Deutsche
Gesellschaft
für Nuklearmedizin
e.V.

SUMMER SCHOOL 2017

Translational Research in Molecular Imaging and Radionuclide Therapy

31 August – 2 September, 2017

Overview Theranostics and Radionuclide Therapy

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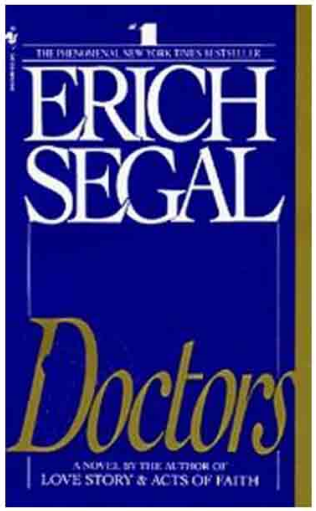
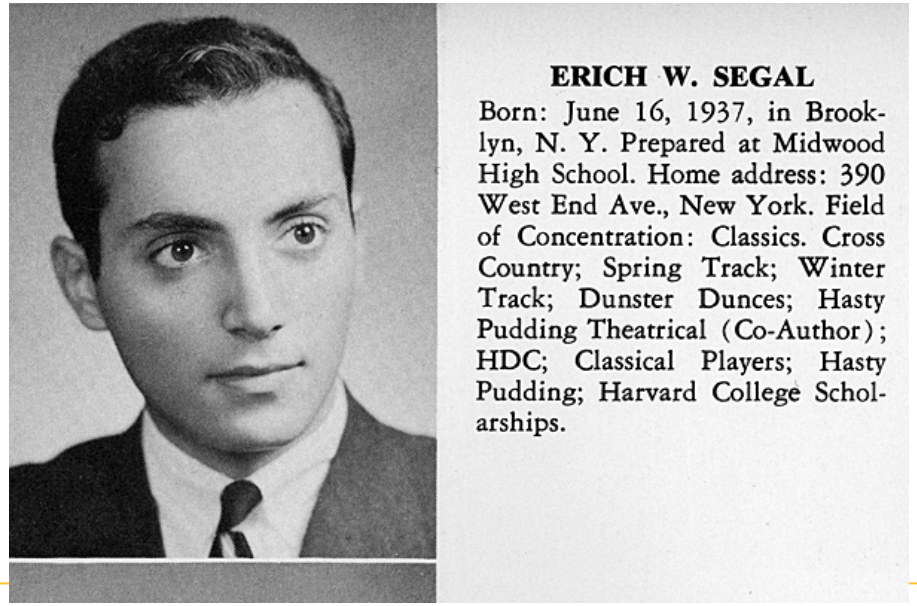
Charité Universitätsmedizin Berlin

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

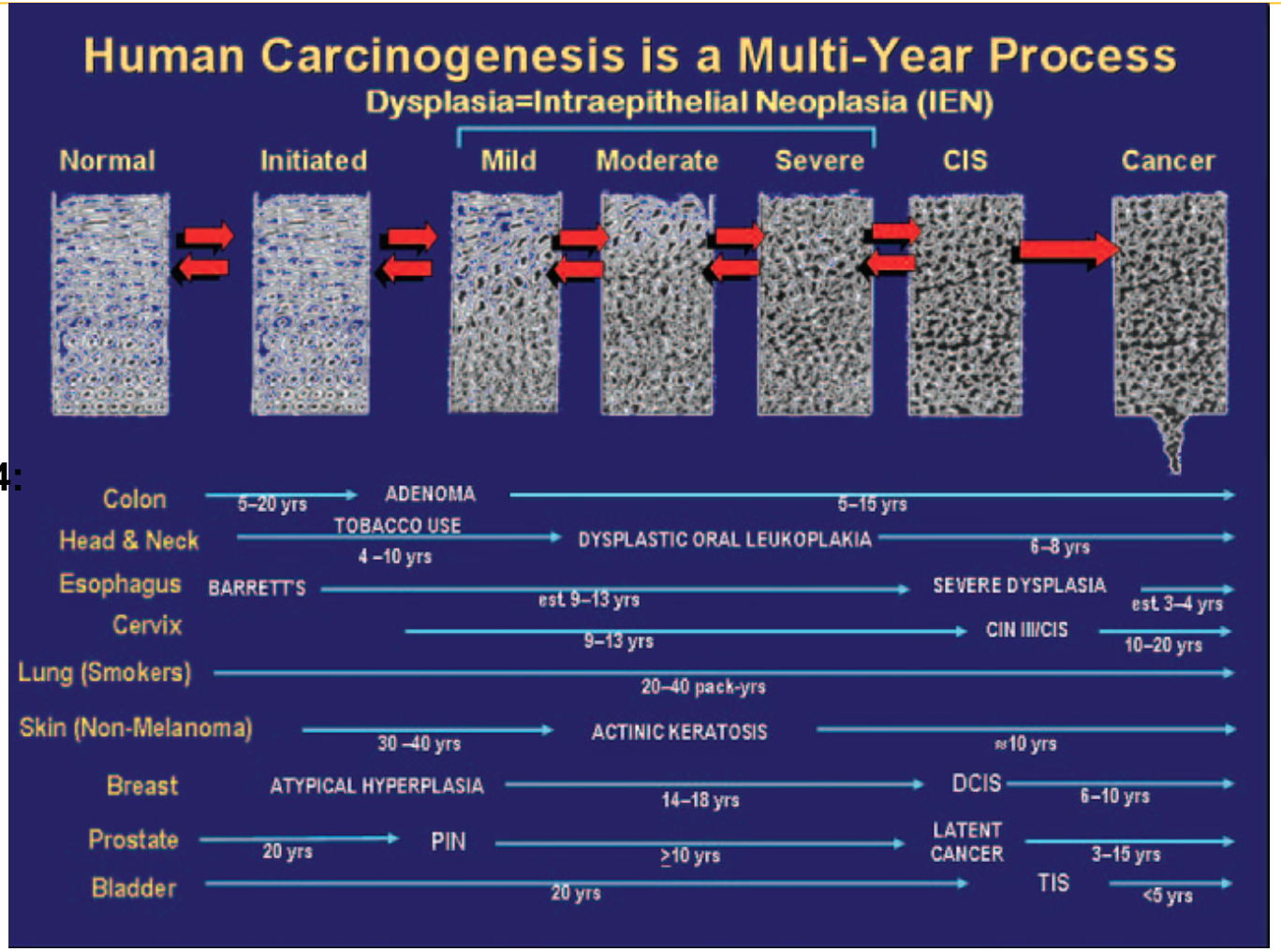
Born: June 16, 1937, in Brooklyn, N. Y. Prepared at Midwood High School. Home address: 390 West End Ave., New York. Field of Concentration: Classics. Cross Country; Spring Track; Winter Track; Dunster Dunces; Hasty Pudding Theatrical (Co-Author); HDC; Classical Players; Hasty Pudding; Harvard College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

Challenges in Oncology

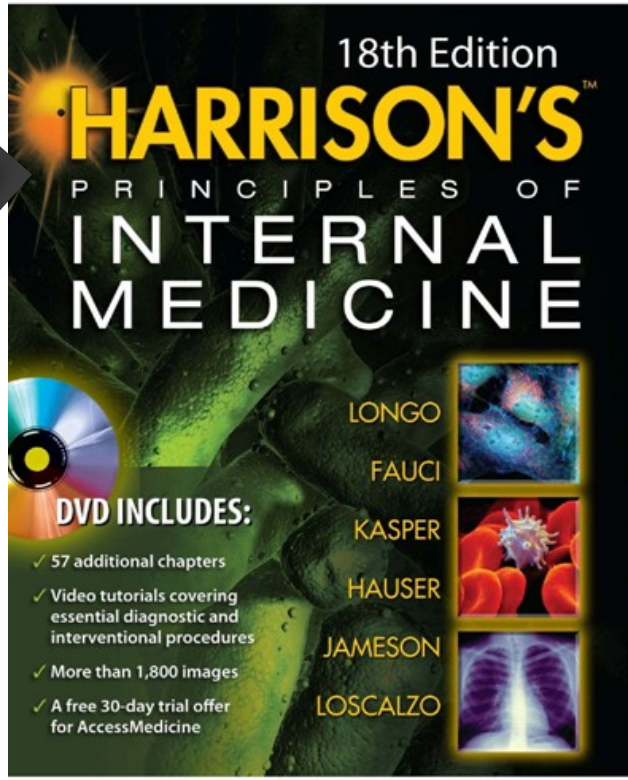
Cancer cells ‚out perform' the normal cells selected through ‚Darwin's theory of evolution'

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

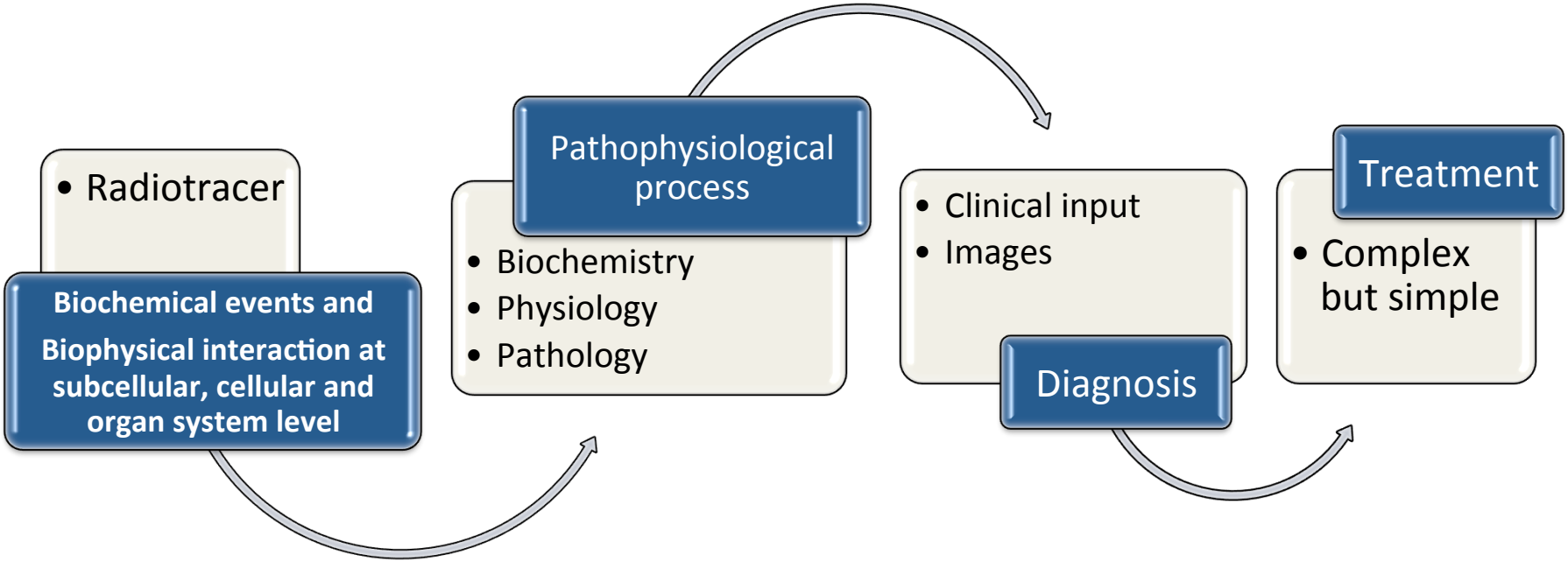
Theranostics is a portmanteau of therapeutics and diagnostics.

Theranostics is a proposed diagnostic methodology for personalizing therapeutic intervention/s

Side Effects

Therapy Response

Nuclear Medicine Definition



Translation and transformation 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

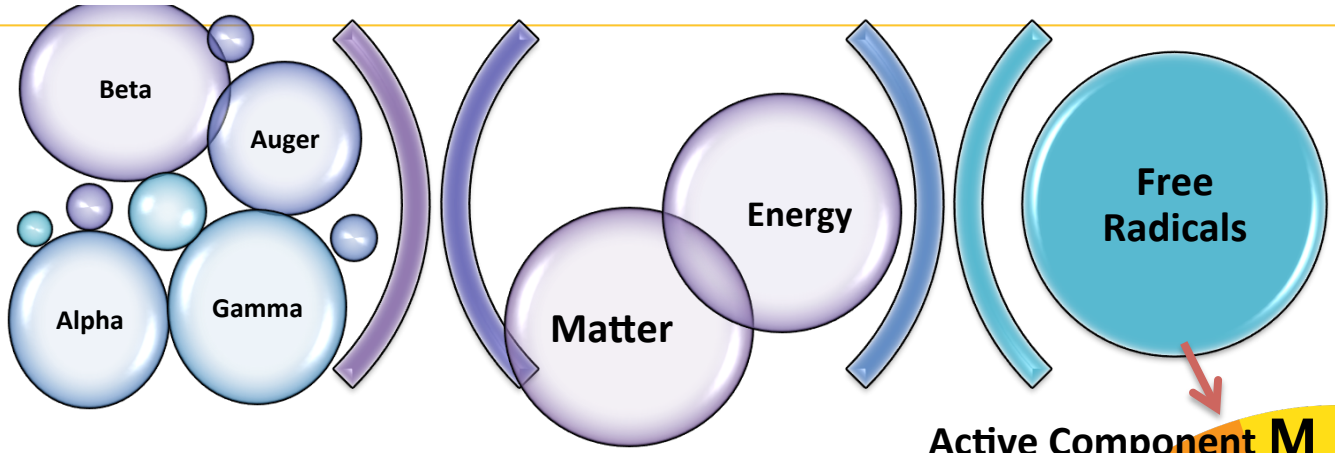
Radionuclides for Therapy

Radionuclide	T ½	Auger	Alpha	Beta	Gamma	Mean Pathlength
I-131	8.04 d			Y	Y	0.9 mm
Lu-177	6.7 d			Y	Y	0.7 mm
Y-90	2.67d			Y		3.9 mm
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			Y	10nm
Ra-223	11.4d		Y			0.06nm
Bi-213	45.6 min		Y			

