SRT Dosimetry Methods/Approaches under Development

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Disclosures

- Yuni Dewaraja is a consultant for MIM Software, Inc.

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SRT Dosimetry Methods under Development: Outline

- Voxel-level dosimetry
- Sub-voxel dosimetry models
- Biological effect models
- Cellular dosimetry (Roger Howell)
- New ICRP Specific Absorbed Fractions (Wes Bolch)
- Simplifications to bring dosimetry to the clinic

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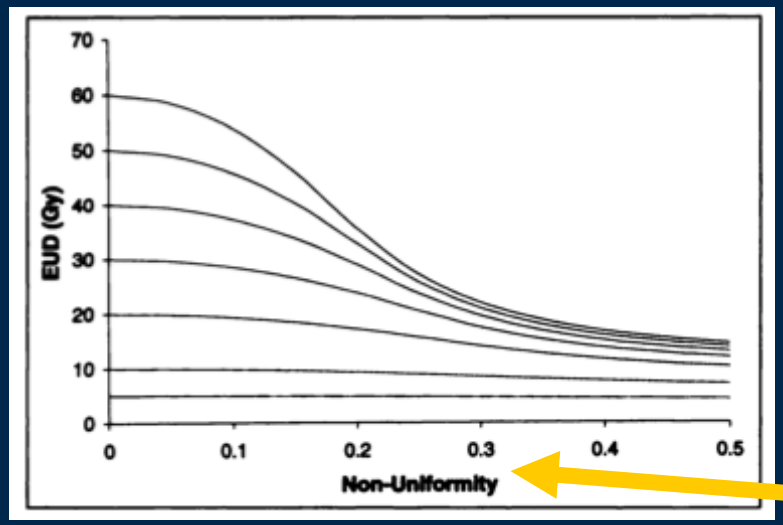
Why Voxel-Level ?

- Voxel-level dosimetry allows calculation of the biological effect of non-uniform absorbed dose distributions
  - Can be less efficient in killing tumor, less toxic to normal tissue
  - Equivalent Uniform Biologically Effective Dose (EUBED)



STD of BED distribution

- Being developed for treatment planning and verification

O'Donoghue JA. Implications of nonuniform tumor doses for radioimmunotherapy. J Nucl Med. 1999 Aug;40(8):1337-41

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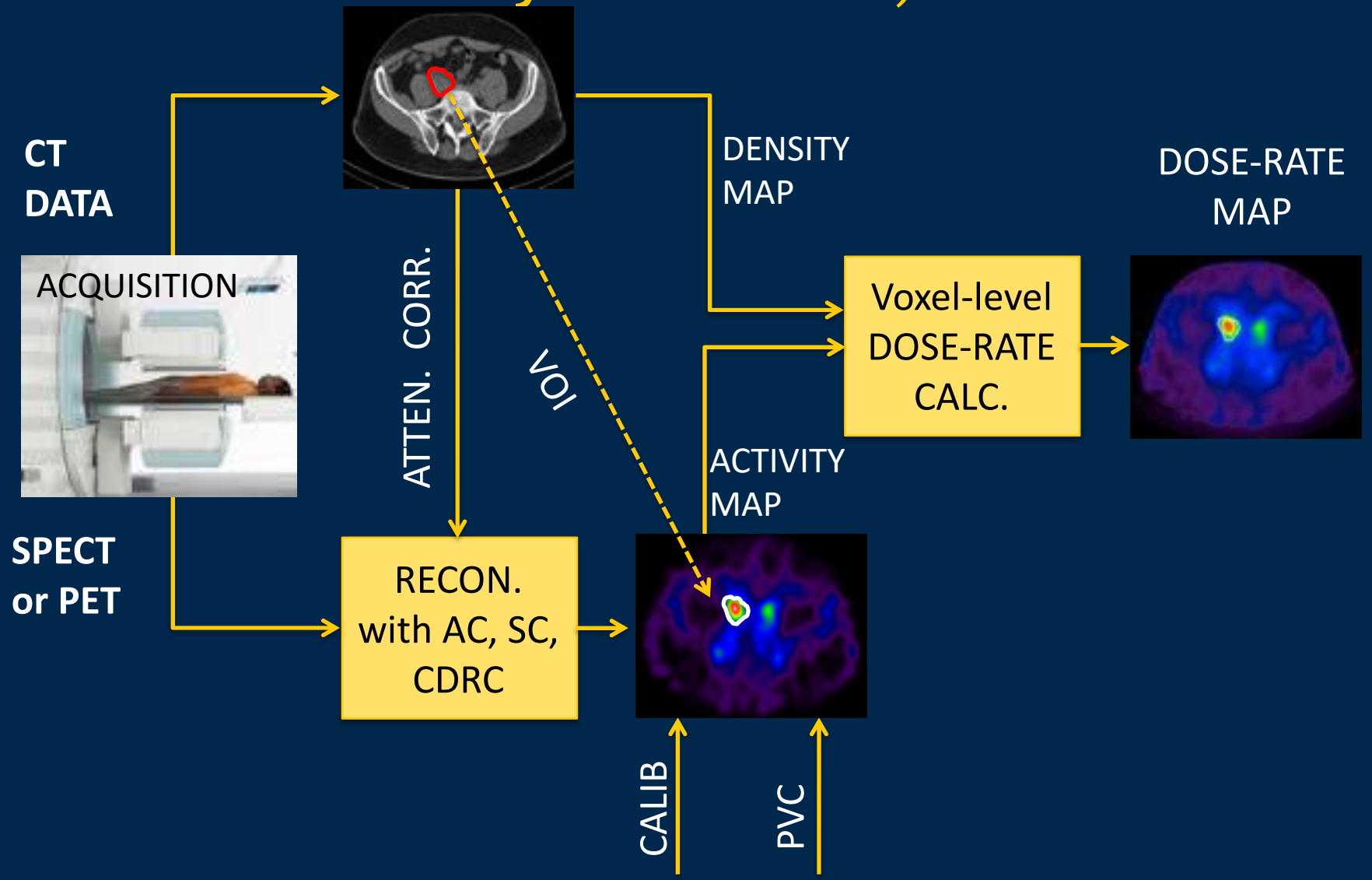
Patient specific voxel-level dosimetry: facilitated by SPECT/CT, PET/CT



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Patient Specific Voxel-level Dosimetry

Examples presented:

1) I-131 tositumomab radioimmunotherpy (RIT) in Non-Hodgkin's Lymphoma (NHL)

2) Y-90 microsphere radioembolization (RE) in hepatocellular carcinoma (HCC) and liver mets

3) I-124 PET as surrogate for radioiodine therapy in thyroid cancer

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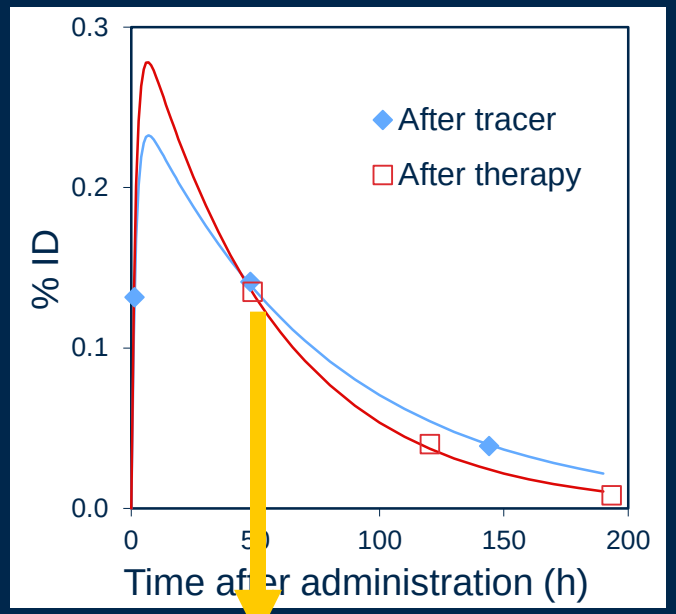
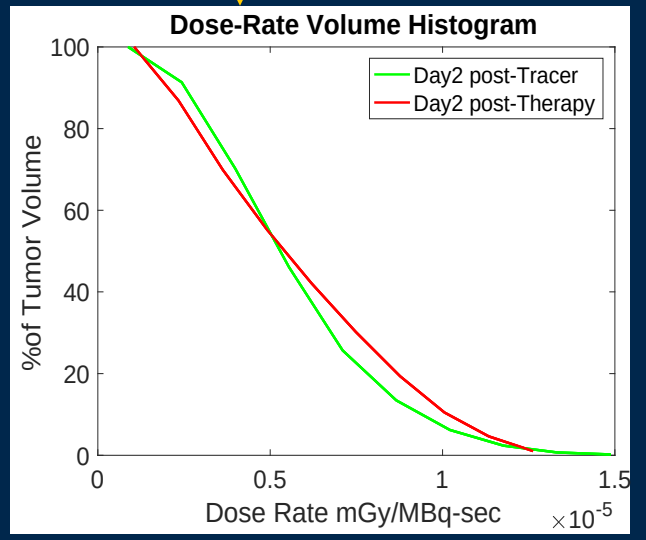
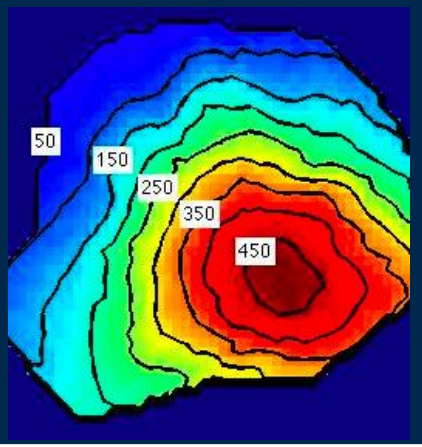
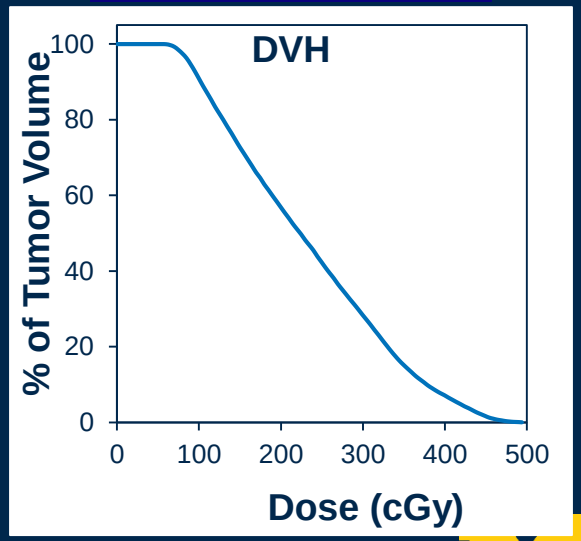
Voxel level dosimetry:I-131 RIT example

