Towards Precision Medicine

The Role of Dosimetry and Theranostics in Radioligand Therapy



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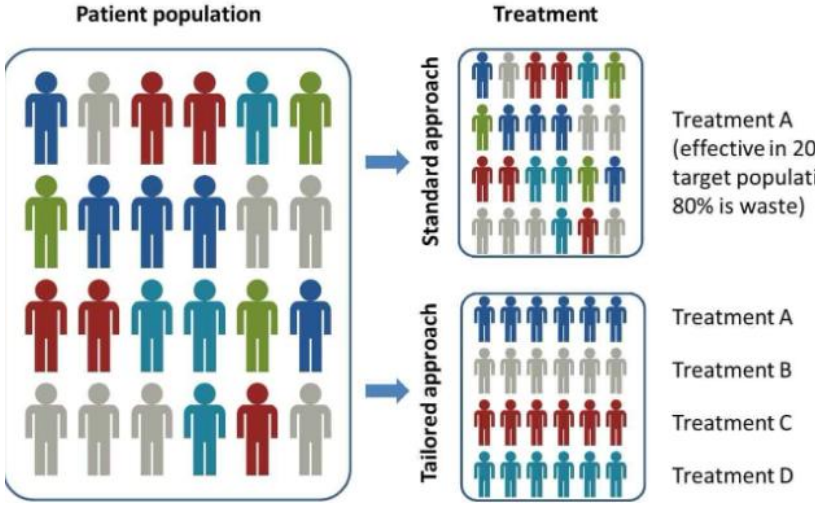
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Precision vs Personalized Medicine

Why precision radionuclide therapy starts with molecular imaging

Precision Medicine	**Personalized Medicine**
Right treatment for the right patient subgroup	**Right treatment for the individual patient**
Based on **measurable biological characteristics**	Integrates **individual clinical context**
Biomarkers • molecular imaging • theranostics • genomics • dosimetry	Biology • comorbidities • preferences • treatment history • dosimetry
Stratification & prediction	**Individualization & adaptation**
Who is likely to benefit?	What is optimal for this patient?



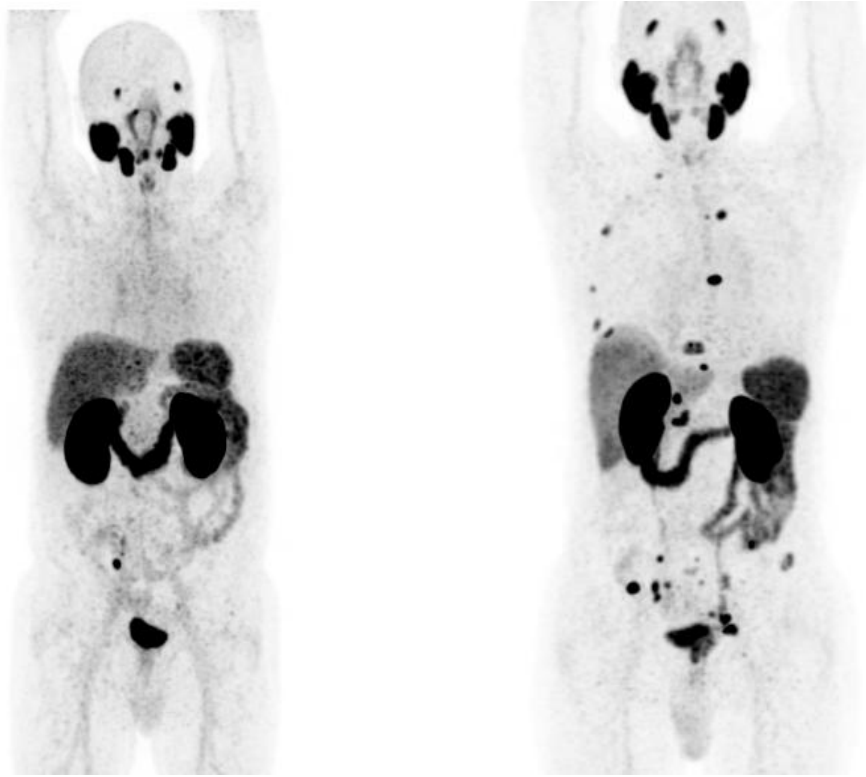
https://www.acobiom.com/en/precision-medicine/

In Radioligand Therapy:
Precision → patient selection | Personalization → treatment optimization

Clinical Applications of Radioligand Therapy (RLT)

Current clinical possibilitess

- ✓ **Neuroendocrine tumors** (NETs): [177Lu]Lu-DOTATATE therapy in somatostatin receptor-positive disease
- ✓ **Prostate cancer**: [177Lu]Lu-PSMA therapy in advanced prostate cancer
- ✓ Emerging applications: **Other** tumor targets and radioligands are being investigated **in clinical trials**



Clinical value: RLT enables targeted treatment, can improve **disease control** and **quality of life** in **appropriately selected patients**, and supports a personalized medicine approach through molecular imaging and patient selection