Challenges#1

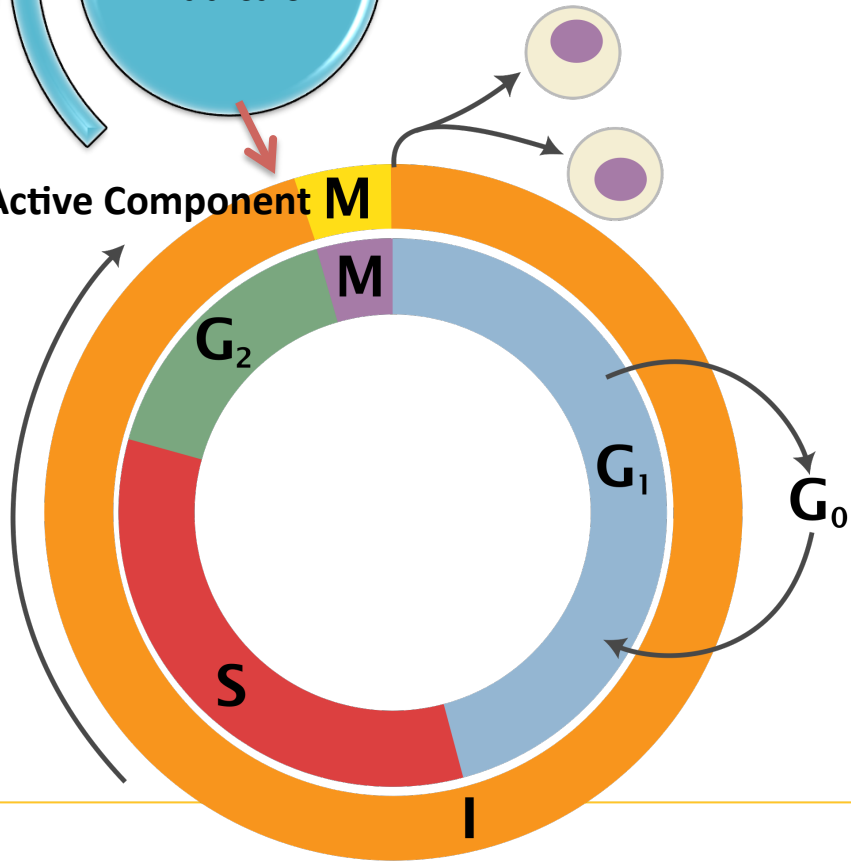
- Dosimetry Protocol

Basic Mechanism of Action: Radiation Induced DNA Double Strand Break



Types of Radiation

Matter Energy Interaction



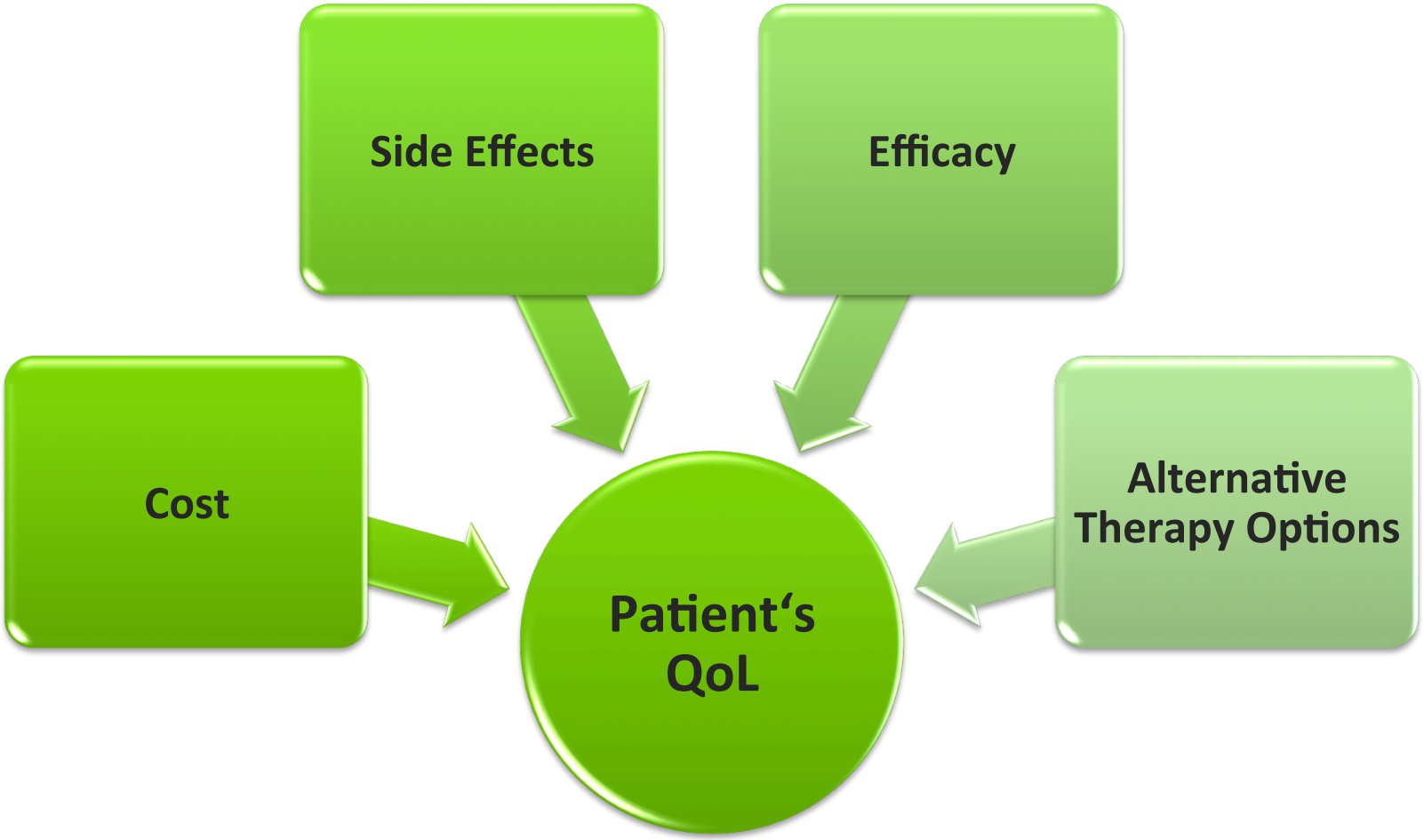
- G2M Phase Most Radiosensitive
- S-Phase and G1 Phase Radioresistant

Is Ki67 the correct proliferation marker?

Challenges#2

- Response Evaluation

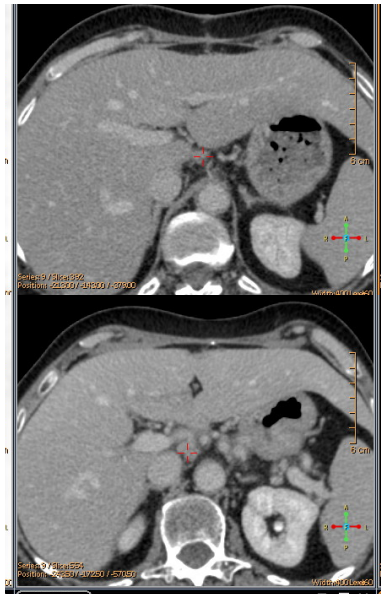
Therapy Response

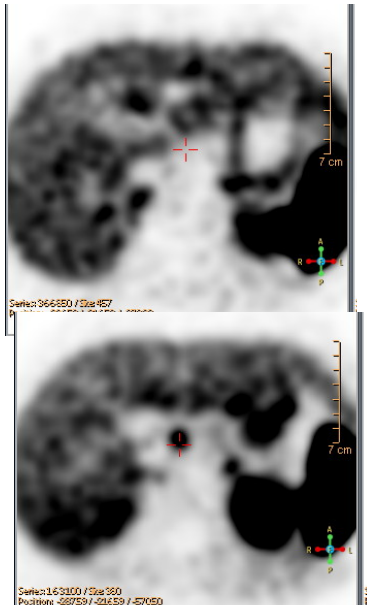


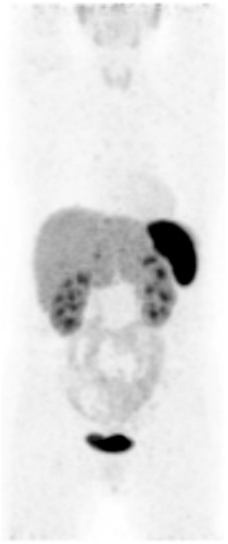
Early Response Prediction
Ga-68 DOTATOC PET/CT vs. 3-Phase CT

Jan 2011

Nov 2011

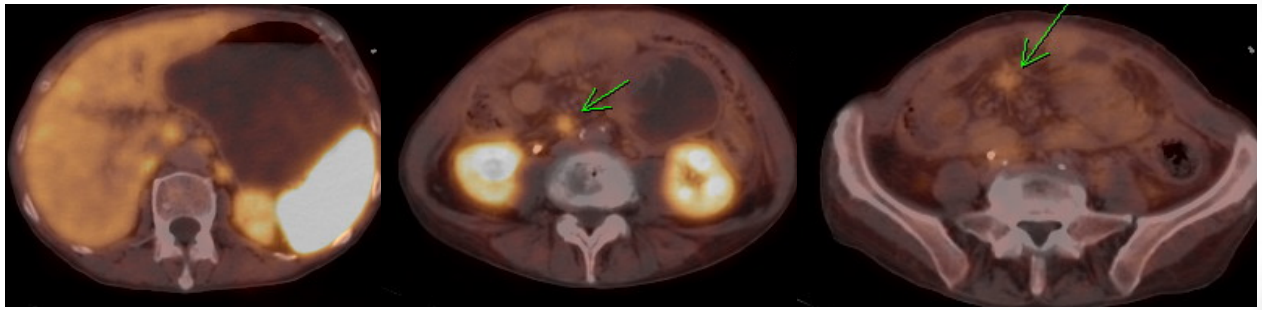


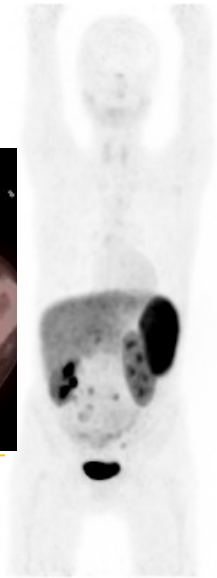




Nov 2011

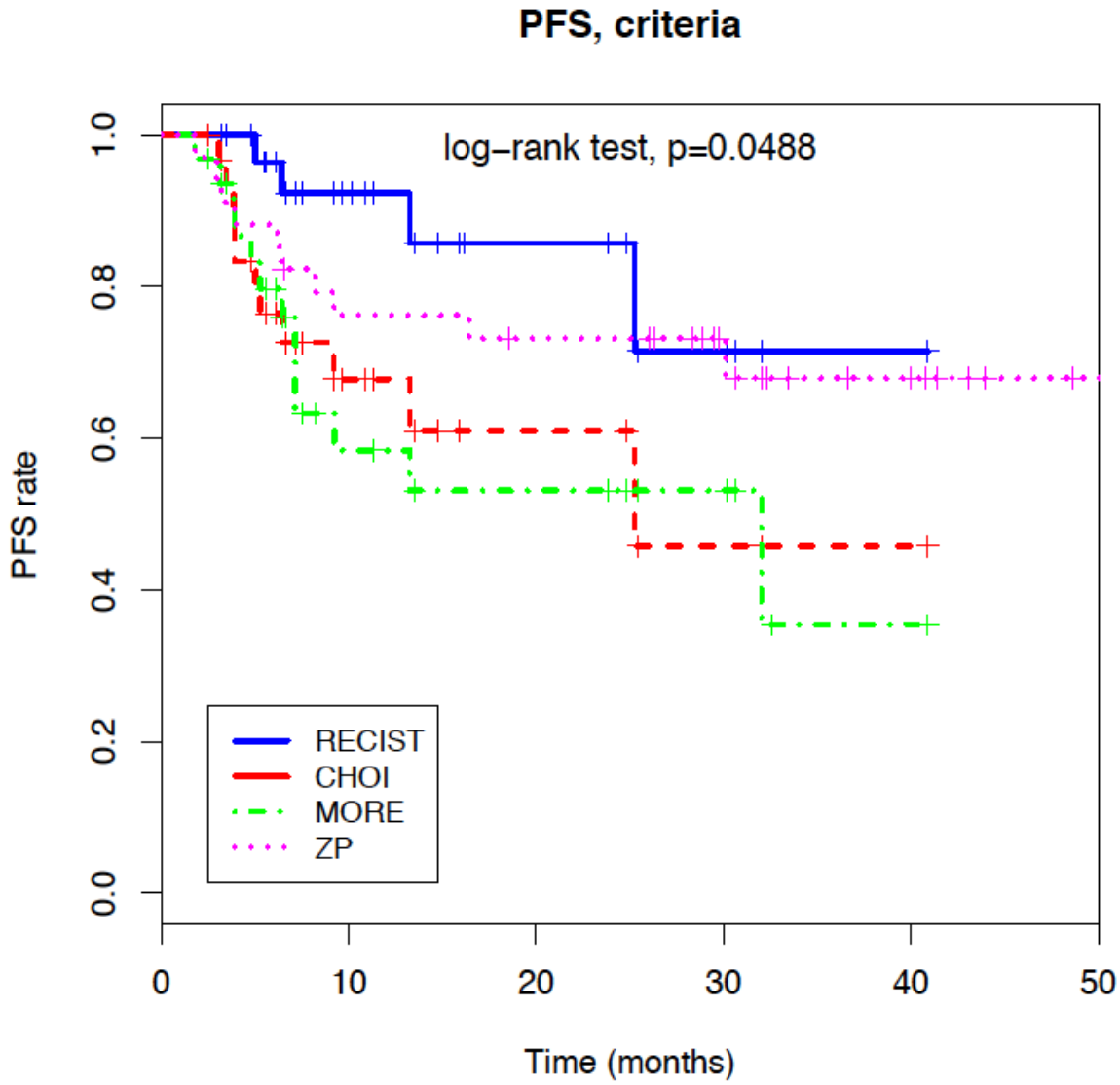
Juni 2013





Juni 2013

RECIST, MORE,CHOI, ZP in response assessment of PRRT (unpublished data, Charite)



Challenges#3

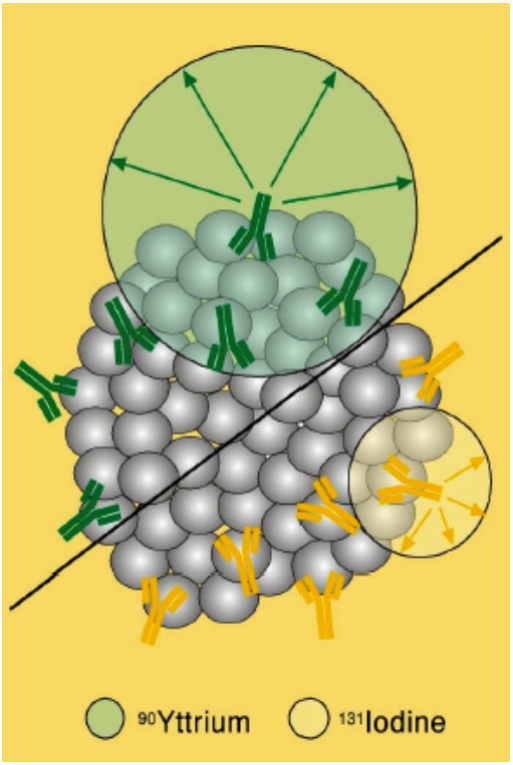
- Cold vs. Radiolabelled (hot) ‚smart molecules‘

Differences Between ‚Cold' and ‚Hot' Smart Molecules

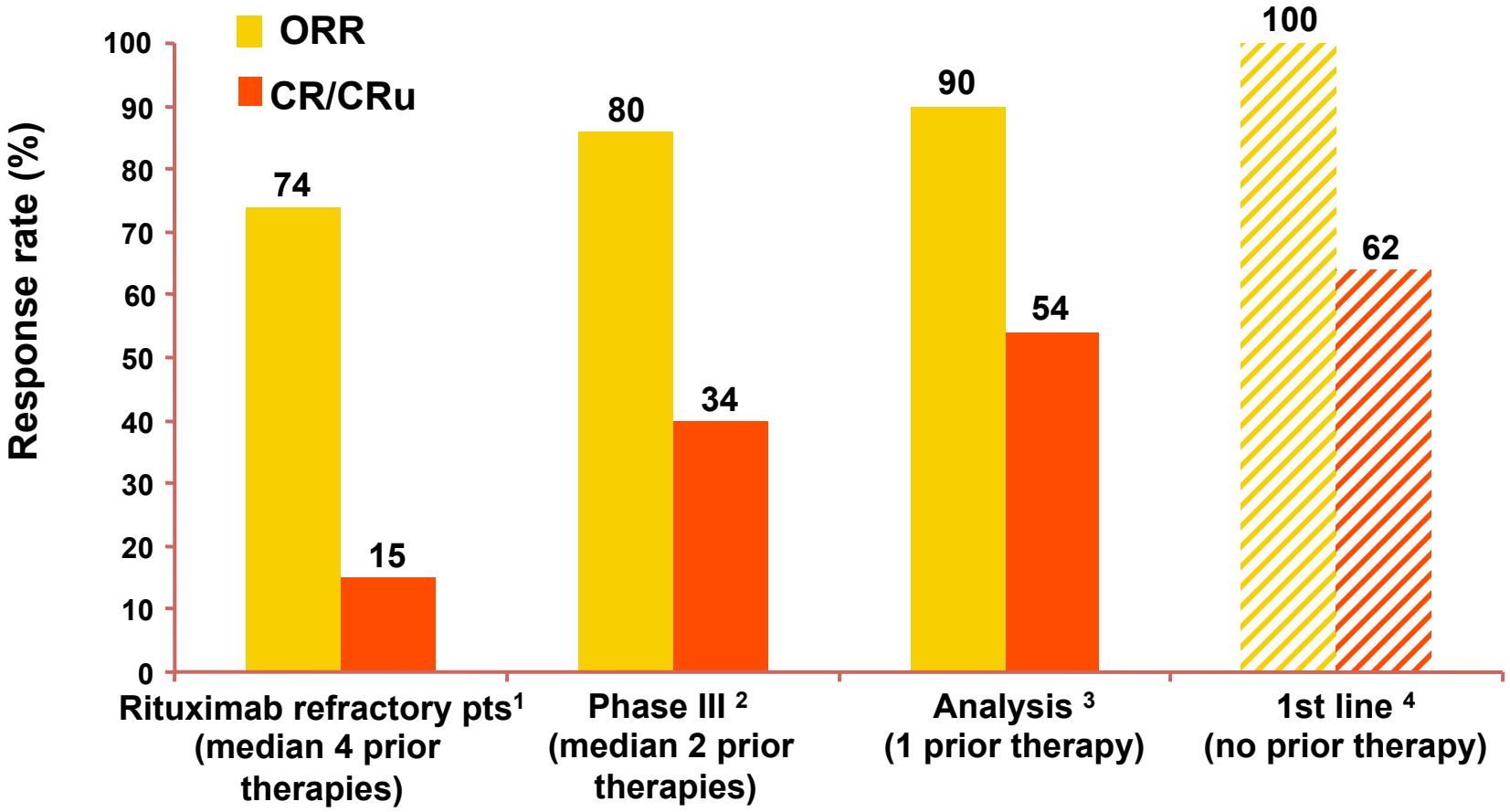
- Concentration
- Penetration
- Effectiveness
- Resistance (Tachyphylaxis)
- Toxicity

