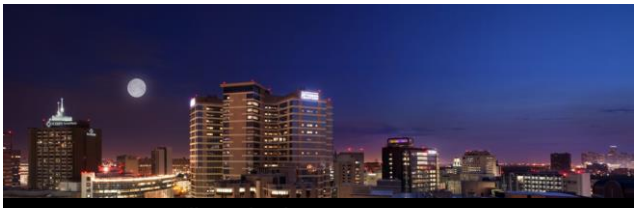

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center Making Cancer History

Offline Adaptive RT

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Professor, Department of Radiation Therapy
Director, Image Guided Cancer Therapy Program
University of Texas MD Anderson Cancer Center

Conflict of Interest

- Funding from the NIH, NCI R01CA221971
- Funding from RaySearch Laboratories (including work in dose mapping and outcomes assessment)
- Research Agreement with Mirada Medical (including work in AI)
- Licensing Agreement with RaySearch Laboratories (deformable registration technology)

Acknowledgments

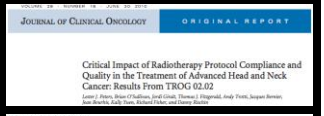
- Image Guided Cancer Therapy Research Program
- Morfeus Lab
  - Guillaume Cazoulat, PhD, Molly McCulloch, PhD, Bastien Rigaud, PhD
- Fuller Lab (PI: C. David Fuller, MD, PhD)
- Chung Lab (PI: Caroline Chung, MD)
- Koay Lab (PI: Eugene Koay, MD, PhD)
- Collaborators at Princess Margaret Hospital and University of Michigan
  - Michael Velec, PhD and Laura Dawson MD
  - James Balter, PhD, Marc Kessler, PhD, Randy Ten Haken, PhD
  - Avi Eisbruch, MD, Ted Lawrence, MD
- Geoff Hugo, PhD – Washington University St. Louis

Motivation

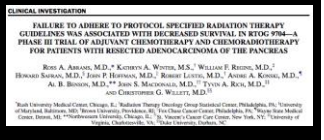
- Mandate for precision medicine
  - Image-guided, personalized, adaptive radiotherapy is the epitome of precision medicine
  - Increasing amount of imaging – for planning, delivery, and assesment
- Precision in design, delivery, and assessment of radiation may have an impact of trial design and outcomes assessment
- QUANTEC:
  - *"To maximize the therapeutic ratio, models relating the true accumulated dose to clinical outcome are needed and robust methods must be developed to track the accumulation of dose within the various tissues of the body."*
- *Goal: Advance the design, delivery, and understanding of radiotherapy*

Precision Delivery/Assessment

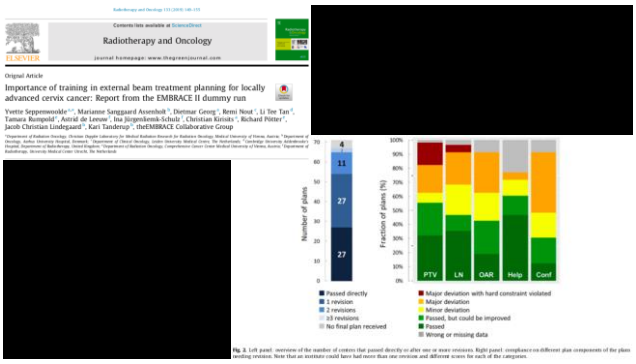
- Evaluation of biological influence on outcomes of treatment, need to ensure that all pts are tx precisely
- Integration of advanced imaging requires patient model and link to dose
- Accurate design and evaluation of clinical trials requires accurate dose assessment

