Radioisotopes in Medical Practice: From There to Here

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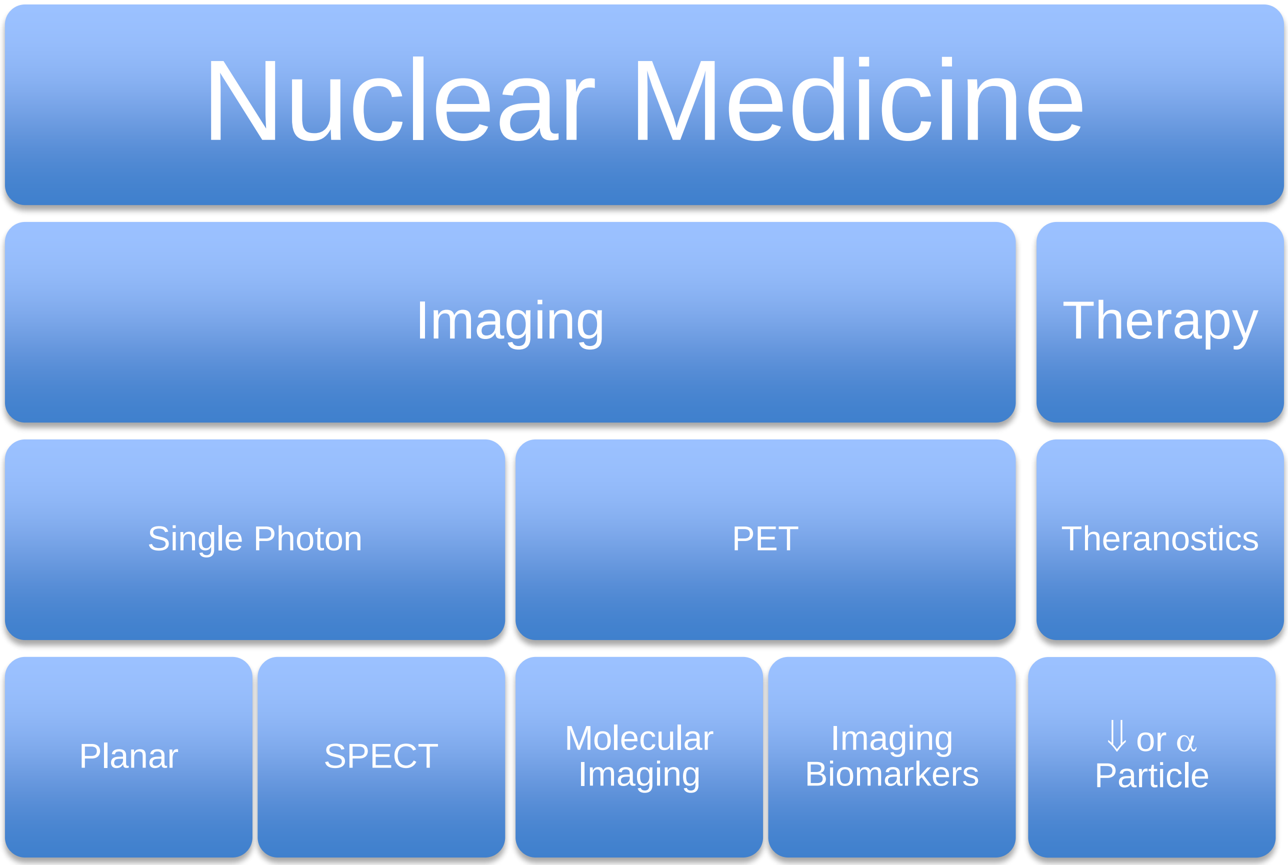
Simplistic View of Medical Imaging

• X-rays	-	Images of Structure
• U/S	-	Images of Structure
• MRI	-	Images of Structure
	-	Images of Function
• Isotopes	-	Images of Function
	-	Biomarkers/Images of Biology


Nuclear Medicine
Imaging
Therapy
Single Photon
PET
Theranostics
Planar
SPECT
Molecular Imaging
Imaging Biomarkers
⇓ or α Particle

Single Photon Imaging

- Radiopharmaceutical/Radiotracer
  - Radionuclide
    - Tc-99m
    - I-131
    - I-123
    - In-111
  - Probe
    - MDP - Bone
    - DTPA - Kidney/transit
    - MIBI - Cardiac perfusion
    - WBC - Infection
    - Peptide - Neuroendocrine cancers

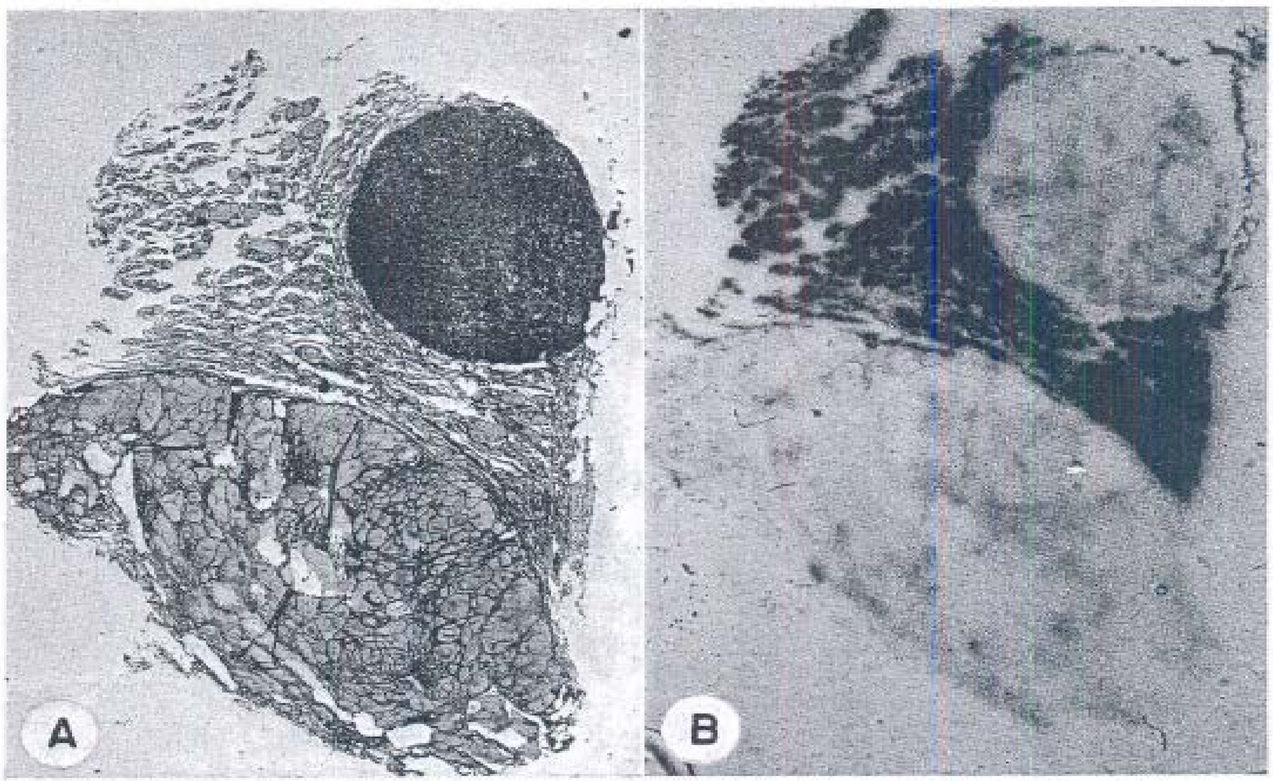
A study of the histopathology and physiologic function of thyroid tumors, using radioactive iodine and radioautography

Dobyns BM and Lennon B.

J Clin Endocrinol 1948; 8:732-748

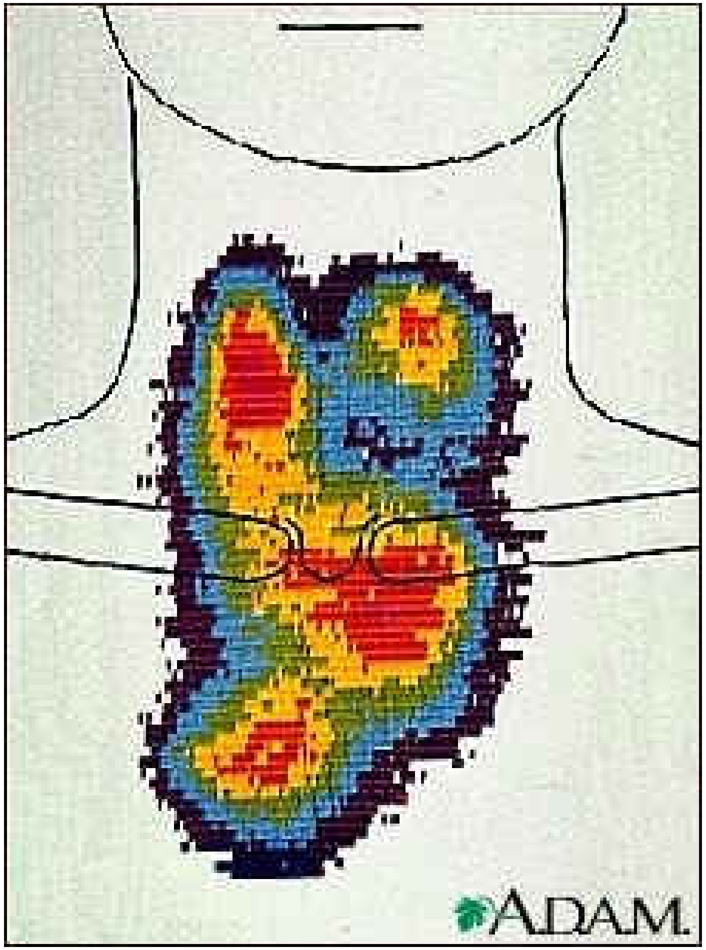
1. The degree of function may be related to the degree of cellular differentiation of adenomas, with certain exceptions.
2. There are hyperplastic adenomas with cellular hypertrophy which are hyperfunctioning but there are also hyperplastic adenomas which are not functioning.
3. Hyperfunctioning adenomas may exist with or without evidence of thyrotoxicosis and probably by their excessive activity suppress otherwise normal thyroid tissue.

Colloid adenoma with relatively little function
A - histologic section; B - radioautograph



Dobyns BM and Lennon B. *J Clin Endocrinol* 1948; 8:732-748

Thyroid Imaging 1976 – Iodine-131: Rectilinear Scanner



Treatment of Thyroid Cancer – 1953 No significant change in 2017

"Principal goal in the treatment of metastatic thyroid cancer is destruction of metastases with radioactive iodine"

- removal of all thyroid tissue
- suppression of iodide production by large doses of thiouracil
- stimulation by TSH

Sturgeon CT, et al. *J Clin Endocrinol Metab* 1953, 13:21391-1407

First Tc-99m Generator – Brookhaven National Laboratory

https://upload.wikimedia.org/wikipedia/commons/2/25/First_technetium-99m_generator_-_1958.jpg

BROOKHAVEN NATIONAL LABORATORY

MEMORANDUM

DATE: December 4, 1958

TO: Addressees Below

FROM: Daniel M. Schaeffer, Head DMS
BNL Patent Office

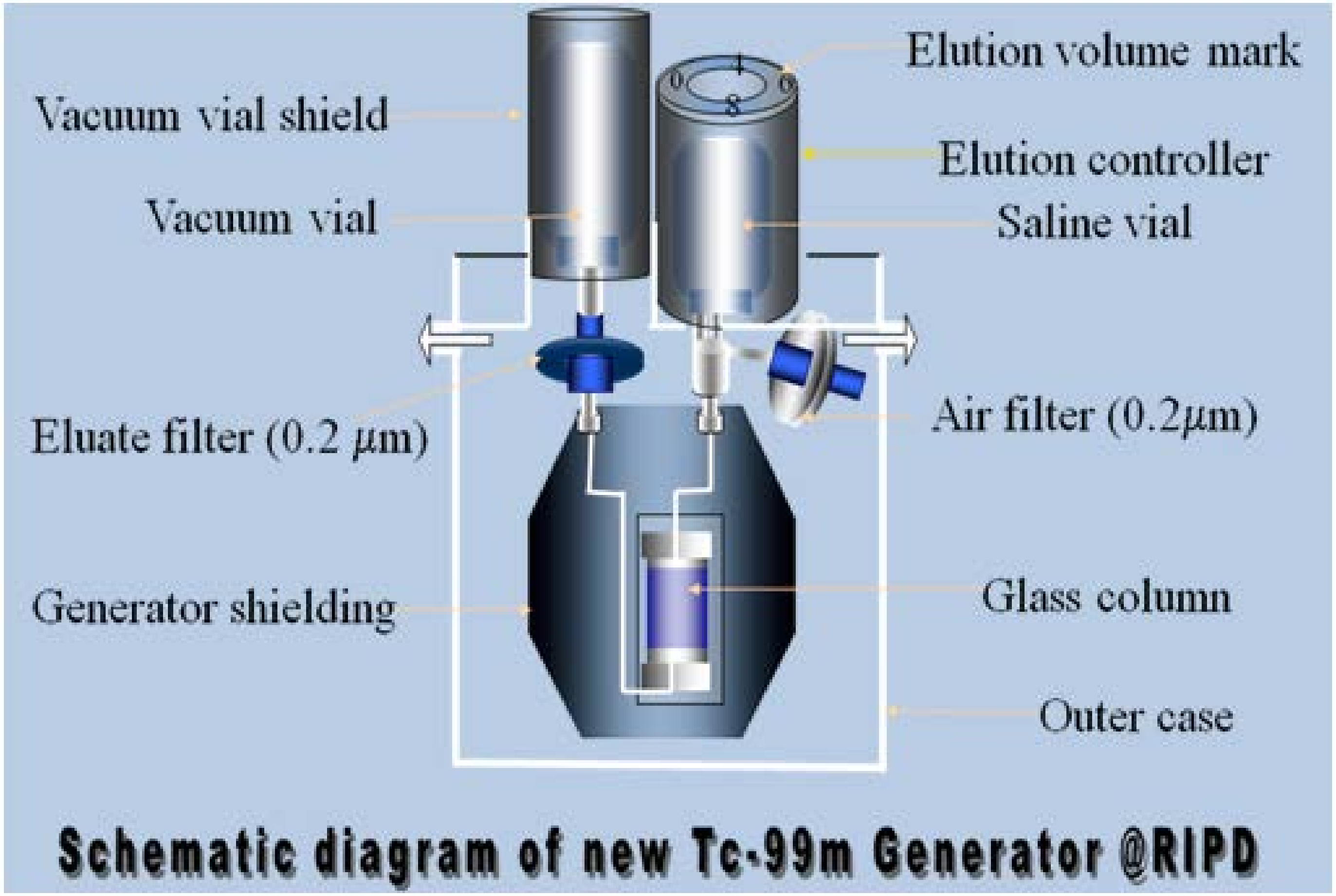
SUBJECT: P-701 and P-702 - PREPARATION OF CARRIER-FREE MOLYBDENUM AND OF TECHNETIUM FROM FISSION PRODUCTS

The New York Patent Group has carefully studied the information available relative to the above-identified item. The AEC does not at present desire to prepare a patent application on this item for the following reason:

"The method of producing carrier-free molybdenum-99 from fission products is disclosed in U. S. Patent Application S.N. 732,108, Green, Powell, Samos & Tucker (BNL Pat No. 58-17). It is noted that molybdenum-99 may be separated from its radioactive daughter, technetium-99, by absorption of a solution of molybdenum-99 on alumina and subsequent elution of its daughter with .1 nitric acid. While this method is probably novel, it appears that the product will probably be used mostly for experimental purposes in the laboratory. On this basis, no further patent action is believed warranted."

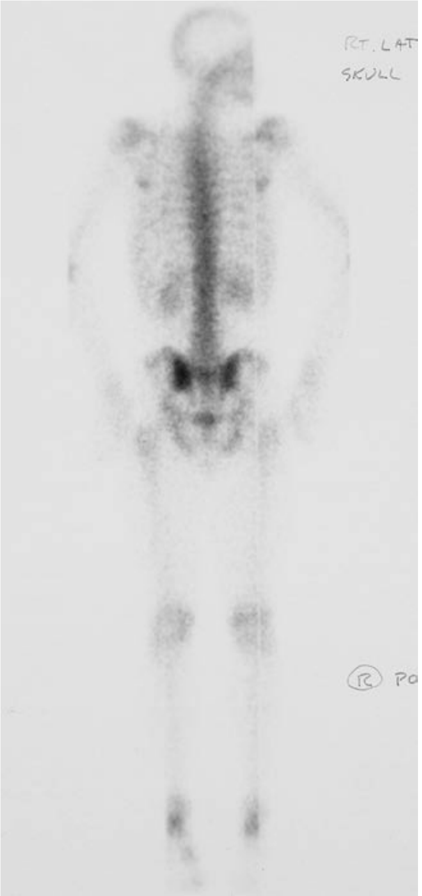
Int J Appl Radiat Isot 33: 793 - 799, 1982