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

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

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

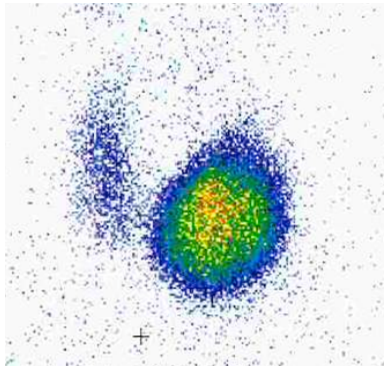
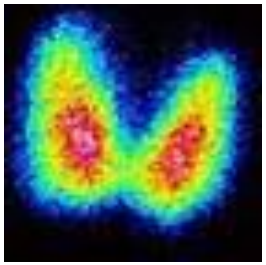
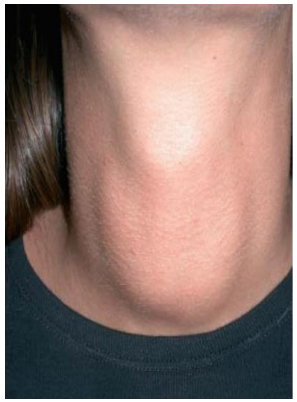
Differences Between ‚Cold' and ‚Hot' Smart Molecules
Life Threatening or Severe Toxicity

	Radionuclide Therapy	mTOR inhibitors	Tyrosine Kinase Inhibitors
MDS/Leukemia	1-3.7%; relative risk persistent hematological disorder under PRRT 3.6	-	-
Renal Insufficiency	1-2%*	-	-
Cardiopulmonary		17%**	< 1 %
Treatment Related Fatal Events	<1%	1.8%	<1%

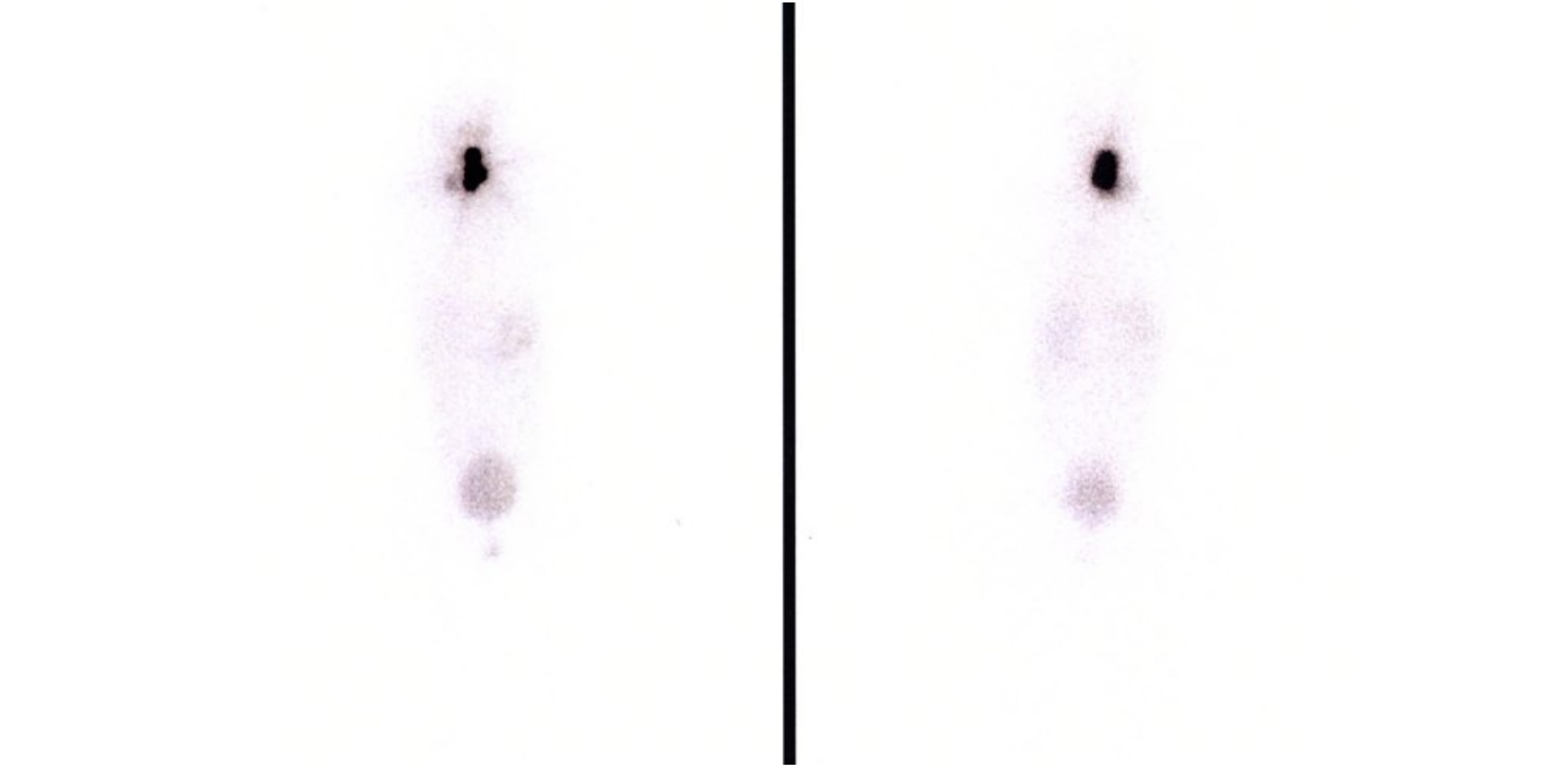
Lessons Learned #1

- Specific Targets= Success

I-131 Therapy of Benign Thyroid Diseases

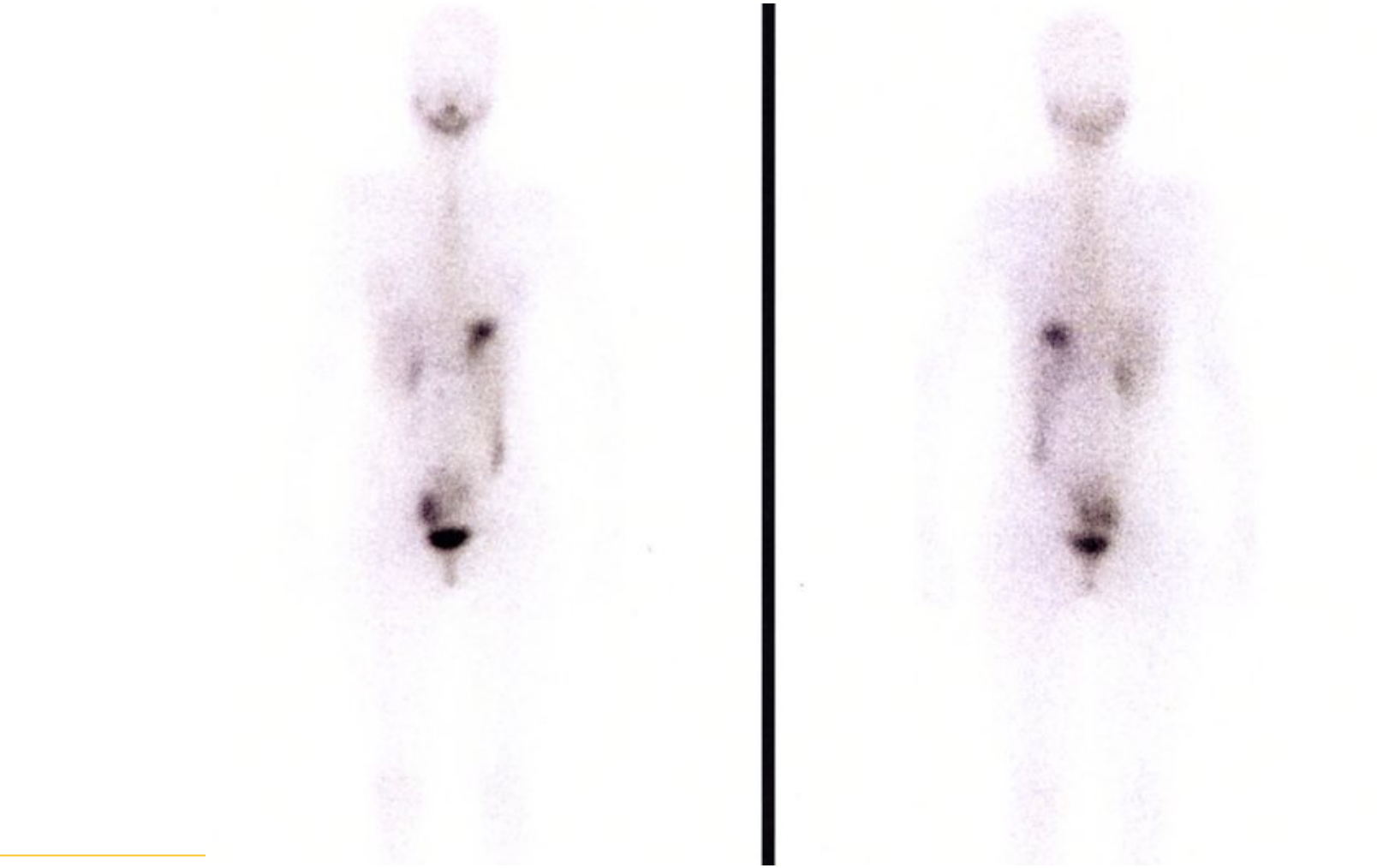
300 - 400 Gy	150 - 300 Gy	100 – 150 Gy
	 	
Focal Autonomy	Morbus Basedow / Graves Disease	Goiter

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



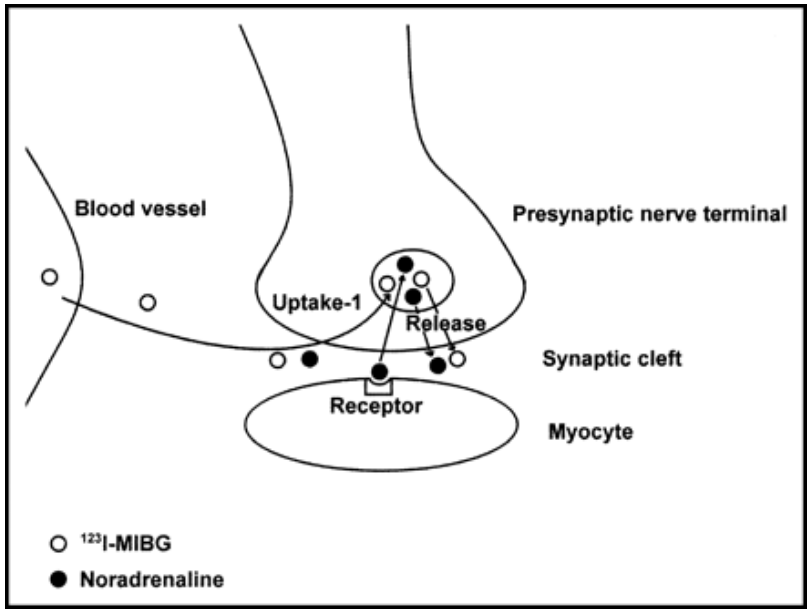
RadionuclideTherapy Of Differentiated Thyroid Cancer

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

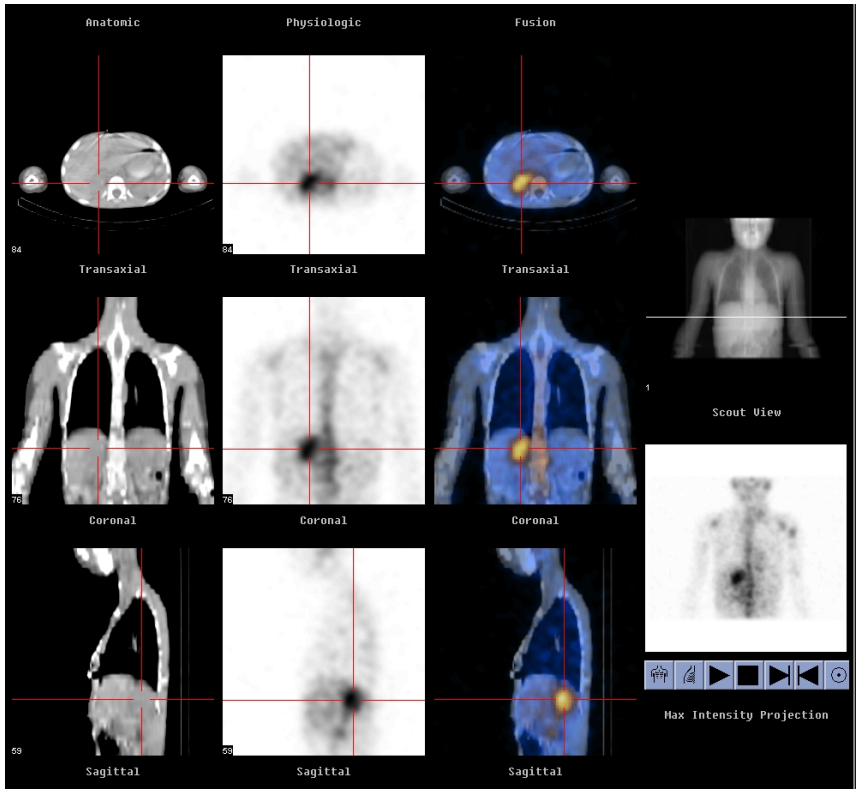


Neuroblastoma
I-123 and I-131 MIBG

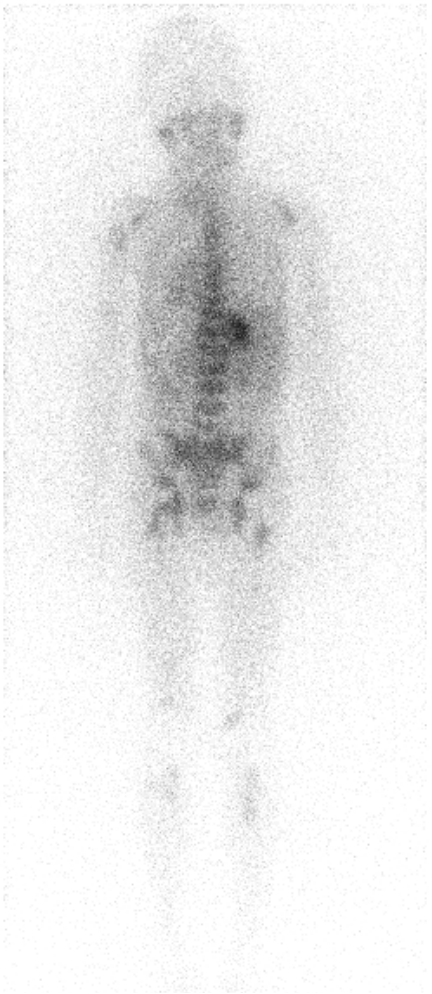
CT: Mass lesion in right adrenal gland
I-123 MIBG Scintigraphy: focal increased uptake in the mass lesion.