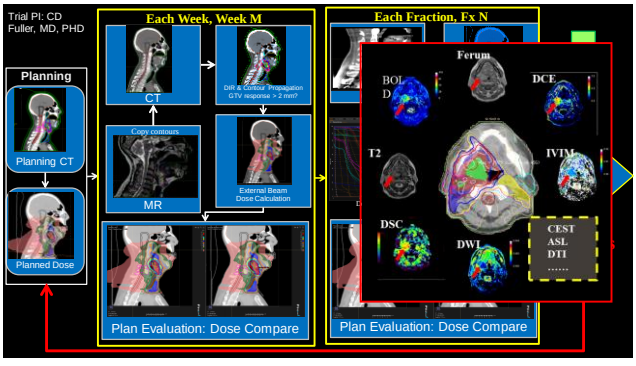

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Critical Impact of Radiotherapy Protocol Compliance and Quality in the Treatment of Advanced Head and Neck Cancer: Results From TROG 02.02


CLINICAL INVESTIGATION

FAILURE TO ADHERE TO PROTOCOL SPECIFIED RADIATION THERAPY GUIDELINES WAS ASSOCIATED WITH DECREASED SURVIVAL IN RTOG 9704—A PHASE III TRIAL OF ADJUVANT CHEMOTHERAPY AND CHEMORADIOTHERAPY FOR PATIENTS WITH RESECTED ADENOCARCINOMA OF THE PANCREAS

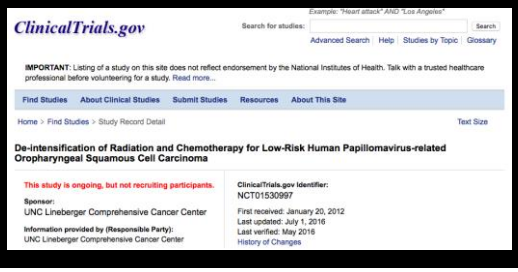


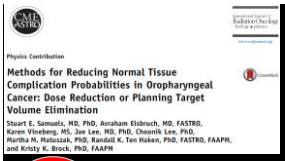


"Vision without action is a daydream. Action with without vision is a nightmare." — Japanese proverb

What is our Vision of Precision in Radiotherapy Design and Delivery?

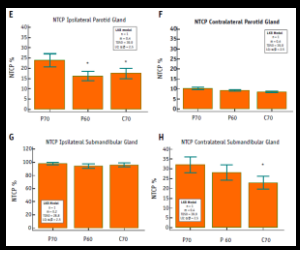
Clinical Trial Design: Importance of Dose Assessment and Outcomes Prediction





With Adaptive RT

- 38 oropharyngeal cancer
- VMAT
- minimal clinically important benefit (MCID): mean change in NTCP of >5%

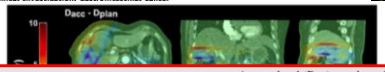


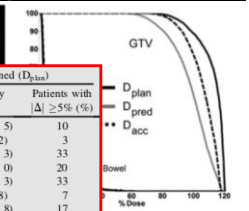
Dose Reduction: iPG was the only structure with an NTCP benefit (MCID >5%, ~40% of Pts)
PTV elimination: iPG and cSMG both benefited (approximately 40% of patients)

Can We Deliver What we Plan?

30 Patients – dose accumulation
21patients (70%) had large dose deviations (>5%) to any tissue or GTV

Clinical Investigation: Gastrointestinal Cancer





	Accumulated (D_{acc}) vs. planned (D_{plan})		
Parameter	Mean, SD, in Gy	Max, Min in Gy (% of Rx)	Patients with $\|\Delta\| \geq 5\%$ (%)
GTV (min to 0.5 cm^3), $n = 54$	−0.2, 1.0	−4.4, 2.3 (−15, 5)	10
Liver (mean), $n = 30$	−0.2*, 0.5	−1.7, 0.9 (−6, 2)	3
Large bowel (max to 0.5 cm^3), $n = 30$	−1.1*, 1.5	−5.3, 1.3 (−15, 3)	33
Small bowel (max to 0.5 cm^3), $n = 15$	−1.3*, 2.2	−7.8, 0 (−26, 0)	20
Duodenum (max to 0.5 cm^3), $n = 30$	−1.5*, 2.6	−12.6, 0.7 (−42, 3)	33
Esophagus (max to 0.5 cm^3), $n = 29$	0.3*, 0.8	−0.8, 2.4 (−3, 8)	7
Stomach (max to 0.5 cm^3), $n = 30$	−0.4, 1.5	−4.3, 4.6 (−14, 8)	17
Right kidney (mean), $n = 30$	−0.4*, 0.7	−2.0, 0.6 (−5, 2)	10
Left kidney (mean), $n = 30$	−0.1*, 0.3	−1.2, 0.4 (−3, 1)	0
Heart (max to 0.5 cm^3), $n = 25$	−0.5*, 1.0	−4.0, 0.8 (−13, 2)	8
Liver (NTCP), $n = 30$	−0.5, 2.5†	−8.3, 8.0†	10