Technetium -99m Generator 2015

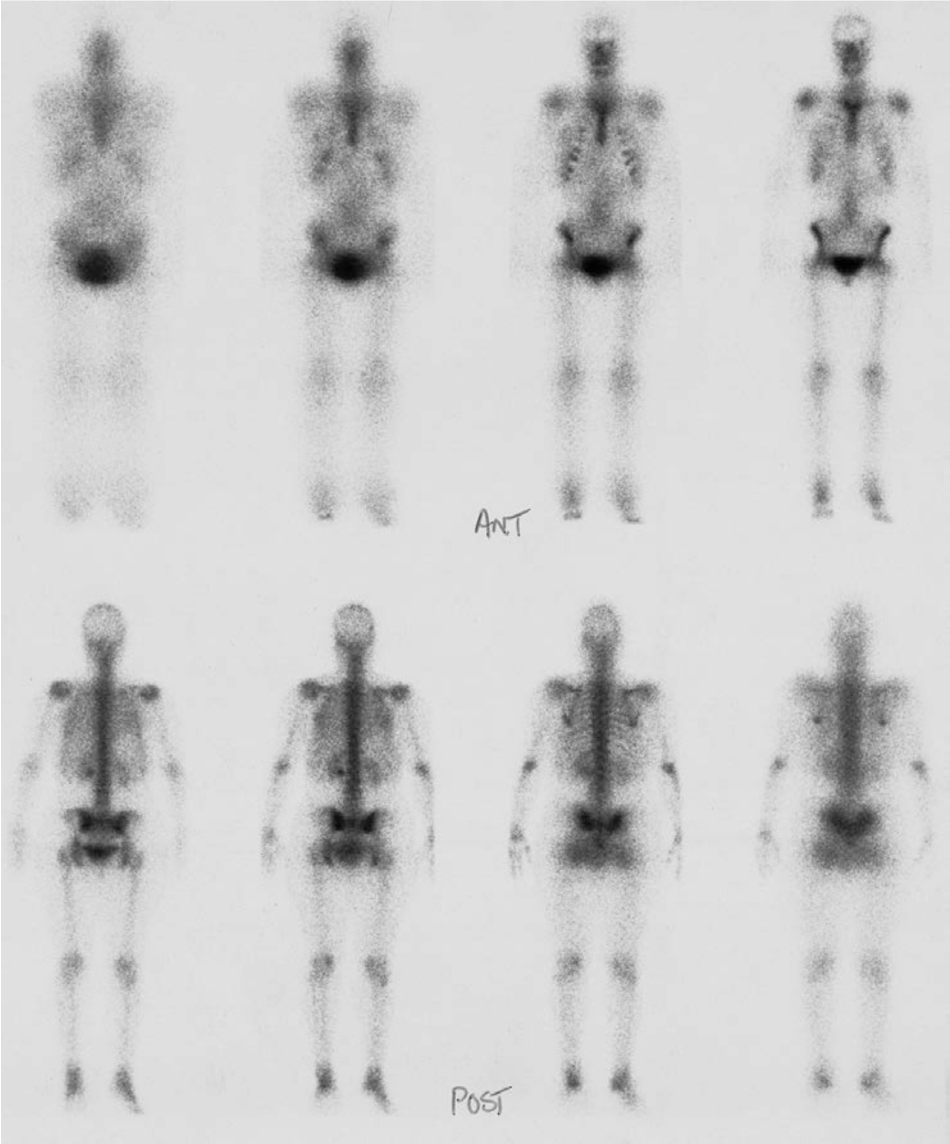


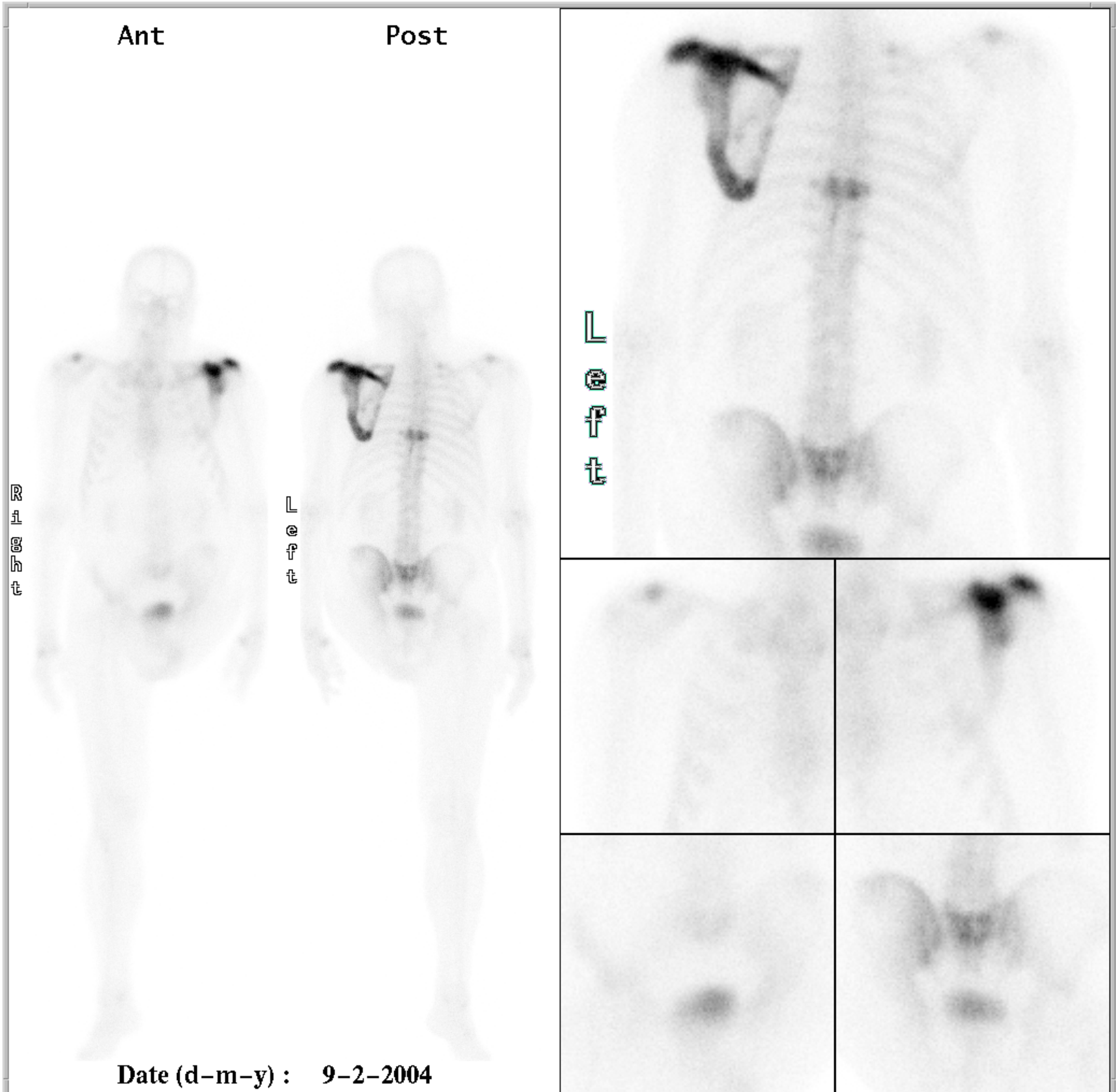
http://www.assignmentpoint.com/science/engineering/generator-hardware-and-accessories.html

Bone Scan 1974 ^{99m}Tc PYP



Linear Tomography 1984 MDP




Ant
Post
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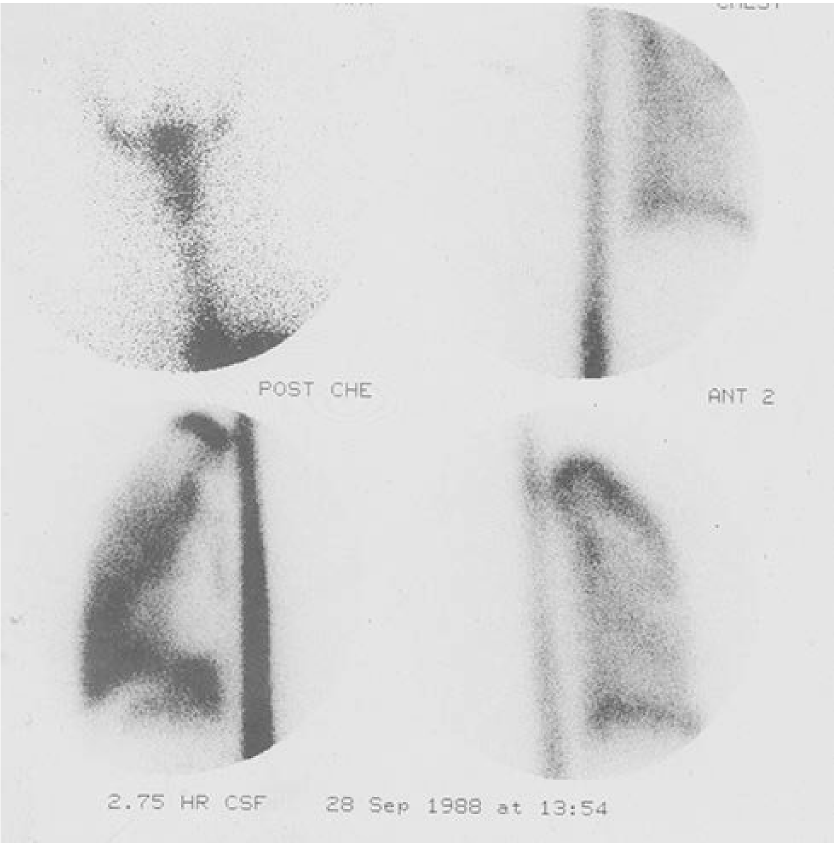
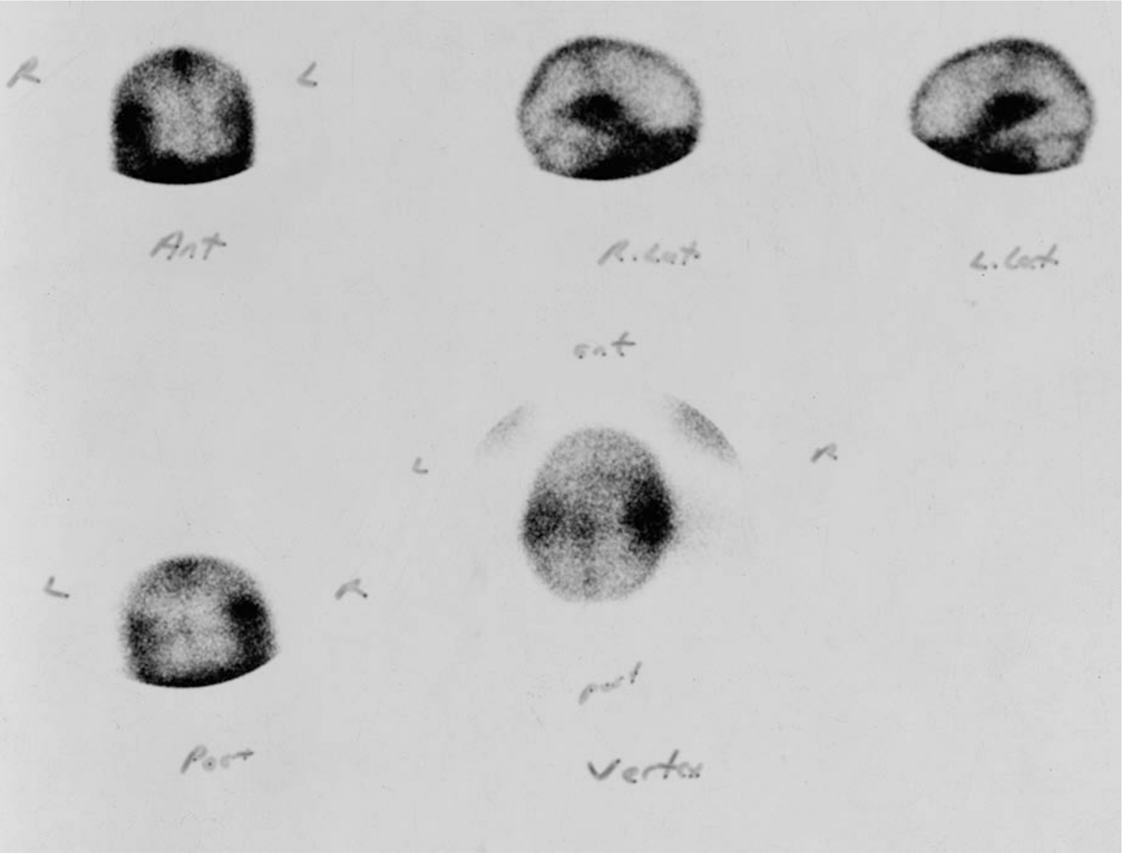
Date (d–m–y) : 9–2–2004

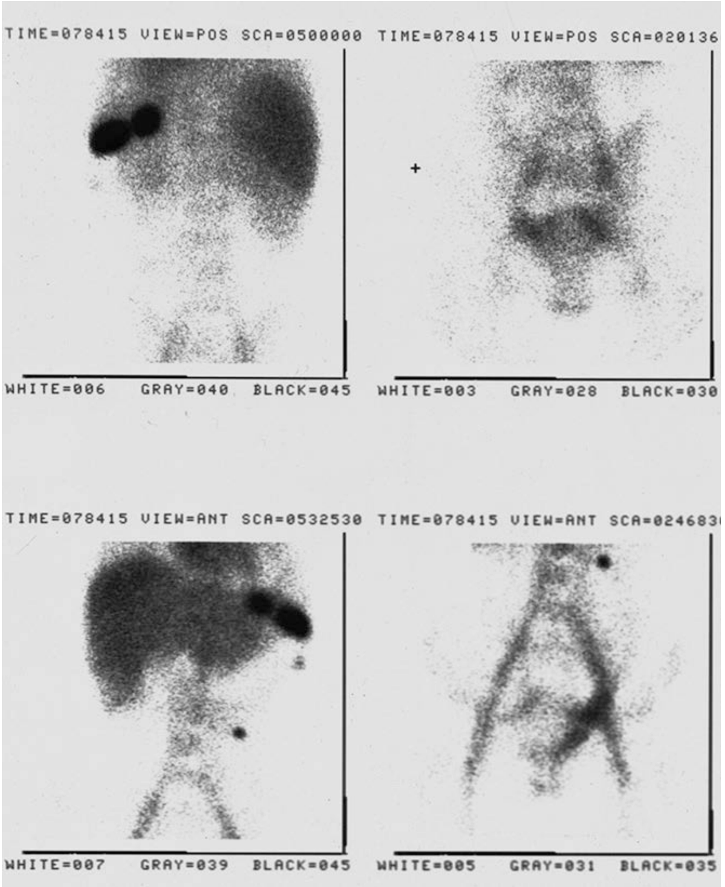
Spinal Pleural Fistula Post Trauma 1989 ^{99m}Tc DTPA



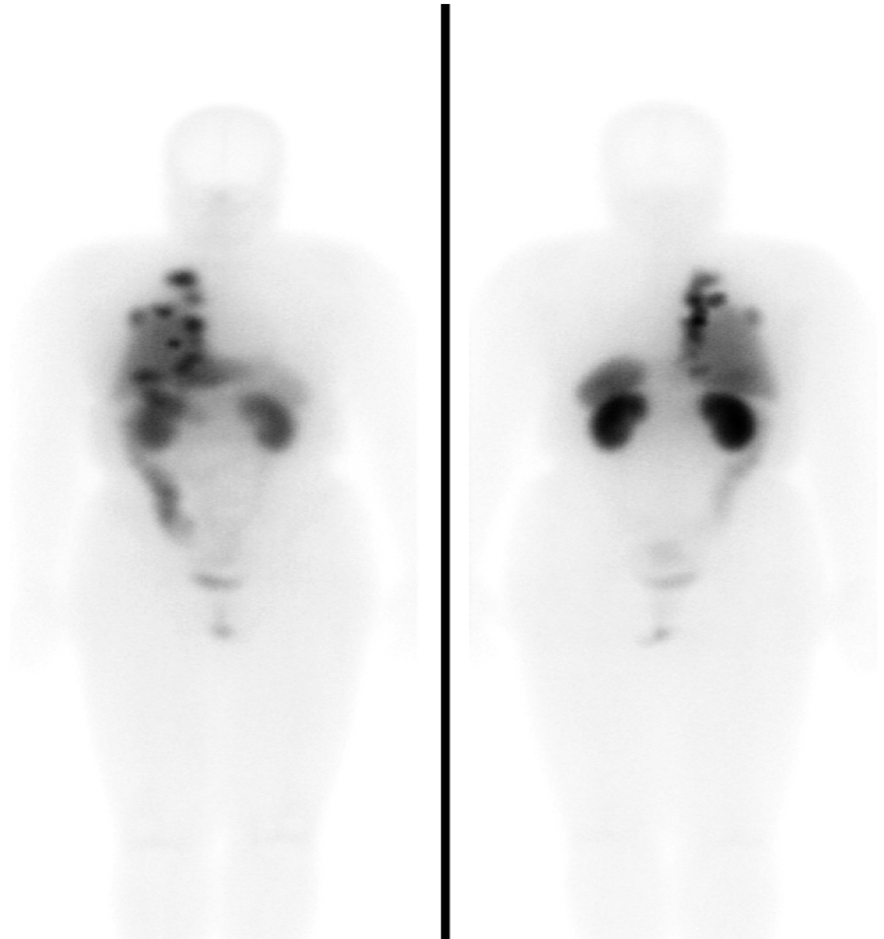
Brain Scan 1988 – $^{99m}TcO_4$



Splenunculi Post Trauma 1990 ^{99m}Tc RBC

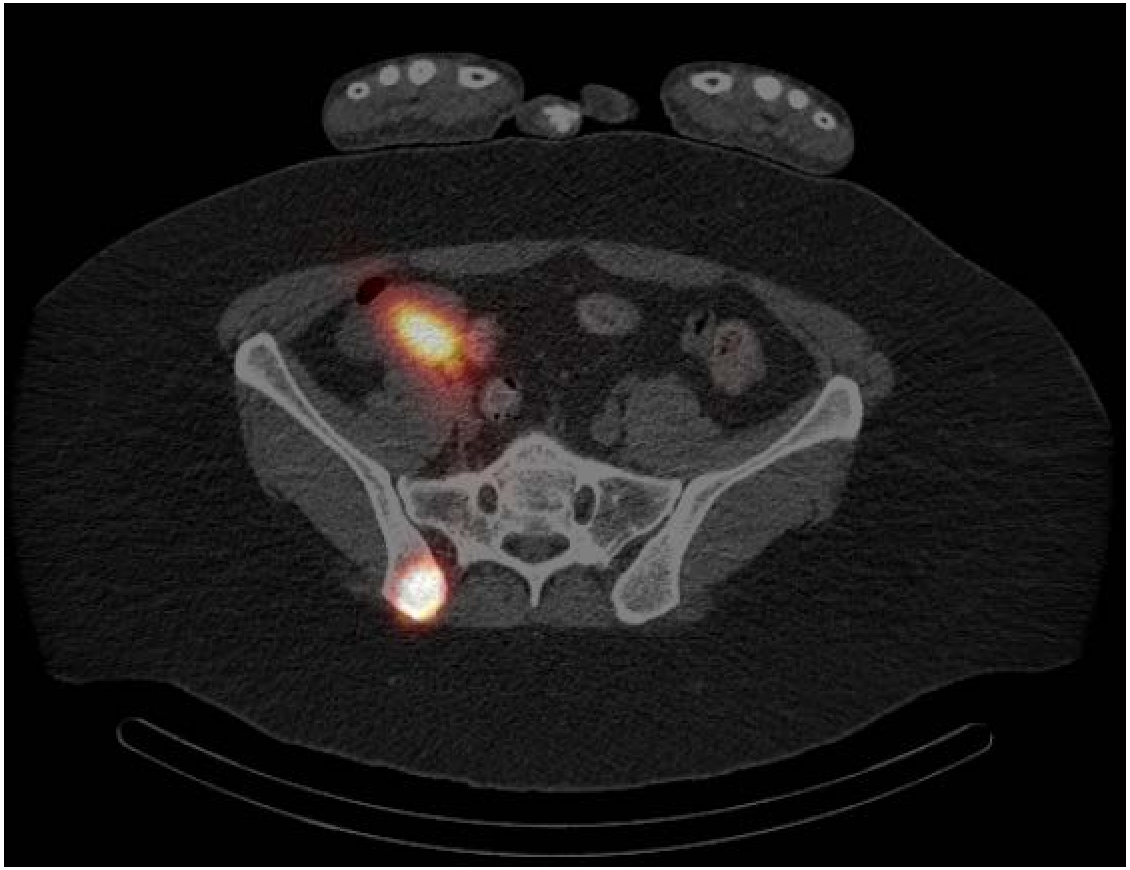


Metastatic Mediastinal Carcinoid: ^{111}In Octreotide



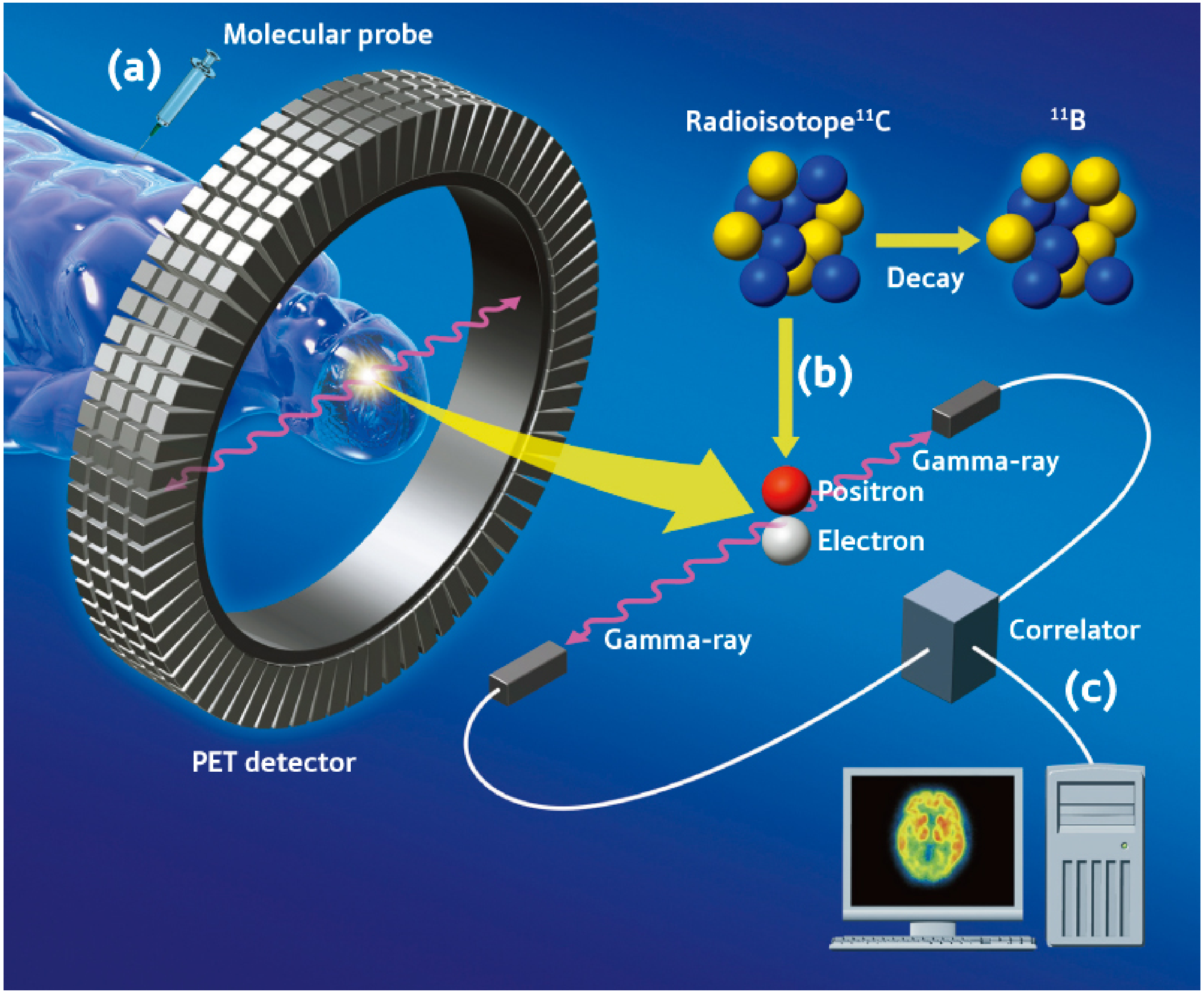
Metastatic Mediastinal Carcinoid: ^{111}In Octreotide SPECT

