Webinar Internal Bapeten,
Rabu, 9 September 2020

Perkembangan Modalitas dan Layanan Kedokteran Nuklir Terkini Nasional dan International

A. Hussein S. Kartamihardja

Department of Nuclear Medicine and Molecular imaging
Faculty of Medicine, Universitas Padjadjaran – Dr. Hasan Sadikin General Hospital

Nuclear Medicine is defined as a medical specialty which uses the nuclear properties of matter to investigate physiology and anatomy, diagnosis diseases, and to treat with unsealed sources of radionuclide.

(IAEA/WHO, 1988).

PMK 780/2008

01

Pelayanan kedokteran nuklir adalah pelayanan **penunjang dan/atau terapi** yang memanfaatkan sumber radiasi terbuka dari disintegrasi inti radionuklida yang meliputi pelayanan diagnostik in-vivo dan in-vitro melalui pemantauan proses fisiologi, metabolisme, dan terapi radiasi internal.

Perka Bapeten 17/2012

02

Kedokteran Nuklir adalah kegiatan pelayanan **kedokteran spesialistik** yang menggunakan sumber radioaktif terbuka dari disintegrasi inti berupa radionuklida dan/atau Radiofarmaka untuk tujuan diagnostik, terapi, dan penelitian medik klinik, yang didasarkan pada proses fisiologik, patofisiologik, dan metabolisme.

KMK 008/2009

03

Pelayanan Kedokteran Nuklir adalah pelayanan **penunjang dan/atau terapi** yang memanfaatkan sumber radiasi terbuka dari disintegrasi inti radionuklida yang meliputi pelayanan diagnotik in-vivo dan in-vitro melalui pemantauan proses fisiologi, , metabolisme dan terapi radiasi internal.

What the different between

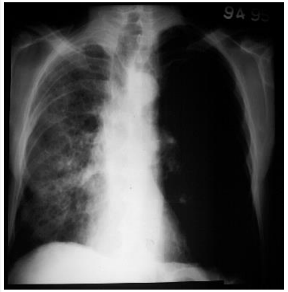
Nuclear Medicine and Radiology

Nuclear Medicine

- Physiology, molecular
- Nuclear properties (gamma, beta, alpha)
- Open source
- Emissions
- Radionuclide therapy (internal radiations, etc)

Radiology

- Anatomy
- Peripheral properties (x-rays)
- Closed source
- Transmissions
- External radiations (for treatment purpose)

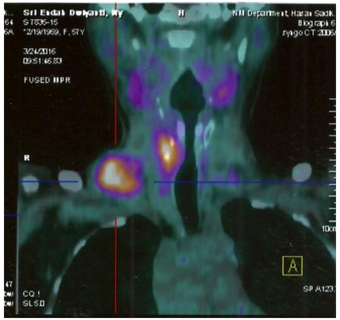


X-ray

IN-VITRO (RIA/IRMA)

- Thyroid Hormones
- Tumor Marker

IMAGING DIAGNOSTICS



THERAPHY Malignant - Benign

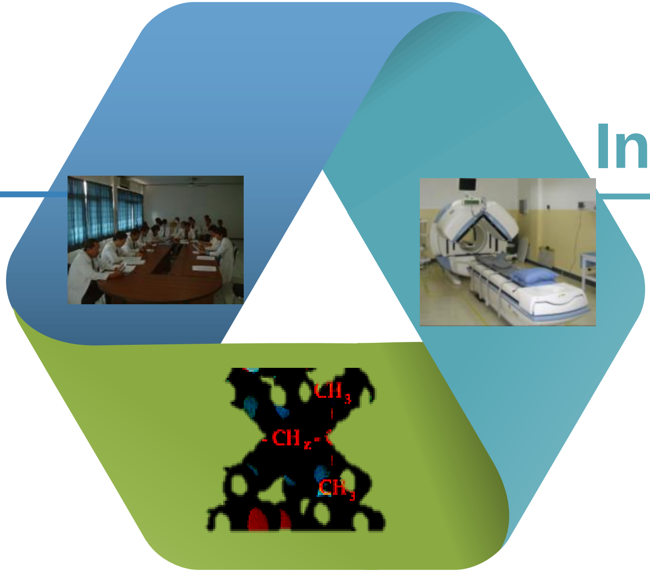
- Hyperthyroidism
- Thyroid Cancer
- Neuroblastoma
- Bone Pain Palliation
- Keloid - heamangioma

Nuclear Medicine Services

left to right: Henri Becquerel, Marie Sklodowska Curie, Georg de Hevesy, Ernest Lawrence and Benadict Cassen. Hal Anger, David Kuhl, Gerd Muehllehner, Ron Jaszczak and Bruce Hasegawa. Gordon Brownell, Michael Phelps, Michael Ter-Pogossian, David Townsend and Ron Nutt.

