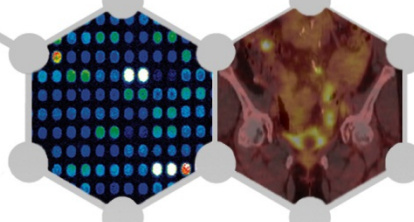

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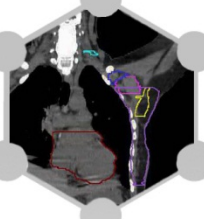

Overview of opportunities of RPT in the NCTN

Radiation dosimetry in RPT trials

Amir Iravani, MD
Assistant Professor of Radiology
Washington University

2021 Winter NRG Radiation Oncology Virtual
01/29/2021

Increasing Importance of RPT


ASCO Connection
The professional networking site for our worldwide oncology community
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Home > Magazine > Features
Clinical Cancer Advances 2019: ASCO Names Advance of the Year, Debuts Research Priorities for the Cancer Community

- **Anaplastic thyroid carcinoma (ATC):** The U.S. Food and Drug Administration (FDA) approved the first treatment for this type of thyroid cancer in nearly 50 years: a targeted-therapy combination of dabrafenib plus trametinib for patients with *BRAF*-mutated ATC.
- **Desmoid tumors:** Research identified sorafenib as the first therapy to improve progression-free survival for patients with this rare form of sarcoma.
- **Neuroendocrine tumors (NETs):** The FDA approved lutetium Lu 177 dotatate, which delivers targeted radiation to tumor cells, for patients with advanced somatostatin receptor-positive NETs in the foregut, midgut, and hindgut.
- **Uterine serous carcinoma:** Research showed that trastuzumab slowed the progression of HER2-positive uterine serous carcinoma, one of the most aggressive forms of endometrial cancer.
- **Tenosynovial giant cell tumor:** Pexidartinib was shown to be the first promising therapy for this rare cancer of the joints.

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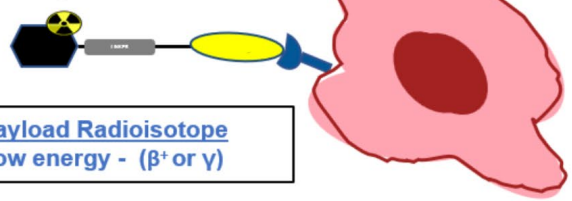
Theranostics :

Imaging a biological target → Therapeutic intervention

Quantitative Imaging

STEP #1 See cancer

Diagnostic



Payload Radioisotope
Low energy - (β^+ or γ)

Scan

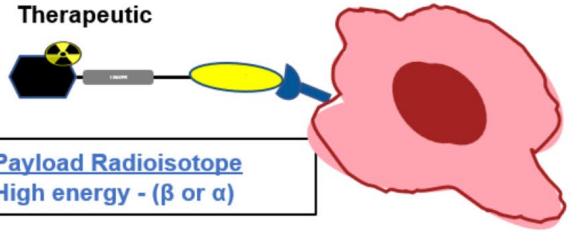
Image

Imaging:
- ✓ Full body
- ✓ Non-invasive
- ✓ Repeatable
- ✓ Instant (~2 hr)

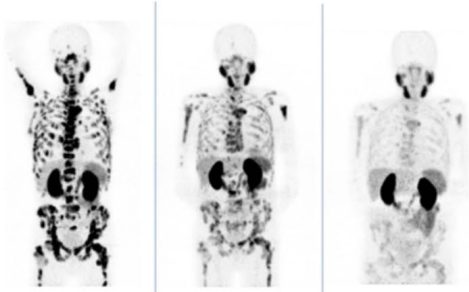
Quantitative Imaging

STEP #2 Kill cancer

Therapeutic



Payload Radioisotope
High energy - (β or α)



Before

6 mth

Therapy:
- ✓ Confirm and hit
- ✓ Time optimization
- ✓ Dose optimization
- ✓ Low dose low toxicity

