RADIOTHERAPY

Todd McNutt PhD
Associate Professor
Radiation Oncology
Johns Hopkins University

Radiation Therapy : Primer

- The use of radiation to eradicate a tumor
  - Optical light: a few eV
  - Diagnostic x-rays: 20 – 80 keV; < ¼” of Pb
  - Therapeutic x-rays: 1 – 6 MeV; 2 ft of concrete, 7” of Pb
- Always try to kill the tumor but not the patient
- Conform dose to the target
- Fractionation: Delivery of dose over several weeks for better normal tissue repair
- Accuracy requirements: 5% change in dose can result in observable biological response

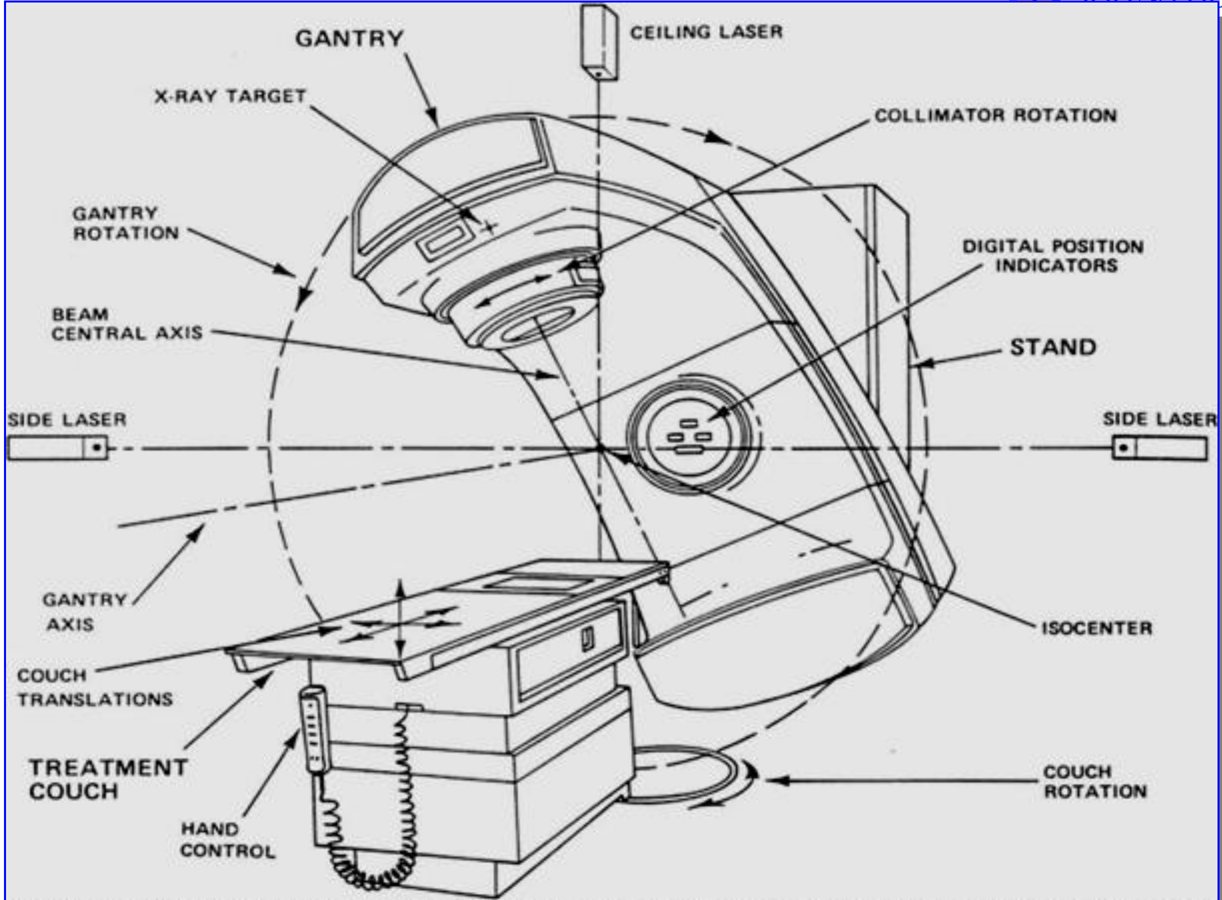
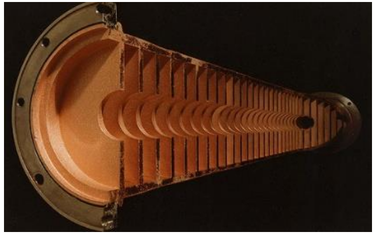


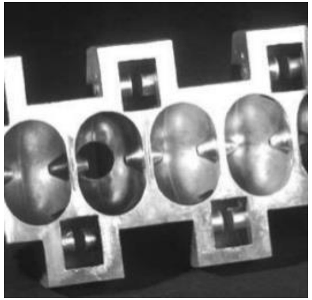
FIGURE 12-1 · Schematic view of a treatment unit emphasizing the geometric relationship of the linac and treatment couch motions. A pedestal type couch is illustrated.

Major Linac Components

- Electron gun: filament emits electrons into the waveguide
- Accelerating waveguide: uses high-energy microwaves to accelerate electrons to within 0.03% of the speed of light
- Bending magnet: steers high-energy electrons from a “waveguide” toward the patient



Travelling wave



Standing wave

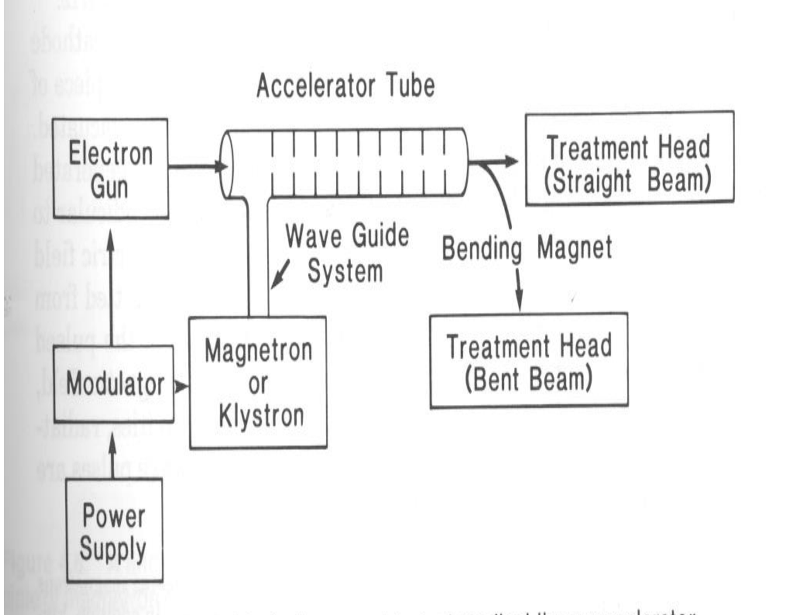


Figure 4.5. A block diagram of typical medical linear accelerator.

JOHNS HOPKINS MEDICINE

Major Linac Components

- **X-ray target**: heavy-metal target that absorbs electron energy to create photons via bremsstrahlung radiation
- **Carousel**: electron scattering foils and photon flattening filters for each beam energy
- **Monitor ion chambers**: measure the amount of radiation emitted from the carousel

Photons

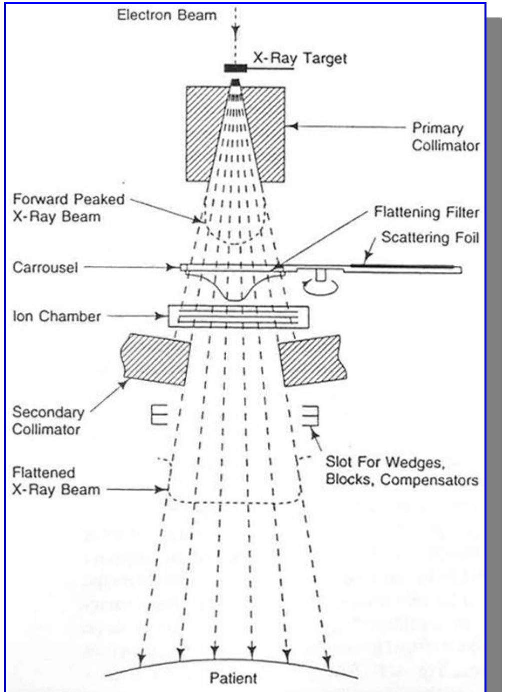


FIGURE 8-6 · Beam subsystem for x-ray beam therapy. Cross section view including central axis of the beam.

Electrons

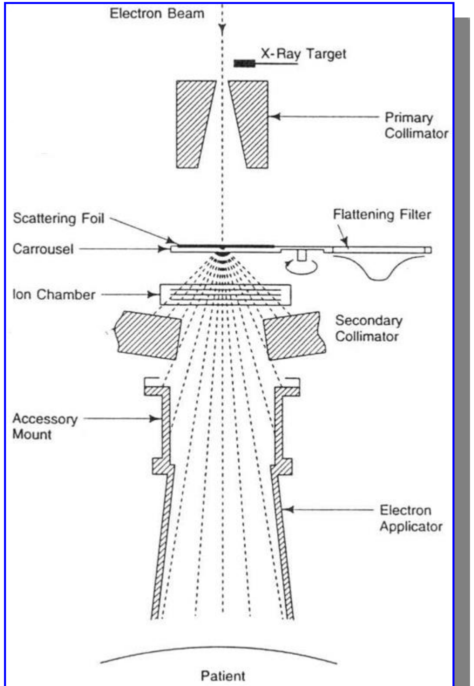
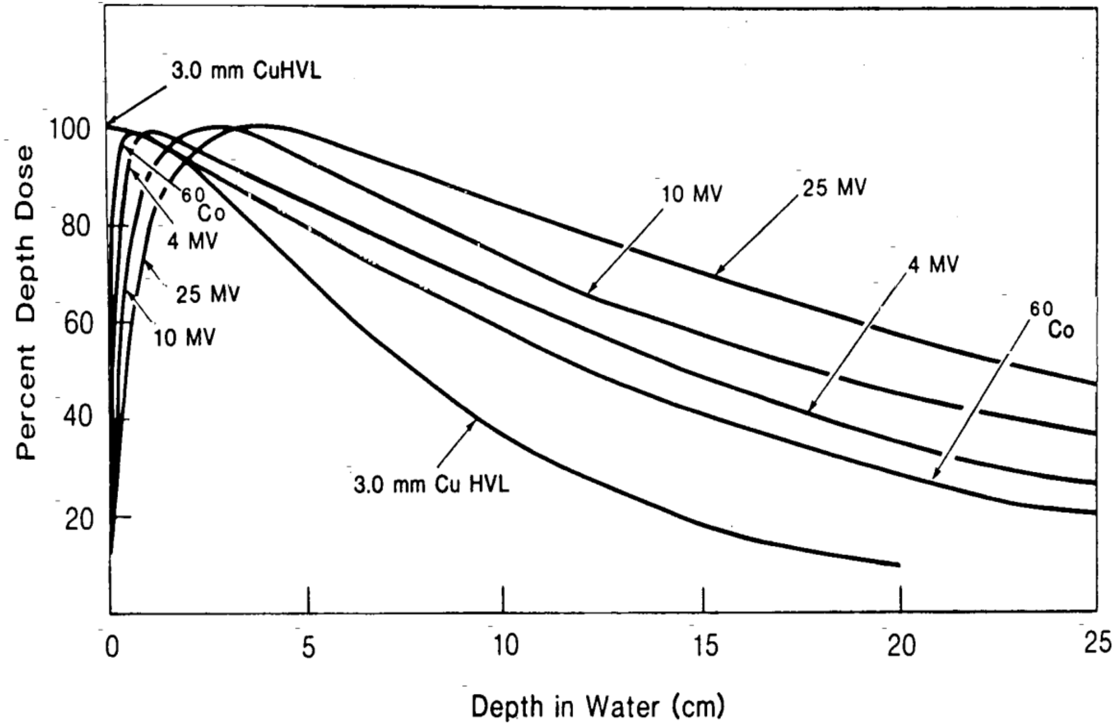


FIGURE 8-4 · Beam subsystem for electron beam therapy. Cross section view including central axis of the beam.

Photon Dose vs Depth, Energy/Beam Quality

JOHNS HOPKINS MEDICINE



- Higher energy ~ Greater penetrating power ~ Higher PDD
- Build up is deeper with higher energy

From Khan F, The Physics of Radiation Therapy, Third Edition, Lippincott Williams and Wilkins 2003

Family of photon beam profiles

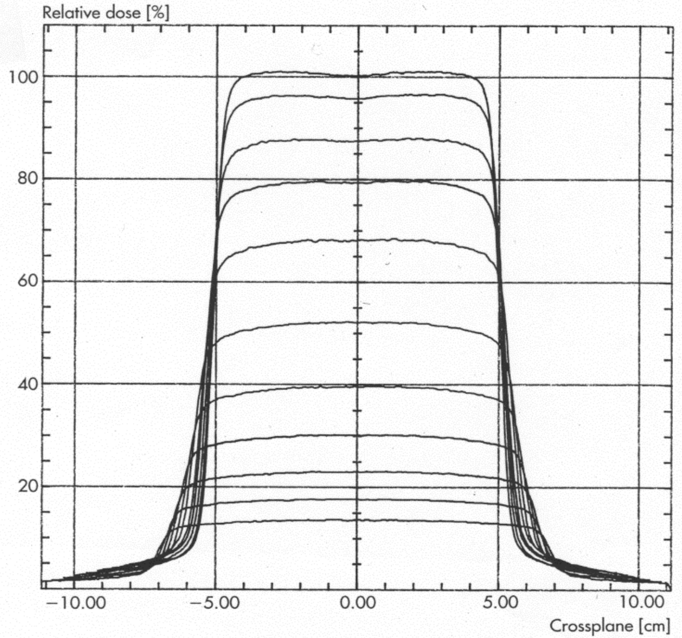
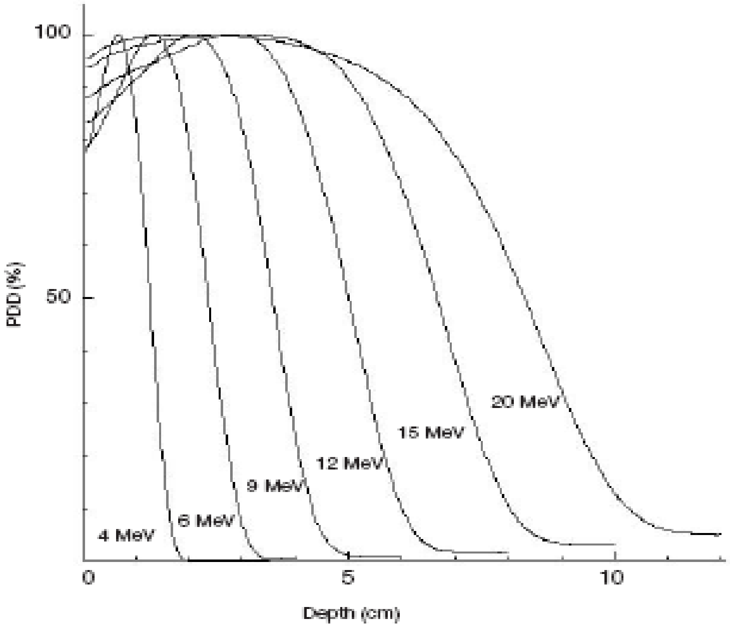


Figure 11-1 Graphic representation of several measured beam profiles of the type often entered into a treatment planning computer. The illustration shows a number of profiles made along lines perpendicular to the central axis at several depths in a water phantom.

- Dose greatest @ CAX
- Dose decreases @ beam edge
- “Horns” common near surface of accelerator beams
- Dose fall of near beam edge
  - Geometric penumbra
  - Reduced scatter

From Khan F, The Physics of Radiation Therapy, Third Edition, Lippincott Williams and Wilkins 2003

Electron Energy Dependence



- Lower surface dose (quick buildup) for lower energy beam
- Dose gradient steeper for lower energy electron
- More x-ray contamination for higher energy beams

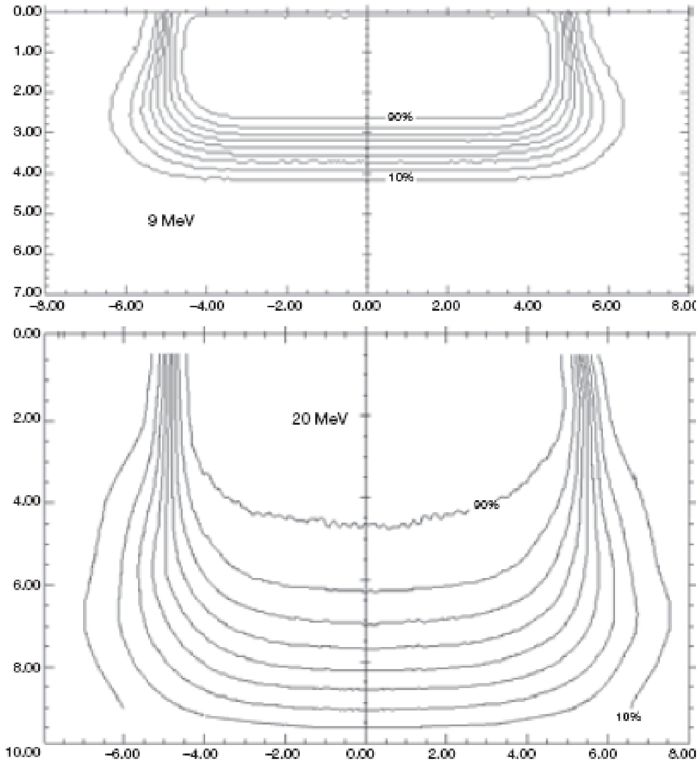
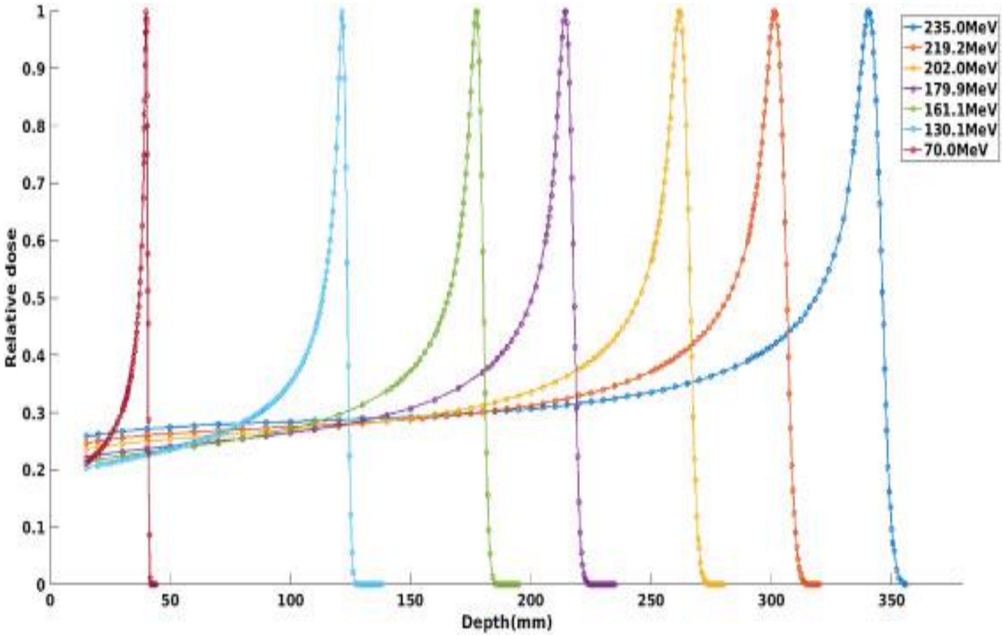


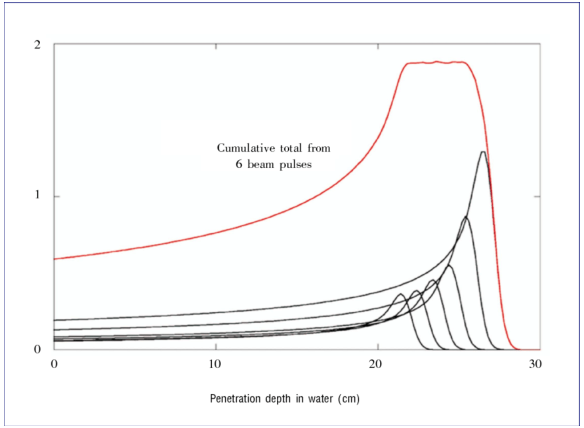
FIG. 8.7. Measured isodose curves for 9 and 20 MeV electron beams. The field size is 10 × 10 cm² and SSD = 100 cm. Note the bulging low value isodose lines for both beam energies. The 80% and 90% isodose lines for the 20 MeV beam exhibit a severe lateral constriction. The abscissa and the ordinate represent distance from the central axis and depth in a water phantom, respectively, measured in centimetres.

Proton depth dose

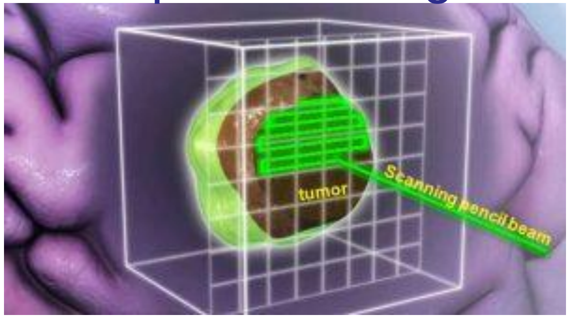
Bragg Peak vs Energy



Spread out Bragg Peak

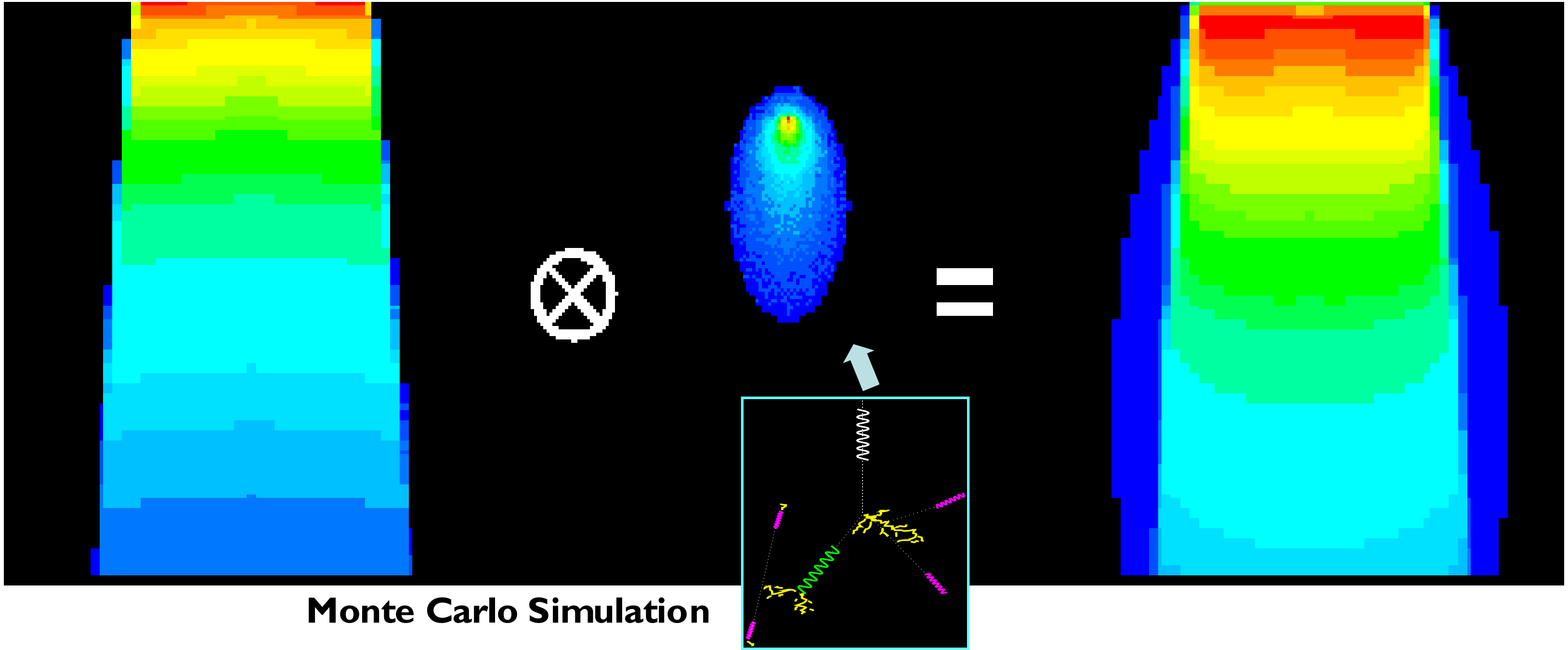


Spot scanning



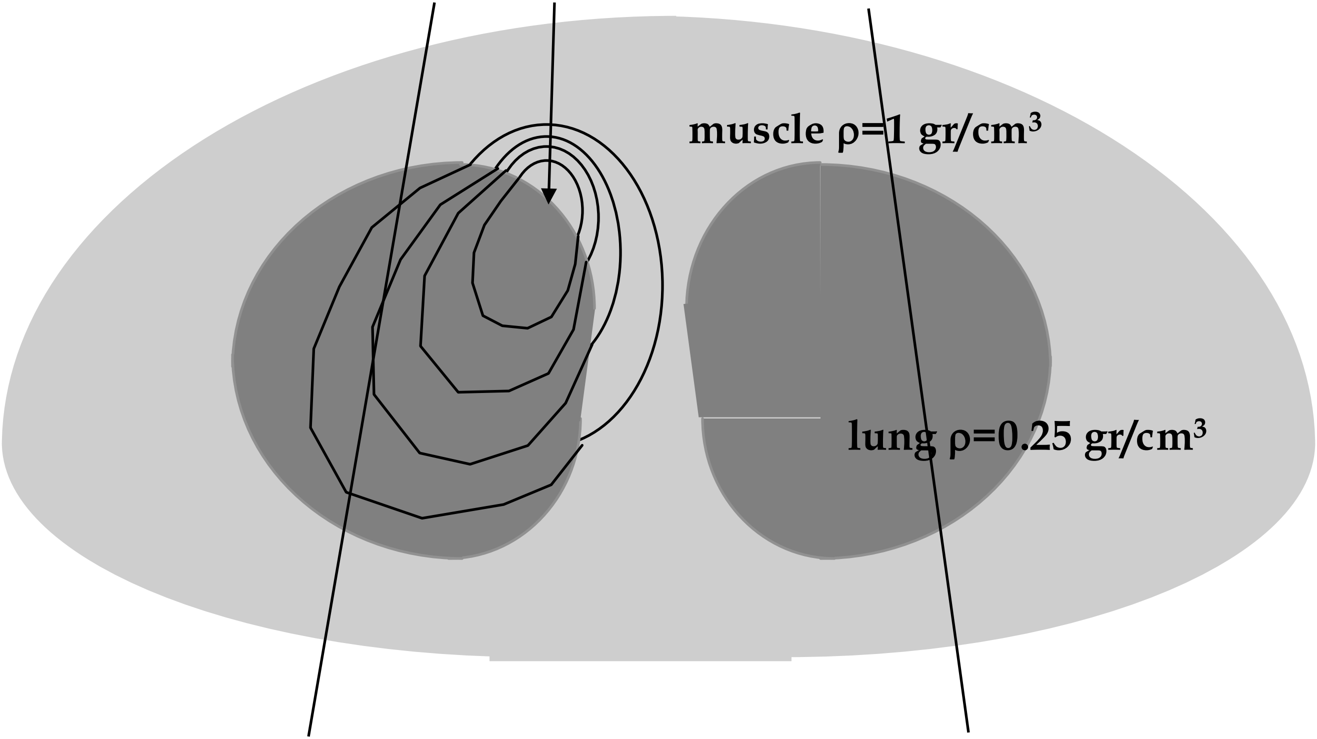
Method: Convolution/Superposition

$$D(\vec{r}) = \int_V \mathrm{T}(\vec{r}\,') \cdot \mathrm{A}(\vec{r} - \vec{r}\,') d^3 r\,'$$