HISTORICAL MILESTONE OF NUCLEAR MEDICINE

The three pillars of nuclear medicine



Man Powers

- Multidiciplinary sklill

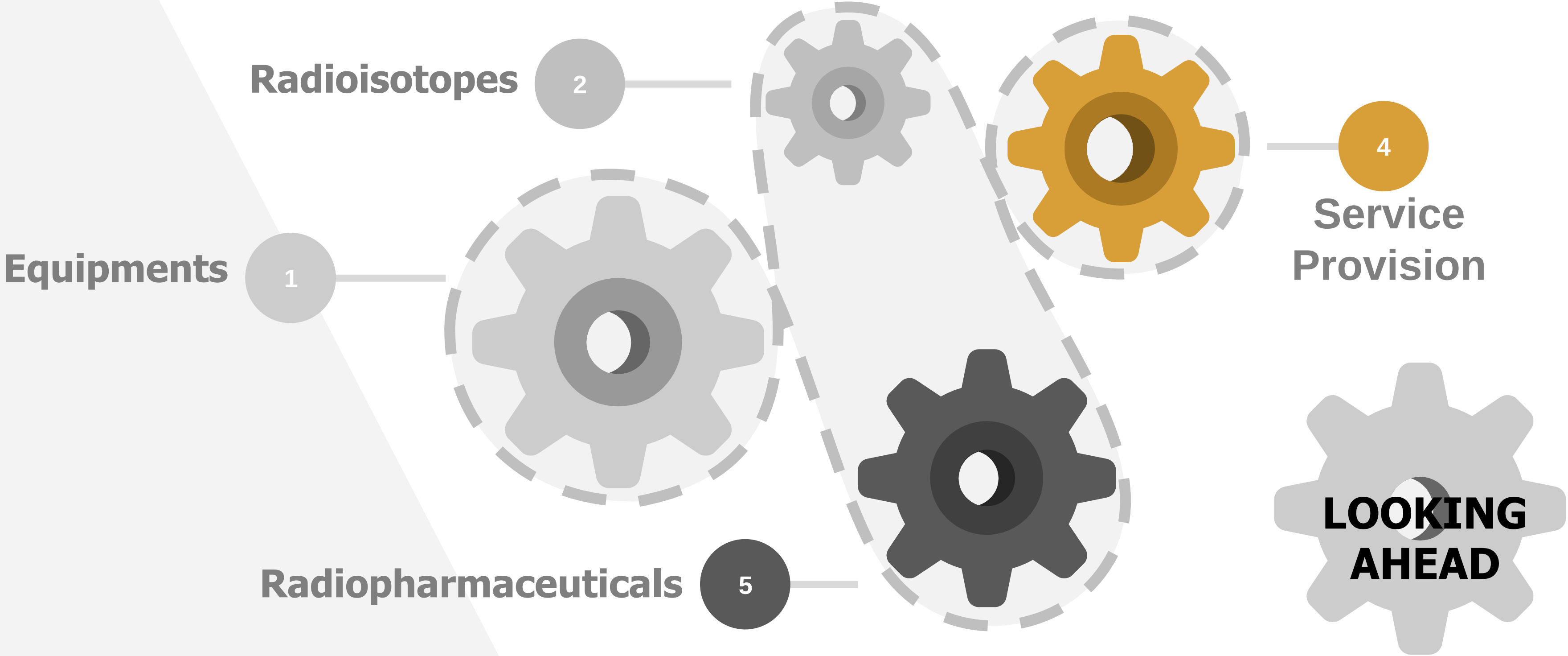
Instrumentations

- Gamma Cameras
- SPECT/CT
- PET/CT
- PET/MR

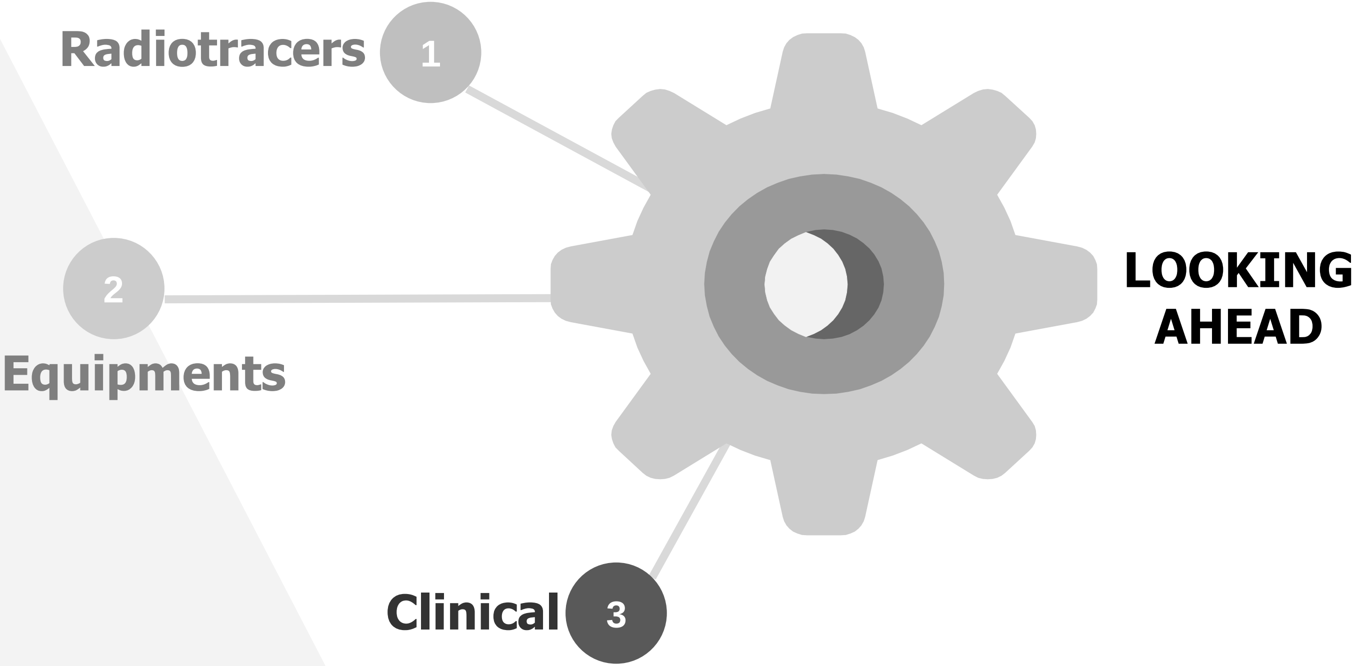
Radiopharmaceutical

- Reactor; Generator
- Cyclotrone

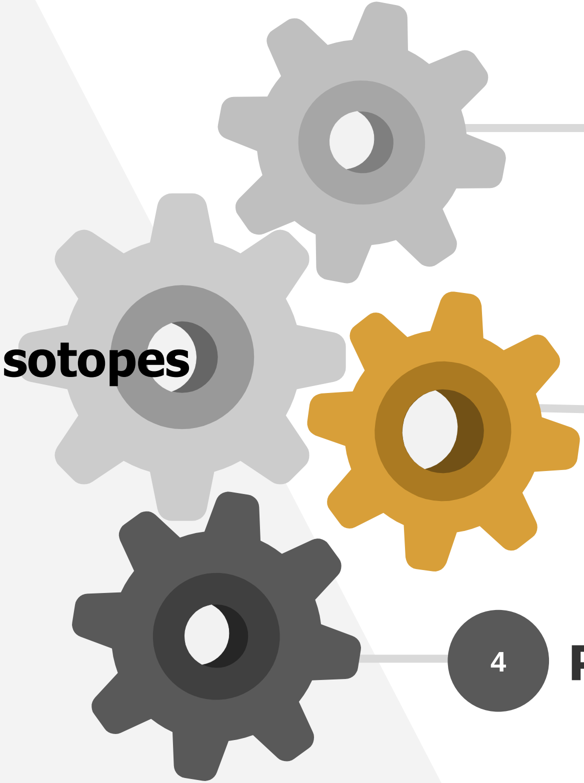
The Future Trends in Nuclear Medicine



The Future Trends in Nuclear Medicine



The Future Trends in Nuclear Medicine



Radioisotopes

1 **Demand and Supply**

- NM Study : 40 m/year
- Tc-99m : 80%
- Radioisotopes demand : increased 5%/yr

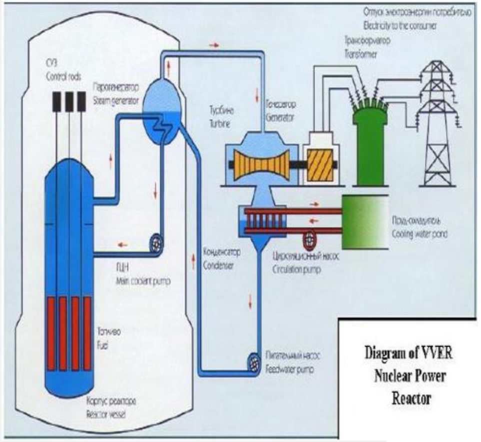
2 **Initiatives**

- Market had substantially restructured following supply crisis

4 **PET Tracers**

- Limited

Radioisotop Production



Reactor

^{99m}Tc- Generator

Gallium-68 Generator

Cyclotron

Radioisotopes

^{90}Sr — Strontium-90
Pain relief

^{111}In — Indium-111
Targeted Diagnostic

^{131}I — Iodine-131
Versatile
Radioiodine

^{32}P — Phosphore-32
Keloid Haemangioma

^{188}Re — Rhenium-188

^{166}Ho — Holmium-166

^{225}Ac

^{201}Tl — Thallium-201
Heart Health

^{133}Xe — Xenon-133
Breathing Easier

^{123}I

^{90}Y — Yttrium-90
Liver Cancer and
radiosynovectomy

^{177}Lu — Luthetium-177
Teranostic
Isotope

^{153}Sm — Samarium-153
Cancer therapy and Pain Relief

^{67}Ga — Gallum-67
Infection/Cancer Detection

^{99m}Tc — Technetium-99m
The most widely used
isotope in the world

PET Tracer

^{18}F

Flour-18
The most widely used PET tracer used in the world for cancer detection

^{15}O

Oxygen-15
Cardiac blood flow

^{68}Ga

Gallum-68
^{99m}Tc like Isotope for PET Targeted Diagnostic

^{13}N

Amonium-13
Cancer

^{82}Rb

Rubidium-82
Myocardial perfusion

^{11}C

Carbon-11
Cancer

The Future Trends in Nuclear Medical Imaging

Radiopharmaceuticals

1

Multimodality Tracers

- Tracers offering dual imaging
- Tc-99m colloid and stain blue

2

Targeted therapy

- PSMA Ga-68 SIRT Y-90
- DOTA Lu-177
- PRRT
- Targeted alpha therapy (BNCT)

4

Future Personalized Medicine

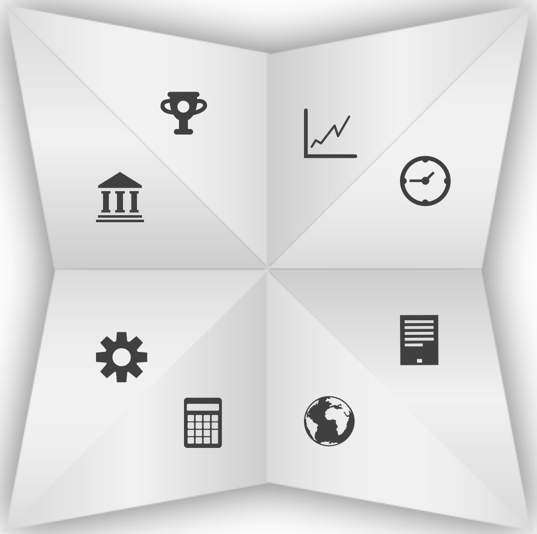
- Molecular genetic imaging
- Monitoring diff cellular process (PET)
- Dynamic imaging of molecular and cell

Ideal Radiopharmaceutical Properties for Diagnosis

Pure gamma emitter

Energy of Gamma Rays
Ideal: 100-250 keV

Localization only in tissue desired



Short half-life isotope
Ideally1.5 times the duration of the diagnostic procedure

High Target to Non target Ratio

Easy preparation and QC

Economy price

Availability

Ideal Radiopharmaceutical Properties for Treatment

Pure beta or alpha particle

High or medium Energy > 1 MeV

Localization only in tissue desired

Relatively long half-life isotope, ideally a couple day

High Target to Non target Ratio

Easy preparation and QC

Economy price

Availability

Radiopharmaceuticals

No	Radiopharmaceuticals	Example
1	Ready to use	I-123 Capsule; I-131 Hippuran; Ga-67 citrate; Tl-201 chloride; Xe-133 gas; Tc-99m pertechnetate
2	Instant Tc-99m kit	DTPA; MDP; GH; MAA; PYP; Tetrofosmin, MIBI, MAG3; Sulfur colloid
3	Requiring significant manipulation	Cr-51; Tc-99m RBC; Tc-99m WBC;
4	Short half life (Cyclotron)	F-18; C-11

Nuclear Medicine

- Cerebrovascular disease
- Alzheimer' s disease
- Schizophrenia, Epilepsy
- Neurotransmitter study

- Sciintimammography
- Sentinel node detection

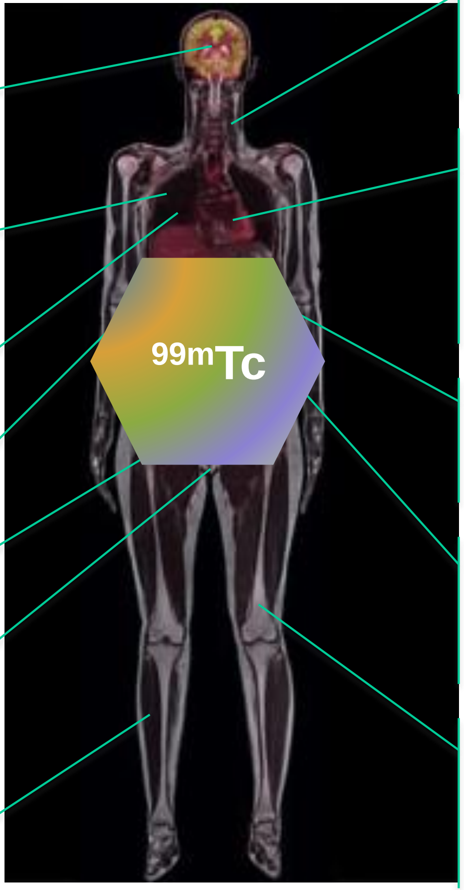
- V/Q Scan --→ PE
- Regional lung function

- Hepatobiliary scan

- Cystography

- Testicular scan

- Flebography
- Venography
- Lymphoscintigrapy



- Thyroid Scan
- Thyroid Uptake
- Neonatal hypothyroidis

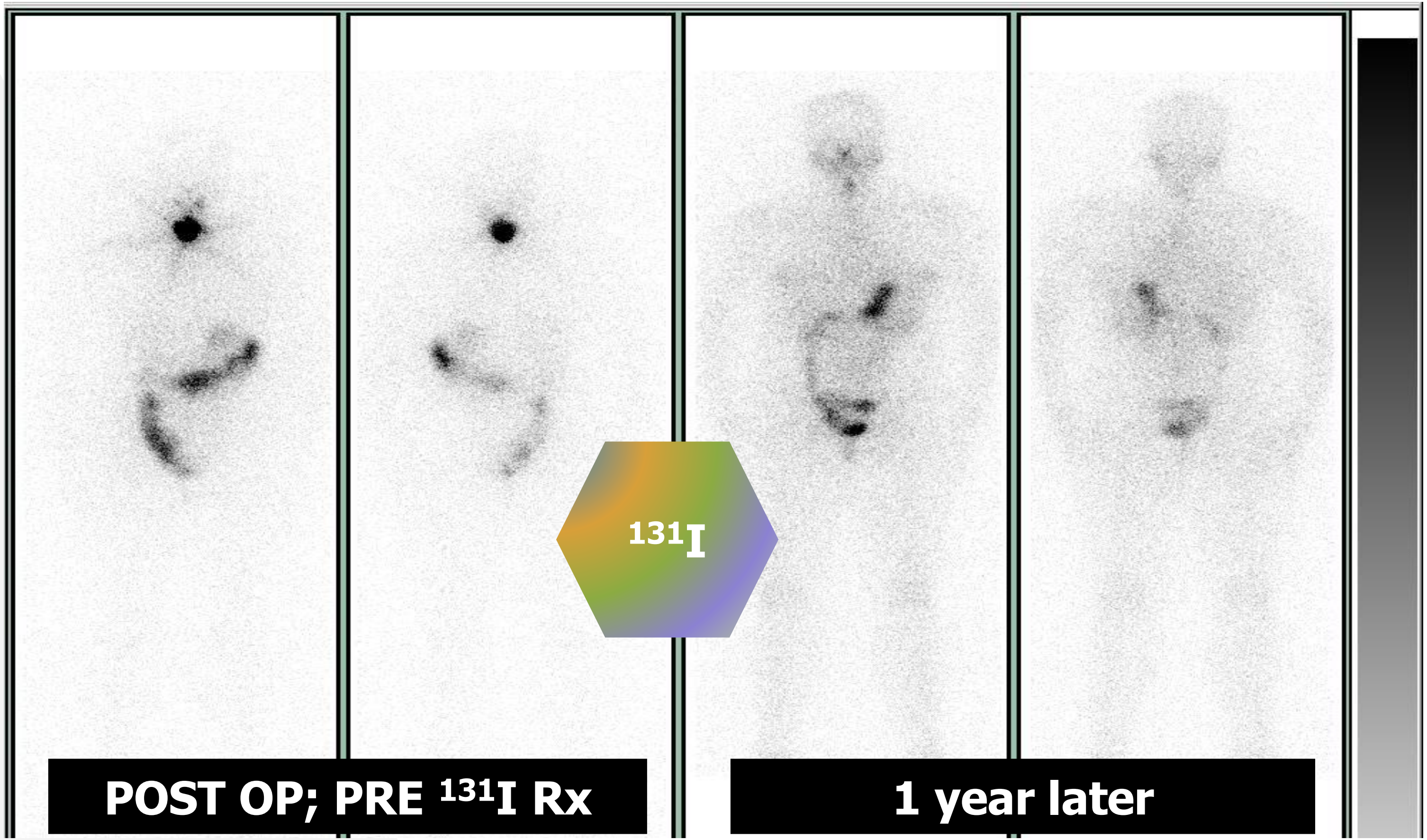
- Myocardial Perfusion
- Viability Study → risk stratification
- Neuroreceptor imaging
- Prevention of restenosis
- Cardiac function

