IEEE NPSS NUCLEAR & PLASMA SCIENCES SOCIETY

2021 IEEE NSS MIC

Short Course 07: PET Kinetic Modeling and Parametric Imaging

Instructors: RN Gunn, M Normandin, GB Wang

Total-Body PET Kinetic Modeling and Applications

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October 16, 2021

Short-Course Agenda

- 08:00 a.m. Roger Gunn (Invicro & ICL):
  Basics of dynamic PET quantification / Compartment modeling

- 09:30 a.m. Marc Normandin (MGH):
  Graphical and linearized models / Reference-tissue modeling methods

- 11:15 a.m. Guobao Wang (UCD):
  Total-body PET kinetic modeling and parametric imaging / potential applications

- 12:30 p.m. Q&A

Disclosure

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

Lecture Outline

I. Dynamic whole-body PET imaging on conventional short scanners

- Whole-body Patlak parametric imaging

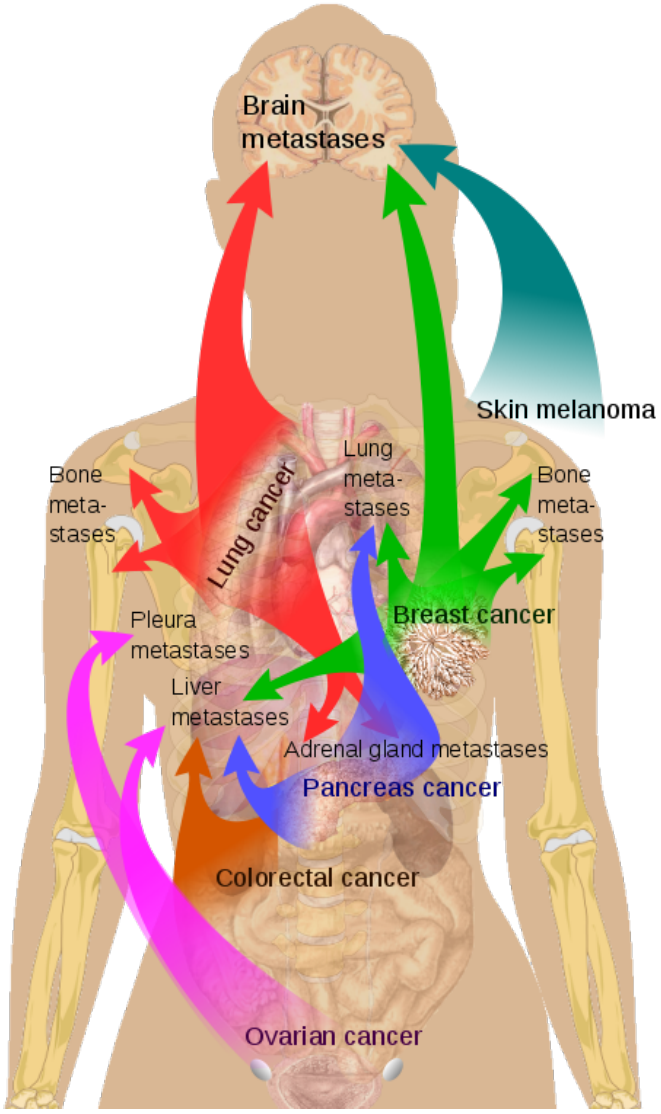
II. Total-body PET kinetic modeling and parametric imaging with long scanners

- Benefits of total-body PET for kinetic modeling
- Technical challenges and solution
- Comparison of compartmental modeling with Patlak plot

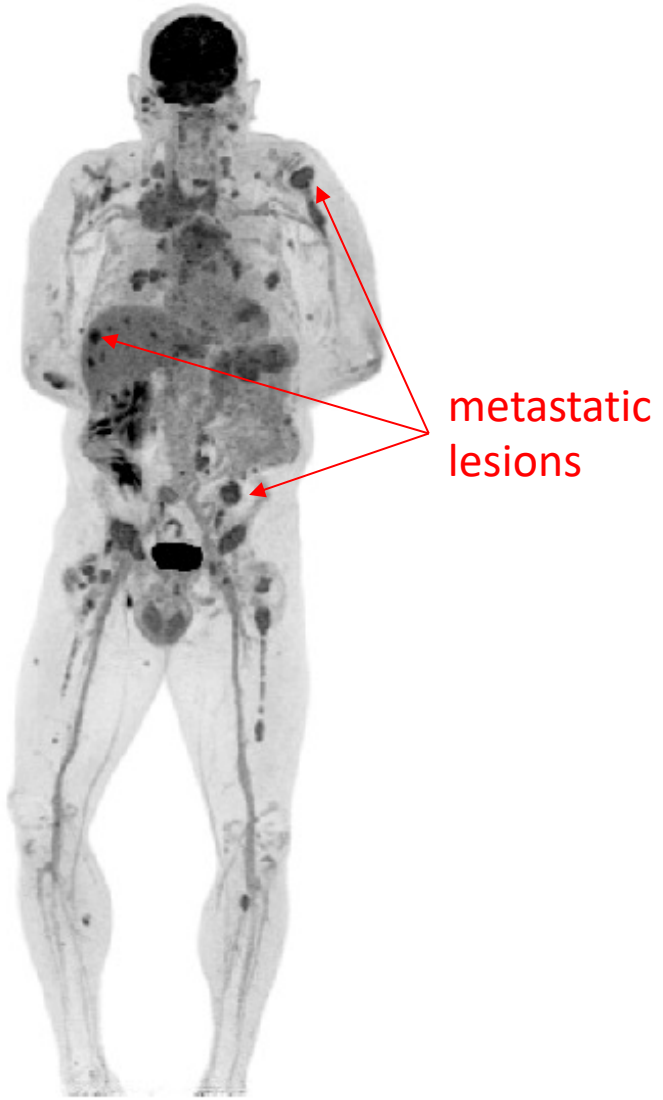
III. Potential benefits/applications of total-body parametric imaging

Why Do We Need Whole-Body Imaging?

- Example: metastatic cancer



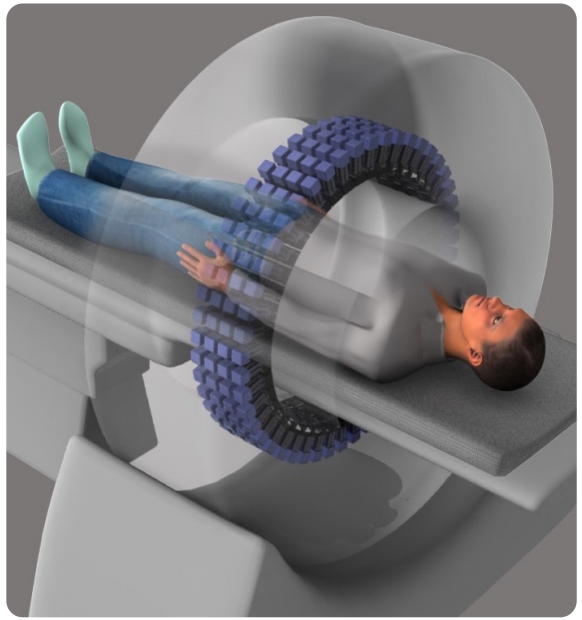
https://en.wikipedia.org/wiki/Metastasis



Axial Length of Standard Clinical PET Scanners

- Standard clinical PET scanners commonly have an axial length of 15-30 cm

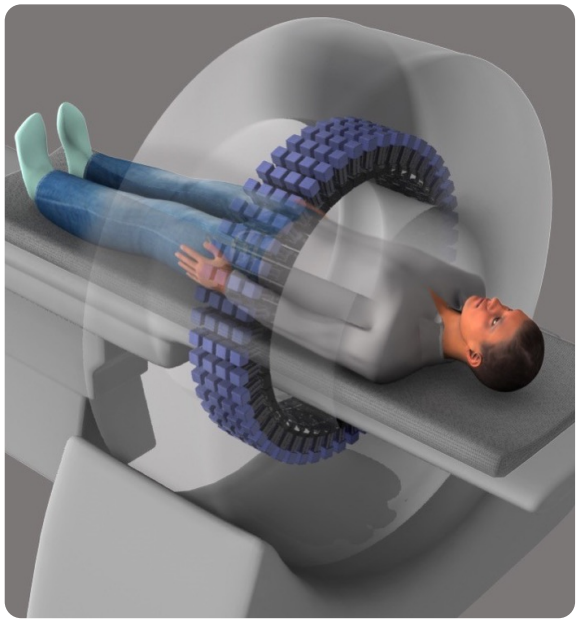
PET Scanner	Year coming into the market	Axial length (cm)
GE Discovery 690	2010	15.9
Philips Vereos	2018	16.4
GE Discovery MI (5-ring)	2018	25
Siemens Biograph Vision	2018	26
Canon Cartesion Prime	2019	27
UIH uMI780	2019	30

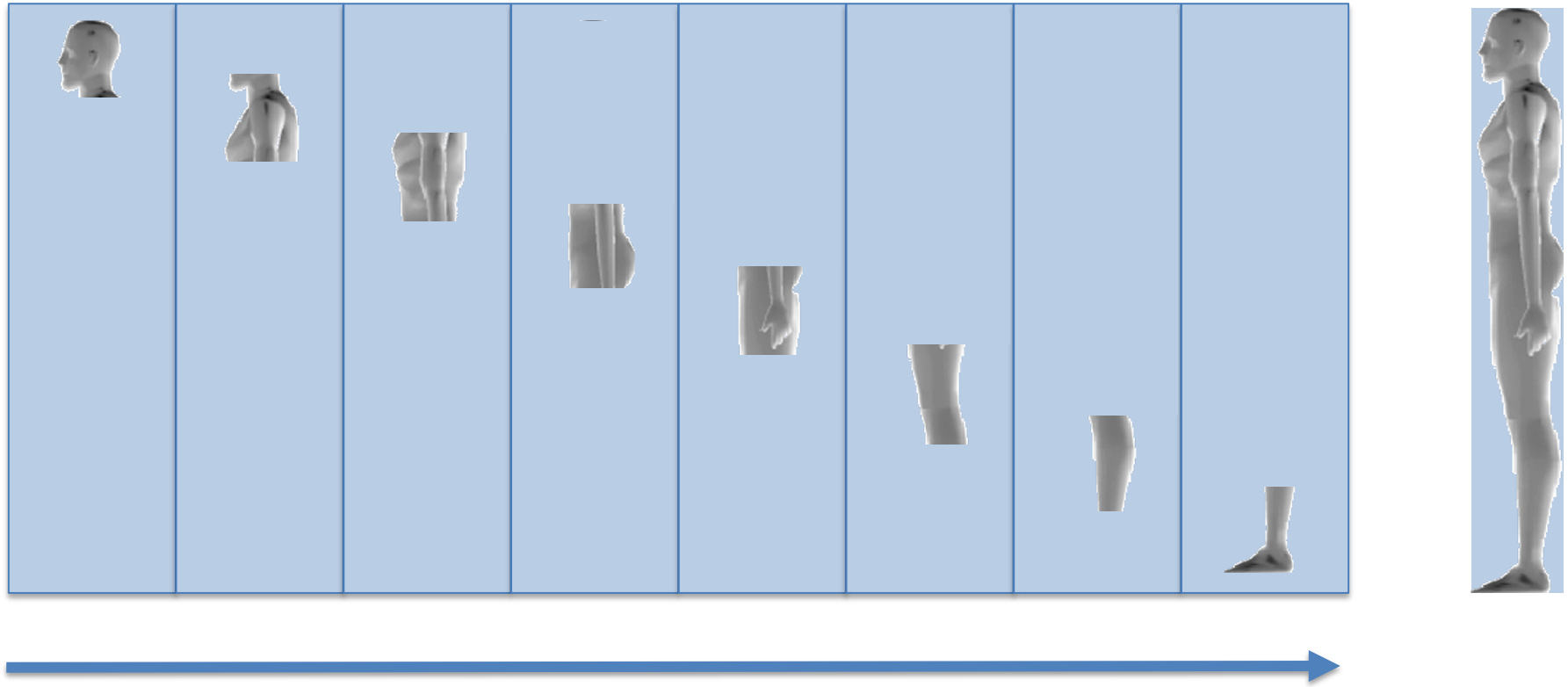


- However, adult human height is about 1.5-2 m

Implementation for Whole-body PET Imaging

- A whole-body scan by a conventional PET scanner requires **multiple bed positions**

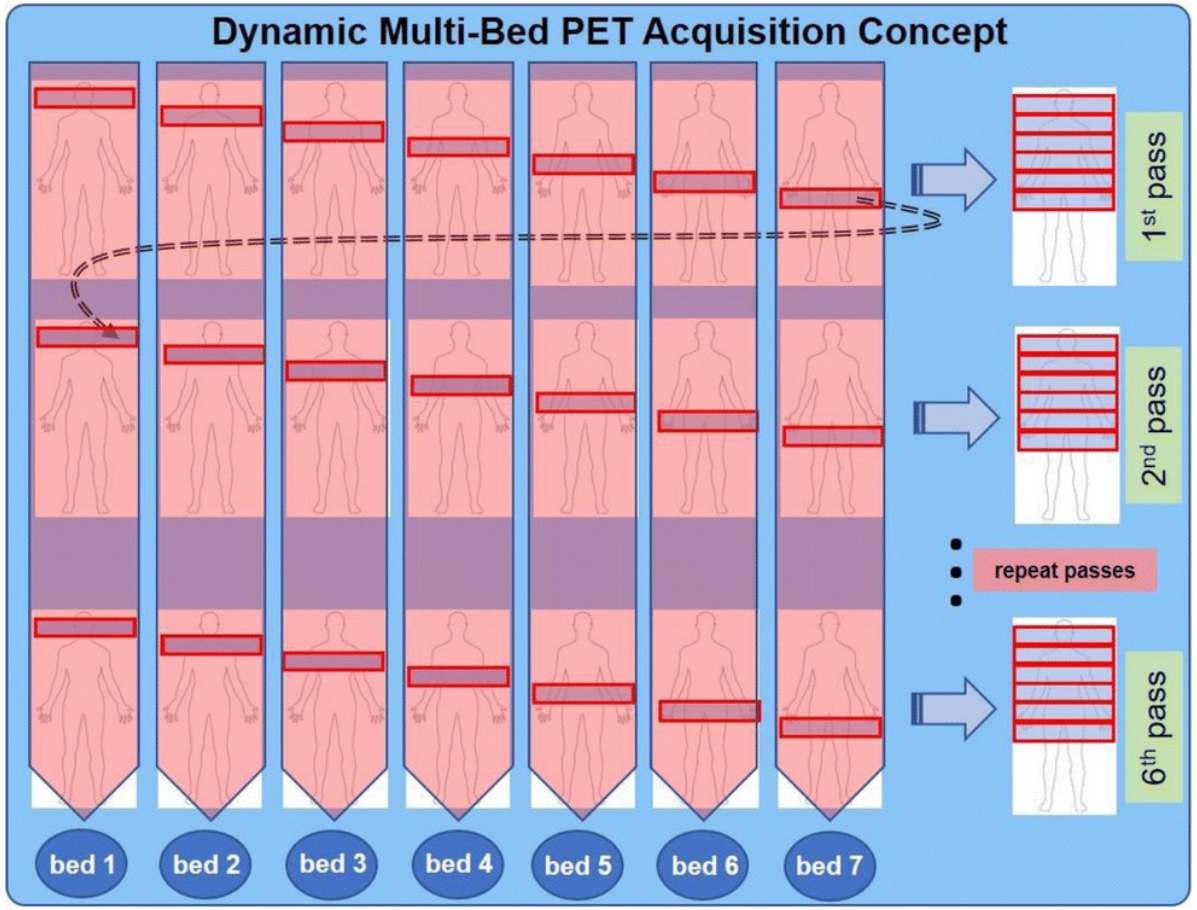




Each takes 2-3 minutes, resulting in a total of 10-20 minutes

Images courtesy of Dr. Ramsey Badawi

Dynamic Whole-Body (WB) PET Imaging

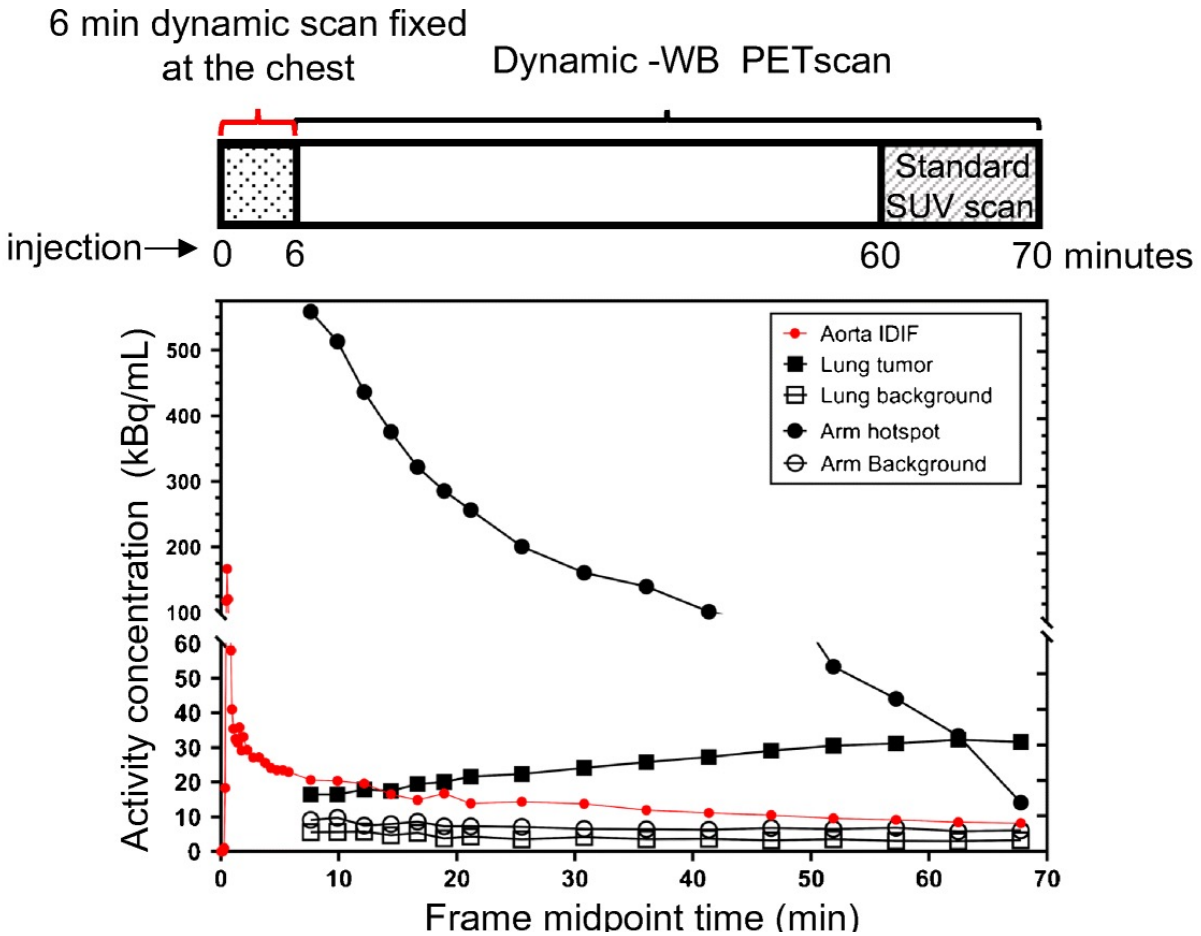


- Dynamic scan of whole body
  - Multi-bed positions
  - Two or multiple passes
  - Mainly late-phase dynamic data
- Blood input function
  - By a short dynamic scan (e.g., 6 minutes) with the bed fixed at the **chest** region
  - or by using a population-based input function

N Karakatsanis *et al.* PMB 2013; Rahmim *et al* EJNMMI 2019

Yao *et al* Med Phys 2020; Wu *et al.* Med Phys 2021

Dynamic WB PET Imaging: Advantages and Limitations



AH Dias *et al.* EJNMMI 2020

- Advantages:
  - Implementable on all existing commercial PET scanners
- Limitations:
  - Limited temporal resolution
  - Lost early-dynamic data for most organs
- But it still enables whole-body Patlak parametric imaging

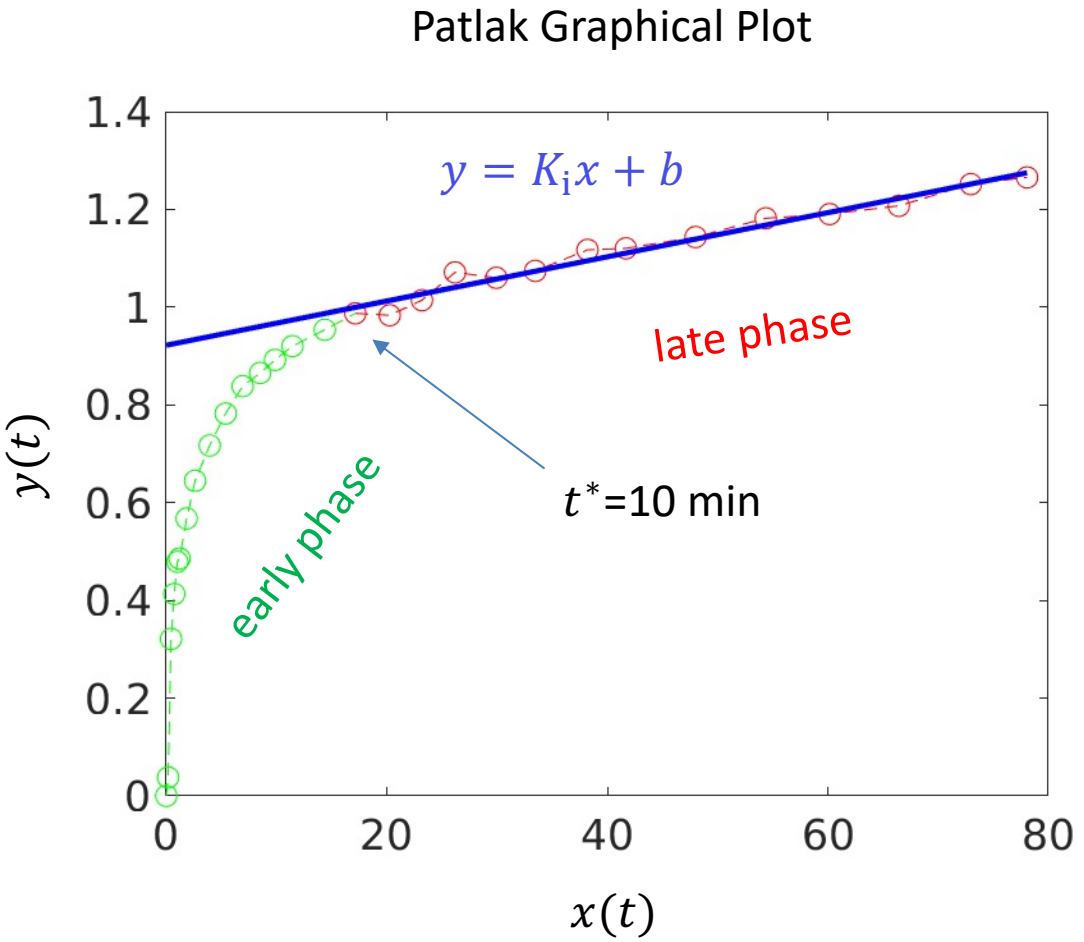
Patlak Graphical Plot

- Model equation (Patlak *et al*. JCBFM 1983):

$$\frac{C_{\mathrm{T}}(t)}{C_{\mathrm{p}}(t)} = K_{\mathrm{i}} \frac{\int_0^t C_{\mathrm{p}}(\tau)d\tau}{C_{\mathrm{p}}(t)} + b, \quad t > t^*.$$

