Department of Medical Physics
UNIVERSITY OF WISCONSIN – MADISON
SCHOOL OF MEDICINE AND PUBLIC HEALTH

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RADIOLOGICAL ENGINEERING
& DESIGN LABORATORY

The Rationale for Dosimetry in Systemic Radiopharmaceutical Therapy

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NCI Workshop on Dosimetry of SRT, Bethesda, MD April 19th, 2018

Disclosures

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I’m the co-founder and Chief Scientific Officer of Voximetry, LCC a Madison based nuclear medicine dosimetry company.

The State of SRT Dosimetry

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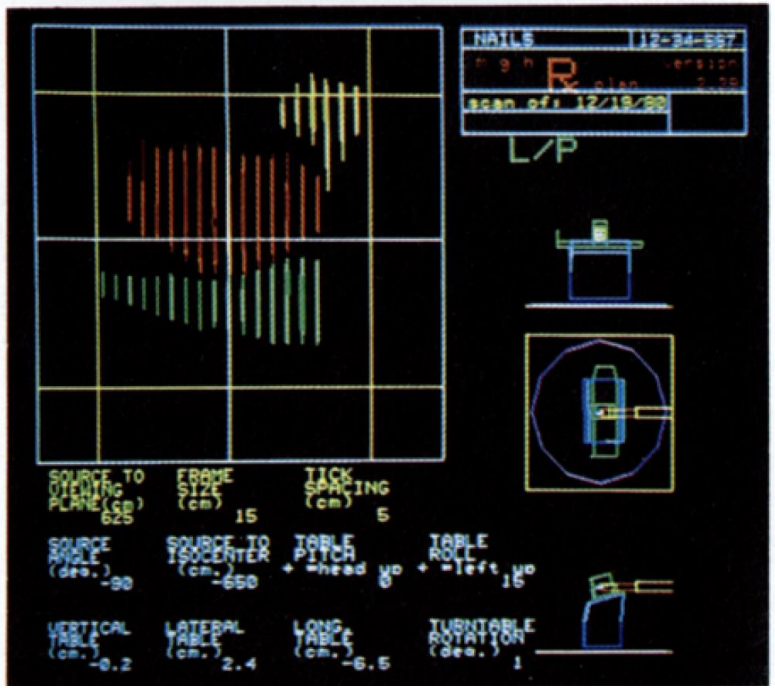
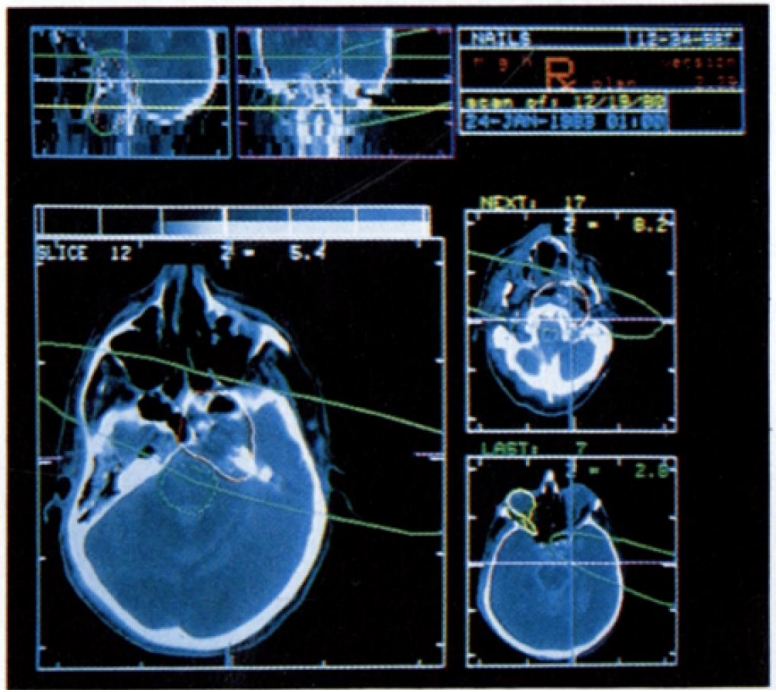
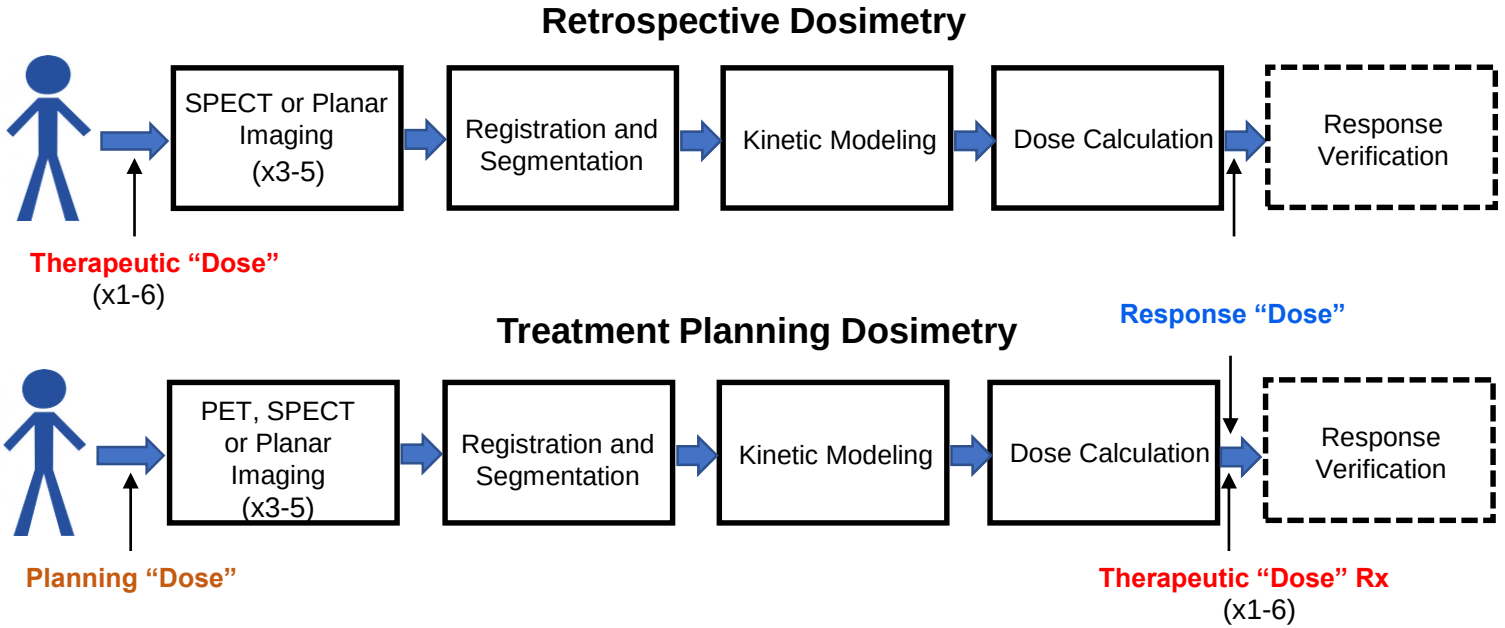




