The Current Trajectory of Personalized Adaptive RT

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THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History

Motivation

- Presidential mandate for precision medicine
  - Image-guided, personalized, adaptive radiotherapy is the epitome of precision medicine
- Radiation therapy initiative to ensure safety
  - Active monitoring of the treatment delivery and evaluation of outcomes is an important piece of this process
- 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*

Personalized Adaptive RT Trajectory

ASTRO Plenary Session 2005

5 **Adaptive Planning and Delivery to Account for Anatomical Changes Induced by Radiation Therapy of Head and Neck Cancer**

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- Set the stage for the importance of adaptive radiotherapy
- Promoted the role of Medical Physics
- Demonstrated the role of adaptive planning to eliminate the PTV
- Demonstrated the need to account for soft tissue changes in dose accumulation
- So what have we done since then…

Clinical Investigation: Head and Neck Cancer

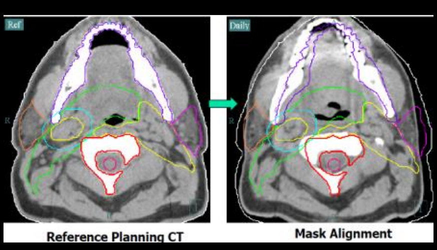
IJROBP 83 (3), pg. 986-993

Adaptive Radiotherapy for Head-and-Neck Cancer: Initial Clinical Outcomes From a Prospective Trial

David L. Schwartz, M.D.,*,†,‡ Adam S. Garden, M.D.,‡ Jimmy Thomas, M.D.,‡ Yipei Chen, B.S.,§ Yongbin Zhang, M.S.,§ Jan Lewin, Ph.D.,‖ Mark S. Chambers, D.M.D.,‖ and Lei Dong, Ph.D.§

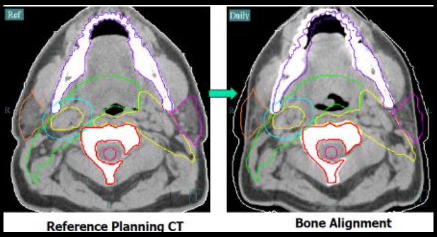
Purpose: To present pilot toxicity and survival outcomes for a prospective trial investigating adaptive radiotherapy (ART) for oropharyngeal squamous cell carcinoma.
Conclusion: This is the first prospective evaluation of morbidity and survival outcomes in patients with locally advanced head-and-neck cancer treated with automated adaptive replan- ning. ART can provide dosimetric benefit with only one or two mid-treatment replanning events. Our preliminary clinical outcomes document functional recovery and preservation of disease control at 1-year follow-up and beyond.

Conventional



Slide Courtesy of Lei Dong

Image Guidance



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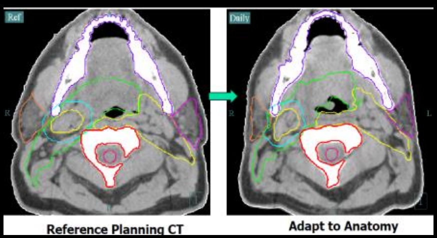
Adaptive



Slide Courtesy of Lei Dong

SUMMARY

1. Images Obtained during Tx
   – Daily CT (CT on-rails)
2. (Auto) Segmentation
   – Auto-segmentation via DIR
3. Deformable Image Registration
   – Modified (dual force accelerated) Thirion's Demons Algorithm
4. Dose Re-calculation & Summation
   – Calculation on Tx Fx CT, no summation
5. Decision Making Tools
   – Replan prompted by changes identified in patient
6. Plan Re-Optimization (including delivered dose)
   – Naïve, empirical adaptive PTV (1 mm)

Replan: Timing and Frequency

<u>1 Replan</u>:
Mean parotid dose sparing was improved by:
- 2.8% (p = 0.003) in the contralateral parotid
- 3.9% (p = 0.002) in the ipsilateral parotid

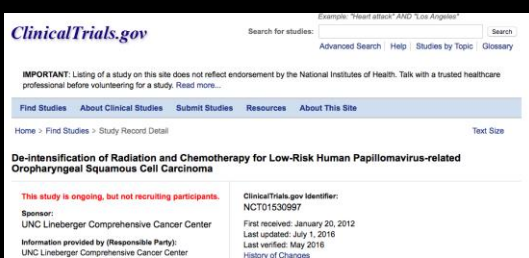
<u>2 Replans</u>:
Mean parotid dose sparing was improved by:
- 3.8% (p = 0.026) for the contralateral parotid
- 9% (p = 0.001) for the ipsilateral parotid

Fig. 3. Timing of adaptive radiotherapy (ART) replanning. Distribution of the triggering fraction for replanning is plotted for both first and second ART events.

