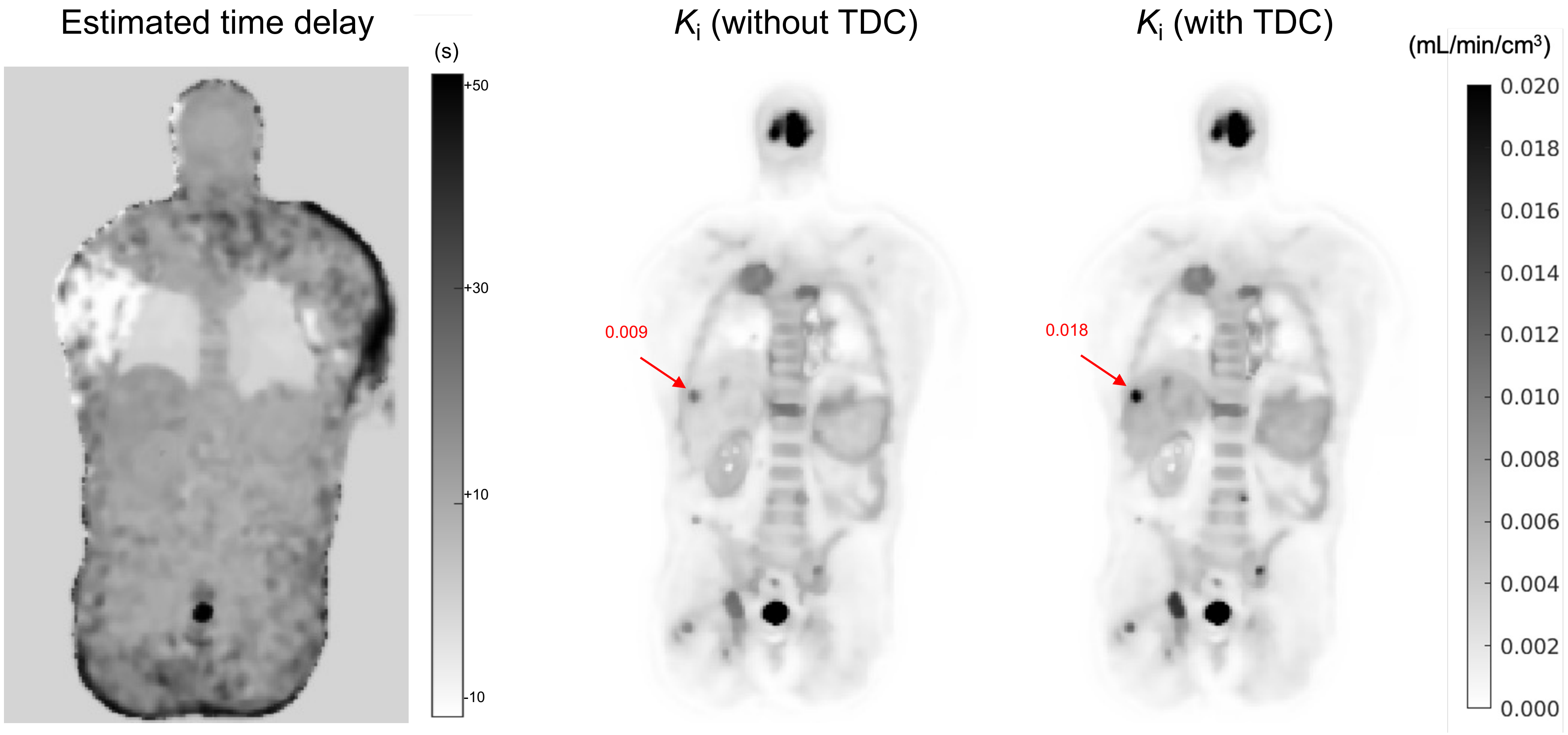
(B) actual arrival in a tissue

Iida *et al.* 1986, 1988, 2000; E. Meyer *et al.* 1989; Lammertsma *et al*. 1990; Feng *et al.* 2020

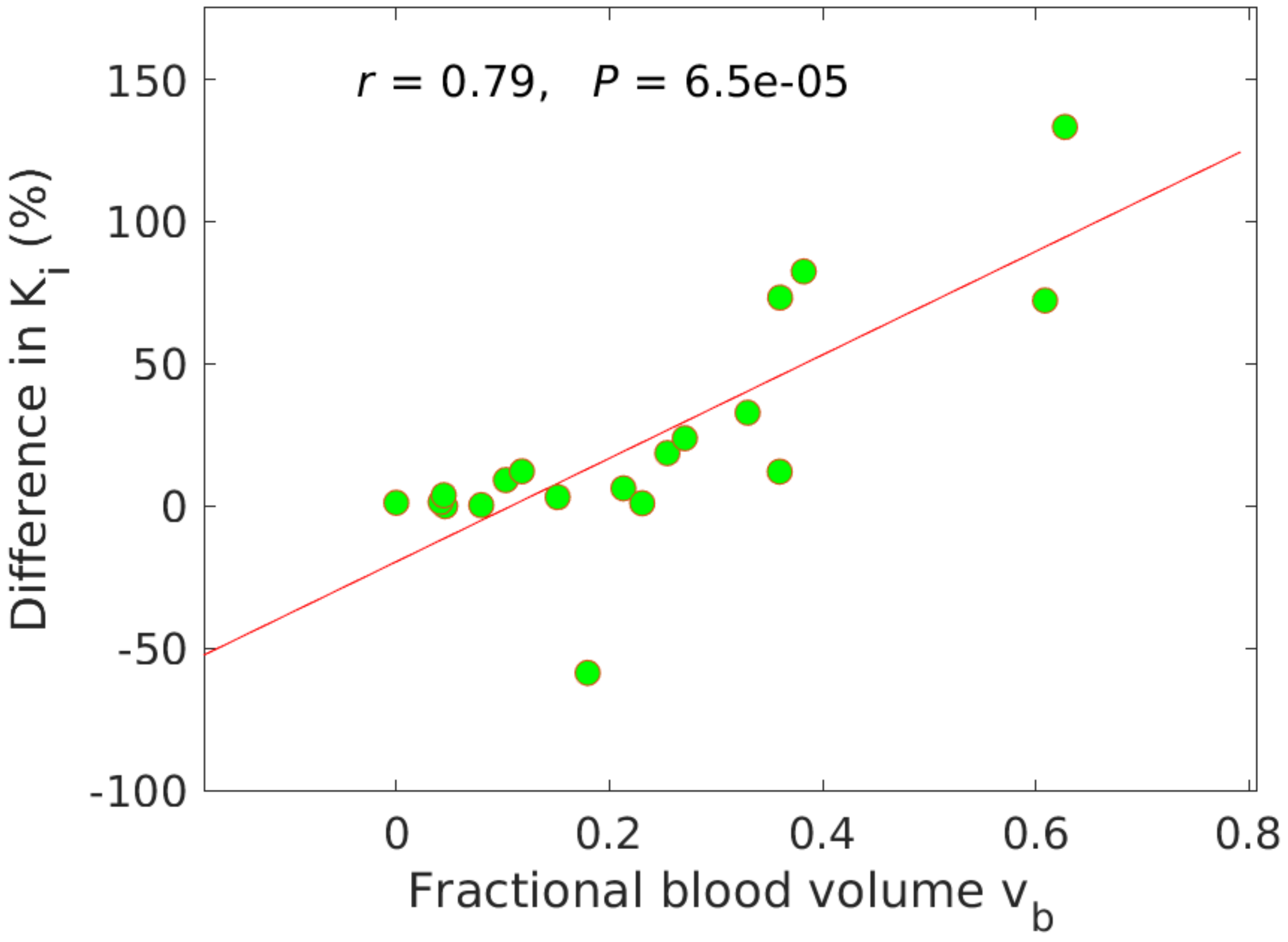
Time-Delay Correction on Total-Body Parametric Imaging



Time-Delay Correction (TDC) Also Impacts on FDG K_i



Impact of Time Delay Correction Correlates with Blood Volume Fraction



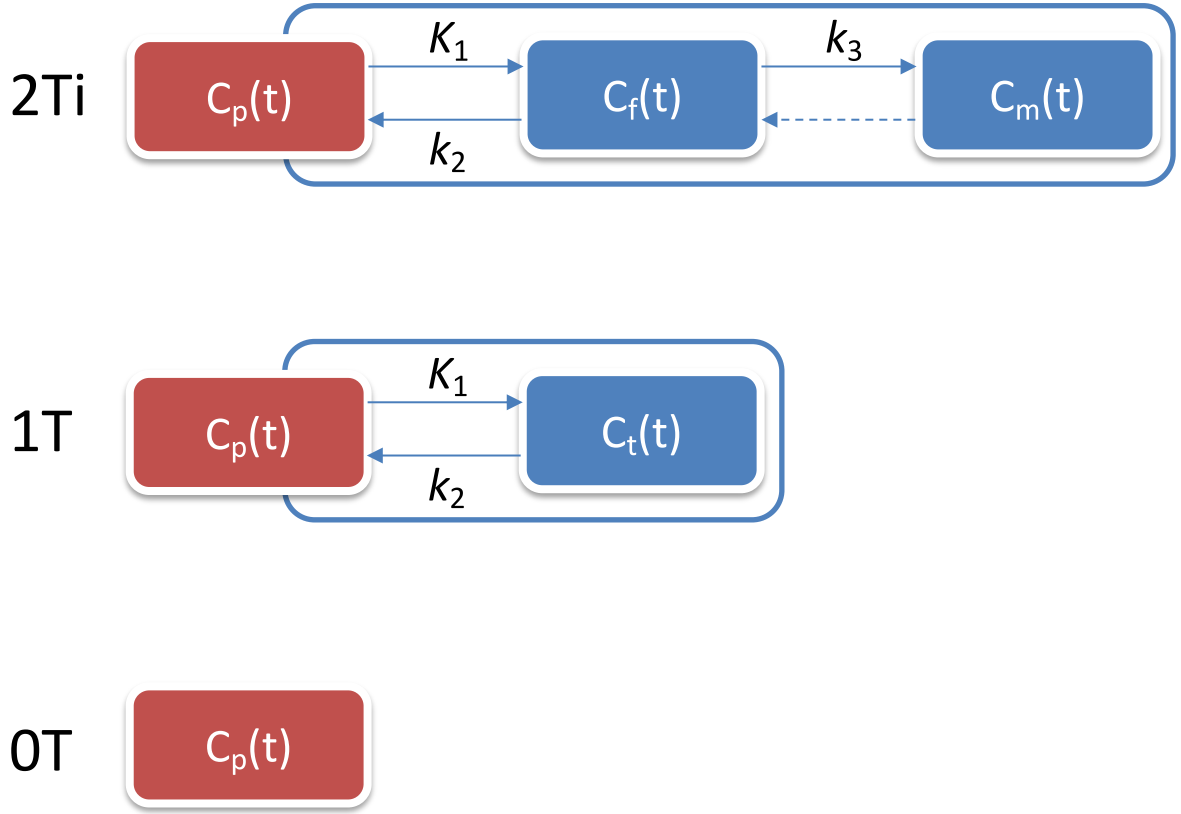
Results from 19 lesions from 5 patients with metastatic genitourinary cancer

