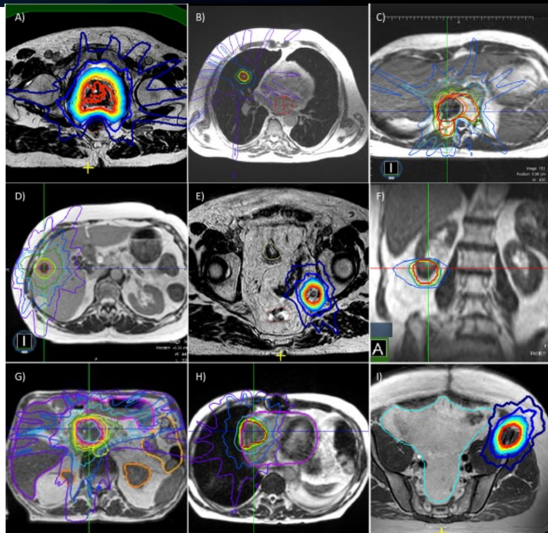
Newer Machines:
A new paradigm for Online Adaptation and Live Tracking

Dr Shikha Goyal
Assistant Professor,
Department of Radiotherapy,
PGIMER, Chandigarh -160012
drshikhagoyal@gmail.com

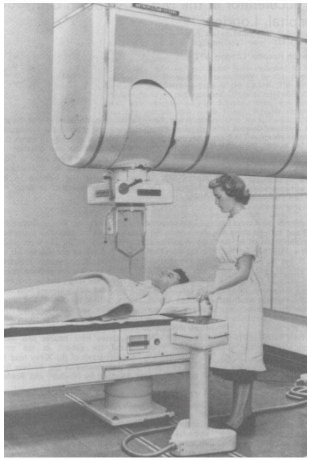


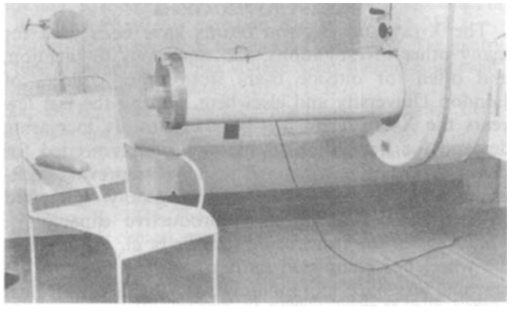
What I shall cover

- Brief history of LINACs and developments
- Image guidance systems (including real time)
- Adaptive Radiotherapy
- MR-LINAC – marriage between
    - Online tracking &
    - Live adaptation

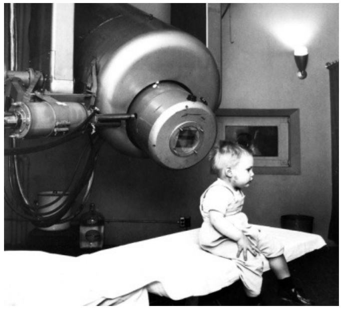
Medical LINAC history dates back 70 years..

- Bill Hanson and Edward Ginzton at Stanford Physics (USA)
  - Developed a 4.5 MeV LINAC in the lab - 1947
  - Called it “Atom smasher”
- DW Fry at Atomic Energy Research Establishment (UK)
  - 8 MeV LINAC
- Both groups developed clinically working LINACs in early 1950s





First treatment at Hammersmith Hospital, London in 1952 (MRC)



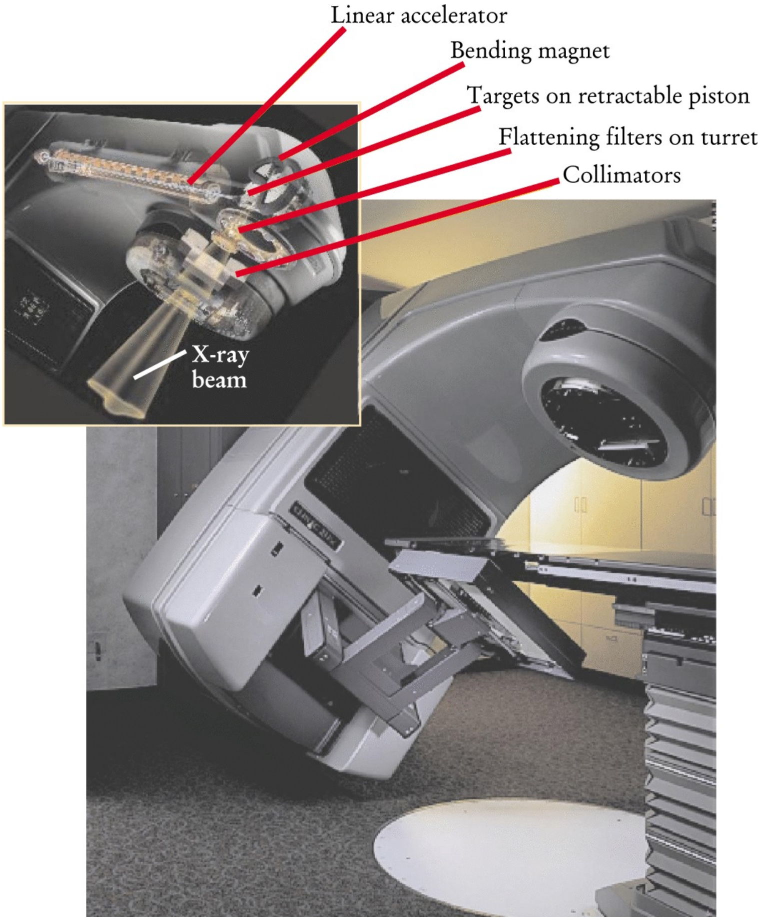
First treatment at Stanford, California in 1956 (Henry Kaplan)