Role of Personalized Adaptive RT

- Localized Oral Cavity and Pharynx Cancer: 83.3% 5 year survival
  https://seer.cancer.gov/statfacts/
- 2015 report from Zeng et al of 208 patients who received IMRT, where xerostomia was recorded in 80.8%, 66.3%, 56%, 40.9% and 40.9% of patients within 1, 2, 3, 4 and 5 years after RT, respectively.

How to Reduce Toxicity?


ClinicalTrials.gov

Example: "Heart attack" AND "Los Angeles"
Search for studies: Search
Advanced Search | Help | Studies by Topic | Glossary

IMPORTANT: Listing of a study on this site does not reflect endorsement by the National Institutes of Health. Talk with a trusted healthcare professional before volunteering for a study. Read more...

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De-intensification of Radiation and Chemotherapy for Low-Risk Human Papillomavirus-related Oropharyngeal Squamous Cell Carcinoma

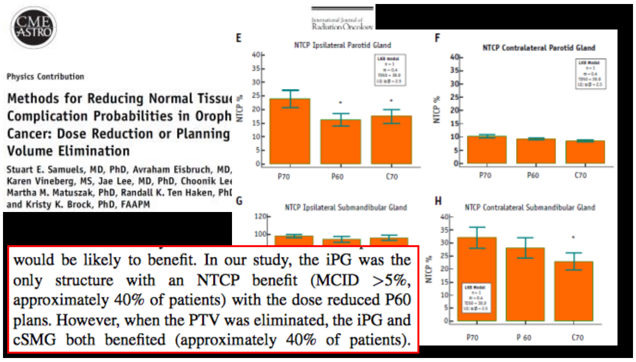
This study is ongoing, but not recruiting participants.

Sponsor:
UNC Lineberger Comprehensive Cancer Center

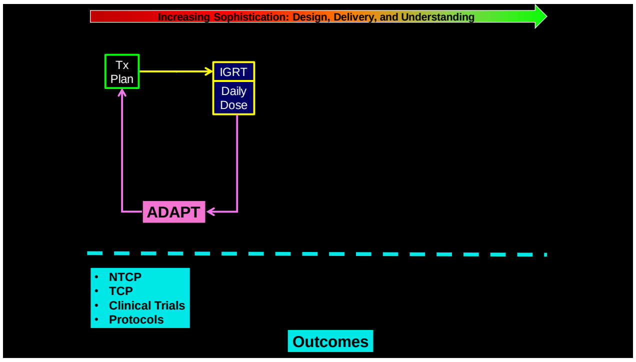
Information provided by (Responsible Party):
UNC Lineberger Comprehensive Cancer Center

ClinicalTrials.gov Identifier:
NCT01530997

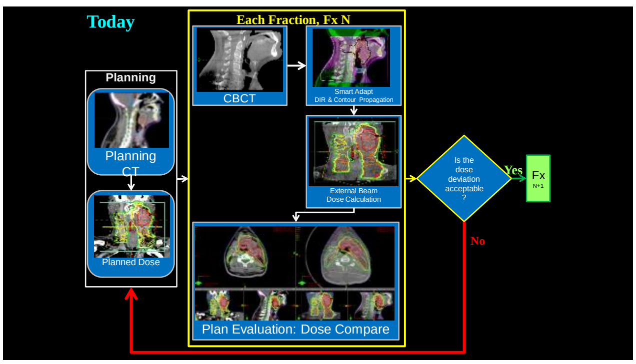
First received: January 20, 2012
Last updated: July 1, 2016
Last verified: May 2016
History of Changes