compromised inferiorly on the
se tissues moved inferior away
ues back toward the high-dose

Accumulation of the delivered treatment dose in volumetric modulated arc therapy
beam co

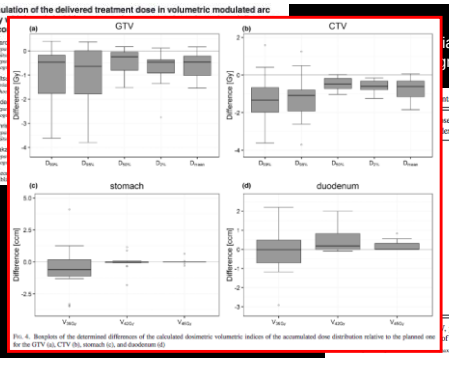


FIG. 4. Boxplots of the determined differences of the calculated dosimetric volumetric indices of the accumulated dose distribution relative to the planned one for the GTV (a), CTV (b), stomach (c), and duodenum (d)

ial marker alignment
gnitude metric

ts for each organ

se-volumetric ex	Per protocol	Acceptable variation
D_{cum}	≤56 Gy	
$D_{95\%}$	≥48 Gy	≥45.6 Gy
$D_{50\%}$	≈51 Gy	≈48 Gy
$D_{98\%}$	≥36 Gy	≥34.2 Gy
$V_{45\ Gy}$	<1 ccm	
$V_{42\ Gy}$	<5 ccm	
$V_{39\ Gy}$	<25 ccm	
$V_{39\ Gy}$	<15 ccm	<30 ccm
$V_{36\ Gy}$	<45 ccm	
D_{max}	<36 Gy	
$D_{2\ ccm}$	<39 Gy	
$V_{20\ Gy}$	<0%	
D_{mean}	<30 Gy	

, planning risk volume; $D_{XX\%(ccm)}$, dose cover- of structure; D_{mean}, mean dose; $V_{XX\ Gy}$, volume ,, maximum dose.

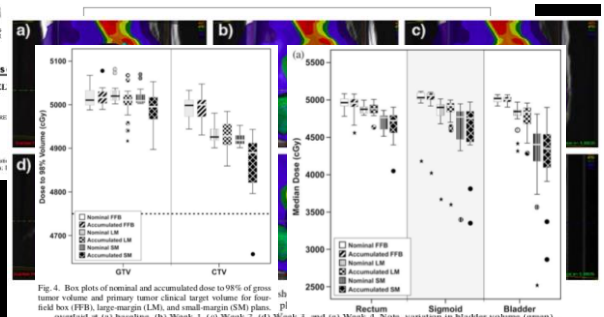
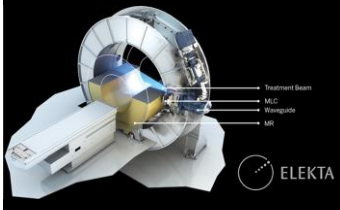


Fig. 4. Box plots of nominal and accumulated dose to 98% of gross tumor volume and primary tumor clinical target volume for four-field box (FFB), large-margin (LM), and small-margin (SM) plans. overlaid at (a) baseline, (b) Week 1, (c) Week 2, (d) Week 3, and (e) Week 4. Note, variation in bladder volume (green), tumor regression (red), and change in uterine position (blue) from upright to anteverted. (f) Final accumulated dose, with organ geometry deformed back to baseline geometry. Dose distribution: red, 5,000 cGy; orange, 4,900 cGy; yellow, 4,750 cGy; green, 4,500 cGy; and blue, 3,000 cGy.

