The Use of Novel Radiotracers in PET
Potential Applications for Dose Painting

John Humm, PhD

Dept. of Medical Physics,
Memorial Sloan-Kettering

AAPM

Session: Practical Considerations of PET

Thursday 22nd July

Which tracers make sense for radiobiologically driven dose painting?

(1) FDG since it provides a general guide to metabolically active tumor

(2) FLT – provides a signal proportional to the tumor cell proliferation.

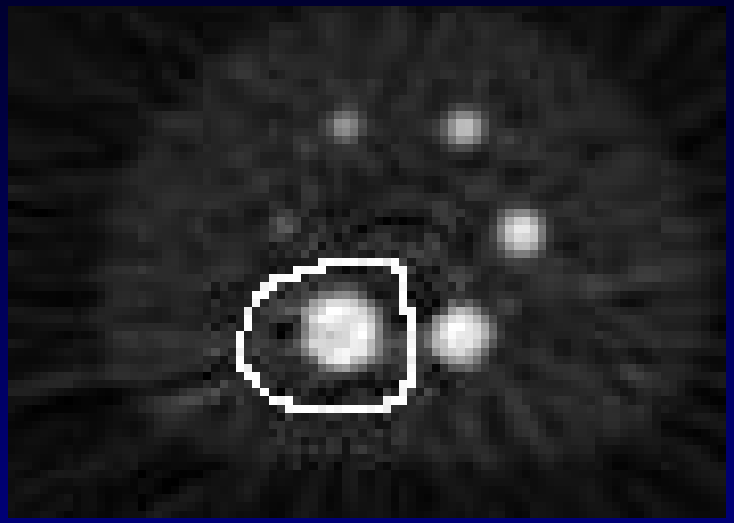
(3) FMISO – provides the distribution of intra-tumoral hypoxia i.e. pockets of radioresistance

(4) Tumor specific Antibodies e.g. ^{124}I-A33,

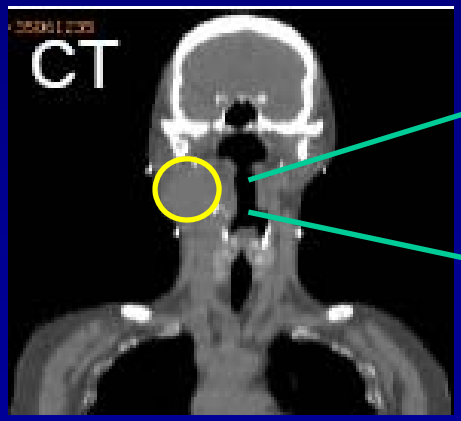
What might be the additional value of PET

- Detection of metastatic spread / staging
- Definition of viable target
- To measure functional response
- Biologically based IMRT

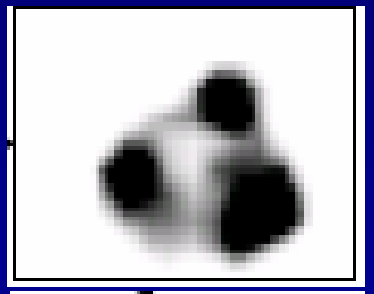
How do we define ROIs on PET Images?
PET Image Segmentation



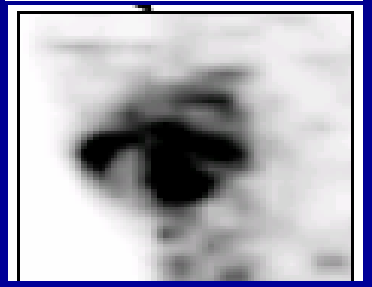
This is all well and good provided the distribution of tracer is uniform

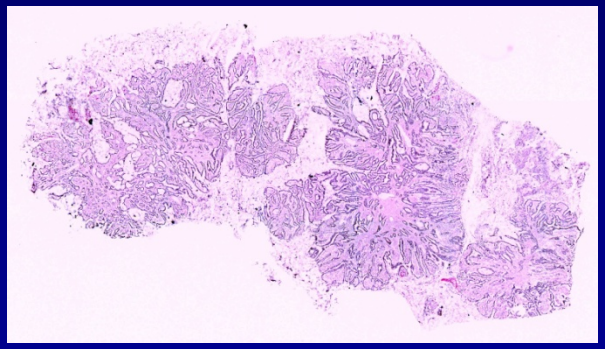


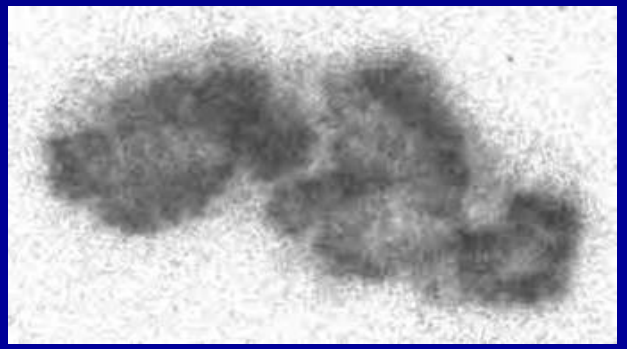
FDG



FMISO



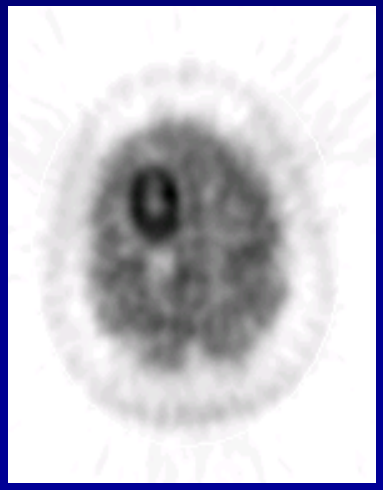




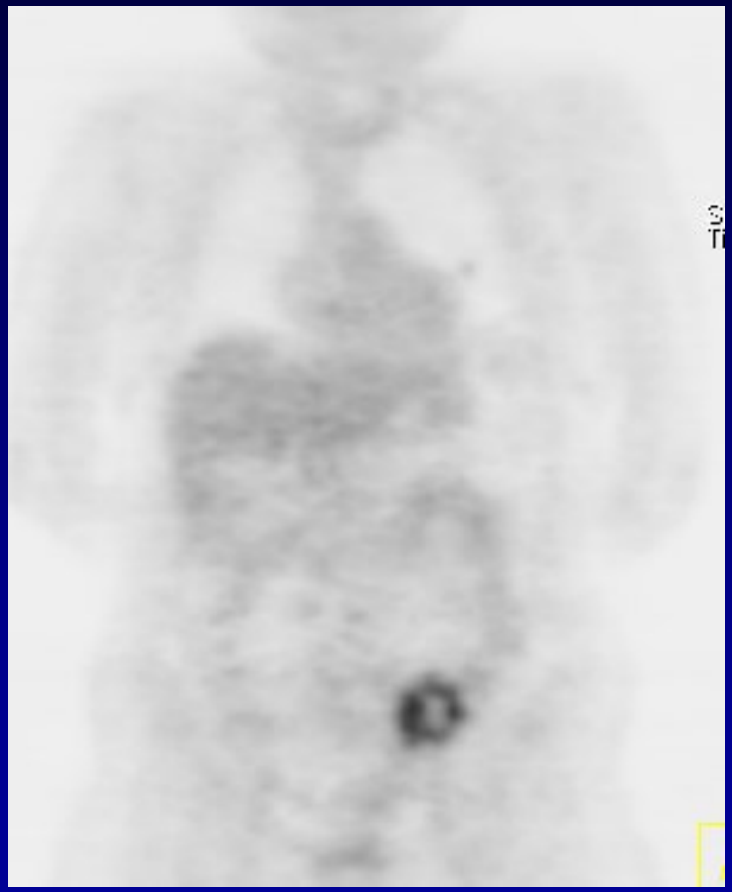
Imaging Glucose Metabolism

FDG Uptake in Different Tumors

Lung



Brain



Colon

Rectal

What determines FDG Uptake Heterogeneity?

- Fraction of tumor/stromal cells
- Proliferation rate
- Inflammatory component
- Hypoxia
- Other

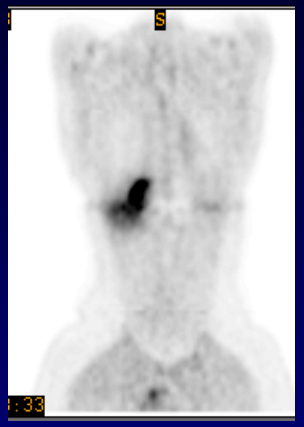
Prostate Cancer FDG after single high dose single fraction

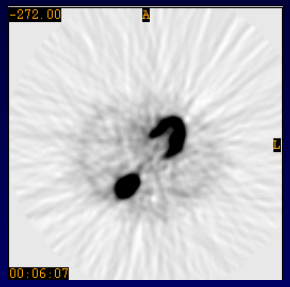
FDG
Pre RT

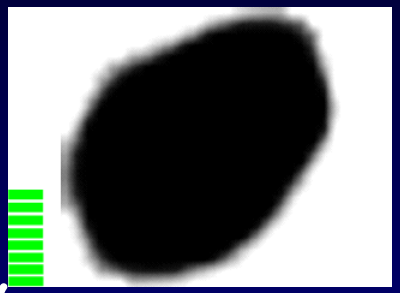
FDG
Post RT

P.I. Dr Zelefsky

Monitoring Radiation Response in Lung Cancer

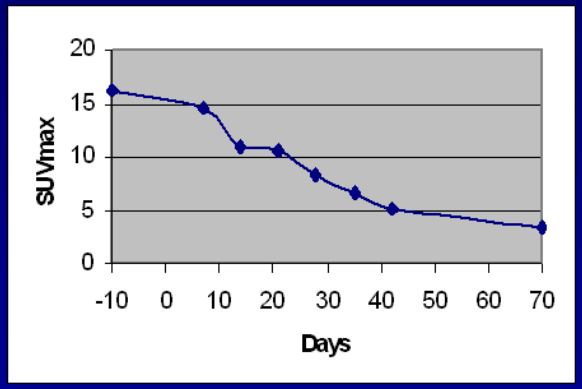


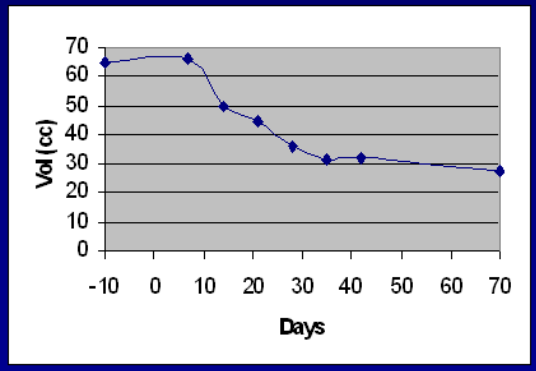




SUV x V

Gy





SUV_{max}

Volume

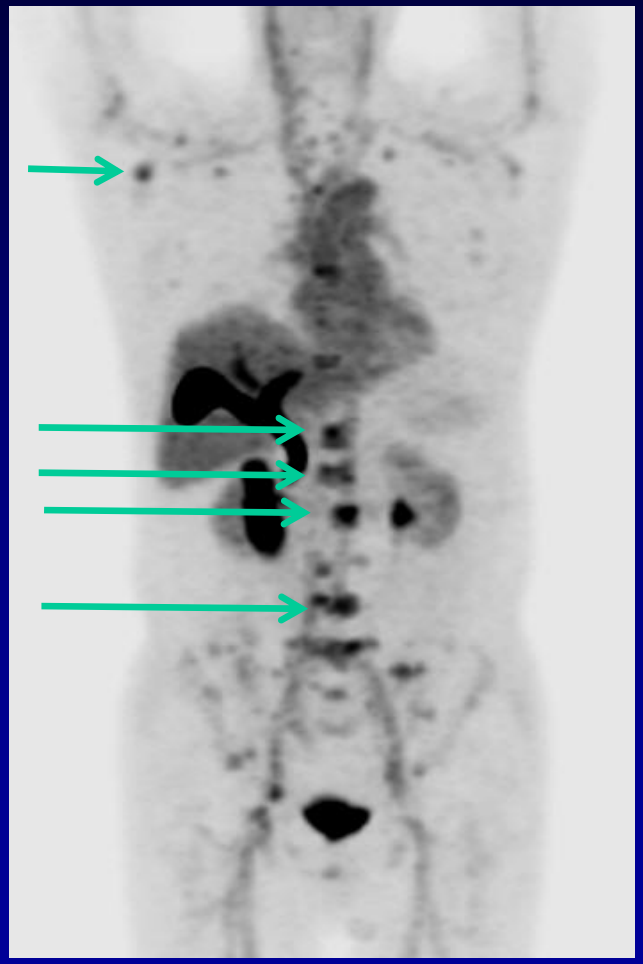
Erdi et al, Eur J Nucl Med. 27(7):861-866, 2000.