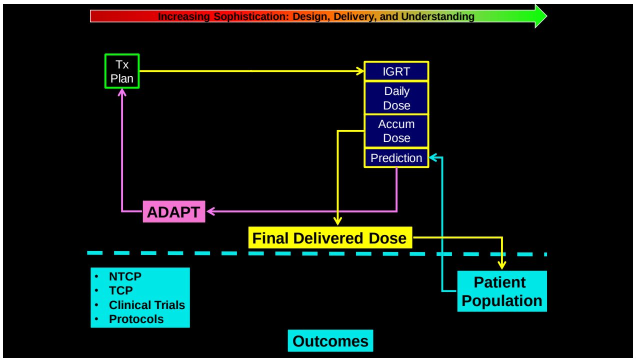
CME ASTRO
International Journal of Radiation Oncology
Physics Contribution
Methods for Reducing Normal Tissue Complication Probabilities in Oroph
Cancer: Dose Reduction or Planning
Volume Elimination
Stuart E. Samuels, MD, PhD, Avraham Eisbruch, MD,
Karen Vineberg, MS, Jae Lee, MD, PhD, Choonik Lee
Martha M. Matuszak, PhD, Randall K. Ten Haken, PhD
and Kristy K. Brock, PhD, FAAPM
E
NTCP Ipsilateral Parotid Gland
F
NTCP Contralateral Parotid Gland
G
NTCP Ipsilateral Submandibular Gland
H
NTCP Contralateral Submandibular Gland
NTCP %
P70
P60
C70
would be likely to benefit. In our study, the iPG was the only structure with an NTCP benefit (MCID >5%, approximately 40% of patients) with the dose reduced P60 plans. However, when the PTV was eliminated, the iPG and cSMG both benefited (approximately 40% of patients).



Increasing Sophistication: Design, Delivery, and Understanding
Tx Plan
IGRT
Daily Dose
ADAPT
NTCP
TCP
Clinical Trials
Protocols
Outcomes



Today
Each Fraction, Fx N
Planning
Planning CT
Planned Dose
CBCT
Smart Adapt
DIR & Contour Propagation
External Beam Dose Calculation
Plan Evaluation: Dose Compare
Is the dose deviation acceptable ?
Yes
Fx N+1
No



Methods and Materials

- 100 H&N (base of tongue) patients Tx with CBCT/VMAT evaluated.
- Phantom used to evaluate CBCT dose calc accuracy
- 4 cases selected for auto-segmentation assessment
- Deviations in the normal tissues were evaluated including:
  - Mean dose: superior (SC) and inferior constrictors (IC)
  - Mean dose: L and R parotid glands (PG)
  - Mean dose: L and R submandibular glands (SMG)
  - Max dose: spinal canal
  - CTV D95

Organ	Planning Constraint [Gy]	Dose Deviation Threshold [Gy]	Organs Included in Model* (N)	Organs Exceeding Deviation (n)	Deviation** at Completion of Tx [Gy]	Deviation** by Fx15 [Gy]
Inf. Constrictor	20	3	12	1	5.62	5.86
Sup. Constrictor	50	7.5	60	0		
Spinal Cord	45	6.75	94	0		
High CTV	Variable*	Variable*	43	0		
Int. CTV	Variable*	Variable*	17	1	-6.65	-4.84
Oral Cavity	30	4.5	56	1	5.18	0.81
Left Parotid	24	3.6	37	1	3.77	3.08
Right Parotid	Setting the threshold at 3.5 Gy at Fx 15 leads to 1 false positive					
SGs	30	4.5	179	7	8.22 (max)	3.5 (min)

*Started with 100 patients and only included organs in the evaluable region of the CBCT and without DIR failure
**Deviation = completed (accumulated) dose – planned dose

Year : 2017 | **Volume** : 13 | **Issue** : 2 | **Page** : 218-223

Changes in pharyngeal constrictor volumes during head and neck radiation therapy: Implications for dose delivery

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Department of Radiation Oncology, Henry Ford Health System, Detroit, MI, USA

- 13 oropharyngeal cancer patients with daily cone beam computed tomography (CBCT) was retrospectively studied
- anterior-posterior PCM thickness was measured at the midline level of C3 vertebral body.
- Delivered dose to PCM was estimated by calculating dose on daily images and performing dose accumulation on corresponding planning CT images using a parameter-optimized B-spline-based deformable image registration algorithm.
- The mean and maximum delivered dose (D_{mean}, D_{max}) to PCM were determined and compared with the corresponding planned quantities.