Can we more closely deliver the planned dose if we improved our technology at the Tx Unit?

Option 1: MR in the Room & Online Next!



Option 2: Better Tools with CBCT

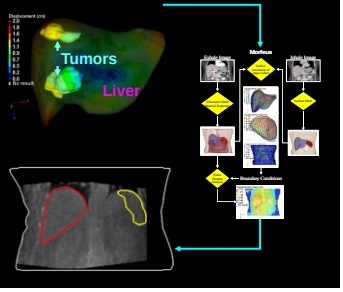
Methods:

1.DIR between exh CT and CBCT

2.Compare 3 alignments:

- *Clinical*
- *Liver*
- *Tumors*

3.Reconstruct the delivered dose for each



Advanced IGRT

- *Results, Accumulated – Predicted dose:*
  - The magnitude of min GTV decreases with clinical IGRT (max: -14%) were reduced by up to 7% (Liver IGRT) and 8% (Tumor IGRT)
  - Dose deviations for normal tissues (within 2Gy of max constraint) with the clinical IGRT (range: -38, 10%), were reduced with Liver IGRT (range: -21, 8%) and Tumor IGRT (range: -21, 8%)

Better delivery of the intended dose!

Can we design a better treatment?

Physics Contribution

Dose Escalated Liver Stereotactic Body Radiation Therapy at the Mean Respiratory Position

Michael Velec, PhD,[*,†] Joanne L. Moseley, BMath,[*] Laura A. Dawson, MD,[*,†,‡] and Kristy K. Brock, PhD[*,†,‡,§]

[*]Radiation Medicine Program, Princess Margaret Cancer Centre; [†]Institute of Medical Science; [‡]Department of Radiation Oncology, University of Toronto, Toronto, Ontario, Canada; and [§]Department of Radiation Oncology, University of Michigan, Ann Arbor, Michigan

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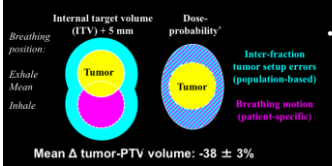
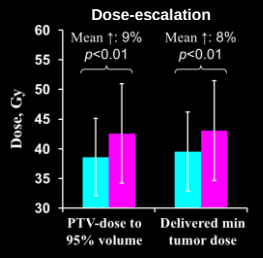


Mean Δ tumor-PTV volume: -38 ± 3%

- Data:
  - 20 patients, 27-49.8 Gy in 6 Fx
    - Tumor motion: 1–21 mm (median: 8 mm)
    - 4D CBCT Daily
- Methods:
  - Optimized new SBRT plans, dose-escalated up to 60 Gy, for an equivalent risk of liver complication and PTV dose-coverage:

1. Exhale 4D CT and ITV-based PTV (ITV + 5 mm)
2. Mid-position CT and Dose-probability PTV

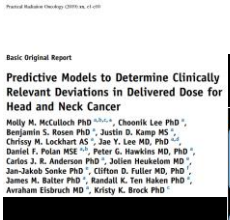
Mean Position Planning

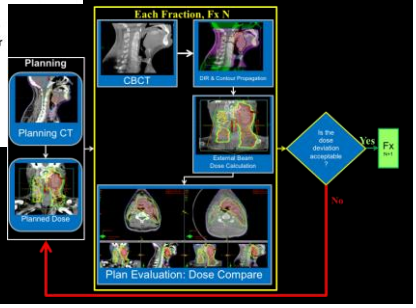


Delivered min tumor dose vs. planned PTV dose	
% patients with delivered min tumor dose > PTV dose (largest tumor dose decrease)	
ITV-based PTV plan	90% patients (-10% dose)
Dose-probability PTV plan	90% patients (-10% dose)

ITV-based PTV plan Dose-probability PTV plan

How can we determine if we are not 'on track' to deliver the intended dose?