$y(t)$ $x(t)$

- No early-phase data of $C_{\mathrm{T}}(t)$ is needed
- Observations (Zhu *et al.* TMI 2014):
  - A linear inverse problem with two unknown kinetic parameters (K_{i}, b)
  - In theory, only two time points are needed to solve the problem
- High temporal resolution is not necessary



Relative Patlak Plot

- Observation: Only the **integral** of the early phase of $C_{\mathrm{p}}(t)$ is needed by the Patlak plot

$$\frac{C_{\mathrm{T}}(t)}{C_{\mathrm{p}}(t)} = K_{\mathrm{i}} \frac{\int_0^t C_{\mathrm{p}}(\tau)d\tau}{C_{\mathrm{p}}(t)} + b, \quad t > t^*$$

$$= \int_0^{t^*} C_{\mathrm{p}}(\tau)d\tau + \int_{t^*}^t C_{\mathrm{p}}(\tau)d\tau$$

- Any error in the early-phase integral only introduces a global scaling factor in the the Patlak slope image

- Relative Patlak plot

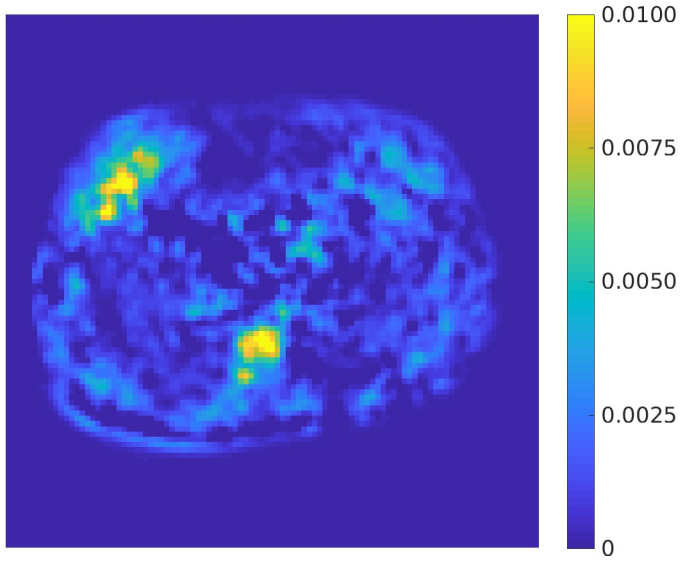
$$\frac{C_{\mathrm{T}}(t)}{C_{\mathrm{p}}(t)} = K_{\mathrm{i}}' \frac{\int_{t^*}^t C_{\mathrm{p}}(\tau)d\tau}{C_{\mathrm{p}}(t)} + b', \quad t > t^*$$

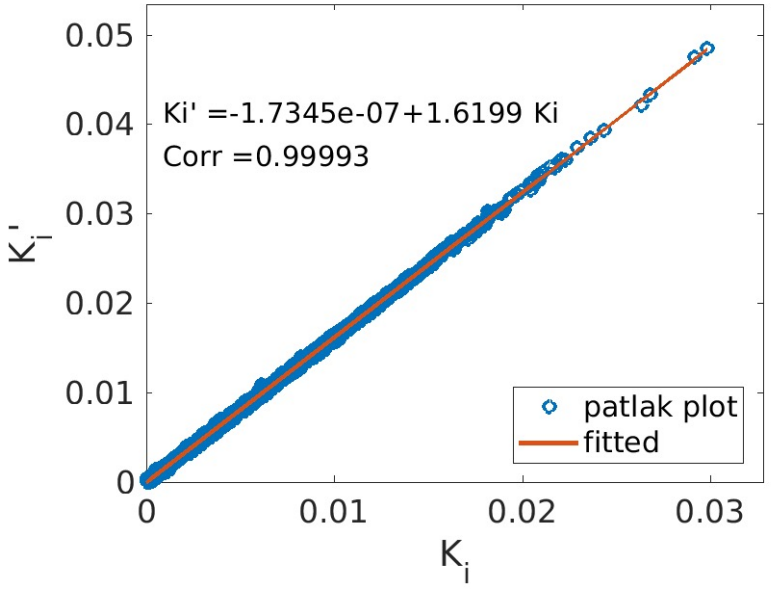
Y Zuo *et al.* PMB 2018; Yao *et al* Med Phys 2020

Difference between Standard and Relative Patlak Slopes: Global Scaling

Standard Patlak plot

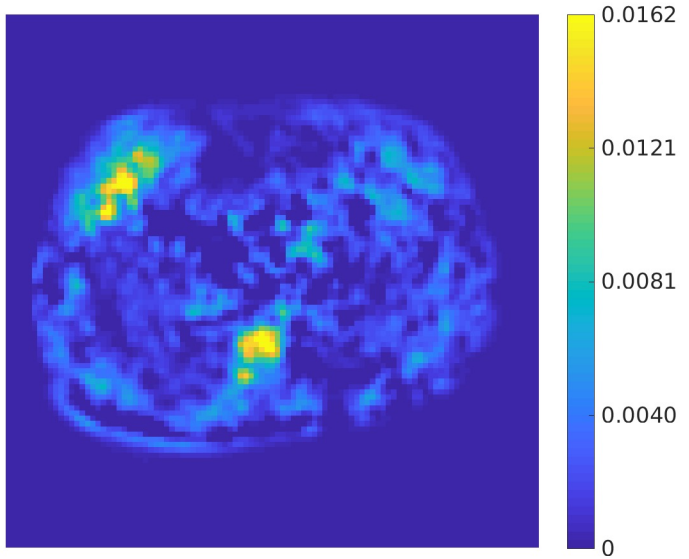
K_i





Relative Patlak plot

K_i'



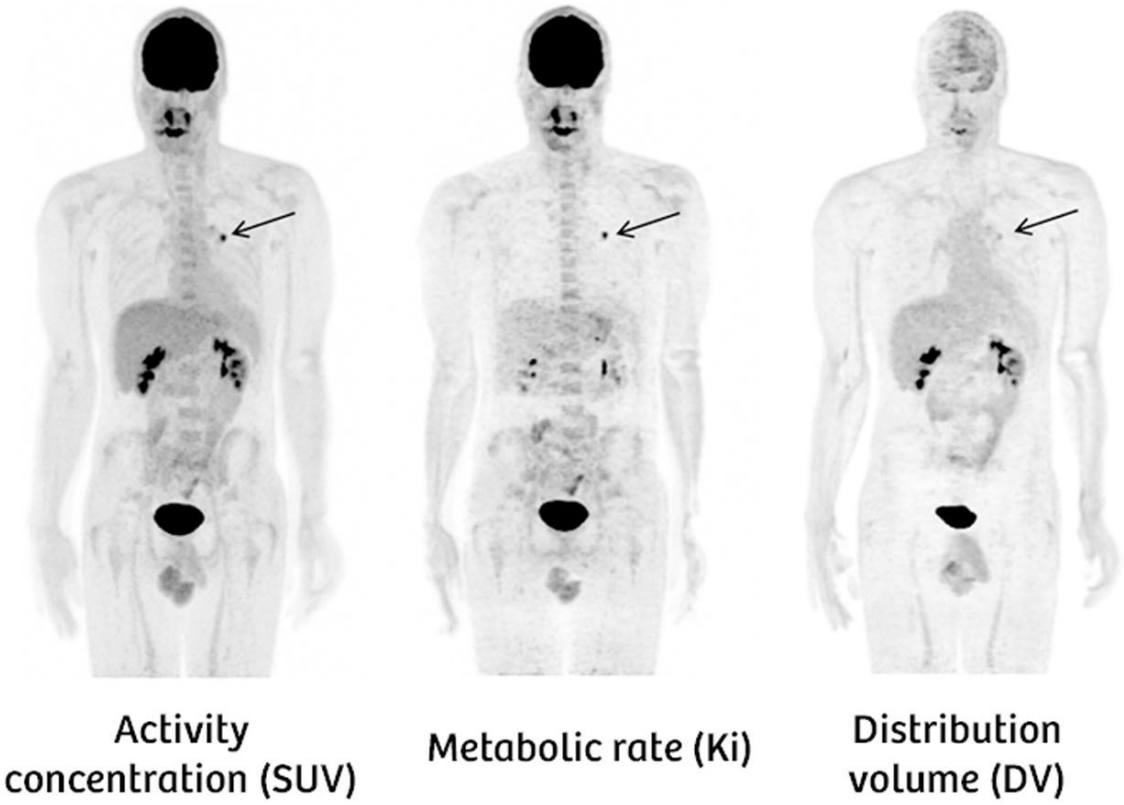
Y Zuo *et al.* PMB 2018

Patlak Parametric Imaging Became Available on Commercial PET Scanners

- Siemens implemented the whole-body Patlak parametric imaging
  (Hu *et al.* IEEE-TRPMS 2020)

- Scan protocol: multibed multi-pass scan
  (Karakatsanis *et al.* PMB 2013)

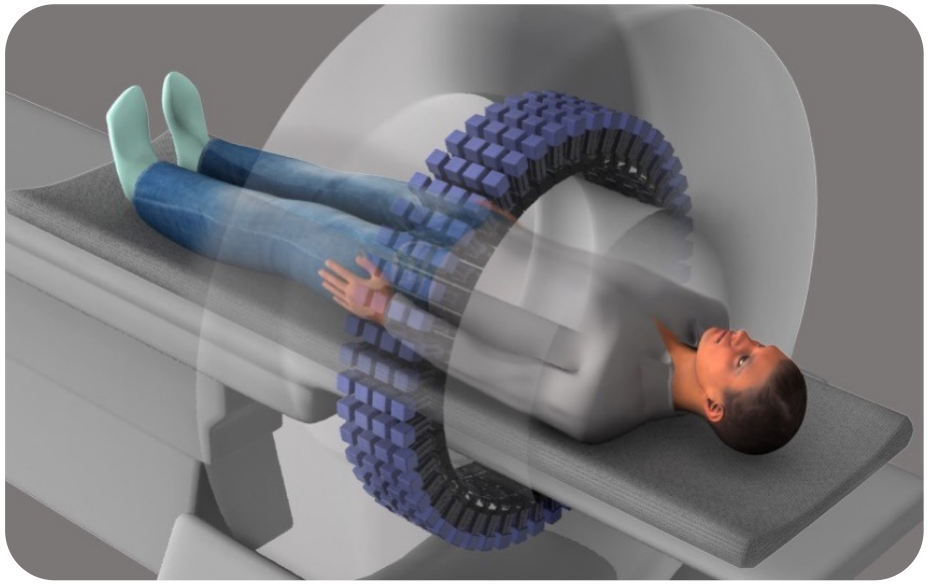
- Direct parametric reconstruction with the Nested EM algorithm (Wang & Qi PMB 2010)



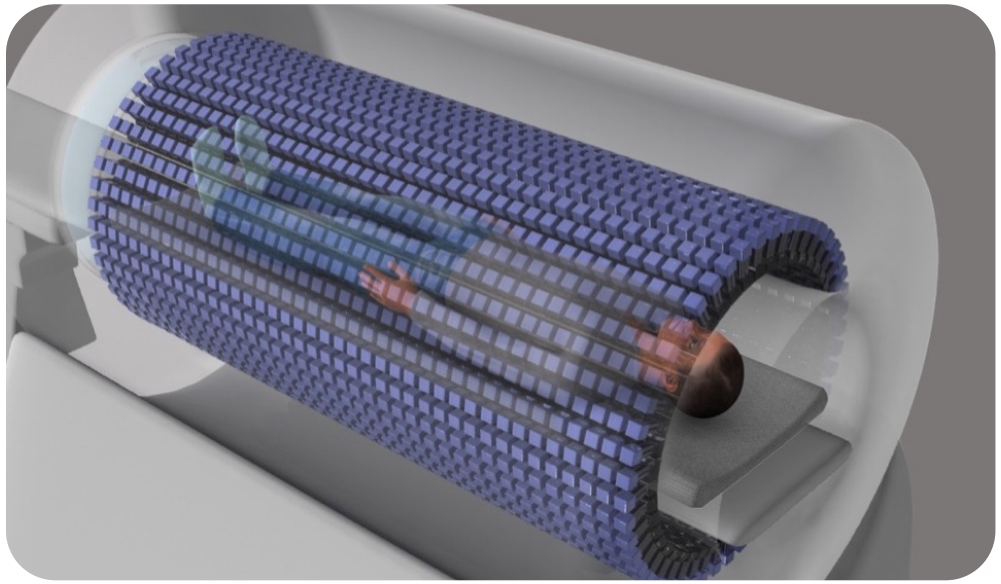
https://www.siemens-healthineers.com/molecular-imaging/options-and-upgrades/software-applications/flowmotion-multiparametricpet-suite

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 dynamic imaging of the entire body

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

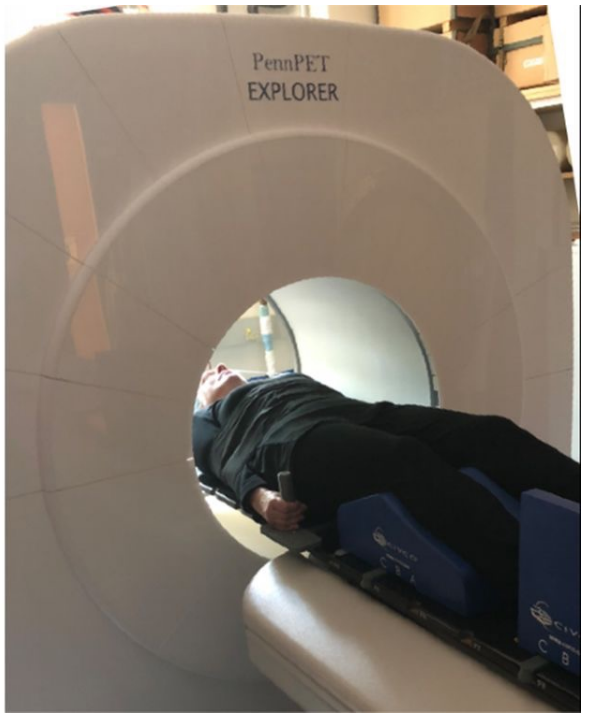
Long Axial FOV PET Scanners

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

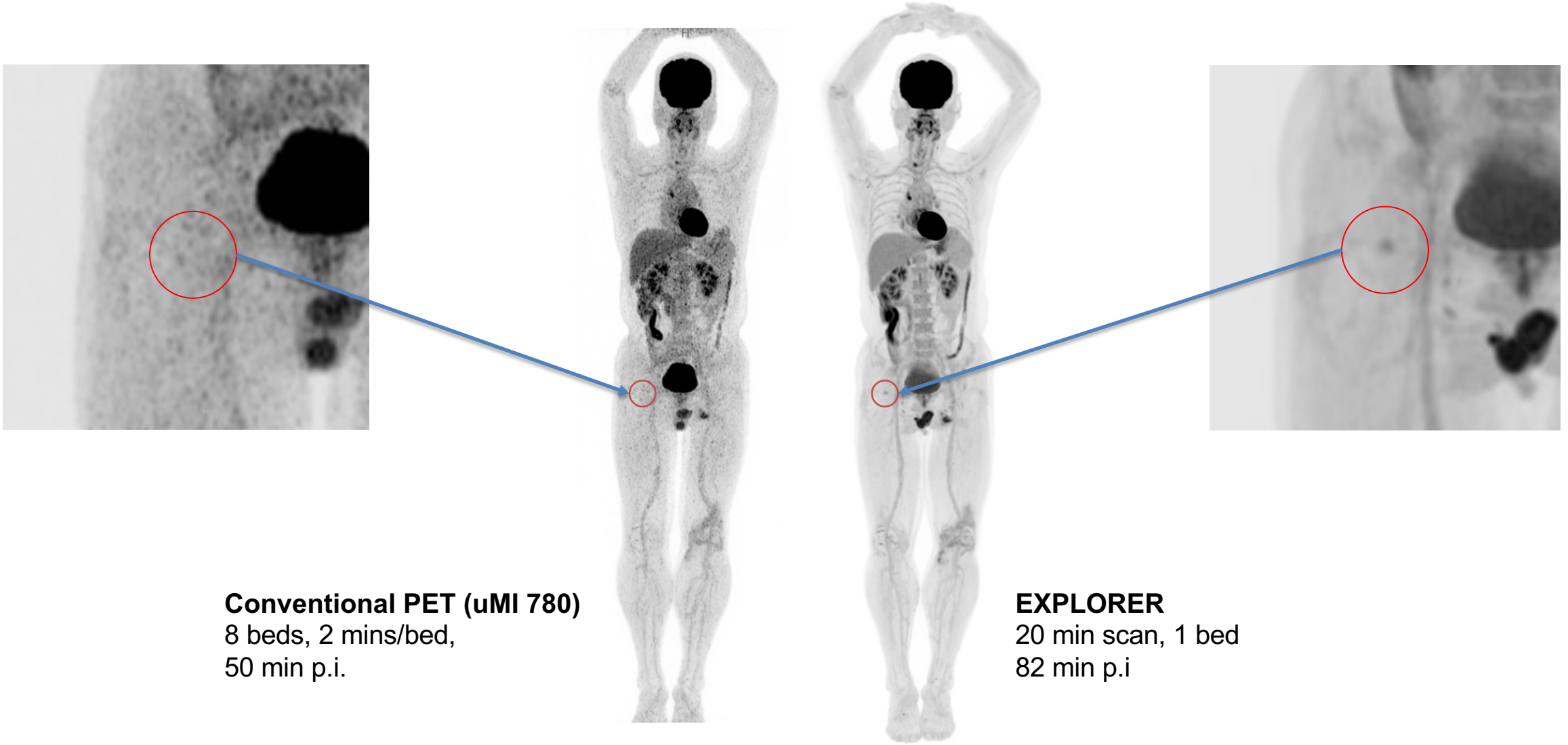
Axial FOV: 106 cm

Alberts *et al.* EJNMMI 2021

Benefits of Total-Body PET for Dynamic Imaging and Kinetic Modeling

- Improved sensitivity
  - makes it more robust to estimate kinetic parameters ⟹ Clinical reliability
  - enables dynamic PET imaging with higher temporal resolution ⟹ Probing physiology
    (Badawi *et al* JNM 2019; Zhang *et al* PNAS 2021)
- Total-body coverage
  - provides *full* time course of tracer activity for *all* organs ⟹ Good image-derived input function ⟹ Total-body parametric imaging of macro- and micro-kinetic parameters

Benefits of Total-Body PET for Dynamic Imaging: High Image Quality

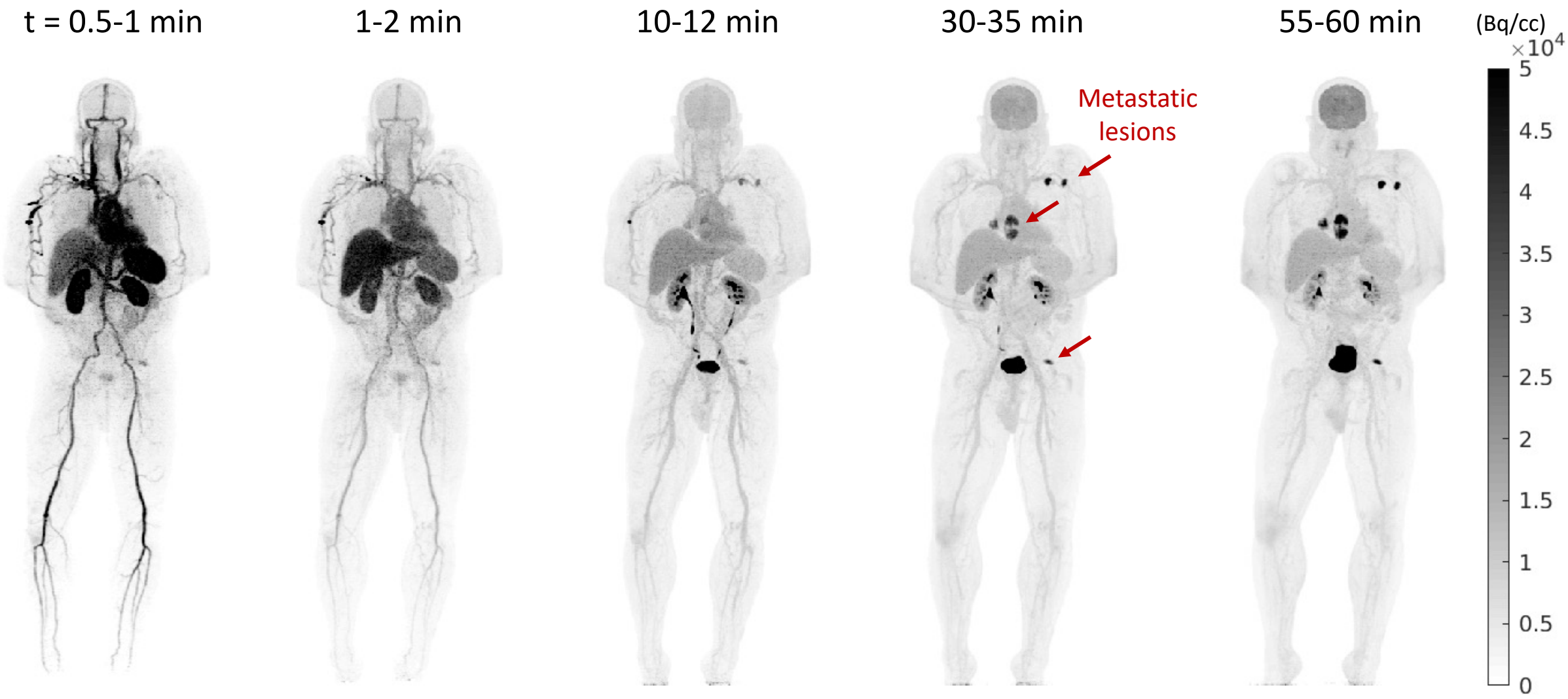


Conventional PET (uMI 780)
8 beds, 2 mins/bed,
50 min p.i.