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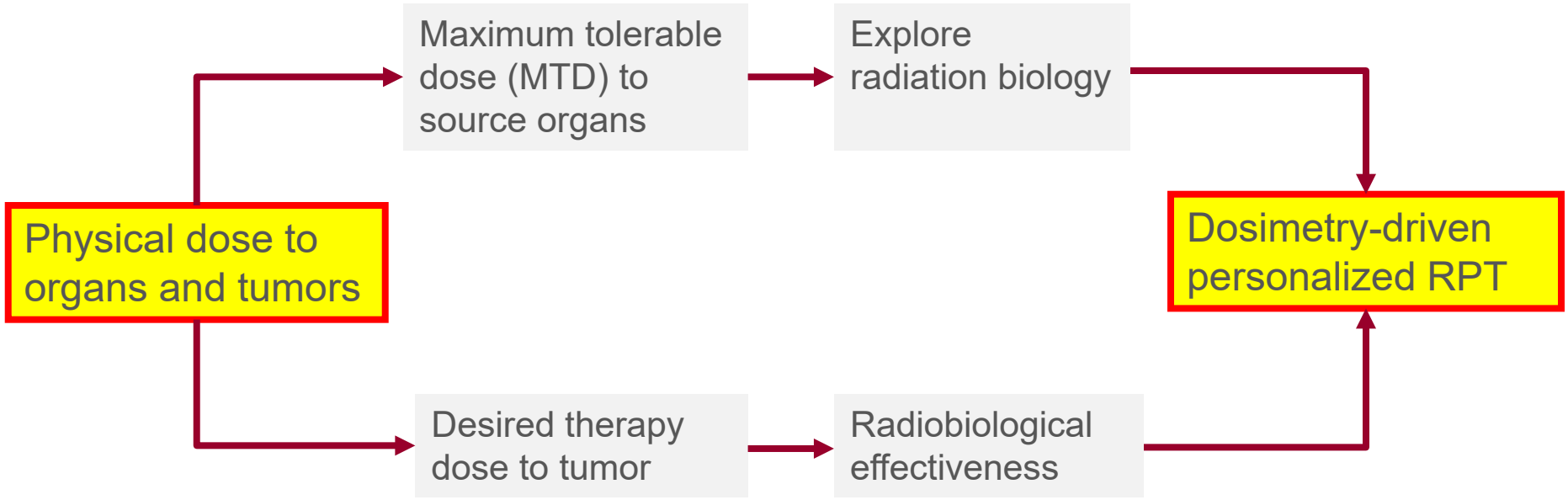
Opportunities Provided by Quantitative Pre- and Post-treatment Imaging



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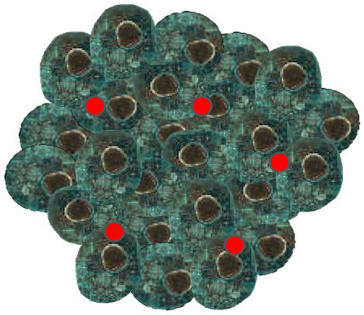
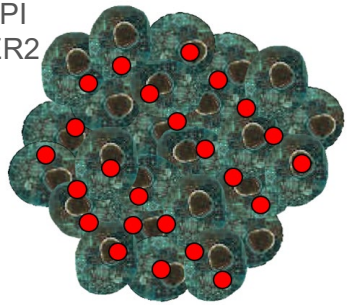
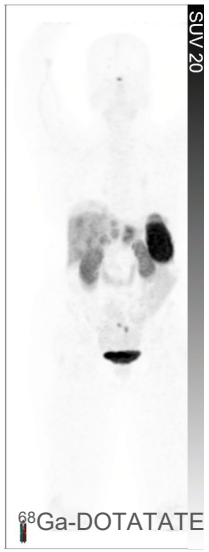
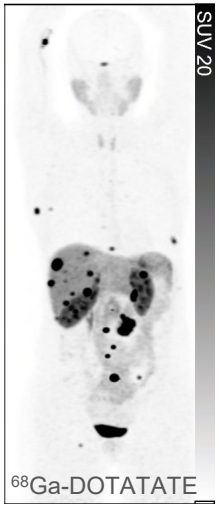
Opportunities Provided by Quantitative Imaging of the Biologic Target

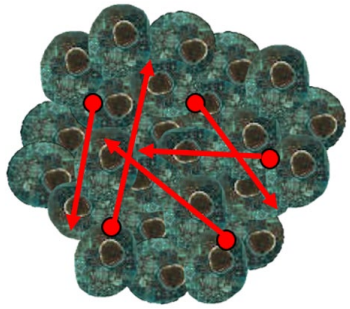


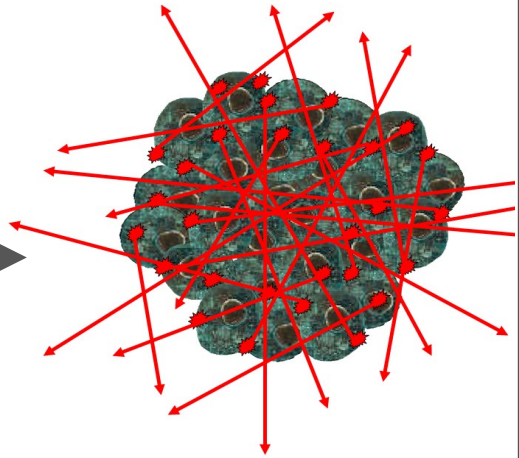
- **Biologic Target**
  - SSTR :NEN
  - PSMA :PCa
  - NaI symporter : DTC
  - Norepinephrine Transporter
  - CXCR4
  - GLP1
  - CCK-2
  - FAPI
  - HER2



