Towards Theragnostic Radiotherapy

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July 31, 2018

Disclosures

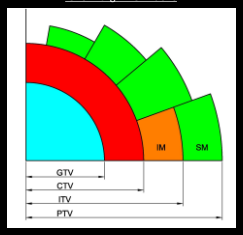
- Research agreement with Siemens Healthineers
- Research agreement with Elekta Instruments, AB
- Research agreement with Philips Healthcare
- Research agreement with MIM Software
- Advancing a Healthier Wisconsin

Theragnostic Radiotherapy

- Multi-dimensional conformal radiotherapy
- Design dose distribution conforming to *both* geometric and biologic attributes of tumor
- Requires association of biological imaging phenotypes to dose
- Hypothesis: non-invasive biological images can be used to derive optimized, non-uniform RT prescription doses

Conventional Radiotherapy

ICRU Margin Definitions



- Pillars of success in RT:
  - Accurate delineation of disease extent
  - Optimal alignment of the treatment beam to the target
- Adaptive therapy based on morphological changes

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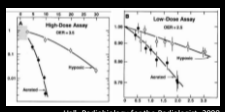
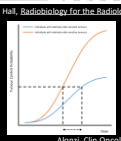
Evidence-based RT Failures

- Tumor burden
- Tumor proliferation:
  - Proliferative *response* rather than proliferation at baseline (Bentzen, PMB, 2011)
- Tumor hypoxia
- Controlled dose escalation shown to overcome radio-resistance for several tumor types



Hall, Radiobiology for the Radiologist, 2008



Alonzi, Clin Oncol, 2015

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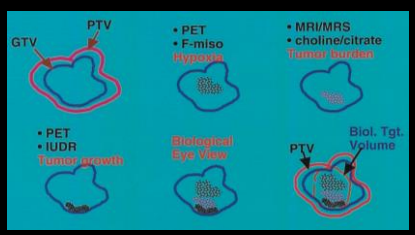
Towards Biological Target Volumes



Ling et al, IJROBP, 2000

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Multi-Parametric qMRI Panel

qMRI Method	Parameter	Phenotype/Biophysical Relevance
IVIM	D_{slow} f	Cell Density
CPMG/MRF	T_2 Map	Edema
MFA/MRF	T_1 Map	Protein
mGRE	R_2* Map	Oxygenation
PK-DCE	K^{trans}, v_e, v_p	Vascular permeability and fraction, blood flow
CEST	pH, others	Aerobic glycolysis, others

- Goal: Robust qMRI panel in <=15 minutes
  - Follow QIBA profiles/QIN recommendations
  - TG-294: Use of Quantitative MR Biomarkers in RT

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Effect of Hardware on qMRI Parameters

- Different field strengths, RF coils, pulse sequences, image reconstructions
- What sort of accuracy, reproducibility, and stability can be expected?

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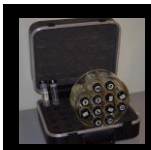
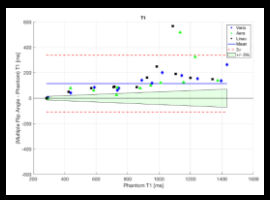
Relaxometry: T1 Bias





- Eurospin TO5 Phantom:
  - 12 tubes (290-1420 msec at 1.5T)
- Temperature monitored
- T1 Mapping:
  - Multiple flip angle method (3,6,10,20,30 deg)
  - TE/TR: 2.4/20 msec

	3T MR Sim	1.5T MR Sim	1.5T MR-Linac
Accuracy	11.4%	13.8%	10.3%
Repeatability	1.1%	-	0.6%

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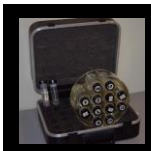
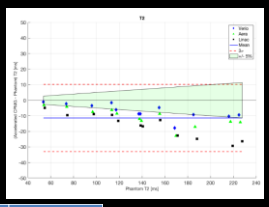
Relaxometry: T2 Bias





