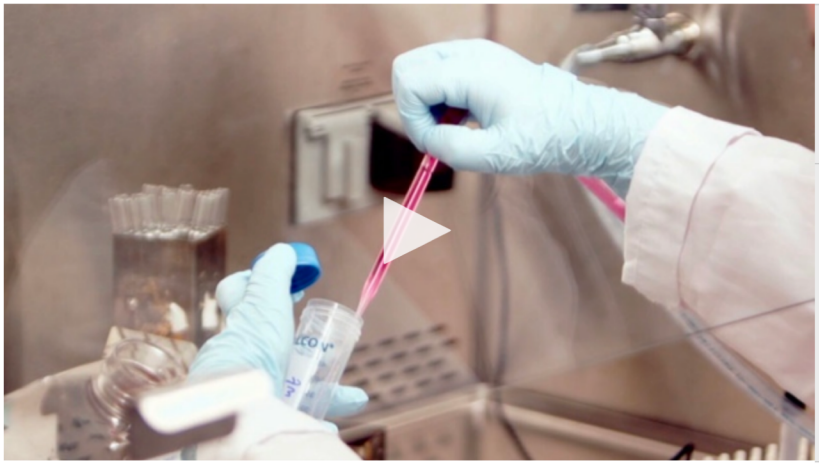

BC CANCER FOUNDATION
CAN
WE IMPROVE THE OUTCOME FOR EVERY CANCER PATIENT
Historic Gift Announcement

New cancer treatment coming to B.C. thanks to $18M donation



BC Cancer Foundation gets huge anonymous donation

An anonymous donor is giving the BC Cancer Foundation a whopping $18 million to help develop an emerging treatment.

CTV Vancouver
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Last Updated Wednesday, October 24, 2018 1:22PM PDT

The BC Cancer Foundation is bringing a cutting-edge cancer treatment to the province after receiving a staggering $18.34 million from an anonymous donor.

The historic act of philanthropy is being used to establish a new Molecular Imaging and Therapeutics program, which will develop radiopharmaceuticals – drugs with radioactivity – through clinical trials.

"Emerging research proves that radioactive particles can deliver drugs directly to the site of metastatic cancers, killing the cancer cells and saving the healthy tissue surrounding them," the BC Cancer Foundation said in a news release.

PHOTOS

The BC Cancer Foundation's Vancouver office is seen in this undated image. (BCCancerFoundation.com)

The program is being led by Dr. François Bénard, leadership chair in functional cancer imaging. Over the next five years, the foundation expects to expand its infrastructure and scale-up development of radioactive isotope treatments.

Bénard said medical isotopes have already been used to treat thyroid cancer for years, but the massive donation will help researchers expand their application.

"We have recently developed probes that bind specifically to cancer cells enabling us to apply this technology to treat many more cancers, notably

VANCOUVER WEATHER | Change city

12°C Scattered Clouds

Full forecast and radar

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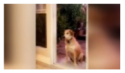


This good boy doesn't understand screen doors so his owners have to pretend to open it

Alleged drug lab uncovered after explosion

CTV News at Six Vancouver for Monday, Nov. 5, 2018

Dentists offer free service

What is Theranostics?

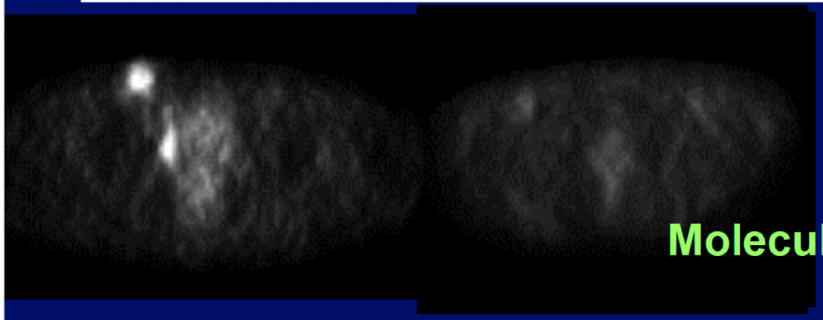
Combination of two words:

- Therapeutic + Diagnostic

Definition:

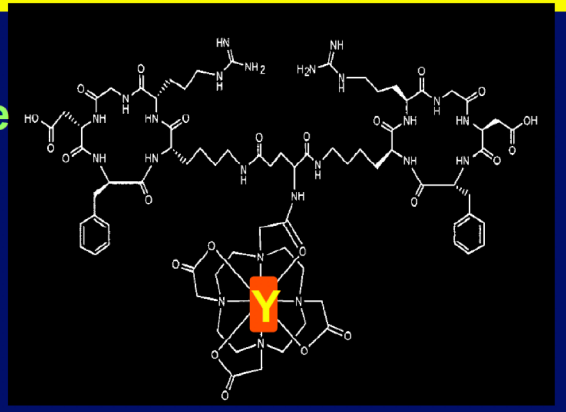
- Combination of a Diagnostic Tool that helps define the right Therapeutic Tool for a specific disease.
- Very natural in nuclear medicine: Use of radionuclide-labeled agents to diagnose disease (imaging) and then use identical or closely related agents to treat these diseases (radioligand therapy)

THERANOSTICS – Diagnostics and Therapy

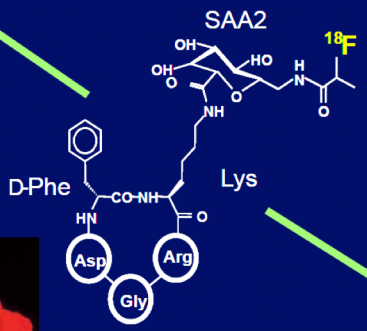


Molecular Imaging Probe

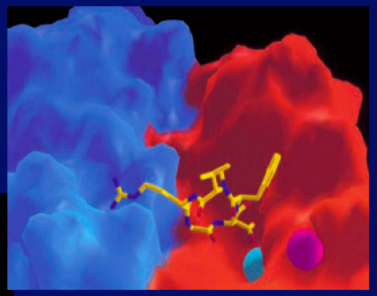
Radionuclide therapy

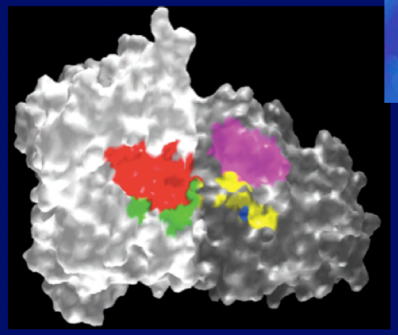


Patient selection



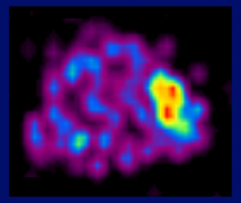
Molecular Target



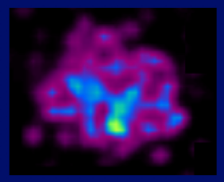


Specific ligand

Therapy monitoring

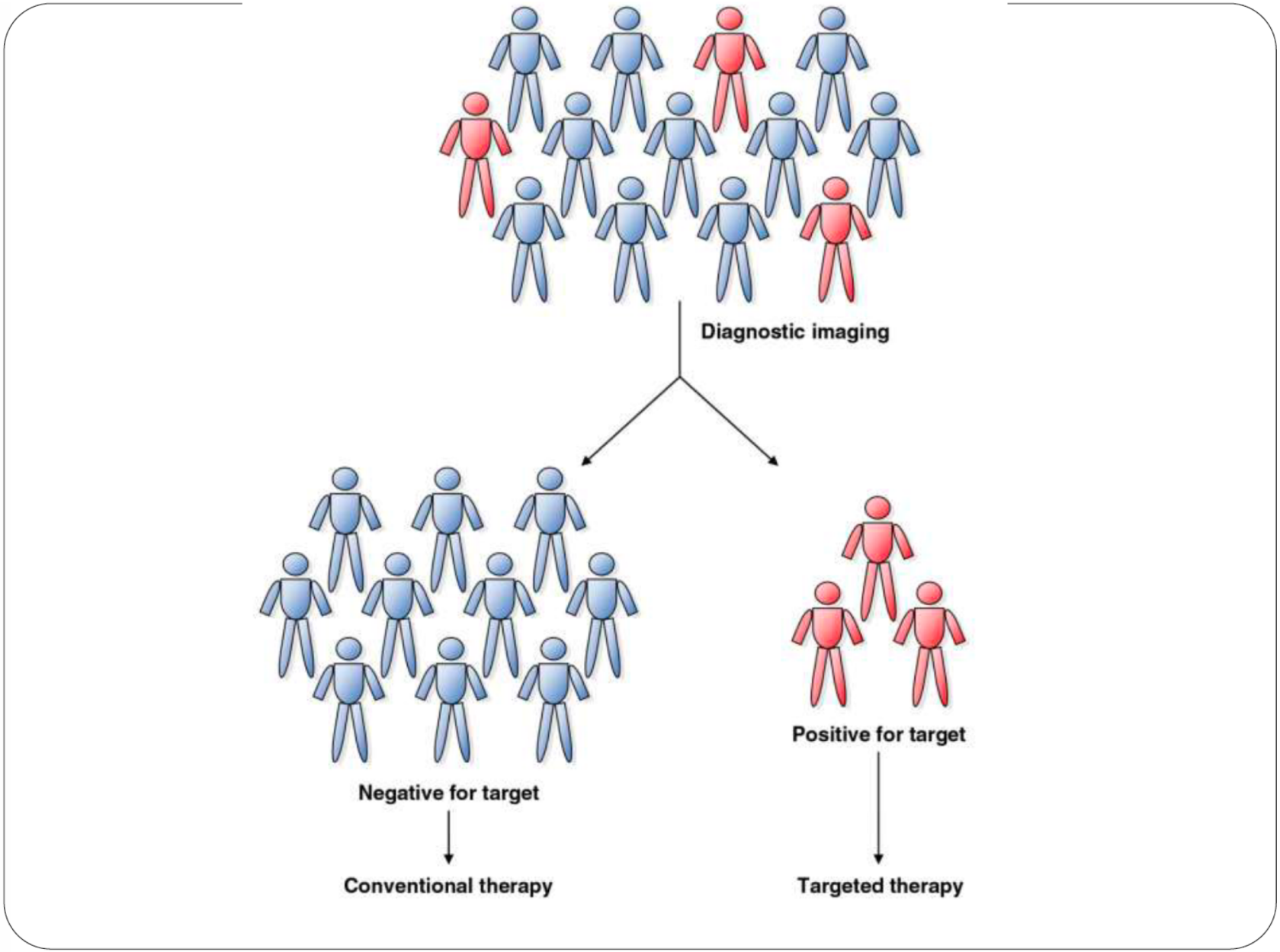


Untreated



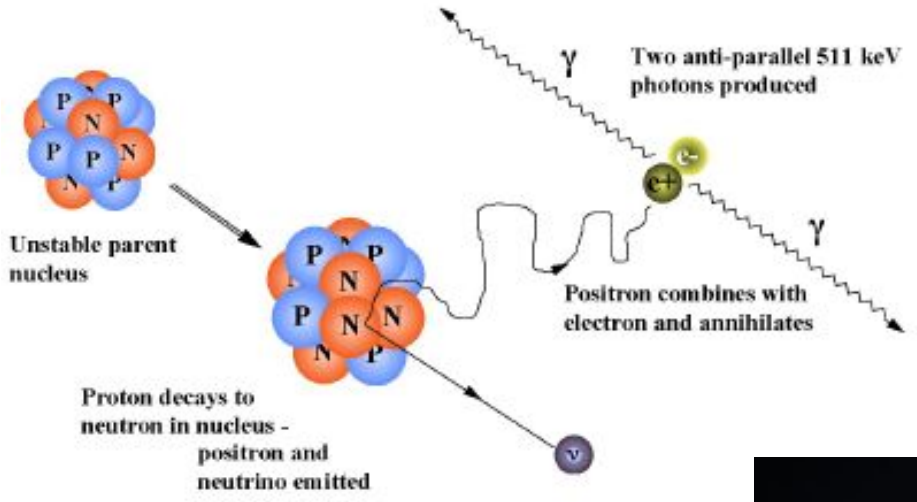
18 mg/kg c(RGDfV)

Courtesy Wolfgang Weber

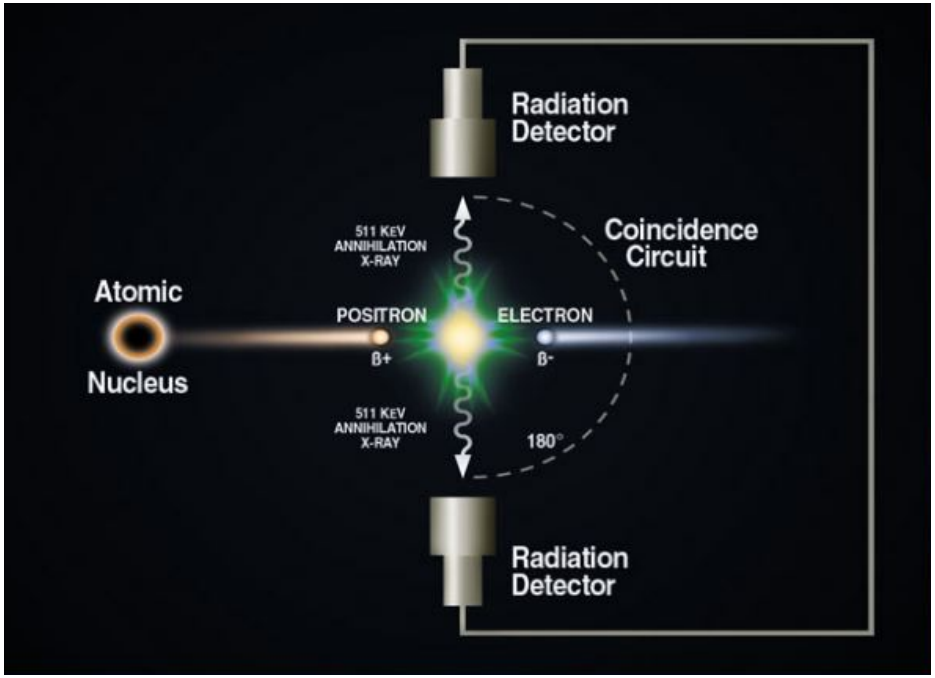


Personalized Medicine:
the right treatment for the right patient at the right time at the right dose