Total-Body Model Selection

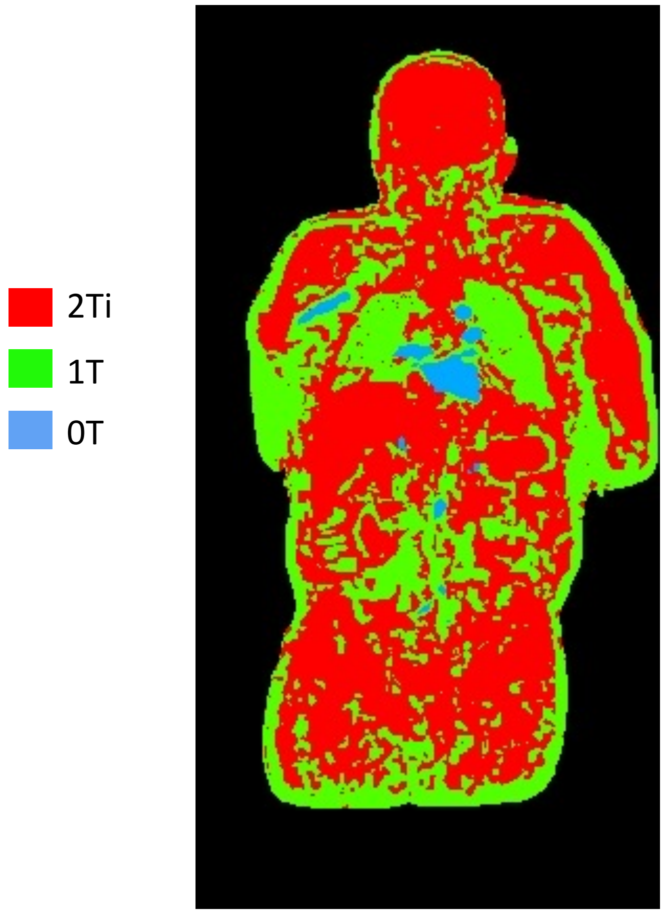
- Conventionally a fixed model is commonly used in organ-specific parametric imaging, e.g.,
  - Brain
  - Myocardium
- Total-body parametric imaging
  - Many different organs
  - Each may follow a different compartmental model

Example of Total-Body Model Selection

Irreversible two-tissue (2Ti) model

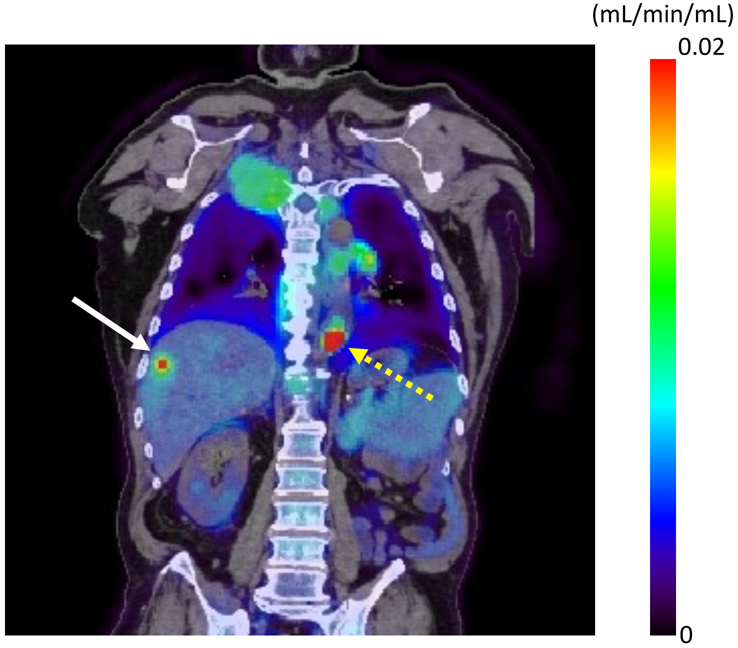


Model selection by Akaike information criterion (AIC)

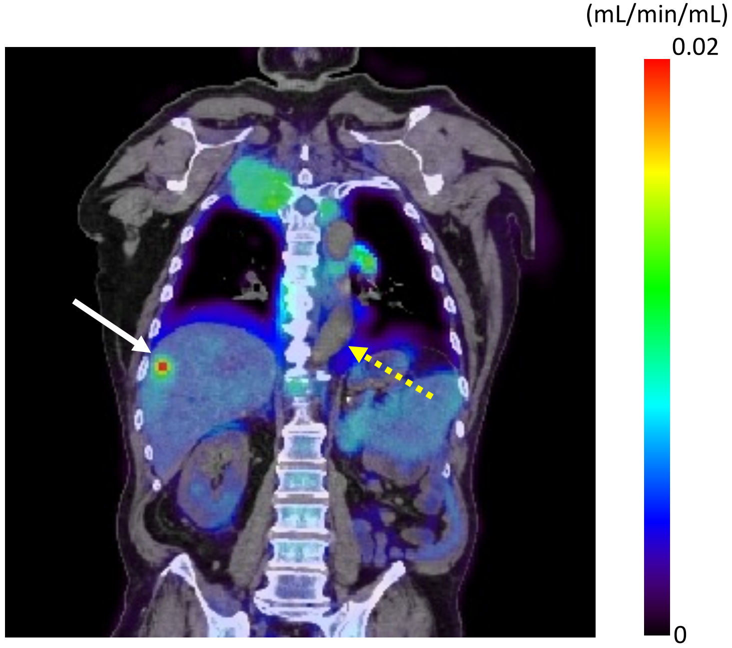


Impact of Model Selection on K_i Imaging of Lesions

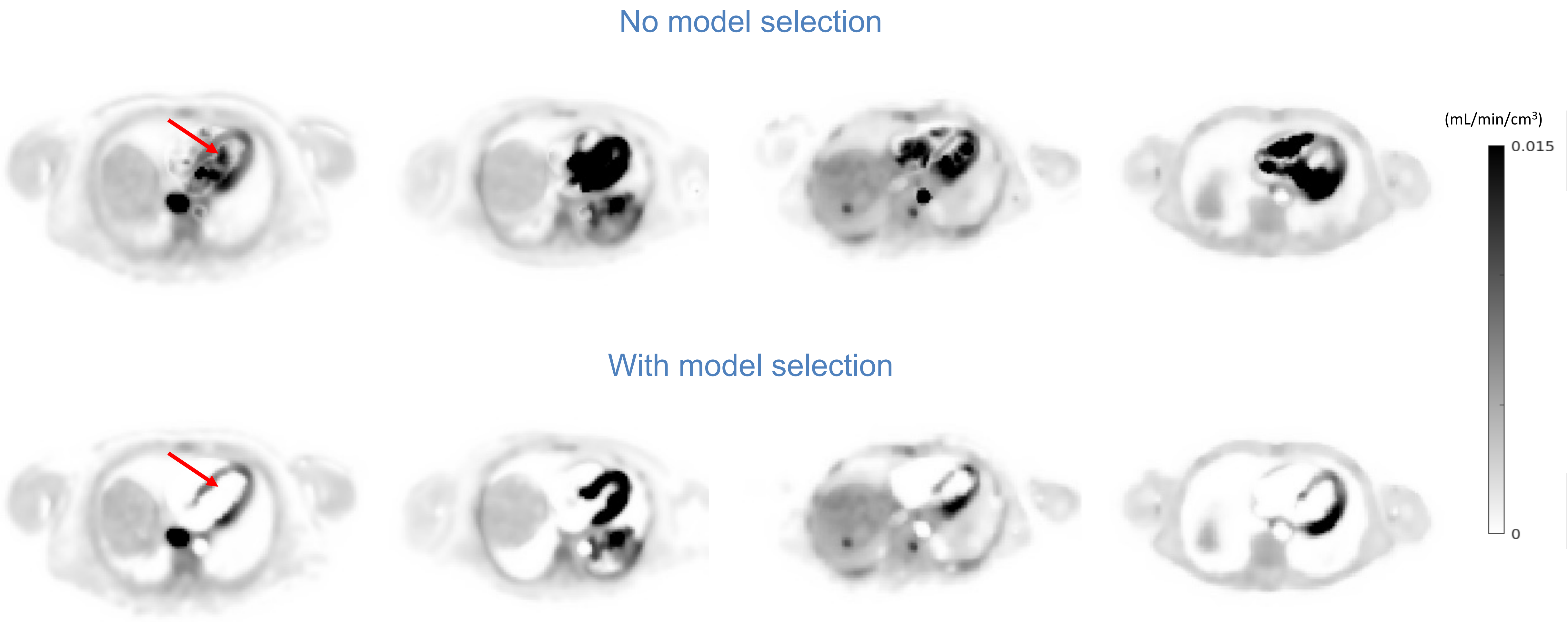
No model selection
(2Ti)



With model selection
(0T, 1T, 2Ti)