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

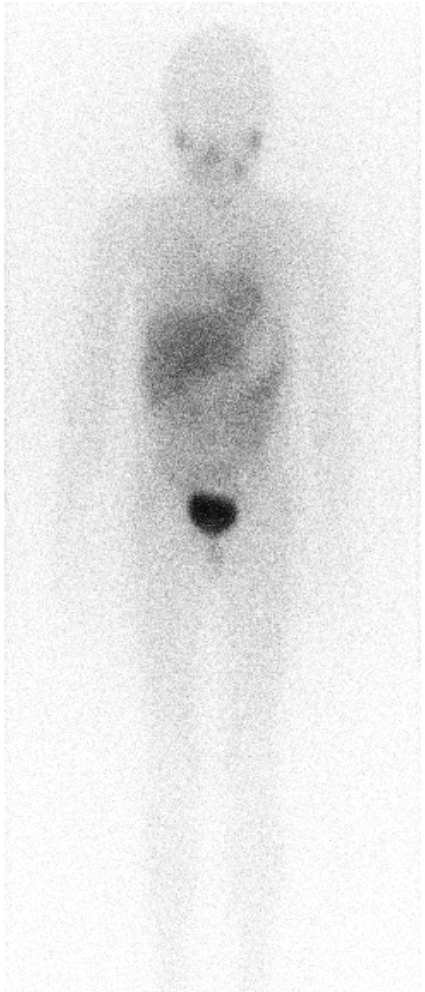


I-131 MIBG Therapy

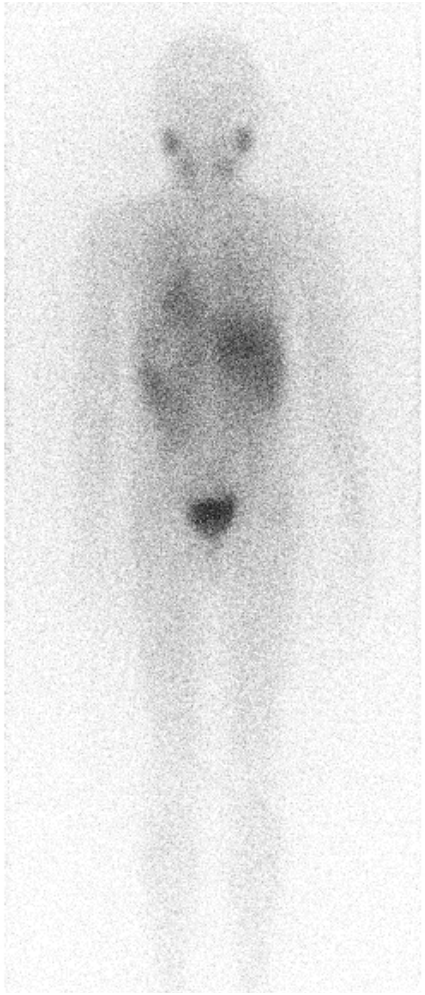


Neuroblastoma patient with disseminated bone marrow metastases

Posttherapeutic I-131 MIBG-Scintigraphy



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



Dose Limiting Factor Is
Bone Marrow Toxicity

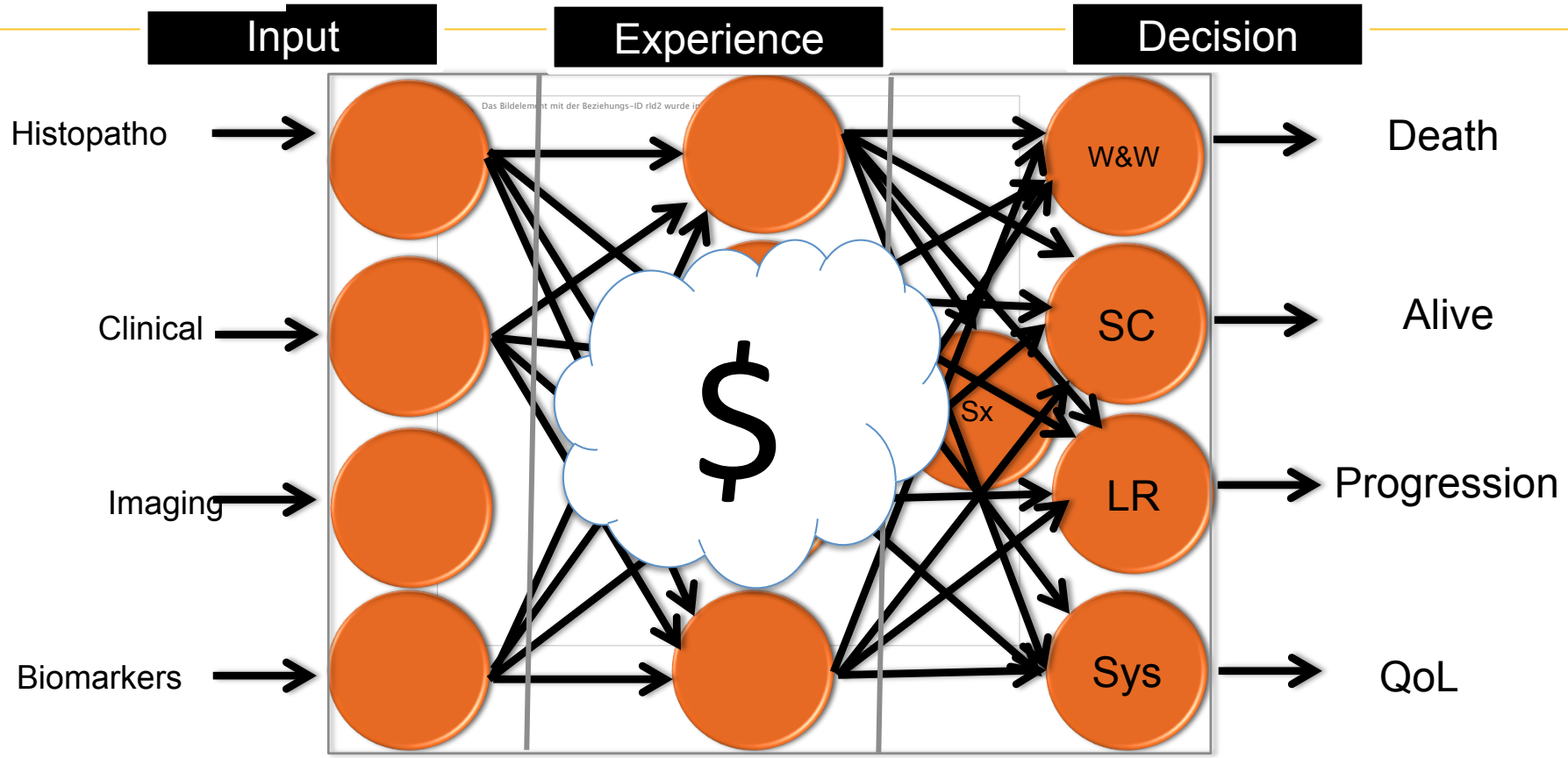
Lessons Learned # 2

- Tumor are heterogeneous = they cannot be tackled through one mechanism only

Neuroendocrine Tumor (NET)

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

Decision and Management Algorithm

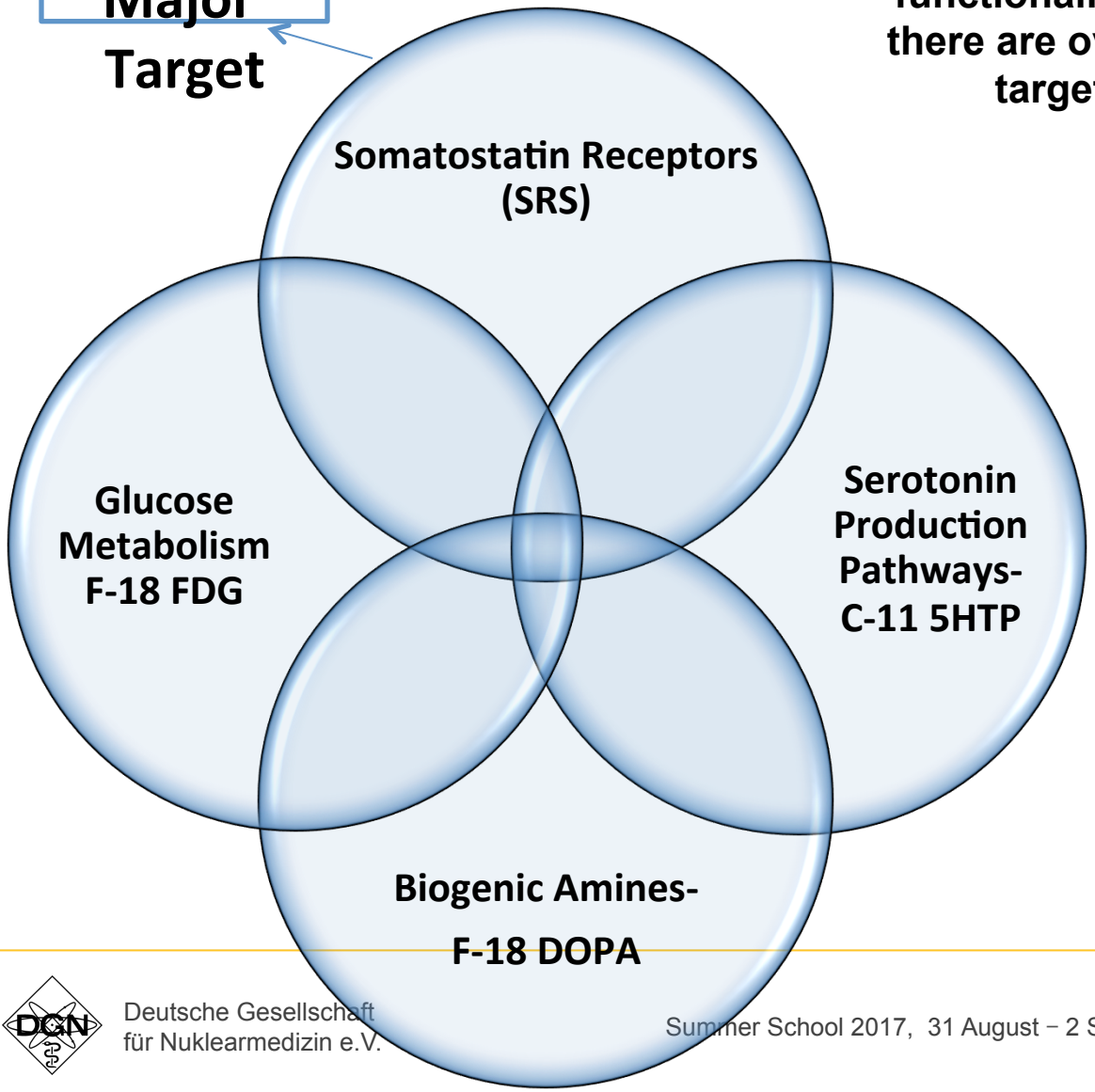


W&W = wait and watch, SC= symptom control, Sx= surgery with curative intent, LR= locoregional therapy (including debulking), Sys = systemic therapy

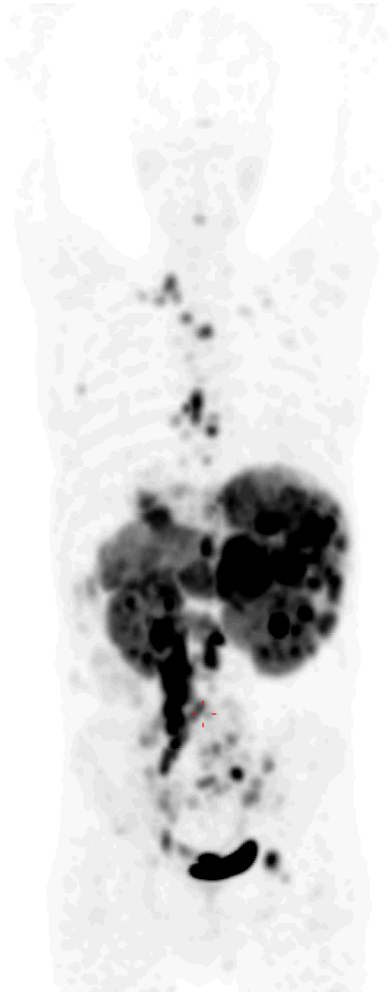
Radiopharmaceuticals-NET

Because of the heterogeneity of neuroendocrine tumors in their functionality, their origin and prognoses, there are overlapping zones amongst the targets for molecular imaging.

Major Target



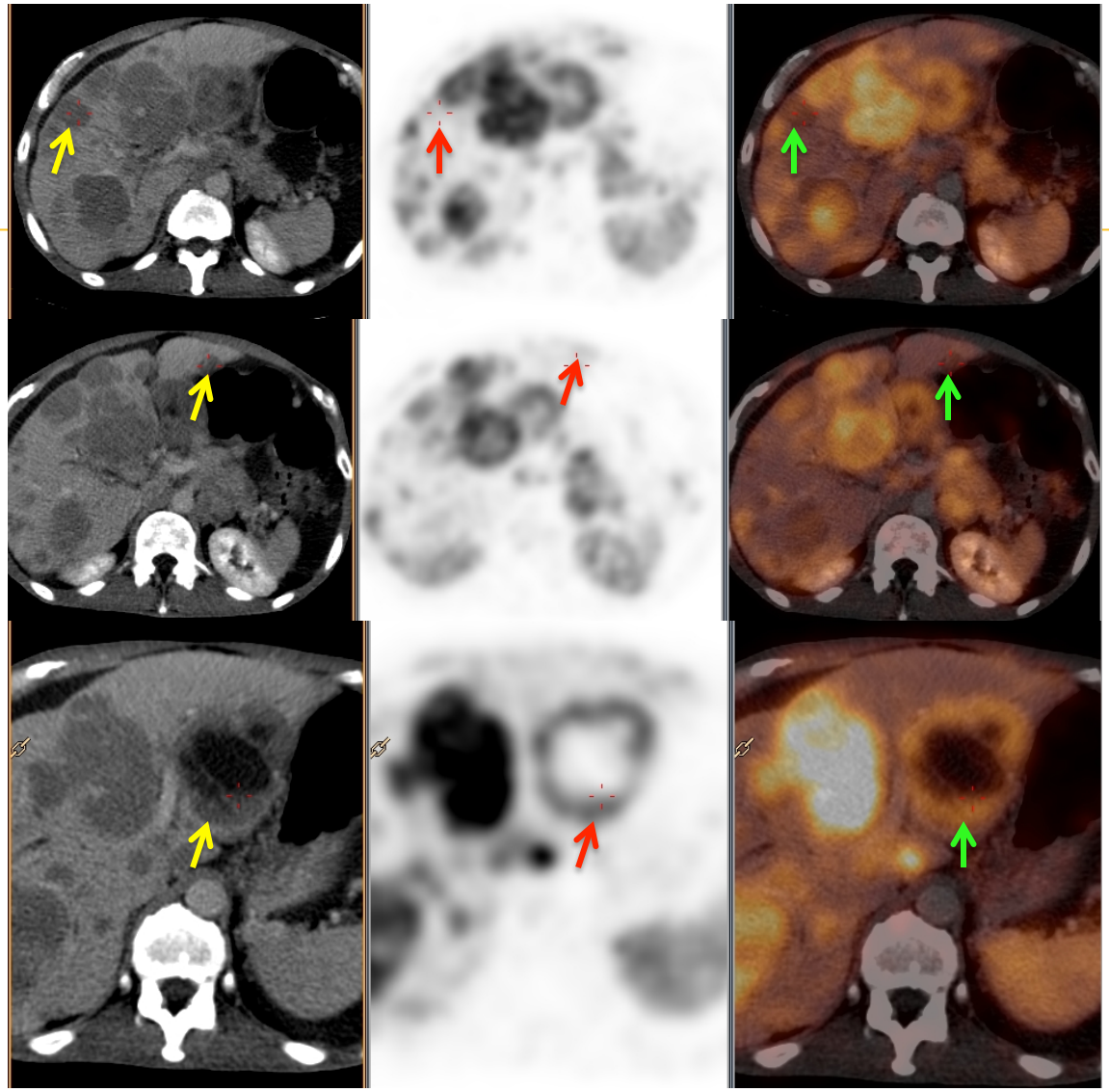
Indication for PRRT?