- Sequential SPECT/CT
- MC dosimetry accounting for tumor shrinkage with radial deformation
- Imaging based marrow dosimet









Dewaraja et al, MIRD 24, JNM 2013:2182-8

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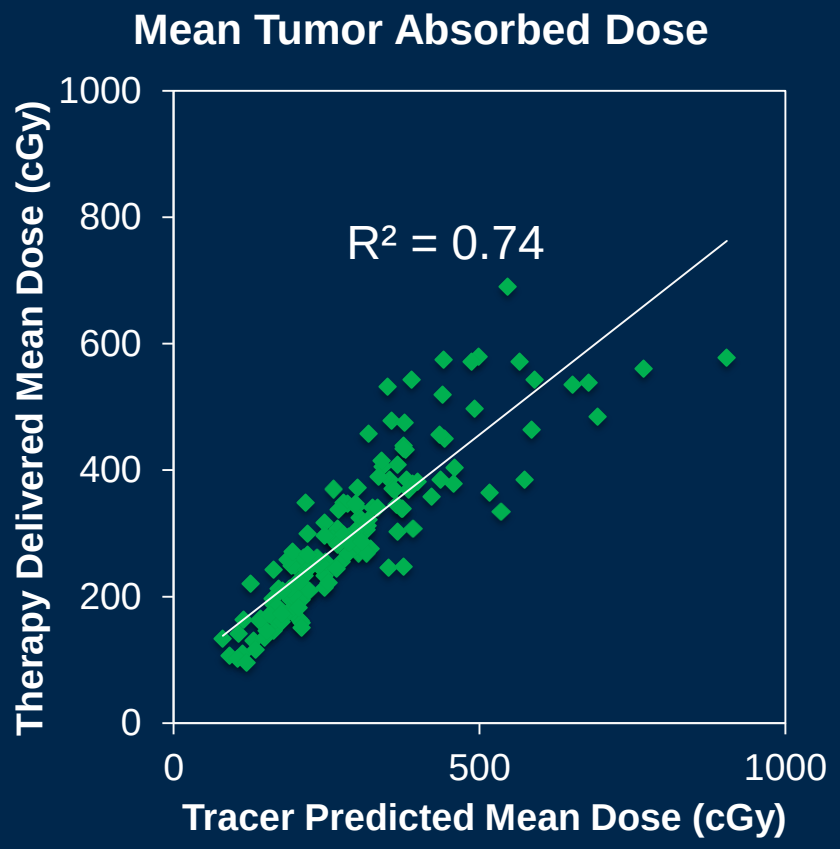
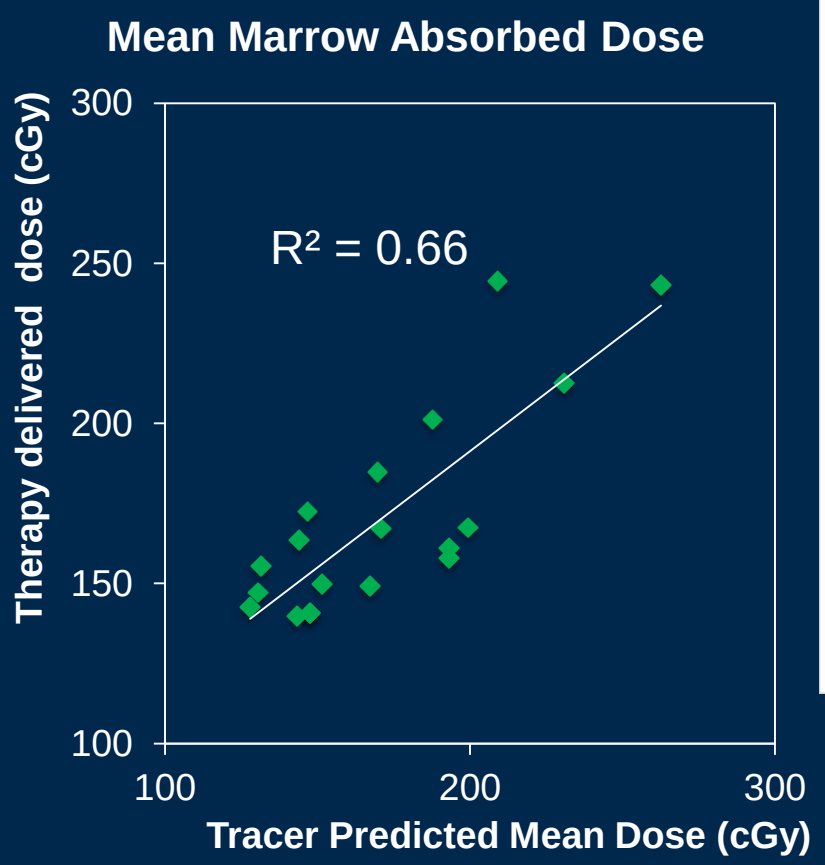
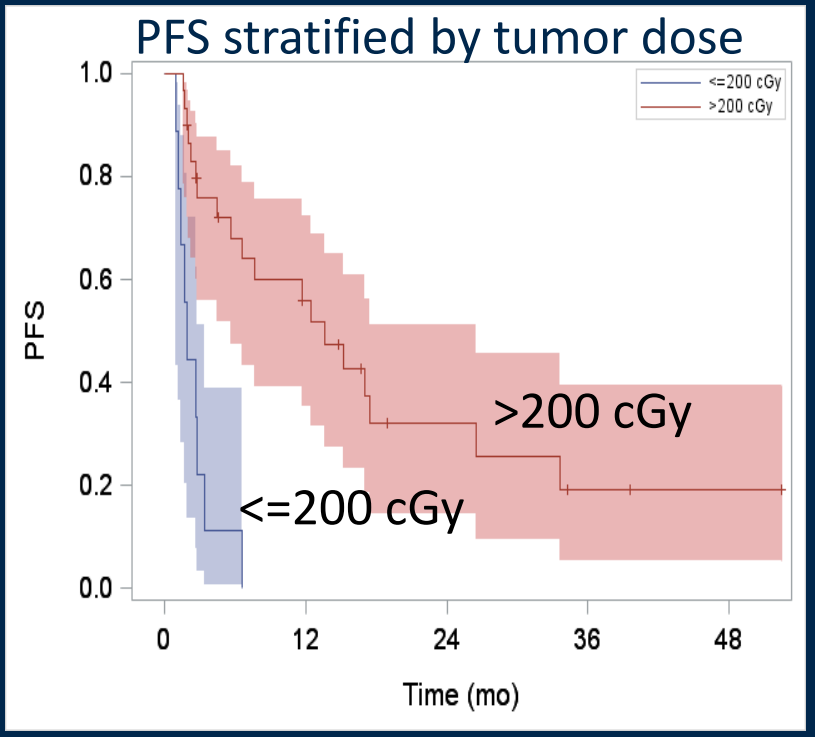
I-131 RIT: Potential for treatment planning

Correlation between tracer and therapy predictions and absorbed dose and outcome







Median PFS

13.6 mo for > 200 cGy

1.9 mo for < 200 cGy

($p < 0.0001$)

Dewaraja et al, JNM 2014, 1047-53

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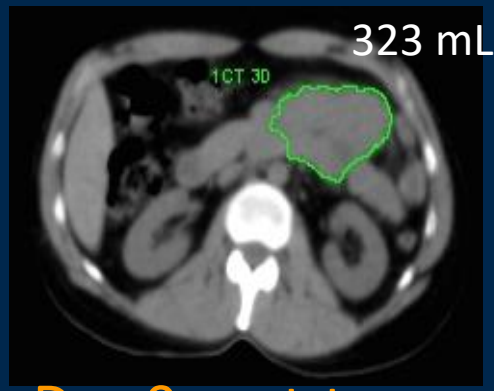
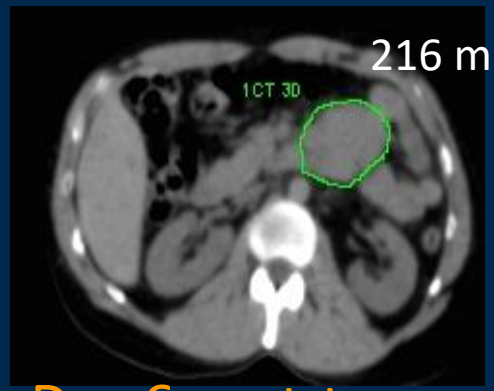
I-131 RIT: 'Cold' (unlabeled) antibody effect

- Outcome is not due to absorbed dose alone

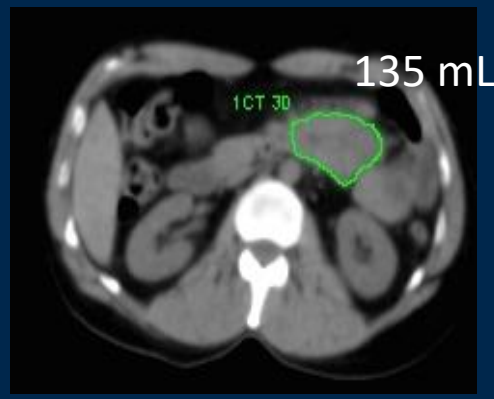
- Tracer (0.2 GBq) and therapy (4 GBq) I-131 tositumomab co-administered with 450 mg unlabeled tositumomab
  - Initial shrinkage likely in response to cold antibody
  - Estimated from CT of SPECT/CT