EXPLORER
20 min scan, 1 bed
82 min p.i

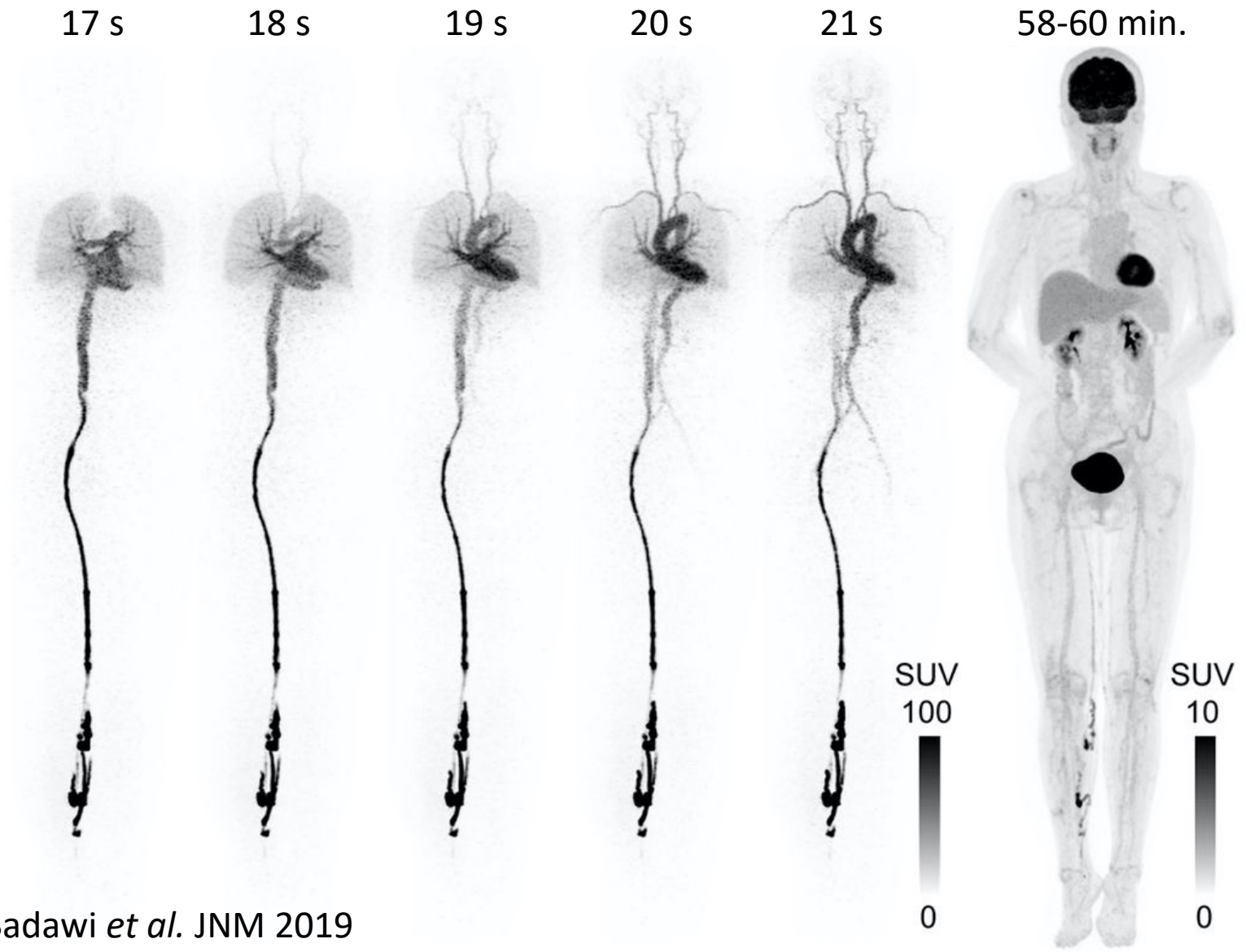
Courtesy of Ramsey D. Badawi

Simultaneous Dynamic Imaging of the Entire Body on EXPLORER



Shown are MIP (maximum intensity projection) images.

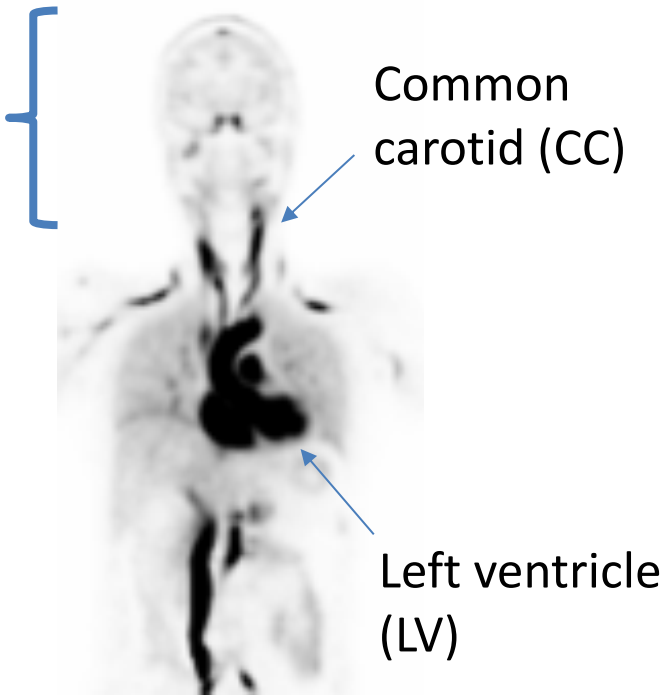
Benefits of Total-Body PET for Dynamic Imaging: High Temporal Resolution



Zhang *et al.* JNM 2020; Badawi *et al.* JNM 2019

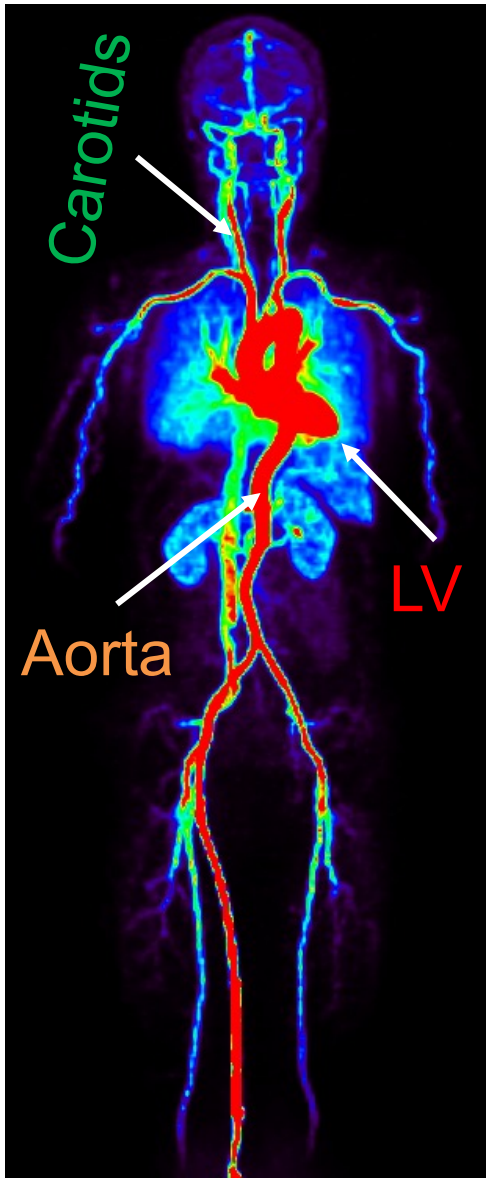
Benefits of Total-Body PET for Kinetic Modeling: Extraction of Input Function

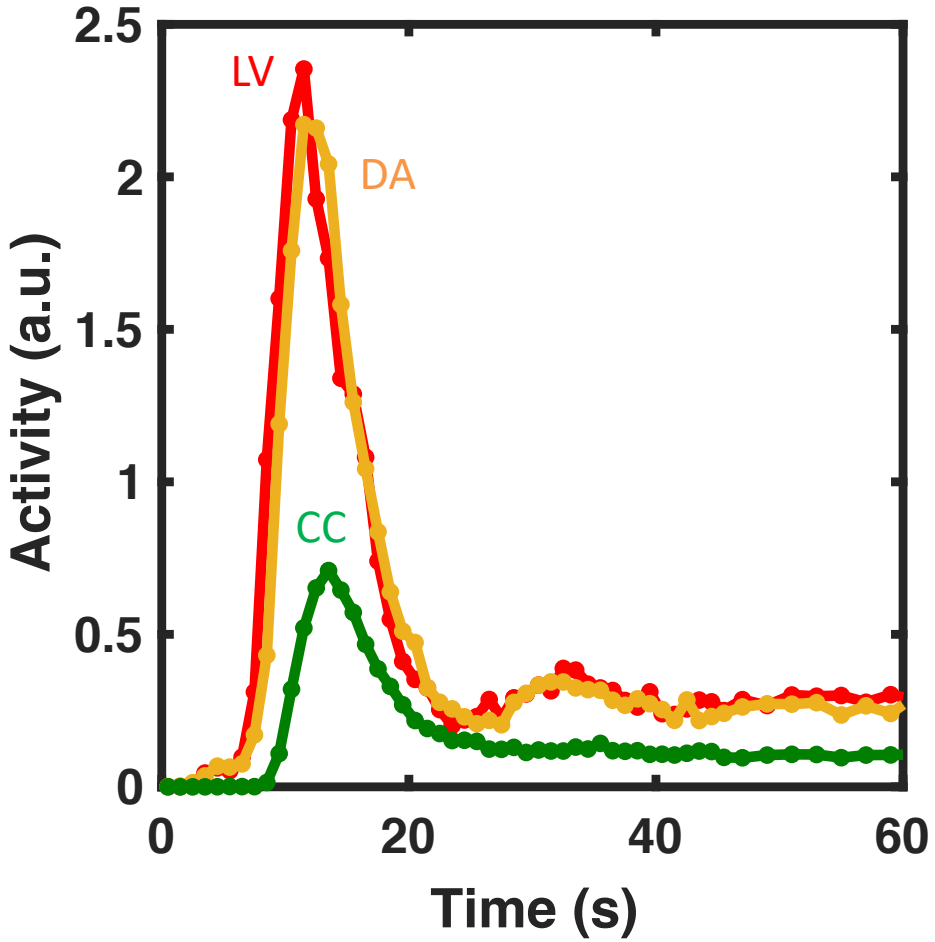
Axial Coverage of Standard PET Scanners



- Blood input function is conventionally obtained with invasive blood sampling
- For brain imaging, best available image-derived input function (IDIF) by conventional PET scanners is from the common carotid artery, which however suffers from severe partial volume effect
- With total-body PET, IDIF is available from a large blood pool, e.g., the left ventricle

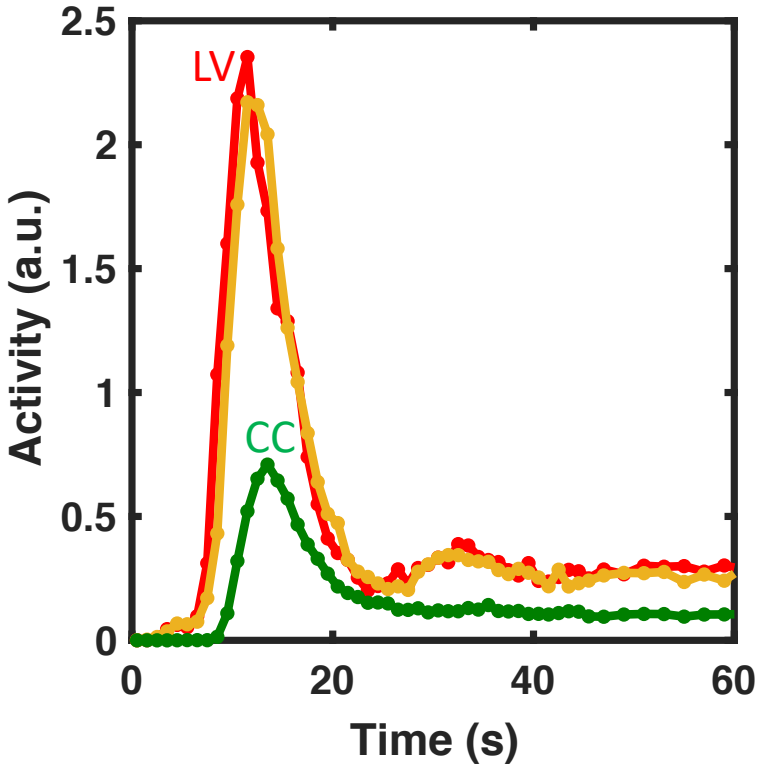
Image-Derived Input Functions (IDIFs) in Total-Body Dynamic PET



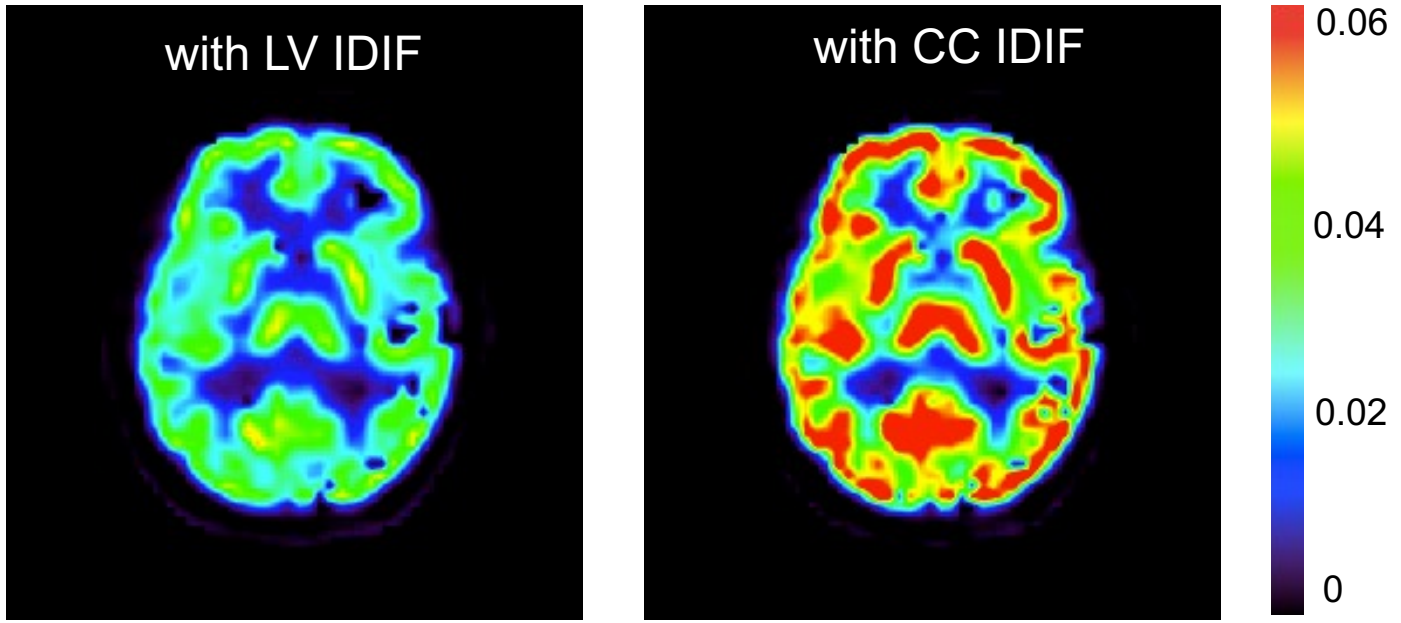


Courtesy of Elizabeth Li

Example of Brain Parametric Imaging

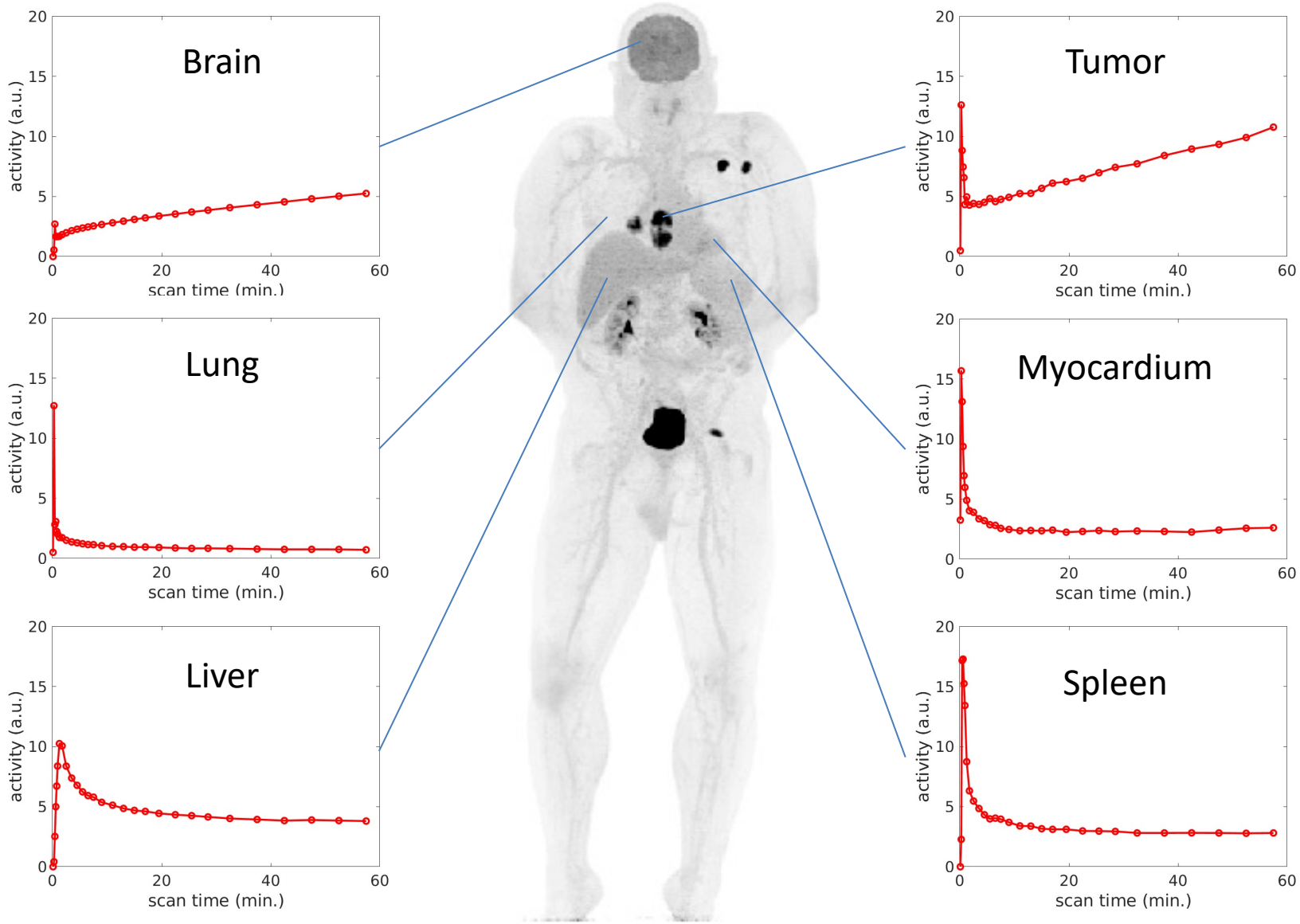


Cerebral FDG K_i

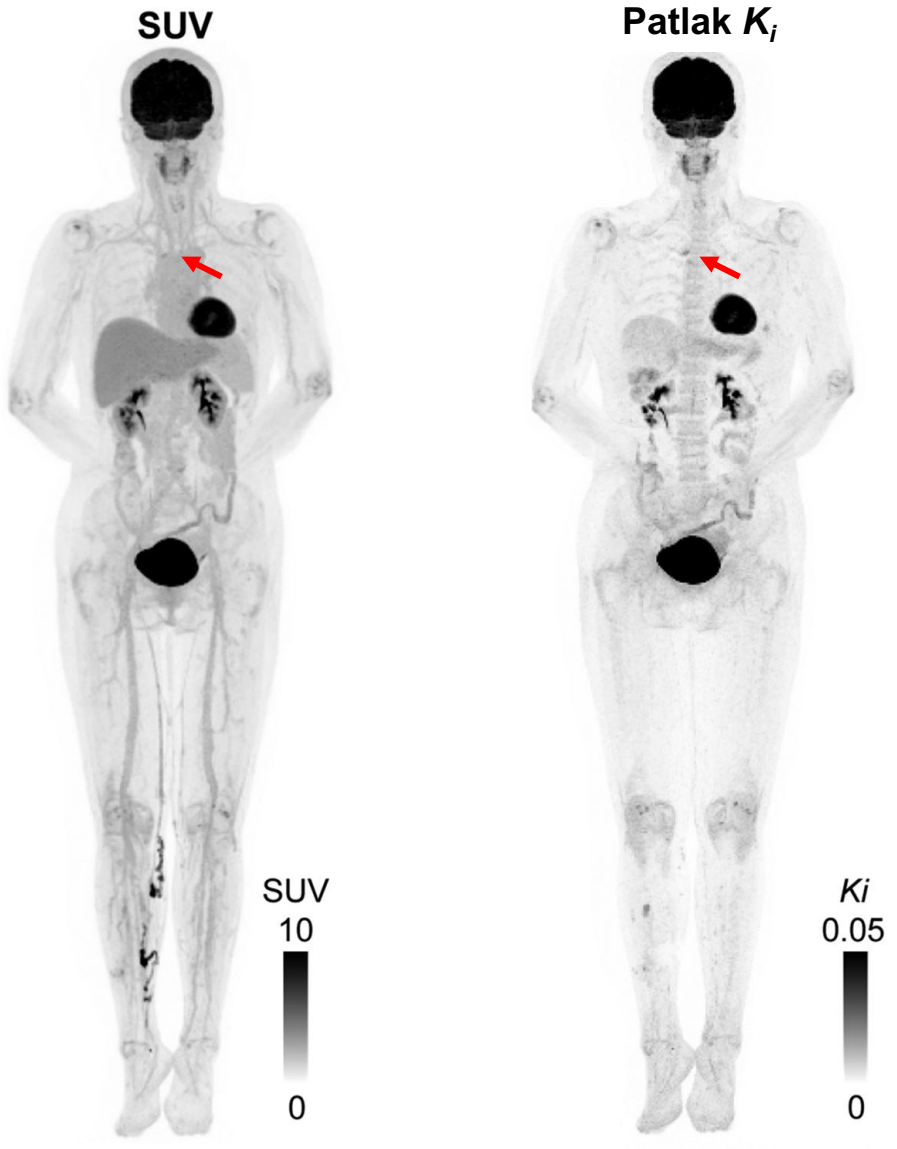


E Li *et al.* 2019 SNMMI

Benefits of Total-Body PET for Dynamic Imaging : Capturing the Full Time Course of Tracer Activity in All Organs

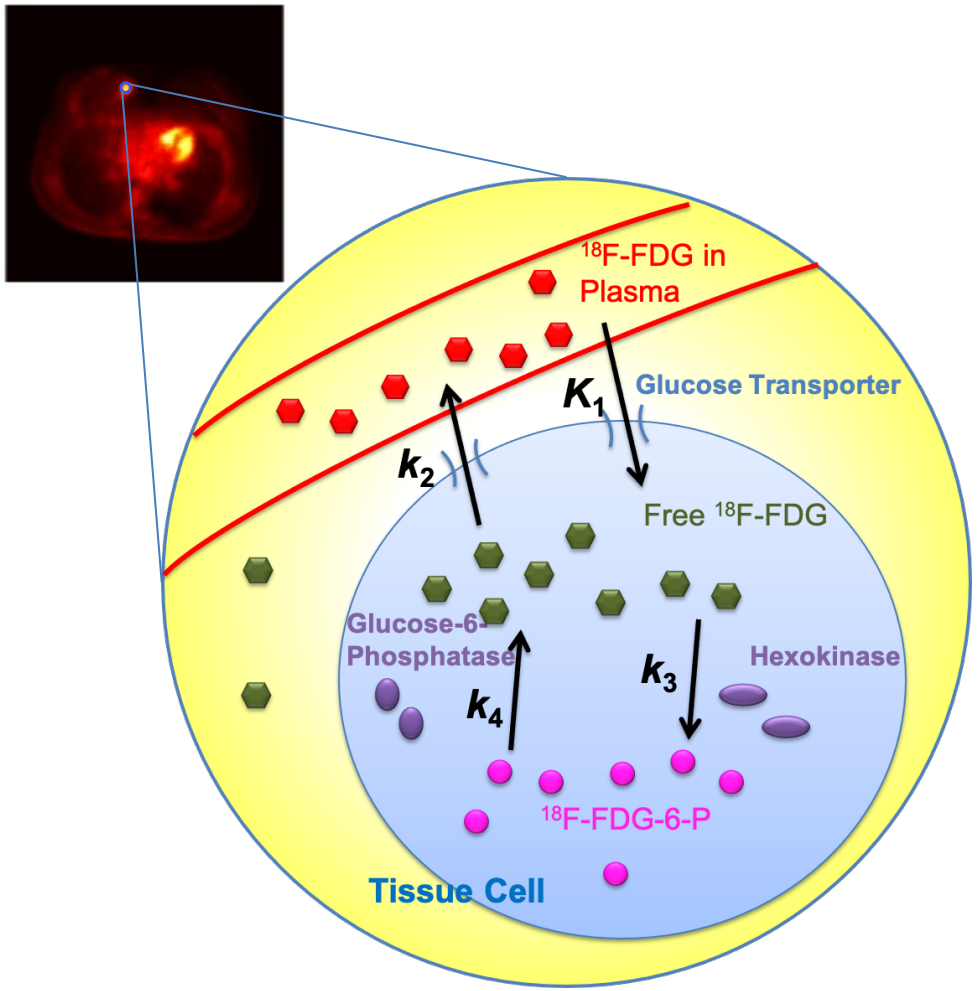


Total-Body Patlak Parametric Imaging on EXPLORER

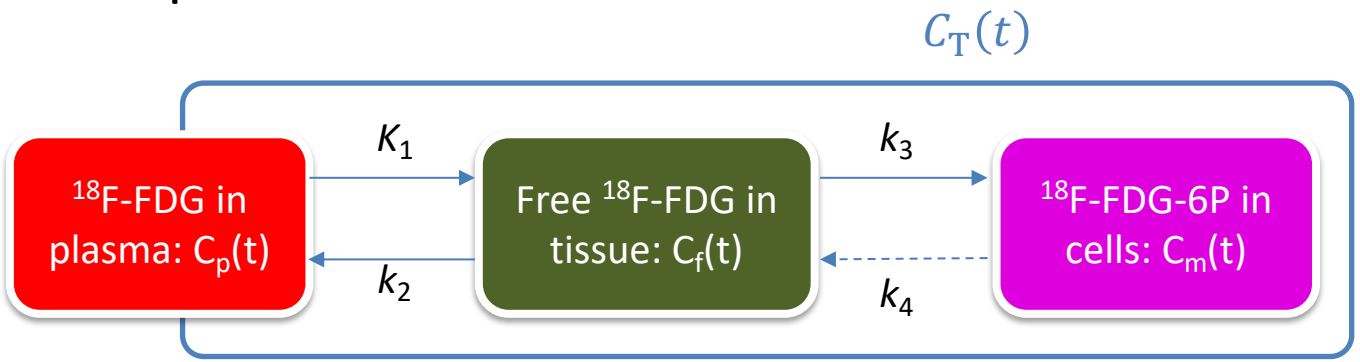


Zhang *et al.* JNM 2020

Benefits of Total-Body PET for Kinetic Modeling: Parametric Imaging with Compartmental Models



