Current Status of SRT

Sara St. James[1] and Bonnie Clarke[2]

[1]Massachusetts General Hospital
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Illustration of internal radionuclide therapy

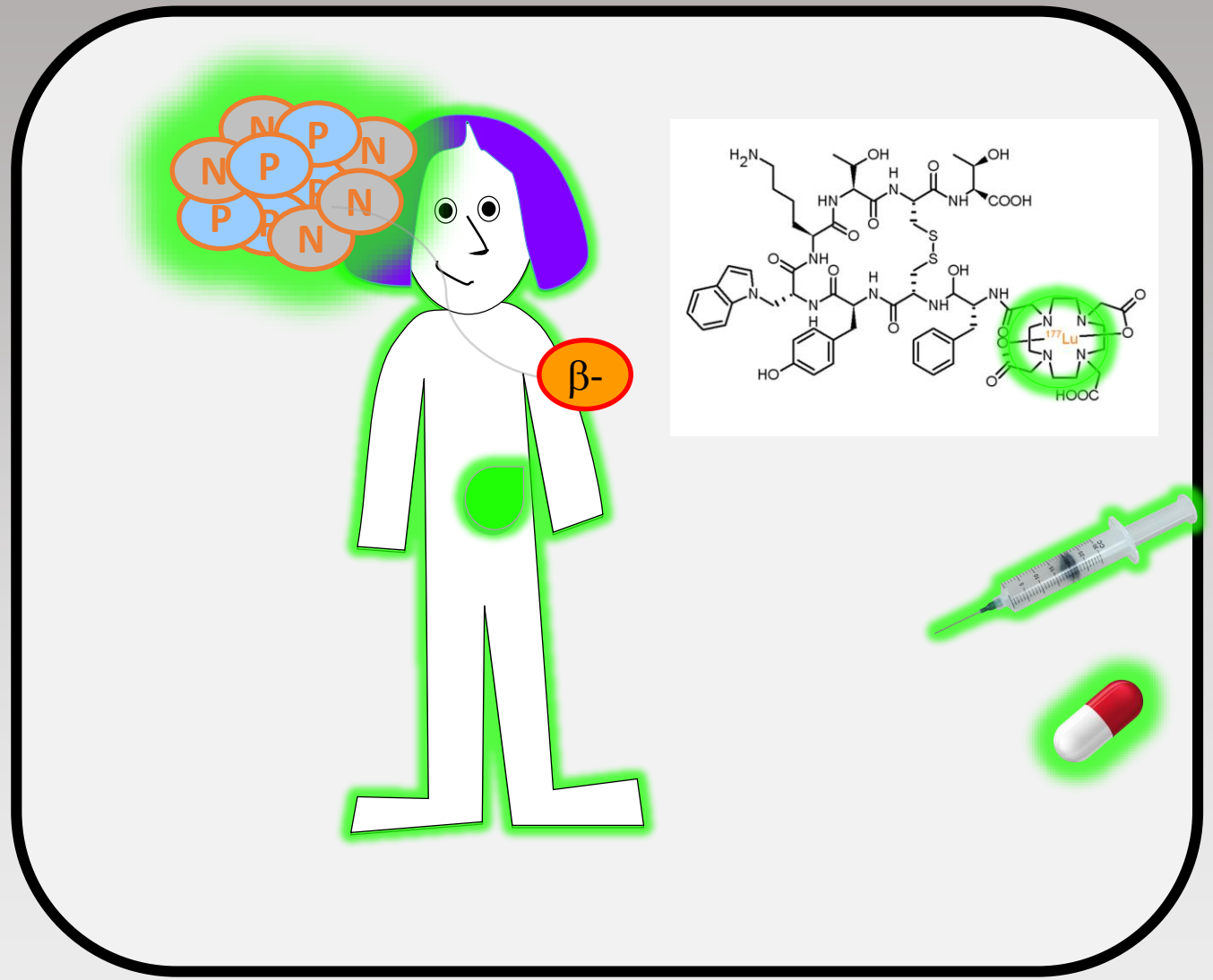
Starting with a radionuclide that decays via alpha or beta decay

The radionuclide may be conjugated to a targeting agent (e.g. small molecule, antibody)

The targeted radionuclide therapy is administered to a patient

With time, the agent has higher accumulation in the target (e.g. tumor)

Unlike conventional radiation therapy, the targeting of the radiation therapy is biologic



What is internal radionuclide therapy?

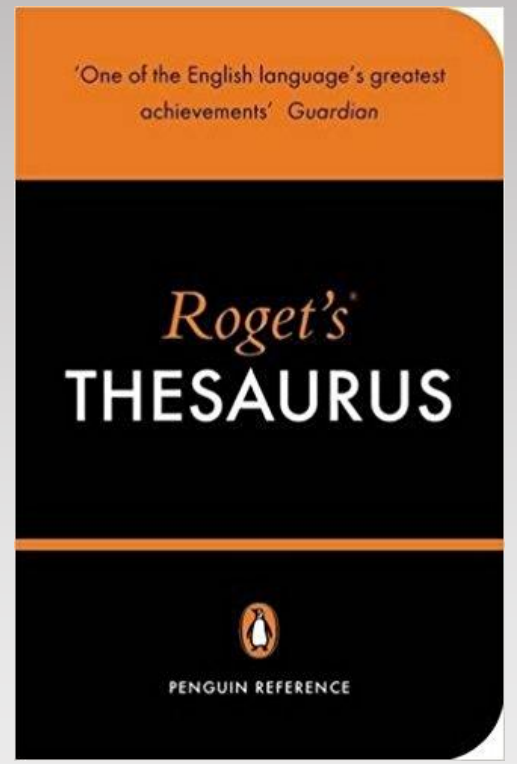
Locally delivered radiation therapy, achieved through biologic targeting....

In addition, sometimes it is called …

Systemic Radionuclide Therapy
Radionuclide Therapy
Radiopharmaceutical Therapy
Targeted Radionuclide Therapy
Molecular Radiation Therapy

and may include…

Selective Internal Radionuclide Therapy
Peptide Receptor Radionuclide Therapy
Radioimmunotherapy…



What radionuclides can be used?

- Local energy deposition (alpha, low energy betas)
- Half-life on the order of days (~5-15 days)
- Imaging analogue (e.g ^{64}Cu & ^{67}Cu)
- Reliable production, simple radiochemistry

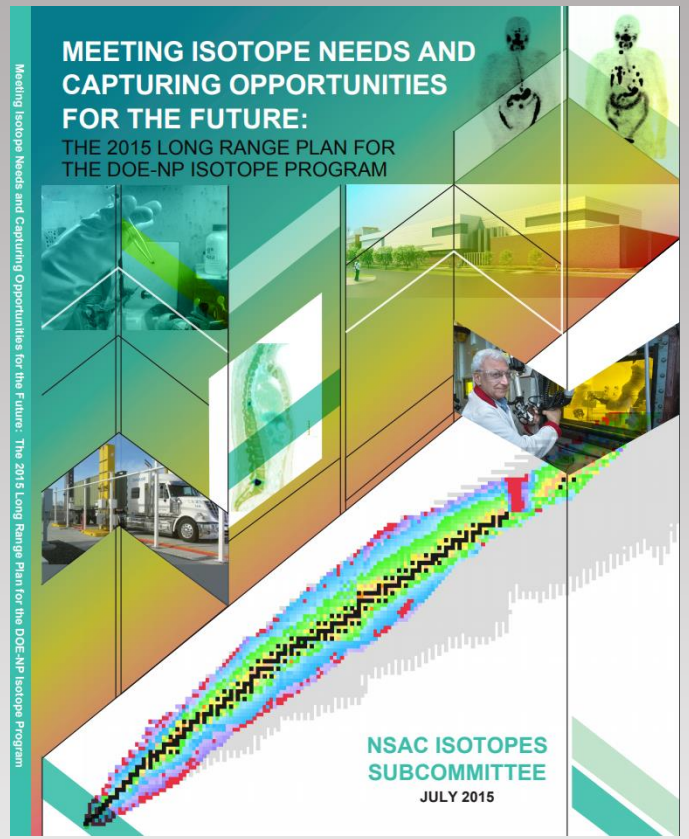
Hot Cell, Photo courtesy of Dr. Jason White