Day 0 post-tracer



Day 6 post-tracer



Day 8 post-therapy

Dewaraja et al, JNM 2010;1155-62 *Roberson et al, EJNMMI 2011:874-83*

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Bio-Effect model

- Sum of relevant quantities affecting therapy outcome

$$BET(v,t) = \alpha \cdot D(v,t) \cdot RE(v,t) + \lambda_p \cdot P(v,t) - \lambda_t \cdot t$$

+ dose effect + cold effect - proliferation

- Parameters (α, λ) determined for each patient from cell survival/clearance model fits to measured tumor shrinkage

- Patient biomarkers (Ki-67, P53, …) investigated to determine parameters pre-therapy

Roberson et al, EJNMMI 2011:874-83

Roberson et al, Cancer Biotherapy and Radiopharmaceuticals. 2017;309-319

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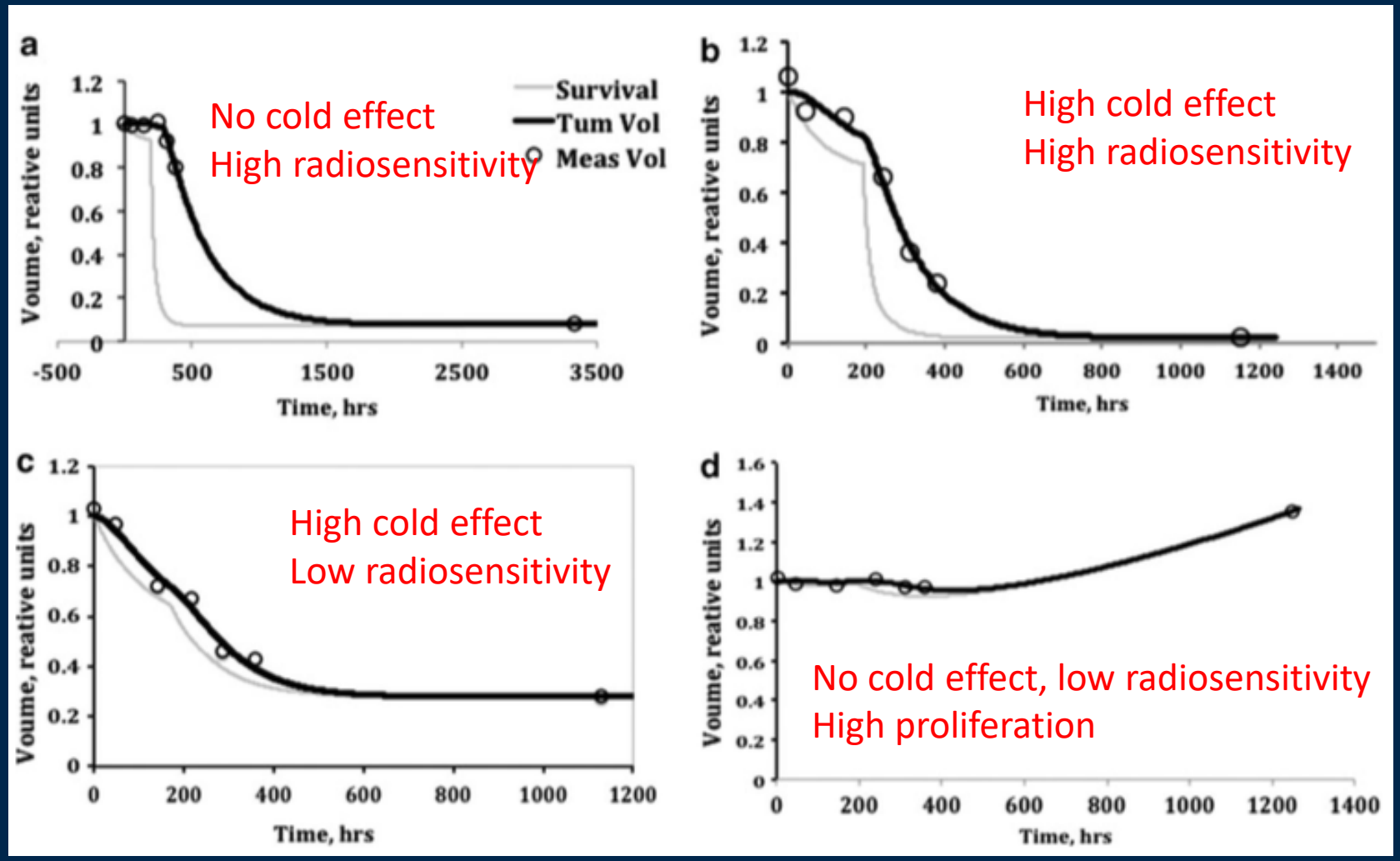
I-131 RIT: model fits to CT-measured tumor shrinkage

- 3 time points after tracer and 3 after therapy (within 15 days)



Roberson et al, Cancer Biotherapy and Radiopharmaceuticals. 2017;309-319

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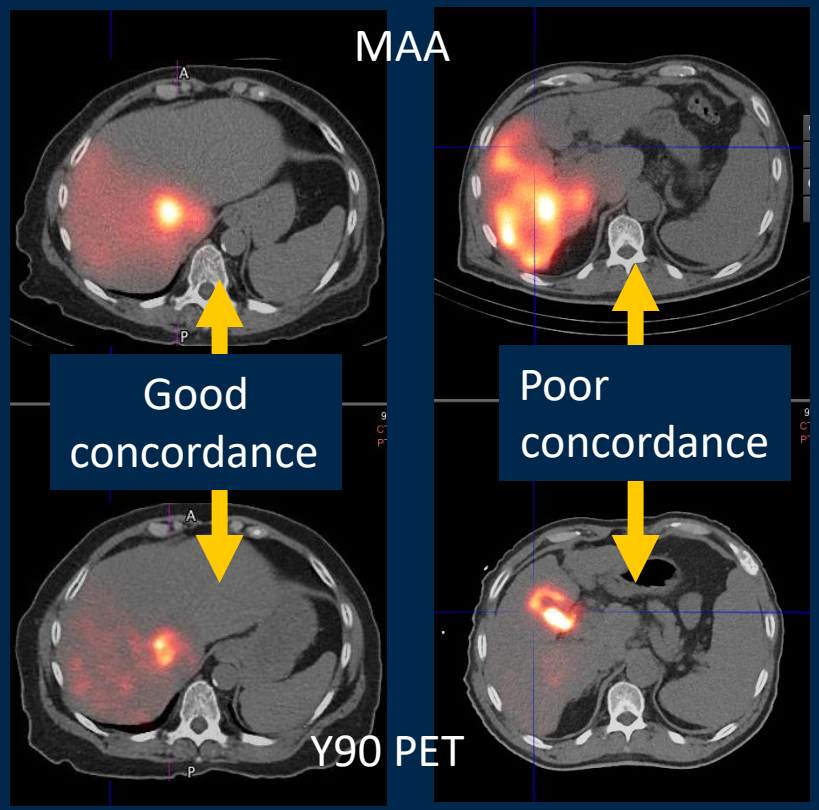
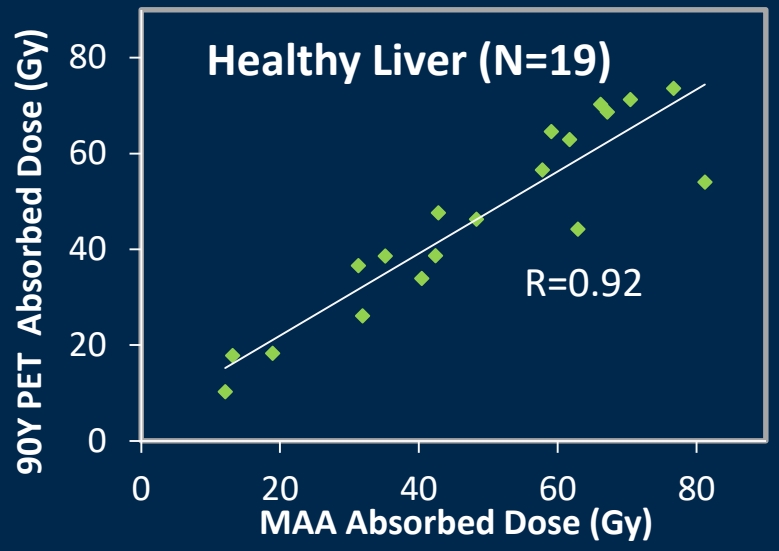
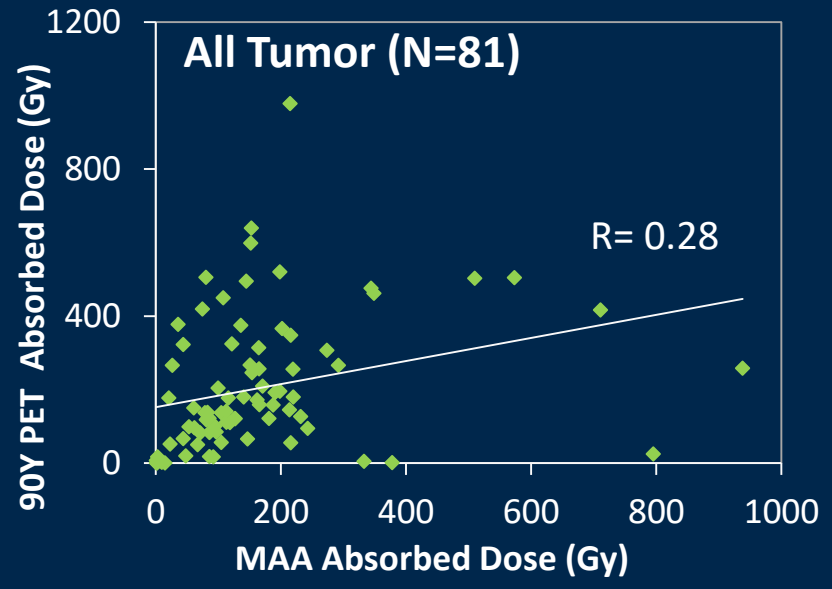
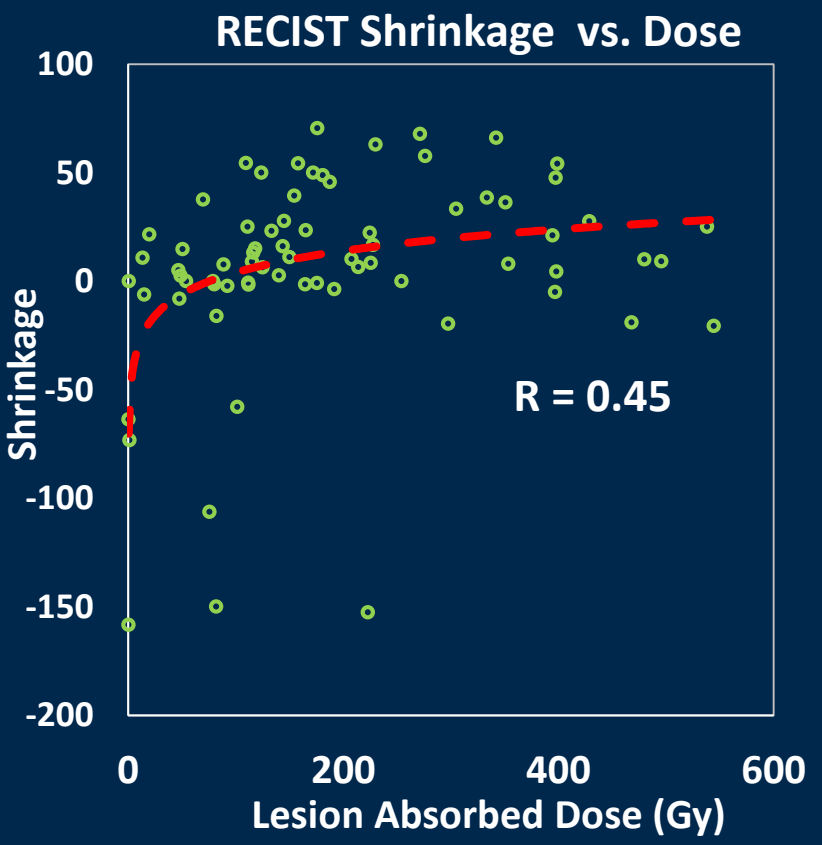
Y-90 RE example: potential for treatment planning?