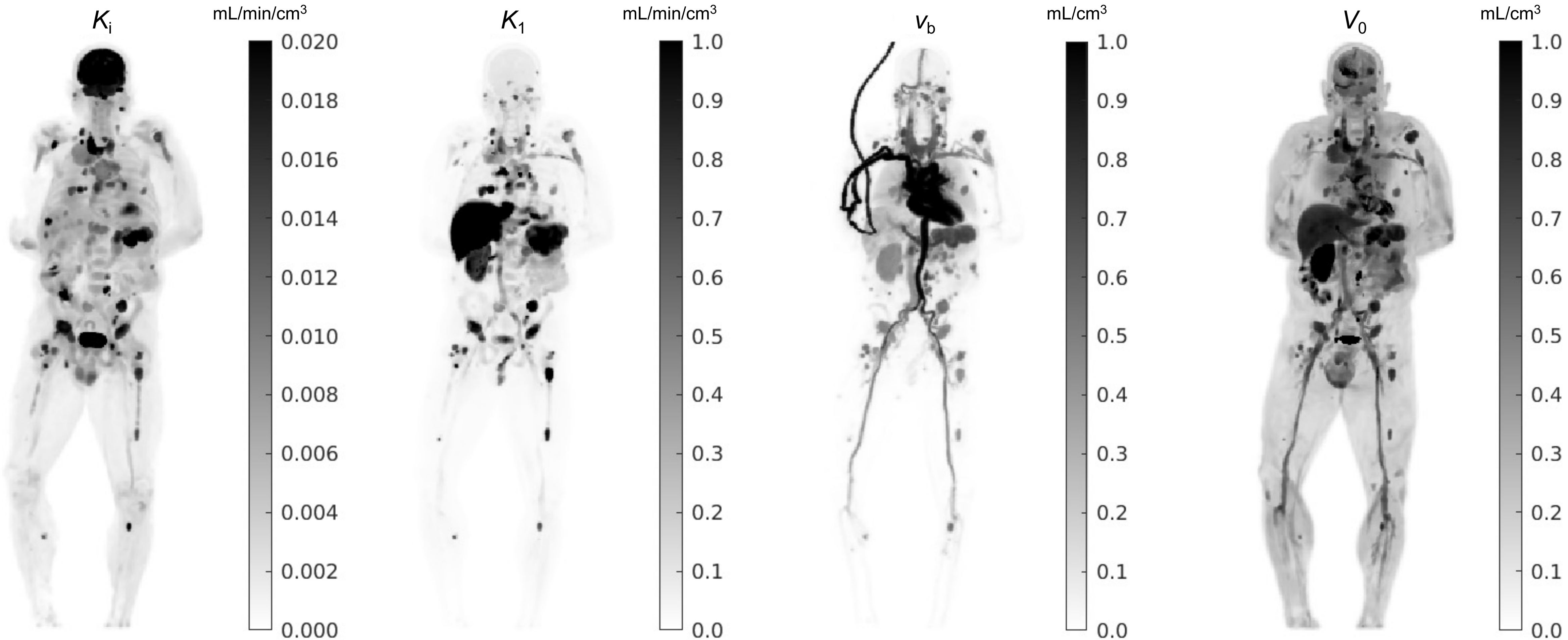


Impact of Model Selection on Myocardial K_i Imaging

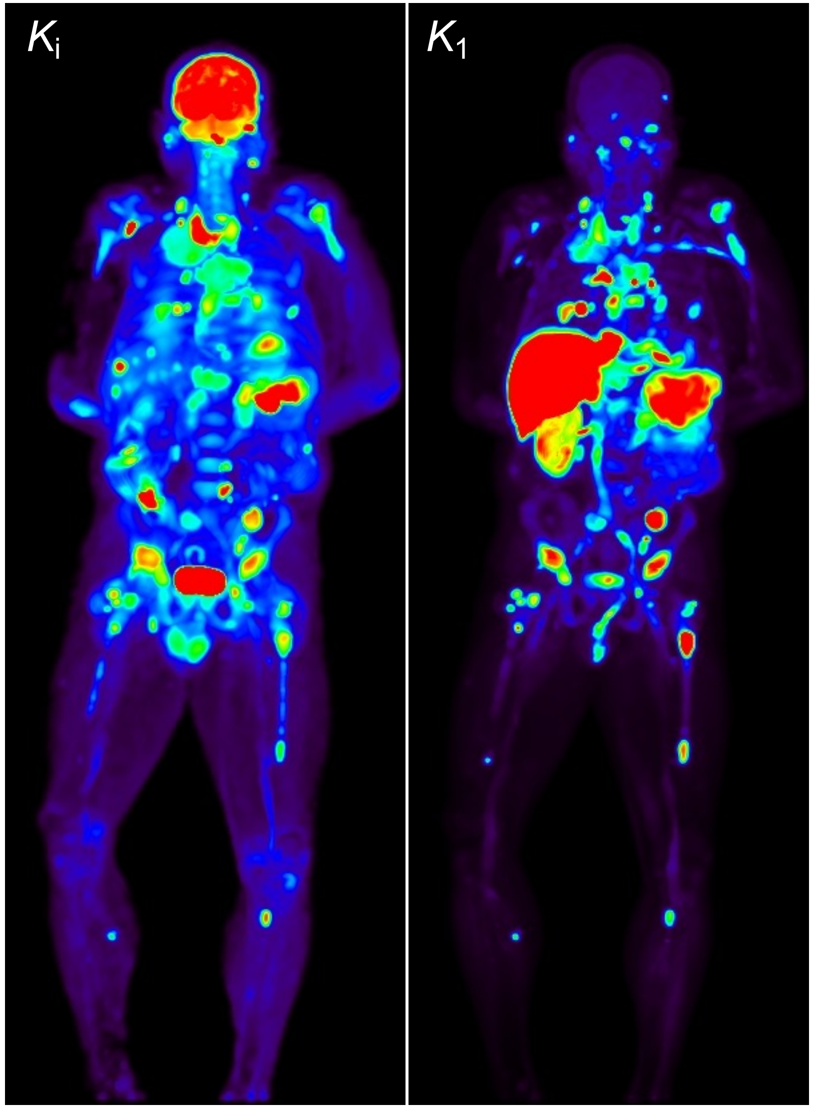


Example of Total-Body PET Multiparametric Imaging in Metastatic Cancer

FDG net influx rate | FDG delivery rate | Fractional blood volume | Volume of distribution



Potential Benefits of Total-Body Multiparametric Imaging



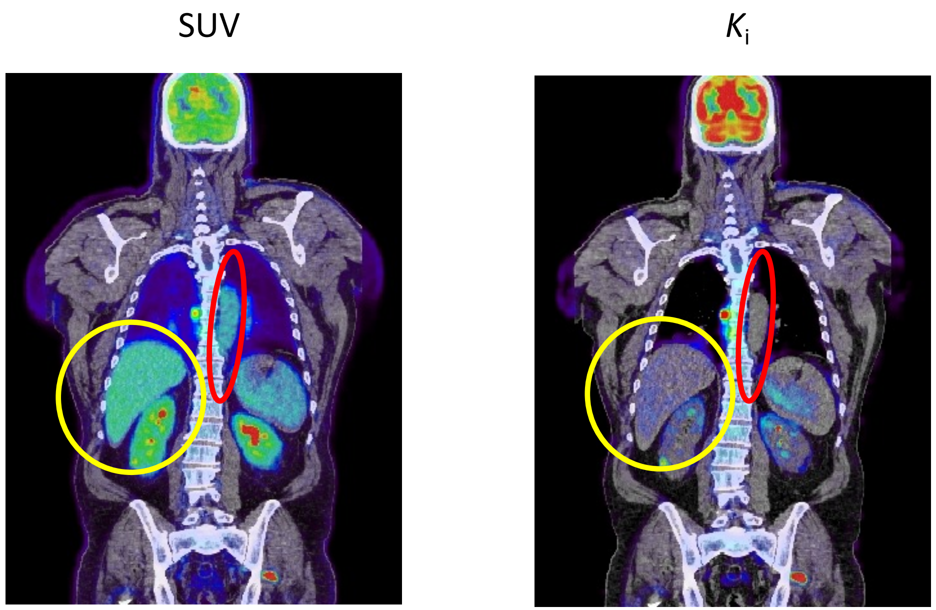
1. Improved lesion contrast

2. Exploring micro kinetic parameters (e.g., K_1) for multiparametric imaging

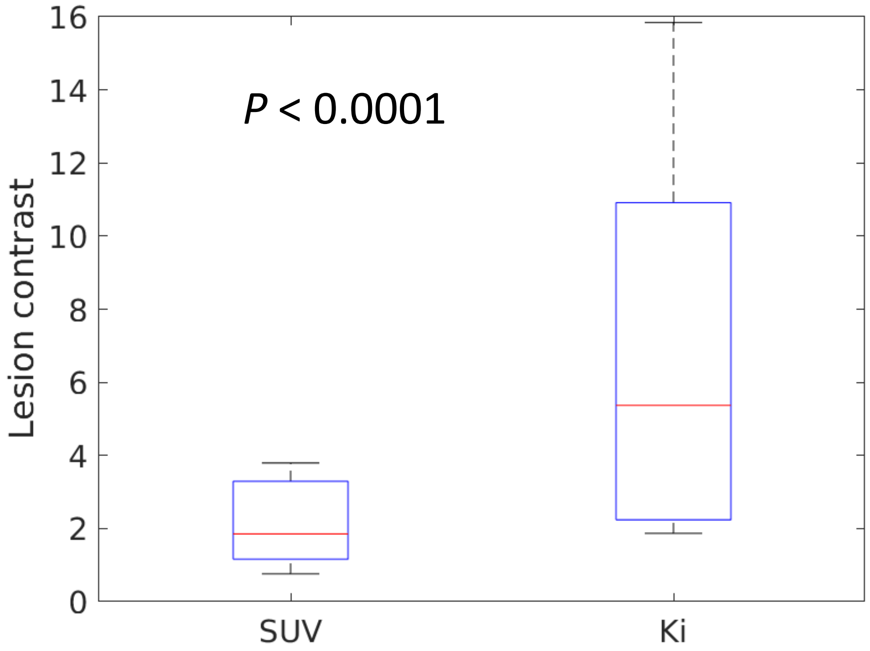
3. Multiorgan quantification in systemic disease