- Oesophageal TT
- Gastric emptying time
- G-E reflux

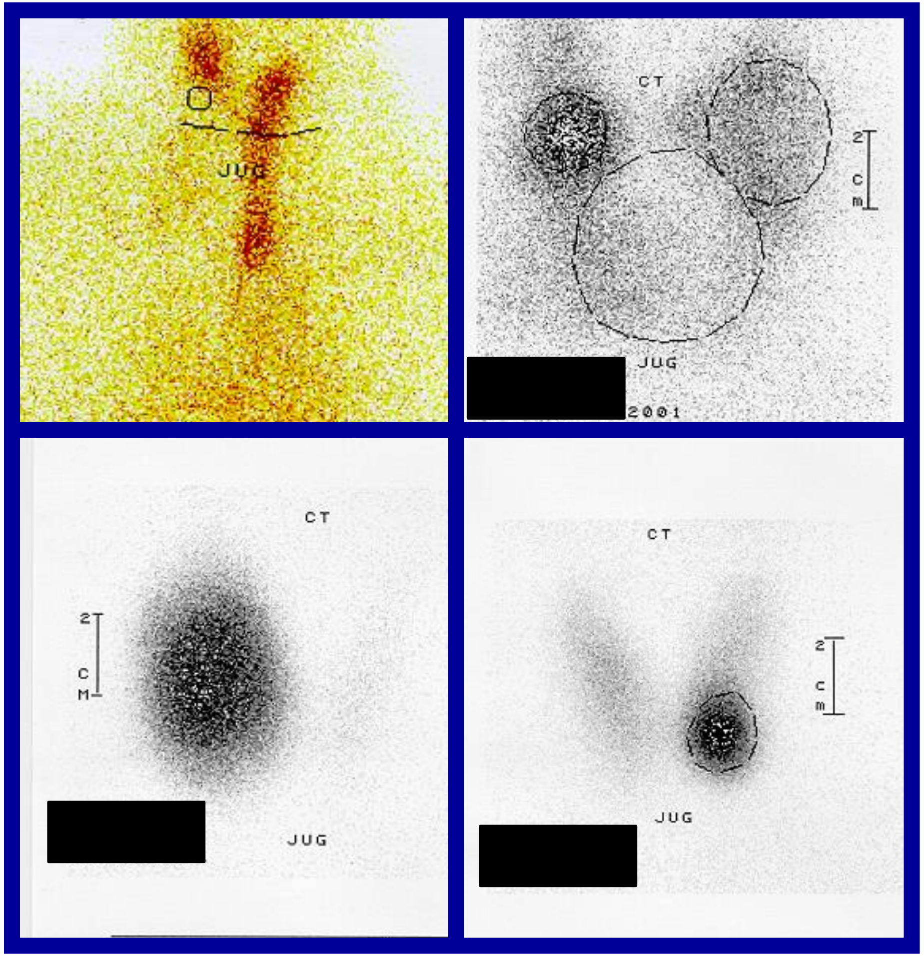
- Renography
- GFR
- ERPF
- Renal scan

Whole body scanning
- Bone scan
- PET
- Infection scan

Well Differentiated Thyroid Carcinoma

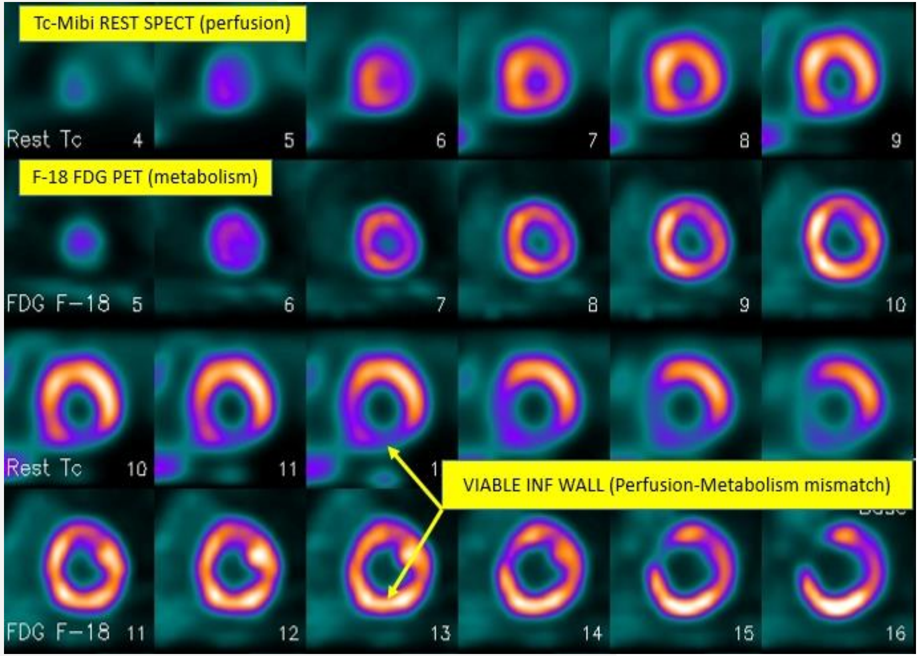


^{131}I

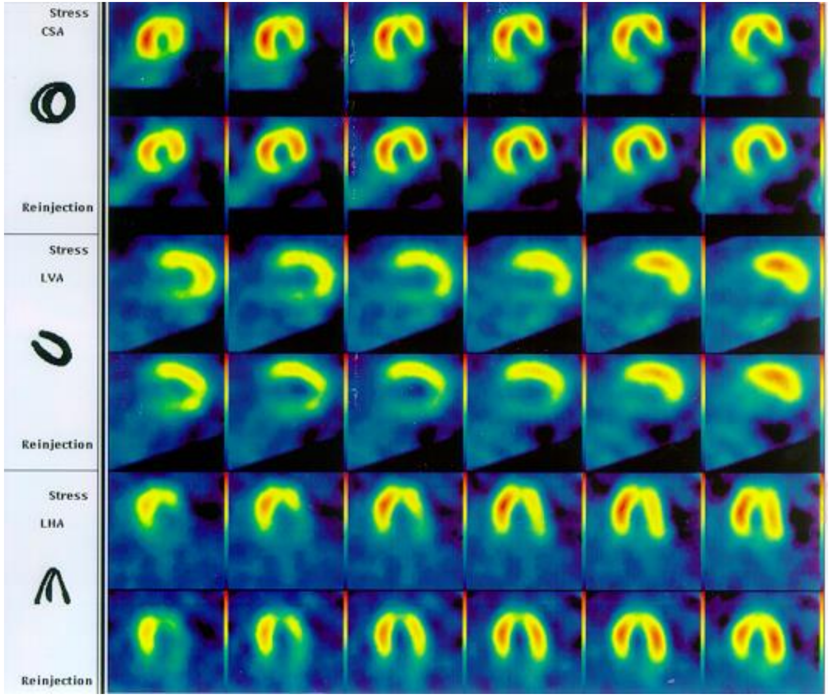


^{123}I

^{99m}Tc


Tc-Mibi REST SPECT (perfusion)
Rest Tc 4
5
6
7
8
9
F-18 FDG PET (metabolism)
FDG F-18 5
6
7
8
9
10
Rest Tc 10
11
FDG F-18 11
12
13
14
15
16
VIABLE INF WALL (Perfusion-Metabolism mismatch)

^{201}Tl


Stress
CSA
Reinjection
Stress
LVA
Reinjection
Stress
LHA
Reinjection

^{18}F

^{32}P

Phosphore-32
Keloid Haemangioma

KELOID TREATMENT

PRE-TREATMENT

POST-TREATMENT

^{90}Y

Yttrium-90

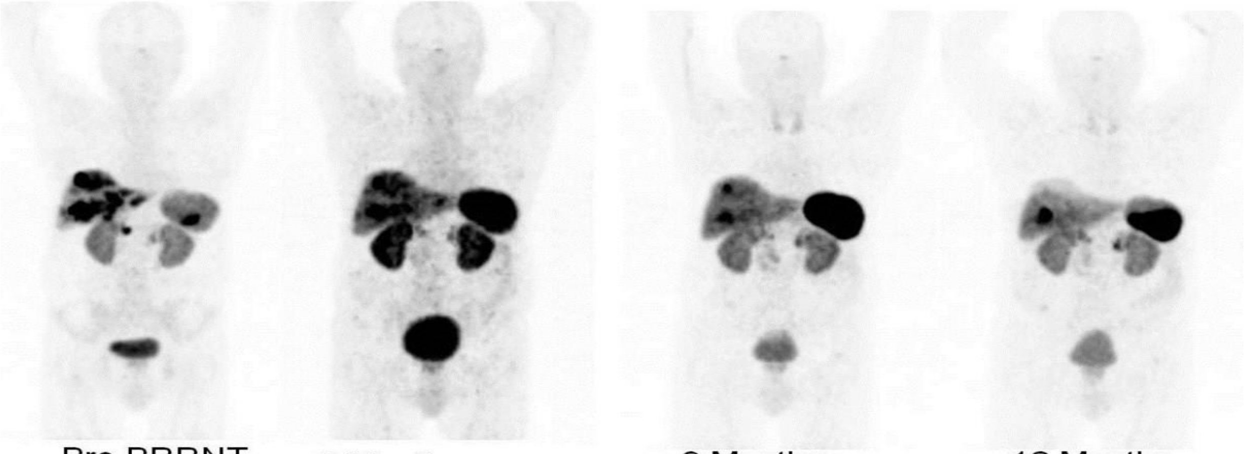


Fig. 5: VIPoma patient with Verner Morrison syndrome (severe watery diarrhoea, hypokalemia), high dose octreotide (Sandostatin LAR) prior to PRRNT. After administration of one single cycle of 5 GBq Y-90 DOTATATE, there was no need of octreotide after 3 months, 15 kg weight gain and significant reduction of tumor burden (partial remission. After follow up of 1 year, the liver and kidney functions were normal and only single liver metastasis remained.