Positron Emission Tomography (PET)



$$^{18}_{9}F \longrightarrow {}^{18}_{8}O + e^{+}$$



Oncologic PET imaging using Fludeoxyglucose: ^{18}F-FDG

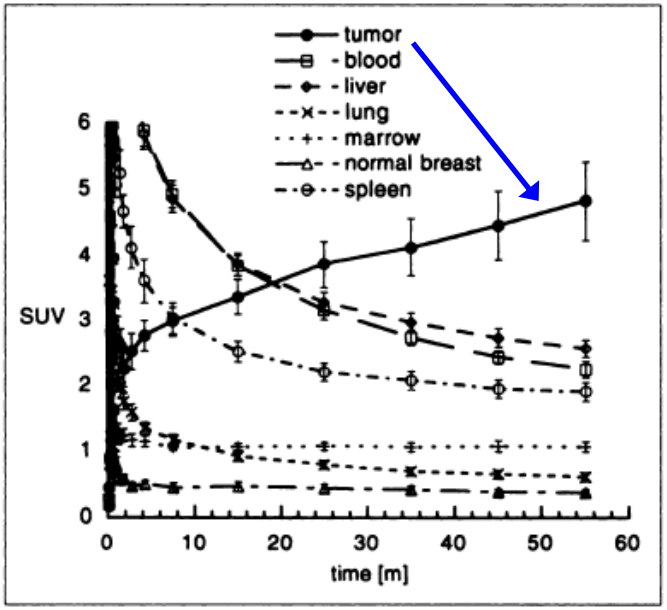
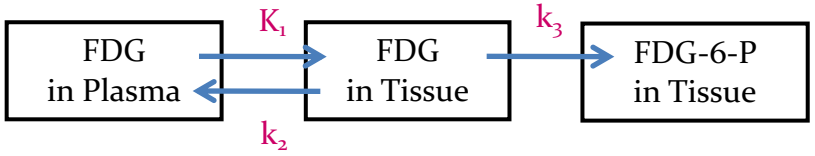
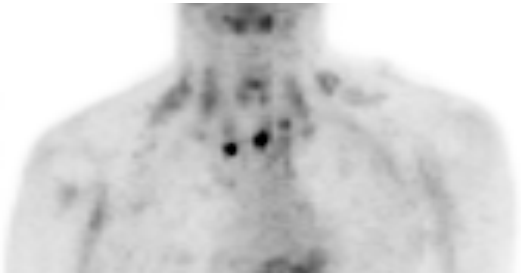
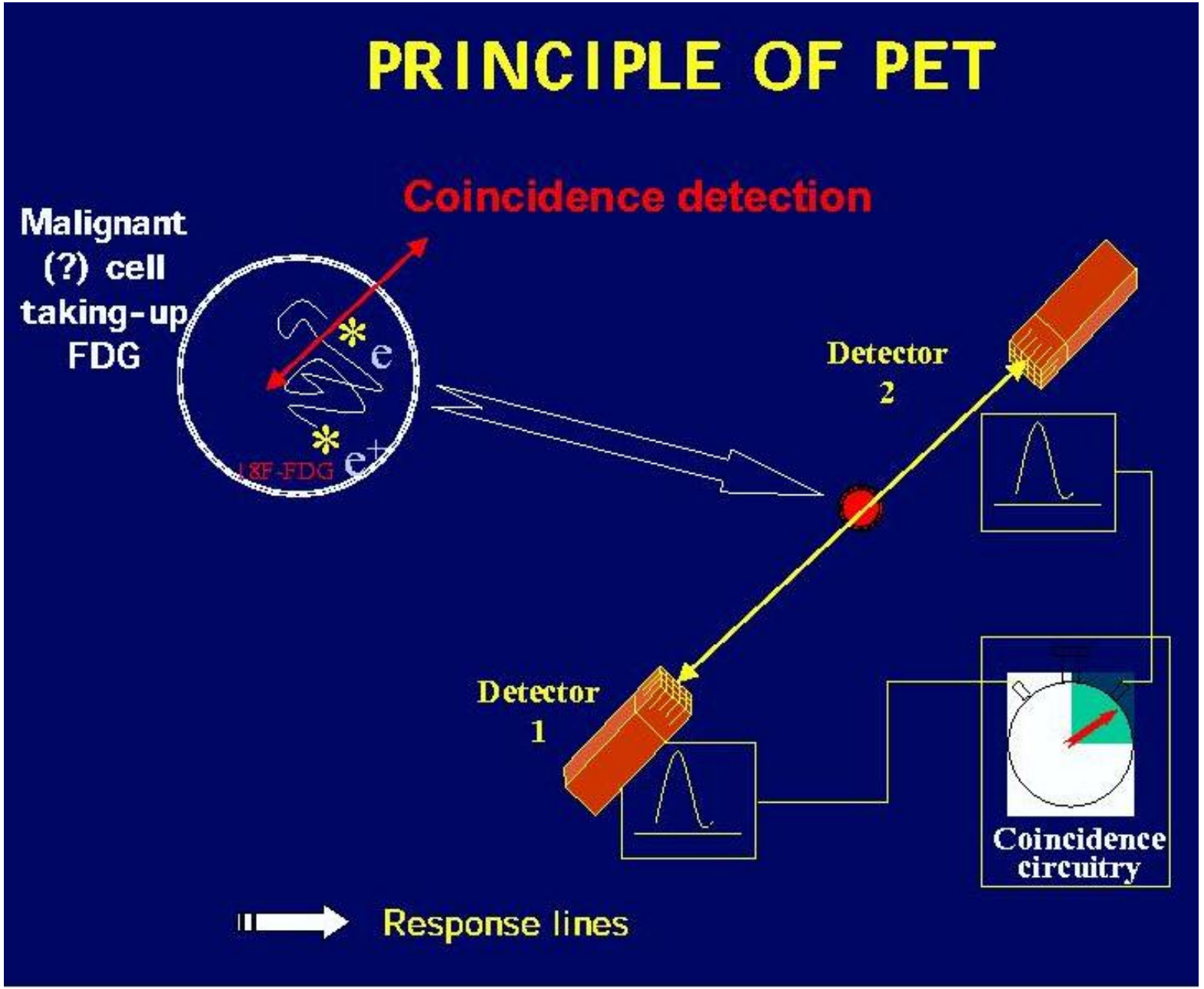


FIGURE 1. Mean time-activity curves (± s.e.m.) for tumor and normal tissues in 18 women with untreated primary breast cancer. On average, tumor activity increased as a function of time relative to blood and normal tissues through 60 min.

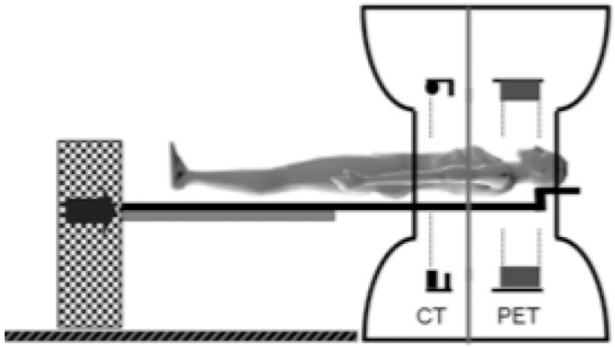
Increased metabolism => increased accumulation of activity over time (increased trapping)



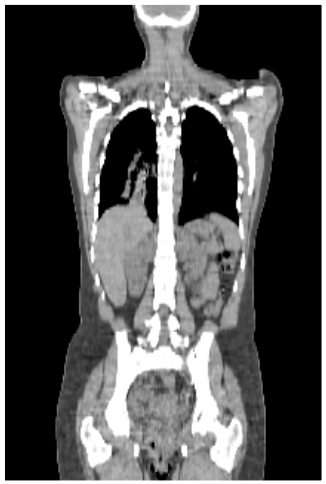



PRINCIPLE OF PET
Coincidence detection
Malignant (?) cell taking-up FDG
e
e+
18F-FDG
Detector 2
Detector 1
Coincidence circuitry
Response lines

Combined PET/CT imaging



- Combined PET/CT scanners provide registered anatomic and functional images.



CT
PET/CT

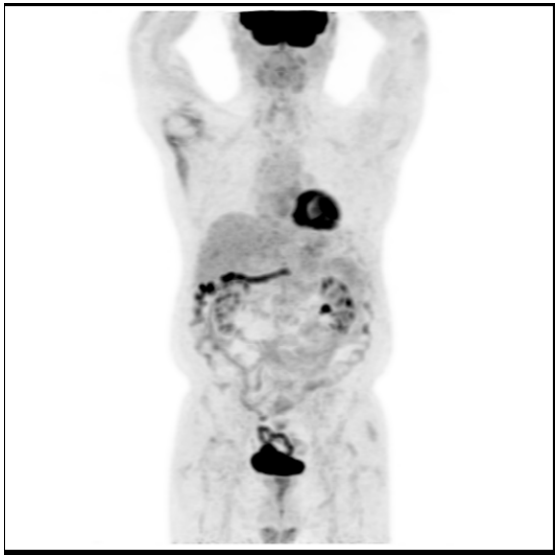
PET

Fused

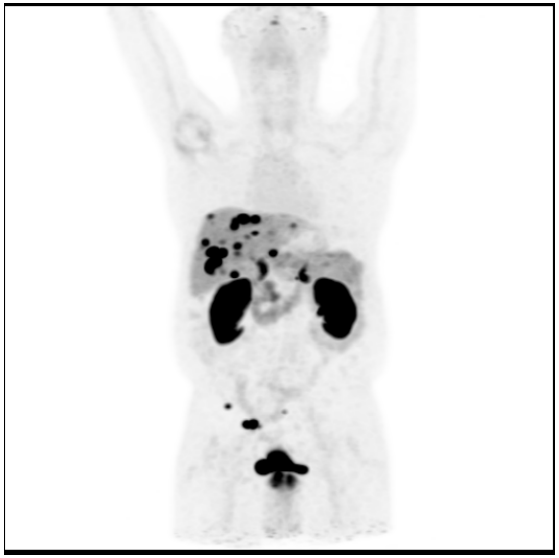
Structure without function is a corpse. . . function without structure is a ghost. —Stephen Wainwright

New Imaging/therapy of Neuroendocrine Tumors (NETs)

- DOTATOC (also DOTATATE) are amino acid peptides that target somatostatin receptors as expressed by NETs.
- They can be can be bound with radionuclides such as gallium-68 (for high resolution PET imaging) and lutetium-177 (for therapy as well as SPECT imaging/dosimetry)
- Significantly improved visualization compared to conventional imaging or regular FDG PET/CT scans



Regular ^{18}F-FDG PET scan



^{68}Ga-**DOTATOC** PET scan

^{68}Ga-DOTA-TOC versus ^{111}In-DOTA-TOC and ^{99m}Tc-HYNIC-TOC

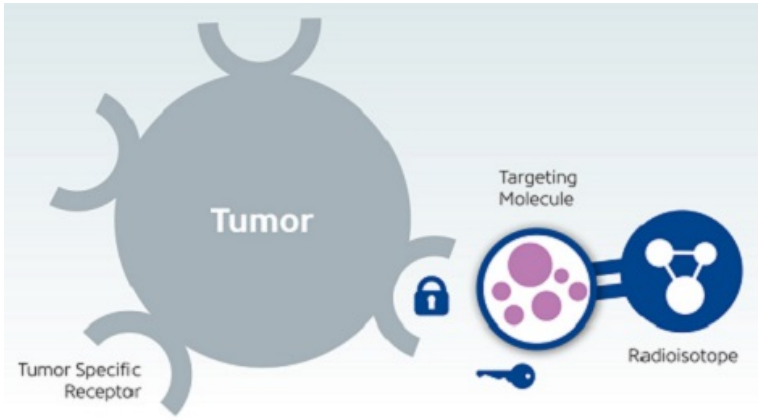
Gabriel et al. J Nucl Med 2007; 48: 508-518