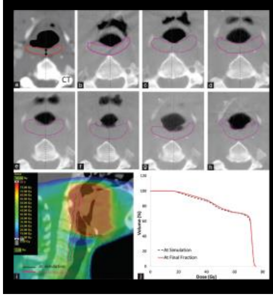


Figure 1: Example case of cross-sections of physician-drawn pharyngeal constrictor in axial view;
(a-h) pharyngeal constrictor contours at C3 level on simulation computed tomography and cone beam computed tomography images of 5, 10, 15, 20, 25, 30, and 35 fractions,
i) contours at simulation and at the last (#35) fraction overlaid on the simulation computed tomography with dose color wash, and
(j) the respective DVHs at simulation (dashed line) and at fraction 35 (solid line). For this case, D_{mean} increased from 62.4 to 63.0 Gy, whereas D_{max} remained unchanged

Pharyngeal constrictor changes for 13 patients during Tx

Patient number	ΔV (%)	Δt (%)	ΔD_{mean} (%)	ΔD_{mean} (Gy)	ΔW (lbs)	Replanned
1	65.3	100	2.1	1.4	1.4	No
2	34.7	−14.3	−0.8	−0.5	1.6	Yes
3	26.2	33.3	0.3	0.1	12.2	No
4	76.7	84.6	2.2	1.4	5.9	No
5	10.5	79.1	2.4	1.2	24.2	No
6	48.6	63.8	0.3	0.2	28.2	Yes
7	66.2	91.1	0.6	0.4	20	Yes
8	102.3	52.2	0.7	0.5	9.2	Yes
9	44.4	36.8	0.9	0.6	17	No
10	38.0	45.2	0.1	0.1	15	Yes
11	106.7	111.1	5.1	3.3	27.8	No
12	−8.9	7.7	0.6	0.3	35.6	Yes
13	94.3	123.8	2.5	1.7	15	No

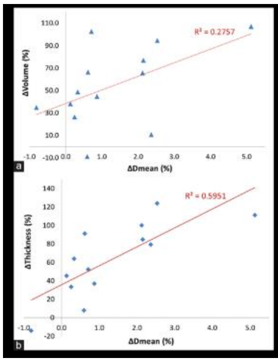
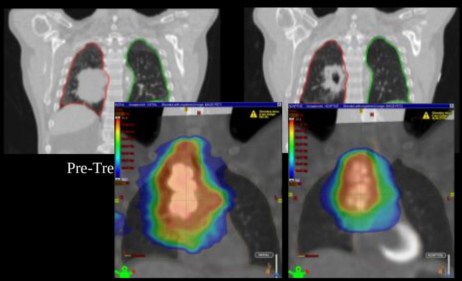


Figure 3: Correlations of (a) volume Δ*V*, and (b) thickness increases Δ*t*, to mean dose increases (ΔD_{mean}). R^2 values from linear regression correlation are also shown

PCM thickness at C3 redicted dose increase, however dose increase is minor to moderate

Adapting to Changing Anatomy



Pre-Tre

and Functional Changes

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Seminars in RADIATION ONCOLOGY

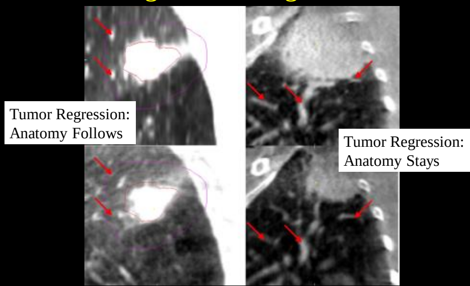
Adaptive Radiotherapy for Lung Cancer

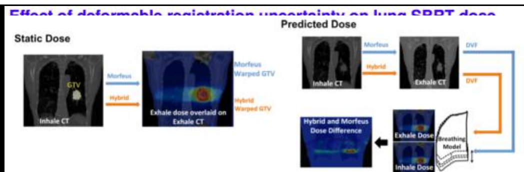
Jan-Jakob Sonke, PhD, and José Belderbos, MD, PhD