Follow-up of 2 years after 3 PRRNT cycles

Response	NETs of non-pancreatic	Pancreatic NETs (pNETs)
Complete/partial and minor remission	**48%**	**52%**
Stabilized Disease	**45%**	**39%**

RP Baum. 2012; 2(5):437-447. doi: 10.7150/thno.3645

^{68}Ga

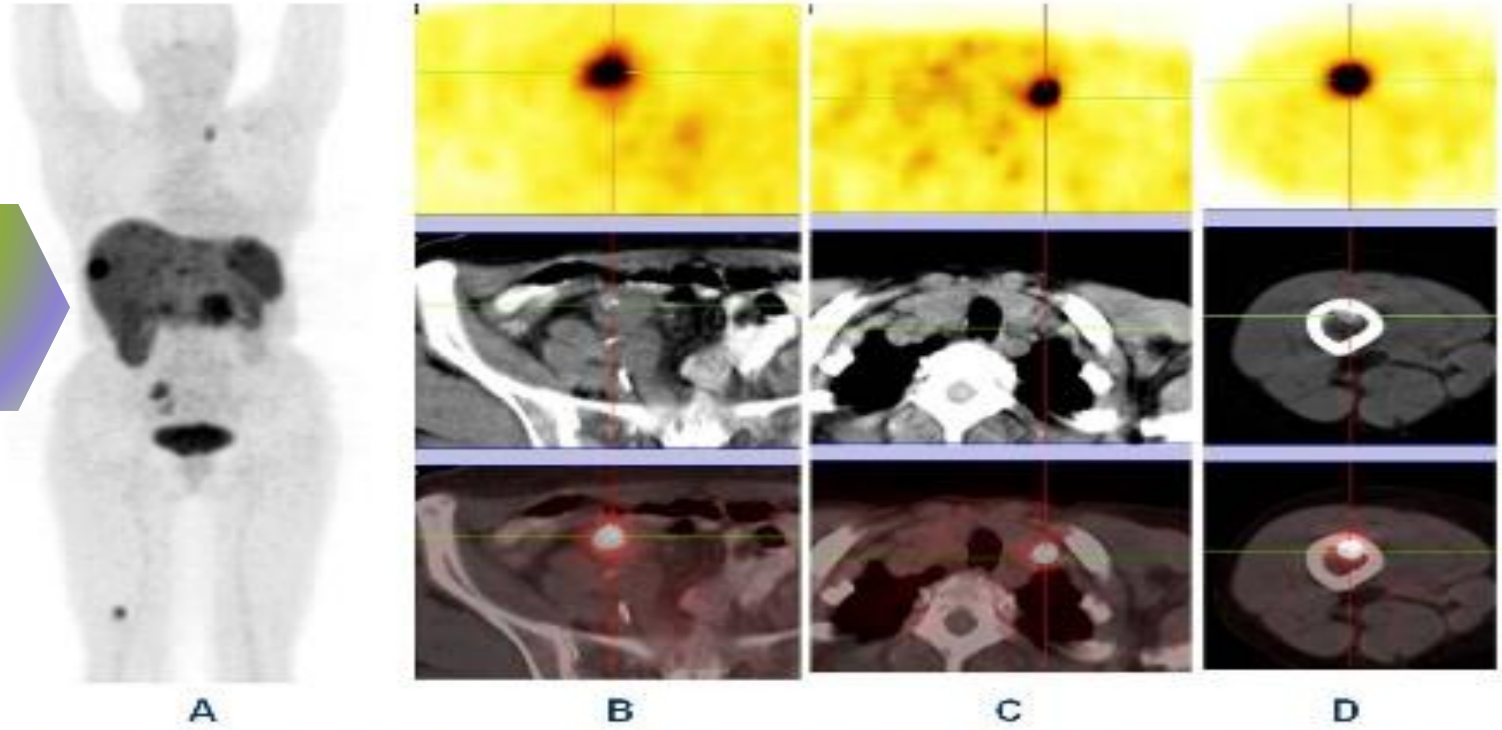
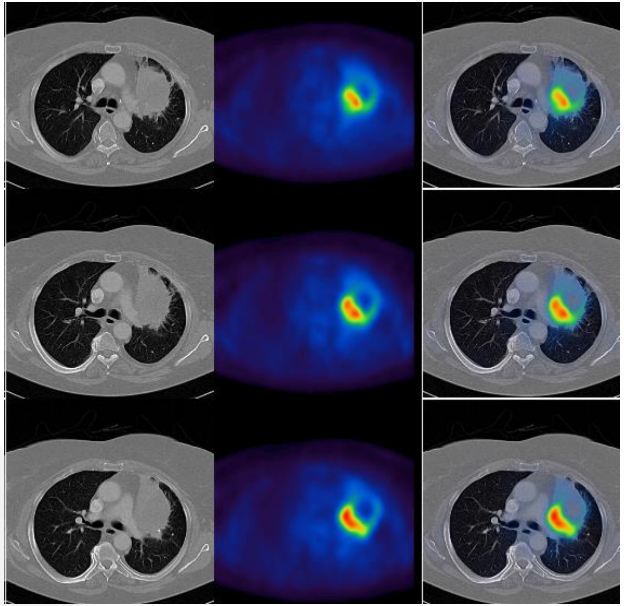


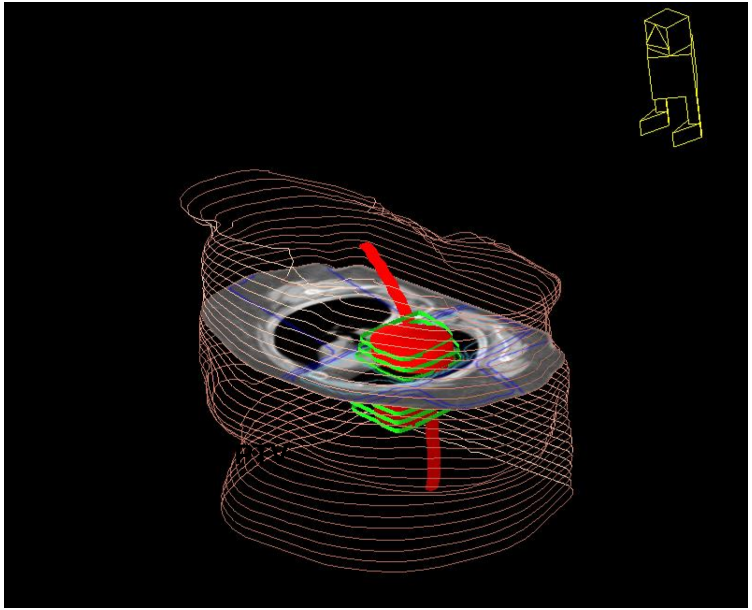
Fig. 2: Whole body "one-stop shop" diagnosis with receptor-PET/CT (A – MIP; B, C and D - PET, CT and fused images) using Ga-68 DOTATOC showing primary neuroendocrine tumor in the ileum (B) with lymph node (C) & bone metastases (D).

RP Baum. 2012; 2(5):437-447. doi: 10.7150/thno.3645

Molecular Radiation Treatment Planning (MRTP)

^{18}F-FDG





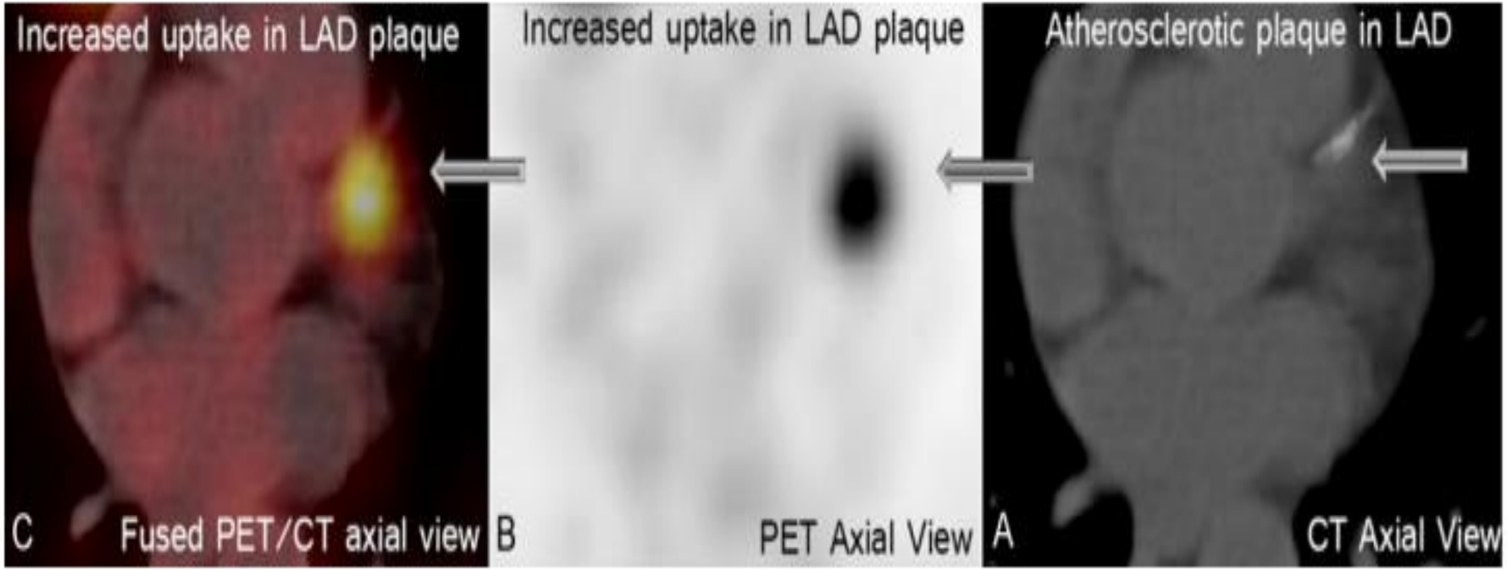
Am J Nucl Med Mol Imaging 2015;5(1):65-71
www.ajnmmi.us /ISSN:2160-8407/ajnmmi0001379

Original Article

Assessment of vulnerable atherosclerotic and fib otic plaques in coronary arteries using ^{68}Ga-DOTATATE PET/CT

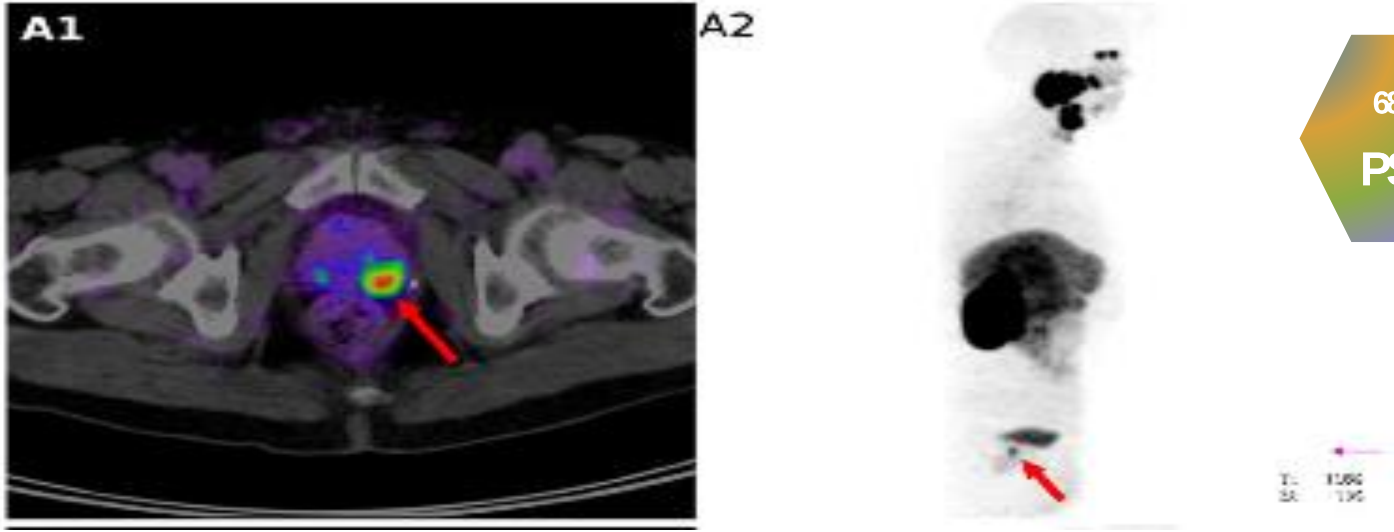
Alireza Mojtahedi[1,2], Abass Alavi[3], Sanjay Thamake[2], Reza Amerinia[1], David Ranganathan[4], Izabela Tworowska[2], Ebrahim S Delpassand[1,2]

^{68}Ga-DOTATATE



- Activated Macrophage → somatostatin receptor-2 (SSTR-2) expression
- **^{68}Ga-DOTATATE** binds to SSTR-2 : High risk plaque detection
- Detect Inflammation and angiogenesis

Eur J Nucl Med Mol Imaging (2012) 39:1085–1086



^{68}Ga-PSMA

The 67-year-old patient had undergone previous radiotherapy of the prostate due to carcinoma and had received androgen therapy since 2002. The patient presented with a continuous increase of PSA values (from 1 ng/ml in 2002 to 7.4 ng/ml in May 2011)

The Future Trends in Nuclear Medicine Imaging

Equipments

- SPECT/PET-CT aligned to anatomical information without the use of external markers or internal landmarks.