Different tracers – different results
FDG vs FDHT

FDHT = fluorodihydrotestosterone - A steroid hormone that binds to the androgen receptor involved in signaling tumor cell division

^{18}FDHT Pre and Post Treatment AR directed therapies

FDHT Jan 24 2008



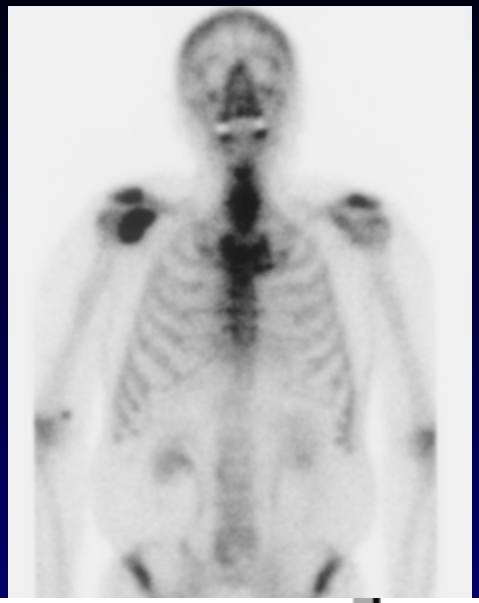
FDHT Feb 25 2008

Scher et al, Lancet. 2010; 375(9724):1437-46.

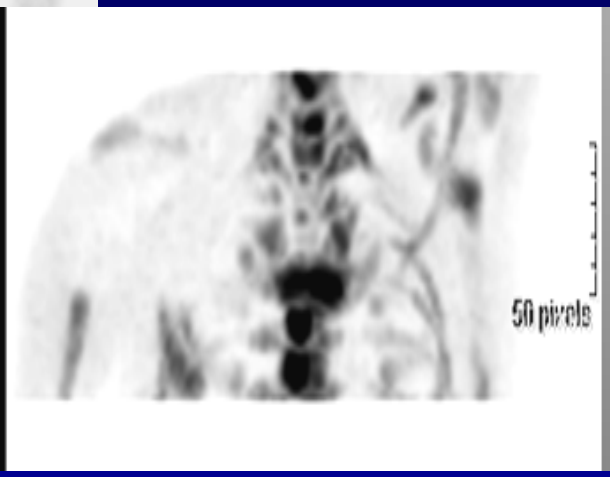
Imaging Cellular Proliferation

FLT for studying radiation response to high dose single fraction RT - prostate bone met

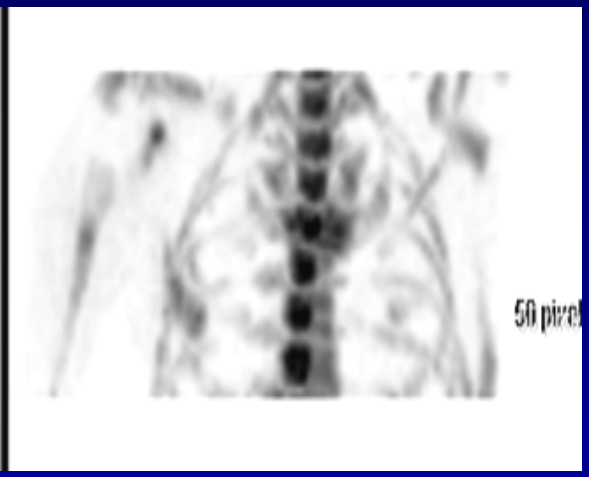
Bone scan



FLT scan pre RT



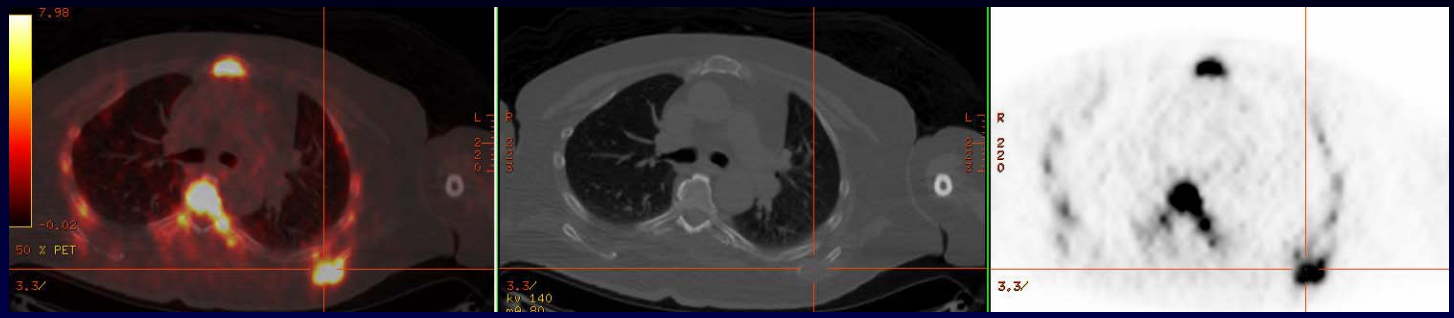
FLT scan 2 days post 24 Gy single fraction RT