- Compartmental model



- Differential equations

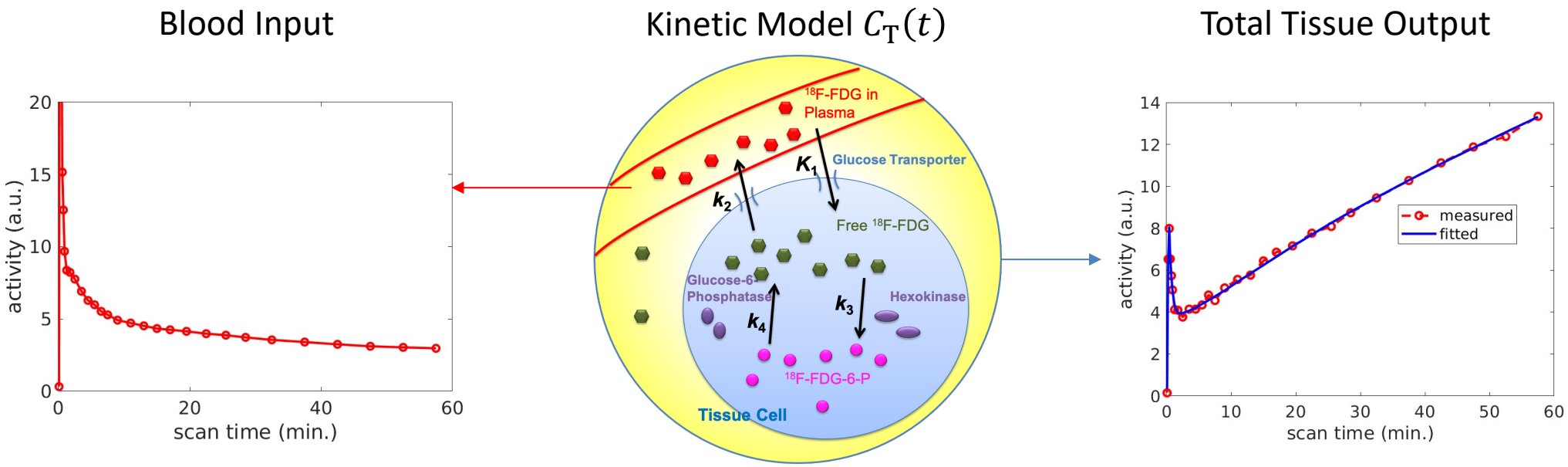
$$\frac{\mathrm{d}}{\mathrm{d}t}\begin{bmatrix} C_\mathrm{f}(t) \\ C_\mathrm{m}(t) \end{bmatrix} = \begin{bmatrix} -(k_2+k_3) & k_4 \\ k_3 & -k_4 \end{bmatrix}\begin{bmatrix} C_\mathrm{f}(t) \\ C_\mathrm{m}(t) \end{bmatrix} + \begin{bmatrix} K_1 \\ 0 \end{bmatrix} C_\mathrm{p}(t)$$

- 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; Gunn *et al* 2002. Online book chapter: Morris *et al.* 2004; Carson 2005

Kinetic Parametric Estimation by Full Time Activity Curve (TAC) Fitting



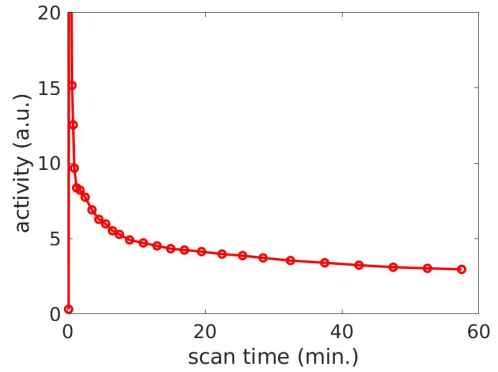
- Micro-kinetic parameters (e.g., K_1, k_2, …) are estimated from TAC fitting
- Macro kinetic parameters can be calculated, e.g., for FDG:

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

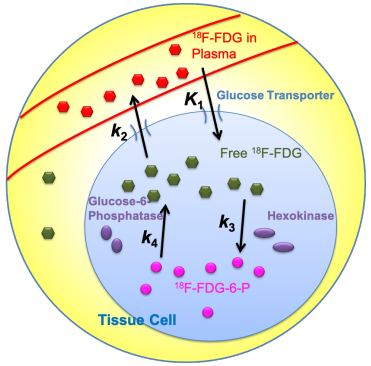
Challenges of Total-Body Kinetic Modeling and Parametric Imaging

Key Components

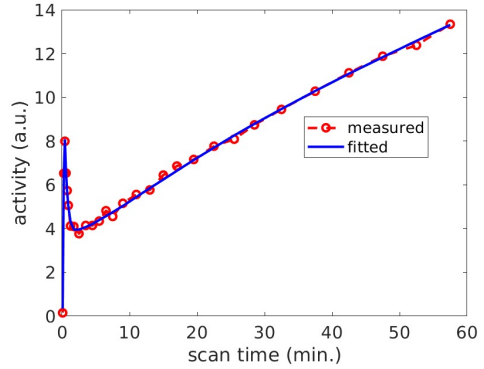
Blood Input Function



Kinetic Model



Tissue TACs and Fitting



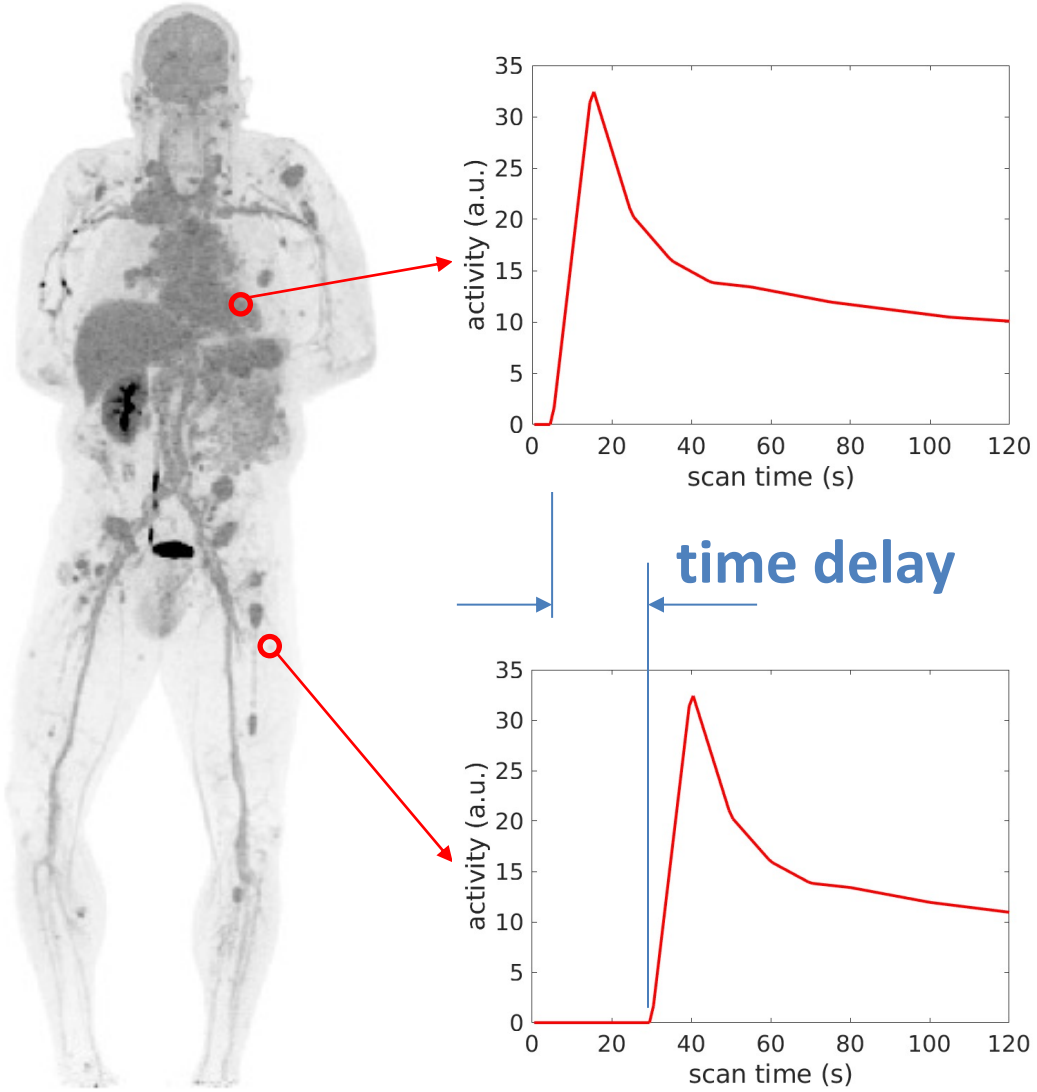
Challenges

- 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

Commonly Neglected in Parametric Imaging

- K_i estimation is more dominated by the late phase instead of early phase of a dynamic scan
- Within a limited axial FOV of 15 cm of conventional PET, time delay can be just a few seconds
- Temporal resolution of dynamic PET was limited (e.g., 10-40 s/frame)
- Mainly considered to be important for estimation of fast kinetics (e.g., cerebral blood flow imaging using ^{15}O-water)

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

Importance for Total-Body Kinetic Modeling

- Time delay in a tissue distant from the left ventricle can be up to 50 seconds

- Metastatic lesions spread to distant organs, which can be far away from the blood pool where a blood input function is extracted

- May significantly affect the estimation of v_{b}, K_1 and K_{i}

Example of time delay map estimated from a ^{18}F-FDG patient scan

Time-Delay Correction by Joint Estimation

- Model TAC <u>without</u> time delay

Impulse response function;
$\boldsymbol{\kappa} = [K_1, k_2, k_3]^T$

$$C_{\mathrm{T}}(t) = (1 - v_{\mathrm{b}})\mathrm{IRF}(t; \boldsymbol{\kappa}) \otimes C_{\mathrm{p}}(t) + v_{\mathrm{b}} C_{\mathrm{b}}(t)$$

- Model TAC <u>with</u> time delay correction

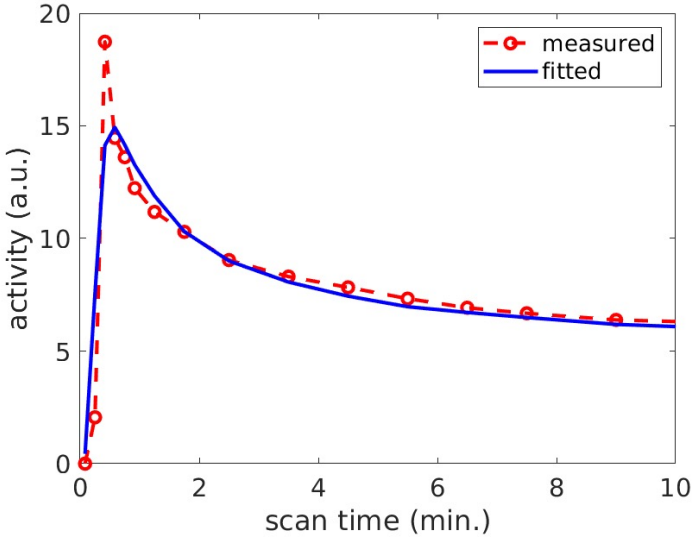
$$C_{\mathrm{T}}(t) = (1 - v_{\mathrm{b}})\mathrm{IRF}(t; \boldsymbol{\kappa}) \otimes C_{\mathrm{p}}(t - t_{\mathrm{d}}) + v_{\mathrm{b}} C_{\mathrm{b}}(t - t_{\mathrm{d}})$$

- $\boldsymbol{\theta} = [\boldsymbol{\kappa}^T, v_{\mathrm{b}}, t_{\mathrm{d}}]^T$ is jointly estimated via nonlinear least-square fitting:

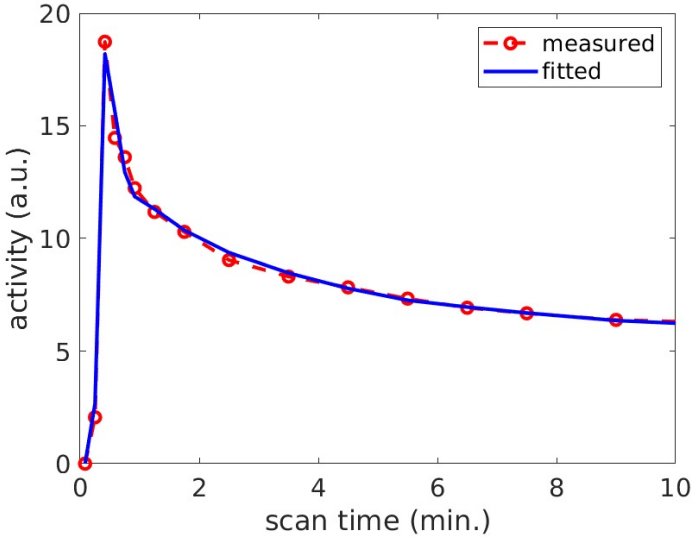
$$\widehat{\boldsymbol{\theta}} = \arg\min_{\boldsymbol{\theta}} RSS(\boldsymbol{\theta}), RSS(\boldsymbol{\theta}) = \sum_{m=1}^{M} w_m \left[\check{C}_{\mathrm{T}}(t_{\mathrm{m}}) - C_{\mathrm{T}}(t_m)\right]^2$$

Example of Fitting a Lesion TAC

A. no time-delay correction

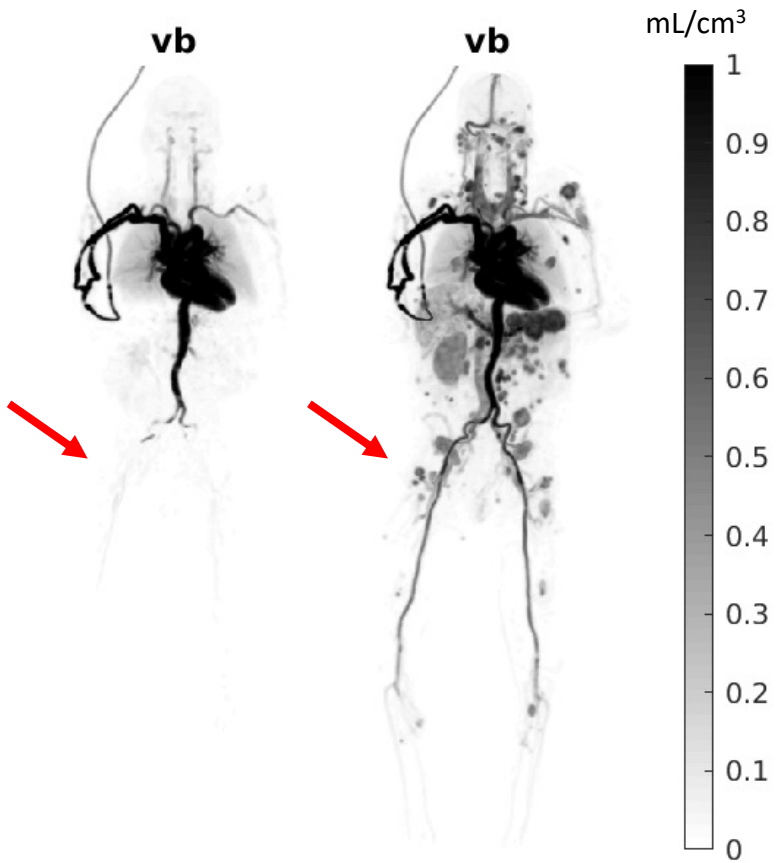


B. with time-delay correction



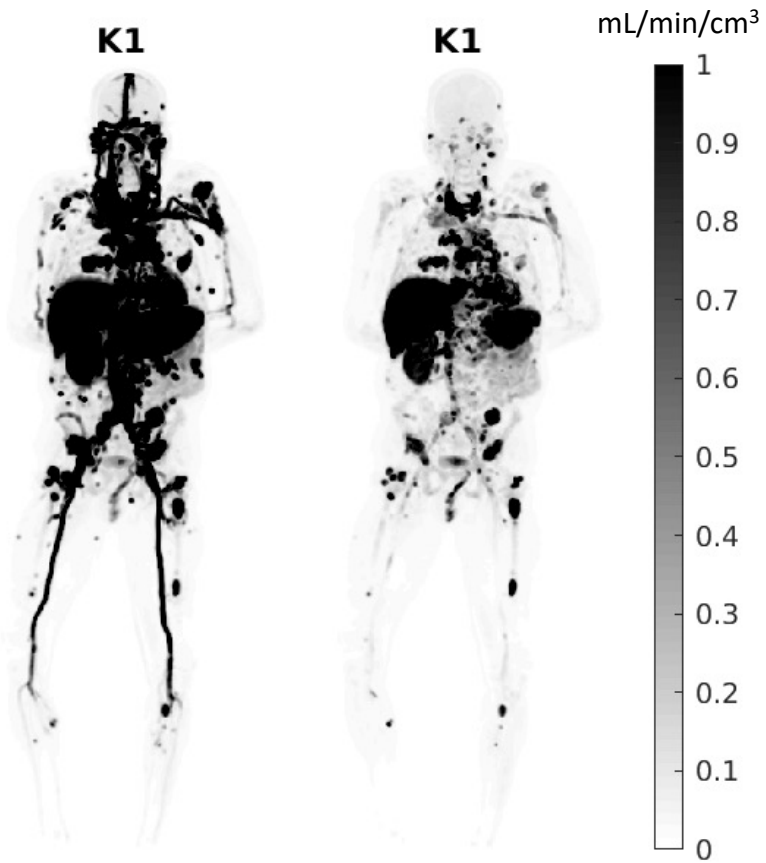
Time-Delay Correction on Total-Body Parametric Imaging

