TREATMENT OPTIMIZATION IN THERANOSTIC RADIONUCLIDE THERAPIES

WORLD CONGRESS IN MEDICAL PHYSICS AND BIOMEDICAL ENGINEERING
JUNE 5TH, 2018

John L. Humm Ph.D.
Vice Chair of Medical Physics
Memorial Sloan Kettering Cancer Center

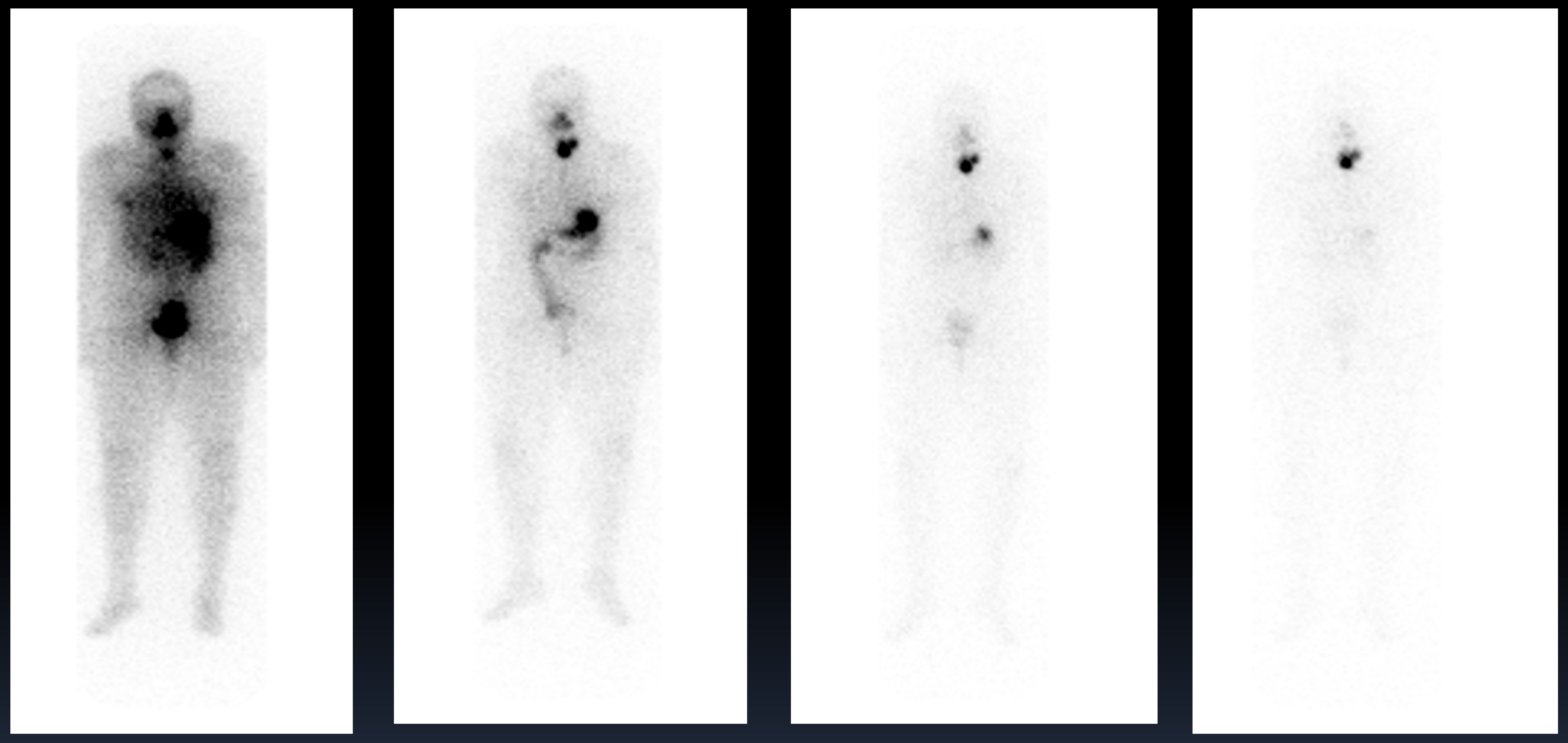
The Content of my talk will includes 3 example vignettes

- 1. Radioiodine in thyroid cancer
- 2. Small peptides in neuroendocrine cancers
- 3. Antibodies in pediatric cancers

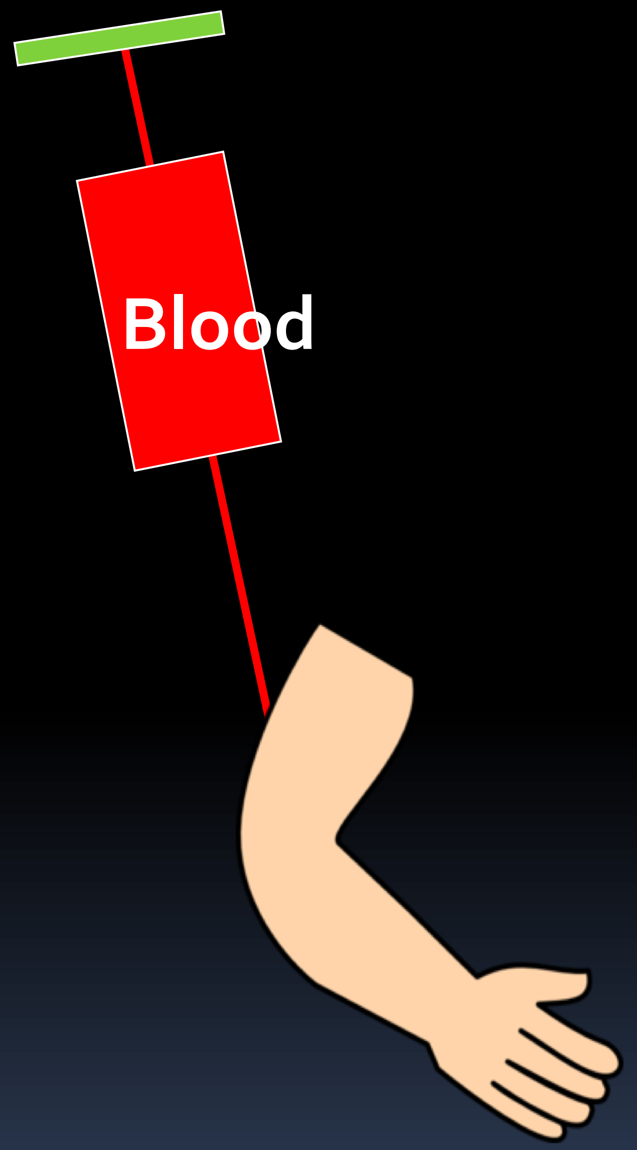
The maximum tolerated activity (MTA)

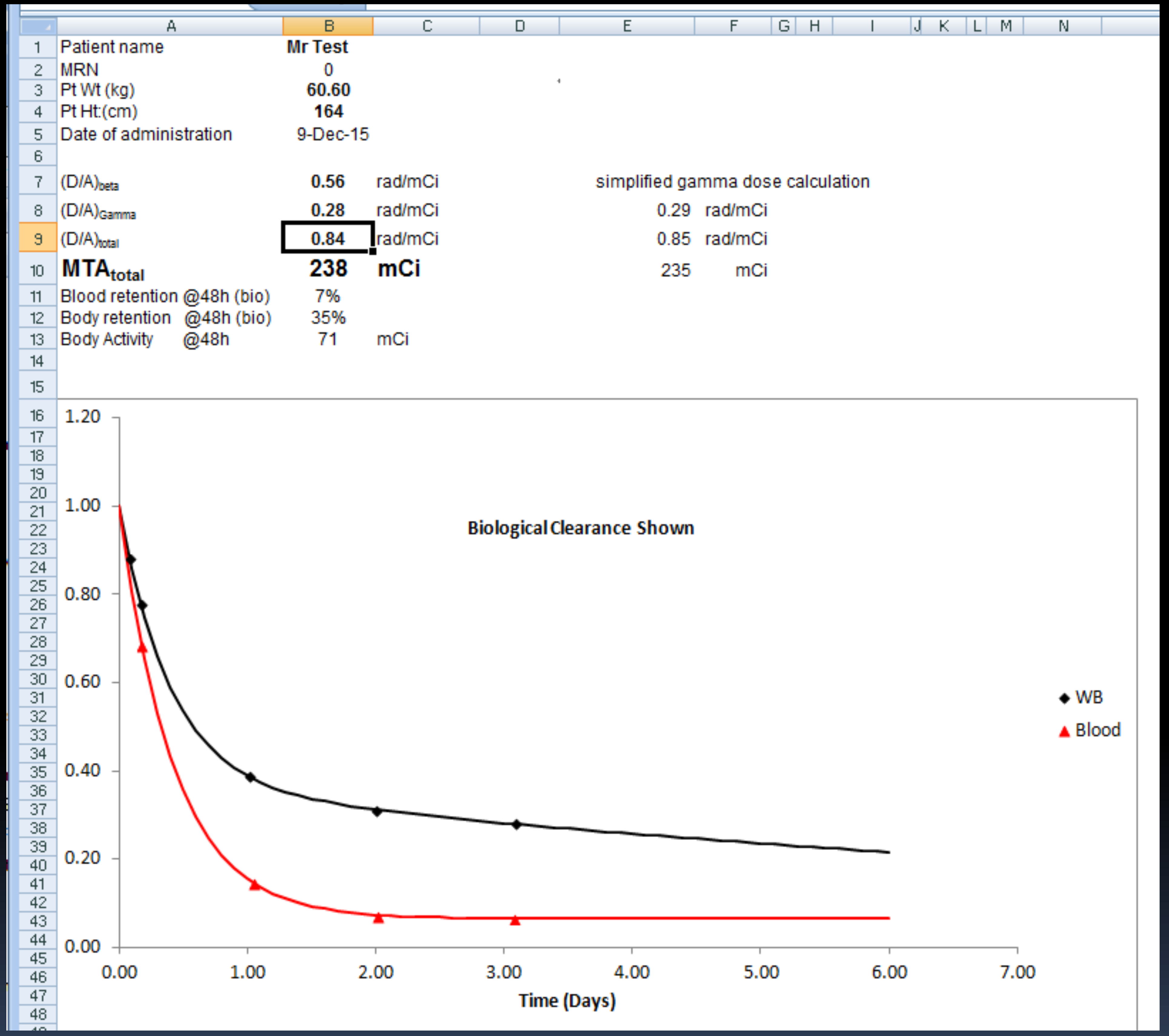
Bone marrow is the dose limiting for many radionuclide therapies