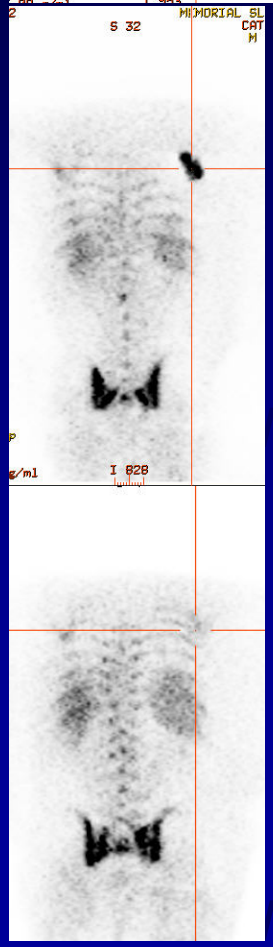
FLT scan 4 weeks post RT

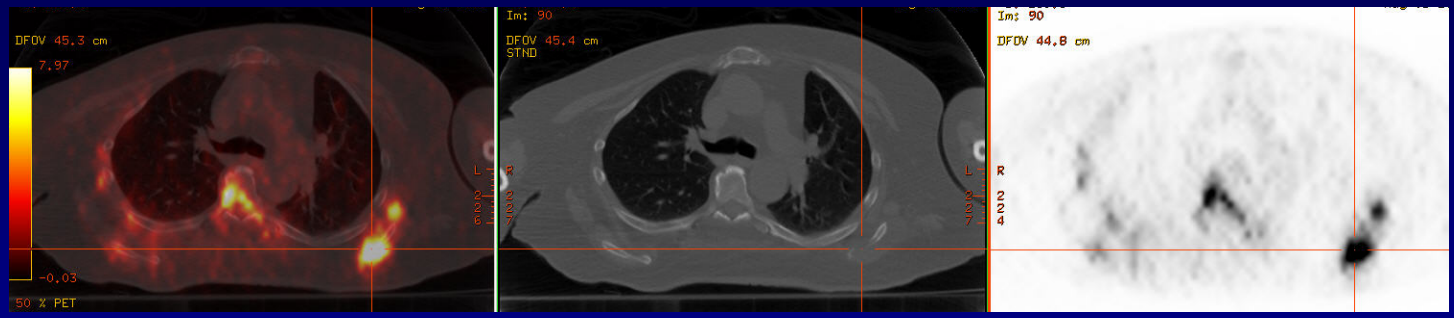
P.I. Dr Zelefsky

FLT: L inferior scapula

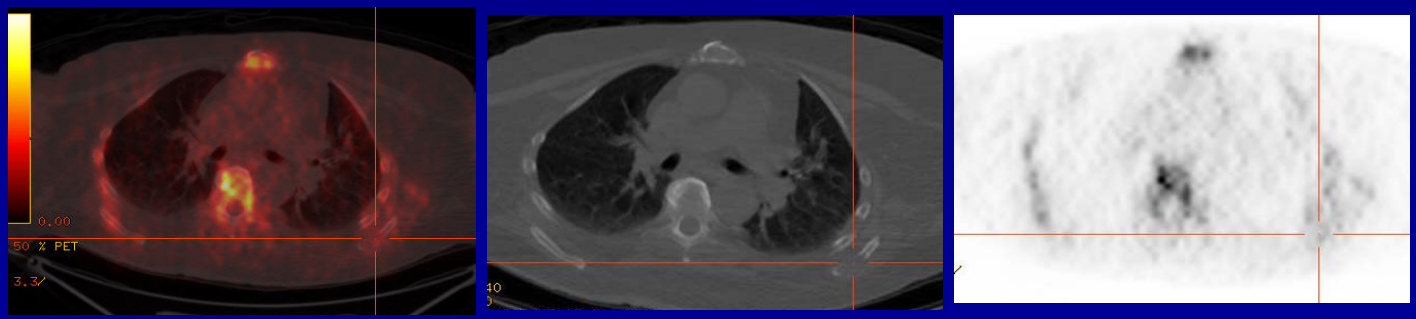


7/25: before RT SUV 19.5





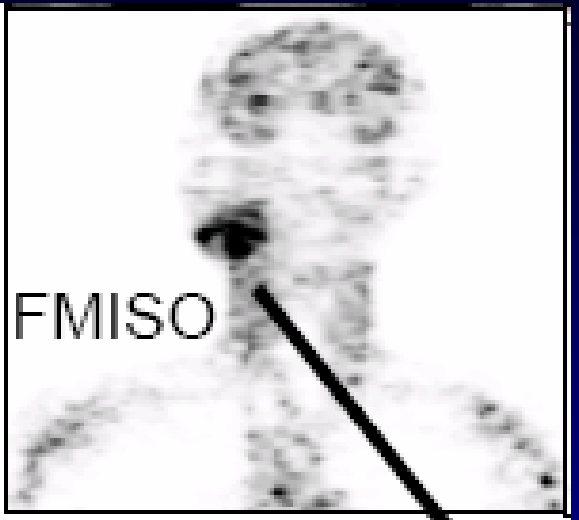
08/01: one day after RT SUV 12.5

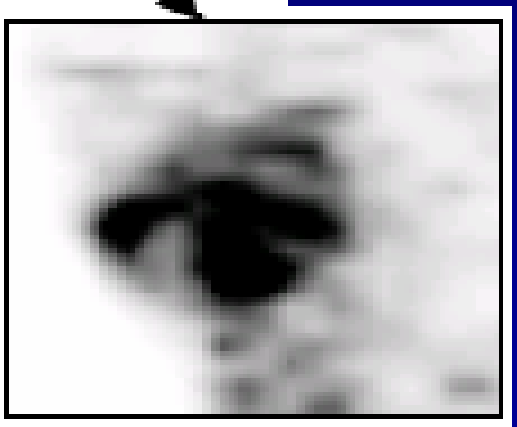


08/22: 21 day after RT SUV 1.5

Hypoxia Imaging

^{18}F-FMISO Scans of H&N Patients

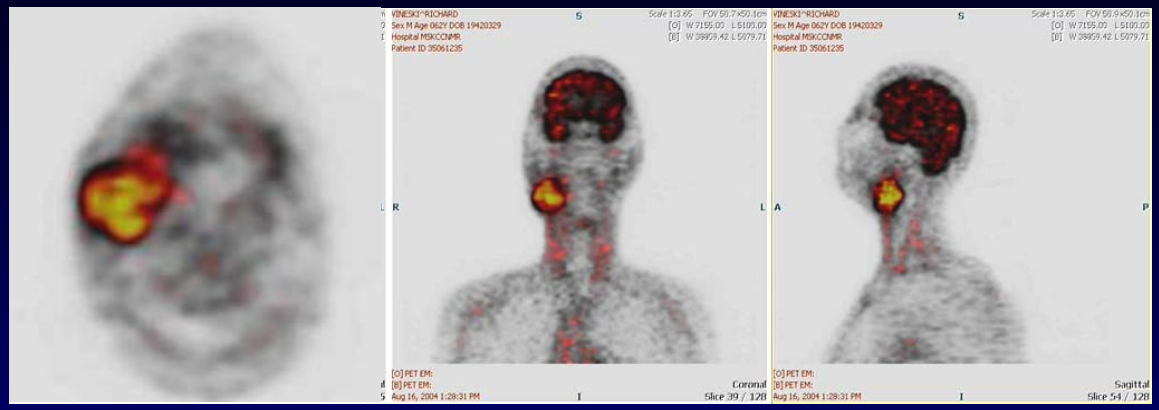




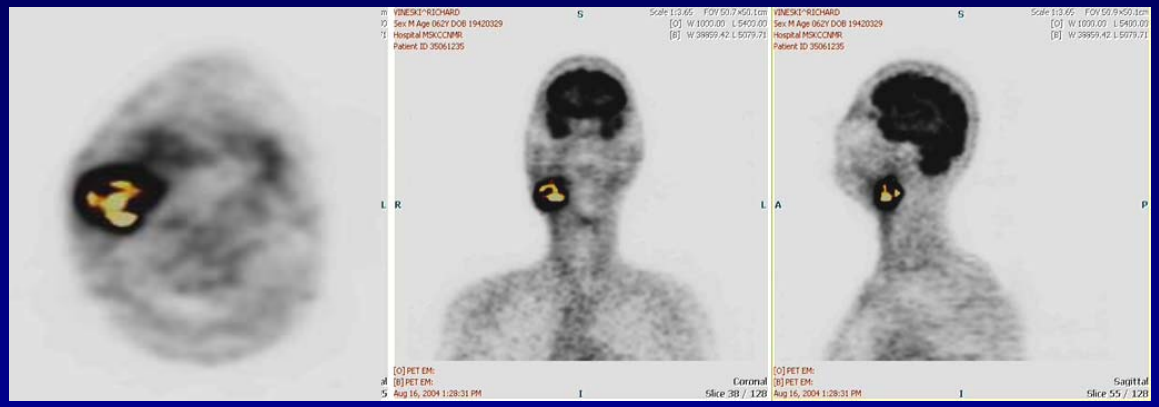
Lee et al, Int.J.Radiat.Onc.Biol.Phys. 2008 70:2-13.