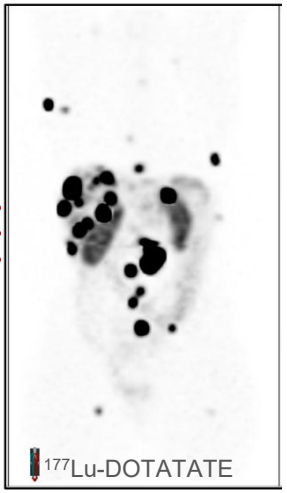








"Crossfire effect"



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Importance of Pre-treatment Imaging

VOLUME 26 · NUMBER 13 · MAY 1 2008

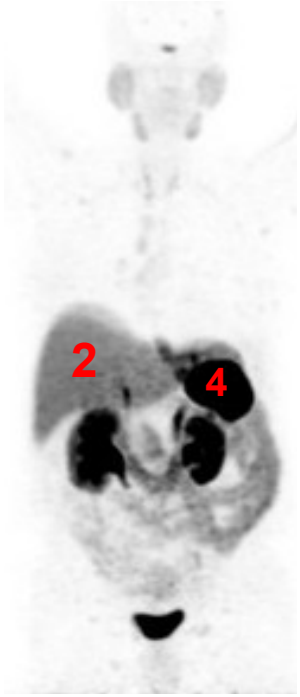
JOURNAL OF CLINICAL ONCOLOGY

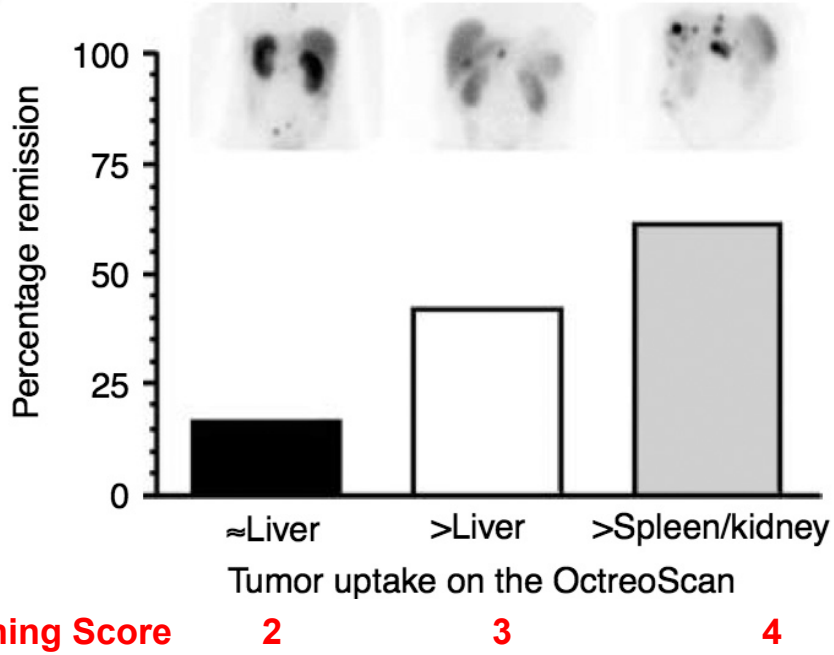
Treatment With the Radiolabeled Somatostatin Analog [^{177}Lu-DOTA^{0},Tyr^{3}]Octreotate: Toxicity, Efficacy, and Surviva

Dik J. Kwekkeboom, Wouter W. de Herder, Boen L. Kam, Casper H. van Eijck, Martijn van Essen, Peter P. Kooij, Richard A. Feelders, Maarten O. van Aken, and Eric P. Krenning