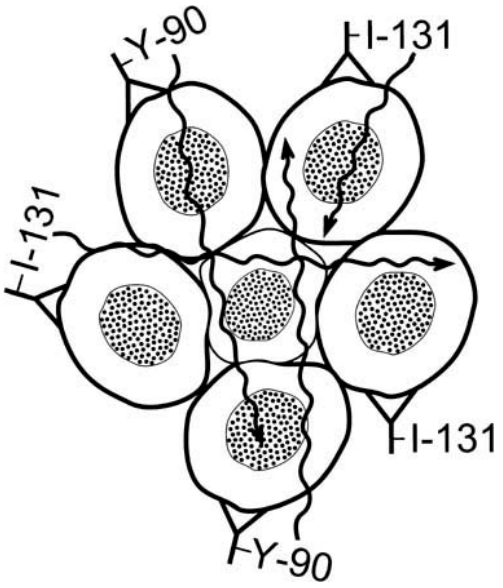
	PET	SPECT	CT
Results (n=84 Patients - NET)			
Sensitivity	97% (69/71)	52% (37/71)	61% (41/67)
Specificity	92% (12/13)	92% (12/13)	71% (12/17)
Accuracy	96% (81/84)	58% (49/84)	63% (53/84)

Combined Use of PET and CT provides the highest accuracy

Radionuclide Therapy

- Also known as (!!):
  - Targeted Radionuclide Therapy (TRT)
  - Radiopharmaceutical Therapy (RPT)
  - Radioligand Therapy (RLT)
  - Molecular Radiotherapy (MRT)
- Agents (e.g., monoclonal antibodies, peptides, microspheres) that target tumors
- Bound to radionuclides whose emissions can kill tumor cells





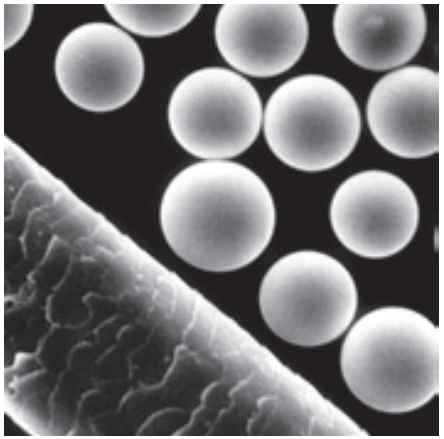
Some Therapeutic Radionuclides for Radionuclide Therapy

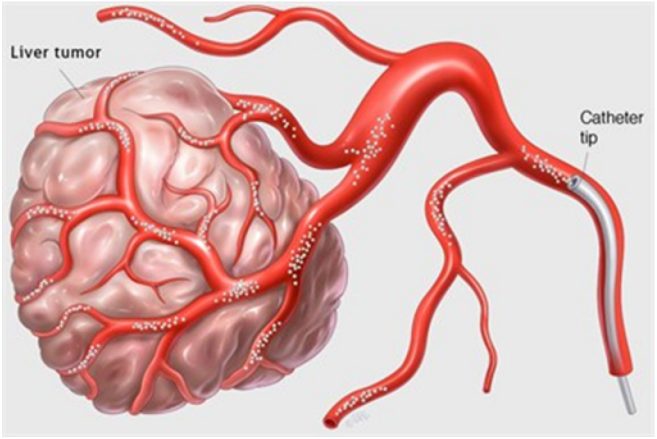
Radionuclide	Halflife (hr)	β- Energy (MeV)
I-131	192.5	0.60
Y-90	64.0	2.28
Sm-153	46.3	0.81
Lu-177	161.5	0.50
Re-188	17.0	2.12

Y-90 Radioembolization
(Selective internal radiation therapy - SIRT)

Y90-SIRT

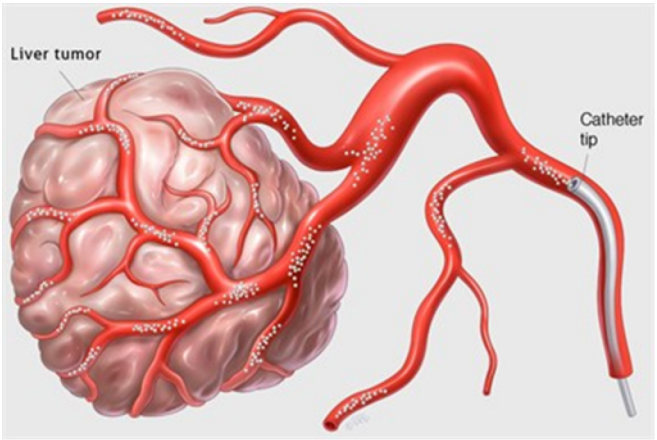
- Treatment is a low toxicity, targeted liver cancer therapy that consists of millions of tiny beads containing radioactive **yttrium-90**. (Y-90 is a decay product of Strontium 90)
- The radioactive beads (20-30 micrometers in diameter – about a third of the width of a human hair) are delivered directly to the liver tumors via a catheter.



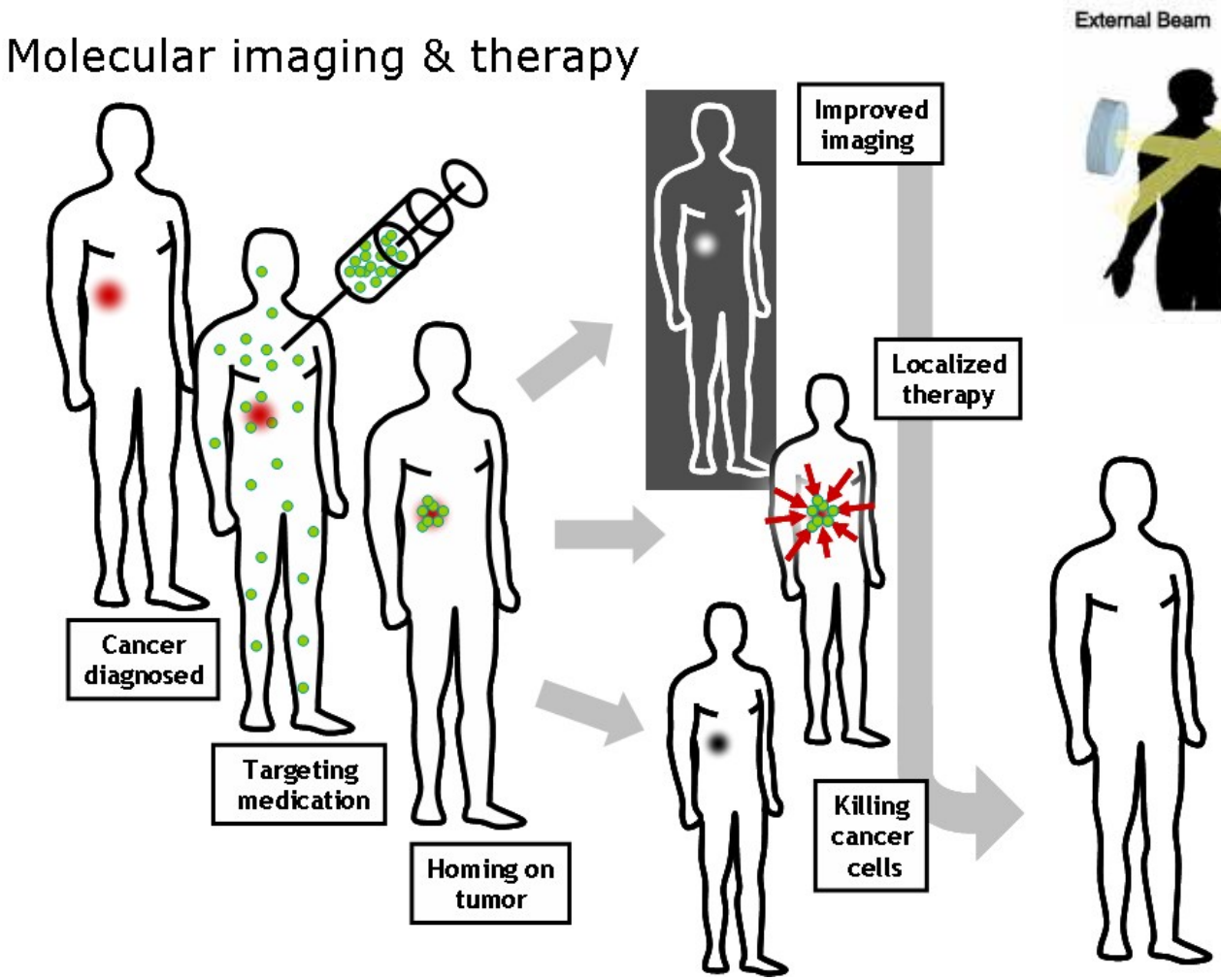


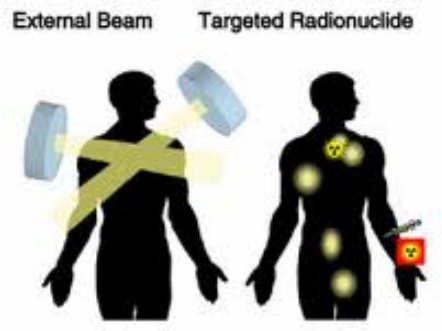
Y90-SIRT

- The tiny radioactive beads flow directly into the liver tumor via its own blood vessels and become permanently lodged in the small blood vessels of the tumor.
- The radiation destroys the tumor cells from within the tumor, with minimal impact to the surrounding healthy liver tissue.
- In addition, embolization of the arteries helps destroy the tumor.

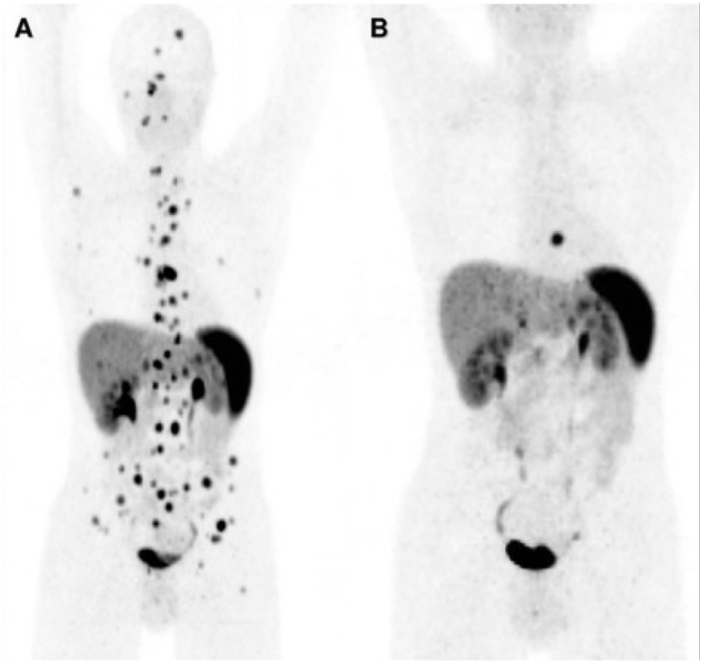


The “Magic Bullet”





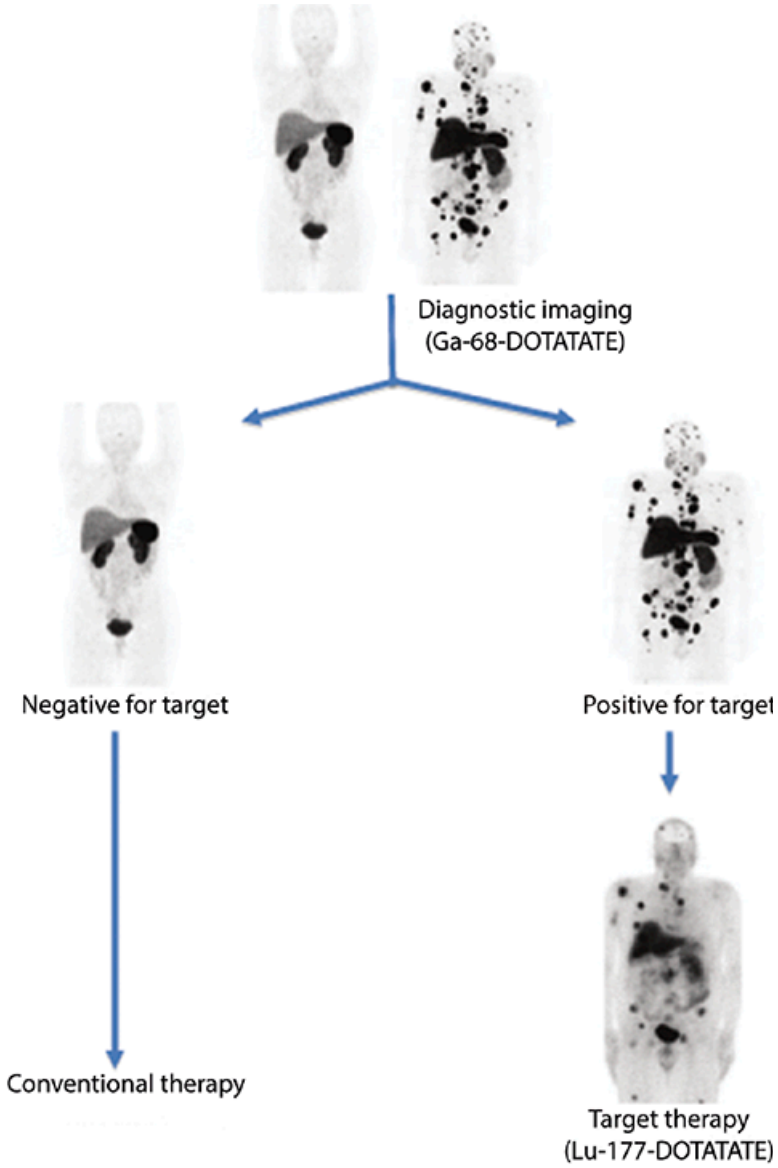
$^{90}Y/^{177}Lu$-DOTATATE Radionuclide Therapy of Patients with NETs