Median AD_{RES} =209 Gy

$AD_{NO\ RES}$ =130 Gy

(p=0.024)

Justin Mikell et al, EANM Annual Meeting 2017

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Why voxel level? Y-90 RE treatment verification

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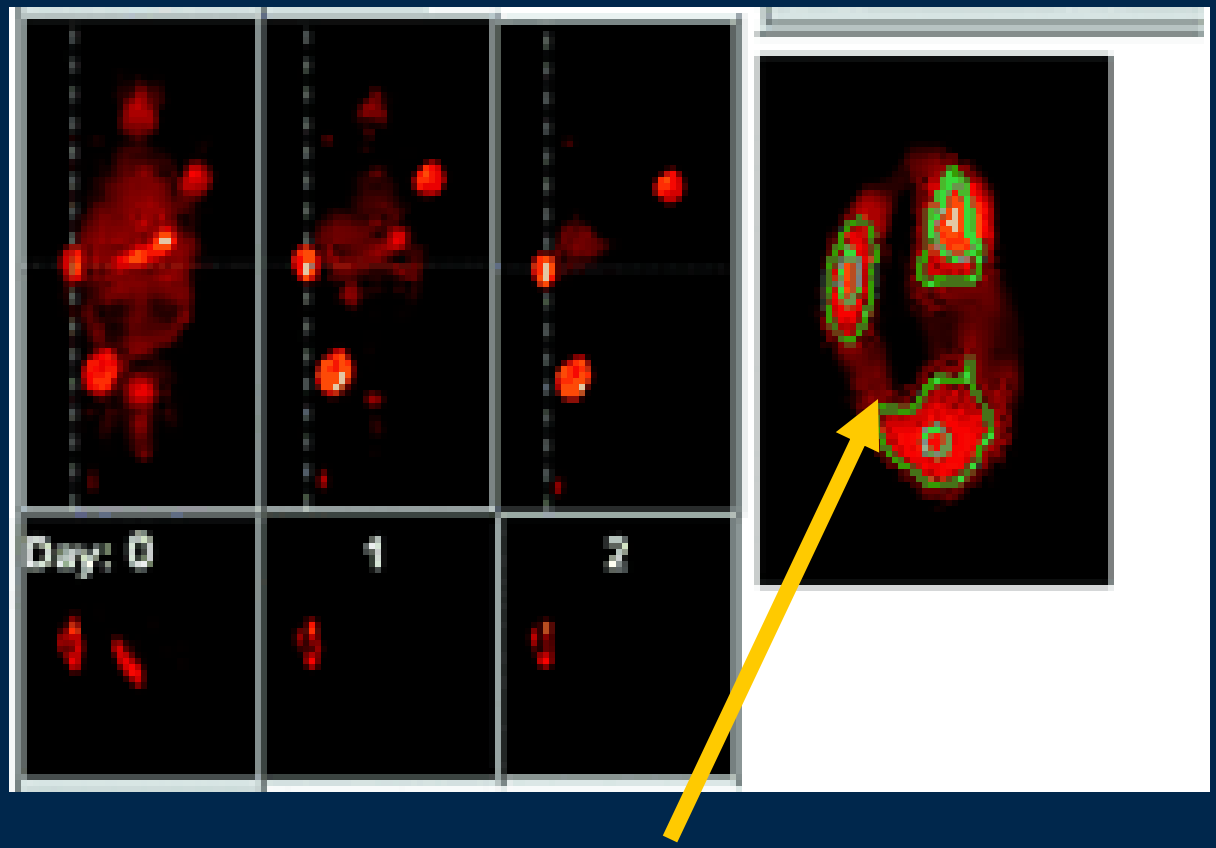
Why voxel level ? I-124 PET example

- PET at 3-4 time points within 7 d
- Importance of fully 3D data
  - If a single PET point was used (assuming static distribution) dose to sub-regions underestimated by up to 56%
  - Limitation of hybrid planar-SPECT approach where all voxels within tumor assigned same kinetics



Time-activity for 3 sub-regions were evaluated

Sgouros et al, JNM 2014;1366-1372

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Sub-voxel dosimetry

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Macro to micro dosimetry

- Activity distributed heterogeneously within voxels
- SPECT, PET, capabilities insufficient to deduce activity distributions at this scale
  - eg. central & portal vein in a liver lobule, glomerulus & tubules in kidney nephron
- Sub voxel model of tissue
  - Relate measured macroscopic activity distributions to micro distributions using a model (eg. pre-clinical model)
- Important when range in tissue is close to microstructure dimensions

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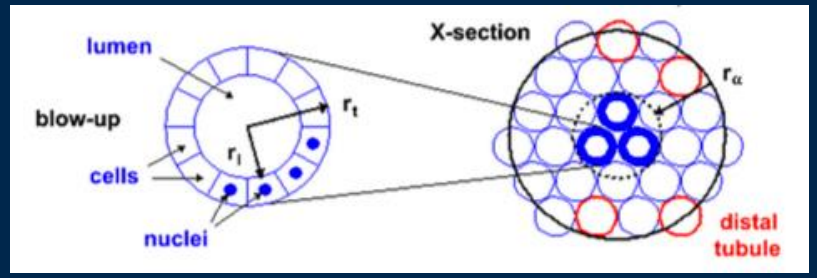
Macro-to-micro dosimetry: nephron model of kidney

- Especially important for targeted alpha particle dosimetry
- Idealized nephron geometry for generating MC based S value
  - Geometric shapes with parameters from ex vivo imaging



- Macro-to-micro (kidney to nephron) model

$$D_{\mathrm{tc}} = \sum_{\mathrm{sc},i} S_{\mathrm{tc}\leftarrow\mathrm{sc},i} \cdot g_{\mathrm{sc},i} \cdot \tilde{A}_k$$

Patient measured kidney activity

Dose to target nephron compartment

Fractional occupancy
Ratio of TIA in compartment to kidney: from activity measured ex-vivo (alpha camera)

Hobbs RF, et al. Phys Med Biol. 2012 Jul 7;57(13):4403-24.

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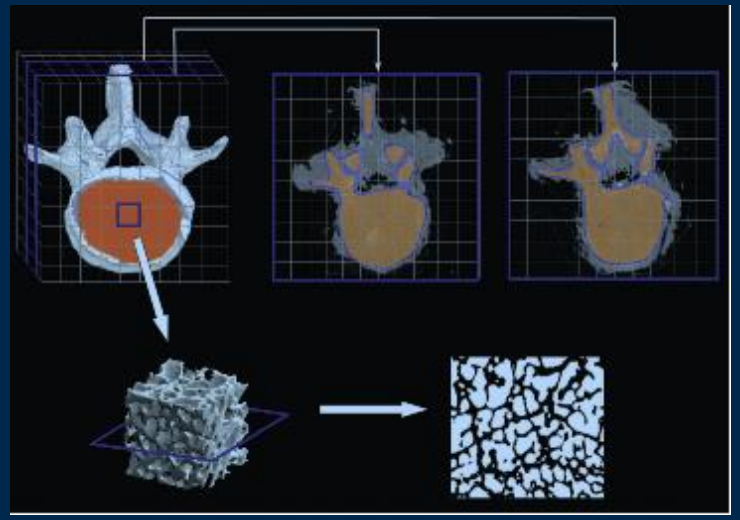
Subvoxel dosimetry model: bone marrow

- Coupling of macro and micro MC particle transport codes
  - Transport handled back and forth between micro and macro codes when particle enters marrow bearing region
  - Trabeculae model from ex-vivo CT & MR microscopy images



- Up to 30% difference in S values compared to conventional chord based model

Shah AP, et al J Nucl Med. 2005;46:344-53.