Fractional blood volume v_b



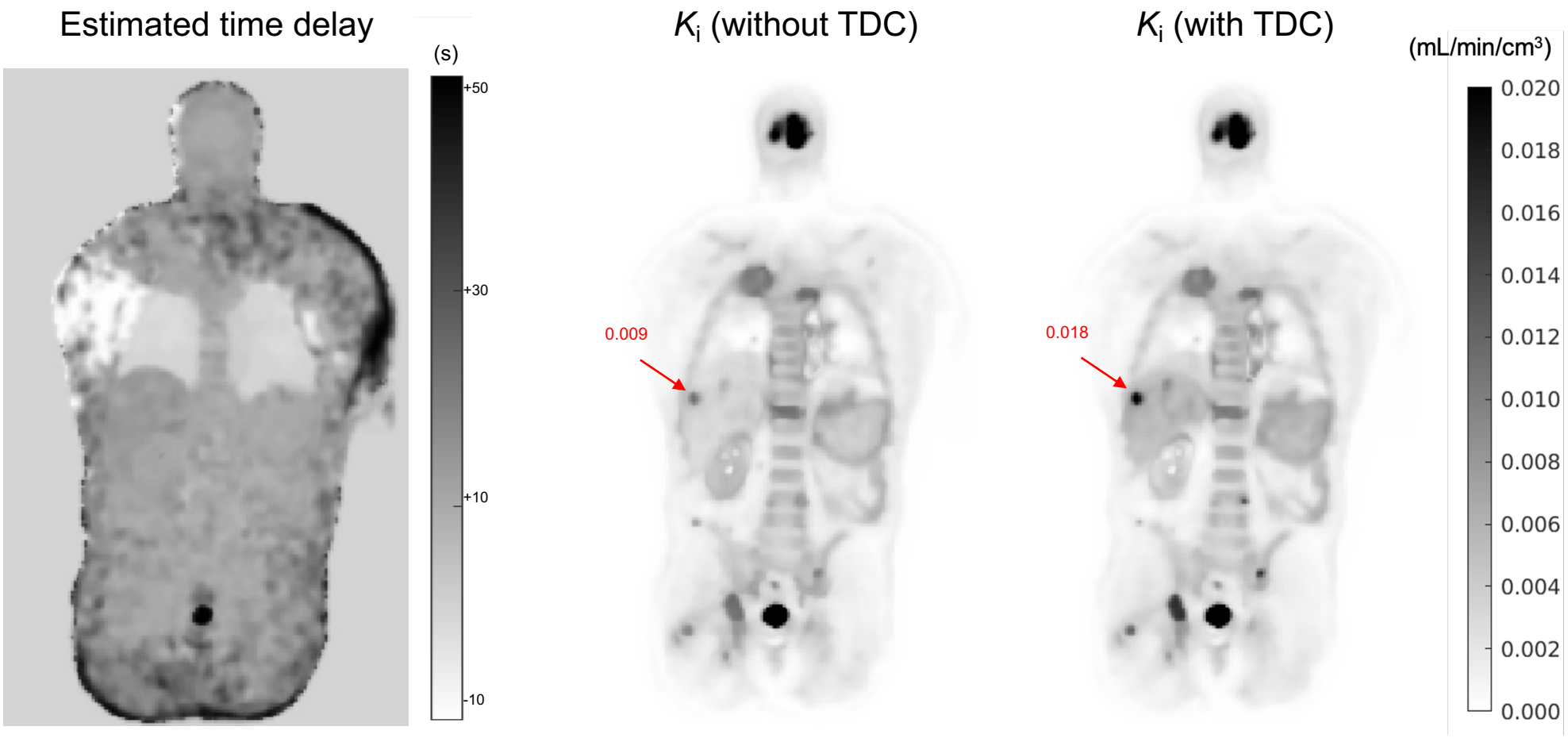
w/o with

FDG delivery rate K_1

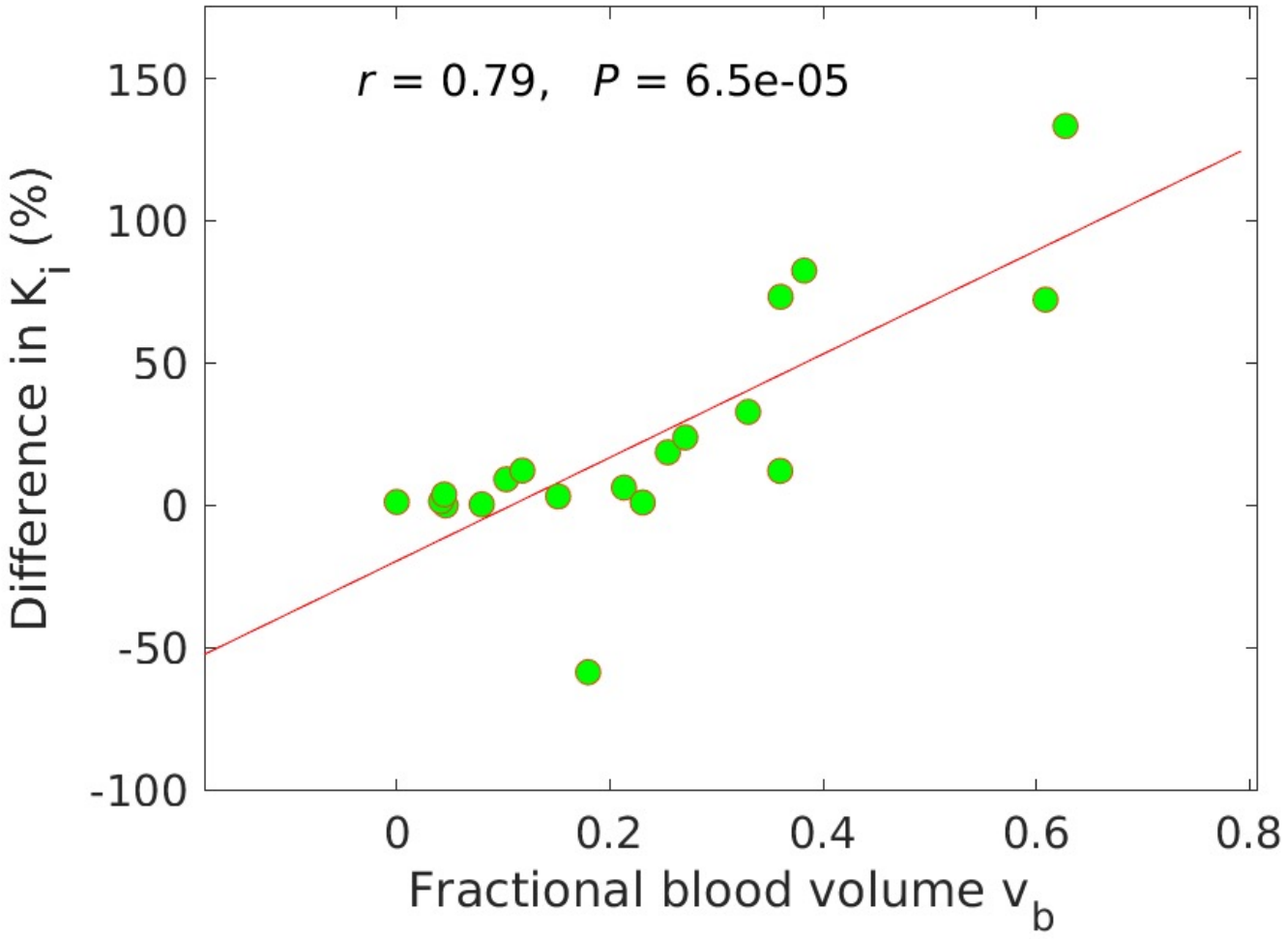


w/o with

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



Impact of Time Delay Correction Correlates with Blood Volume Fraction

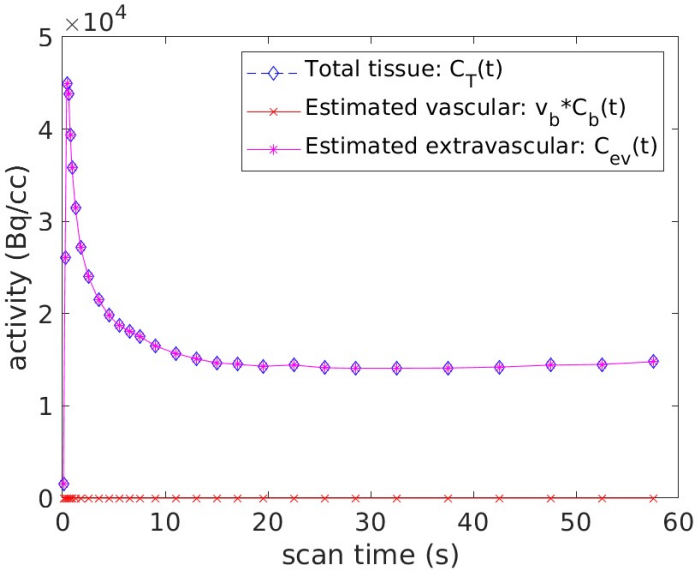


Results from 19 lesions from 5 patients with metastatic genitourinary cancer

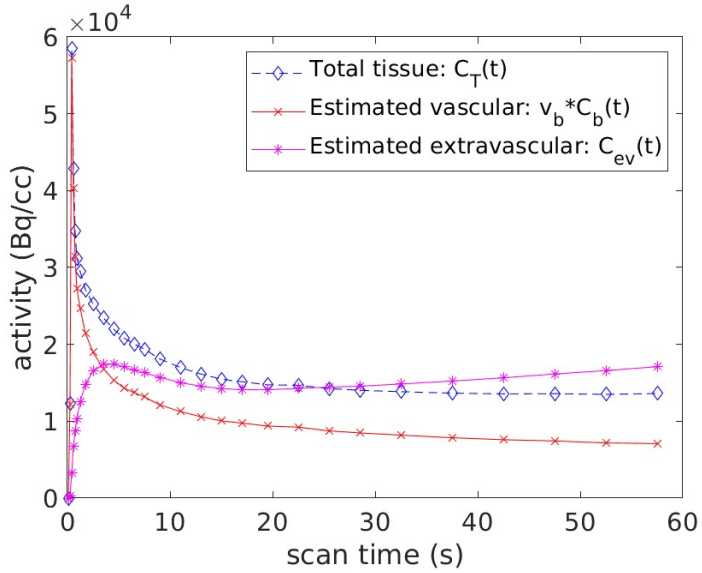
Why Time-delay Correction May Impact K_i Estimation?

$$C_{\mathrm{T}}(t) = (1 - v_{\mathrm{b}})\underbrace{\mathrm{IRF}(t;\boldsymbol{\kappa}) \otimes C_{\mathrm{p}}(t - t_{\mathrm{d}})}_{C_{\mathrm{ev}}(t)} + v_{\mathrm{b}} C_{\mathrm{b}}(t - t_{\mathrm{d}})$$

A. No time delay estimation



B. With time delay estimation

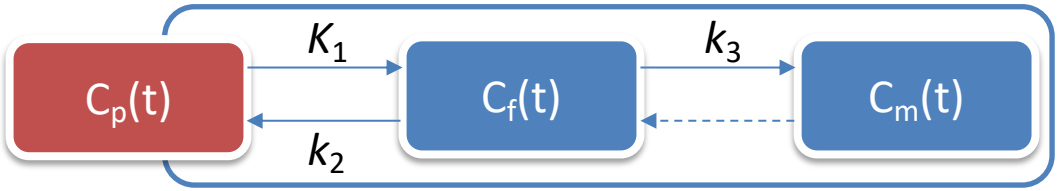


Total-Body Model Selection

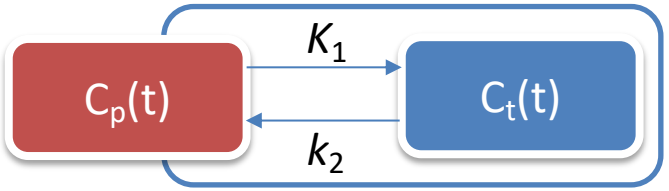
- Conventionally a fixed model is commonly used in organ-specific parametric imaging, e.g.,
  - Brain
  - Myocardium
- Total-body parametric imaging
  - Many different organs
  - Each may follow a different compartmental model

Example of Candidate Compartmental Models

A. 2T



B. 1T

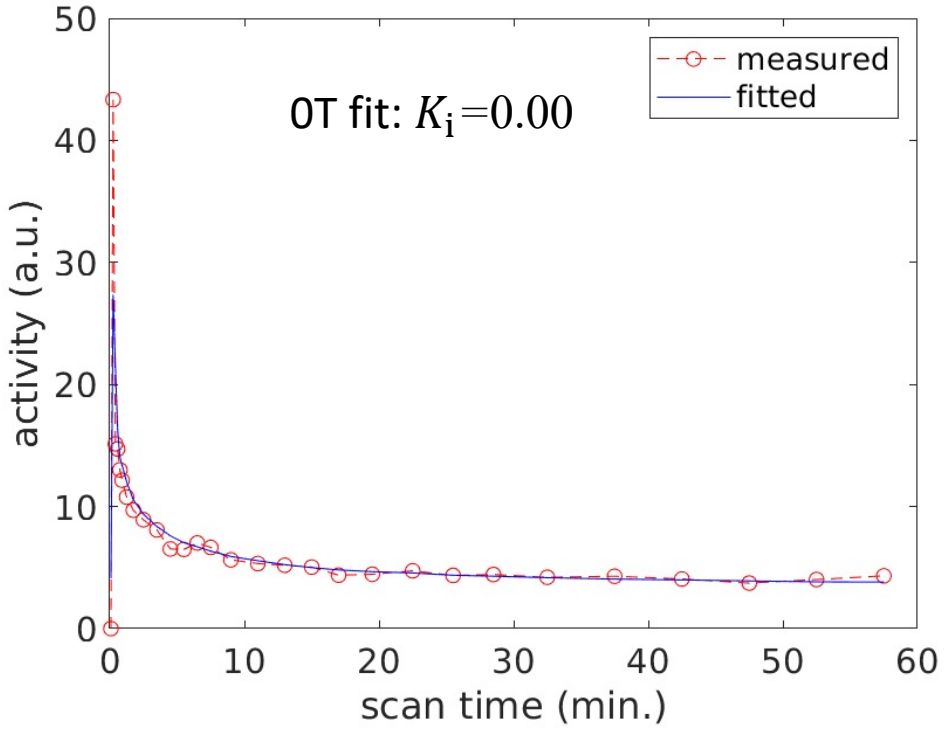


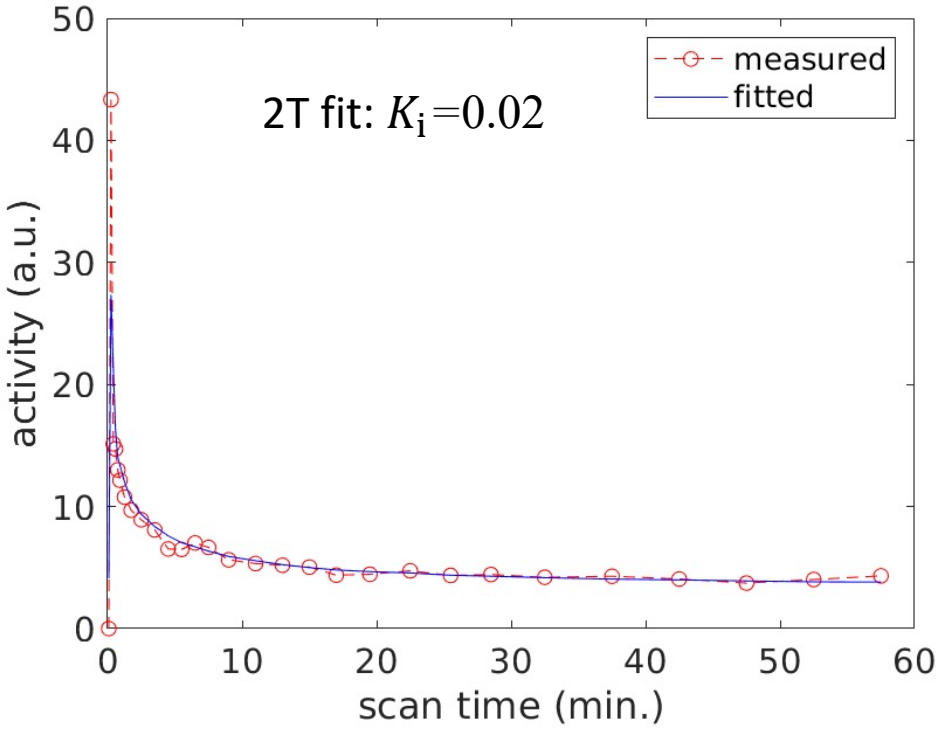
C. 0T

(blood voxels)

Which Model Is the Best?

- Similar fits, but very different K_i results





Akaike Information Criteria (AIC)

- Definition

$$\mathrm{AIC} = M \ln\left(\frac{RSS}{M}\right) + 2n$$

Goodness of fit

Penalty on a more complex model

where *RSS* denotes the residual sum of squares

$$RSS = \sum_{m=1}^{M} w_m \left[\check{C}_{\mathrm{T}}(t_{\mathrm{m}}) - C_{\mathrm{T}}(t_m)\right]^2$$

with *M* the number of frames and *n* the number of unknown kinetic parameters.

AIC for Small Sample Size

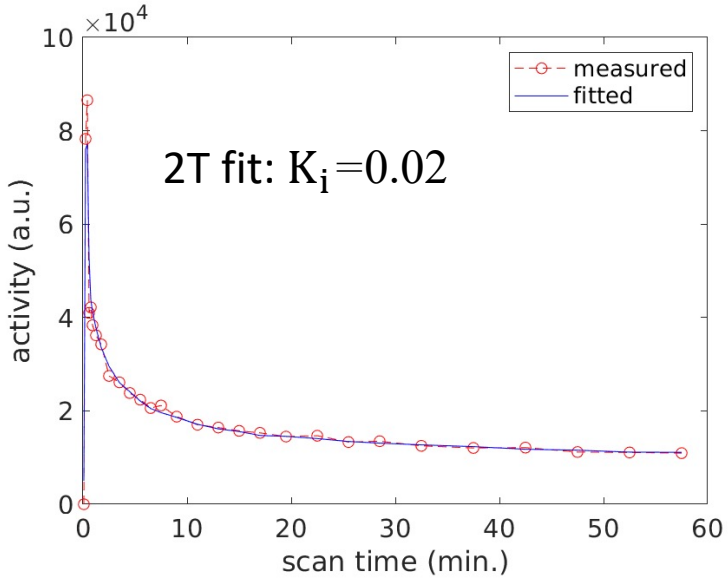
- Correction for small sample size:

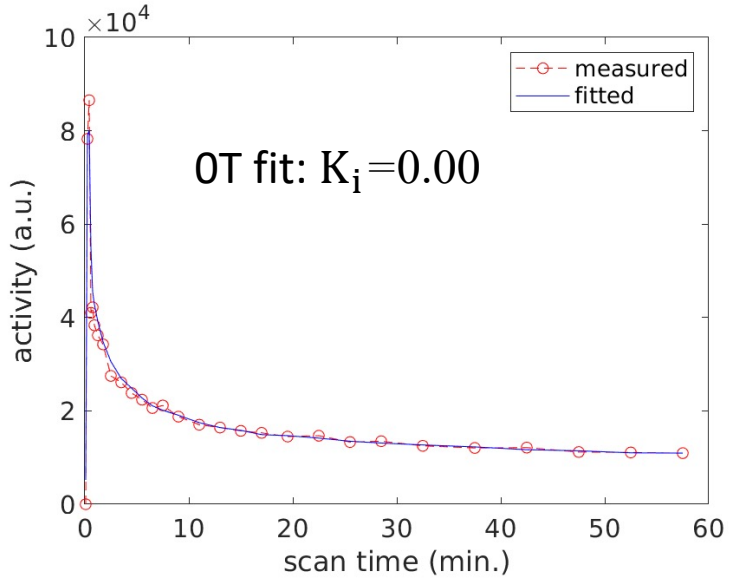
$$\mathrm{AICc} = \mathrm{AIC} + \boxed{\frac{2n(n+1)}{M-n-1}}$$

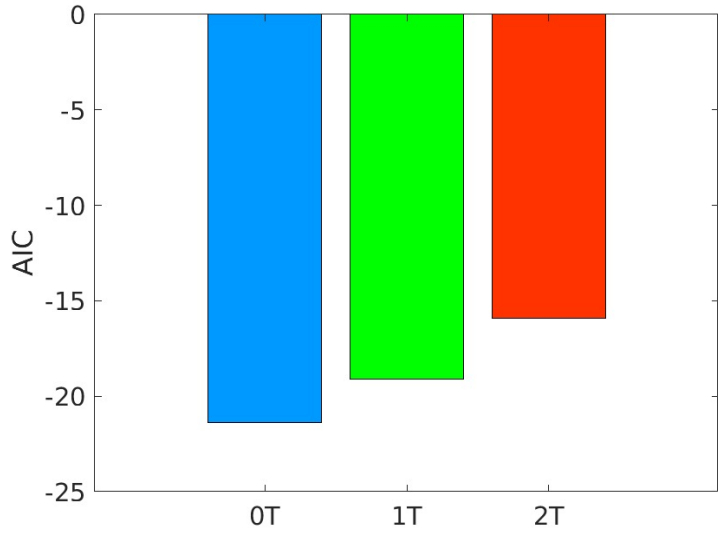
Extra penalty to avoid overfitting

- AIC includes *n*, thus the first-order estimate of the information loss
- AICc includes n^2 and is a second-order estimate
- Lower value of AIC (or AICc) indicates a better fit

Test for Fitting a Blood TAC

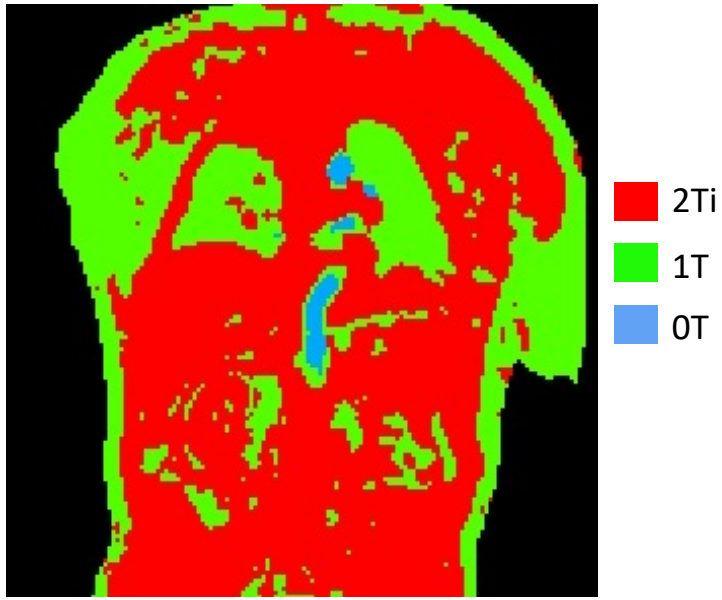




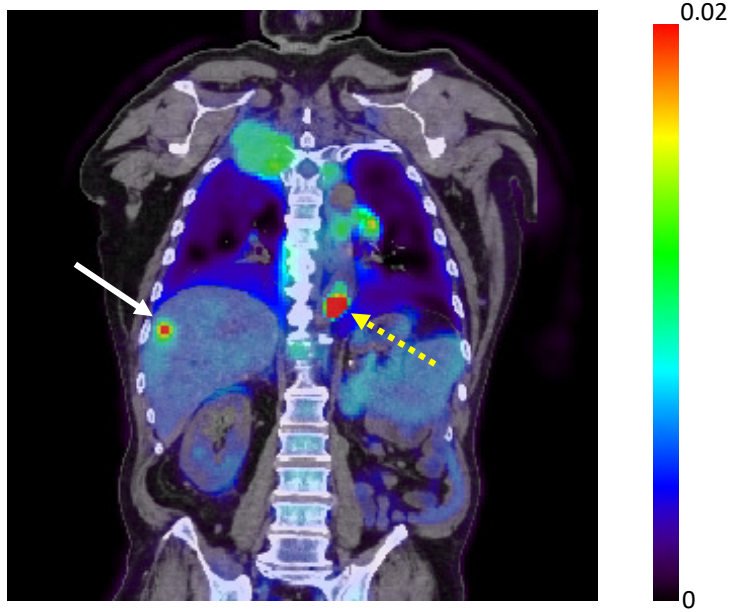


Impact of Model Selection on K_i Imaging of Lesions

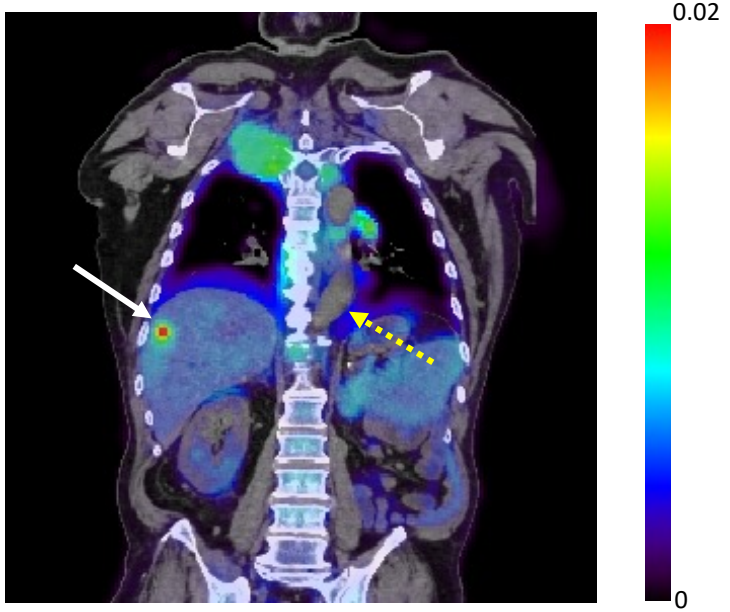
Model selection map



No model selection
(2Ti)



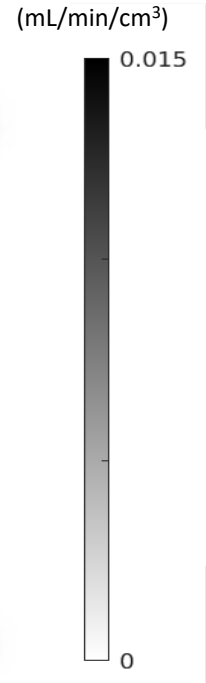
With model selection
(0T, 1T, 2Ti)