Benefit 1: Parametric Image of K_i Can Improve Lesion Contrast

- FDG K_i can clean background signal in the liver and blood pool

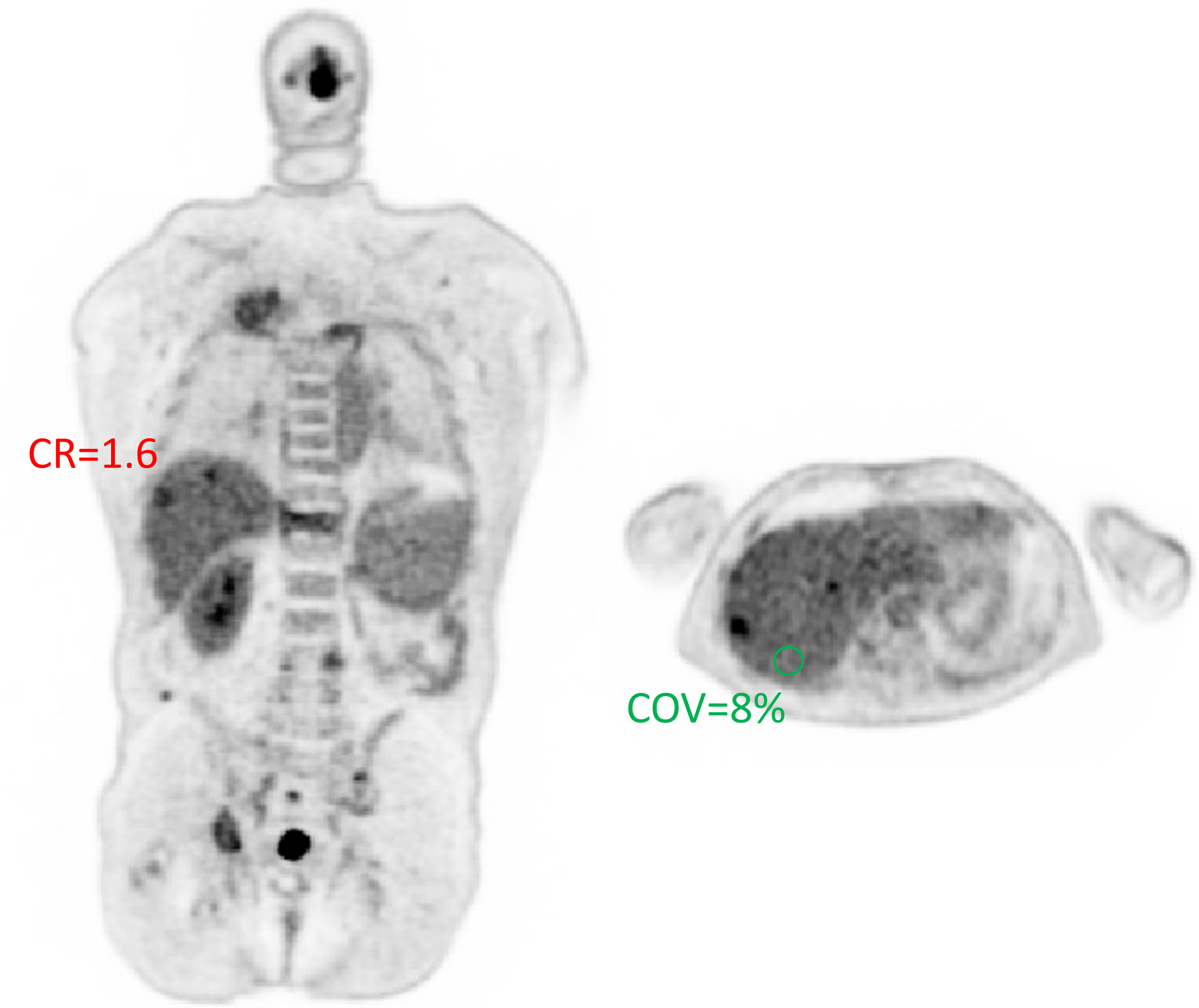


Results from 19 lesions from 5 patients with metastatic genitourinary cancer

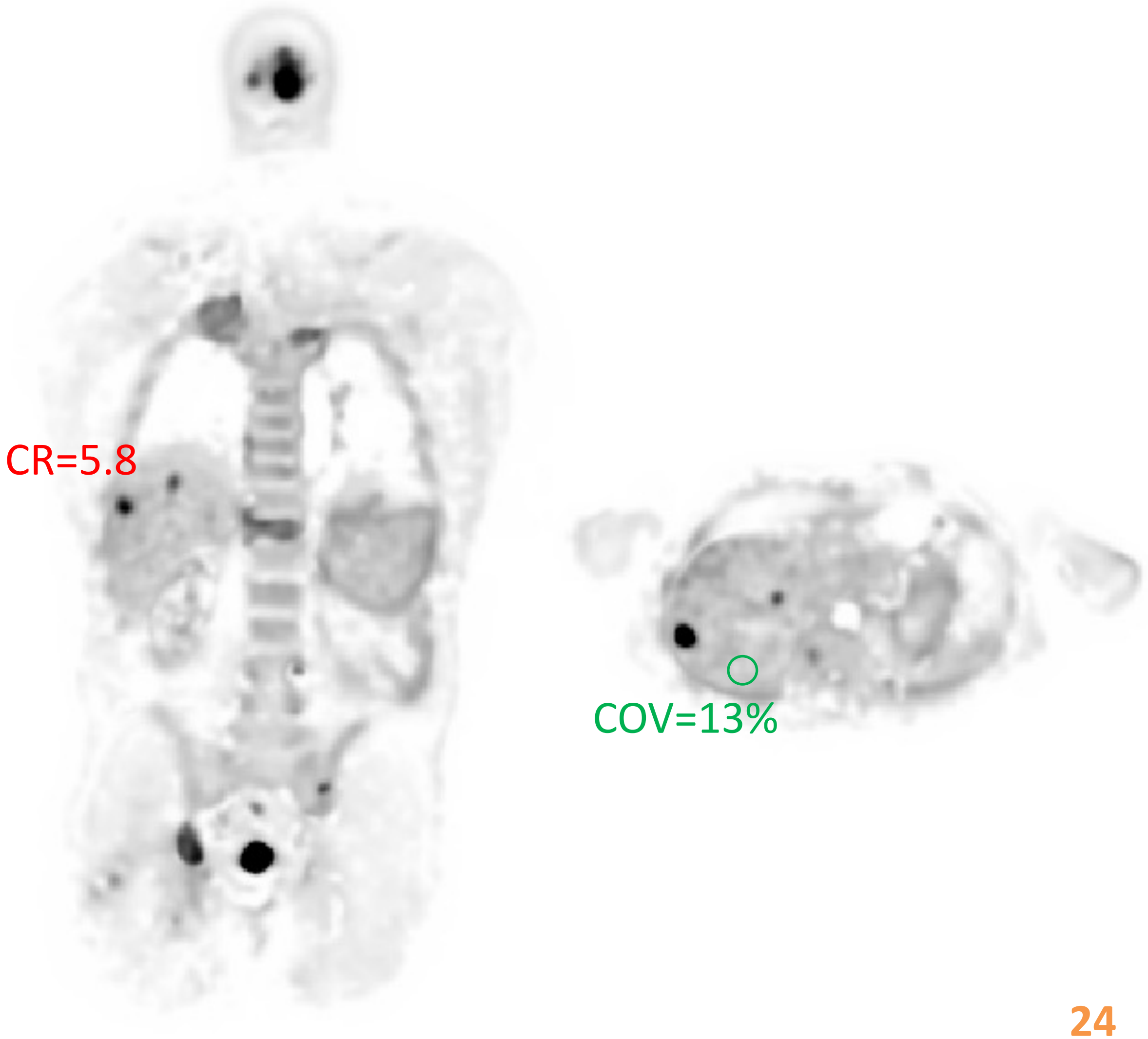


Example of Liver Lesions

SUV



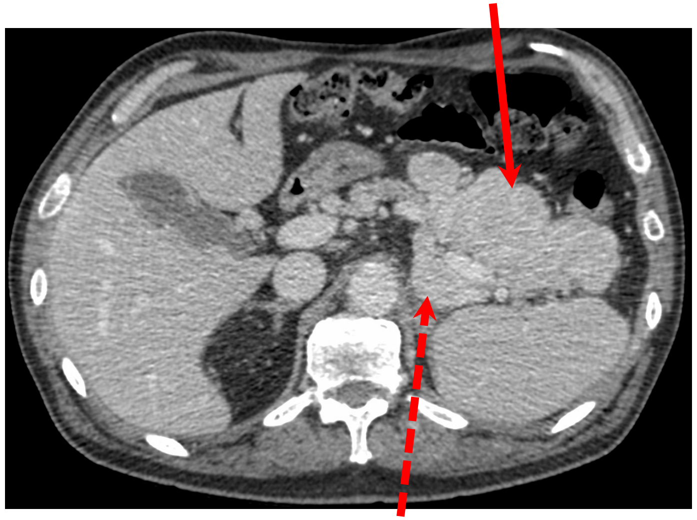
FDG influx rate K_i



Example of Abdominal Lesions

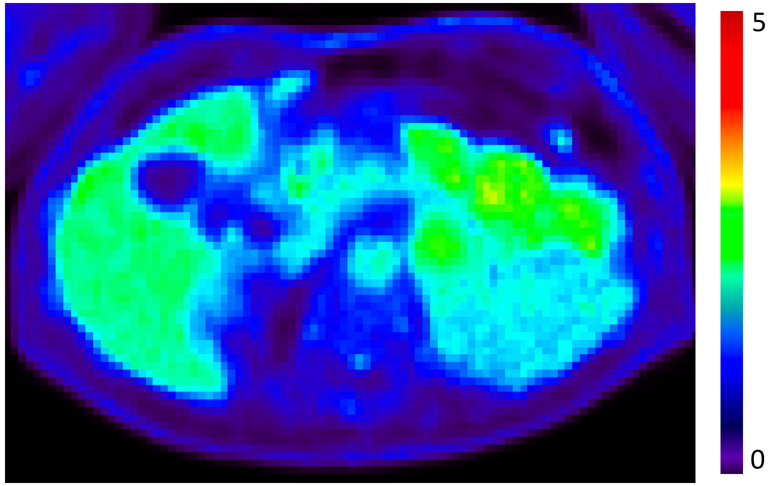
Contrast-enhanced CT

Peritoneal mass

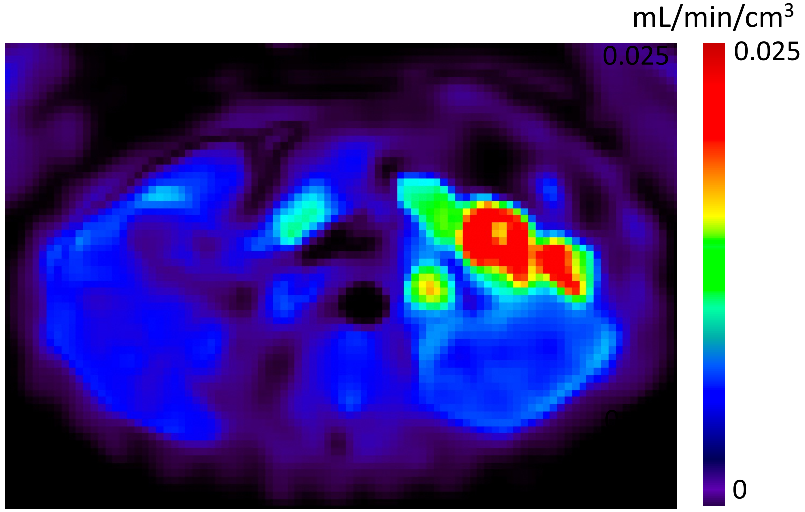


para-aortic lesion

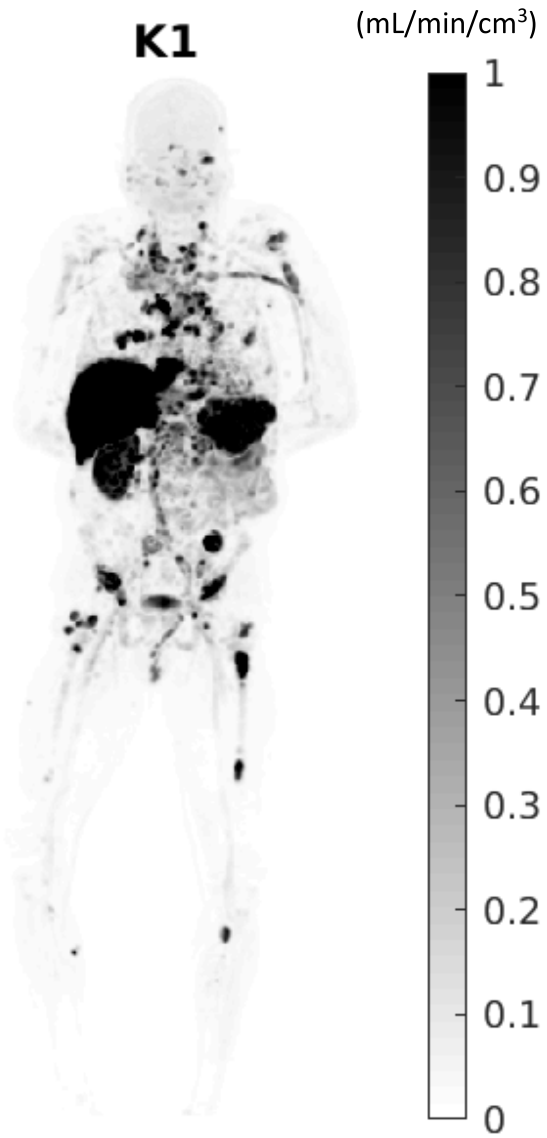
SUV



FDG K_i



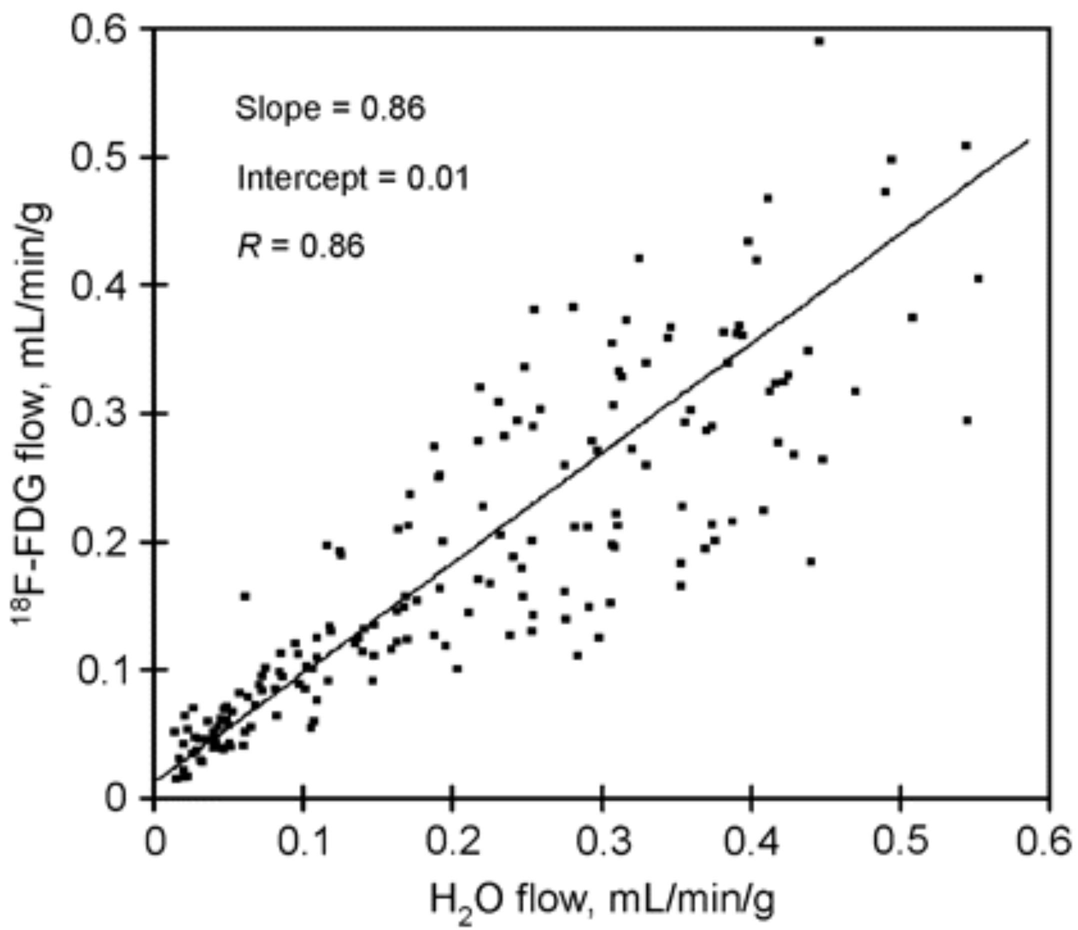
Benefit 2: Exploring Micro-kinetic Parameters for Multiparametric Imaging



- SUV and K_i characterize glucose metabolism
- FDG delivery rate K_1 generally reflects a mix of blood flow and glucose transport