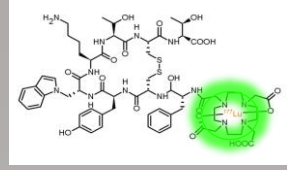
Radionuclide	Half-life	Decay mode	E or E(max) (MeV)	Photon Energy (keV)
^{32}P	14.3 d	β-	1.7	None
^{64}Cu	12.7 h	β-, EC + β+	$^{-}$: 0.58; $^{+}$: 0.65	None
^{67}Cu	2.58 d	β-	0.58	91(7%), 93(16%), 185(49%)
^{67}Ga	3.26 d	EC		91(3%), 93(39%), 185(21%), 300(17%), 394(5%)
^{68}Ga	67.6 min	β+	1.9	1077
^{89}Sr	50.5 d	β-	1.49	None
^{90}Y	2.67 d	β-	2.28	None
^{111}In	2.8 d	EC		171(90%), 245(94%)
^{117m}Sn	13.6 d	IT		159(86%)
^{124}I	4.18 d	EC, b+		603 (60%), 723 (10%), 1325 (1.4%), 1376 (1.7%), 1509 (3%), 1691 (10.4%)
^{131}I	8.02 d	β-	0.61	80(2.6%), 284(6%), 364(82%), 637(7%), 723(1.8%)
^{153}Sm	1.95 d	β-	0.81	103(30%)
^{166}Ho	26.8 h	β-	1.85	81(7%), 1379(0.93%), 1582(0.19%), 1662(0.12%)
^{177}Lu	6.71 d	β-	0.5	113(6), 208(11%)
^{186}Re	3.72 d	EC^{-}	1.07	137(9%)
^{188}Re	17.0 h	β-	2.12	155(15%), 478(1%), 633(1%)
^{211}At	7.2 h	EC, α	7.45	X rays 77(12%), 80(20%)
^{213}Bi	45.6 min	B-, α	8	440(16.5%)
^{223}Ra	11.4 d	β-,α	7.53	82(20%), 154(15%), 270(10%), 351, 405
^{225}Ac	10.0 d	α		

Radionuclide
^{32}P
^{64}Cu *
^{67}Cu *
^{67}Ga
^{68}Ga
^{89}Sr *
^{90}Y
^{111}In
^{117m}Sn
^{124}I
^{131}I
^{153}Sm
^{166}Ho
^{177}Lu *
^{186}Re
^{188}Re
^{211}At *
^{213}Bi
^{223}Ra *
^{225}Ac *

Isotope Development

The Department of Energy continues to develop isotopes for use in medical applications.



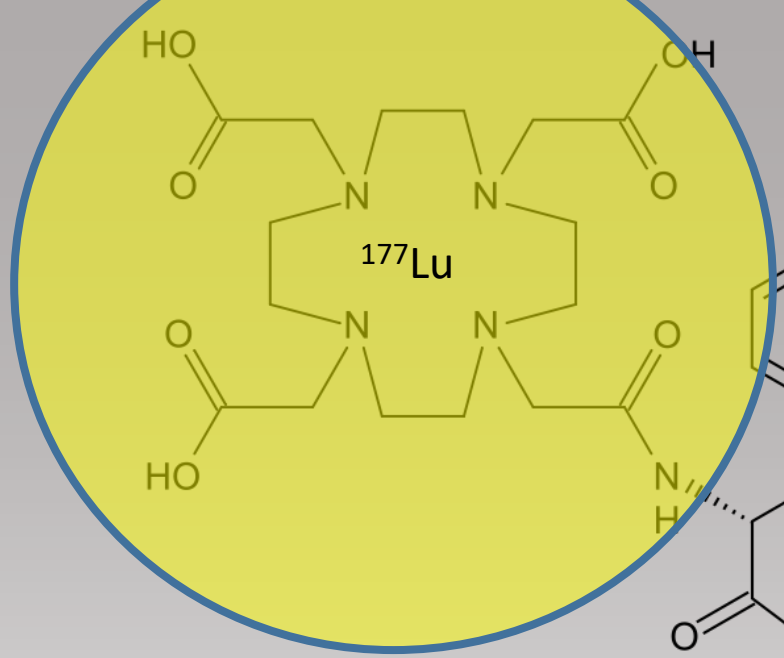


Targeting Agents

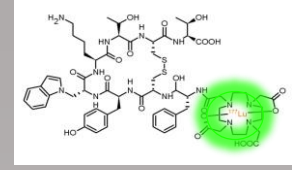
- Potential of employing advances in pharmacologic targeting, for radiation therapy.
- If an alpha or beta emitting radionuclide can be conjugated with a targeted agent, this results in targeted radionuclide therapy.
- The level of targeting varies from simplistic (e.g. ^{131}I, ^{223}Ra-dichloride), to very complicated (e.g. conjugating radionuclides to peptides and antibodies)

Targeting Agents

DOTA



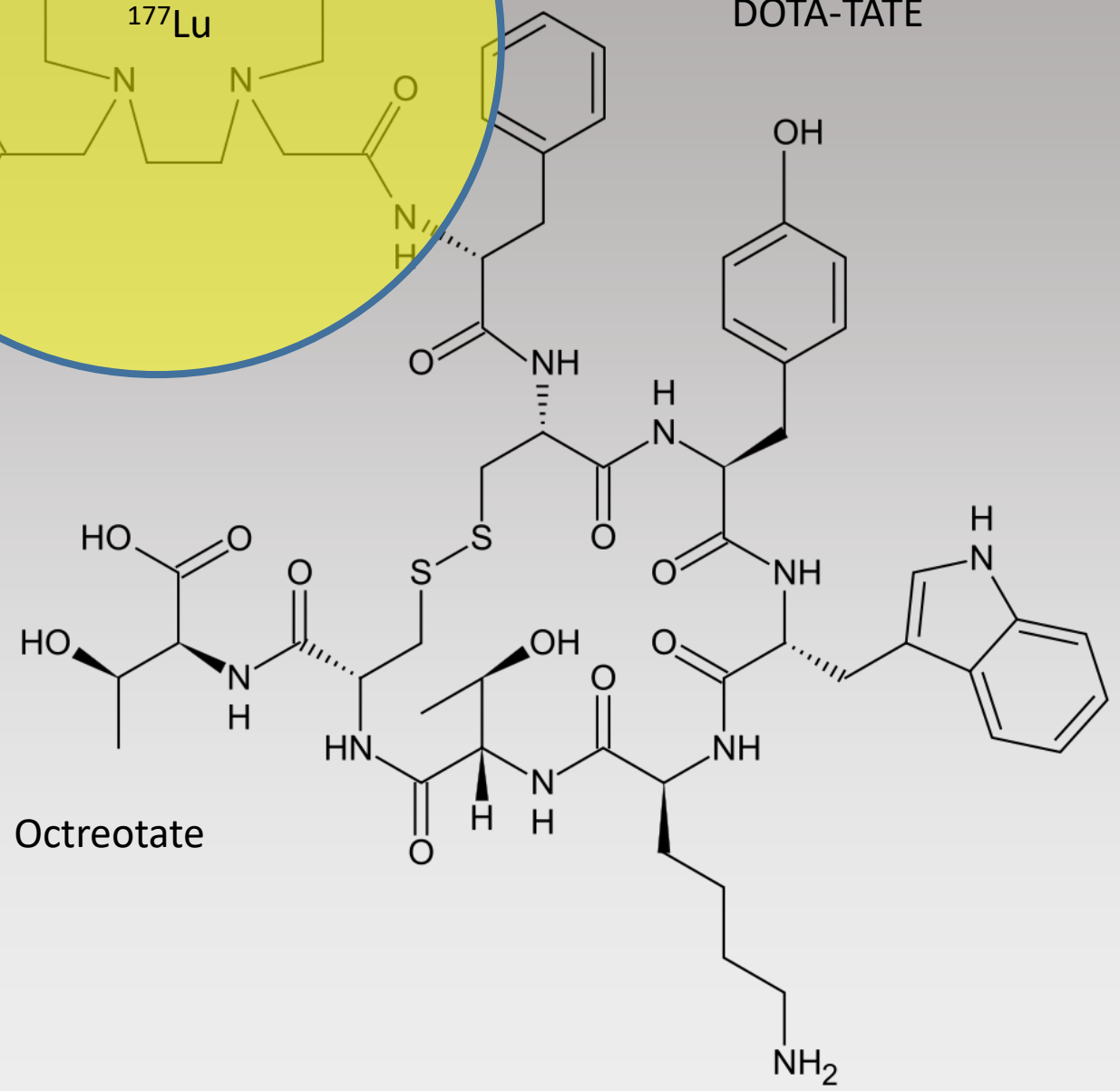
DOTA-TATE



Example (1)

Peptide Receptor Targeting

(^{177}Lu-Dotatate)



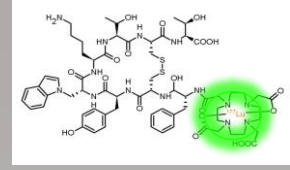
Octreotate

Targeting Agents

Example (2)

Prostate Specific Membrane Antigen

(^{177}Lu-PSMA-617)