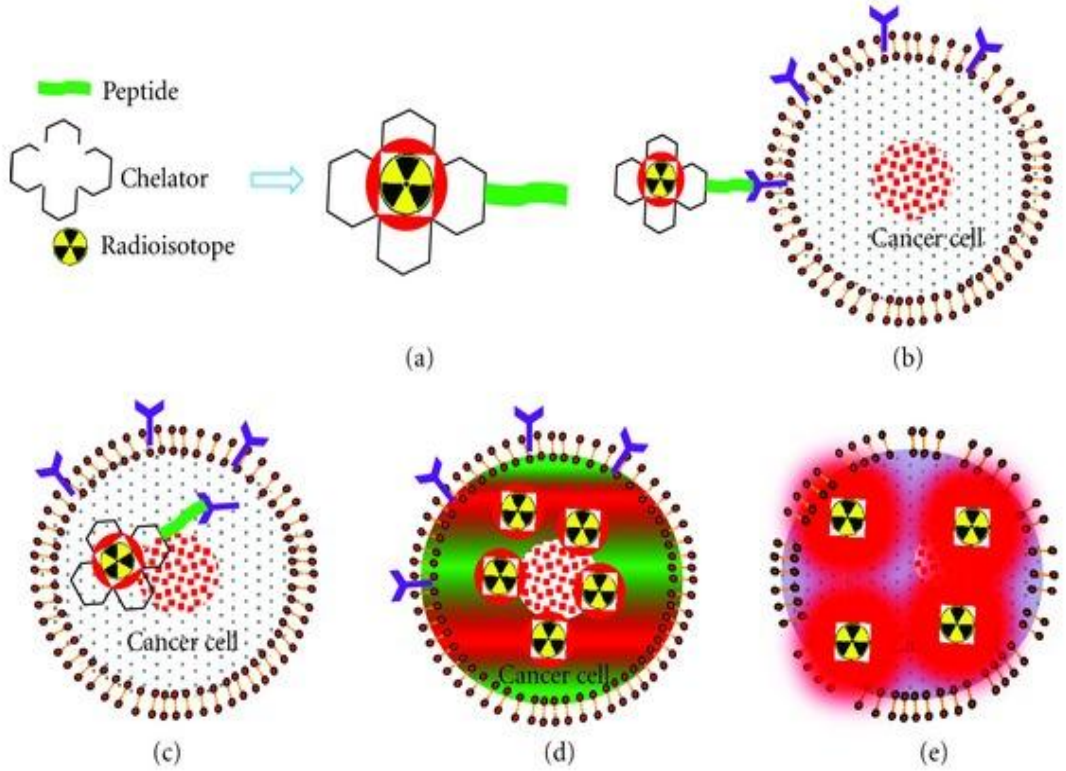
RLT in the treatment of neuroendocrine tumors

The Present and Future of Nuclear Medicine

RLT is **a systemic** treatment method that uses a radiopharmaceutical that binds to receptors on tumor cells and delivers therapeutic radiation directly to them

How does RLT work?

A somatostatin analogue, such as DOTATATE, binds to somatostatin receptors (SSTRs), primarily SSTR2
When coupled with the radionuclide f.e. lutetium-177 (^{177}Lu), it emits beta-minus (β^-) radiation, damaging tumor cells.
This leads to inhibition of tumor growth and may reduce tumor burden



Only individuals with somatostatin receptor-positive tumors can get this type of molecular radiation therapy.
Many neuroendocrine tumors, although not all, express one or more somatostatin receptor subtypes.

Precision and Personalization in RLT

Current possibilites

- Theranostics
- Dosimetry

Precision Medicine Starts with Theranostics

Theranostics = Therapy + Diagnostics

A personalized approach that combines molecular imaging and targeted therapy using the same or closely related biological target

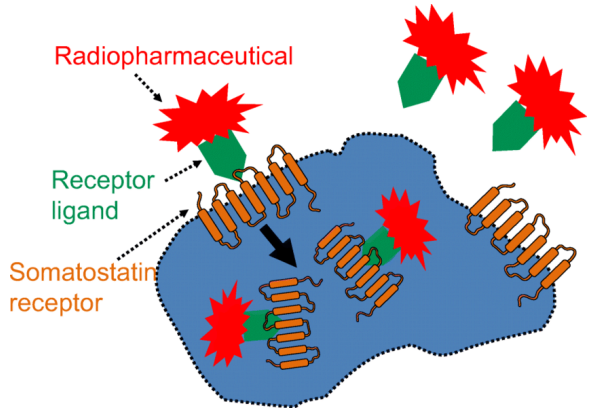
1. IDENTIFY
Diagnostic radiopharmaceutical
Visualizes the molecular target and confirms its expression

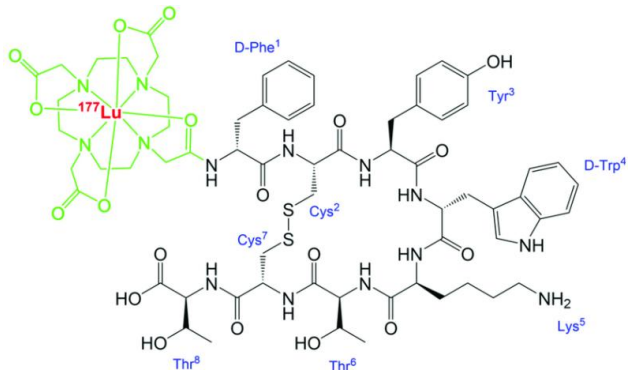
2. SELECT
Patient selection & dosimetry
Identifies patients likely to benefit and estimates radiation delivery

3. TREAT
Therapeutic radiopharmaceutical
Delivers targeted radiation directly to tumor cells

Why is it important?

