Deutsche
Gesellschaft
für Nuklearmedizin
e.V.

SUMMER SCHOOL 2014

Overview Theranostics and Radionuclide Therapy

September 4, 2014

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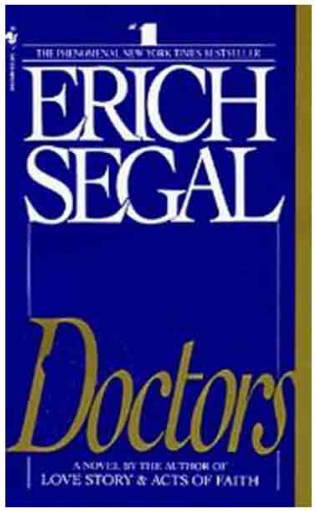
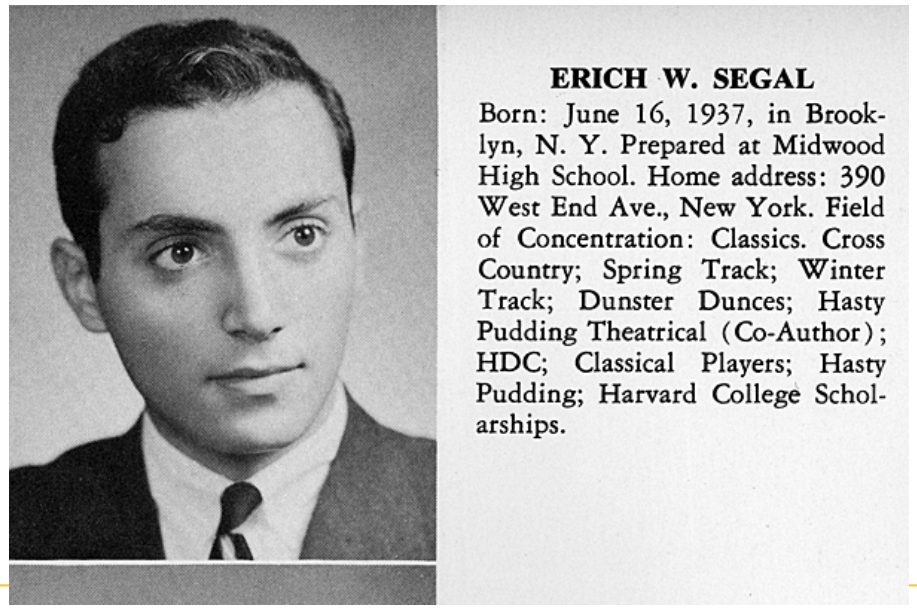
Overview Theranostics and Radionuclide Therapy

Dr. Holmes, Dean Harvard Medical School addressing the medical graduates of the class of 1958:

‚Gentlemen, I urge you to engrave this on the template of your memories: there are thousands of diseases in this world but the medical science only has an **empirical cure for twenty-six** of them. The rest is...guesswork'





ERICH W. SEGAL

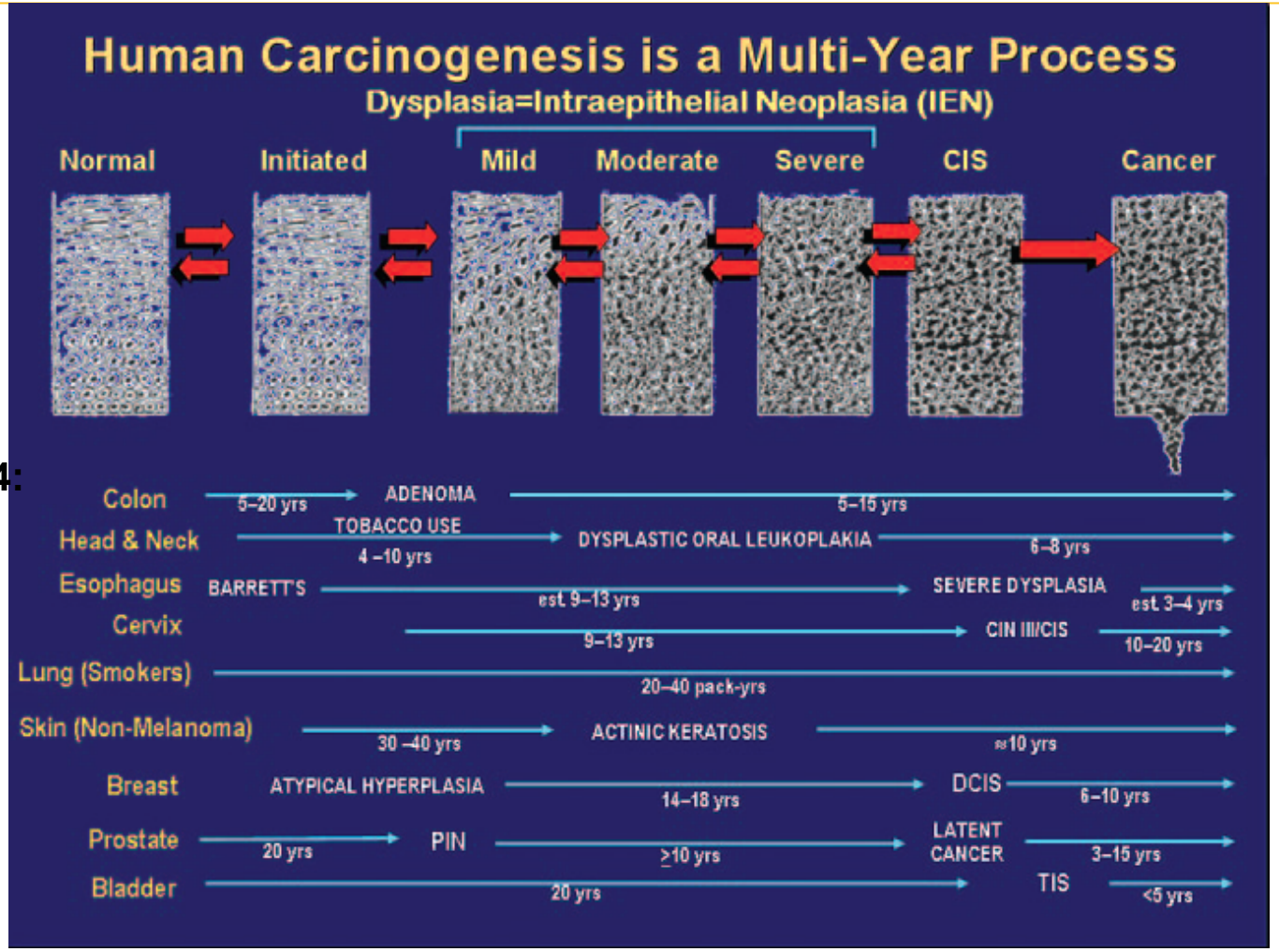
Born: June 16, 1937, in Brooklyn, N. Y. Prepared at Midwood High School. Home address: 390 West End Ave., New York. Field of Concentration: Classics. Cross Country; Spring Track; Winter Track; Dunster Dunces; Hasty Pudding Theatrical (Co-Author); HDC; Classical Players; Hasty Pudding; Harvard College Scholarships.

Challenges in Oncology

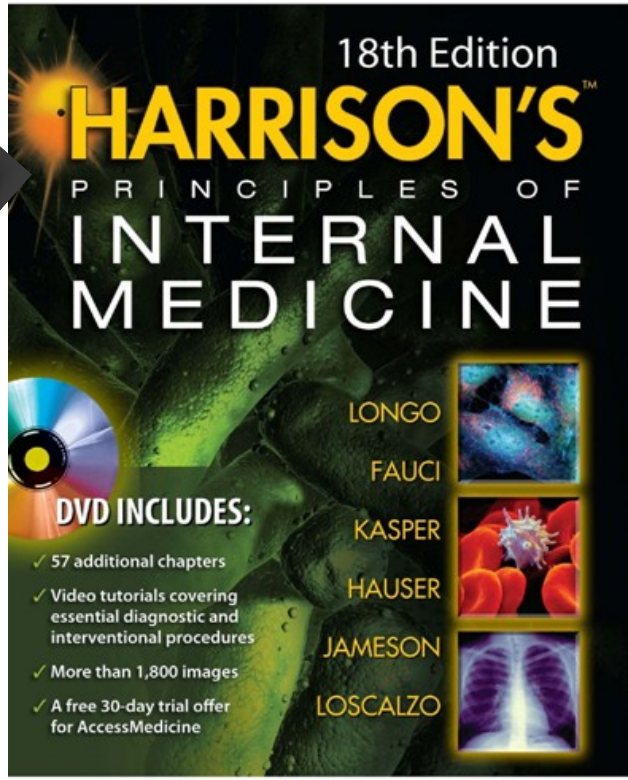
Cancer cells ‚out perform' the normal cells selected through Darwin's theory of Evolution'

Prasad, Brenner, Modlin: Eur J Nucl Med Mol Imaging. 2014 Feb;41(2):202-4

Radiology: Vol 244: Number 1



Evolved Cancer Cells Need To Be Tackled Smartly!



Theranostics (or Theragnostics) Definition

Personalized Medizin ----- Therapeutic Index

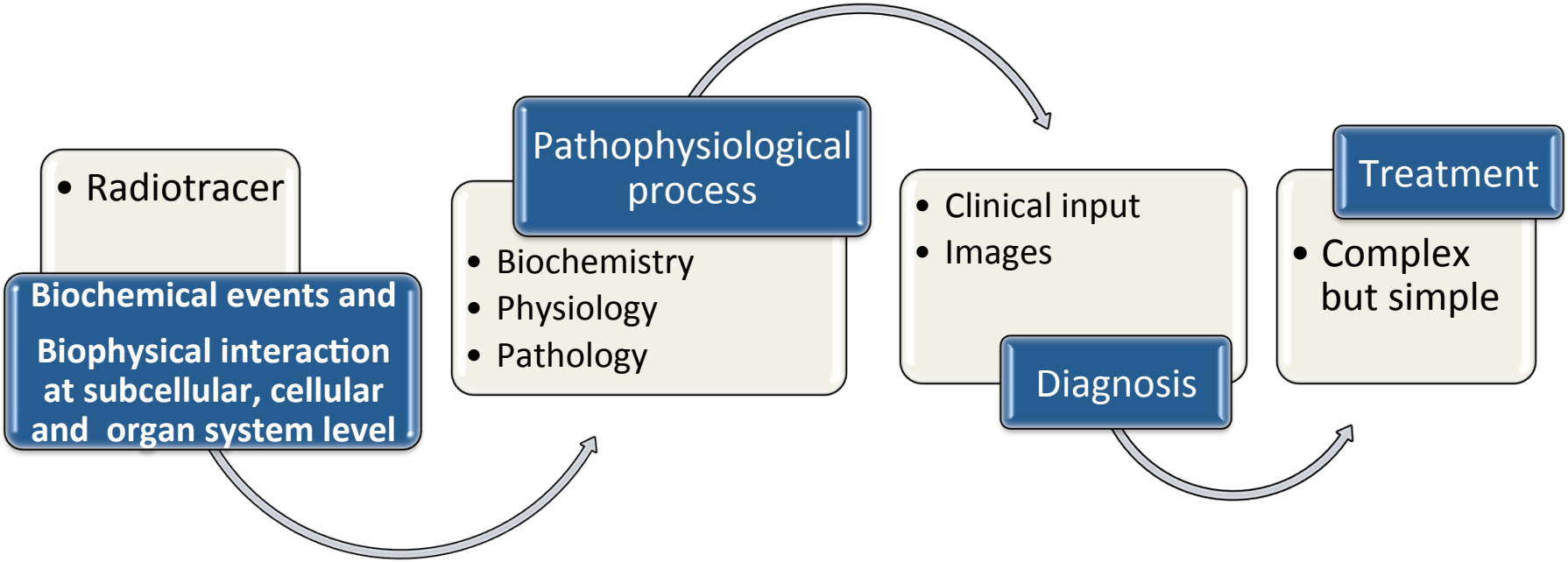
Theranostic is a portmanteau of Therapeutics and Diagnostics.

Theranostics is a proposed diagnostic methodology for personalizing therapeutic intervention

Side Effects

Therapy Response

Nuclear Medicine
Definition



Translation and transofrmation of events taking place at subcellular, cellular or organ-system level through physical devices (radiation and scanners) into understanding complex pathophysiological process behind diseases or diseased organ (diagnosis) and using the same process for treatment using radionuclides is ‚Nuclear Medicine'.

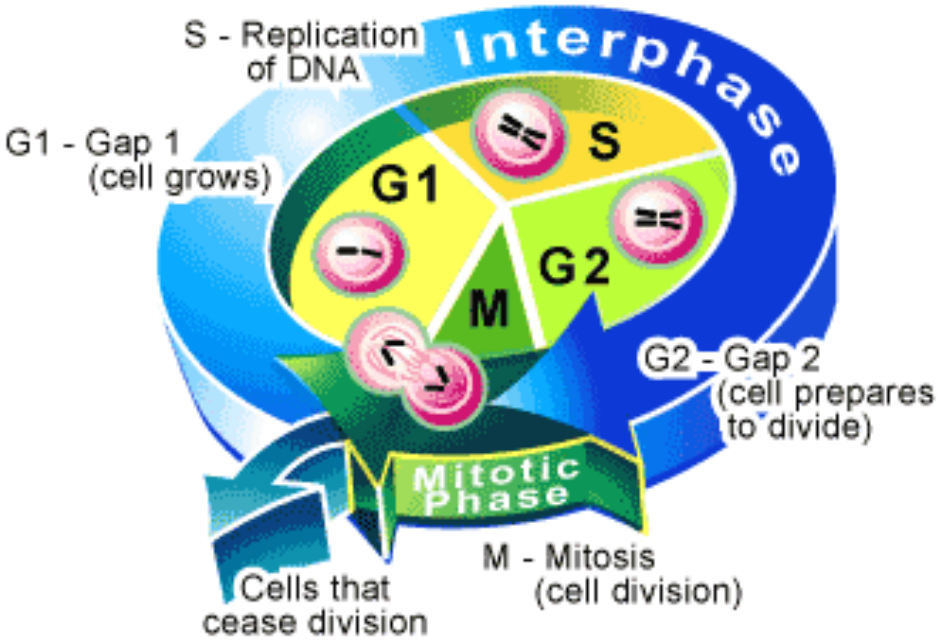
Nuclear Medicine: First Exponent Of Theranostics Concept