Why is SRT almost 40 years behind EBRT with regard to 3D treatment planning?

Goitein et al, Int. J. Rad. Onc. Bio. Phys. 9 (1983)

Current Approaches



Current Approaches

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- Historically, four main patient-specific dose calculation methods have been used for SRT:
  - Traditional MIRD method
  - Dose point kernel convolution
  - Voxel S-values based on MIRD method
  - Direct Monte Carlo radiation transport

*All of these methods rely on Monte Carlo methods


NBSIR 73-107 (R)

Improved Point Kernels for Electron and Beta-Ray Dosimetry

Martin J. Berger

Center for Radiation Research
Institute for Basic Standards
National Bureau of Standards
Washington, D. C. 20234

February 1973

Progress Report

Prepared for
U. S. Atomic Energy Commission
Division of Biomedical and Environmental Research
Washington, D. C. 20545

Zanzonico P., J. Nuc. Med. Vol. 41 (2000)

Commercial Dosimetry Software

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Name of Software	Name of Distributor	Approval Status	Dosimetry Method
OLINDA/EXM 2.0	HERMES Medical	510(k) Clearance (July 2017)	OLINDA/EXM 2.0
SurePlan – LiverY90*	MIM Software Inc.	510(k) Clearance (Nov. 2017)	Local Deposition or Voxel S Values
Rapidsphere – Part of Velocity*	Varian	510(k) Clearance (Apr. 2018)	“3D voxel dose conversion”
STRATOS – Part of Imalytics	Philips	Not Approved	Dose Point Kernel
Automated Int. Dos. Research Tool	Siemens	Not Approved	Dose Point Kernel
PLANET Dose	Dosisoft	CE Mark	Dose Point Kernel
DOSEFX	Comecer	CE Mark	Unknown
Simplicit^{90}Y*	Mirada	CE Mark	Unknown