Effect of Threshold

FDG-FMISO2



FDG-FMISO2
T/B = 1.2

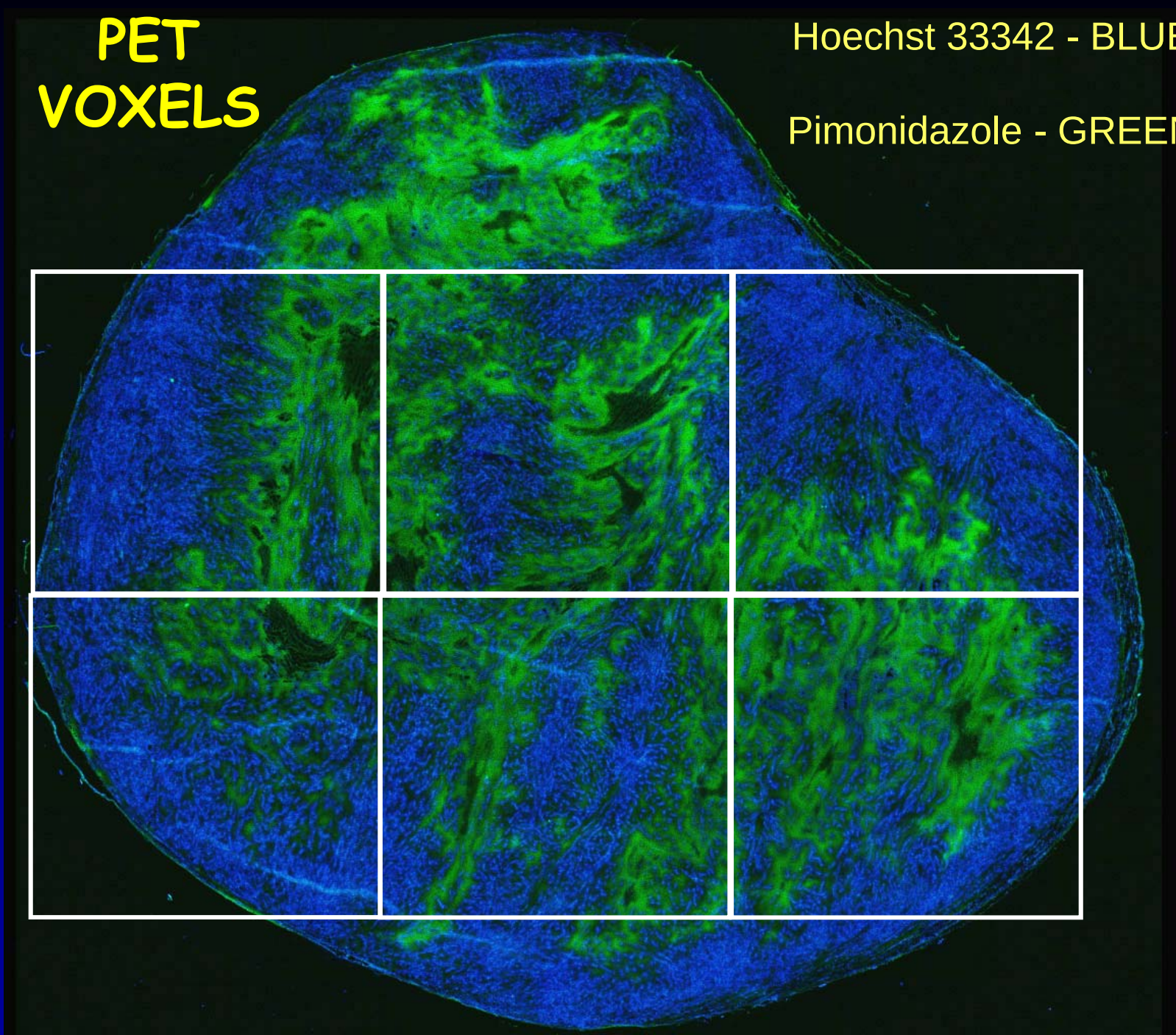


FDG-FMISO2
T/M = 1.4

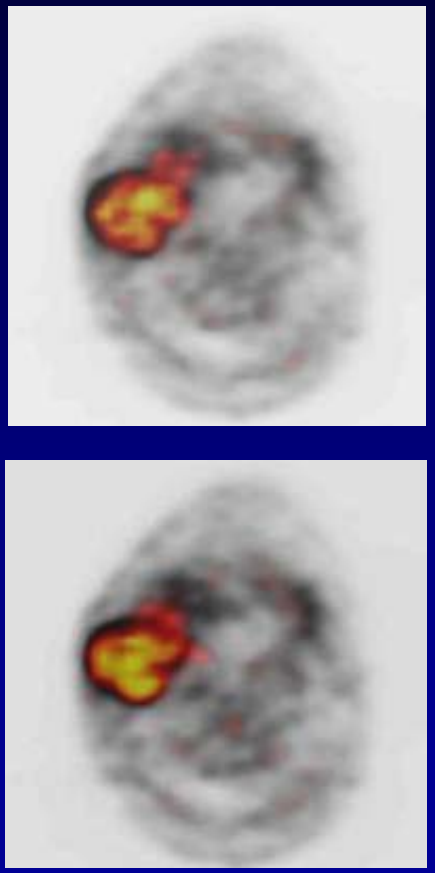
PET VOXELS

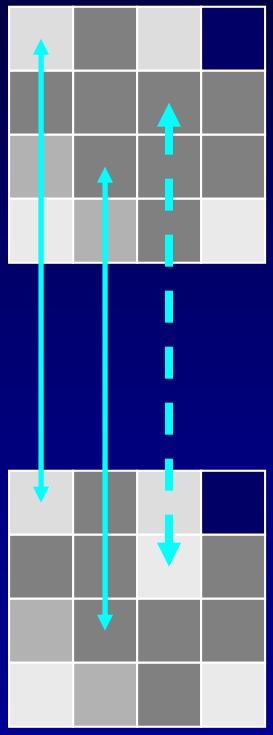
Hoechst 33342 - BLUE

Pimonidazole - GREEN



How reproducible are two ^{18}F-FMISO studies performed 3 days apart



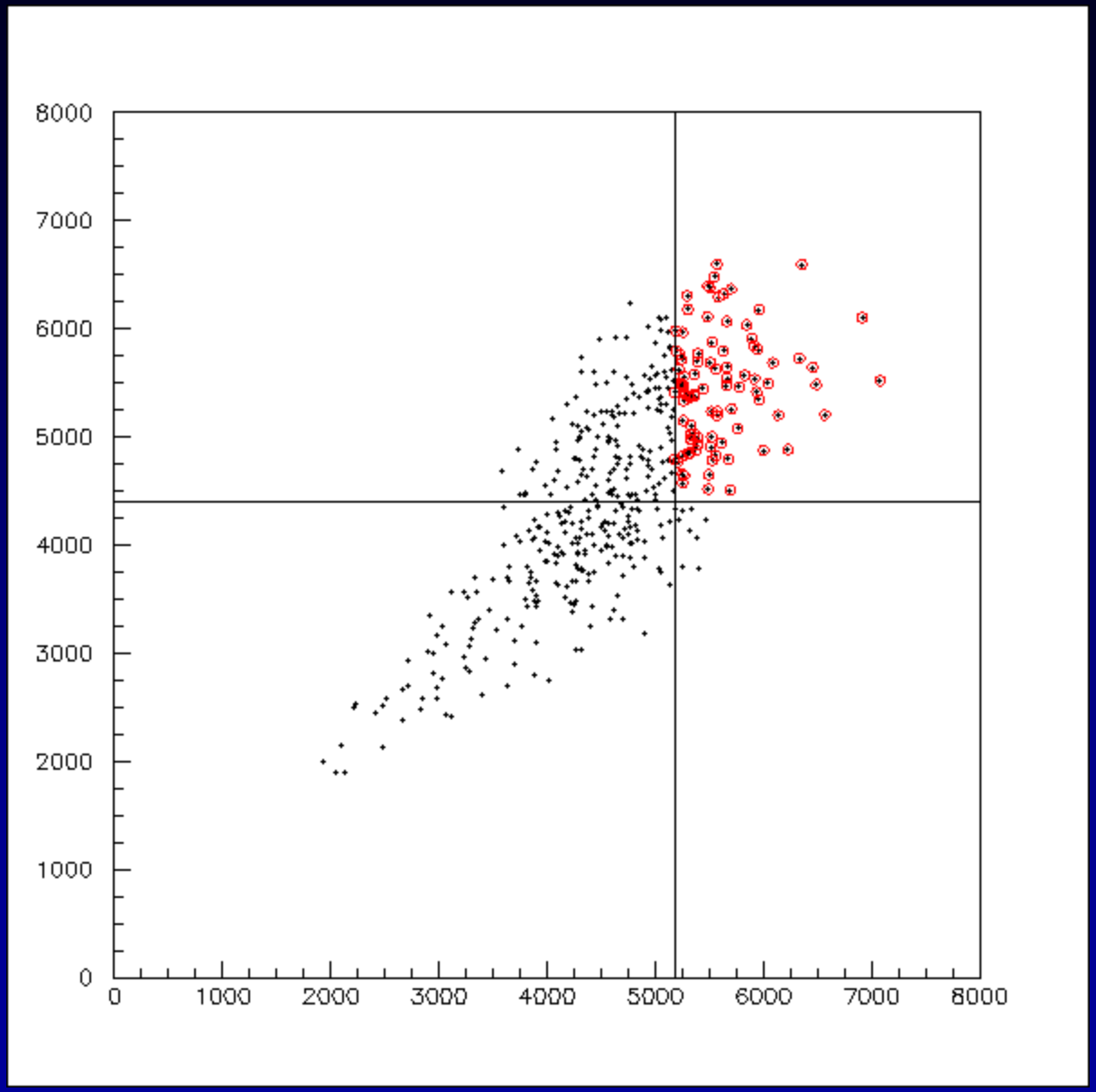


Day0
FMISO image

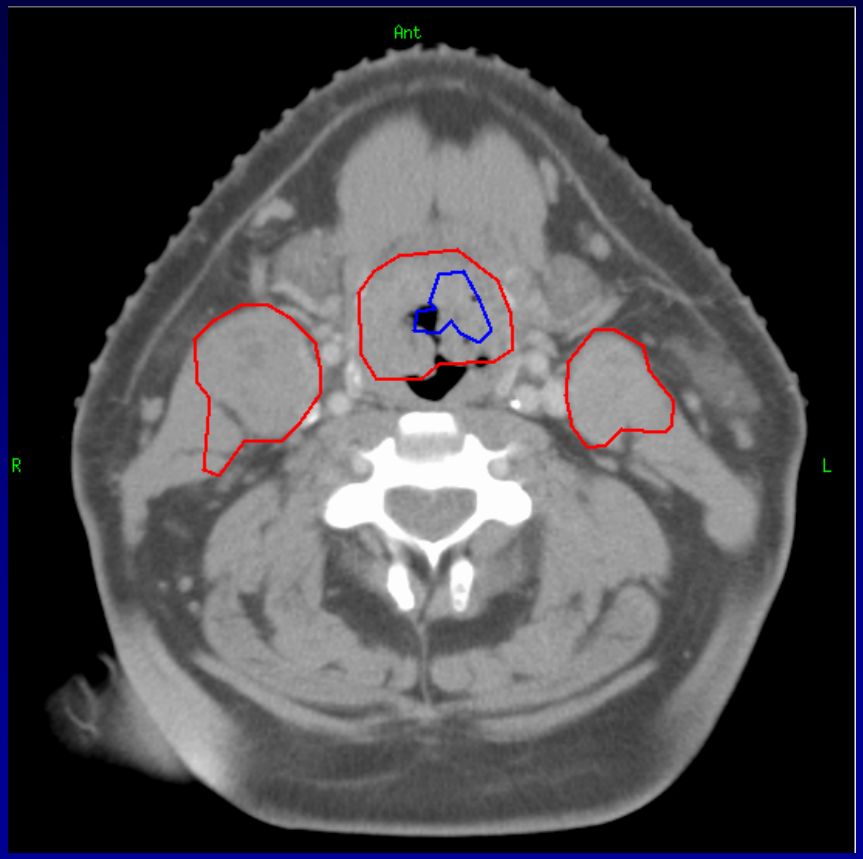
Day3
FMISO image

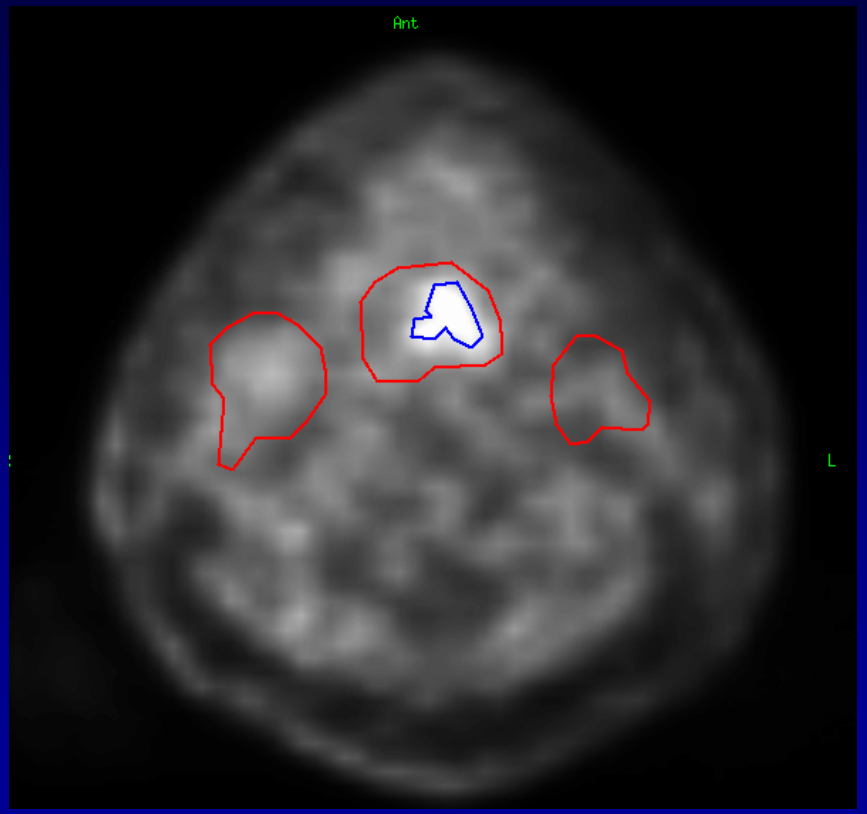
Plot registered voxel intensities from 1st FMISO image with the 2nd

FMISO2 vs FMISO1



The concept of a GTV_h

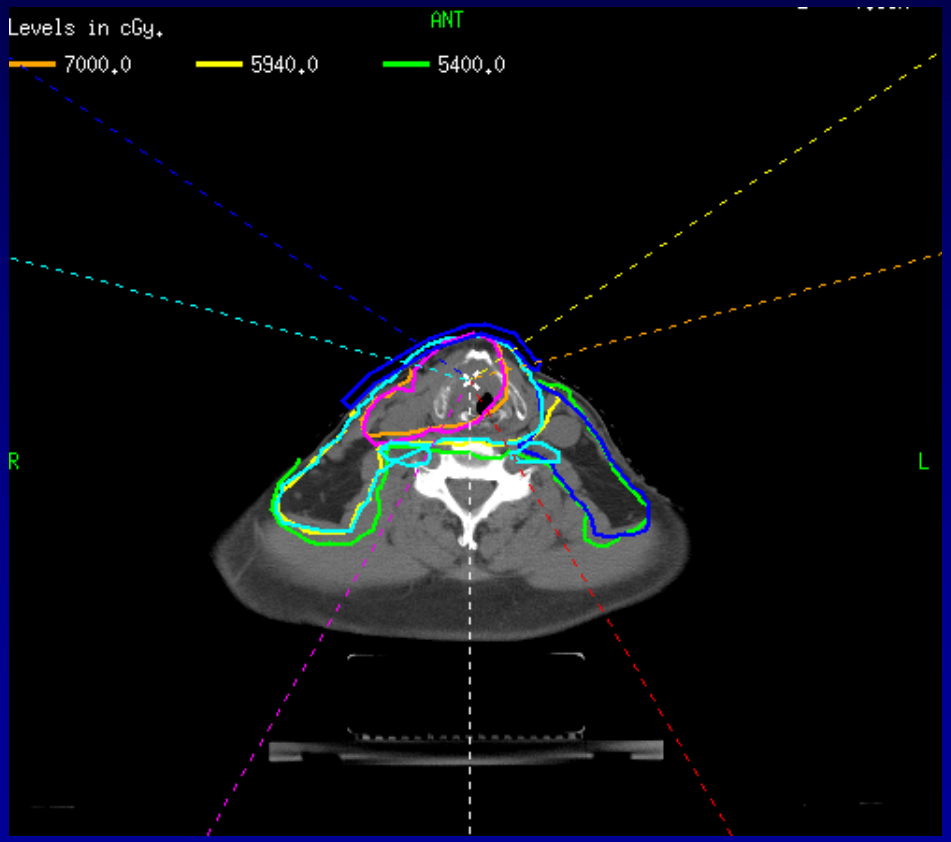




Lee et al, Int.J.Radiat.Onc.Biol.Phys. 2008 70:2-13.