- Eurospin TO5 Phantom:
  - 12 tubes (~49-212 ms at 1.5T)
- Temperature monitored
- T2 Mapping:
  - Accelerated CPMG (mTE: ~20 – 200 msec)
  - TR: 5000 msec

	3T MR Sim	1.5T MR Sim	1.5T MR-Linac
Accuracy	4.5%	6.8%	11.7%
Repeatability	0.1%	-	0.7%

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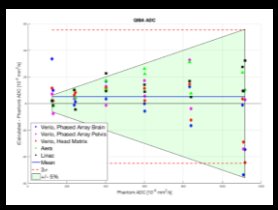
ADC Bias



- QIBA DWI phantom
- Temperature maintained at 0 deg C
- QIBA Profile:
  - SE-EPI (R=2)
  - b=0, 500, 900, 2000 s/mm²

	3T MR Sim	1.5T MR Sim	1.5T MR-Linac
Accuracy	2.6%	2.1%	2.0%
Reproducibility		1.4%	

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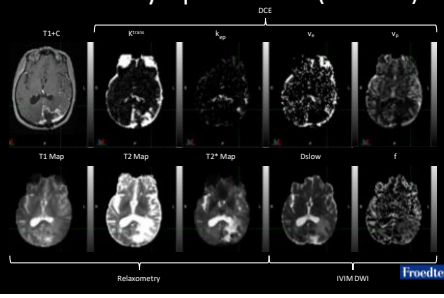
Feasibility: qMRI Panel (Glioma)



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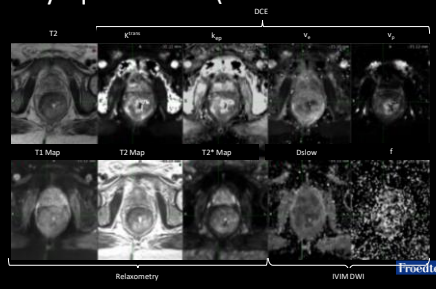
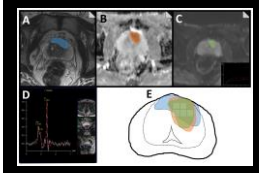
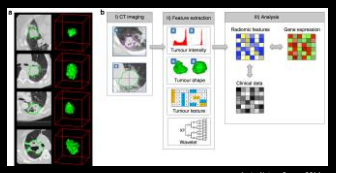
Feasibility: qMRI Panel (Rectal Adenocarcinoma)



From qMRI to Target Phenotypes



Alonzi, Clin Oncol, 2015



Aerts, Nature Comm, 2014

- Individual parameters (SUV, ADC), logistic regression models (multi-parametric)
- Thresholding, texture analysis, radiomics, deep learning
- Which parameters to use requires prospective evaluation in each tumor site

Dose Prescription Functions

- Requires understanding:
  - Relationship between qMRI parameter and risk of recurrence
  - Dose-response relationship for a particular tumor type

$$D_{p,i} = D_{0,i} + \frac{1}{\alpha} \cdot \ln p_i$$

Thorwarth et al, Med Phys, 2017

- No consensus in literature:
  - Some use radiobiological modeling
  - Linear, quadratic, exponential
  - OER: 1.4-1.8 for fractionated RT

$$D_{\text{presc}} = D_{\min} + (D_{\max} - D_{\min}) \cdot \text{TP}^n$$

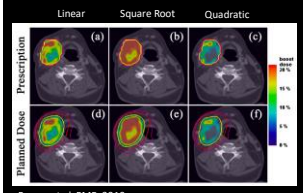
Bowen et al, PMB, 2009

$$D(I) = D_{min} + \frac{I - I_{min}}{I_{max} - I_{min}} \cdot (D_{max} - D_{min})$$

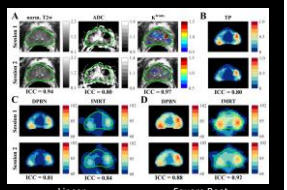
Bentzen et al, PMB, 2011

- All employ minimum and maximum dose constraints:
  - Errors in qMRI parameter intensities may translate into dose errors
- Phase I, II trials ongoing (HNSCC, NSCLC):
  - PET-defined escalation or redistribution