SPECT/CT I-131 Scan Thyroid Metastasis



Characteristics of PET/CT - Molecular Imaging; Imaging Biomarkers

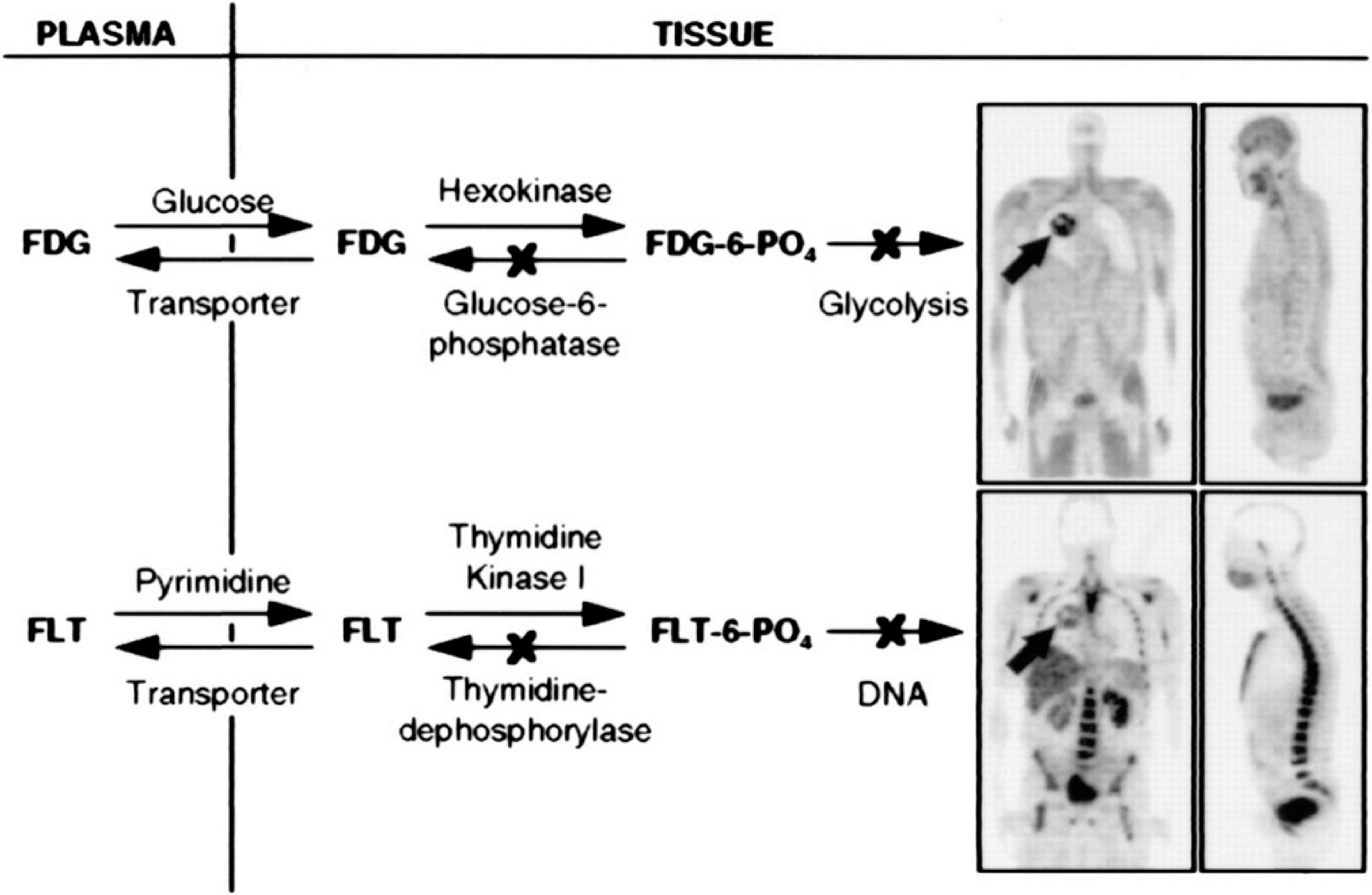
- Assay of biological and functional tumor characteristics
  - Molecular medicine
- Targeted
  - To tumor
  - To biological process or target
  - To metabolic, biochemical, genomic, proteomic pathway
- Quantitative
  - Relative, absolute or temporal
- Diagnostic and predictive
  - Stratifies for treatment
  - Demonstrates early changes in response to therapy
  - Predicts treatment response



https://3c1703fe8d.site.internapcdn.net/newman/gfx/news/hires/figure1molec.jpg

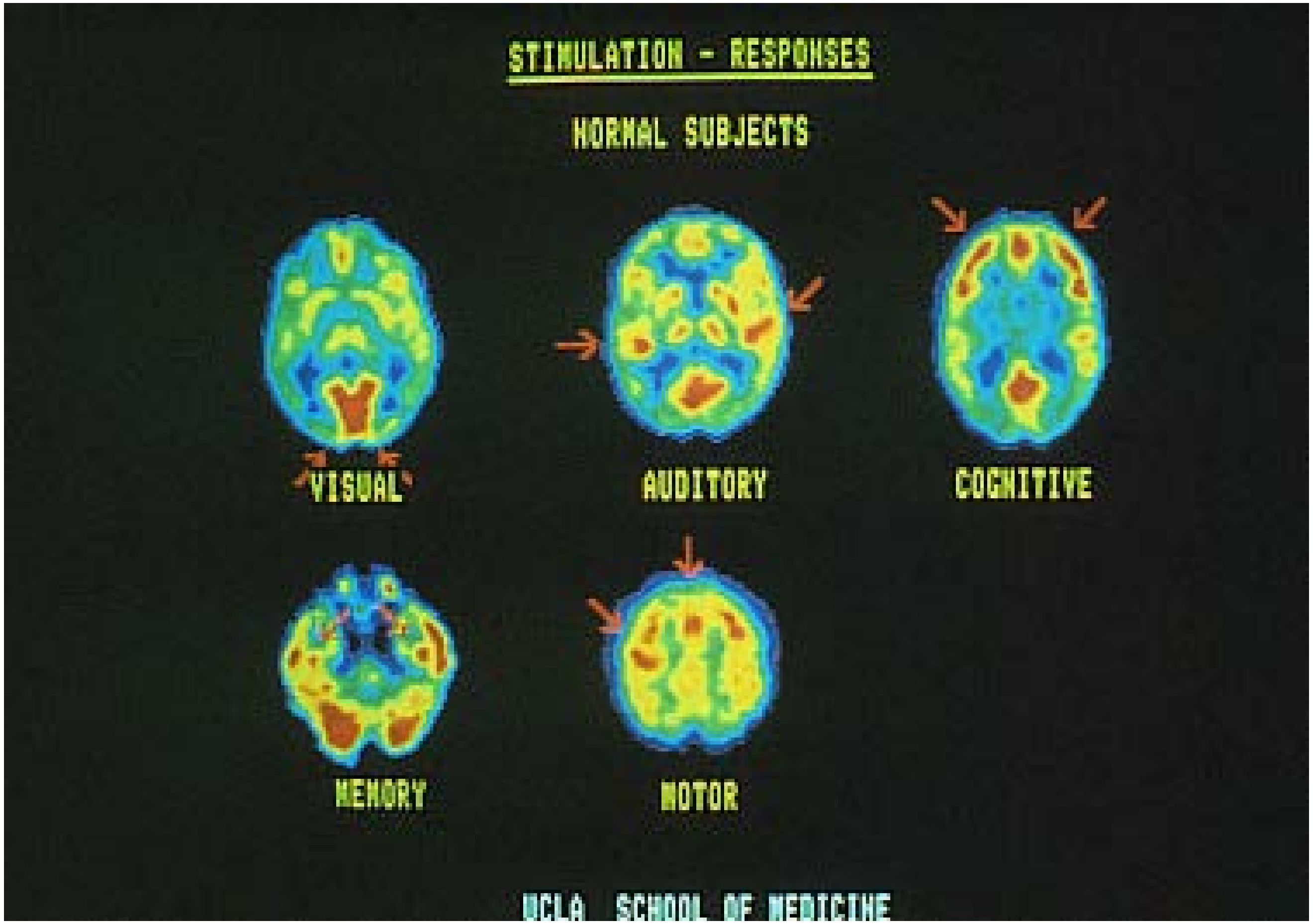
Characteristics of PET/CT - Molecular Imaging; Imaging Biomarkers

- Radiopharmaceutical/Radiotracer
  - Radionuclide
    - F-18
    - C-11
    - Ga-68
    - Rb-82
  - Probe
    - FDG - glucose metabolism
    - FAZA - hypoxia
    - FLT - proliferation
    - Peptide - neuroendocrine and prostate cancers
    - Carfentanil - opioid recpetors

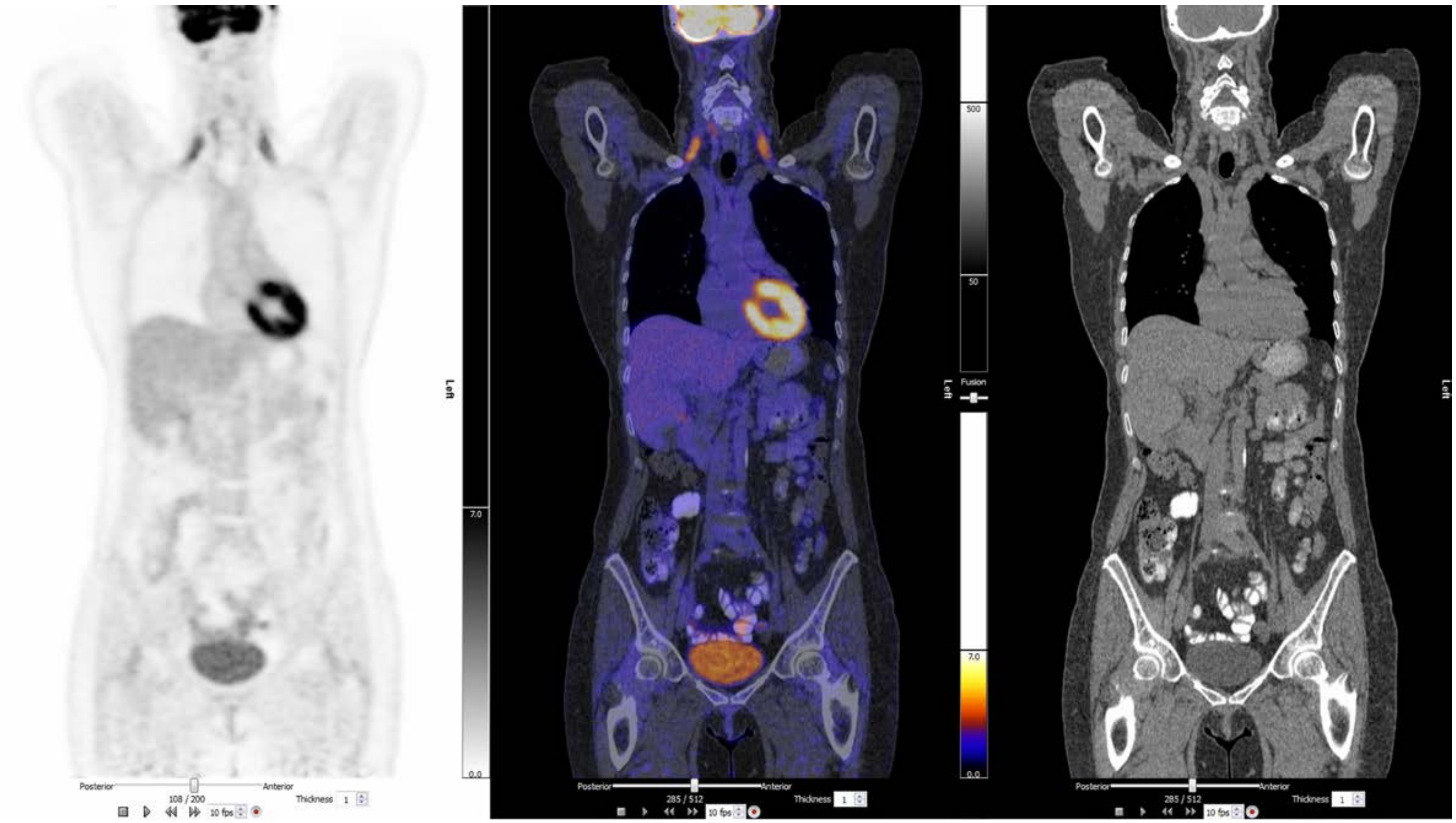


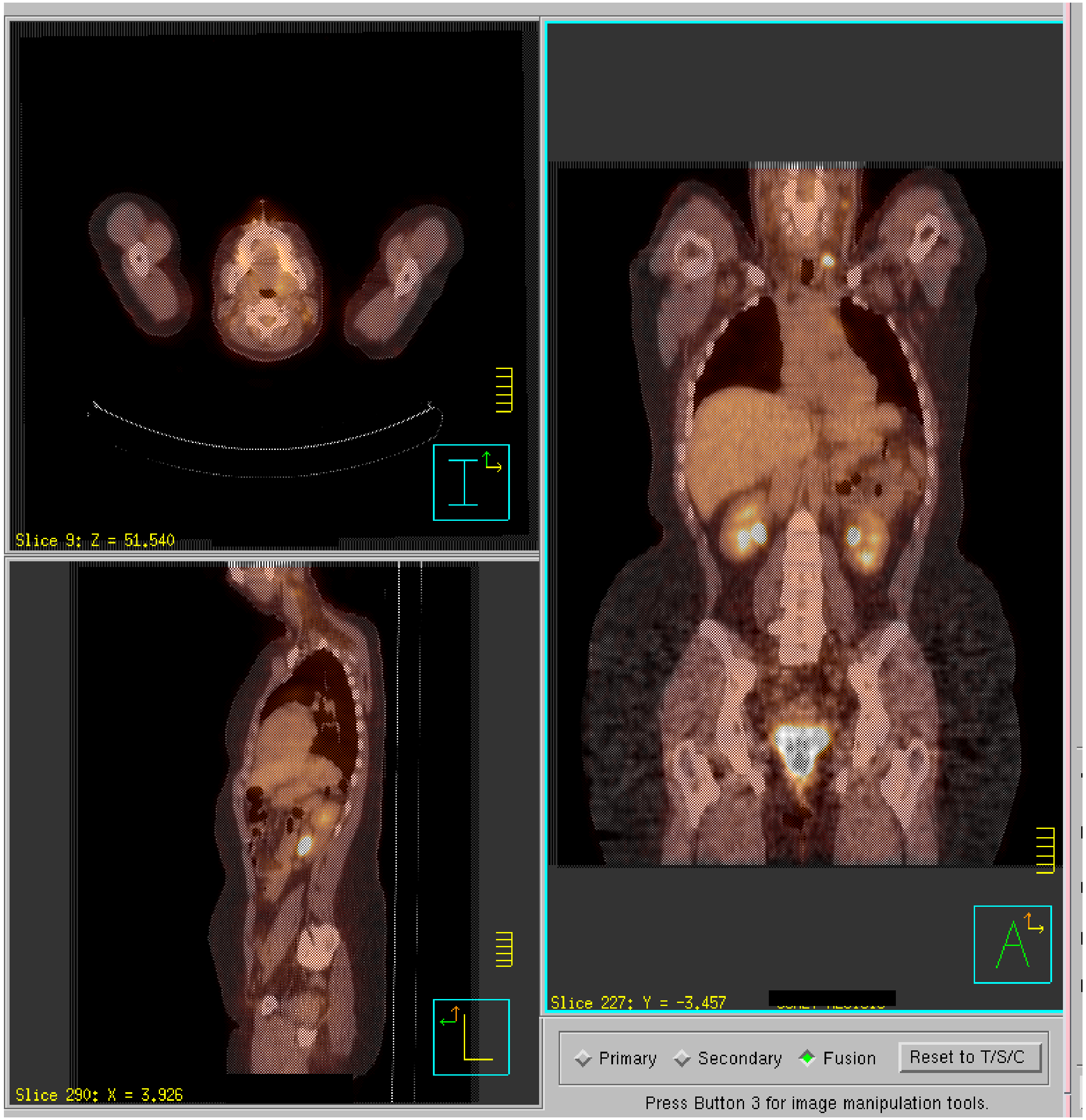
Anthony F. Shields (Wayne State, Detroit) and John R. Grierson (U. Washington, Seattle)

Bernhard M. Dohmen and H-Juergen Machulla (Tuebingen PET Center, Germany)

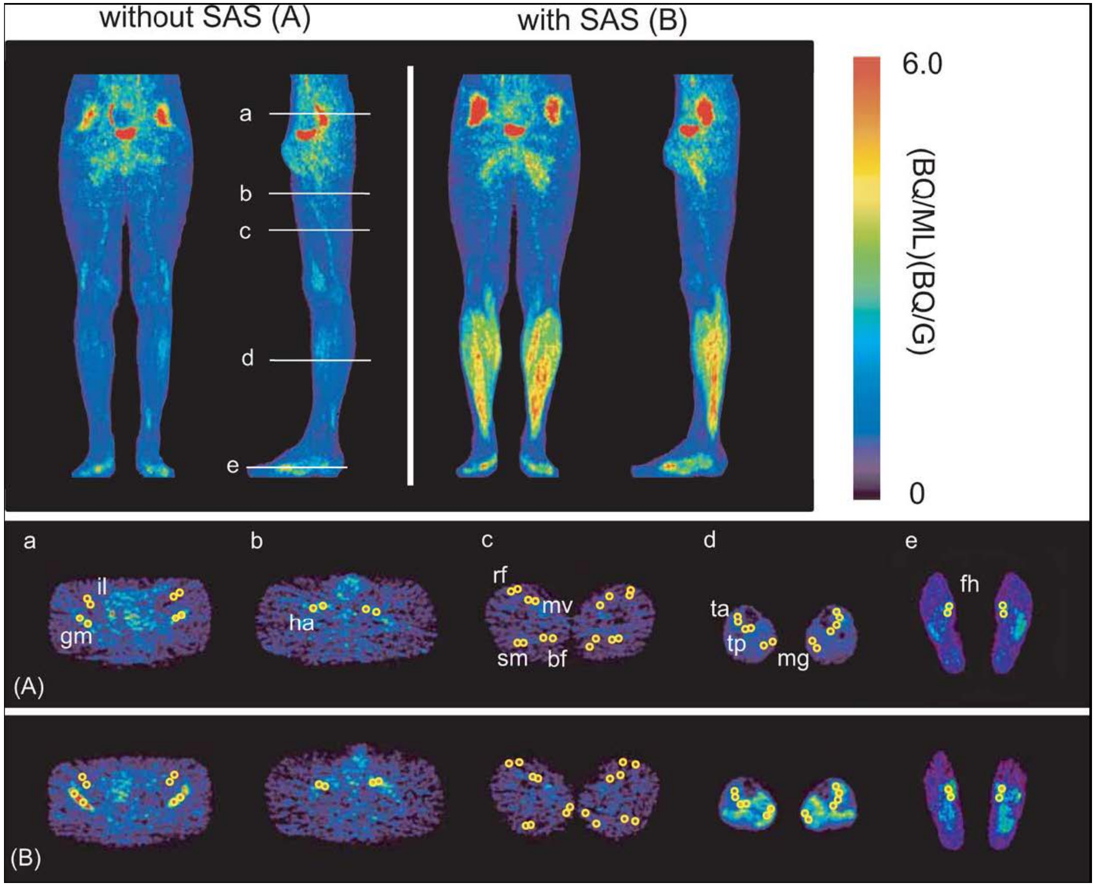

STIMULATION - RESPONSES
NORMAL SUBJECTS
VISUAL
AUDITORY
COGNITIVE
MEMORY
MOTOR
UCLA SCHOOL OF MEDICINE

Coronal Slices of PET FDG Images




Slice 9: Z = 51.540
Slice 290: X = 3.926
Slice 227: Y = -3.457
[redacted]
Primary
Secondary
Fusion
Reset to T/S/C
Press Button 3 for image manipulation tools.