PET /CT

SPECT /CT

PET /MR

SPECT /MR

- Find the design of different geometries and various detector technologies of SPECT and PET scanners

PET/MR more challenging

1

Hybrid Imaging

- Systems are being designed for "low cost" and very high-resolution

2

Multimodality

- The design of a prototype small animal PET scanner

- **Function and Structure**
- **Blurred boundaries**
- **Efficient**

- PET has become of more interest for clinical practice

The Camera

Rectilinear Scanner

Planar Gamma Camera

Double Head SPECT Camera

SPECT/CT

PET/CT – PET/MR

Molecular Pathology
- Ligands, Targets
  Digitalization of images
- Data analysis
- Gene analysis

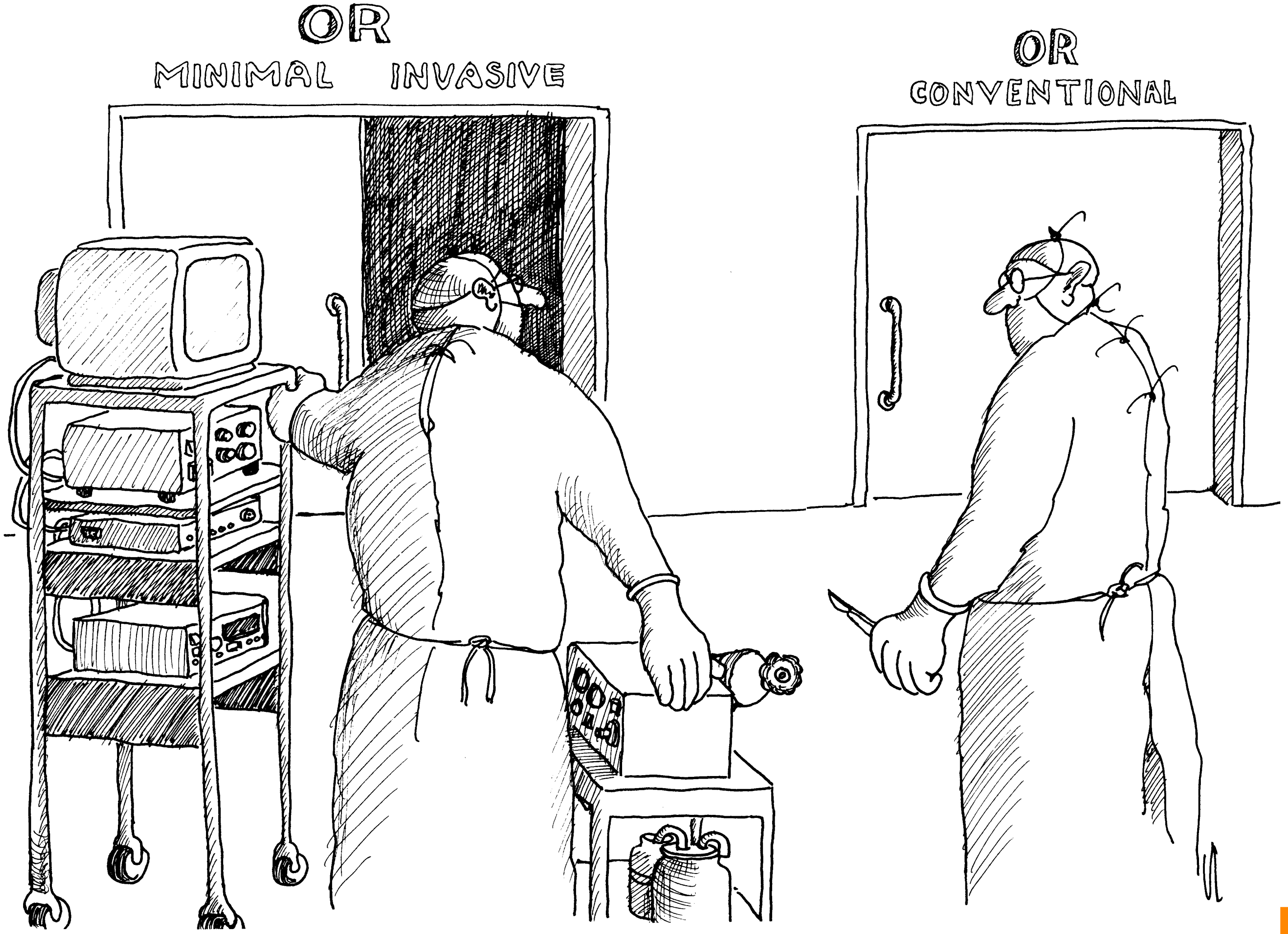
Preclinical Imaging
- Animal PET/CT, PET/MRI,
- SPECT/CT

THERANOSTICS

Molecular Imaging
- PET/CT, PET/MRI
- Novel tracers
- Clinical studies

Molecular Therapy
- 4D-dosimetry
- Medicial physics
- Clinical studies
- Multicenter trials

PATIENTS


OR
MINIMAL INVASIVE
OR
CONVENTIONAL

TREATMENT PARADIGM

Breaking the cycle

Observation → Test → Action → Predictable Response

Trial and error medicine

One-medicine-fits-all

- Trial and error medicine
- One-medicine-fits-all

→ Personalized Medicine → Personalized Health Care

Targeted Therapy -Thera(g)nostics

“THERAGNOSTICS”

The combination of a ***diagnostic*** tool that helps to define the right ***therapeutic*** tool for a specific disease

Easy to apply and to understand in ***Nuclear Medicine***

an easy ***switch of the radionuclide*** from diagnostic to therapy on the same vector

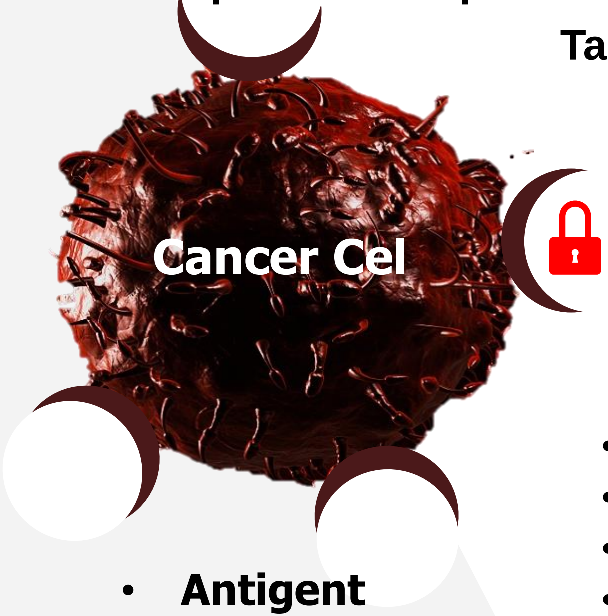
The most prominent and oldest application is ***radioiodine***

The concept of ***Personalized Medicine*** appeared

THERANOSTIC PAIRS

The Key-Lock Principle

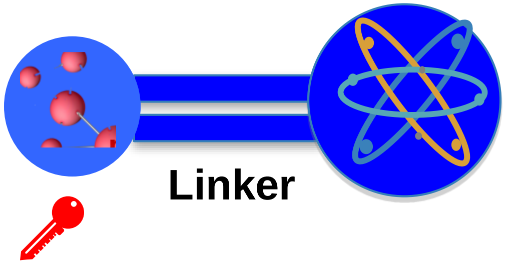
Tumor Specific Receptor



- Antigent
- Transporters
- Enzyme
- Inhibitor

Target Molecule (ligant)

Radionuclide (Chelator)



- Antibodies,
- Minibodies,
- Aptamer
- Peptides
- Amino acids

Reporting Unit

- ^{68}Ga
- ^{99m}Tc
- ^{111}In
- ^{18}FDG

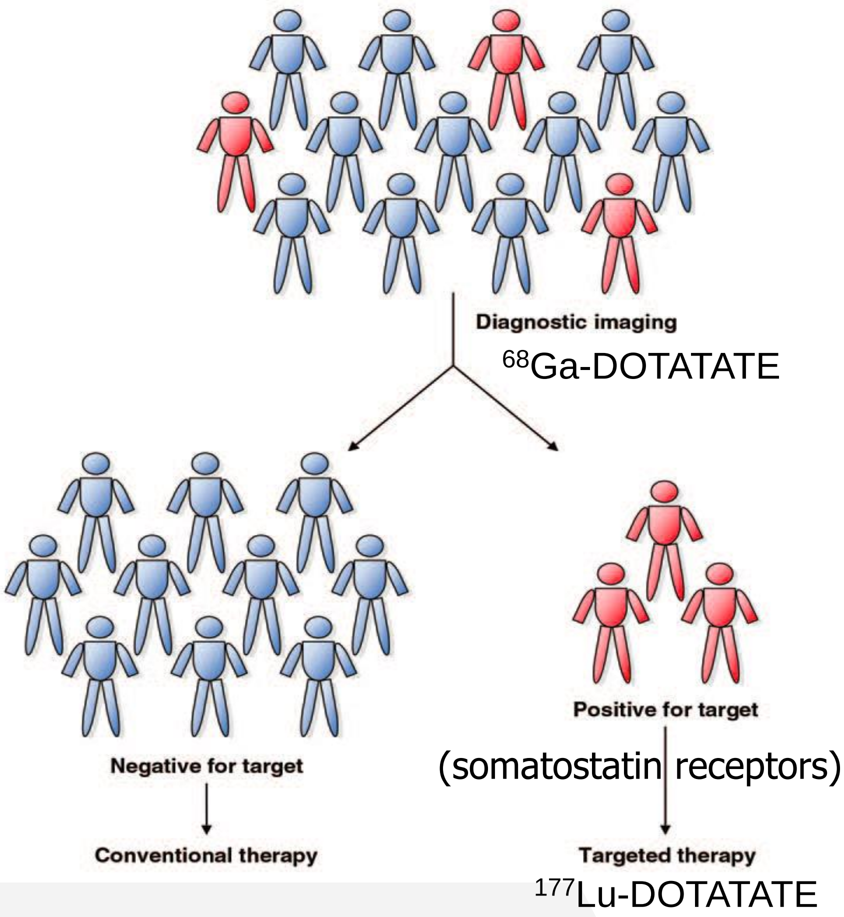
Cytotoxic Unit

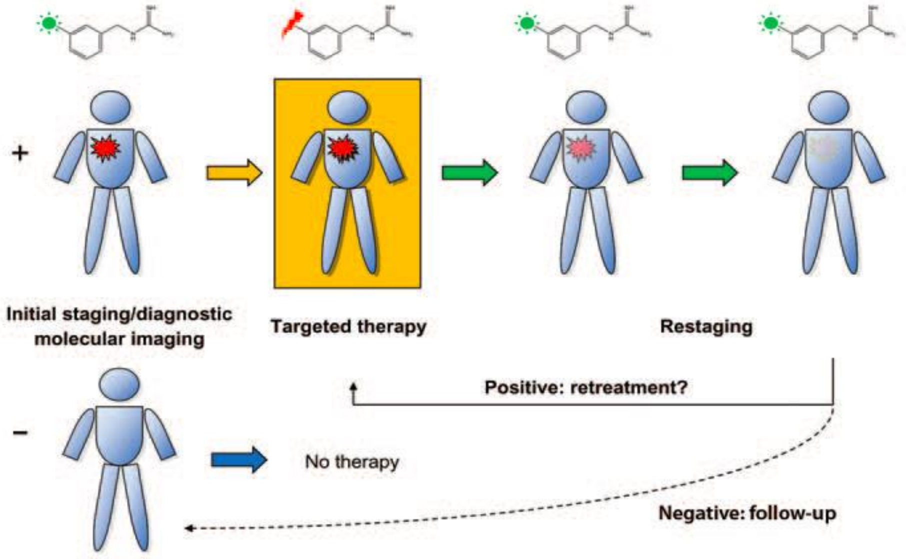
- ^{90}Y
- ^{177}Lu
- $^{186,\ 188}$Re

"See and Treat Concept"