DOI: 10.1200/JCO.2007.15.2553

Krenning Score





Krenning Score 2 3 4

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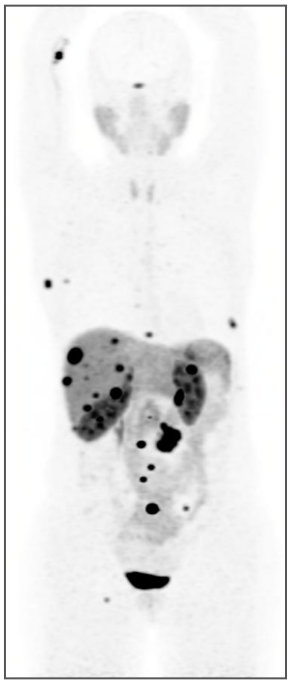
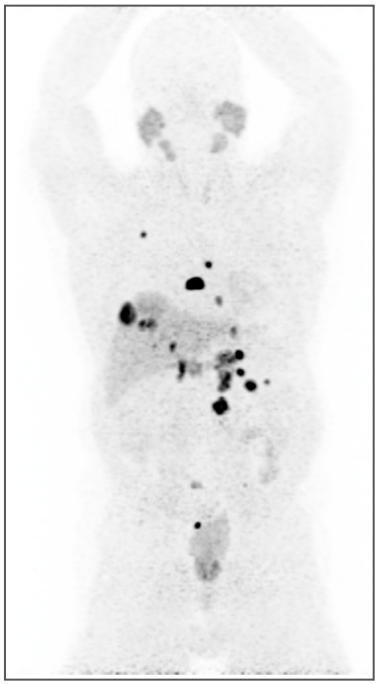
From Qualitative to Quantitative Imaging

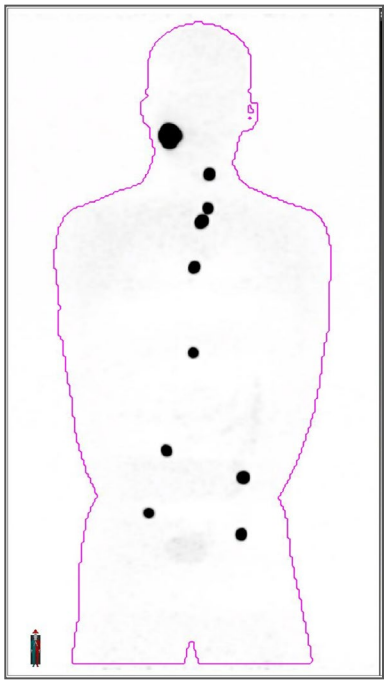


^{68}Ga-DOTATATE

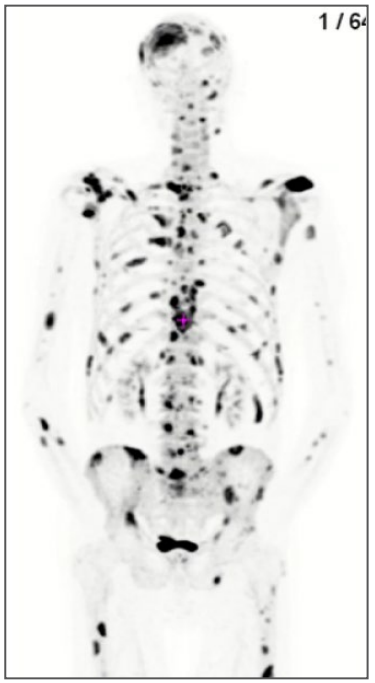
^{68}Ga-PSMA-11



^{124}I MIBG



^{124}I NaI



^{18}F-NaF

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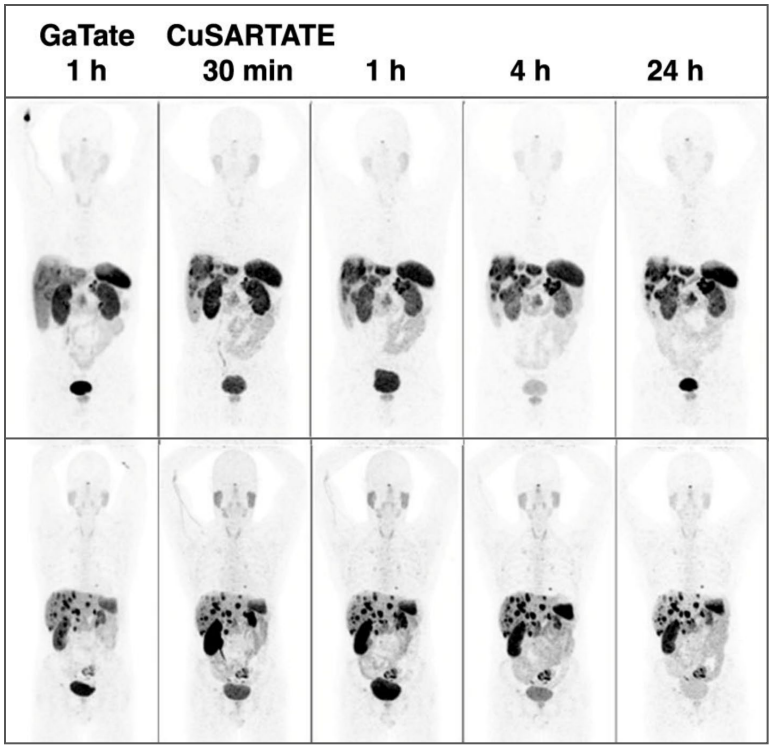
Prospective Dosimetry: Pre-treatment Quantitative Imaging

