AAPM 2018 JUL 29–AUG 2
BEYOND THE FUTURE!
60TH ANNUAL MEETING & EXHIBITION | NASHVILLE, TN

PET in Radiation Oncology: Advances in Chemistry, Biology, and Physics

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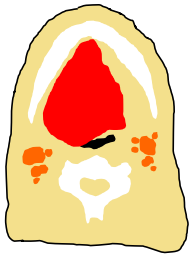
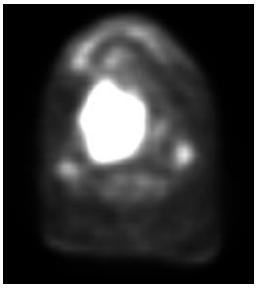
Molecular Imaging Program @ Stanford | Cancer Biology Program | Bio-X

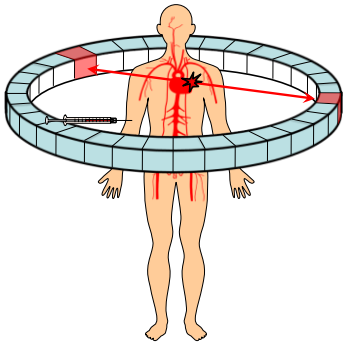
Imaging in Radiation Oncology



Imaging in Radiation Oncology



Positron Emission Tomography



- **Positron emitters and radiochemistry**
- **Imaging technology**
- **Imaging targets and radiotracers**
- **Quantitation**

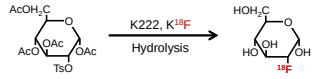
Positron Emitters

Isotope	Half life (hours)	Decay	Maximum β^+ energy (keV)	Mean β^+ energy (keV)
^{11}C	0.34	β^+ (99.8%)	960	386
^{13}N	0.17	β^+ (99.8%)	1198	492
^{15}O	0.03	β^+ (99.9%)	1732	735
^{18}F	1.83	β^+ (96.7%)	634	250
^{64}Cu	12.70	β^+ (17.4%) β^- (39.0%) EC (43.6%)	653	278
^{68}Ga	1.13	β^+ (88.9%) EC (11.1%)	1899	836
^{89}Zr	78.40	β^+ (22.7%) EC (76.2%)	902	396
^{124}I	100.20	β^+ (22.7%) EC (77.3%)	2138	819

P. McQuade *et al.*, *Cur Med Chem*, 2005

PET Radiochemistry

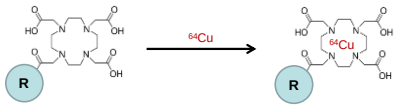
Organic synthesis/ Radiolabeling :



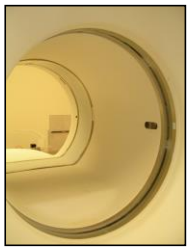
^{11}C, ^{18}F, ^{124}I

^{64}Cu, ^{89}Zr ^{68}Ga

Chelation/ Conjugation :

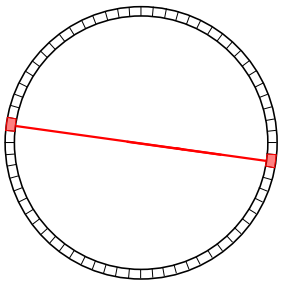


PET/CT Hardware



Current clinical PET performance: Spatial resolution ~5 mm
Sensitivity <pM

TOF PET



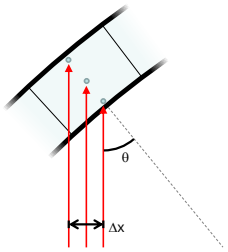
Early PET scanners utilized coincidence detector timing to localize events along a line-of-response, however these detectors were abandoned due to poor sensitivity.

Philips introduced the Gemini TF in 2006 taking advantage of detector improvements to revisit time-of-flight PET.

TOF resolution 300-500 ps (9-15 cm)

S. Vandenberghe *et al.*, *EJNMMI Phys*, 2016

DOI PET

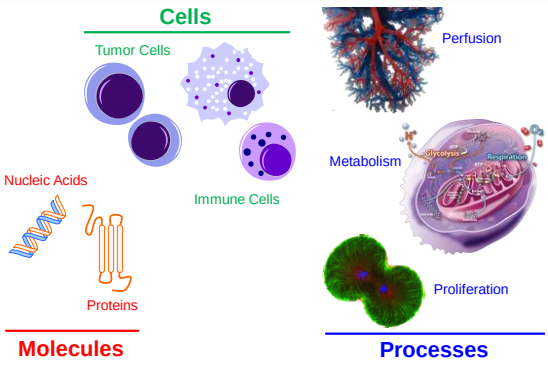


Increasing PET detector thickness is a standard approach to improving sensitivity. However, this comes with an increase in parallax error.