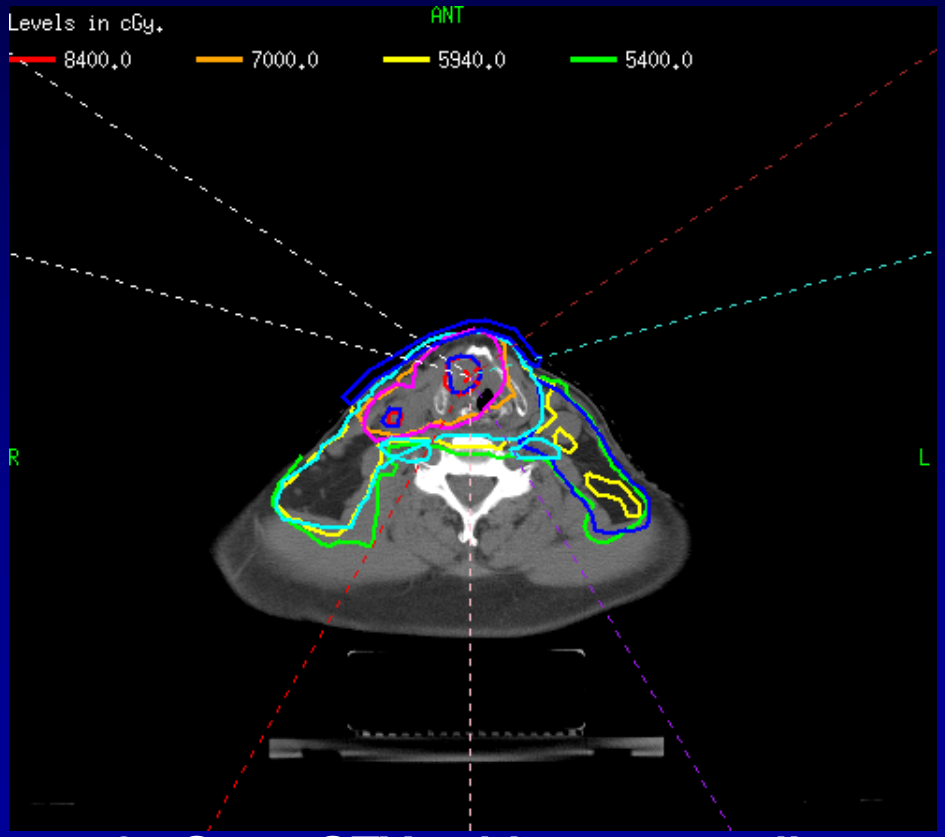
IMRT plan for a loco-regionally advanced supraglottic carcinoma:

Delivered Treatment Plan



70 Gy to GTV

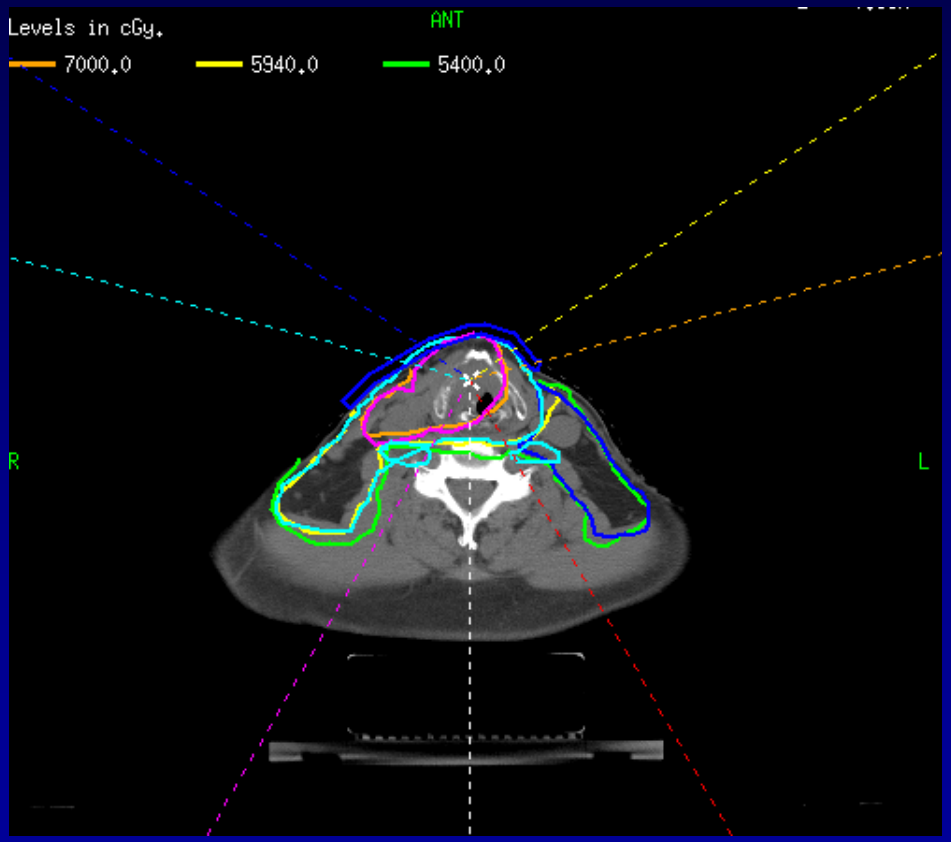
Hypothetical Plan escalating dose to the GTV_h



84 Gy to GTV_h without exceeding normal tissue tolerances

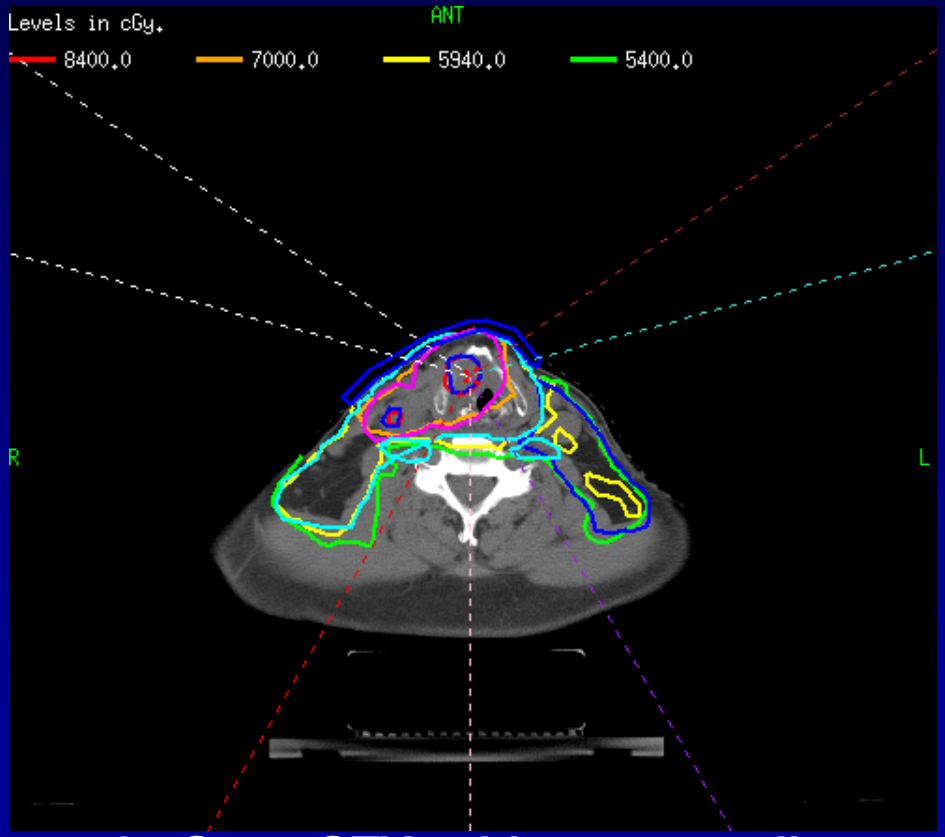
IMRT plan for a loco-regionally advanced supraglottic carcinoma:

Delivered Treatment Plan



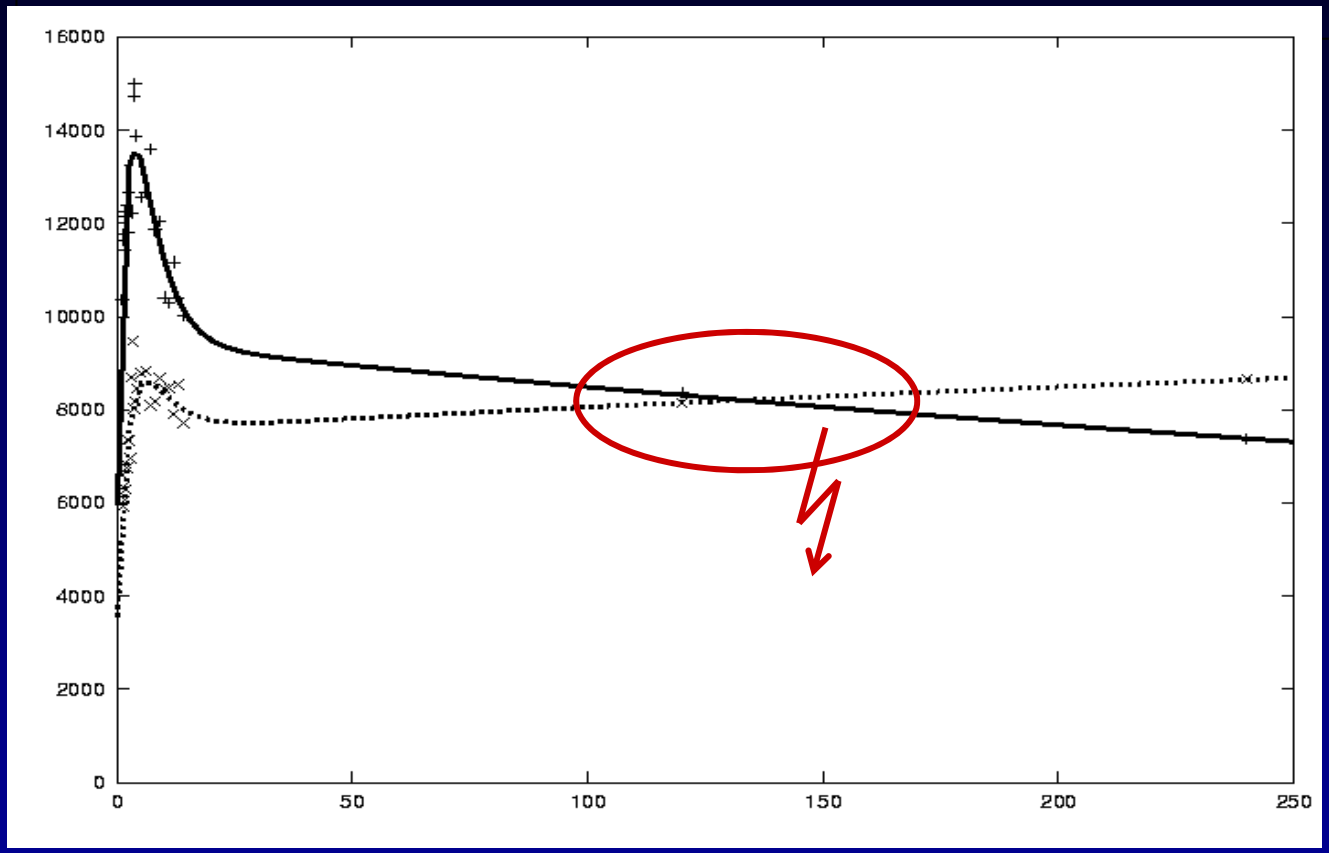
70 Gy to GTV

Hypothetical Plan escalating dose to the GTV_h



84 Gy to GTV_h without exceeding normal tissue tolerances

Analysis of ^{18}F-FMISO Dynamic PET



Hypoxia criterion

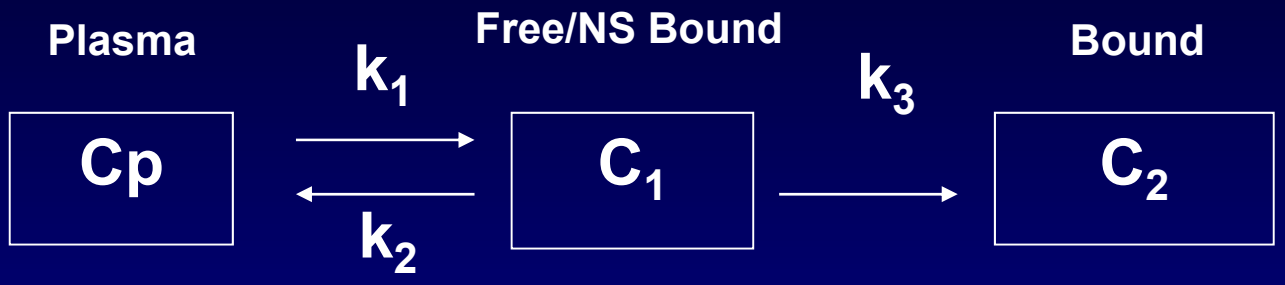
Tumor-Blood Ratio(T:B) ≥1.4

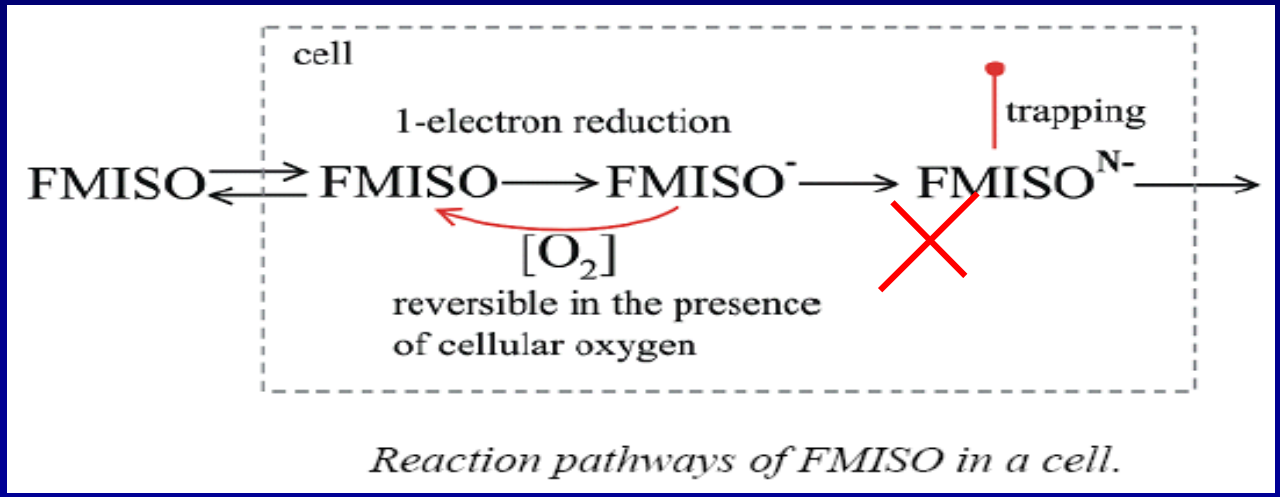
not reliable

Kinetic analysis of Time-Activity Curves (TAC) is necessary

Thorwarth et al, BMC Cancer. 2005 Dec 1;5:152.

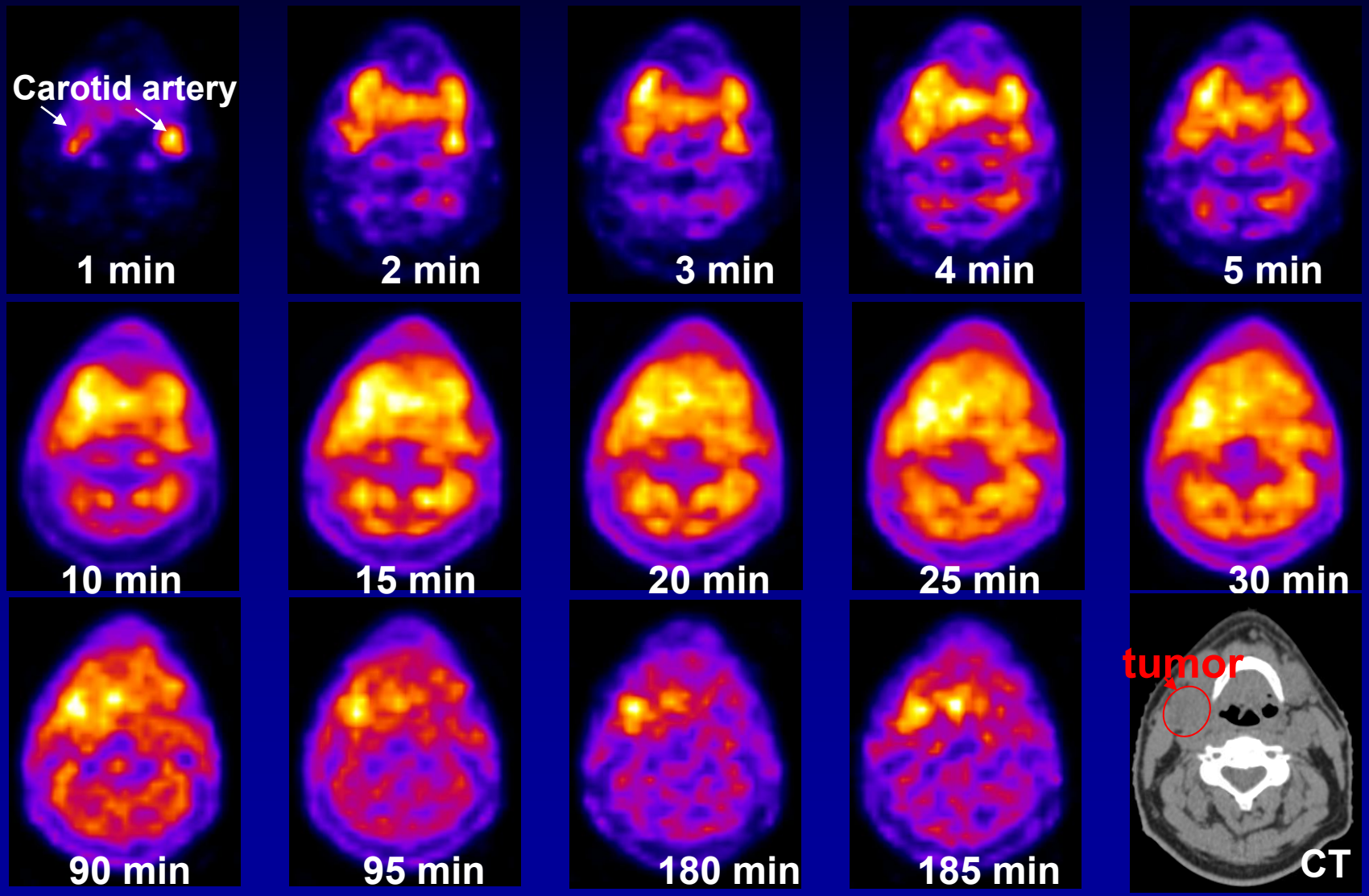
A compartmental model to mimic FMISO metabolism.



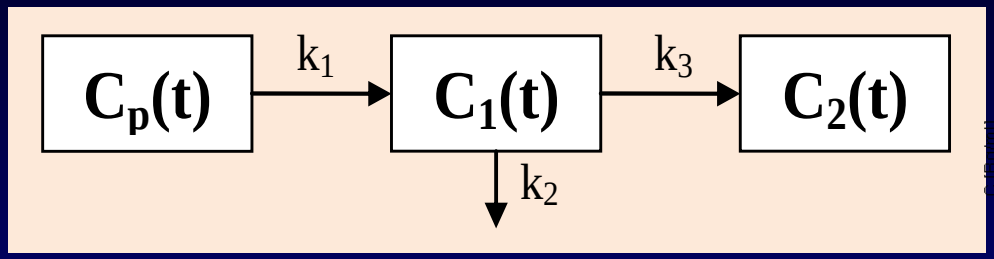


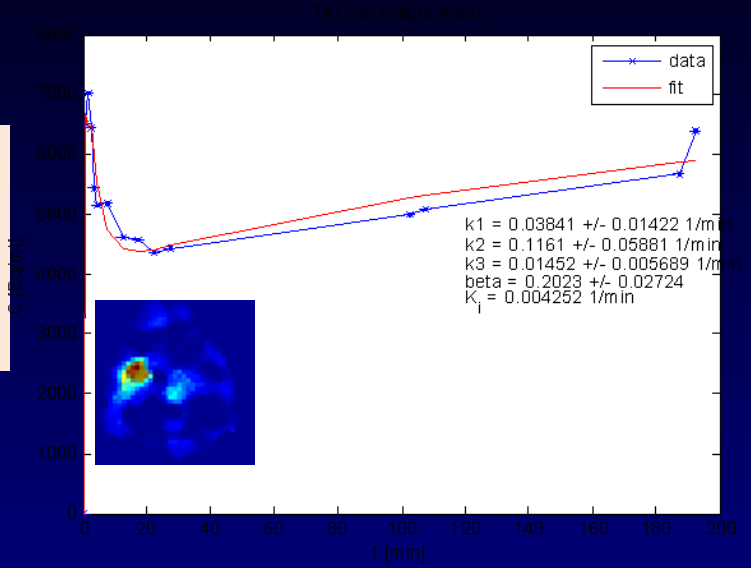
Reaction pathways of FMISO in a cell.

H&N Patient Dynamic PET Images

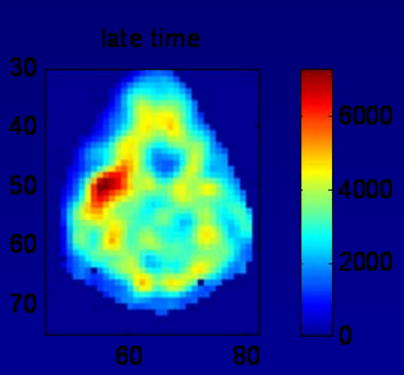


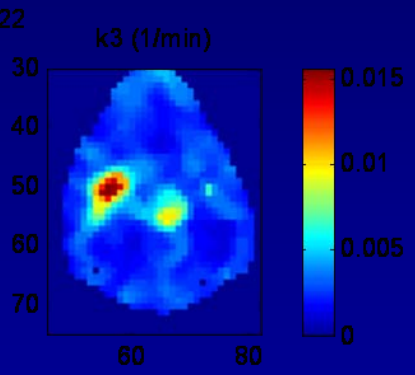
Parametric Images of ^{18}F-FMISO

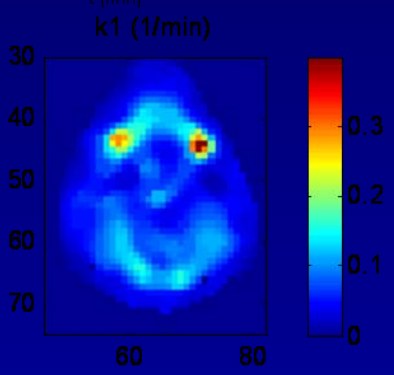




Concordance





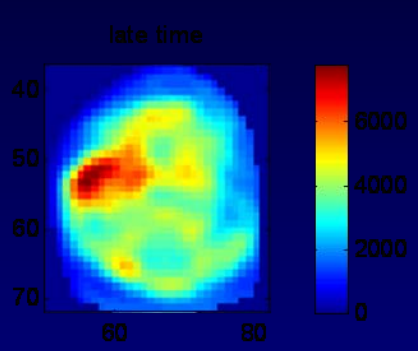


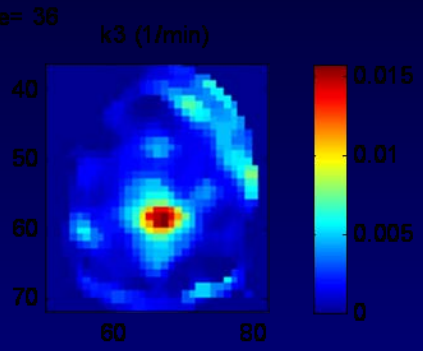
CT **3hr FMISO** **k3 map** **k1 map**

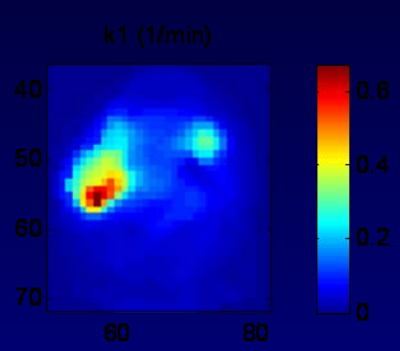
Wang et al, Phys Med Biol. 2009; 54: 3083-99.