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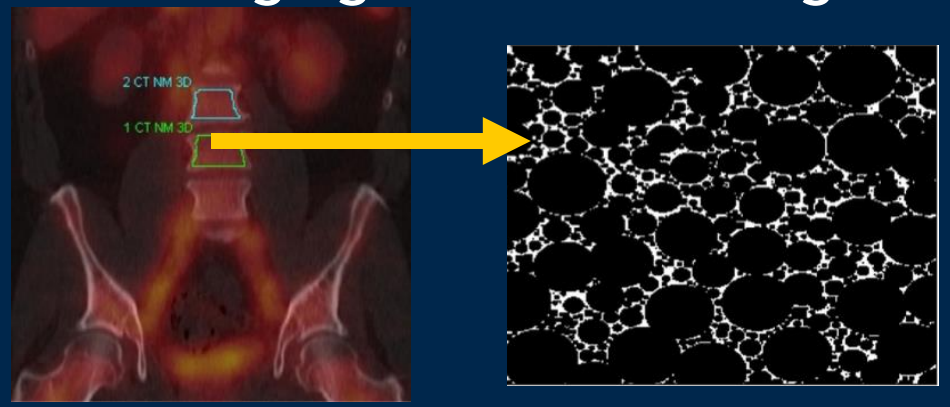
Bone marrow: spongiosa model with voxel-level variations

- ‘Faster’ approach: MC derived energy absorption fractions
  - Tabulated for arbitrary bone fractions and cellularities
  - 3 component (bone, red or yellow marrow) model of spongiosa
  - Module added to existing MC (DPM) algorithm

- Red marrow doses in I-131 RIT patients imaged with SPECT/CT
  - Patient specific cellularity (biopsy) and CT-based bone volume fractions
  - 20% different from imaging based assuming homogeneous spongiosa



Wilderman SJ, Roberson PL, Bolch WE, Dewaraja YK. Phys Med Biol. 2013;58:4717-31.

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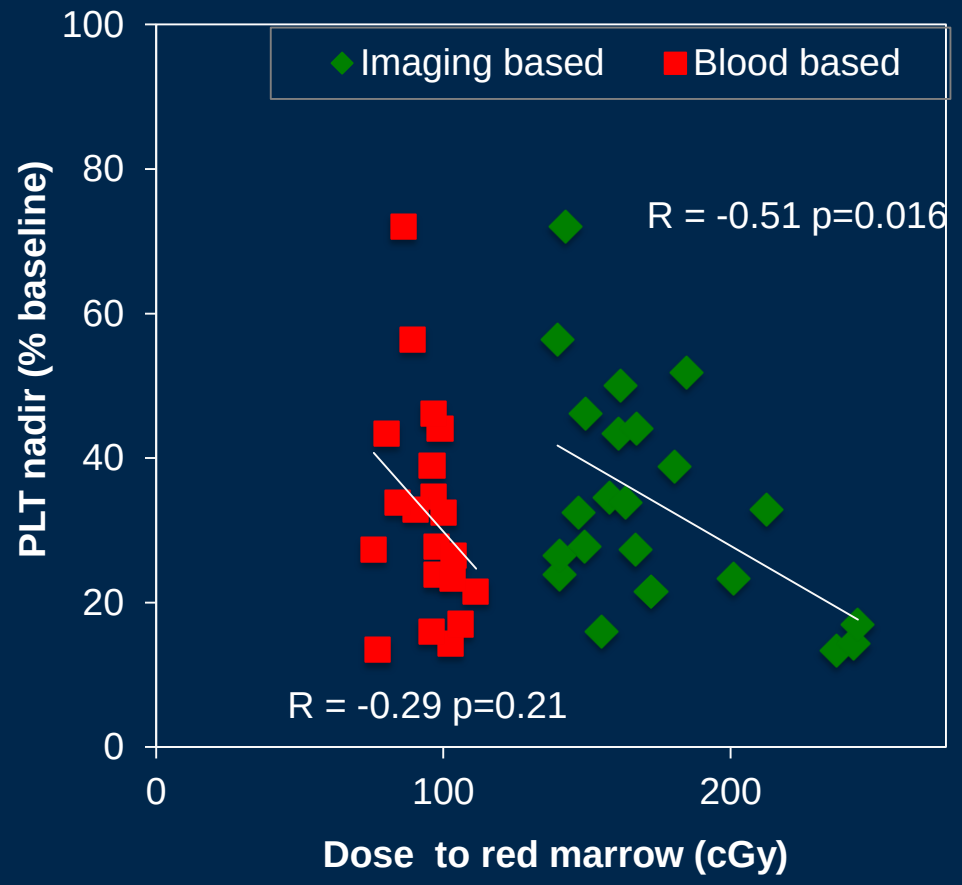
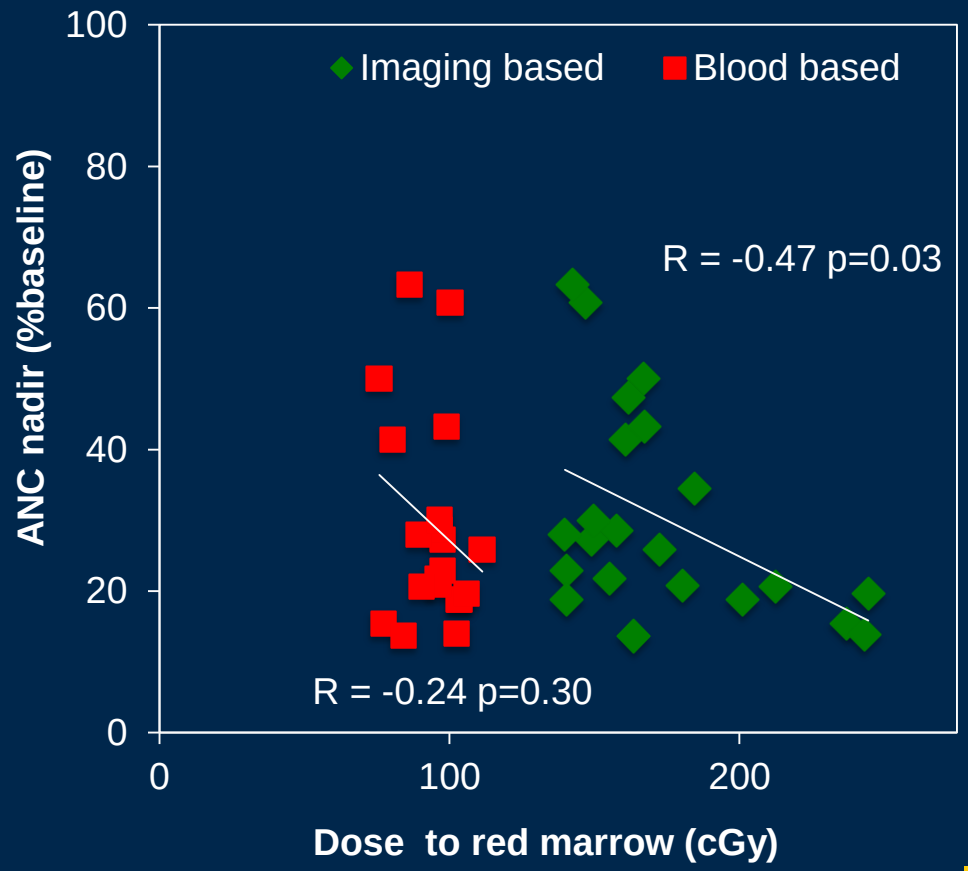
Patient results with sub voxel bone marrow dosimetry

- Dose – toxicity in NHL patients treated with I-131 tositumomab





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Liver microdosimetry in Y-90 radioembolization

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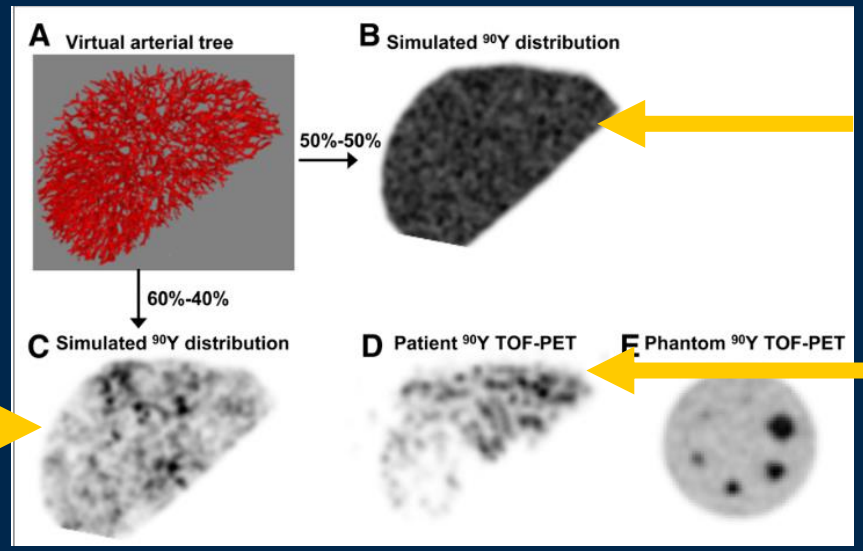
Liver microdosimetry in Y-90 radioembolization

- Low hepatic toxicity (per Gy) of Y-90 RE compared with EBRT
  - Similar toxicity with resin 70 Gy, glass 100 Gy and EBRT 40 Gy
  - Potentially due to non-uniformity in dose distribution

