Novel Advances in Radiation Oncology Beyond SRS and Proton Therapy: What Is Next?

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Miami Cancer Meeting 2023

The Intersection of Adaptive Radiotherapy and Big Data Initiatives

“Leveraging Advanced Technologies and Biology to Advance Cancer Therapy Outcomes for True Personalized Therapy”

How can we improve cancer therapy?

What does it mean to improve cancer therapy?

Why do we want to improve cancer therapy?

Why do we want to improve cancer therapy?

Improve how long our patients live

Improve patient Quality of Life

What does it mean to improve cancer therapy?

Optimal dosing of tumor

Less dose to normal tissues

What does it mean to improve cancer therapy?

Optimal dosing of tumor -

Not too much treatment for a durable response

Not too little treatment for a durable response

Less dose to normal tissues

AI will solve these questions – BUT NEED DATA ON PATIENTS

What does it mean to improve cancer therapy?

Optimal dosing of tumor

Less dose to normal tissues – Obvious – ultimately we want to bring normal tissue doses to as little as technically possible

How can we improve cancer therapy?

For chemo, simple – replace with immunotherapy

For radiation therapy:

CT- and MR-based adaptive radiotherapy

Biologically-guided adaptive radiotherapy

AI-driven adaptive radiotherapy

What are the metrics to demonstrate better therapy?

Less toxicity

Optimized tumor control

Better QoL

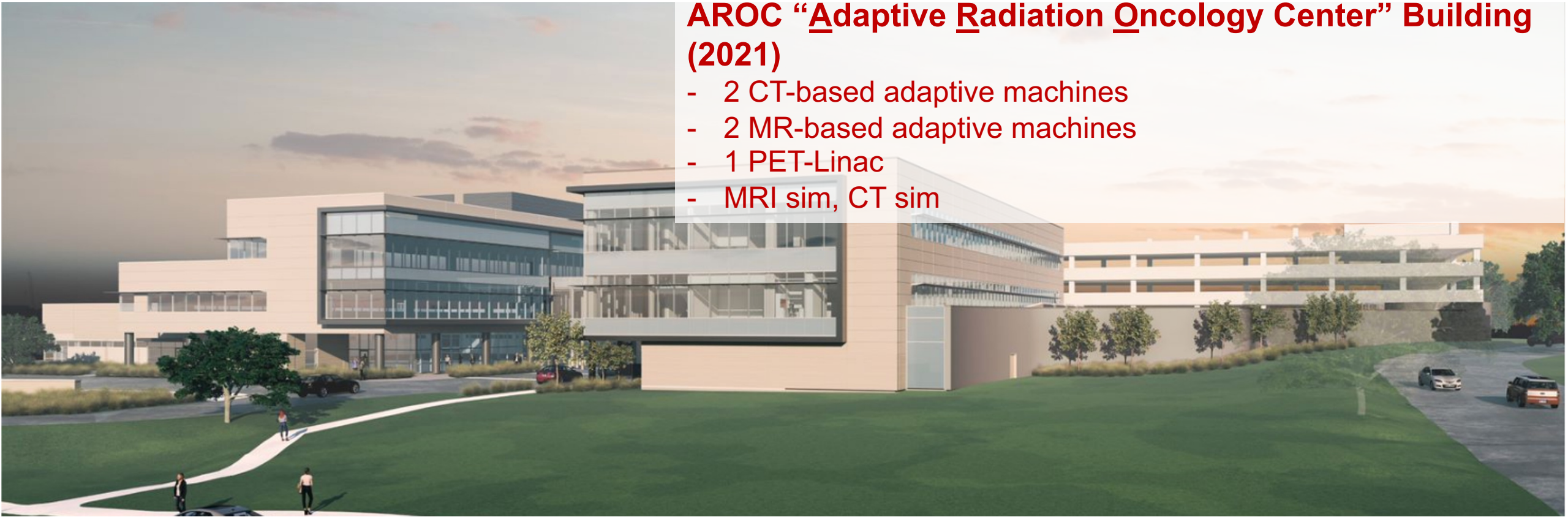
Better survival

BUT NEED DATA FROM PATIENTS

Adaptive Radiotherapy

UTSW Overview

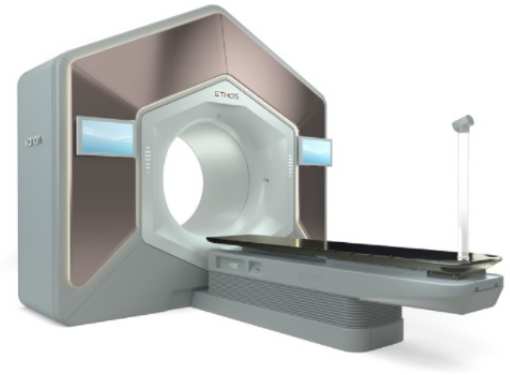
- Summary of adaptive machines



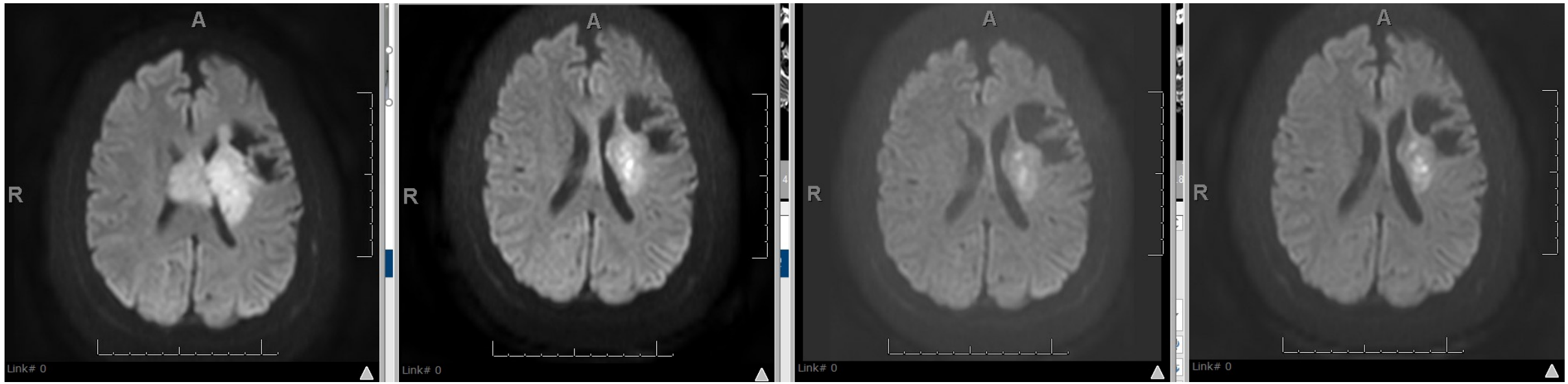
AROC "Adaptive Radiation Oncology Center" Building (2021)

- 2 CT-based adaptive machines
- 2 MR-based adaptive machines
- 1 PET-Linac
- MRI sim, CT sim

Adaptive RT Responds to CHANGE



- These machines can identify changes in the patient's anatomy (via special imaging) including the patient's tumor and changes in patient tumor biology ("functional imaging")
  - React to those changes by re-planning the treatment (very quickly)
  - Will educate regarding the need to treat more or less, different part of the tumor, timing, etc. among variables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Keys

To identify patients who may benefit from adaptive radiotherapy – prediction and prognostication

“Personalized/Precision” Medicine

To consider novel (near) future applications of adaptive radiotherapy

The 3 ways we can make our mark for adaptive tx:

1) Presenting the facts – presenting practice patterns

2) Identifying how adaptive tx provides clinical benefit

3) Identifying which patients will need adaptive therapy

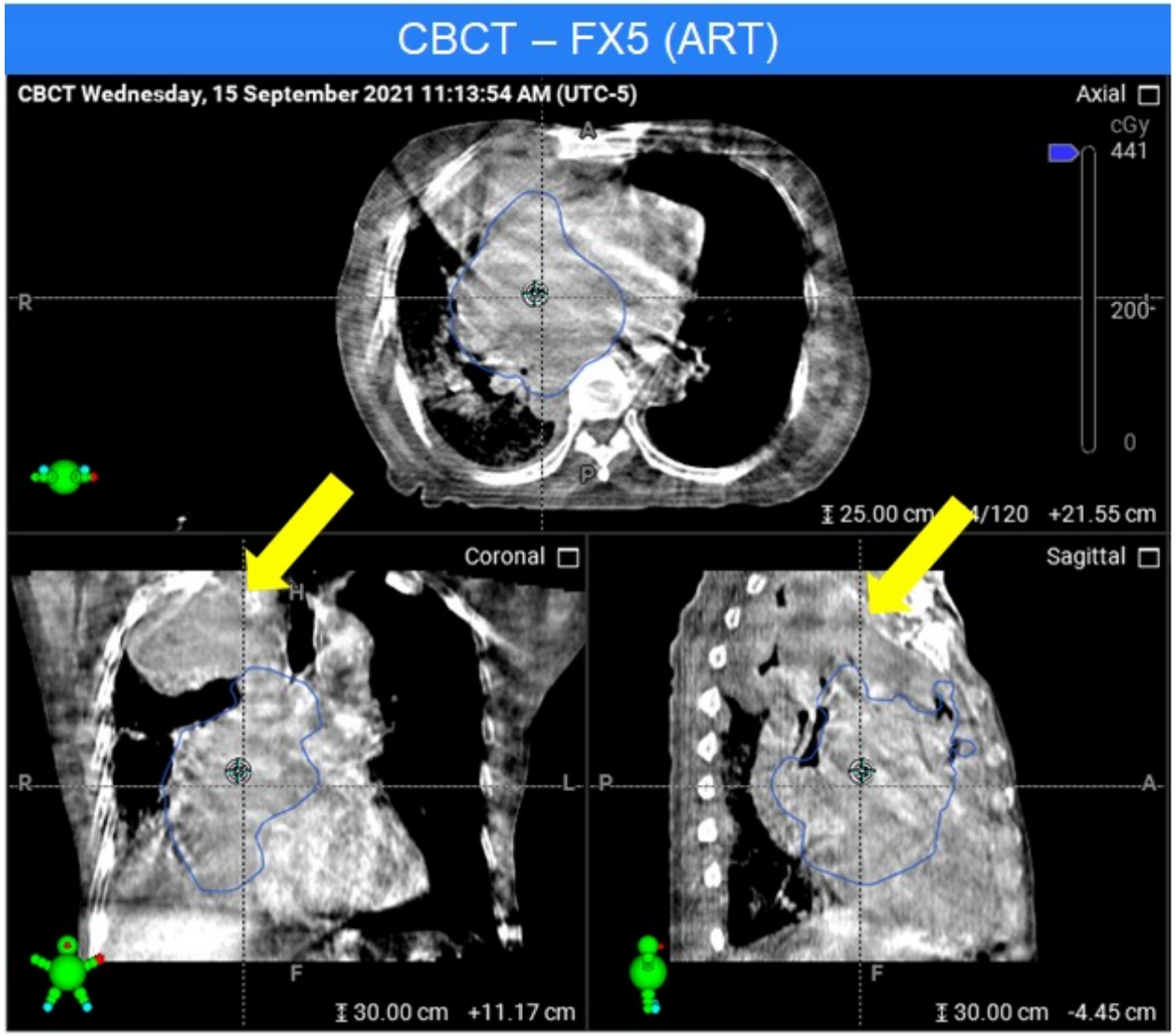
Who Benefits from Adaptive Radiotherapy?