Parametric Images of ^{18}F-FMISO

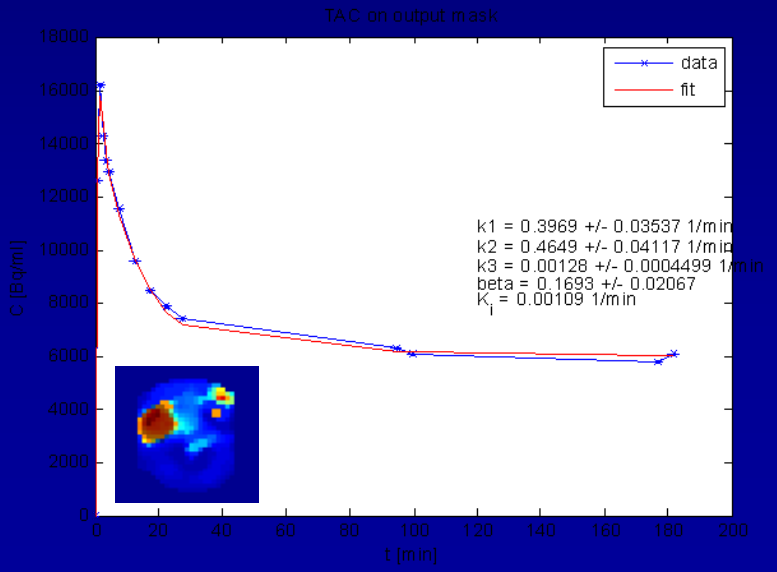
Discordance



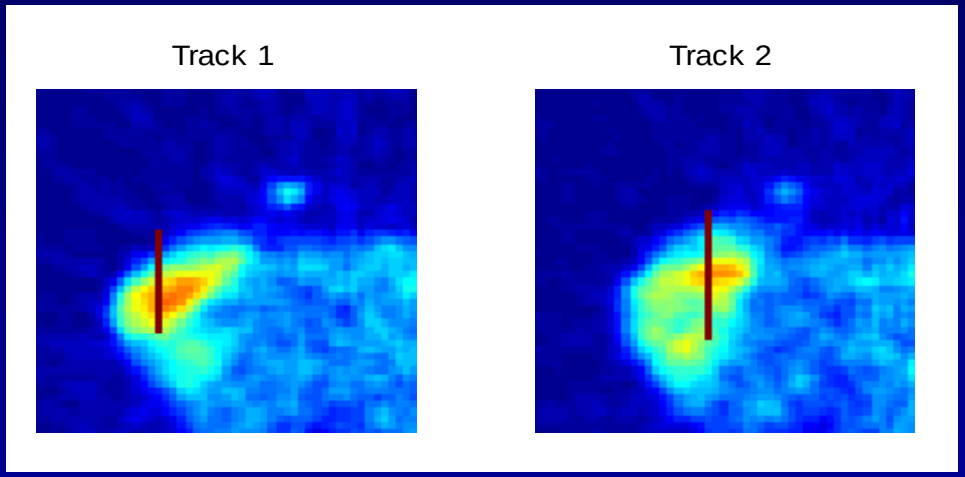




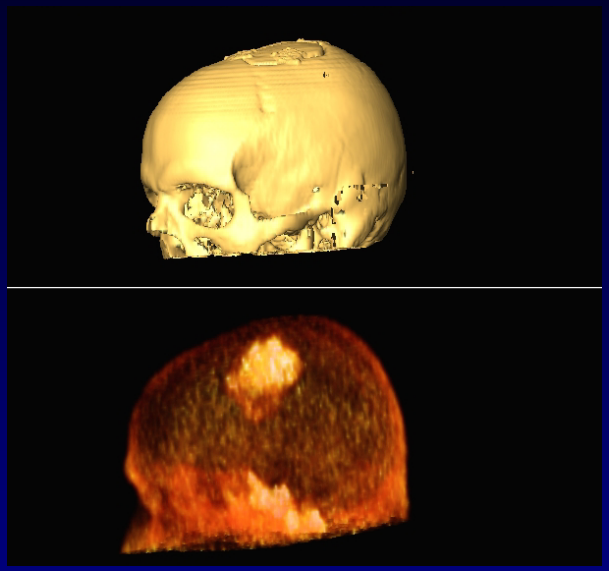
CT 3hr FMISO k3 map k1 map



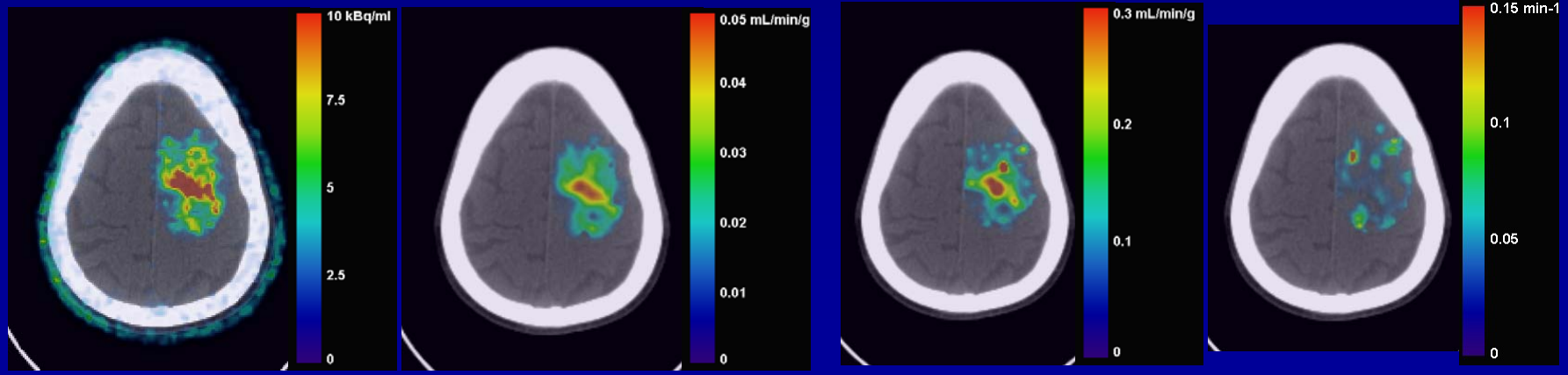
Parametic vs late time-point images
Which are correct?



FLT in Brain Tumors

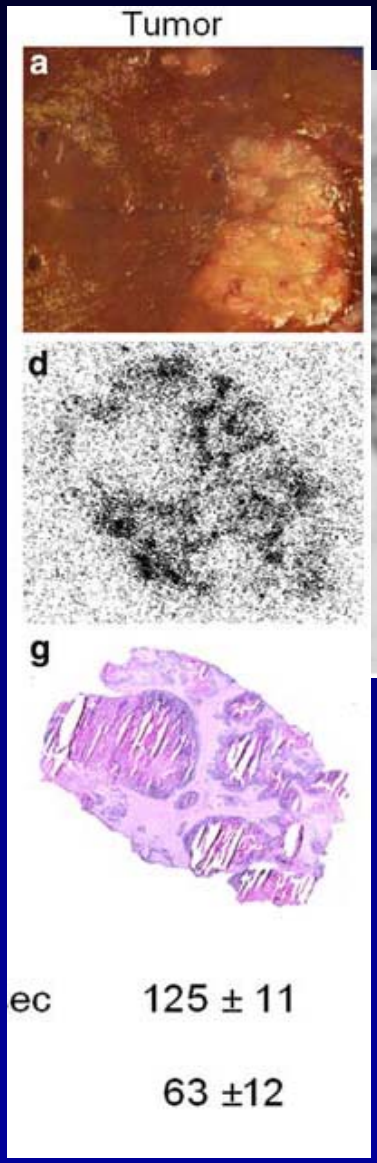


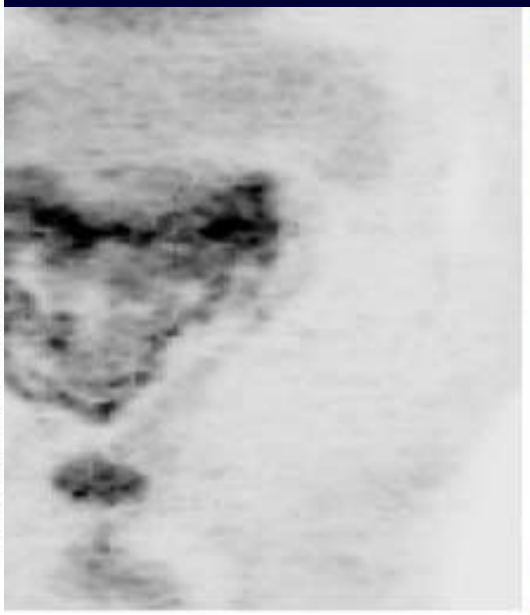
PET/CT FLUX/CT K_1/CT K_3/CT

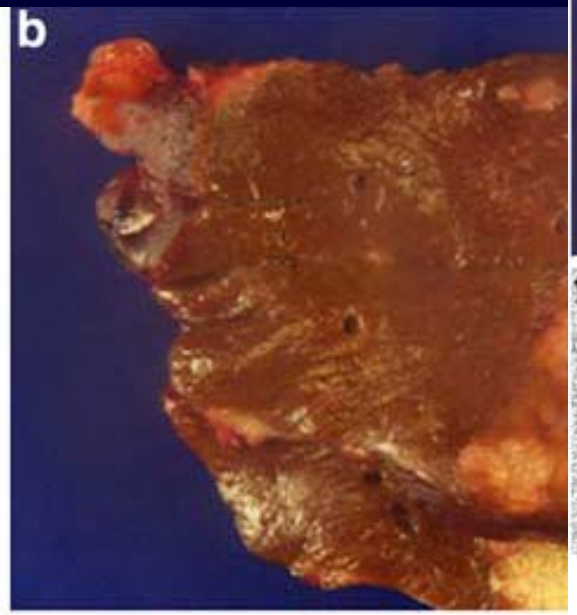


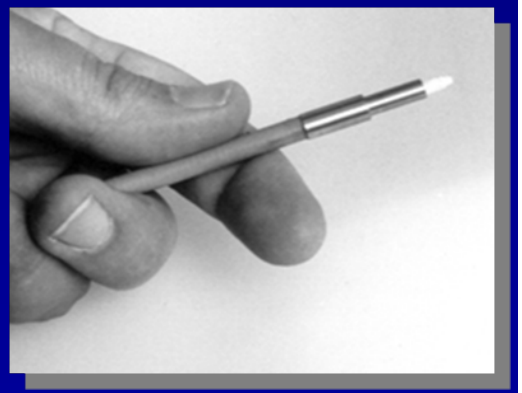
Tumor Specific Antibodies RadioimmunoPET