Planning CT | First week CBCT

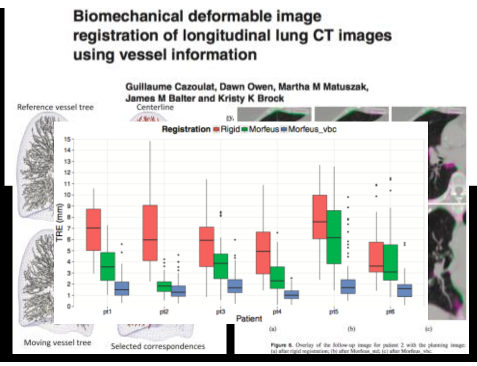
Figure 7 Example of progressive anatomical changes requiring plan adaptation depicting the planning CT (left) and first week CBCT (right) aligned on the bony anatomy. Pretreatment GTV (red) and PTV (purple) delineations are overlaid on both scans. Due to shrinkage of the tumor the atelectasis (seen on the planning CT scan) dissolved and a shift of mediastinal structures to the normal position occurred (seen on the CBCT scan). As a consequence, the dose distribution changed, the dense tissue of the collapsed lung dissolved, the tumor, and subcarinal lymph node moved outside the PTV and excessive irradiation of normal lung tissue occurred.

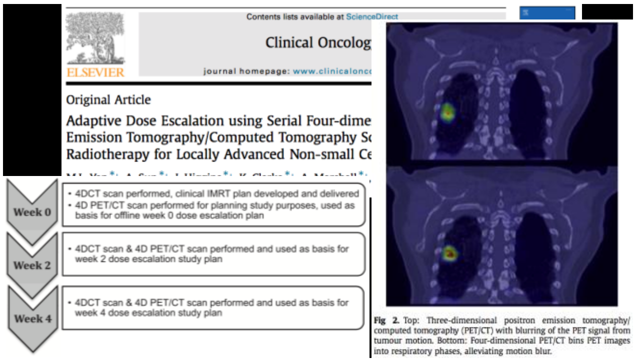
Lung Tumor Regression





- 1.5 mm reduction of DIR error translated to >1 Gy differences in Dmin in up to 50% of a patient population with the following characteristics:
  1. Dose homogeneity index > 15
  2. DIR-induced Dice differences > 0.08
- These characteristics were specific criteria but not highly sensitive since there were cases that met the criteria without resulting in >1 Gy differences (in accumulated dose).

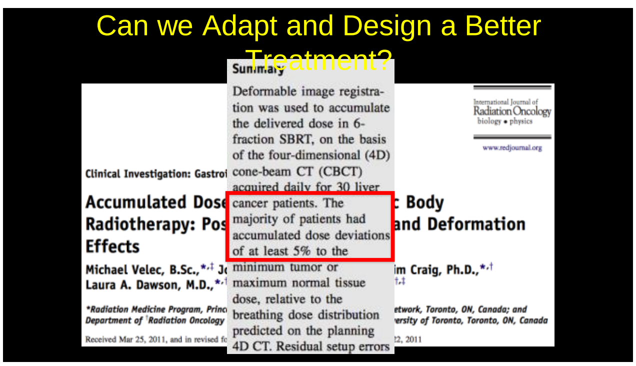




Adaptive 4D PET Results

- 32 patients were recruited, 27 completing all scans.
- 25 patients (93%) were boosted successfully above the clinical plan doses at week 0, 23 (85%) at week 2 and 20 (74%) at week 4.
- The median dose received by 95% of the planning target volume (D95) at week 0, 2 and 4 to PET-T were 74.4 Gy, 75.3 Gy and 74.1 Gy and to PET-N were 74.3 Gy, 71.0 Gy and 69.5 Gy.

- Conclusions: Using 18F-FDG-4DPET/4DCT, it is feasible to dose escalate both primary and nodal disease in most patients. Choosing week 0 images to plan a course with an integrated boost to PET-avid disease allows for more patients to be successfully dose escalated with the highest boost dose.