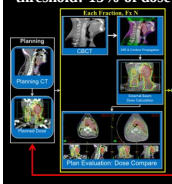




How do we know if the deviation is acceptable?

Developing Predictive Model

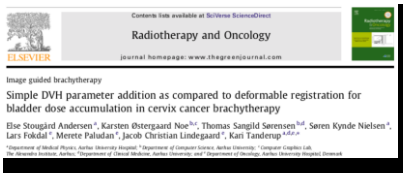
Clinically defined deviation threshold: 15% of dose constraint



100 Patients Retrospective Accumulation of Dose → **8 SGs Δ>4.5 Gy**

Deviation at Fx 15 To Identify Deviations → **Δ>3.5 Gy 1 False + 100% Sens., 98.7% Specif.**

Independent Validation 52 Patients → **Sensitivity: 100% Specificity: 98%**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Radiotherapy and Oncology

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Image guided brachytherapy

Simple DVH parameter addition as compared to deformable registration for bladder dose accumulation in cervix cancer brachytherapy

Else Stougård Andersen [a], Karsten Østergaard Noe [b,c], Thomas Sangild Sørensen [b,d], Søren Kynde Nielsen [a], Lars Fokdal [e], Merete Paludan [e], Jacob Christian Lindegaard [e], Kari Tanderup [a,b,e,*]

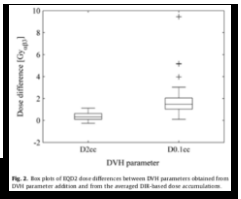


Fig. 2. Box plots of EQD2 dose differences between DVH parameters obtained from DVH parameter addition and from the averaged DIR-based dose accumulation.

Materials and methods: 47 patients treated for locally advanced cervical cancer. EBRT + with 2 individually planned 3D IG adaptive BT Fx. D2cm^3 and D0.1cm^3 were estimated by DVH parameter addition vs dose accum

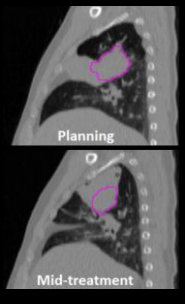
Results: DIR-based DVH analysis was possible in 42/47 patients. DVH parameter addition resulted in mean dose deviations relative to DIR of 0.4 ± 0.3 Gy (1.5 ± 1.8%) and 1.9 ± 1.6 Gy (5.2 ± 4.2%) for D2cm^3 and D0.1cm^3 , respectively. Dose deviations greater than 5% occurred in 2% and **38%** of the patients for D2cm^3 and D0.1cm^3 , respectively. Visual inspection showed that hotspots were located in the same region of the bladder during both BT Fx for the majority of patients.

Conclusion: DVH parameter addition provides a good estimate for D2cm^3 , whereas D0.1cm^3 is less robust

What about complex deformation?

Problems with Traditional DIR

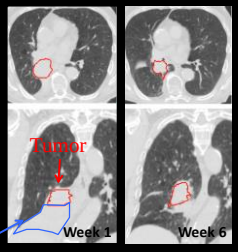
- Need high DIR accuracy
  - near the PTV for dose mapping
  - At structure boundaries for contour mapping
- 'Traditional' DIR algorithms rely on assumption of corresponding features between the images to be registered
- Atelectasis appearance in CT challenges this assumption.
- *Goal: To develop a DIR algorithm that can handle missing / incomplete correspondence in the lung.*



Chris Guy (VCU) & Geoff Hugo (WashU)

Atelectasis / large tissue change

- Atelectasis (partial collapse)
- Pleural effusion (fluid)
- Large volume changes in atelectasis (~150cc) during RT
- Associated with large tumor shifts (> 5mm in 83% of pts)
- Associated with large dose changes to OARs (5-10 Gy single fx change in cord max, MED, MLD)



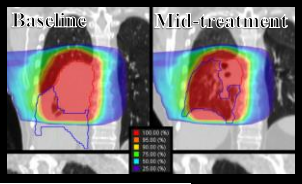
Chris Guy (VCU) & Geoff Hugo (WashU) *Guy Med Phys 2016, Tennyson Adv RO 2016*