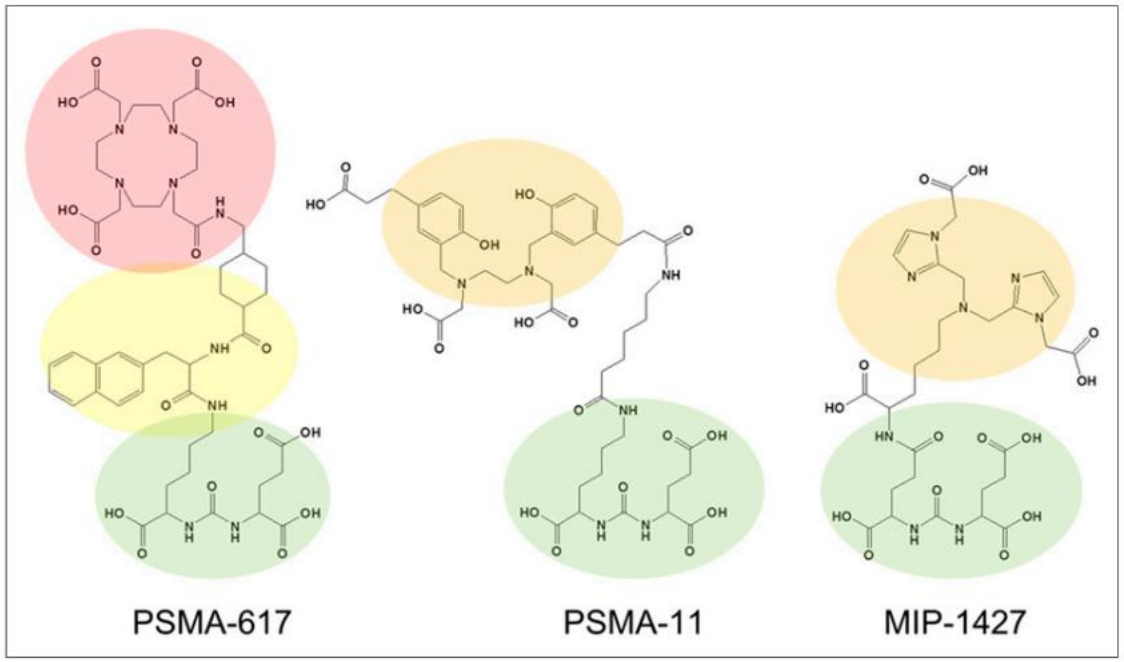


FIGURE 1. PSMA equals enzyme glutamate carboxypeptidase II. Its proteolytic domain can be targeted with Glu-urea motif (green). Hydrophobic pocket accessory to proteolytic domain adversely interacts with highly polar chelates such as DOTA (red) but favors more lipophilic chelates (orange) such as CIM (MIP-1427) for labeling with ^{99m}Tc or HBED-CC (PSMA-11) for labeling with ^{68}Ga. In PSMA-617, aromatic linker (yellow) exploits lipophilic accessory pocket to keep more universal DOTA-chelate remote to Glu-urea binding site.

PSMA-Targeted Radionuclide Therapy of Metastatic Castration-Resistant Prostate Cancer with ^{177}Lu-Labeled PSMA-617

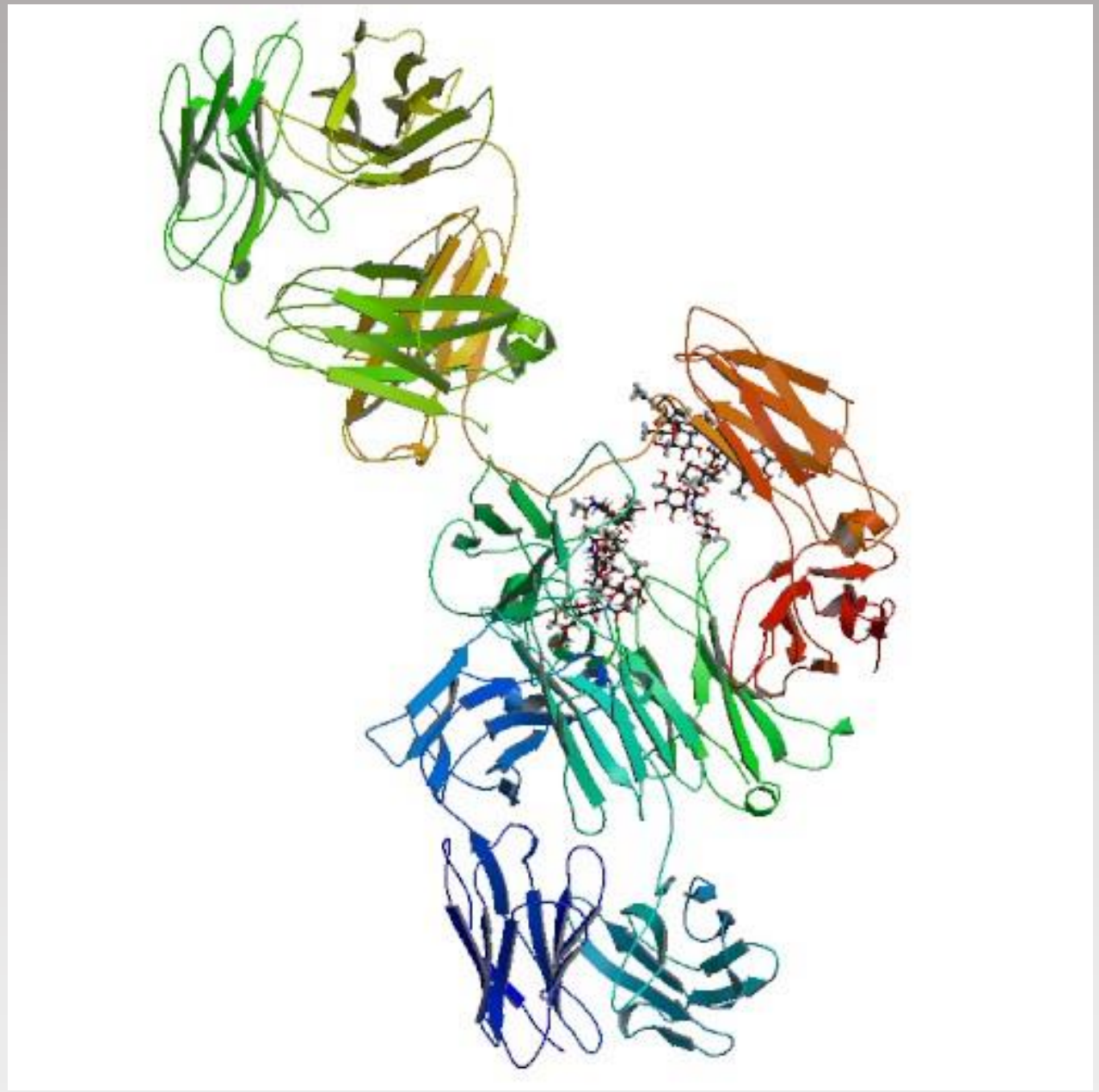
Clemens Kratochwil[1], Frederik L. Giesel[1,2], Melsa Stefanova[1], Martina Benešová[3], Marcus Bronzel[4], Ali Afshar-Oromieh[1,2], Walter Mier[1], Matthias Eder[3], Klaus Kopka[3], and Uwe Haberkorn[1,2]

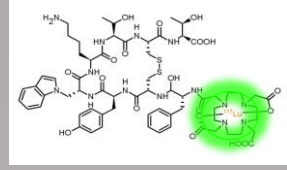
Targeting Agents

Example (3)

Antibody targeting

(^{90}Y Ibritumomab tiuxetan)





Targeting : What can we treat?

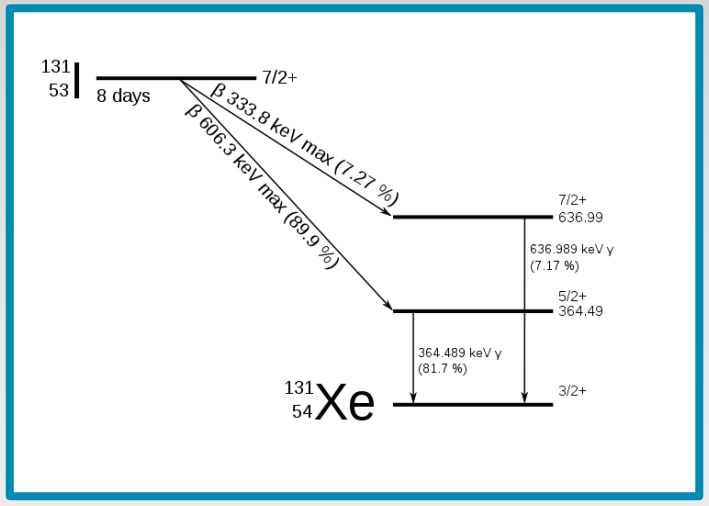
Radionuclide therapy can be targeted in the same manner as other pharmaceuticals

Targeted radionuclide therapy isn't new

^{131}I is routinely used in the treatment of papillary and follicular thyroid cancer

(30-100 mCi dose)

Part of routine clinical practice (Nuclear Medicine)



An Analysis of "Ablation of Thyroid Remnants" with I-131 in 511 Patients from 1947–1984: Experience at University of Michigan

William H. Beierwaltes, Roya Rabbani, Carl Dmuchowski, Ricardo V. Lloyd, Patti Eyre, and Shirley Mallette

University of Michigan Medical Center, Ann Arbor, Michigan

Between January 1947 and June 1983, 511 patients were given treatment doses of I-131 after surgery for thyroid cancer in the presence of I-131 uptake in thyroid remnants. Thirty-four patients were removed from the study leaving 462 patients with a 99% follow-up at 1 or more yr, with a mean follow-up of 15 yr. Of 267 patients with radioiodine uptake confined to the thyroid bed, 233 (87%) had ablation from the first dose of I-131 ranging from 100 to >200 mCi. The higher the percent uptake, the more difficult it was to achieve ablation. In the percentages of successful ablation, there were no significant differences between I-131 doses of: 100–149 mCi, 150–174 mCi, 179–199 mCi, and 200 mCi or more. The 100–149 mCi ablative dose may furnish "adjuvant" therapy for occult metastases.