- Many potential applications of FDG K_1:
  - Serve as a surrogate of blood flow
  - Independent imaging biomarker
  - Create lesion contrast

Cancer: FDG K_1 May Highly Correlate with Tumor Blood Flow

- Due to generally high extraction fraction of FDG in tumors

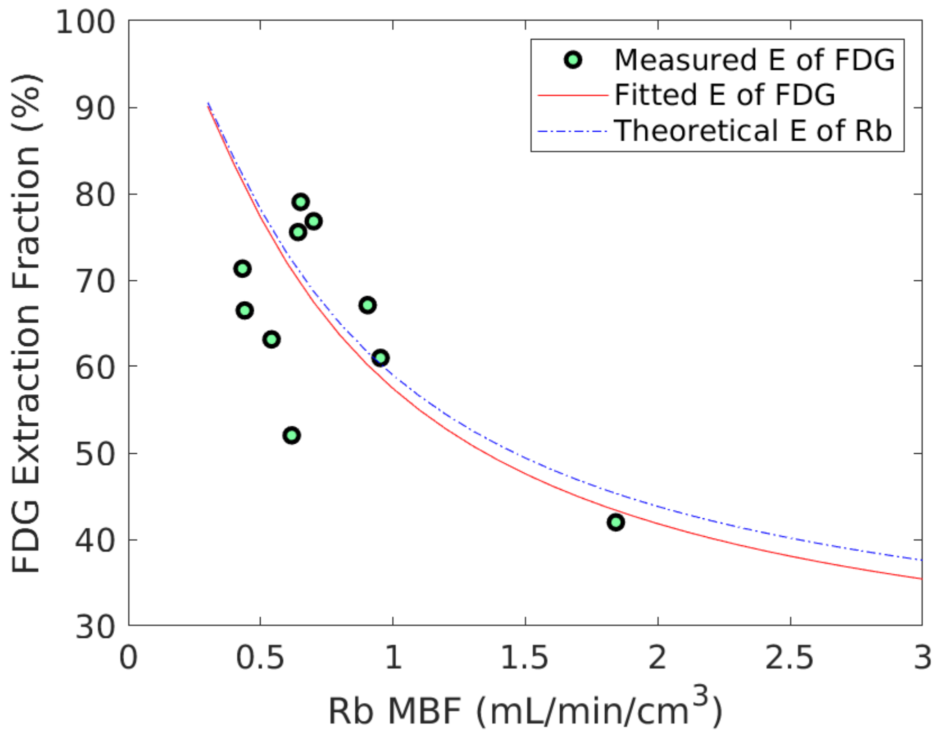


Enabling single-tracer (FDG) evaluation of flow-metabolism mismatch

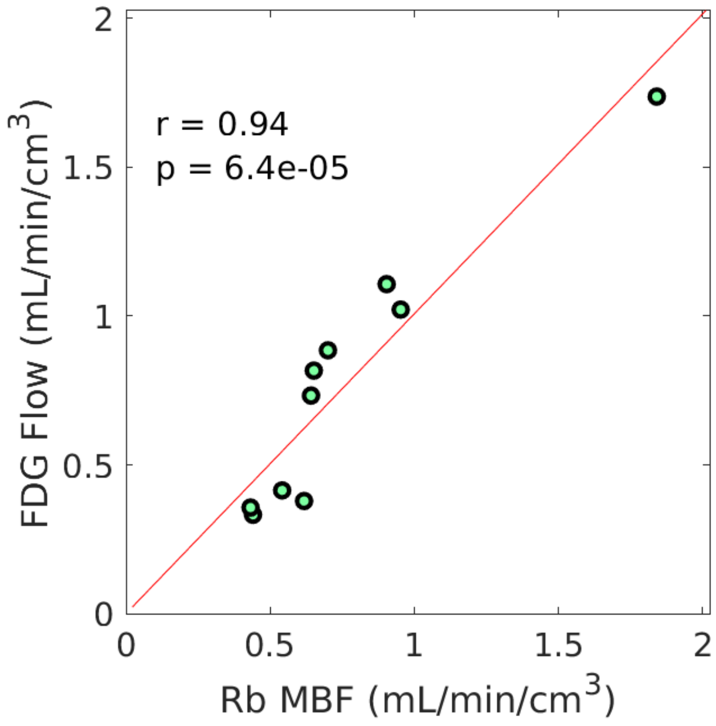
Mullani *et al*, 2008; Zeng *et al* 2004

Heart: Measuring Myocardial Blood Flow (MBF) Using FDG K_1

- FDG may have a very similar first-pass extraction fraction as ^{82}Rb-chloride in myocardium



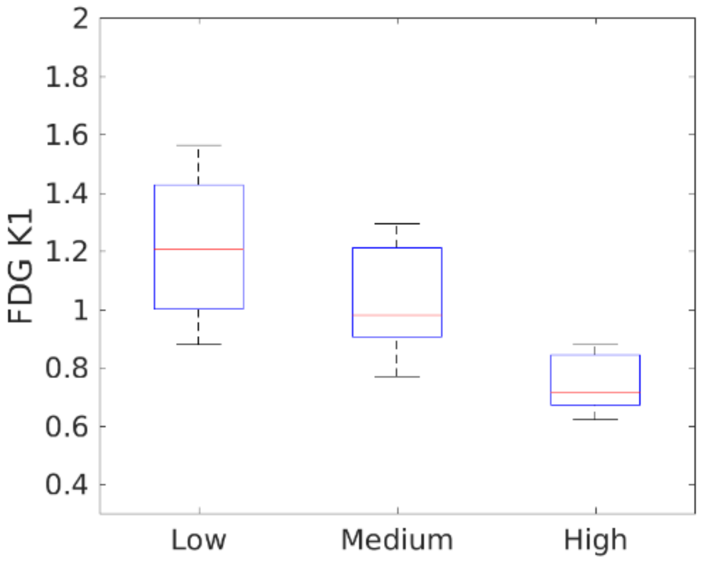
- Correlation of FDG-derived MBF with Rb MBF



Zuo *et. al.*, Phys Med Biol 2021

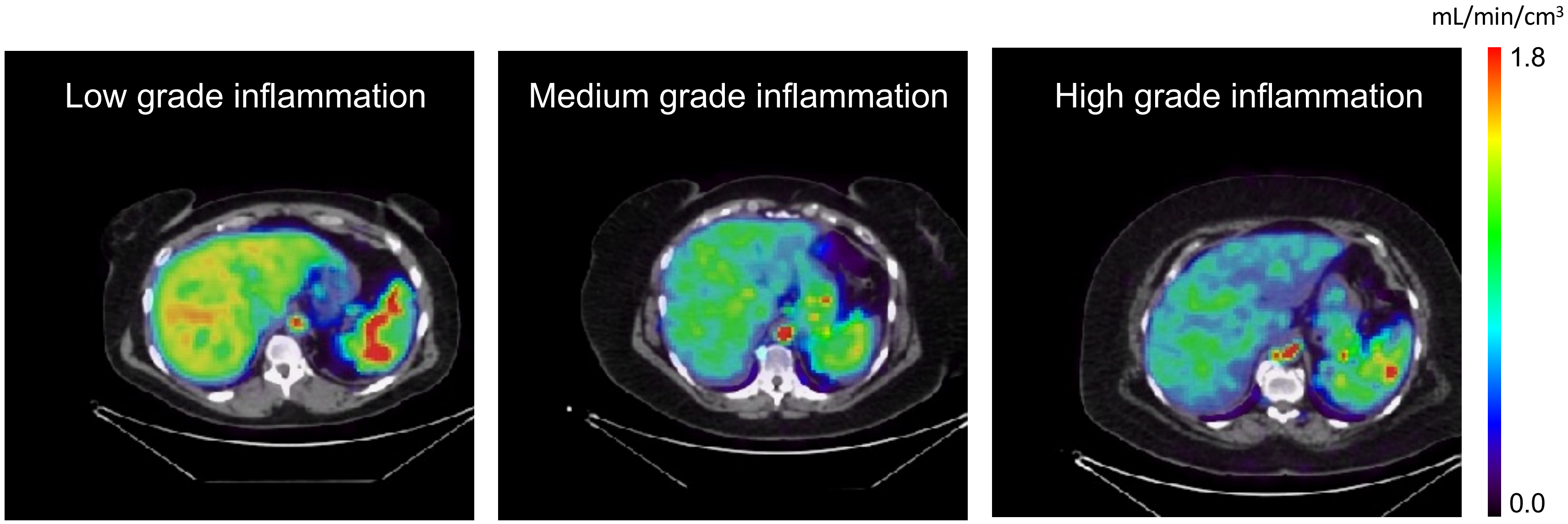
Liver: FDG K_1 May Be a Potential Biomarker of Liver Inflammation