Atelectasis / large tissue change

Dose recalculated on mid-treatment image
- Aligned to both bone and carina
- Compared to planned dose

Worst-case estimate

Dose changes can be significant
- Highlights need for ART/DIR



			Bone aligned				Carina aligned			
Structure	Metric	Units	Mean	Stdev	Min	Max	Mean	Stdev	Min	Max
Spinal cord	D_{max}	Gy	0.67	2.99	−2.78	10.93	0.14	1.80	−2.94	4.29
Esophagus	D_{mean}	Gy	0.99	2.69	−3.72	7.92	0.77	2.95	−4.56	7.07
Lungs	D_{mean}	Gy	0.50	2.05	−2.89	5.69	0.06	1.71	−3.35	4.56

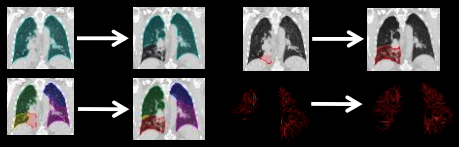
Guy Med Phys 2016, Tennyson Adv RO 2016

Lung DIR Algorithm

Multi-resolution B-spline framework (elastix)

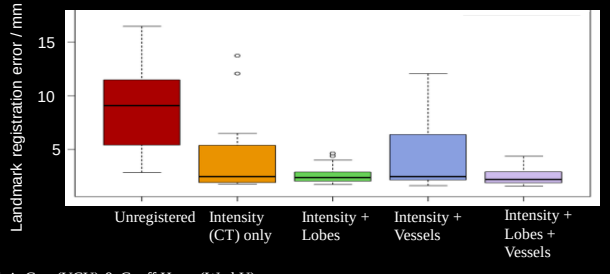
Mass-preserving metric within healthy lung
±
Intensity-based similarity metric within atelectasis
±
Co-registration of lobe label images
±
Co-registration of vesselness measure images

- SSTVD
- SSRVD
- SSD
- MI



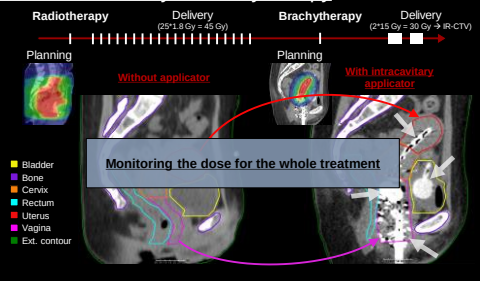
Chris Guy (VCU) & Geoff Hugo (WashU)

Lung DIR Algorithm



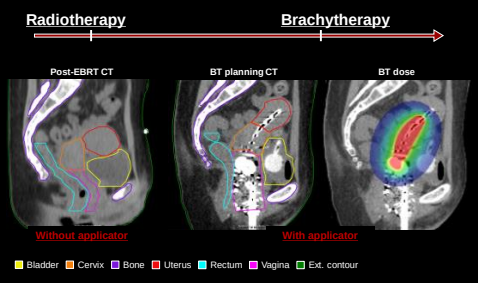
Chris Guy (VCU) & Geoff Hugo (WashU)