Impact of Model Selection on Myocardial K_i Imaging

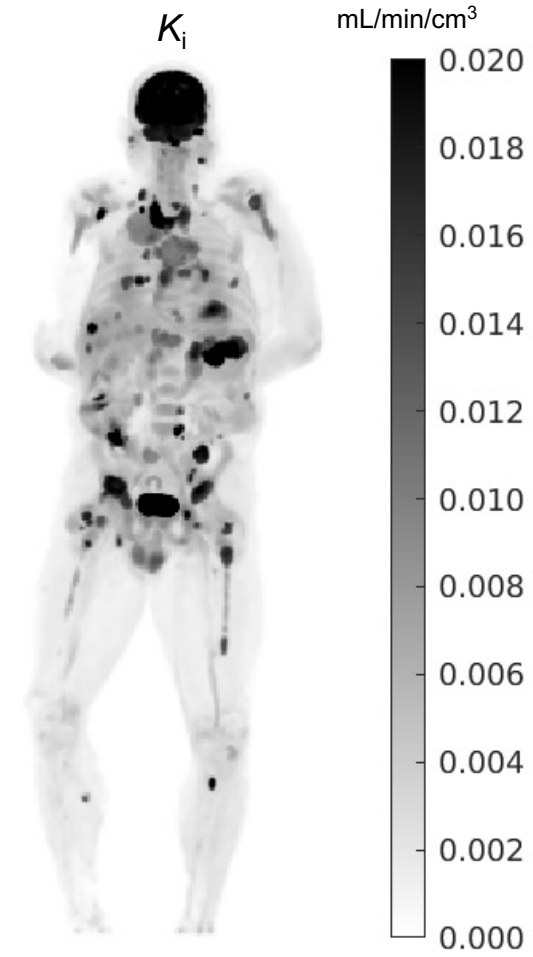
No model selection

With model selection

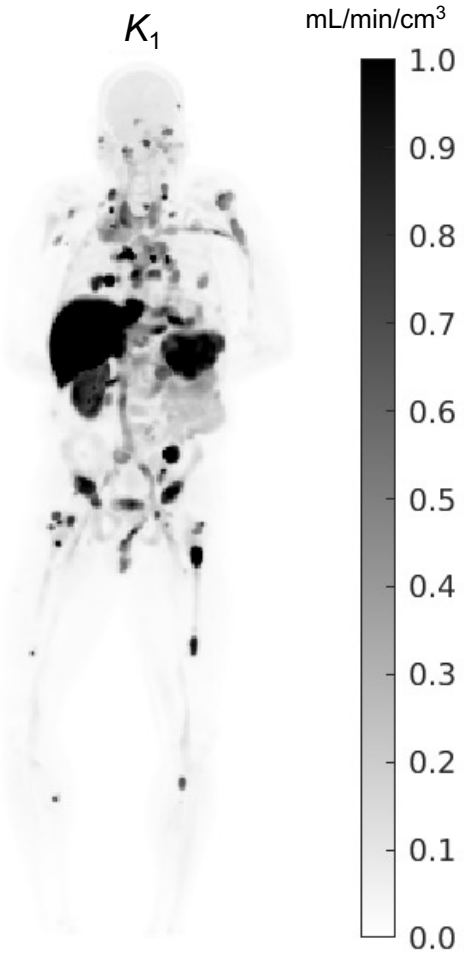


Example of Total-Body PET Multiparametric Imaging Using Compartmental Modeling (CM)

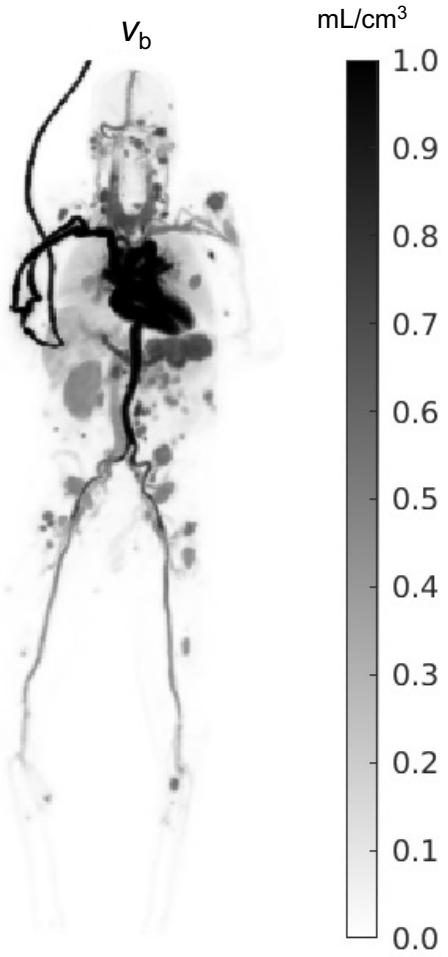
FDG net influx rate



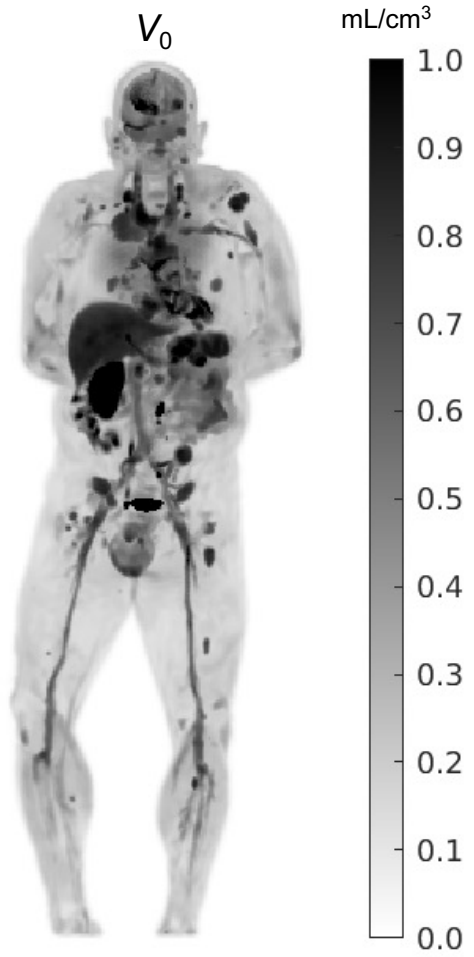
FDG delivery rate



Fractional blood volume



Volume of distribution



Comparison of 2T CM with Patlak Plot

Irreversible 2T CM

$$C_{\mathrm{T}}(t) = (1 - v_{\mathrm{b}})\mathrm{IRF}(t;\boldsymbol{\kappa}) \otimes C_{\mathrm{p}}(t) + v_{\mathrm{b}}C_{\mathrm{wb}}(t)$$

Patlak plot

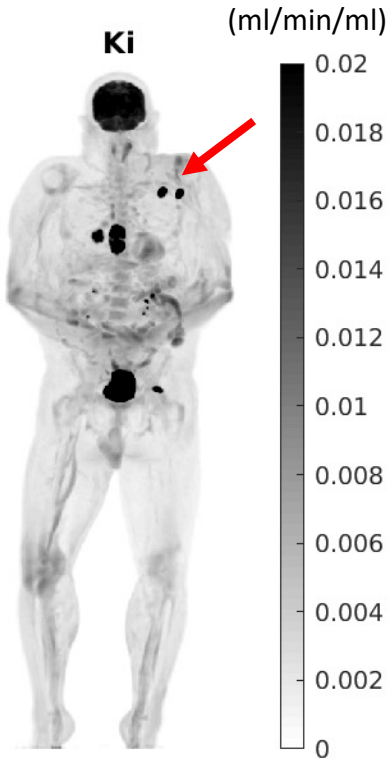
$$\frac{C_{\mathrm{T}}(t)}{C_{\mathrm{p}}(t)} = K_{\mathrm{i}}\frac{\int_0^t C_{\mathrm{p}}(\tau)d\tau}{C_{\mathrm{p}}(t)} + b, \quad t > t^*$$

- Pros
  - Better modeling of the blood component (v_{b})
  - The Patlak slope is not exactly equal to $K_{\mathrm{i}} = \frac{K_1 k_3}{k_2 + k_3}$ of the 2T model, but $(1 - v_{\mathrm{b}})K_{\mathrm{i}}$
  - Allowing parametric imaging of micro-kinetic parameters (e.g., K_1, v_{b})
- Cons
  - Computationally less efficient
  - Additional **corrections** are needed in order to explore the benefits

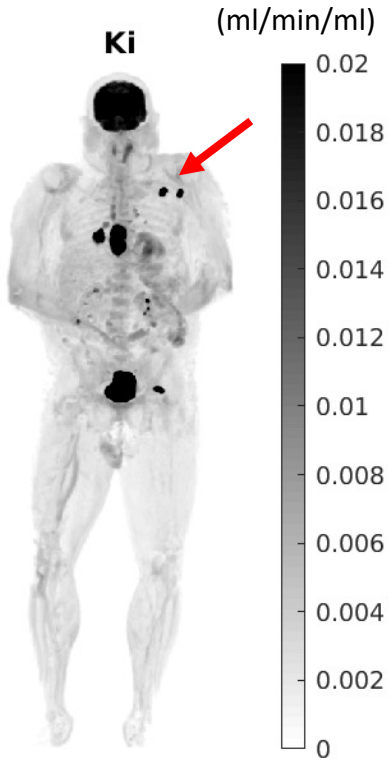
When Similar and When Different Between Compartmental Modeling and Patlak Plot?

Similar

Patlak

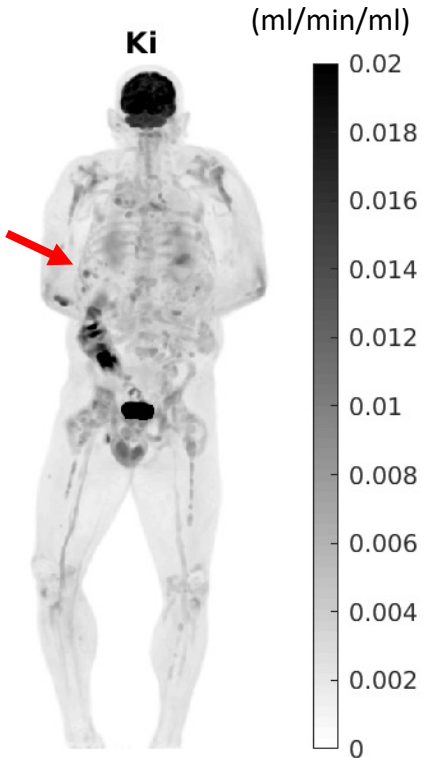


2Ti

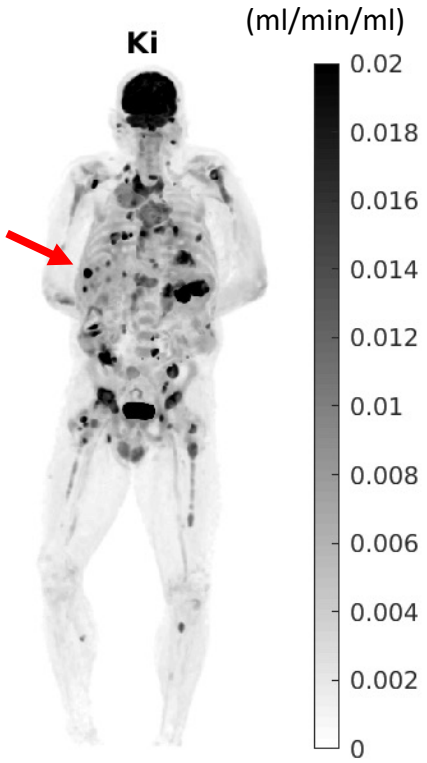


Different

Patlak

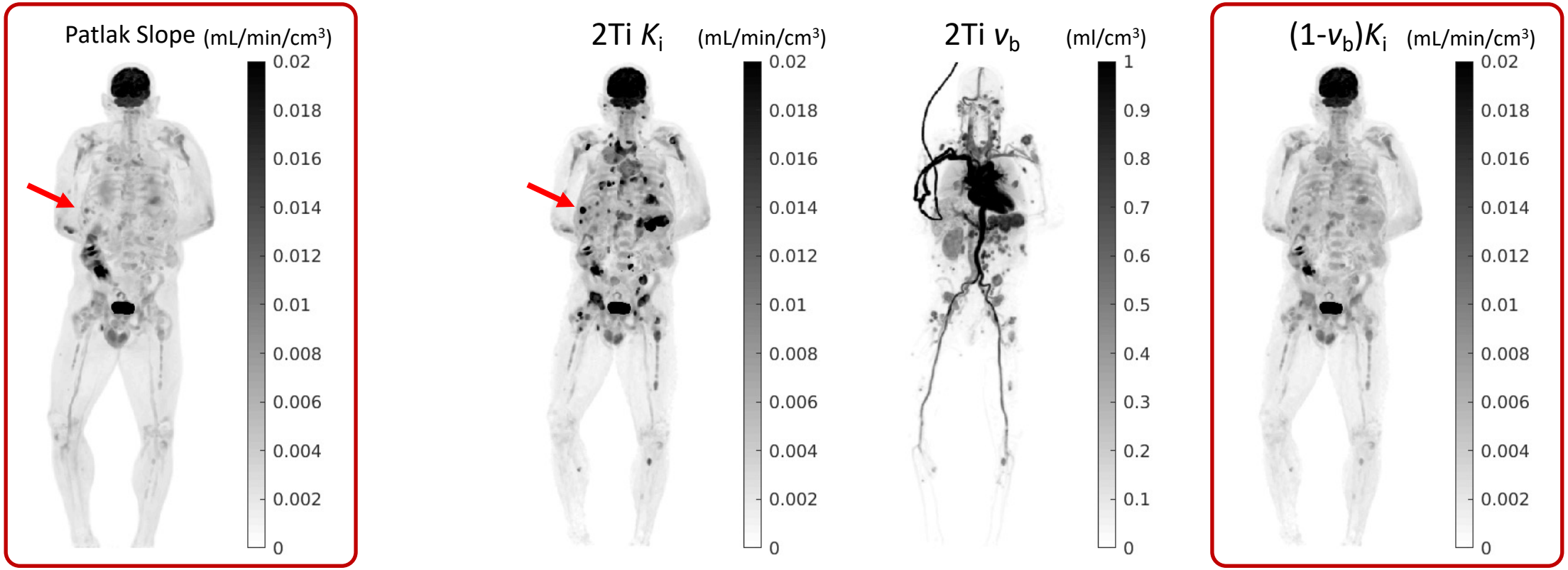


2Ti



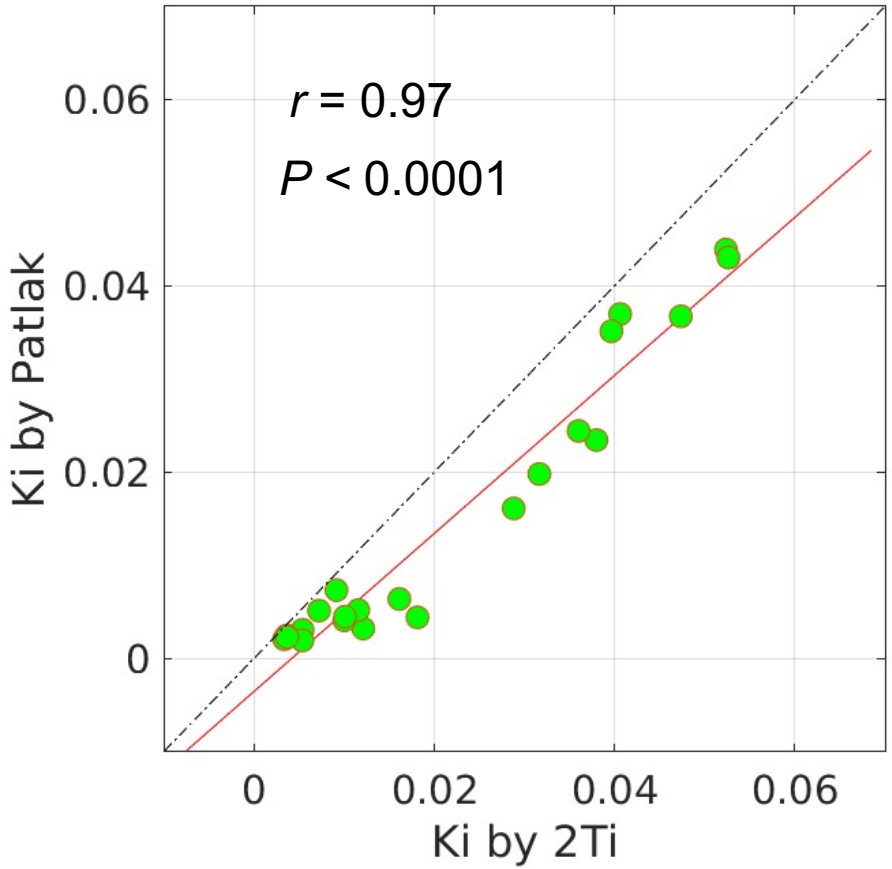
The Relationship Depends on Vascular Fraction

- Compartment modeling allows separate estimation of K_i and v_b
- Patlak slope $\approx (1\text{-}v_b)K_i$, which does not make the separation
- The difference becomes nonnegligible if v_b is large

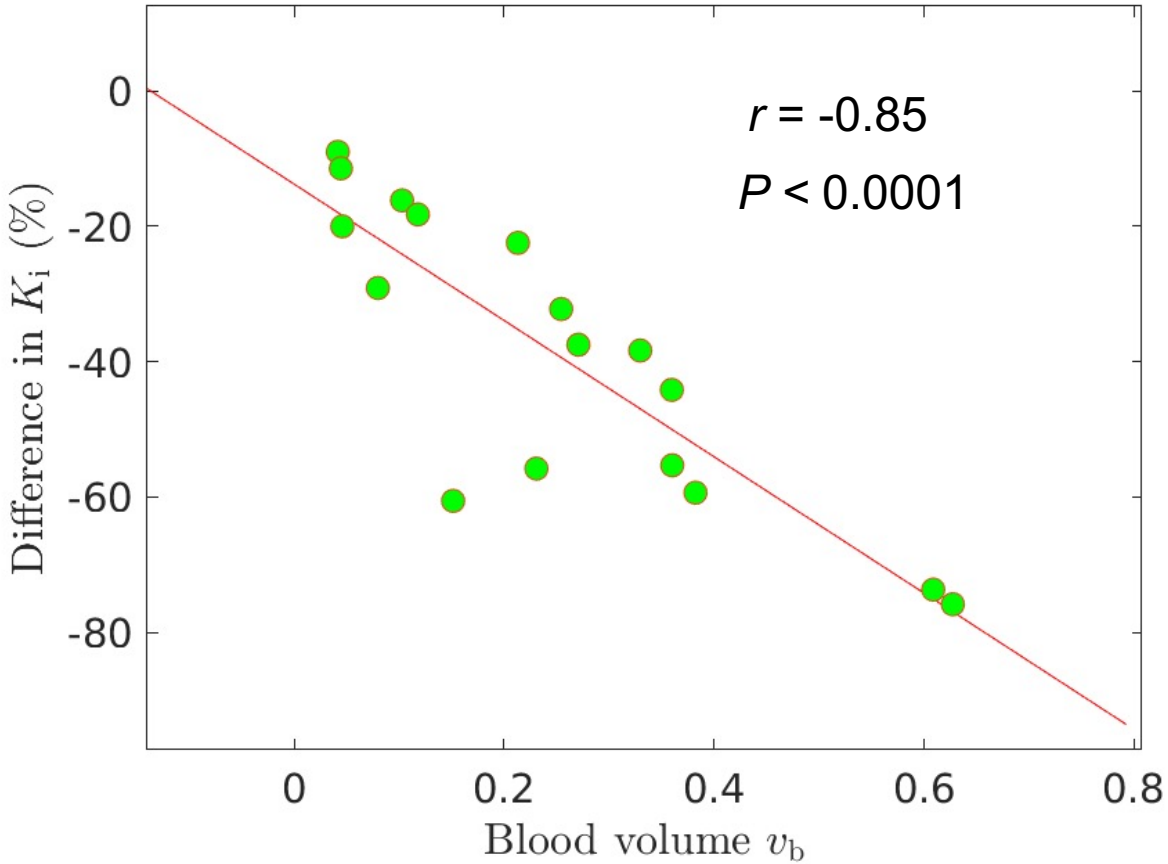


Patlak Underestimation Correlates with Blood Volume

Patlak plot underestimates K_i but highly correlates with it

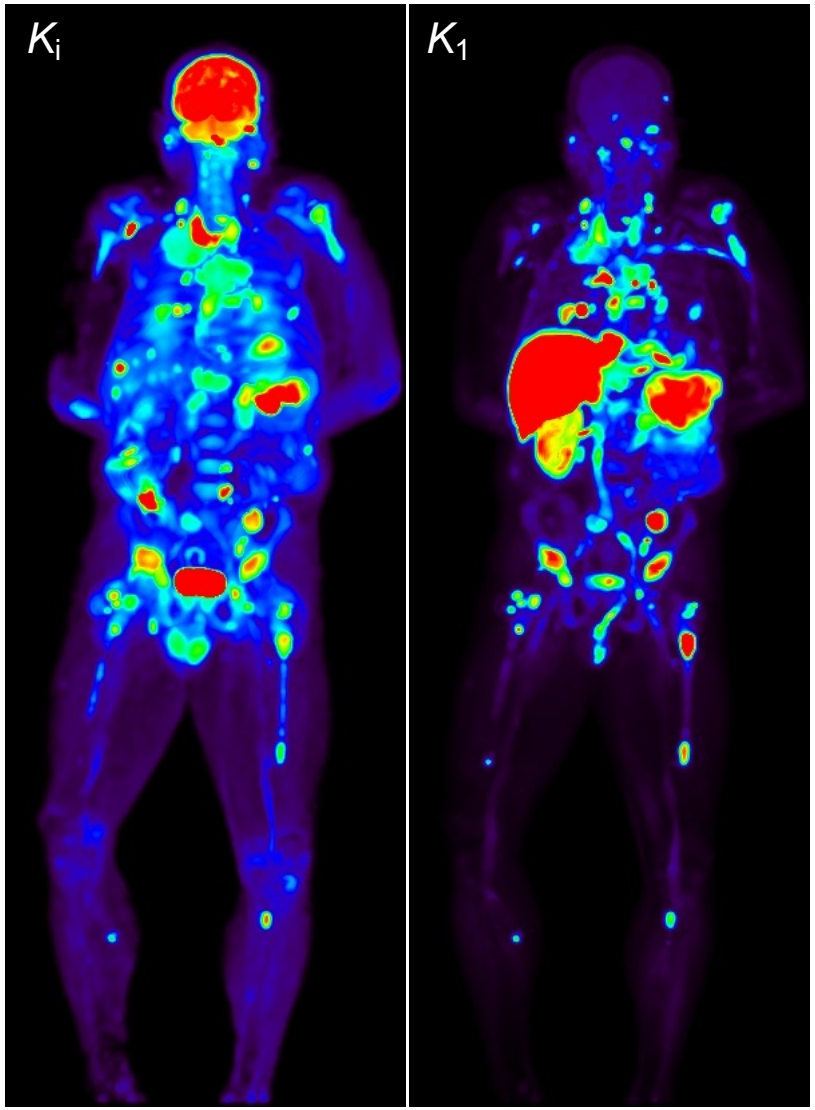


The underestimation is increased as blood volume increases



19 lesions from 5 patients with genitourinary cancer

Potential Benefits of Total-Body Multiparametric Imaging



1. Improved lesion contrast

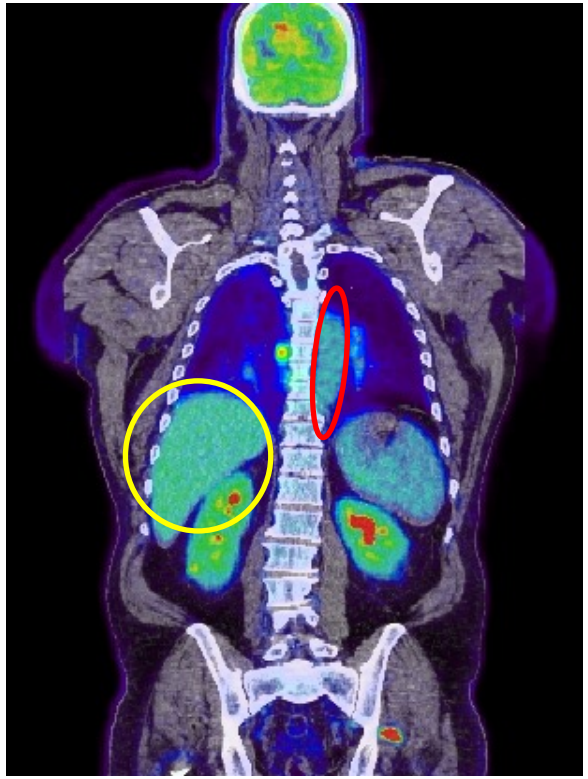
2. Exploring micro kinetic parameters (e.g., K_1) for multiparametric imaging