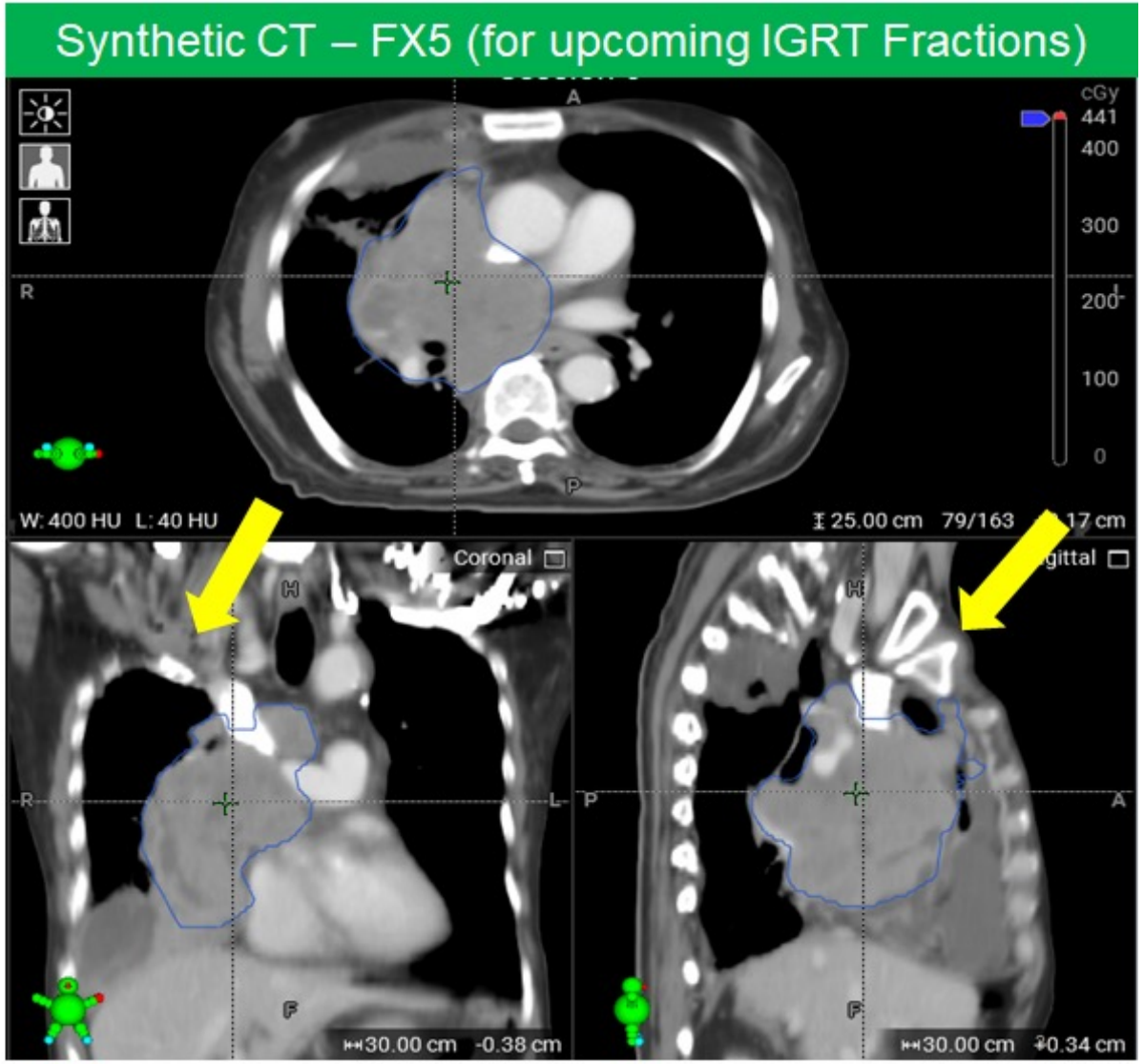
- Anatomy adaptation (target and/or OAR)
  - GYN/GU/GI (organ motion, bladder filling, rectal gas)
  - Head and neck (weight loss, anatomy change)
  - Any target abutting critical structure or prior RT field (i.e. lung target adjacent to BP)

- Response adaptation (changes in tumor size/shape)
  - i.e. radiosensitive tumors, PULSAR treatment

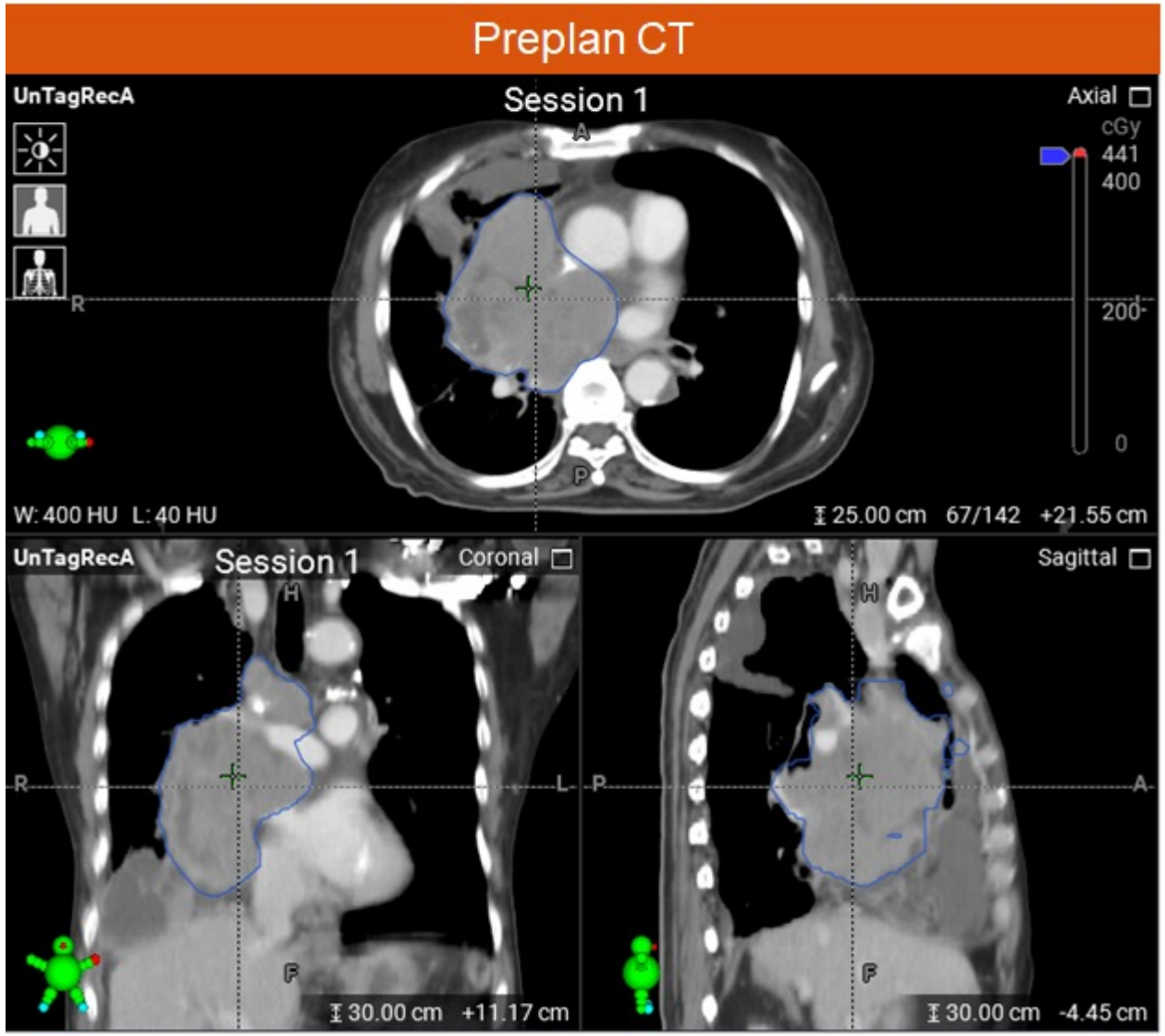
- Goals of ART
  - More accurate treatment (↑ efficacy, ↓ toxicity)
  - PTV margin reduction (↓ toxicity)
  - GTV reduction from tumor shrinkage (↓ toxicity)
  - Dose escalation? (↑ efficacy)
  - Shorter treatments i.e. more SAbR/PULSAR? (↑ convenience, ↑ efficacy?, ↓ toxicity?)