- Targeted: preferential delivery to tumor tissue
- Personalized: treatment based on tumor biology
- Quantifiable: imaging assesses target expression and biodistribution
- Adaptable: β−, α or Auger-electron therapy options



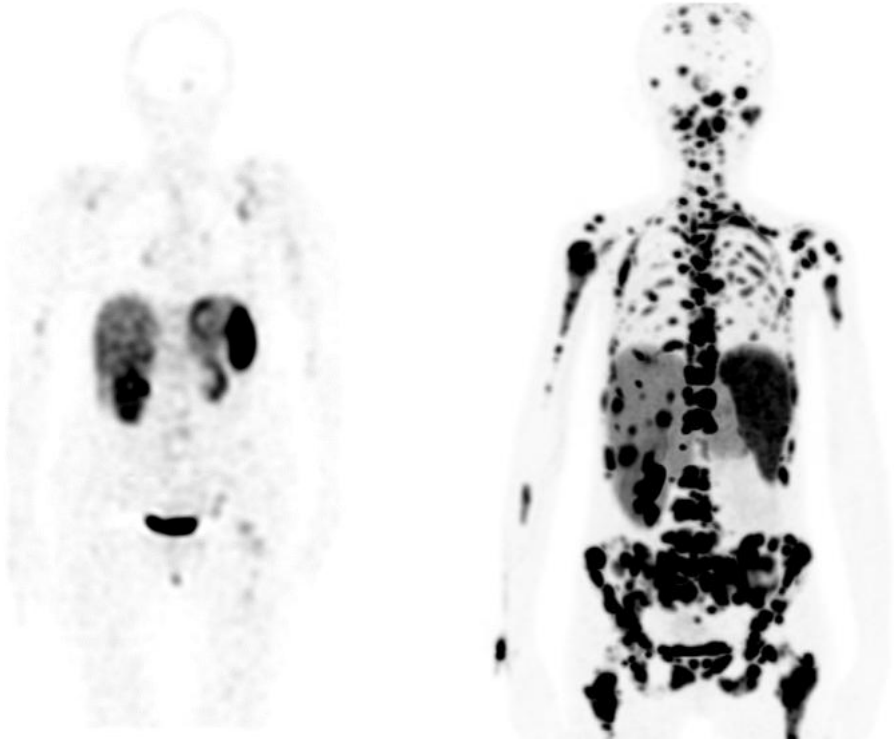


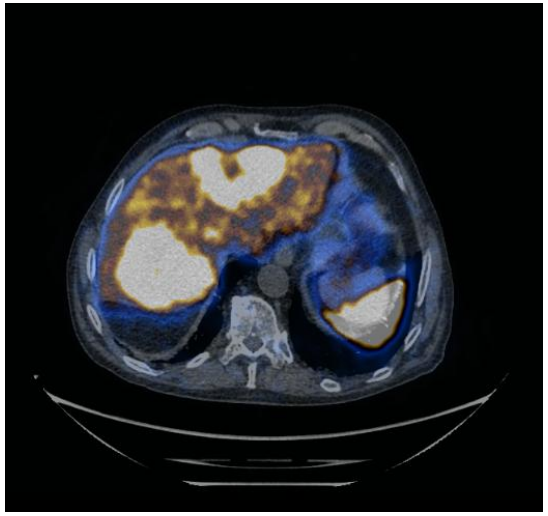
Example: ^{68}Ga-DOTATATE PET → SSTR-positive NET → ^{177}Lu-DOTATATE therapy

Petersenn, et al. Targeted systemic and peptide radio-ligand therapy for aggressive pituitary tumors and carcinomas. Rev Endocr Metab Disord 21, 277–286 (2020).
Hennrich U, et al. Lutathera®: The First FDA- and EMA-Approved Radiopharmaceutical for Peptide Receptor Radionuclide Therapy. Pharmaceuticals (Basel). 2019 Jul 29;12(3):114

Theranostics

See what you treat, treat what you see





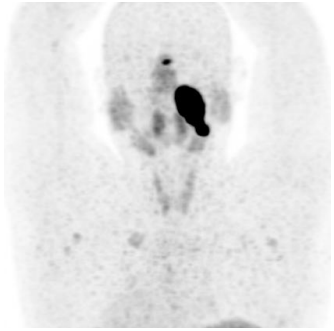
PET/CT [68Ga]Ga-DOTA-TATE

PET-Based Krenning Score		
Category	**Score**	**Interpretation**
Negative	Score 0	no uptake
	Score 1	very low uptake
Positive	Score 2	uptake less than or equal to that of the liver
	Score 3	uptake greater than the liver
	Score 4	uptake greater than that of the spleen