Baseline 22 months post treatment

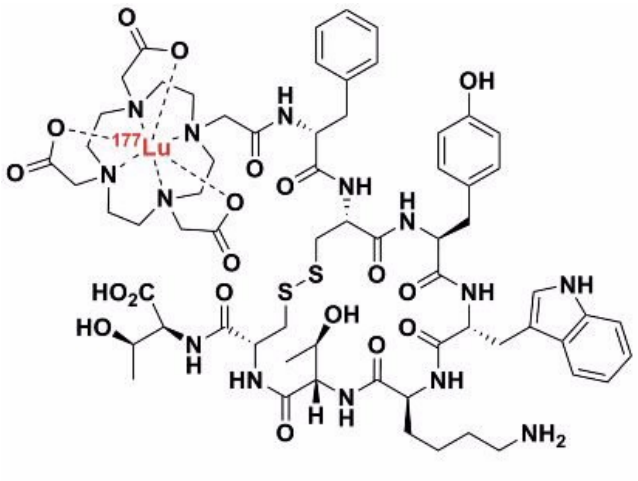
Prasad et al., EJNMMI Research 2015 **5**:53 **DOI:** 10.1186/s13550-015-0130-2

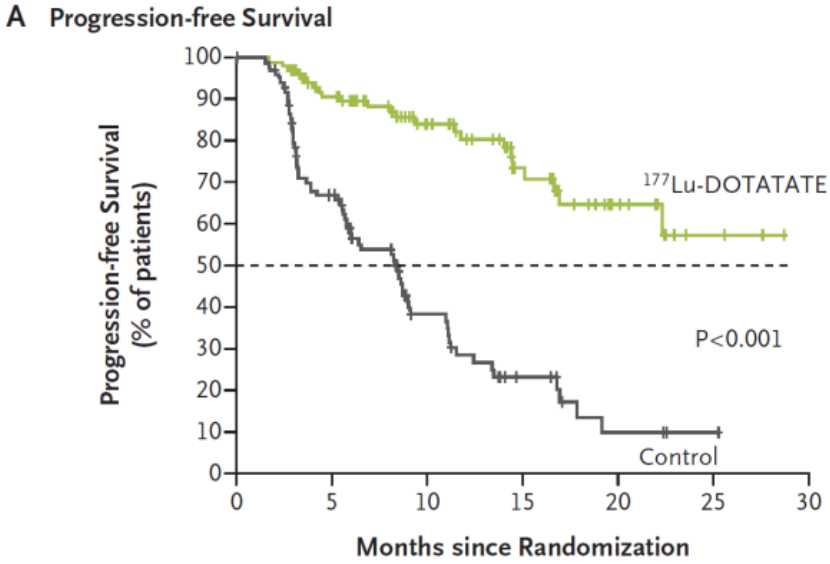
Theranostic Approach



^{177}Lu - Lutathera

Somatostatin-targeted theranostic for neuroendocrine tumor treatment



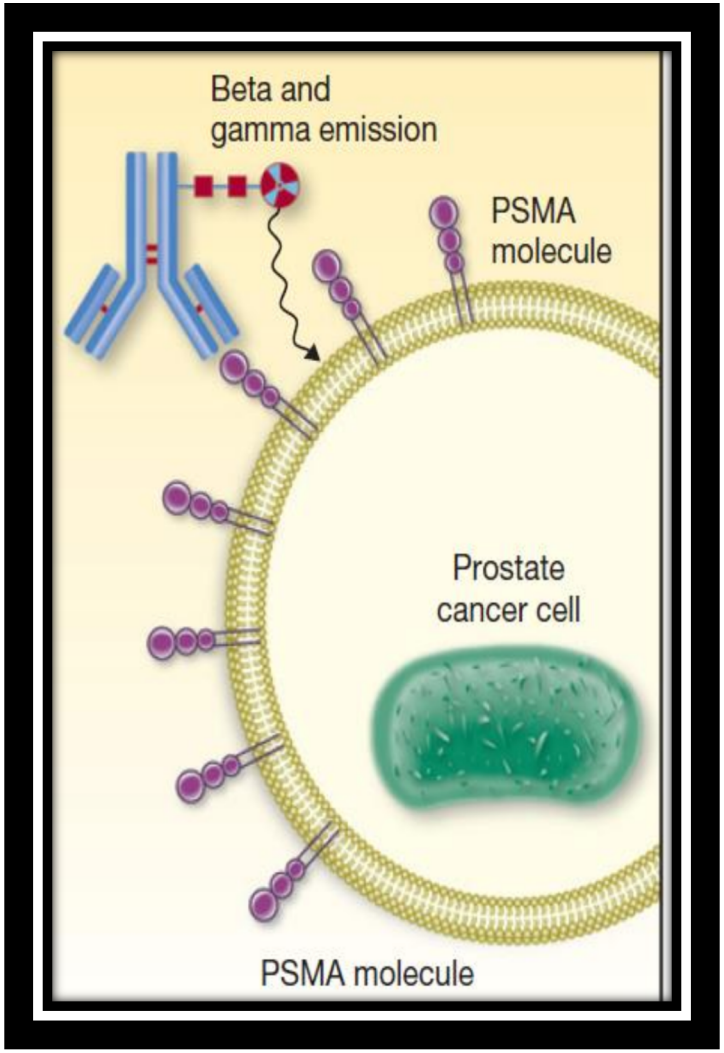


NEJM 2017; 376:125-135

Prostate-Specific Membrane Antigen (PSMA)

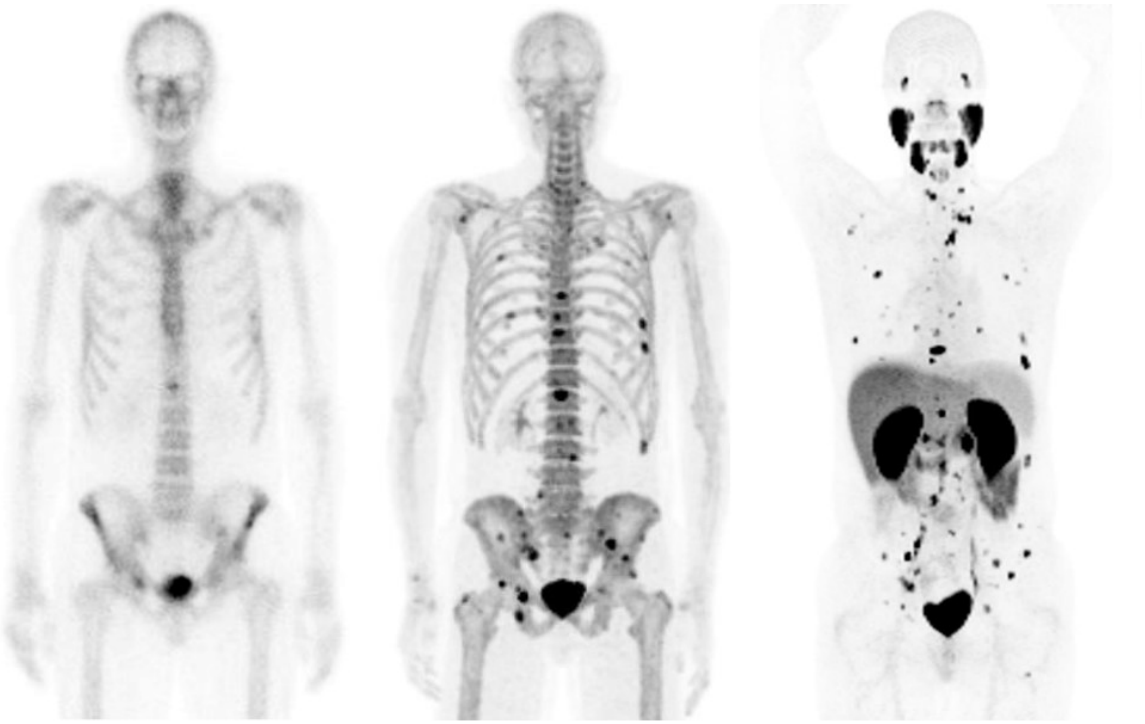
- Protein overexpressed in prostate cancer (~10 times compared to normal prostate)
- Observed in more than 95% of prostate cancer tumors.
- Direct correlation between expression levels and tumor aggressiveness.

PSMA Theranostics



PSMA PET Imaging

Comparison to Bone Scan and Conventional PET

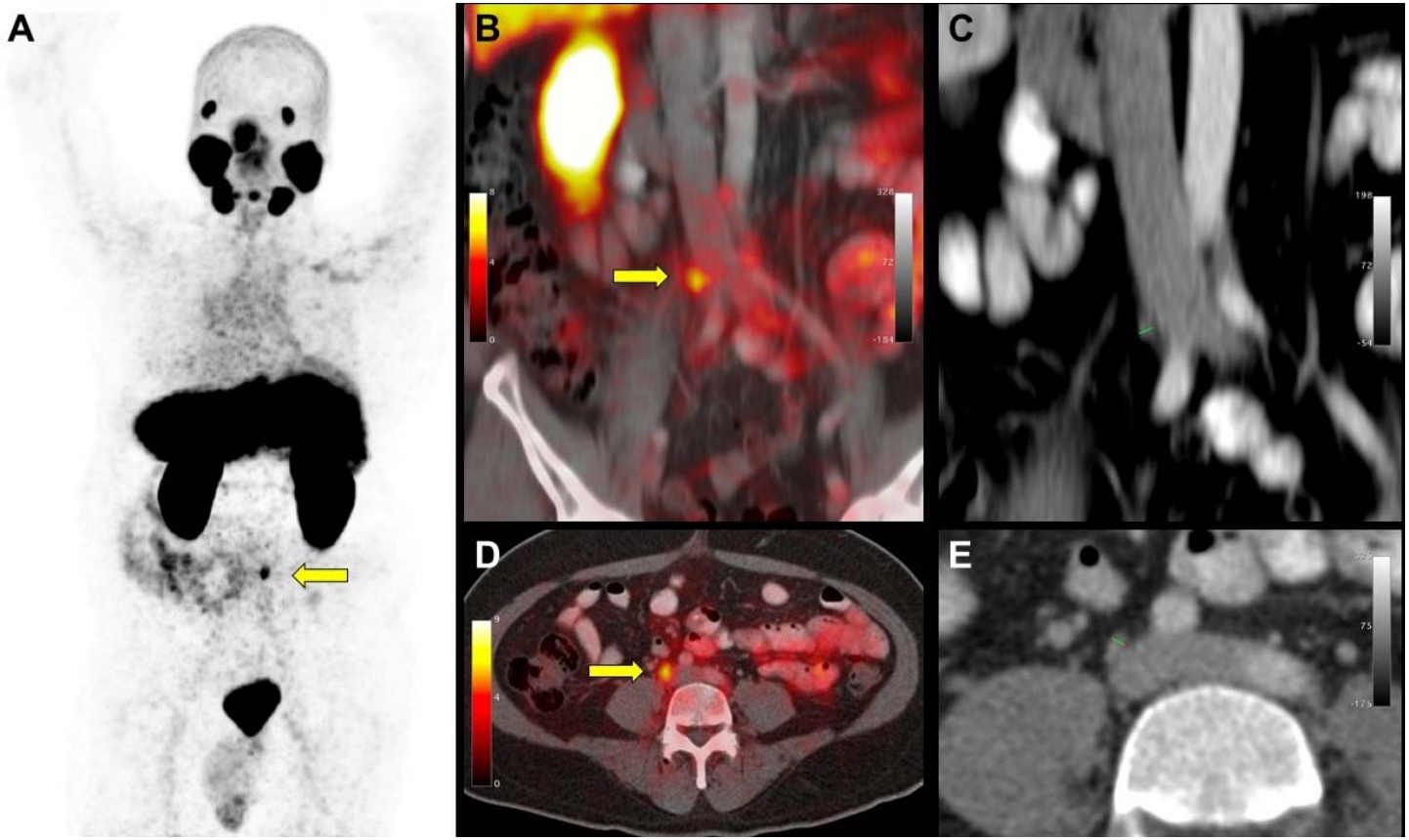


Number of Detected Bone Lesions:

Bone Scan: 12 $Na^{18}F$ PET: 39 ^{18}F-DCFPyL PET: 87

Rowe SP, Mana-ay M, Javadi MS, et al. *Clin Genitourin Cancer*. **2016**;*14*:e115-e118.