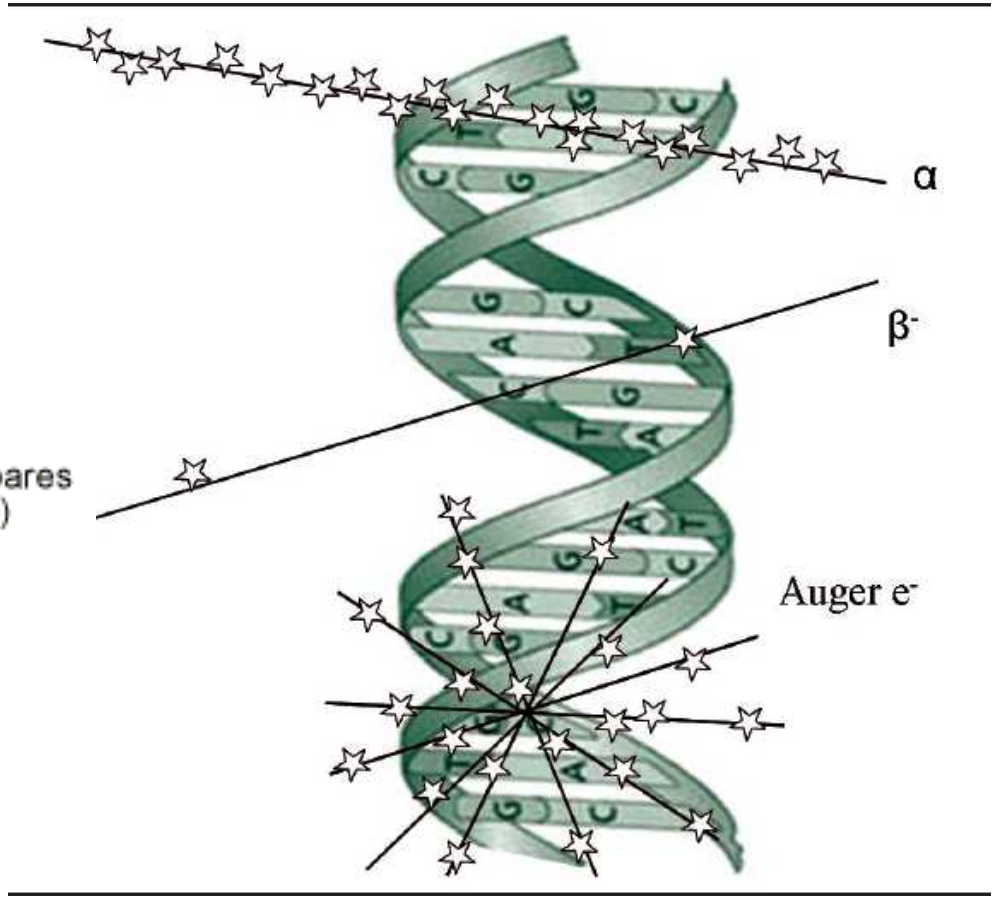
- Na-I symporter
- Diagnosis of benign and malignant thyroid diseases using I-123 and I-131
- Treatment using I-131

Radionuclides For Therapy

Radionuclide	T ½	Auger	Alpha	Beta	Gamma	Mean Pathlength
I-131	8.04 d			Y	Y	0.9 mm (3mm diameter)
Lu-177	6.7 d			Y	Y	0.7 mm
Y-90	2.67d			Y		3.9 mm (2 cm diameter)
Sm-153	1.95d			Y	Y	1.2 mm
Re-188	17 hrs			Y	Y	3.5 mm
I-125	60.0d	Y				10 nm
In-111	2.8d	Y				10nm
Ra-223	11.4d		Y			0.06nm
Bi-213	45.6 min	Y				

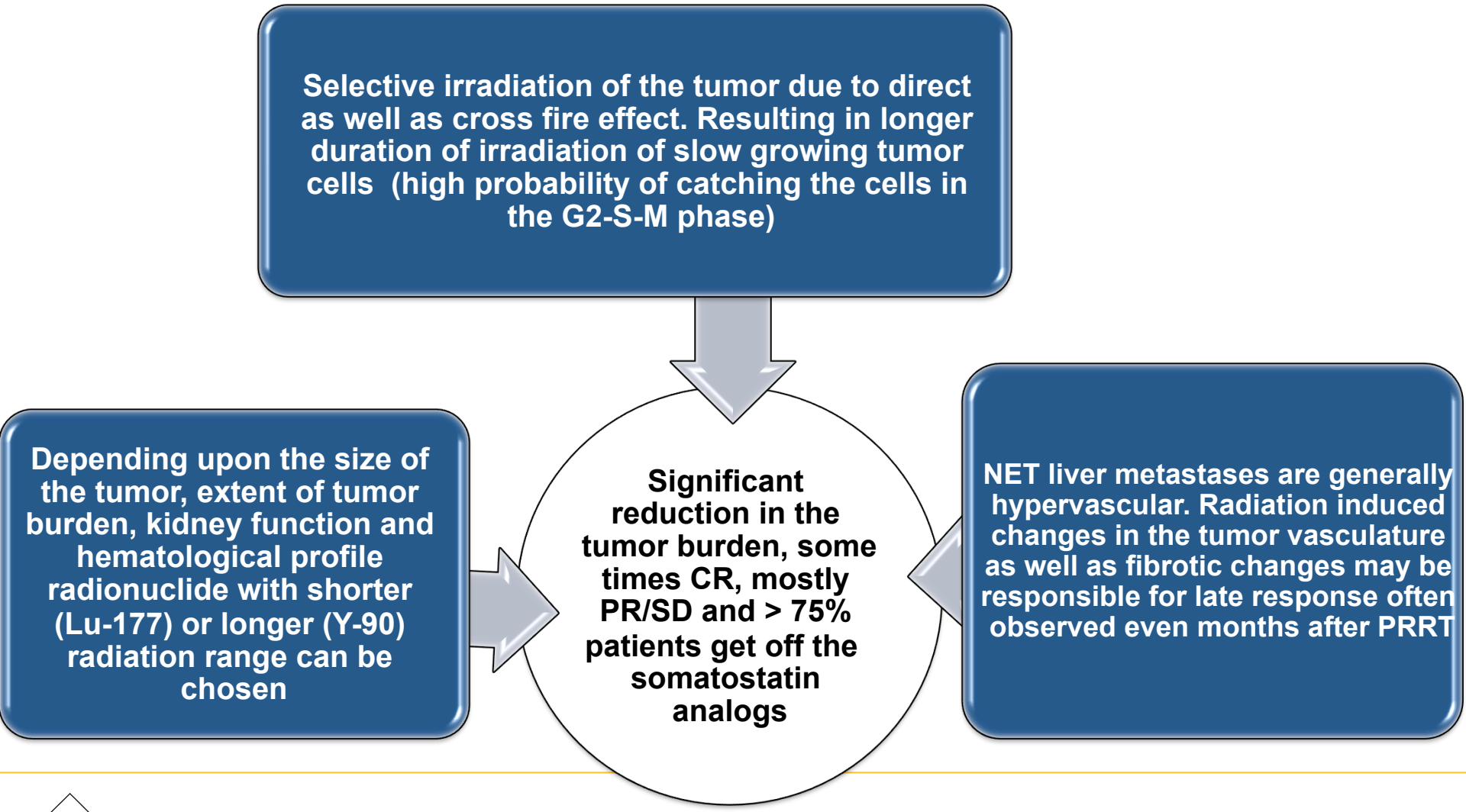
Basic Mechanism Of Action: Radiation Induced DNA Double Strand Break



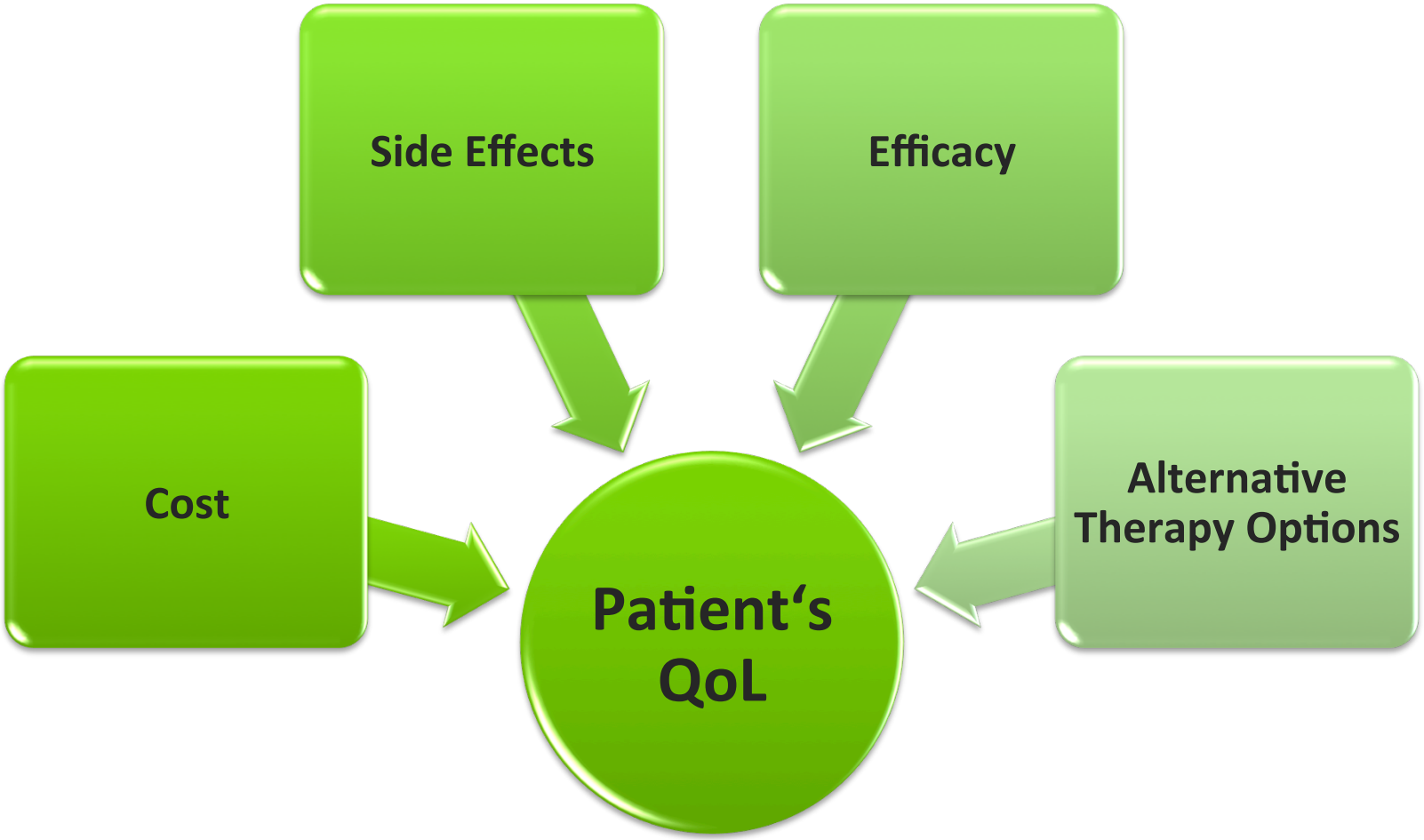


Differences Between External And Internal Radiotherapy

Example : Neuroendocrine Tumor (NET)



Therapy Response

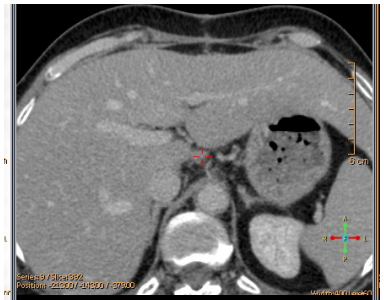


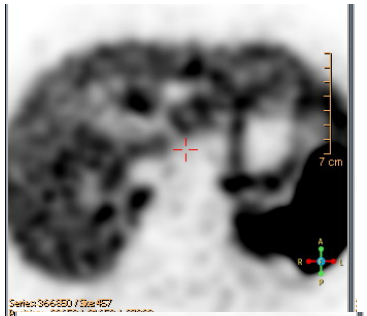
Targets On Cancer Cells

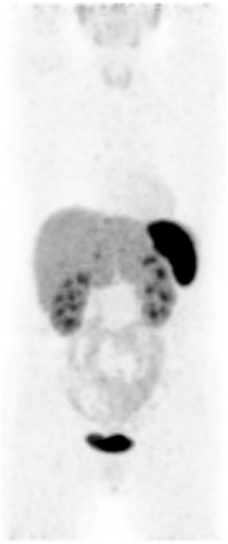
- Genes
- Receptors
- Antigens
- Enzymes
- Metabolic Pathways