First-in-human trial of ^{64}Cu-SARTATE PET imaging of patients with neuroendocrine tumours demonstrates high tumor uptake and retention, potentially allowing prospective dosimetry for peptide receptor radionuclide therapy

Rodney John Hicks, Price Jackson, Grace Kong, Robert E. Ware, Michael S Hofman, David A Pattison, Tim Akhurst, Elizabeth Drummond, Peter Roselt, Jason Callahan, Roger Price, Charmaine Jeffery, Emily Hong, Wayne Noonan, Alan Herschtal, Lauren J. Hicks, Matthew Harris, Amos Hedt, Brett M. Paterson and Paul Donnelly

J Nucl Med.
Published online: November 15, 2018.
Doi: 10.2967/jnumed.118.217745



Using PET agents with longer physical half-life (^{64}Cu :12.7 hrs)

- Inherent quantitative ability of PET technology
- Clearance kinetics within source organs and tumor tissues potentially beyond 24 hours
- Prospective dosimetry
- Potential to use theranostic pair (^{67}Cu)

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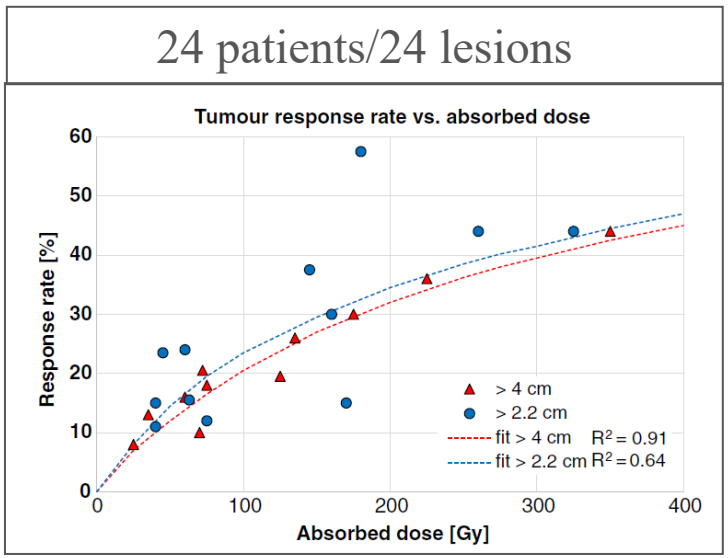
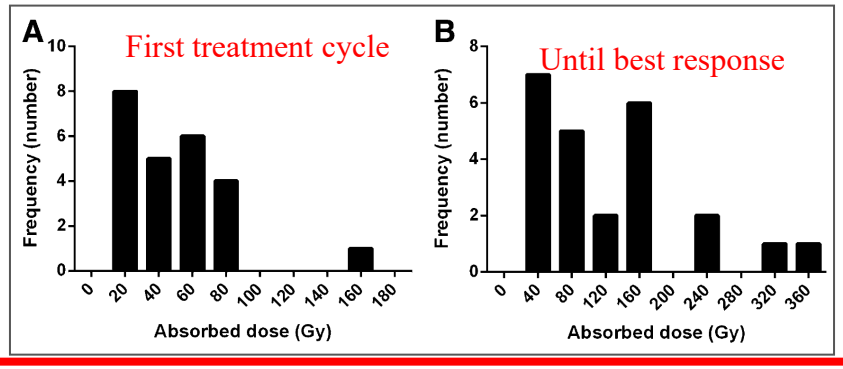
Post-treatment Quantitative Imaging: Dose-response relationship

Dose Response of Pancreatic Neuroendocrine Tumors Treated with Peptide Receptor Radionuclide Therapy Using ^{177}Lu-DOTATATE

Ezgi Ilan[1,2], Mattias Sandström[1,2], Cecilia Wassberg[1,3], Anders Sundin[1,3], Ulrike Garske–Román[1,3], Barbro Eriksson[4], Dan Granberg[4], and Mark Lubberink[1,2]