1) Blood clearance (beta dose)
2) Whole Body Clearance (gamma dose)



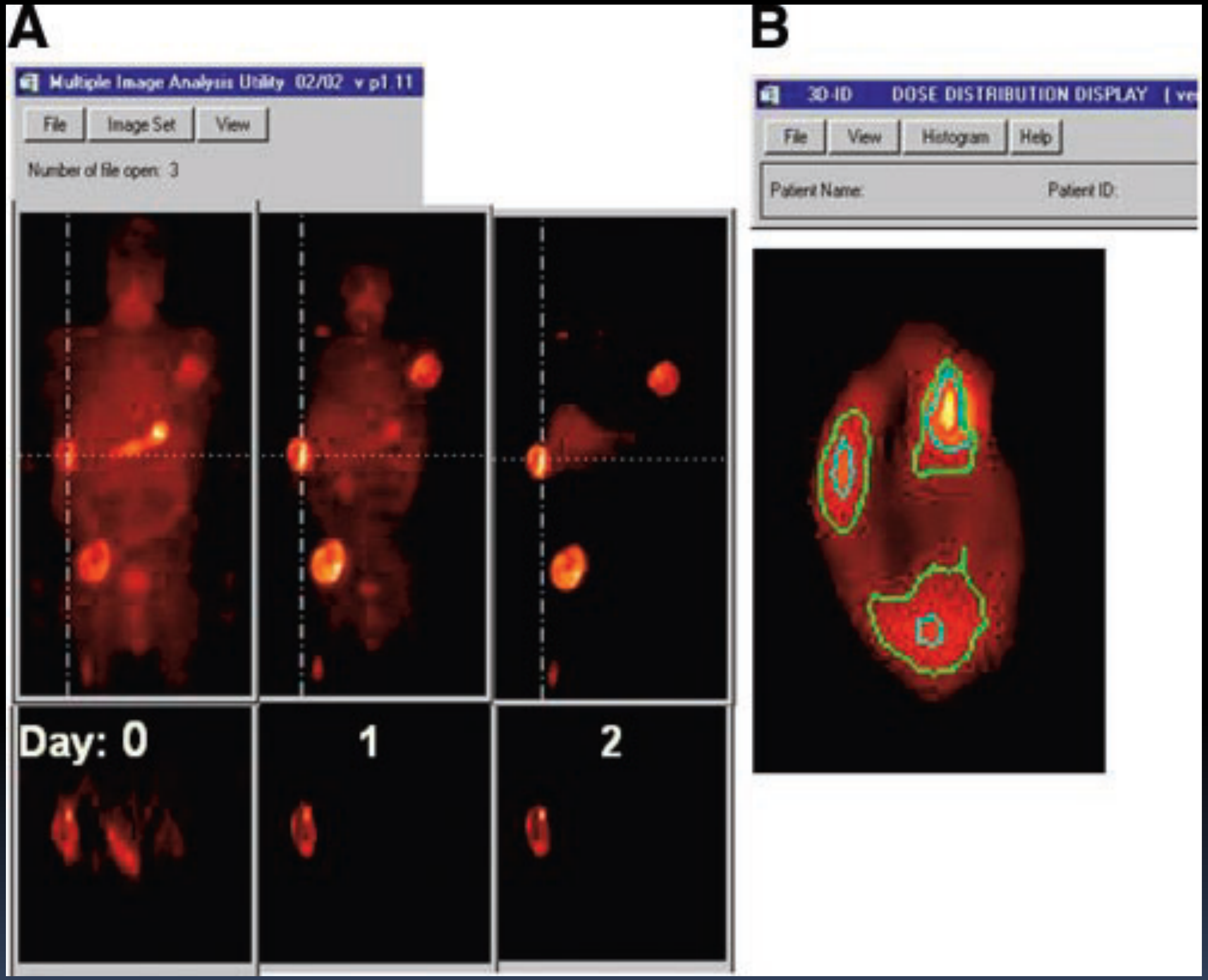
2hr 24hr 48hr 96hr





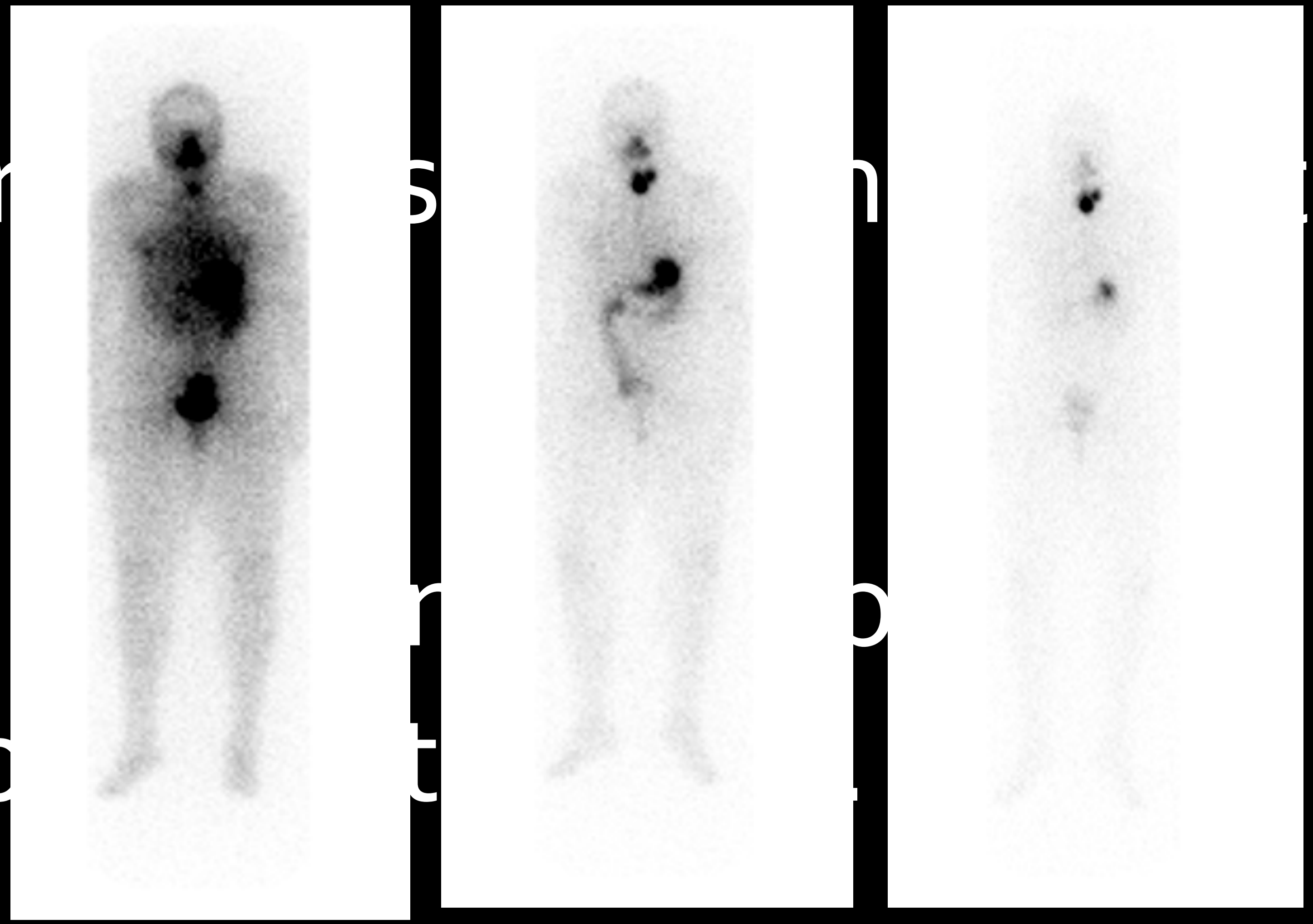
Benua RS et al, The relation of radioiodine dosimetry to results and complications in the treatment of metastatic thyroid cancer. **American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine,** 87 171–182. 1962
Furhang EE, Larson SM, Buranapong P, and Humm JL, Thyroid dosimetry using clearance fitting. J.Nucl.Med.40: 131-136, 1999.