Early Response Prediction
Ga-68 DOTATOC PET/CT vs. 3-Phase CT

Jan 2011

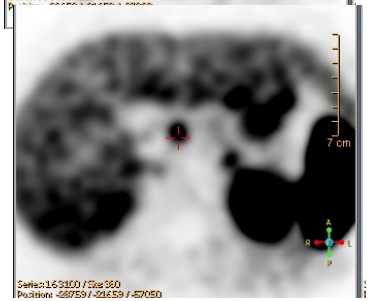




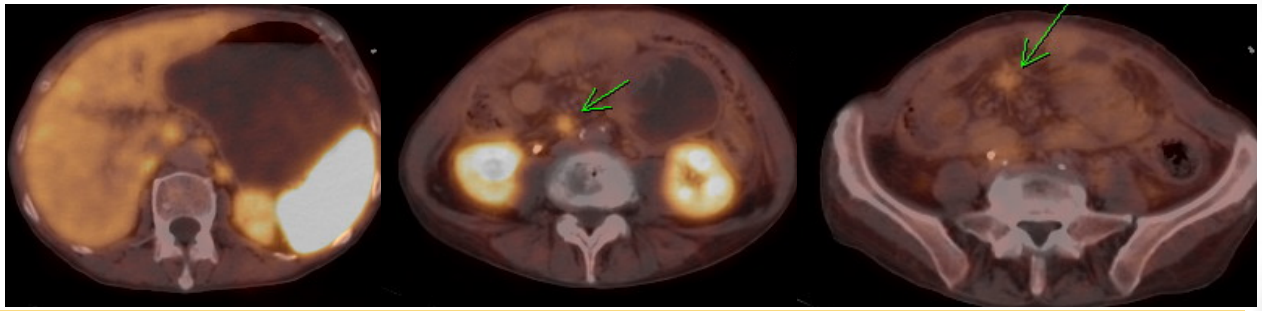


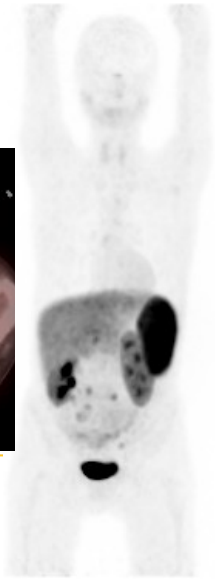
Nov 2011

Nov 2011



Juni 2013





Juni 2013

Targets in Nuclear Medicine

Direct

- Antigens
- Receptors
- Transporters (symporters)
- Enzymes

Indirect

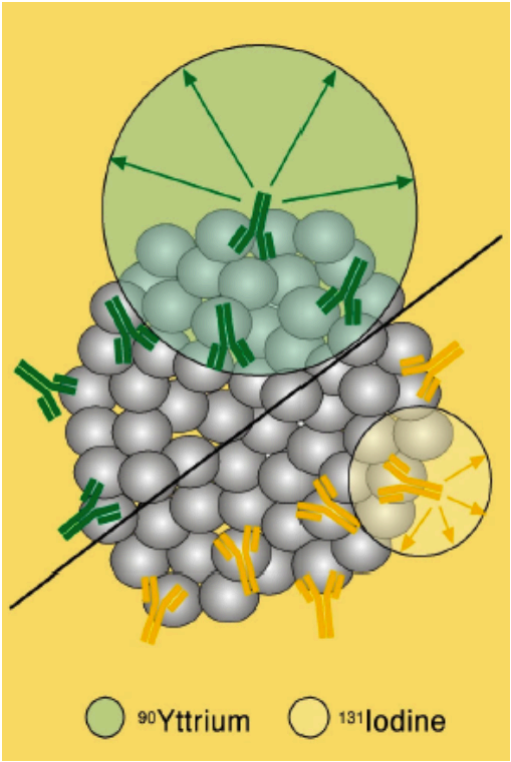
- Increased bone metabolism

Differences Between ‚Cold' and ‚Hot' Smart Molecules

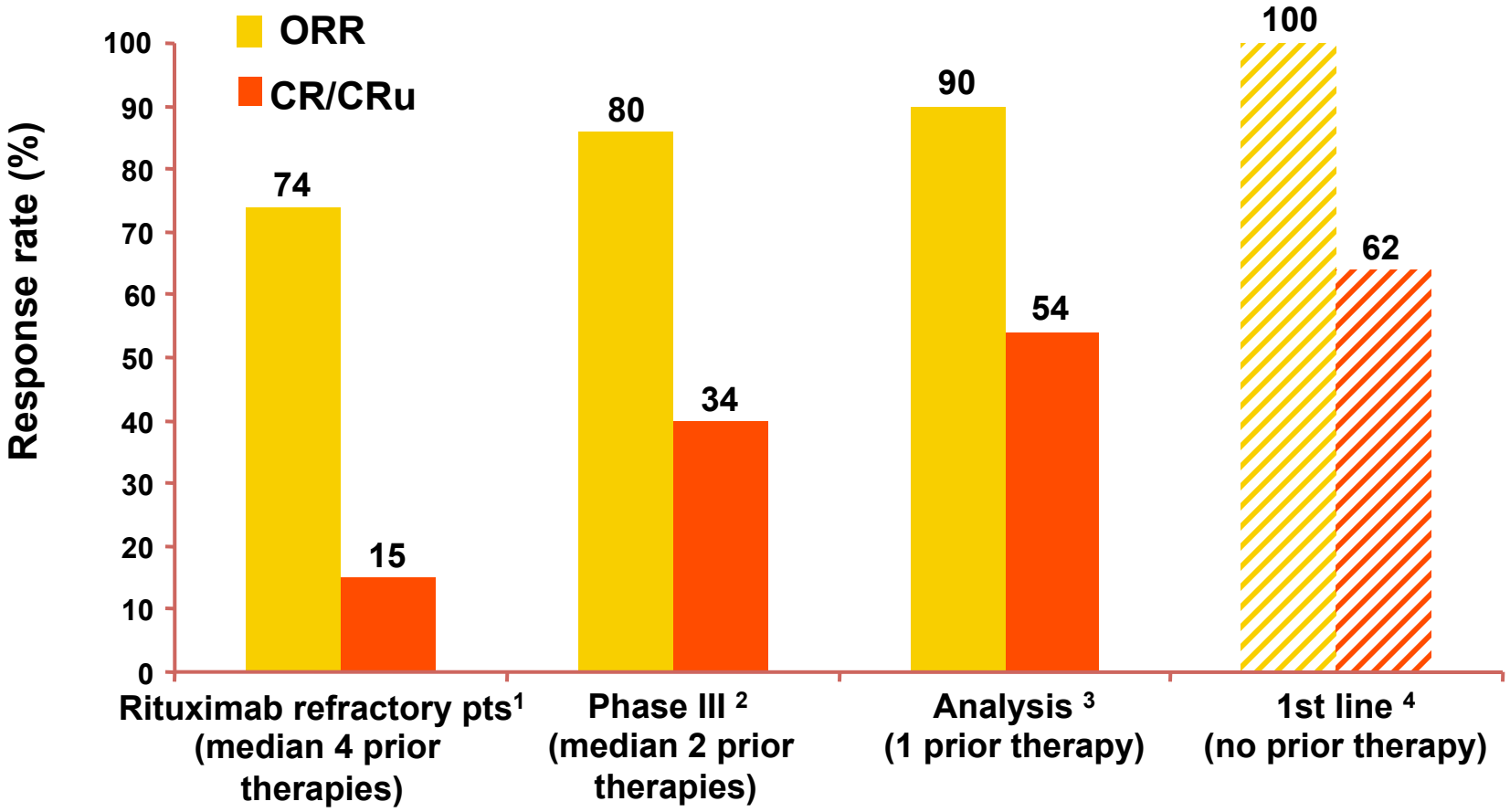
- Concentration
- Penetration
- Effectivity
- Resistance
- Tachyphylaxis
- Toxicity

Differences Between ‚Cold' and ‚Hot' Smart Molecules
Concentration, Penetration, Effectivity
Zevalin (Y-90 Ibritumomab-Tiuxetan ant CD20 antibody) vs. **Rituximab**

- **Non-Hodgkin's Lymphoma are extremely radiosensitive**
- **The radiotherapy is curative in early stage of indolent NHL.**
- **Penetration of non radiolabelled lymphoma is poor.**
- **Radiolabelled antibodies bind specifically on NHL cells**
- **Lymphoma cells sitting in the center / NHL cells not binding the radiolabelled antibodies can be killed due to the cross fire effect of Y-90.**
- **Small macroscopically not visible NHL cells are additionally killed.**



Zevalin As First Line Therapy Is More Effective!!



[1]Witzig et al., J Clin Oncol 2002
[2]Gordon et al., Clin Lymph 2004
[3]Emmanouilides et al., Blood 2003
[4]Sweetenham et al., Blood 2004

Differences Between ‚Cold' and ‚Hot' Smart Molecules
Resistance and Tachyphylaxis
PRRT vs. ‚Cold' Somatostatin Analogs

Y-90 DOTATOC therapy in NET patients resistant to cold somatostatin analogues

Table 3. Duration of Symptom Response to ^{90}Y-Edotreotide

Symptoms (7-point scale: 0-6)	Patients With Baseline Symptoms		Duration (weeks)				Durable Response*	
	No.	%	Mean	Median	Minimum	Maximum	%	No.
Diarrhea	63	70	12.2	13.8	5.7	21.1	60	38/63
Hot flushes	65	72	10.5	9.7	4	19.5	51	33/65
Abdominal pain	59	66	10.7	9.3	4.1	21.1	58	34/59
Nausea/vomiting	35	39	11.0	12	4.1	18	60	21/35
Feeling tired	75	83	9.5	8.1	4.0	18	47	35/75
Decreased strength	62	69	11.1	12.5	4	15.6	52	32/62
Heartburn	24	27	10.3	9.6	4.8	19.5	54	13/24
Loss of appetite	40	44	12.1	13.0	5.7	18.0	55	22/40
Difficulty sleeping	44	49	13.2	13.9	4.0	19.5	43	19/44
Muscle/joint pain	47	52	10.5	10.6	4.0	17	55	26/47
Shortness of breath	35	39	12.1	13.6	4.0	21.1	54	19/35
Fever	14	16	11.1	12.1	4	14.7	64	9/14

*A durable response is measured as 4 or more weeks in length.

J Clin Oncol. 2010 Apr 1;28(10):1652-9

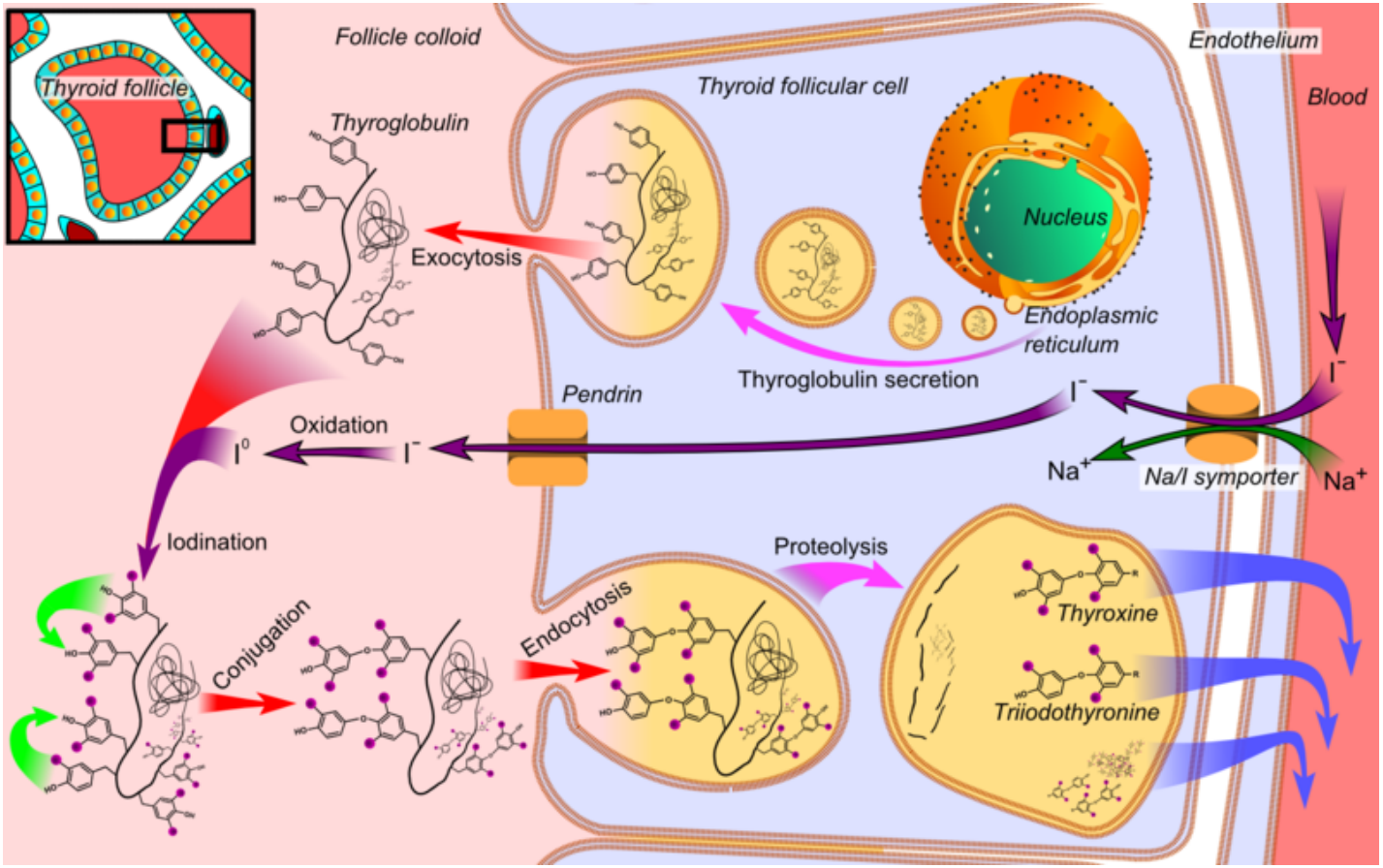
Differences Between ‚Cold' and ‚Hot' Smart Molecules
Life Threatening or Severe Toxicity

	Radionuclide Therapy	mTOR inhibitors	Tyrosine Kinase Inhibitors
MDS	1-2%	-	-
Leukemia	Extremely rare; <0.01%		
Renal Insufficiency	1-2%*	-	-
Cardiopulmonary		17%**	< 1 %
Treatment Related Fatal Events	<1%	1.8%	<1%

Metabolic Targets In Radionuclide Therapy

- Amino Acid Transporter
- Folate/Nucleotide Metabolism

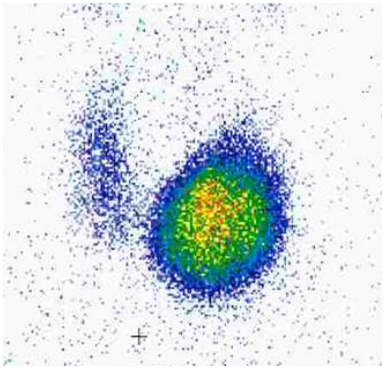
I-131 Therapy of Malignant And Benign Thyroid Diseases



Adapted from M. Häggström

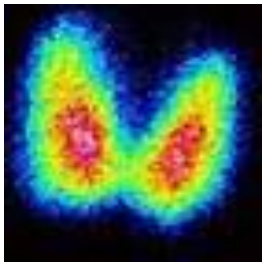
I-131 Therapy of Benign Thyroid Diseases