J Nucl Med 2015; 56:177–182
DOI: 10.2967/jnumed.114.148437





Radiopharmaceutical therapy

Administered activity ≠ Absorbed dose ≠ Response

Wide range of absorbed dose

- Heterogeneity in binding affinity
- Receptor density
- Hypoxia and necrosis
- Tumor volume

Tumor-specific radiosensitivity and Outcome

Wide range of tumor shrinkage

- Proliferation rate Ki 67
- Primary site
- Microenvironment
- Hypoxia and necrosis

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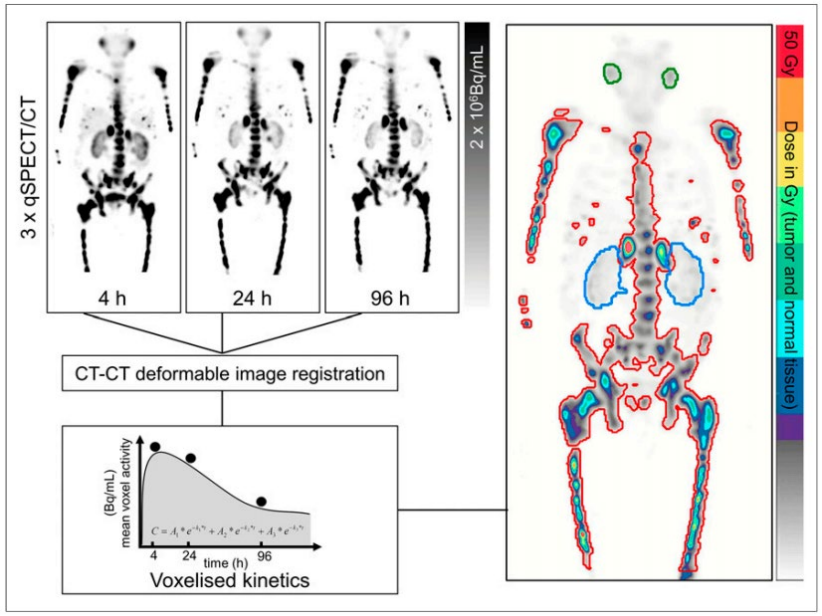
Combining Pre- and Post-treatment Quantitative Imaging

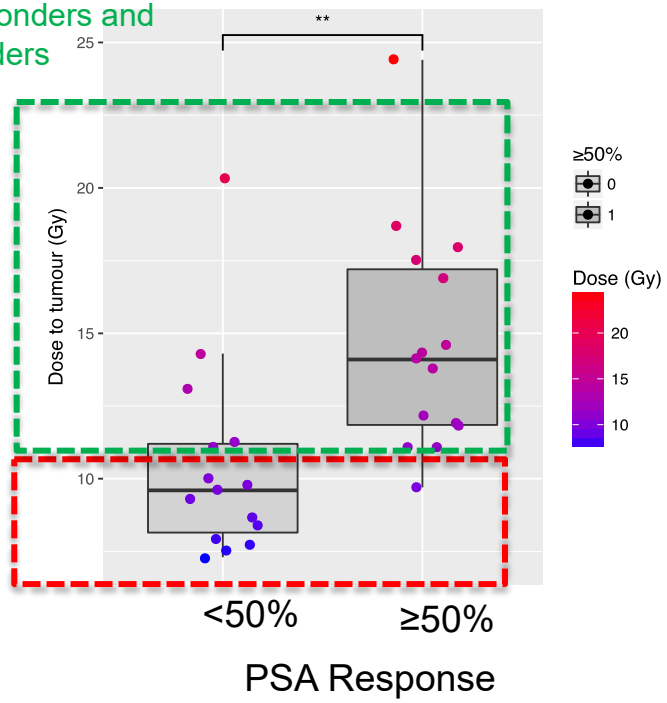
Dosimetry of ^{177}Lu-PSMA-617 in Metastatic Castration-Resistant Prostate Cancer: Correlations Between Pretherapeutic Imaging and Whole-Body Tumor Dosimetry with Treatment Outcomes

John Violet[1], Price Jackson[1,2], Justin Ferdinandus[2], Shahneen Sandhu[3], Tim Akhurst[2], Amir Iravani[2], Grace Kong[2], Aravind Ravi Kumar[2], Sue Ping Thang[2], Peter Eu[2], Mark Scalzo[2], Declan Murphy[4,5], Scott Williams[1,5], Rodney J. Hicks[2,5], and Michael S. Hofman[2,5]