*^{90}Y Microspheres

Note: Rapid, LLC (Baltimore, MD) web-based service oriented dosimetry company

Voximetry, LLC (Madison, WI) Treatment planning software that uses GPU-based Monte Carlo dose engine

The State of SRT Dosimetry

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Treatment	No. of Patients	Endpoints
^{131}I-NaI (Thyroid Cancer)	885	Ablation, Response, Toxicity
^{131}I-NaI (Benign Disease)	523	Response
^{131}I-mIBG	148	Partial Response, Toxicity
DOTATAC/DOTATATE	88	Response, Toxicity*
^{131}I-tositumab	176	Response, Toxicity
^{90}Y microspheres	549	Partial Response, Response, Toxicity

*Renal Toxicity

48 out of 79 studies found an absorbed dose-effect correlation.

Strigari et al Eur J Nucl Med Mol Imaging 41 (2015)

The State of SRT Dosimetry

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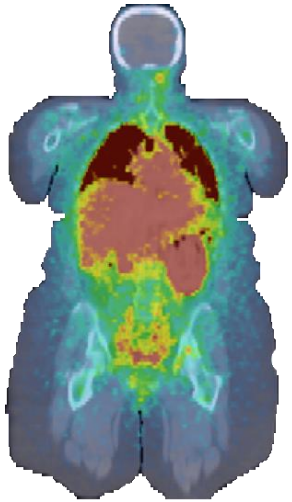
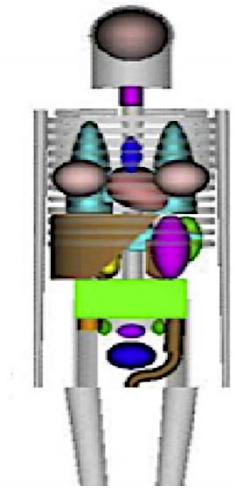
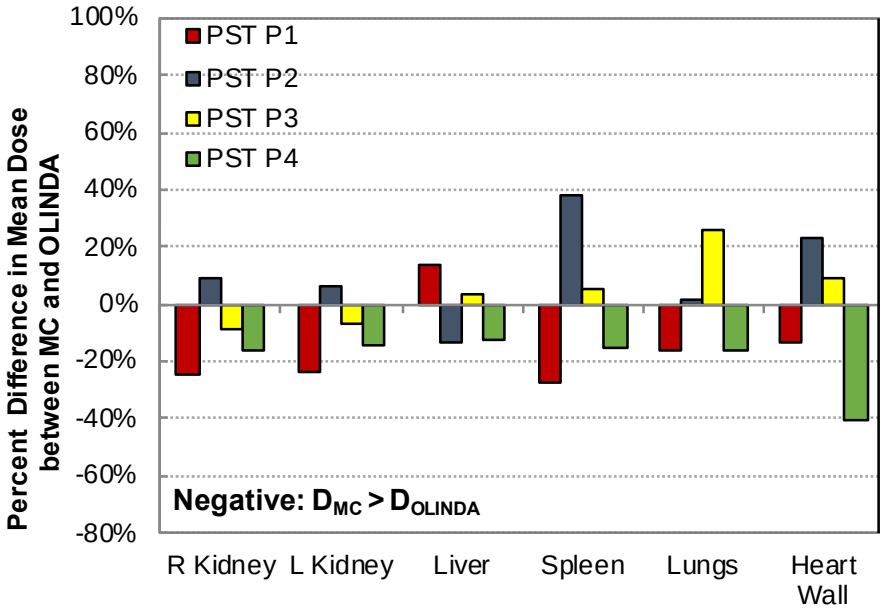
Dosimetry analysis of 5 patients enrolled in a ^{131}I-CLR1404 Phase 1 Clinical Trial



PST P1 SPECT/CT



MIRD



*MC dosimetry done with UW RAPID platform.