Theranostic Limitations

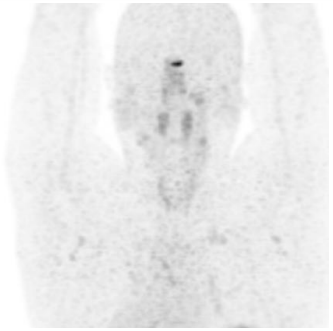
Imaging Current Limitations

- Mismatch between diagnostic and therapeutic radionuclides (e.g. 68Ga → 177Lu)
- Limited capability for accurate pre-therapy assesmet of treament outcome
- Trade-off between radiation range and precision
- Limited availability and production of novel radionuclides
- Tumor heterogenity [SomaKit **TOC** for diagnosis, Luthathera **TATE** for treatment]



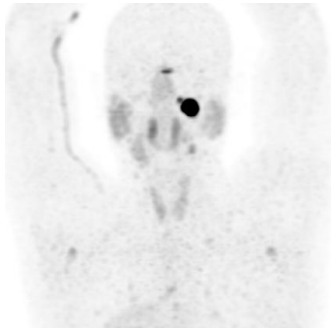
[^{68}Ga]Ga-DOTA-TATE

2016



[^{68}Ga]Ga-DOTA-TOC

2018



[^{68}Ga]Ga-DOTA-TATE

2020

Radiopeptyd	SSTR1	SSTR2	SSTR3	SSTR4	SSTR5
^{68}Ga-DOTATATE	**>10 000**	**0.20**	**>1000**	**300**	**377**
^{68}Ga-DOTATOC	>10 000	2.5	613	>1000	73
^{68}Ga-DOTANOC	>10 000	1.9	40	260	7.2
^{177}Lu-DOTATATE	**>1000**	**2.0**	**162**	**>1000**	**>1000**

Pauwels E, et al.. Somatostatin receptor PET ligands - the next generation for clinical practice. Am J Nucl Med Mol Imaging. 2018.

Theranostic Radionuclides

Emerging Opportunities

✓ Same vector and chemistry

✓ Patient selection & dose planning

✓ Radiation matched to tumor size

✓ Lower dose to healthy tissues

✓ Choice of β−, α and Auger emitters

New opportunities

✓^{64}Cu → ^{67}Cu (PET → β^-)

✓^{61}Cu → ^{67}Cu (PET → β^-)

✓^{43}Sc → ^{47}Sc (PET → β^-)

✓^{44}Sc → ^{47}Sc (PET → β^-)

✓^{203}Pb → ^{212}Pb (SPECT → α/β^-)

Terbium family:

✓152Tb → 161Tb (PET → β− + Auger)

✓152Tb → 149Tb (PET → α)

Is a theranostic pair enough for precision and personalized medicine?

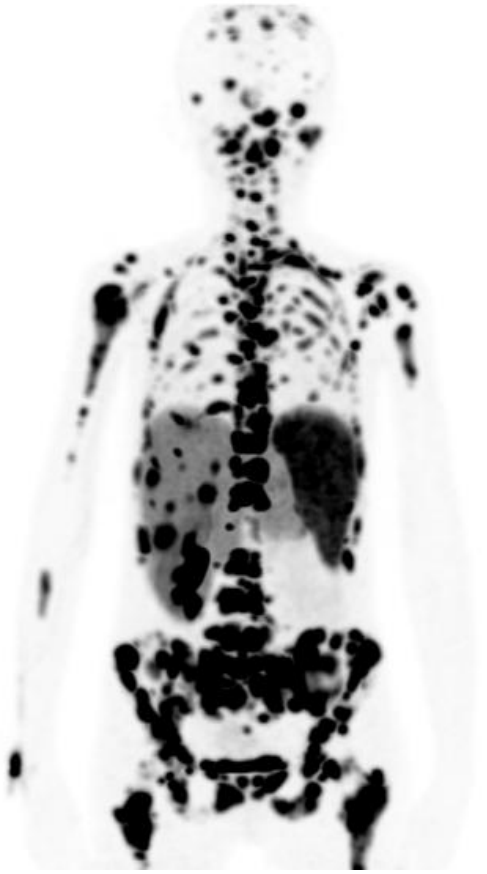
The next step - dosimetry

Current standard practice in RLT uses fixed radiopharmaceutical doses, regardless of patient-specific factors such as:

- Tumor burden (the total volume and distribution of cancer in the body)
- Primary tumor location (may affect pharmacokinetics)
- Disease stage (from early, localized disease to widespread metastatic involvement)
- Biological heterogeneity of tumors and metastases (impact receptor expression and radiotracer uptake)

• This “one-size-fits-all” approach, while effective in some cases, may:

- Lead to **suboptimal therapeutic outcomes**
- Increase the **risk of adverse effects**



Does a radionuclide metters?

Different phiscial properities – different clinical outcome

Feature	^{90}Y	^{177}Lu	^{161}Tb
Physical half-life	2.67 d	6.65 d	6.9 d
Main therapeutic emission	β^-	β^-	β^- + **Auger electrons**
Mean β^- energy	**~933 keV**	~133 keV	~154 keV
Maximum β^- range in tissue	**~11 mm**	~2 mm	~0.3 mm
Auger / conversion electron emission	Very low	Moderate	**High**
Imaging capability	Limited	**Yes (γ: 113, 208 keV)**	Yes, limited
Best suited for	**Large / bulky tumors**	Small–large lesions	**Small lesions / micrometastases**
RLT status	Clinically established	**Clinically established**	Emerging
Main advantage	Long β^- range → strong **cross-fire effect**	**Good balance** of range, energy and dosimetry	**High local energy deposition** + β^-
Main limitation	Higher irradiation of surrounding healthy tissue	Limited effect in very small lesions	Limited clinical experience and availability

Does a radionuclide metters?