Effect of Dose Prescription Function Choice



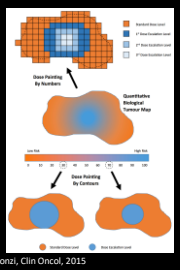
Bowen et al, PMB, 2010



Linear Square Root

van Schie, et al, PMB, 2017

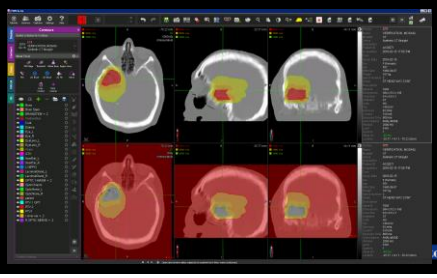
Approaches for Theragnostic RT Planning



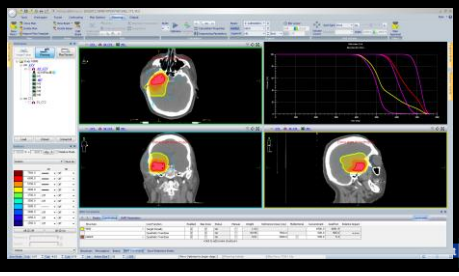
- Dose Painting by Contours (discrete):
  - Threshold applied to stratify into low and high risk regions
  - Robust against statistical noise in images
- Dose Painting by Numbers (continuous):
  - Contour-free
  - Each tumor voxel assigned a specific dose based on phenotype (level of risk)
- Both result in non-uniform dose distributions, escalating dose only where needed
- How to handle voxel-wise objective functions?

Alonzi, Clin Oncol, 2015

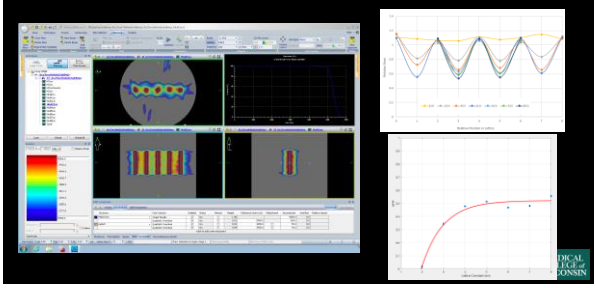
Feasibility: Dose Prescription Map Generation



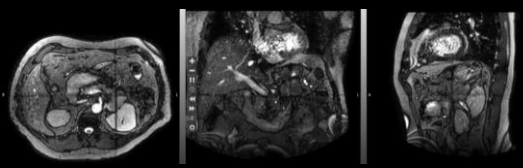
Dose Painting by Numbers in Monaco



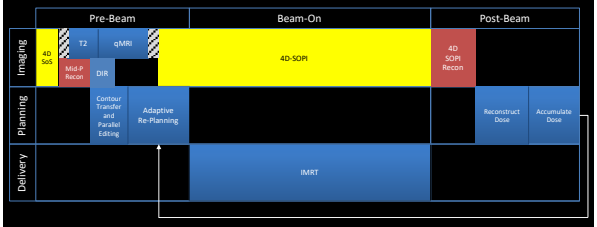
Monaco "Modulation Transfer Function"



Intrafraction Motion Management Critical

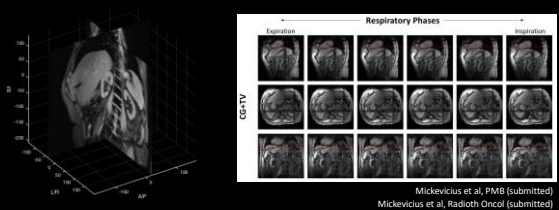


Potential Workflow for MR-gRT



- What is anatomy and motion of the day?
- Truth-in-delivery: How much dose did target and OARs actually receive?