Besemer A., Dissertation, UW-Madison (2016)

Addressing Barriers for Implementation

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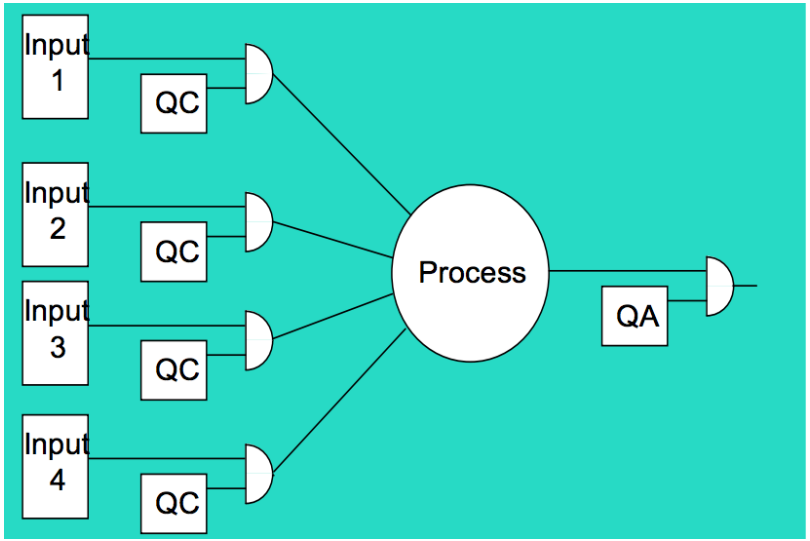
- “Proof is in the pudding”
- Sub-optimal quality management (QC/QA) in therapeutic workflow
- Logistically challenging workflow in clinical setting
- Uncertainties in radiation biology
- Inadequate training
- Cost

Emphasizing Quality Management

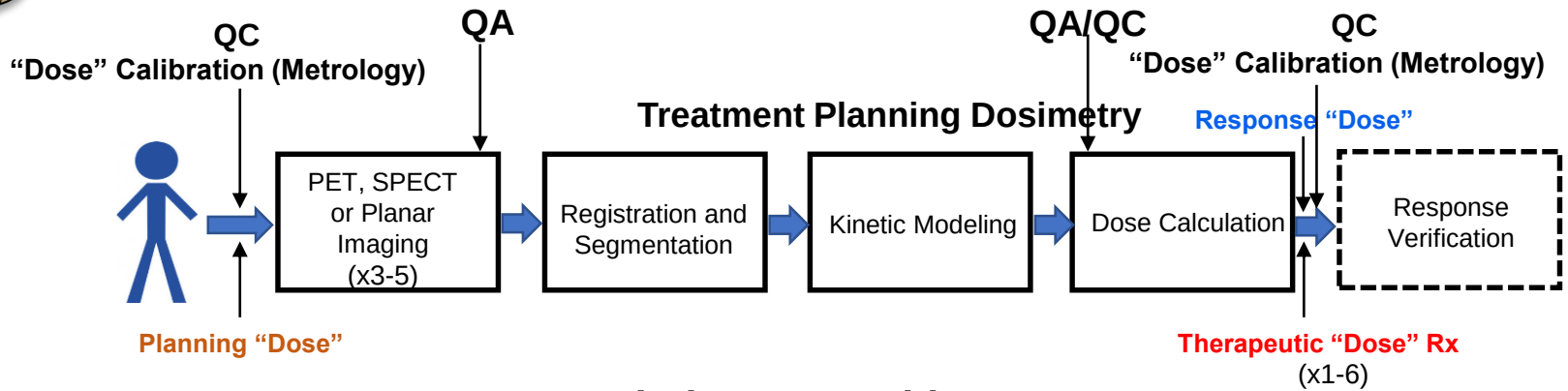
- Quality management is all activities designed to achieve a desired quality in treatments.



Quality Control (QC): Tends to focus on failure prevention
Quality Assurance (QA): Tends to focus on failure interception

*Courtesy of B. Thomadsen

Emphasizing Quality Management



Uncertainties to consider:

- Dose calibration
- Dose administration
- Image acquisition
- Post-processing
- Radionuclide impurities
- Operator errors

*SNMMI Clinical Trial Network

Emphasizing Quality Management

Journal of Nuclear Medicine, published on January 11, 2018 as doi:10.2967/jnumed.117.202861