^{68}Ga-PSMA-PET/CT



3 mm iliac node in a PCa patient with PSA=0.3 post-RP

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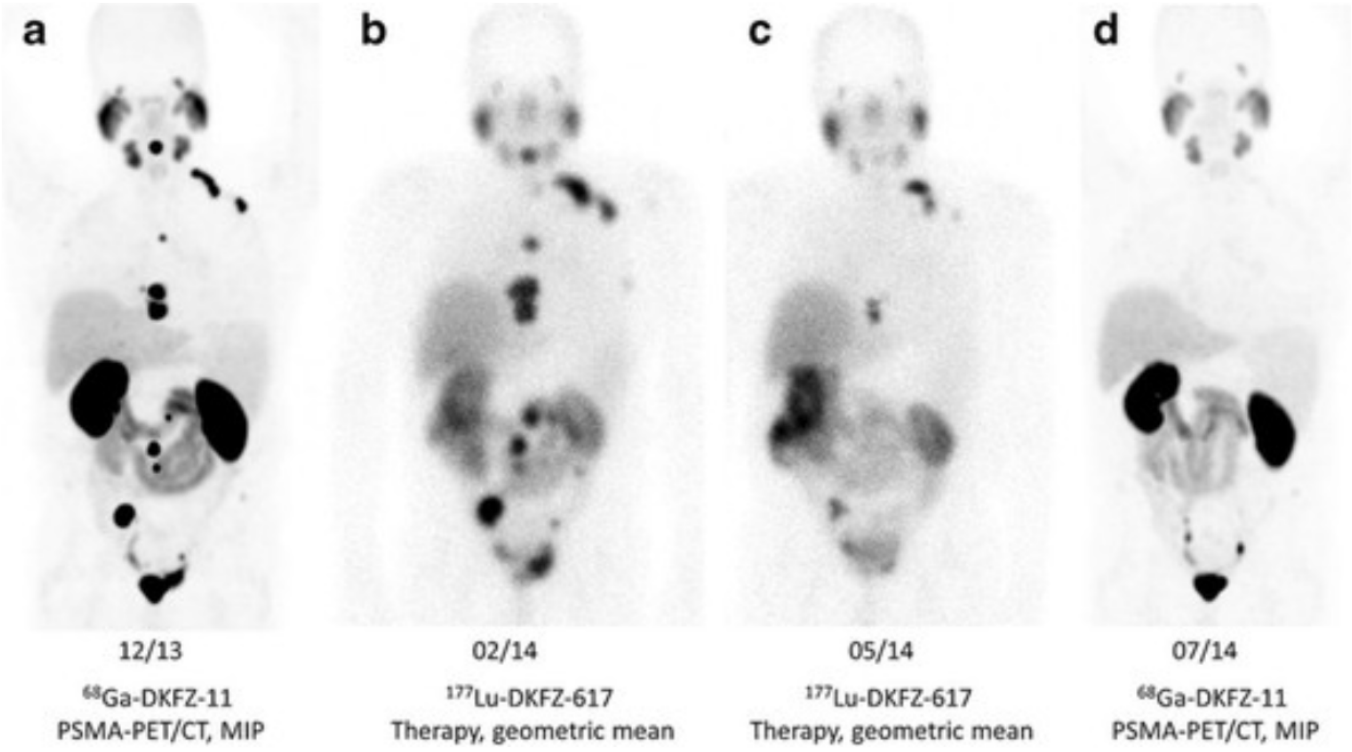
Calais J. *J Nucl Med* 2017; epub

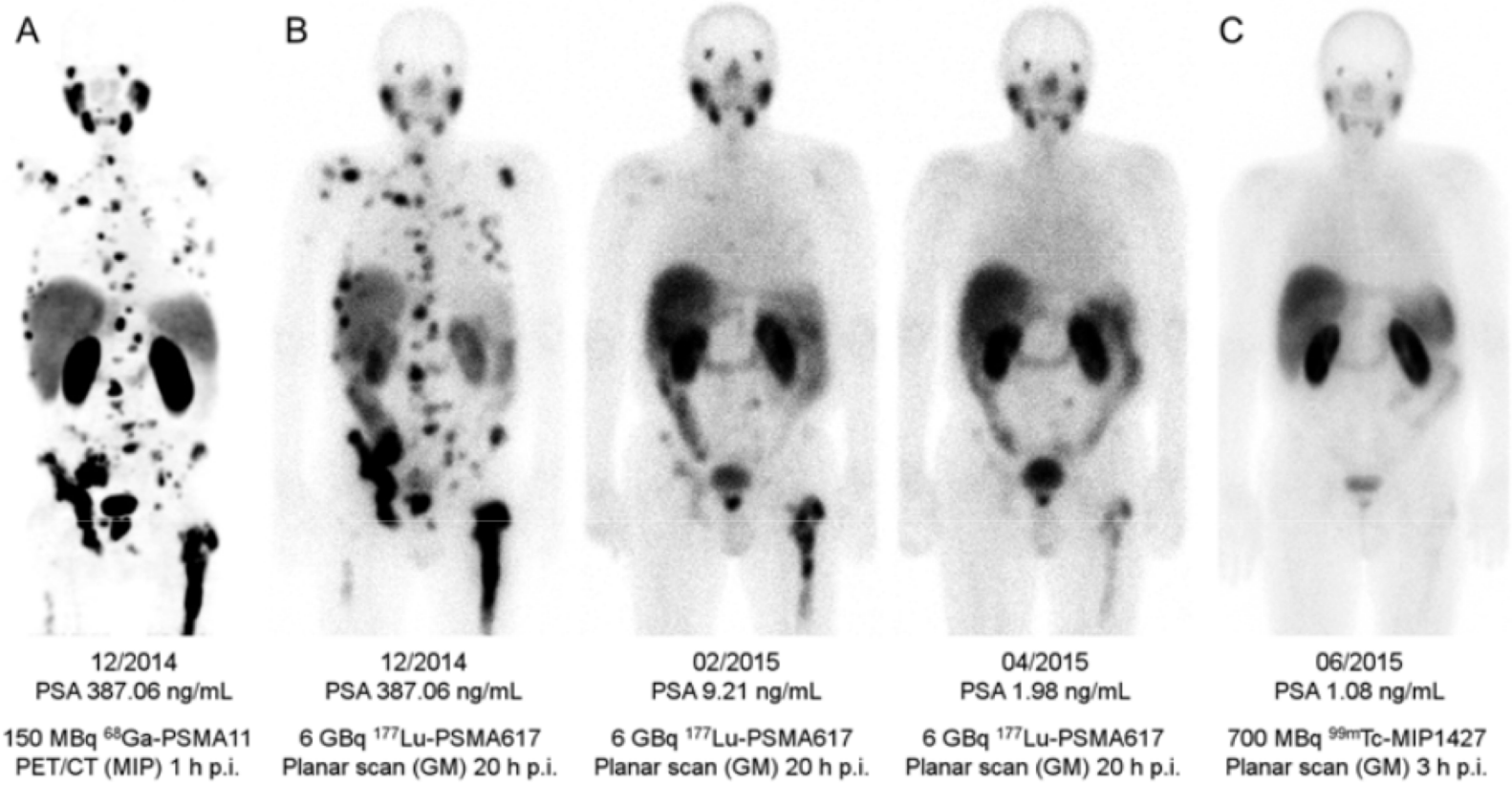
^{177}Lu – PSMA-617 for tumor treatment in metastatic castration-resistant prostate cancer (mCRPC)



[Lu]Lutetium-labelled PSMA ligand-induced remission in a patient with metastatic prostate cancer.

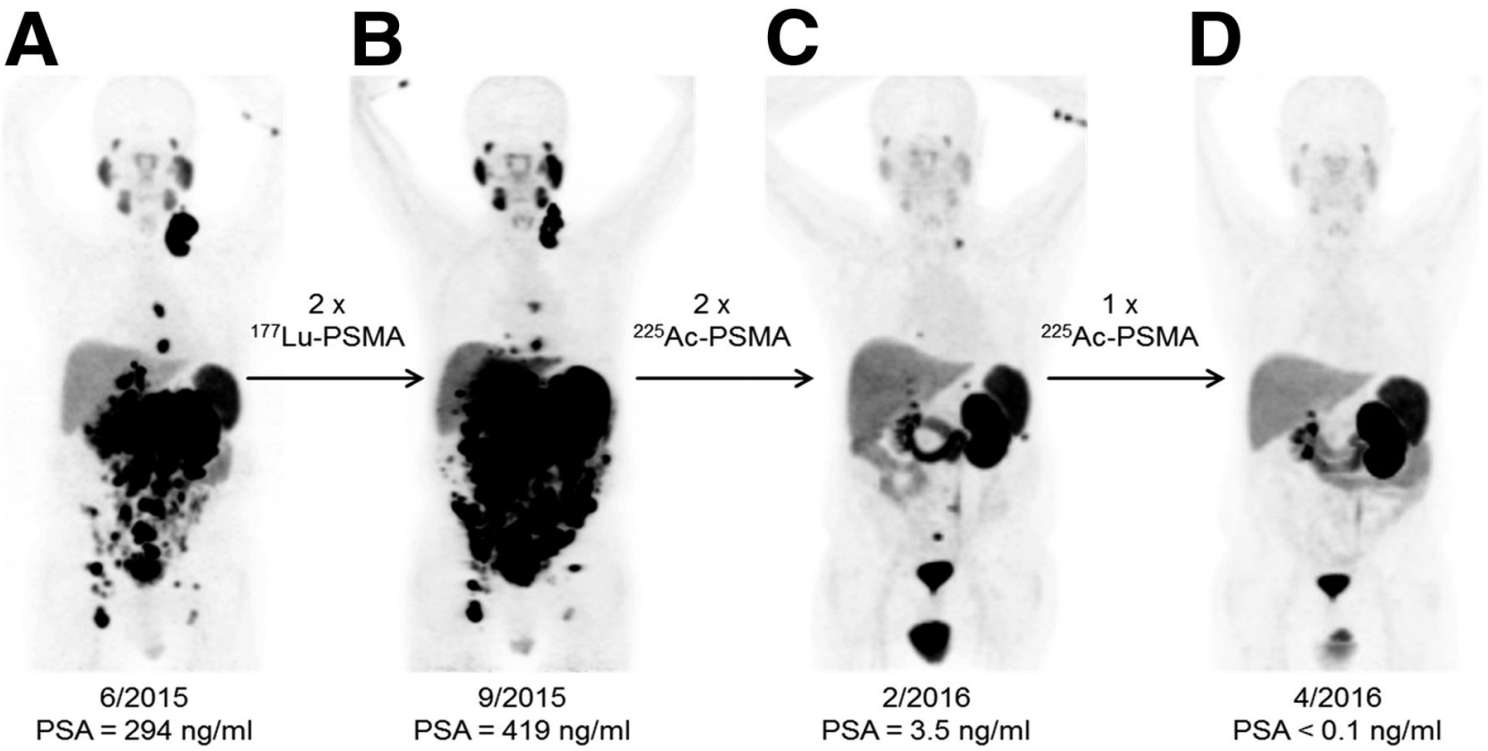
Eur J Nuc Med Mol Imag 2015; 42: 987-988

Response to PSMA Therapy



Krachtowil et al., J Nucl Med. 2016.

Response to PSMA Therapy



68Ga-PSMA-11 PET/CT scans of patient B. In comparison to initial tumor spread (A), restaging after 2 cycles of β-emitting 177Lu-PSMA-617 presented progression (B).

Clemens Kratochwil et al. J Nucl Med 2016;57:1941-1944

Melbourne Trial

Peter MacCallum Cancer Centre

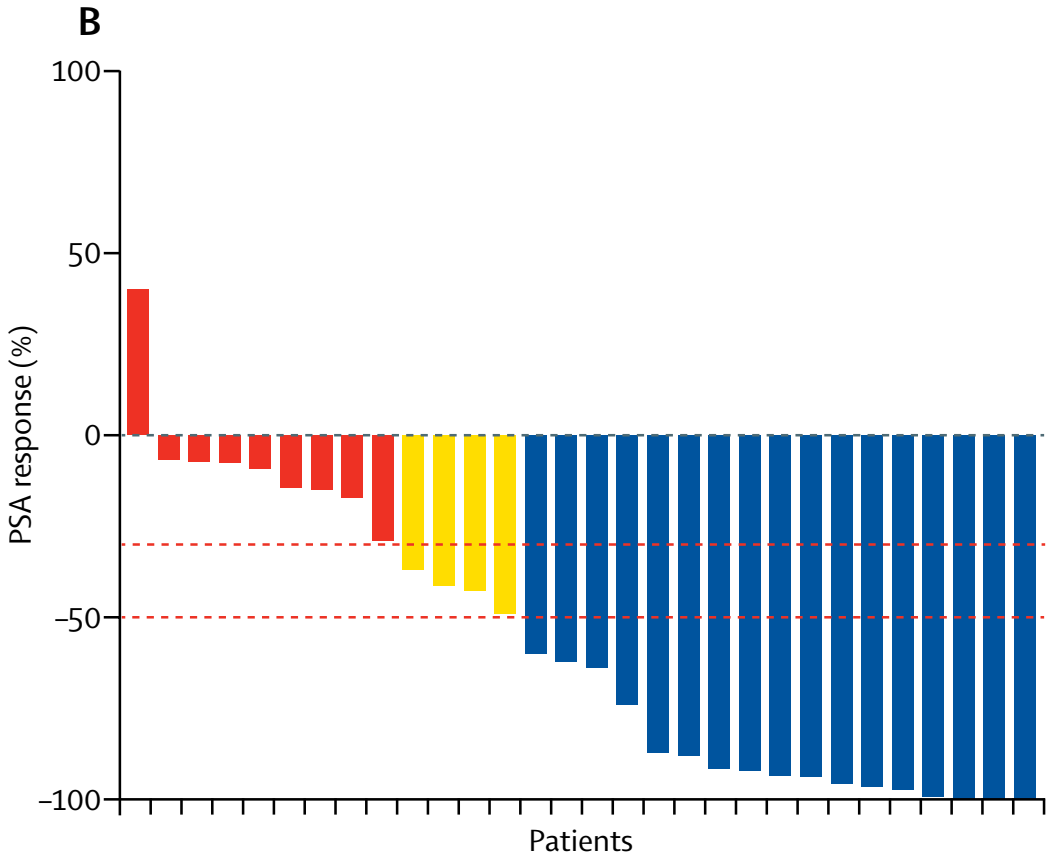
- Prospective, investigator-initiated phase 2 study
- 30 patients with progressive mCRPC after taxanes and abiraterone/enzalutamide
  - Positive ^{68}Ga-PSMA-11 PET/CT, No discordance of FDG-PET
- Up to 4 induction cycles of ^{177}Lu-PSMA-617 RLT
  - Median 7.5 [4.4 – 8.7] GBq per cycle, q 6 weeks
- Responders allowed to received further cycles upon re-progression
- Primary endpoints: PSA response and toxicity