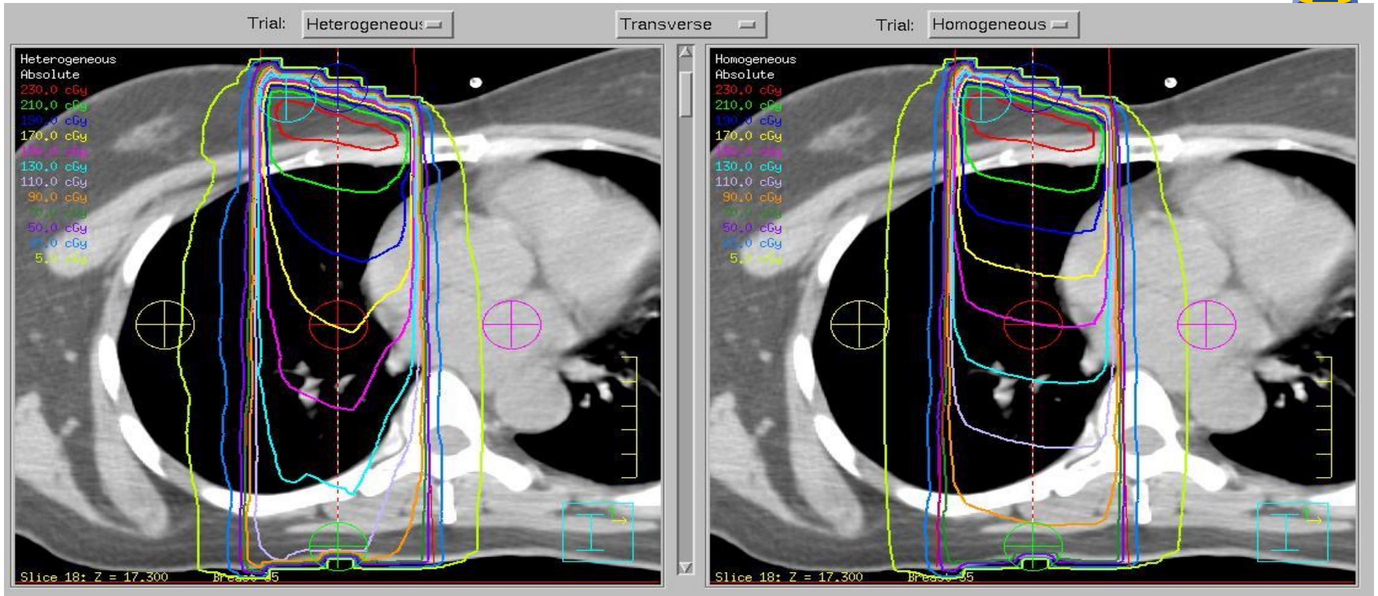


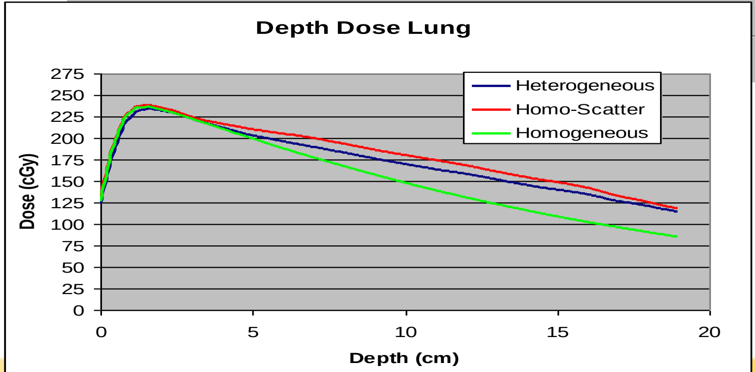
Monte Carlo Simulation

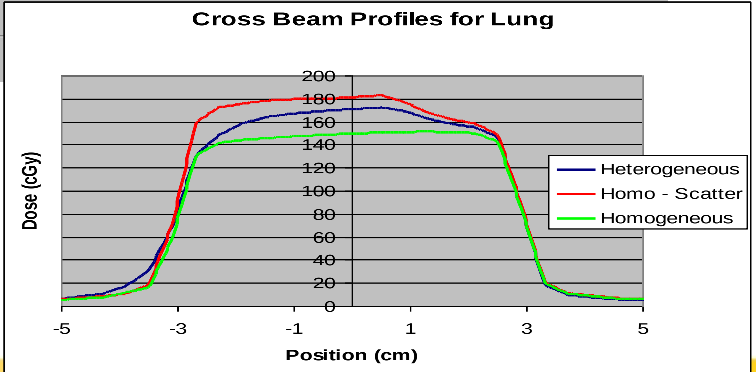
Convolution/Superposition: Heterogeneities



Open anterior beam



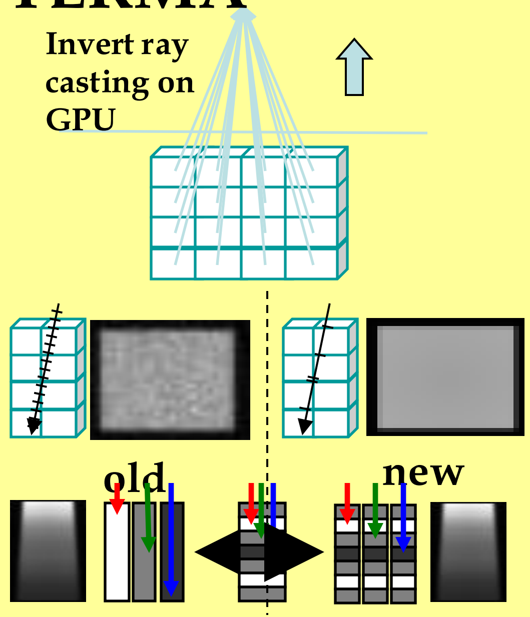




Fast Convolution/Superposition Dose Computation on GPU

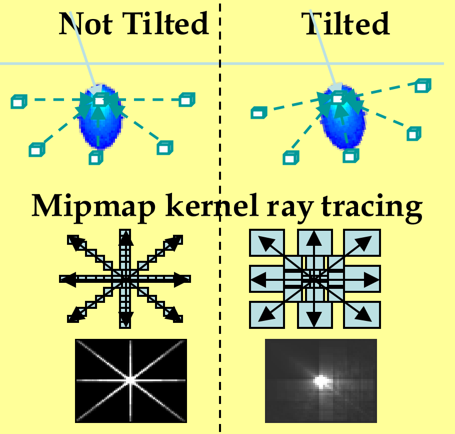
JOHNS HOPKINS MEDICINE

TERMA



Stepwise beam hardening

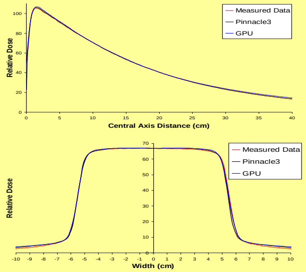
Superposition

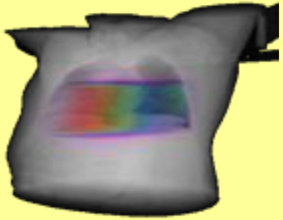


Performance

			64^3			128^3	
Engin	Kernel Type	Rays	Time (s)	VPS	Speedup	Time (s)	Speedup
GPU	CCK, Tilting*	72	0.198	5.051	41.8x	2.801	33.7x
GPU	CCK, Non-tilting	80	0.159	6.289	52.0x	2.254	41.9x
GPU	CCK, Tilting*	32	0.086	11.628	96.1x	1.246	75.8x
GPU	CCK, Multi-Reso	80	0.097	10.309	85.2x	0.963	98.1x
GPU	CCK, Multi-Reso	32	0.042	23.810	N/A	0.411	N/A
Pinna	CK, Non-tilting	80	8.268	0.121	1.0x	94.51	1.0x

Accurate





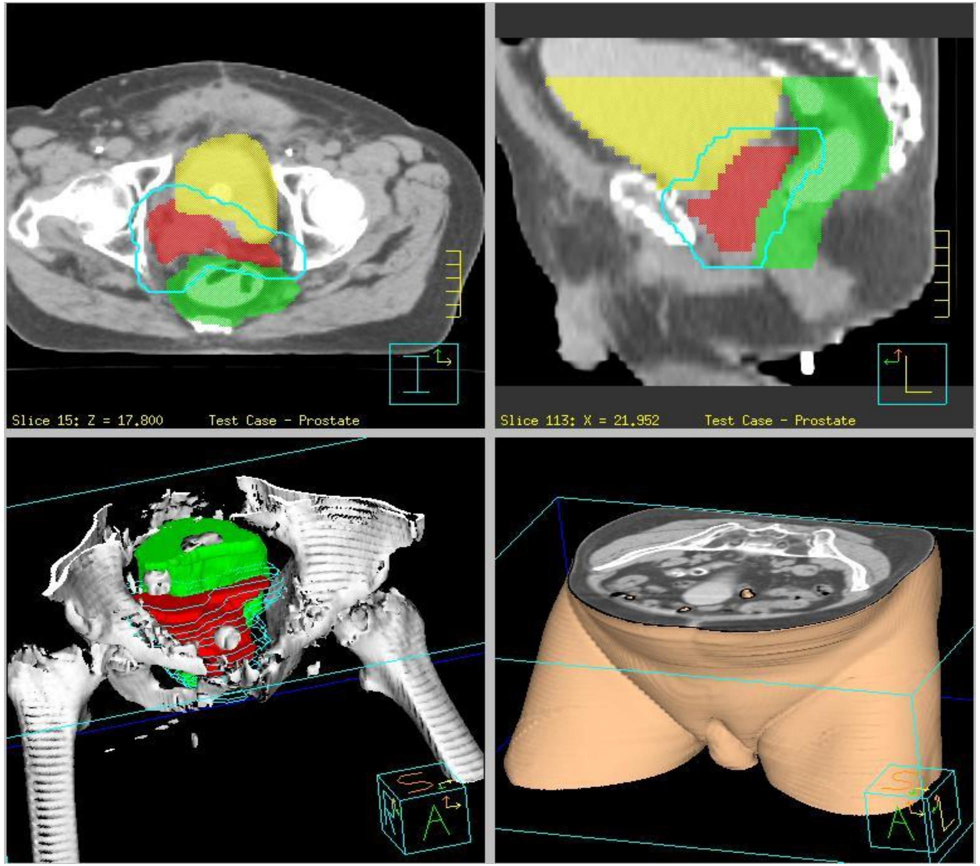
Target and Clinical Structure Definition

- Planning begins by defining the regions of interest within the patient

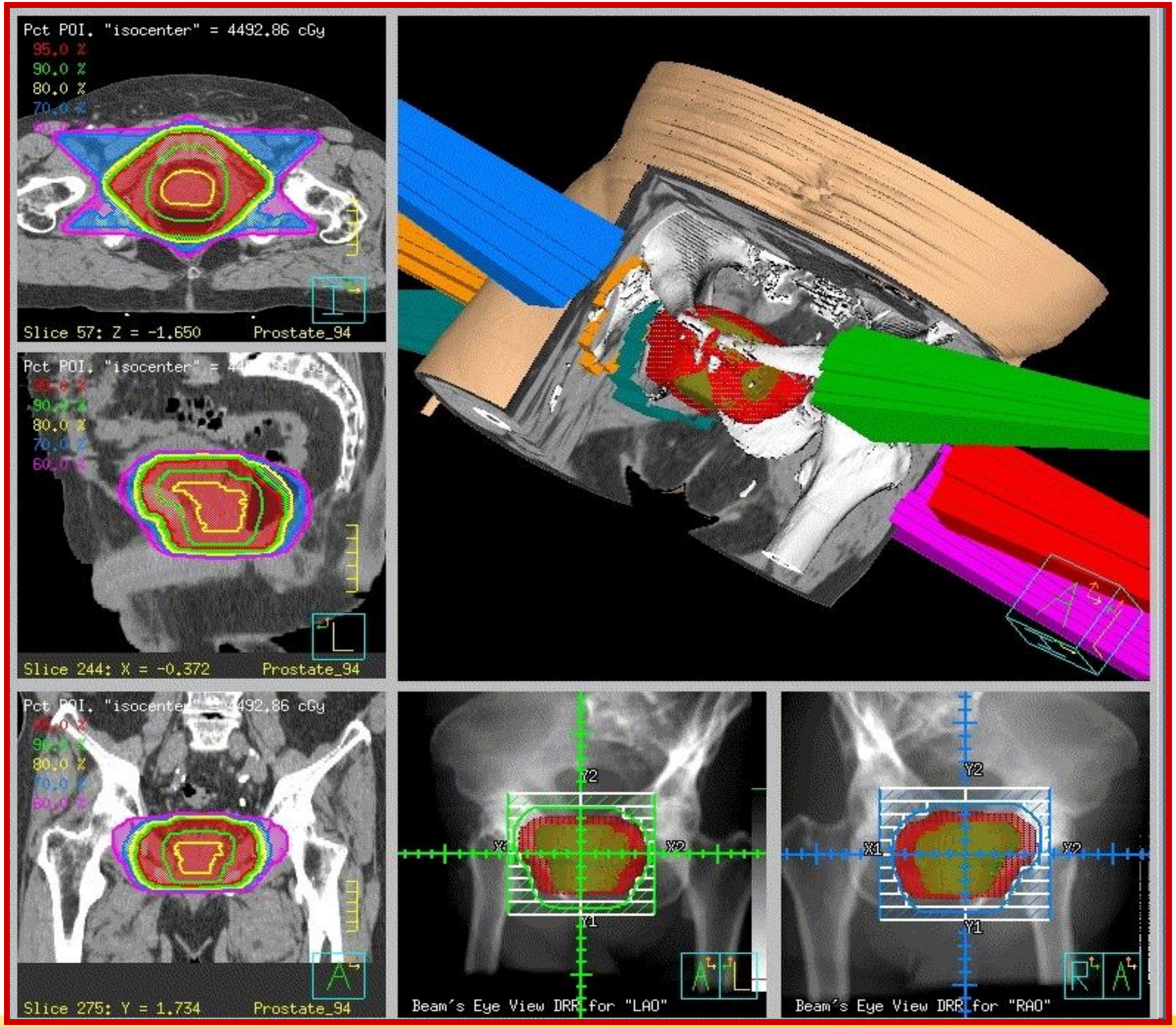
Manual Tools
- Line Drawing
- Paint Brush
- 3D tools

Auto Contouring
- Threshold
- Gradient/Edge detection
- Model based

Display
- Contours
- Colorwash
- Polygons (2D and 3D)

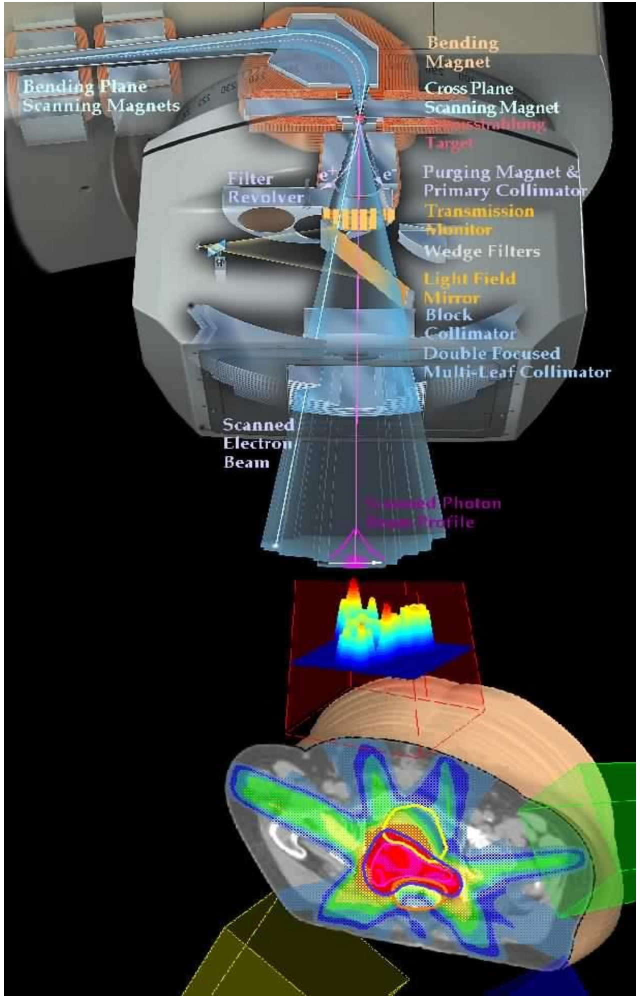


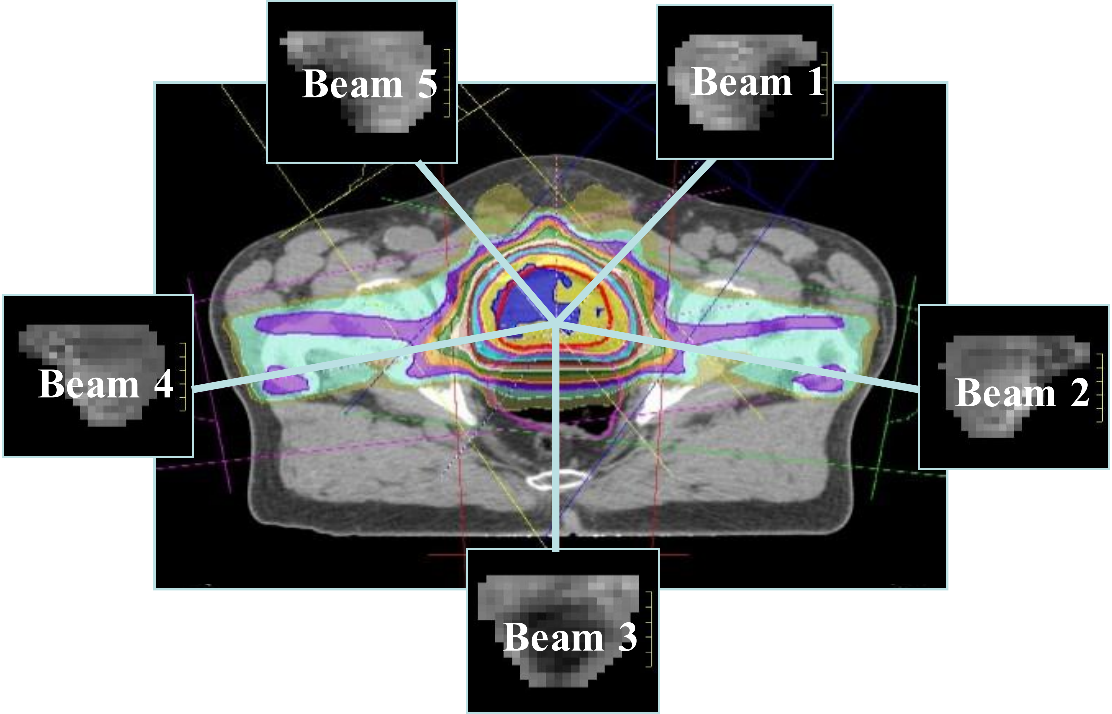
3D



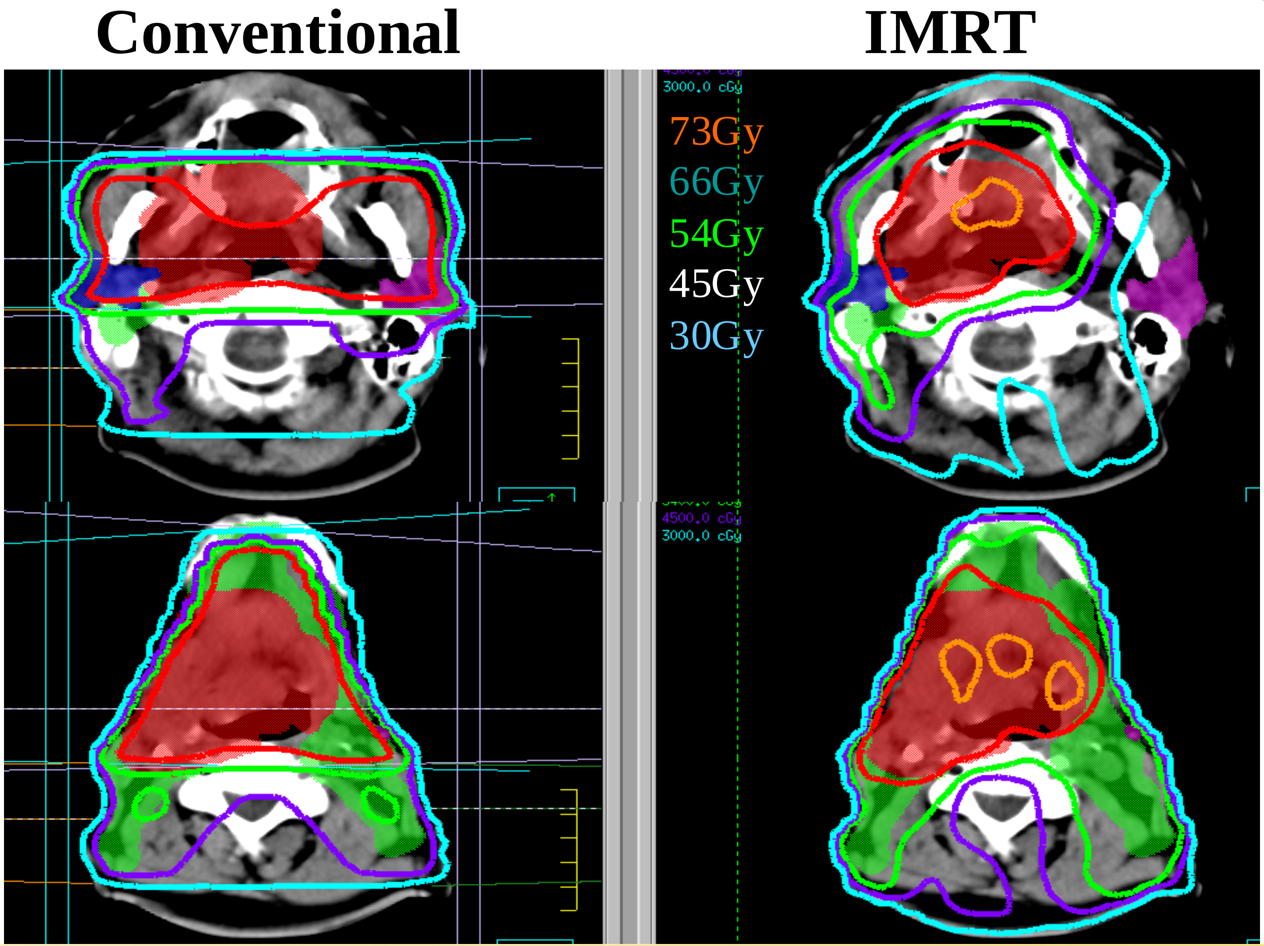
JOHNS HOPKINS MEDICINE

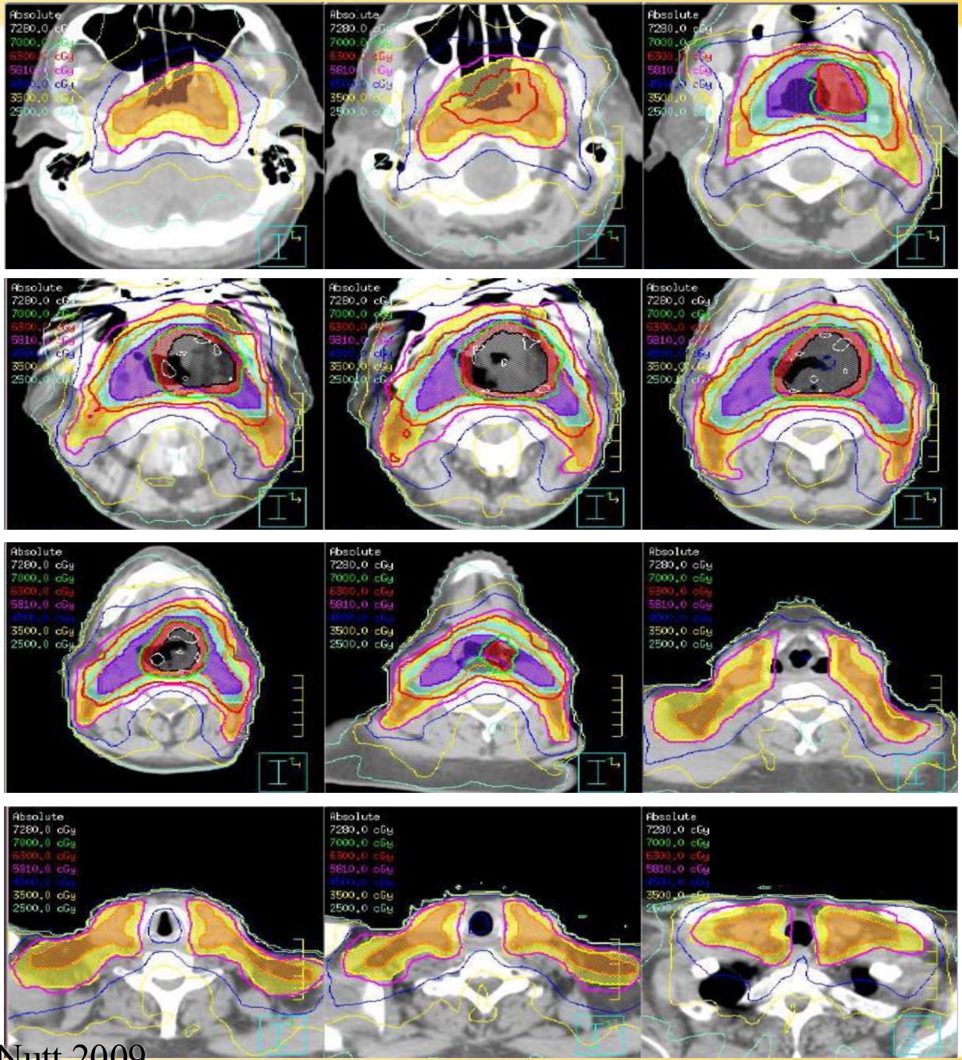
Modern Medical Accelerator and Intensity Modulation (IMRT)