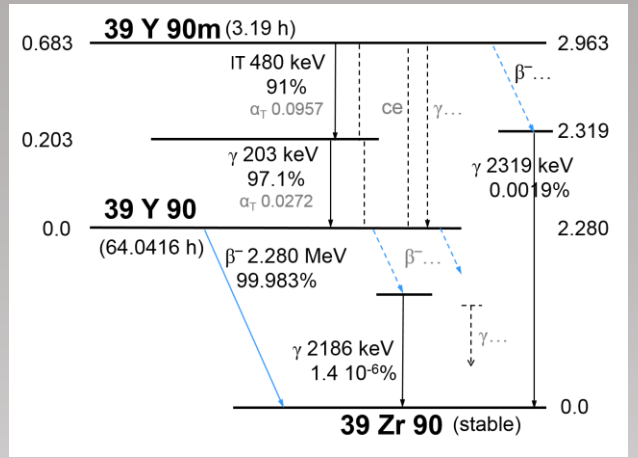
J Nucl Med 25: 1287–1293, 1984

Targeted radionuclide therapy isn't new (cont'd)

- Y-90 microspheres are used for the treatment of liver cancers.
- Administered activity is based on the liver mass and the required dose (e.g. 80-150 Gy for TheraSpheres)

$$Activity(GBq) = \frac{Dose(Gy) * LiverMass(Kg)}{50}$$

- Part of routine clinical practice; may be a part of interventional radiology, nuclear medicine or radiation oncology



"Treatment of Inoperable Cancer of the Liver by Intra-Arterial Radioactive Isotopes and Chemotherapy", I.M. Ariel and G.T. Pack, Cancer, 1967

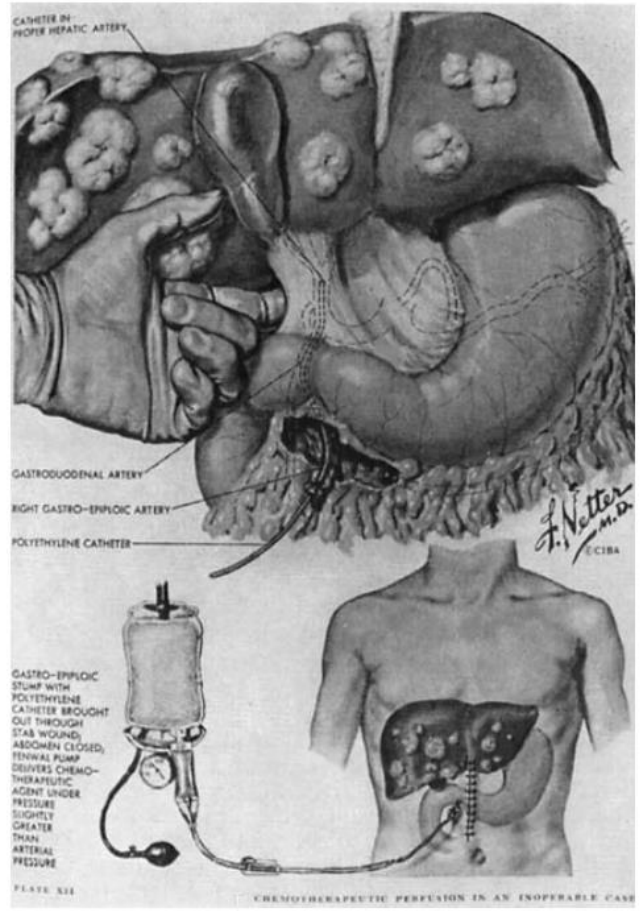
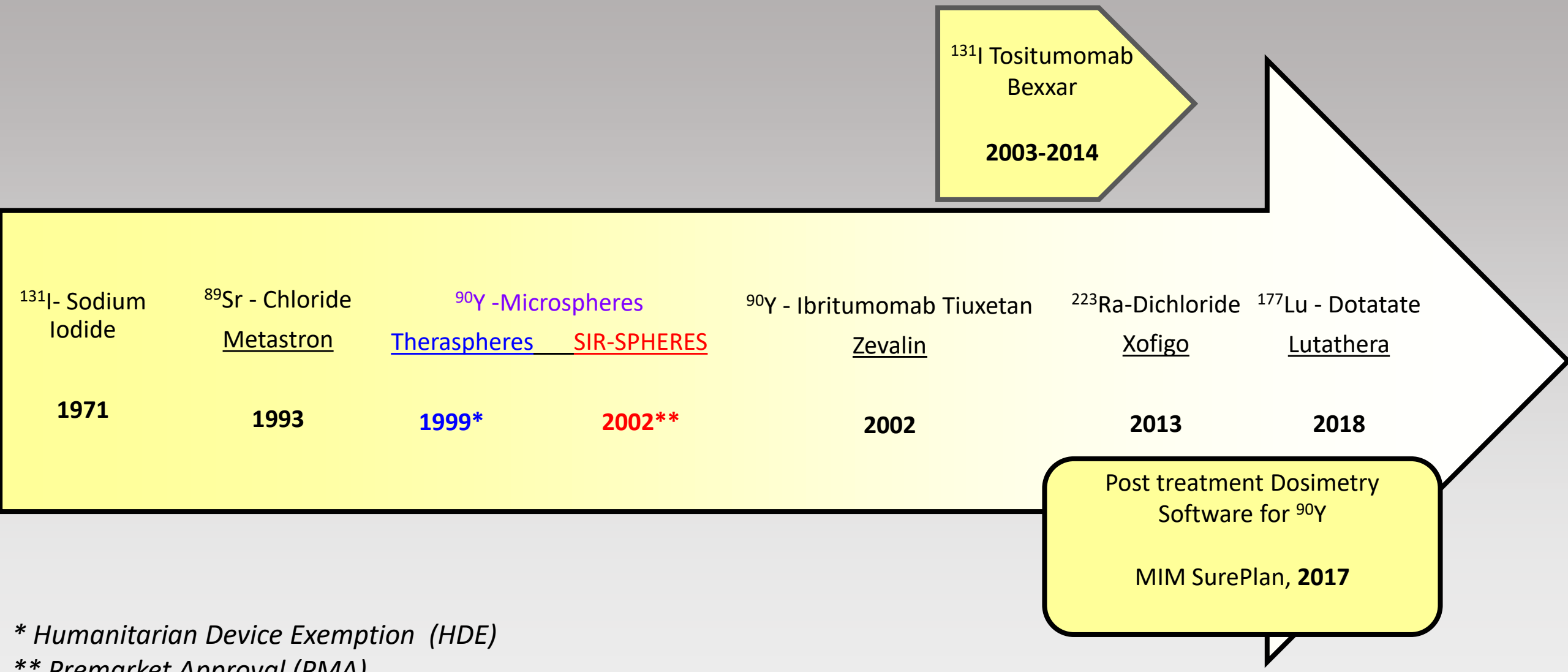


FIG. 2. Top, technique of hepatic artery catheterization by insertion of catheter into right gastroepiploic artery and threading it retrograde into hepatic artery. Bottom, Fenwall infuser attached to stump of gastroepiploic artery for constant intrahepatic artery infusion of anticancer drugs and radioactive isotopes. Copyright Clinical Symposia, by Frank H. Netter, MD, published by CIBA Pharmaceutical Company.