Anatomical variability in brachytherapy



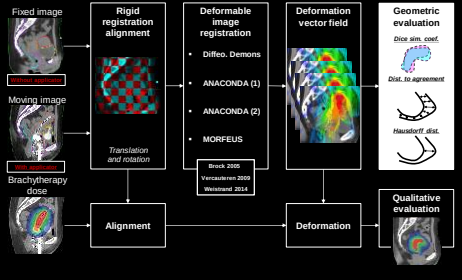
Bastien Rigaud, PhD

Data: 20 patients



Bastien Rigaud, PhD

Study workflow



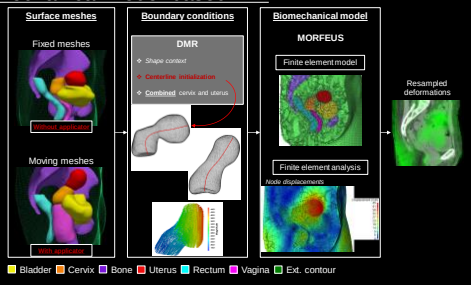
Bastien Rigaud, PhD

Deformable registration methods

Diffeomorphic Demons	ANACONDA	MORFEUS
Intensity	Combined information	Biomechanical model
▪ Metric: sum of squared difference	▪ Non-linear optimization	▪ Surface mesh
▪ Gaussian regularization	▪ Metric: correlation coefficient	▪ Boundary conditions
▪ Fast convergence	▪ Jacobian constraint	▪ Finite element model
▪ Theoretically invertible	▪ Mesh regularization (contour and grid)	▪ Mechanical properties
	▪ Contours constraint	▪ Discontinuities between organs

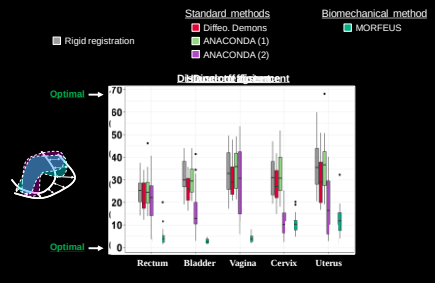
Bastien Rigaud, PhD

Biomechanical model-based DIR



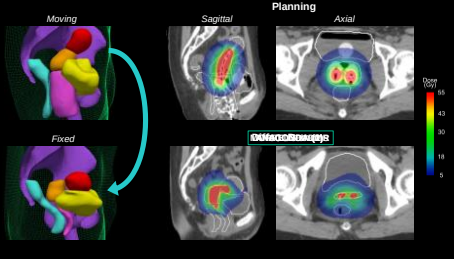
Bastien Rigaud, PhD

DIR methods comparison



Bastien Rigaud, PhD

Qualitative evaluation: BT dose deformation



Bastien Rigaud, PhD

"However beautiful the strategy, you should occasionally look at the results." —Sir Winston Churchill

Advancing our understanding of outcomes

Clinical Investigation

Accumulated Delivered Dose Response of Stereotactic Body Radiation Therapy for Liver Metastases

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Does Improved Accuracy in Dose Matter for Outcomes?

- 81 patients, 142 liver metastases
- accGTV calculated using DIR and daily CBCTs
- accGTV dose is a better predictor of TTLP compared to minPTV dose for liver metastases SBRT
- Univariate HR for TTLP for increases of 5 Gy in accGTV versus minPTV was 0.67 versus 0.74

Scientific Article

A simulation study to assess the potential impact of developing normal tissue complication probability models with accumulated dose

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- Hypothesis: The use of accumulated dose will change NTCP models

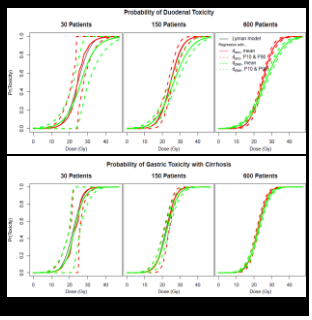
Results

- Lyman NTCP
- Mean NTCP based on simulations with accumulated dose
- Mean NTCP based on simulations with planned dose

→For the duodenal toxicity model:

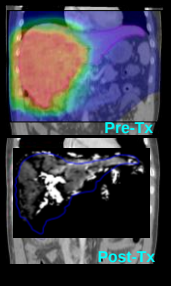
- Under 22 Gy, the planned dose under-predicts toxicity and above 22 Gy over-predicts toxicity
- Average deviation of 6%, max error of 16%

→Little difference between planned and acc dose models for the stomach.