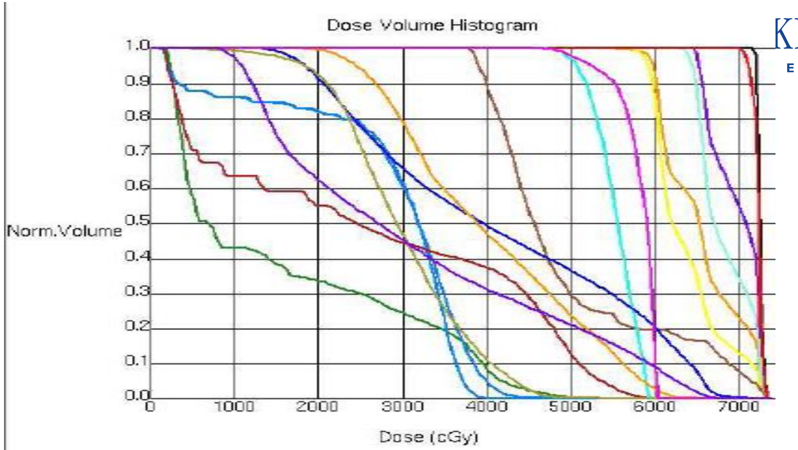




Isodose Lines Comparing 3D and IMRT



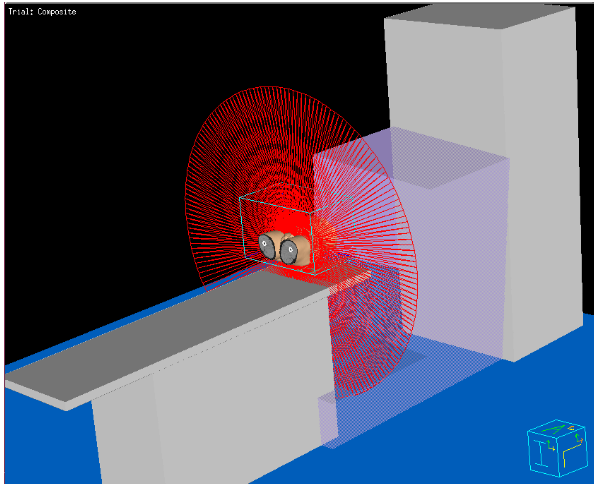


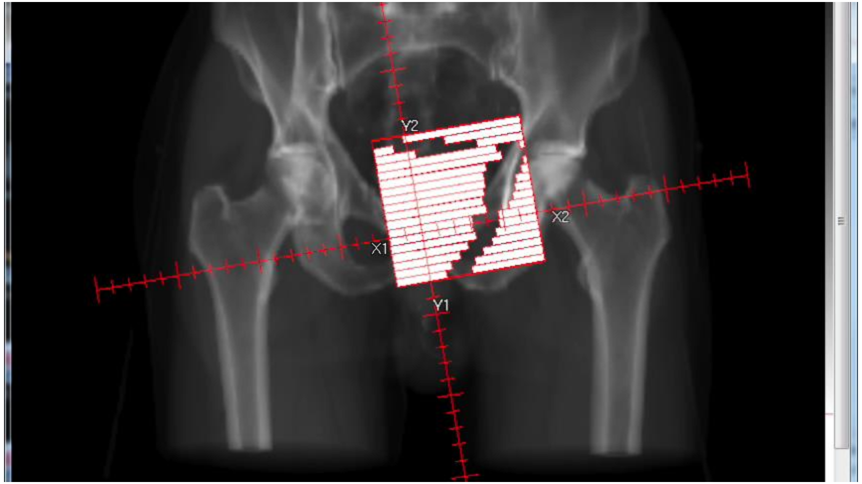


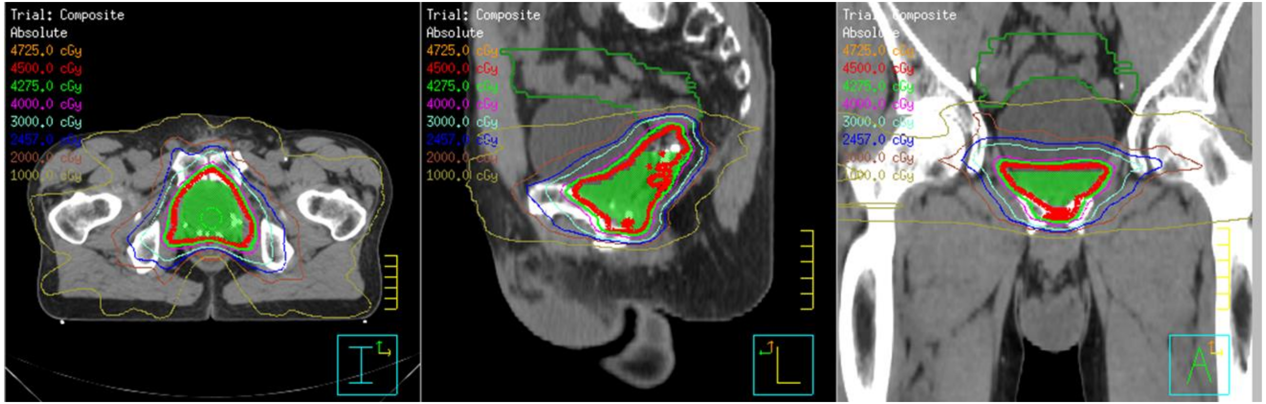
Dose Volume Histograms are used to analyze treatment plan quality by determining what percent of a region of interest receives how much dose.

McNutt 2009

VMAT – Volumetric Modulated Arc Therapy

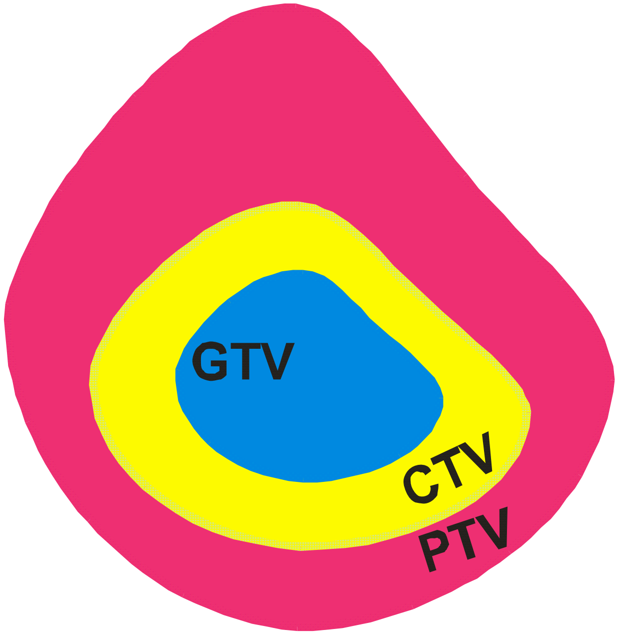




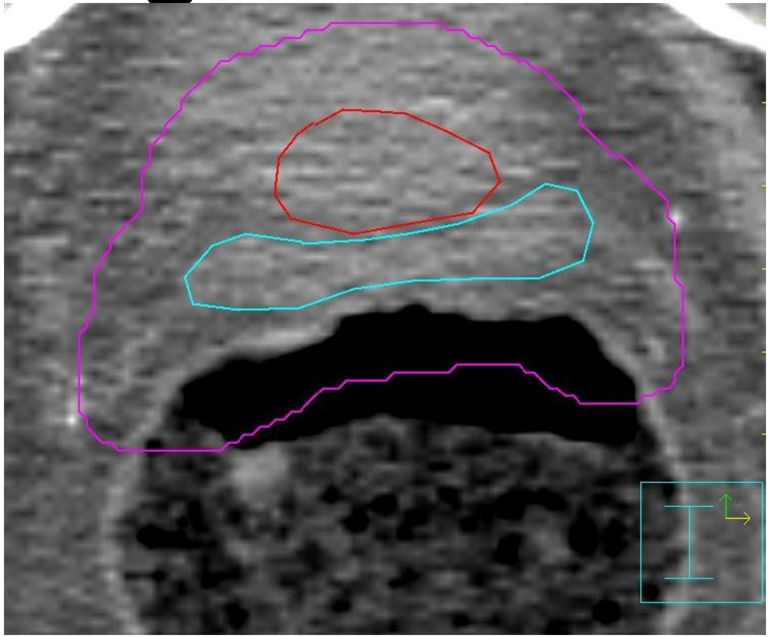


Target Volume Specification *(late 80's)*

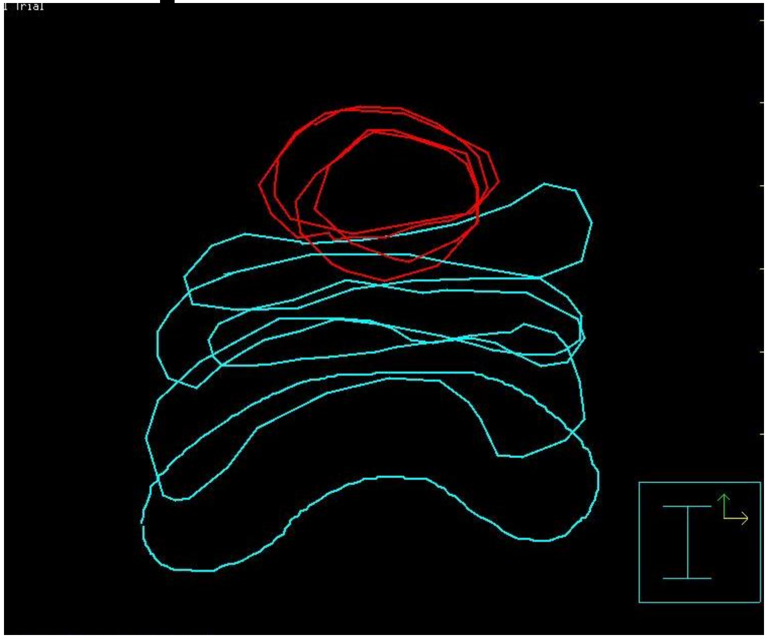
- GTV - Gross Tumor Volume
- CTV - Clinical Target Volume
- PTV - Planning Target Volume
  - – Accounts for internal organ motion and patient setup variations during the course of treatment.
- All 'TVs are a statement of the uncertainties (or our ignorance) ---- research opportunities



Organ Motion : Repeat CTs



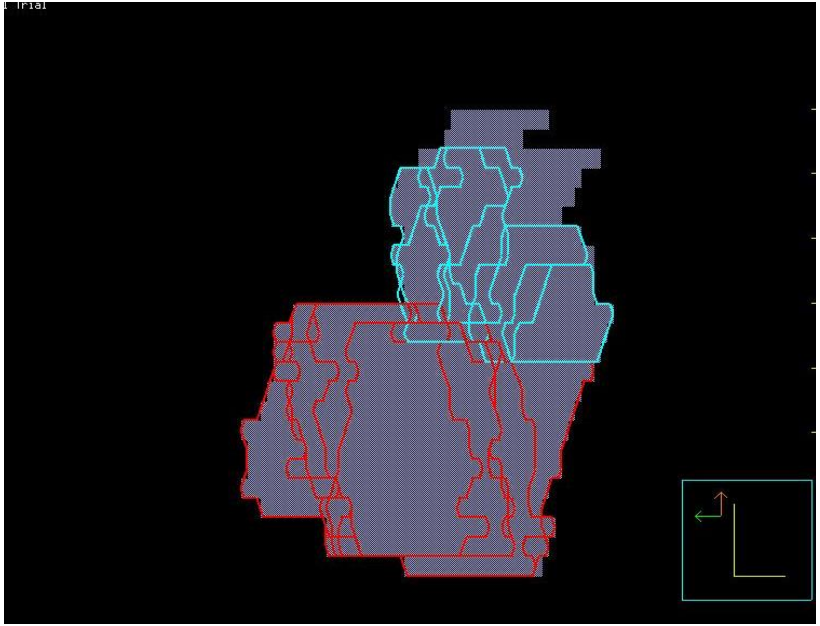
PTV prescribed with 1st day CT

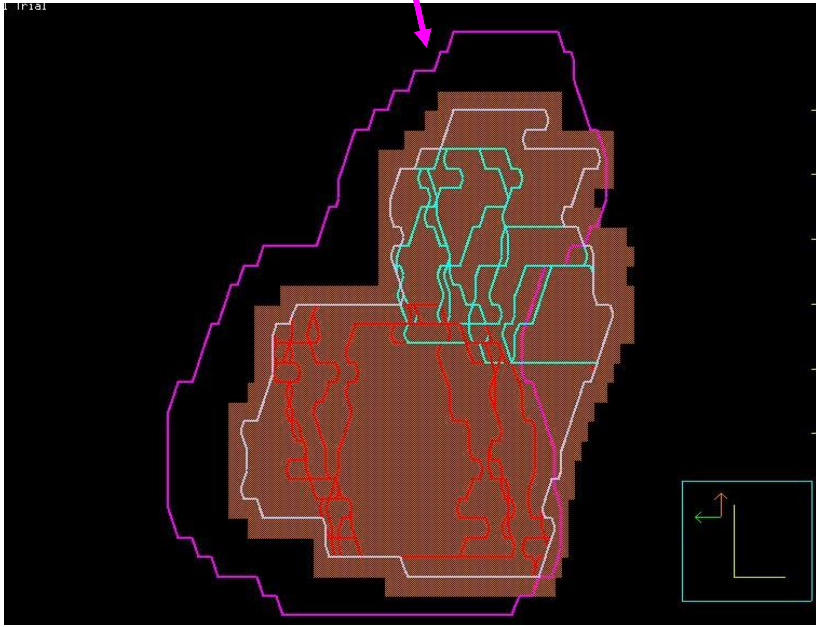


Organ motion detected on first 5 days

Patient Specific cl-PTV after 5 days

Original PTV :CTV + 1.0 cm



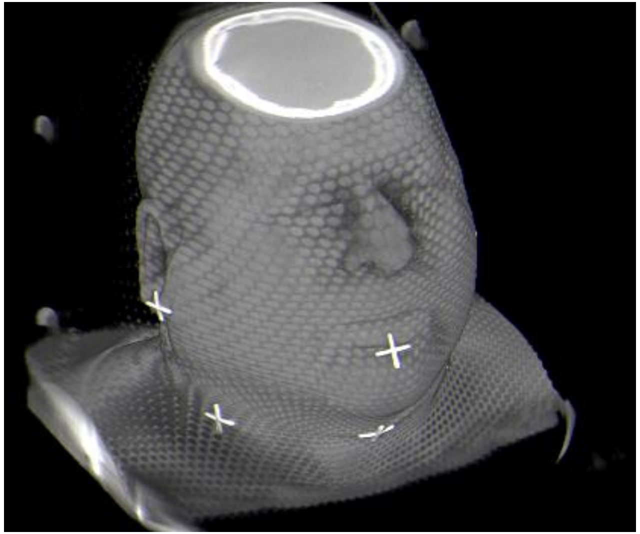


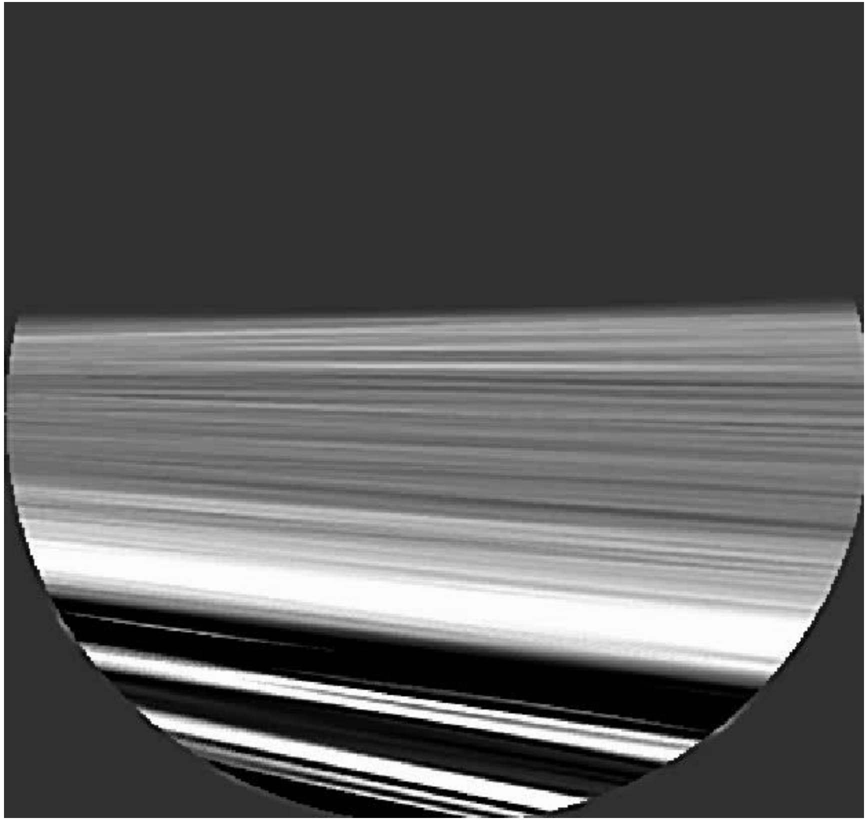
Convex-hull to account for organ motion

Final PTV (setup and organ motion)

Cone Beam CT Accelerator for On-line intervention

JOHNS HOPKINS MEDICINE

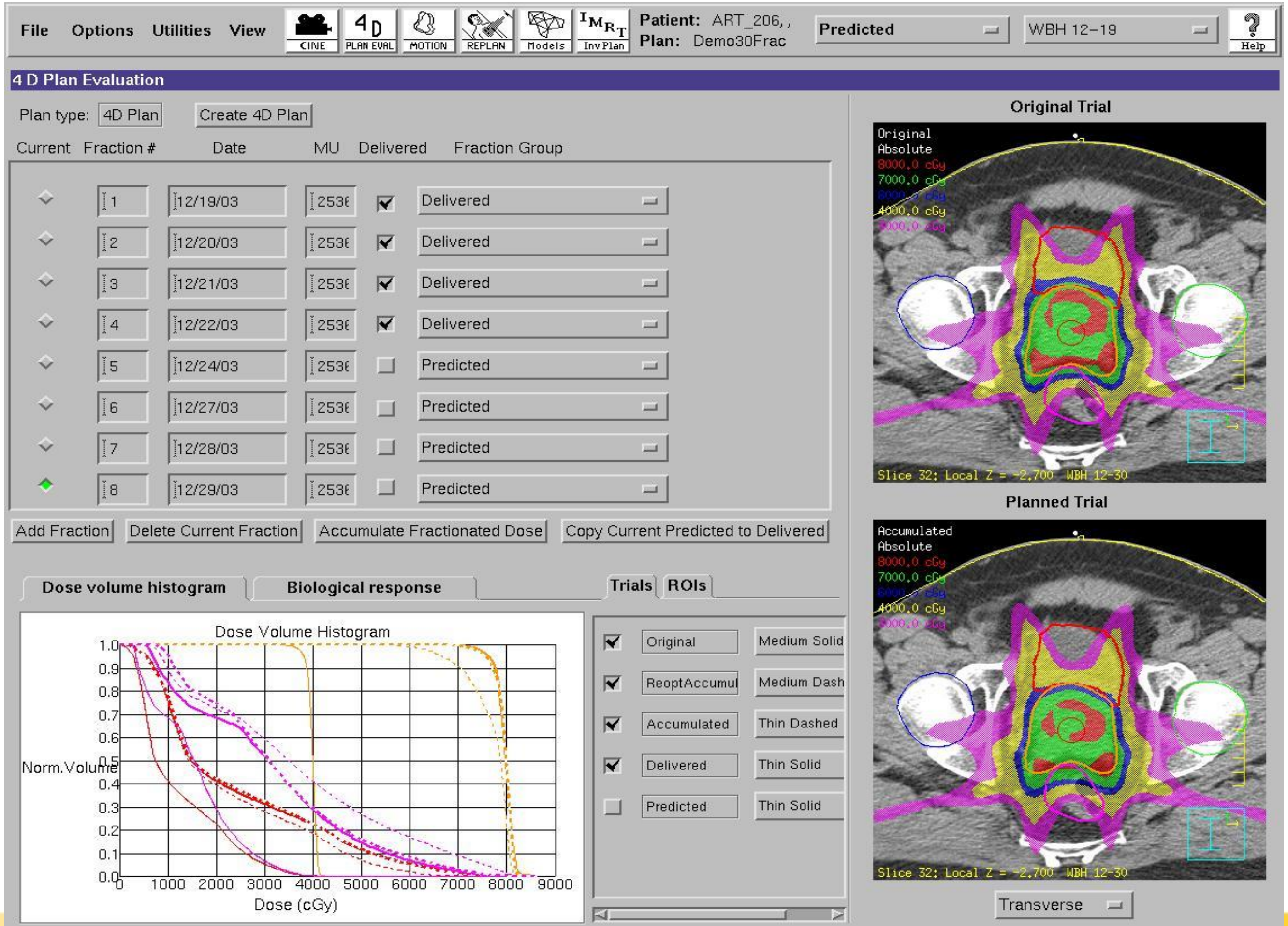




JOHNS HOPKINS
MEDICINE

Adaptive Planning Prototype

JOHNS HOPKINS
MEDICINE

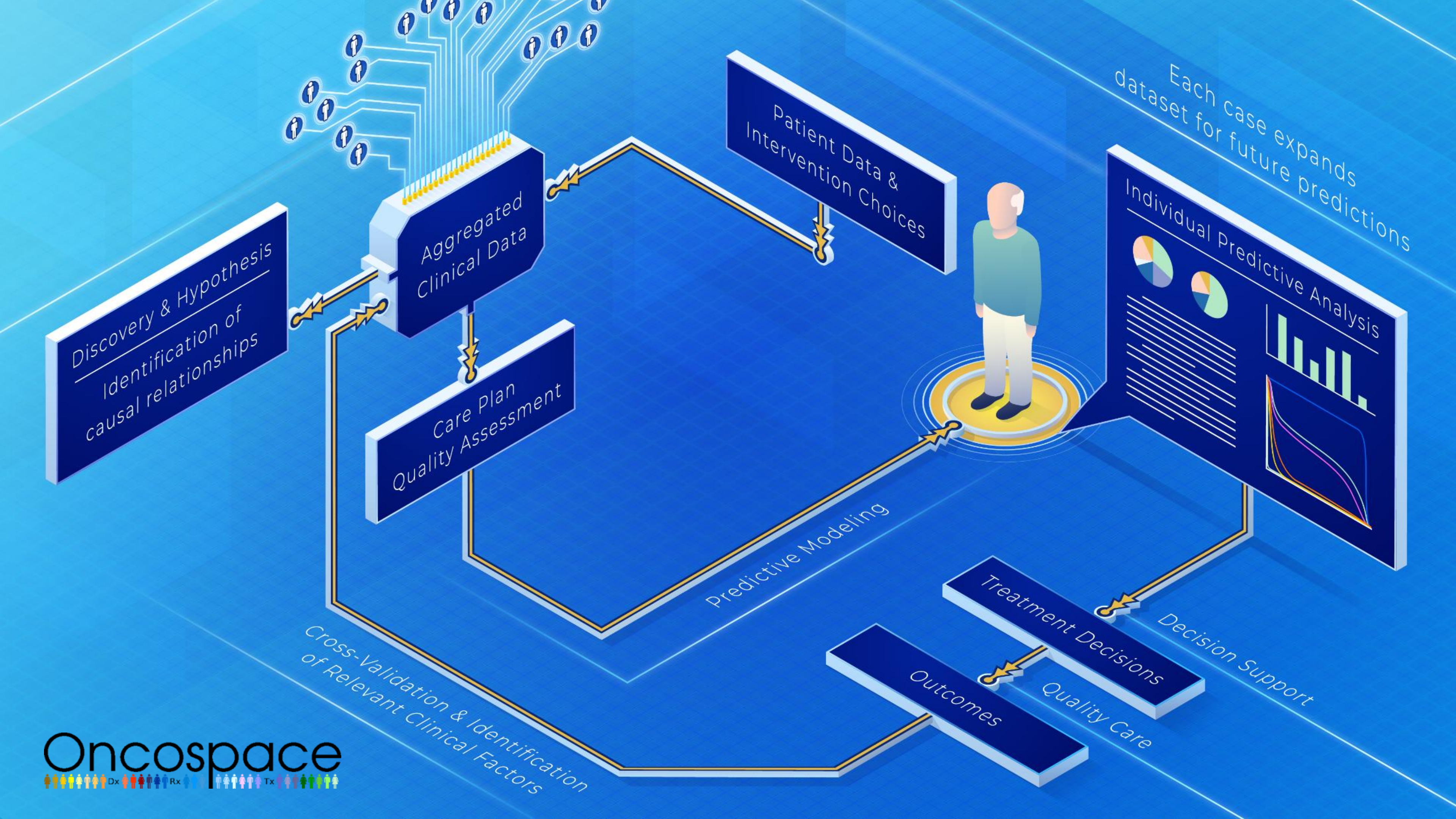


Commercial on-line adaptive

JOHNS HOPKINS MEDICINE

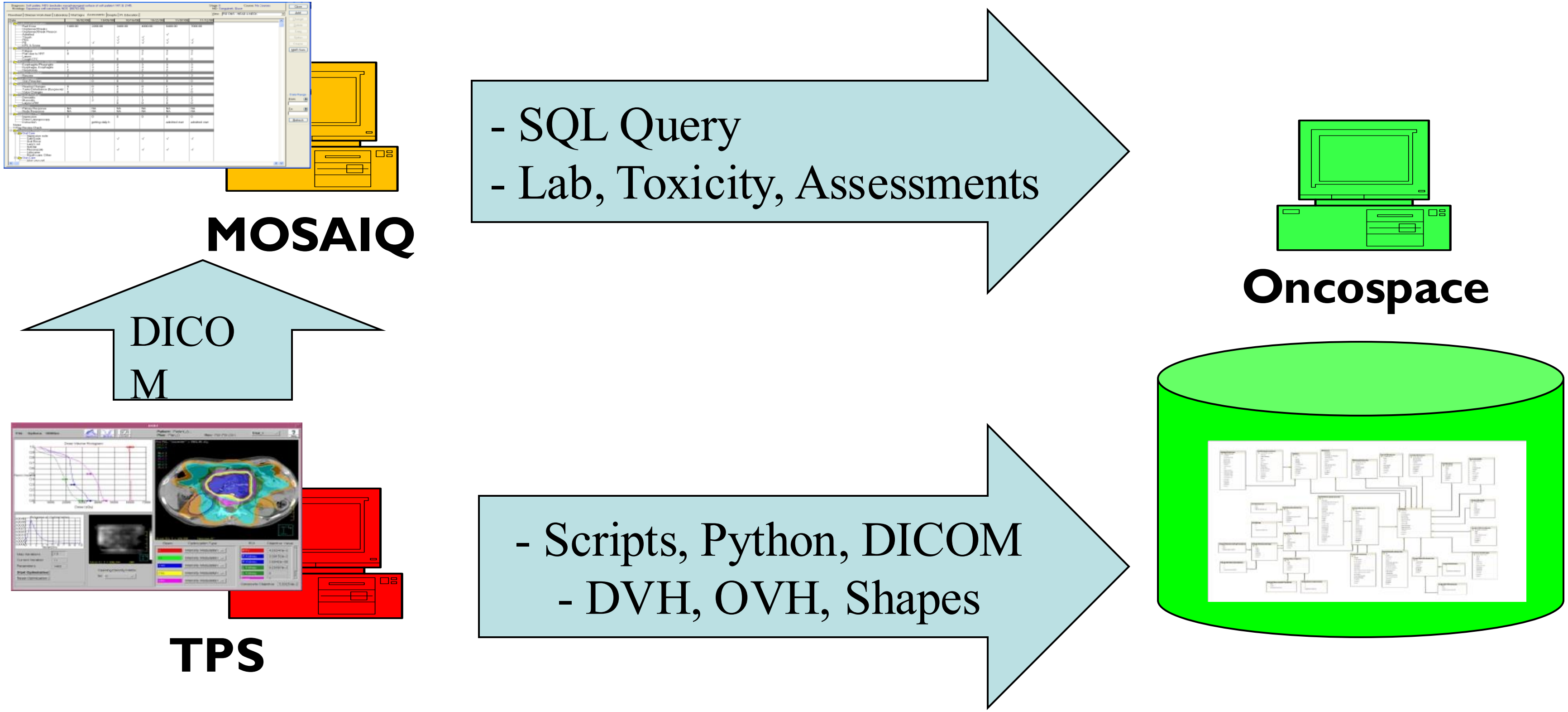
(a) MRIdian (ViewRay, Cleveland, OH, US) (b) Unity (Elekta AB, Stockholm, Sweden) (c) Ethos (Varian Medical Systems, Palo Alto, CA, US)