The use of ^{124}I PET for thyroid lesion dosimetry



Sgouros et al, Patient-Specific Dosimetry for 131I Thyroid Cancer Therapy Using 124I PET and 3D –Internal Dosimetry (3D–ID) Software, J Nucl Med 2004; 45:1366–1372

Difference between external beam radiotherapy and radionuclide therapy



- In XRT the treatment planner use a CT (and other s n t volume defined by the radiation oncologist.
- In XRT there are normal tissue constraints and so o jostle with the beam directions and weights to op t
- In radionuclide therapy, the planner! studies the biodistribution and pharmacokinetics of a tracer quantity of the intended therapeutic.
- In radionuclide therapy, there is no way to modulate the radionuclide distribution
- Or is there?

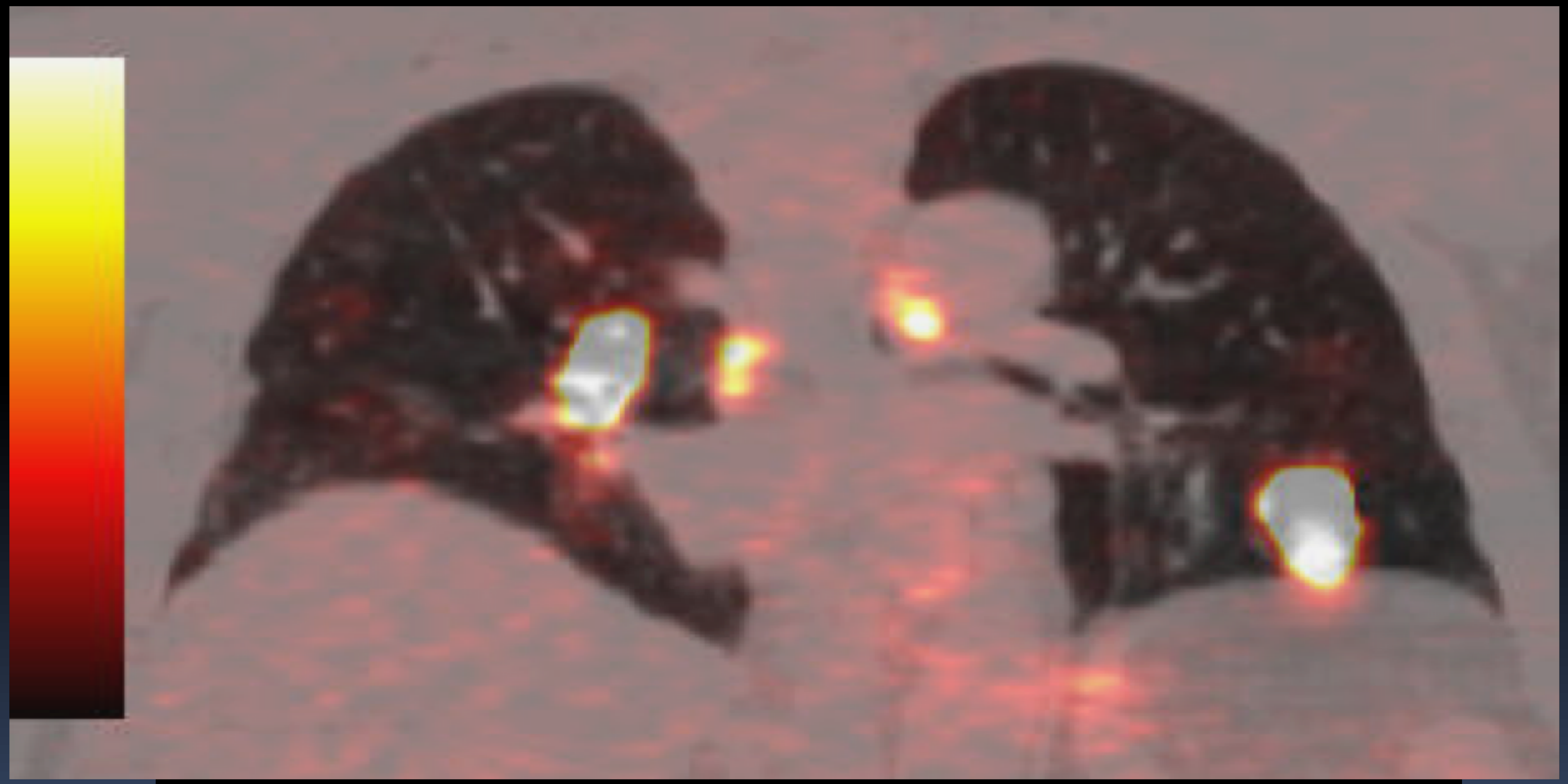
Restoring Radioiodine Uptake in Thyroid Cancer

A Paradigm Shift

New drugs are under development, such as selumetinib, that is a mitogen-activated protein kinase (MEK) inhibitor, that may restore the NaI symporter expression.

This can restore radioiodine uptake in metastatic thyroid cancer.

^{124}I PET/CT
Baseline



^{124}I PET/CT
After Selumetinib

1 R01 CA201250-01

^{124}I-NAI PET: Building block for precision medicine in metastatic thyroid cancer

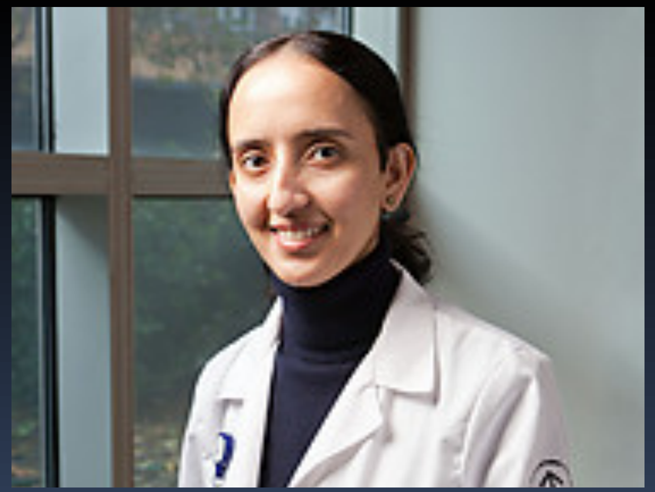
John Humm

Steve Larson (Contact PI)