Different phiscial properities – different clinical outcome

✓ **90Y-RLT** (240 patients)

- DRR (Durable Response Rate) 22,81 - 56,1%, średnio 42,92%,
- DCR (Disease Control Rate) **100%**

✓ **177Lu-RLT** (440 patients)

- DRR 27,63 - 57,35%, mean **33,41%**,
- DCR 71,88 - 100%, mean **79,32%**

DRR = complete or partial objective response

Meta-Analysis > Nucl Med Commun. 2017 Dec;38(12):1085-1093.
doi: 10.1097/MNM.0000000000000758.

The efficacy of the available peptide receptor radionuclide therapy for neuroendocrine tumors: a meta-analysis

Shorouk F Dannoon [1], Saud A Alenezi, Abdelhamid H Elgazzar

✓ tandem-RTL (97 patients)

- DRR 42,11 do 66,67%, mean **50,52%**
- DCR 93,33 - 100%, mean **98,97%**

What makes radionuclide therapy personalized?

Precision is a chain, not a single technology

The use of tandem therapy with LutaPol/ItraPol (177Lu/90Y-DOTATATE) as an effective tool in the treatment of neuroendocrine tumors, DuoNen, 2019/ABM/01/00077

(a multicenter, randomized phase III clinical trial)



Świętokrzyskie Centrum Onkologii

Maria Skłodowska-Curie National Research Institute of Oncology

Military Institute of Medicine – National Research Institute – WIM

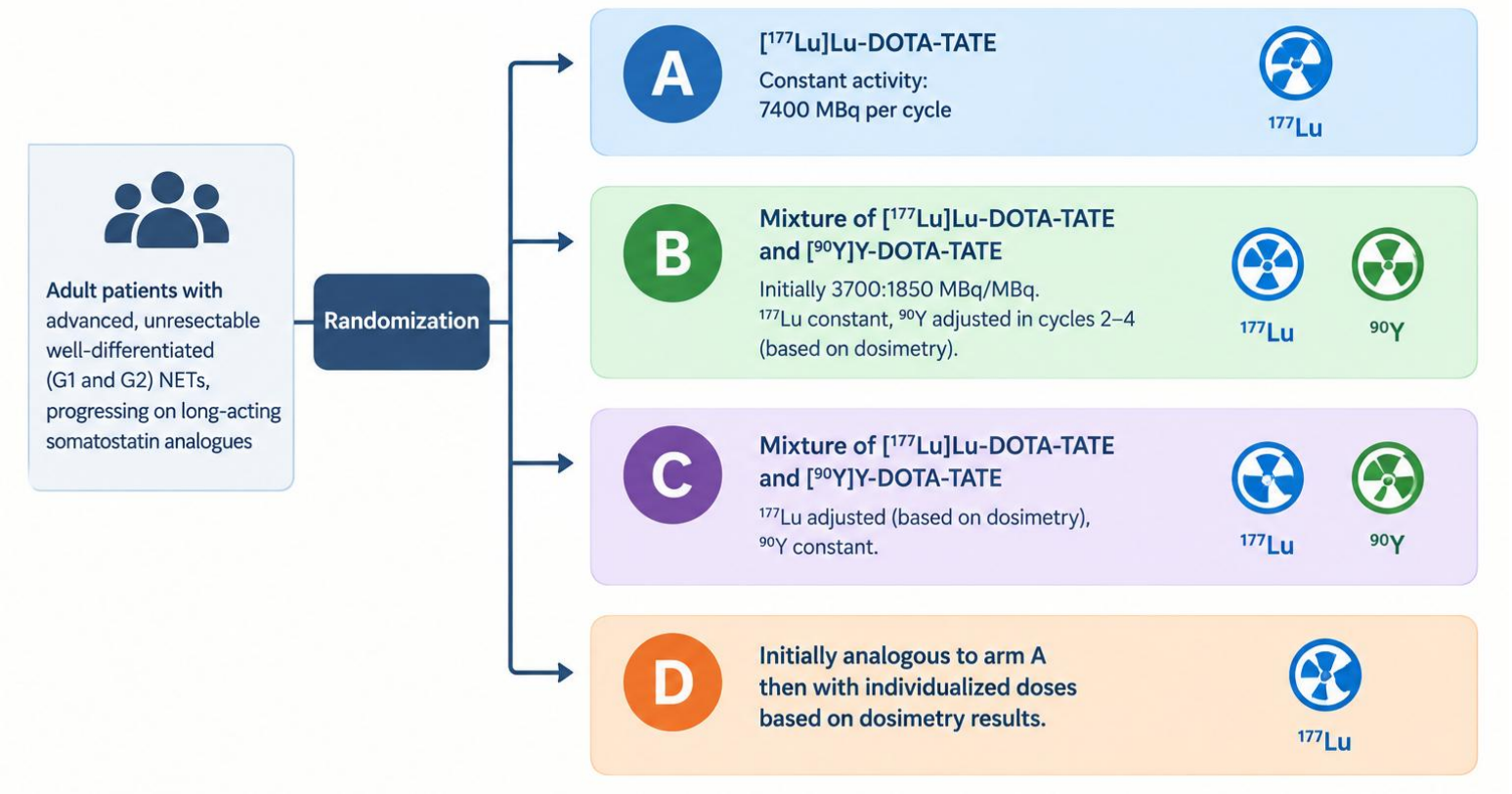
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University Hospital in Krakow