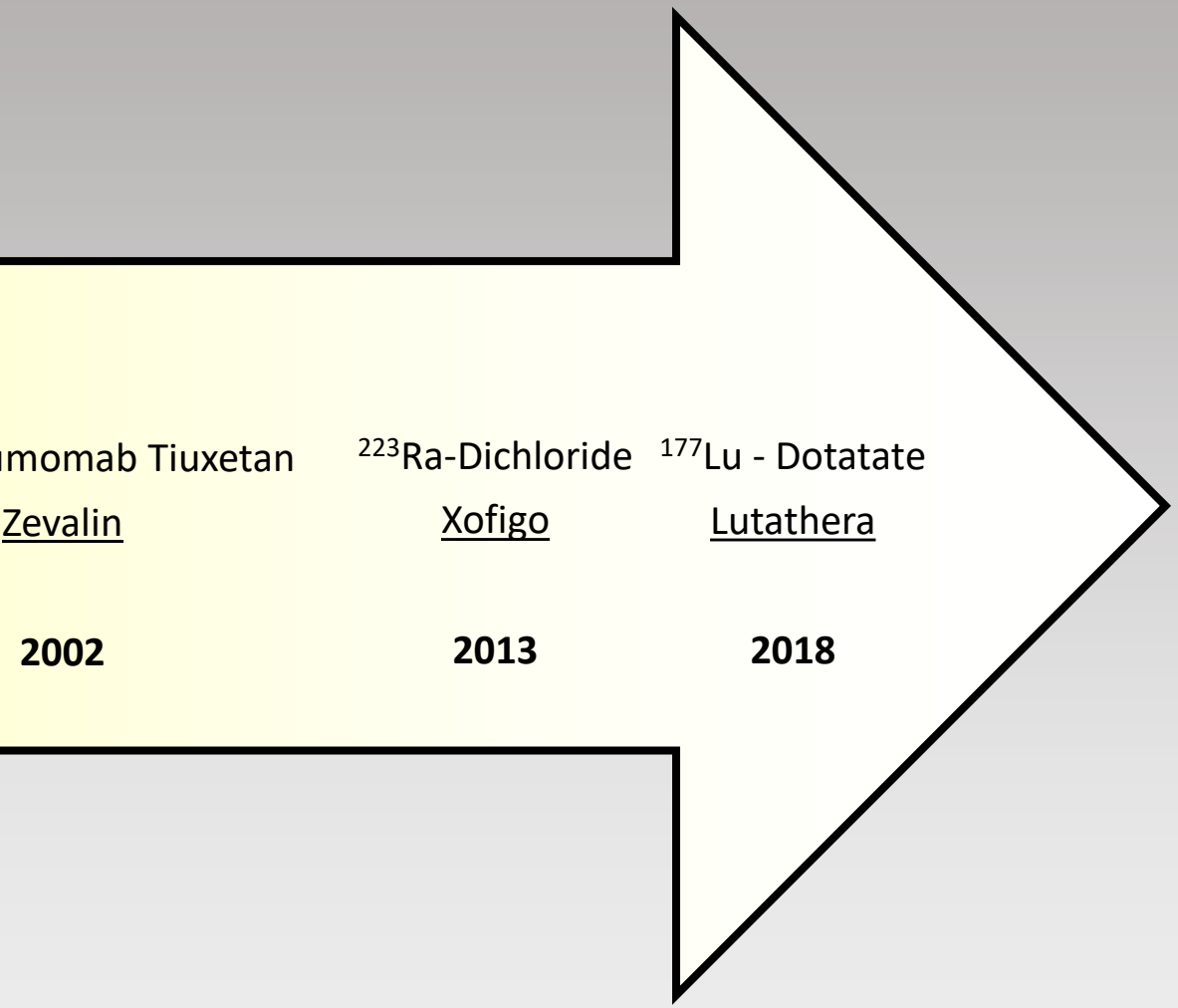
FDA approvals of targeted radionuclide therapy



** Humanitarian Device Exemption (HDE)*

*** Premarket Approval (PMA)*

FDA approvals of targeted radionuclide therapy



There are many agents that are currently in clinical trials

Clinical Trials: SRT in Development

Isotope	Conjugate Labeled	Indication
Lutetium-177	PSMA	Metastatic Castration Resistant Prostate Cancer
Lutetium-177	Girentuximab	Metastatic Clear Cell Renal Cell Carcinoma
Lutetium-177	dis-HSG-DOTA peptide IMP-288	Colorectal Cancer
Lutetium-177	Lilotomab (Betalutin®)	Radioimmunotherapy for Treatment of Relapsed Non-Hodgkin Lymphoma
Lutetium-177	DOTA- cG250	Metastatic Renal Cell Carcinoma
Indium-111	DOTA-cG250	Metastatic Renal Cell Carcinoma
Iodine-131	CLR1401	Glioma
Iodine-131	monoclonal antibody BC8	Non-Hodgkin Lymphoma

Clinical Trials: SRT in Development

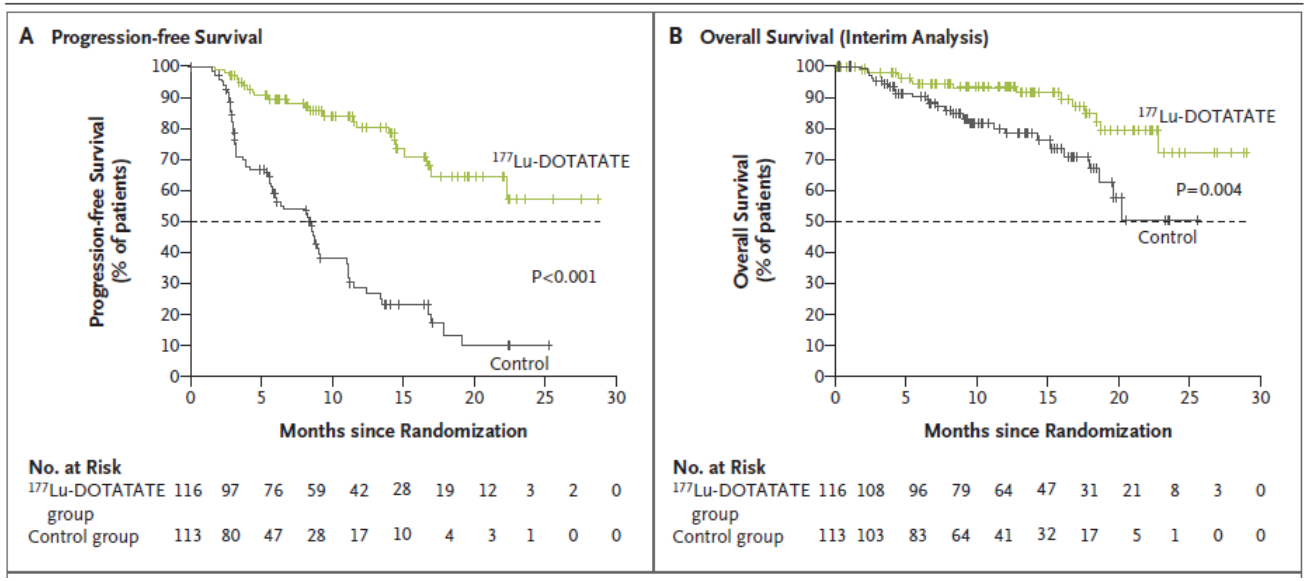
Isotope	Conjugate Labeled	Indication
Actinium-225	Lintuzumab	Acute Myeloid Leukemia, Multiple Myeloma
Yttrium-90	DOTATOC	Neuroendocrine Tumor
Yttrium-90	In combination with immune modulation therapy	Hepatocellular Ca
Holmium-166	DOTMP	Ewing's sarcoma
Lead-212	Trastuzumab	Multiple neoplasms
Lead-212	AlphaMedix®	Neuroendocrine Tumor
Bismuth-213	monoclonal M195	Leukemia, Myelodysplastic syndromes

Clinical Trials: SRT alone or in combination for multiple indications

Drug	In combination with:	Indication(s)
Xofigo (Ra 223 dichloride) <u>Approved indication:</u> mCRPC	Abiraterone	mCRPC
	Enzalutamide	
	Stereotactic body radiation	
	Paclitaxel	Neoplasms, bone diseases
	Hormonal Tx and Denosumab	Breast cancer with bone mets
	N/A	Osteosarcoma
		Clear-cell Metastatic Renal Cell Ca
		Non-Small Cell Lung Ca
Lutathera (Lu 177 dotatate) <u>Approved indication:</u> GEP-NETs	Nivolumab	Small cell lung cancer
	N/A	Pheochromocytoma/paraganglioma

Outcomes of SRT clinical trials

- For the mentioned clinical trials, the endpoints vary.
- The outcomes of the clinical trials may be:
  - Maximum tolerated dose
  - Progression free survival
  - Overall survival
  - Quality of life metrics
- Dosimetry for tumor volumes and organs at risk may not be included in the studies