"Targeted Therapy"

Targeted radionuclide therapy in theragnostic systems





Theragnostics and Targeted Therapy

- offering the right treatment
- for the right patient
- at the right time

Personalized Medicine

- with the right dose
- providing a more targeted
- efficient pharmacotherapy

Not targeting the “specific disease” but the “specific tumor of a patient”.
Selectively deliver radiation to cancer cells with minimal toxicity to surrounding normal tissues

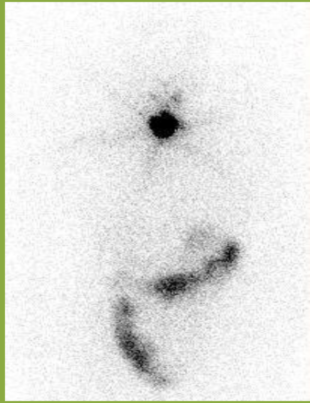
Early Theranostics in Nuclear Medicine

Hyperthyroidism

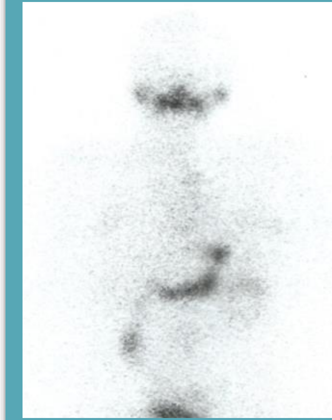
High Uptake

Low Uptake

Differentiated Thyroid Carcinoma

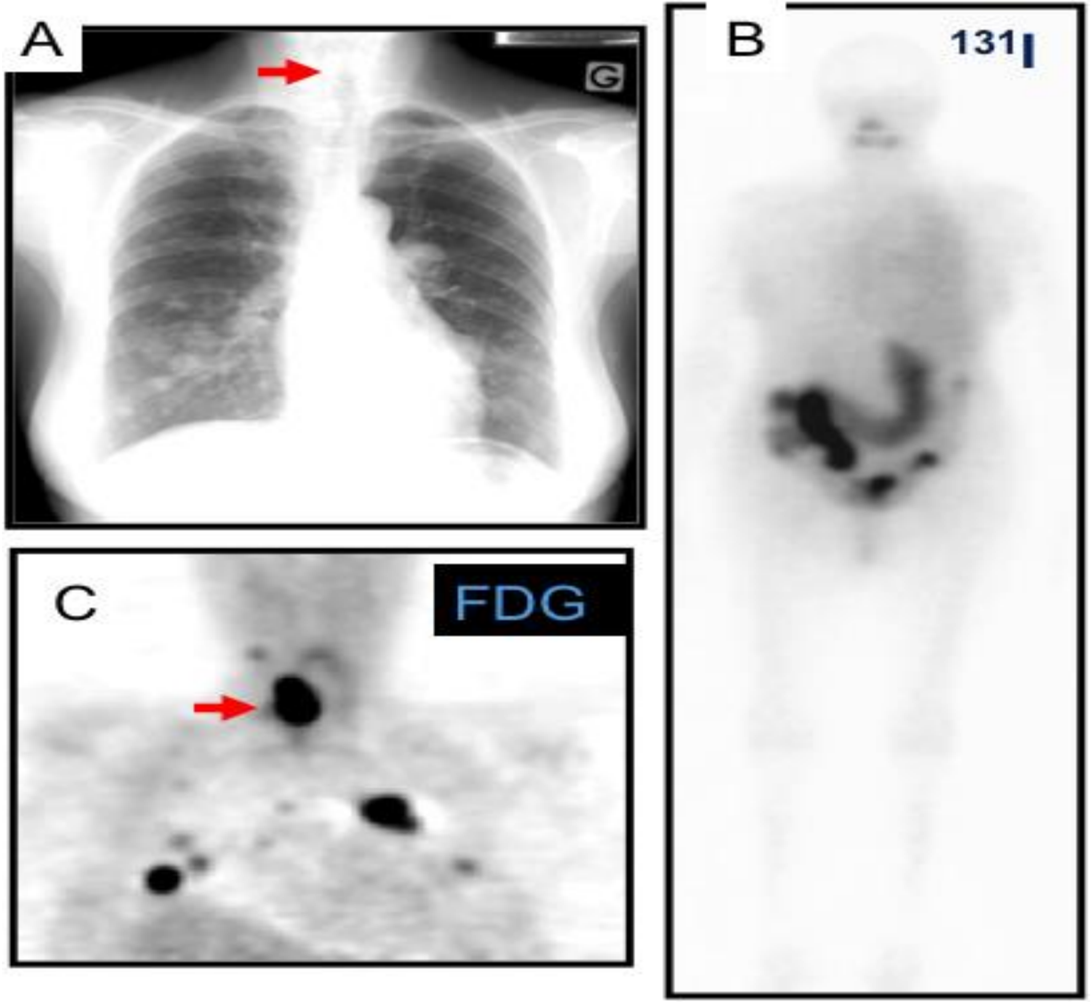


Positive Uptake



Negative Uptake

NaI-131



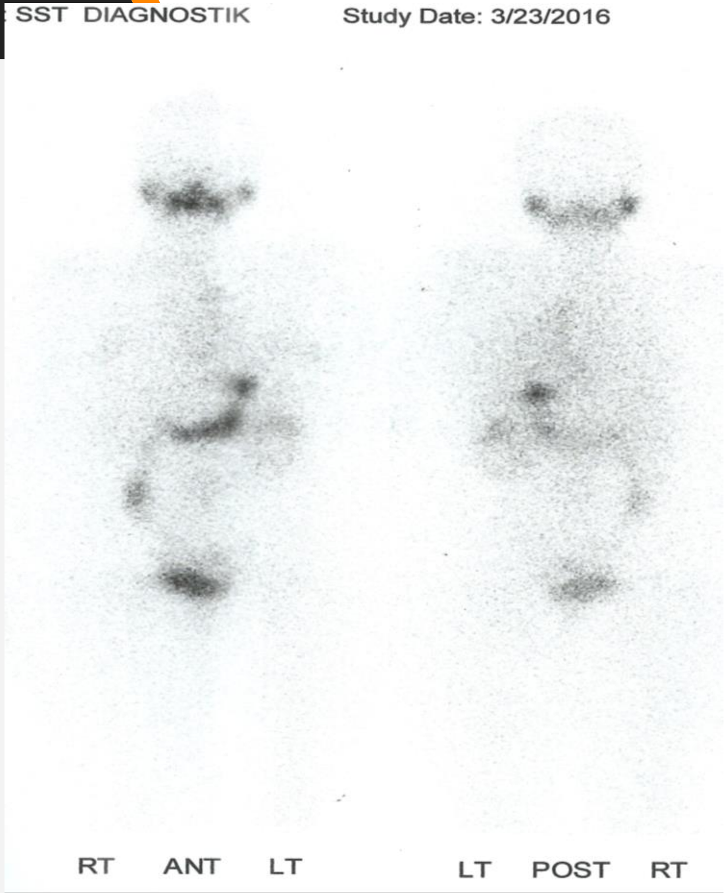
68-yrs old female with prior of follicular thyroid cancer.

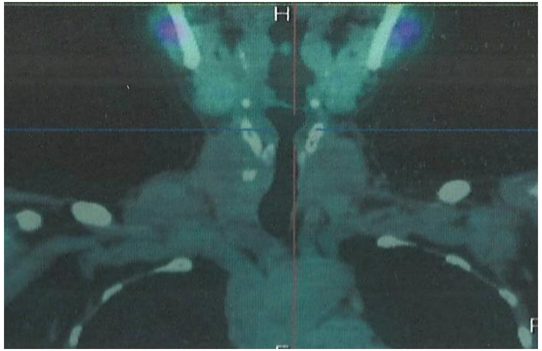
A. CXR:
multiple pulmonary nodules and tracheal deviation (arrow)

B. Post I-131 ablation (250 mCi) WBS was negative.

C. FDG-PET:
clearly demonstrated a para-tracheal tumor and pulmonary metastases.

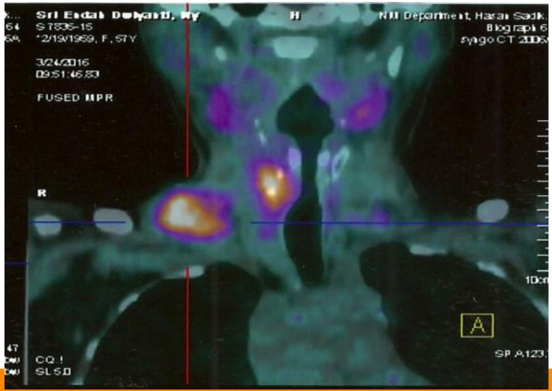
This lesion was resected, with resolution of dyspnoe.
Pathology follicular thyroid cancer





- Negative ^{131}I- scan
- Tg : 18.5 ng/dL
- Anti-Tg: > 3000 U/mL

F 56 yrs papillary thyroid ca Post Total Thyroidectomy and ^{131}I ablation (100 mCi)



I-131 MIBG in NETs

Iodine-131 meta-iodobenzylguanidine

- a radiopharmaceutical used for both ***imaging and treating*** certain types of ***neuroendocrine tumors***.
  - Neuroblastomas,
  - Paragangliomas
  - pheochromocytomas.
- the compound MIBG is very ***similar to norepinephrine/noradrenaline***,
- a neurotransmitter chemical that is ***taken up by*** certain ***neuroendocrine cells***.
- ***selectively targeting and killing*** neuroendocrine tumors that take up MIBG.

Theragnostics of NETs

- Most differentiated NETs over-express somatostatin receptors (SSTRs).
- Somatostatin receptor scintigraphy (SRS) using In-111 penetreotide has been used for the diagnosis of NETs.
- The development of somatostatin analogs for labeling with Ga-68 and also Lu-177 and Y-90 has enabled highly specific targeting of NETs for theranostics.
- The Ga-68 labeled DOTA-peptides binding to SSTRs with high affinity,

^{68}Ga- SSTR PET/CT

- Provides a "one-stop shop" whole-body investigation of NETs for staging, including evaluation of liver, lymph nodes, bone, lung, brain and other possible tumor sites.
- Have a potential role in small cell lung cancer as this tumor is known to express SSTRs.
- The follow up and evaluation of molecular response (MORE) to therapy by assessing the molecular tumor volume and by quantification of the SSTR density in vivo before and after PRRNT
- Helps in restaging, e.g. in patients with rising tumor markers and for detection of recurrences.