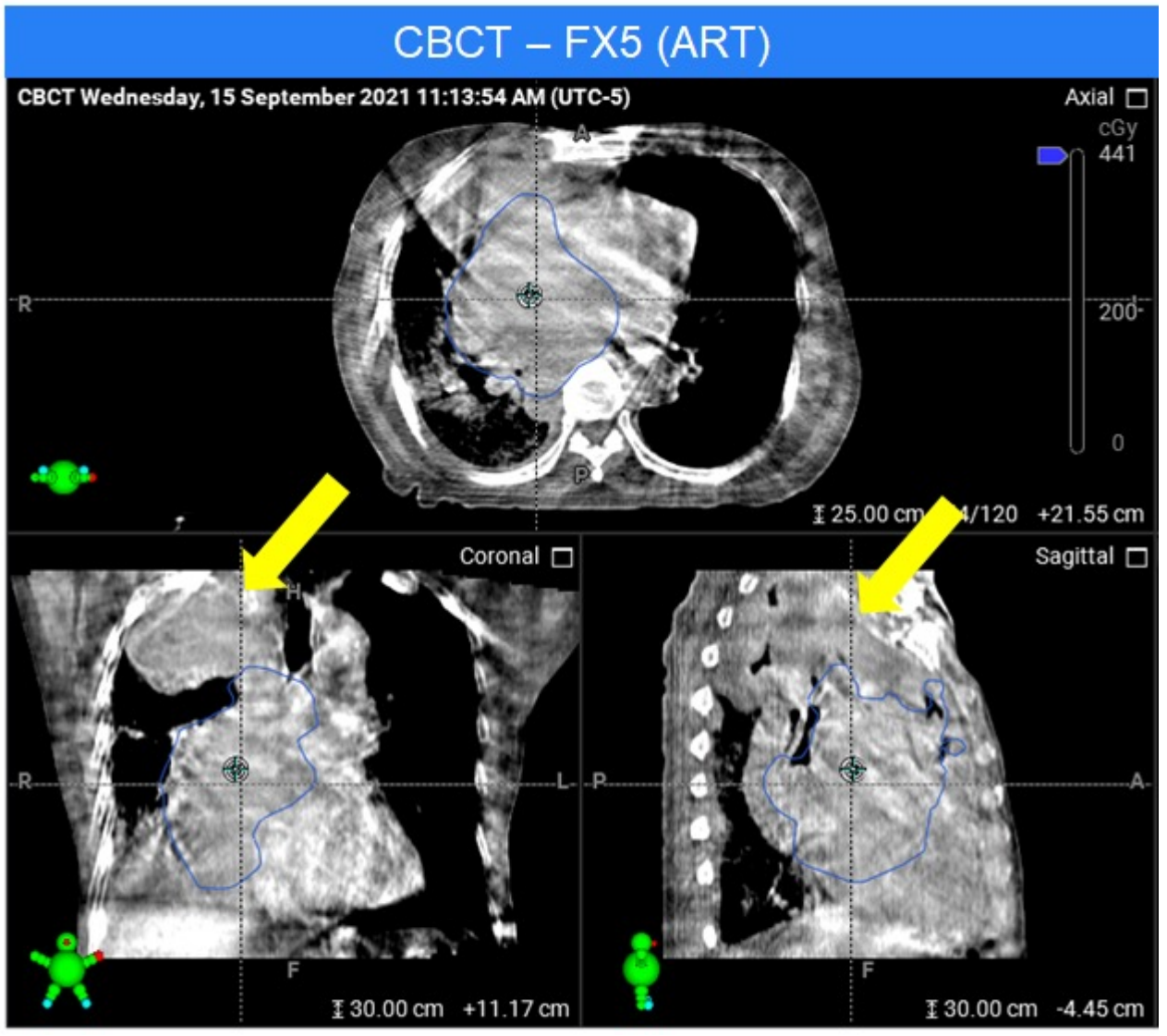
CT Adaptive Machine





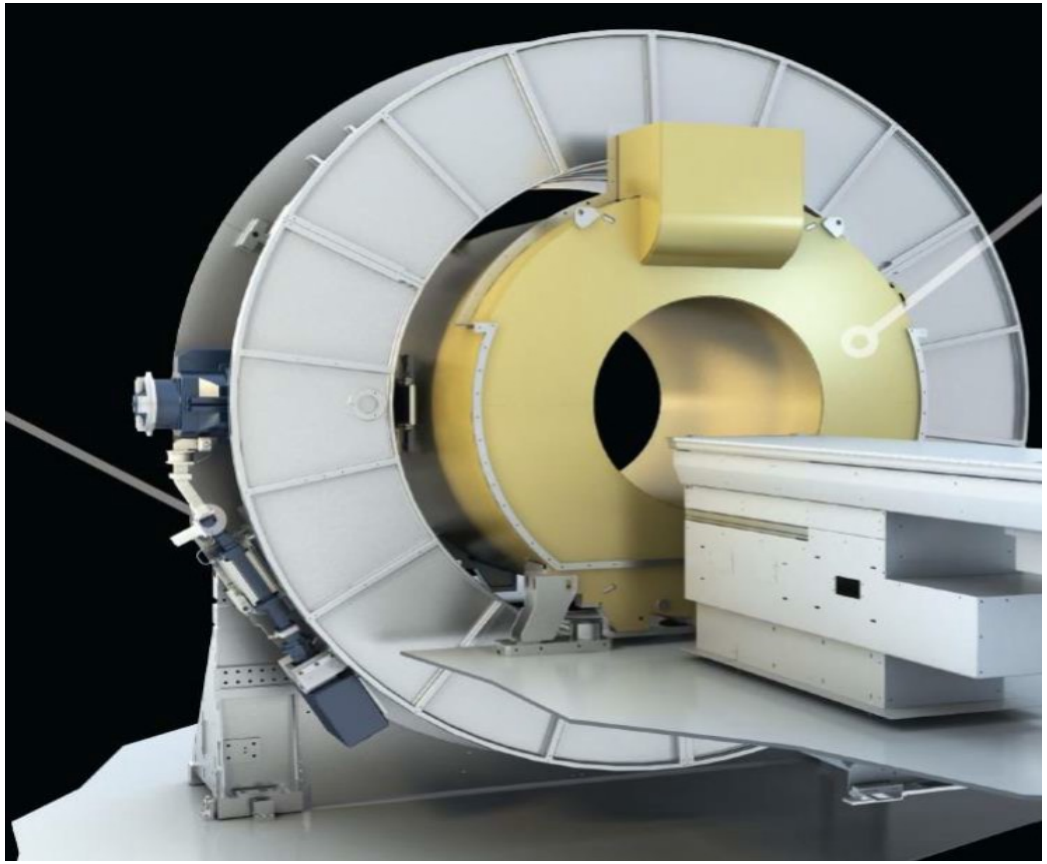
Patient Anatomy Change During Course





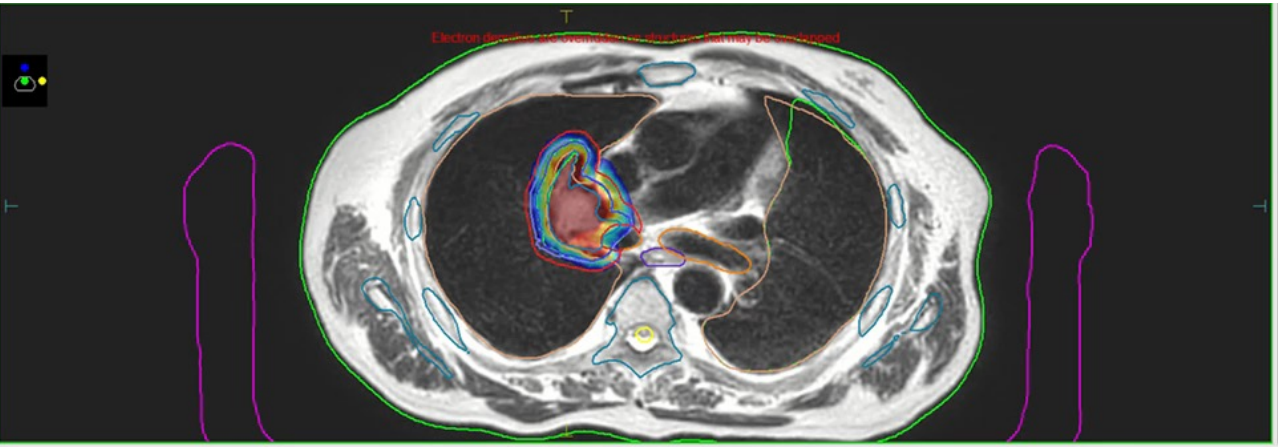
MR-guided radiotherapy

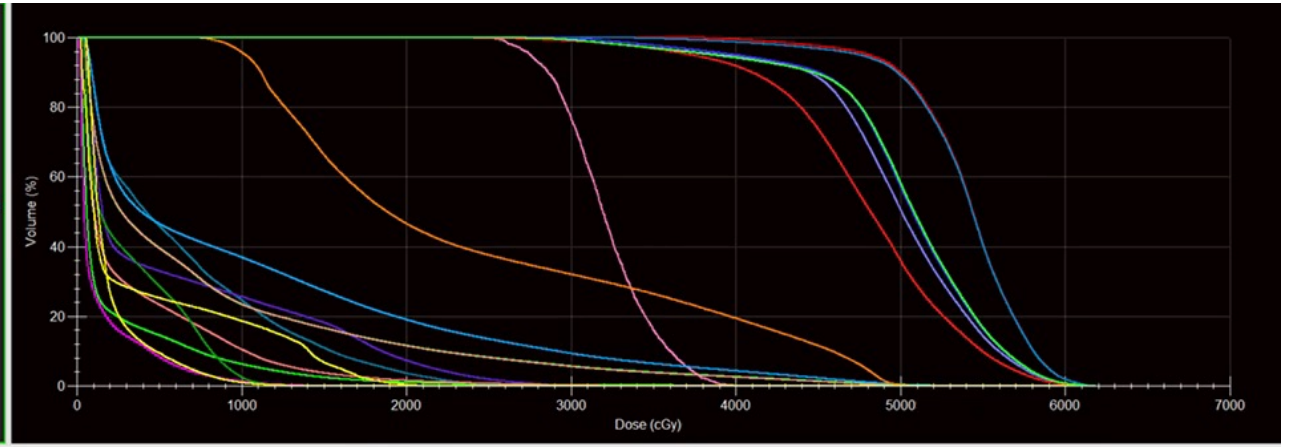
- MR linac integrates a magnetic-resonance imaging (MRI) scanner with a radiotherapy linac
- Challenging to integrate these two systems!
  - Electrons accelerated by linac can be affected by magnetic fields
  - MR scanner is sensitive to linac EM noise
- *But* MR provides
  - Unmatched soft-tissue visualization, allowing better tumor targeting and normal-tissue avoidance (eg: brain, pancreas/bowel)
  - No-dose repeat imaging, and no-dose real-time imaging during Tx