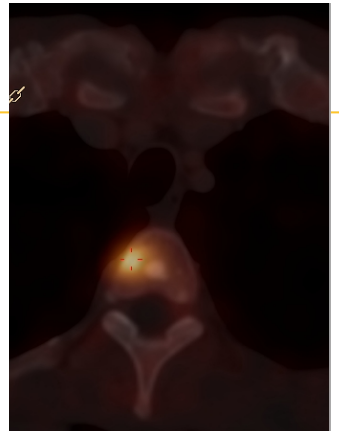


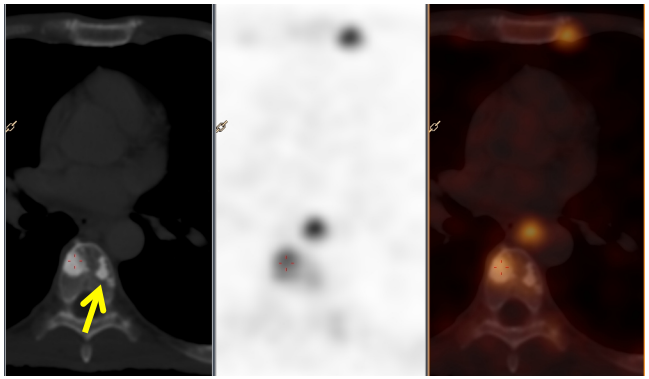
53 year / male
Resident of Cypern
pancreatic NET (Ki67 10%), KI 60%, FD 04/2012
Best response after 3 cycles of 5FU/Strepto- SD
In Cypern sutent and everolimus not available
Ga-68 DOTATATE- multiple somatostatin receptor positive lesions

According to the ENETS guidelines he is suitable for PRRT

Ga-68 DOTATATE PET/CT



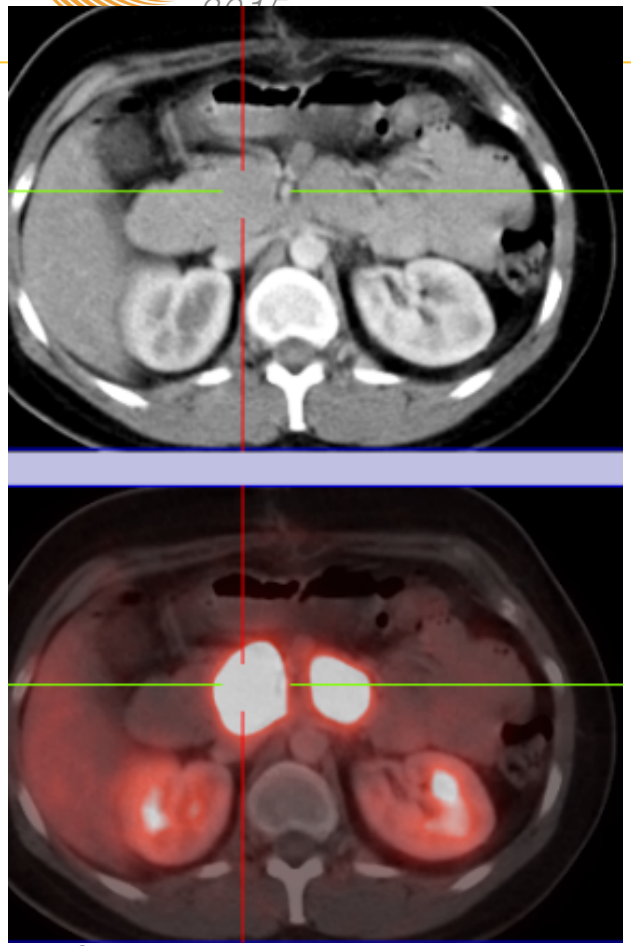




Clinically G3 (loss of 15 Kg in 6 months), glucagonoma not ruled out

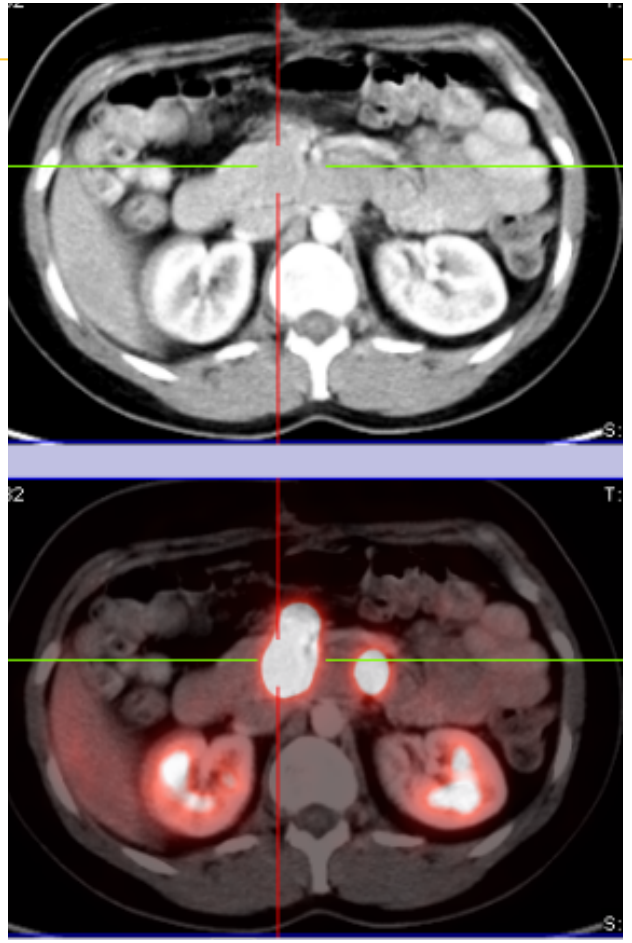
Lesions had highly heterogeneous somatostatin receptor profile

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



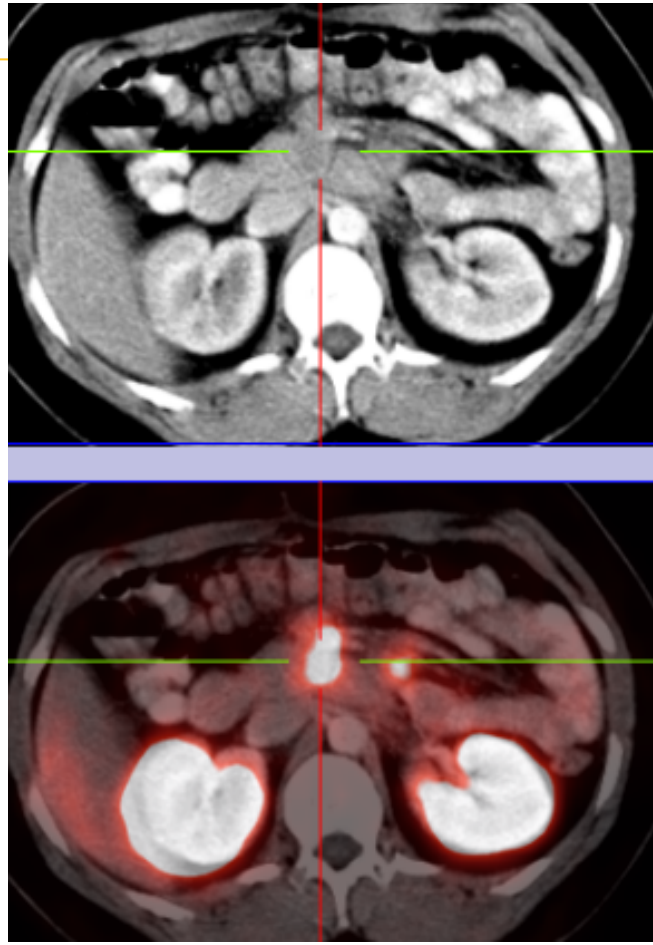
Before PRRT-1
6 GBq Y-90

Jan. 2007



Before PRRT-2
4.5 GBq Y-90

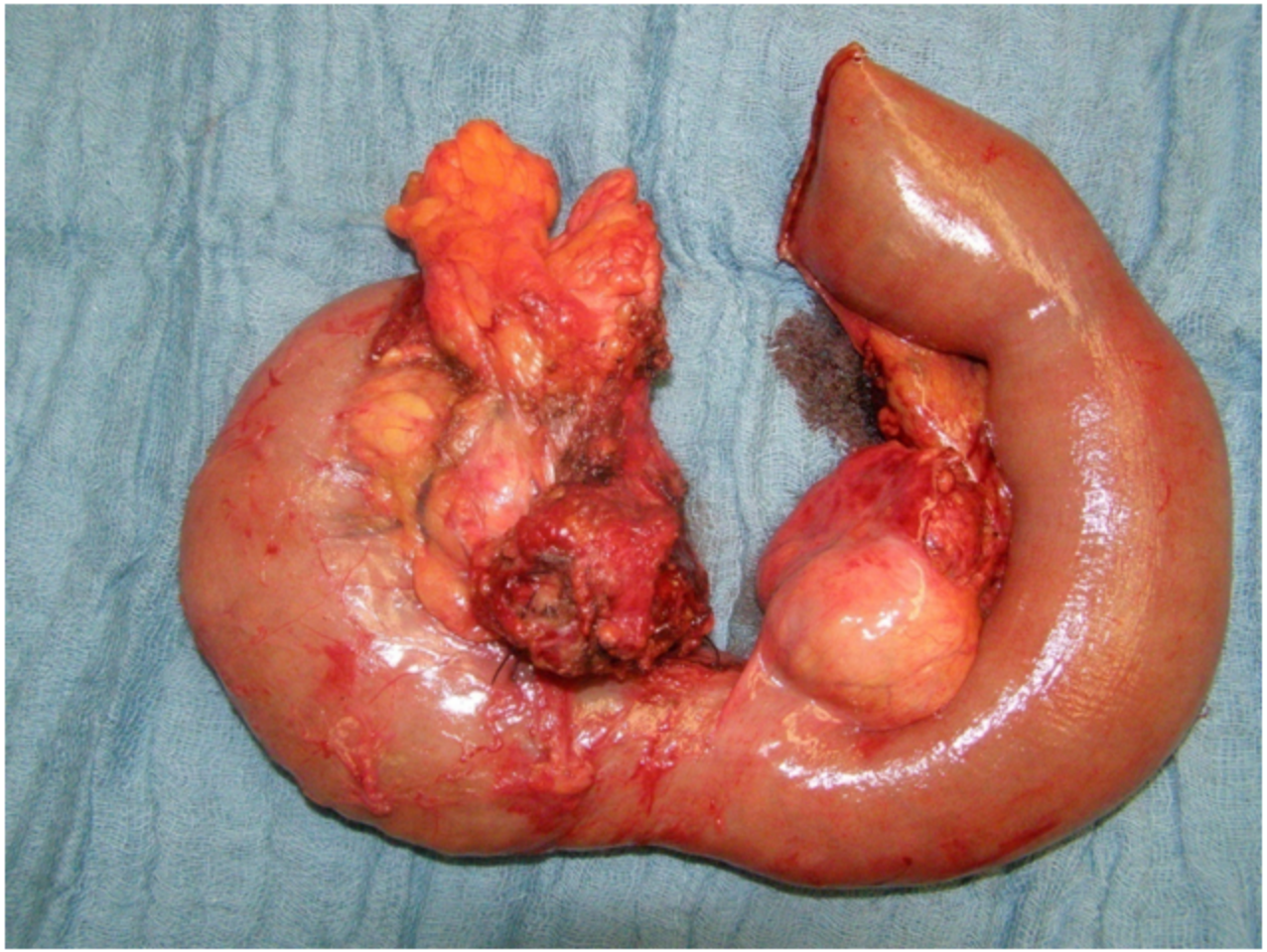
May 2007



5-mo after PRRT-2
pre Op.

Oct. 2007

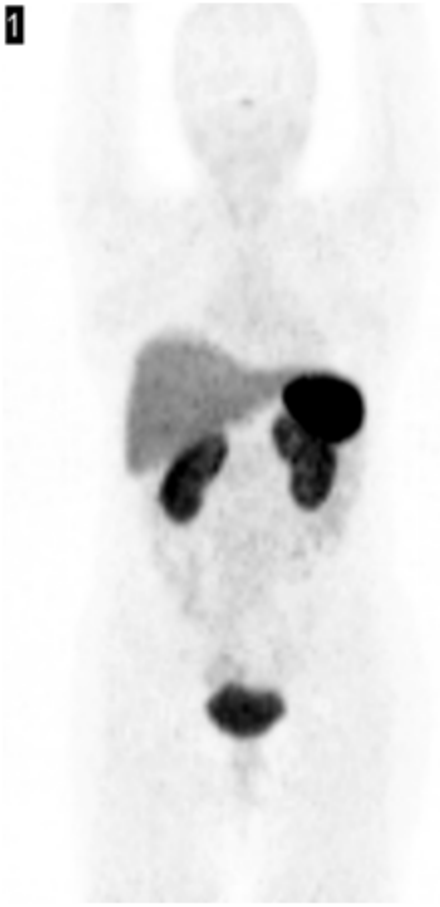
Whipple' Operation – Complete Resection of Pancreatic NET after Neoadjuvant PRRT



Histology revealed nearly total tumor necrosis typical for radiation necrosis

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

1



Follow up at 48 months – complette remission

Progression-Free Survival

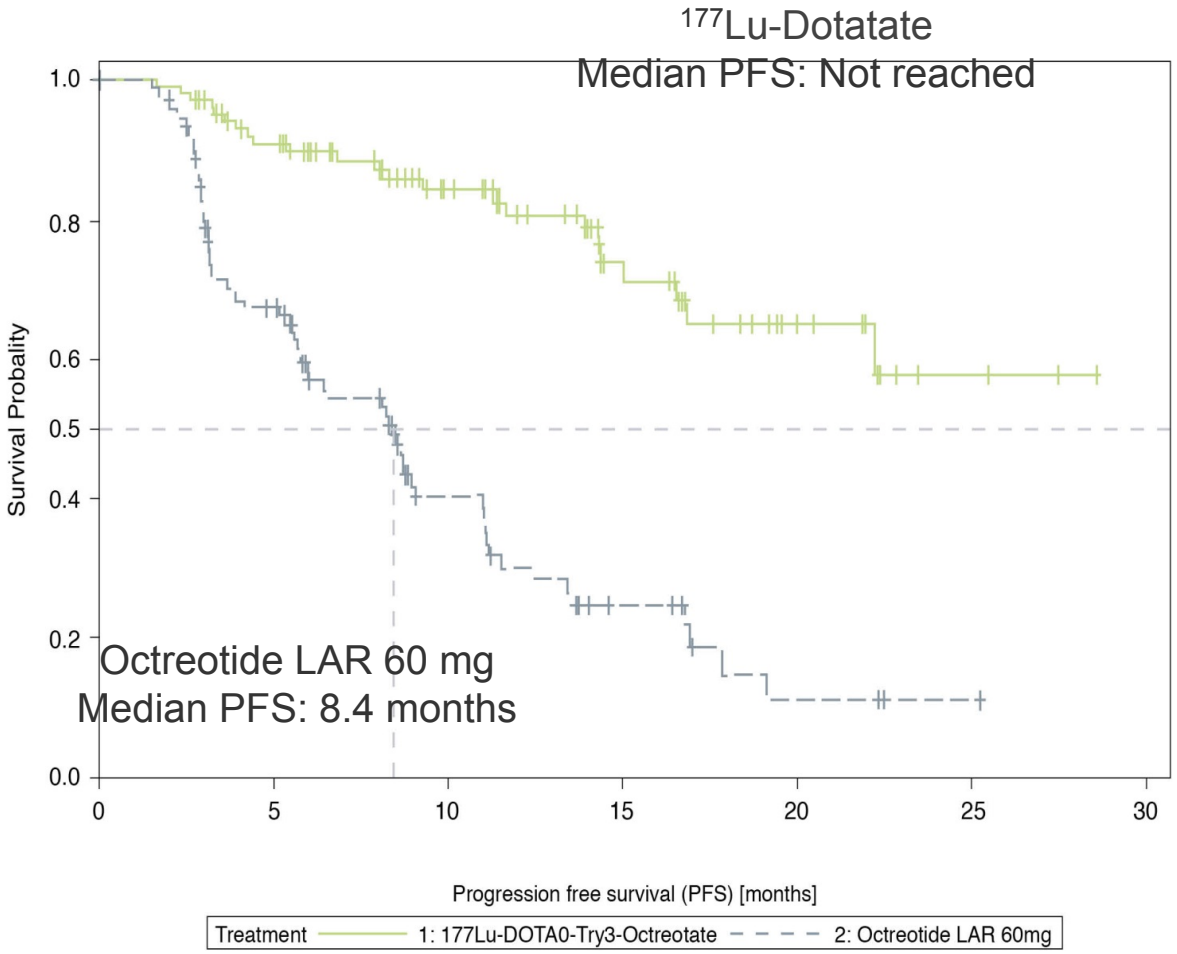
N = 229 (ITT)
Number of events: 90

- ^{177}Lu-Dotatate: 23
- Oct 60 mg LAR: 67

Hazard ratio : **0.21** [0.129 – 0.338] **p < 0.0001**

79% reduction in the risk of disease progression/death

Estimated Median PFS in the Lu-DOTATATE arm
≈ 40 months



All progressions centrally confirmed and independently reviewed for eligibility (SAP)