^{68}Ga- DOTATOC PET/CT

- superior to ^{111}In- DTPA-OC in the detection of NET metastases in the skeleton and other organs
- the accuracy (96%) was found to be significantly higher than that of CT and ^{111}In- DOTATOC SPECT
- the staging was better than CT or SPECT, it picked up more lesions in lymph nodes, liver and bones.
- Provided clinically relevant additional information

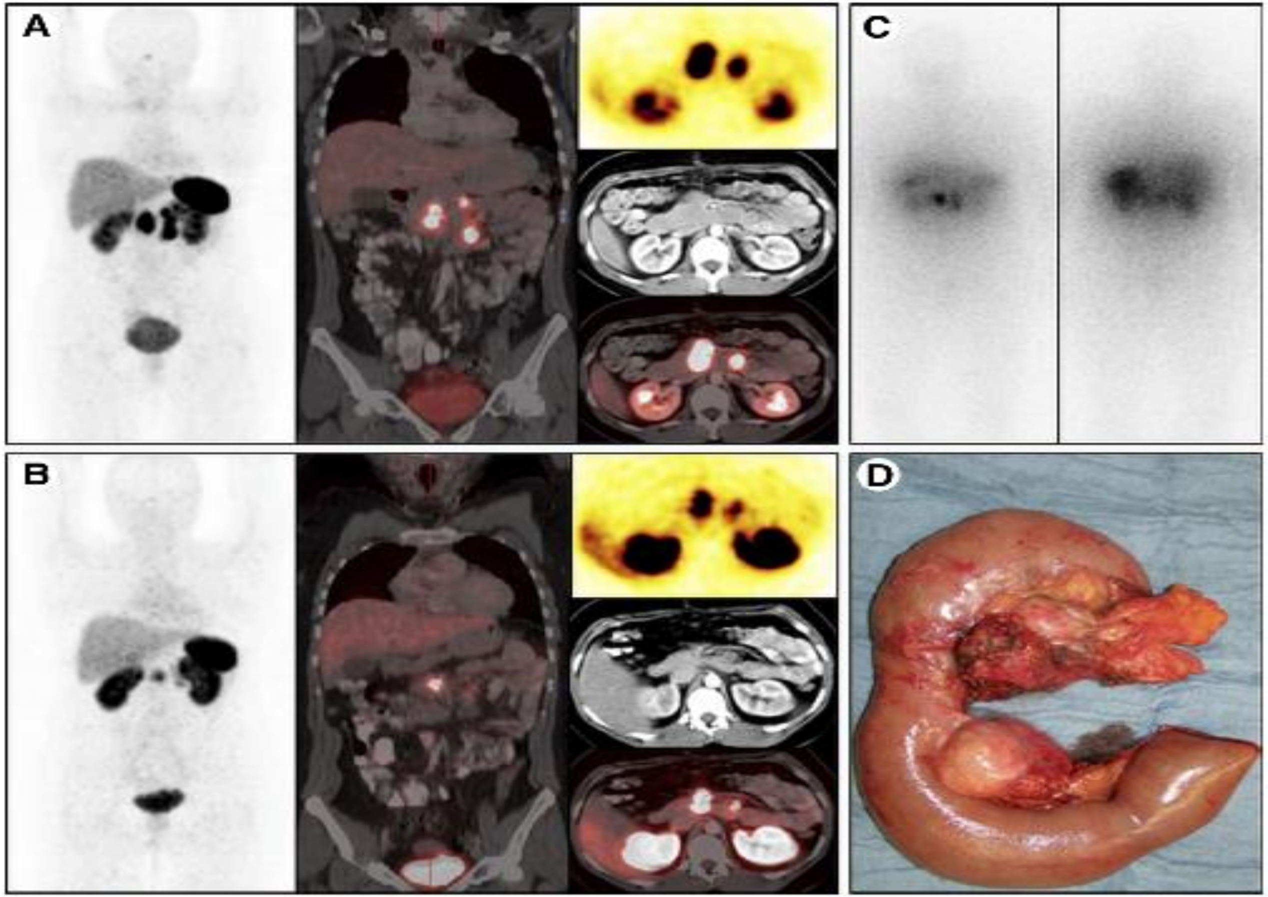


Figure 9 ^{68}Ga-DOTANOC PET/CT maximum intensity projection images before (A) and after (B) neoadjuvant PRRNT in a 36-year-old woman presenting with a well-differentiated, inoperable primary tumor of the pancreas and lymph node metastases encasing the great abdominal vessels (Ki-67/MiB1 proliferation rate: 8%, CgA+). The images show an excellent response (partial remission) to PRRNT after 2 cycles of ^{90}Y-DOTATATE administering 6 GBq and 4.5 GBq, respectively (C, posttherapy scans in anterior [left] and posterior [right] views after the second cycle). The patient then underwent a Whipple procedure (D, operative specimen of primary tumor mass with necrotic lymph node metastases) and showed persistent complete remission 4 years after neoadjuvant PRRNT and surgical tumor excision.

RP Baum.icrt –jeju 2013

PSMA (Prostate-Specific Membrane Antigen) THERANOSTICS for prostate ca.

- A cell membrane glycoprotein,
- Expressed at higher levels in prostate cancer.
- Provides a promising target for specific imaging and therapy
- Expressed in the neovasculature of many solid tumours

^{68}Ga-PSMA PET/CT Imaging

- Molecular imaging may contribute to the reduction of morbidity and mortality
- PET ^{18}F-FDG non specific fails in diagnosis of slowly growing tumours

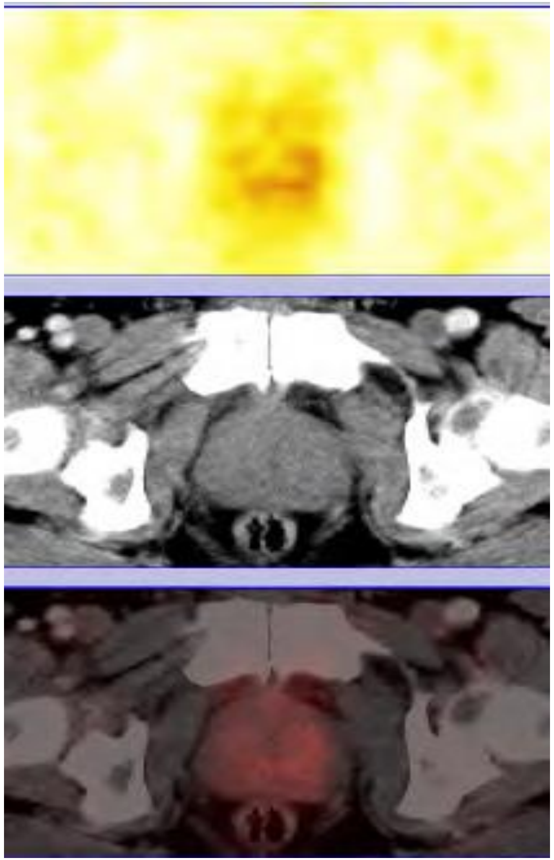
^{177}Lu-PSMA Therapy

- The 2nd most common cancer worldwide in male
- 5-year survival rate :
- localised metastases 100 %
- distant metastases 31 %
- Deaths are due to advanced disease,

^{68}Ga- PSMA PET

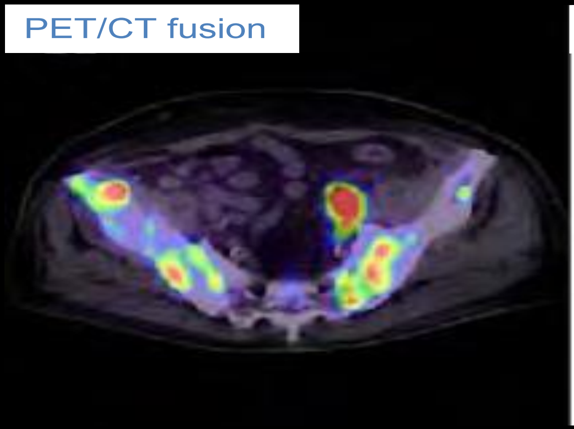
- Identifies tumor cells expressing PSMA antigen with excellent sensitivity & specificity, Detecting lesions remaining unidentified by conventional methods.
- Can present lesions suspicious for prostate cancer with excellent contrast and a high detection rate even when the level of PSA is low
- A potentially valuable marker in the treatment of patients with prostate cancer
- Promising potential for restaging in recurrence/ biochemical failure after definitive treatment of prostate cancer.
- Could be used as a marker of patient response to anti-androgen drugs.

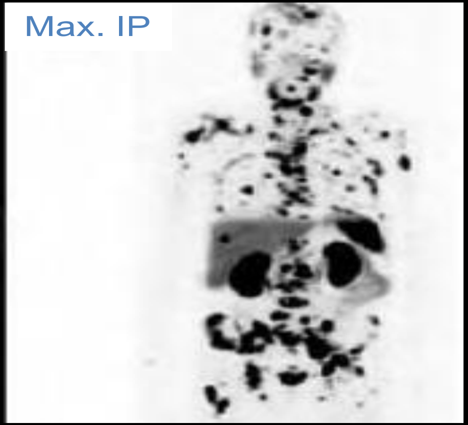
Benign prostatic hyperplasia: Enlarged prostate (6.2 x 5.6 cm), PSA 50 ng/ml. No evidence of a PSMA-avid primary tumor or metastases



RP Baum.icrt –jeju 2013

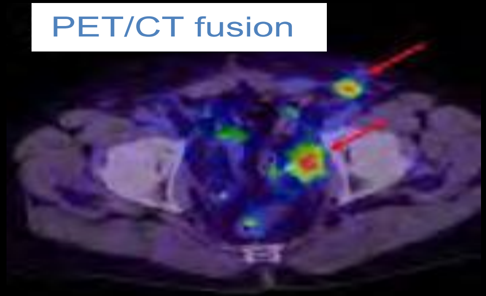
^{68}Ga-PSMA PET/CT





^{68}Ga-PSMA PET/CT

Patient representative for disseminated lymph node and bone metastases of prostate cancer.