Mike Tuttle

James Fagin

Alan Ho



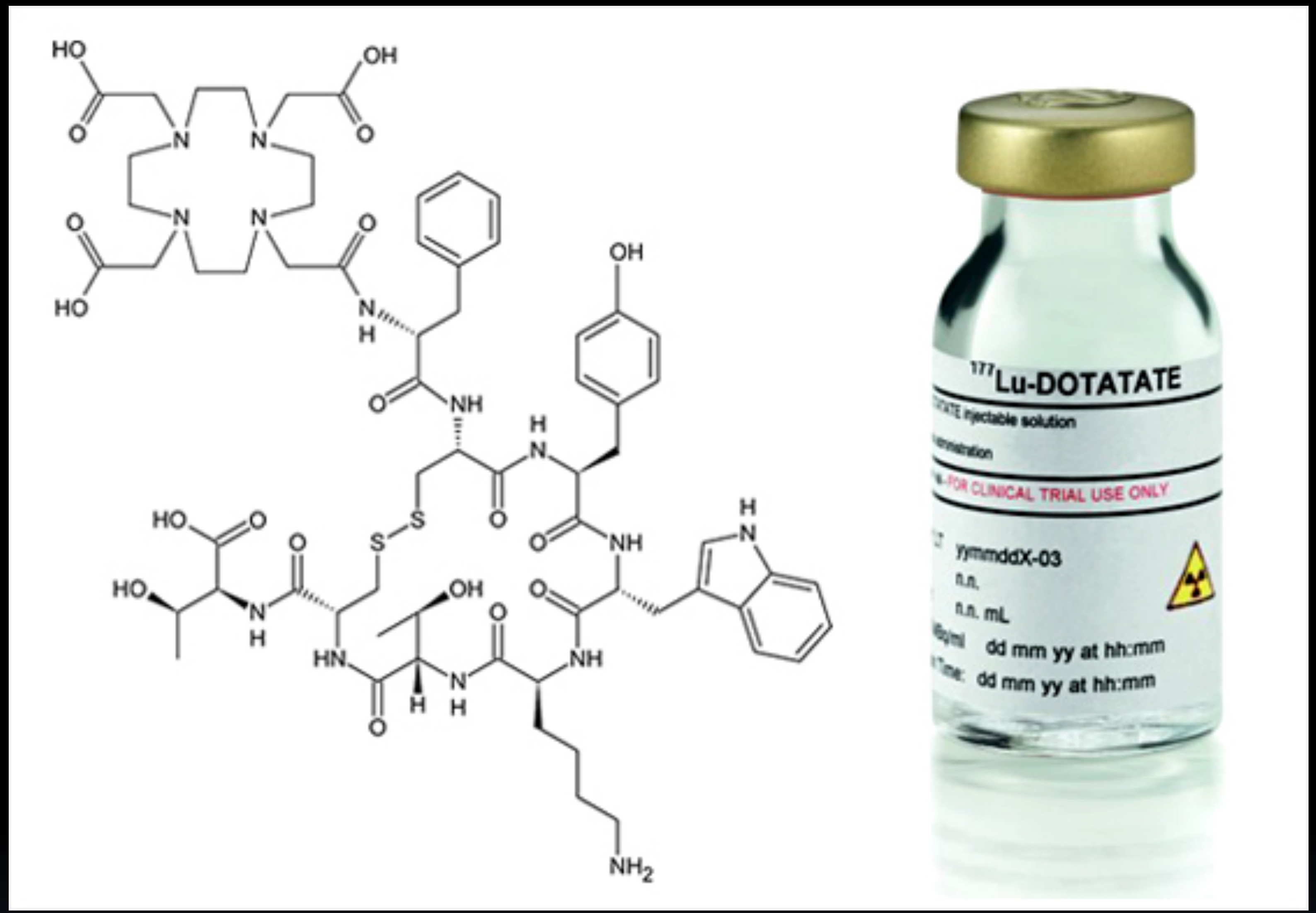
Ravi Grewal

Keith Pentlow

Part 2 - Peptide Theranostics

Peptide Receptor Radionuclide Therapy (PRRT)

- There is been a recent explosion of interest is small molecule targeted therapies.
- Radiolabeled somatostatin receptor (sst) agonists, e.g. ^{177}Lu-DOTATATE, have become an integral part of therapeutic management in patients with neuro-endocrine tumors .
- These are ideal theranostic agents, where the molecular can be labeled with ^{68}Ga for diagnosis and ^{177}Lu for dosimetry and therapy.



Somatostatin (sst) agonist vs antagonist

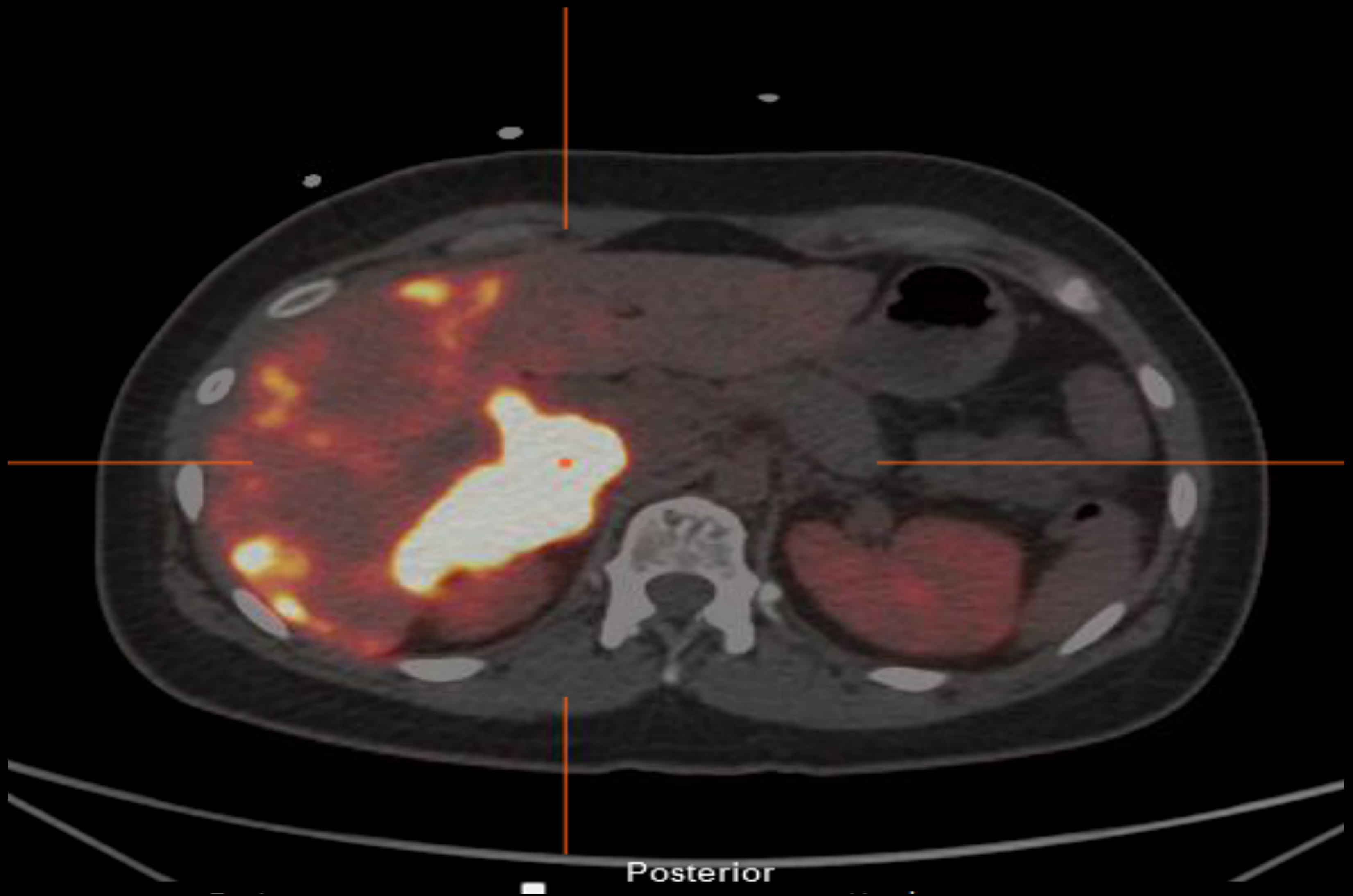
Wolfgang Weber performed a head to head comparison of the radiolabeled sst antagonists ^{177}Lu-JR11 against an sst agonist ^{177}Lu-DOTATATE.
A favorable tumor-to-organ dose ratios were found.

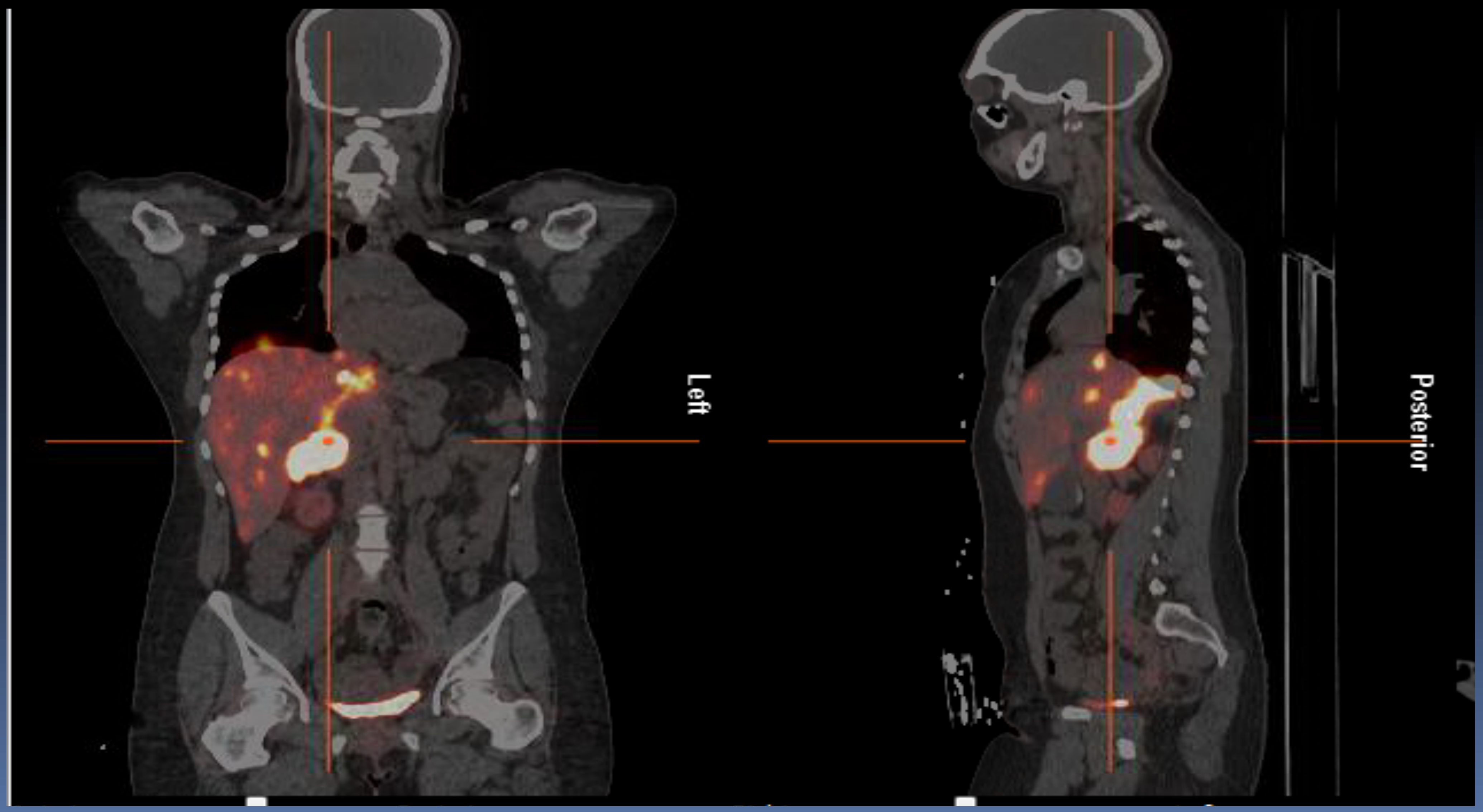
Wild D, Fani M, Fischer R, Del Pozzo L, Kaul F, Krebs S, Fischer R, Rivier JE, Reubi JC, Maecke HR, Weber WA. J Nucl Med. **Comparison of somatostatin receptor agonist and antagonist for peptide receptor radionuclide therapy: a pilot study.** 2014 Aug;55(8):1248-52.