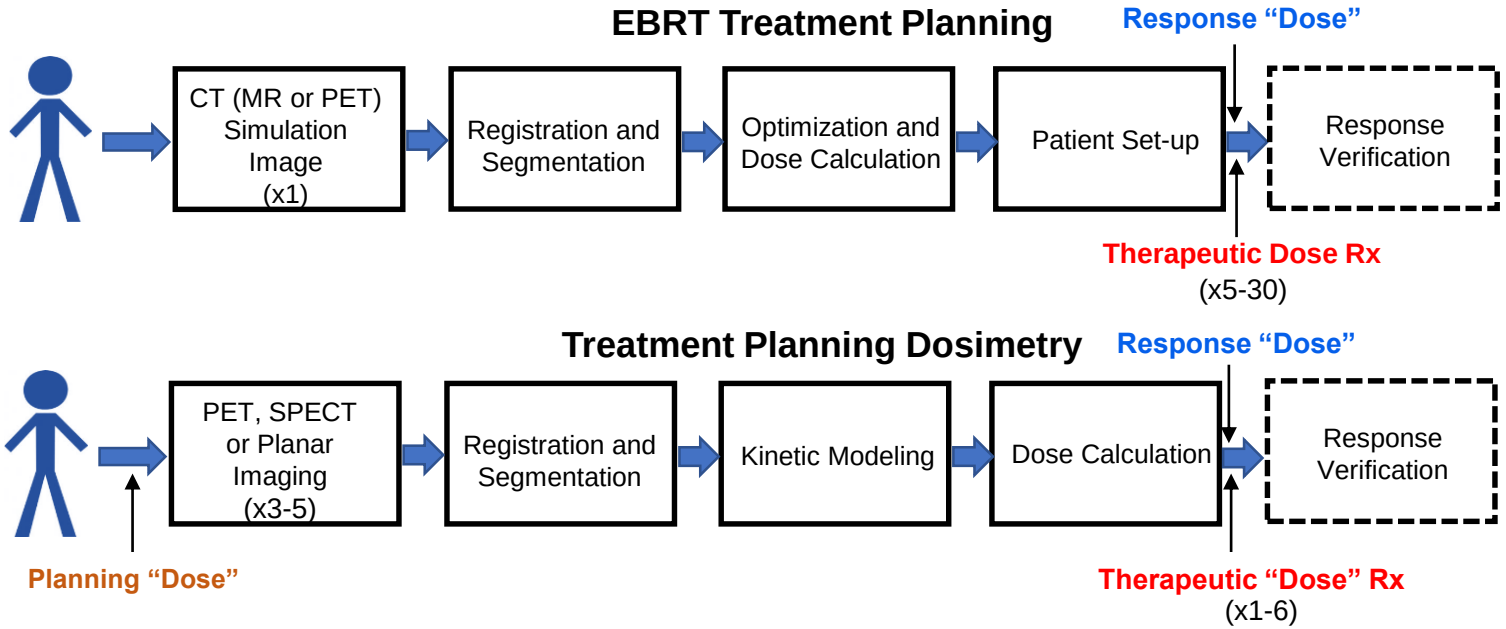
BRIEF COMMUNICATION

ACCURACY OF DOSE CALIBRATORS FOR GALLIUM-68 PET IMAGING: UNEXPECTED FINDINGS IN A MULTI-CENTRE CLINICAL PRE-TRIAL ASSESSMENT

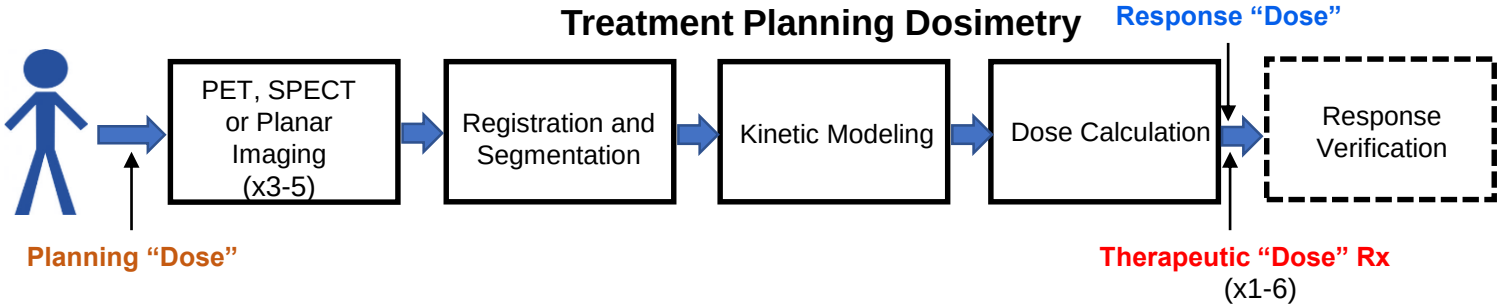
Dale L Bailey[1,2], Michael S Hofman[3], Nicholas J Forwood[1,2], Graeme J O'Keefe[5], Andrew M Scott[5,6], Winifred M van Wyngaardt[7], Bonnie Howe[7], Olga Kovacev[4] and Roslyn J Francis[4,8] on behalf of ARTnet[4] and the ProPSMA Trial Investigators