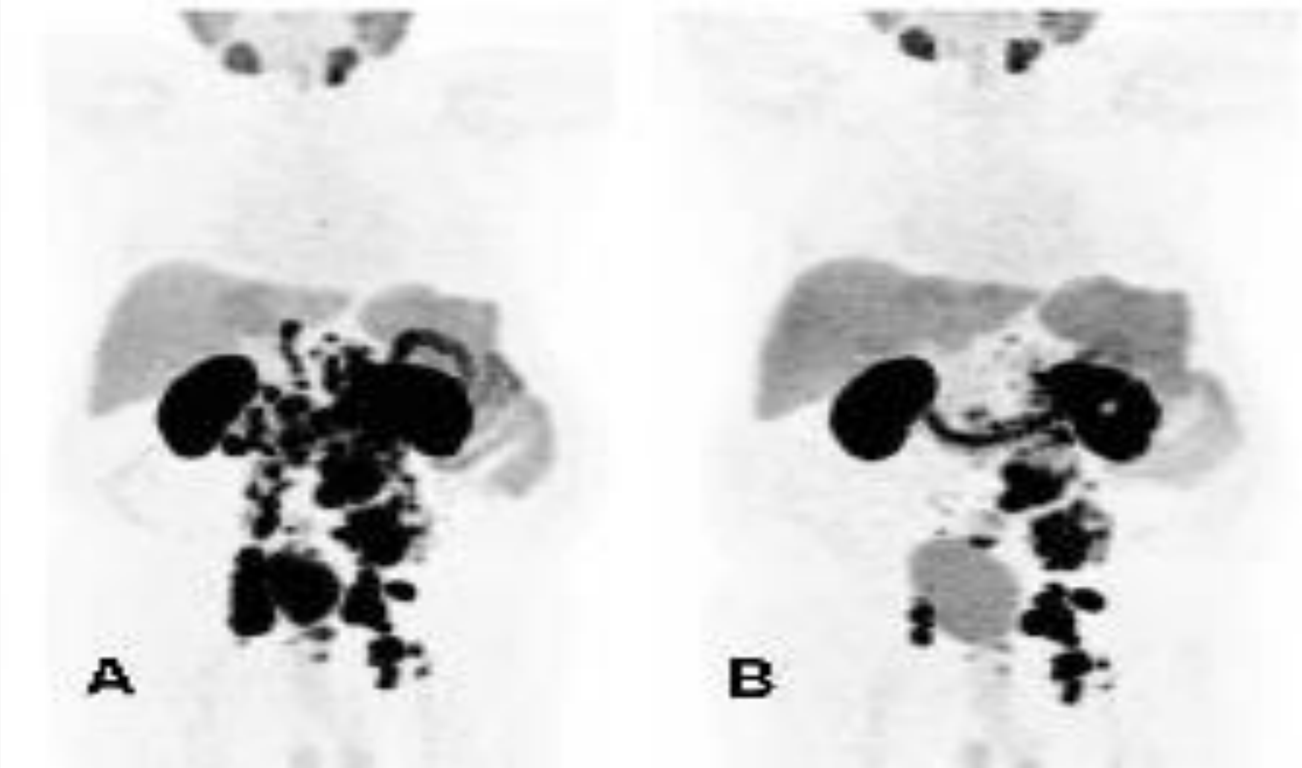
^{68}Ga-PSMA PET/CT

Patient with low PSA level (0.01 ng/ml) and lymph node metastases.
Minimal PSA elevation despite visible tumor lesions suggests dedifferentiation of prostate cancer metastases.

At PSA levels < 2.2 ng/ml, lesions suspicious for cancer were observed in 60 % of the patients.
At PSA levels > 2.2 ng/ml, lesions were detected in all patients.

A. Afshar-Oromieh et al. EJNM MI 2012

Chemo-refractory Prostate Cancer



A 74-year old patient with hormone and ***chemo-refractory prostate cancer*** underwent PSMA PET/CT. (A) : which showed diffuse abdominal and iliacal lymph node metastases. The patient underwent RLT with ***5.7 GBq 177Lu-PSMA***. The PSA level was at the time of the therapy 790 ng/ml. (B): A ***partial response*** 7 weeks after RLT with 63% PSA decline at this time, the PSA level was 293 ng/ml

The Benefit of Theranostics

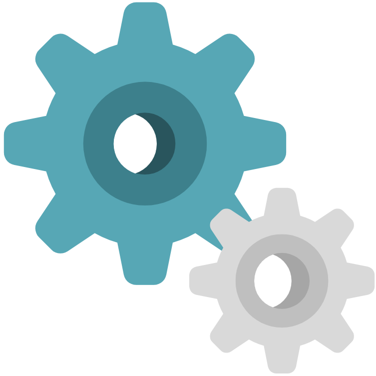
- shift from 'trial and error' medicine to personalized medicine
- holds great promise for improved patient outcomes.
- provides a valuable tool for identifying and selecting patients
- help improve drug efficacy, which patients serve to benefit the most from treatment.
- The precise targeting properties
- minimizing off-target effects to normal tissues,
- lead to more cost effective and efficient drug programs,
- guiding pre-clinical drug development or clinical trial eligibility to help maximize the likelihood of successful outcomes.

The basis for successful personalized medicine radionuclide therapy is a theranostic approach

The Future Trends in Nuclear Medicine

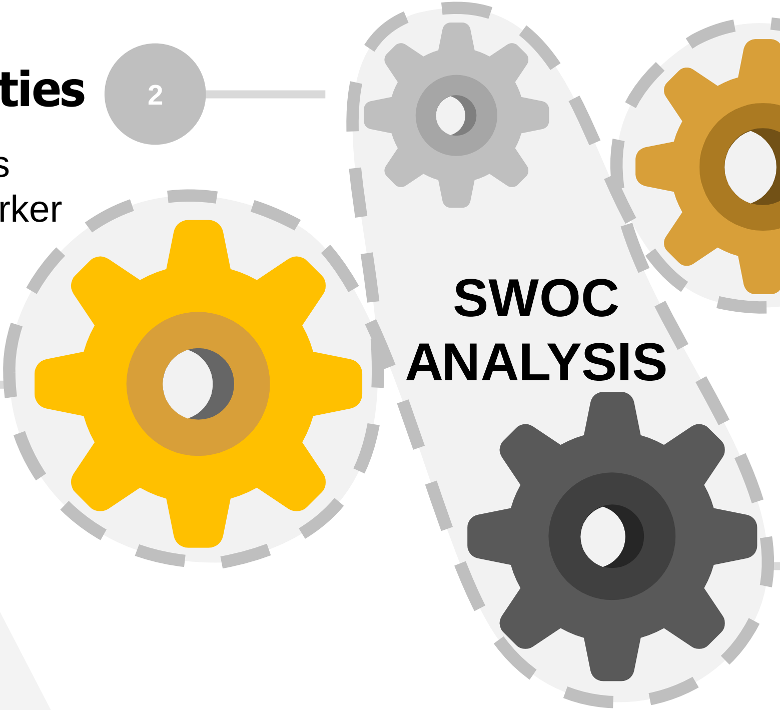
New advances in clinical research suggest a boom in nuclear imaging applications

Service Provision



Great people with great equipment will lead to great healthcare

The Future Trends in Nuclear Medicine



Opportunities
2

- Nuclear theranostics
- New imaging biomarker

Weaknesses
3

- Lack of strict licensing requirement
- Insufficient training
- Nuclear medicine community

Strengths
1

- **Molecular Imaging (PET and SPECT**
  - Oncology
  - Nuclear Cardiology
  - Neuroimaging
  - Other application
- **Established NM therapies**

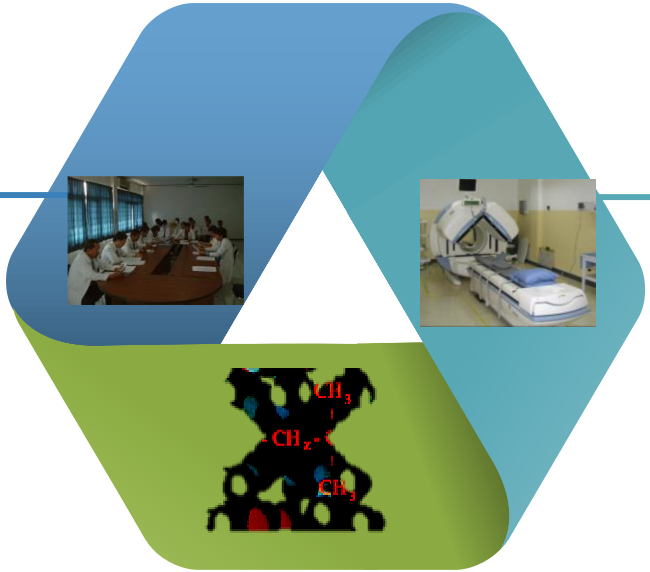
Challenges
4

- Takeover by other specialities of various NM application
- Lost of ownership
- Compensation model

Indonesian Particular Problems

Man Powers

- Multidiciplinary skill
- Insufficient training



Equipments

- High cost

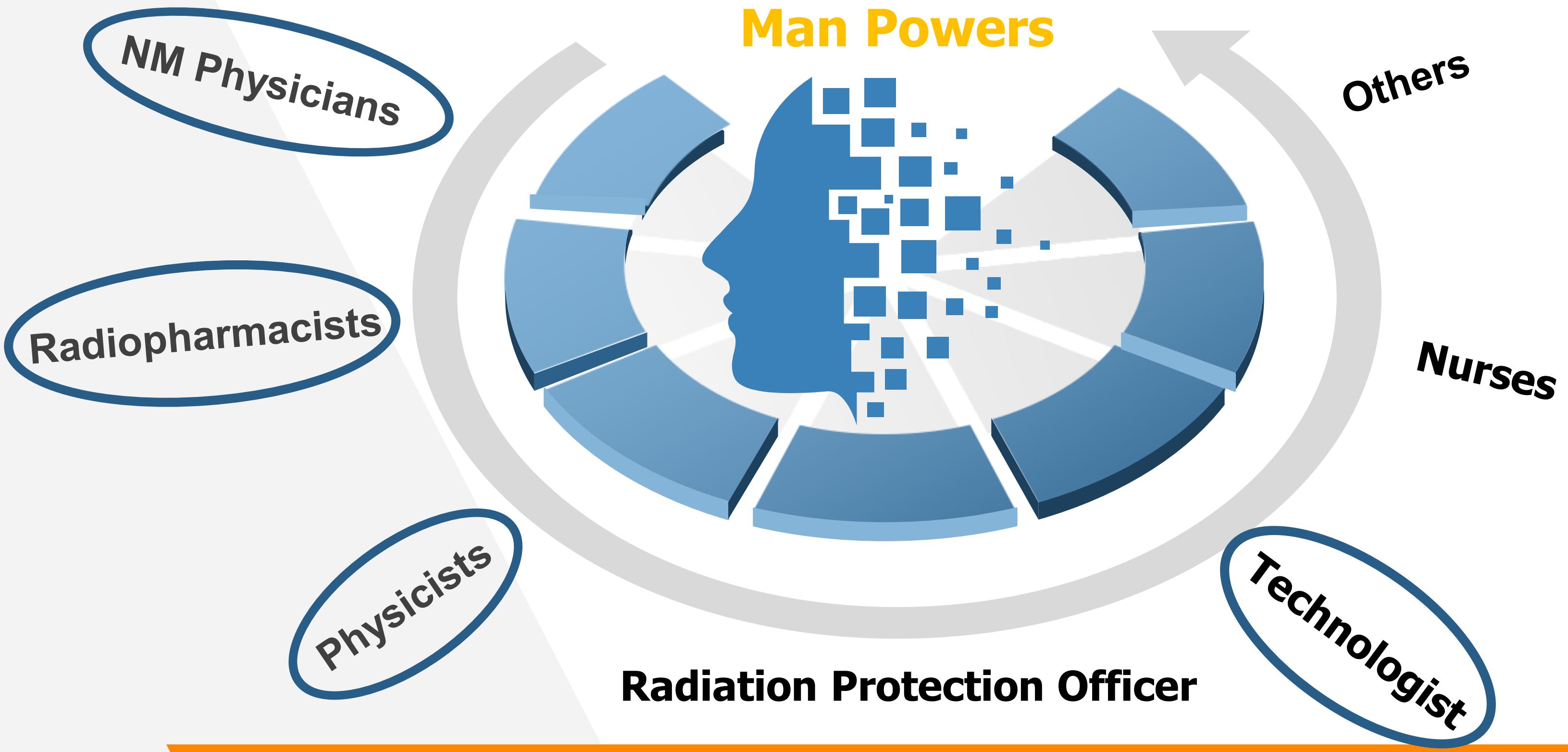
Government Policy

- Not priority
- Strict licensing requirement

Radiopharmaceutical

- Mostly depend on imported production

The Future Trends in Nuclear Medicine



Thank You

For Your Attention

"A new scientific truth is not usually presented in a way that convinces its opponents…..
Rather the opponents gradually die off, and rising generation becomes familiar with the truth from the start"