An overlap
among responders and non-responders

<10 Gy:
10 non-responders
1 responder



Whole-body tumor SUVmean | **Whole-body tumor absorbed dose** | **PSA response at 12 wks**

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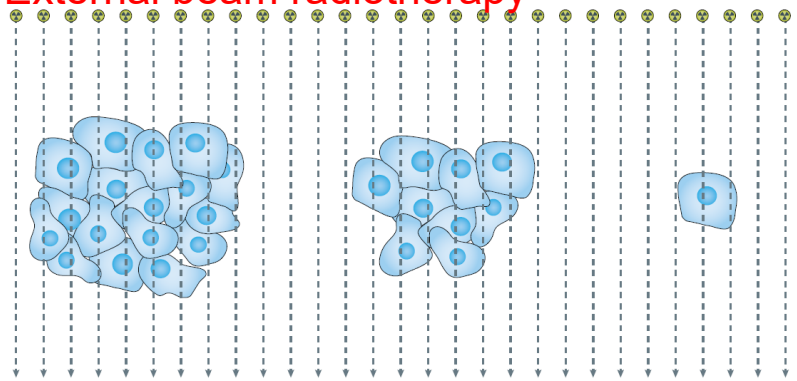
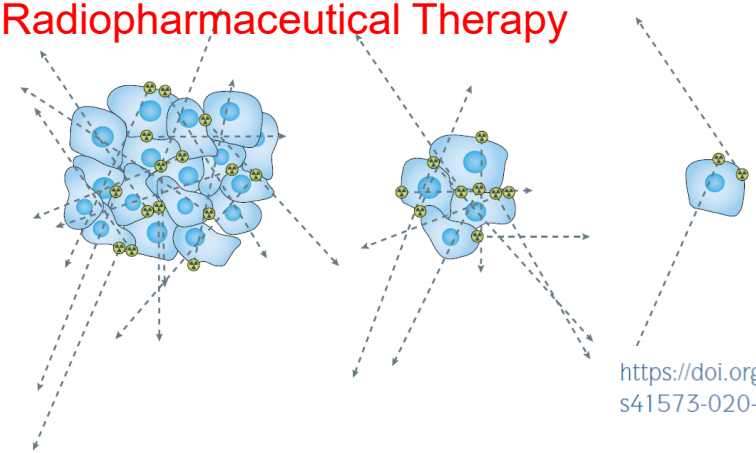
From Macrodosimetry to Microdosimtery

Lesion geometry and dosimetry

External beam radiotherapy

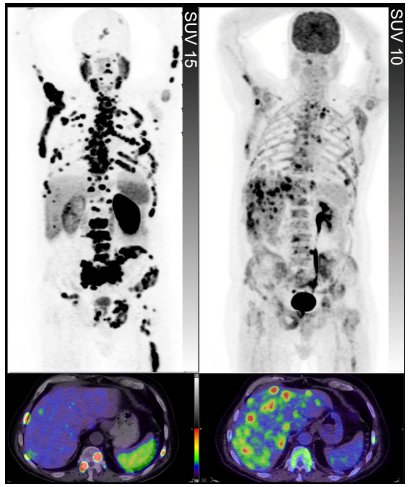


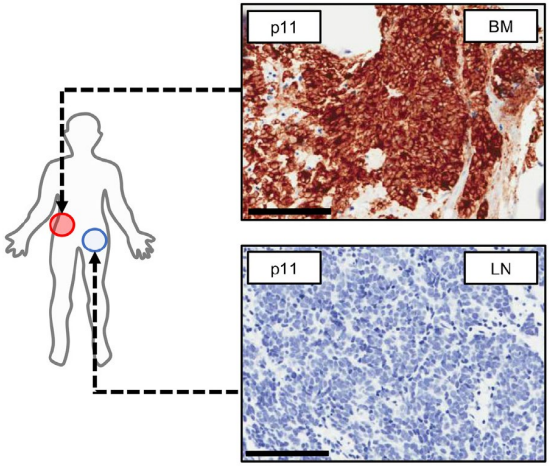
Radiopharmaceutical Therapy



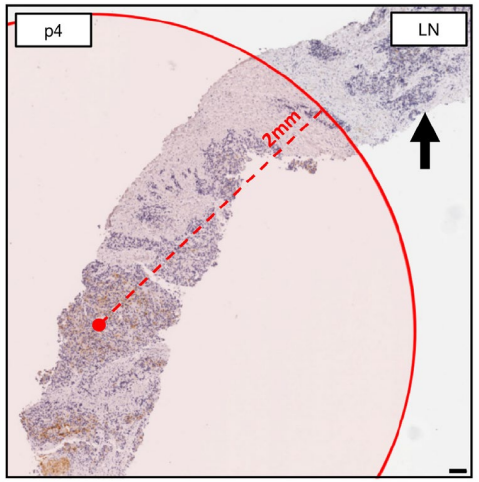
https://doi.org/10.1038/s41573-020-0073-9

