Advances in Nuclear Medicine Theranostics

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Contents

- The use of radioiodine in thyroid cancer
- Peptides in neuroendocrine and prostate cancer

Disclosures

None

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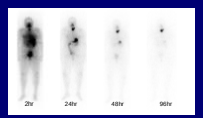
^{124}I-NaI PET: Building block for precision medicine in metastatic thyroid cancer

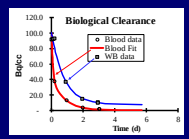
(PIs: Larson/ Humm / Tuttle)

The Concept of Maximum Tolerated Activity (MTA)

Bone marrow is the dose limiting for most radionuclide therapies.
Blood is commonly used as a surrogate for marrow

1) Blood clearance (beta dose)
2) Whole Body Clearance (gamma dose)



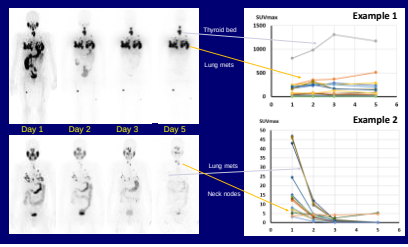


D_T (cGy/MBq) = D_B (blood) + D_Y (WB)

MTA (MBq) = 200cGy / D_T (cGy/MBq)

Benua RS et al, The relation of radioiodine dosimetry to results and complications in the treatment of metastatic thyroid cancer. American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine, 87 171 -182. 1962

Thyroid lesion dosimetry (by ^{124}I PET)



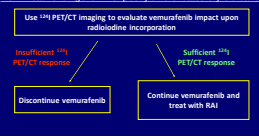
Restoring Radioiodine Uptake in Thyroid Cancer

A Paradigm Shift

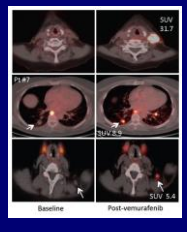
But what about thyroid lesions with poor radioiodine uptake?

New drugs are under development, such as selumetinib and vemurafetnib, that have the potential to restore the NaI symporter expression, and thus reverse the refractoriness to radioiodine in some patients with metastatic thyroid cancer.

New Treatment Algorithm for poorly differentiated thyroid cancer



Measuring ^{124}I Avidity change by PET after Vemurafenib



Based on simple assumptions e.g. 70 kg man, 48hr biological half-life, lesion doses would be

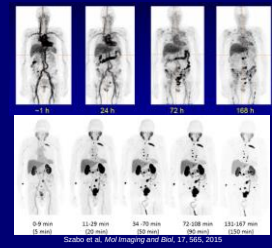
D = 202 Gy

D = 57 Gy

D = 34 Gy

Peptides theranostics for neuroendocrine and prostate cancer

Comparing Antibody Against Peptide

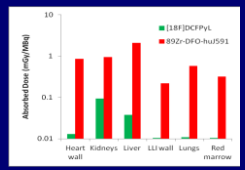


^{89}Zr-anti PSMA antibody

^{18}F-DCFPyL PSMA binding peptide

Szabo et al, *Mol Imaging and Biol*, 17, 565, 2015

Dosimetric Implications for diagnostic imaging and treatment follow-up

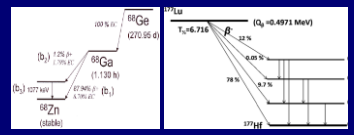


ImmunoPET requires long lived radionuclide (^{89}Zr or ^{124}I) because tumor uptake is slow.
Peptides localize rapidly into tumor allowing short lived radionuclides (^{68}Ga and ^{18}F).

Radiolabeled Peptides in Current Use

Molecule		Applications
SSTR-targeting agents		
Imaging	^{68}Ga-DOTATATE	Neuroendocrine Tumors
Therapy	^{177}Lu-DOTATATE (Lutathera)	Neuroblastoma/Pheochromocytoma
	^{177}Lu-JR11 (Satoreotide Tetraxetan)	
PSMA-targeting agents		
Imaging:	^{68}Ga-PSMA-11/HBED-CC	Prostate Cancer
	^{18}F-DCFPyL	Vascular Tumors
Therapy:	^{131}I-MIP-1095	
	^{177}Lu-PSMA-R2 / PSMA-617	
	^{225}Ac-PSMA-617	

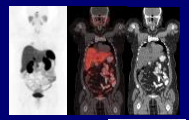
Theranostic Imaging Isotopes



^{68}Ga (68 min half-life)	^{177}Lu (6.7 day half-life)
90% positron yield	Mean β ray energy of 0.159MeV (1.6mm range)
Produced by a ^{68}Ge generator	10% yield of 208 keV photons for imaging