Phase 3 Trial of ^{177}Lu-Dotatate for Midgut Neuroendocrine Tumors

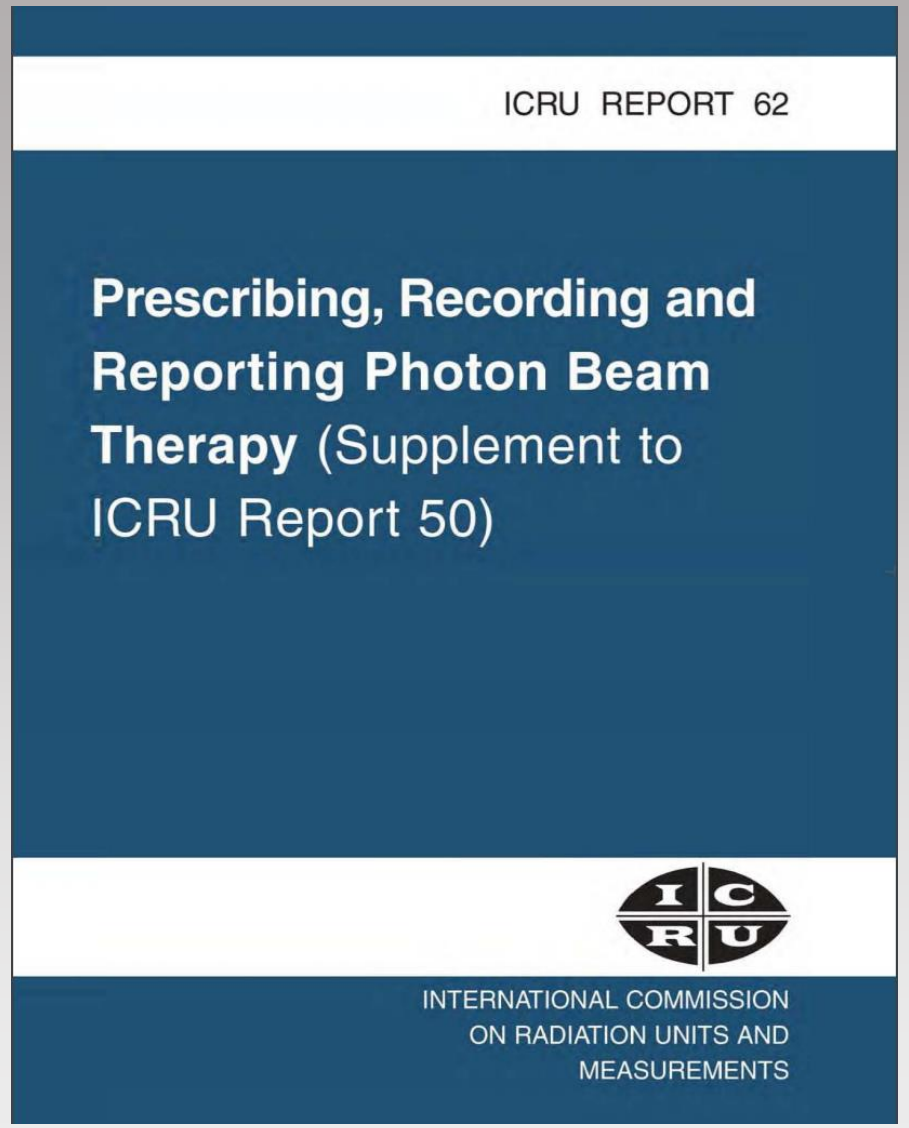
J. Strosberg, G. El-Haddad, E. Wolin, A. Hendifar, J. Yao, B. Chasen, E. Mittra, P.L. Kunz, M.H. Kulke, H. Jacene, D. Bushnell, T.M. O'Dorisio, R.P. Baum, H.R. Kulkarni, M. Caplin, R. Lebtahi, T. Hobday, E. Delpassand, E. Van Cutsem, A. Benson, R. Srirajaskanthan, M. Pavel, J. Mora, J. Berlin, E. Grande, N. Reed, E. Seregni, K. Öberg, M. Lopera Sierra, P. Santoro, T. Thevenet, J.L. Erion, P. Ruszniewski, D. Kwekkeboom, and E. Krenning, for the NETTER-1 Trial Investigators*

Targets and Organs at Risk

In External Beam RT, we follow ICRU guidelines

- Include how we define where the radiation is prescribed (targets)
- Include how we report the radiation dose received by normal tissues (organs at risk)

- It should be noted that a target can be encompassed by an organ at risk.

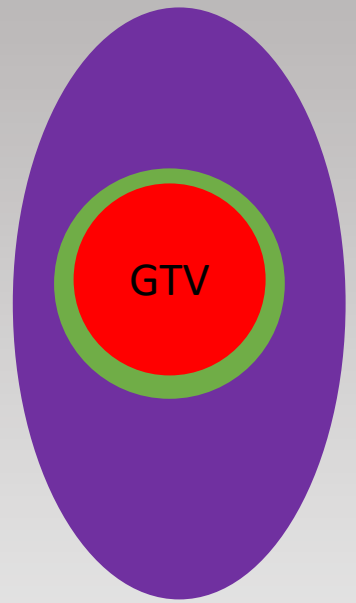


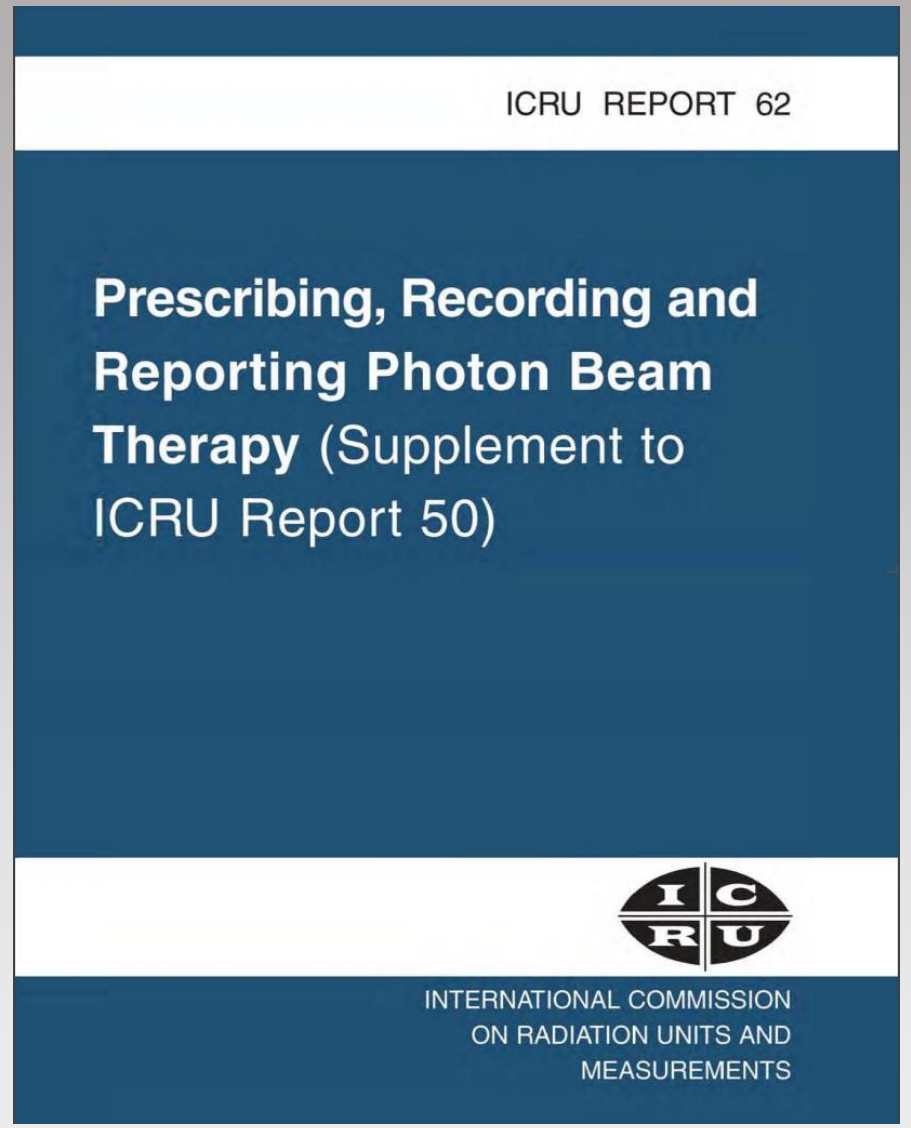
Targets and Organs at Risk

In External Beam RT, ICRU guidelines are followed

Treatment planning volumes

1. **GTV: Gross tumor volume**
2. **CTV: Clinical target volume**
3. **PTV: Planning target volume**





Targets and Organs at Risk

What we do with the Organs at Risk Data

There are guidelines for maximum dose tolerances for high dose per fraction treatments (e.g. SBRT)

There are guidelines for what is used in conventional fractionation schemes as well.

In addition, there are guidelines on how to contour organs at risk (e.g. bowel)

Table 1. QUANTEC Summary: Approximate Dose/Volume/Outcome Data for Several Organs Following Conventional Fractionation (Unless Otherwise Noted)*

Organ	Volume segmented	Irradiation type (partial organ unless otherwise stated)†	Endpoint	Dose (Gy), or dose/volume parameters†	Rate (%)	Notes on dose/volume parameters
Brain	Whole organ	3D-CRT	Symptomatic necrosis	Dmax <60	<3	Data at 72 and 90 Gy, extrapolated from BED models
	Whole organ	3D-CRT	Symptomatic necrosis	Dmax = 72	5	
	Whole organ	3D-CRT	Symptomatic necrosis	Dmax = 90	10	
	Whole organ	SRS (single fraction)	Symptomatic necrosis	V12 <5–10 cc	<20	Rapid rise when V12 > 5–10 cc
Brain stem	Whole organ	Whole organ	Permanent cranial neuropathy or necrosis	Dmax <54	<5	
	Whole organ	3D-CRT	Permanent cranial neuropathy or necrosis	D1–10 cc‖ ≤59	<5	
	Whole organ	3D-CRT	Permanent cranial neuropathy or necrosis	Dmax <64	<5	Point dose <<1 cc
	Whole organ	SRS (single fraction)	Permanent cranial neuropathy or necrosis	Dmax <12.5	<5	For patients with acoustic tumors
Optic nerve / chiasm	Whole organ	3D-CRT	Optic neuropathy	Dmax <55	<3	Given the small size, 3D CRT is often whole organ‡‡
	Whole organ	3D-CRT	Optic neuropathy	Dmax 55–60	3–7	
	Whole organ	3D-CRT	Optic neuropathy	Dmax >60	>7-20	
	Whole organ	SRS (single fraction)	Optic neuropathy	Dmax <12	<10	
Spinal cord	Partial organ	3D-CRT	Myelopathy	Dmax = 50	0.2	Including full cord cross-section
	Partial organ	3D-CRT	Myelopathy	Dmax = 60	6	
	Partial organ	3D-CRT	Myelopathy	Dmax = 69	50	
	Partial organ	SRS (single fraction)	Myelopathy	Dmax = 13	1	Partial cord cross-section irradiated
	Partial organ	SRS (hypofraction)	Myelopathy	Dmax = 20	1	3 fractions, partial cord cross-section irradiated
Cochlea	Whole organ	3D-CRT	Sensory neural hearing loss	Mean dose ≤45	<30	Mean dose to cochlear, hearing at 4 kHz
	Whole organ	SRS (single fraction)	Sensory neural hearing loss	Prescription dose ≤14	<25	Serviceable hearing
Parotid	Bilateral whole parotid glands	3D-CRT	Long term parotid salivary function reduced to <25% of pre-RT level	Mean dose <25	<20	For combined parotid glands¶
	Unilateral whole parotid gland	3D-CRT	Long term parotid salivary function reduced to <25% of pre-RT level	Mean dose <20	<20	For single parotid gland. At least one parotid gland spared to <20 Gy¶

What data do we have on radiation dose response?