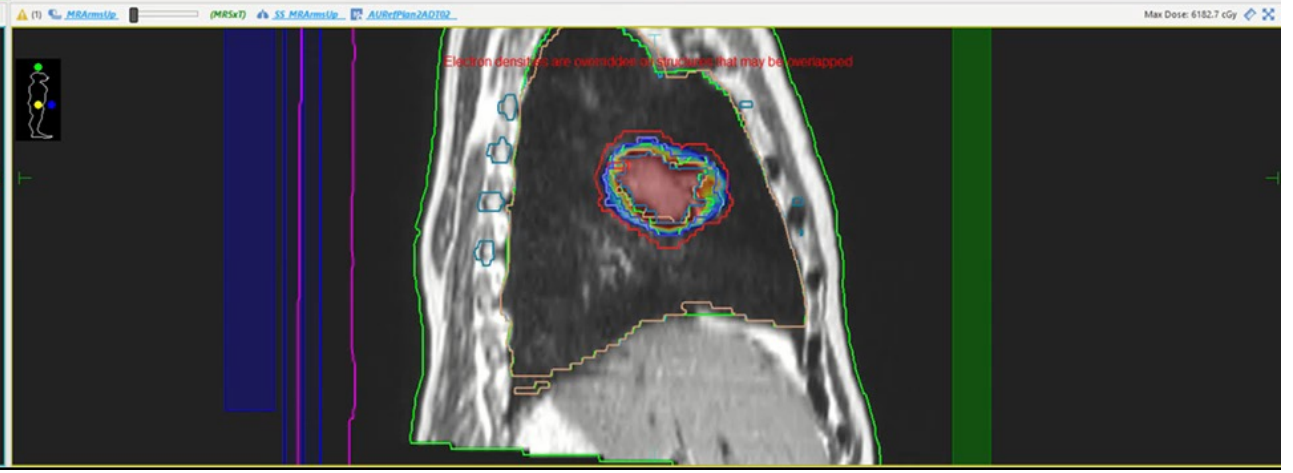


MR Linac : First Initial Experience

- **Lung PULSAR** 9 Gy x 5

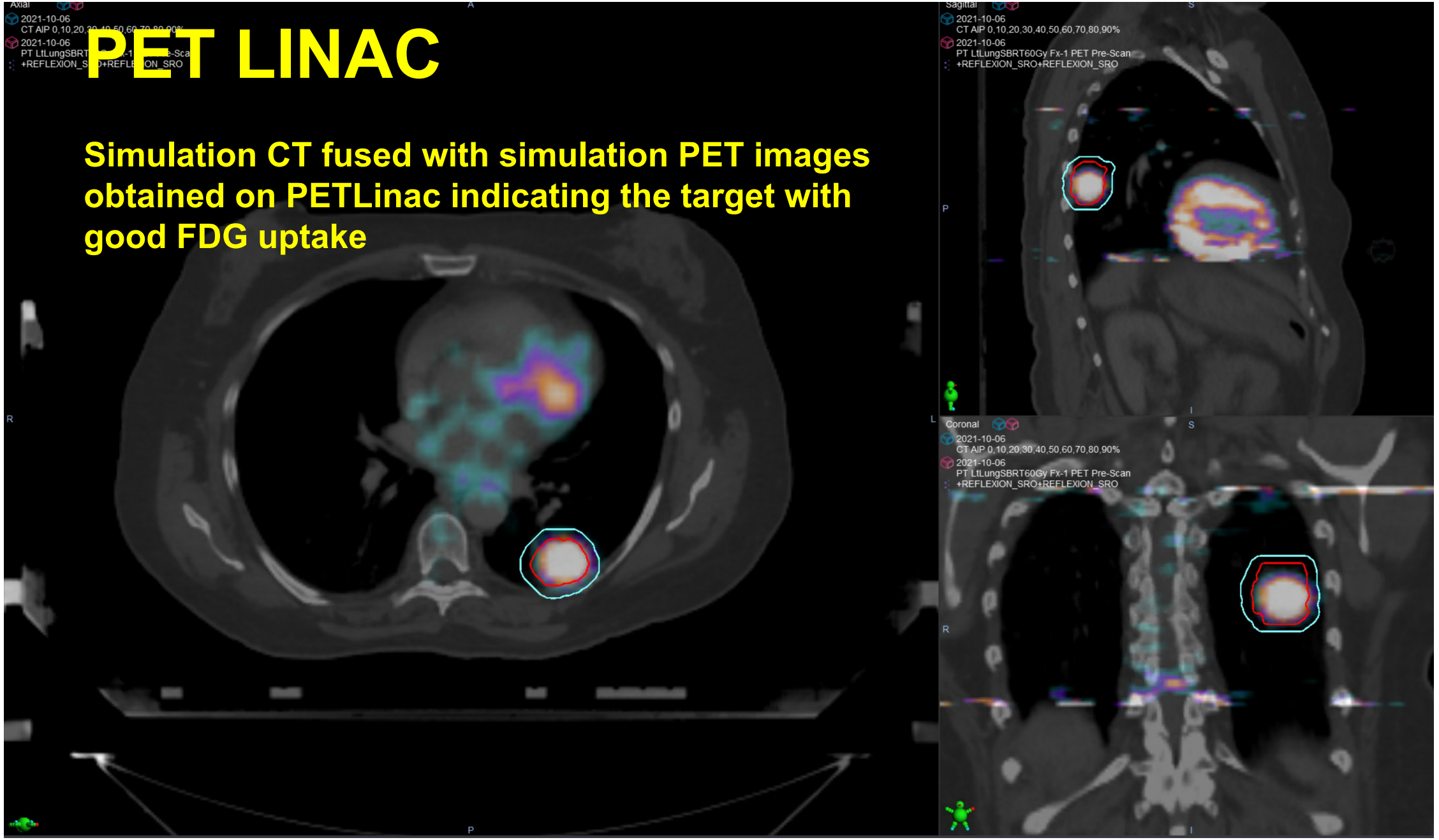






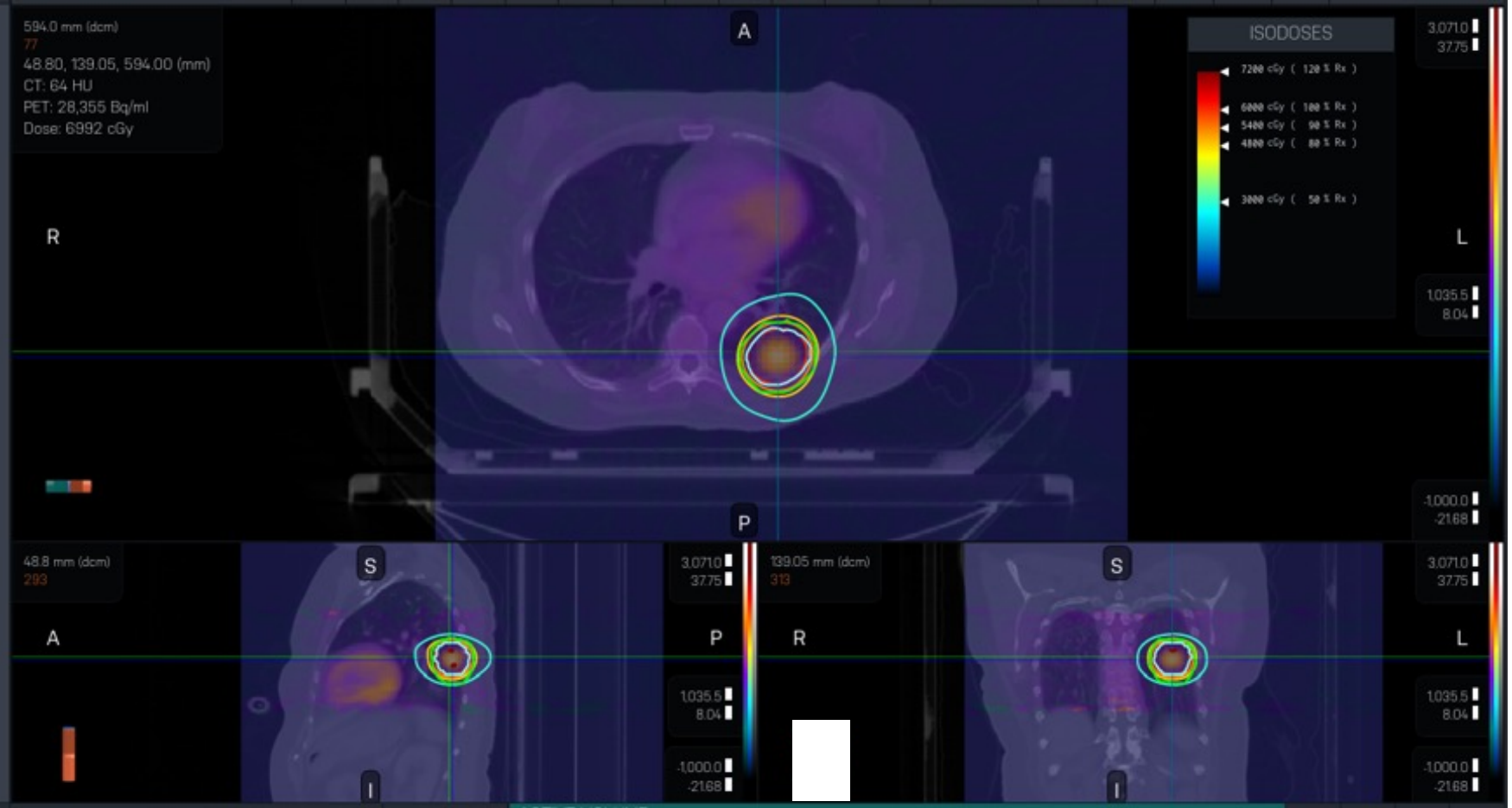
PET LINAC

Simulation CT fused with simulation PET images obtained on PETLinac indicating the target with good FDG uptake

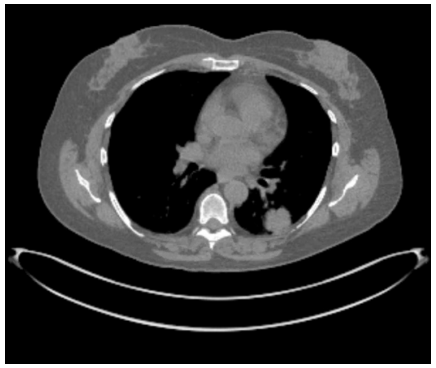


Dose Scope:	PLAN
Dose Purpose:	TREATMENT
Dose Source:	PLANNED
Radiation Absorption Model:	IMAGE
Effective Tissue Composition:	WATER
Algorithm Type:	Convolution
Max Dose:	7,227.0 cGy
Prescription Dose:	6000 cGy
Coverage:	94.2%
CI:	1.0
CI80:	2.3
CI50:	6.0
nCI:	1.1
HI:	1.2

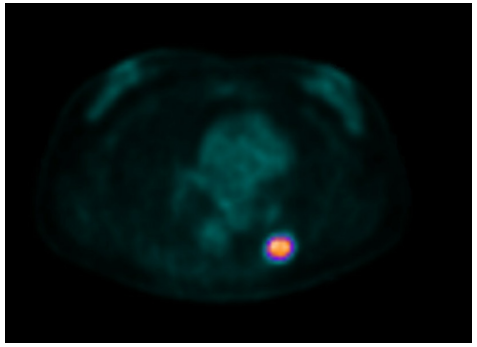
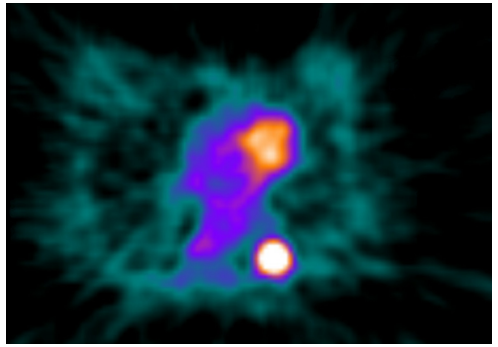
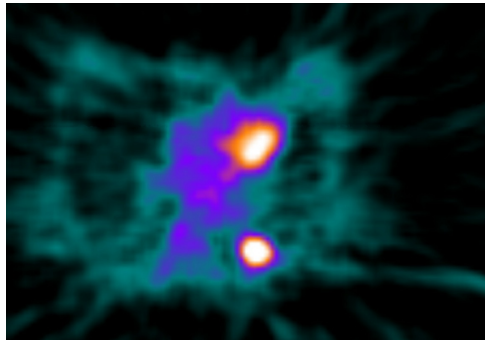
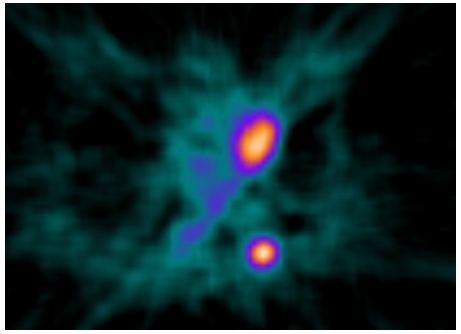
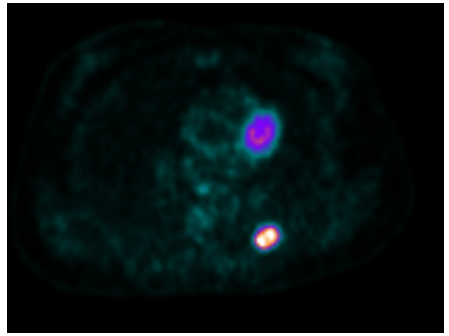
A BgRT plan was generated based on simulation CT and PET images



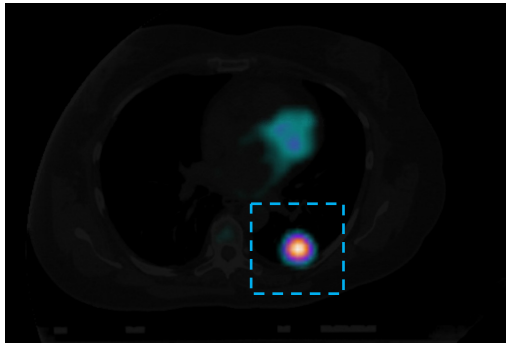
13 CONCEPTUAL VOLUMES	VOL (cc)	DOSE (cGy)		
		MAX	MIN	MEAN
PTV	41.9	7,227.0	5,574.0	6,575.0
SpinalCord	47.4	1,910.0	0.0	251.0
Lungs-ITV	2,569.2	6,962.0	0.0	746.0
Esophagus	27.8	2,002.0	0.0	539.0
Heart	690.9	2,292.0	40.0	723.0
Ribs	31.2	6,591.0	306.0	2,773.0
Skin	2,181.2	3,323.0	0.0	145.0
Trachea	19.2	144.0	0.0	38.0
20mmshell	28.9	3,806.0	707.0	2,262.0
5mmshell	11.8	5,813.0	4,397.0	5,224.0