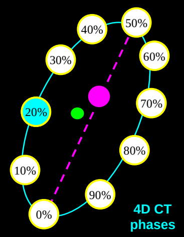


Dose-Escalated Liver SBRT @ Mean Position

Clinical Relevance:

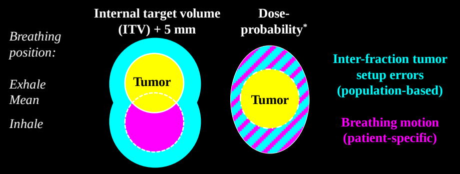
- Mean position PTV margins are smaller in volume than the standard ITV approach
- Reduction in volume will also reduce the overlap with luminal GI structures

- *Purpose: Quantify the dosimetric improvement in liver SBRT delivery with mean position planning and targeting.*



Velec M, et al. 'Dose-escalated liver SBRT at the mean respiratory position,' IJROBP, 89(5): 1121-8, 2014

Mean Respiration Model



Mean Δ tumor-PTV volume: -38 ± 3%

Dose-probability PTV* $= 2.5\Sigma + 1.28(\sigma - \sigma_{penumbra})$

Σ, σ: residual tumor error after liver alignment on CBCT(≈3–5 mm)

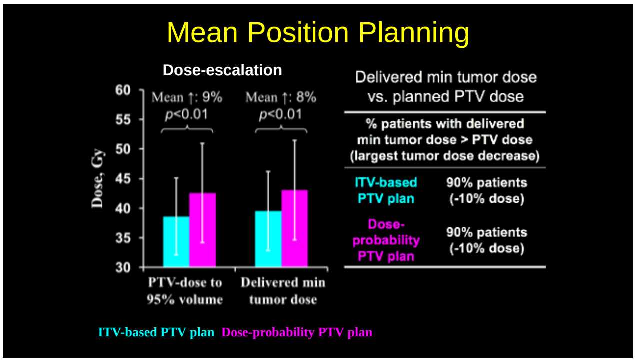
Σ: ≈0 from Mid-position CT, σ: ≈1/3 breathing amplitude

*van Herk. *IJROBP* 2000;84(4): 1121-1135

Dose-Escalated Liver SBRT @ Mean Position

- Data:
  - 20 patients, planned on exhale 4D CT for 27-49.8 Gy in 6 fractions
    - Treated free-breathing; tumor amplitude: 1–21 mm (median: 8 mm)
    - Daily 3D CBCT registration of the liver (retrospective 4D sorting)
- 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



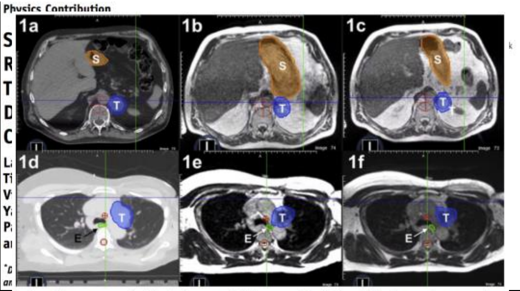


Fig. 1. Patient anatomy at simulation (a, d) compared with "anatomy of the day" revealed by the magnetic resonance image set at fraction 1 (b, e) versus "anatomy of the day" revealed by magnetic resonance imaging at fraction 2 (c, f). In frames a-c, large interfractional shifts occur in the position of the stomach (S) relative to the adrenal tumor (T). Similarly, in a separate patient (d-f), interfractional variability in esophageal position (E) relative to a para-aortic lymph node tumor (T) was observed.