Wolfgang Weber

Joe O'Donoghue

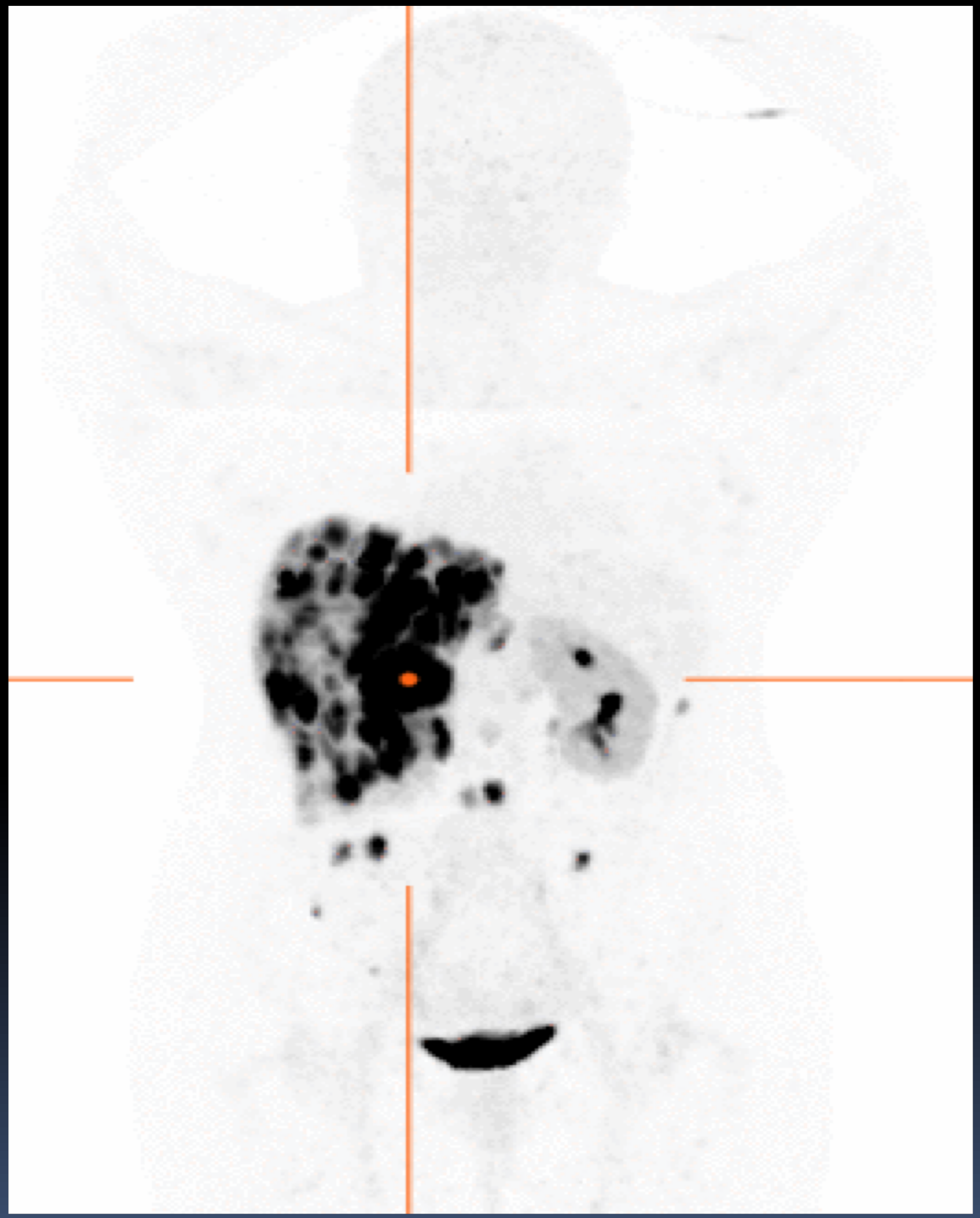
^{68}Ga-DOTA-JR11





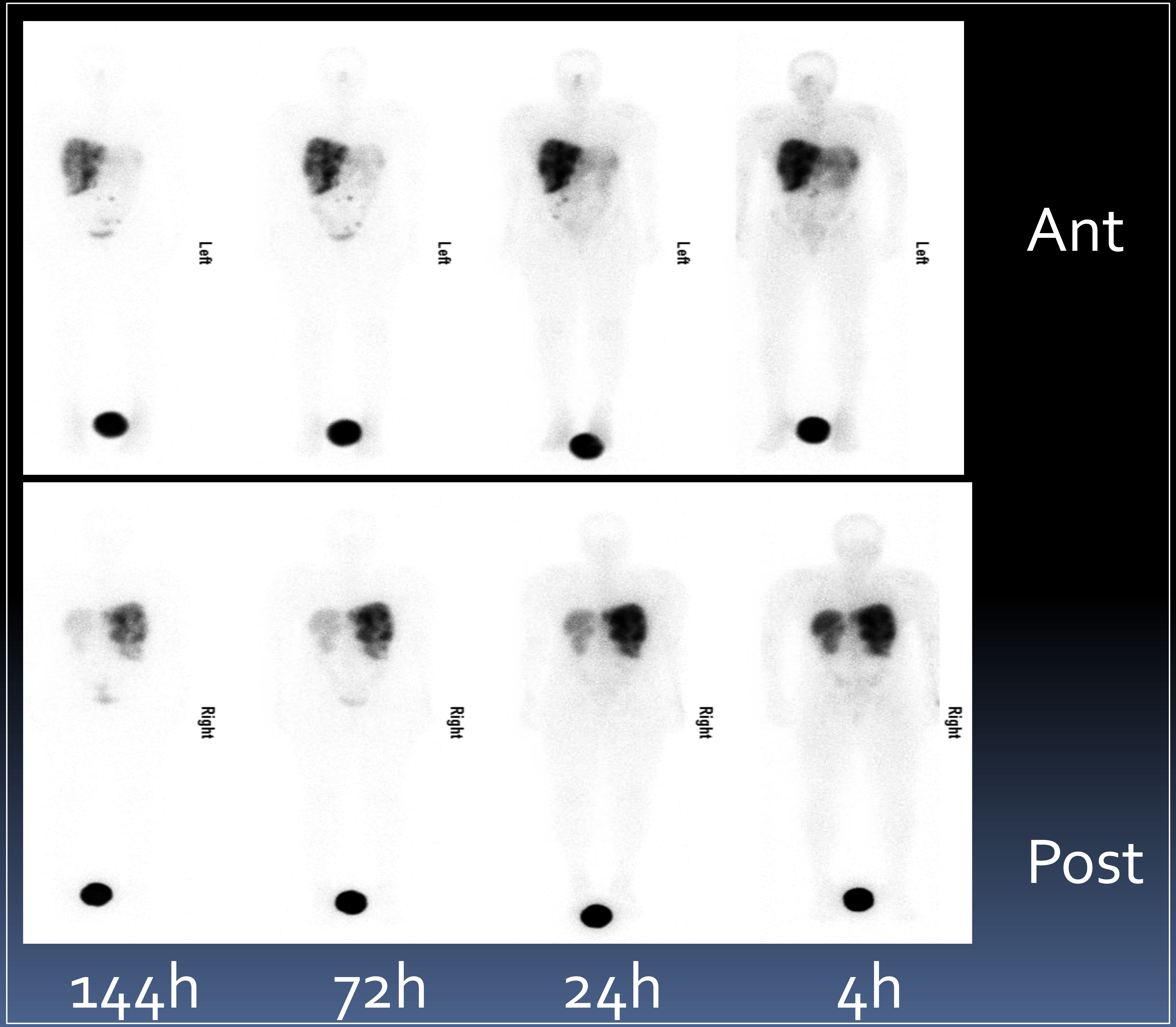
Administered Activity: 4.4 mCi (163MBq)