Commercial online adaptive radiotherapy systems. **a** MRIdian (ViewRay, Cleveland, OH, USA), **b** Unity (Elekta AB, Stockholm, Sweden), **c** Ethos (Varian Medical Systems, Palo Alto, CA, USA)



Each case expands dataset for future predictions
Patient Data & Intervention Choices
Aggregated Clinical Data
Discovery & Hypothesis
Identification of causal relationships
Care Plan Quality Assessment
Individual Predictive Analysis
Predictive Modeling
Treatment Decisions
Decision Support
Outcomes
Quality Care
Cross-Validation & Identification of Relevant Clinical Factors
Oncospace

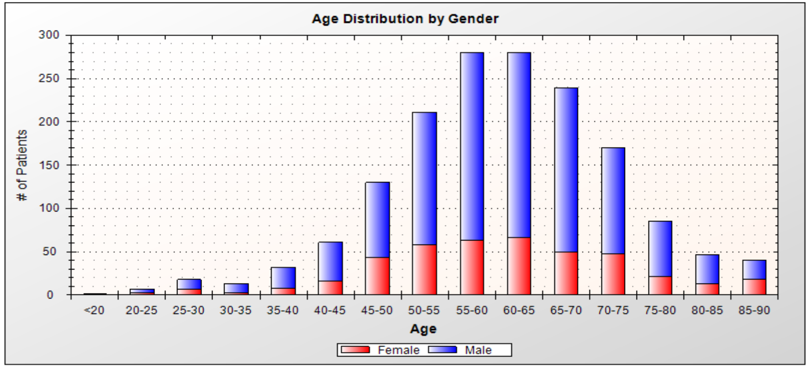
Extract, Transform, Load



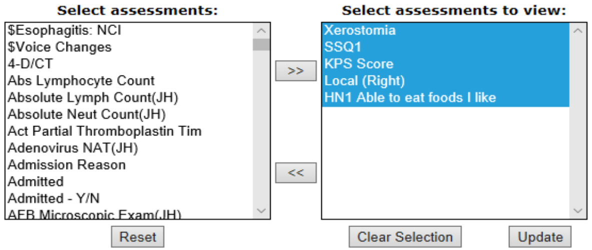
Head and Neck Inventory

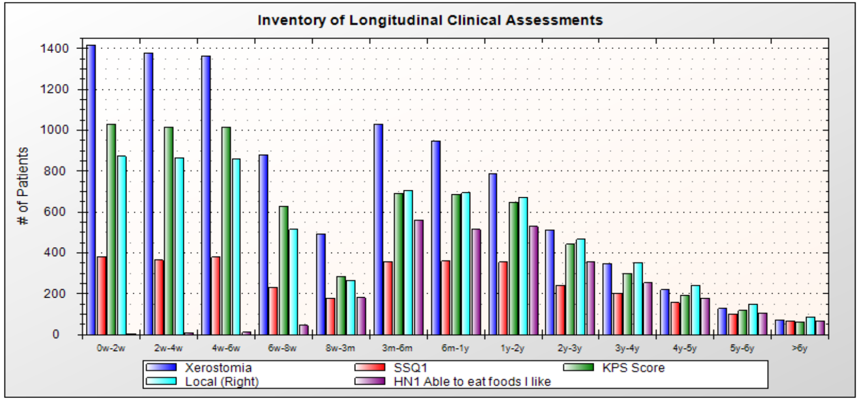
JOHNS HOPKINS MEDICINE

Age Distribution



Totals:
418 female
1195 male
1613 total





Total: 29579 assessments shown

>6 yrs

Targets

ptv_6300	723
ptv_7000	556
ptv_6000	435
ptv_5400	390
ptv_5425	234
ptv_6600	233
ptv_5810	230
ptv_6240	117
ptv_5940	115
ptv_5520	105
ptv_6720	97
ptv_6120	75
ptv_7200	70
ptv_5760	66
ptv_6996	60
ptv_5600	56

Normals

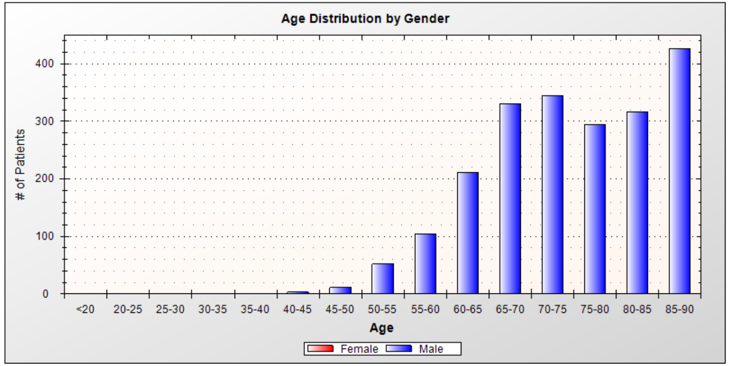
cord	1512
brainstem	1499
mandible	1457
l_parotid	1448
r_parotid	1437
r_eye	1436
l_eye	1431
brain	1411
r_lens	1382
l_lens	1373
chiasm	1358
l_optic_nerve	1317
r_optic_nerve	1314
l_submandibular	1131
r_submandibular	1108
thyroid	1022

l_ear_inner	932
esophagus	879
cricopharyngeal_muscle	827
r_ear_middle	758
oral_cavity	756
l_ear_middle	746
soft_palate	688
cord_avoidance	637
glottis	600
constr_muscle_pharyngeal	575
ctv_6300	567
comb_parotids	566
l_cochlea	558
r_cochlea	543
endolarynx	527
midline_avoidance	493
sublingual	476
[illegible]	[illegible]

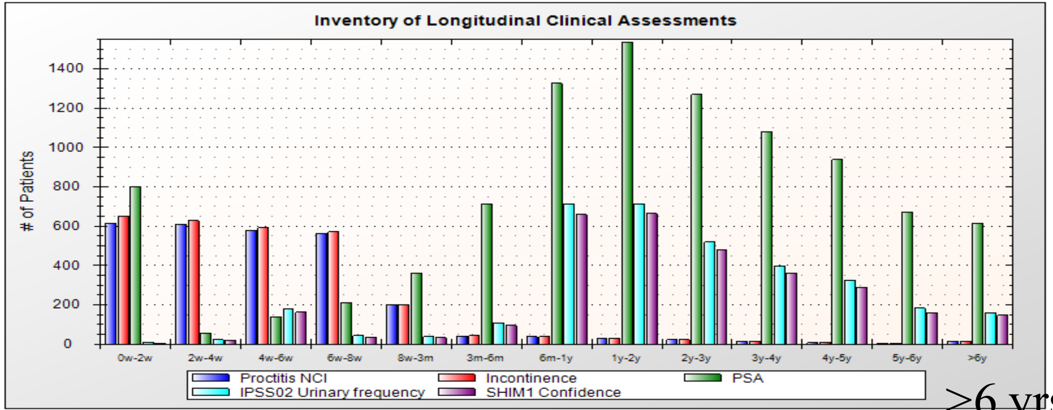
Prostate Inventory

~2100 pts - ~1500 with dose

Age Distribution



Totals:
0 female
2096 male
2096 total



Total: 21743 assessments shown

>6 yrs

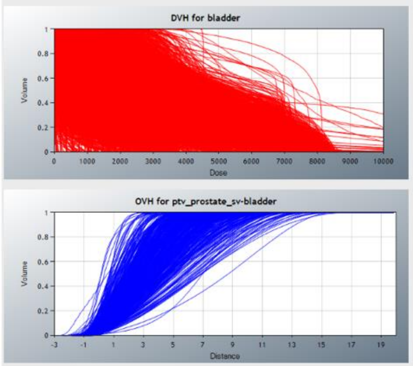
Targets

ptv_prostate_sv	568
ptv_prostate_bed	448
ptv_prostate	387
ptv_nodes	349
ptv_prostate_brachy	237
ptv_prostate_bed_cd	207
ptv_prostate_sv_nodes	150
ptv_prostate_bed_nodes	87

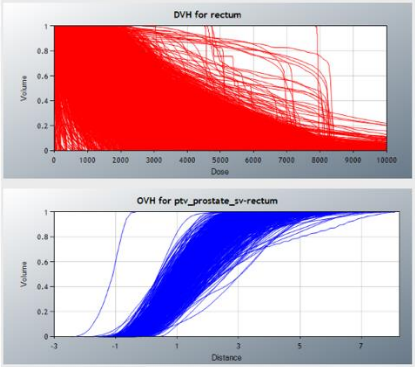
Normals

rectum	1798
bladder	1472
l_head_femur	1418
r_head_femur	1414
bowel	817
penile_bulb	511

Bladder



Rectum

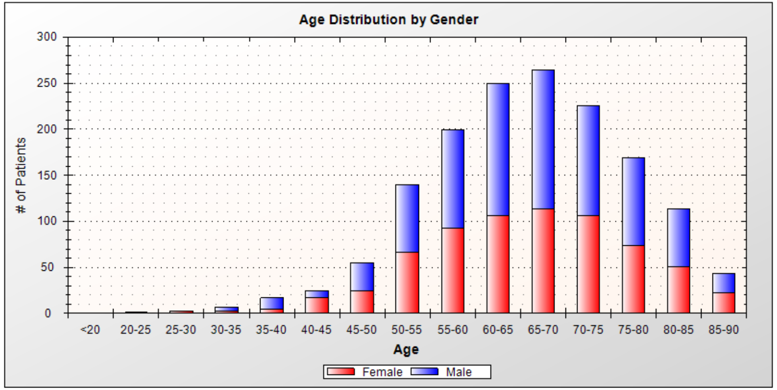


Thoracic Inventory

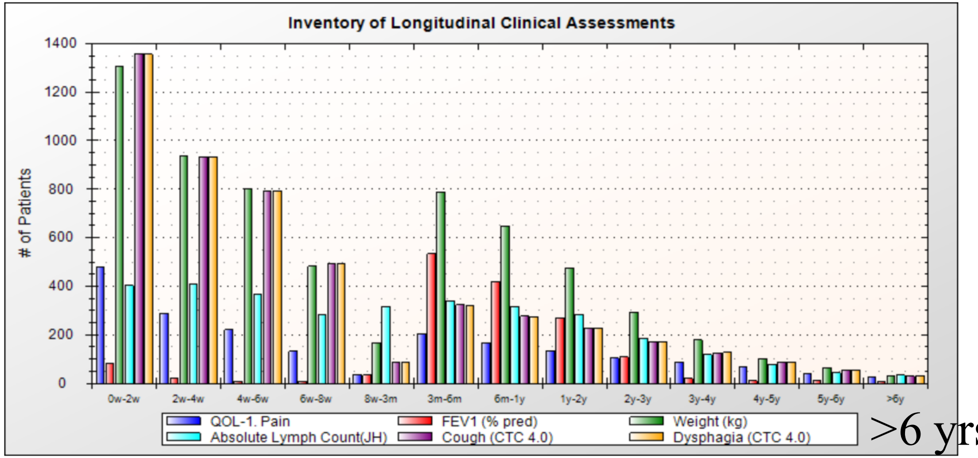
JOHNS HOPKINS MEDICINE

~1700 pts

Age Distribution



Totals:
682 female
831 male
1513 total



>6 yrs

Total: 22894 assessments shown

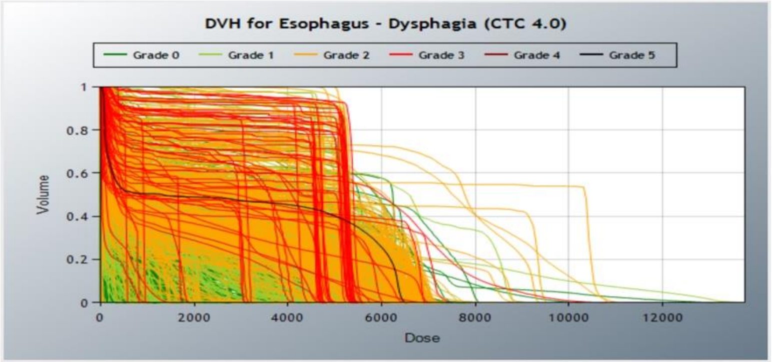
Targets

gtv_fb	675
gtv_0pct	549
PTV	418
ptv_final	323
gtv_60pct	311
gtv_50pct	215
GTV	211
ptvexp	178
ptv_5mm_exp	164
gtvroi	148
gtv_min	83
gtv_max	83

Normals

R_Lung	1633
L_Lung	1629
Esophagus	1452
Lungs	1385
Trachea	1322
Heart	836
SpinalCord	823
Pericardium	711
Liver	349
R_Kidney	267
L_Kidney	264
Thyroid	135

Esophagus DVH vs Dysphagia CTCAE



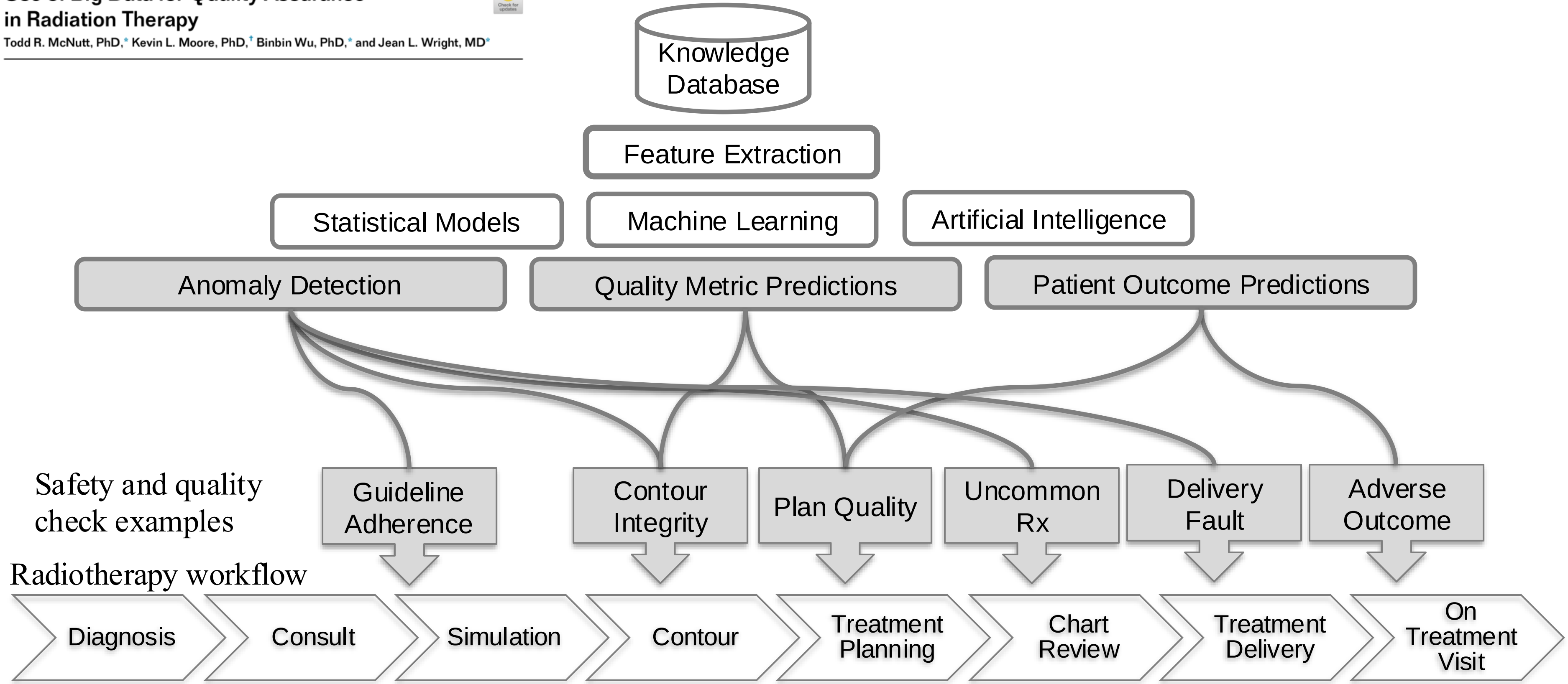
Seminars in RADIATION ONCOLOGY

ELSEVIER

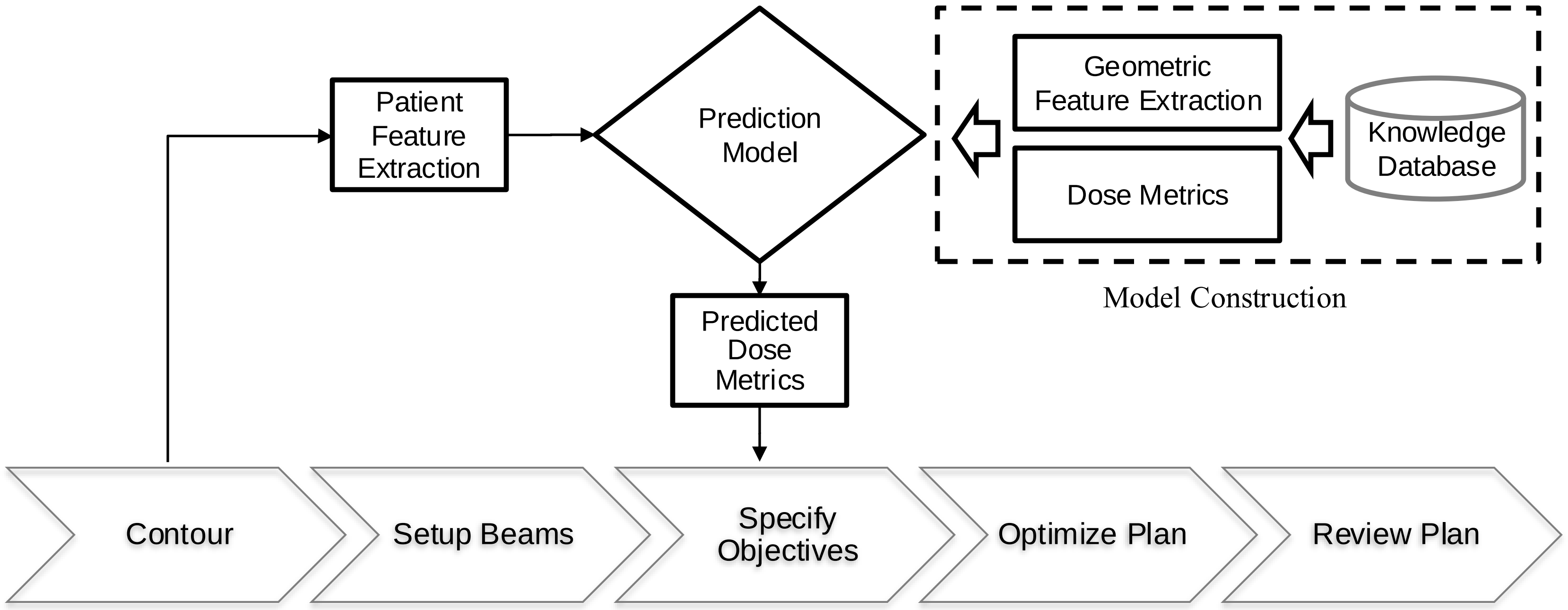
Use of Big Data for Quality Assurance in Radiation Therapy

Todd R. McNutt, PhD,* Kevin L. Moore, PhD,† Binbin Wu, PhD,* and Jean L. Wright, MD*

JOHNS HOPKINS MEDICINE

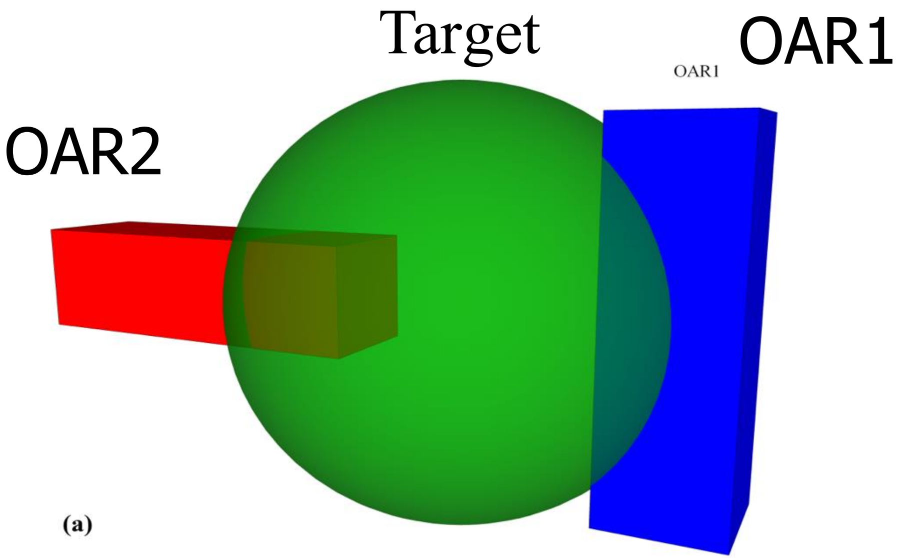


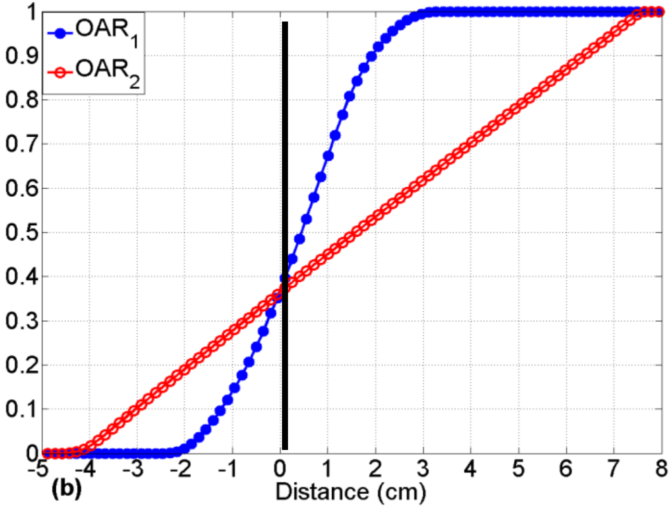
Knowledge based planning



Overlap Volume Histogram

OVH: serial vs parallel (Wu, Taylor, Kazhdan, Simari, McNutt)





For parallel organs, **OAR2** is more easily spared.