CHU de Québec Université Laval

Hofman MS et al. *Lancet Oncol* 2018; 19(6):825-33

PSA response

- Any decline in 97%
- >50% decline in 57%
- PSA nadir <0.2 lasting >1 year in 2 patients



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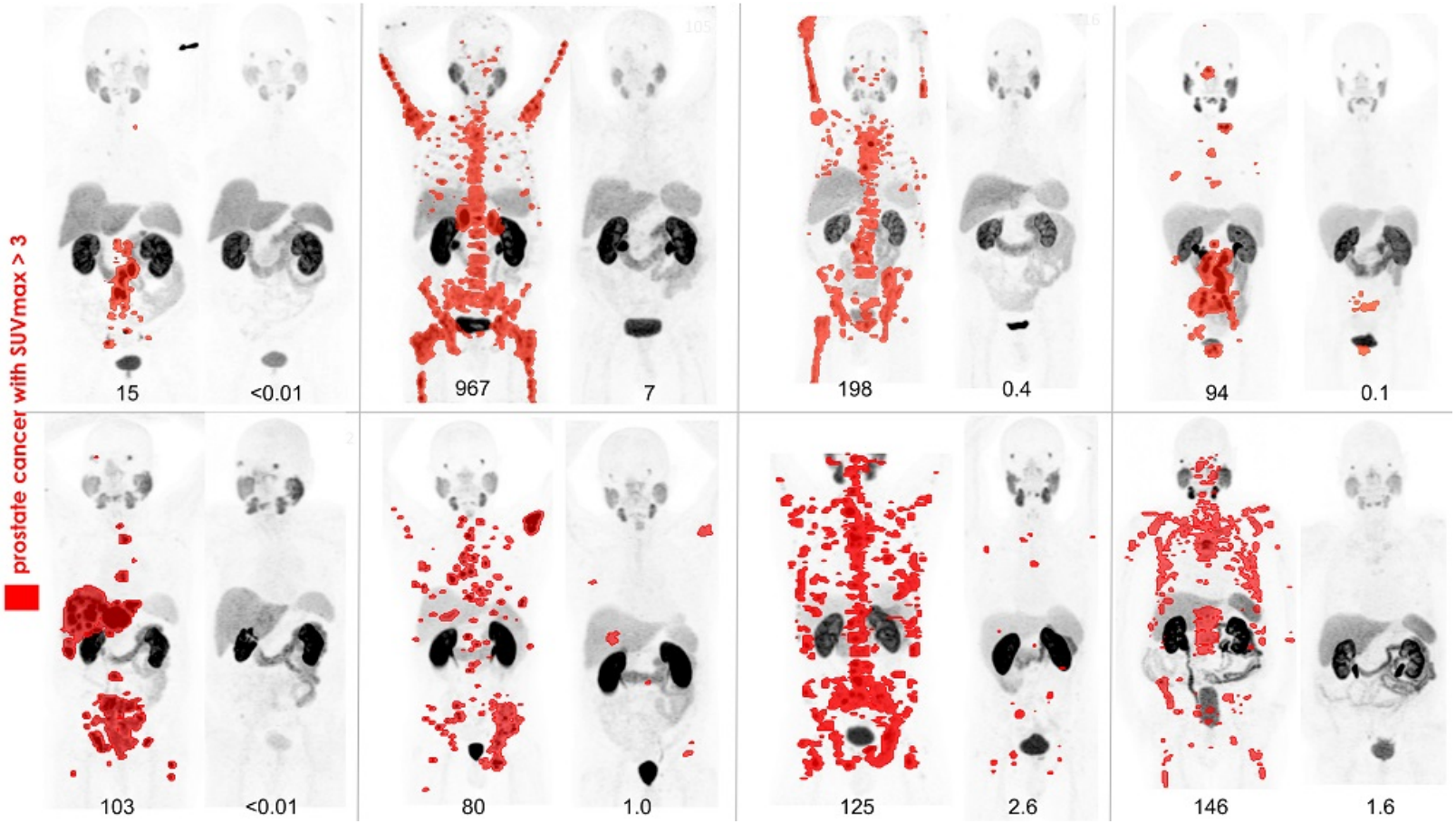
Hofman MS et al. *Lancet Oncol* 2018; 19(6):825-33



Credit: [Michael Hofman](), et. al. Peter MacCallum Cancer Centre, Melbourne, Australia.

Efficacy & Toxicity

- Some pain relief in all of 90% of patients with pain at baseline
- Median PSA-PFS: 7.6 mo.
- Median OS: 13.5 mo.

- Side effects (limited to Grade 1/2):
  - Nausea, limited to 24-48 h
  - Dry mouth in 87%
  - Dry eyes in 17%
- Grade 3/4 toxicity:
  - Thrombocytopenia in 13%
  - Anemia in 13%
  - Neutropenia in 7%

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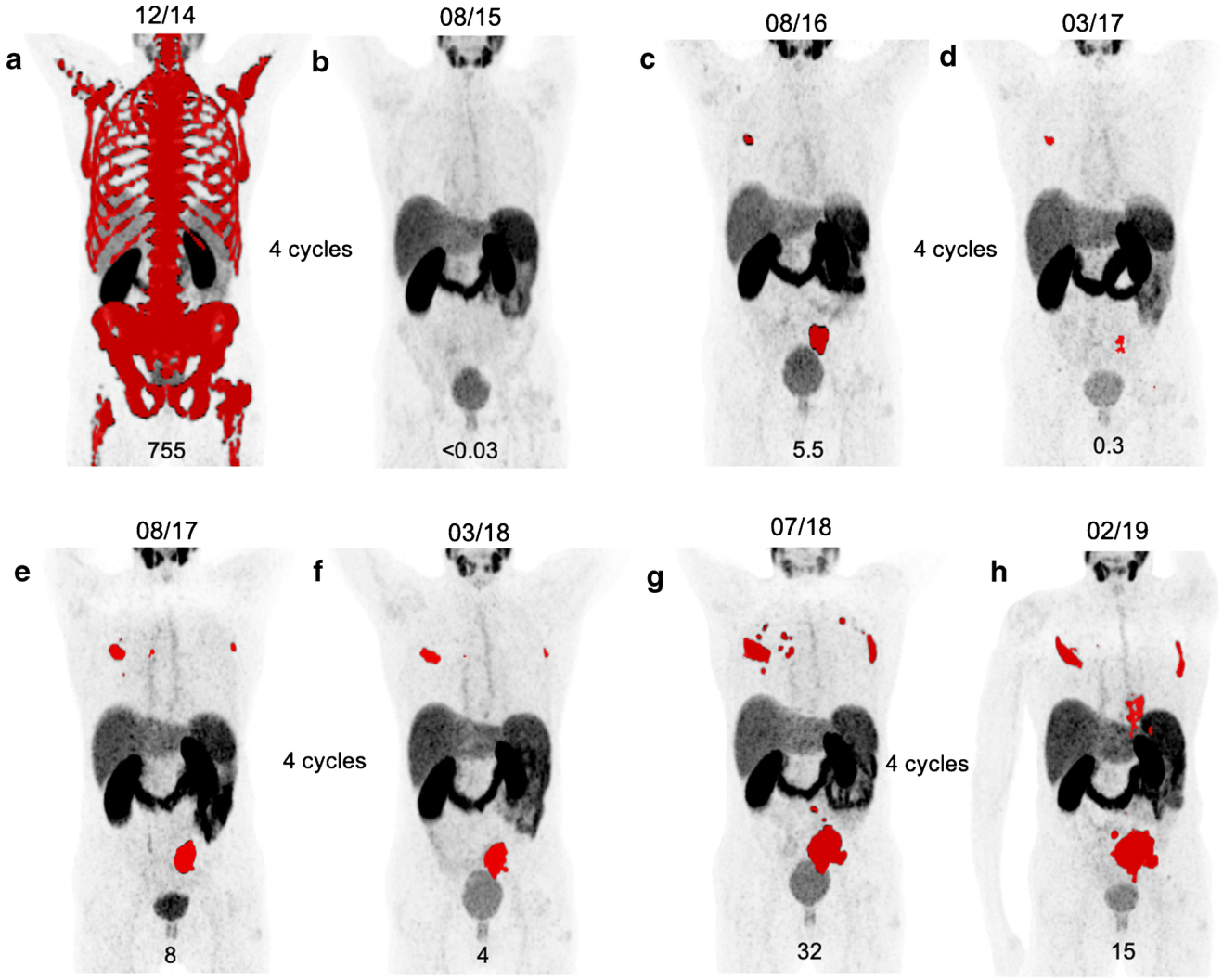
Hofman MS et al. *Lancet Oncol* 2018; 19(6):825-33

An example: 4-year response to ^{177}Lu-PSMA radioligand therapy in mCRPC patient



Gafita et al, EJNMMI, 2019.

Clinical PET Program at BC Cancer

- Currently 37 patient studies per day on 2 scanners
  - From 8 am to 10 pm, 6 days a week
- > 70,000 studies performed to date
- Expanding to Victoria in 2019 and Kelowna in 2020
- Multiple clinical trials, notably:
  - ^{18}F-FDG in lymphoma and numerous clinical trials
  - ^{18}F-DCFPyL in recurrent prostate cancer
  - ^{11}C-methionine in parathyroid adenomas (complete)
  - ^{18}F-Fluorodeoxygalactose for hepatocellular carcinoma
  - ^{68}Ga-DOTATOC for neuroendocrine tumours
  - ^{18}F-DOPA for neuroendocrine tumours

Institu AMI)

- New Inst
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Justin Trudeau ✓
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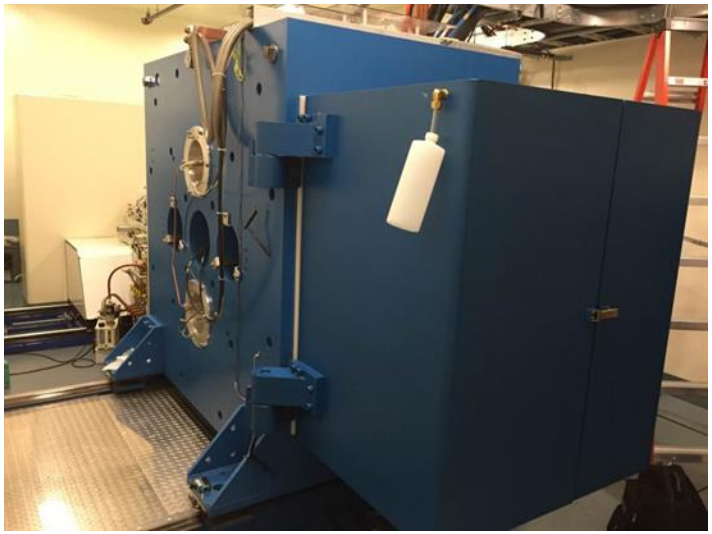
For Canada to lead in an ever-evolving economy & create the jobs of tomorrow, we have to invest in our scientists & the institutions that support them. That's why we're at @TRIUMFLab today announcing our support for a new home for nuclear medicine at @UBC: bit.ly/2P2YDDg

5:16 PM - 1 Nov 2018

Centre of Excellence for Functional Cancer Imaging Clinical



TR19 cyclotron
(ACSI, Richmond, BC)

Two GE PET/CT Scanners

- D600
- D690

Centre of Excellence for Functional Cancer Imaging Preclinical

Inveon PET/CT scanner (Siemens)

USPECT/CT II scanner (MILabs)

PET/CT Clinical Trials

In addition to performing routine clinical PET/CT scans, the Functional Imaging program in Vancouver also conducts clinical trials investigating new PET radiotracers.

These trials are approved by the UBC BC Cancer Research Ethics Board and Health Canada.

For more information, click "+" on the trials below.

18F-DCFPyL (PSMA) PET/CT for Assessment of Recurrent Prostate Cancer −

^{18}F-DCFPyL (PSMA) PET/CT for Assessment of Recurrent Prostate Cancer

Principal Investigator: Dr. François Bénard
BC Cancer
600 W 10th Ave., Vancouver, BC, V5Z 4E6
PET Reception/Booking: 604-707-5951 (toll-free 1-800-663-3333, ext. 5951)
Fax Referrals to: 604-877-6245

We hold clinical trials at all six regional cancer centres. For more information, click the button below.