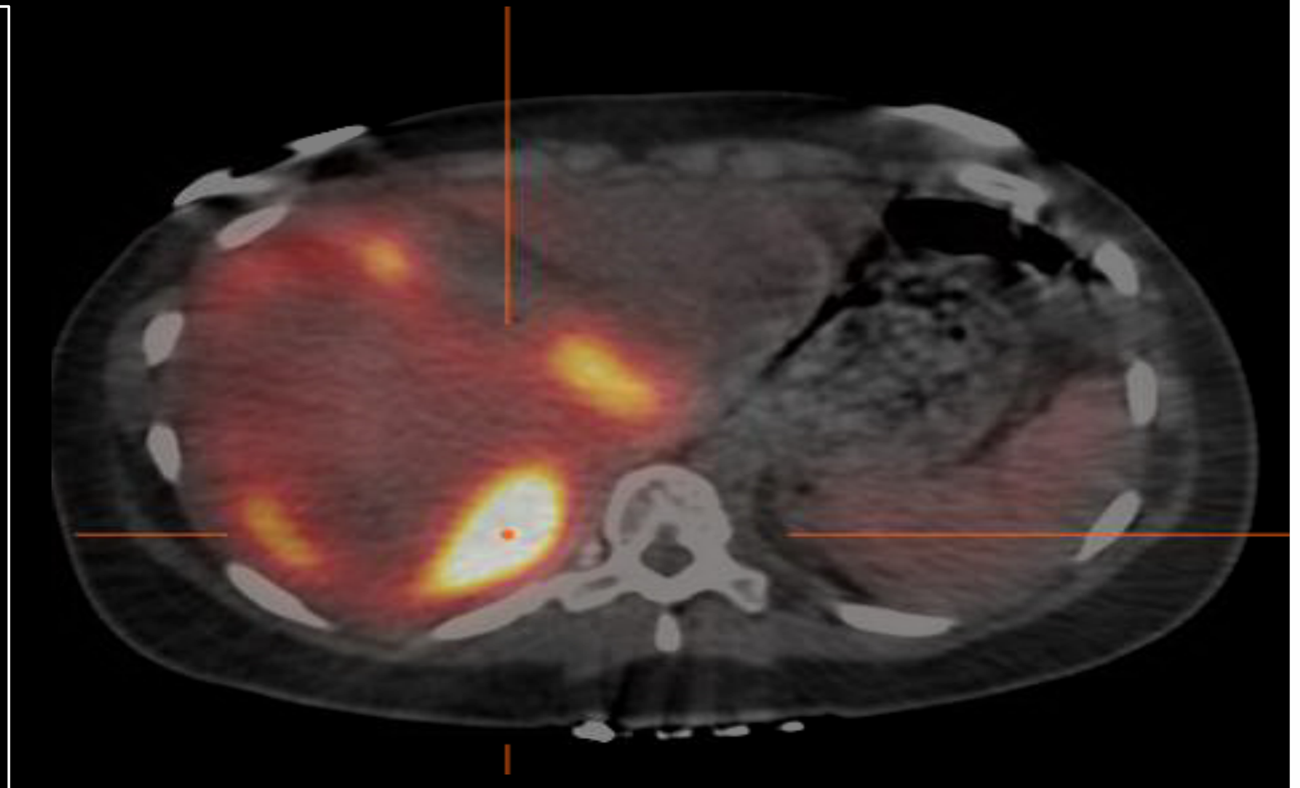
Acquired 60 min pi
3 min per bed
Q.clear recon (350)

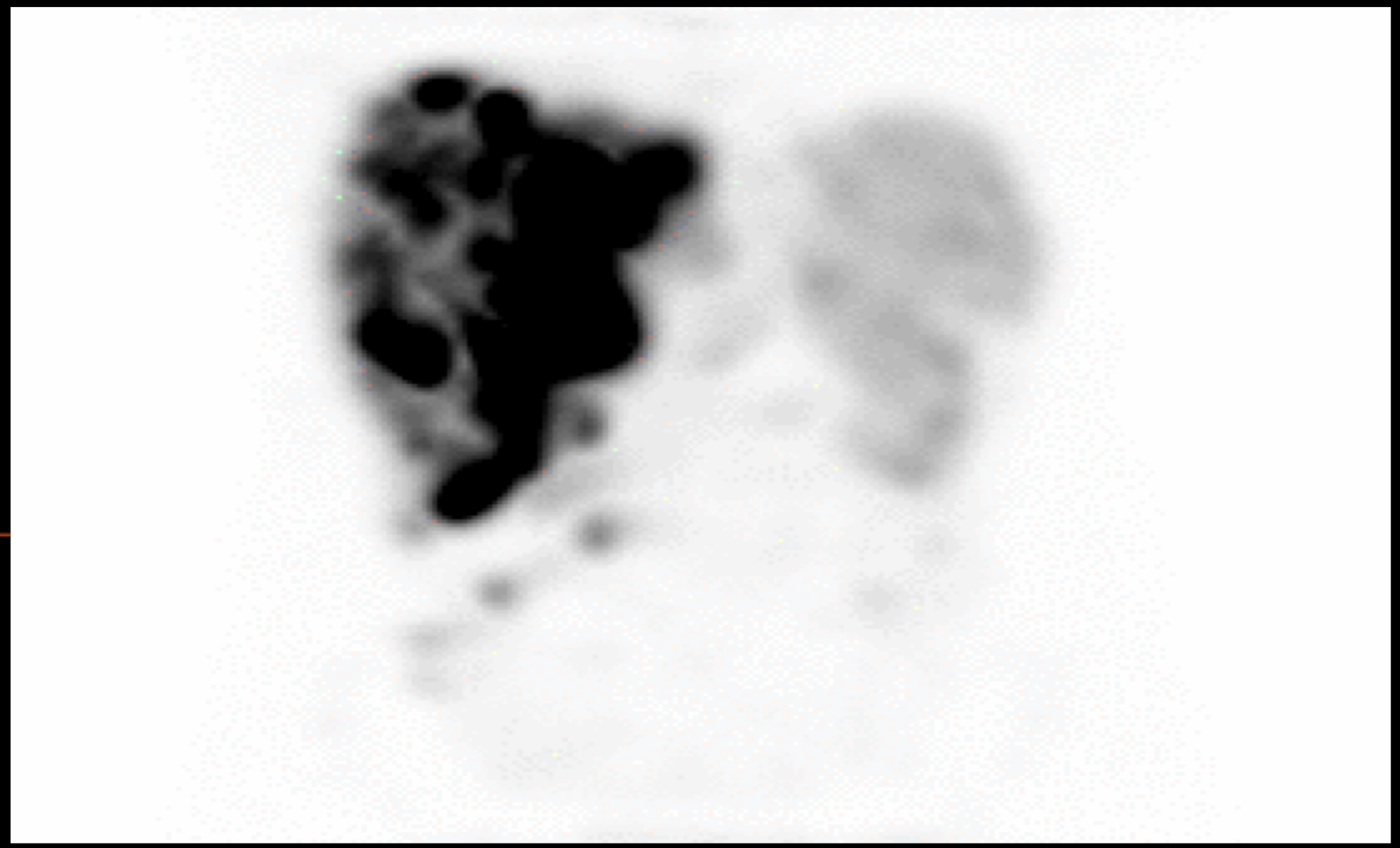


^{177}Lu-DOTA-JR11

Dosimetry Administration: 49 mCi (**1.81 GBq**)







Projections for Therapy:

Activity limits: 789 mCi (RM); 861 mCi (Kidney)

29 GBq **32 GBq**

Index Lesion: 22 cGy/mCi

Lesion dose @ 200 mCi: 44 Gy

Lesion dose @ 789 mCi: 174 Gy

Part 3 - Antibody Theranostics

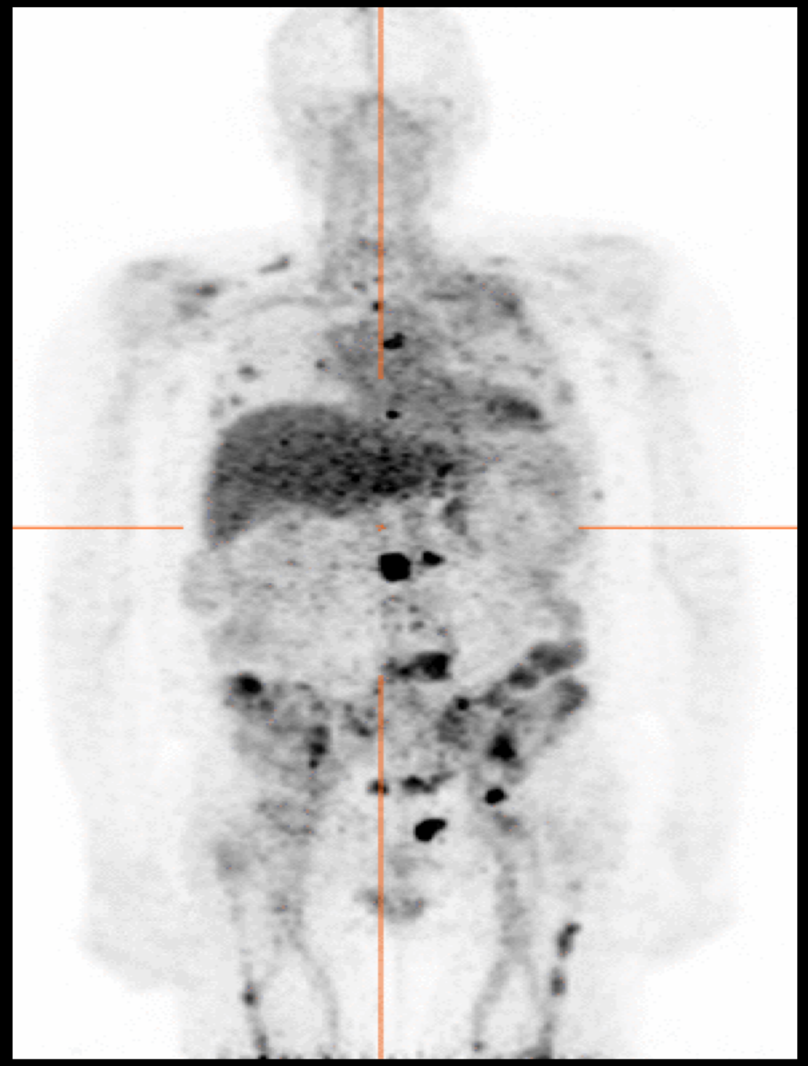
Long-lived β^+ emitting (^{89}Zr and ^{124}I) radionuclides for ImmunoPET