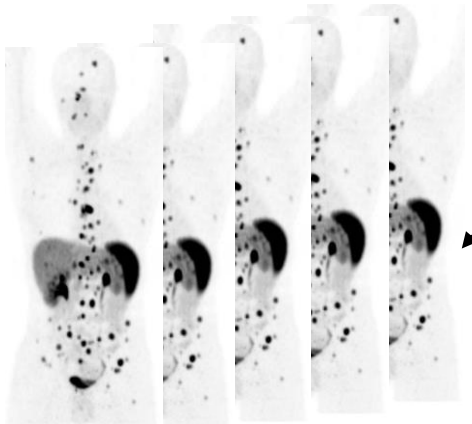
- Systematic miscalibration during site validation of a multi-center ^{68}Ga clinical trial
- 10 out of 14 PET systems underestimated the SUV by 15% on average (13%-23%).
- Due to an incorrect factory-shipped dose calibrator setting from a single manufacturer.

Logistical Challenges



Logistical Challenges





> 180 Lesions per scan!

Ga-68 DOTATOC or DOTATATE

Current Development Needs:

- Automated Registration/Segmentation
- AI/Machine Learning
- GPU Dose Computing

Dose Engines are “Embarrassingly Parallelizable”

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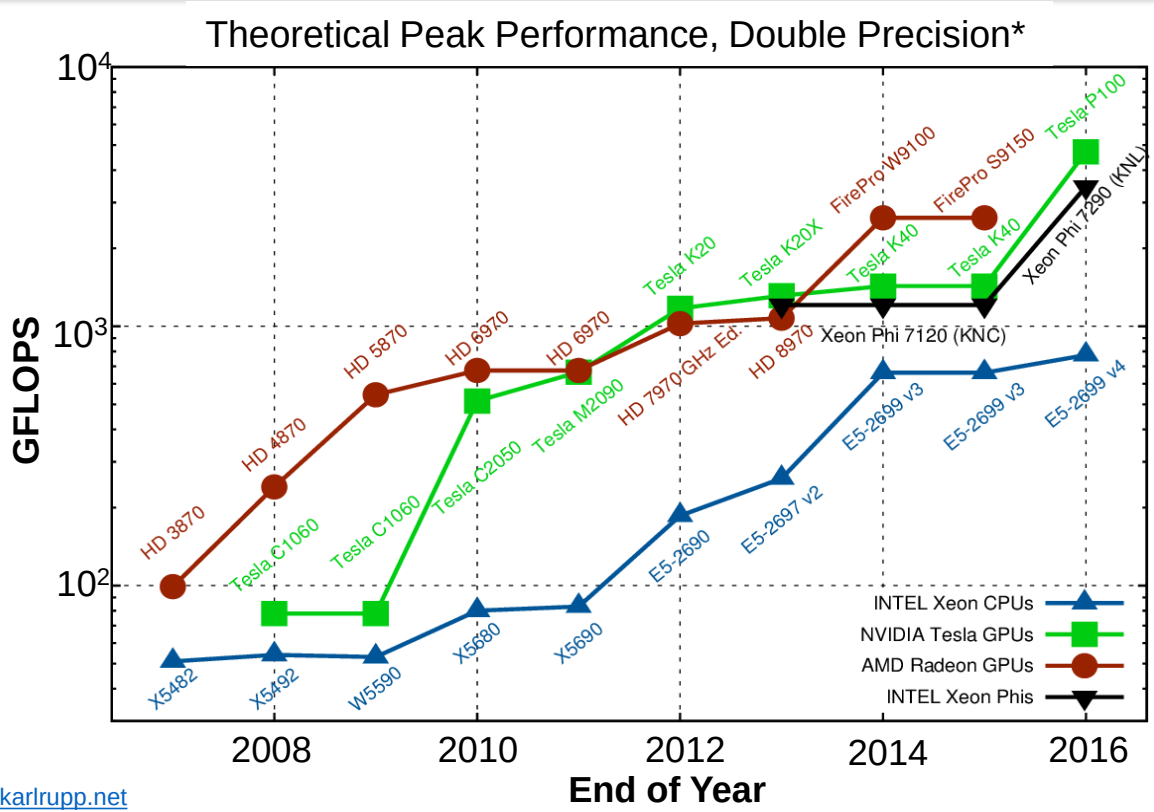
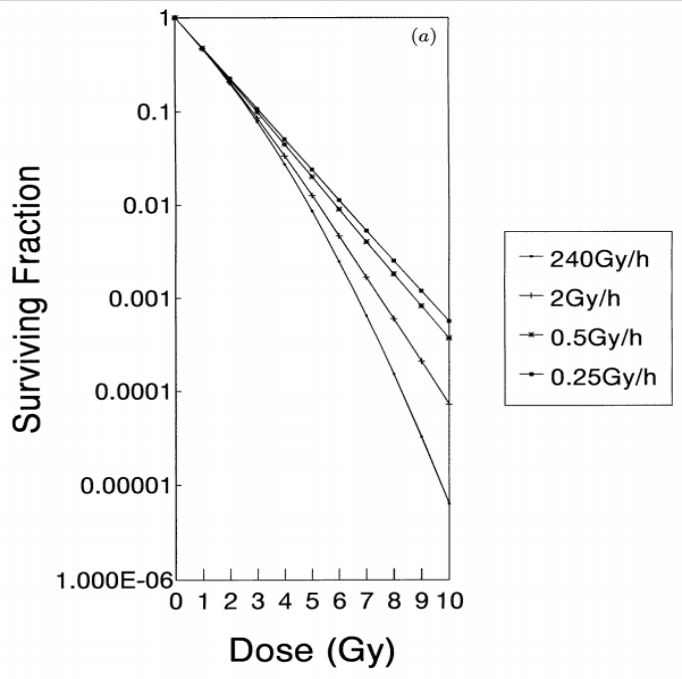