Open Clinical Trials >

BC Cancer: A Prospective Study on ^{18}F-DCFPyL PSMA PET/CT Imaging in Biochemical Recurrence of Prostate Cancer

- N=130 subjects
- ^{18}F-DCFPyL PET/CT localized recurrent prostate cancer in 60% (PSA ≥0.4 to <0.5), 78% (≥0.5 to <1.0), 72% (≥1.0 to <2.0), and 92% (≥2.0) of cases
- Change in treatment intent occurred in 65.5% of subjects
- Disease stage changed in 65.5%
- Management plans changed in 87.3% of subjects
- N=22 subjects reported mild adverse events after the scan; all resolved completely.

Conclusion: ^{18}F-DCFPyL PET/CT is safe and sensitive for the localization of biochemical recurrence of prostate cancer. This test improved decision making for referring oncologists and changed management for the majority of subjects.

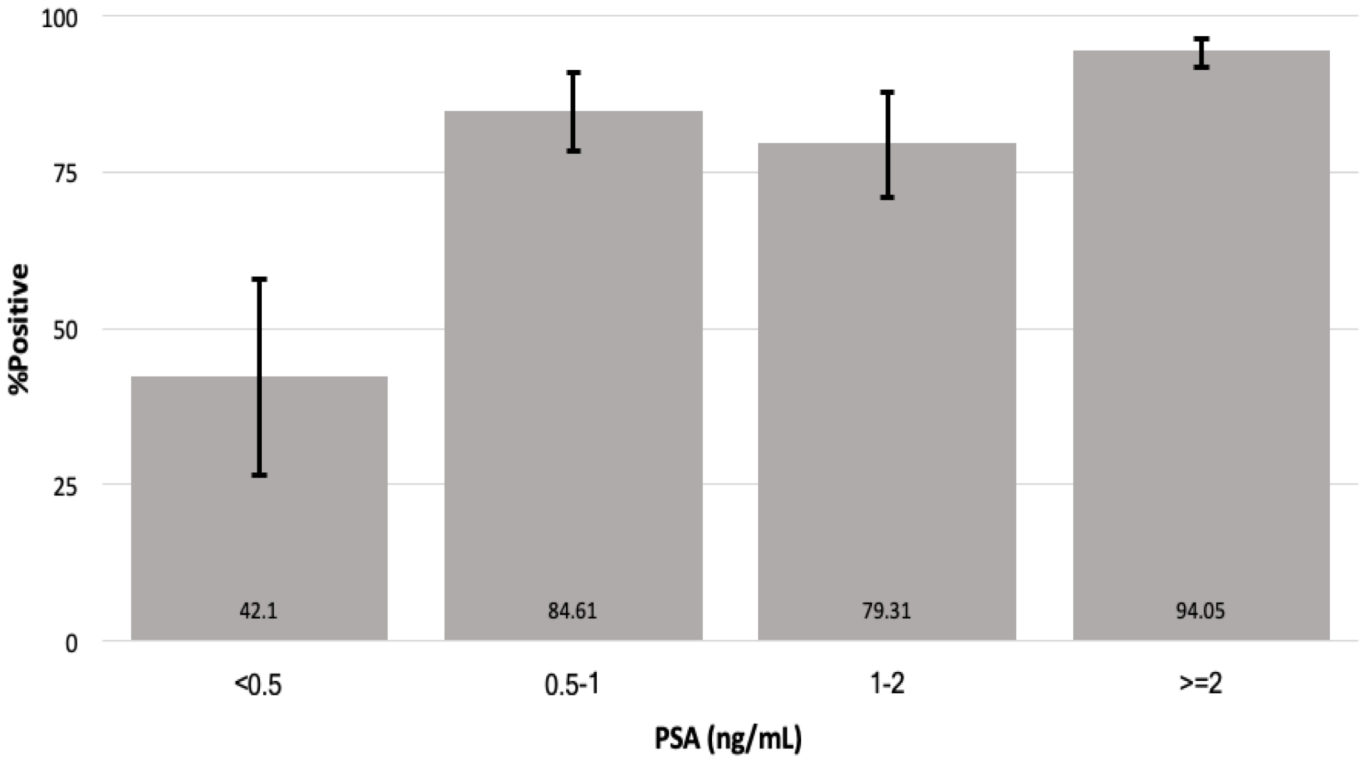
Etienne Rousseau et al, JNM 2019

BC Cancer: Updates Analysis

- ✓ 430 subjects included in the analyses
  - 307 subjects (71.4%) with BR after radical prostatectomy
  - 123 subjects (28.60%) with BR after radiation therapy
- ✓ Prior treatments:
  - Surgery (71.4% of cases)
  - Radiotherapy (62.09%)
  - Androgen deprivation therapy (ADT) (27.44%)
  - Chemotherapy (1.86%)
    - Some participants having received more than one type of therapy.
- ✓ 267 subjects received one or more types of radiotherapy:
  - Brachytherapy administered to 57/267
  - External beam radiotherapy to 176/267
  - Intensity-modulated radiation therapy (IMRT) to 33/267
  - Proton therapy to 1/267
- ✓ Mean PSA of 5.41±7.62 ng/mL with a doubling time of 12.3±10.8 months.

Adverse Events

- No adverse events during scans.
- A total of 52/508 reported mild adverse events after the scan
    - All resolved completely



Proportion of positive scans based on PSA levels. Error bars represent 95% confidence interval.

Radioligand Therapy Research

- Multiple trials on $^{223}RaCl_2$
- New program in Neuroendocrine Tumours
  - Imaging program has started
  - Validation batches underway for ^{177}Lu – start date early 2019
- New $4.5M Prostate Cancer Canada/Movember grant for multicentre study on prostate cancer therapy
  - Randomized comparison with docetaxel
  - Start date 2019-20
- Participation in Endocyte Phase III trial
- New funding for in-house prostate cancer clinical trials
  - Personalized dose-adjusted prostate cancer therapy
  - Phase 1/2 study of ^{225}Ac-PSMA therapy

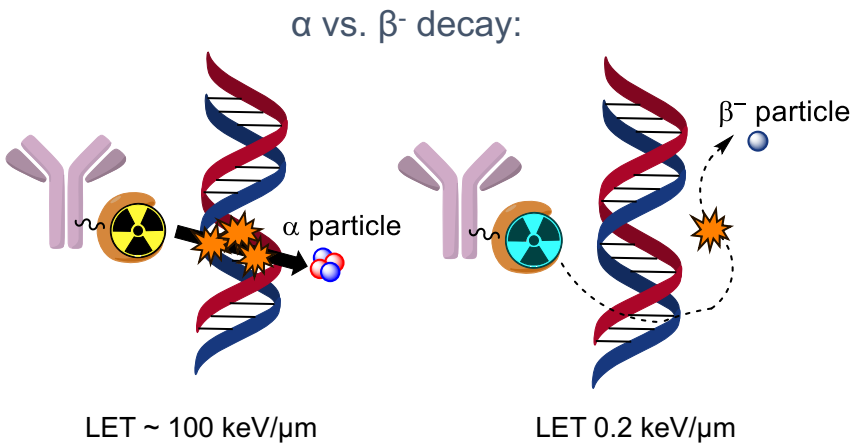
VISION: AN INTERNATIONAL, PROSPECTIVE, OPEN-LABEL, MULTICENTER, RANDOMIZED PHASE 3 STUDY OF ^{177}LU-PSMA-617 IN THE TREATMENT OF PATIENTS WITH PROGRESSIVE PSMA-POSITIVE METASTATIC CASTRATION-RESISTANT PROSTATE CANCER (MCRPC)

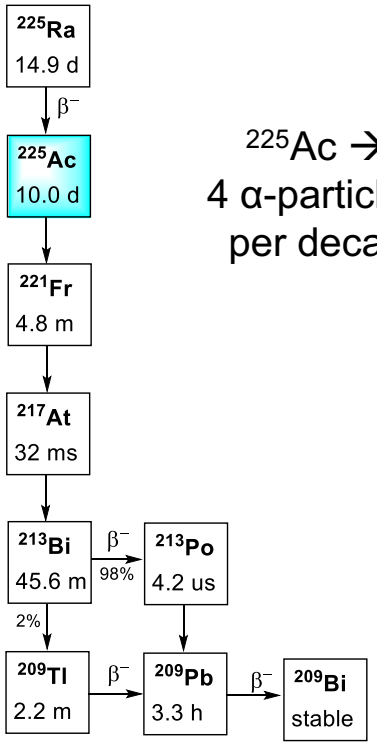
17 Jan 2019

BCCA CODE: GUTVISION

Targeted Alpha Therapy

α-particles have **high LET** (~100 keV/μm) and typical range in tissue of 50 – 100 μm (**< 10 cell diameters**)





^{225}Ac → 4 α-particles per decay

M. Miederer, D. Scheinberg, M. McDevitt, *Advanced Drug Delivery Rev.,* **2008**, *60*, 1371.; J. Elgqvist, S. Frost, J.-P. Pouget, et al. *Frontiers in Oncology,* **2014**, *3*, 324.; M. W. Brechbiel, *Dalton Trans.,* **2007**, 4918.; Y.-S. Kim, M. W. Brechbiel, *Tumor Biol.*, **2012**, *33*, 573. J.-P. Pouget, I. Navarro-Teulon, et al. *Nat. Rev. Clin. Oncol.* **2011**, *8*, 720.

^{225}Ac-PSMA

German Prostate Cancer Study:

^{225}Ac-PSMA-617 for PSMA-Targeted α-Radiation Therapy of Metastatic Castration-Resistant Prostate Cancer

J Nucl Med 2016; 57:1941–1944
DOI: 10.2967/jnumed.116.178673

Clemens Kratochwil*[1], Frank Bruchertseifer*[2], Frederik L. Giesel[1], Mirjam Weis[2], Frederik A. Verburg[3], Felix Mottaghy[3], Klaus Kopka[4], Christos Apostolidis[2], Uwe Haberkorn[1], and Alfred Morgenstern[2]

Study conclusions:

- Two patients in highly challenging clinical situations who showed a complete response to ^{225}Ac-PSMA-617 therapy
- Both patients experienced a PSA decline to below measurable levels and showed a complete response on imaging
- No relevant hematologic toxicity was observed
- Xerostomia was the only mentionable clinical side effect

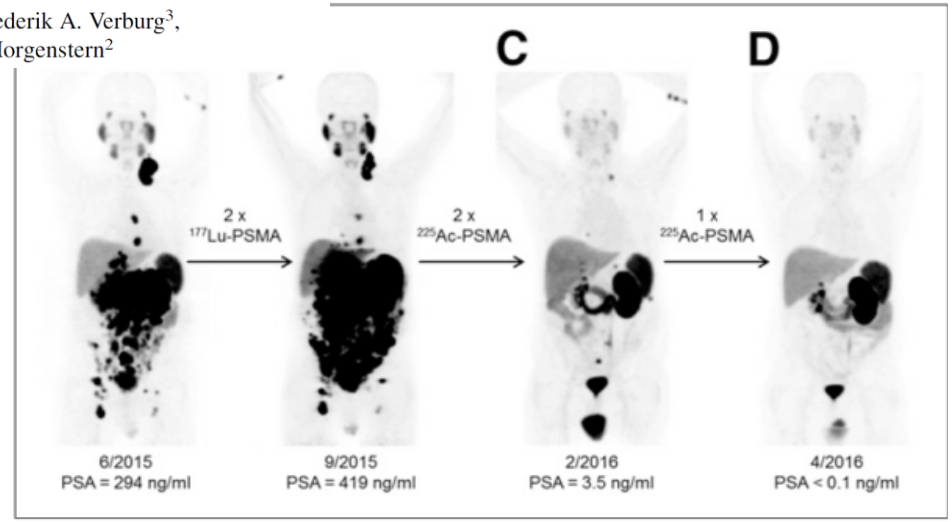
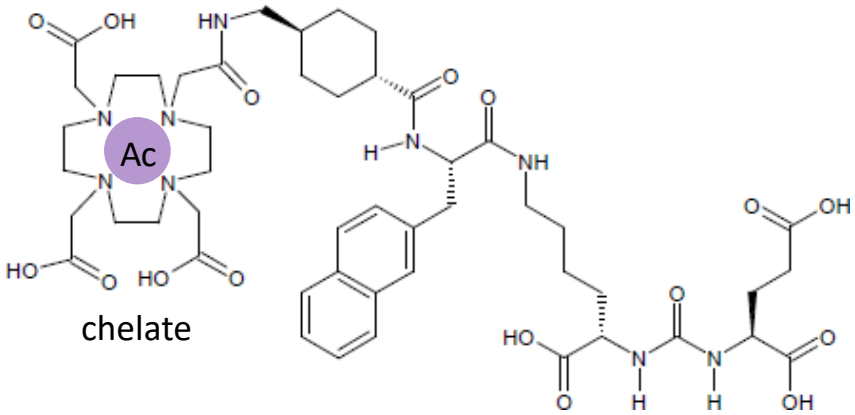


FIGURE 3. ^{68}Ga-PSMA-11 PET/CT scans of patient B. In comparison to initial tumor spread (A), restaging after 2 cycles of β-emitting ^{177}Lu-PSMA-617 presented progression (B). In contrast, restaging after second (C) and third (D) cycles of α-emitting ^{225}Ac-PSMA-617 presented impressive response.