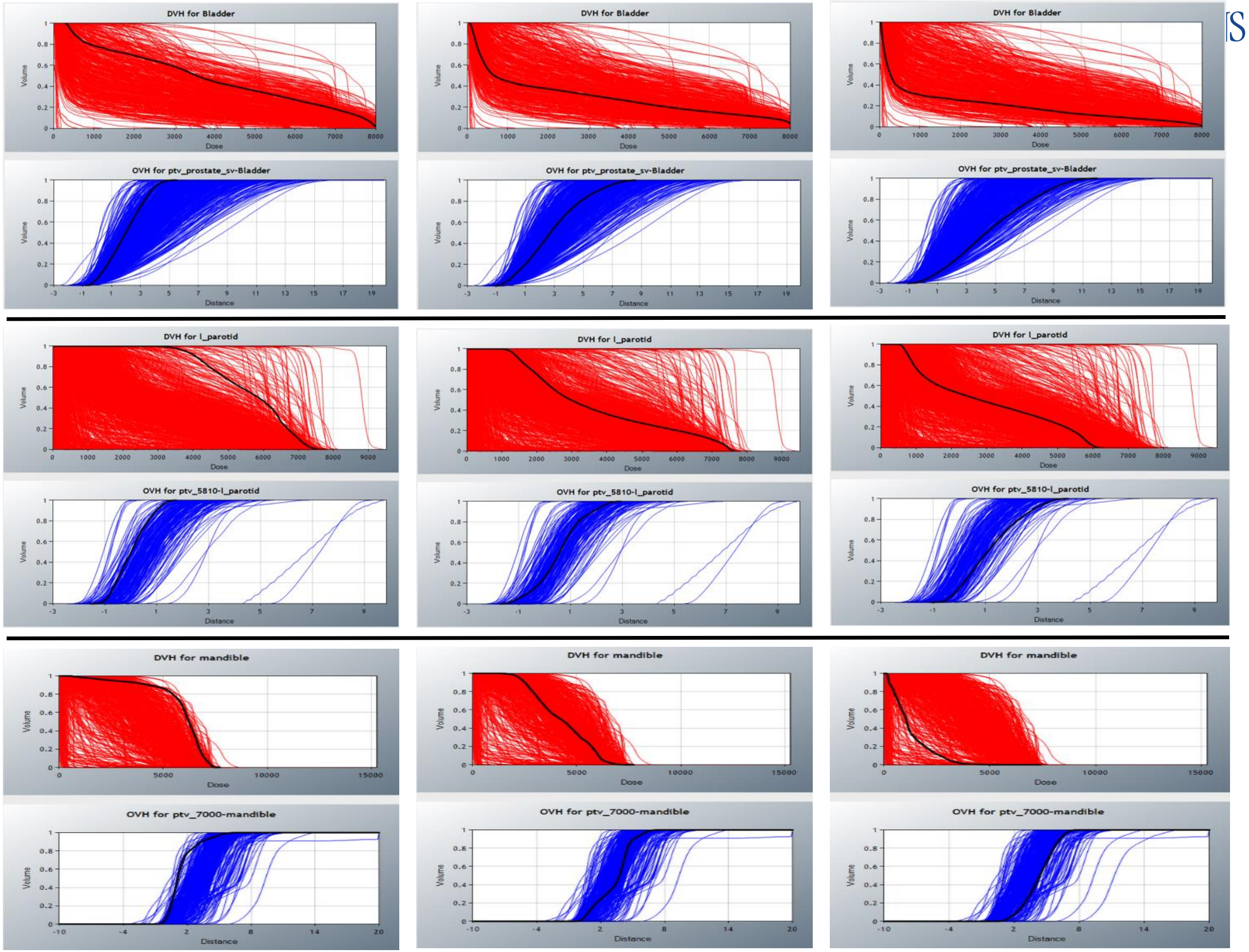
For serial organs, **OAR1** is more easily spared.

OVH vs DVH

Bladder vs ptv_prostate_sv

Left parotid vs ptv_5810

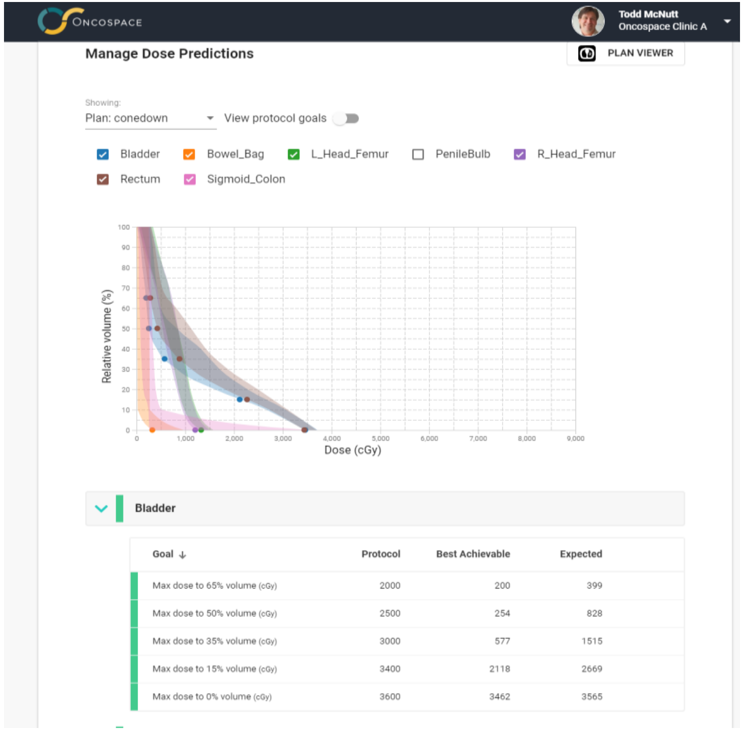
Mandible vs ptv_7000



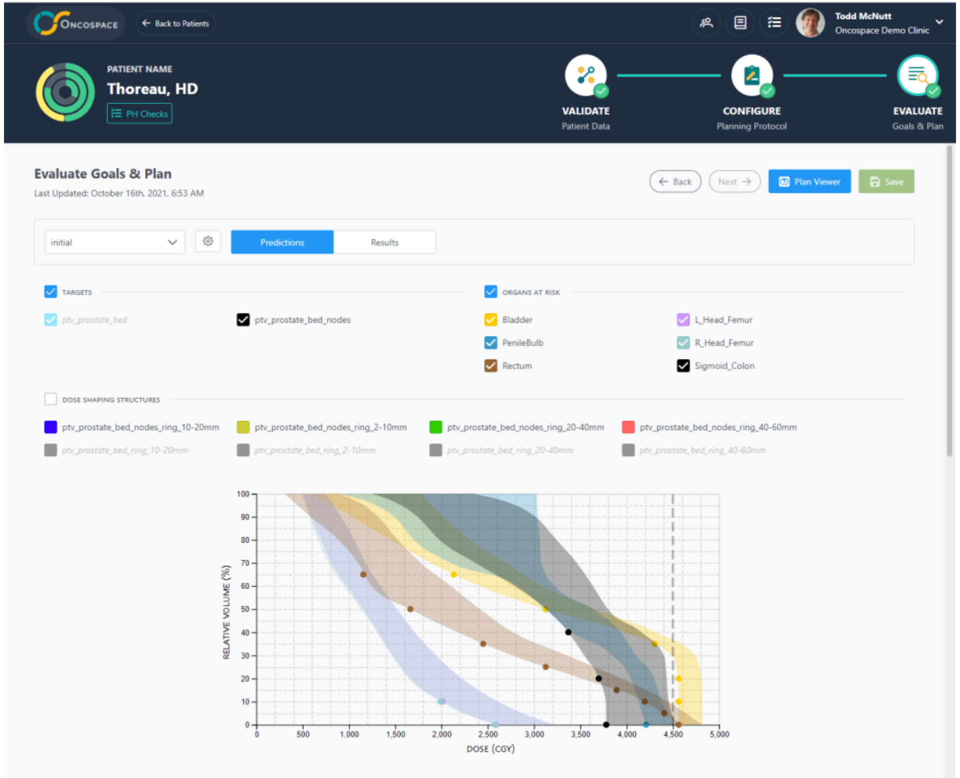
New model predictions with Random Forest

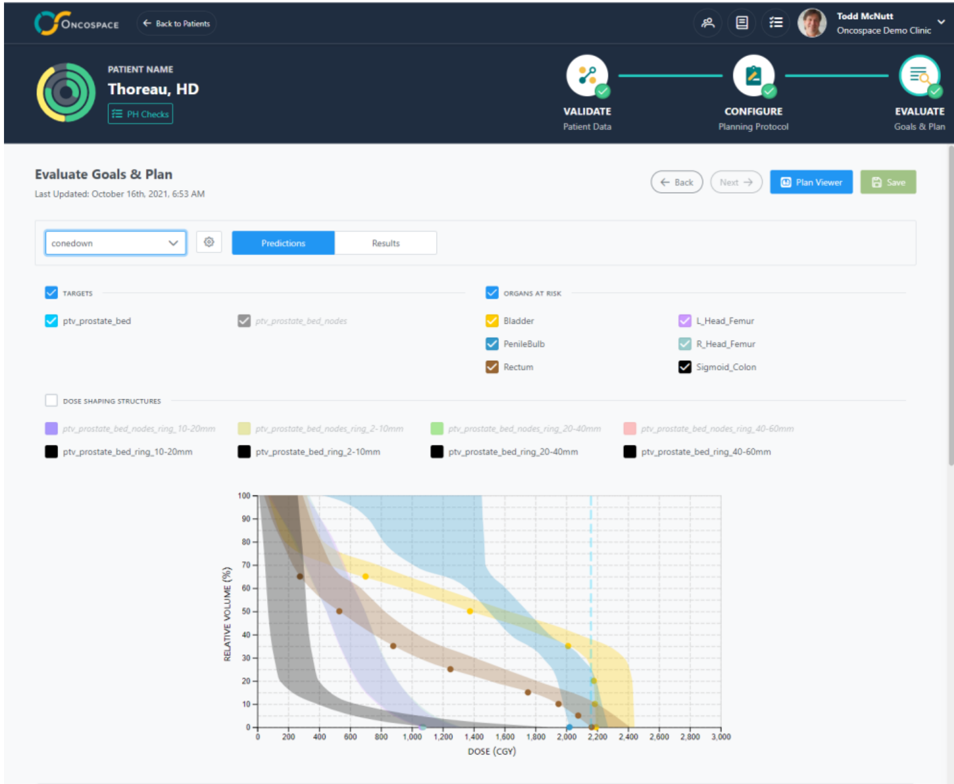
Features: OVH-xyz, OVH-xy, OVH-z, PTV-Volume, PTV-Concavity…

Lowest achievable = Predicted median of the 5th percentile of doses given a set of input features at each %v
Expected = Predicted value of prior similar plans

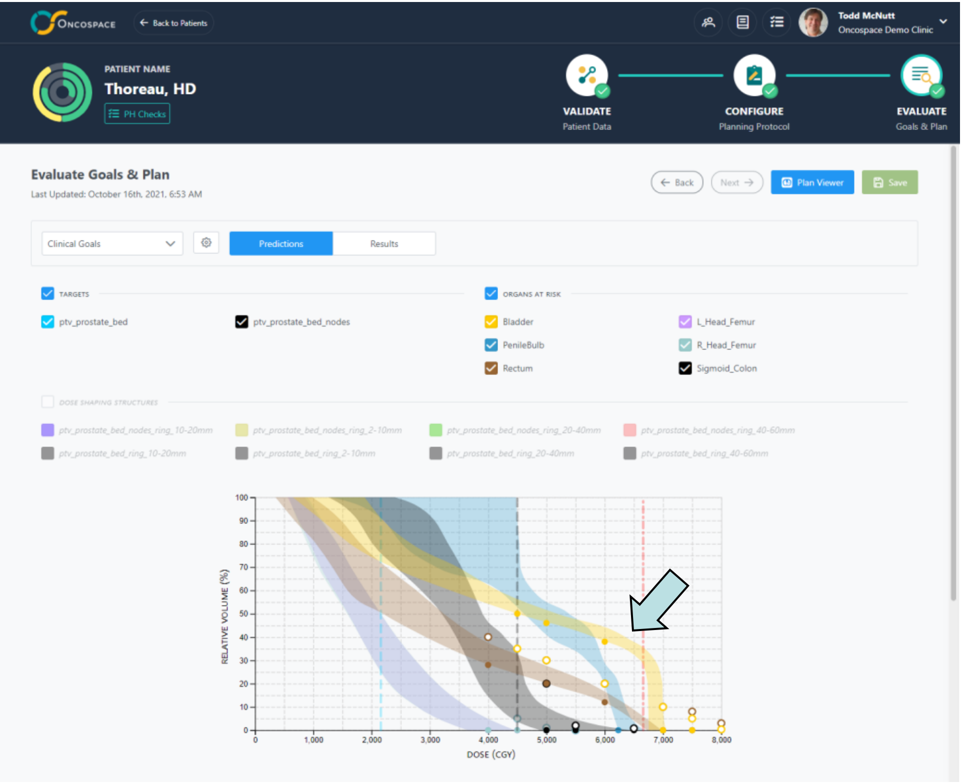


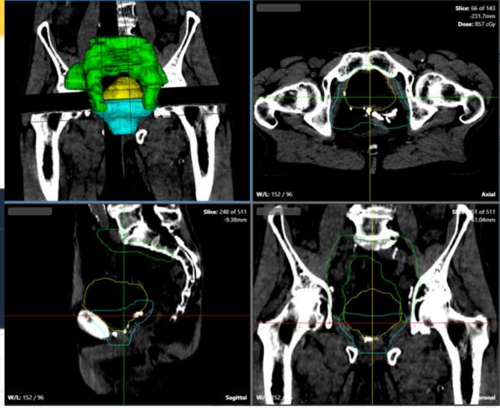
Predicted Plan objectives





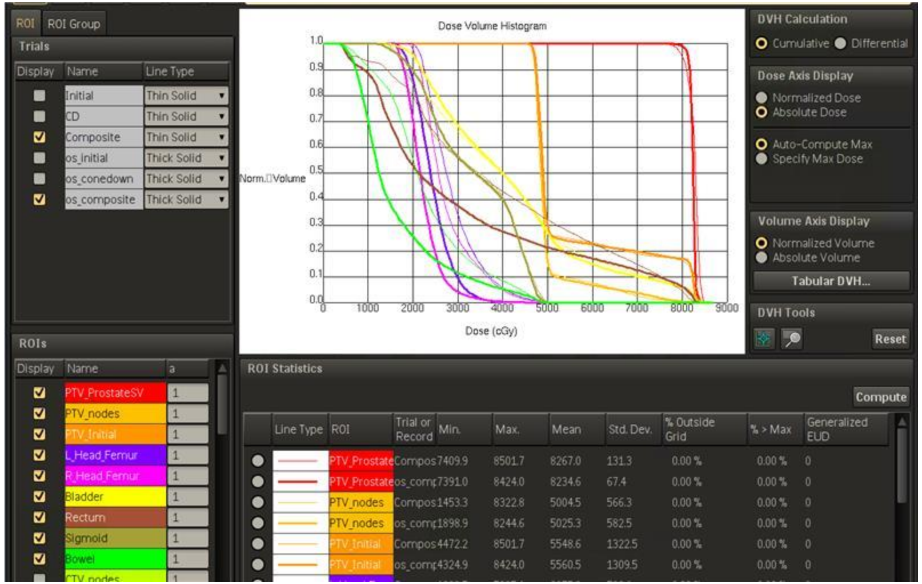
Course Predictions

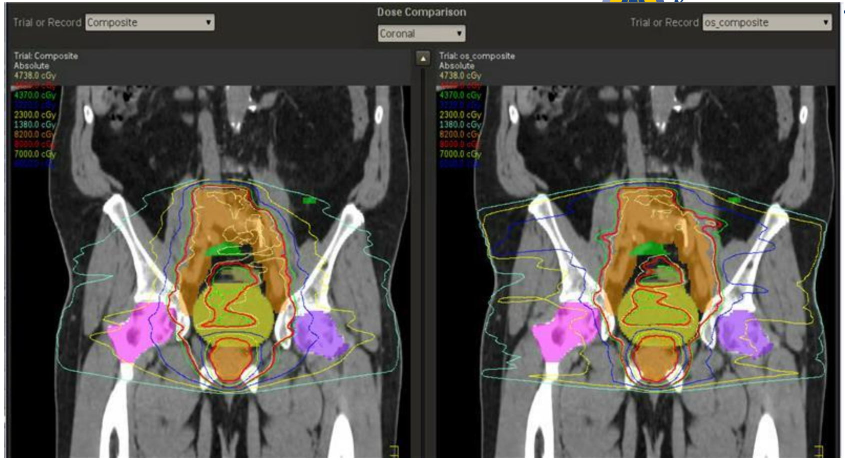


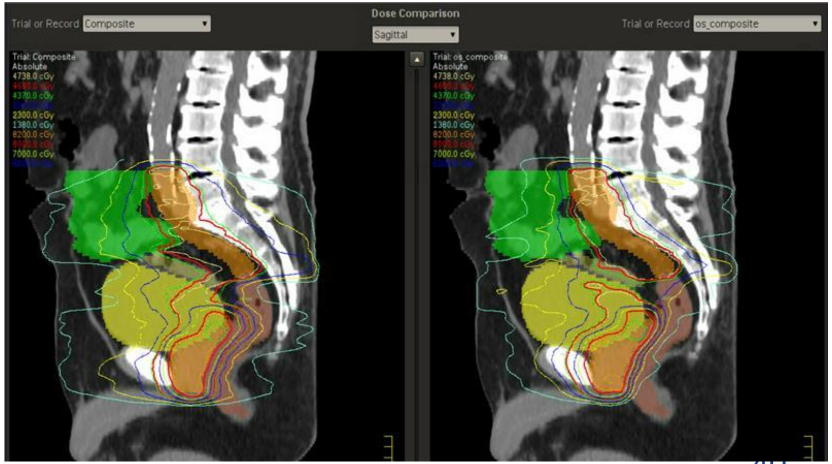


JOHNS HOPKINS

Autoplan result



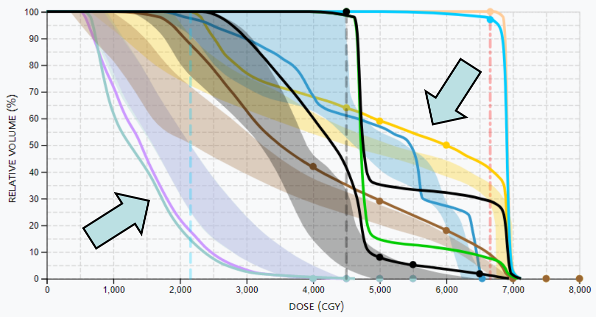




Comparison

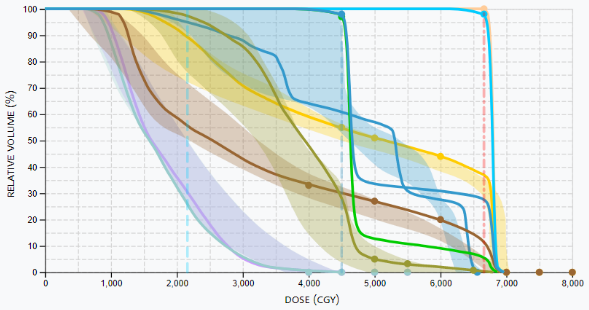
Bladder
PenileBulb
Rectum
L_Head_Femur
R_Head_Femur
Sigmoid_Colon

Clinical Plan



Goal	Protocol	Predicted Range	Plan Value	Comparison
Bladder				
V8000cGy[cc]	≤ 1-7.5 cc	0 – 0	0	
V4500cGy[%]	≤ 35-55%	50 – 56	64	
V5000cGy[%]	≤ 30-50%	46 – 51	59	
V6000cGy[%]	≤ 20-40%	38 – 44	50	
V7000cGy[%]	≤ 10-30%	0 – 2	1	
V7500cGy[%]	≤ 5-25%	0 – 0	0	

Predictive Plan



Goal	Protocol	Predicted Range	Plan Value	Comparison
Bladder				
V8000cGy[cc]	≤ 1-7.5 cc	0 – 0	0	
V4500cGy[%]	≤ 35-55%	50 – 56	55	
V5000cGy[%]	≤ 30-50%	46 – 51	51	
V6000cGy[%]	≤ 20-40%	38 – 44	44	
V7000cGy[%]	≤ 10-30%	0 – 2	0	
V7500cGy[%]	≤ 5-25%	0 – 0	0	

AI prostate planning results

Song, Ennis, Showalter

RadOnc A, High Risk Patient #1

APFLDO (P1 High) Feature Ratings (1 worst – 5 best)			
Category	**Feature**	**Score**	*Ave cat.*
Overall	overall quality	3	*3*
Targets	tumor coverage	5	*5*
	tumor homogeneity	5	
OARs	bladder sparing	2	*4.2*
	rectum sparing	4	
	femur head sparing	5	
	bowel sparing	5	
	penile bulb sparing	5	
Non-ROIs	dose outside ROIs	2	*2*
	Plan clinically acceptable?	marginal	
Comments: Dose extends anterior to pubic symphysis			

JCILHD (P1 High) Feature Ratings (1 worst – 5 best)			
Category	**Feature**	**Score**	*Ave cat.*
Overall	overall quality	4	*4*
Targets	tumor coverage	5	*5*
	tumor homogeneity	5	
OARs	bladder sparing	3	*4.4*
	rectum sparing	4	
	femur head sparing	5	
	bowel sparing	5	
	penile bulb sparing	5	
Non-ROIs	dose outside ROIs	3	*3*
	Plan clinically acceptable?	yes	
Comments: Better than APFLDO, but high dose fully includes pubic bone			

Comparison of plan **APFLDO** vs **JCILHD (P1 High)**	
Which plan is preferable?	**JCILHD**
Which aspect was most relevant in that selection? Lower dose rectal volumes better; less anterior coverage beyond pubic bone	

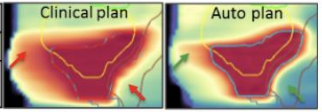
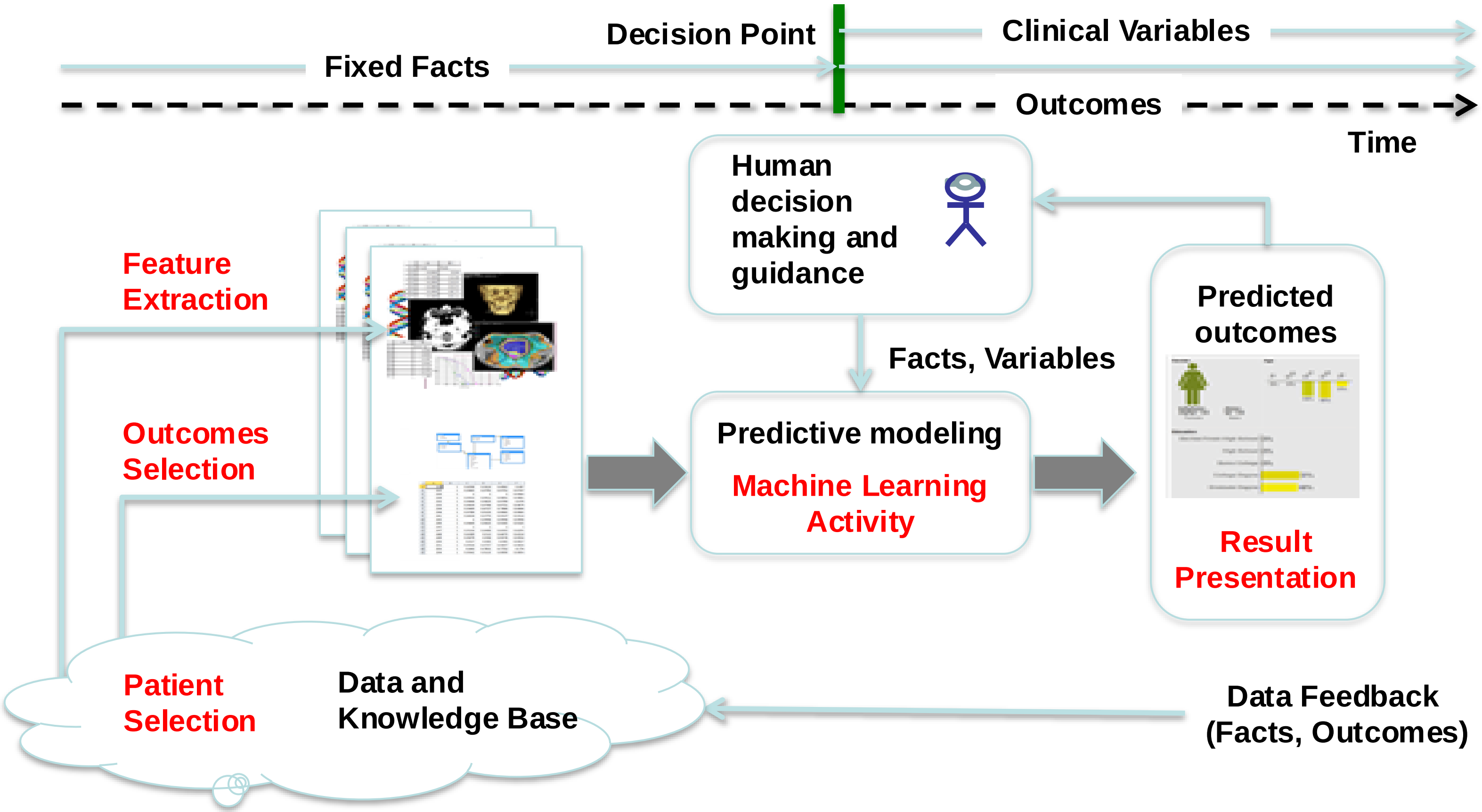


Figure 13. Example of ratings and overall preference for the pair of plans for high risk patient #1. Dose overlay indicates the advantages of the auto plan commented on in green.