*Reproduced from https://www.karlrupp.net

Radiobiological Considerations



$$SF = \exp(-\alpha \times BED)$$

Absorbed Dose

Lea-Catcheside

$$BED = D + \frac{G}{(\alpha/\beta)} D^2$$

$$G = \frac{\lambda}{\mu + \lambda}$$

Repair Rate Constant

$(\alpha/\beta)_{RBM}$ = 7-26 Gy[1]

$(0.693/\mu)_{RBM}$= 0.5-1.5 hrs[2,3]

[1]Fowler JF Brit. J. Radiol. 62 (1989)
[2]Wilder et al Euro. J. Nuc. Med. 23 (1996)
[3]Dale RG Brit. J. Radiol. 58 (1985)
[4]Dale RG Phys. Med. Biol.

*Neglects cell repopulation, bystandard effects, immunostimulation, and immunosuppression

Training

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- Implementation of routine patient-specific dosimetry will require a well trained workforce.

- The AAPM/SNMMI Task Force on Nuclear Medicine Physics Training states:
  - Less than 10% of total number of medical physicist in the US are nuclear medicine physicist
  - The median age of current medical physicist is quite high
  - There is a critical need for CAMPEP-accredited residencies for clinical training in nuclear medicine

- A solid didactic training in therapeutic nuclear medicine is currently missing from CAMPEP-accredited medical physics graduate programs.

Closing Thoughts

- Good clinical evidence of absorbed dose-effect relationships in SRT.
- Further improvements can be made by capitalizing on the improving accuracy of quantitative nuclear medicine systems.
- Lessons can be learned from EBRT, but unique challenges and needs associated with patient-specific dosimetry for SRT.
- The advancement of patient-specific dosimetry for SRT will ultimately depend on key stakeholders including: physicians, physicist, industry, regulatory agencies, and NIH.