Intra-patient heterogeneity and dosimetry





Intra-lesion heterogeneity and dosimetry



https://doi.org/10.1016/j.eururo.2019.06.030

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Goal: Personalized RPT Based on Dosimetry

European Journal of Nuclear Medicine and Molecular Imaging (2018) 45:970–988
https://doi.org/10.1007/s00259-018-3945-z

ORIGINAL ARTICLE

Prospective observational study of ^{177}Lu-DOTA-octreotate therapy in 200 patients with advanced metastasized neuroendocrine tumours (NETs): feasibility and impact of a dosimetry-guided study protocol on outcome and toxicity

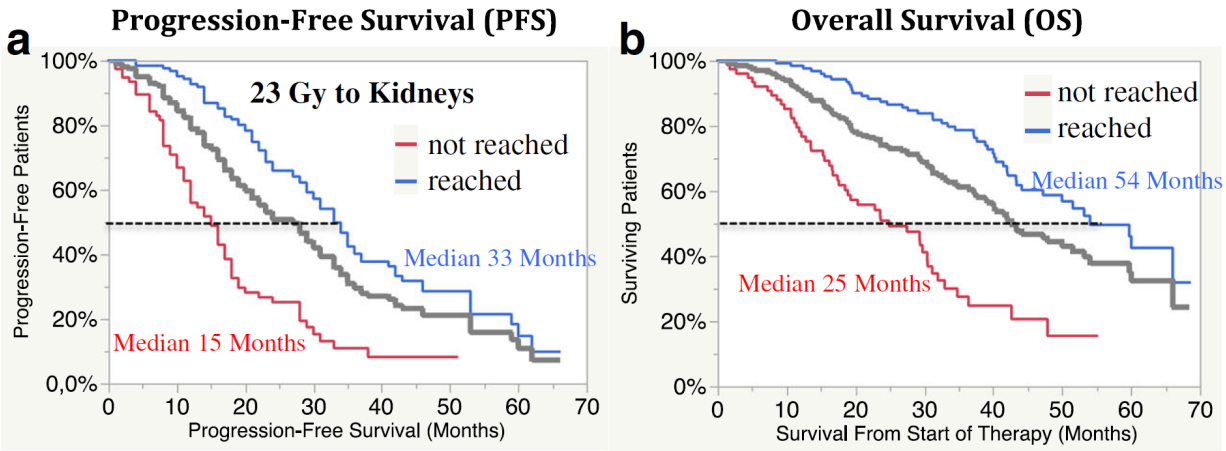
Ulrike Garske-Román[1,2] · Mattias Sandström[3] · Katarzyna Fröss Baron[4] · Lars Lundin[2] · Per Hellman[2] · Staffan Welin[4] · Silvia Johansson[4] · Tanweera Khan[4] · Hans Lundqvist[3] · Barbro Eriksson[4] · Anders Sundin[2] · Dan Granberg[4]

Received: 29 September 2017 / Accepted: 11 January 2018 / Published online: 1 March 2018

Dosimetry driven personalized RPT

- Stop criterion: aiming at an absorbed dose of 23 Gy to the kidneys
- Kidney absorbed dose a surrogate tumor dose and maximum tolerability of patient

Entire population



Longer PFS and OS in patients achieved 23 Gy to kidneys

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Concluding Remarks

- Radiation dose from RPT is a measure that is expected to correlate with tumor control probability and normal tissue complication probability

- Dose to tumors and normal tissues can vary widely among patients for a given administered activity level due to differences in
  - Tissue mass
  - Pharmacokinetics
  - Tissue geometries
  - Tumor phenotype and microenvironment

It is critical to monitor patient-specific radiation absorbed dose by established dosimetry techniques, whereby appropriate changes in management may be made

Opportunities and Future Directions

- Development of radiopharmaceuticals with potential to perform prospective dosimetry
- Inclusion of post-treatment dosimetry in RPT trials to establish the dose-response relationships
- Macro and microdosimetry to enhance the understanding of RPT radiation biology
- Trials designs with the goal of personalization of RPT based on pre-treatment or post-treatment dosimetry