300 - 400 Gy



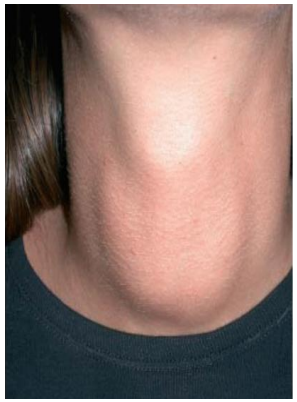
Focal Autonomy

150 - 300 Gy



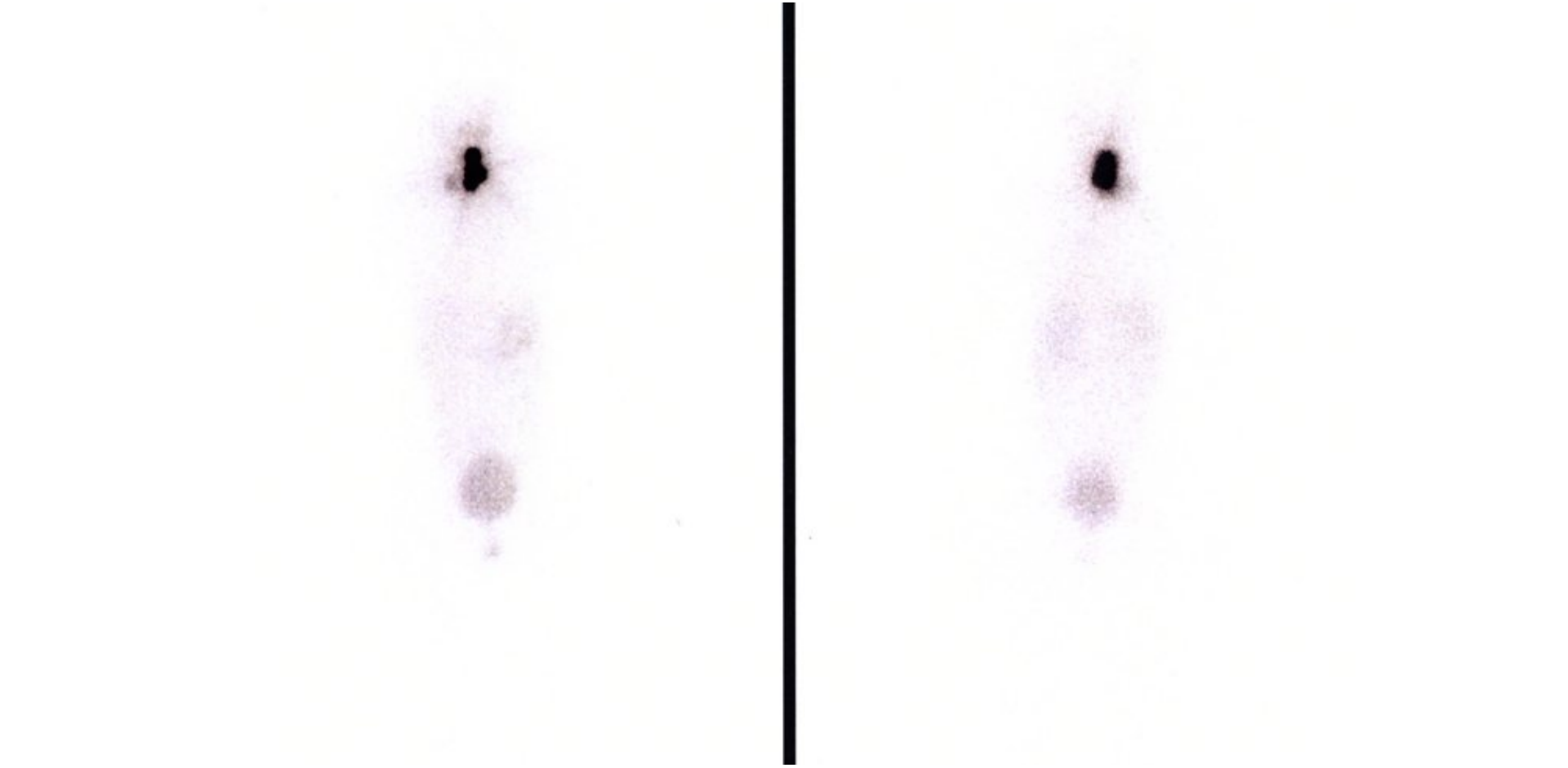
Morbus Basedow / Graves Diseases

100 – 150 Gy



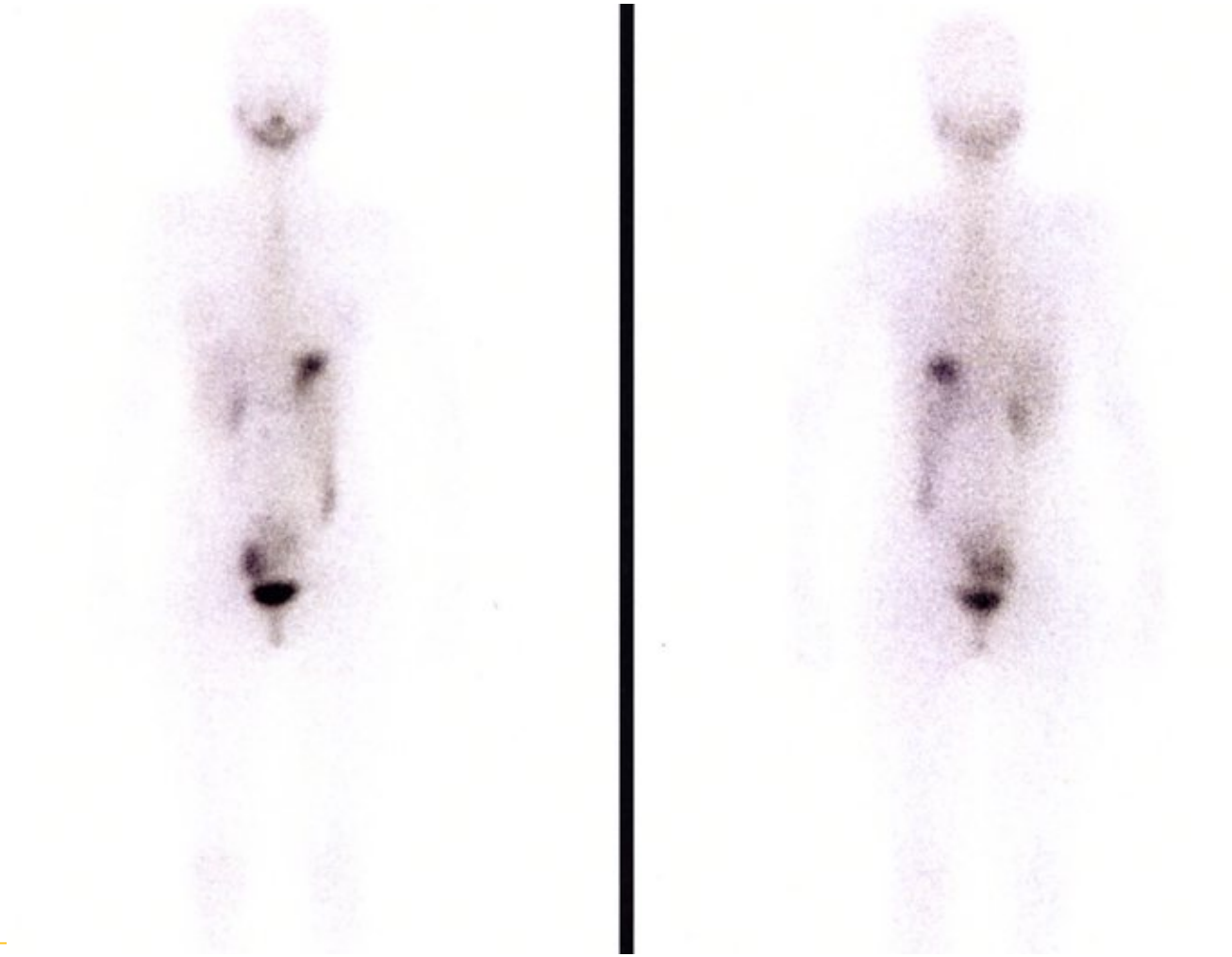
Goiter

Radionuclide Therapy Of Differentiated Thyroid Cancer
I-131 Whole Body Scan After 1st Radioiodine Therapy



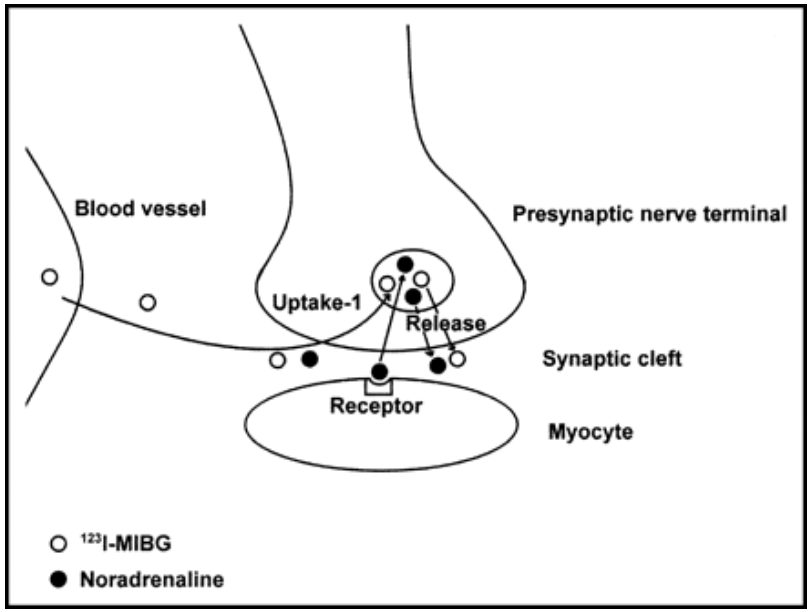
RadionuclideTherapy Of Differentiated Thyroid Cancer

I-131 Whole Body Scan After 2nd Radioiodine Therapy
Complete Remission

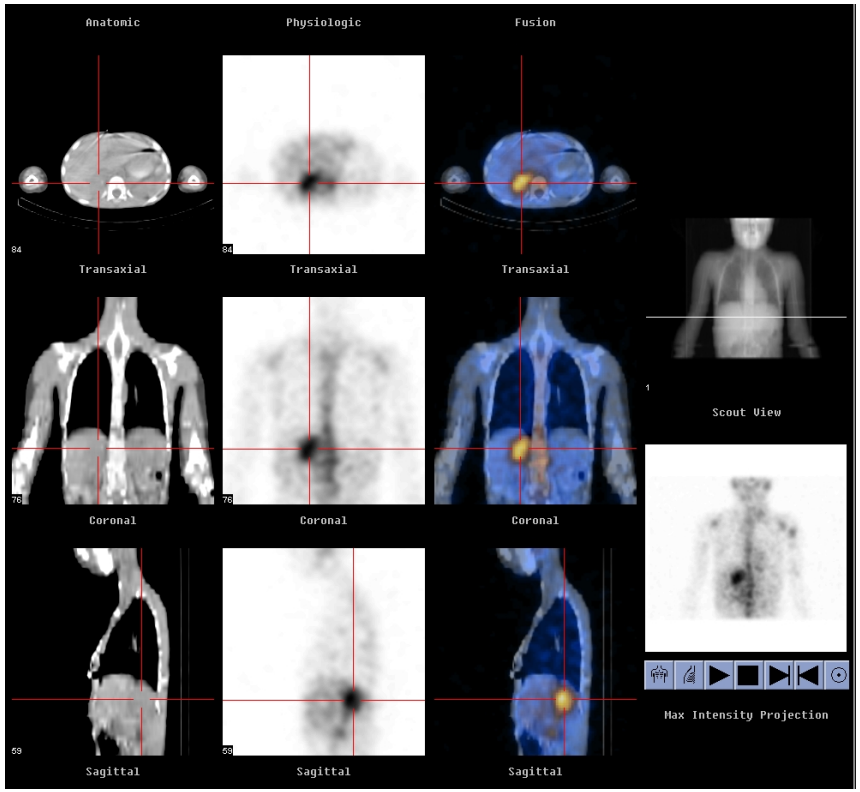


Neuroblastoma
I-123 and I-131 MIBG

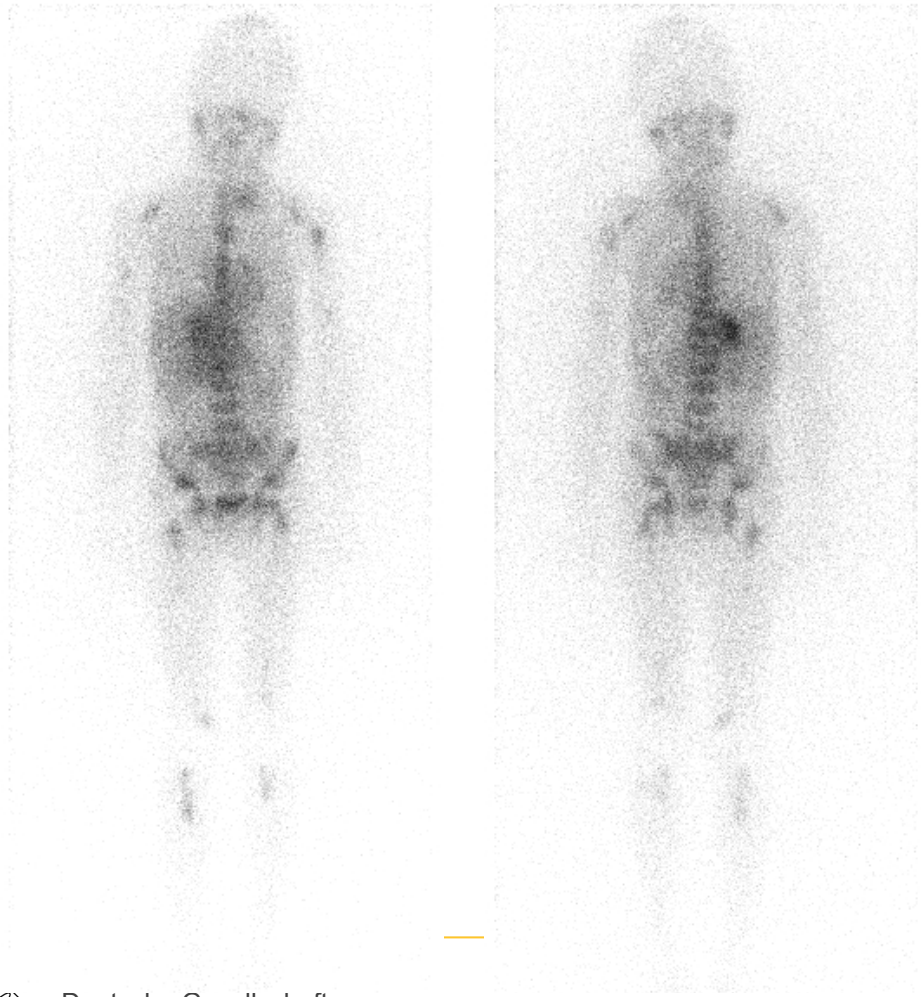
CT: Mass lesion in right adrenal gland
I-123 MIBG Scintigraphy: focal increased uptake in the mass lesion.