Slides Dr. J Strosberg
N Engl J Med. 2017 Jan 12;376(2):125-135. doi: 10.1056/
36

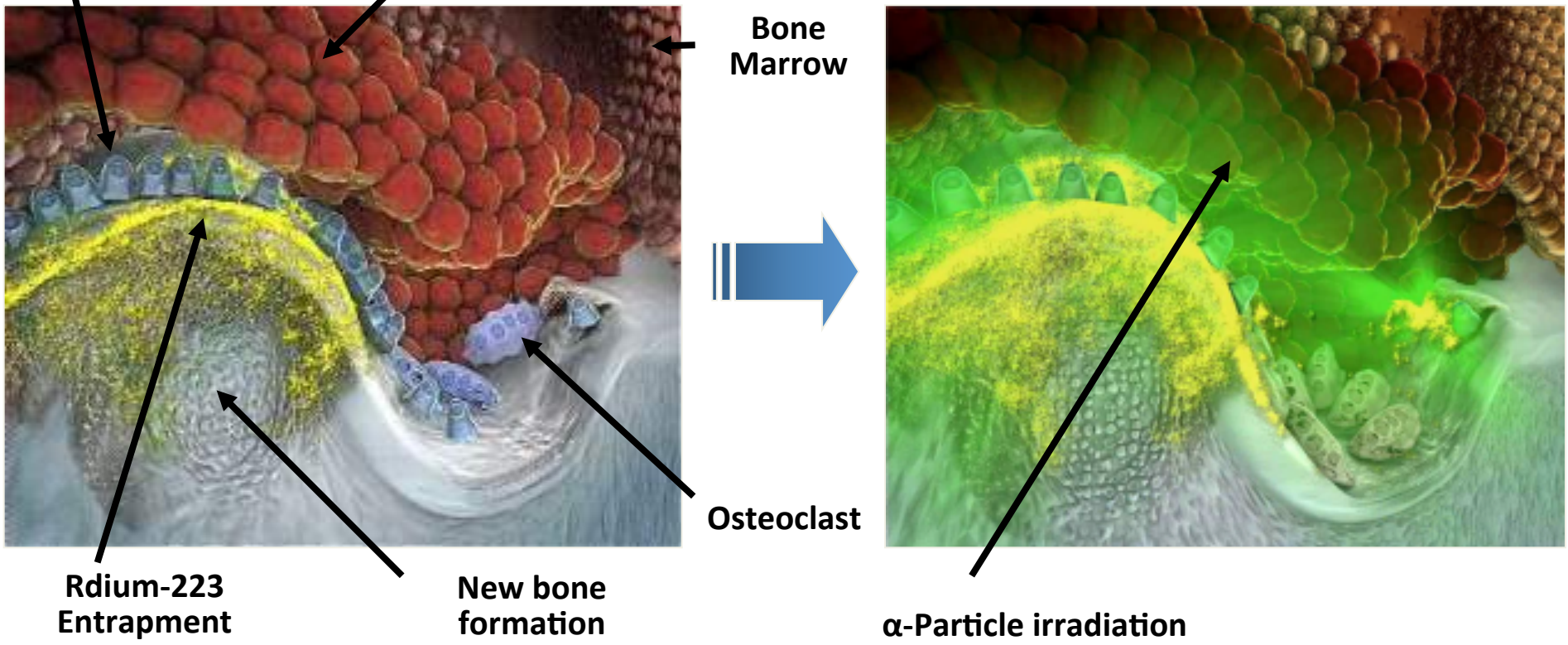
Lessons Learned # 3

- Radionuclide therapy works even when other therapies are not effective anymore.

Prostate Cancer
Ra-223 Working Principle

Actively taken up in area of new bone formation

Irradiates nearby tumor cells → high energy transfer



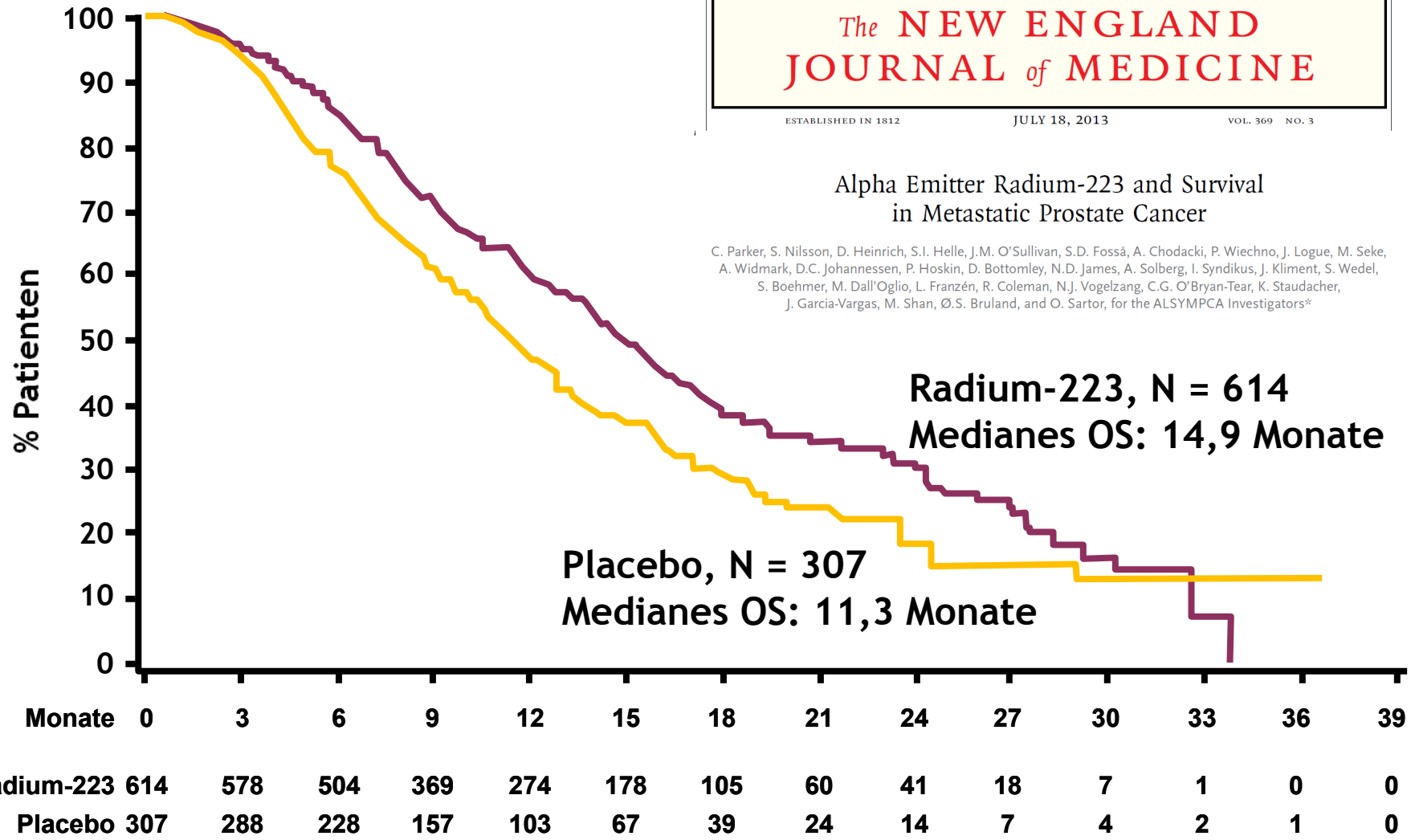
Bruland OS, et al. Clin Cancer Res. 2006;12(20):6250s–57s

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

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 JULY 18, 2013 VOL. 369 NO. 3

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*



Monate	0	3	6	9	12	15	18	21	24	27	30	33	36	39
Radium-223	614	578	504	369	274	178	105	60	41	18	7	1	0	0
Placebo	307	288	228	157	103	67	39	24	14	7	4	2	1	0

HR = 0,695, p = 0,0007

Parker C, et al. ASCO 2012 LBA4512.

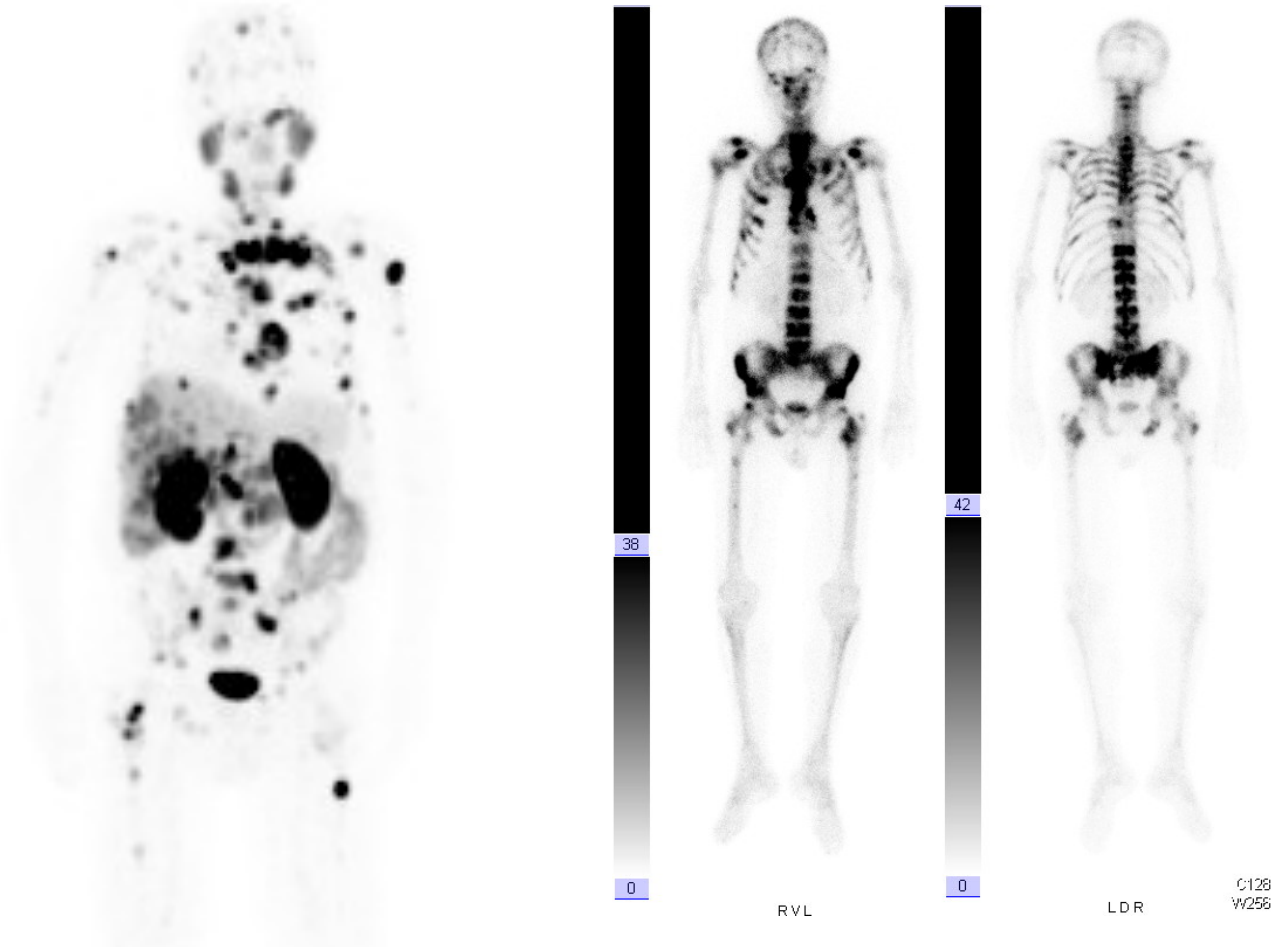
Prostate Cancer Response To Ra-223

Before recruitment in ALSYMPCA Studie

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

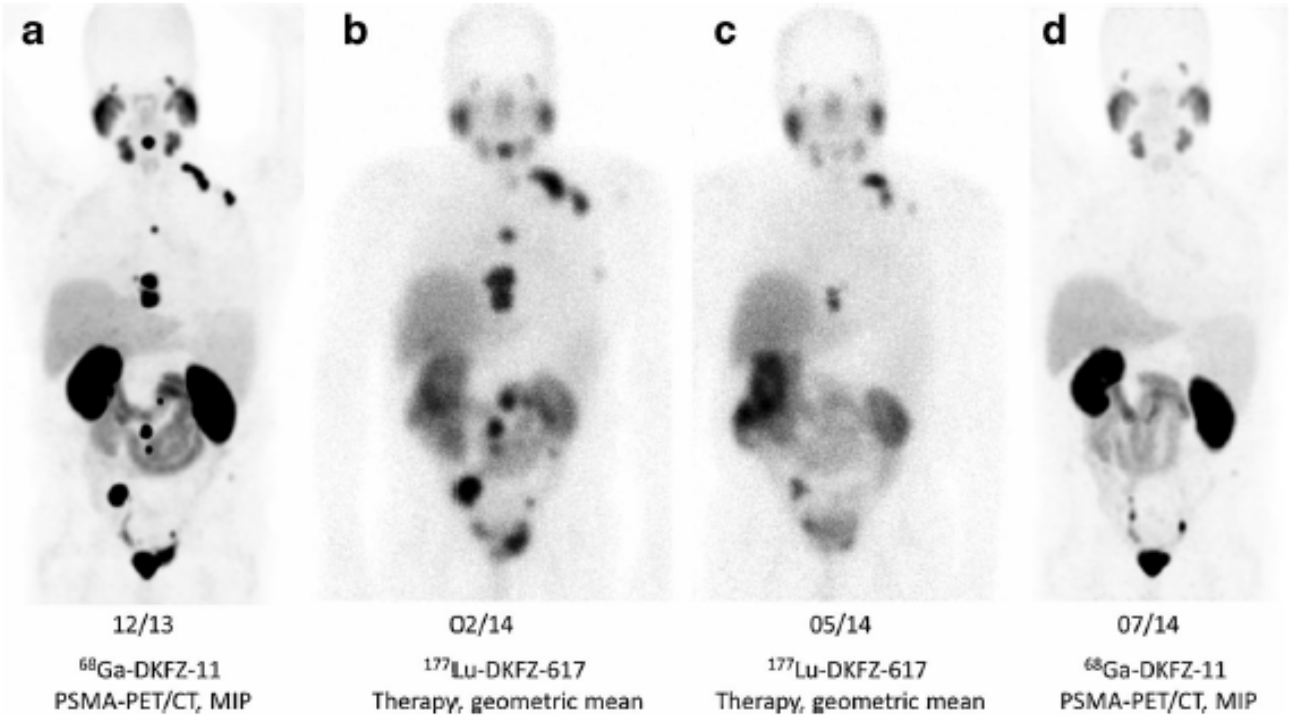
PSMA PET and Therapy

Patient with multiple bone metastases and PSA 660 ng/dl referred for the evaluation of Lu-177 PSMA therapy. Ga-68 PSMA PET/CT showed not only disseminated bone lesion but also liver and lymph node lesions. Patient was progressive under all standard therapy including chemotherapy