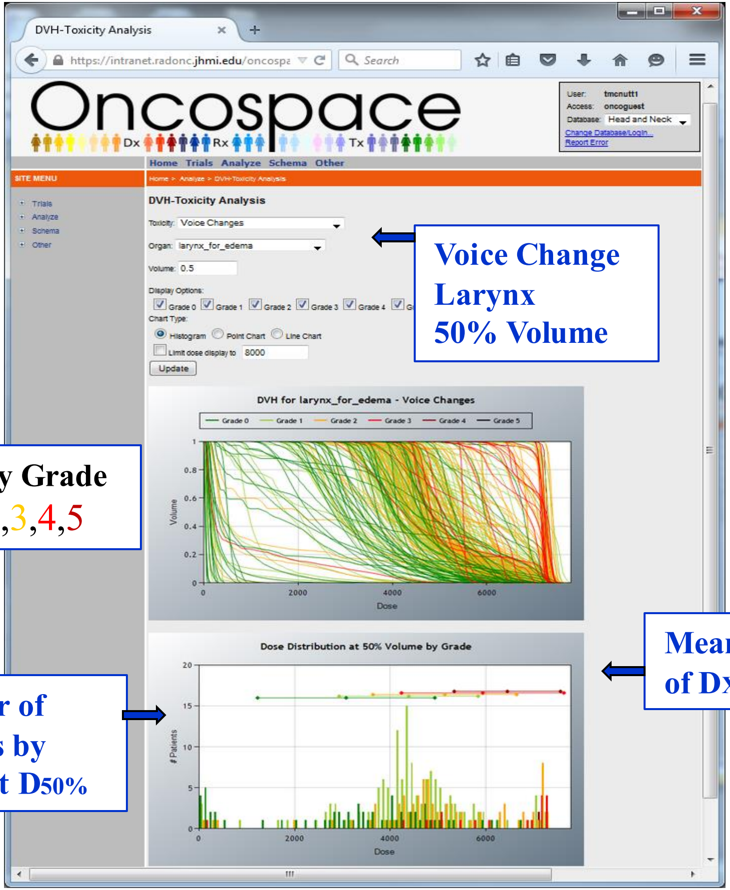
	Clinical Acceptability of Plan						**Preferable Plan**			
	RadOnc A		**RadOnc B**		**RadOnc C**		**RadOnc A**	**RadOnc B**	**RadOnc C**	**Overall**
	Auto	**Clin**	**Auto**	**Clin**	**Auto**	**Clin**				
Pilot										
P1 Low	Yes	Yes	Yes	Yes	Marginal	Yes	Clin	Auto	Clin	Clin
P1 Int	No	No	No	No	Marginal	Yes	Clin	Auto	Clin	Clin
P2 Int	Yes	Marginal	Yes	Yes	Yes	Yes	Auto	Clin	Auto	Auto
Test							Auto 12-0	Auto 10-2	Auto 9-3	**Auto 12-0**
P2 Low	Yes	Marginal	Yes	Yes	Yes	Yes	Auto	Auto	Auto	**Auto**
P3 Low	Yes	Yes	Yes	Yes	Yes	Yes	Auto	Auto	Clin	**Auto**
P4 Low	Yes	No	Yes	No	Yes	No	Auto	Auto	Auto	**Auto**
P3 Int	Yes	Yes	Yes	Yes	Yes	Yes	Auto	Auto	Clin	**Auto**
P4 Int	Yes	Yes	Yes	Yes	Yes	Marginal	Auto	Auto	Auto	**Auto**
P5 Int	Yes	Yes	Yes	Yes	Yes	Yes	Auto	Auto	Auto	**Auto**
P1 High	Yes	Marginal	Yes	No	Marginal	Marginal	Auto	Auto	Clin	**Auto**
P2 High	Yes	Yes	Yes	Yes	Yes	Yes	Auto	Clin	Auto	**Auto**
P3 High	Yes	Yes	Yes	Yes	Yes	Yes	Auto	Clin	Auto	**Auto**
P4 High	No	No	No	No	Marginal	No	Auto	Auto	Auto	**Auto**
P5 High	Yes	Marginal	Yes	Yes	Yes	Yes	Auto	Auto	Auto	**Auto**
P6 High	Yes	Marginal	Yes	Yes	Yes	Yes	Auto	Auto	Auto	**Auto**

Learning health system – Decision Support



DVH, Toxicities and Grade distributions

JOHNS HOPKINS MEDICINE

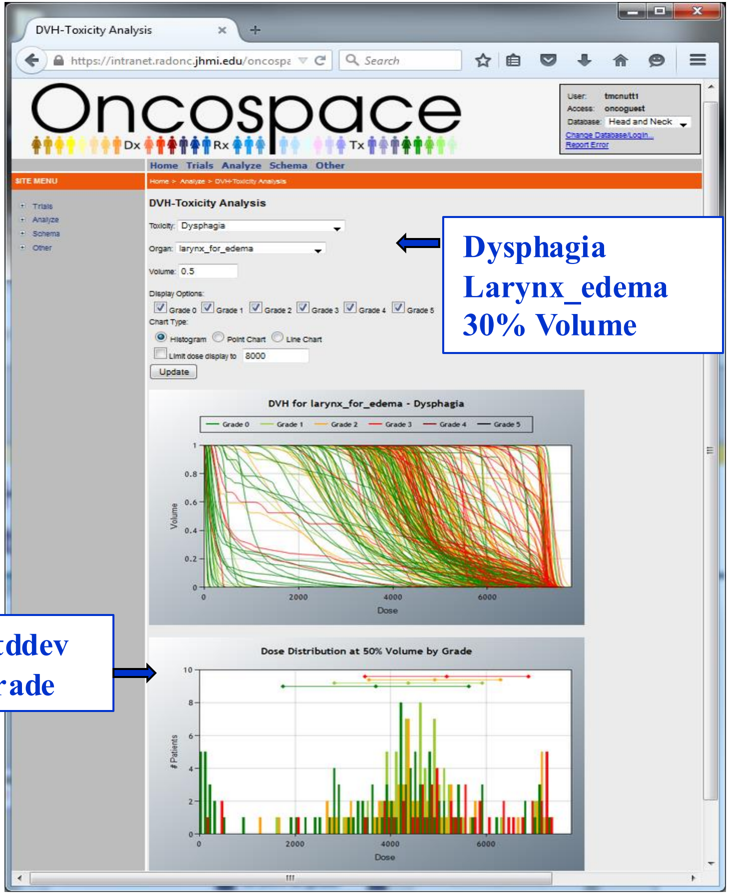


Voice Change
Larynx
50% Volume

Toxicity Grade
0,1,2,3,4,5

Number of patients by grade at D50%

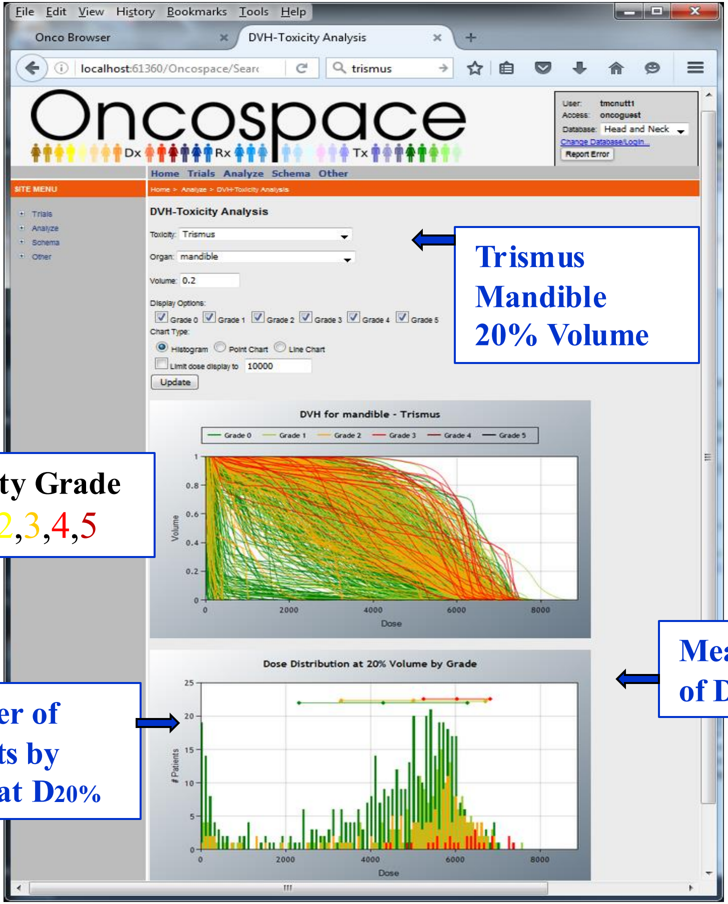
Mean and stddev of Dx% at grade



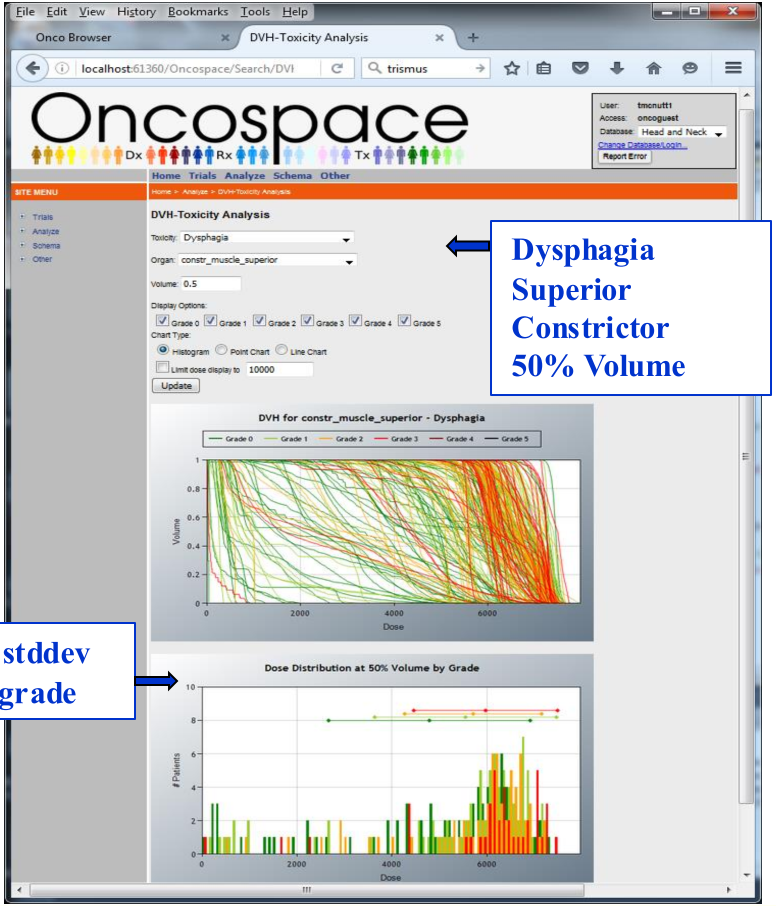
Dysphagia
Larynx_edema
30% Volume

DVH, Toxicities and Grade distributions

JOHNS HOPKINS MEDICINE



Trismus
Mandible
20% Volume



Dysphagia
Superior
Constrictor
50% Volume

Toxicity Grade
0,1,2,3,4,5

Number of patients by grade at D20%

Mean and stddev of Dx% at grade

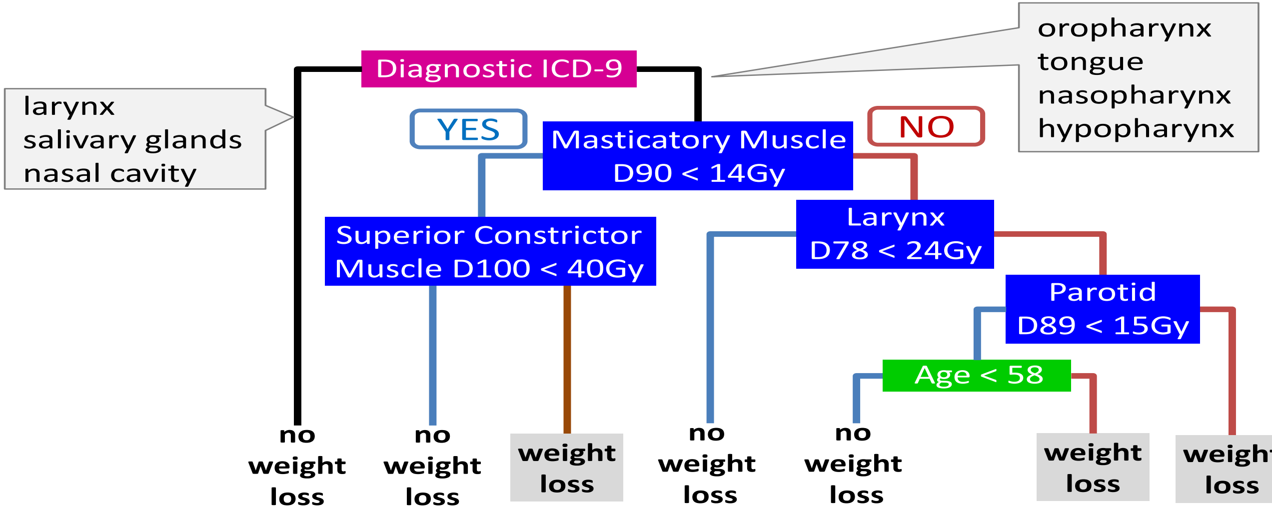
Longitudinal measures

Results: Weight loss prediction at planning

Endpoint: > 5kg loss at 3 months post RT

Sierra Zhi Cheng MD MS
Minoru Nakatsagawa PhD

- Predictors:
  - **(1: Diagnosis)** ICD-9 code
  - **(2: Dosimetry)** dose to swallowing muscles, larynx, parotid
  - **(3: Patient)** age
- Prediction result: High negative predictive value
  - The model can screen out patient without weight loss
  - Physicians can focus on patients with high probability of weight loss



Prediction result

AUC	0.773
Sensitivity	0.766
PPV	0.426
NPV	0.901

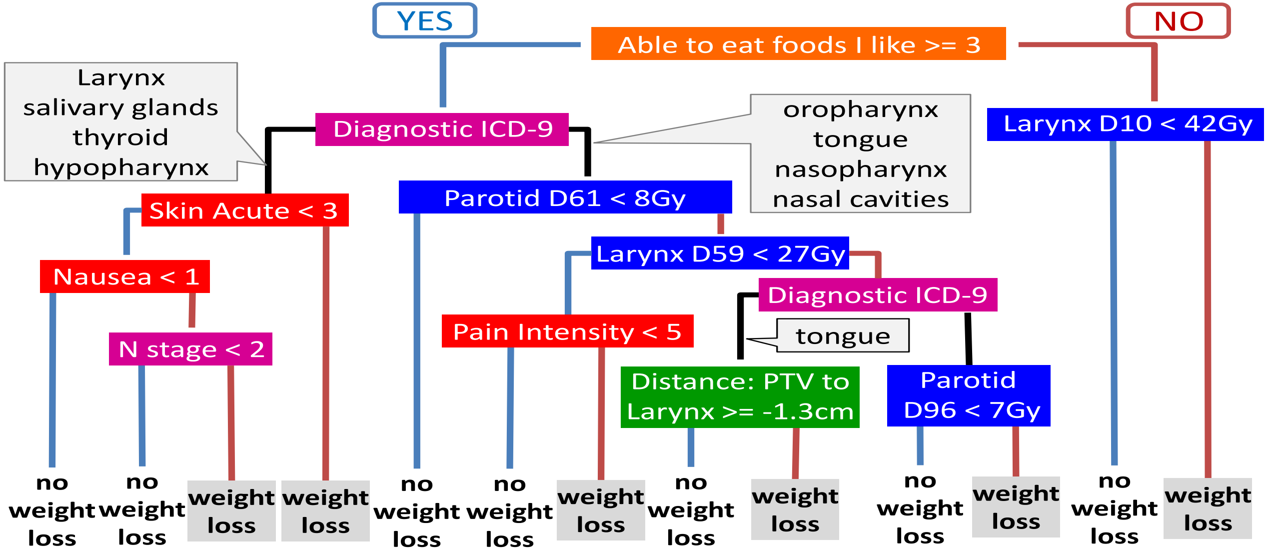
Results: Weight loss prediction during RT

JOHNS HOPKINS MEDICINE

Endpoint: > 5kg loss at 3 months post RT

- Predictors:
  - (1: QOL) patient reported oral intake
  - (2: Diagnosis and staging) ICD-9, N stage
  - (3: Dosimetry) dose to larynx, parotid
  - (4: Toxicity) skin toxicity, nausea, pain
  - (5: Geometry) minimum distance b/w PTV, larynx

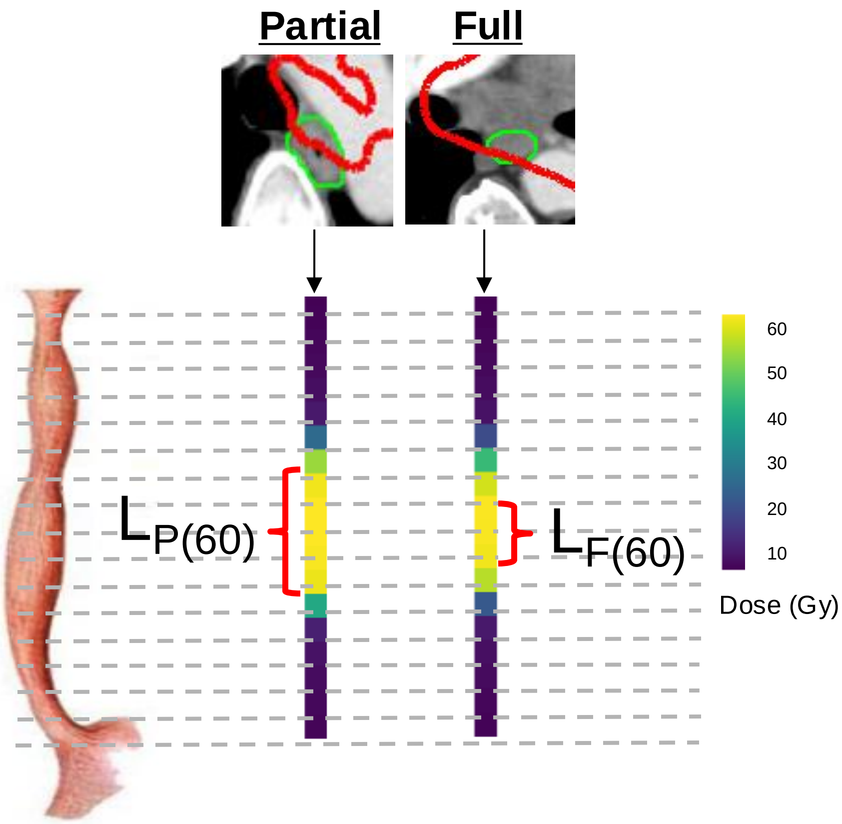
Sierra Zhi Cheng MD MS
Minoru Nakatsagawa PhD



Prediction result

AUC	0.821
Sensitivity	0.977
PPV	0.462
NPV	0.986

Length of circumferential esophageal dose vs weight loss P. Han et al.



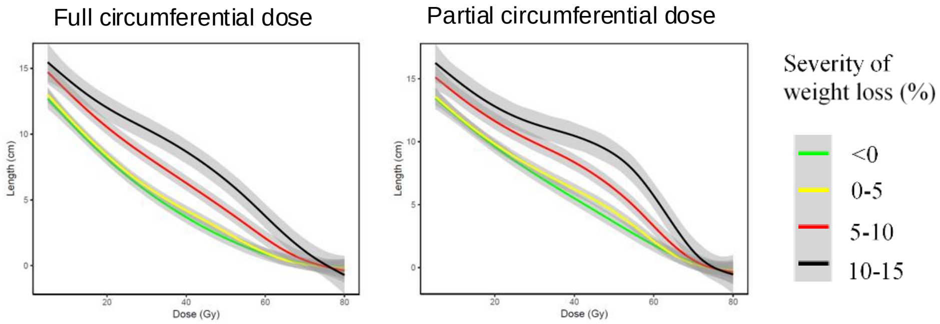


Table 2. Weight loss prediction using Ridge

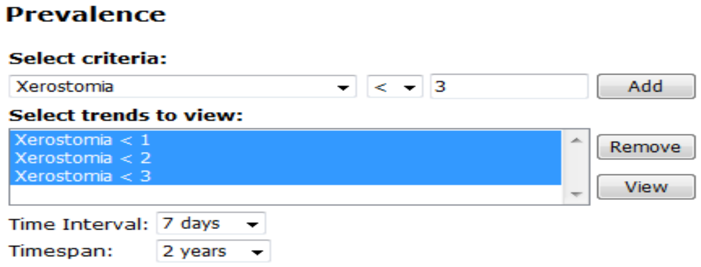
Variable	importance*
Pre-treatment albumin	100
$L_{F(65)}$	85
Marital status	53
$L_{F(60)}$	45
$L_{P(65)}$	42
ECOG performance status	36
$L_{F(55)}$	35
Chemotherapy (full dose vs. none)	32
$L_{P(60)}$	31
Race	24

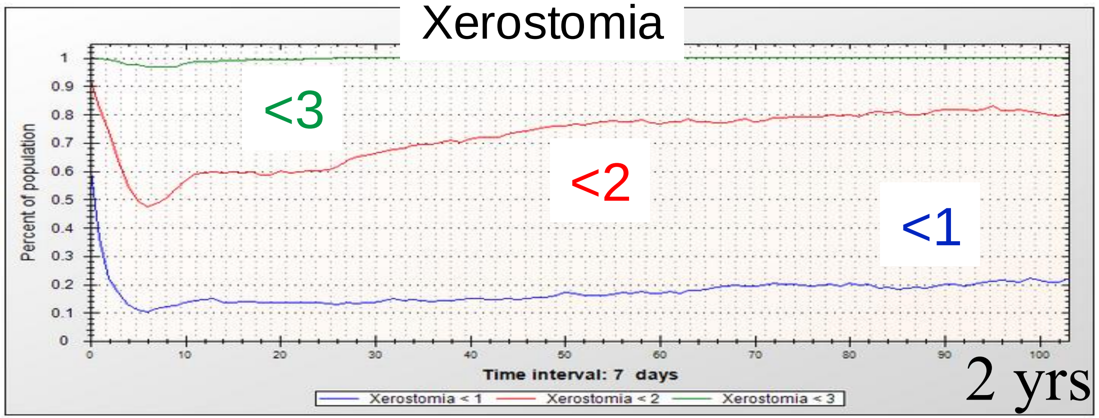
Our Xerostomia Story

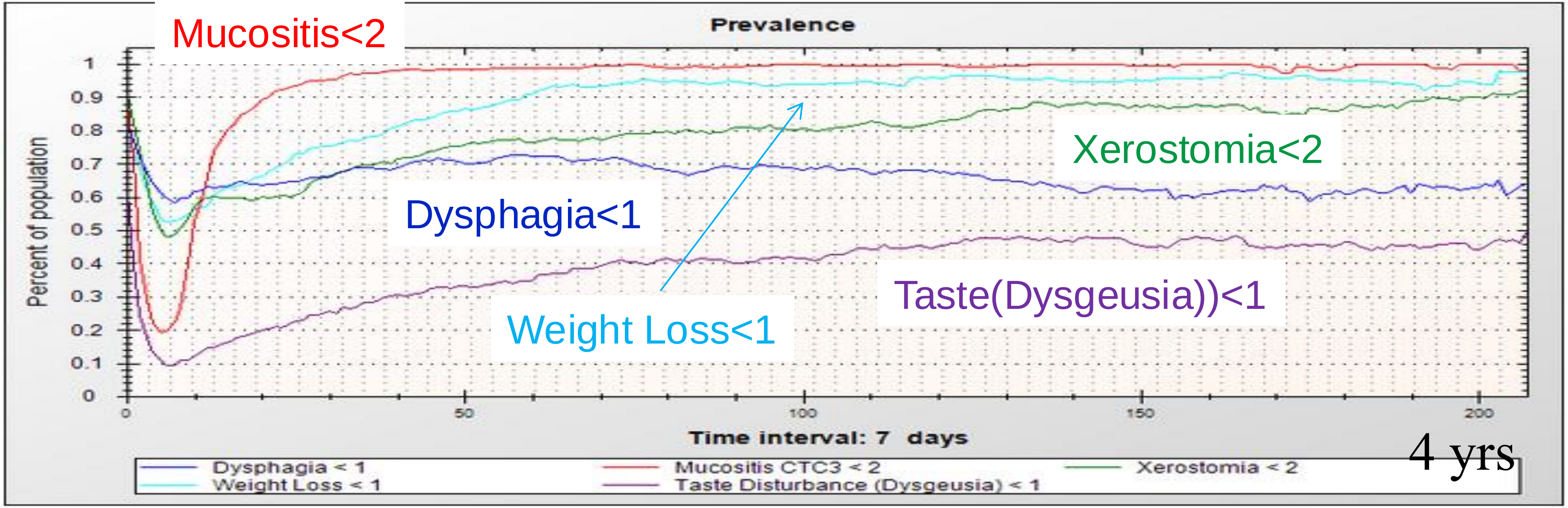
an example of possibilities for data-driven outcome-based planning

Toxicity Prevalence

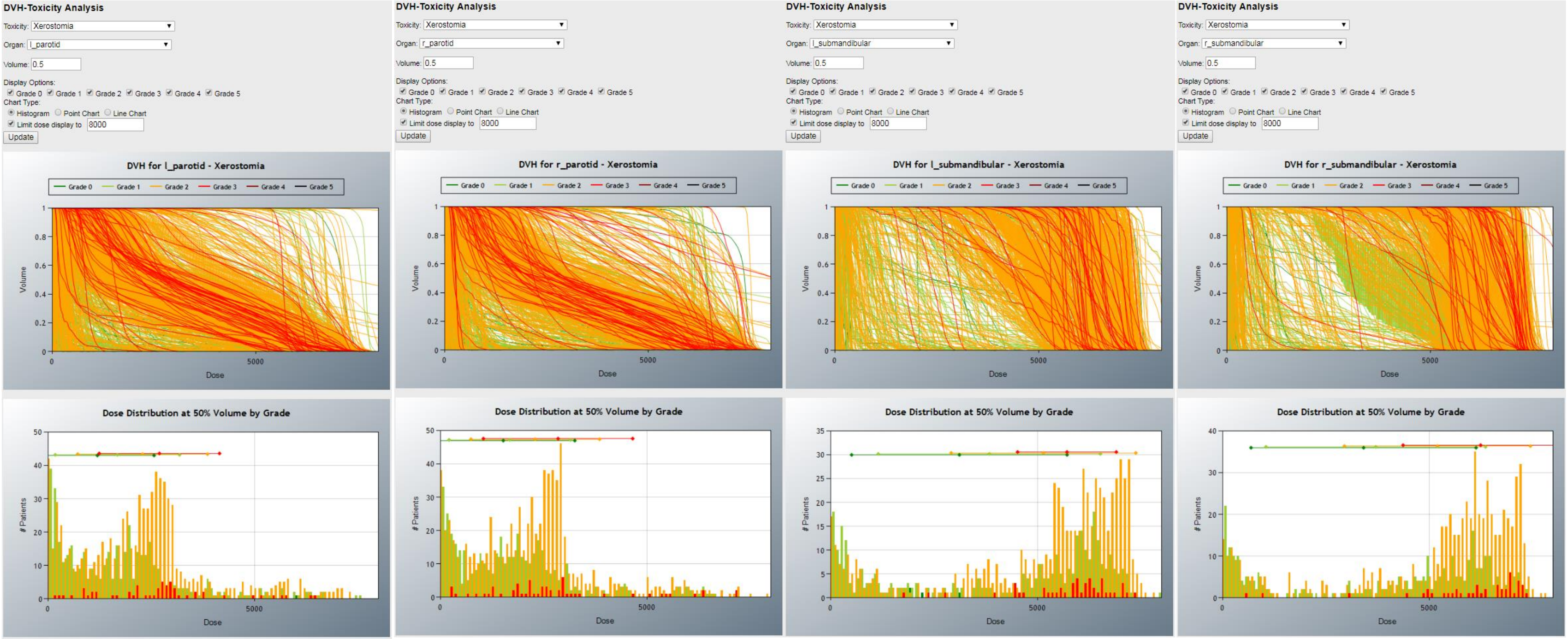
(P. Lakshminarayanan)