- Decreased liver FDG K_1 is associated with increased liver inflammation in nonalcoholic fatty liver disease



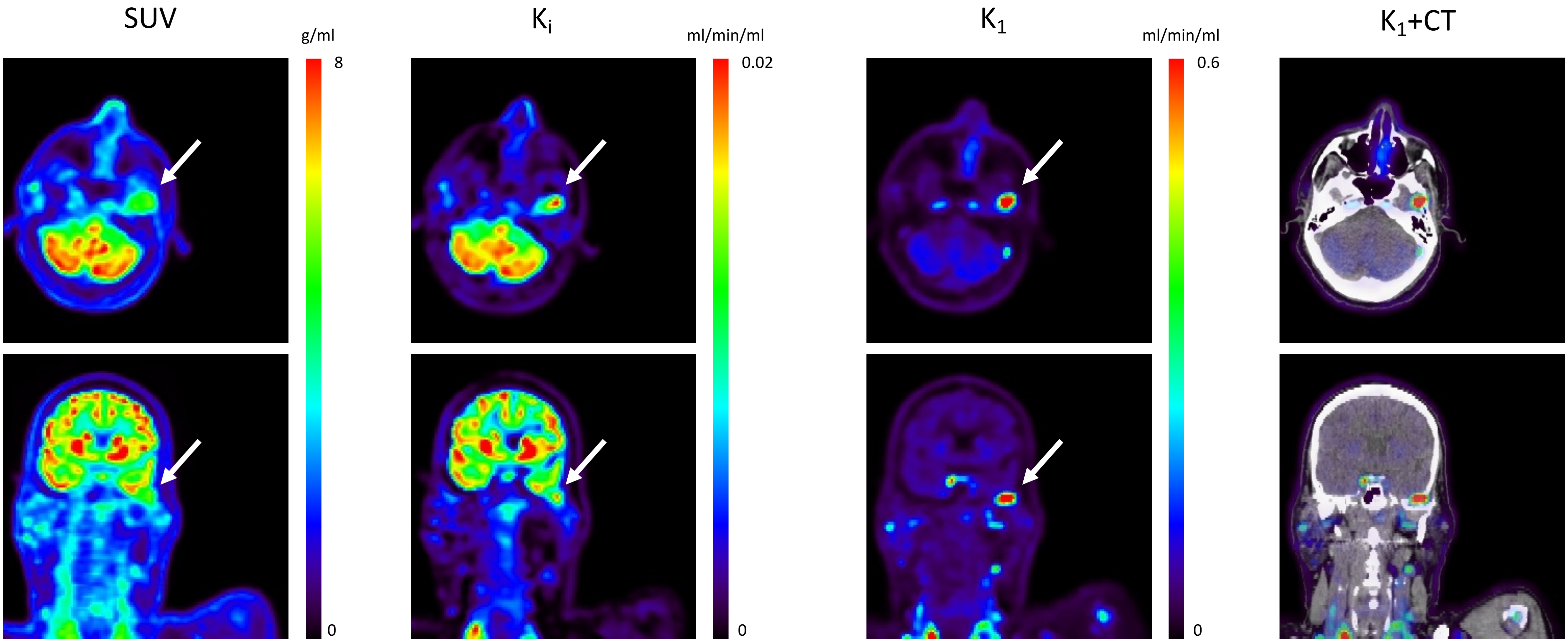
Liver inflammation grade

Liver FDG K_1 Images



Sarkar *et al* CGH 2021; Sarkar *et al.* AJR 2019; Zuo *et al.* PMB 2019; Wang *et al.* PMB 2018;

Brain/Skull: FDG K_1 Has Potential to Better Detect Tumors



Wang *et al.* unpublished EXPLORER data

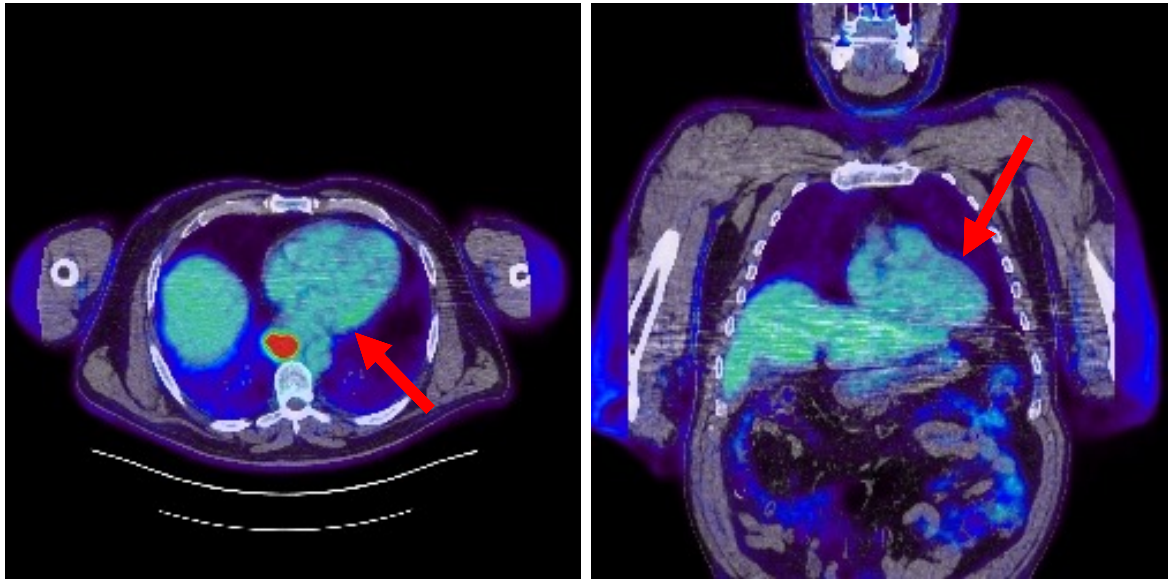
Benefit 3: Enabling Multi-Organ Evaluation in Systemic Disease

- Simultaneous evaluation of myocardium in cancer patients?

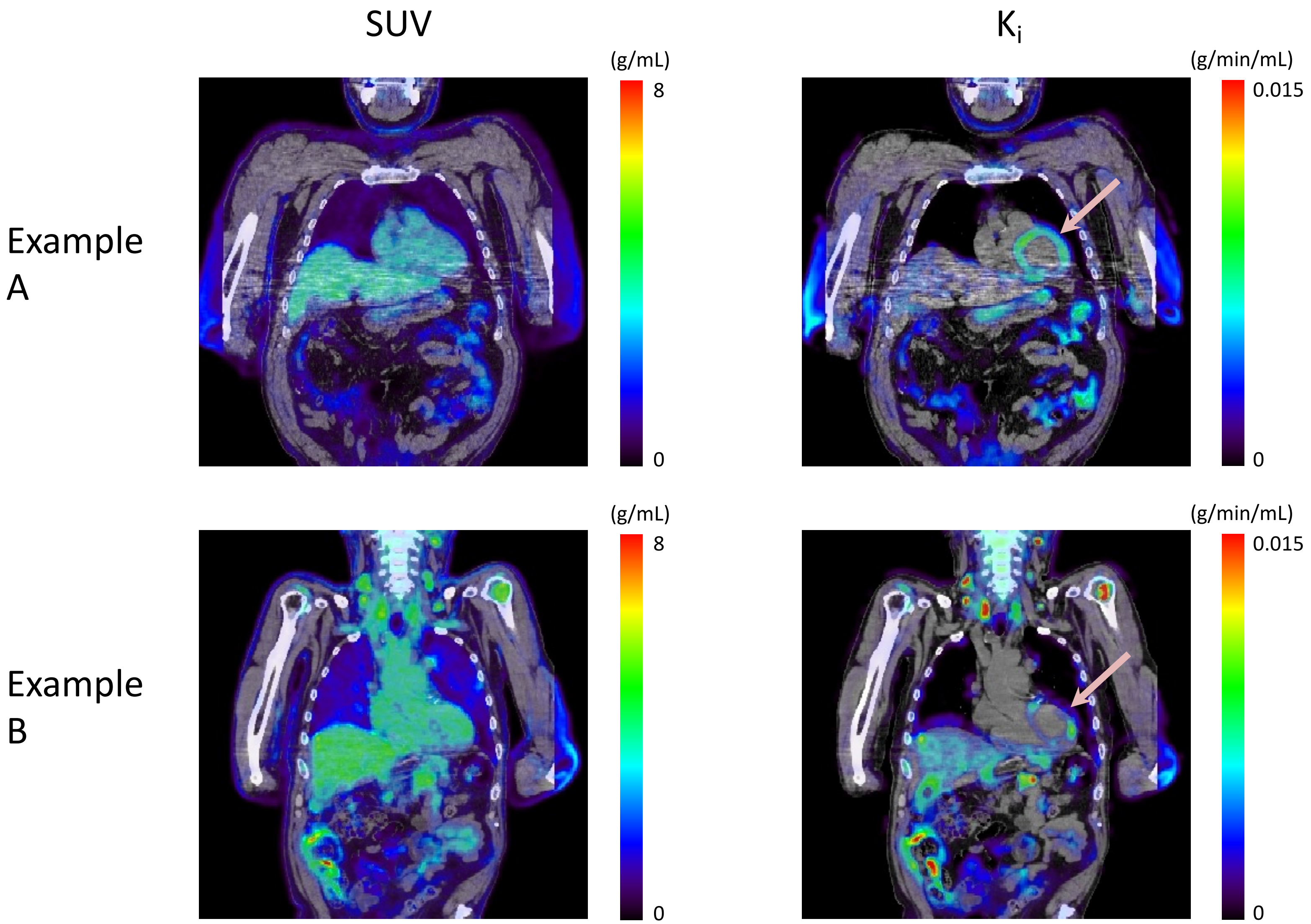
- **Problem**: 30-40% of standard oncological FDG-PET scans do not show visible myocardium

- Parametric imaging can help

SUV (60 min. p.i.)