J. Nucl. Med. Technol. June 1, 2004 vol. 32 no. 2 66-71



I-131 MIBG Therapy

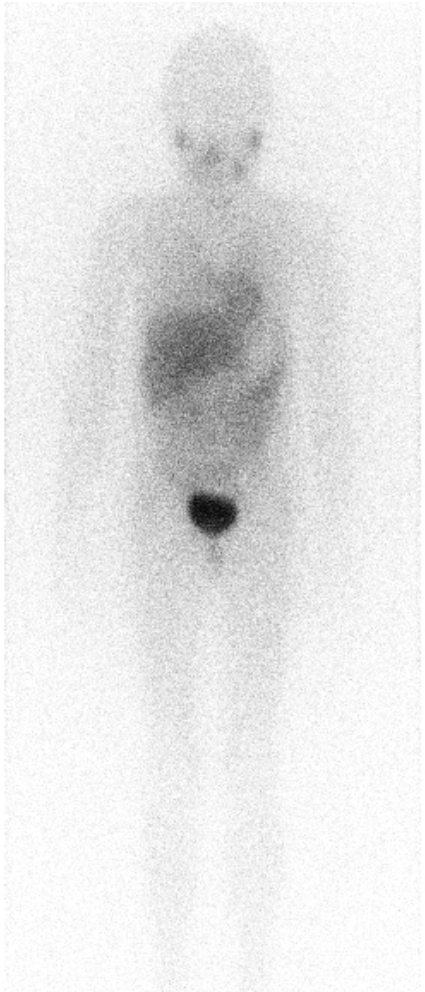


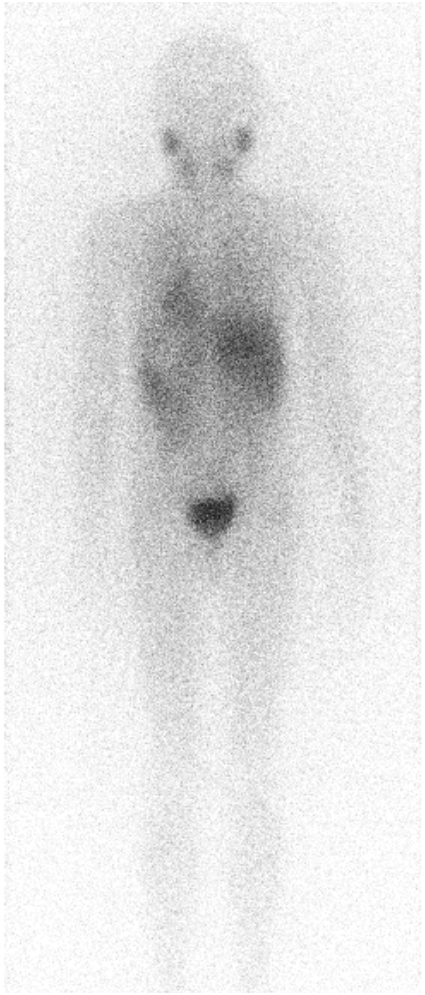
Neuroblastoma patient with disseminated bone marrow metastases

Dose Limiting Factor Is
Bone Marrow Toxicity

I-131 MIBG-Scintigraphy After Therapie

Normal Finding After
Chemotherapy, MIBG-Therapy
and Bone Marrow Transplantation

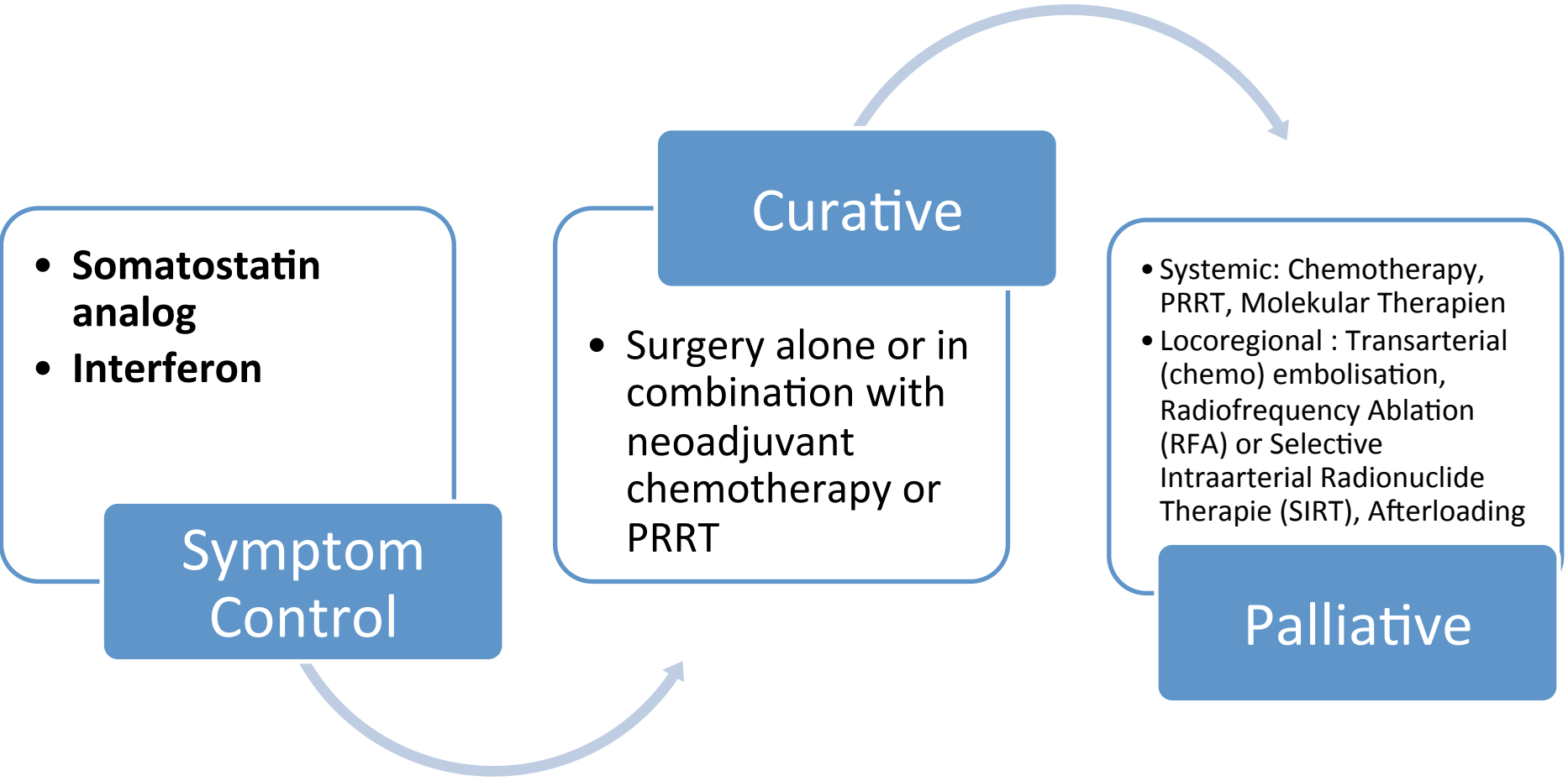




Neuroendocrine Tumor (NET)

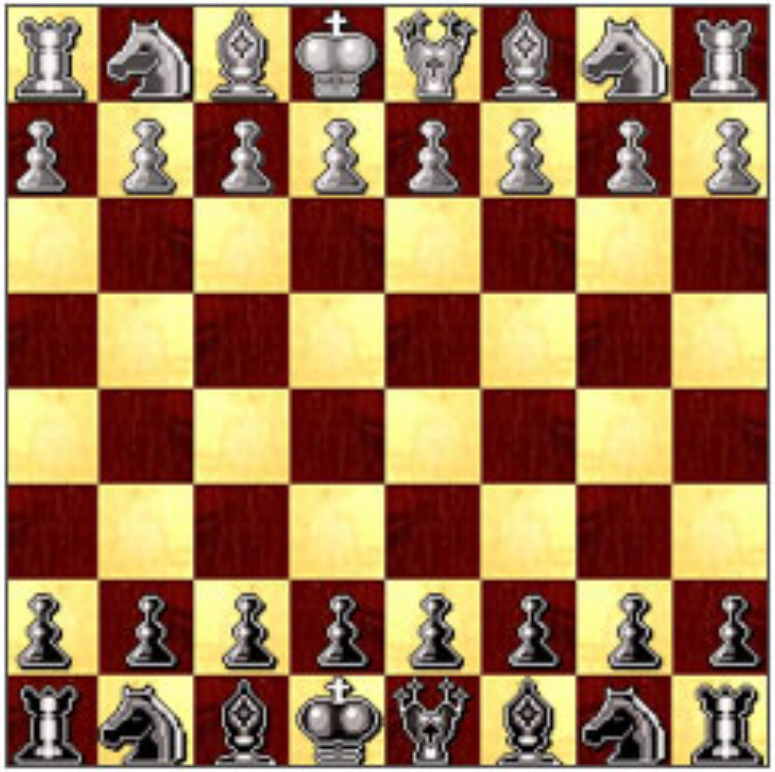
- Heterogenous, relatively indolent
- Most of the good to moderately differentiated NET show increased somatostatin receptor expression

Therapy Options: NET

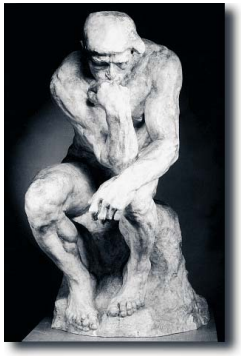


Sequence and Combination of Therapies

Doctor



Neuroendocrine Tumor



1. Line Therapy
2. Line Therapy
3. Line Therapy

Ideal- white wins (doctor)
(NET- Complete Remission)

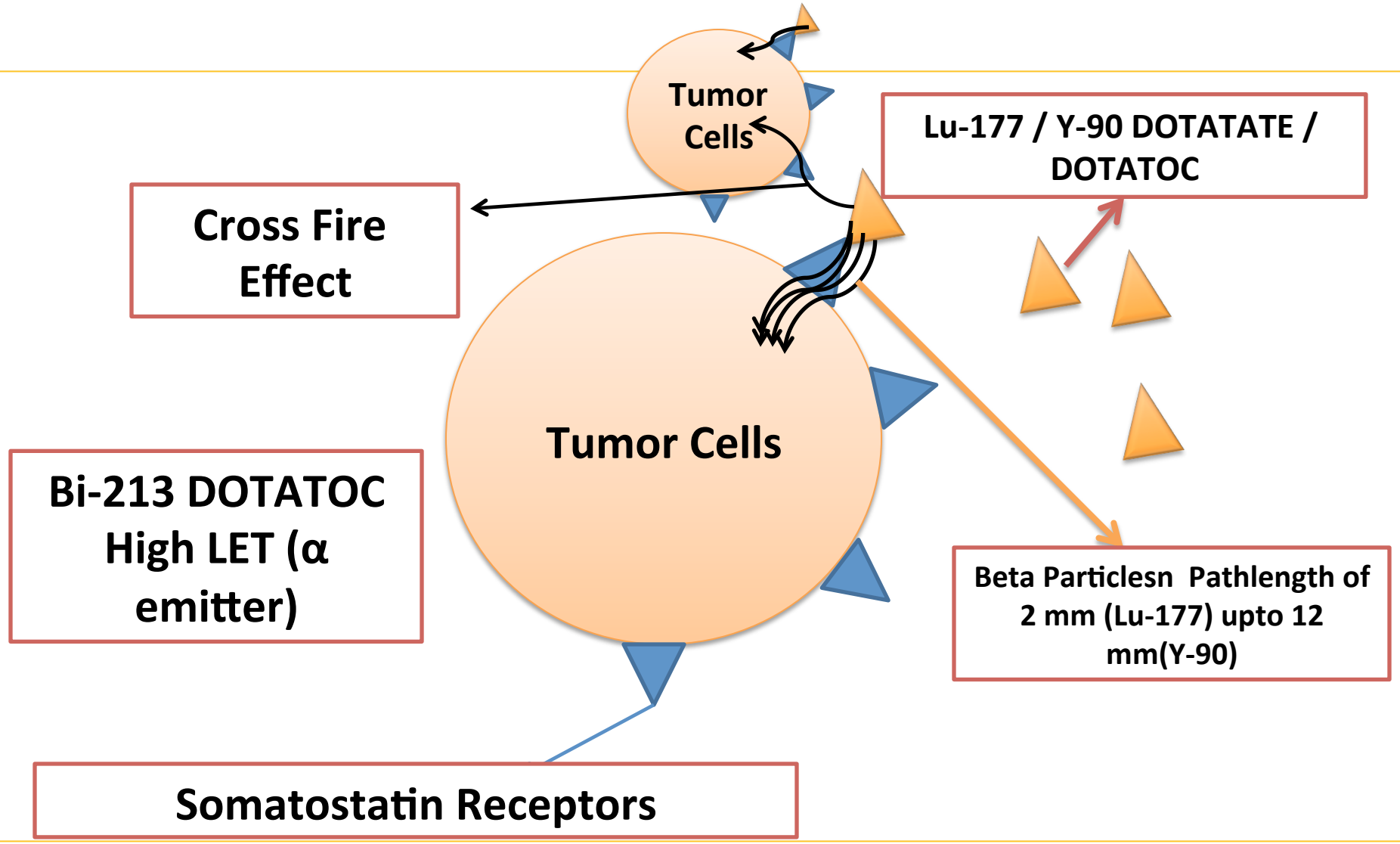
Most common result
(Stable Disease)

Sequence and combination of therapies

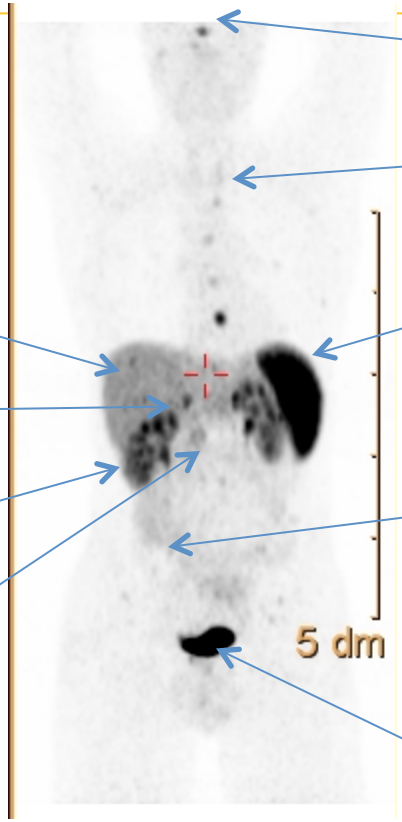
Aggressive? Curative? Palliative?

- **Most of the NET patients have good OS**
- **Therapies are not without side effects**