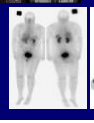
Lutathera Treatment at MSKCC

^{68}Ga-DOTATATE PET scan

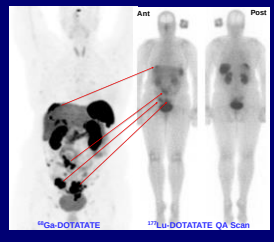


Amino acid solution (Lysine 2.5% + Arginine 2.5%) – 250ml/hr for 30 min

^{177}Lu DOTATATE infused over 30min using Graseby syringe pump



^{68}Ga / ^{177} Lu concordance



^{68}Ga-DOTATATE

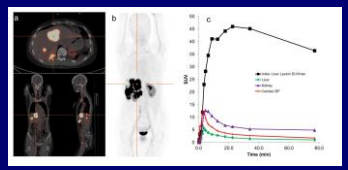
^{177}Lu-DOTATATE QA Scan

Improving peptide targeting
The example of JR11

- Preliminary clinical studies (Wild et al 2014) with JR11 indicated higher tumor uptake and retention of SSTR antagonist compared to DOTATATE agonist.
- MSK Study (20 pts) imaged with ^{68}Ga-DOTA-JR11 followed by therapy with ^{177}Lu-DOTA-JR11.
  1.85 GBq 7.4 GBq
- Dosimetry admin (50 mCi) followed by 2 x therapy admin (~200 mCi) with absorbed dose limits (23 Gy to kidney, 1.5 Gy to red marrow).

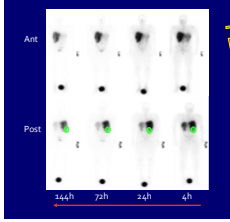
Wild D, Fani M, Fischer R, Del Pozzo L, Kaul F, Kreb S, Fischer R, Reubi JC, Maecke HR and Weber WA, Comparison of somatostatin receptor agonist and antagonist for peptide receptor radionuclide therapy: a pilot study. JNM. 2014 Aug;55(8):1248-52.

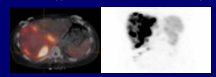
^{68}Ga-DOTA-JR11 Uptake and Biodistribution



No significant uptake in any normal tissues except kidney
High uptake of ^{68}Ga-DOTA-JR11 in liver disease
Rapid disease uptake with prolonged retention

Determining the MTA for ^{177}Lu-DOTA-JR11 (treatment planning)





Pre-Therapy Administration: 49 mCi (1.81 GBq)

Projections for Therapy:

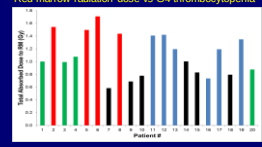
Activity limits: 789 mCi (RM); 861 mCi (Kidney)
29 GBq 32 GBq

Index Lesion: 22 cGy/mCi (600 cGy/GBq)

Lesion dose @ MTA: 374 Gy
Lesion dose @ 200 mCi: 44 Gy

^{177}Lu-DOTA-JR11 Toxicity after 20 patient clinical trial

Red marrow radiation dose vs G4 thrombocytopenia



Red: G4 thrombocytopenia after two cycles (3 months apart)
Green: no G4 thrombocytopenia after two cycles (3 months apart)
Blue: no G4 thrombocytopenia after two cycles (> 3 months apart)
Black: no G4 thrombocytopenia after one cycle (did not have second cycle)

Combining EBRT with Targeted Radionuclide therapy

Rationale: Use radionuclide therapy to treat micrometastases and use EBRT to boost the dose to bulky disease inadequately treated by radionuclide therapy.

Minimal overlap in dose limiting toxicity: For targeted radionuclide therapies it is usually marrow, kidney and salivary glands.

Summary 1

- Radioiodine was the 1st targeted radionuclide theranostic.
- It led to the foundation of a dosimetric method with which to estimate the maximum tolerated activity (MTA) and the use of an imaging dose being used to guide the selection of a therapy dose.
- The ability of PET to quantify radioiodine uptake and the emergence of new thyroid differentiation agents offer the new potential to use imaging to select which patients benefit from radionuclide therapy.

Summary 2

- ImmunoPET requires long-lived radionuclides e.g. ^{89}Zr and ^{124}I commensurate with the slow targeting pharmacokinetics of antibodies.
- Small peptides have faster uptake and clearance kinetics relative to antibodies which allows the short half-lived radionuclides e.g. ^{68}Ga and ^{18}F for imaging that results in lower radiation doses.
- Two promising peptide therapies are SSTR (neuroendocrine tumors) and PSMA (prostate cancer).
- Most currently favored theranostic radionuclide ^{177}Lu, which has a 6.7 day half-life and a low yield of photon emissions but ideal for imaging.
- Lutathera was FDA approved in 2018. PSMA theranostic agents approved in Europe and Australia and likely soon in the U.S.

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