FDG PET Images Taken After Walking Without (A) or With (B) a Stride Assistance System



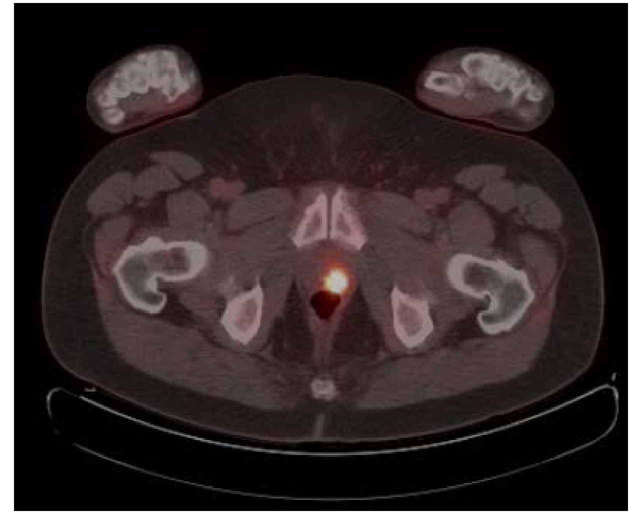
Shimada H, et al. *IEEE Transactions on Neural Systems and Rehabilitation Engineering* 2007; 15(3):442-448

FDG Uptake by Lower Extremity Muscles During Walking With or Without a Stride Assistance System

	Without the SAS Mean	With the SAS Mean	Ratio with ÷ without	*p* Value
Flexor hallucis longus	2.08	2.36	1.25	0.43
Tibialis anterior	1.71	2.54	1.74	0.08
Tibialis posterior	1.44	2.92	2.13	0.04
Medial gastrocnemius	1.54	2.91	2.36	0.01
Rectus femoris	0.43	0.41	0.97	0.56

Shimada H, et al. *IEEE Transactions on Neural Systems and Rehabilitation Engineering* 2007; 15(3):442-448


Left



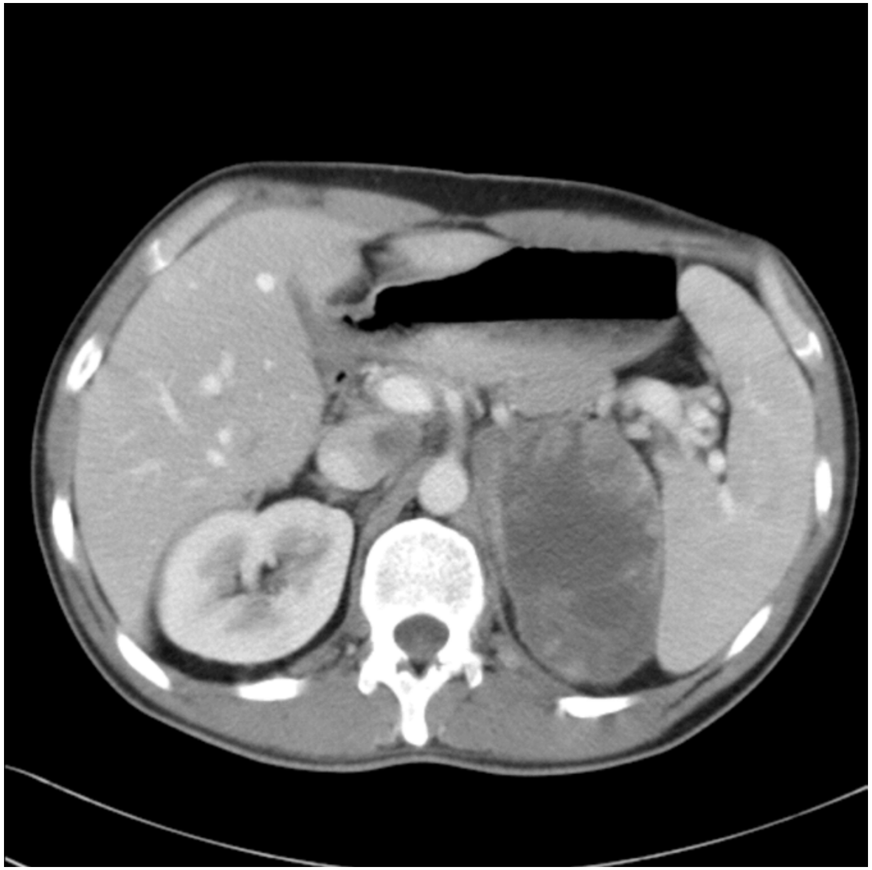

Left

Molecular Profiling of Cancer – the Future of Cancer Medicine: a Primer on Cancer Biology and the Tools Necessary to Bring it to the Clinic

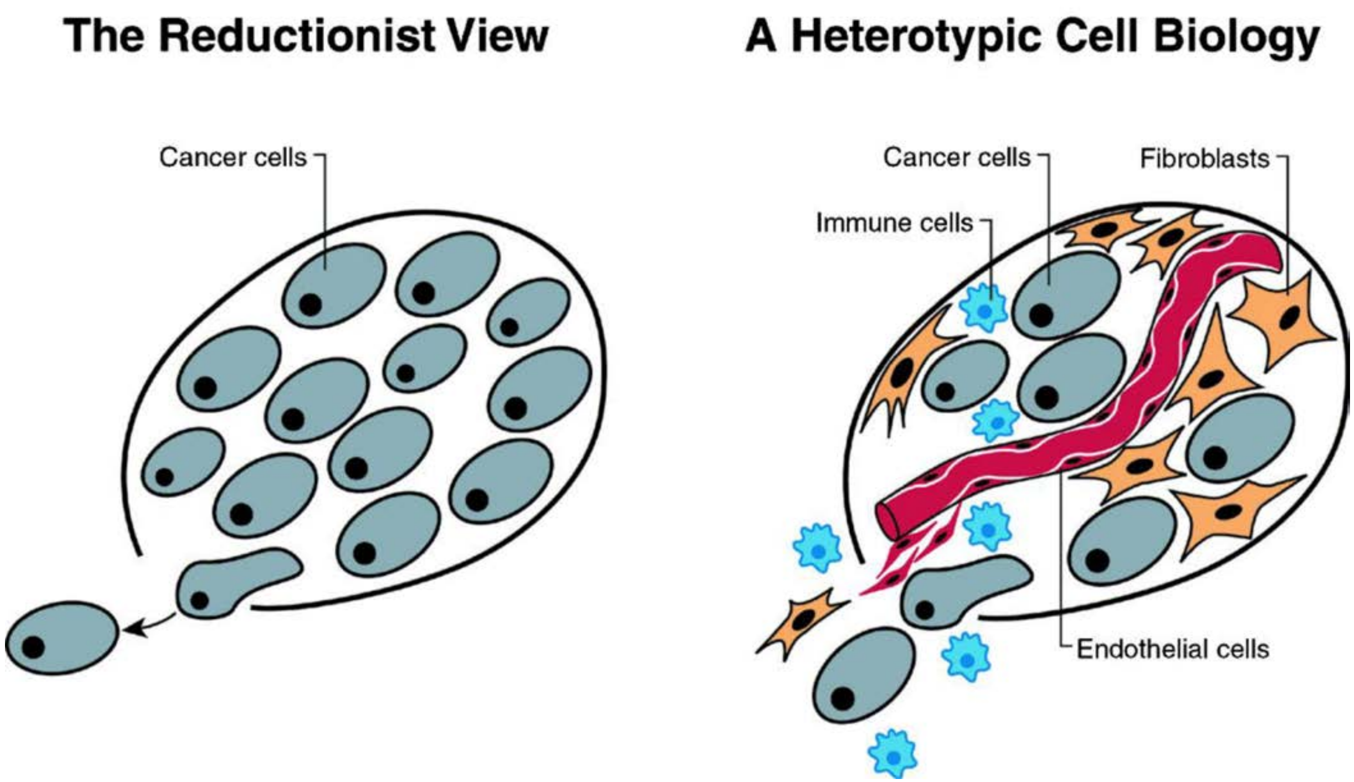
"The goal of personalized cancer medicine is to understand the relevant characteristics underlying a particular individuals disease (both disease and host factors) and then tailor therapy to that individual disease. The right drug, at the right dose, for the right patient at the right time is the goal of personalized medicine."

Stricker T et al. Semin Oncol 38: 173 - 185

Assessment of Response

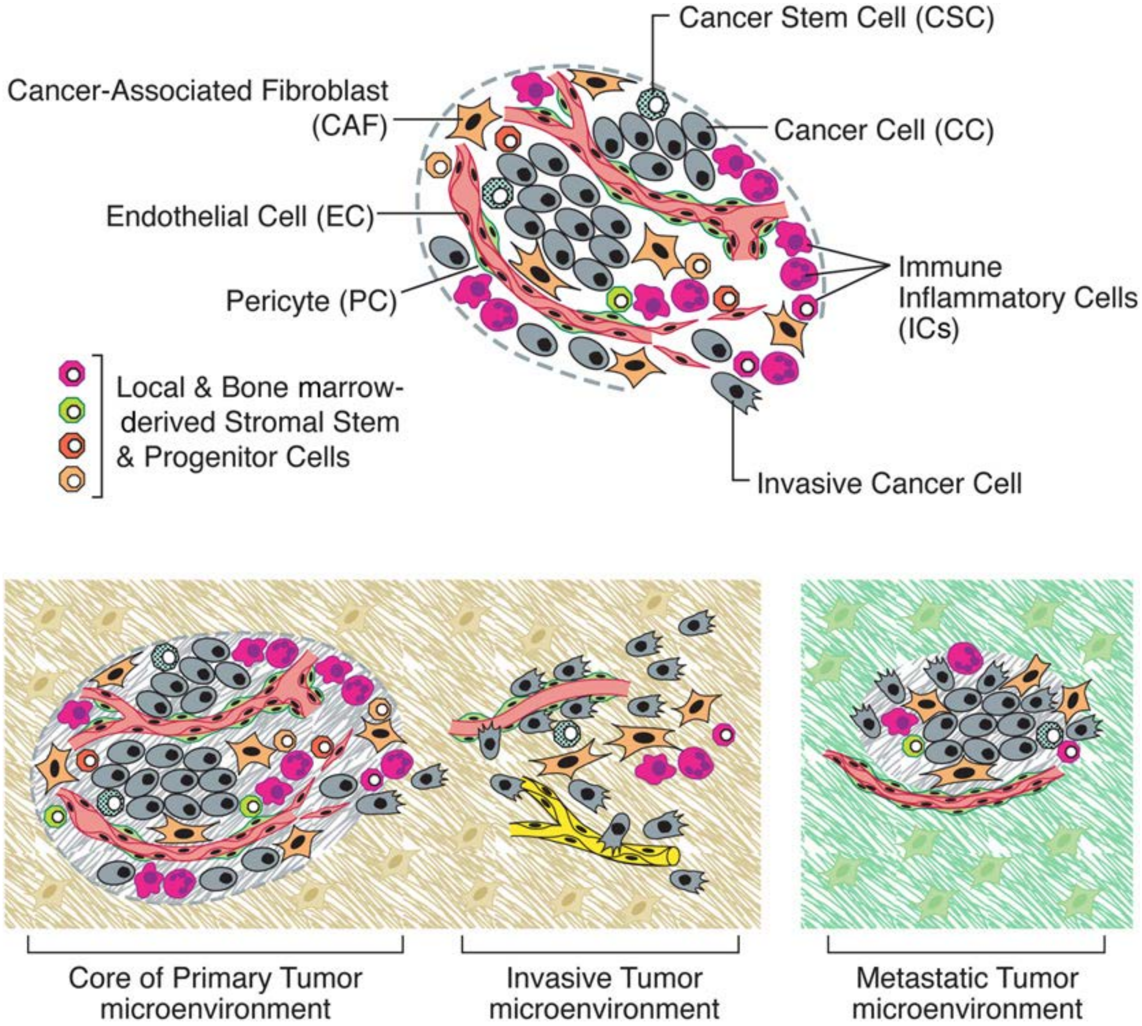


Tumors as Complex Tissues



Hanahan D and Weinberg RA. *Cell* 2000; 100:57-70

Tumors as Complex Tissues



Hanahan D and Weinberg RA. *Cell* 2011; 144:646 - 674

What is Measurable with Molecular Imaging

Workman P, et al. JNCI, 2006; 98(9):580-598

Objectives	Measurable Endpoints
Patient selection	Expression of molecular target (erbB2), Physiologic state (hypoxia)
↓	↓
Concentrations needed for activity at the site of action	Pharmacokinetic properties in plasma and/or tissue
↓	↓
Specific action on the molecular target or pathway	Target inhibition in tumors and/or surrogate normal tissue
↓	↓
Induction of the desired biologic effect	Inhibition of proliferation, invasion, angiogenesis, induction of apoptosis, differentiation or senescence
↓	↓
Resulting clinical response	Tumor regression, cytostasis
↓	↓
Patient outcome	Disease-free survival, performance status, quality of life, overall survival

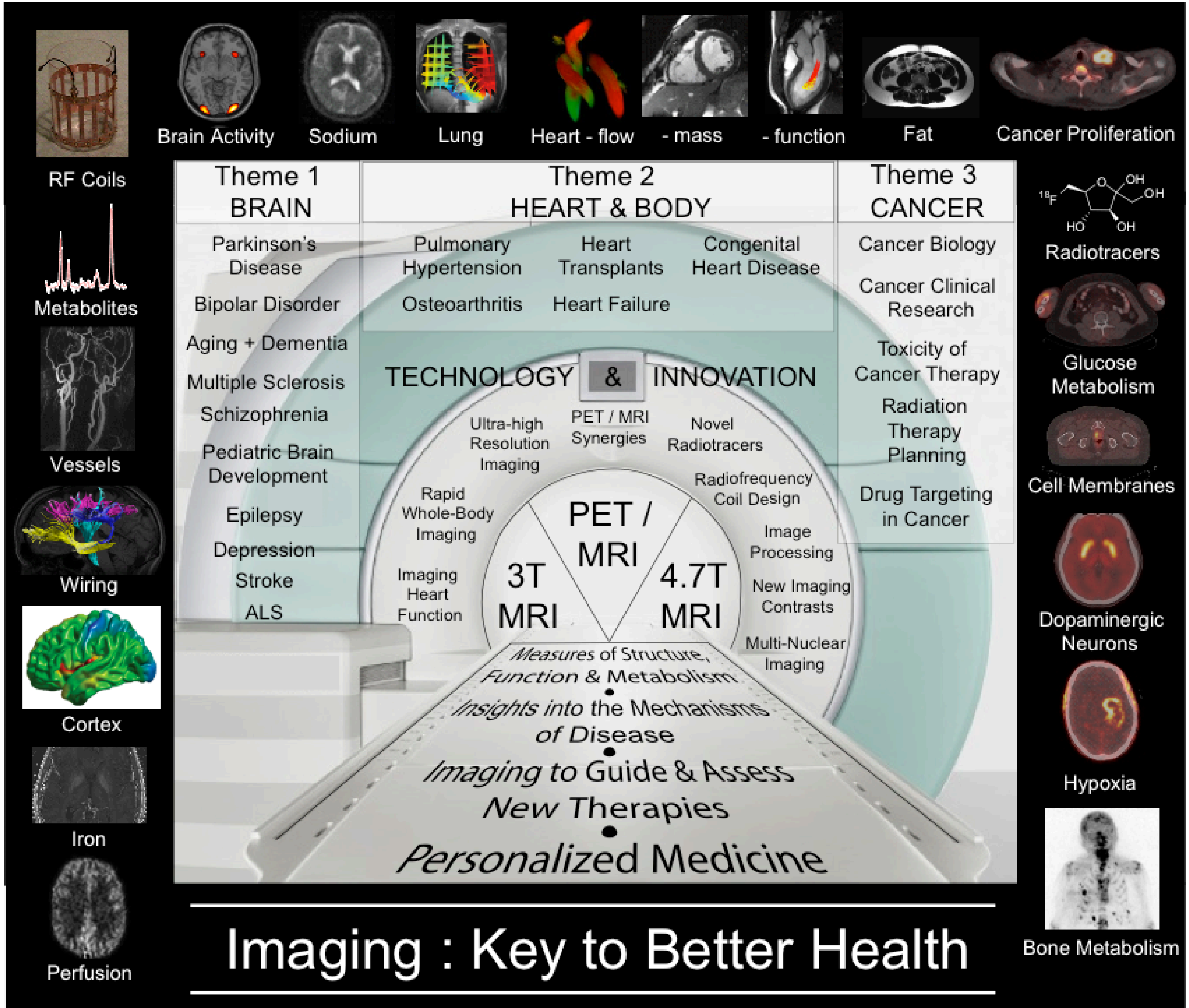
Molecular Imaging/Imaging Biomarkers in Oncology

Current Paradigm

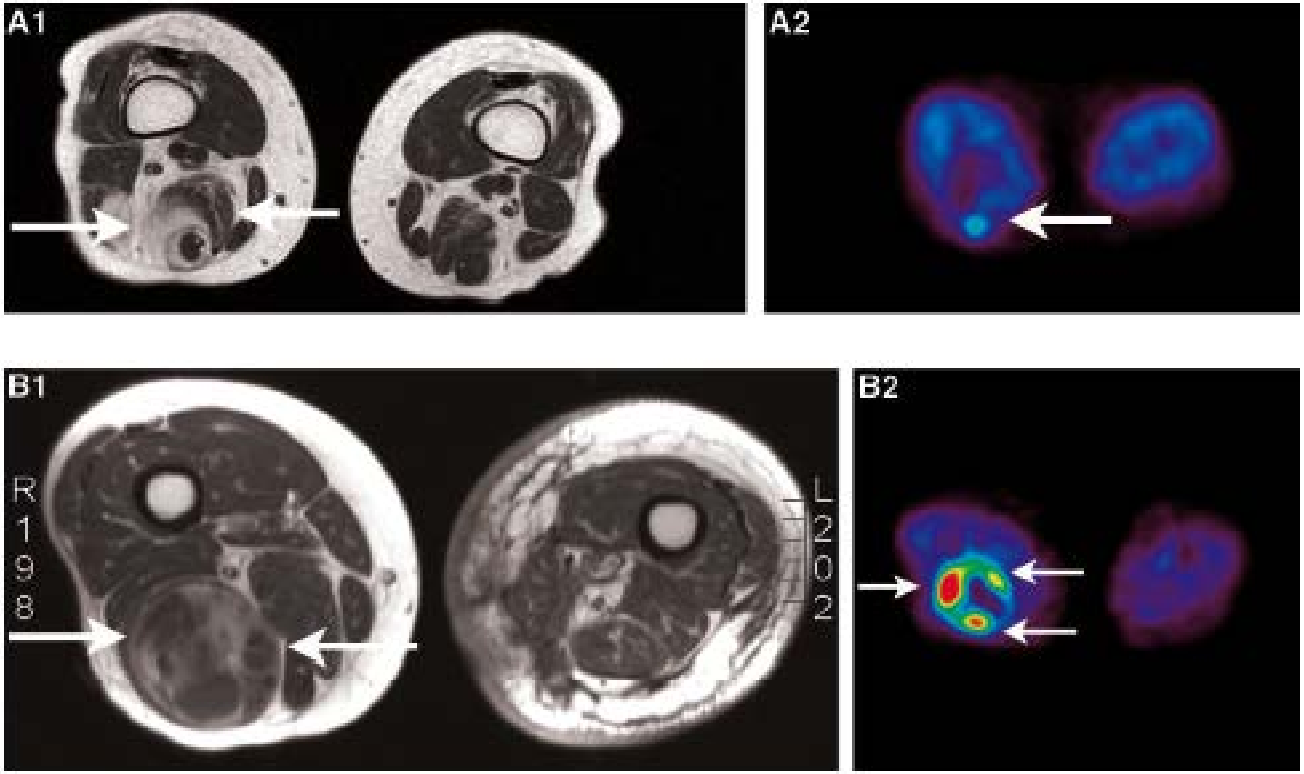
- Identify the presence or absence of tumor
  - Primary diagnosis and staging
  - Treatment effect
  - Monitoring
  - Recurrence
  - Follow-up and restaging
- Assessing toxicity
- Screening