3. Multiorgan quantification in systemic disease

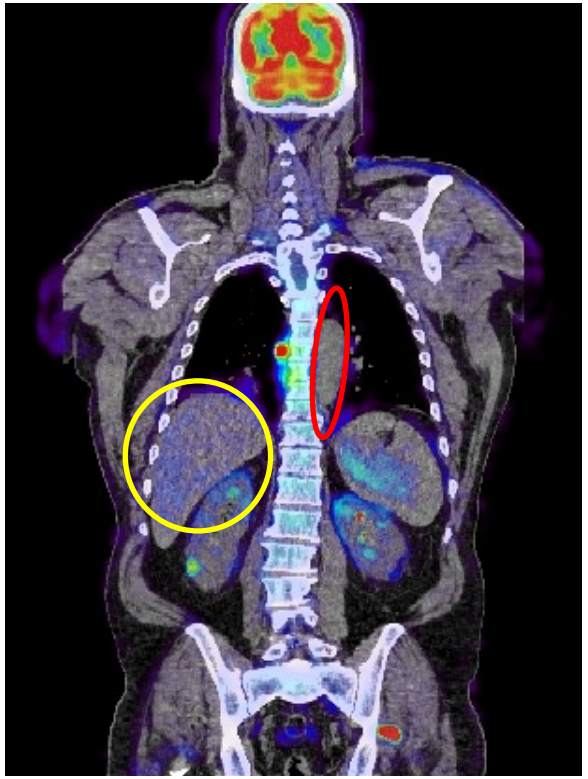
Benefit 1: Parametric Image of K_i Can Improve Lesion Contrast

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

SUV

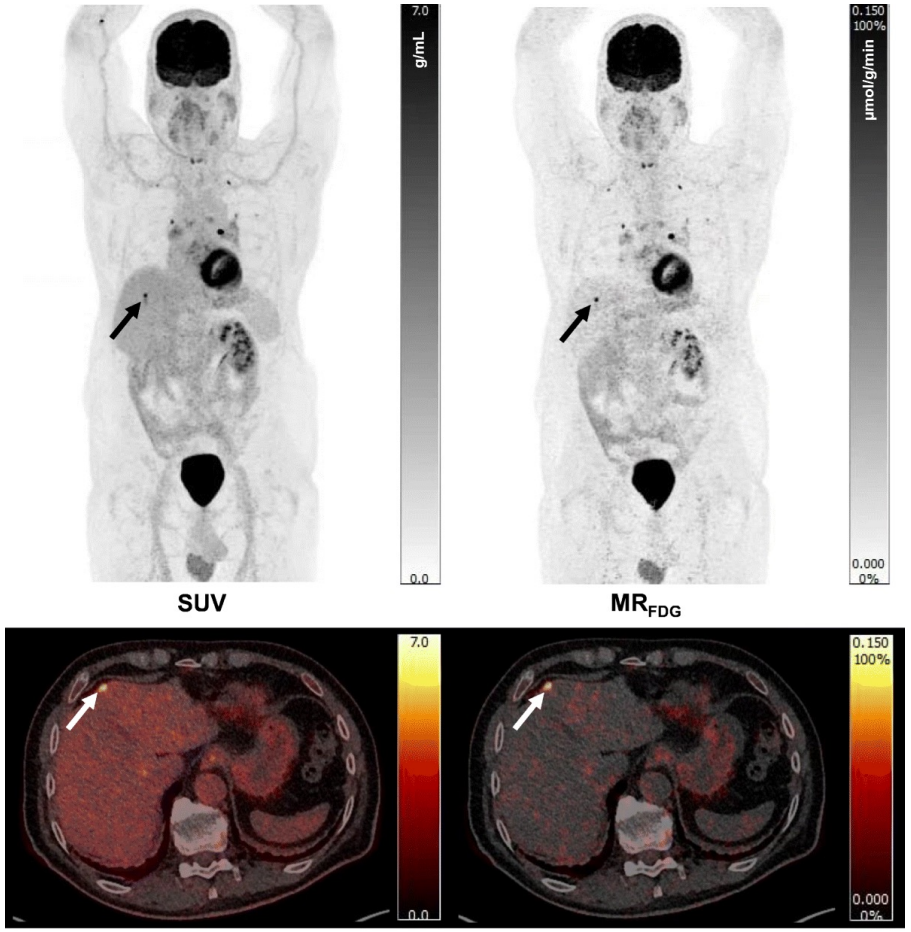


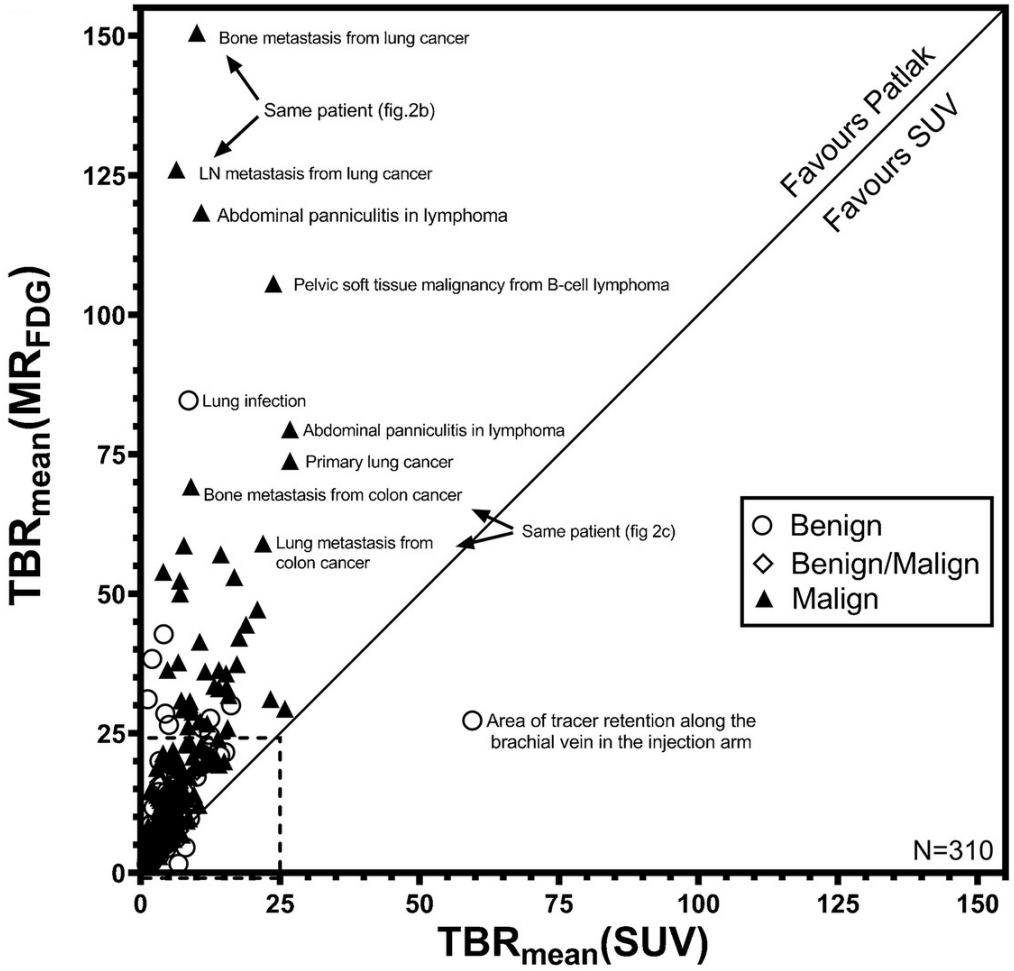
K_i



Results from Whole-body Patlak Imaging on Conventional PET Scanners

Improved tumor-to-background ratio (TBR)

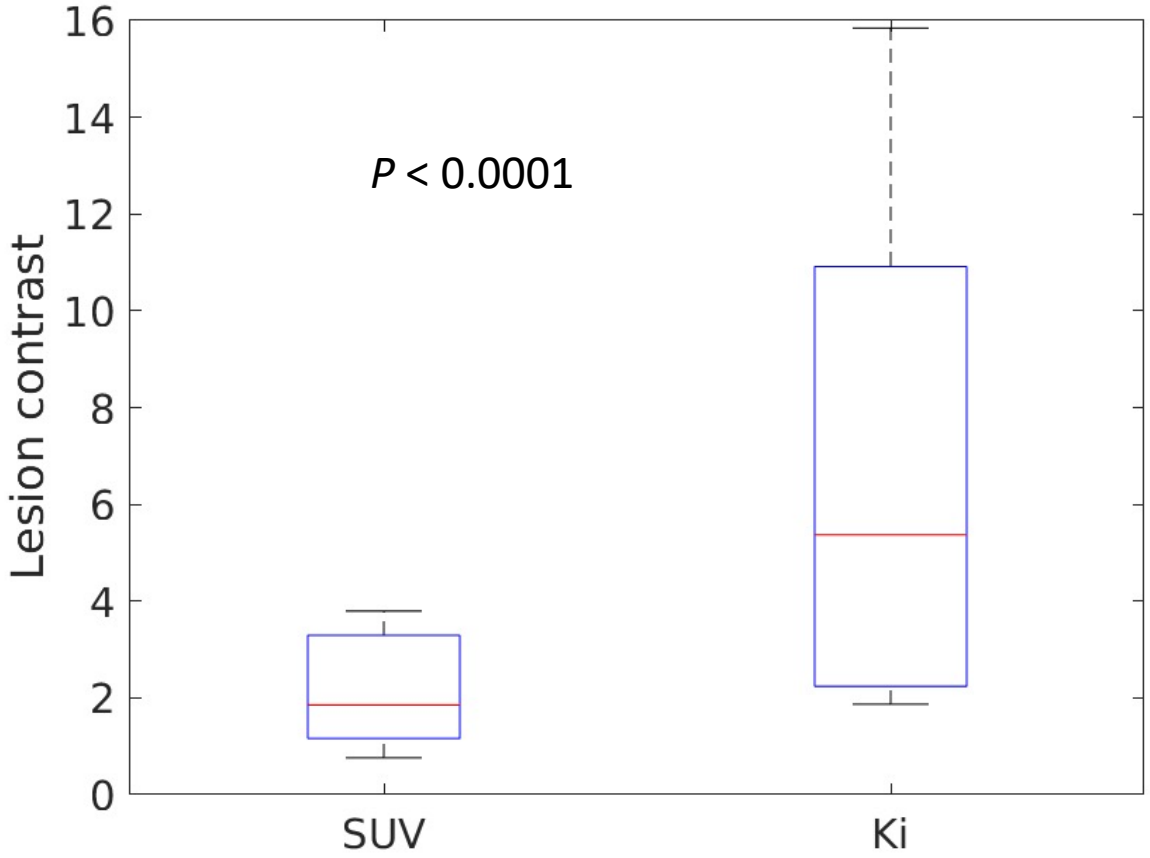




AH Dias *et al.* EJNMMI 2020

Initial Results from Total-Body Parametric Imaging with Compartmental Modeling on EXPLORER

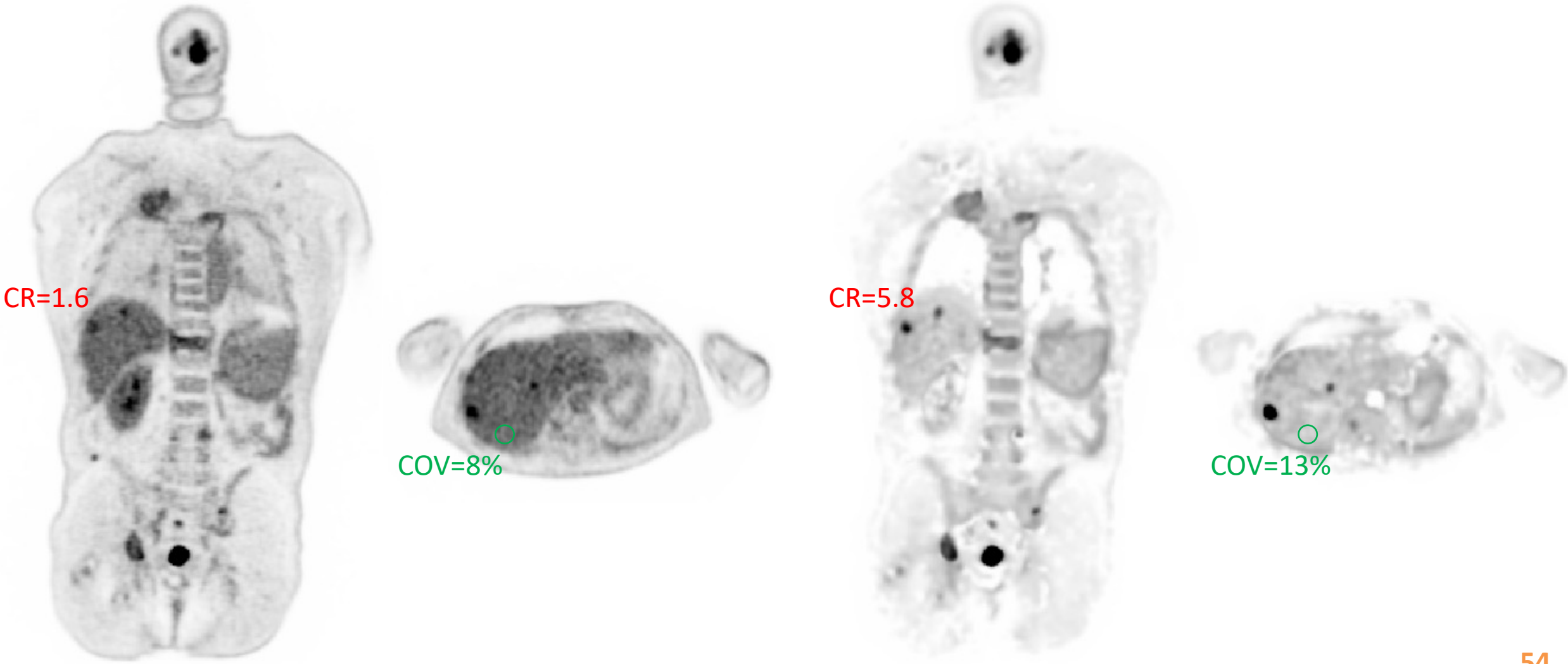
Results from 19 lesions from 5 patients with metastatic cancer



Example of Liver Lesions

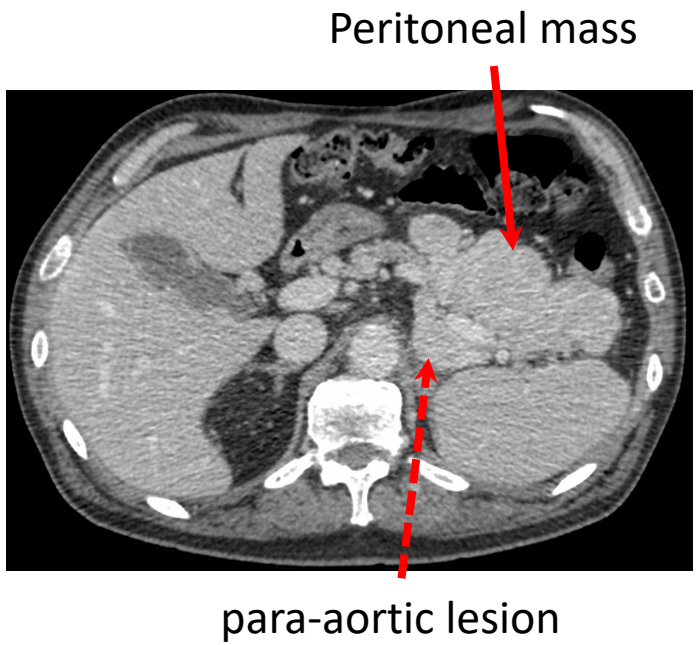
SUV

FDG influx rate K_i

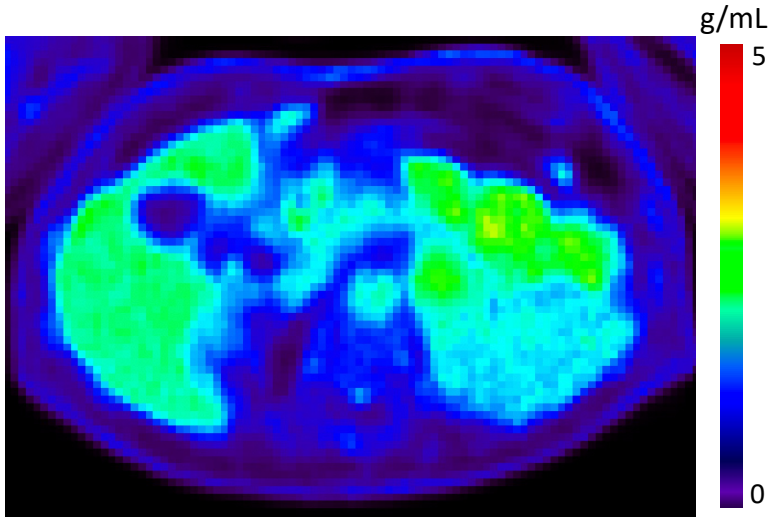


Example of Abdominal Lesions

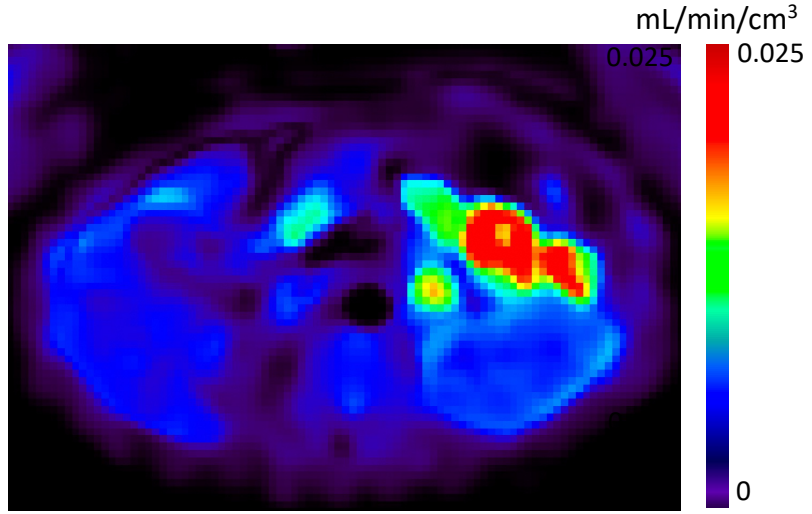
Contrast-enhanced CT



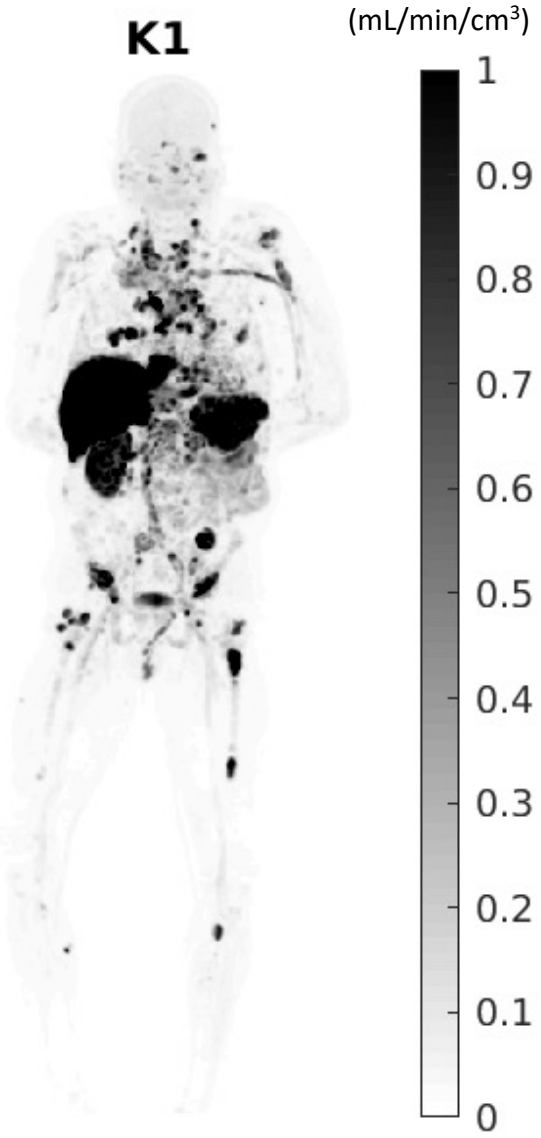
SUV



FDG K_i



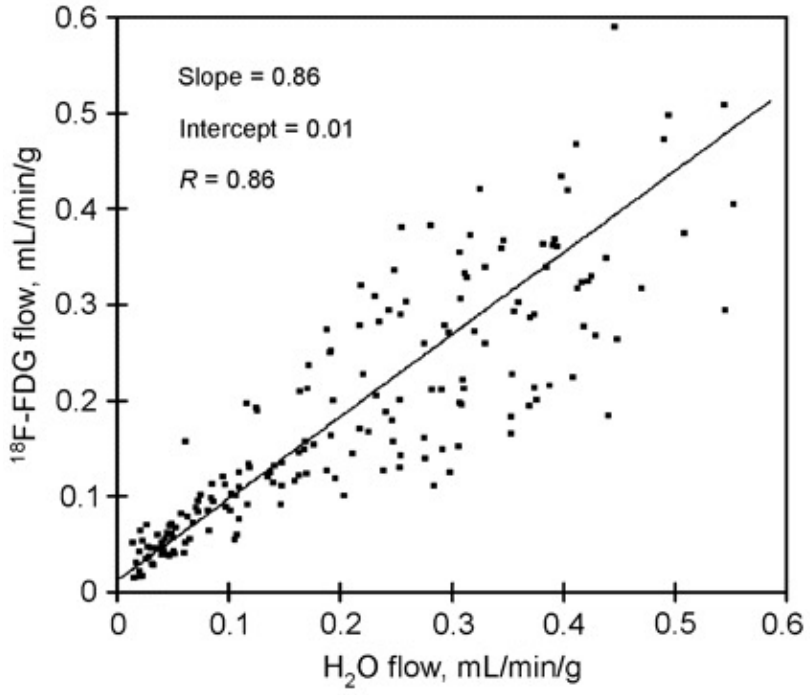
Benefit 2: Exploring Micro-kinetic Parameters for Multiparametric Imaging



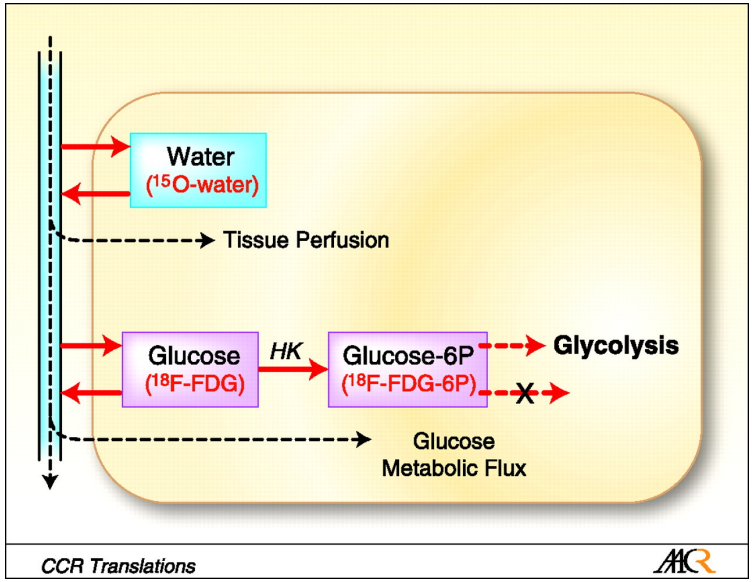
- SUV and K_i characterize glucose metabolism
- FDG delivery rate K_1 generally reflects a mix of blood flow and glucose transport
- Many potential applications of FDG K_1:
  - Serve as a surrogate of blood flow
  - Independent imaging biomarker
  - Create lesion contrast