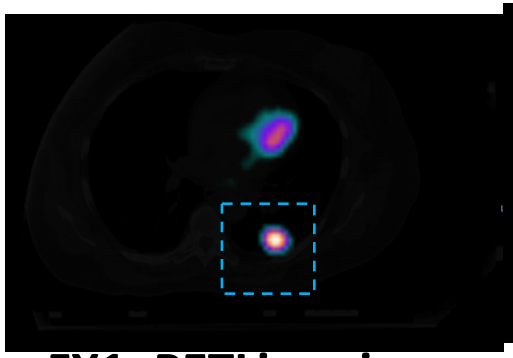


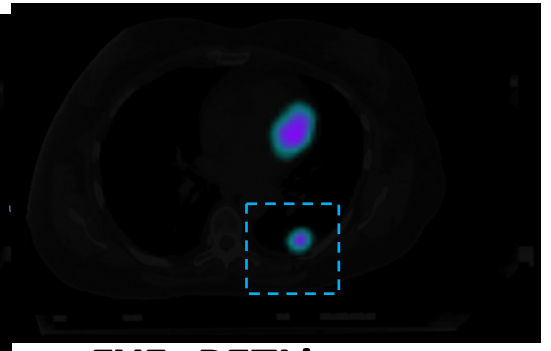
Pretreatment Diagnostic PET/CT



FX0: PETLinac image



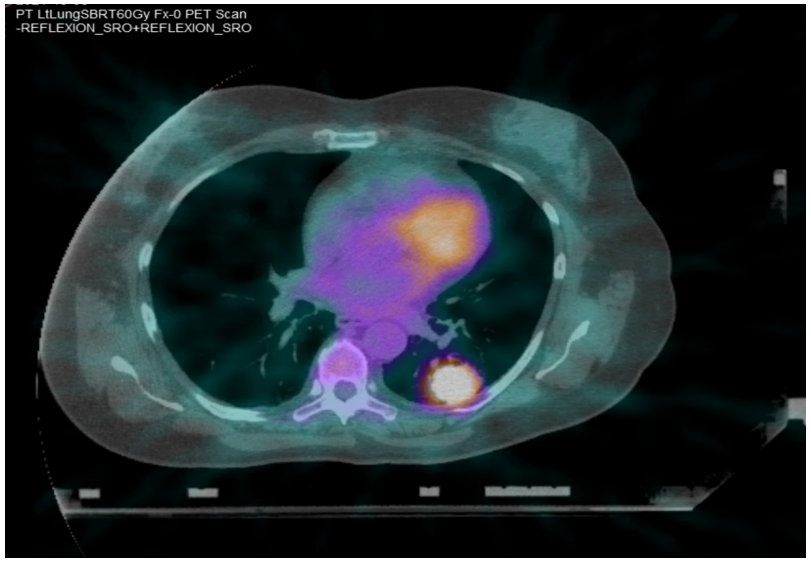
FX1: PETLinac image



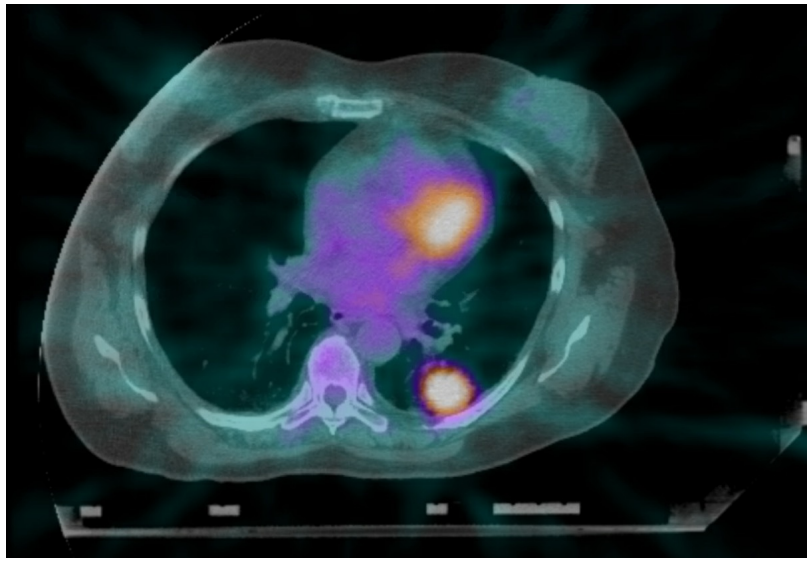
FX5: PETLinac image

Post treatment on FX5 Diagnostic PET/CT

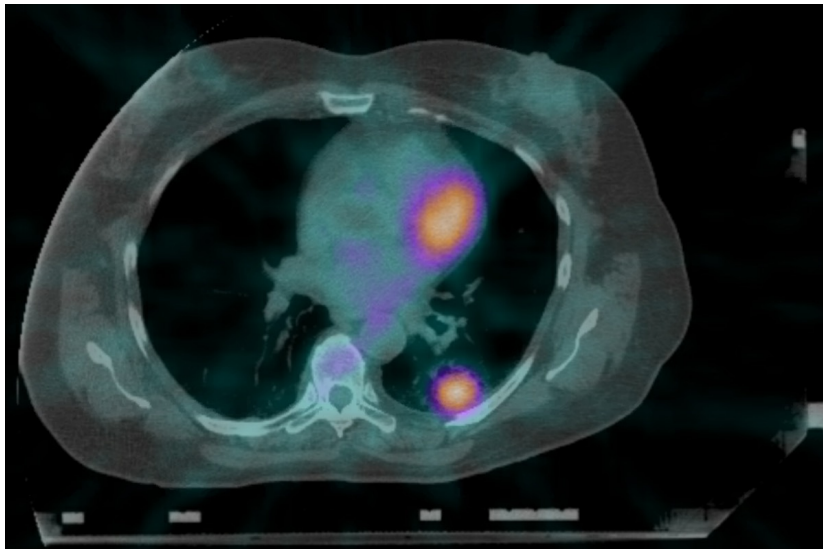
Emulated delivery shows the delivered dose/DVH within bounded DVH as planned



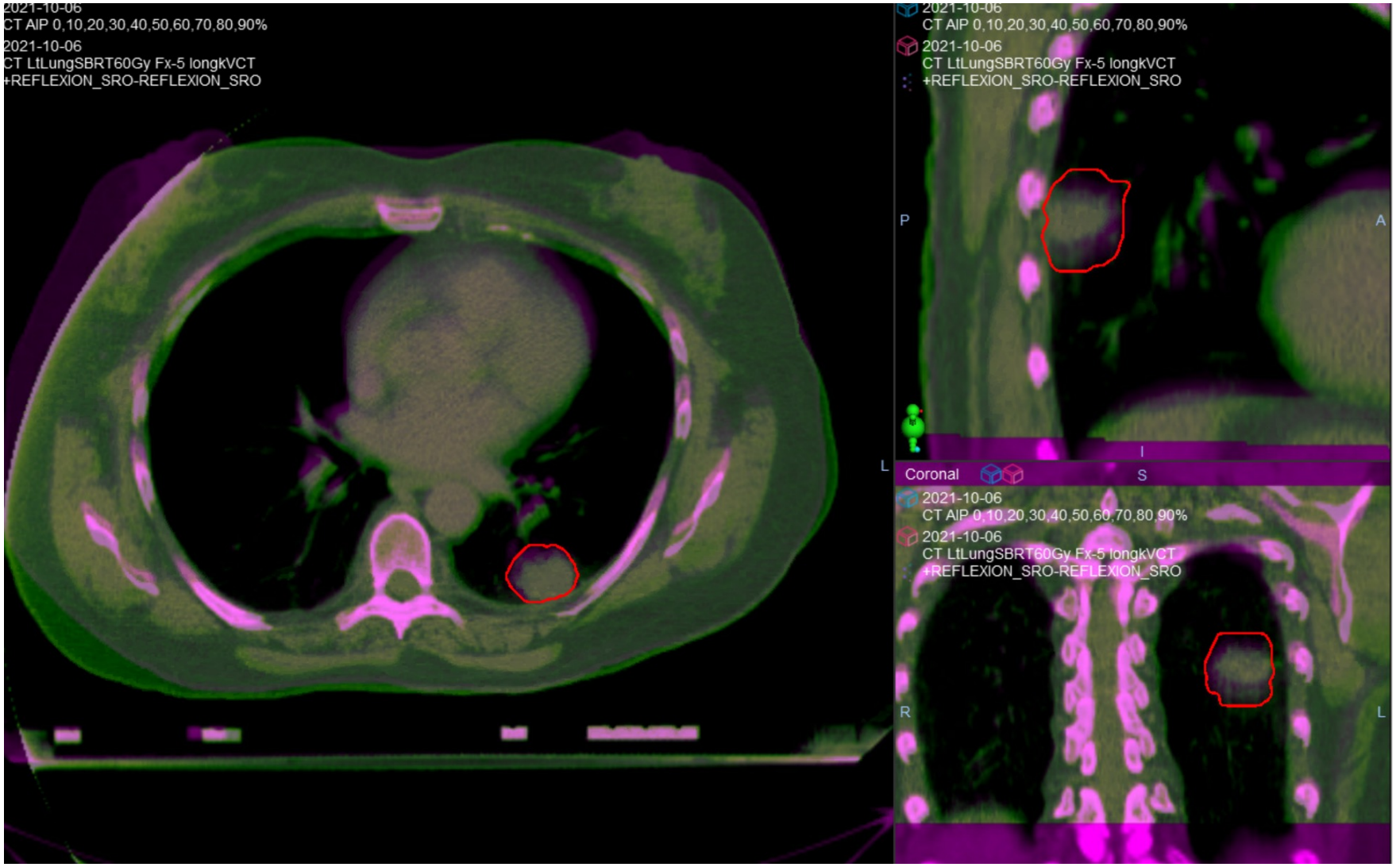
FX0: PETLinac kVCT and PET image



FX1: PETLinac kVCT and PET image



FX5: PETLinac kVCT and PET image



Simulation CT (red) fused with FX5 kVCT (green) on PETLinac: possible tumor shrinkage

JAMA Oncology | Original Investigation

Magnetic Resonance Imaging–Guided vs Computed Tomography–Guided Stereotactic Body Radiotherapy for Prostate Cancer
The MIRAGE Randomized Clinical Trial

Amar U. Kishan, MD; Ting Martin Ma, MD, PhD; James M. Lamb, PhD; Maria Casado, BS; Holly Wilhalme, MSc; Daniel A. Low, PhD; Ke Sheng, PhD; Sahil Sharma, BS; Nicholas G. Nickols, MD, PhD; Jonathan Pham, PhD; Yingli Yang, PhD; Yu Gao, PhD; John Neylon, PhD; Vincent Basehart, BS; Minsong Cao, PhD; Michael L. Steinberg, MD

CONCLUSIONS AND RELEVANCE In this randomized clinical trial, compared with CT-guidance, MRI-guided SBRT significantly reduced both moderate acute physician-scored toxic effects and decrements in patient-reported quality of life. Longer-term follow-up will confirm whether these notable benefits persist.

Table 2. Incidence of Acute Highest-Grade Treatment-Related Toxic Effects 3 Months or Less After SBRT[a]

	Patients, No. (%) (N = 154)								
	CT-guided SBRT (n = 76)				MRI-guided SBRT (n = 78)				
Adverse event	Grade 1	Grade 2	Grade 3	Grade ≥2	Grade 1	Grade 2	Grade 3	Grade ≥2	*P* value[b]
Genitourinary									
Any[c]	34 (44.7)	32 (42.1)	1 (1.3)	33 (43.4)	39 (50.0)	19 (24.4)	0	19 (24.4)	.006
Cystitis	2 (2.6)	2 (2.6)	0	2 (2.6)	0	0	0	0	.12
Hematuria	1 (1.3)	1 (1.3)	0	1 (1.3)	2 (2.6)	1 (1.3)	0	1 (1.3)	.50
Urinary frequency	32 (42.1)	24 (31.6)	0	24 (31.6)	28 (35.9)	12 (15.4)	0	12 (15.4)	.01
Urinary incontinence	9 (11.8)	3 (3.9)	0	3 (3.9)	4 (5.1)	2 (2.6)	0	2 (2.6)	.34
Urinary retention	10 (13.2)	20 (26.3)	1 (1.3)	21 (27.6)	7 (9.0)	9 (11.5)	0	9 (11.5)	.006
Urinary tract infection	0	0	0	0	0	0	0	0	.50
Urinary urgency	20 (26.3)	9 (11.8)	0	9 (11.8)	19 (24.4)	5 (6.4)	0	5 (6.4)	.14
Dysuria	9 (11.8)	5 (6.6)	0	5 (6.6)	1 (1.3)	5 (6.4)	0	5 (6.4)	.50
Gastrointestinal									
Any[c]	34 (44.7)	8 (10.5)	0	8 (10.5)	23 (29.5)	0	0	0	.001
Colitis	1 (1.3)	2 (2.6)	0	2 (2.6)	0	0	0	0	.12
Constipation	3 (3.9)	0	0	0	3 (3.8)	0	0	0	.50
Diarrhea	22 (28.9)	5 (6.6)	0	5 (6.4)	15 (19.2)	0	0	0	.01
Nausea	0	0	0	0	0	0	0	0	.50
Proctitis	15 (19.7)	5 (6.6)	0	5 (6.4)	9 (11.5)	0	0	0	.01
GI hemorrhage	4 (5.3)	3 (3.9)	0	3 (3.8)	1 (1.3)	0	0	0	.06
Rectal pain	2 (2.6)	2 (2.6)	0	2 (2.6)	1 (1.3)	0	0	0	.12
Sexual									
Any[c]	2 (2.6)	0	0	0	0	0	0	0	.50
Erectile dysfunction	2 (2.6)	0	0	0	0	0	0	0	.50

The Intersection of Adaptive Radiotherapy and Big Data Initiatives

ALL CANCER THERAPIES GENERATE ENORMOUS DATA

CAN WE LEVERAGE DATA TO OPTIMIZE PATIENT THERAPY TO GET BEST RESULTS USING AI

BASIC PRINCIPLES OF OUR FEATURE ACQUISTION PROGRAM

Types and Sources of Data

1. **FUNDAMENTAL** – Clinical data reflexively collected for any patient as part of functioning clinic:

   a. Traditional Oncologic – primary cancer, stage, basic treatment information, SOC molecular and traditional pathology, survival outcomes, toxicity, imaging, EBUS findings, any type of scope, PFTs, any ancillary evaluation, labs, patient demographics, etc.

      SOURCE: UTSW and Parkland Tumor registries, EMR.

   b. Radiation-specific – primary cancer or met, dose, fractionation, volumes, DVH, toxicity, adaptive vs not, PULSAR vs not, etc.

      SOURCE: Equivalent treatment planning systems, data (including imaging) from machines, simulation relevant data, adaptive registry, etc.

Types and Sources of Data continued

2. **ACQUIRED** – Collected as part of UTSW Rad Onc Database longitudinal efforts to collect relevant samples/data before, during, and after a given radiation and/or other therapy:

   a. Biologic – blood collected and processed for serum and cells for proteins/cytokines, immune cells, macromolecules (lipids, amino acids, metabolites), circulating tumor cells, circulating tumor DNA, etc.

   Tissue – Tumor and normal – from clinical bx, research bx, circulating cells, skin, from bronch or other scope Stool (microbiome, bacteria, cells, etc.), Urine, CSF.

   Types of data – transcriptomics, genomics, proteomics, metabolomics, -omics.

   b. Physics-related – additional research imaging (MRI, PET or other functional imaging, CT-based, U/S, etc.), additional sources of data for AI-based efforts, extra data collected during the course of radiation therapy that would not normally be collected as part of treatment planning and/or treatment delivery.

   c. Alternative – Activity sensors, QoL measures, Patient satisfaction measures, times through clinic as determined by RTLS.