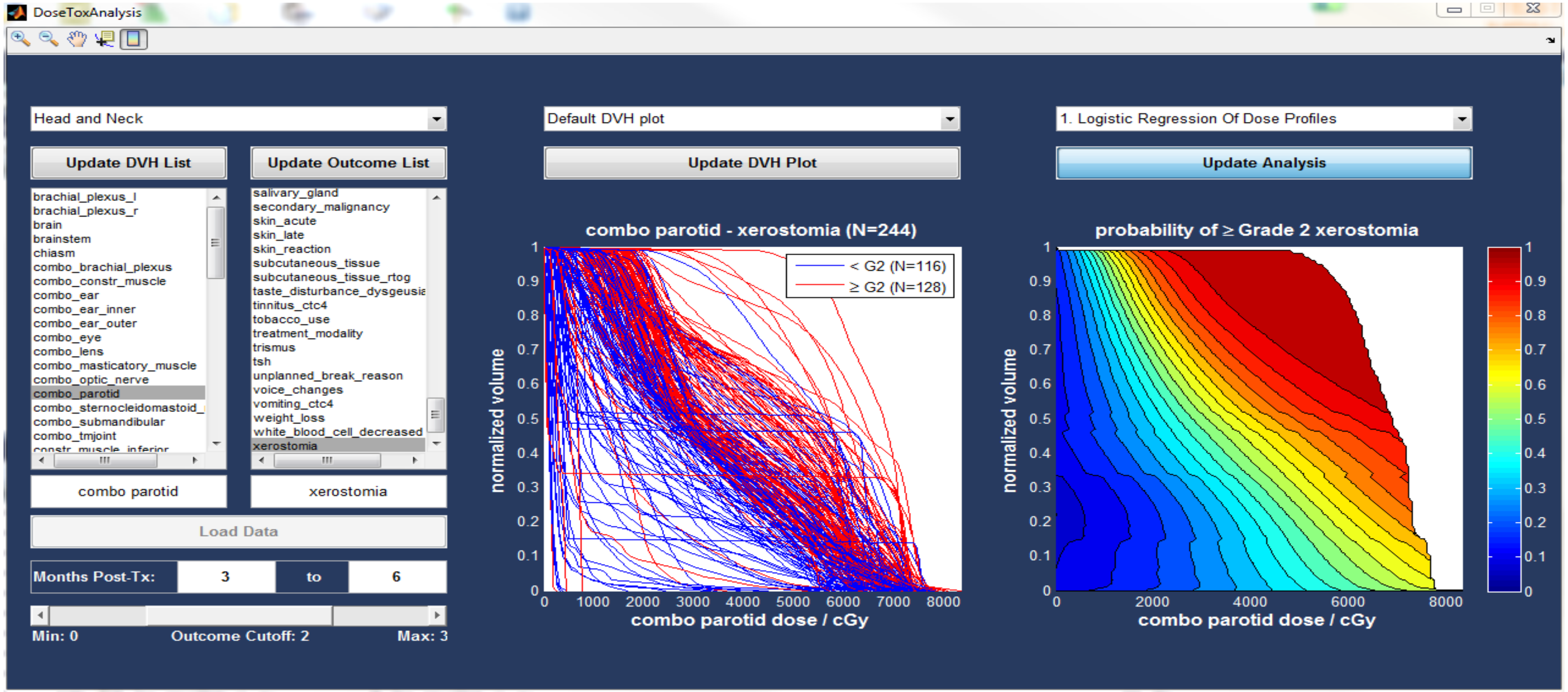


Raw DVH data for salivary glands



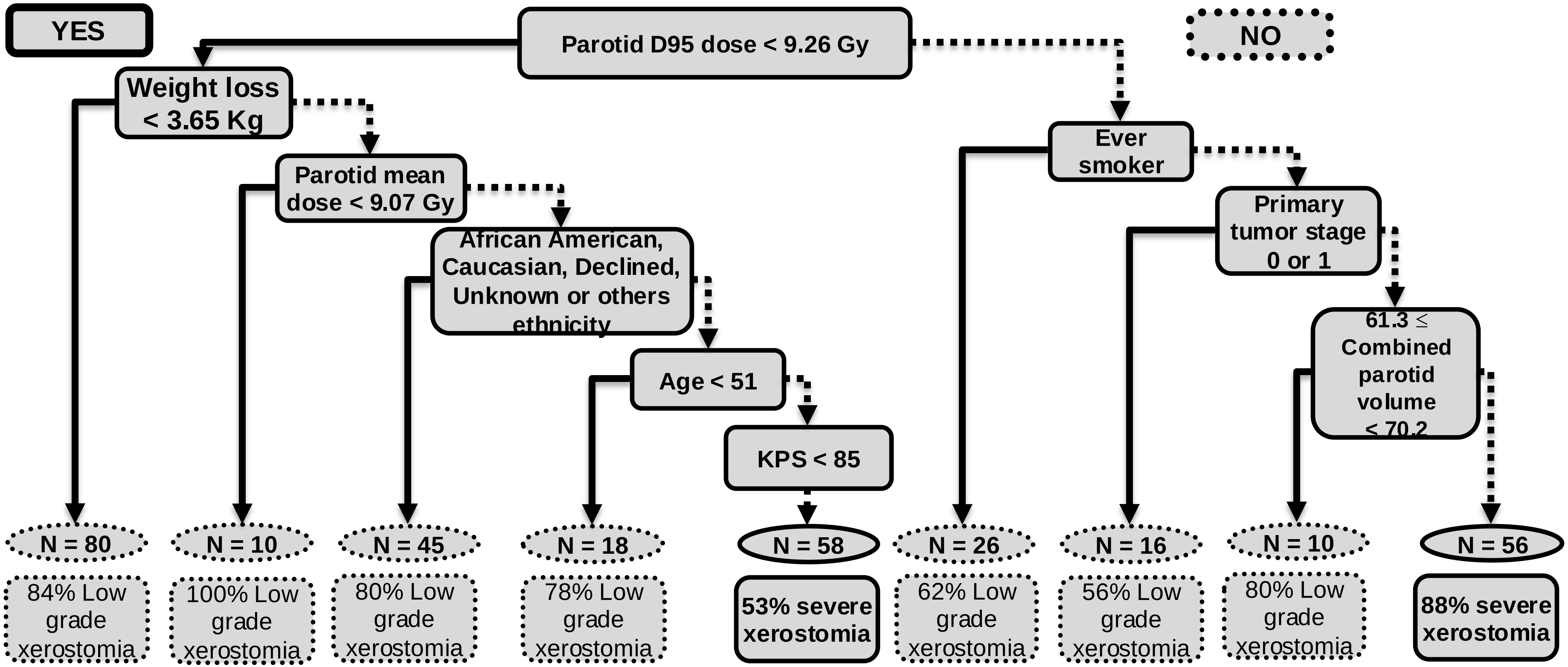
Toxicity and Dose Volume Histogram

(Scott Robertson et al…)



Xerostomia Prediction (3-6 Months post RT)

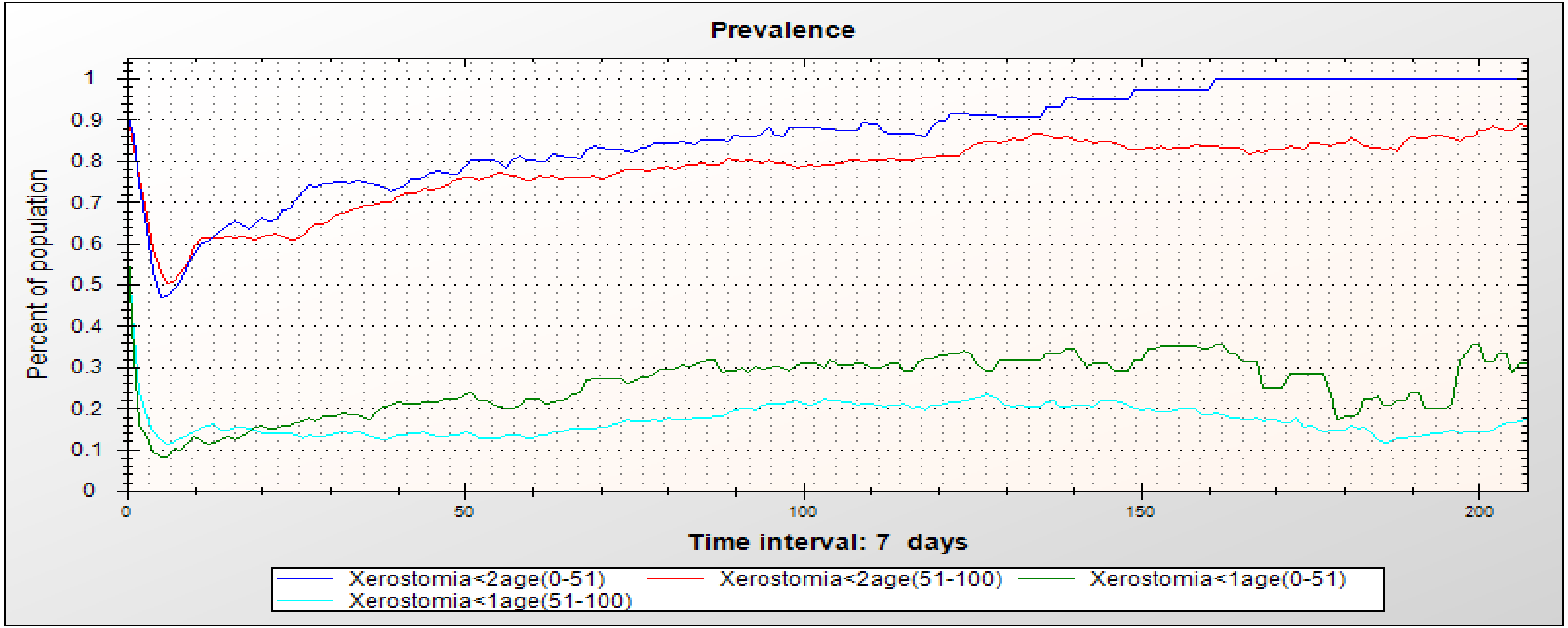
JOHNS HOPKINS MEDICINE



AUC	Accuracy	Sensitivity	Specificity
0.627	0.687	0.536	0.784

Xuan Hui MD MS

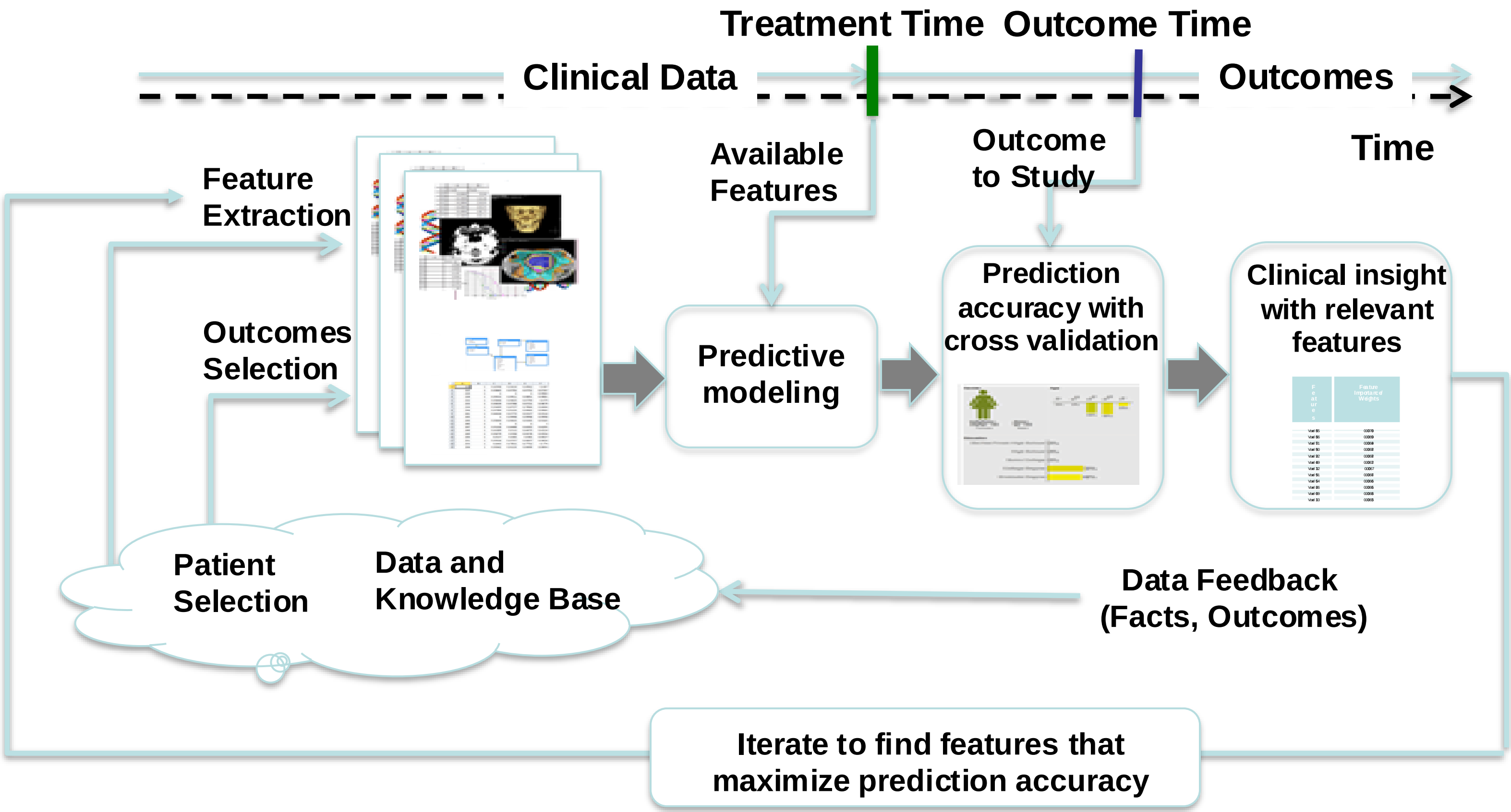
Xerostomia prevalence separated by age = 51



Xerostomia<2age(0-51) :
Initial size: 175
25% lost follow up at time: 26
50% lost follow up at time: 74

Xerostomia<2age(51-100) :
Initial size: 654
25% lost follow up at time: 27
50% lost follow up at time: 64

Learning health system – Hypothesis Derivation



Radiation dose transformed to standard atlas

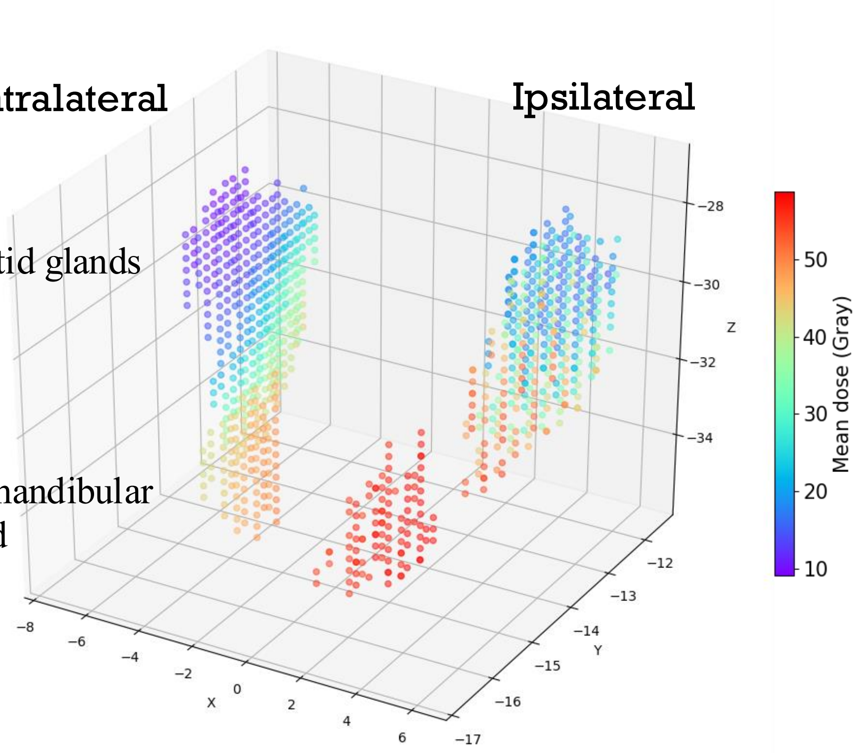
Average dose to each voxel

Contralateral

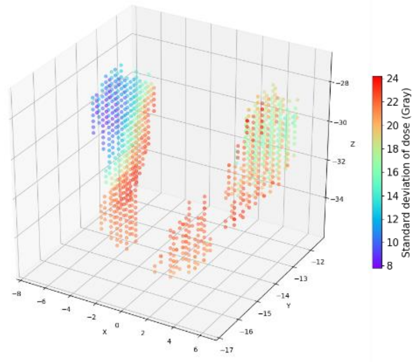
Ipsilateral

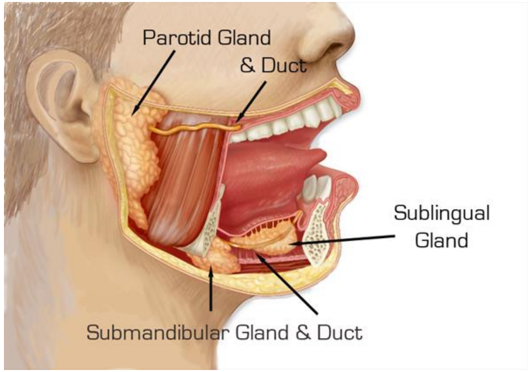
Parotid glands

Submandibular gland



Standard Deviation of Dose

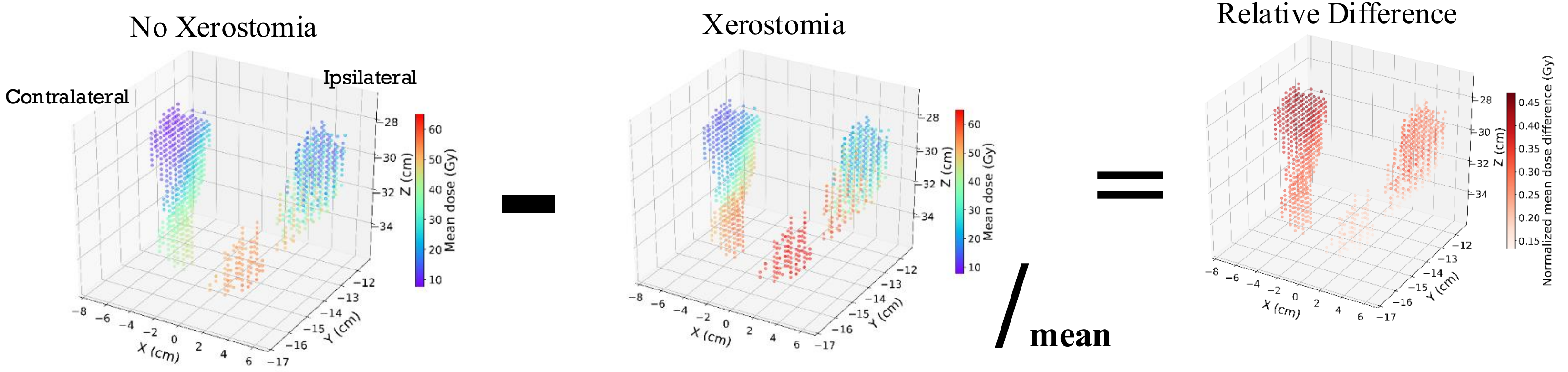




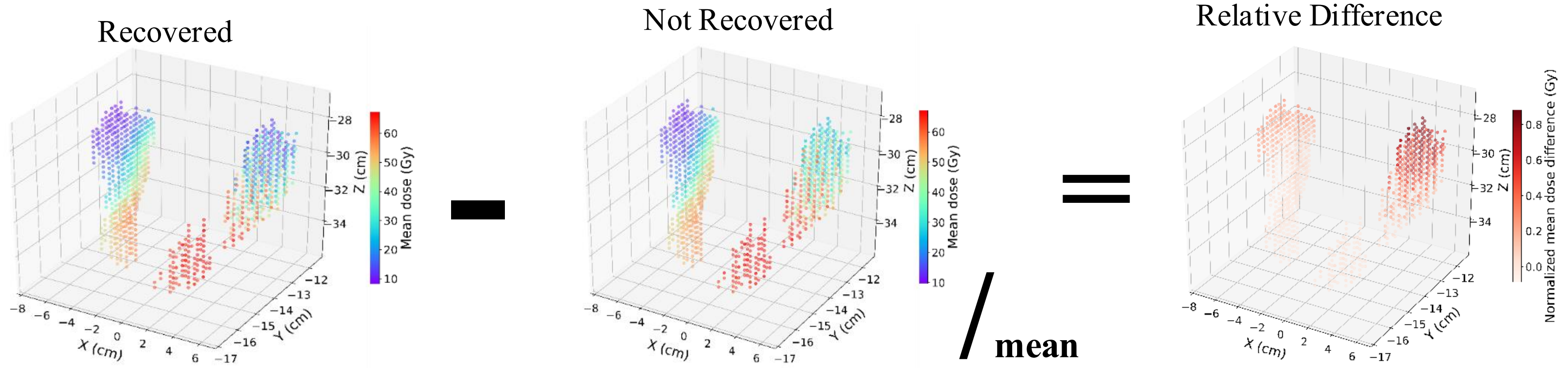
Mean voxel doses and normalized difference

JOHNS HOPKINS MEDICINE

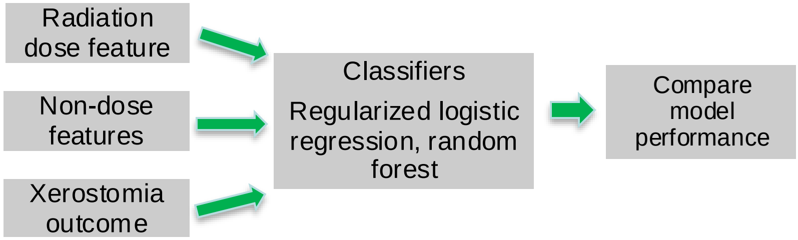
Acute Xerostomia



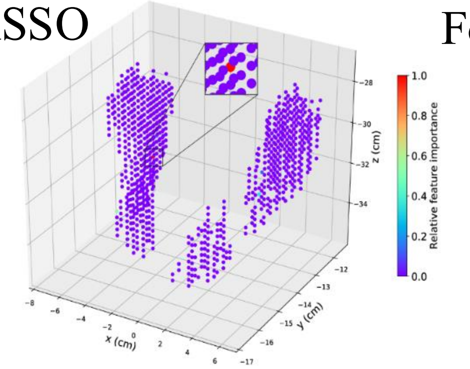
Recovery



Voxel importance pattern comparisons by machine learning Acute Xerostomia (Injury)

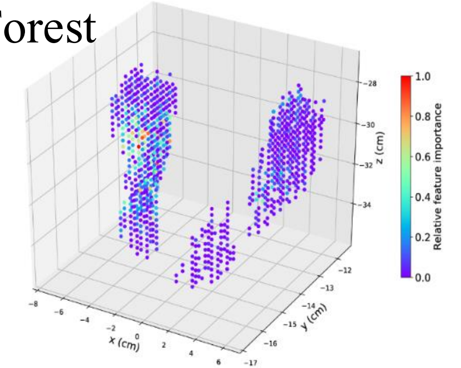


LASSO



(a) Voxel importance pattern from lasso logistic regression

Random Forest

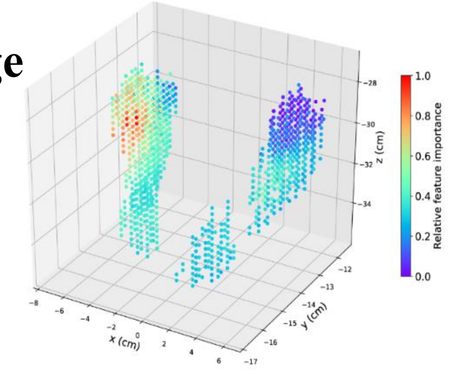


(b) Voxel importance pattern from random forest

*** **Ridge** is most appropriate to handle correlated dose variable

Models	Data set (dimension: 427*961)
	AUC (10-fold cross-validation) Out-of-sample score
Ridge logistic regression	**0.70 ±0.04**
Lasso logistic regression	0.67±0.04
Random forest	0.69±0.06

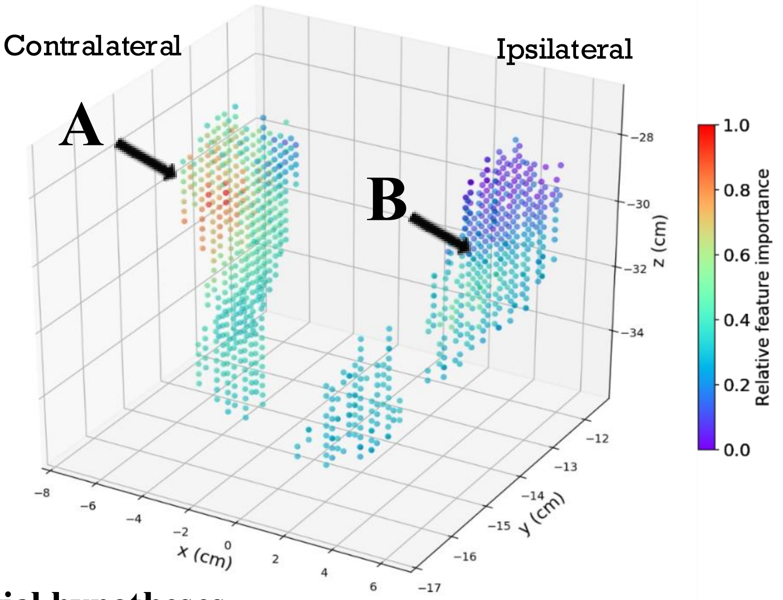
Ridge



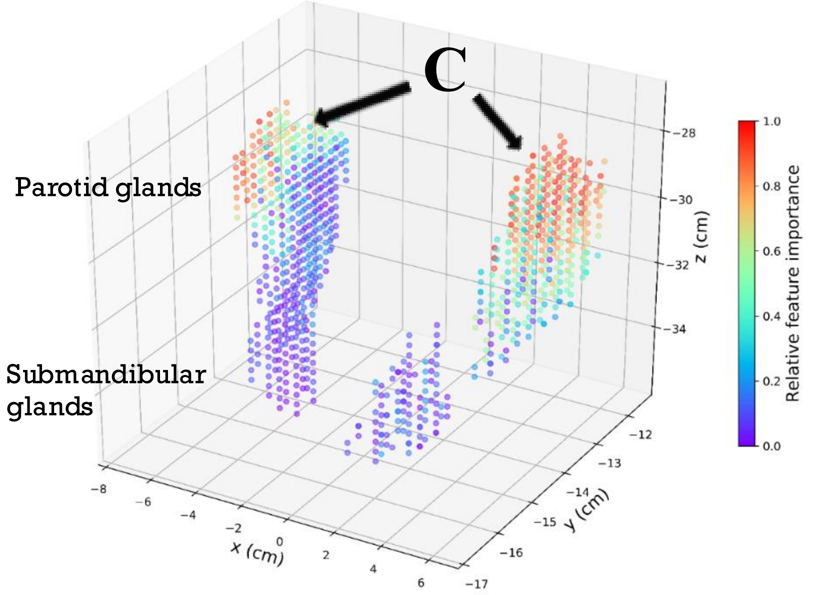
(c) Voxel importance pattern from ridge logistic regression

Voxels importance from Ridge logistic regression

Acute Xerostomia (Injury)



Recovery



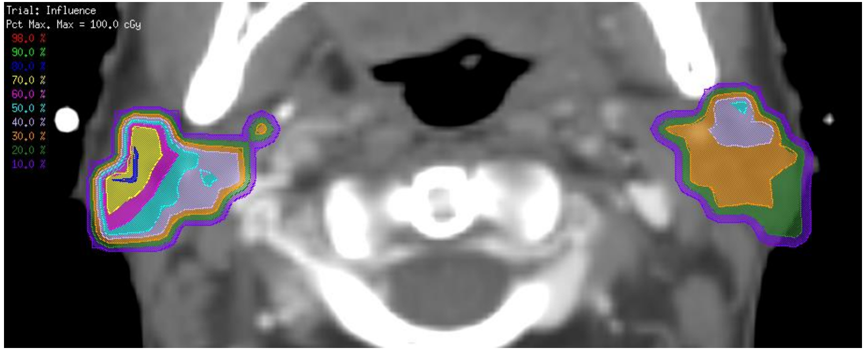
Potential hypotheses

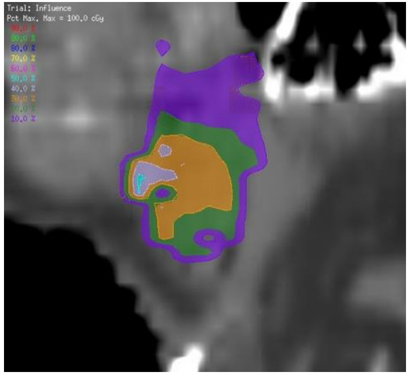
A. The superior portion of the contralateral parotid is the last region to be able to spare (lowest mean dose). If a high dose, there is likely high dose everywhere else, increasing xerostomia.