National Centre for Nuclear Research Świerk

DUONEN trial design

Material and Methods



Dosimetry outline

Five post-therapy imaging:

- whole-body (WBS) imaging **3.5 hours** after radiopharmaceutical administration
- SPECT/CT **4, 24, 48, and 192 hours** after radiopharmaceutical administration

For **bone marrow** dosimetry: blood samples measurements at five time points: **5, 15, and 40 minutes, and 4 and 24 hours** after RLT

RLT dose in subsequent cycles dependent **on individual dosimetry results for** critical organs (bone marrow, kidneys)

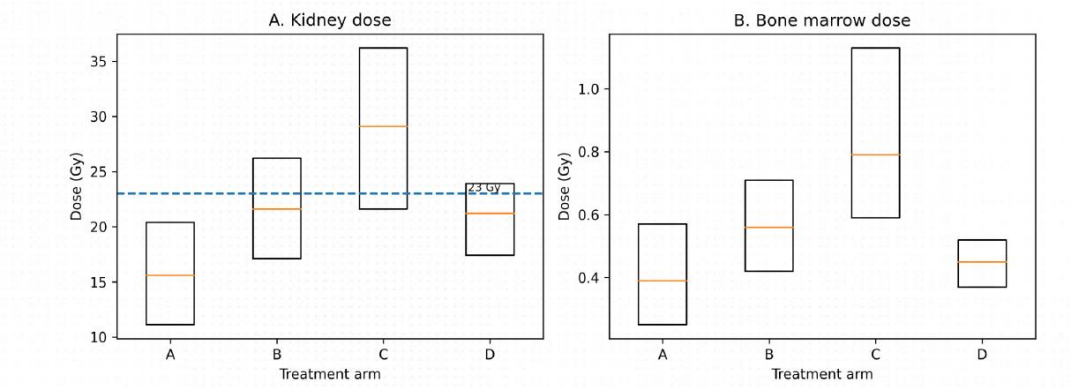
- ✓ **Kidneys** dose limit for for the entire RLT 23Gy
- ✓ **Bone marrow** dose limit of 2 Gy for the entire RLT (no more than 0.5 Gy per cycle)

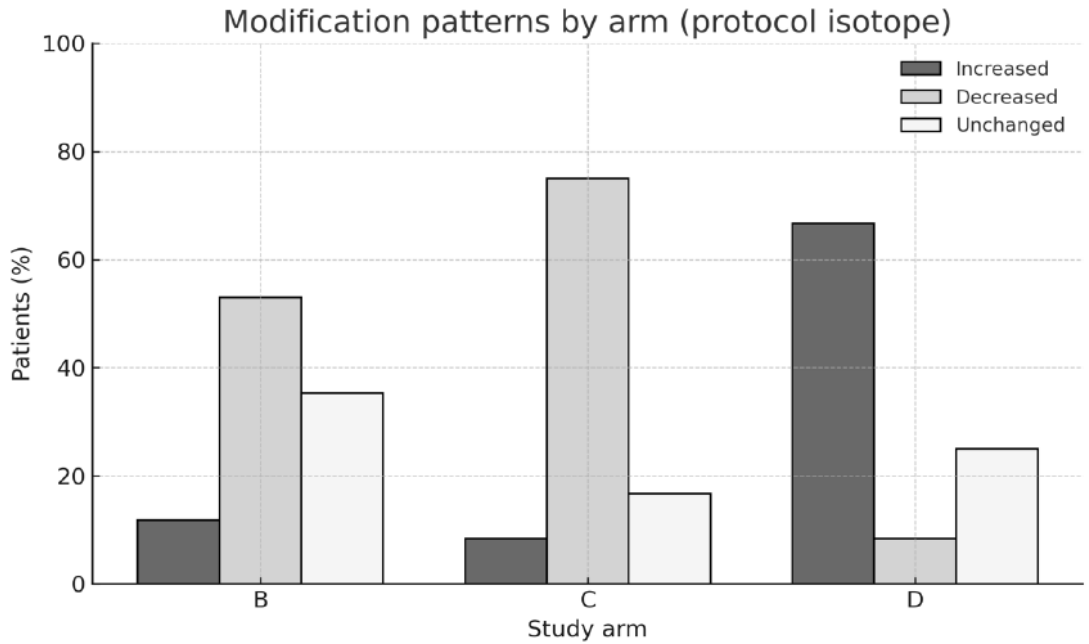
Clinical Role of Dosimetry

DUONEN intertim results

There is **significant inter individual variability** in absorbed doses – clinical benefits can be expected from adjusting RLT doses in subsequent treatment cycles