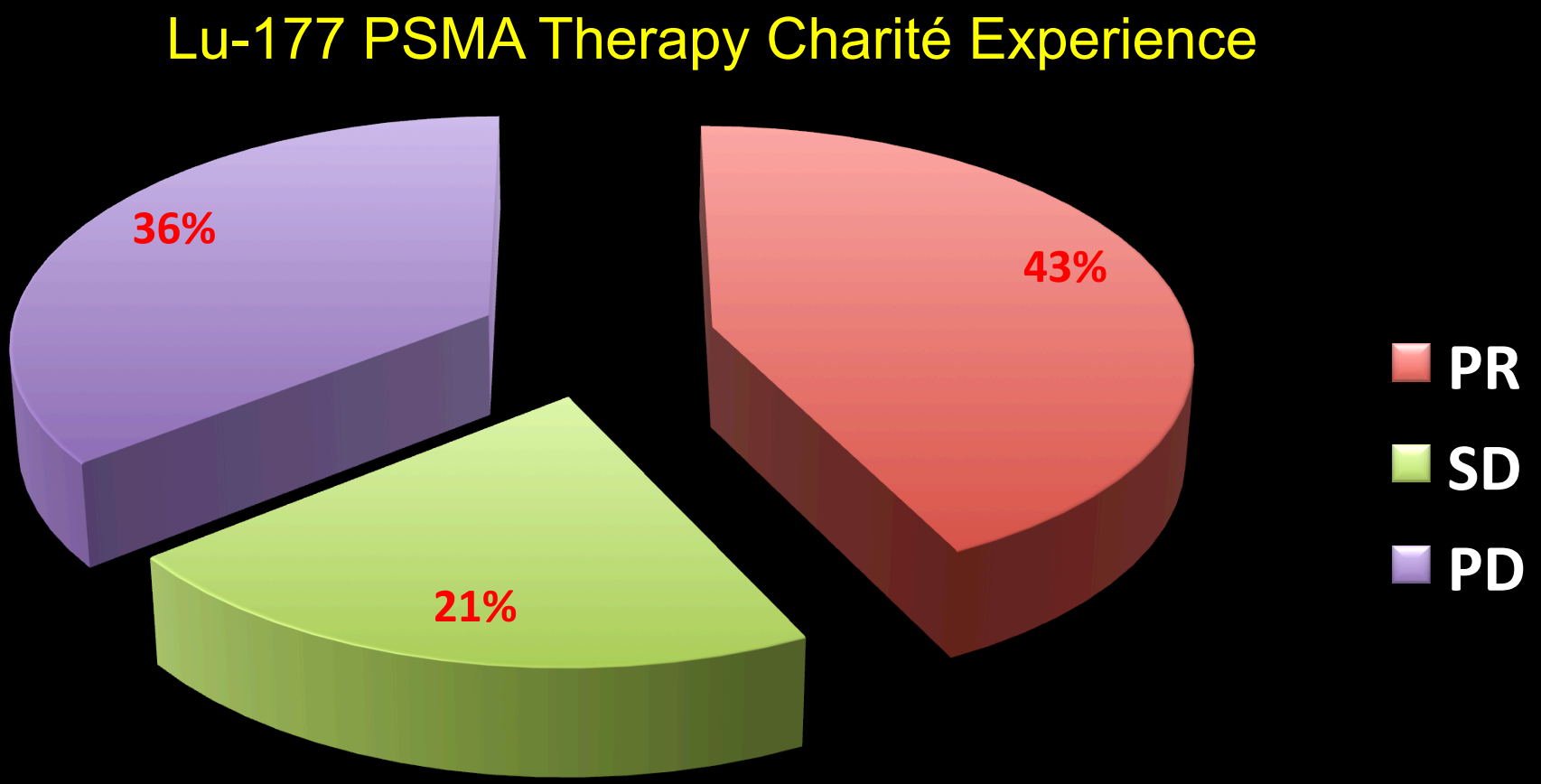
[^{177}Lu]Lutetium-labelled PSMA ligand-induced remission in a patient with metastatic prostate cancer

Clemens Kratochwil · Frederik L. Giesel · Matthias Eder · Ali Afshar-Oromieh · Martina Benešová · Walter Mier · Klaus Kopka · Uwe Haberkorn

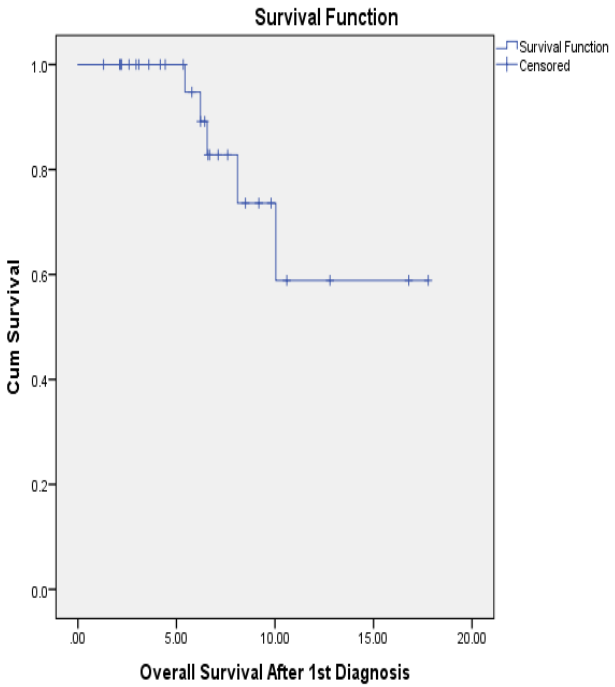


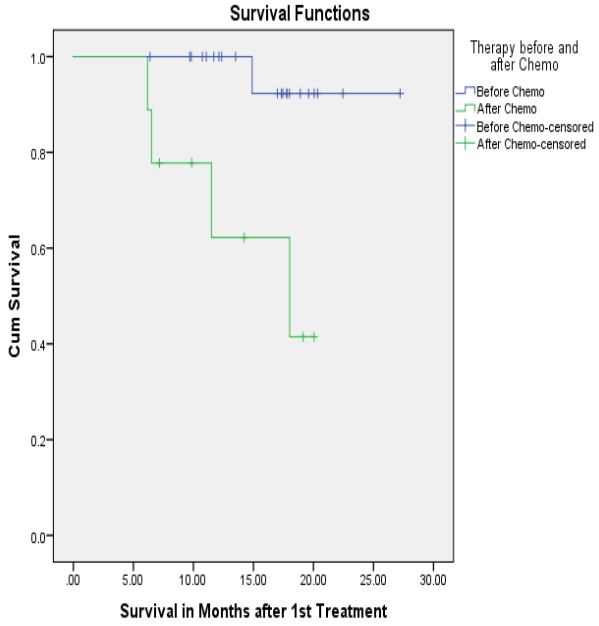
Eur J Nucl Med Mol Imaging

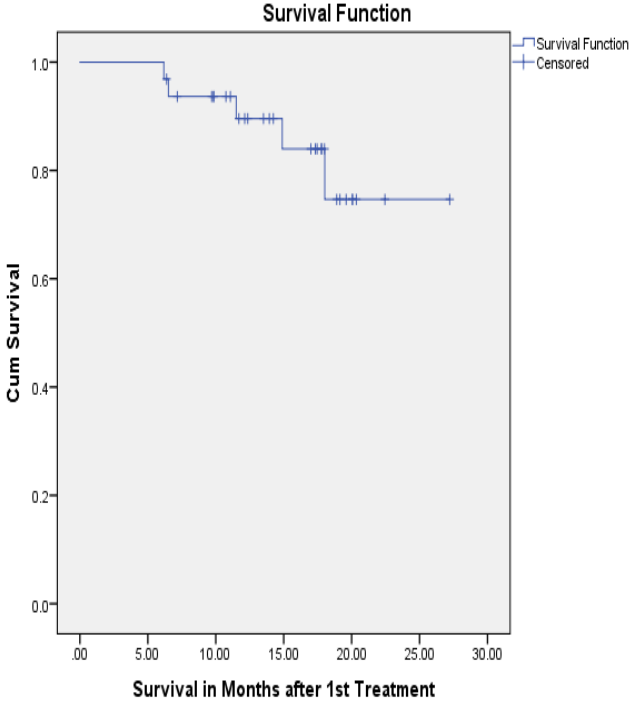
Image Based Response after 2nd Cycle (N=28)



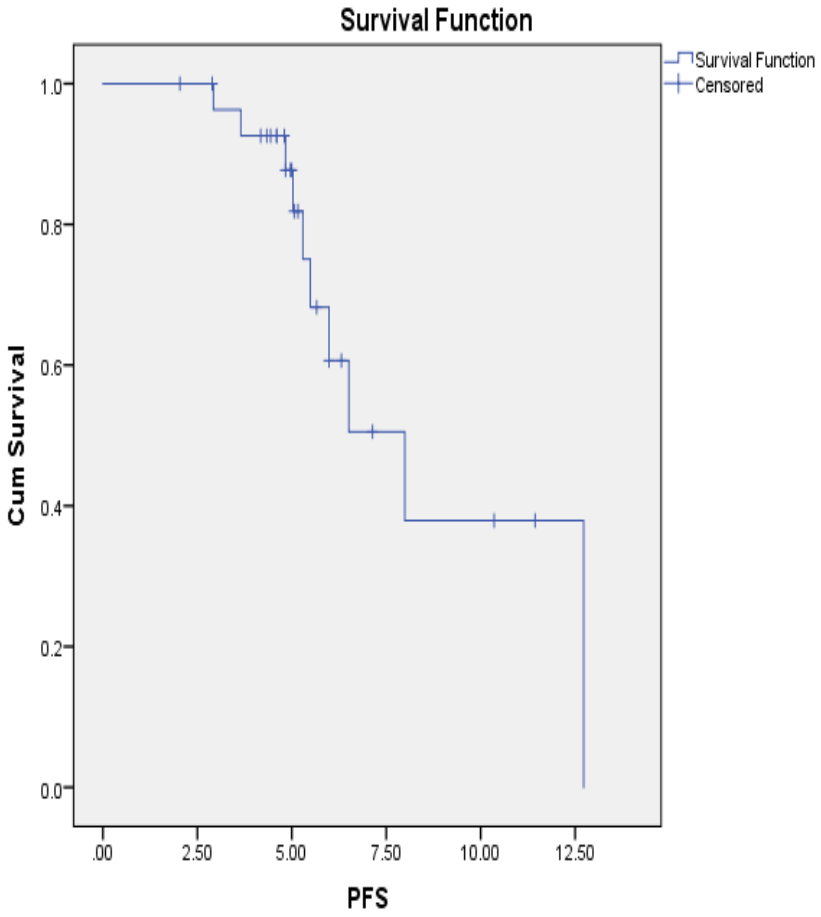
Lu-177 PSMA Therapy Charité Experience

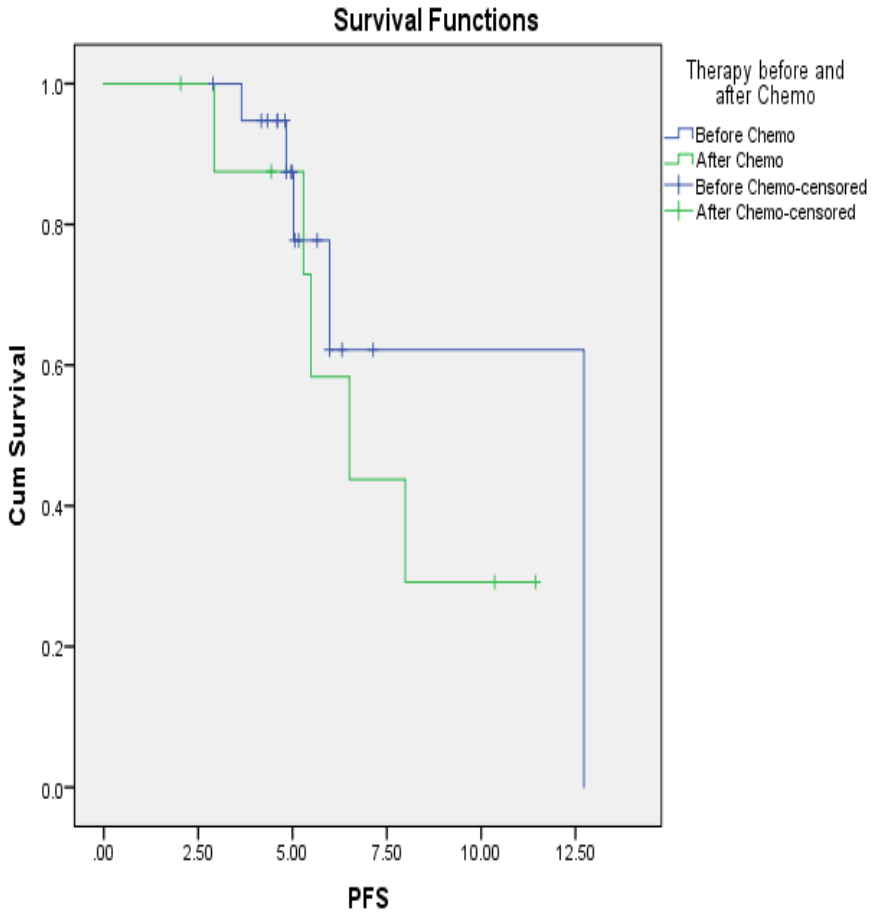






Lu-177 PSMA Therapy Charité Experience

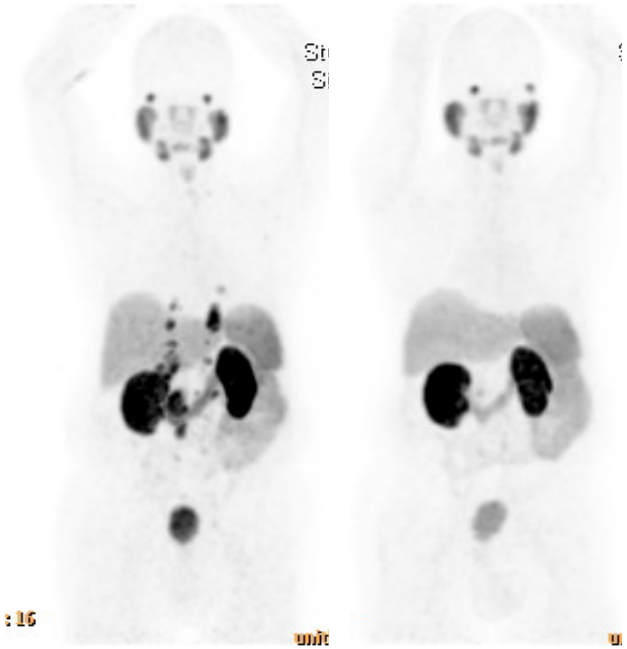




Lu-177 PSMA Therapy Charité Experience

09/2015 Pre therapy PET

02/2016 post therapy PET

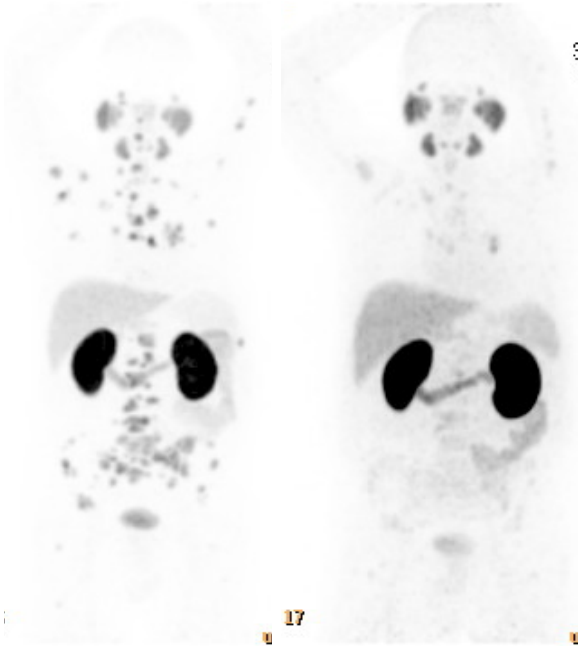


PSA 46.43

PSA 1.36

09/2015 Pre therapy PET

02/2016 post therapy PET



PSA 138.4

PSA 2.45

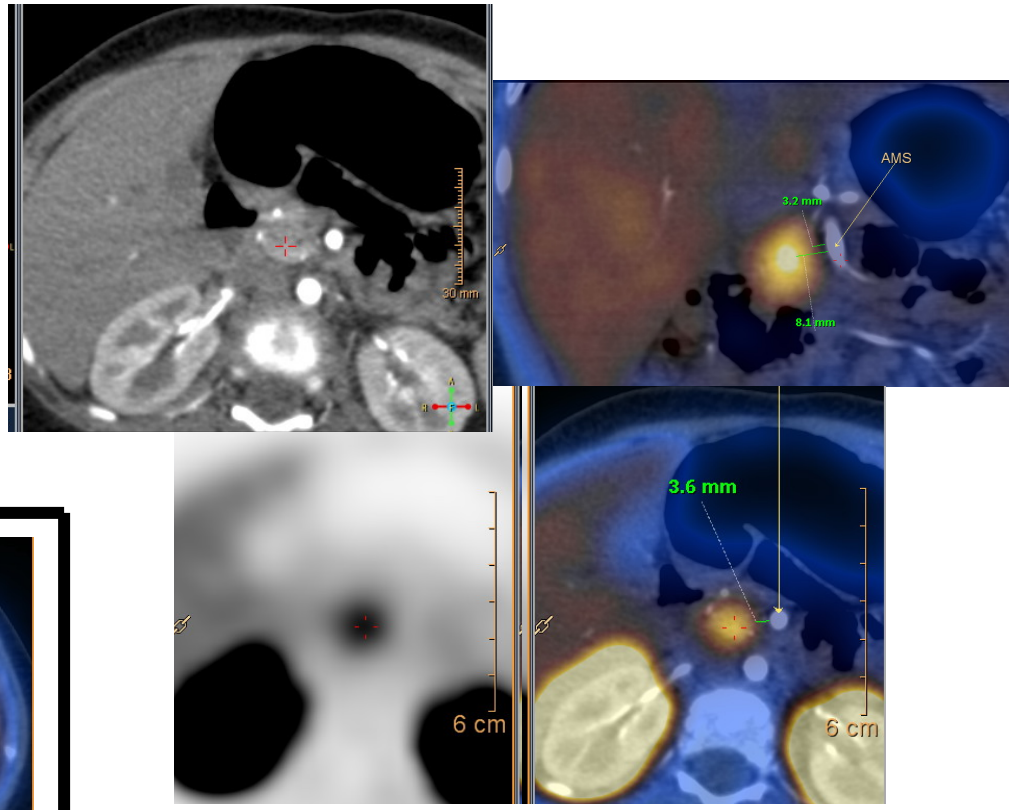
Other Areas of Theranostic Applications of Radionuclide Probes