Future Paradigm

- Current indications
- Biological characterization
  - Tumor
  - Individual
- Predicting progression/outcome
- Predicting/assaying Rx response
- Treatment stratification
- Predicting /assaying toxicity
- Personalized medicine


Brain Activity
Sodium
Lung
Heart - flow
- mass
- function
Fat
Cancer Proliferation
RF Coils
Metabolites
Vessels
Wiring
Cortex
Iron
Perfusion
Radiotracers
Glucose Metabolism
Cell Membranes
Dopaminergic Neurons
Hypoxia
Bone Metabolism
Theme 1 BRAIN
Parkinson's Disease
Bipolar Disorder
Aging + Dementia
Multiple Sclerosis
Schizophrenia
Pediatric Brain Development
Epilepsy
Depression
Stroke
ALS
Theme 2 HEART & BODY
Pulmonary Hypertension
Heart Transplants
Congenital Heart Disease
Osteoarthritis
Heart Failure
Theme 3 CANCER
Cancer Biology
Cancer Clinical Research
Toxicity of Cancer Therapy
Radiation Therapy Planning
Drug Targeting in Cancer
TECHNOLOGY & INNOVATION
Ultra-high Resolution Imaging
PET / MRI Synergies
Novel Radiotracers
Rapid Whole-Body Imaging
Radiofrequency Coil Design
Image Processing
Imaging Heart Function
New Imaging Contrasts
Multi-Nuclear Imaging
PET / MRI
3T MRI
4.7T MRI
Measures of Structure, Function & Metabolism
Insights into the Mechanisms of Disease
Imaging to Guide & Assess New Therapies
Personalized Medicine
Imaging : Key to Better Health

FLT Uptake in Low- and High-Grade Sarcoma



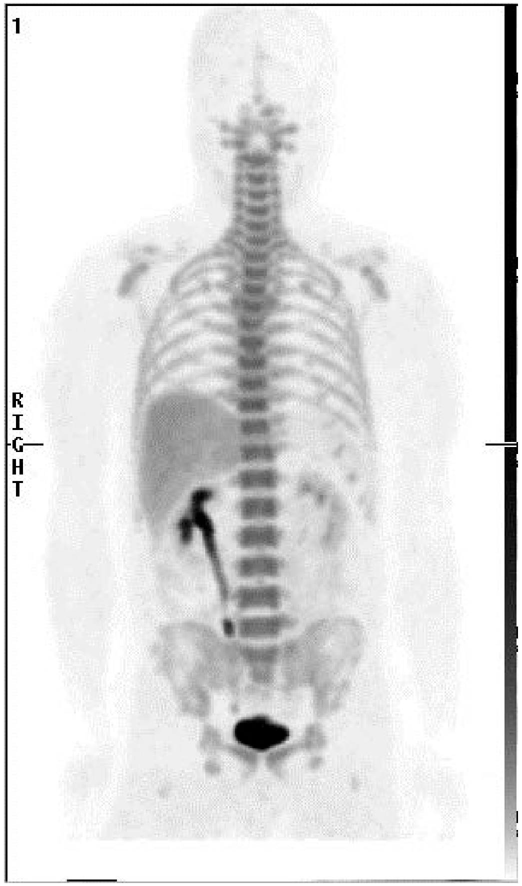
Cobben DCP, et al. *Clin Cancer Res*, 2004; 10:1685-1690

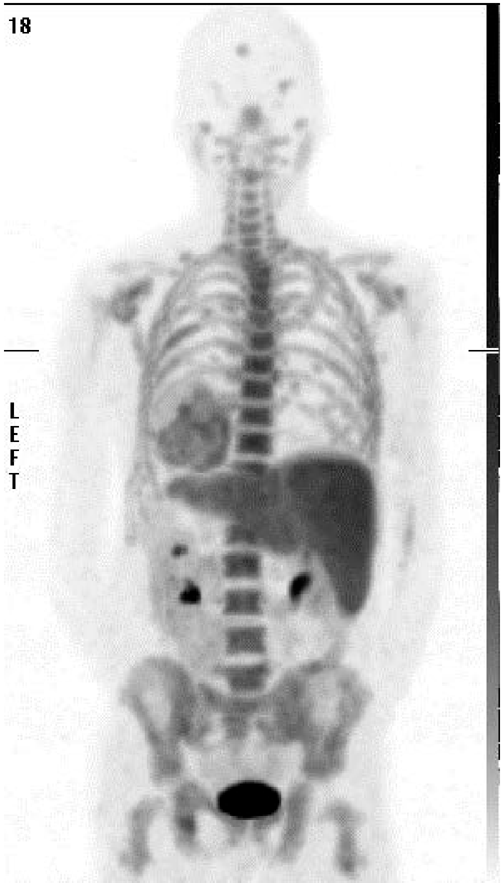
Mean and Maximal SUV and Tumor/NonTumor Ratio in Japanese Grading System

	Grade 1 (*n*=7)	Grade 2 (*n*=5)	Grade 3 (*n*=8)	Low Grade vs High
Mean SUV	1.0	2.1	2.8	0.011
Maximal SUV	1.3	2.8	3.3	0.014
TNT	2.1	3.4	6.0	0.008

Cobben DCP, et al. *Clin Cancer Res*, 2004; 10:1685-1690

Imaging with FLT in 2 Patients with NSCLC





Normal Distribution

Abnormal Distribution

Metabolic Assessment of Gliomas using ^{11}C-Methionine, $[^{18}F]$-Fluorodeoxyglucose, and ^{11}C-Choline Positron-Emission Tomography

AJNR 29: 1176 – 1182, 2008

Metabolic Assessment of Gliomas

- 95 patients with presentation with glioma
  - Brain stem and grade 1 excluded
- Presurgical evaluation with MET, FDG, CHO, contrast enhanced MRI
- Correlation with WHO histological classification

AJNR 29: 1176 – 1182, 2008

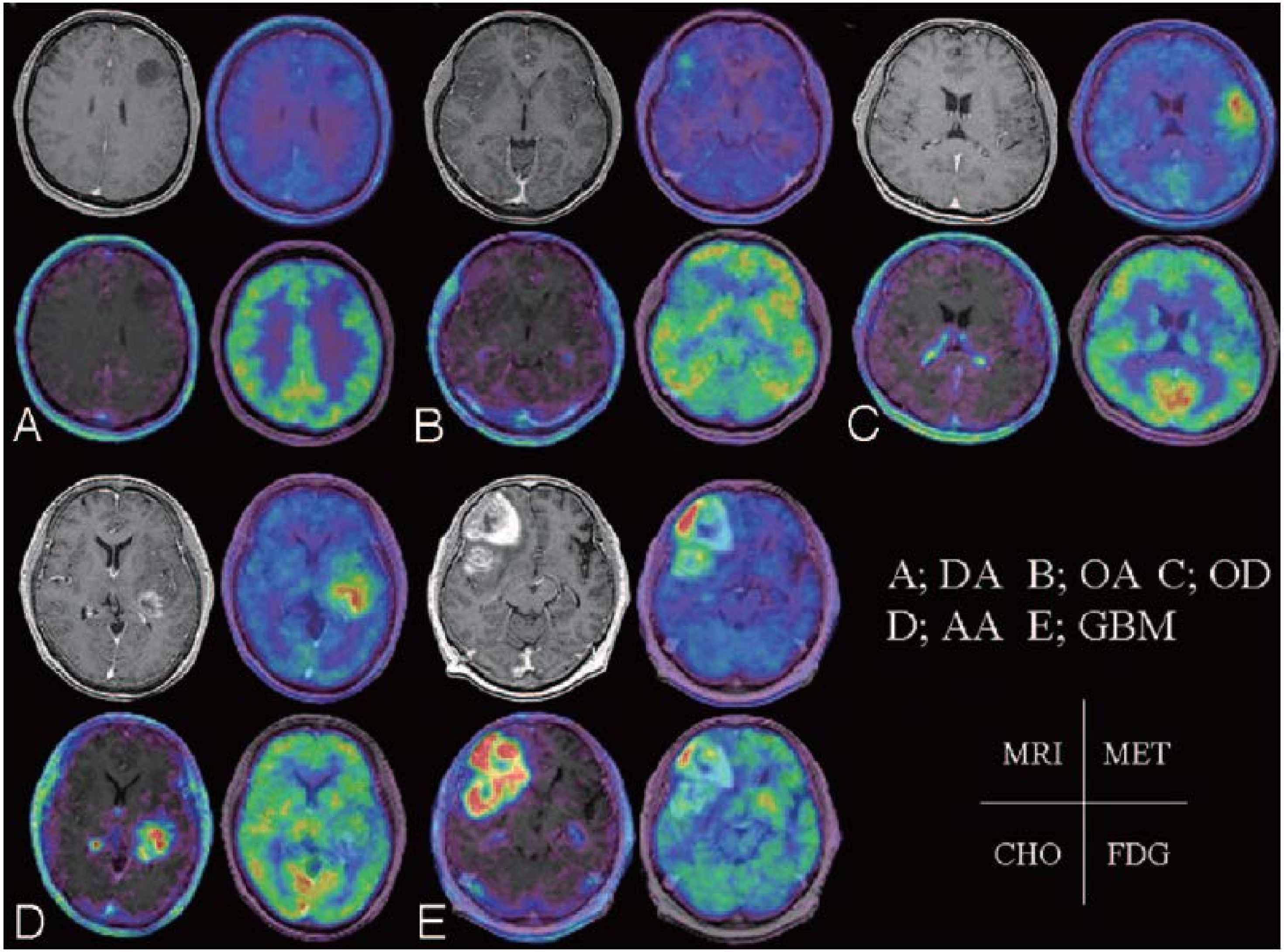
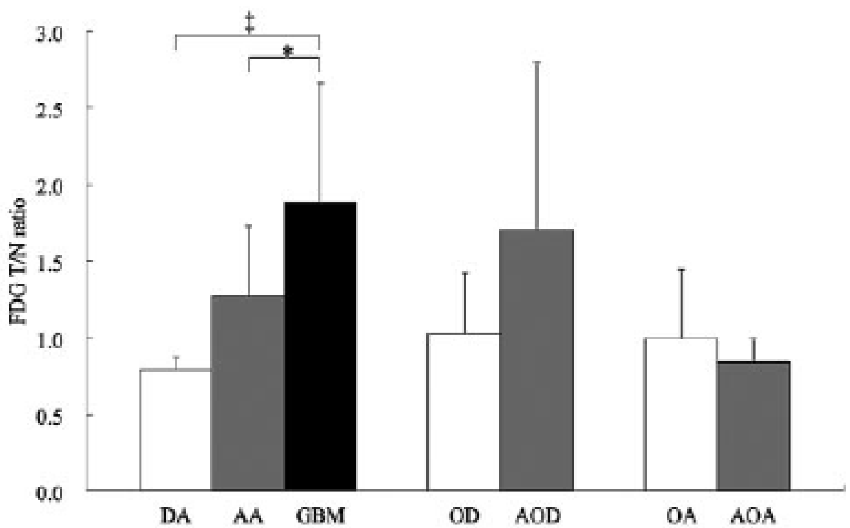


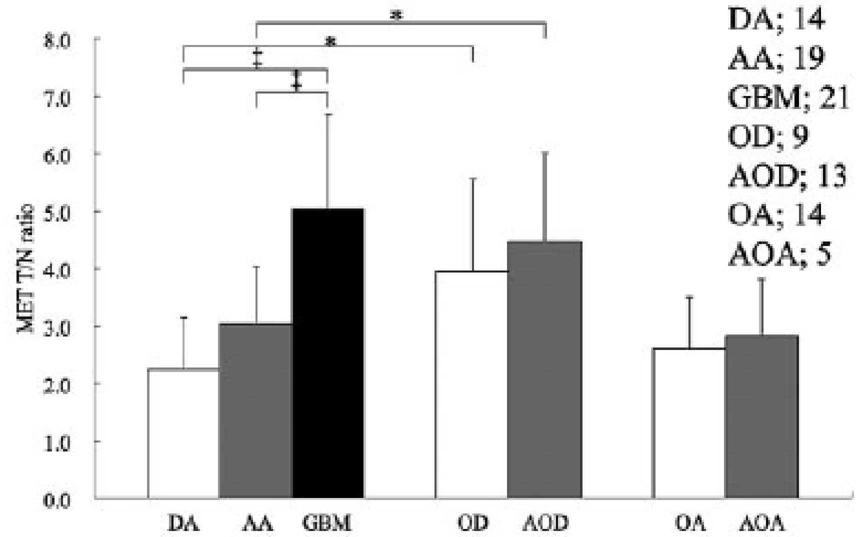
Fig 2. *Left top,* Contrast-enhanced, T1-weighted image. *Right top,* MET PET is superimposed on MR imaging. *Left bottom,* CHO PET is superimposed on MR imaging. *Right bottom,* FDG PET is superimposed on MR imaging. *A,* A 32-year-old woman presented with diffuse astrocytoma. MET T/N ratio = 1.72, CHO T/N ratio = 1.38, and FDG T/N ratio = 0.66. *B,* A 23-year-old woman presented with oligoastrocytoma. MET T/N ratio = 2.76, CHO T/N ratio = 1.82, and FDG T/N ratio = 0.92. *C,* A 44-year-old man presented with oligodendroglioma. MET T/N ratio = 3.71, CHO T/N ratio = 2.74, and FDG T/N ratio = 1.07. *D,* A 62-year-old woman presented with anaplastic astrocytoma. MET T/N ratio = 4.26, CHO T/N ratio = 10.17, and FDG T/N ratio = 1.24. *E,* A 68-year-old man presented with glioblastoma multiforme. MET T/N ratio = 6.85, CHO T/N ratio = 33.38, and FDG T/N ratio = 2.55.

AJNR 29: 1176 – 1182, 2008

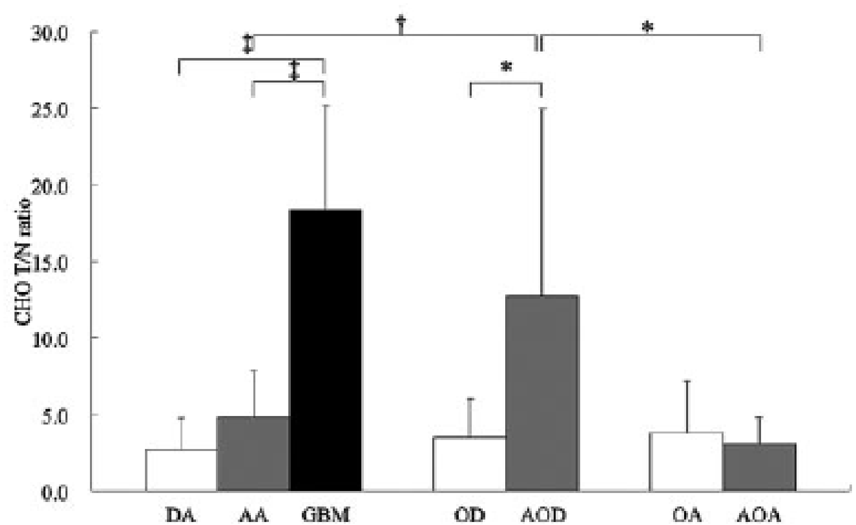
Correlation Between Tracer Uptake and Tumour Grade



FDG



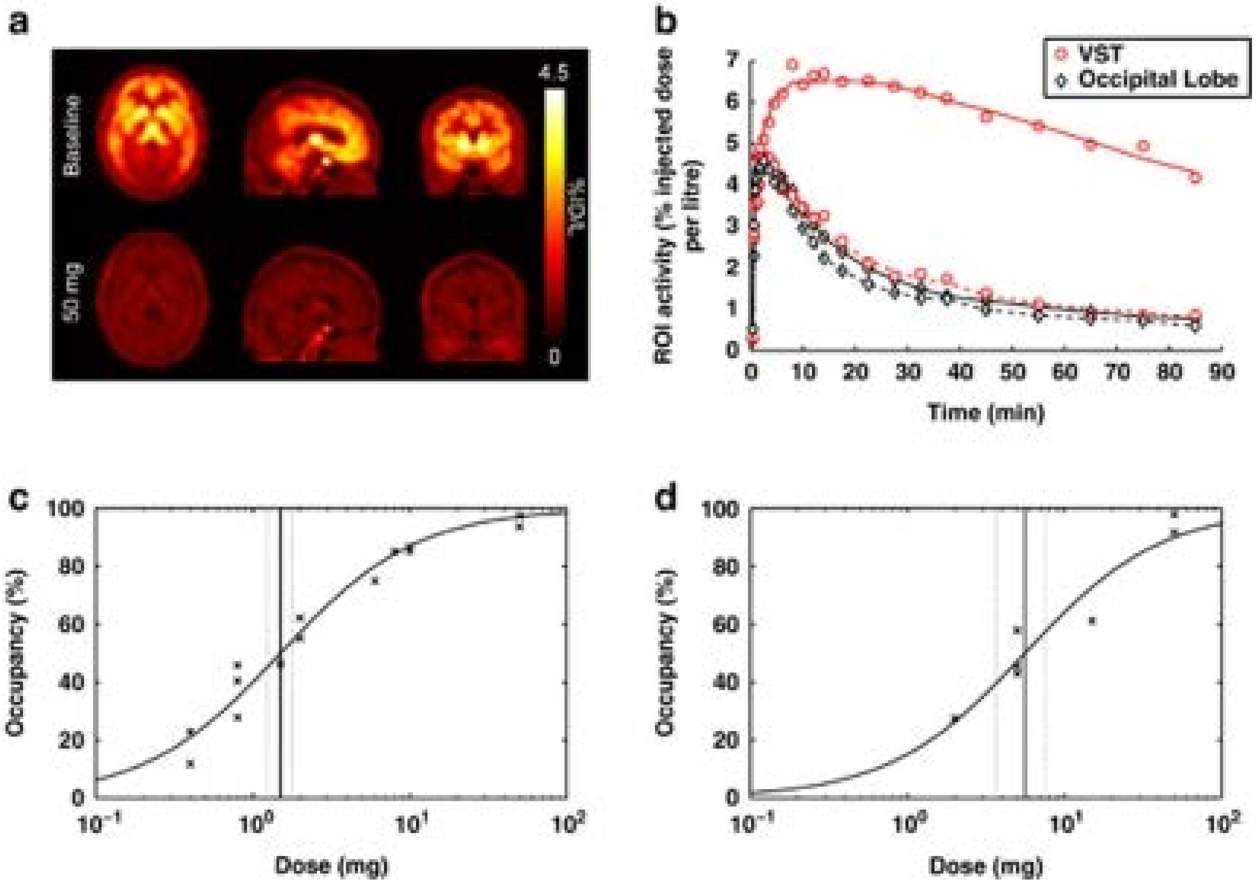
MET



CHO

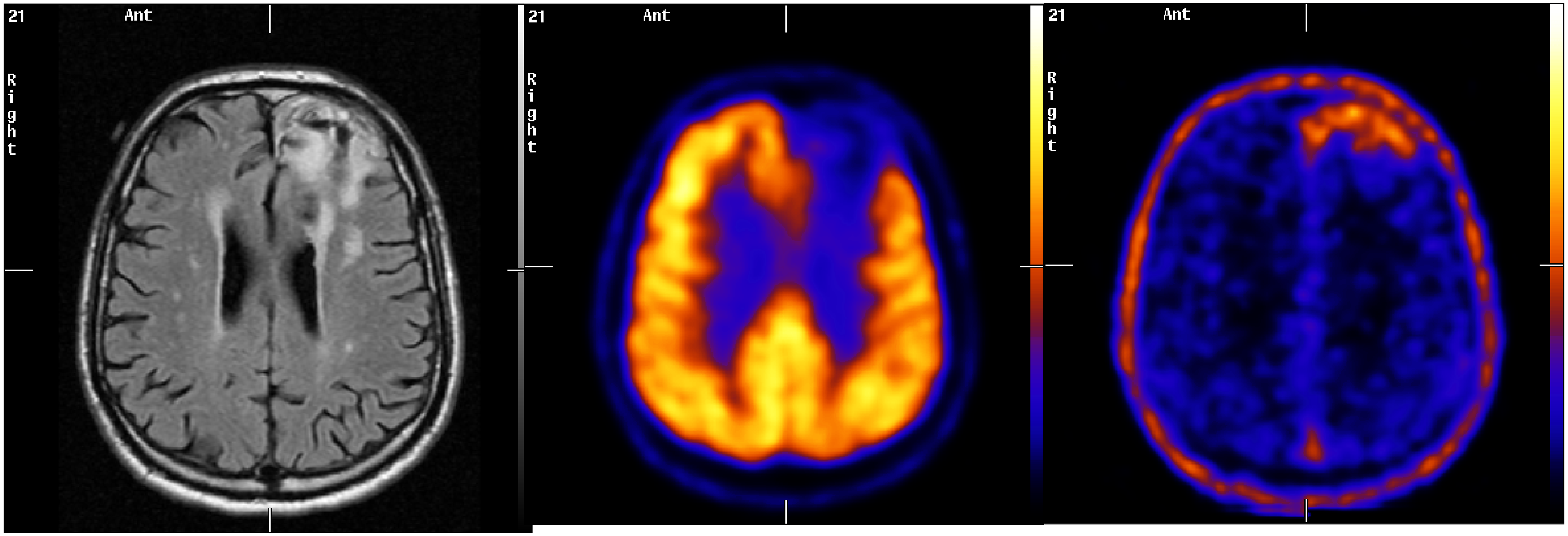
AJNR 29: 1176 – 1182, 2008

^{11}C-Carfentanil Distribution in Brain



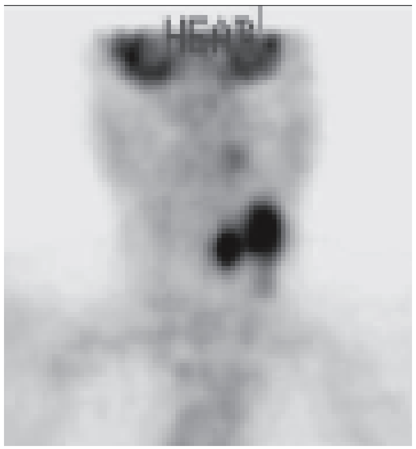
Mol Psychiatry. 2011 Aug; 16(8): 826–835.