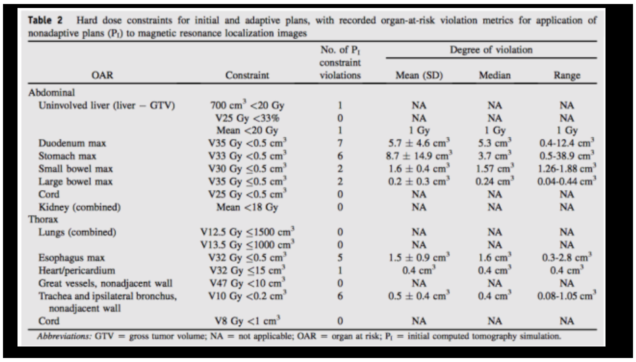


Table 2 Hard dose constraints for initial and adaptive plans, with recorded organ-at-risk violation metrics for application of nonadaptive plans (P_I) to magnetic resonance localization images

			Degree of violation		
OAR	Constraint	No. of P_I constraint violations	Mean (SD)	Median	Range
Abdominal					
Uninvolved liver (liver − GTV)	700 cm^3 <20 Gy	1	NA	NA	NA
	V25 Gy <33%	0	NA	NA	NA
	Mean <20 Gy	1	1 Gy	1 Gy	1 Gy
Duodenum max	V35 Gy <0.5 cm^3	7	5.7 ± 4.6 cm^3	5.3 cm^3	0.4-12.4 cm^3
Stomach max	V33 Gy <0.5 cm^3	6	8.7 ± 14.9 cm^3	3.7 cm^3	0.5-38.9 cm^3
Small bowel max	V30 Gy ≤0.5 cm^3	2	1.6 ± 0.4 cm^3	1.57 cm^3	1.26-1.88 cm^3
Large bowel max	V35 Gy ≤0.5 cm^3	2	0.2 ± 0.3 cm^3	0.24 cm^3	0.04-0.44 cm^3
Cord	V25 Gy <0.5 cm^3	0	NA	NA	NA
Kidney (combined)	Mean <18 Gy	0	NA	NA	NA
Thorax					
Lungs (combined)	V12.5 Gy ≤1500 cm^3	0	NA	NA	NA
	V13.5 Gy ≤1000 cm^3	0	NA	NA	NA
Esophagus max	V32 Gy ≤0.5 cm^3	5	1.5 ± 0.9 cm^3	1.6 cm^3	0.3-2.8 cm^3
Heart/pericardium	V32 Gy ≤15 cm^3	1	0.4 cm^3	0.4 cm^3	0.4 cm^3
Great vessels, nonadjacent wall	V47 Gy <10 cm^3	0	NA	NA	NA
Trachea and ipsilateral bronchus, nonadjacent wall	V10 Gy <0.2 cm^3	6	0.5 ± 0.4 cm^3	0.4 cm^3	0.08-1.05 cm^3
Cord	V8 Gy <1 cm^3	0	NA	NA	NA

Abbreviations: GTV = gross tumor volume; NA = not applicable; OAR = organ at risk; P_I = initial computed tomography simulation.

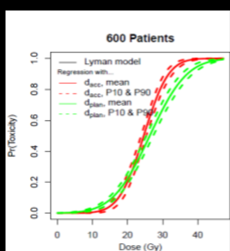
Does Improved Accuracy in Dose Matter for Outcomes?

- 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

Swaminath, Brock, Dawson, et al. IJROBP 2015

What about Normal Tissue?

- Simulation of the impact of using accumulated dose in toxicity models
- Under 22 Gy, acc-dose NTCP model using the planned dose yields a more accurate prediction of duodenal toxicity than the standard model:
  - → Standard, planned-dose NTCP models: Avg error 6.3%, SD 6.5%
  - → Max error 16%



Work by Molly McCulloch

Summary

- This is a very exciting time for precision radiotherapy!
- Advances in treatment planning allows for the sculpting of dose around normal tissue to reduce toxicity risk and improve the probability of local control.
- The combination of volumetric imaging and anatomical modeling enables assessment of the delivery and potential adaptation of the treatment plan, based on anatomical and functional changes.
- Calculation of the delivered dose has the potential to improve our understanding of the impact of radiation dose on normal tissue toxicity and tumor control.
- Completing the loop… we can use this information to further advance the safe, optimization of radiotherapy.

Acknowledgement
Michael B. Sharpe, PhD, FAAPM: Friend, Mentor, Colleague

Mike taught me so much… state of the art image-guided treatment planning, how to engage in clinically meaningful, translational research, but even more, that if you are very lucky, you will have amazing friends in your life, who will teach you and challenge you.

A friend that will remind you to not take a single day for granted and will make your life better through their friendship, even when that friendship becomes cherished memories.