- Radioguided Surgery
- Photodynamic Therapy (e.g. BetaCure EU Project)
- Drug Development

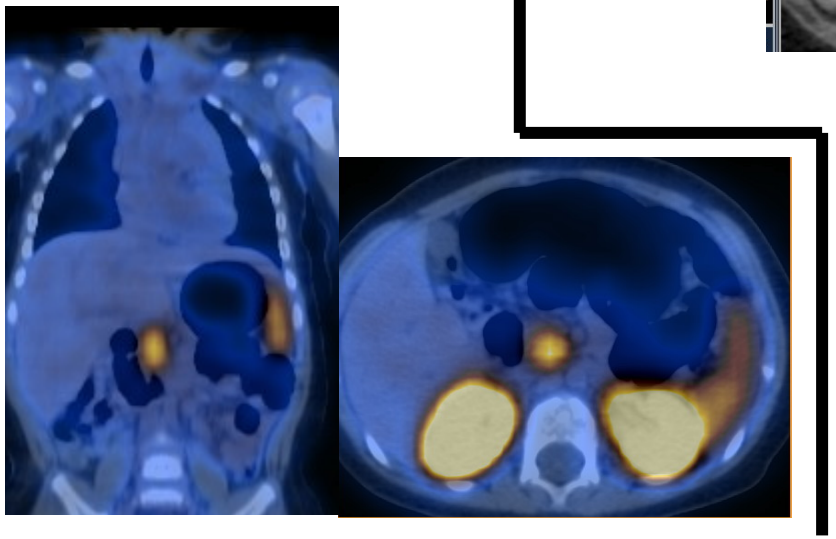
Radioguided Surgery In Congenital Hyperinsulinism Can Reduce The Surgery Time

- 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



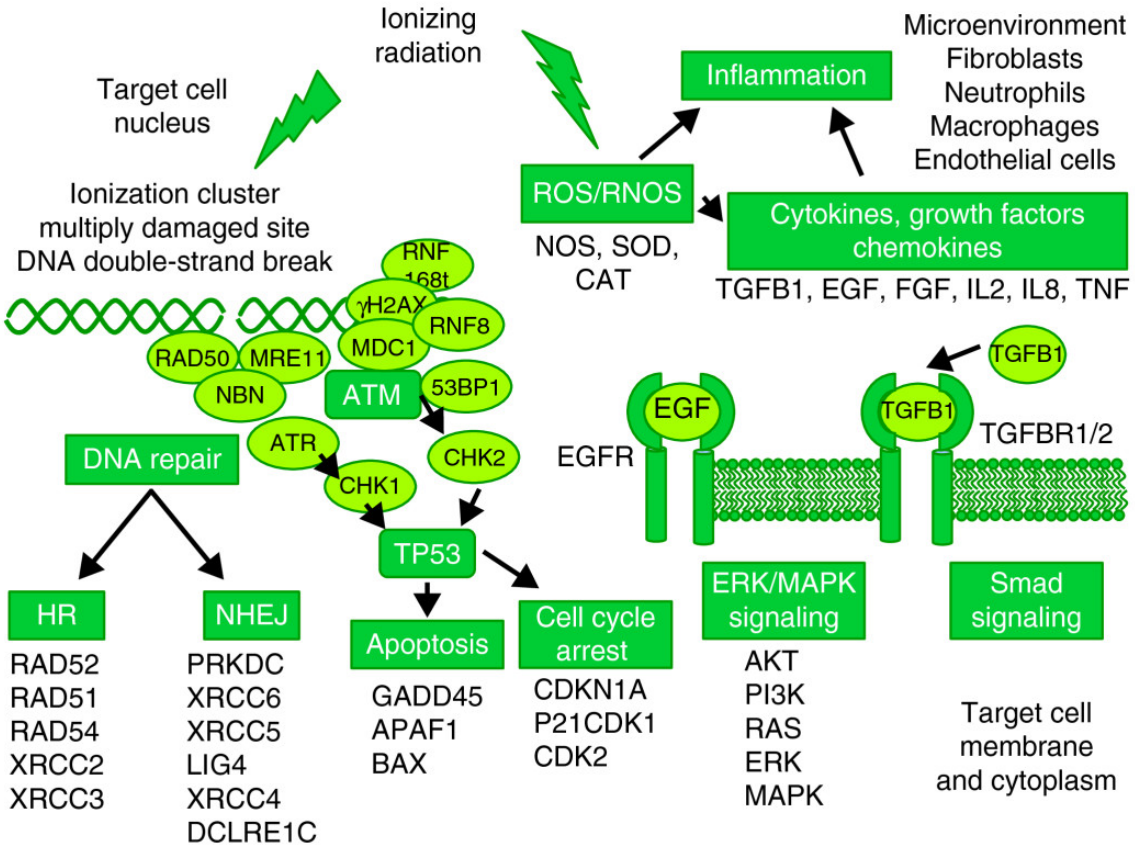
Ga68DOTATOC PET/CT



Future

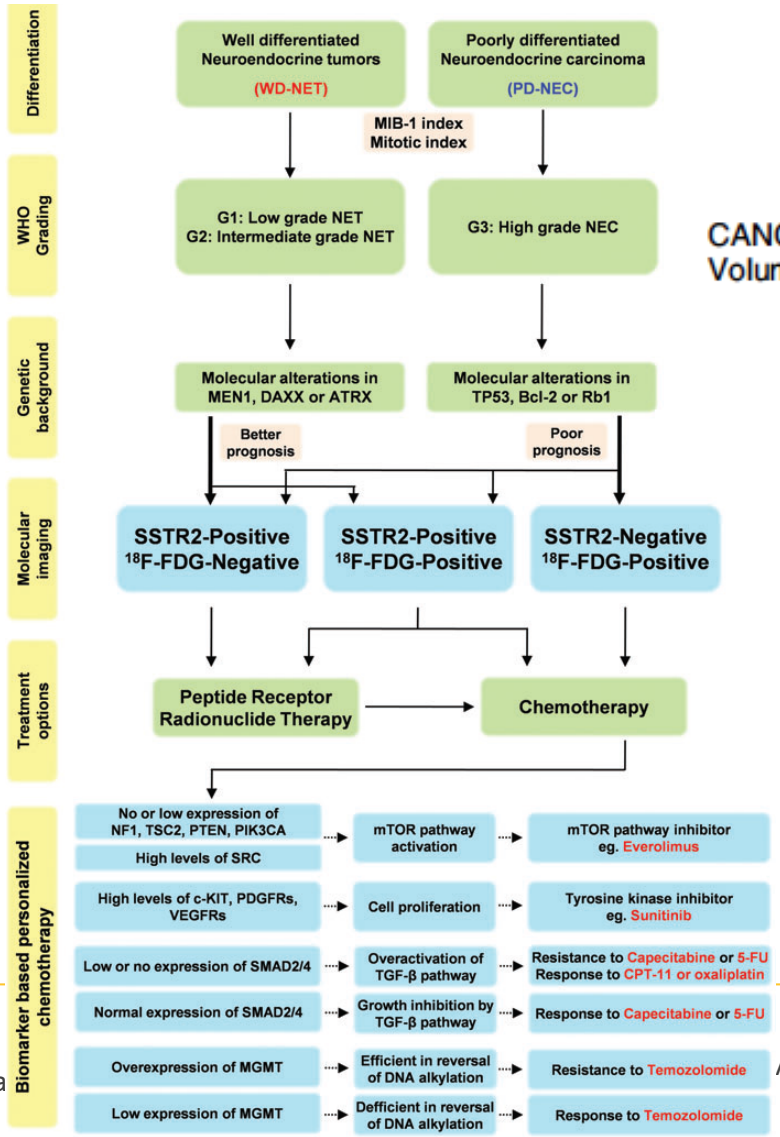
- Avoid tunnel view and open up for interdisciplinary approach combining several therapy options (cocktail)
- Combine genetic information to outsmart the evolved cancer cells from getting resistant
- Data mining using artificial neuronal networking (MIBG, NETTest)
- Think beyond.....

Summary of The Pathways and Mechanisms Involved in Cell and Tissue Response to Radiotherapy



Genome Medicine 2011 **3**:52

Correlating and Combining Genomic and Proteomic Assessment with *In Vivo* Molecular Functional Imaging: Will This Be the Future Roadmap for Personalized Cancer Management?



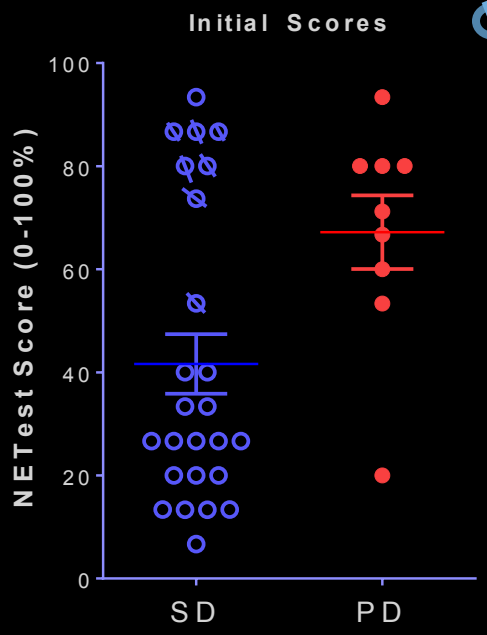
Bhakti Basu[1] and Sandip Basu[2]

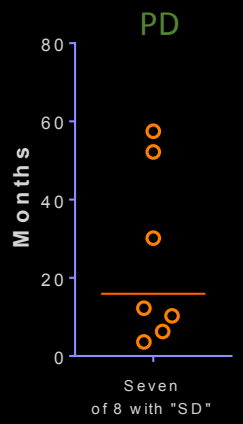
CANCER BIOTHERAPY AND RADIOPHARMACEUTICALS
Volume 31, Number 3, 2016

Long-term role of NETest scores

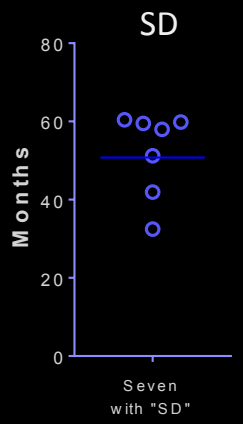
Stable to disease progression

- Seven of eight SD with high disease activity developed disease progression





3.6-54 months
median 12.2 months



33-60 months
median 58 months

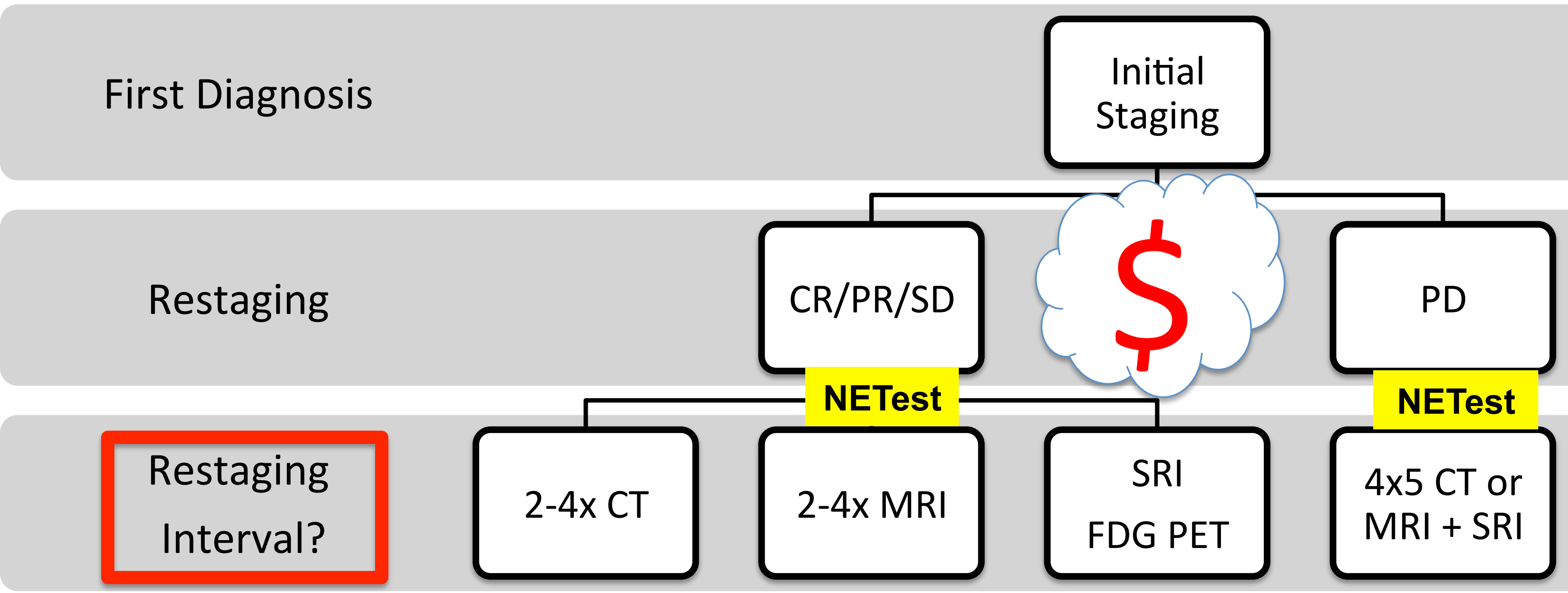
Elevated NETest activity can predict clinical status

Slide Dr. Mark Kidd

Neuroendocrinology. 2016 Apr 15. [Epub ahead of print]

Rough estimate of radiation burden and cost of follow-up of G1 and low grade G2 (Ki67 < 10%) NET

G1-G2 GEP NET PFS under standard therapy 18-40 months
Radiation Exposure: worst case scenario i.e. PFS of 18 months (100-150mSv)
Cost of Imaging alone: approximately 6.000 -10.000 Euro/ Year



A Delphic Consensus assessment: Imaging and Biomarkers in Neuroendocrine Tumor Disease Management
Accepted for Publication in Endocrine Connections; Impact Factor 4.498

Oberg K, Krenning E, Sundin A, Bodei L, Kidd M, Tesselaar M, Ambrosini V, Baum R, Kulke M, Pavel M, Cwikla J, Drozdov I, Falconi M, Fazio N, Frilling A, Jensen R, Klaus K, Korse T, Kwekkeboom D, Maecke H, Paganelli G, Ramon S, Severi S, Strosberg J, **Prasad V**, Scarpa A, GrossmannS, Walenkamp A, Cives M, Virgolini I, Kjaer A, Modlin IM

PILLARS OF NUCLEAR MEDICINE

Mathematics

Biology

Chemistry

Physics

From Theory To Theranostics: Connecting The Dots In The Firmaments Of Nobel Prizes

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

SUMMER SCHOOL 2017

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