Working Principle Of Peptide Receptor Radionuclide Therapy



Normal Biodistribution of Radiolabelled Somatostatin Analogs



Pituitary

Thyroid

Liver

Spleen

Adrenal Glands

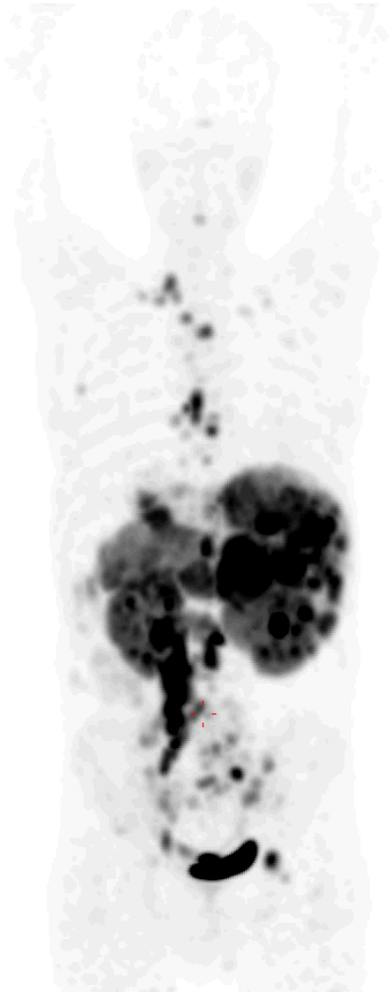
Intestine

Kidneys

Processus Uncinatus of Pancreas

Urinary Bladder

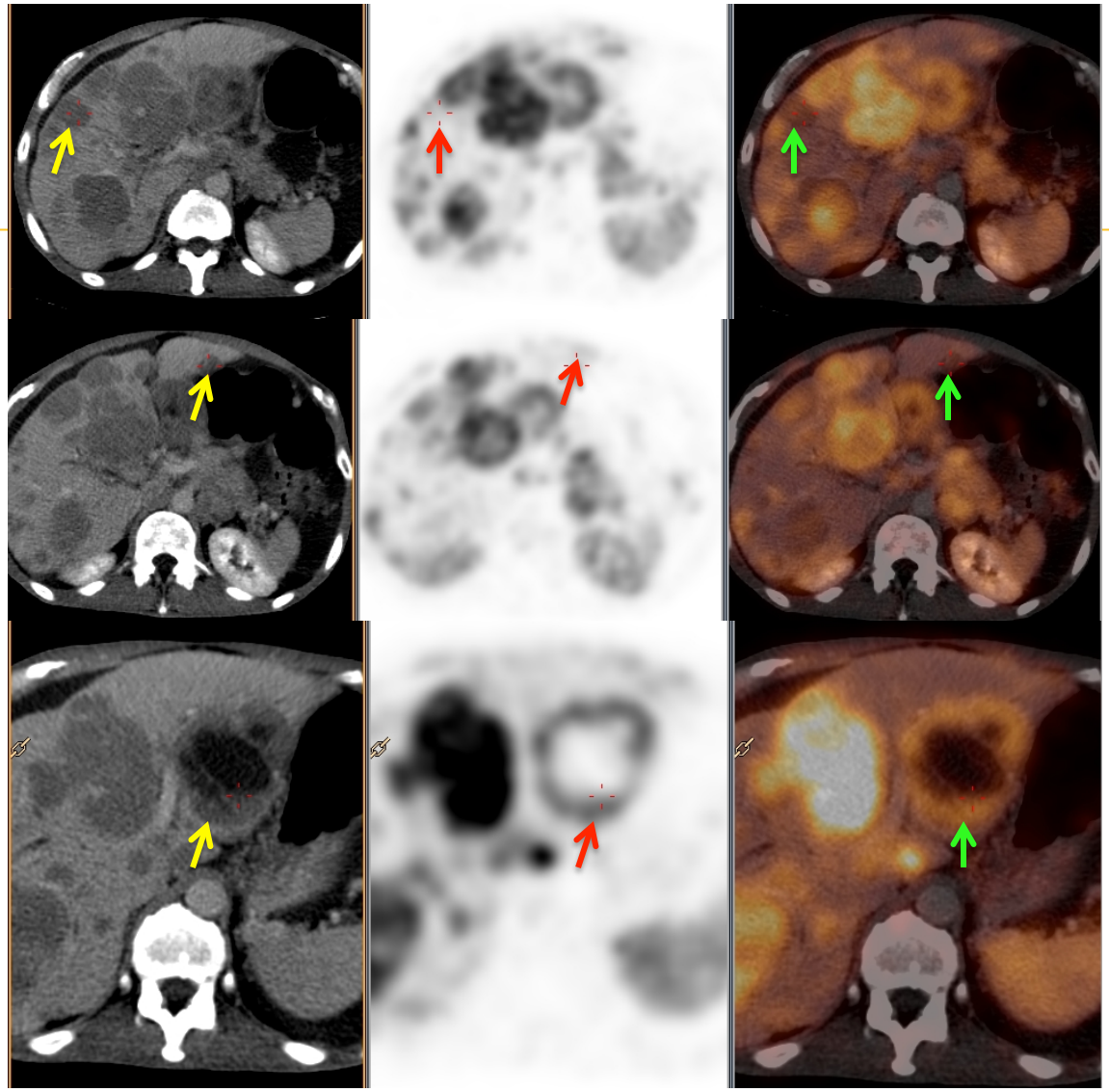
Indication For PRRT?

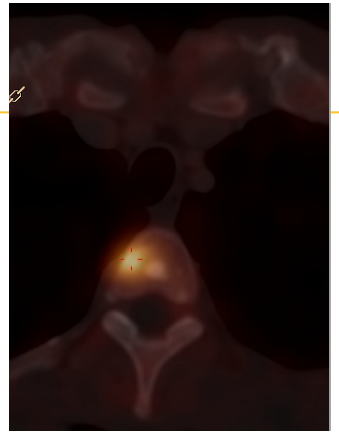


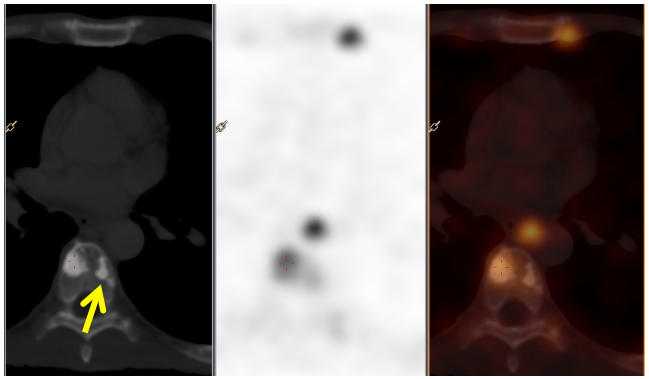
53 year / male
Resident of Cypern
pancreatic NET (Ki67 10%), KI 60%, FD 04/2012
Best Response after 3 cycles of 5FU/Strepto- SD
In Cypern Sutent and Everlomis not available
Ga-68 DOTATATE- multiple somatostatin receptor positive lesions

According to the ENETS guidelines he is suitable for PRRT

Ga-68 DOTATATE PET/CT



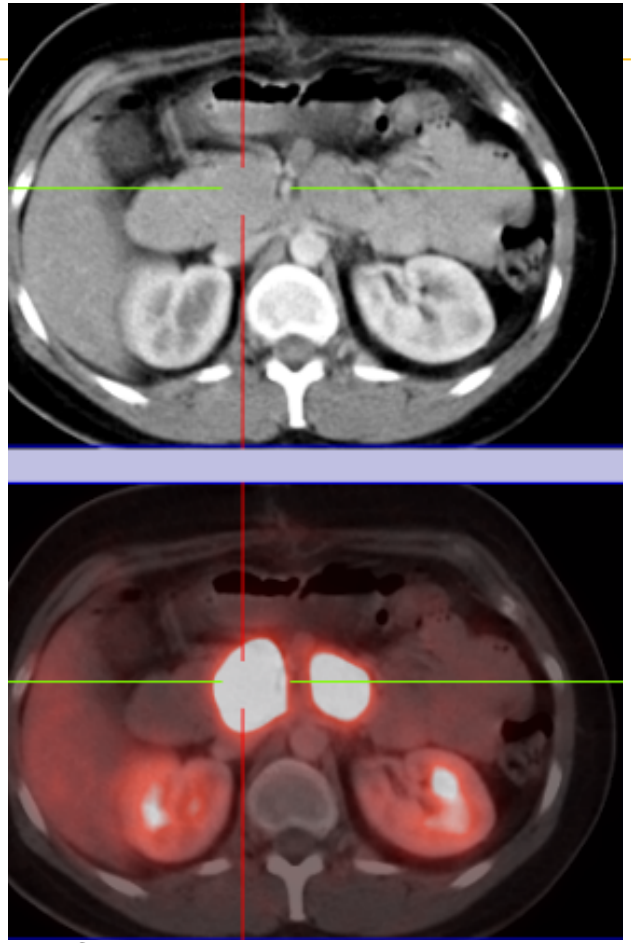




Clinically G3 (loss of 15 Kg in 6 months), glucagonoma not ruled out

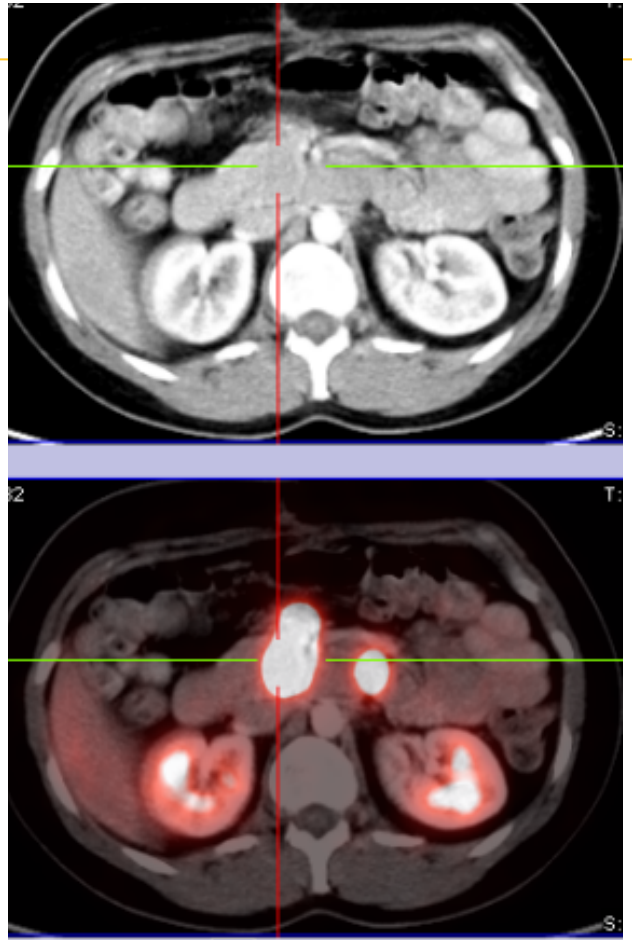
Lesions had highly heterogeneous somatostatin receptor profile

Sequential PRRT (Y-90 DOTA-TATE) of Inoperable Pancreatic NET



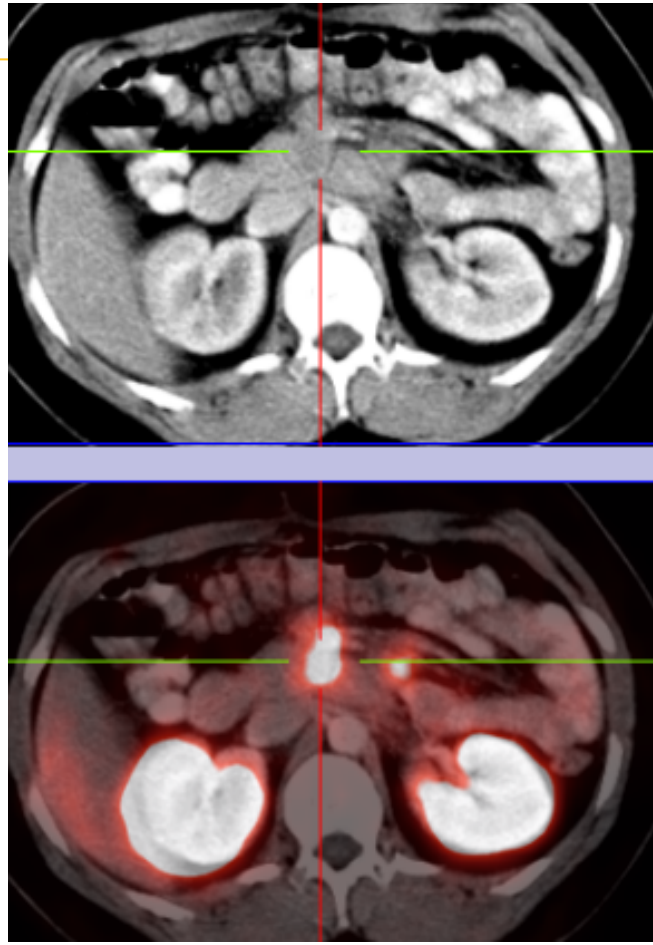
Before PRRT-1
6 GBq Y-90

Jan. 2007



Before PRRT-2
4.5 GBq Y-90

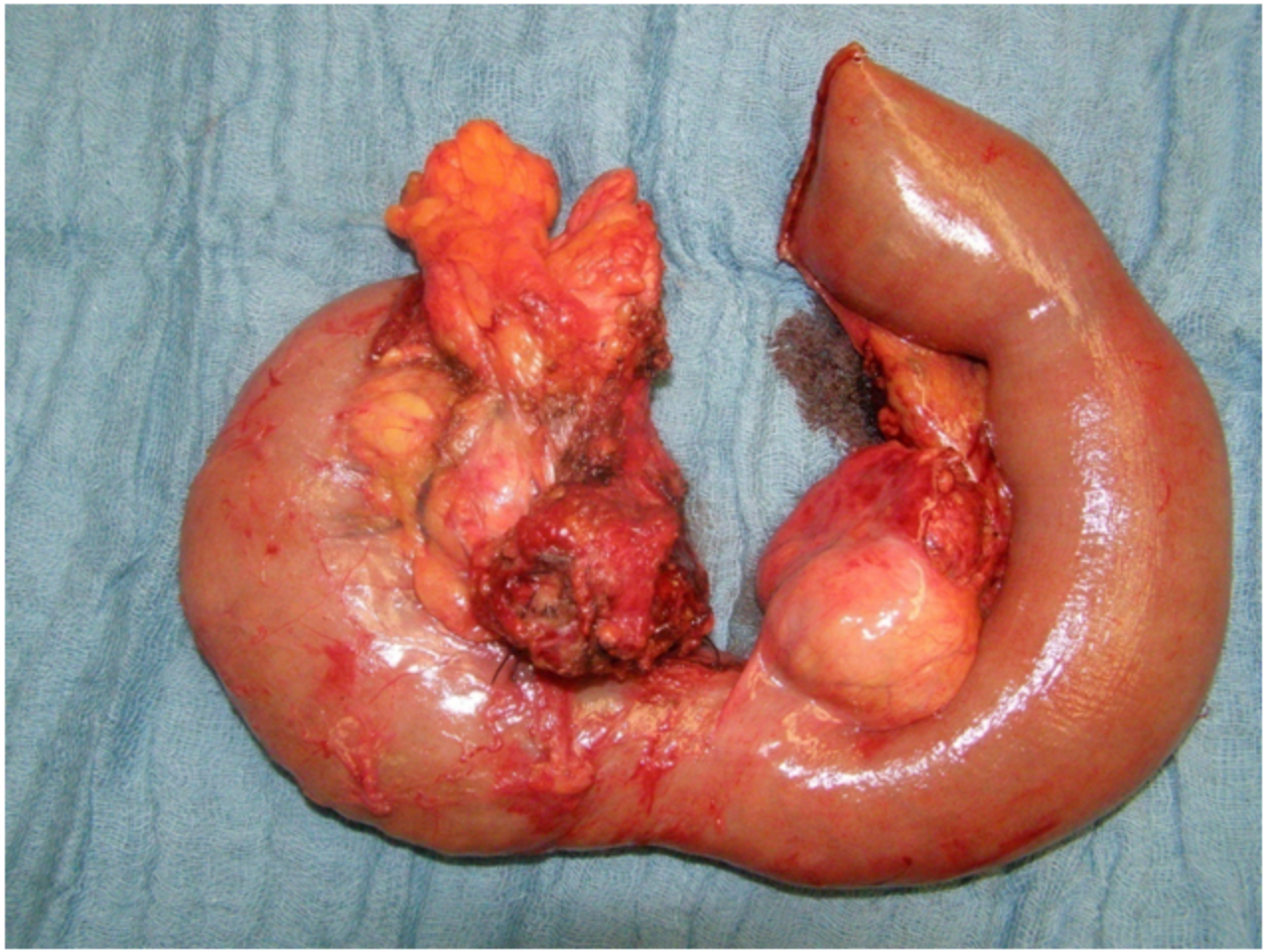
May 2007



5-mo after PRRT-2
pre Op.