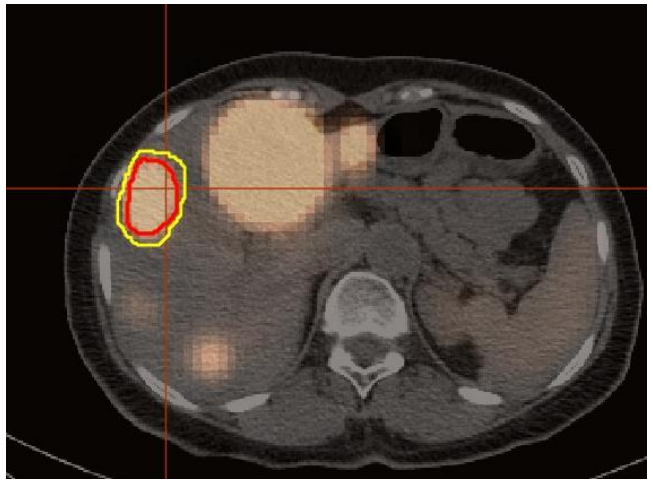
- in study arms treated with [^{177}Lu]Lu-DOTA-TATE, dose escalation was possible in 60% of cases, while dose reduction was indicated in 16%





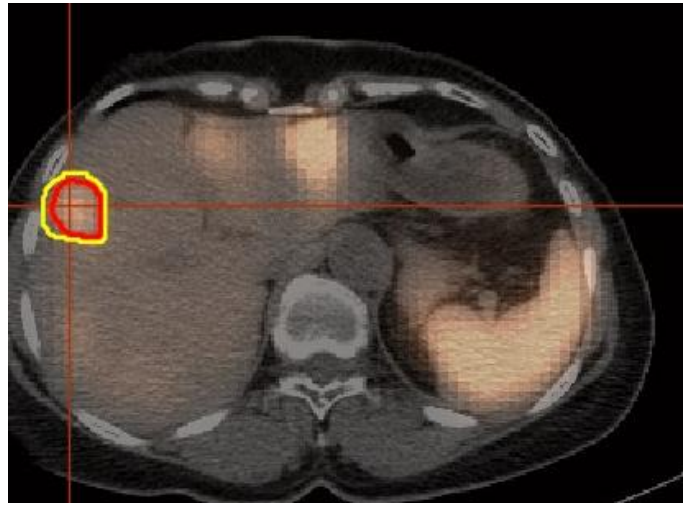
Results - Patient 1

		CI	CII	CIII	CIV
		7354 MBq	4742 MBq	4551 MBq	4157 MBq
Kidneys	Absorbed dose (Gy)	7,21	5,49	5,91	6,35
Bone marrow		0,17	0,10	0,08	0,15
T1	Absorbed dose (Gy)	55	4,9	6,6	4,7
T2	Absorbed dose (Gy)	65,4	6,15	4,73	5,9
T3	Absorbed dose (Gy)	57,4	11,5	10,4	10,5
T4	Absorbed dose (Gy)	58,1	0	0	0



Female 75 years old, NET of pancreas, G2, Ki67 approximately 9%, arm D

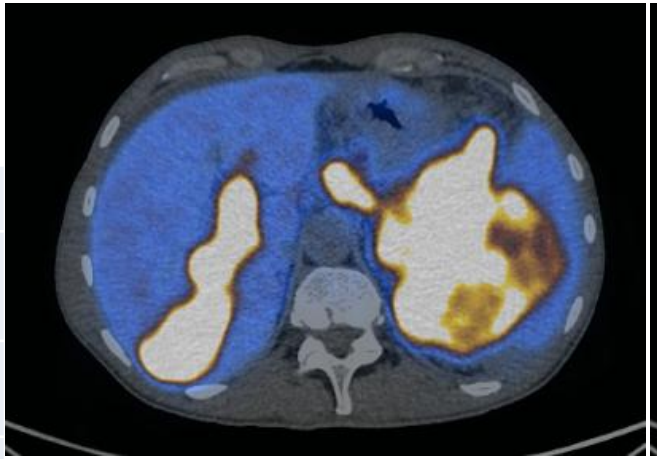
High renal exposure → decrease of the dose of [177Lu]-DOTA-TATE total dose approximately 20.8 GBq) → a very good radiological response without biochemical complications