Simultaneous Visualization of Myocardium by Parametric Imaging

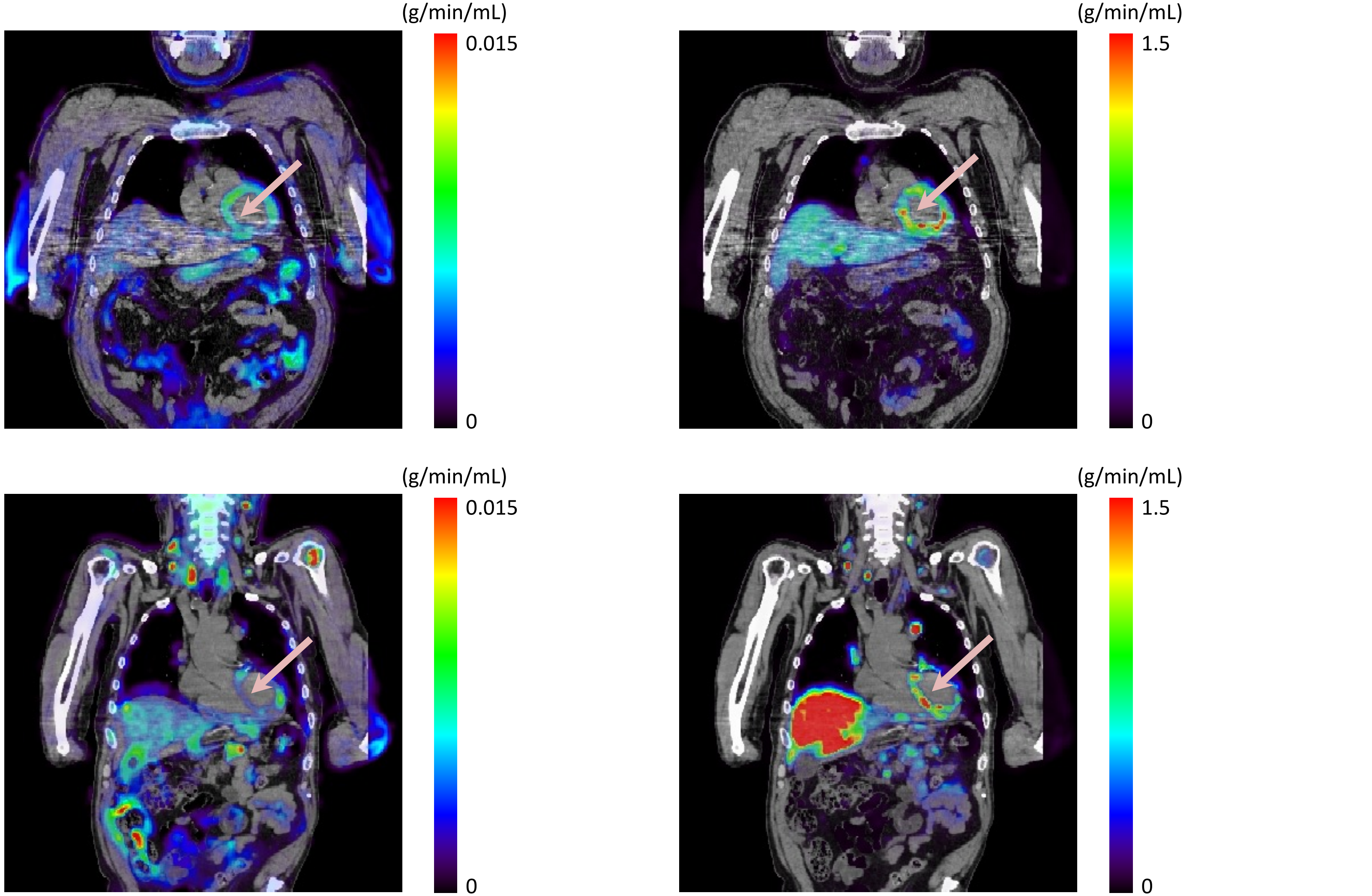


Allowing Evaluation of Perfusion-Metabolism Coupling/Mismatch

K_i (metabolism) | **K_1 (perfusion/transport)**

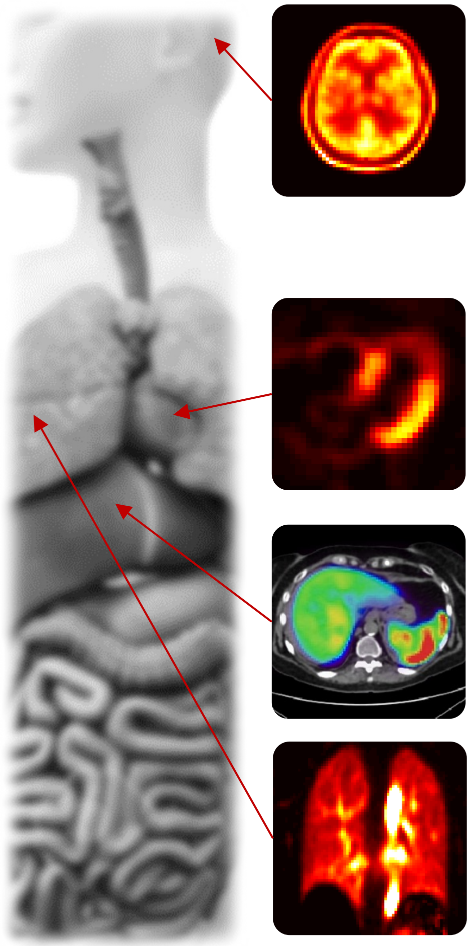
Example A

Example B



Putting All Puzzles Together

<u>Single-tracer (^{18}F-FDG) Multiorgan Multiparametric Evaluation by EXPLORER</u>



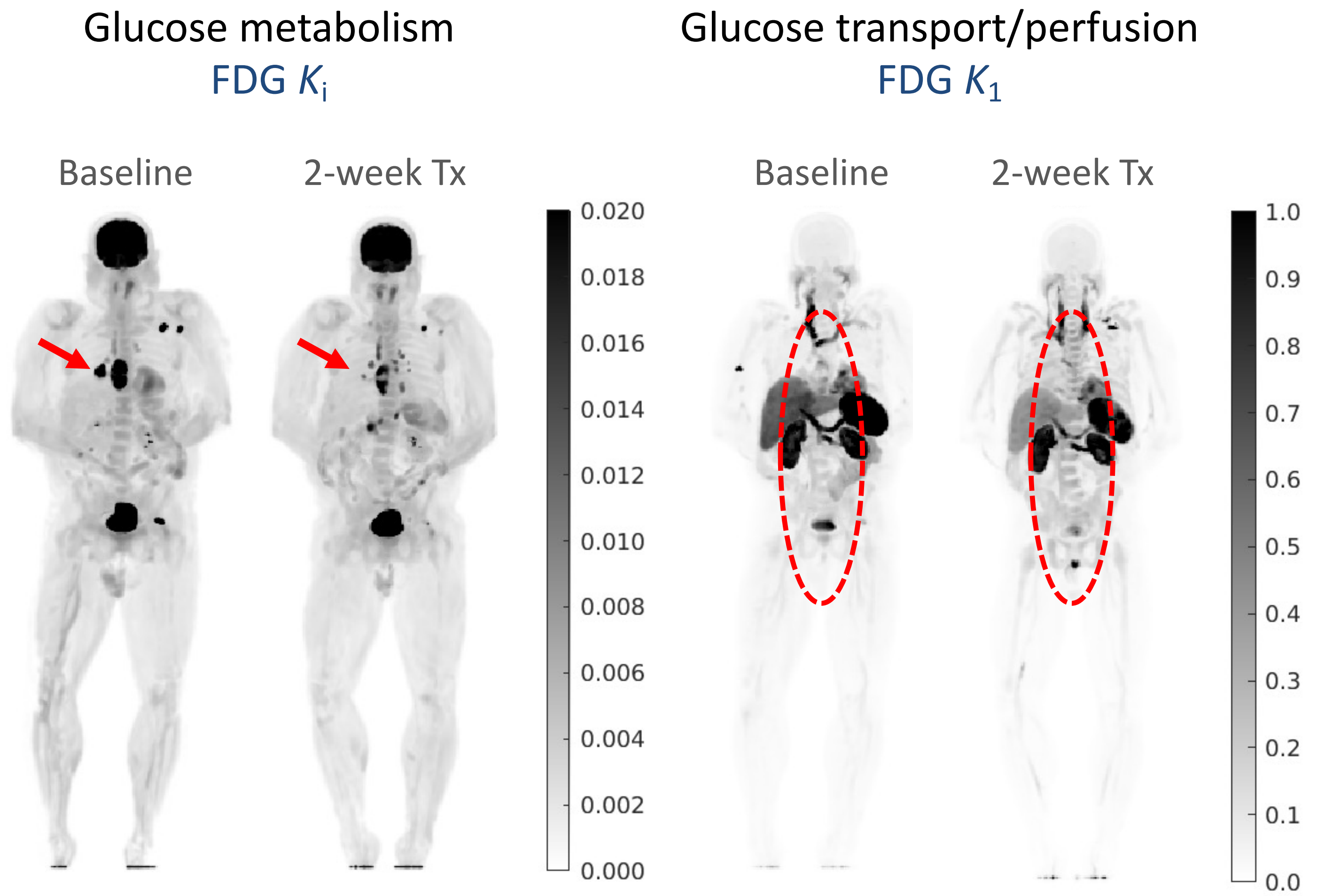
Multi Organs

- Myocardium
- Liver
- Lung
- Brain
- Bone marrow
- Spleen
- Kidney ...

Multiparametric Imaging

- Glucose metabolism
- Glucose transport / perfusion
- and potentially more

Example of Ongoing Studies: Total-Body Evaluation of Response to Cancer Immunotherapy