Hypoxia Imaging in GBM - FAZA

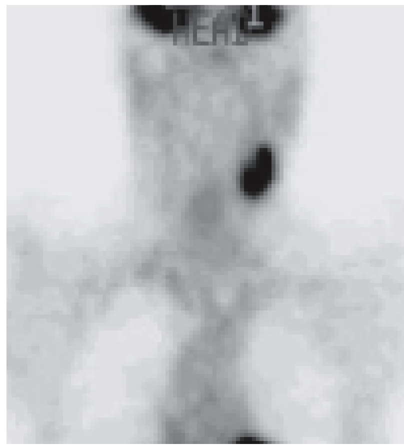


Hypoxia Imaging: Tirapazamine Trial

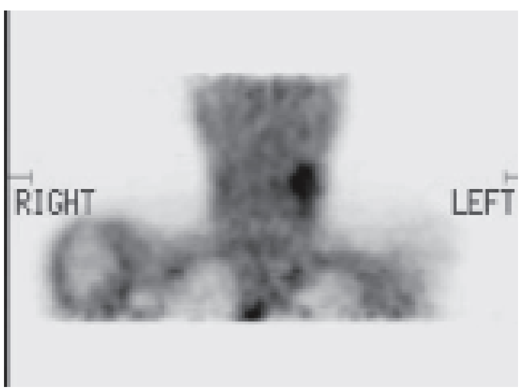
Rischin D, et al. J Clin Oncol; 2006; 23(13): 2098-2104



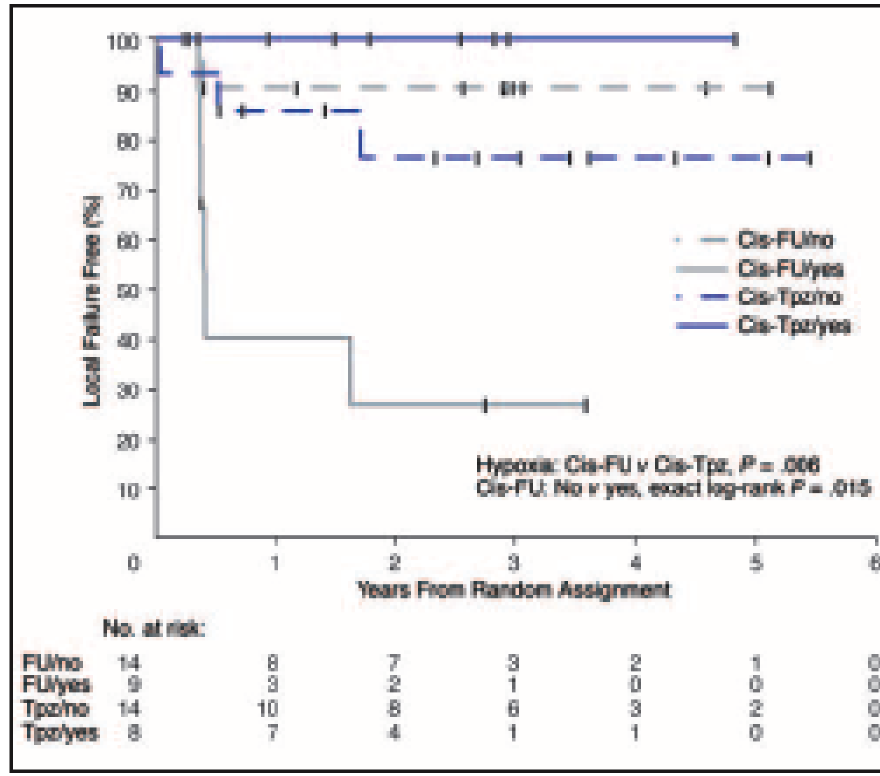
FDG Pre Rx



FDG Post Rx



FMISO Pre Rx



KM Survival Standard of Care
–v – SOC + Tirapazamine

Functional imaging of neuroendocrine tumors with combined PET/CT with ^{68}Ga-DOTATATE and ^{18}F-FDG

Kayani I, et al. *Cancer* 2008;112:2447-2455

- 38 patients with prior diagnosis of NETs
  - 34 GEP
  - 4 Unknown primary
- Gold standard: Histology, markers, Progressive imaging
- Ga-68 sensitivity: 82%
- FDG sensitivity: 66%

Imaging Biomarkers for Cancer Biology

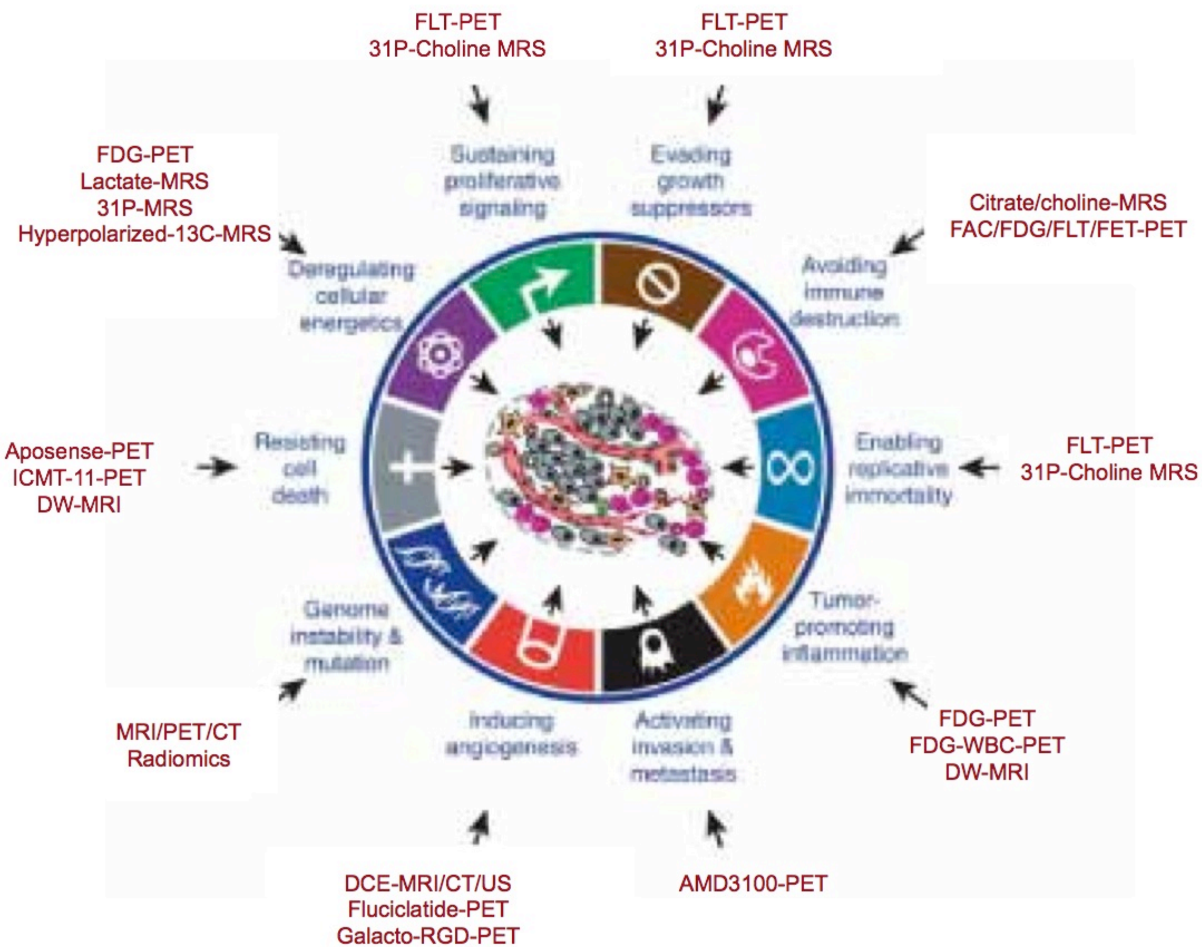


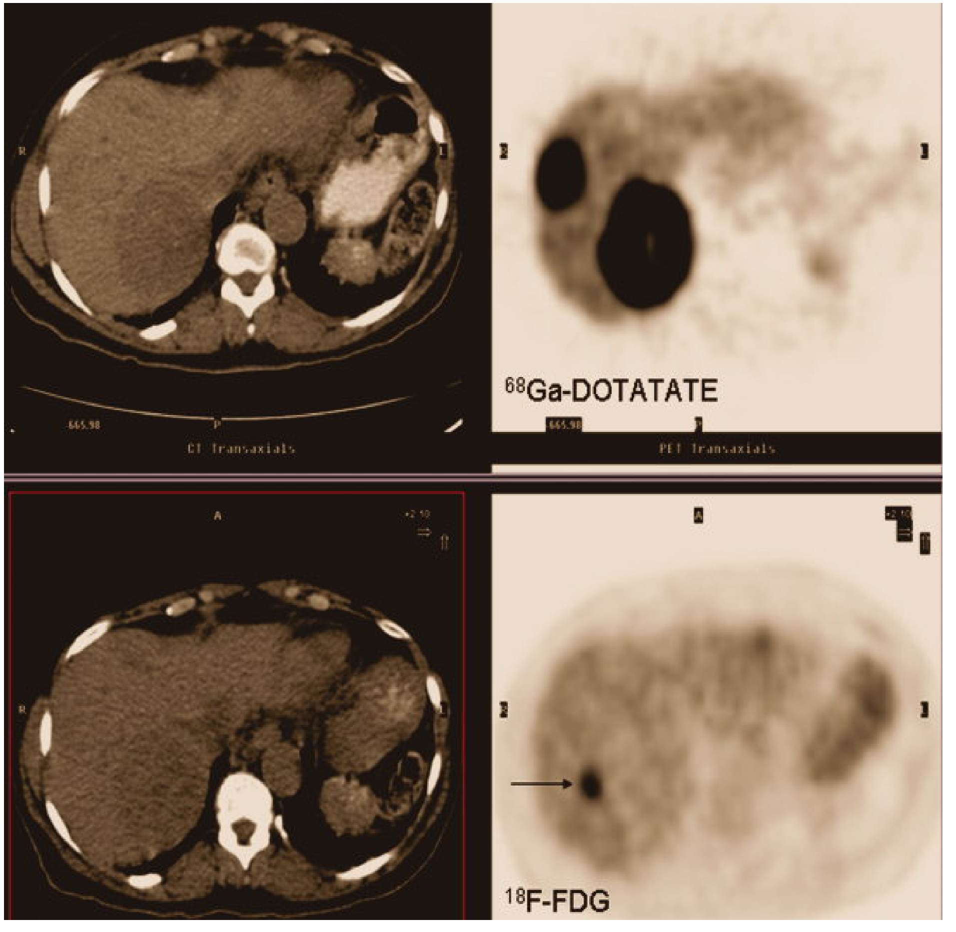
Figure: Hanahan D and Weinberg R, 2011, Cell, ***144****:646-674, adapted by Adapted by E Aboagye, R Maxwell and DR Newell*

Criteria for Assessing the Prognosis of Neuroendocrine Tumors of the Gastrointestinal Tract

Bioliogical behaviour	Meta- stases index	syndrome	Histological Invasion	Tumor differenti-	Angio- ation	Ki-67 size	Hormonal invasion
Benign	-	-	Well	≤ 1 cm	-	< 2%	-
Benign or low grade	-	-	Well	≤ 2 cm	-/+	< 2%	-
Low grade malignant	+	+	Well	> 2 m	+	>2%	+
High grade malignant	+	+	Poorly	Any	+	>30%	-

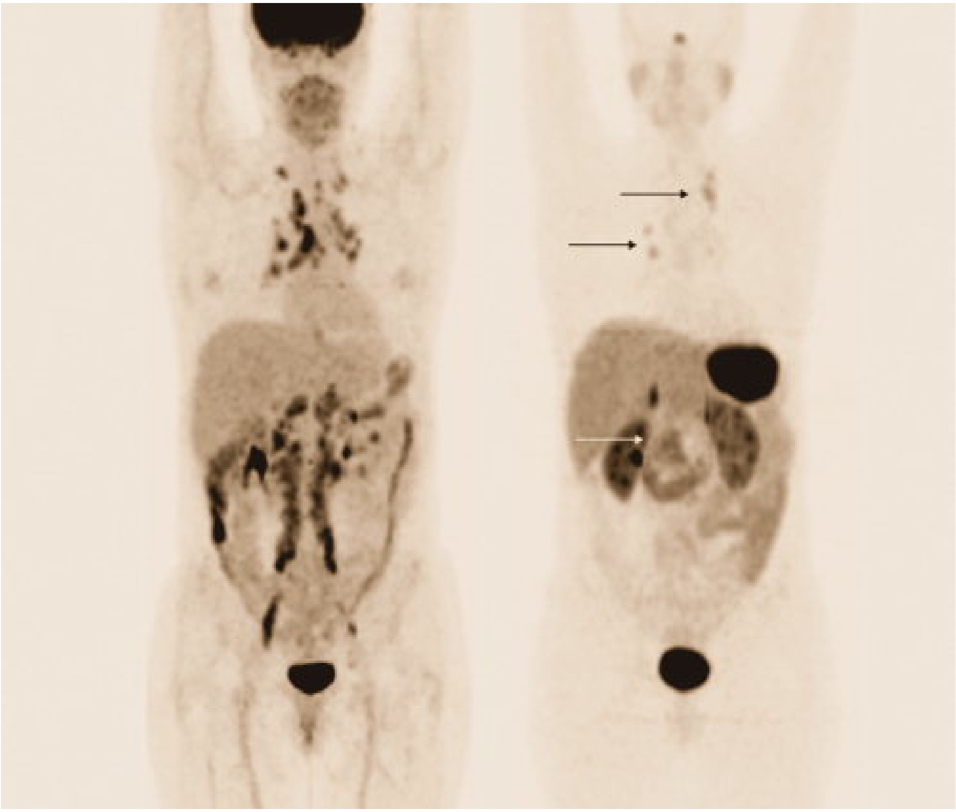
Klöppel G, et al. Ann NY Acad Sci. 2004; 1014:13-27.

54-year-old Female Patient with Metastatic Carcinoid Tumor (Primary Cecal Carcinoma)



Kayani I, et al. *Cancer* 2008;112:2447-2455

55--yer-old Female Patient with Metastatic Neuroendocrine Carcinoma with Unknown Primary



FDG **Ga-68**

Kayani I, et al. *Cancer* 2008;112:2447-2455

SUVmax of ^{68}Ga-DOTATATE and ^{18}F-FDG According to Tumor Grade

	^{68}Ga-DOTATATE	^{18}F-FDG	*P*
All NET	16.9 (1.6-50)	4.2 (1.4-16.4)	.005
Ki67 index ≤2%	29 (3.3-45)	2.9 (1.5-12)	<.001
Ki67 index 3%-20%	15.5 (1.8-50)	10.5 (2.0-13.9)	NS
Ki67 index >20%	4.4 (1.6-8.9)	11.7 (4.1-16.4)	.03

Kayani I, et al. *Cancer* 2008;112:2447-2455

Radioisotope Therapy (RIT)

Lu-177 DOTATATE Treatment for Patients with Neuroendocrine Tumours

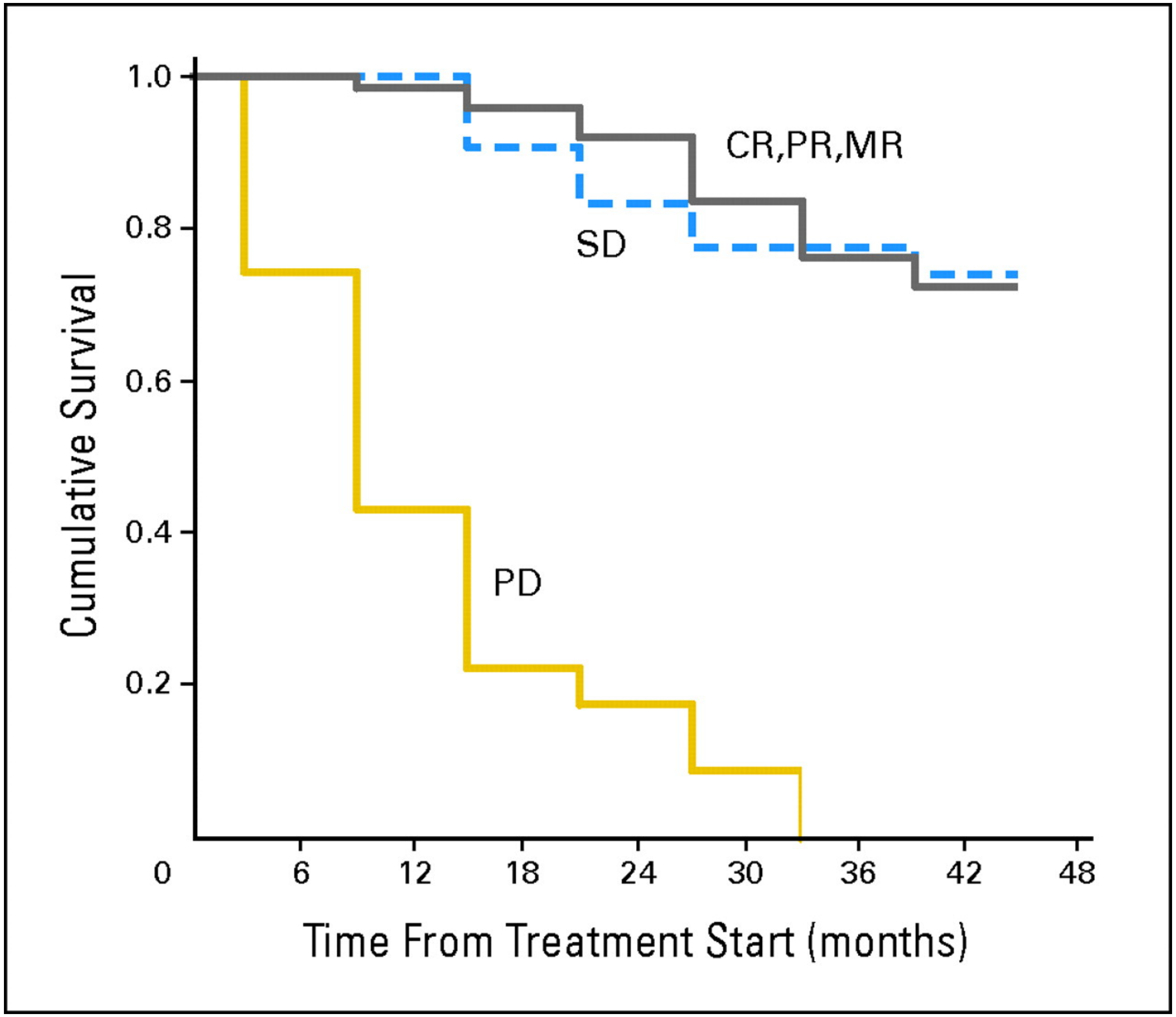
Sandy McEwan, M.B. F.R.C.P.C
Chair, Department of Oncology
University of Alberta