- Arterial tree model with non-uniform trapping
  - 40% - 60% spreading between 2 daughter vessels shifted lobule distribution to lower doses



Predicted for
50% - 50% spreading

Predicted distribution
for 60% - 40% spreading

Observed

Walrand S et al, JNM 2014;55:135-140

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Cellular dosimetry

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ICRP Absorbed Fractions using Realistic Phantoms

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Simplifications to bring dosimetry to the clinic

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Potential simplifications

- When voxel-level dosimetry is not feasible and quantity of interest is the mean absorbed dose the procedure can be simplified, yet remain patient specific to some extent

- Time integrated activity
  - Commercial availability of quantitative SPECT/CT (output Bq/mL)
  - Reduced time points (mixed model fitting or single time point)
  - Hybrid planar-SPECT imaging

- Absorbed dose calculation
  - Commercial software coupling images directly with dosimetry
  - New SAFs and S values from realistic ICRP phantom

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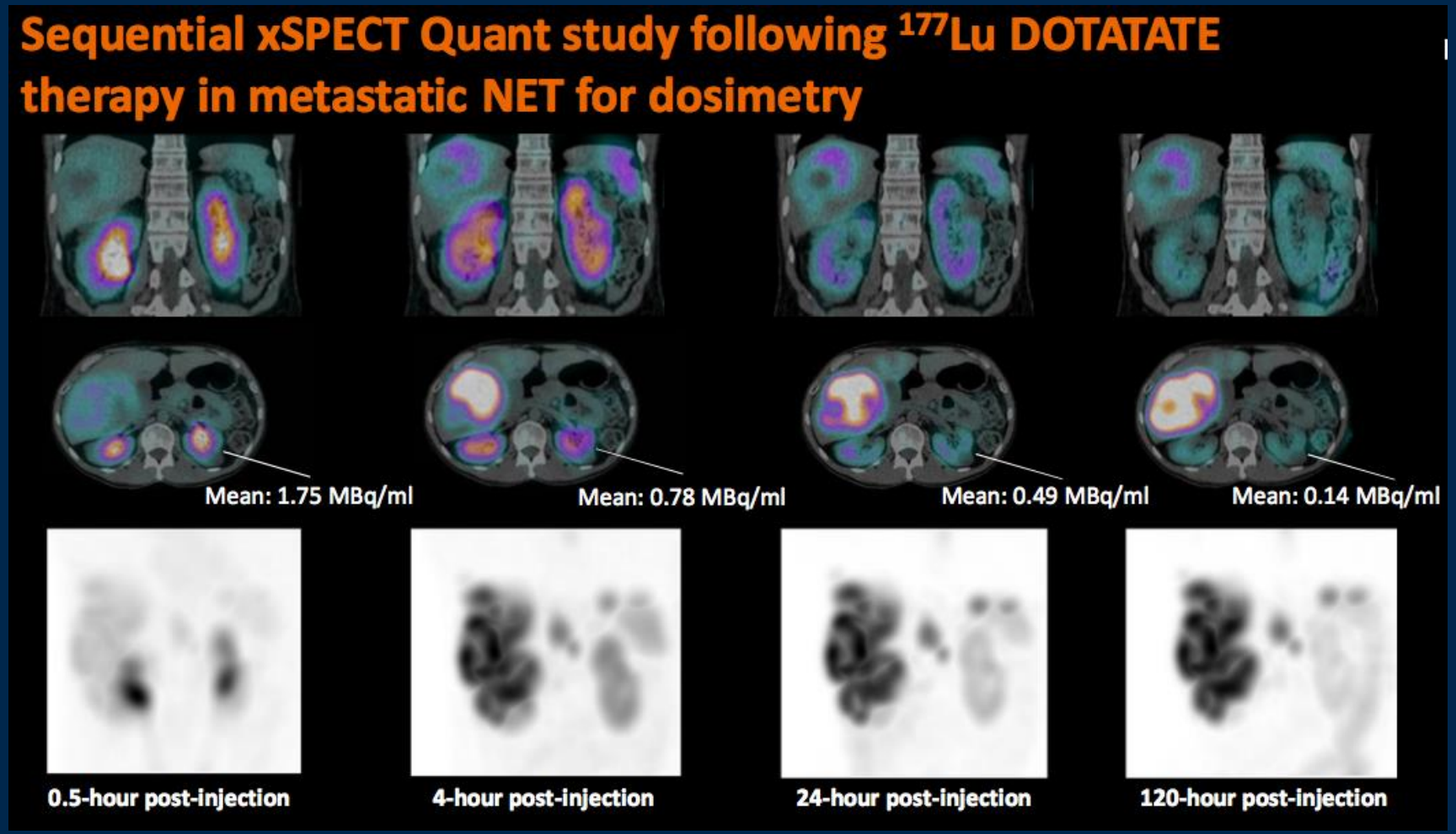
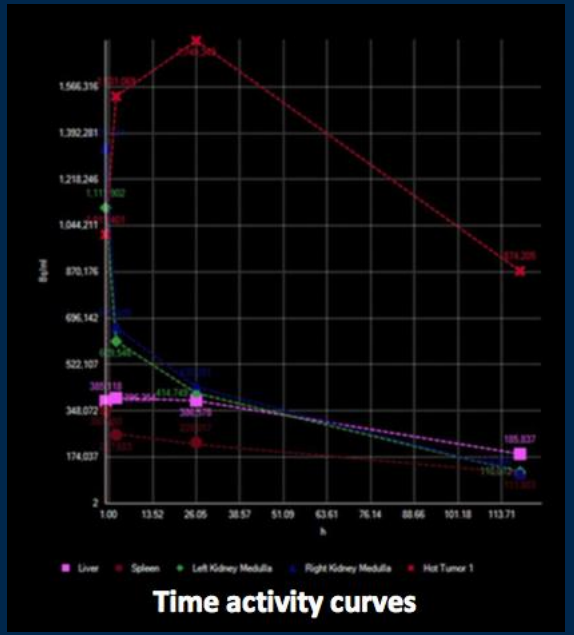
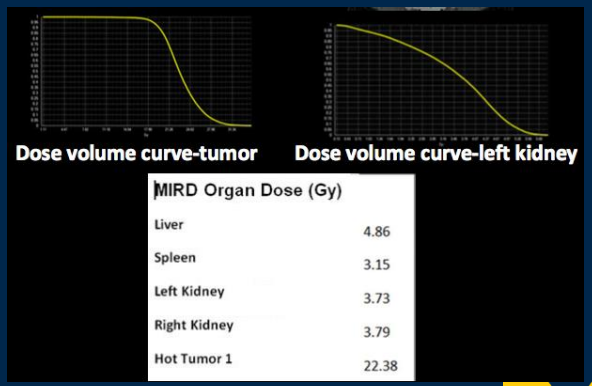
Commercially available tools: Siemens xSPECT Quant







Courtesy of Johannes Zeintl, Siemens Healthineers

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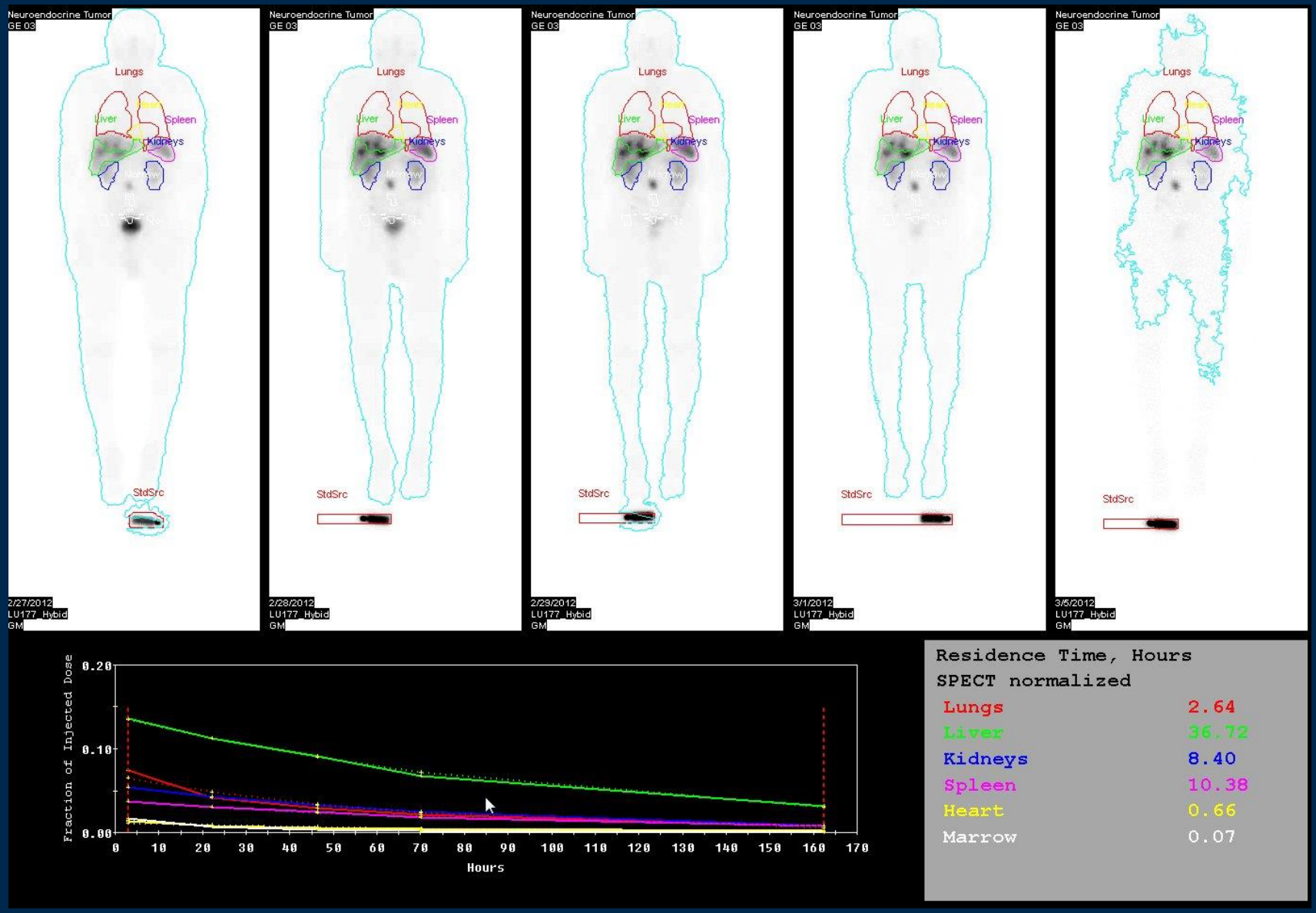
Commercially available tools: GE Dosimetry Toolkit