Common Features Across DOTs - FUNDAMENTAL

General

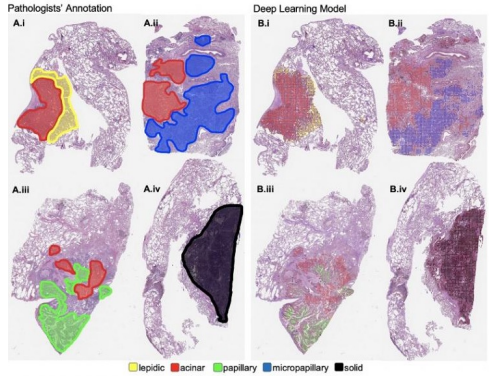
MRN
Other MRN
External MRN
Date of birth
Sex
Diagnosis code
Diagnosis date
Primary site
Laterality
Histology Type
Grade
Lymph-vascular Invasion
Regional Nodes Examined
Regional Nodes Positive
TNM Clinical T
TNM Clinical N
TNM Clinical M
TNM Clinical Stage Group
TNM Pathology T
TNM Pathology N
TNM Pathology M
TNM Pathology Stage Group
CS Mets at DX
CS Mets at DX-Brain, Bone
CS Mets at DX-Liver
CS Mets at DX-Lung, Other Sites
Surgery Site
Surgery Date
Surgical Margin
Chemo/IO/Targeted Therapy Date
RX Summary-Chemo
Hormone Date
RX Summary-Hormone
Lab Test Date
Lab Test Summary
Date of Last Contact
Vital Status
Diagnostic Imaging
Diagnostic Imaging Date
Diagnostic Imaging Accession #
Diagnostic Imaging Process Name
Diagnostic Imaging Summary
Pathology Report Date
Pathology Report Summary
Depth of Tumor invasion
Surgery Type
Biopsy type
Country of origin for patient
Language spoken
Family income
HEI (Healthy Eating Index)
Symptom onset date
Symptom history
Family history of X cancer
Body mass index (current, prior)
Physical activity (current, prior)
Smoking history
Race/Ethnicity
Age
Diabetes Status (HgbA1c)
Insurance Status
Employment Status
TOXICITY Metrics

Common Features Across DOTs - FUNDAMENTAL

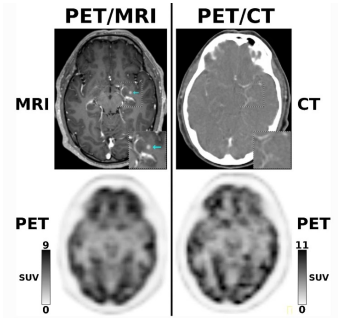
General

SOC CBC
SOC CHEM7/10
SOC LFTs
SOC Renal function tests
SOC Lab tests

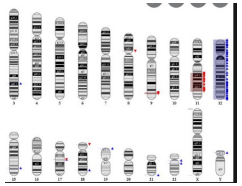
Pathology



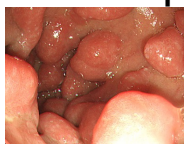
SOC Staging
Pre-tx PET/CT of various tracers
- CT of different anatomy
- MRI brain, chest, pelvis, abdomen, liver, etc.
- U/S of different anatomy
- Any other functional imaging

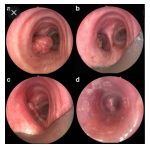


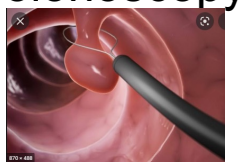
SOC Molecular Testing on Tumor



SOC PFTs, Endoscopy, Bronchoscopy, EGD, EUS, Colonoscopy, etc.



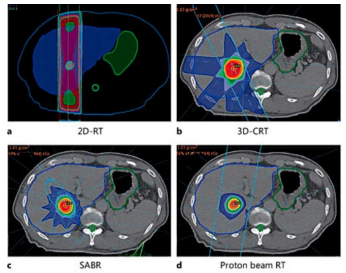


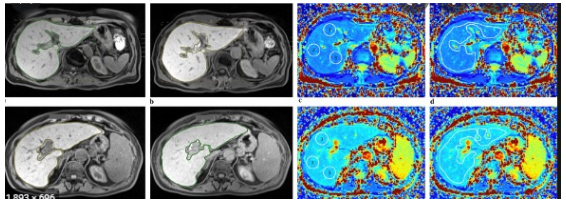


Common Features Across DOTs - FUNDAMENTAL

Radiation/Treatment-Related

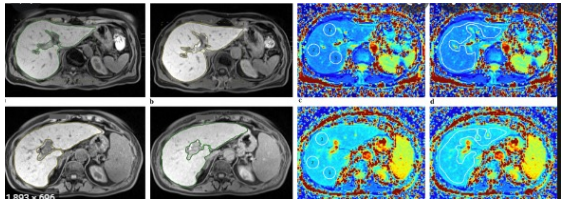
Number of Courses
Physician
Planned Dose (cGy)
Planned Fractions
Actual Dose (cGy)
Actual Fractions
RT Plan
RT Structure
Planning CT
DVH (Dose Volume Histogram)
DRR
Modality
Energy
Clinical Trial
PI of Clinical Trial
Summary of clinical trial
Techniques
Treatment site
Treatment Intent
Sequence? SIB/BST
Treatment Start Date
Treatment End data
Elapse Days
Treatment Date
Dose delivered at each treatment fraction (cGy)
Setup Imaging – kV or MV
Setup Imaging – CBCT
Shift Delta X (mm)
Shift Delta Y (mm)
Shift Delta Z (mm)
Bladder filling (prostate)
QA
QA Date
QA-Description
QA-Summary
OTV Date
OTV Vitals
OTV Toxicity
Plan Revision
RT Plan-Revised
RT Dose-Revised
RT Structure-Revised
Replanning CT
Objectives
CBCTs during treatment





Common Features Across DOTs - ACQUIRED

Imaging



Longitudinal – before, during, after different treatments

PET/CT with F18, PSMA, DOTATATE, FES, Fatty acids, novel tracers

Novel MRI protocols and approaches - DCE/CEST, T1, T1, DWI, with O2 enhancement, ASL

CT-based imaging

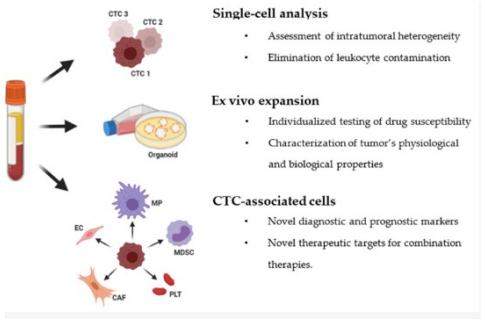
Spectroscopy – 13C NMR Spectral Analysis, 2HG NMR Spectral Analysis, 13C Pyruvate

Dopamine Scan

Optoacoustics

Common Features Across DOTs - ACQUIRED

Blood

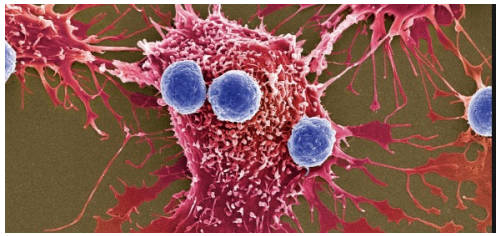


Longitudinal – before, during, after different treatments

- CTCs
- ctDNA
- PBMCs
- Multiplex cytokines
- Metabolic panels – lipids, amino acids, macromolecules, trigs, exosomes
- Proteomics Signatures
- PD-L1
- Circulating RNAs
- T cells, immune cell repertoire, MDSCs
- ESR1, MYB, WISP3, PRDM1, Leptin, LDH, CRP, Uric Acid

Common Features Across DOTs - ACQUIRED

Tumor



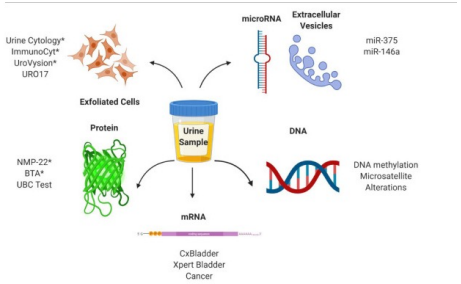
Longitudinal – before, during, after different treatments
- p53 status (mutation status – WT, disruptive, non-disruptive)
- p53 status (EA score)
- Digital pathology
- Tumor microbiome
- RNAseq, scRNAseq, ATTACseq, all seqs
- Tumor immune cell repertoire
- Metabolomics
- Multiplex IHC
- Mutation analysis
- Whole exome sequencing
- Whole transcriptome sequencing
- TILs
- Immuneseq

Common Features Across DOTs - ACQUIRED

Urine

Longitudinal – before, during, after different treatments

Nothing common. Only requested by GU. Maybe relevant to GI and GYN as well?

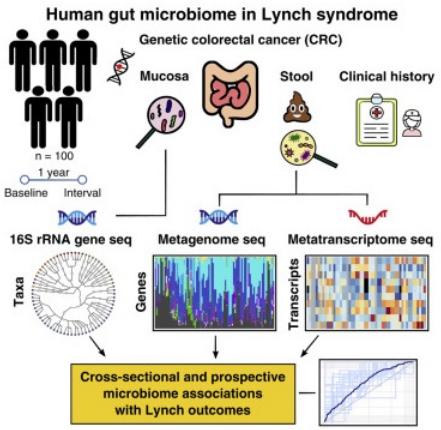


Common Features Across DOTs - ACQUIRED

Stools

Longitudinal – before, during, after different treatments

Nothing common. Only requested by GI and Breast. Maybe relevant to GU and GYN as well?

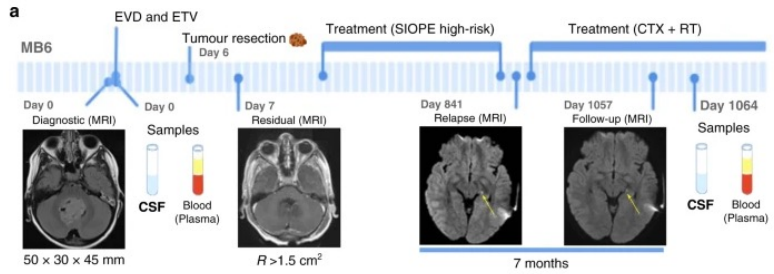


Common Features Across DOTs - ACQUIRED

CSF

Longitudinal – before, during, after different treatments

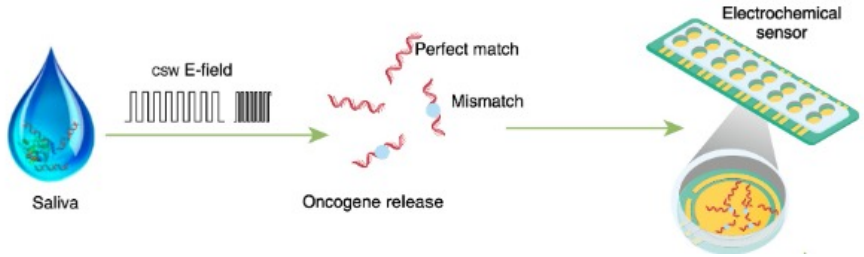
Fig. 4: CSF ctDNA characterises the primary tumour and identifies minimal residual disease in patients that respond to treatment.



Nothing common. Only requested by CNS. May be relevant to Thoracic and H&N?

Common Features Across DOTs - ACQUIRED

SALIVA AND ANY OTHER BODY FLUIDS



Longitudinal – before, during, after different treatments

Nothing common. Only requested by H&N. May be relevant to Thoracic and CNS?