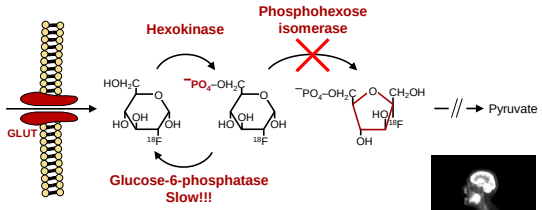
DOI detectors are capable of measuring the location of interaction of a 511 keV photon within a scintillation crystal.

M. Ito, *Biomed Eng Letters*, 2011
M.F. Bieniosek *et al.*, *Phys Med Bio*, 2017
M.S. Lee, *Phys Med Bio*, 2017

Imaging Targets



Fluorodeoxyglucose

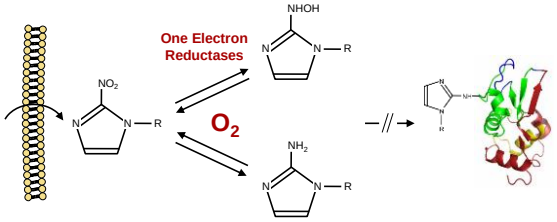


FDG PET signal is dependent on:

- Vascular delivery
- Cell number
- GLUT expression
- Hexokinase expression
- Excretion pathways

Hypoxia PET

Radiochemistry • Imaging Technology • **Targets and Radiotracers** • Quantitation

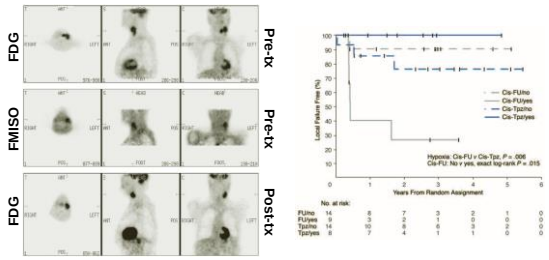


2-nitroimidazole uptake is dependent on:

- Vascular delivery
- Cell number
- Reductase expression
- Oxygen
- Excretion pathways

Hypoxia PET and Prognosis

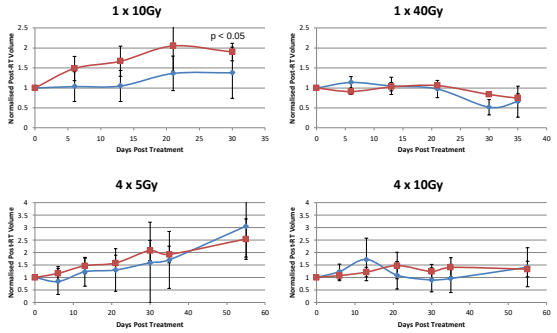
Radiochemistry • Imaging Technology • **Targets and Radiotracers** • Quantitation



D. Rischin *et al.*, *J Clin Onc*, 2006

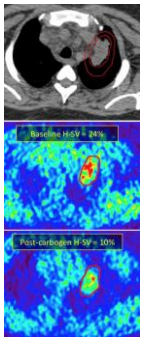
Hypoxia PET and RT Response

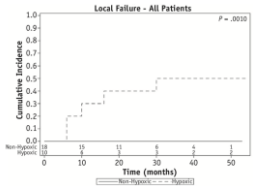
Radiochemistry • Imaging Technology • **Targets and Radiotracers** • Quantitation



R.S. Ali *et al.*, *PLoS One*, 2015

Hypoxia PET and RT Response





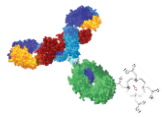
Y. Qian *et al.*, *Int J Radiat Oncol Biol Phys*, 2018

Radiotracer Design

Small molecules

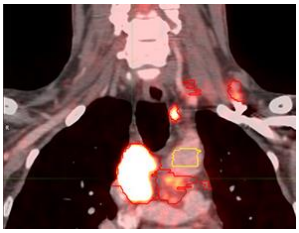
- **Require organic synthesis/radiolabeling**
- **Short blood half life/clearance time**
- **Can use short-lived positron emitters**
- **Unsuitable for conjugation to large labels such as chelators**

Biologics and Nanoparticles



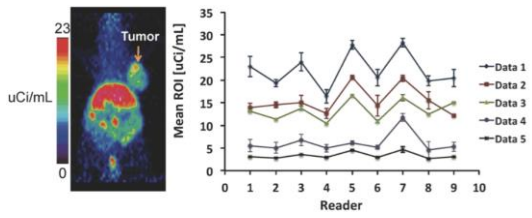
- **Typically expensive to manufacture**
- **Long blood half life/clearance time**
- **Require long-lived positron emitter**
- **Suitable for non-specific labeling, chelators**