^{225}Ac-PSMA



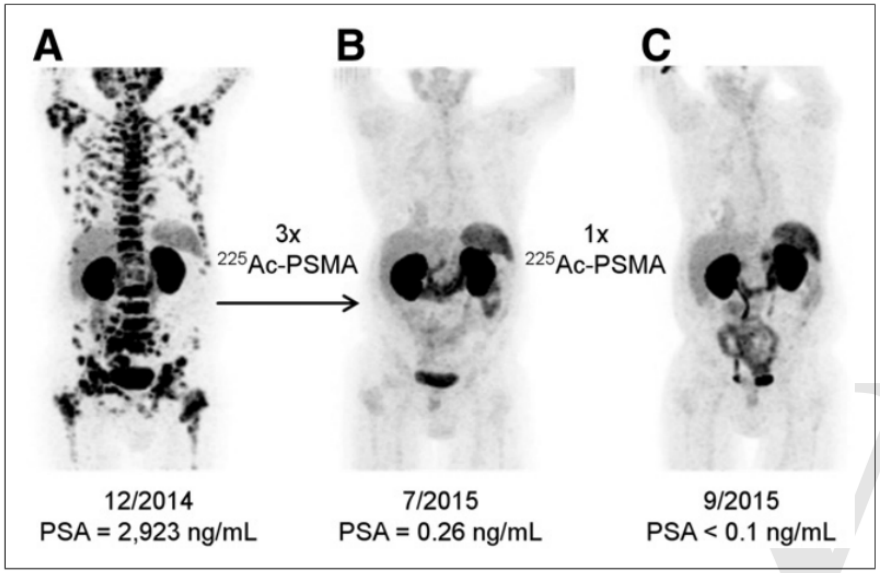


Image: Kratochwil et al. **^{225}Ac-PSMA-617 for PSMA-Targeted α-Radiation Therapy of Metastatic Castration-Resistant Prostate Cancer.** J Nucl Med. 2016 Dec;57(12):1941-1944.

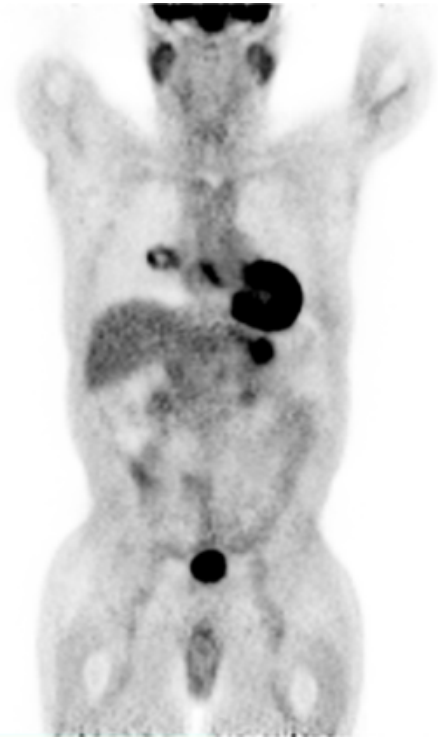
Note: [^{225}Ac]PSMA agent shows curative properties for late-stage, metastatic prostate cancer
Goal: Apply similar principle to treat other incurable cancers

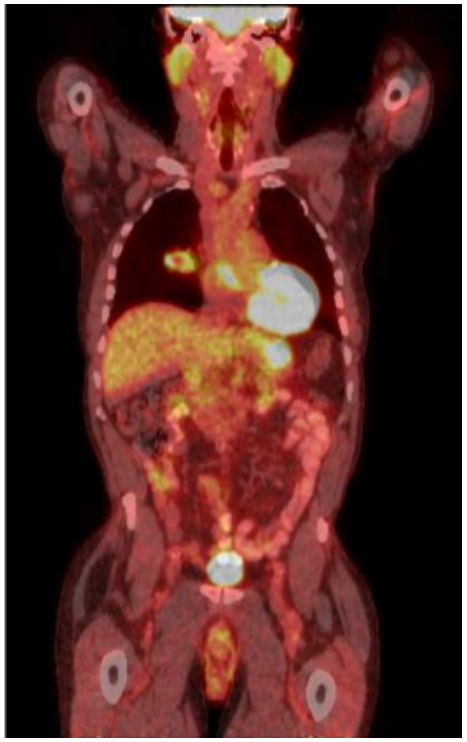
Problem: The global supply of ^{225}Ac is limited to 1.7 Ci per year from US/Europe.
- Sufficient to treat <5k patients/year

Images Are More than Pictures, They Are Data!

Visual Interpretation

- Visual interpretation is the primary method of clinical PET image analysis.
  - Incorporates clinical experience
  - Knowledge of normal variants.
  - Knowledge of artifacts.

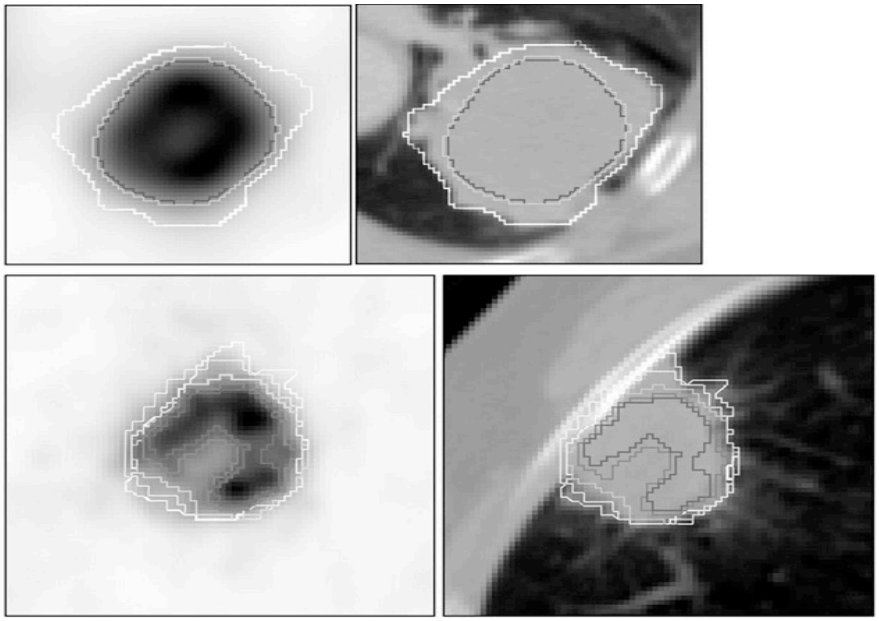




- Although visual assessment continues to be the mainstay of PET interpretation, it has some potential limitations.
  - Particularly for assessing response to treatment.

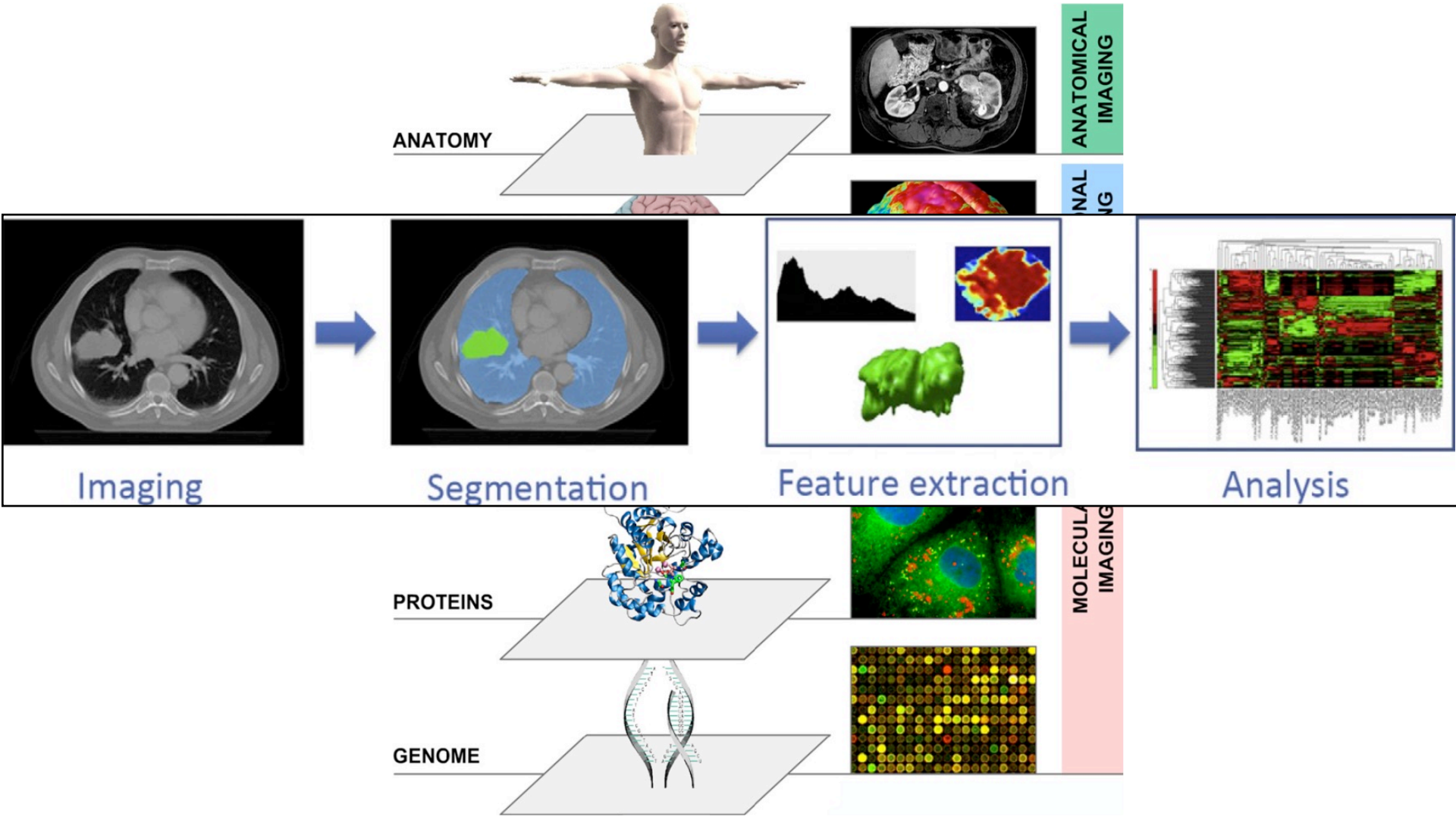
Tumor Heterogeneity

- Intra-tumor heterogeneity due to regional variations in proliferation, cell death, vascular structure, etc.
- Implications in disease progression & treatment response



Hatt et al., JNM11

Radiomics



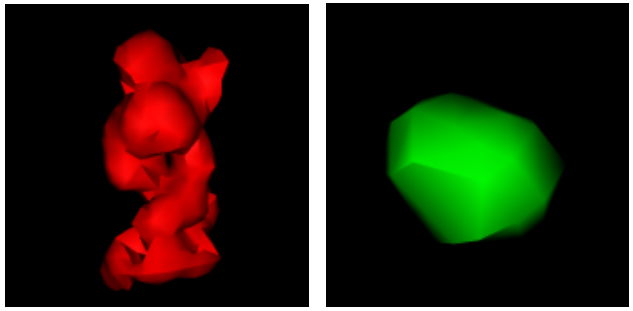
P Lambin, *et al*. **Radiomics: extracting more information from medical images using advanced feature analysis**. *Eur J Cancer* 2012

Multimodal characterization of tumors

Characterization: geometrical shape

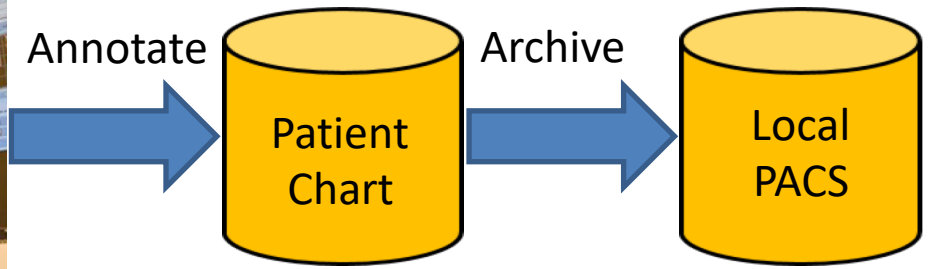
- 3D geometrical shape:

$$Sphericity = \frac{\sqrt[3]{36\,\pi\,Volume^2}}{Surface}$$



1. Hatt, *et al*. **A fuzzy locally adaptive Bayesian segmentation approach for volume determination in PET.** *IEEE Trans Med Imaging*. 2009
2. El Naqa, *et al*. **Exploring feature-based approaches in PET images for predicting cancer treatment outcomes**. *Pattern Recognit*. 2009

Current Practice



Reading Room of the Future

Annotate

Patient Chart

Archive

Local PACS

Segment

Extract Features

Genomic Data

Medical Data

Radiomic Data

Database

Mining & Decision Support

Key Points

- Significant excitement over PSMA-targeted imaging and therapy (theranostics)
  - "Treat what you see and see what you treat"
- Significant potential especially for mCRPC patients
- Both imaging and therapy agents involved in multiple clinical trials in Canada and elsewhere
  - expected to be approved for wide usage

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