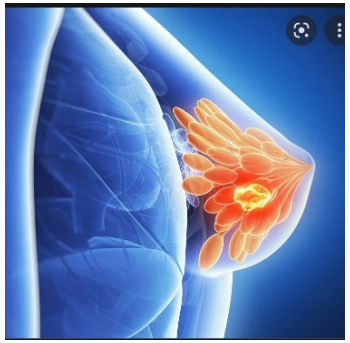
CNS Features – FUNDAMENTAL & ACQUIRED

Functional MRI- DCE/CEST	Imaging	Prior to/during/after treatment
DOTATATE PET	Imaging	q2 week PET + MRI(DCE)
13C NMR spectral analysis	Imaging	Pre-treatment and surveillance
2HG NMR spectral analysis	Imaging	Pre-treatment and surveillance
Dopamine Scan	Imaging	Baseline and following treatment
Next generation sequencing	Tumor	At time of surgery
PD-L1 (circulating)	Plasma	Baseline and following treatment
CTC	Blood	Baseline and following treatment
ctDNA	Blood	Baseline and following treatment
CSF	CSF	Baseline and following treatment
Carbonic Anhydrase	Plasma	Baseline and following treatment
Endocrine	Blood	Baseline and following treatment
Neurocognitive testing	Hopkins Verbal Learning	Baseline and following treatment
Fatigue	Qol	Baseline/during/following treatment
Vision	Visual fields	Baseline and following treatment
Hearing	Audiogram	Baseline and following treatment

H&N Features - FUNDAMENTAL & ACQUIRED

Pre-treatment PET-CT	Imaging	Pre-treatment
Pre-treatment simulation CT	Imaging	Pre-treatment
Weekly CBCT	Imaging	On-treatment
Post-treatment PET-CT	Imaging	Post-treatment
p53 status (WT, disr, non-disr)	Tissue pathology	Pre-treatment
p53 status (EA score)	Tissue pathology	Pre-treatment
ctHPVDNA	Blood	Pre, On, Post-treatment
ctnonHPVDNA	Blood	Pre, On, Post-treatment
Pre-treatment MRI - sequence TBD	MRI	Pre-treatment
On-treatment MRI - sequence TBD	MRI	On-treatment (week 3)
UWO3 score	Tissue pathology	Pre-treatment
Circulating tumor cell capture	Blood	Pre, On, Post-treatment
Salivary HPV quantification	Saliva	Pre, On, Post-treatment
Oral microbiome	Saliva	Pre-treatment
Digital pathology	Tumor biopsy or excision	Pre-treatment

BREAST Features – FUNDAMENTAL & ACQUIRED



DVH metrics	TPS/Scriptable	Upon plan approval
DVH metrics for ART	TPS/manual	Every ART
DICOM files ART	Imaging/manual	Upon plan approval
DICOM files non ART	Imaging/scriptable	Every ART
Dose accumulation	Log files/CBCT	End of treatment?
MRI for response assessment	Imaging	Pre, During, Post RT
Motion montoring/4D	MR	
RTLS(?)	Patient's mobility & vital	Before, During, Post RT
MRI (DCE)	Imaging MRI	Pre-RT, Pre-surgery, Post RT
MRI (OE)	Imaging MRI	Pre-RT, Pre-surgery, Post RT
MRI (ASL)	Imaging MRI	Pre-RT, Pre-surgery, Post RT
MRI Delta T1/T2	Imaging MRI	Pre-RT, Pre-surgery, Post RT
MR Spect 13C- pyruvate	Imaging MRI	Pre-RT, Pre-surgery, Post RT
MRI T1 and T2 Relaxation	Imaging MRI	Pre-RT, Pre-surgery, Post RT

BREAST Features – FUNDAMENTAL and ACQUIRED

Circulating RNAS	Blood	Prior to Radiation/ 1 month post radiation
ctDNA and RNA	Blood	Prior to Radiation and during all follow-up visits
CTCs	Blood	Prior to Radiation/ 1 month post radiation
CD4:CD8	Blood	Prior to Radiation/ 1 month post radiation
ESR1	Blood	Prior to Radiation and during all follow-up visits
MYB	Blood	Prior to Radiation and during all follow-up visits
WISP3	Blood	Prior to Radiation and during all follow-up visits
PRDM1	Blood	Prior to Radiation and during all follow-up visits
Gut microbiome	Stool	Prior to radiation and 1 month post-radiation
Tumor biopsy	Tumor	Prior to radiation and 2 weeks after radiation
Residual disease s/p Neoadj	Tumor	Once, at the time of surgery
EKG	Patient	Before radiation and at each follow-up
Echo	Patient	Before radiation and at each follow-up
Oncogenotyping	Tissue	Once, at the time of surgery or biopsy
Tumor microbiome	Tumor	Baseline preo patients, post RT
HIF 1 alpha	Tumor	Pre-treatment biopsy pre-op pts and post op
BRD4	Tumor	Pre-treatment biopsy pre-op pts and post op
CMP	Blood	Baseline
HGBa1c	Blood	Baseline
Fasting Glucose	blood	Baseline
Leptin	blood	Baseline

BREAST Features – FUNDAMENTAL AND ACQUIRED

Endotrophin	Blood	Baseline
BMI	Patient history	Baseline
Fasting Insulin	Blood	Baseline
Plasma IgF1	Blood	Baseline
Parity	Patient History	Baseline
Insurance status	Mosaic/EPIC	Baseline
Family Income	Patient history	Baseline
Employment Status	Patient history	Baseline
Race/Ethnicity	Patient history	Baseline
Age	Patient history	Baseline
Optoacoustics	Imaging US	Prior to surgery and/or radiation
FES-PET	Imaging	Pre-op radiation patients
Can pt speak English	Patient history	Baseline
Cytokine/chemokine	Plasma	All patients
Autoantigen array	Plasma	All patients
Serum metabolic panels	Plasma	All patients
cytometry by time of flight (CyTOF)	PBMC	Pre-op radiation patients
Proteomics signature	Serum	Pre-op radiation patients
Metabolomics	Fresh frozen tumor	Pre-op radiation patients
Cardiac substructure	Dosimetry	Radiation plan

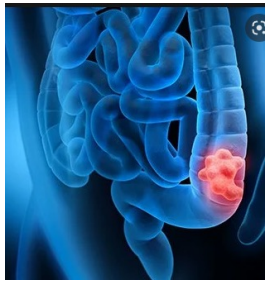
THORACIC Features – FUNDAMENTAL & ACQUIRED

Cytokine/chemokine	Plasma	Before, during and after RT
Autoantigen array	Plasma	Before, during and after RT
Serum metabolic panels	Plasma	Before, during and after RT
CyTOF	PBMC	Before, during and after RT
Proteomics	Serum	After pulsar treatments
Metabolomics	Fresh frozen tumor	Diagnosis and Recurrence/metastasis
RNA seq	Fresh frozen tumor	Diagnosis and Recurrence/metastasis
Multiplex IHC	Paraffin embedded tumor	Diagnosis and Recurrence/metastasis
Microbiome	Saliva and stool	Diagnosis and Recurrence/metastasis, RT
PET/CT	Imaging	Baseline and Longitudinally
LAD dosimetry	Radiation plan	Baseline and Longitudinally
All Lab values	Blood	Baseline and Longitudinally
Date of diagnosis	EMR	Baseline
Age and gender	EMR	Baseline
Histology	EMR	Baseline
TNM staging	EMR	Baseline

THORACIC Features – FUNDAMENTAL & ACQUIRED

Performance status	EMR	Longitudinal
Smoking history	EMR	Longitudinal
Major comorbidities	EMR	Longitudinal
FEV1 (absolute)	PFTs	Longitudinal
FEV1 (predicted)	PFTs	Longitudinal
DCLO	PFTs	Longitudinal
Targetable mutations (positive and negative)	Tumor	Longitudinal
IO tumor marker status	Tumor	Longitudinal
First line chemotherapy	EMR	At Tx
Second line chemotherapy	EMR	At Tx
Date of death	EMR	x 1
QOL	Surveys	Longitudinal
ART volumes and dosimetry	RT Records	Longitudinal

GI Features – FUNDAMENTAL & ACQUIRED

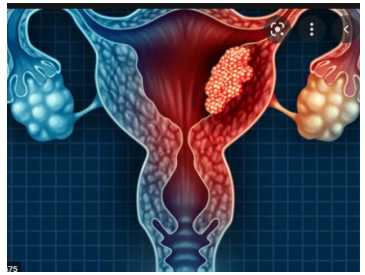


cfDNA	Plasma/blood	3 X per treatment course and on follow up
Gut microbiome	Stool	Baseline, mid treatment, post RT
Tumor microbiome	Tumor	Baseline, post RT (can be at surgery)
Tumor tissue	Biopsy and surgical specimen	Whenever samples are obtained
Circulating tumor cells	Blood draw/buffy coat	3 X per treatment course, and on follow up
Tumor scRNAseq	Sx specimen/Pre-tx bx	2 max
PBMCs from blood	Blood	NA cases x3 pre, short post, and then NA completed
Plasma/Serum	Blood	NA cases x3 pre, short post, and then NA completed
CA 19-9/CEA	Blood	2-10x
PET SUV primary/mets	Imaging	Longitudinal
MRI Scans	Imaging	x2 Pretreatment, post treatment
MRI Unity Scans	Unity	During each fraction
CT scans	Radiology	2-5x
PHYSICS/DOSI		
Tumor volume	Planning system	Baseline, post RT

GI Features – FUNDAMENTAL & ACQUIRED

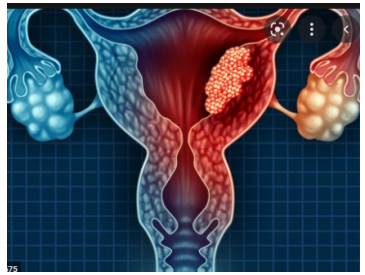
CLINICAL		
Country of origin	EMR	Baseline
Language spoken	EMR	Baseline
Family income	EMR	Baseline
HEI (Healthy Eating Index)	EMR	Baseline - https://www.fns.usda.gov/healthy-eating-index-hei
LARS score	EMR	Baseline - https://www.escp.eu.com/news/focus-on/beyond-colorectal-cancer/1579-lars-score
Symptom onset date	EMR	Baseline
Symptom history	EMR	Baseline
Family CA history	EMR	Baseline
Body mass index	EMR	Baseline, each follow-up
Physical activity	EMR	Baseline
Antibiotic use	EMR	Baseline
Smoking history	EMR	Baseline
Alcohol history	EMR	Baseline
Diabetes Status	EMR	Initial, end of treatment, fu

GYN Features – FUNDAMENTAL & ACQUIRED



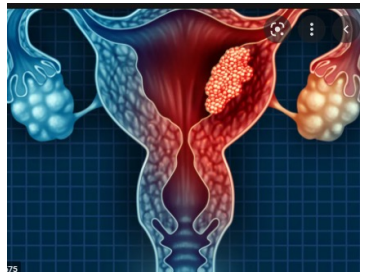
Biomarkers - treatment resistance	Tumor/Blood	Before EBRT, during week 4/before 1st BT, after 2nd BT
Vagina microbiome	Vaginal swabs	Before EBRT, during week 4/before 1st BT, after 2nd BT
Tumor microbiome	Tumor	Before EBRT, during week 4/before 1st BT, after 2nd BT
Tumor tissue	Bx/Tumor	Before EBRT, during week 4/before 1st BT, after 2nd BT
CTCs	Blood	Before EBRT, during week 4/before 1st BT, after 2nd BT
Plasma/Serum	Blood	Before EBRT, during week 4/before 1st BT, after 2nd BT
MRI imaging		
DWI	MR images	treatment planning, once during treatment, post treatment
IVIM	MR images	treatment planning, once during treatment, post treatment
Volumetrics	MR images	treatment planning, once during treatment, post treatment
DCE	MR images	treatment planning, once during treatment, post treatment
T1,T2	MR images	treatment planning, once during treatment, post treatment
QOL assessment	QoL	Tx start, before BT, 3month, 1yr
Pre-treatment PET-CT	Imaging	Pre-treatment
Pre-treatment simulation CT	Imaging	Pre-treatment
Weekly CBCT	Imaging	On-treatment

GYN Features – FUNDAMENTAL & ACQUIRED



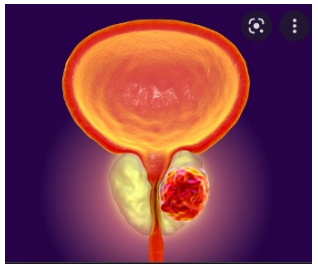
Microbiome	Stools	Before EBRT, during week 4/before 1st BT, after 2nd BT
ctHPVDNA	Blood	Pre, On, Post-treatment
ctnonHPVDNA	Blood	Pre, On, Post-treatment
Physics Metrics	DVH metrics	Eclipse TPS/Scriptable
	DVH metrics for ART	Ethos TPS/manual
	DICOM files ART	Imaging/Ethos/manual
	DICOM files non ART	Imaging/Eclipse/scriptable
	Dose accumulation (Delivered dose) - log files + CBCT + deformable registration	
Country of origin	EMR	Baseline
Language spoken	EMR	Baseline
Family income	EMR	Baseline
HEI (Healthy Eating Index)	EMR	Baseline - https://www.fns.usda.gov/healthy-eating-index-hei
Symptom onset date	EMR	Baseline
Symptom history	EMR	Baseline
Family history of X cancer	EMR	Baseline
BMI	EMR	Baseline, each follow-up
Physical activity	EMR	Baseline
Smoking history	EMR	Baseline