Quantitation



- **Maximum intensity**
- **Minimum intensity**
- **Mean intensity**
- **Median intensity**
- **Integrated intensity**
- **75th percentile**
- **90th percentile**
- **Standard deviation**
- **Variance**
- **Skew**
- **Kurtosis**
- **ROI volume**

Variability in PET



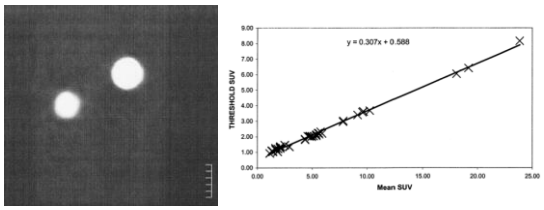
F. Habte *et al.*, *Am J Nuc Med Mol Im*, 2006

Variability in PET

Category	Procedure	Uncertainties	Quality control
Scanning protocol	Patient preparation	Metabolism: levels (↑F-FDG)	Limit physical activity
		Blood glucose levels (↑F-FDG)	Measure fasting blood glucose with exclusion criteria
		Bowel voids/positioning	Use fasting protocol
	Radiotracer injection	Residual activity in syringe	Measure/correct for residual activity
		Decay correction errors	Synchronize scanner clock
Acquisition	Patient positioning	Spatial offset between PET and treatment-planning CT	Ensure consistent patient positioning using identical positioning devices
		Quantitative uncertainties from attenuating objects	Avoid placing objects outside image field of view
	Scanning	Patient motion	Implement motion management strategies
		Attenuation correction uncertainties from iodine contrast material	Acquire separate low-dose CT scan or apply corrections
		Equipment failure or electronic drift	Calibrate detector and equipment frequently
		Increased SUV because of longer uptake period	Apply strict protocol for uptake period
Reconstruction	Reconstruction	Selection of optimal image reconstruction method/parameters	Benchmark algorithms using phantoms (task-specific)
		Randoms, scatter, attenuation, detector sensitivity, and partial-volume effect	Apply appropriate calibrations and corrections
Analysis	Segmentation	Differentiation of normal tissue and tumor uptake	Know radiotracer's normal biodistribution
		Segmentation uncertainties	Develop segmentation protocol; benchmark algorithms with phantoms
		Lim ted spatial resolution and sensitivity	Include margins
	Quantification	Quantitative accuracy	Calibrate PET scanner to dose calibrator
		Selection of relevant quantitative measures	Compare semi-quantitative metrics with kinetic analysis-derived parameters; consult literature
		Quantitative differences between scanners/institutions	Quantitatively harmonize scanners
Treatment planning	Target definition	Registration errors	Benchmark algorithms using physical or digital phantoms; crop images
		Motion	Use same motion management method as was used during imaging

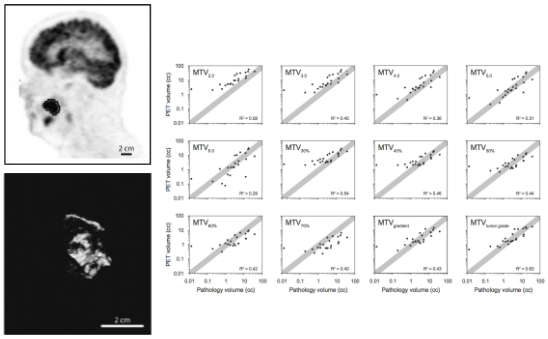
R. Jeraj *et al.*, *J Nuc Med*, 2015

Image Segmentation



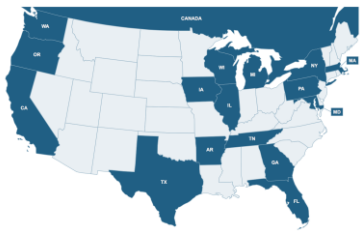
Q. Black *et al.*, *Int J Rad Onc Biol Phys*, 2004

Validation



J. Murphy *et al.*, *Radiother Onc*, 2011

Quantitative Imaging Network



The QIN is an NCI-sponsored collective of 21 research teams spanning 19 institutions working to standardize imaging acquisition and analysis methods in order to facilitate the widespread use of imaging as a quantitative biomarker for cancer research and treatment.

Summary

- **Radiochemistry of a large number of PET probes is established and translatable.**
- **Clinical PET/CT scanners are capable of imaging positron-emitting probes at sub-picomolar levels with spatial resolutions of 4-5 mm.**
- **A variety of molecular and cellular processes are imageable with PET.**
- **Current challenges to integration of PET images in radiotherapy planning are establishment of robust segmentation methods and the cost of multicenter deployment and evaluation of these methods.**