Oct. 2007

Whipple‘ Operation – Complete Resection of Pancreatic NET after Neoadjuvant PRRT



Histology revealed nearly total tumor necrosis typical for radiation necrosis

Kaemmerer, Prasad et al; World J Gastroenterol. 2009 Dec 14;15(46):5867-70

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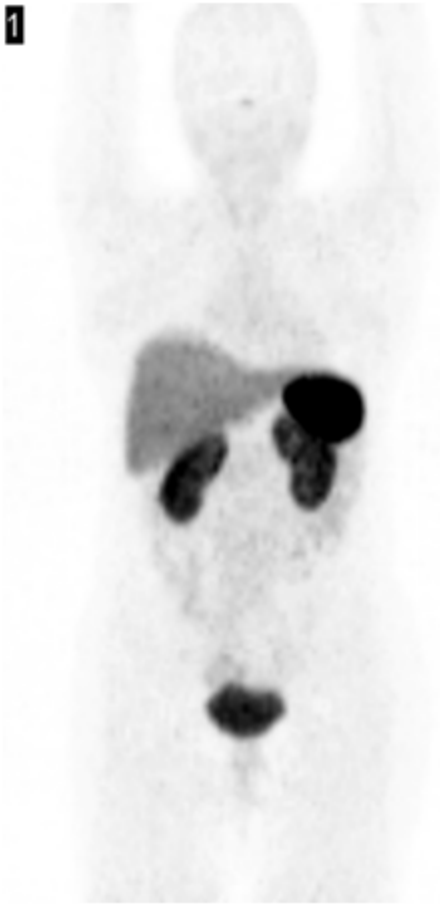
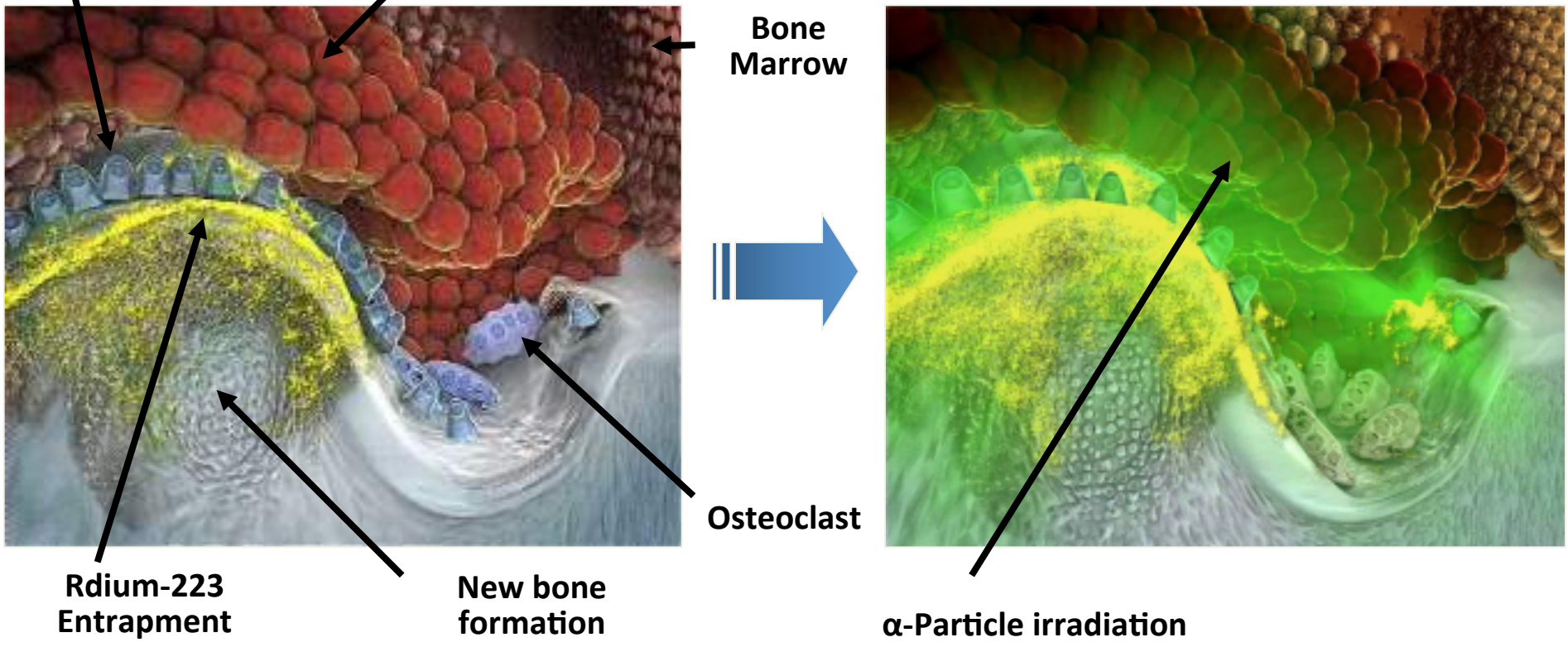


Follow up at 36 months – complette remission

Prostate Cancer
Ra-223 Working Principle

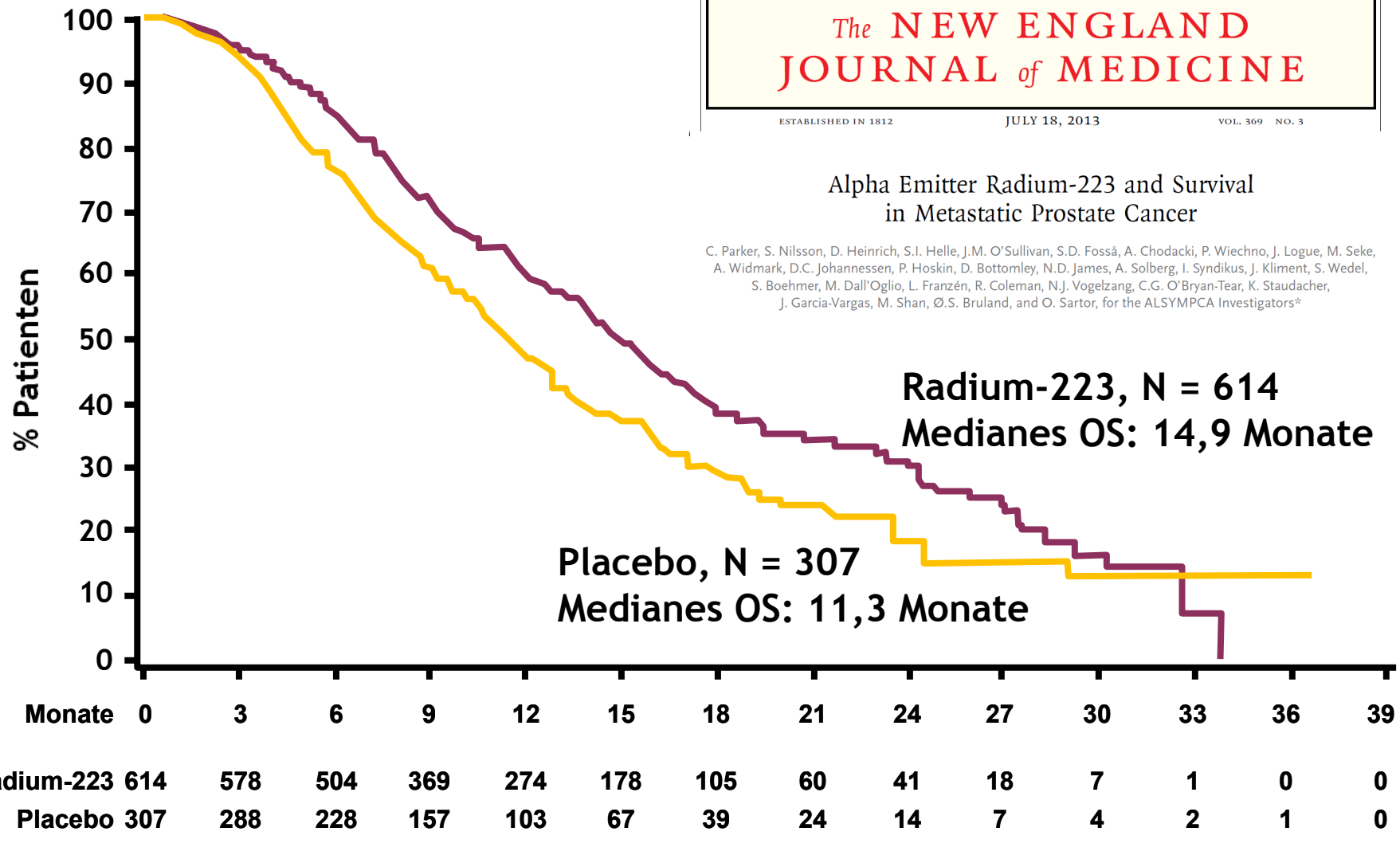
Actively taken up in area of new bone formation

Irradiates nearby tumor cells → high energy transfer



Bruland OS, et al. Clin Cancer Res. 2006;12(20):6250s–57s

ALSYMPCA: Overall Survival in Castrate Resistant / Hormone Refractory Prostate Cancer Patients With Bone Metastases After Ra-223 Therapy



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Alpha Emitter Radium-223 and Survival in Metastatic Prostate Cancer

C. Parker, S. Nilsson, D. Heinrich, S.I. Helle, J.M. O'Sullivan, S.D. Fossâ, A. Chodacki, P. Wiechno, J. Logue, M. Seke, A. Widmark, D.C. Johannessen, P. Hoskin, D. Bottomley, N.D. James, A. Solberg, I. Syndikus, J. Kliment, S. Wedel, S. Boehmer, M. Dall'Oglio, L. Franzén, R. Coleman, N.J. Vogelzang, C.G. O'Bryan-Tear, K. Staudacher, J. Garcia-Vargas, M. Shan, Ø.S. Bruland, and O. Sartor, for the ALSYMPCA Investigators*

HR = 0,695, p = 0,0007

Parker C, et al. ASCO 2012 LBA4512.

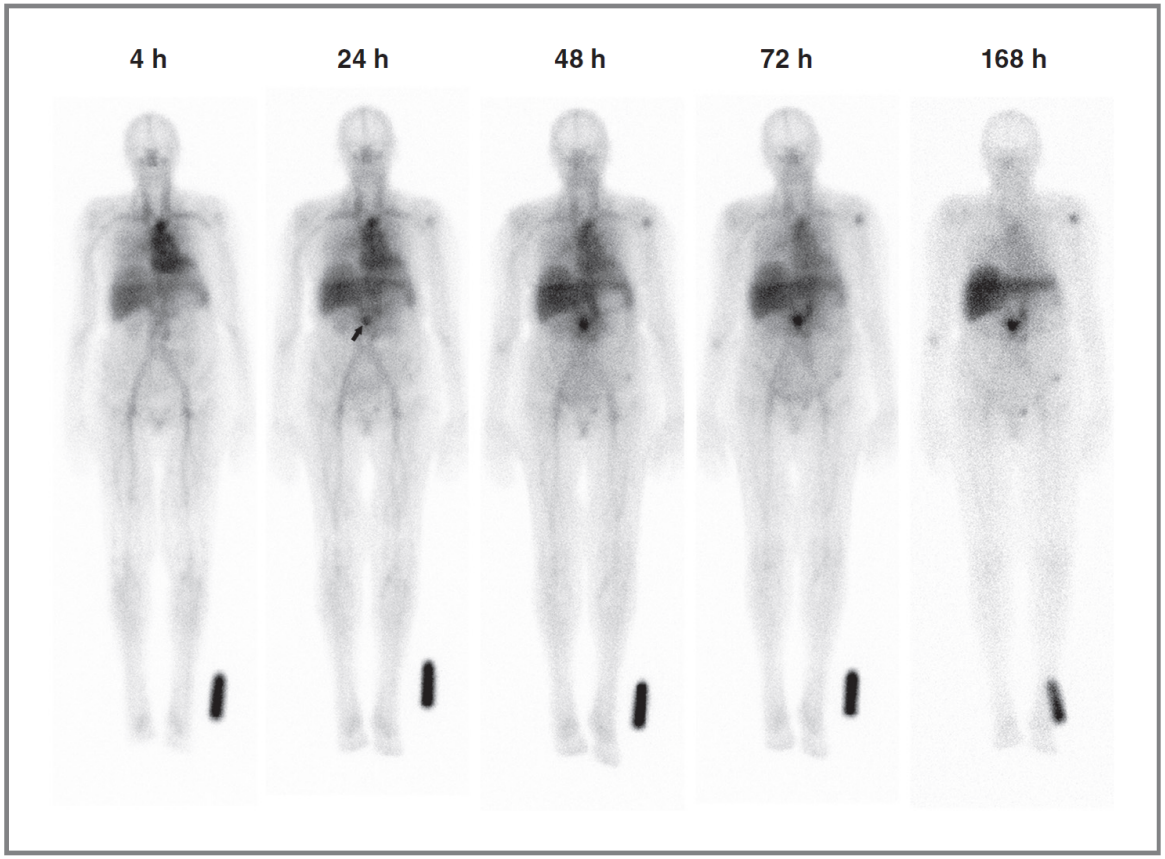
Prostate Cancer
Response To Ra-223

Before Recruitment
ALSYMPCA Studie

After 6x i.v. of Radium-223
(50 kBq/kg)

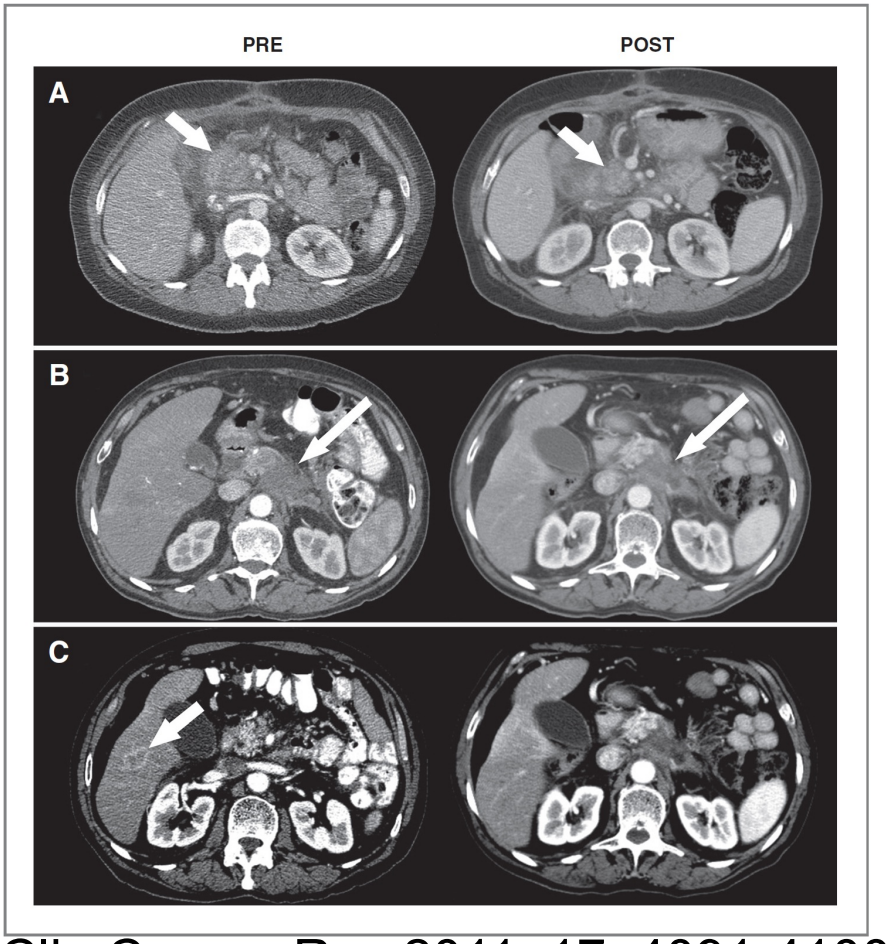
Pancreas Adenocarcinoma

In-111 hPAM4 Dosimetry Scan Of A Pancreas Adeno Ca Resistant To Gemcitabine



Clin Cancer Res 2011; 17: 4091-4100

Patient With Pancreas Adenocarcinoma After Treatment With Y-90 hPAM4 Antibody



Clin Cancer Res 2011; 17: 4091-4100

Figure 2. CT image examples before (PRE) and after treatment with ^{90}Y-hPAM4 (POST). A, a 63-year-old female diagnosed 5 months earlier with locally advanced pancreatic cancer was previously treated with gemcitabine and external radiation therapy. At study entry, the patient had a 6.3-cm mass in the head of the pancreas which reduced to 3.0 cm by 4 weeks after ^{90}Y-hPAM4 (arrows). B and C, a 70-year-old male diagnosed 4 months earlier with locally advanced disease received 5-FU and external radiation therapy initially and then gemcitabine. At study entry, the patient had a 4.5-cm mass in the body of the pancreas which reduced to 3.3 cm after treatment with ^{90}Y-hPAM4 (long arrows) and a 2.3-cm lesion in the liver (short arrow) that was no longer measurable.