Courtesy of Prof. Kreissl and Dr. Grosser, University Hospital Magdeburg, Germany

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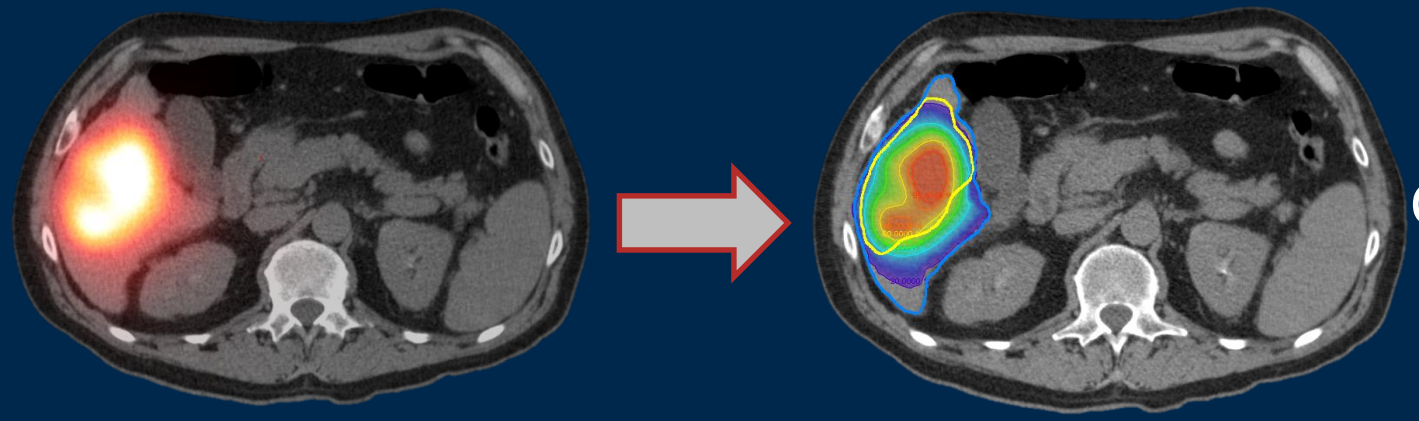
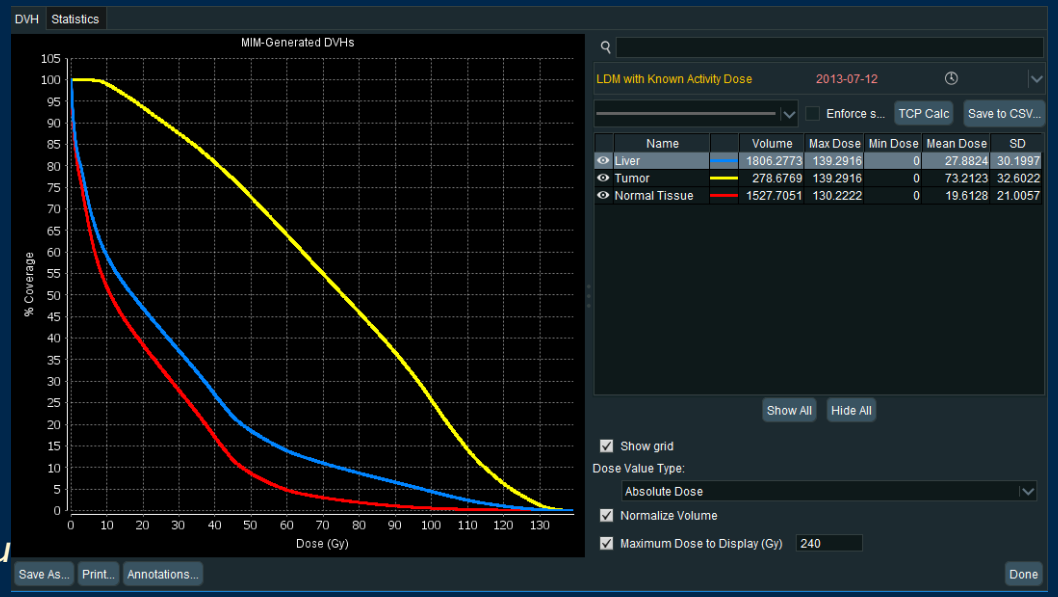
Commercially available tools: MIM (vendor neutral)

Example: Y90 microsphere bremsstrahlung SPECT/CT



Convert the SPECT to a dose object



View dose volume histograms for each region of interest

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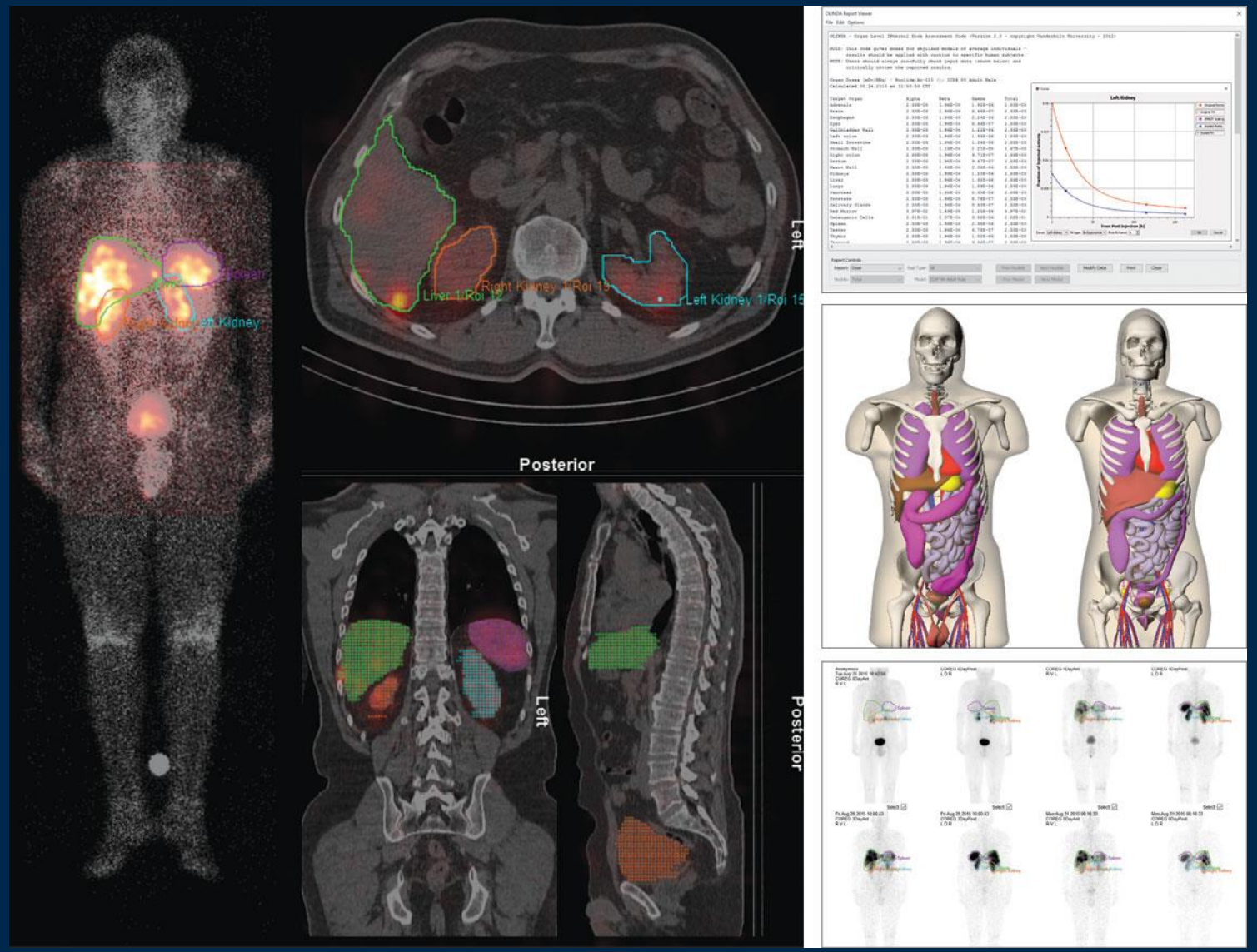
Commercially available tools: Hermes (vendor neutral)