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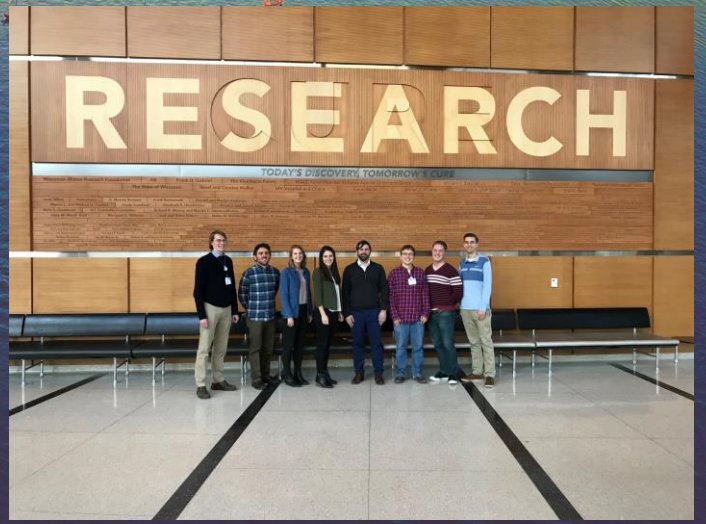

Voximetry, LLC

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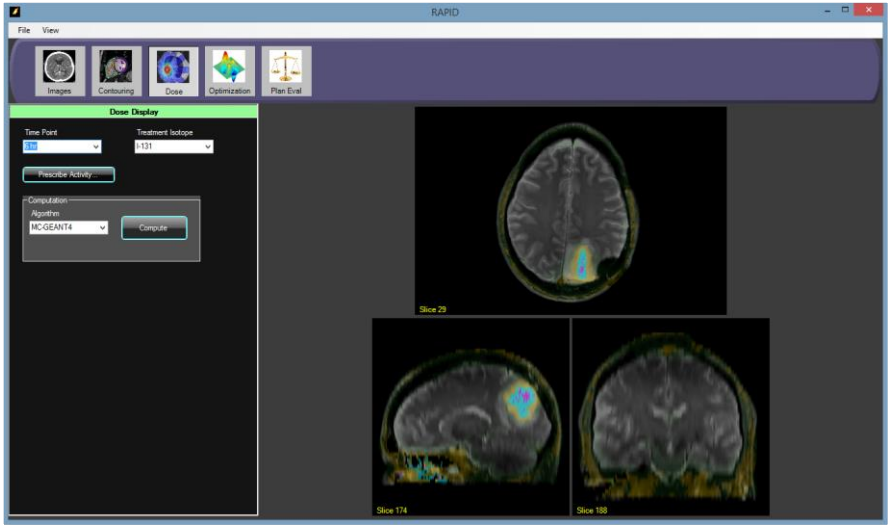
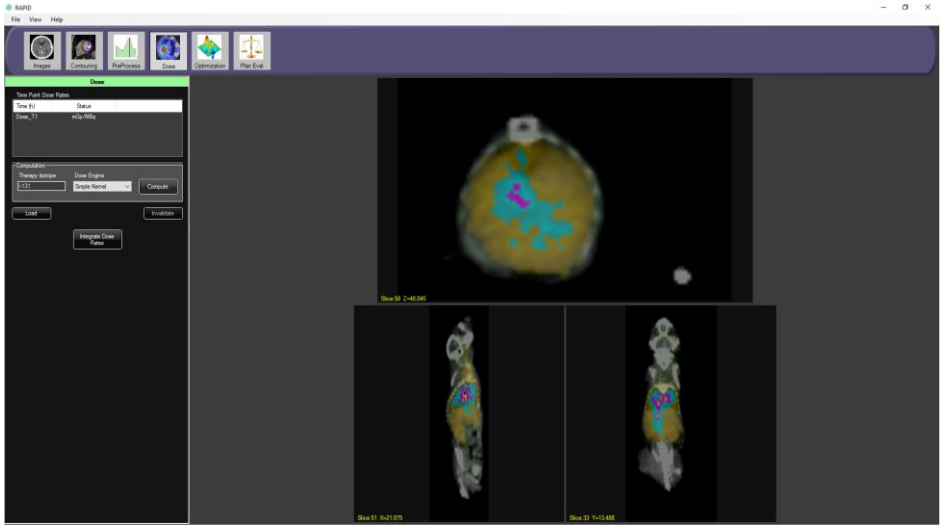
Voximetry Treatment Planning Software





^{131}I-CLR1404 dose distributions in human (left) and mouse (right)

Courtesy of P. Wickre (Voximetry, LLC, Madison, WI)