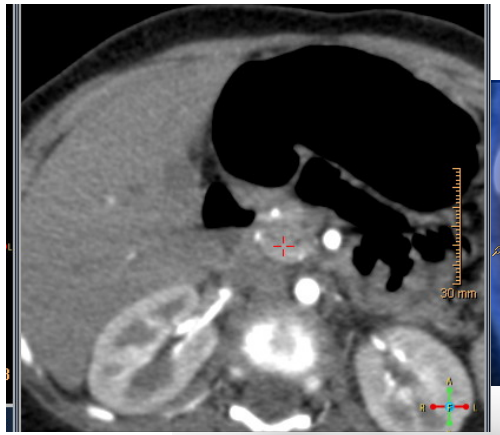
Other Areas Of Theranostic Applications Of Radionuclide Probes

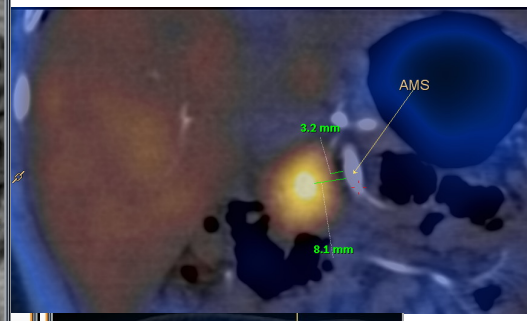
- Radioguided Surgery
- Photodynamic Therapy
- Drug Development

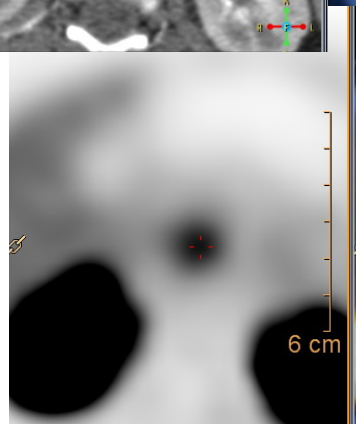
Radioguided Surgery In Congenital Hyperinsulinism Can Reduce The Surgery Time

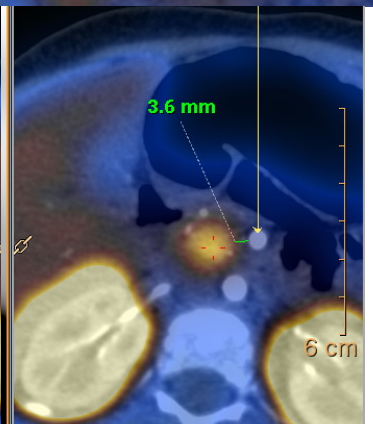
- Life threatening
- Surgery for focal form only curative option
- Surgery because of small size and no definite visible changes in pancreas is time consuming and challenging needing 8-12 hrs

F-18 DOPA PET/CT

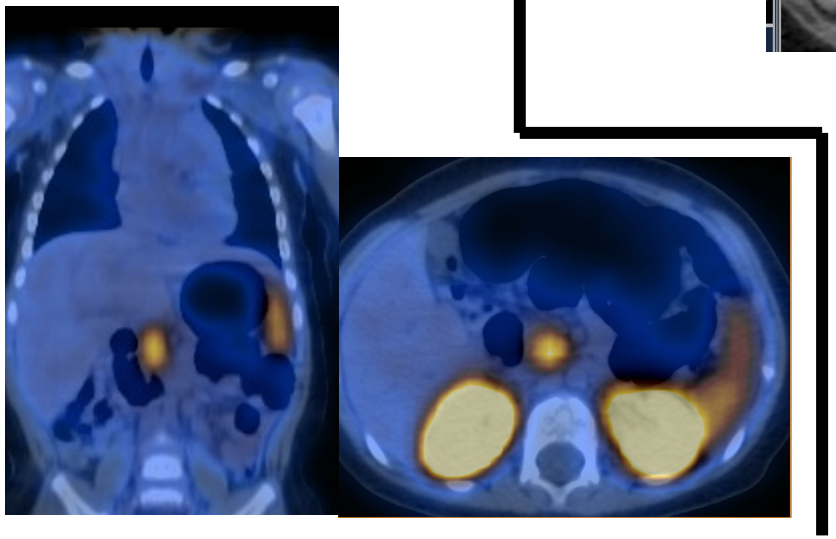








Ga68DOTATOC PET/CT

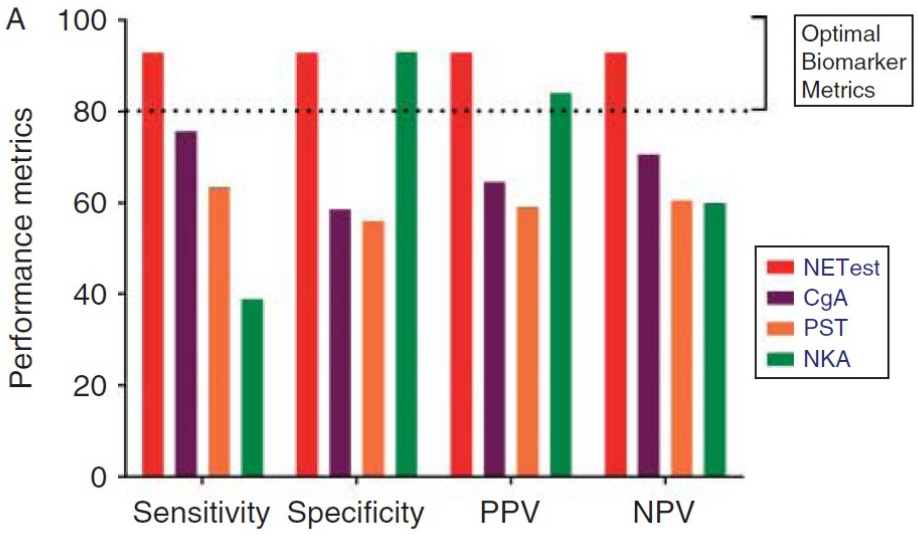


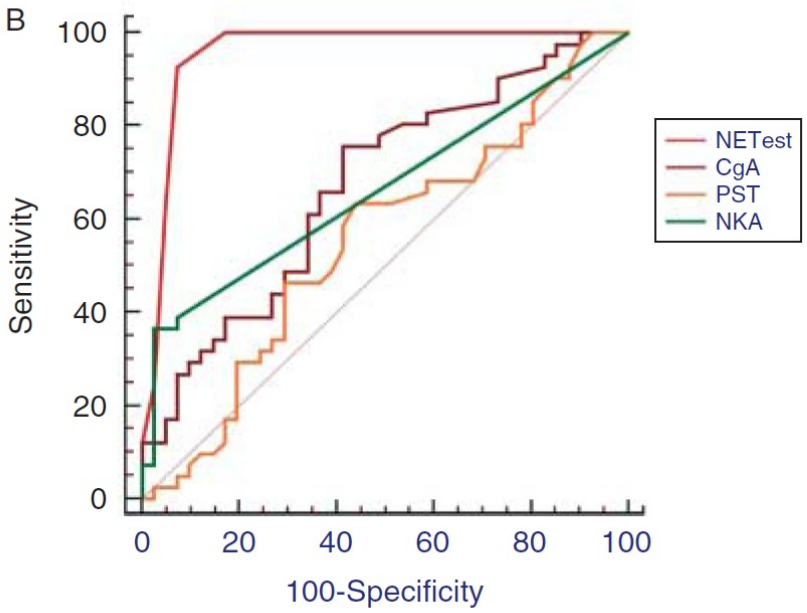
Future

- Avoid tunnel view
- Combine genetic information to outsmart the evolved cancer cells from getting resistant
- Data mining using artificial neuronal networking (MIBG, NETTest)
- Think beyond.....

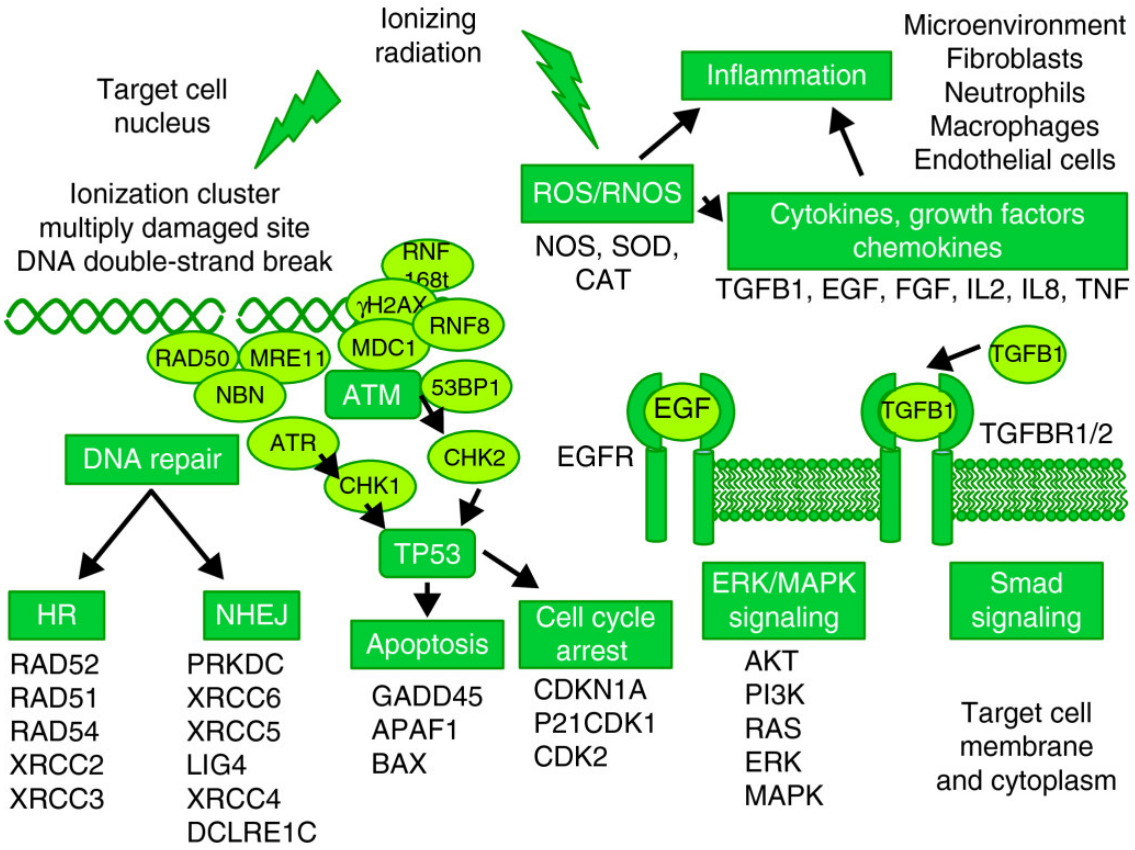
A Multianalyte PCR Blood Test Outperforms Single Analyte ELISAs (CgA, Pancreastatin, Neurokinin A) For NET Detection
I.M. Modlin, L. Bodei, M. Kidd et al

Endocr Relat Cancer 2014; 21:615-28





Summary Of The Pathways And Mechanisms Involved In Cell And Tissue Response To Radiotherapy



Genome Medicine 2011 **3**:52

‚Make Sure You Have A Good Mentor‘

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Boat House
of
Prof. Modlin
New Haven
June 2014

PILLARS OF NUCLEAR MEDICINE

Mathematics

Biology

Chemistry

Physics

From Theory To Theranostics: Connecting The Dots In The Firmaments Of Nobel Prizes (To Be Submitted)

Vikas Prasad, Lisa Bodei, Mark Kidd, Irvin M Modlin

Physiology or Medicine:

1909: Emil Theodor Kocher- Thyroid Physiology:
1946: Hermann Joseph Muller- X-ray induced mutation
1972: Gerald M. Edelman and Rodney R. Porter – chemical structure of antibodies
1977: Rosalyn Yalow- Radioimmunoassay
1979: Allan M Cormack and Godfrey N. Hounsfield- CT
1984: Niels K. Jerne, Georges J.F. Köhler and César Milstein- Monoclonal Antibody
2003: Lauterbur and Mansfield

Physics:

1901: Wilhelm Conrad Röntgen
1903: Antoine Henri Becquerel- discovery of spontaneous radioactivity
1921: Albert Einstein-law of photoelectric effect
1922: Niels Henrik David Bohr- investigation of the structure of atoms and of the radiation emanating from them
1936: Carl David Anderson- discovery of the positron
1938: Enrico Fermi-existence of new radioactive elements produced by neutron irradiation
1939: Ernest Orlando Lawrence- Cyclotron
1952: Bloch and Purcell: nuclear magnetic precision measurements
1992: Georges Charpak- multiwire proportional chamber

Chemistry:

1908: Ernest Rutherford- discovery of radioactive substances
1911: Marie Curie- discovery of radium and polonium
1921: Frederick Soddy- knowledge of chemistry of radioactive substance:
1935:Frédéric Joliot and Irène Joliot-Curie- synthesis of new radioactive substance-
1943: Georde de Hevesy-Tracer principle
1944: Otto Hahn- fission of heavy nuclei
1952: Archer John Porter Martin and Richard Laurence Millington Synge- partition chromatography:
1997: Jens C. Skou-Na-K ATPase
2012: Robert J. Lefkowitz and Brian K. Kobilka- G- protein coupled receptors