In external beam radiation therapy, 7% is often quoted as the accuracy needed for modern radiation dosimetry.

There are also ways to externally verify our dosimetry (e.g IROC phantoms)

What data do we have on radiation dose response?

Very little data is available on dose response in patients receiving radionuclide therapy.

In radionuclide therapy, the one variable controlled is the administered activity.

This may be determined based on a calculation of the patient's body surface area

Do not typically get dose to targets or OARs, and doses are rarely reported in Gy.

Input	Dose Calculation	Optimization Parameters	Radiation Biology	End-Points
Diagnosis Time-integrated activity in reference organs	Reference phantom based MIRD calculation	Administered activity	Risk models that relate equivalent or effective organ dose to risk: BEIR VII, ICRP, NCRP, EPA	Cancer risk and other health risks
RPT Longitudinal activity, density and composition images	Monte Carlo/analytical methods, MIRD voxel S-Values.		Adjustments for radiosensitivity and repair of tissue (α/β) and dosing schema (BED).	Organ toxicity; tumor response
External Beam RT Patient Anatomy; Complete CT and contoured structures	Monte Carlo/analytical dose calculation algorithms.	Beam parameters (number of beams, weight, fluence, energy, etc.) optimized to meet dose volume histogram constraints.		

^{177}LU-DOTATATE PHASE 3 TRIAL IN MIDGUT NEUROENDOCRINE TUMORS

SUPPLEMENTARY APPENDIX

TABLE OF CONTENTS

Supplementary Table S2. ^{177}Lu-DOTATATE Exposure.*

Patients who completed treatment phase (N=103†)	no. (%)
Number of administrations	
4	79 (77)
3	6 (6)
2	12 (12)
1	5 (5)
0	1 (1)
All treated patients (N=111)	
No DMT	103 (93)
DMT	8 (7)

* DMT denotes dose-modifying toxicity.

† Excluding patients still under treatment (n=8) or no treatment (n = 5).

Phase 3 Trial of ^{177}Lu-Dotatate for Midgut Neuroendocrine Tumors

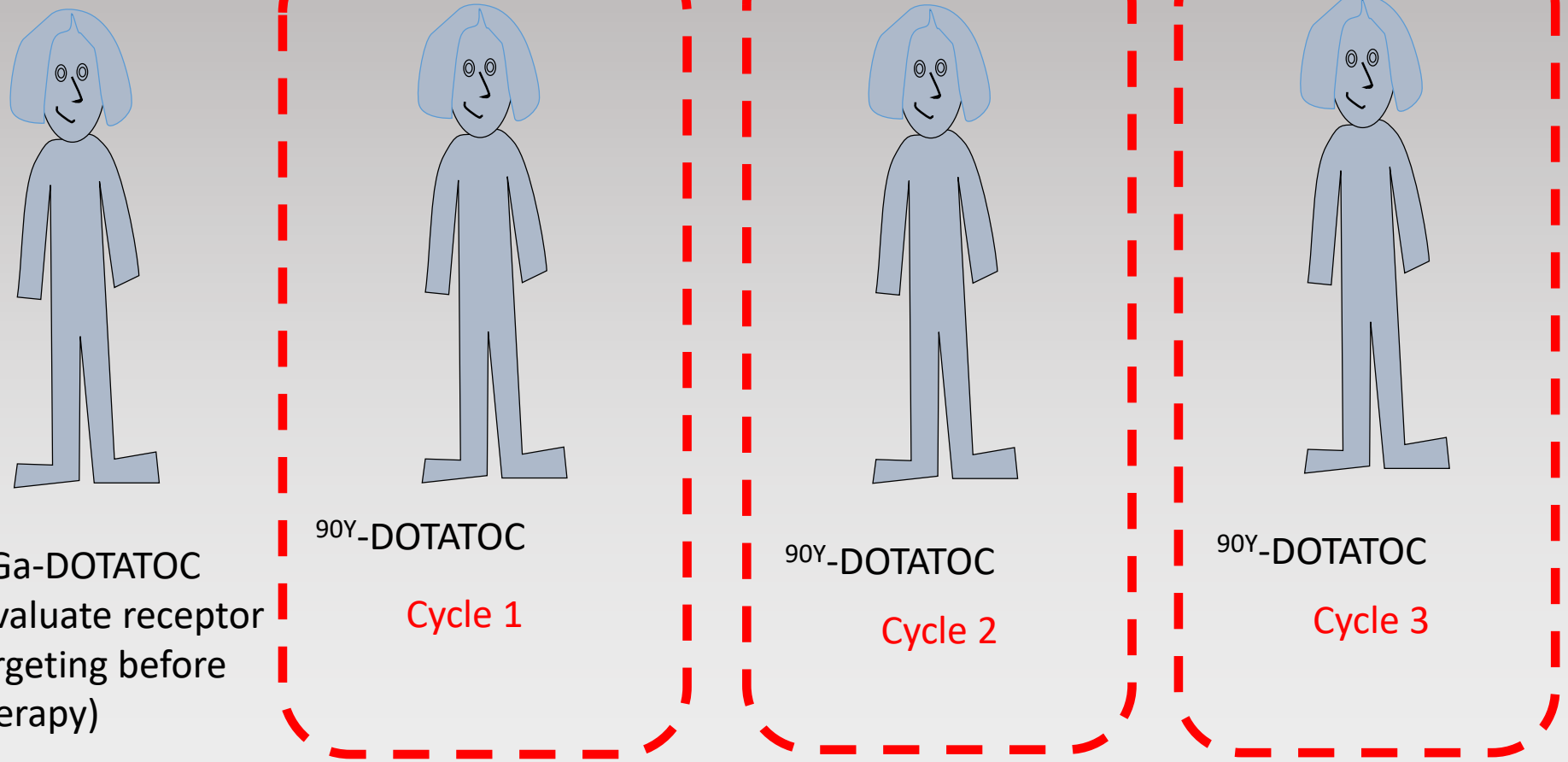
J. Strosberg, G. El-Haddad, E. Wolin, A. Hendifar, J. Yao, B. Chasen, E. Mittra, P.L. Kunz, M.H. Kulke, H. Jacene, D. Bushnell, T.M. O'Dorisio, R.P. Baum, H.R. Kulkarni, M. Caplin, R. Lebtahi, T. Hobday, E. Delpassand, E. Van Cutsem, A. Benson, R. Srirajaskanthan, M. Pavel, J. Mora, J. Berlin, E. Grande, N. Reed, E. Seregni, K. Öberg, M. Lopera Sierra, P. Santoro, T. Thevenet, J.L. Erion, P. Ruszniewski, D. Kwekkeboom, and E. Krenning, for the NETTER-1 Trial Investigators*

What do we learn (or change) when accurate dosimetry is performed?

What do we learn (or change) when accurate dosimetry is performed?