- Required for imaging because of antibody kinetics

- Problematic for normal tissue dosimetry

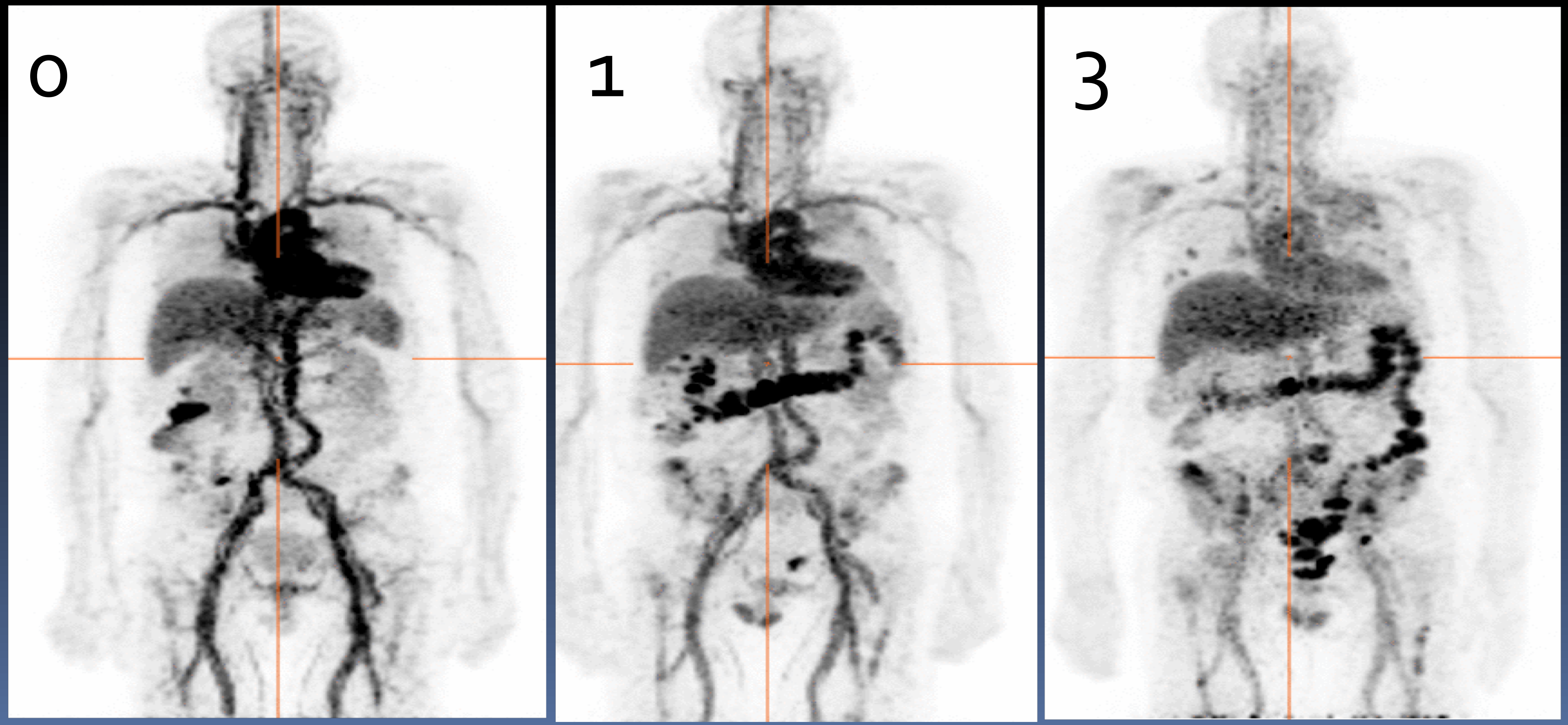
ImmunoPET: Timecourse

CRPC: ^{89}Zr-anti-STEAP antibody: 185 MBq (5mCi)



7 days pi

- Soon after injection all antibody is in the circulation - uninformative
- Slow clearance from circulation - metabolism/excretion and slow take up in target tissues – mostly uninformative
- Circulation continues to clear, ongoing take up in target tissues – informative but suboptimal
- Circulation almost clear - antibody distribution reaches “final” state – maximally informative



Consequences for radiolabeled antibodies

- For solid tumors, even in the highest antigen density expressing tumors (CA-IX in renal cell carcinoma), radioimmunotherapy failed.

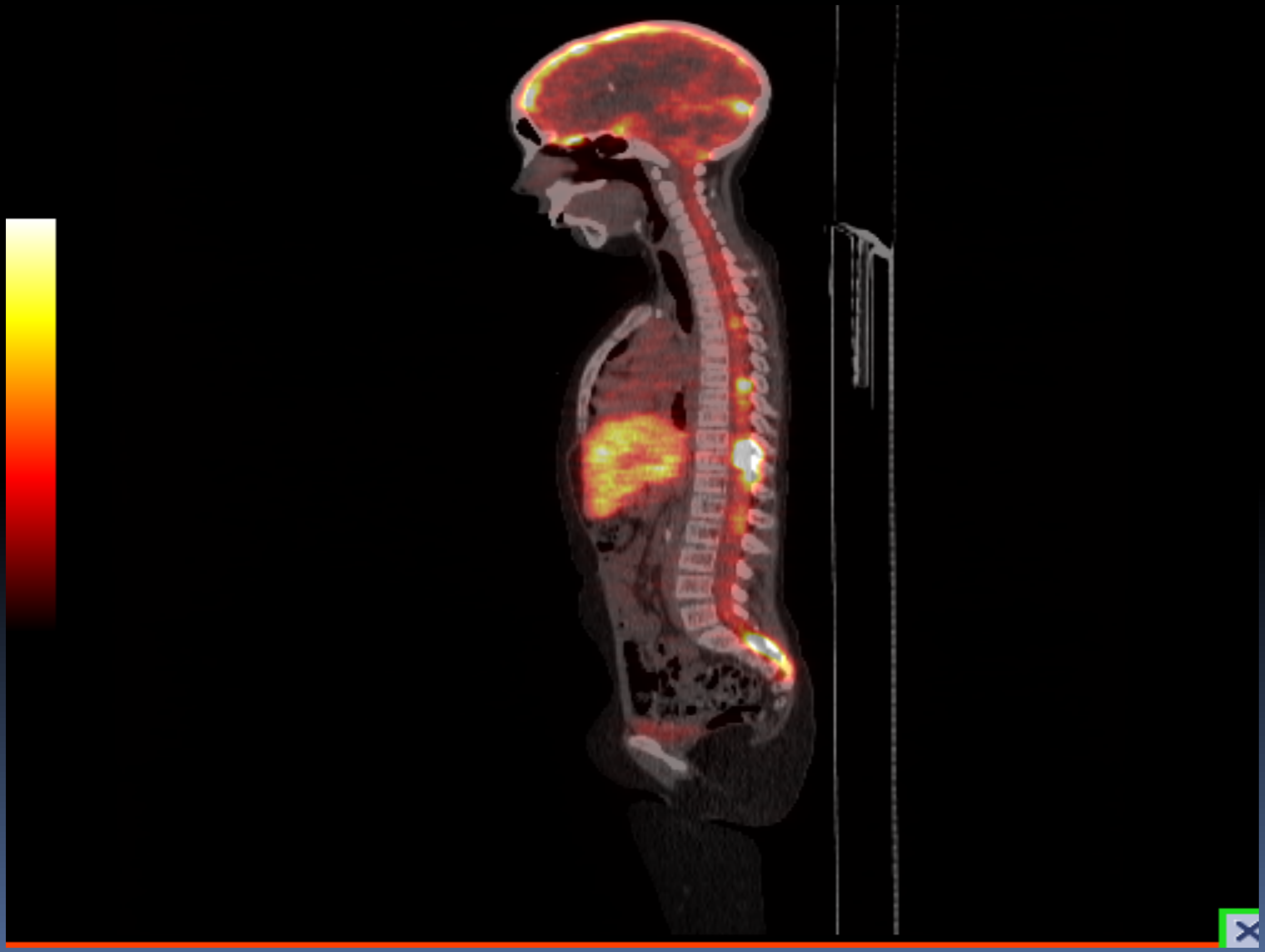
- So does it work or where might it work?