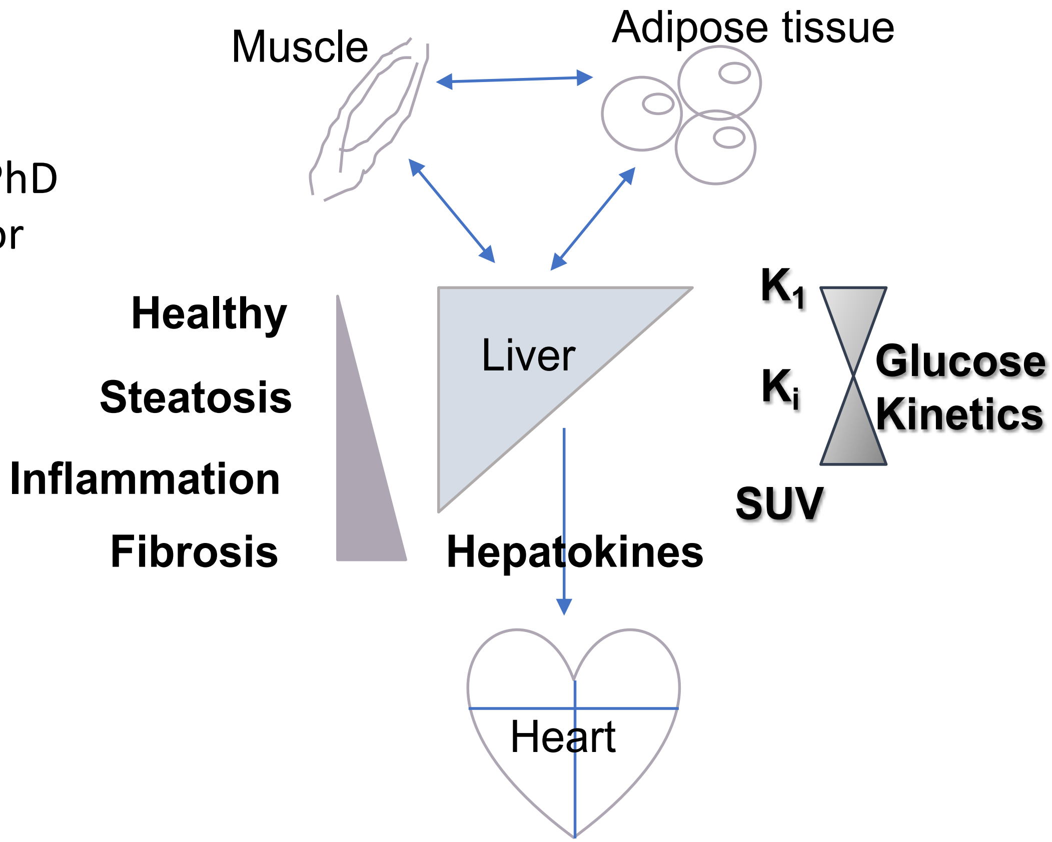


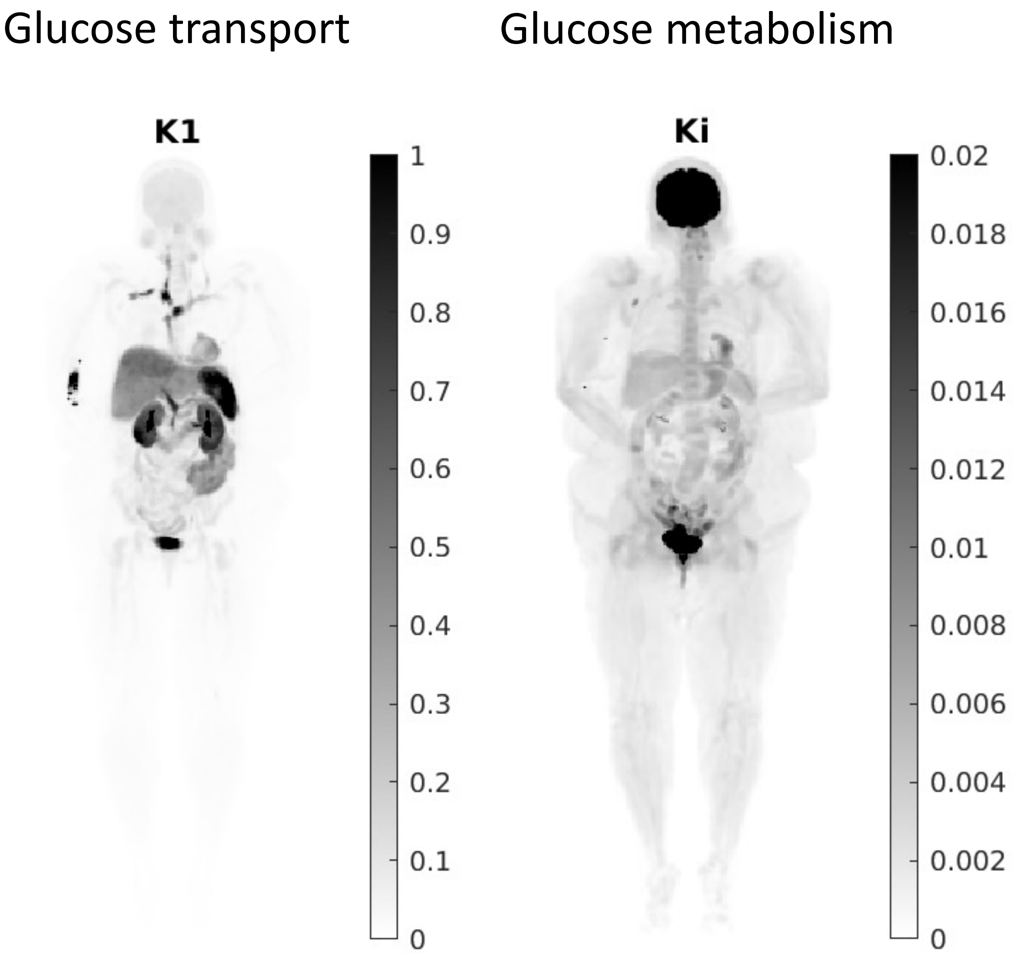
- Response of tumor
- Response of immune organs
  – Bone marrow
  – Spleen
- Drug effects
  – Heart: cardiotoxicity
  – Brain: cognitive impairment

Collaboration with L Nardo MD, RD Badawi PhD, M Parikh MD, R Verma MD

Example of Ongoing Studies: Organ Crosstalk in Nonalcoholic Steatohepatitis (NASH)

Souvik Sarkar, MD, PhD
Associate Professor
UC Davis Health



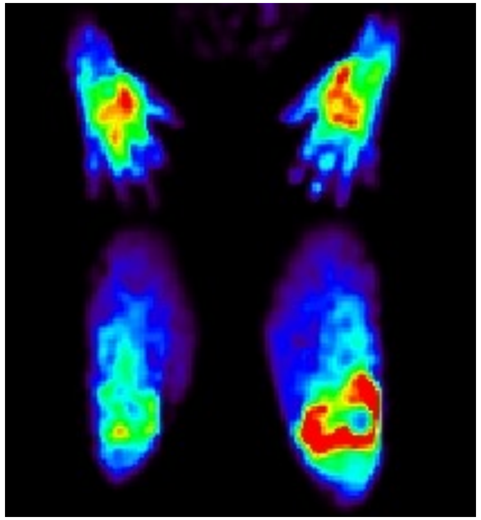


Example of Ongoing Studies: Low-Dose Total-Body PET of Rheumatoid Arthritis

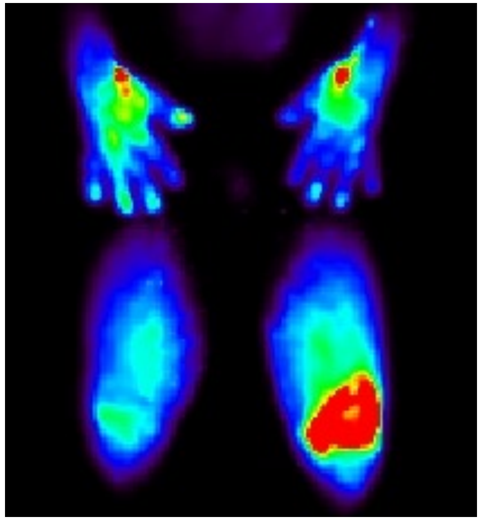
Abhijit Chaudhari, PhD
Professor, UC Davis

Rheumatoid Arthritis

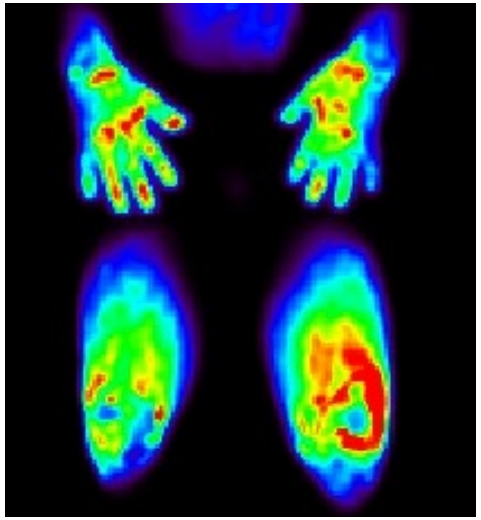
FDG K_i



FDG K_1

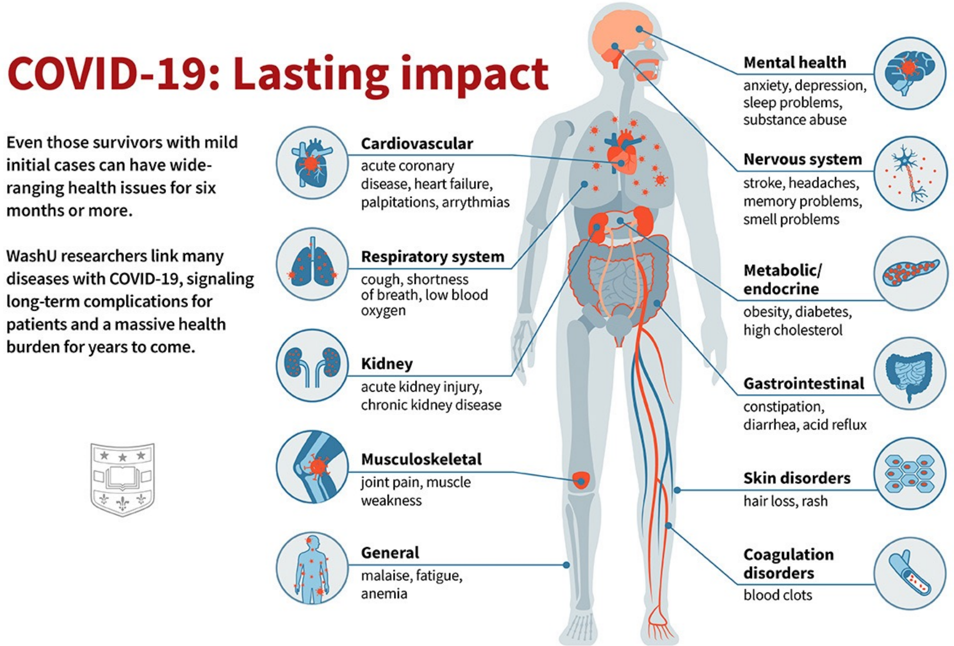


Volume of Distribution V_0



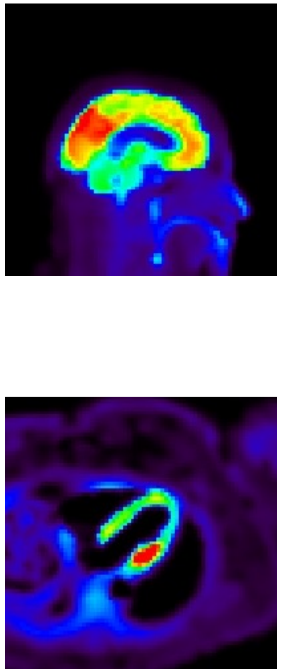
2 mCi ^{18}F-FDG injection

Example of Ongoing Studies: Metabolic Imaging of COVID-19 Recovery



https://medicine.wustl.edu/

FDG transport K_1 FDG metabolism K_i



5 weeks after COVID diagnosis

Collaboration with L Nardo MD, SR Cherry PhD

Acknowledgements

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Abhijit Chaudhari
Ben Spencer
Xuezhu Zhang
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Yasser Abdelhafez
Souvik Sarkar
Javier Lopez
Chong-xian Pan
Primo N. Lara
Mamta Parikh
Rashimi Verma

UC Davis EXPLORER Molecular Imaging Tech Team

All UC Davis MiPET Group members