Liver Response to Radiotherapy: Understanding Radiation Effects

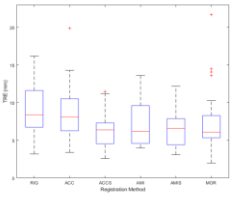
- Patients with oligometastases often have multiple courses of SBRT
  - Need: map previously delivered dose
- Advancements in functional imaging (e.g. DCE-MRI) can predict/describe function
  - Need: correlate the delivered dose
- Challenging due to the volumetric response of the tissue to radiation
  - Often variable across the tissue as a function of dose



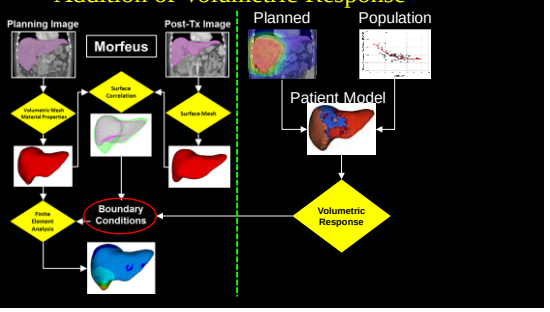
Hypothesis

Results Summary – TREs for the six methods

	RIG	ACC	ACCS	AMI	AMIS	MOR
Mean TRE (mm)	9.1	8.6	6.3	7.1	6.4	7.5
Standard Deviation (mm)	3.5	3.5	2.3	2.7	2.4	4.0
Median TRE (mm)	8.4	8.1	6.4	6.2	6.6	6.1
Minimum (mm)	3.2	3.4	2.6	4.0	3.1	2.0
Maximum (mm)	16.2	19.9	11.5	13.6	12.2	21.7
Best performing cases (#)	2	0	7	4	9	7



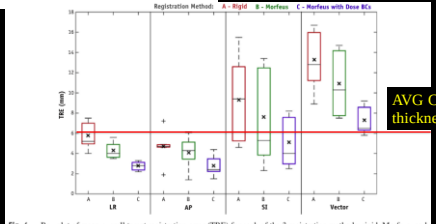
Addition of Volumetric Response



Physics Contribution

Implementing Radiation Dose-Volume Liver Response in Biomechanical Deformable Image Registration

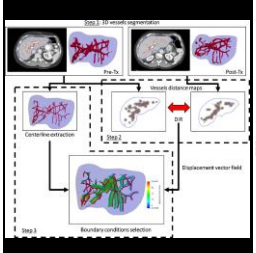
Daniel F. Polan, MSE,* Mary Feng, MD,*,† Theodore S. Lawrence, MD, PhD,* Randall K. Ten Haken, PhD,* and Kristy K. Brock, PhD*,†

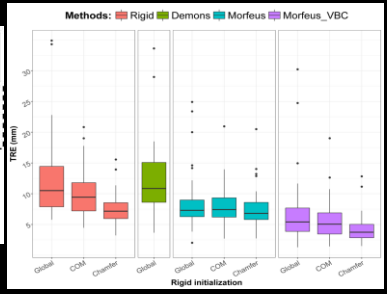


AVG CT slice thickness

Fig. 4. Box plot of mean overall target registration error (TRE) for each of the 3 registration methods: rigid, Morfeus, and Morfeus with dose boundary conditions (BCs). The newly developed method, Morfeus with dose BCs, showed improvements in TRE for each direction and the overall vector when compared with rigid and standard Morfeus registrations. *Abbreviations:* AP = anterior-posterior; LR = left-right; SI = superior-inferior.

Addition of Internal Structures





Guillaume Cazoulat, PhD

Summary

- This is a very exciting time for DIR, dose accumulation, and adaptive RT!
- We need to proceed, but proceed with caution, education, and safety
- Adaptive is not just about advanced technology, but also about improving our understanding of the impact of radiation on tumor and normal tissue
- Data shows that what we plan is NOT what we deliver and this has the potential to impact correlation with outcomes
  - Need to move toward including dose accumulation in clinical trials
- As we seek to understand the biological aspects of the treatment and design and evaluate novel clinical trials, we need to ensure that we are
  - Planning the optimal therapy
  - Precisely delivering and tracking the delivered dose
  - Linking the delivered dose to retreatments, functional imaging, and outcomes
- Need to continue to advance predictive modeling and correlation with outcomes
  - Enable improved treatment and link with re-treatment and imaging outcomes