Treatment With the Radiolabeled Somatostatin Analog [^{177}Lu-DOTA^{0},Tyr^{3}]Octreotate: Toxicity, Efficacy, and Survival

Dik J. Kwekkeboom, et al

JCO, 2008:2124-2130

Lutetium Octreotate Rx Survival in GEPNETS



Kwekkeboom, D. J. et al. J Clin Oncol; 26:2124-2130 2008

Previous PRRT monotherapy studies in NET

Reference	Type	Patients	Compound	Primary Tumor	Mean Dose (GBq)	Mean Cycles (N)	DCR (%)	PFS (M)	OS (M)
MEDICAL THERAPIES									
Yao 2011 (19)	P	207	Everolimus	P-NET	10mg	daily	78	11	>28
Raymond (20)	P	86	Sunitinib	P-NET	37.5 mg	daily	72	11.4	>20
Rinke (22)	P	42	Octreotide	GE-NET	30 µg	4-weekly	NA	14.3	>75
Martin-Richard 2013 (21)	R	30	Lanreotide	ALL NET	120 mg	4-weekly	89	12.9	NA
PRRT									
Waldherr 2001 (2)	P	41	^{90}Y-TOC	ALL NET	6/m^2	4	85	>26	>24
Imhof 2011 (3)	R	1109	^{90}Y-TOC	ALL NET	3.7/m^2 *Cycle	2 (1-10)	39.3	NA	NA
Kwekkeboom 2008 (4)	R	310	^{177}LU-TATE	ALL NET	28.7	4	80.3	33	46
Bodei 2011 (9)	P	51	^{177}LU-TATE	ALL NET	25.2-26.4	4-6	82	36	36>
Sansovini 2013 (10)	P	52	^{177}LU-TATE	P-NET (all)			81	29	>30
Ezziddin 2014 (8)	R	68	^{177}LU-TATE	P-NET	32	4	85	34	53
Paganeli 2014 (11)	P	43	^{177}LU-TATE	GE-NET	18.4 - 25.7	5	84	36	> 60
Romer 2014 (6)	R	141	^{177}LU-TOC	ALL NET	13.5	2	NA	NA	45.5
Present Study	R	56	^{177}LU-TOC	ALL NET	13.1	2.1	66.1	17.4	34.2
		24	1 Cycle	ALL NET	6.9	1	29.2	3.8	3.9
		32	> 1 Cycle	ALL NET	18.5	2.6	94	32	35
		24	> 1 Cycle	GEP_NET	19.4	2.7	100	34.5	34.7
		8	> 1 Cycle	Other NET	15.9	2.4	75	11.9	16.2
BL SD - Percept Patients with Stable Disease at Baseline									

Theranostics 2016. 6(4) 501-510 DOI: 10.7150/thno.13702

Radioisotope Therapy (RIT)

The systemic administration of a targeted radionuclide utilizing short range beta (alpha) particle or electron emissions to achieve a clinically important outcome for a patient with primary or metastatic cancer:

- Symptom control; improved quality of life
- Stable disease
- (Good) partial remission
- Complete remission
- Prolonged response times
  - Increased progression free survival
  - Increased overall survival

Treatment Delivery in RIT

- Current paradigm continues to be governed by:
  - Classical radiobiology
  - Classical dosimetry
  - Fixation on tumor dose
- Emulation of classical external beam radiation oncology principles
- "First dose is best (only) chance of clinical benefit"
- Lack of appropriate clinical trial methodology
- Lack of robust clinical outcomes data

Two Paradigms for RIT

- **“Big Bang”**

  High unit dose

  Toxicity rescue

  Single treatment

  Possibly precludes further treatments

  High complexity

  Always inpatient

Paradigm of Physics

- **“Steady State”**

  Low unit dose

  High cumulative dose

  Multiple treatments

  Titrate to toxicity

  Delayed Response

  Low complexity

  Usually outpatient

Paradigm of Biology

The Edmonton Protocol

The Edmonton Lu-177 Protocol

Hypothesis: Induction & long-term maintenance therapy with Lu-177 improves outcomes in patients with NETs, and is effective and safe for these patients.

Clinical Protocol: up to 12 cycles in total

- ***Induction*****:** 4 cycles of up to 6.11 GBq/cycle every 2.5 – 3.5 months
- ***Maintenance*****:** up to 8 cycles of up to 4.07 GBq/cycle every 5.5 – 10 months

Edmonton Protocol

Therapy Number	Year	Frequency	Evaluations
Induction 1 - 4	1	Every 10 - 12 weeks	CT/MRI scans and blood work/urine 4 months after therapy 4.
Maintenance 5 - 6	2	Every 6 months (range 5 – 8 months)	CT/MRI scans and blood work/urine 4 months after therapy 5 & 6.
7 - 8	3	Every 6 months (range 5 – 9 months)	CT/MRI scans and blood work/urine 4 months after therapy 7 & 8.
9 +	4	Every 9 months (range 7 – 12 months)	CT/MRI scans and blood work/urine 4 months after each subsequent therapy.

Distribution of Lu-177 patients at CCI - GEPNETS

Subjects with at least 1 treatment	n = 138
Primary	PNET n=44; GNET n=84, presumptive GNET n=10
Age (yrs) at treatment onset (mean, range)	61.3 (26.5 – 84.4)
Gender (M/F)	74/64

Current Active Patients: March 31, 2016

Patients	Number
Active Therapy	109
No Longer on therapy	29
Deceased	13
Progressive Disease	9
On Hold - Toxicity	5
Complete Remission	2

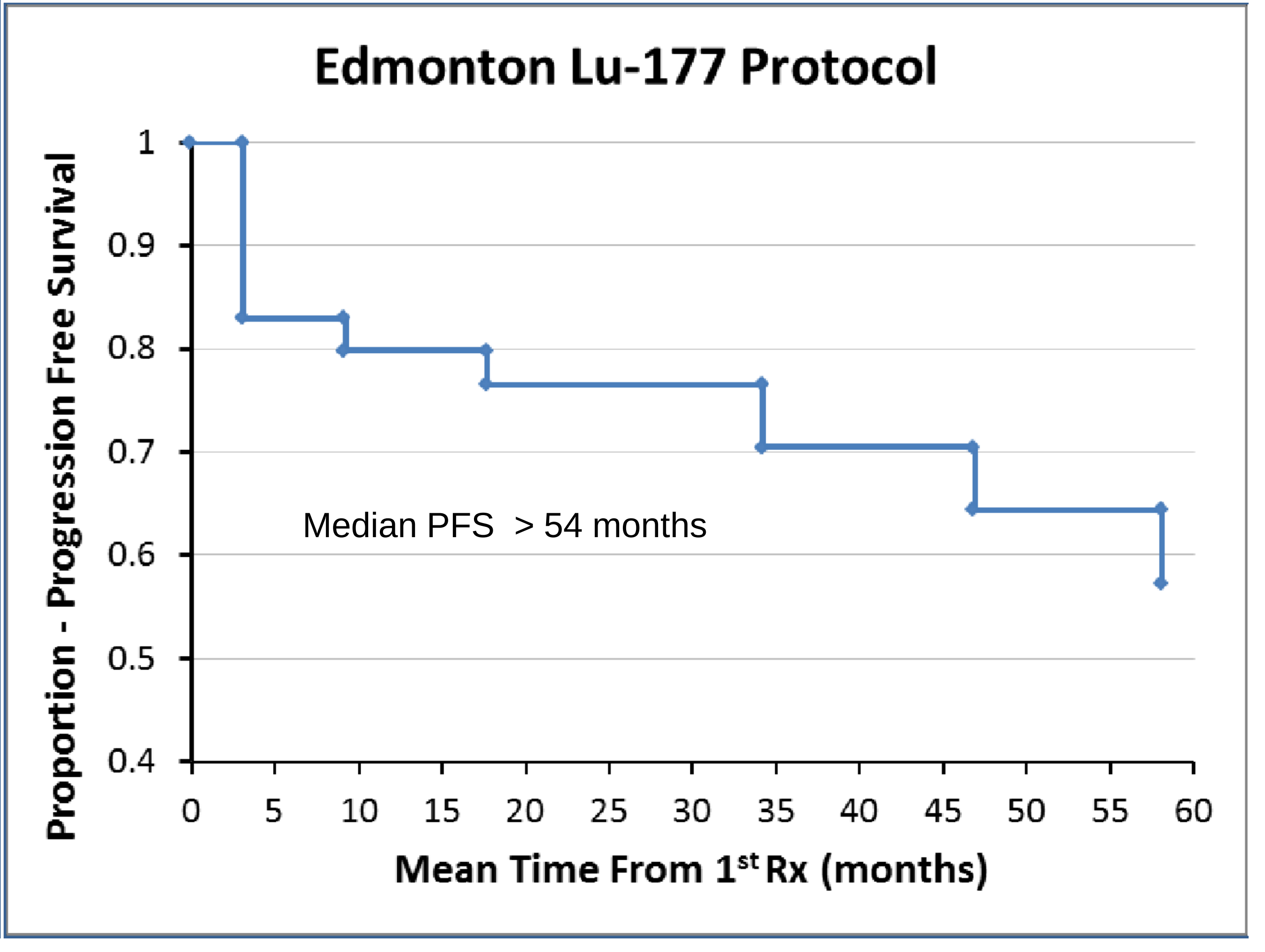
Cumulative Administered Lu-177 Doses

Total # Lu-177 Doses	Cumulative Lu dose (GBq) (mean ± SD)
1 - 2	5.76 (2.4)
3 - 4	17.90 (3.4)
5 - 6	23.49 (3.9)
7 - 8	31.98 (4.3)
9 - 10	40.25 (2.9)
11 - 12	48.88 (6.0)

Rx Failures by Primary Site

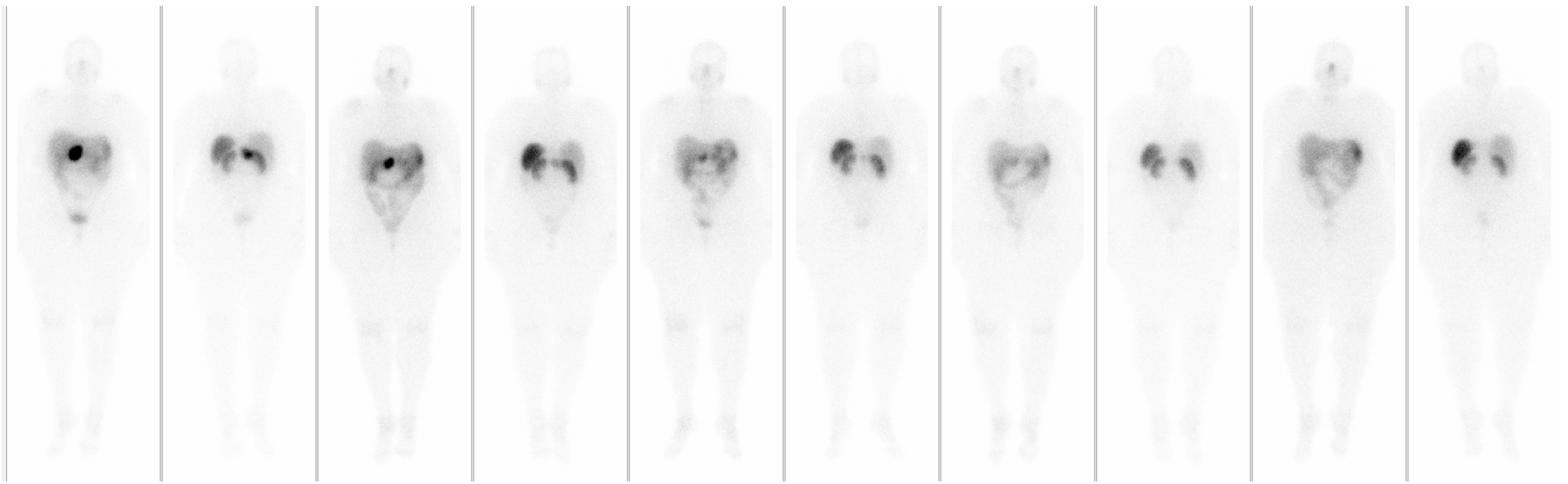
Site	No Longer on Rx	Deceased	PD	CR	On Hold
PNET	11	5	4	0	2
GNET	15	6	4	2	3
pGNET	3	2	1	0	0