Cancer: FDG K_1 May Highly Correlate with Tumor Blood Flow

- Due to generally high extraction fraction of ^{18}F-FDG in tumors



- Enabling single-tracer imaging of **tumor flow-metabolism mismatch**



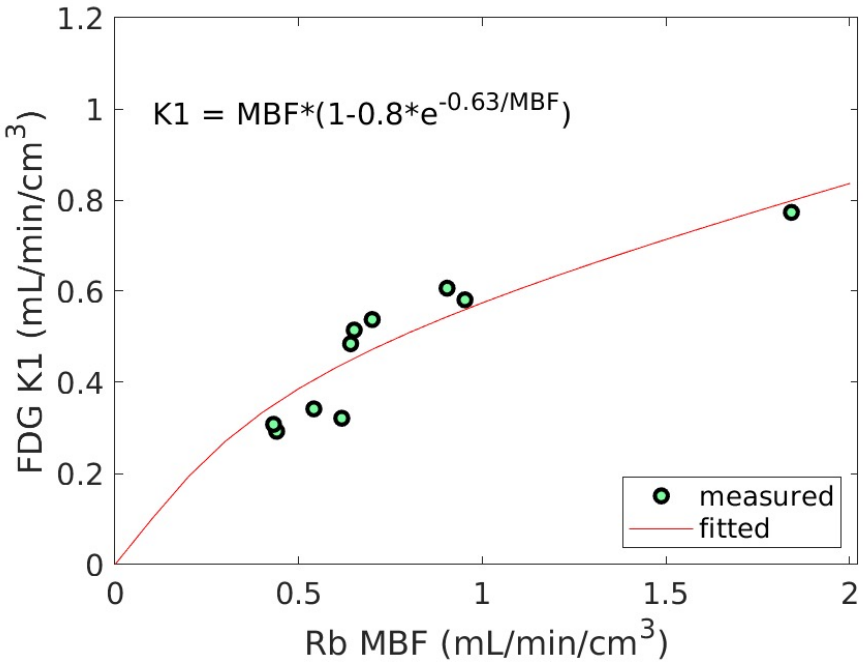
Mankoff *et al* CCR 2009

FDG flow: Mullani *et al*, JNM 2008; Tseng *et al* JNM 2004;
Flow-metabolism mismatch: Komar *et al* CCR 2009; Mankoff *et al* CCR 2009

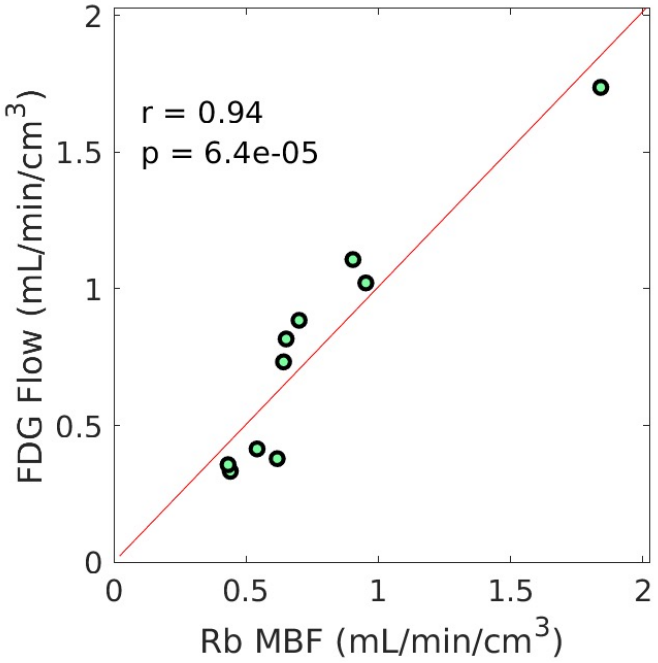
Heart: Measuring Myocardial Blood Flow (MBF) Using FDG K_1

- FDG K_1 is closely associated with blood flow in the myocardium

Pilot study using Rb-82 PET on a conventional scanner



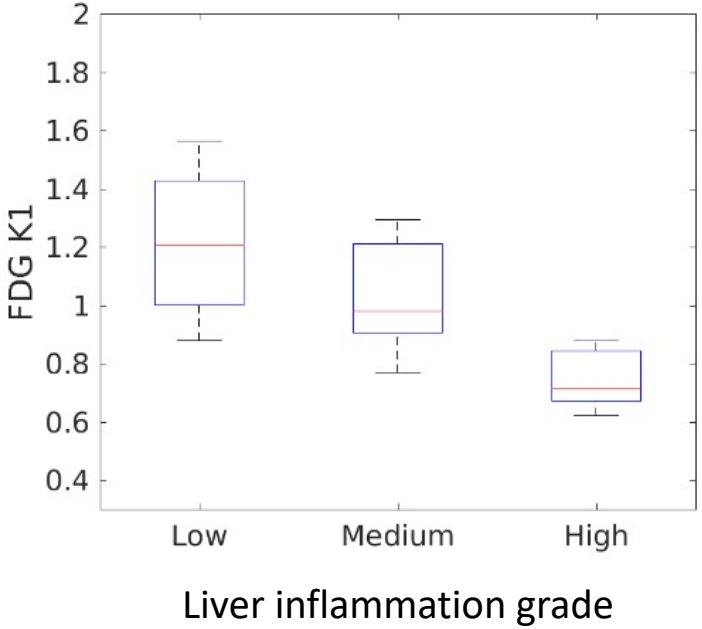
- Correlation of FDG-derived MBF with Rb MBF after the nonlinearity correction



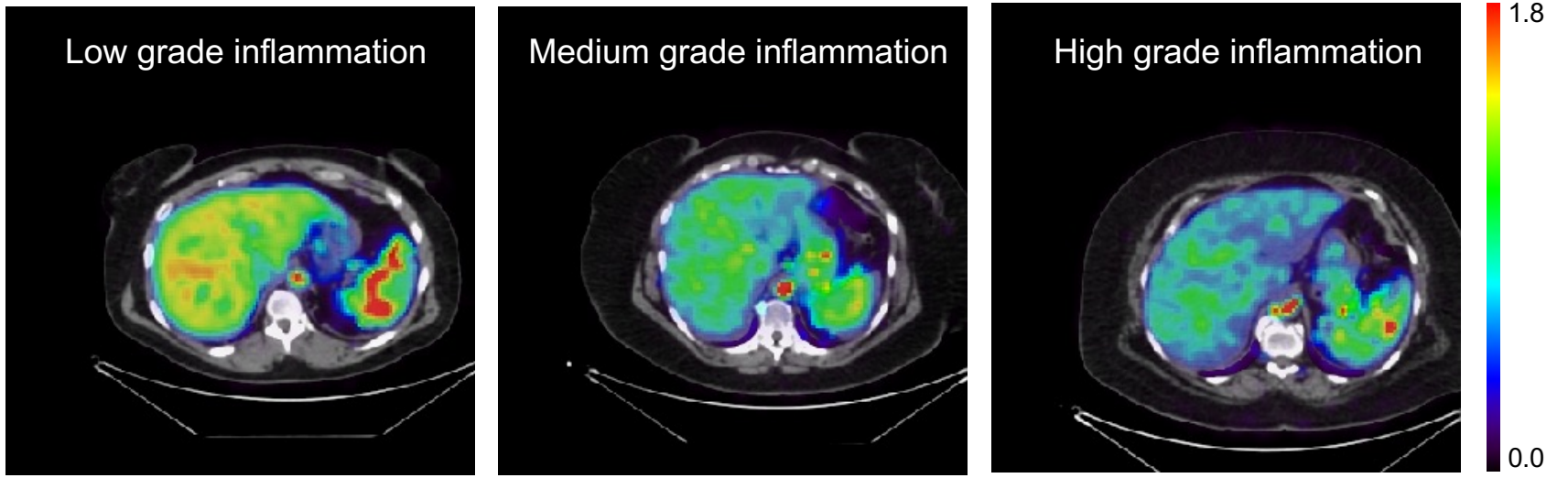
Zuo *et. al.*, Phys Med Biol 2021; Zuo *et al*. IEEE TRPMS 2020

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

- Decreased liver FDG K_1 is associated with increased liver inflammation

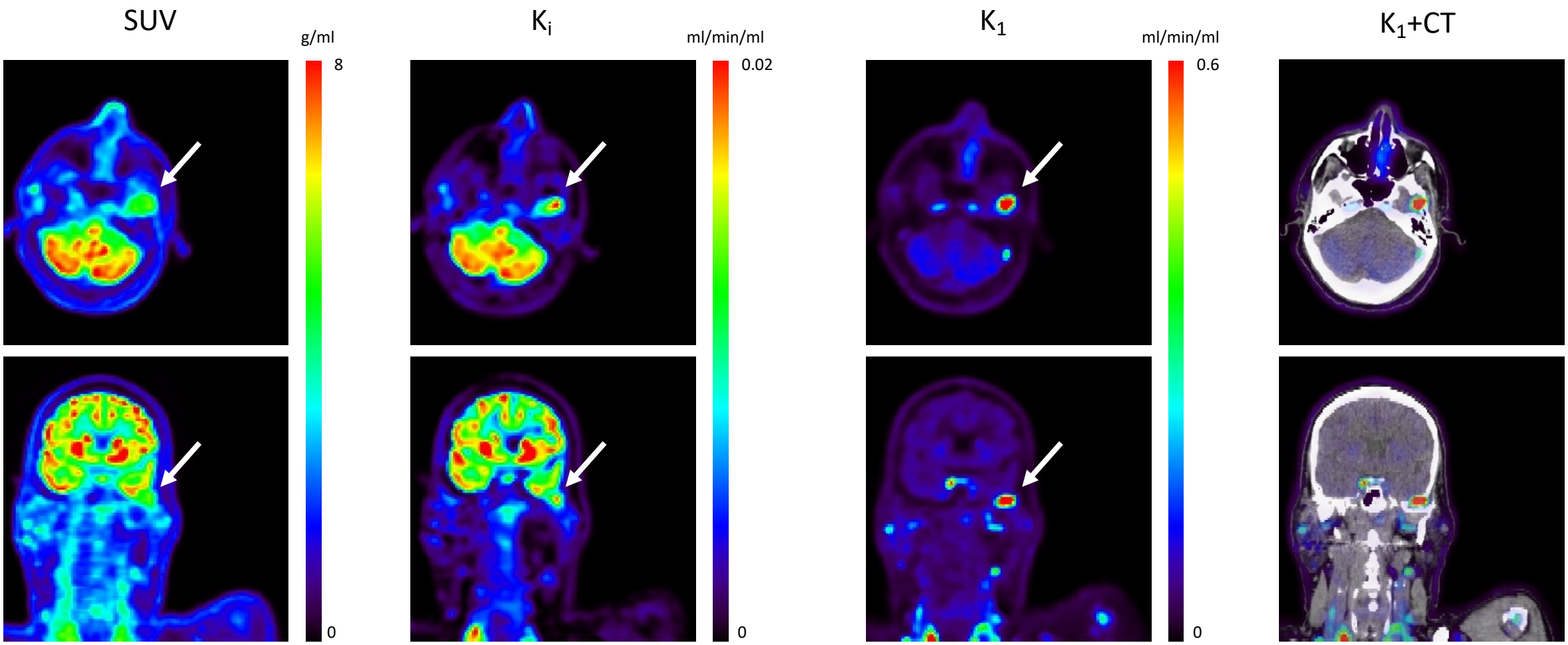


Liver FDG K_1 Images



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

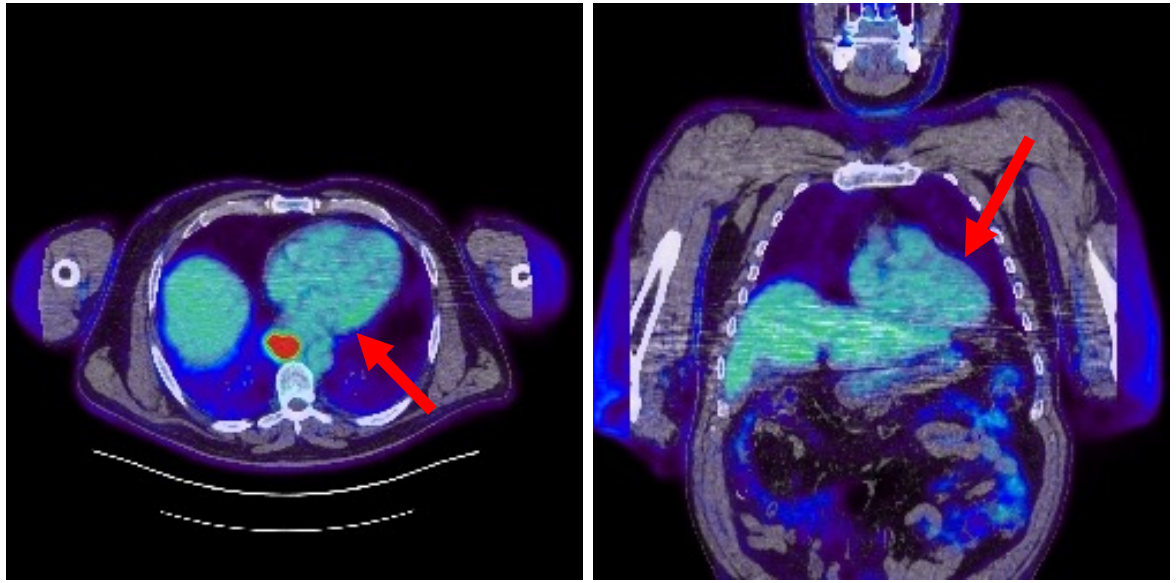


Wang *et al.* unpublished EXPLORER data

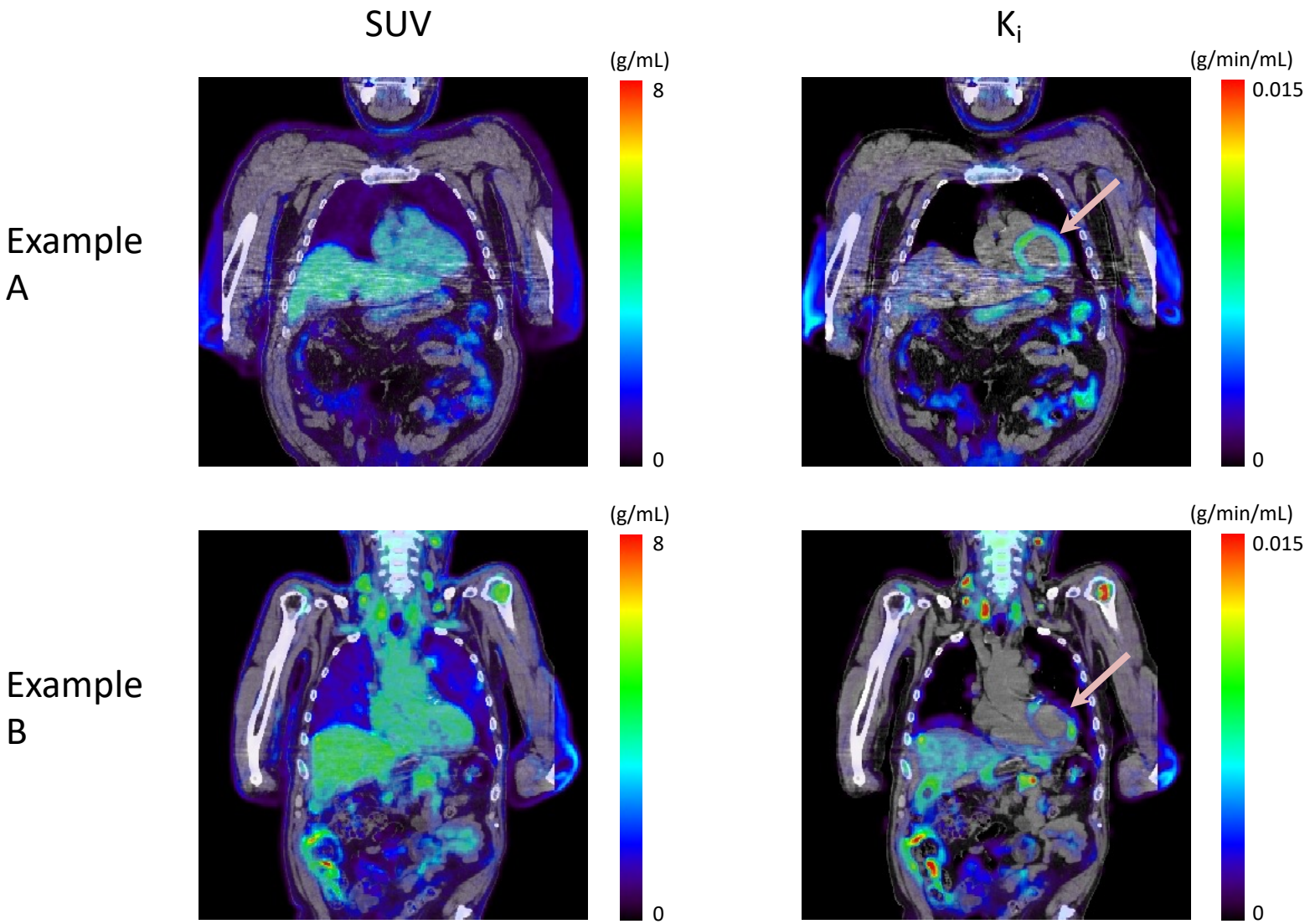
Benefit 3: Enabling Multi-Organ Evaluation in Systemic Disease

- 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

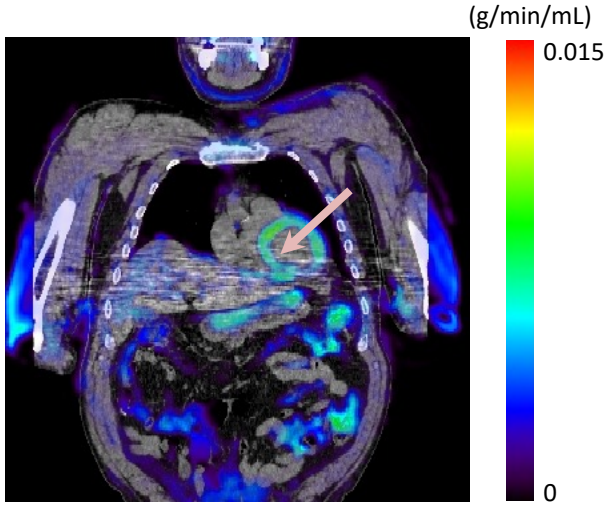
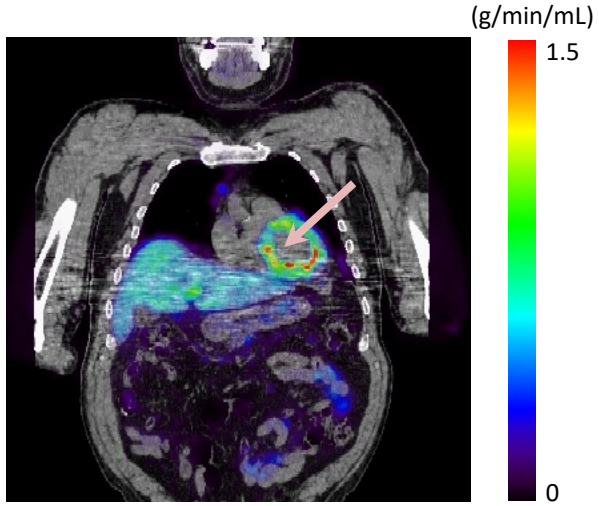
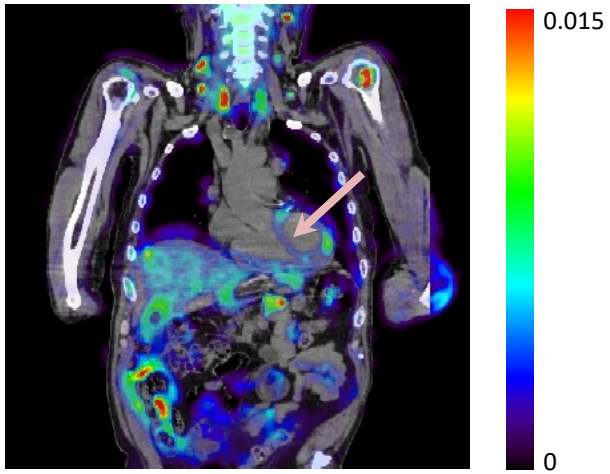
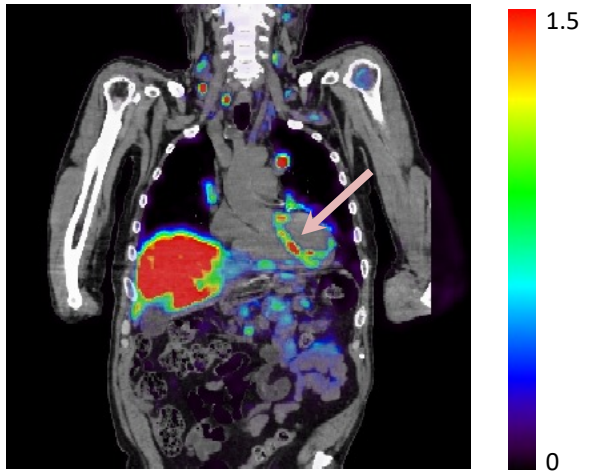
SUV (60 min. p.i.)



Simultaneous Visualization of Myocardium by Parametric Imaging

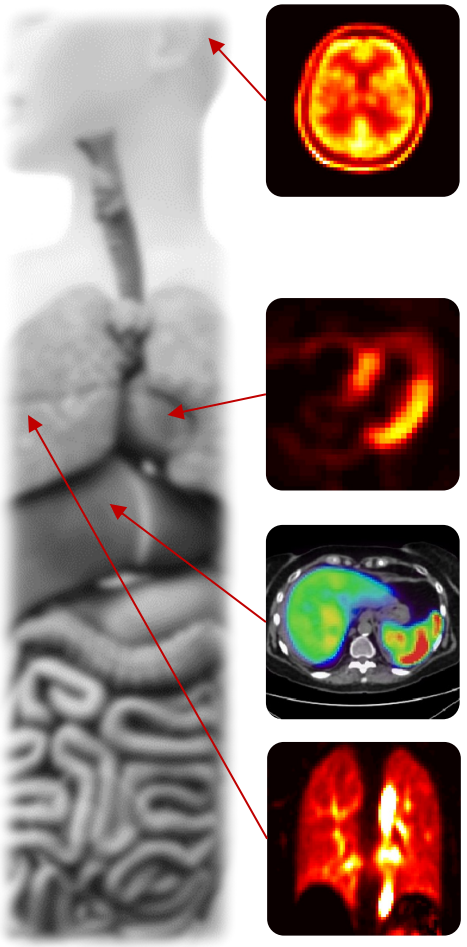


Allowing Evaluation of Perfusion-Metabolism Coupling/Mismatch

	K_i (metabolism)	K_1 (perfusion/transport)
Example A		
Example B		

Putting All Puzzles Together

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



Multi Organs

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

Multiparametric Imaging

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

Advanced Topics in Total-Body Modeling and Analysis

- Metabolite correction using total-body compartmental modeling
- Motion correction for total-body parametric imaging
- High-temporal resolution (e.g., 1s/frame) kinetic modeling
- 4D parametric imaging with cardiac/respiratory modulation
- Total-body dual-tracer and multi-tracer dynamic imaging
- Total-body organ network analysis and connectomes
- and many more …

Thank you for your attention!

Questions?

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