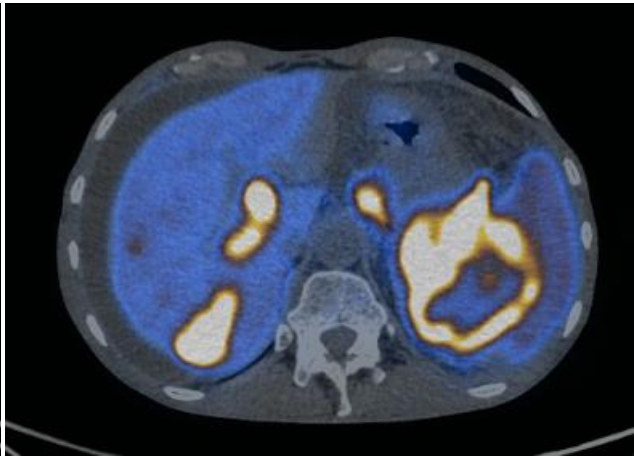


Results - Patient 2

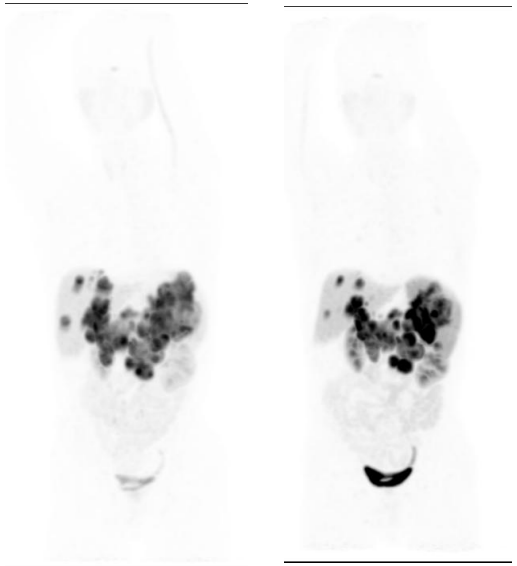
Male, 49 years of age, NET pancreas, G2, arm C

		CI	CII	CIII	CIV
		3689/1846 MBq	4917/1854 MBq	5238/1904 MBq	4109/1786 MBq
kidnes	Absorbed dose (Gy)	4,46	5,53	7,7	7,37
bone marrow	Absorbed dose (Gy)	0,45	0,45	0,65	0,51
T1	Absorbed dose (Gy)	51,6	38,3	28,6	18,4
T2	Absorbed dose (Gy)	57,6	49,3	36,0	28,9
T3	Absorbed dose (Gy)	48,6	39,0	30,7	11,1





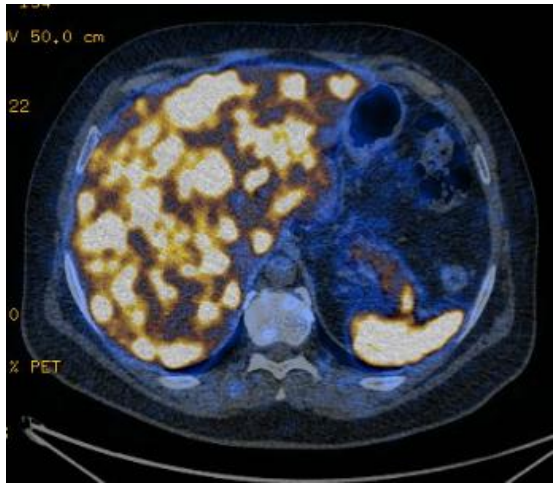
Good dosimetric results lead to low dose escalation in subsequent cycles with a good radiological and biochemical response.Chromogranin A (baseline): 113.6 nmol/L [0.0–6.0](post-PRRT): 35.5 nmol/L [0–6]. Therapy was complicated by persistent thrombocytopenia (PLT: 47×10³/µL [150–440]).(total dose approx. 25.4 GBq)



Results - Patient 3

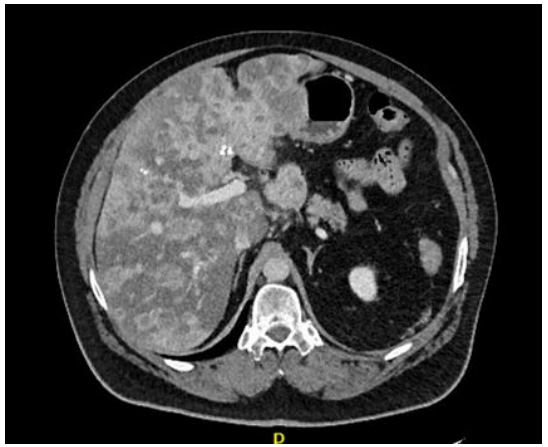
Male 57 years old, NET pancreas, G2, arm D

		CI	CII	CIII	CIV
		7200MBq	11996MBq	14000MBq	14000MBq
kidneys	Absorbed dose (Gy)	2,76	5,03	5,40	5,48
Bone marrow	Absorbed dose (Gy)	0,17	0,26	0,25	0,32
T1	Absorbed dose (Gy)	50,9	63,4	66,9	52,1
T2	Absorbed dose (Gy)	48,9	75,8	104,0	58,2
T3	Absorbed dose (Gy)	38,1	50,6	80,1	61,7



Very good dosimetric results → significant dose escalation in subsequent cycles [total almost 52GBq] → radiological stabilization of the disease, no biochemical complications





Summary

The Role of Dosimetry and Theranostics in Radioligand Therapy

- **Theranostics** is evolving from established ^{68}Ga / ^{177}Lu applications toward a broader portfolio of radionuclide platforms
- **New pairs** such as ^{64}Cu / ^{67}Cu, **^{44}Sc / ^{47}Sc, terbium** isotopes and ^{203}Pb / ^{212}Pb offer different combinations of imaging and therapeutic physics —but they are at different stages of translation
- **Dosimetry** is essential for optimizing RLT, but we need **faster and more efficient** computational **algorithms** to enable its routine clinical implementation
- **Precision radionuclide therapy** is ultimately **a chain**: accelerator capability + radionuclide production + radiochemistry + molecular targeting + dosimetry + clinical decision-making