- We have seen such successive in radiosensitive tumors e.g. B-cell lymphoma (Bexxar and Zevalin)

How can we break out of this impasse?

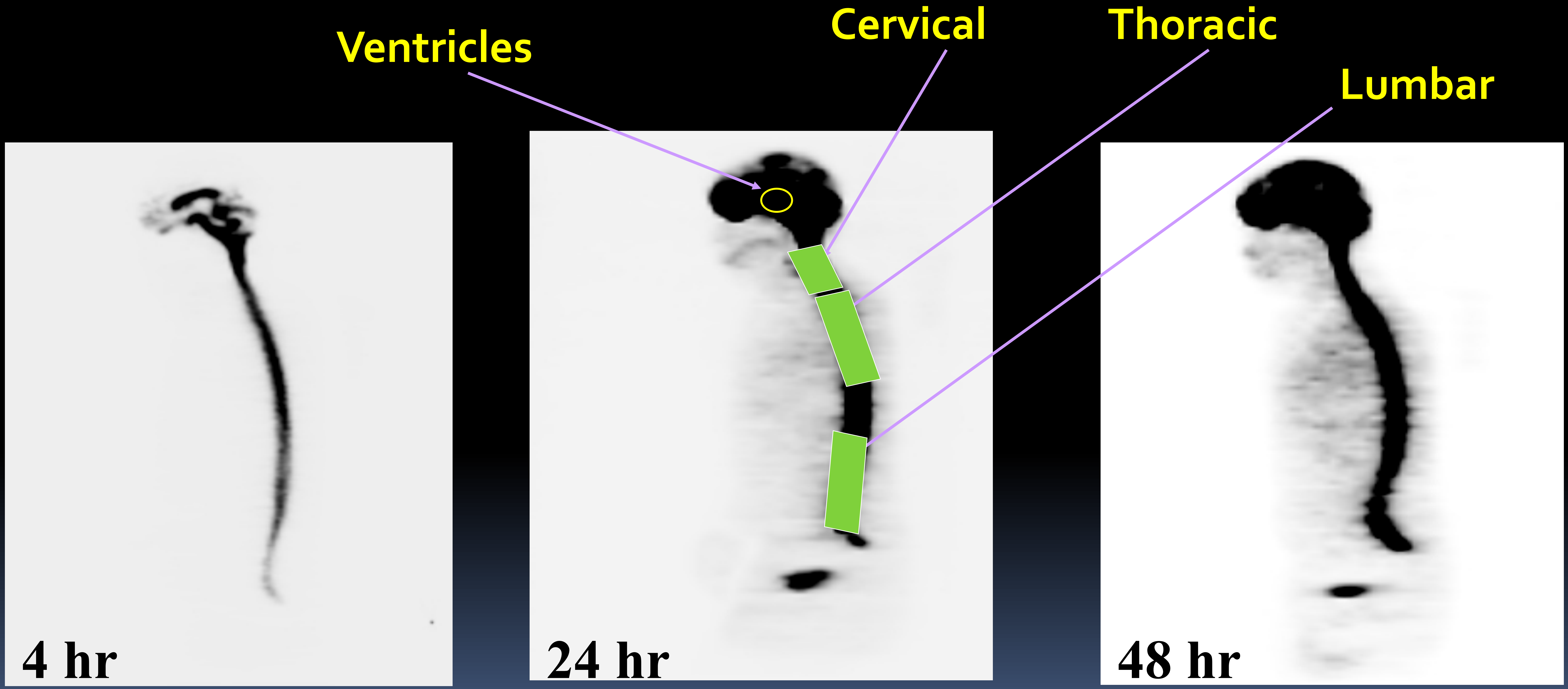
- Intra-compartmental / intra-tumor administration

Intrathecal antibody therapy for leptomeningeal Disease
Pre-Therapy Dosimetry using ^{124}I or ^{131}I labeled Ab



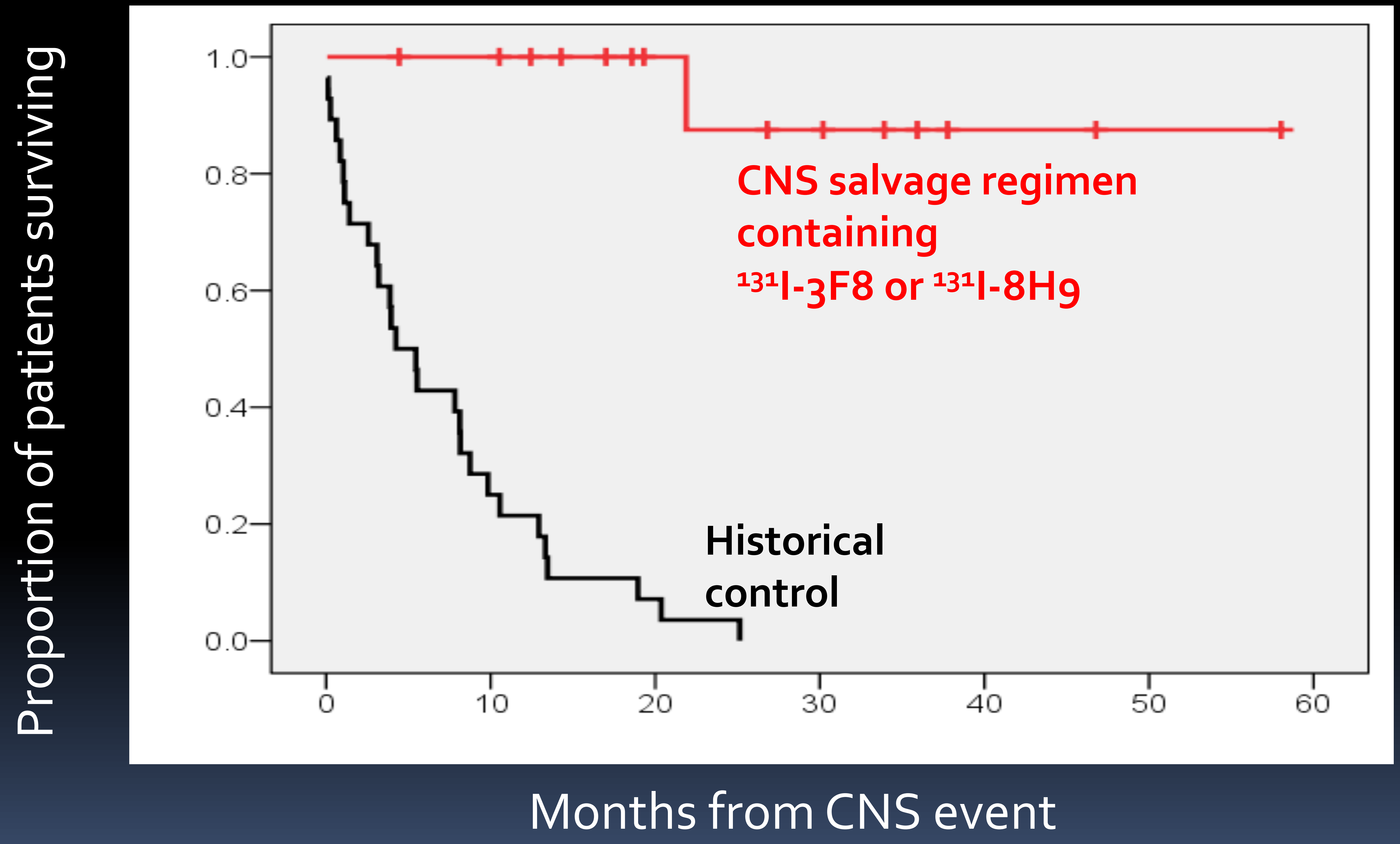
Kim Kramer

Serial whole body ^{124}I labeled Ab PET scans



Perform ROI analysis on each of the 3 time point images

Recurrent neuroblastoma metastatic to the CNS



Radiolabeled antibodies added to conventional chemoradiation therapy may dramatically improve outcome in this disease.

Kramer et al, J. Neurooncology, 2010;97(3):409-18. **Compartmental intrathecal radioimmunotherapy: results for treatment for metastatic CNS neuroblastoma.**

Summary

- The management of patients with poorly differentiated metastatic thyroid cancer is undergoing a revolution due to the emergence of new targeted drugs that cause thyroid re-differentiation.
- The use of peptide theranostic agents is a remarkable success story in radionuclide therapies that will continue to grow and improve.
- Early hiccups in the field of radioimmunotherapy could have heralded the end of an era. However, new radiolabeled antibody theranostic agents are emerging that combine immunoPET (^{89}Zr, ^{124}I) with therapy isotopes.
- The poor AUCs tumor/blood ratios (only 5 to 1 for macromolecular targeting agents) may be improved by intra-compartmental administration.
- This is a new era of personalized medicine where the quantitative capability of nuclear medicine may provide new therapeutic opportunities.