4D-SOPI



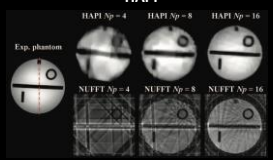
Mickevicius et al, PMB (submitted)
Mickevicius et al, Radioth Oncol (submitted)

- Simultaneous real-time 2D + retrospective 4D imaging:
  - Gating, tracking, trailing, and truth-in-delivery analysis

WE-FG-KDBRB1-3, Mickevicius et al (MRI Guided Radiotherapy)

Toward Real-Time Volumetric Imaging

HAPI



Ersoz et al, Med Phys, 2013

DL-HAPI

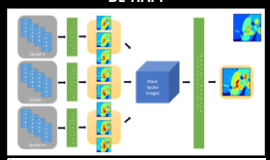


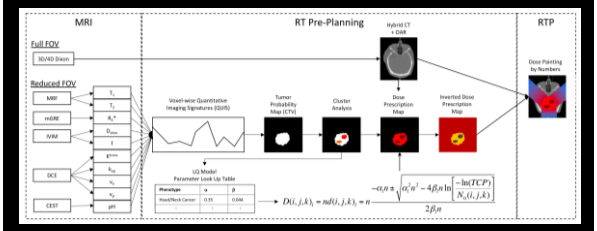
Table 1: Reconstruction time comparison

Algorithm	8-spoke reconstruction time (per slice)
NUFFT	0.16 sec (averaged from 100 reconstructions)
SENSE	47.89 sec (averaged from 2 reconstructions)
SENSE+TV	55.32 sec (averaged from 2 reconstructions)
HAPI+TV	2.59 sec (averaged from 100 reconstructions)
HAPI-DL	0.0015 sec (average of 30,000 reconstructions)

Nencka et al, MRM, (in preparation)

- Goal: 3D volumetric imaging <= 0.5 sec frame rate

MR-guided Theragnostic RT Workflow



- Dose distributions optimized with DPBN once per week not significantly different from daily DPBN optimization (Gago-Arias, PLoS ONE, 2018)

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Summary

- Theragnostic radiotherapy has great potential to further personalize radiation therapy.
- Biologically-based treatment planning using existing planning systems is technically feasible, though the amount of dose modulation may be limited.
- Significant progress in a number of areas is still required before large multi-center clinical trials using theragnostic radiotherapy can begin.

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Acknowledgements

- Nikolai Mickevicius
- Zach Boyd
- Christopher Schultz
- X. Allen Li
- Beth Erickson
- Bill Hall
- Xinfeng Chen
- Ergun Ahunbay
- Doug Prah
- Carmen Bergom
- Cathy Marszalkowski
- Colette Gage
- Britta Nelson
- Brooke McMichael
- Paul Knechtges
- Andrew Nencka
- Tugan Muftuler
- Amit Joshi
- Anubha Wadhwa
- Steve Censky
- David Hotchkiss (MCW IS)
- Mike Gill (MCW IS)
- Greg McQuestion (MCW RCC)
- Kalpa Vithalani (MCW OTD)
- Uulke van der Hiede (NKI-AVL)
- Rob Tijssen (UMC Utrecht)
- Geoff Ibbott (MD Anderson)
- Hannah Lee (MD Anderson)

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Learning Objectives

- Appreciate the challenges involved with biologically optimized radiotherapy.
- Describe a biologically adaptive MR-guided radiotherapy workflow.
- Understand strategies to generate biologically adaptive radiation treatment plans from fully quantitative MR images.

PET-based Theragnostic Radiotherapy

- Metabolism:
  - FDG
- Proliferation:
  - FLT
- Hypoxia:
  - FMISO, FAZA, Cu-ATSM
- Challenges:
  - Poor spatial resolution (3.5-5mm; hypoxia on order of 100 um)
  - Lack of consensus on analysis
  - Hard/expensive to perform repeat imaging

Other Geometries?