Progression Free Survival

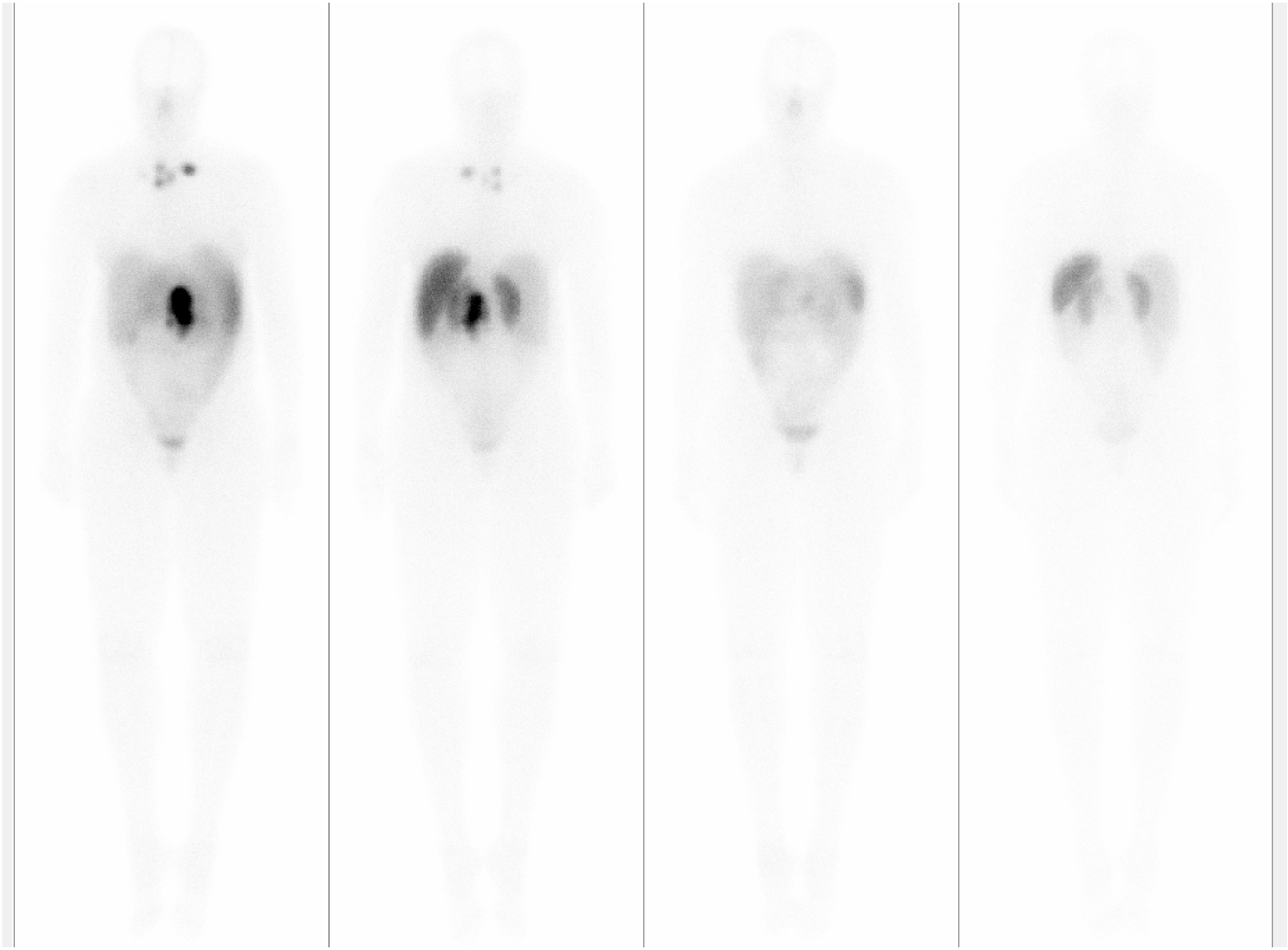


Surgical CR After 6 Cycles

Aug 2014 Nov 2014 Feb 2015 Apr 2015 Apr 2016

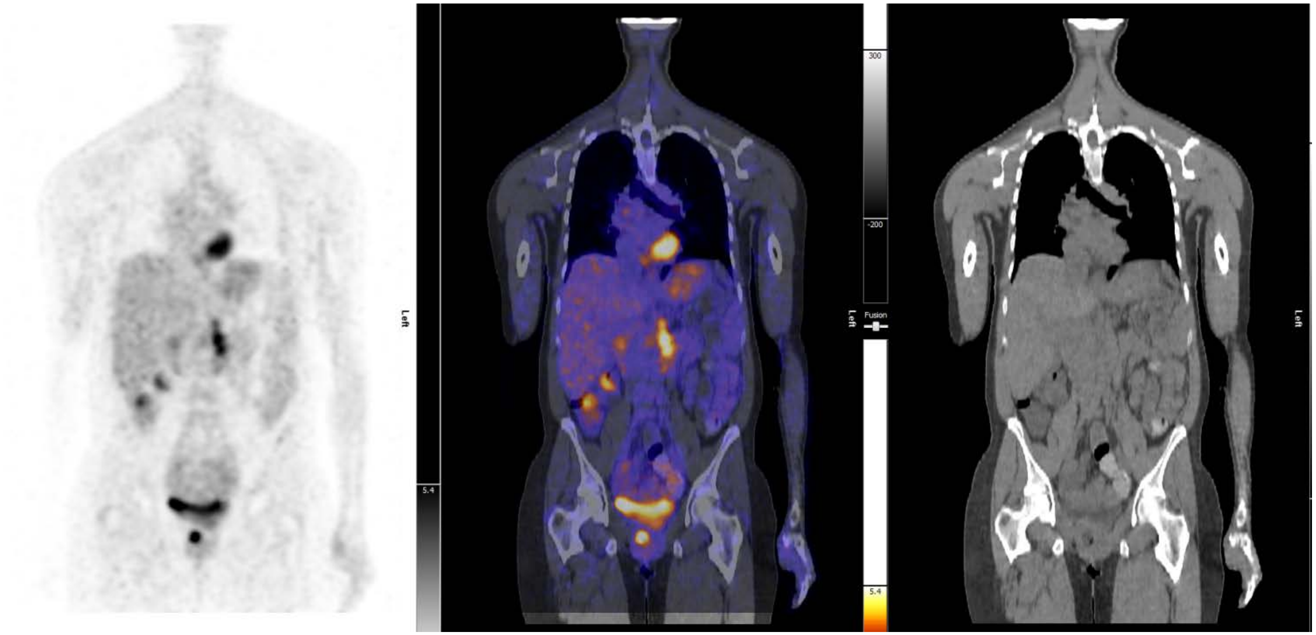


NM “CR” After 6 Cycles

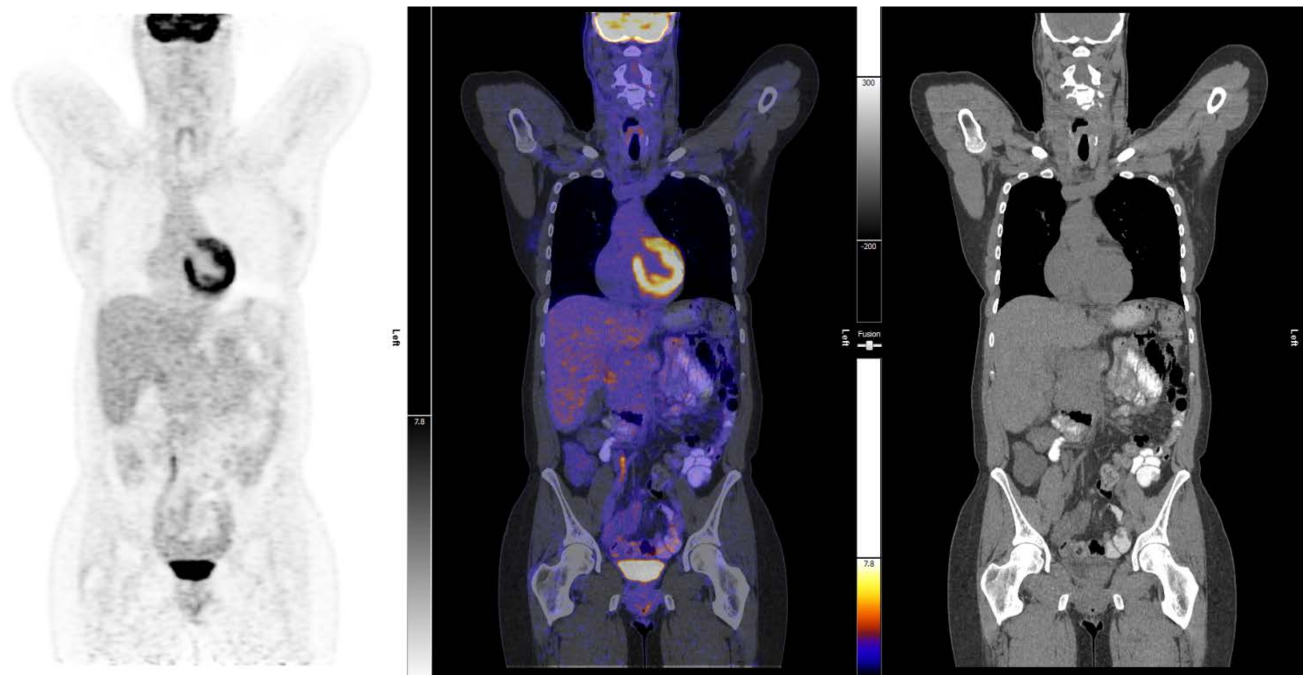


PET "CR"
After 6
Cycles

Jan 2013



Jan 2015



Lu-177 Therapy Overview All Diagnoses

- Data support hypothesis that induction and maintenance therapy with Lu-177 improves PFS in patients with GEPNETS.
- This regimen is more effective than literature reported treatment regimens.
- In this cohort, median PFS has not been reached at 54 months.
- GNET response rate > PNET
  - 80% -v- 62%

Edmonton Protocol Toxicity

- Lymphocytes ≥ grade 3: n = 10
- Platelets ≥ grade 3: n = 1
- White cells ≥ grade 3: n = 1
- Renal ≥ grade 3: n = 4
- No myelodysplasia or leukemia has been observed

Clinical Outcomes after Steady State RIT (Biological Hypothesis; Edmonton Protocol)

- Stable disease is common
- Palliative responses are the norm
    - There appears to be a cumulative dose benefit
    - Treatments may be sustained for several years
    - There appears to be limited cumulative dose risk
    - Treatments may continue as maintenance
    - Response may be sustained for several years
- Unequivocal progression free survival benefit
- Probable overall survival benefit
- Toxicity is very limited; is acceptable at the doses administered and should not reduce therapy goals of improving long term responses
- ? Implications for combination therapies

How Does it Work

(Biological Hypothesis)

Characteristics of Radioisotope Therapy

Clinical Characteristics

- **Systemic administration**
- **Retreatment**
- **Low toxicity**
- Low complexity
- Adjuvant treatment (?)

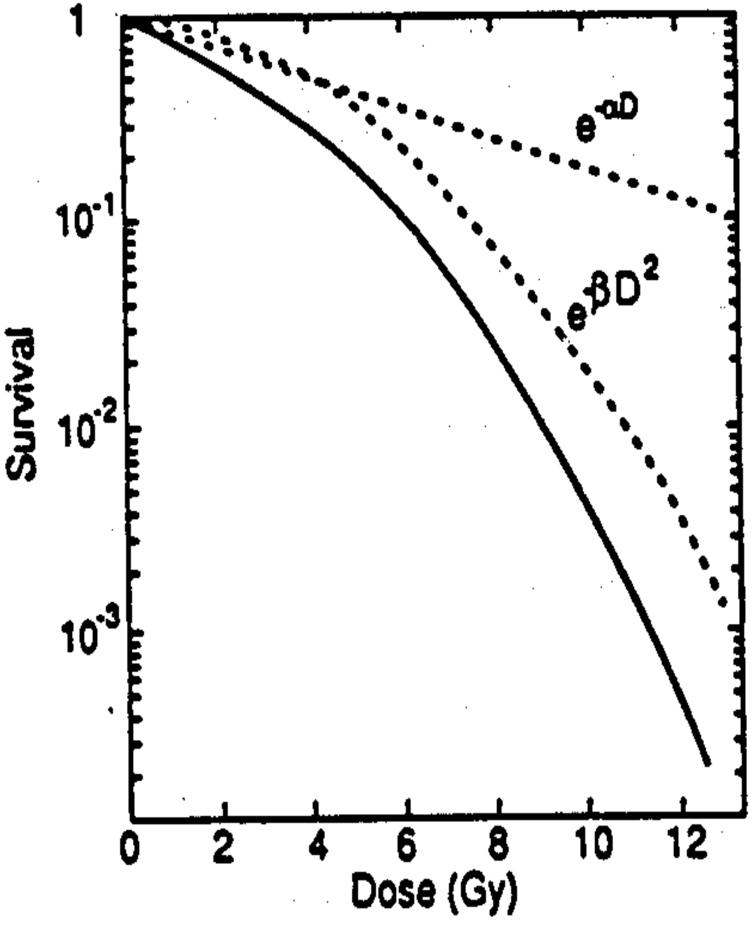
Scientific Characteristics

- **VLDR/LDR**
- ***Microdosimetry (biology)***
- T_p correlates with T_b
- Low proliferation rate (?)
- Ability to image (theragnostic)
- Specific targeting

“Classical” Cell Survival Curves

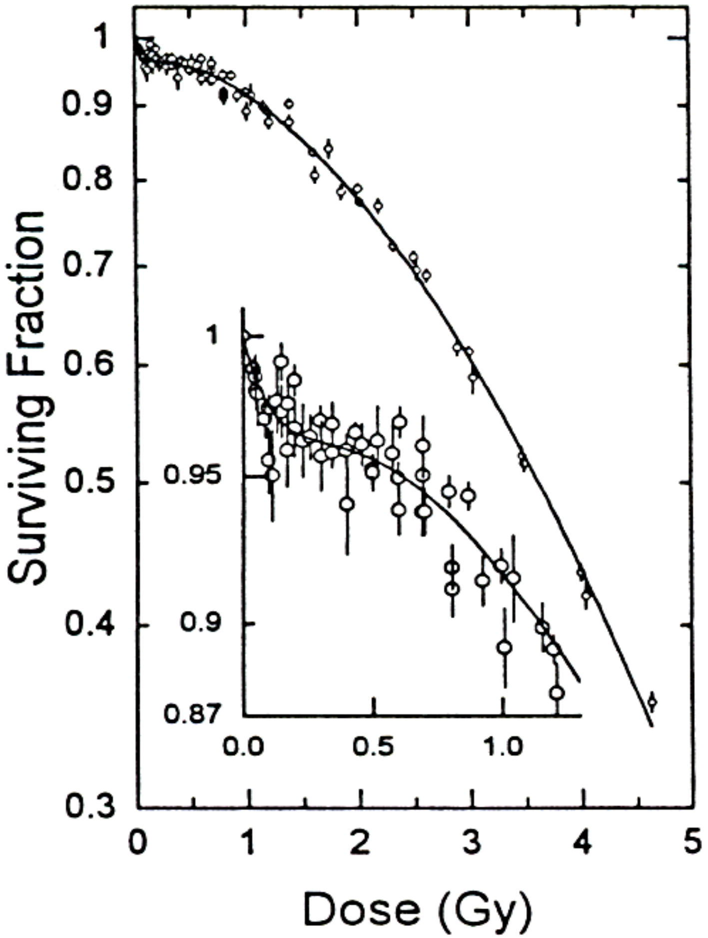
- Cell killing is well described by shouldered models such as multi-target [MT] or linear-quadratic [LQ].

- Cells must be “hit” to be killed, and DNA is the principal “target”.



Paradigm Revision:
Low dose hypersensitivity-inducible radioresistance (LDH-IRR)

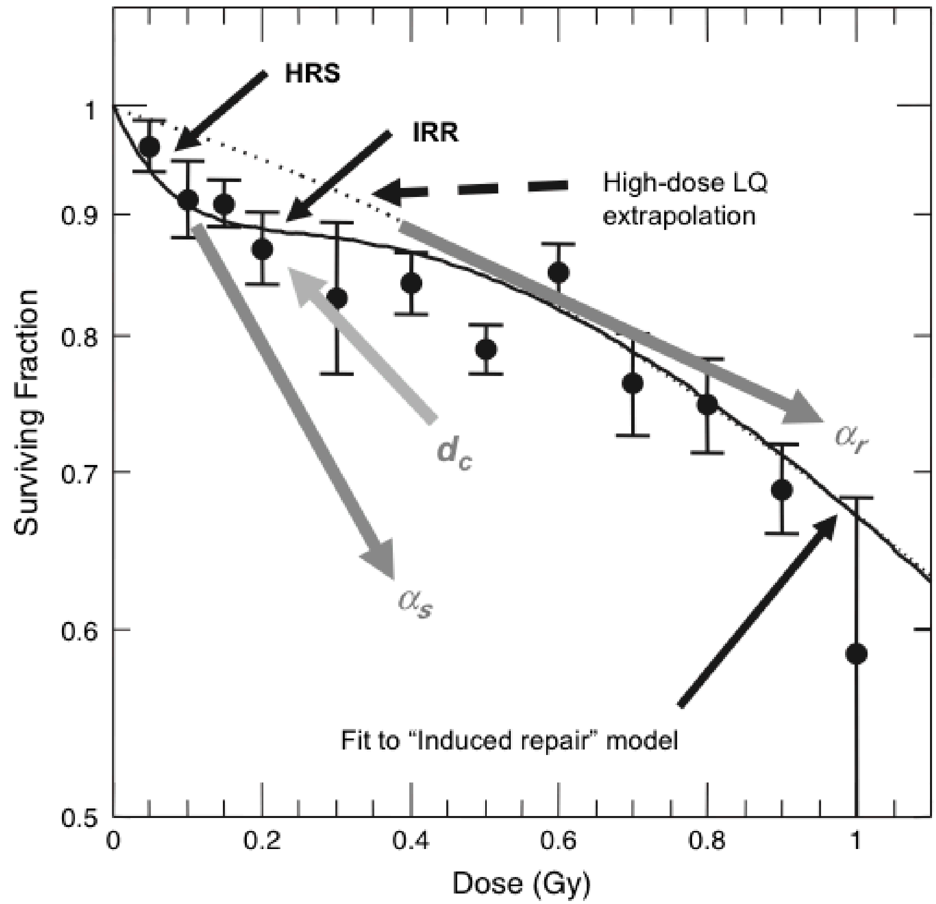
- Most cell types exhibit fine structure in their survival curves at low doses.



Survival curves for HT-29 cells

Ref: Wouters B *et al.* Radiat Res 146:399, 1996.

Survival Curves - LDHRS



Int. J. Radiation Oncology Biol. Phys., 70: 1310 - 1318, 2008

Clinical relevance for LDH in RIT

- If localized dose/dose rate is below the threshold for triggering IRR, cell killing should follow the initial slope of the survival (α_s) rather than α_r estimated from high-dose LQ model
- If so RIT should exert much greater cytotoxicity than would be predicted by conventional LQ models.
- Is RIT effectively “ultra fractionation” which fails to activate IRR

LDR Evades DNA Repair Sensors

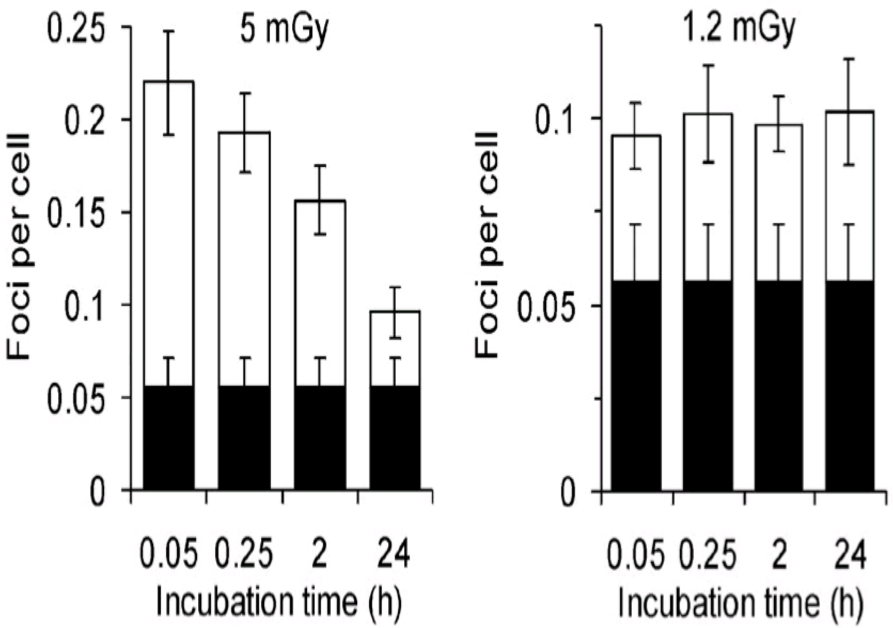
- Reduced activation of ATM following LDR
- Reduced activation of downstream target gH2AX
- Increased cell killing after LDR

“Failure to activate ATM-associated repair pathways contributes to the increased lethality of continuous LDR radiation exposures”

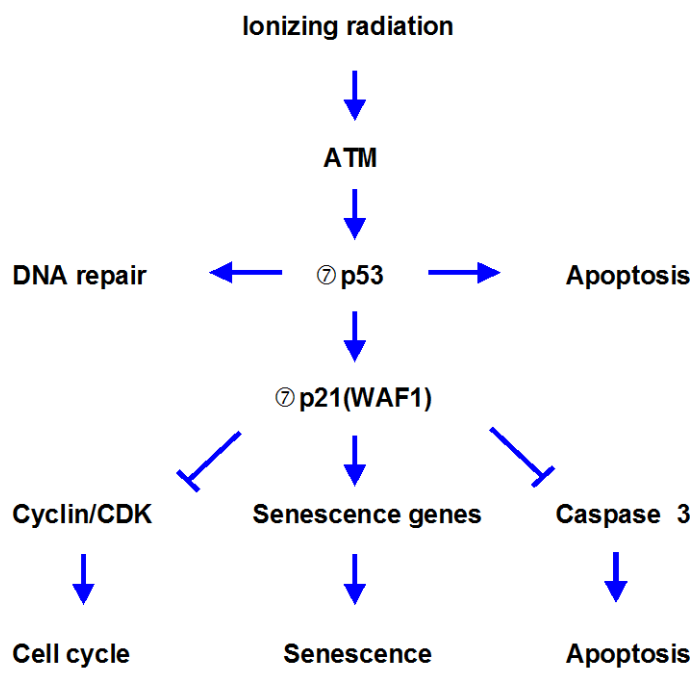
Collis SJ, et al. *J Biol Chem* 2004, Sept 17

Lack of DSB Repair After Very Low Doses

- Rothkamm and Löbrich (2003) observed a decreasing capacity for DSB repair with decreasing dose
- Between 2 Gy and 5 mGy, H2AX foci were extensively repaired.
- Below 1.2 mGy, repair of foci did not occur up to 24 h.

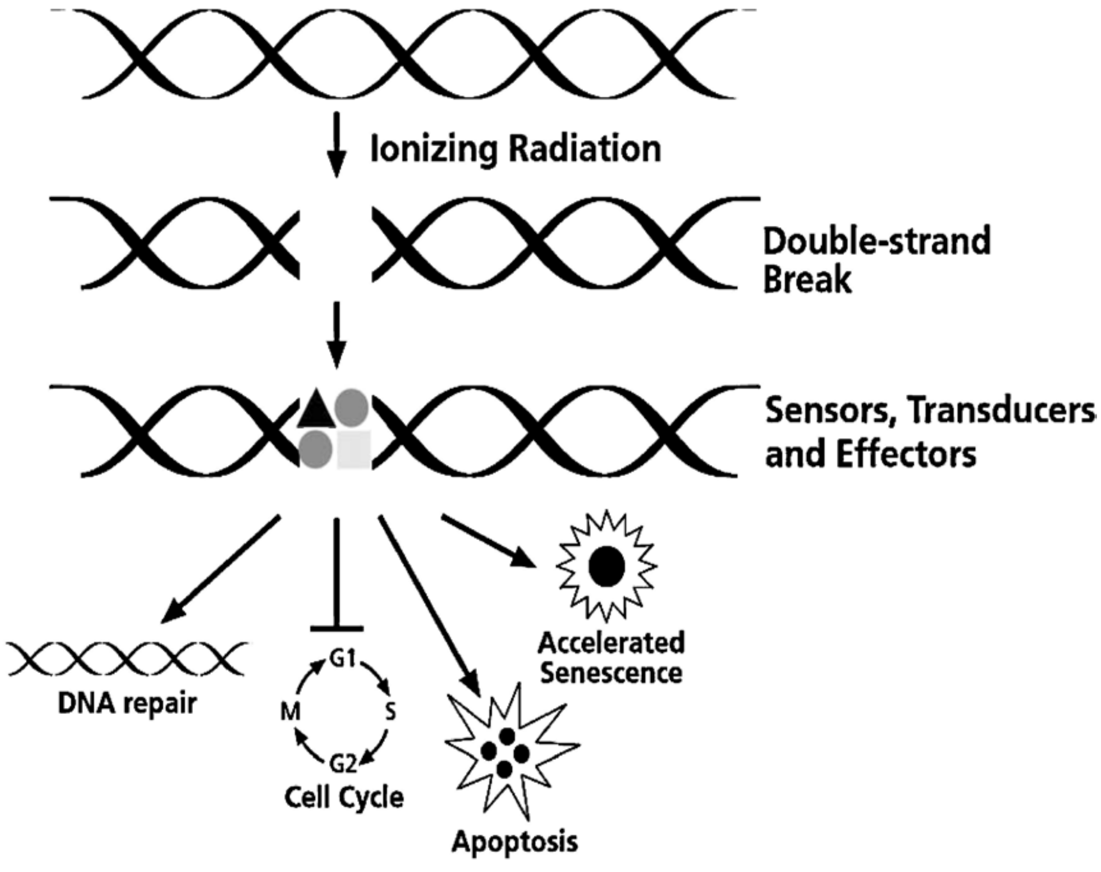


Normal cell responses to ionizing radiation



- p53 also transcriptionally transactivates genes such as *p21*$^{waf1/cip1}$.
- Different types of normal cells lose their clonogenic potential by several different mechanisms (necrosis, apoptosis, replicative senescence).
- Many human tumor cells have mutant p53 and fail to properly execute these responses … can this be exploited therapeutically?

DNA Damage - Cellular Responses



Murray and McEwan. Cancer Biother Radiopharm 2007 Feb;22(1):1-23.

To Cure Sometimes
To Help Often
To Care Always