GYN Features – FUNDAMENTAL & ACQUIRED



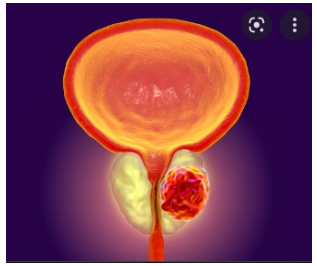
Diabetes Status	EMR	Initial, end of treatment, fu
Cardiovascular disease	EMR	Initial, end of treatment, fu
Clinical details/follow-up		Ongoing data base
POST OP		
QOL		
BRACHYTHERAPY		
CTV volumes	DICOM RT structure	Every treatment fraction
OAR contours	DICOM RT structure	Every treatment fraction
DVH metrics	DICOM RT plan file	Every treatment fraction
CT images	DICOM RT CT files	Every treatment fraction
MR images	DICOM RT CT files	Every treatment fraction

GU Features – FUNDAMENTAL & ACQUIRED



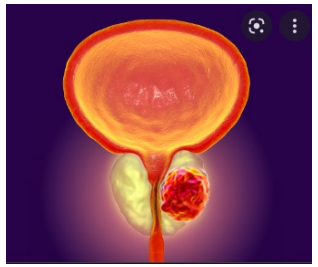
PSA Total	Blood	Baseline and Q6M
PSA Free	Blood	Baseline and Q6M
Testosterone	Blood	Baseline and Q6M
LDH	Blood	Baseline and Q6M
CRP	Blood	Baseline and Q6M
Uric Acid	Blood	Baseline and Q6M
CBC with diff	Blood	Baseline and Q6M
MDSC	Blood	Baseline and Q6M
PD-L1 (circulating)	Plasma	Baseline and Q6M
CTC	Blood	Baseline and Q6M
ctDNA	Blood	Baseline and Q6M
Genomics	Tumor tissue	Baseline
PORTOS	Tumor tissue	Baseline
Oncogenotypes	Tumor tissue	Baseline
-omics	Tumor tissue	Baseline
Whole exome sequencing	Tumor tissue	Baseline
Whole transcriptome sequencing	Tumor tissue	Baseline
Tumor infiltrating lymphocyte	Tumor tissue	Baseline
scRNA and immune seq	Tumor tissue	Baseline
Side effect/toxicity	EMR/Patient	Baseline and Q6M
Overall Survival	EMR/Patient	Baseline and Q6M

GU Features – FUNDAMENTAL & ACQUIRED



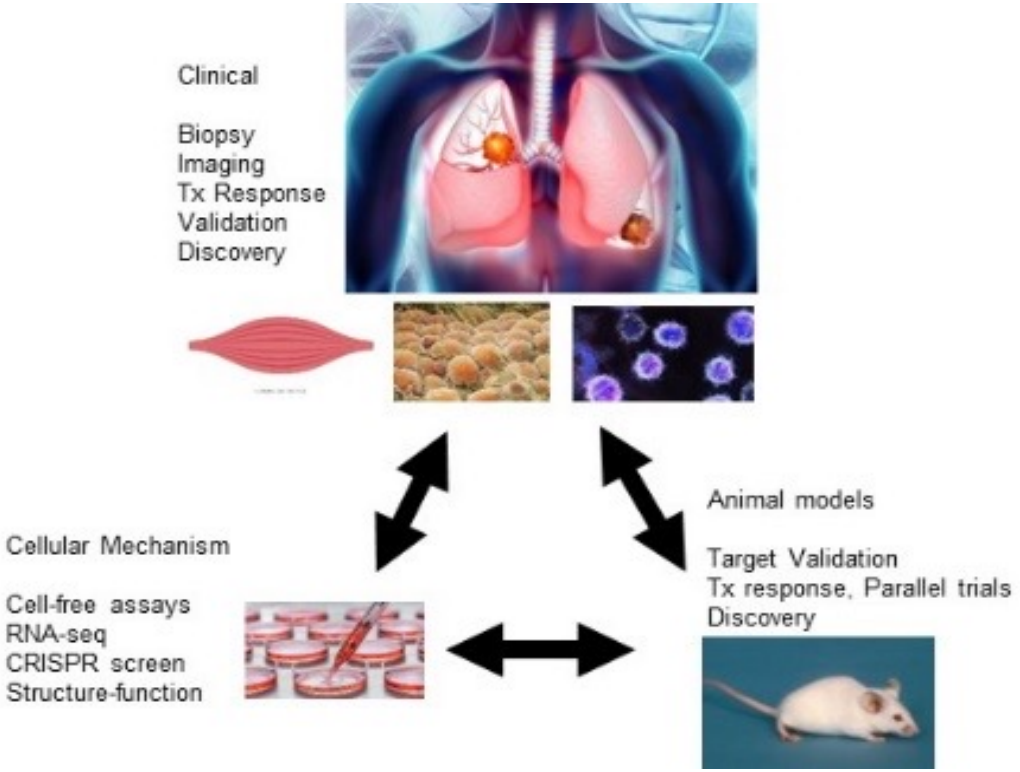
Patient Reported Outcome		
EPCI-26	Patient	Baseline and Q6M
EQ-5D	Patient	Baseline and Q6M
FKSI	Patient	Baseline and Q6M
Expense		
Insurance expense	Health insurance	Treatment and follow up
patient's out-of pocket expense	Health insurance	Treatment and follow up
Radiology/Imaging		
PSMA scan	Imaging	Baseline and Q6M
CT	Imaging	Baseline and Q6M
MRI	Imaging	Baseline and Q6M
Dosimetric data:		
Treatments	Treatment planning system	
DVH	Treatment planning system	
DICOM.RT	Treatment planning system	
Reconstructed delivered dose	need in-house development	
Imaging:		
diagnosis	MRI PACS	
simulation	MRI/CT PACS	
weekly CBCT	Planning System	
in-treatment MRI		
Treatment Response	MRI	
Pathology Slides	Tissue pathology	

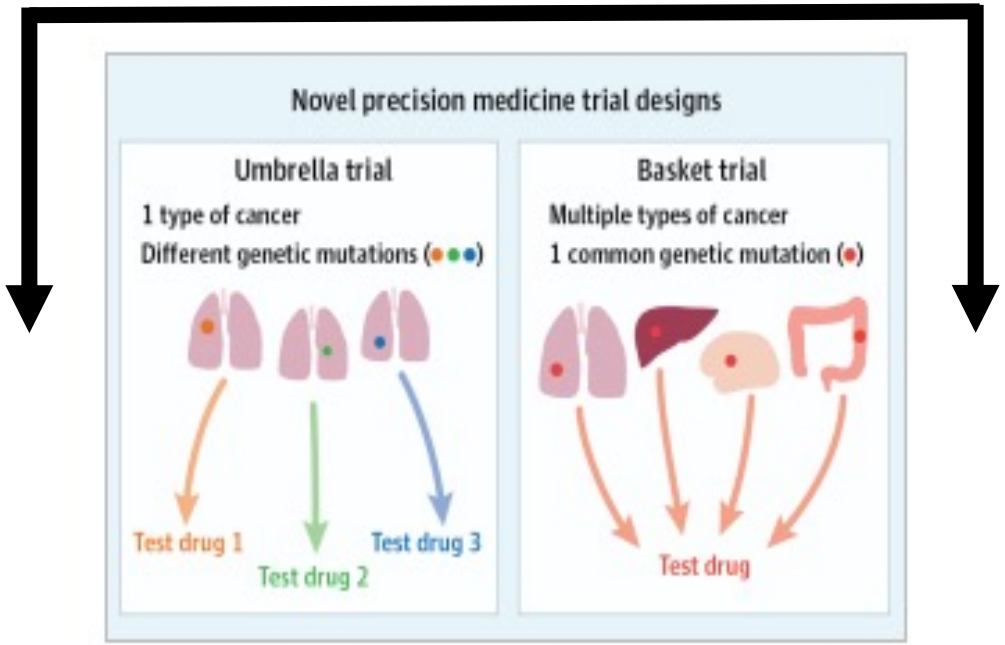
GU Features – FUNDAMENTAL & ACQUIRED



Bladder Tumour Antigen (BTA)	Urine
Aneuploidy of chromosomes 3, 7, and 17 and loss of the p16 gene at the 9p21 locus	Urine
Nuclear Matrix Protein (NMP) 22	Urine
Urine cytology	Urine
FISH test	Urine
IRAK3, Li-MET, and SOX1 (three-marker DNA methylation test)	Urine
Bladder cancer–specific nuclear matrix protein-4 (BLCA-4)	Urine
CxBladder	Urine
CYFRA21-1	Urine
Histone tail modifications (HTF) trimethylation of lysine 27 on histone H3 (H3K27me3)	Urine
HS3ST2, SEPTIN9, and SLIT2/FGFR3	Urine
Hyaluronic acid/Hyaluronidase	Urine
MCM5 protein	Urine
miR-135a, miR-135b, miR-148a, miR-204, miR-34 Has-let-7c	Urine
miRNA-assay: 25-target diagnostic signature	Urine
miRNA-assay: miR-187, miR-18a, miR-25, miR-92a, miR-125b; miR142-3p	Urine
sFas	Urine
Survivin	Urine
Urinary Bladder Cancer (UBC) Rapid Test	Urine
URO17	Urine

How to finish studies with greater insight and urgency?



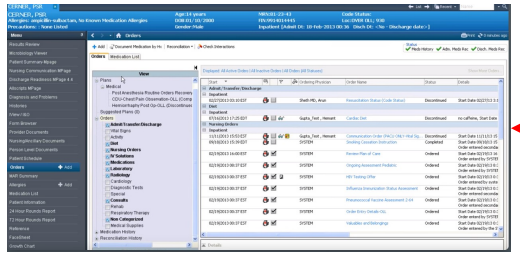


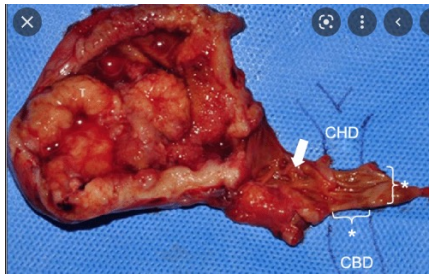
Early-phase, translational-heavy trials
SMART trials

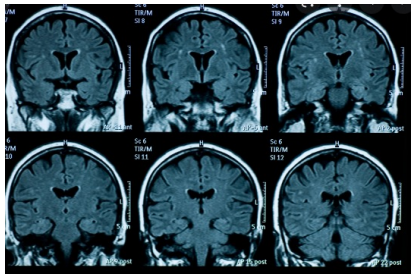
How will the quality of the data be validated?

How will the data be collected (in context), stored (virtual database), collated, and easily retrievable in customized formats?

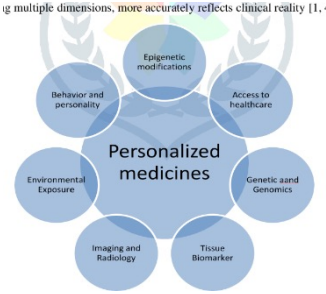
How will the data be interrogated with AI?

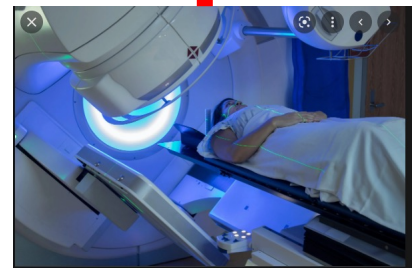


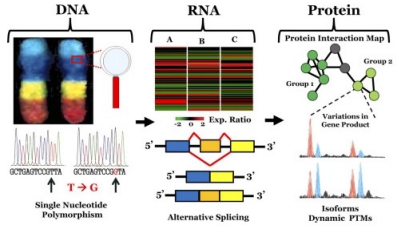




g multiple dimensions, more accurately reflects clinical reality [1,







The Wheel of Personalization