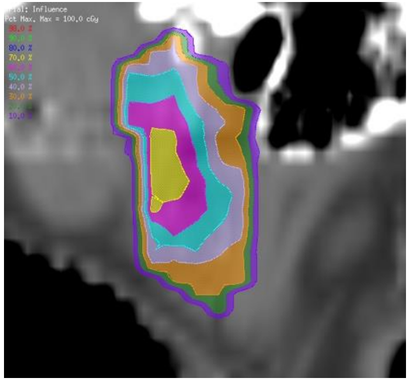
B. Ductal region of ipsilateral parotid has high influence, where the superior portion has very low importance suggesting possible occlusion of duct or serial component of organ function related to injury.

C. The superior (lower dose) portions of both parotids influence recovery whereas the higher dose regions have little influence. This suggests a lower dose threshold for preserving the ability to recover salivary function if injured.

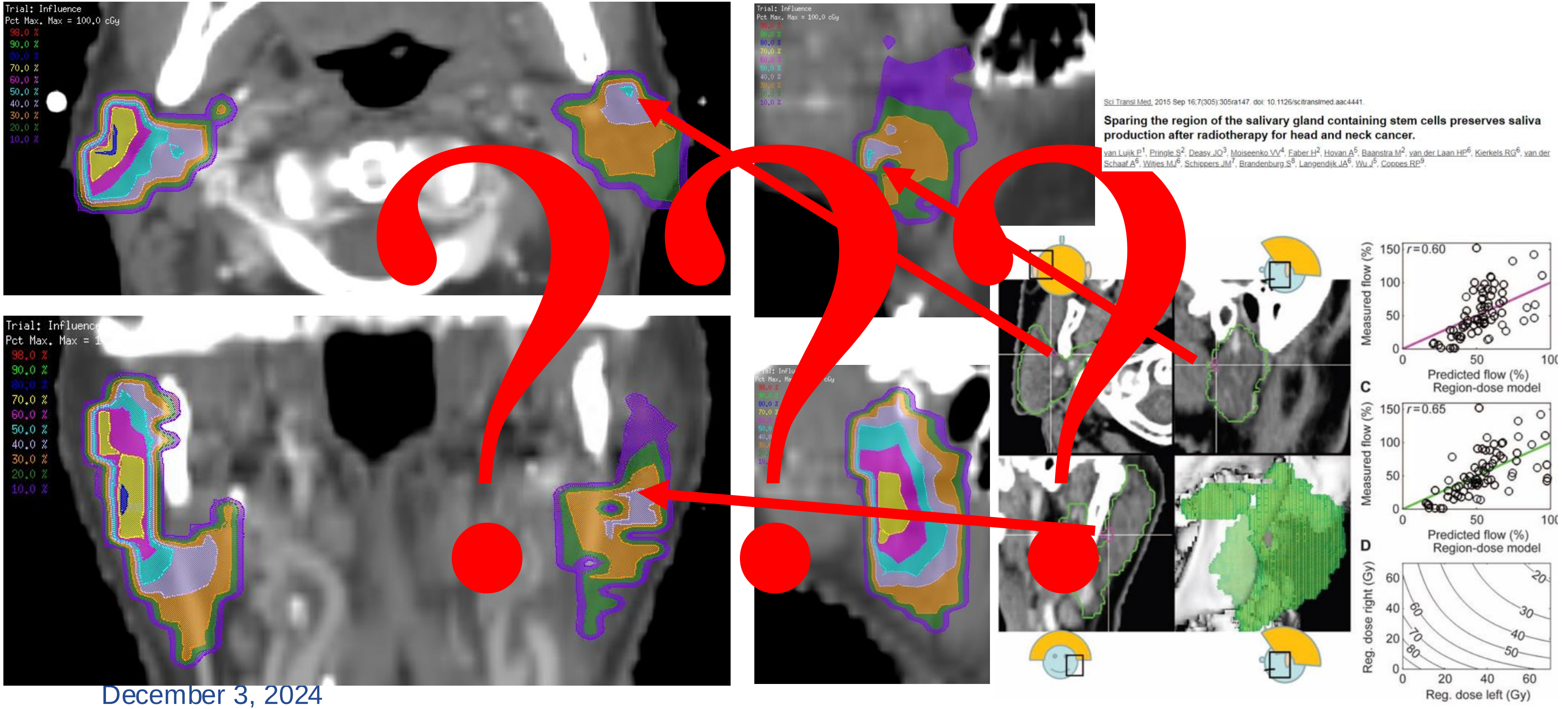
Influence on CT for Injury

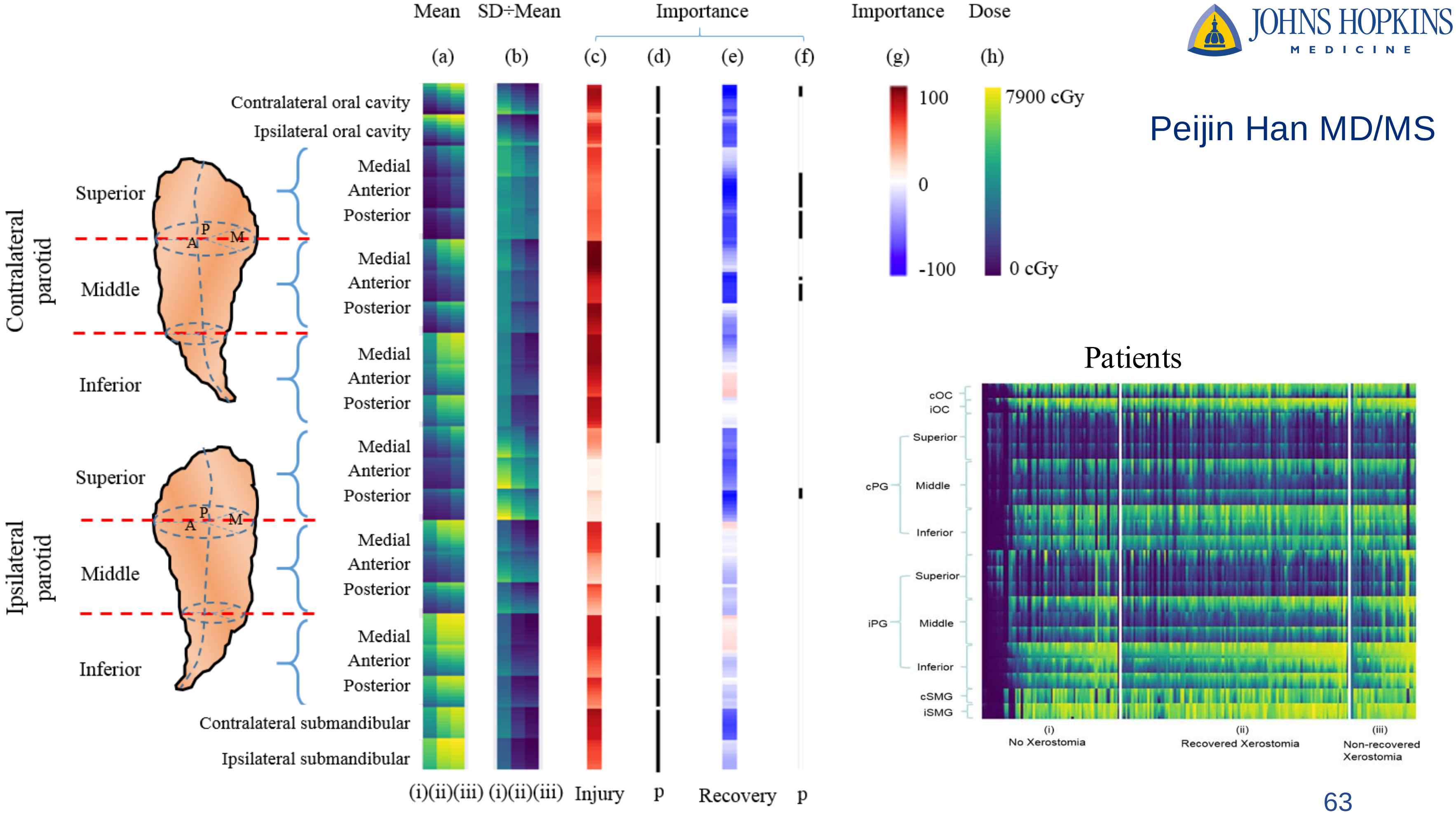






Influence on CT for Injury

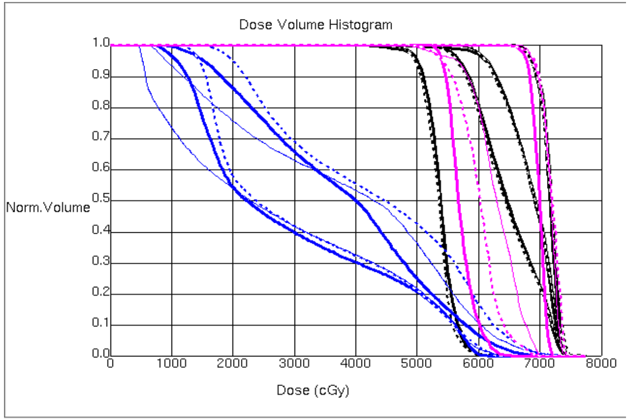




Peijin Han MD/MS

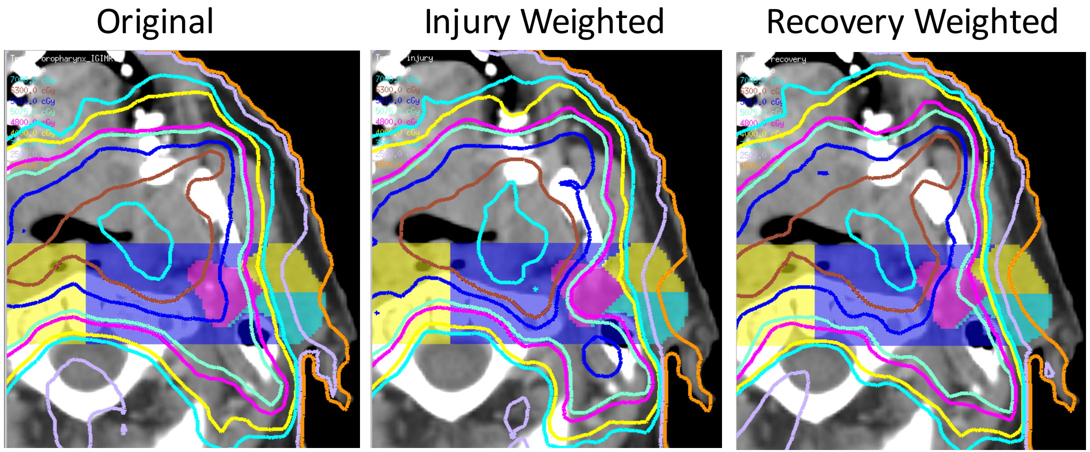
IMRT plans driven by predictions

(McNutt, Lee, Sheikh, Quon)



Original – dashed
Injury – thick
Recovery – thin

Targets – black
Parotids – blue
Submandibulars – pink



	Injury Percentile	Recovery Percentile
Original	81.8	13.5
Injury Wt	64.3	18.1
Recovery Wt	69.7	32.0

How to stay safe and maintain quality?

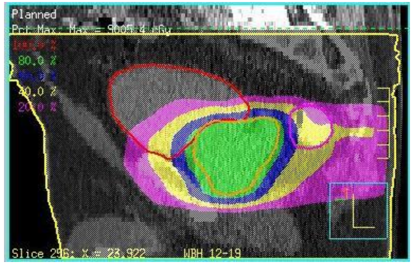
- Data is not always the highest quality – must make sure methods/models don't assume it is
- Data does not contain all knowledge. Existing knowledge is often absent
  - If all patients in database meet a dose goal, then there is no knowledge outside of that goal contained in the data.
  - Be wary of situations where you may be outside of the available data bounds
- Data gets old
  - How to keep models current?
  - Do we want to be treated the way patients were treated 2 decades ago?
  - The Rx anomaly may be using an old Rx that has been superseded.

Acknowledgments

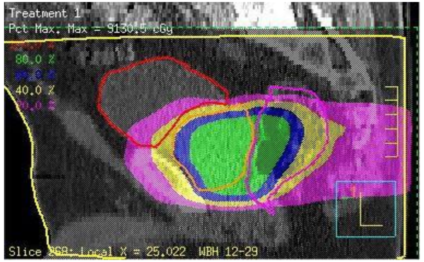
- **JHU-RO**
  - Sierra Cheng MD
  - Michael Bowers BS
  - Joseph Moore PhD
  - Scott Robertson PhD
  - Pranav Lakshminarayanan
  - Xuan Hui MD
  - John Wong PhD
  - Theodore DeWeese MD
- GI Team
  - Joseph Herman MD
  - Amy Hacker-Prietz PA
- H&N Team
  - Harry Quon MD
  - Ana Keiss MD
- **Toronto-Sunnybrook**
  - William Song PhD
  - Patrick Kwok
- **JHU - CS**
  - Russ Taylor PhD
  - Misha Kazhdan PhD
  - Fumbeya Murango BS
- **Philips PROS**
  - Karl Bzdusek BS
- **Toshiba**
  - Minoru Nakatsugawa PhD
  - Bobby Davey PhD
  - Rachel-Louise Koktava
  - John Haller
- **Elekta**
  - Bob Hubbell
- **University of Washington**
  - Kim Evans MS
  - Mark Philips PhD
  - Kristi Hendrickson PhD

Deformable dose accumulation

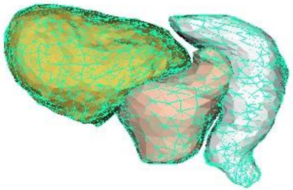
Primary dataset

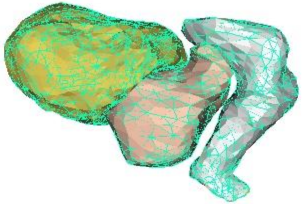


Secondary dataset with primary IMRT beam arrangement



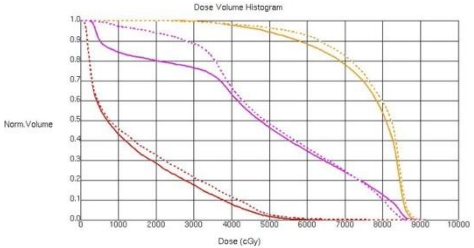
Model-based segmentation



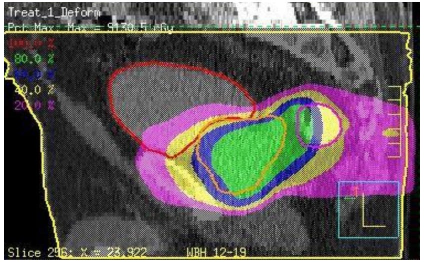


Deformable registration

Dose warping



Secondary dose deformed back to primary plan

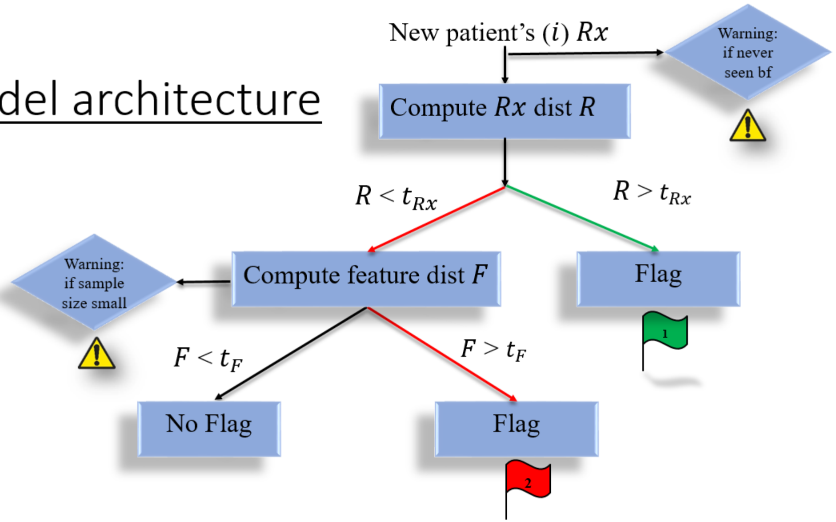


Radiation Prescription Anomalies

A novel data-driven algorithm to predict anomalous prescription based on patient's feature set

Qiongge Li, R. Voong, R. Hales, J. Wright, T. McNutt (Submitted)

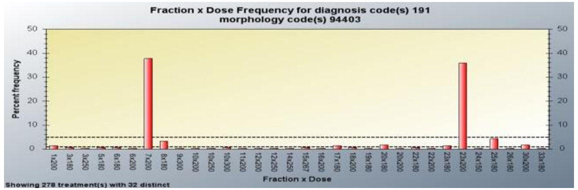
Model architecture



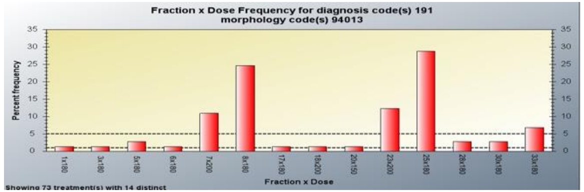
Automated Cross-Referencing of Radiation Prescriptions to Diagnosis: A Proposed Mechanism to Improve Patient Safety

A. Sharabi, T. McNutt, and T. DeWeese; *The Johns Hopkins University School of Medicine, Baltimore, MD*

191 Brain
AND
Pathology of Glioblastoma



191 Brain
AND
Pathology of Anaplastic Astrocytoma

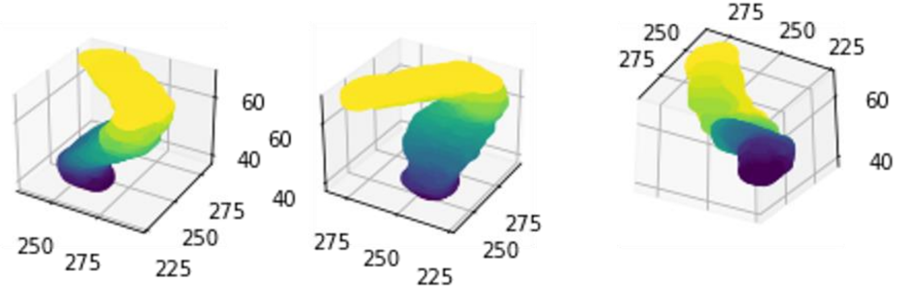


Contour Anomalies

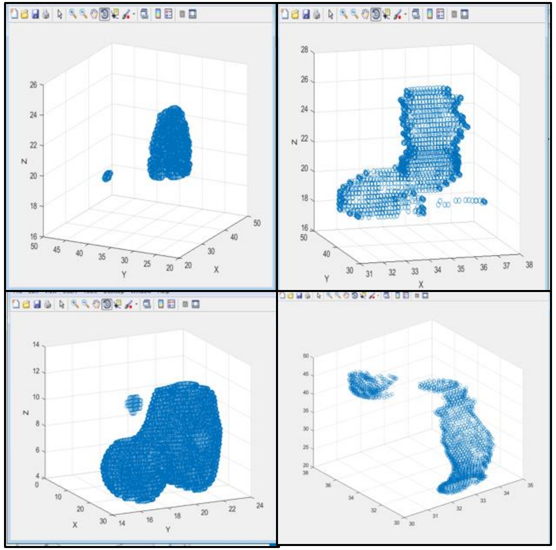
Anomaly types:

- Discontinuities
- Size/extent inconsistency
- Shape inconsistency
- Anatomic relationships

e.g. Rectum contoured into Sigmoid Colon



Kevin Gorman et. al.



RADIATION ONCOLOGY PHYSICS

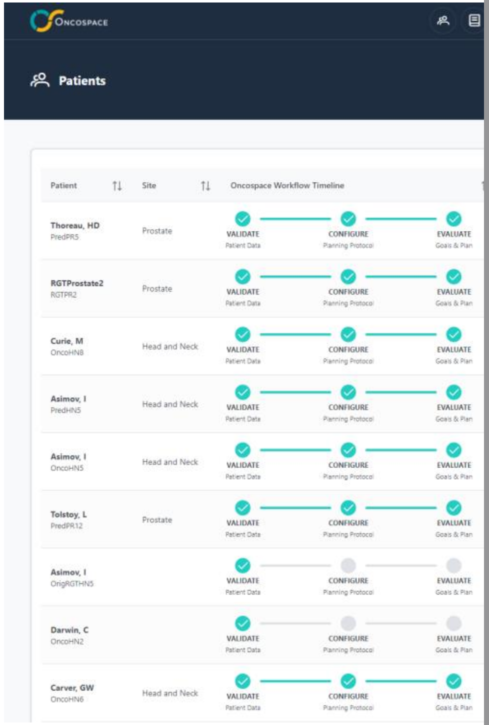
WILEY

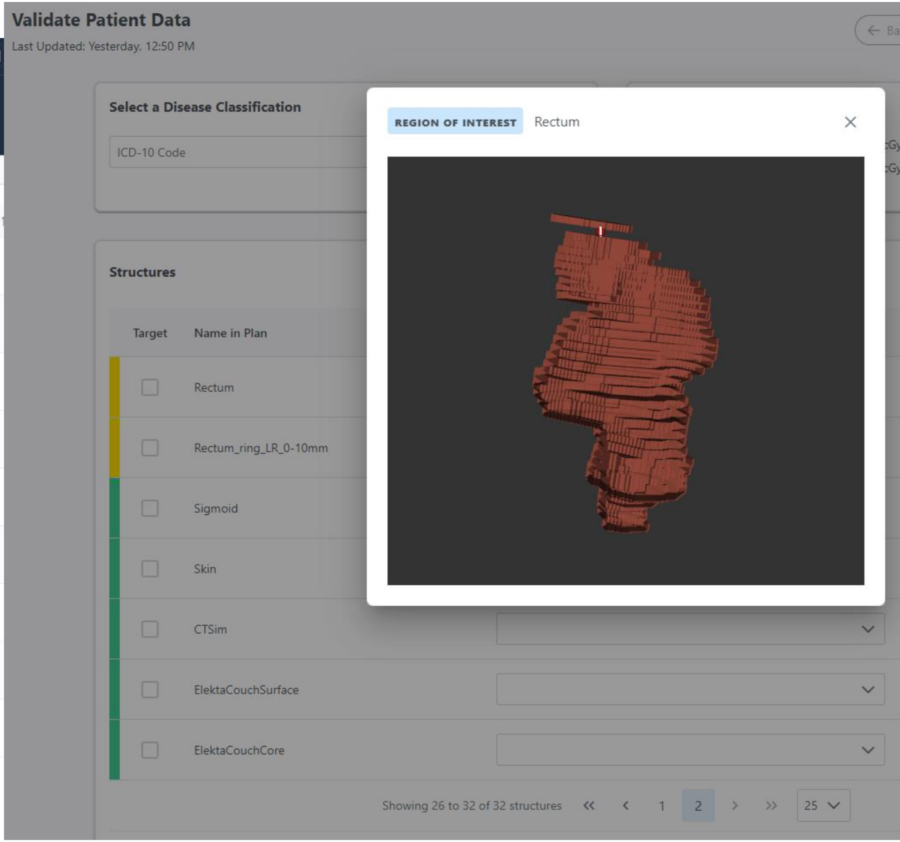
Data integrity systems for organ contours in radiation therapy planning

Veeraj P. Shah[1] | Pranav Lakshminarayanan[2] | Joseph Moore[3] | Phuoc T. Tran[1,3] | Harry Quon[1] | Curtiland Deville[1] | Todd R. McNutt[1]

Putting it together…

- Send contours to system
- Map ROI names (auto)
- Evaluate contour integrity
    - Discontinuity
    - Unexpected volume
    - Unexpected shape
- Select Tx protocol





Causality

(Shpitser)

Semi-Parametric Causal Sufficient Dimension Reduction Of High Dimensional Treatments

Razieh Nabi, T. McNutt, I. Shpitser • Published 2017 • Mathematics • arXiv: Methodology

Cause-effect relationships are typically evaluated by comparing the outcome responses to binary treatment values, representing cases and controls. However, in certain applications, treatments of interest are continuous and high dimensional. For example, understanding the causal relationship between severity of radiation therapy, represented by a high dimensional vector of radiation exposure values at different parts of the body, and post-treatment side effects is a problem of clinical interest… Expand

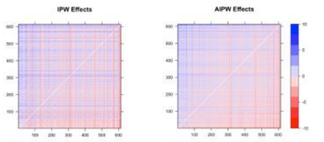


Fig. 4: Heatmaps to illustrate the causal effect of radiation on weight loss, where effects are computed by estimating β via (a) IPW estimator, and (b) AIPW estimator. Heatmaps are antidiagonally symmetric with opposite color tones.

- Notion of Dimension Reduction with consideration of Causal Inference
  - DVH point is dimension reduction
  - Principle Components…
- Can we blend with anatomical/physiological understanding?
- Does it work with the inherently controlled treatment?
- Spawned interest with van Herk and Christie Hospital – Manchester, UK

Decision Support Efforts

JOHNS HOPKINS MEDICINE

- Weight loss prediction
  - Head and neck (PEG Tube ?)
  - Thoracic with Image features
- Alcorn BMETS example
- Challenges
  - Clinical decisions that impact trajectory of care