https://www.hermesmedical.com/product-showcase/olinda/

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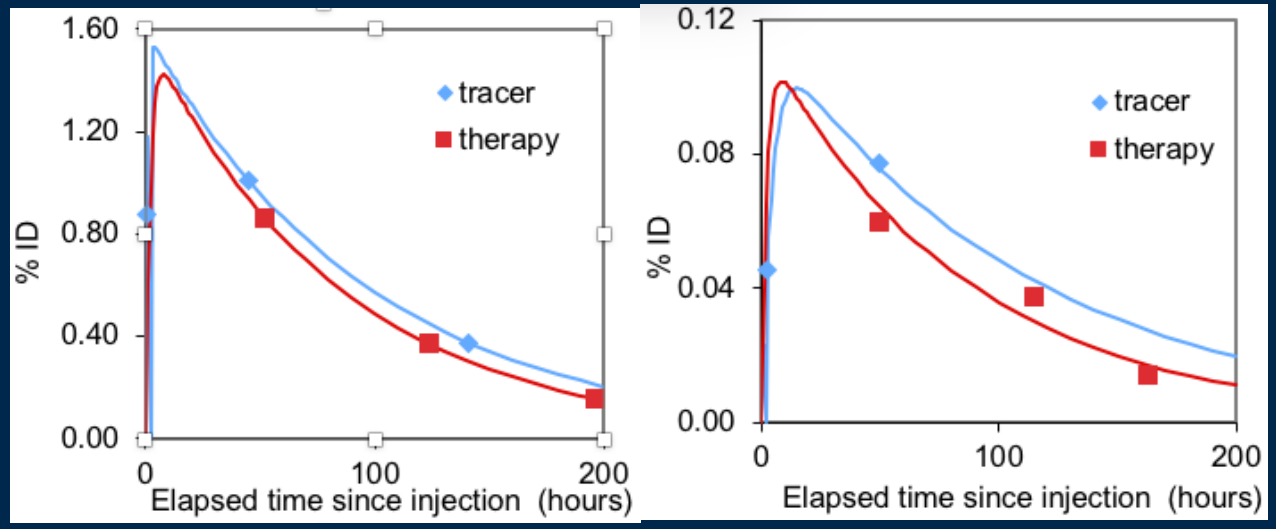
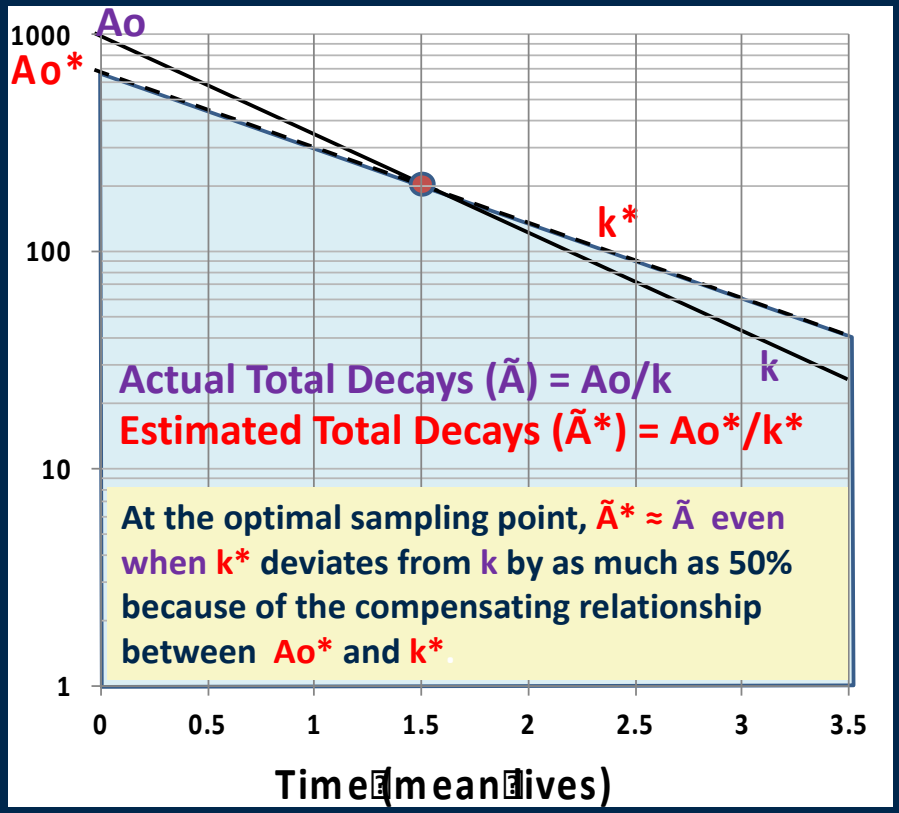
Simplifications for generating time integrated activity

- Mixed model fitting
  - curves from multiple subjects are jointly estimated



- Single time point method
  - Need estimate of population average of parameters
  - Dose estimates 10 - 20%



Schipper et al, Cancer Biotherapy Radiopharm, 2012

Courtesy Mark Madsen, PhD University of Iowa (Accepted to Med Phys)

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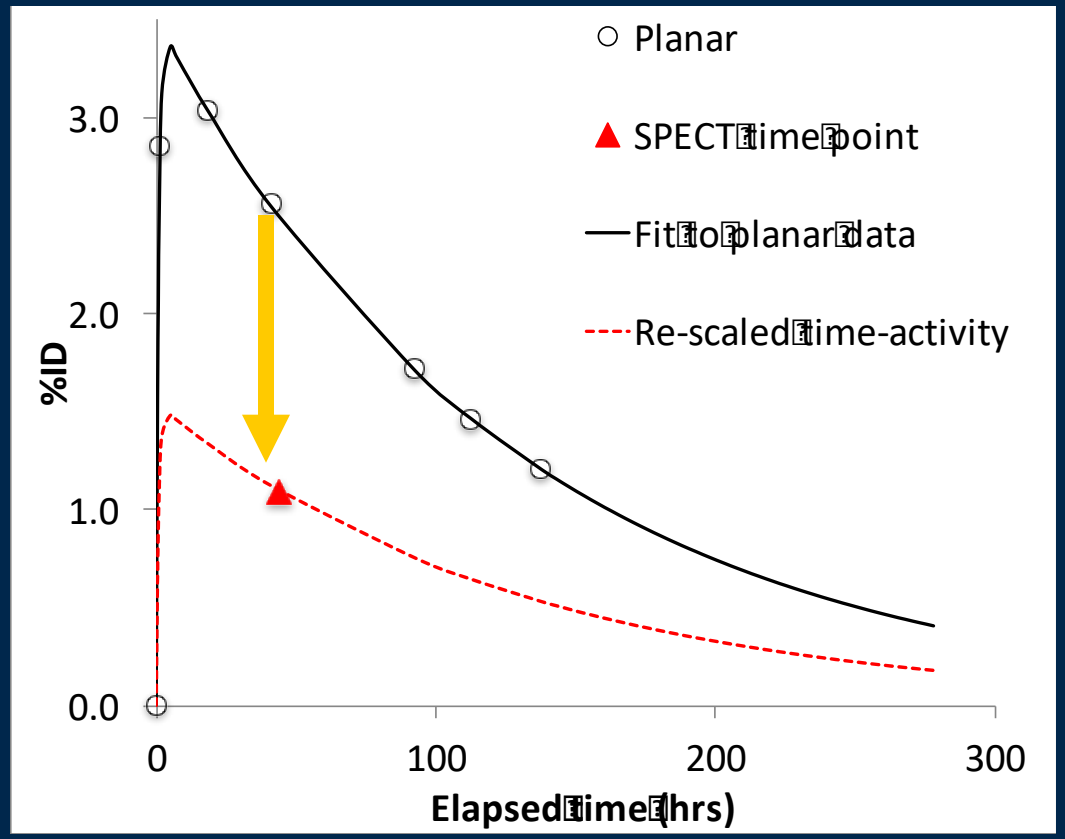
Simplifications: Hybrid planar – SPECT

- Normalization of planar derived time-activity to single SPECT
  - Assuming static distribution



Patient imaged after I-131 tositumomab RIT

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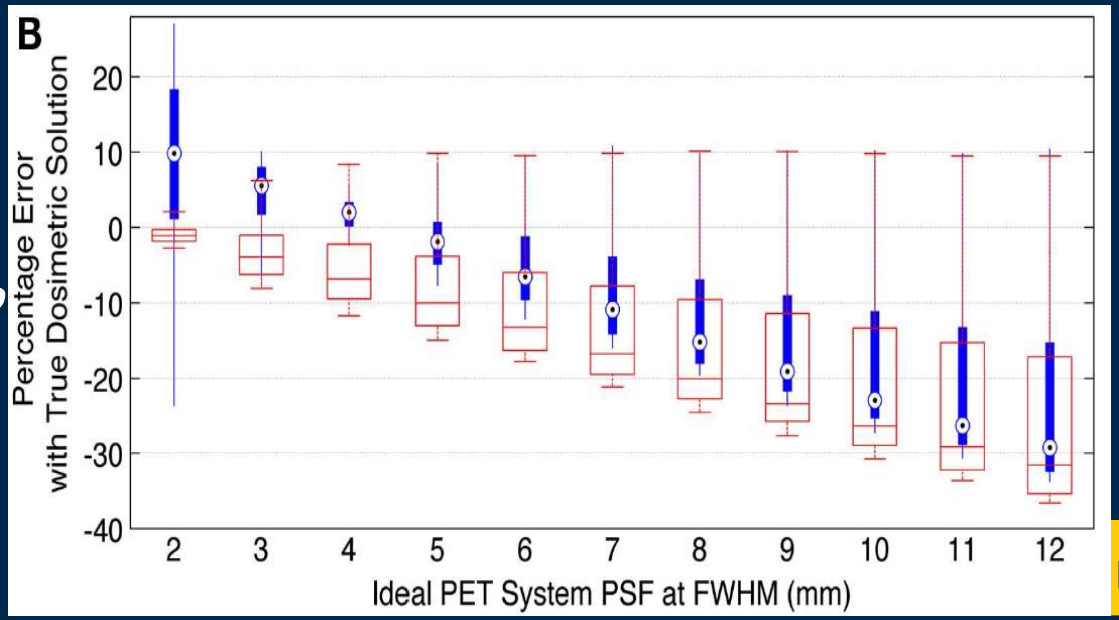
Simplification: 'full' dosimetry vs. local energy deposition

- For particles with short path-length and low intensity or no gamma-ray emissions
  - 3D dosimetry assuming energy absorbed locally within voxel where decay occurred vs. radiation transport
  - Activity map converted to absorbed dose simply using a conversion factor

- Differences between the 2 methods depend on voxel size, spatial resolution, noise



Pasciak et al, Frontiers in Oncology, May 2014

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Thank You

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