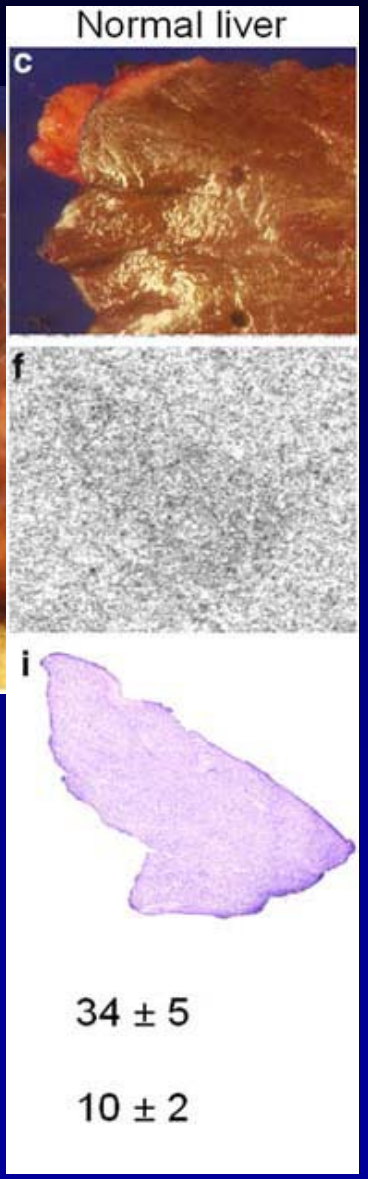
Use of PET and intra-operative probes in the O.R.



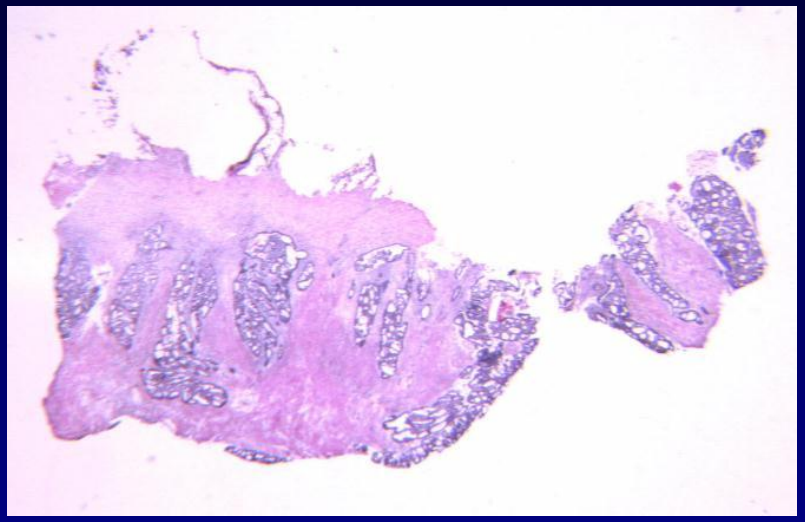


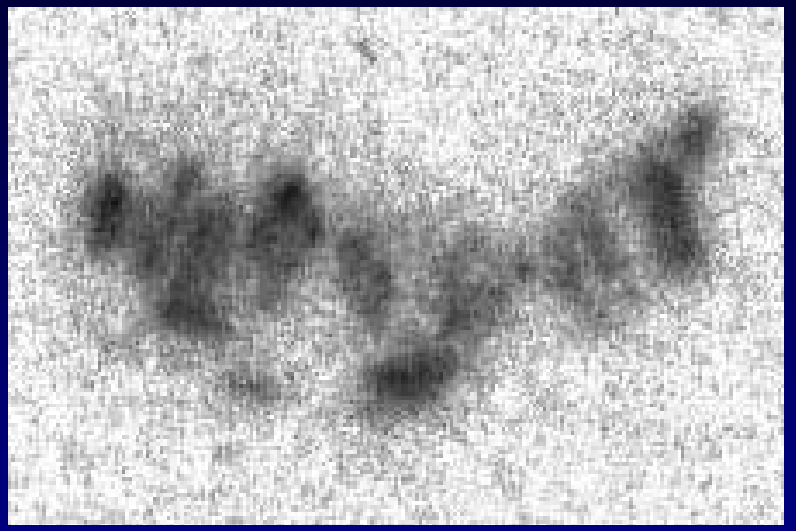


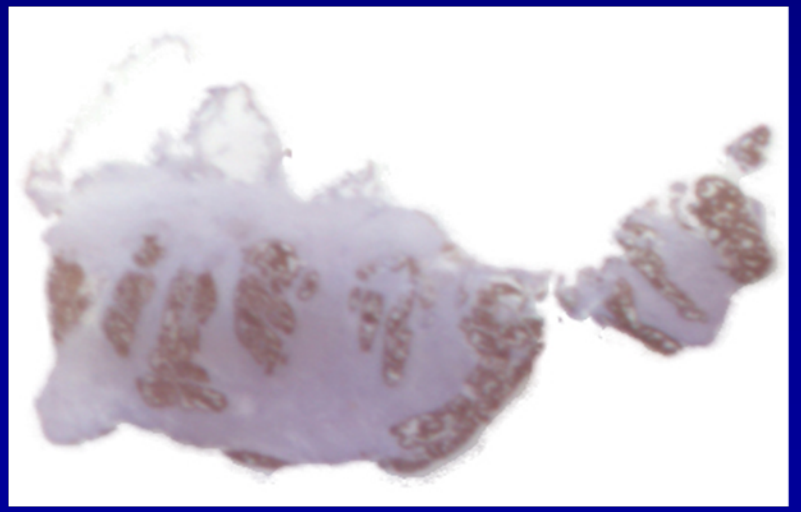




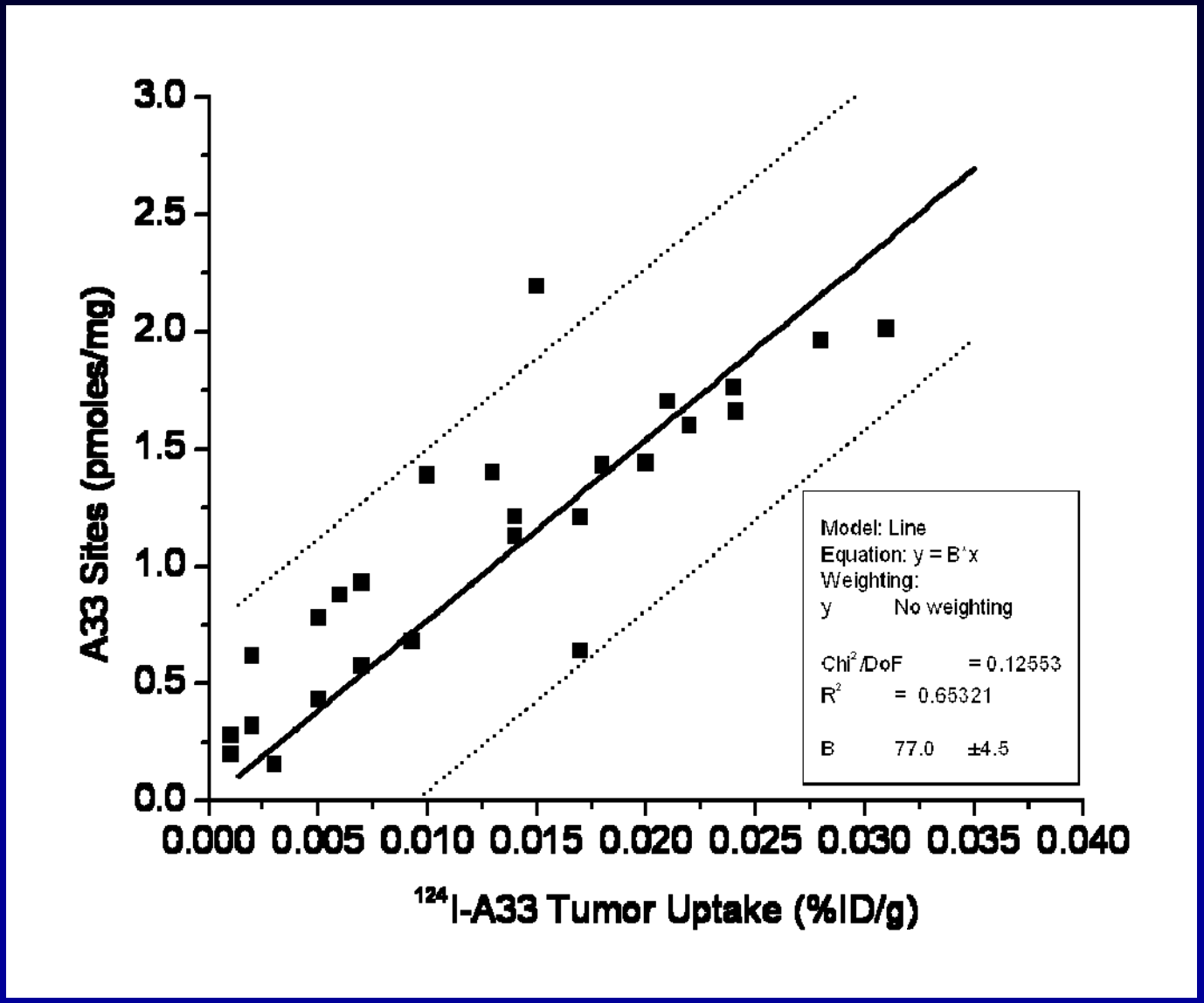
Does ^{124}I-A33 correspond to microdistribution of tumor location?







PET signal may provide a measure of the number of tumor cells per voxel



Conclusions

- Ideally we would like to perform single time point imaging and directly derive radiobiological information for radiotherapy planning.
- This may not work in all cases.
- FDG easiest to perform but signal uptake dependent upon many factors.
- FLT may be more specific to viable tumor cells.
- Hypoxia tracers are expected be prognostically relevant.
- Tumor specific antibodies may provide accurate map of tumor cell distribution.

Acknowledgements

MSKCC

Dept of Medical Physics
Sadek Nehmeh, Ph.D.
Jim Mechalakos, Ph.D.
Pat Zanzonico, PhD
Joseph O'Donoghue, PhD
Andrei Pugachev PhD
Shutian Ruan, MD
Sean Carlin, Ph.D.
Bixui Wen, MD
Olivia Squire RN
Kelin Wang, Ph.D.
Clifton Ling, PhD

Nuclear Medicine Service
Steven M Larson, MD
Heiko Schoder, MD

Cyclotron / Radiochemistry Facility
Ron Finn, PhD
Shangde Cai, PhD

Radiation Oncology
Nancy Lee, MD

Fox-Chase Cancer Center
J. Donald Chapman, PhD*
Richard Schneider, PhD