Technical aspects of peptide receptor radiotherapy (PRRT) with 90Y-DOTATOC for neuroendocrine tumors using PET/CT and SPECT/CT

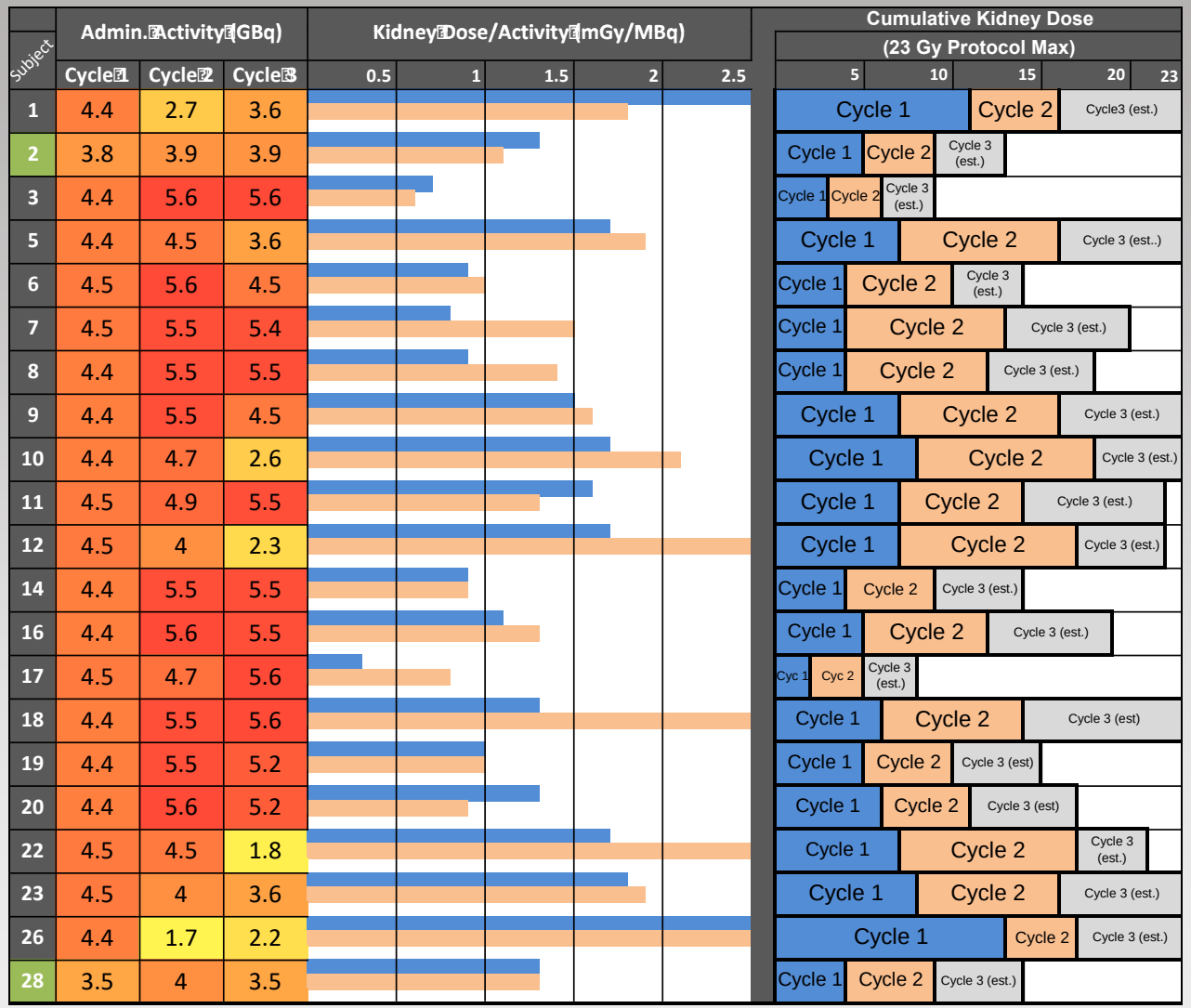
Lisa Dunnwald[3], John Sunderland[2], Yusuf Menda[1], John Richmond[3], Julie Riggert[3], Christine Mundt[3], Kelli Schlarbaum[3], Alyssa Martocci[3] and Mark Madsen[2]



After each treatment, the uptake of 90Y-DOTATOC was imaged using PET/CT and SPECT/CT (renal imaging)

Doses for subsequent cycles were adjusted using renal dose estimates from previous cycles, maintaining total renal dose < 23 Gy.

What do we learn (or change) when accurate dosimetry is performed?



10/21 Patients had Cycle 2 Dose Increased > 20% as a result of 90Y-DOTATOC PET/CT Measurement

4/21 Patients had Cycle 2 Dose Decreased by >10% as a result of 90Y-DOTATOC PET/CT Measurement

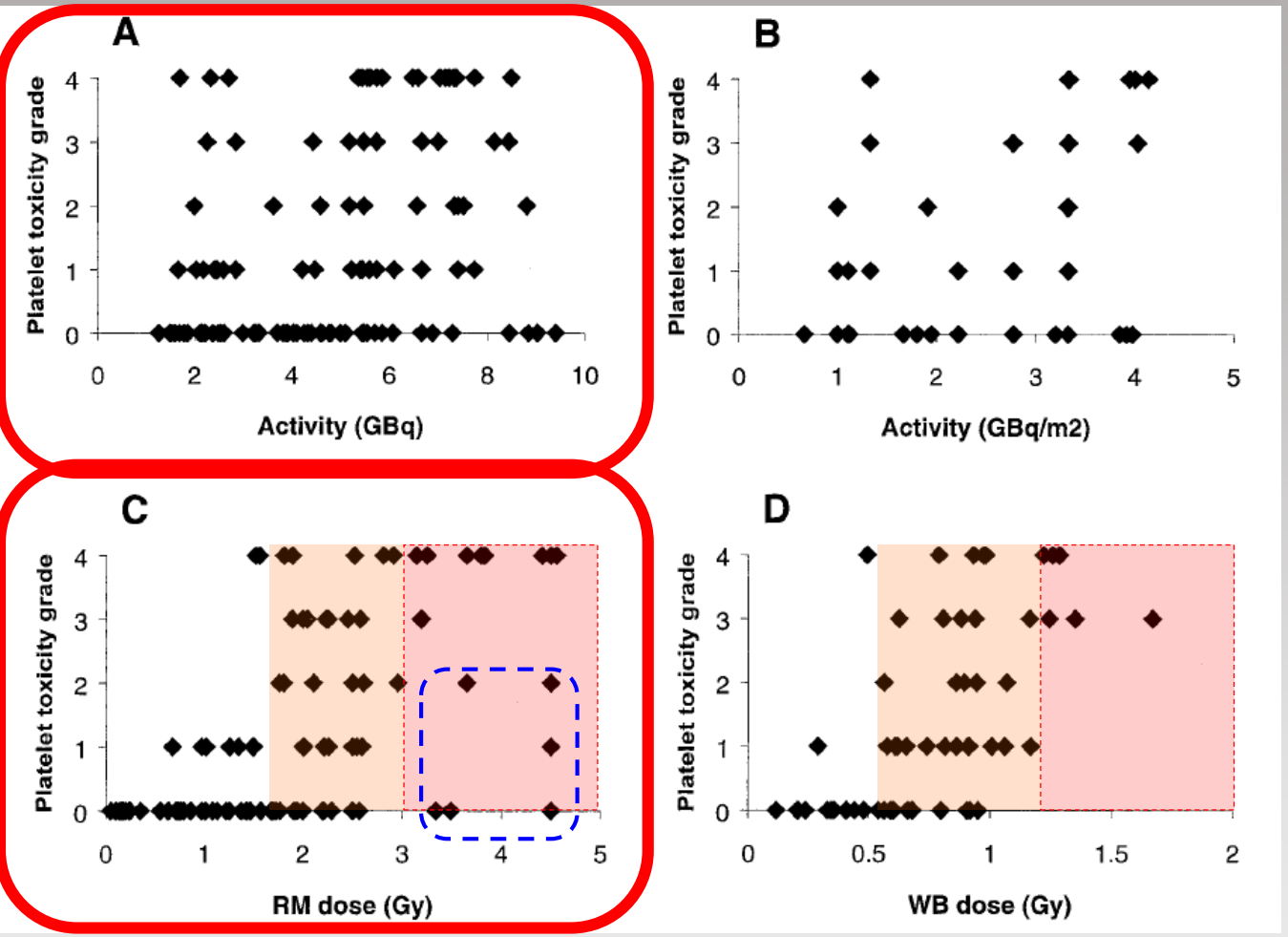
3/21 Patients had Cycle 3 Dose Decreased by > 30% to keep Total Cumulative Kidney Dose < 23 Gray

Dose escalation prohibited by protocol in 2 pediatric cases

9/21 Patients likely would have benefited from even higher administered therapeutic doses, but were limited by protocol maximum injected dose of 5.6 GBq (150 mCi) [^{90}Y]DOTATOC

Slide courtesy of M. Madsen

What data do we have on dose response?



A. Platelet toxicity as a function of administered activity
B. Platelet toxicity as a function of administered activity normalized to body surface area
C. Platelet toxicity as a function of marrow dose
D. Platelet toxicity as a function of whole body radiation dose

Hematologic Toxicity in Radioimmunotherapy: Dose-Response Relationships for I-131 Labeled Antibody Therapy

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Targeted radionuclide therapy has a promising future

- The radiation is targeted and may spare healthy tissues
- Less dependent on user skill
- Targeting developments can follow pharmaceutical targeting developments
- May be cost effective …. (TBD)

Outlook

For the success of radionuclide therapy we need:

① Available radionuclides

② Ability to target the radiation

① Accurate dosimetry for targets and organs at risk

① Workflows (and dosimetry tools) that can be integrated into clinical environments

For accurate dosimetry, we need quantitative imaging

- For accurate dosimetry we need volumetric images of our patients (CT, MRI) to accurately determine target structures and organs at risk
- We also need functional imaging studies to determine the activity of the radiotracer in the volumes of interest
- Additional challenges include quantification of nuclear medicine studies, spatial resolution and kinetic modeling