Advances in LINAC Technology

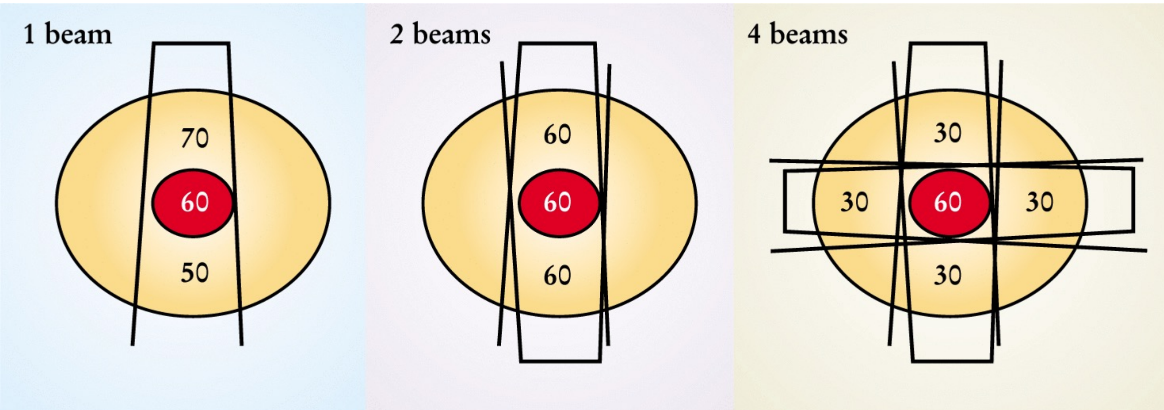
- Treatment planning – 3DCRT, IMRT/VMAT, AI
- Beam constituents (energy type) – photon, electron, particle therapy
- Beam shaping – cones, MLC, micro-MLC
- Treatment delivery and stability
  - Dynamic/static jaws
  - Moving gantry
  - Moving couch
  - Respiratory motion management – DIBH, Gating
- Treatment verification
  - KV, MV, USG, Electromagnetic transponders, Camera-based
- Online adaptive radiotherapy
- MR LINAC
- Under evaluation
  - Mobile LINAC units
  - Biology guided radiotherapy platforms

Modern standard LINAC

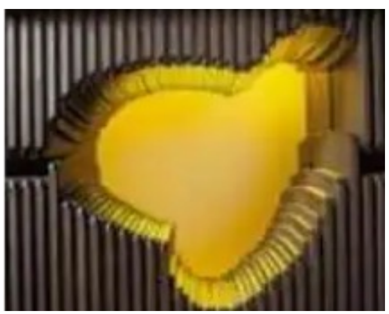
- Electrons (energy 4-25 MeV) accelerated in wave guide
- Strike a suitable target to produce X-rays by bremsstrahlung
- X-ray beam made uniform by a flattening filter
- Beam shaped by jaws and MLC for delivery
- Accelerator, beam transport system, and beam-shaping devices - mounted on a gantry capable of 360° rotation about a horizontal axis
- Patient positioned on a couch mounted on an accordion structure and capable of horizontal movement and some degree of rotation
- Appropriate combination of gantry and couch adjustments can help direct radiation beam at the target along almost any direction
- Image detectors of various types can help in treatment verification

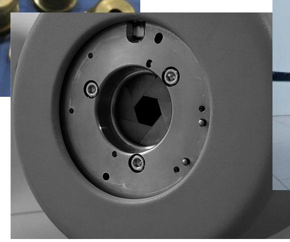


Conformal RT



Multiple beams



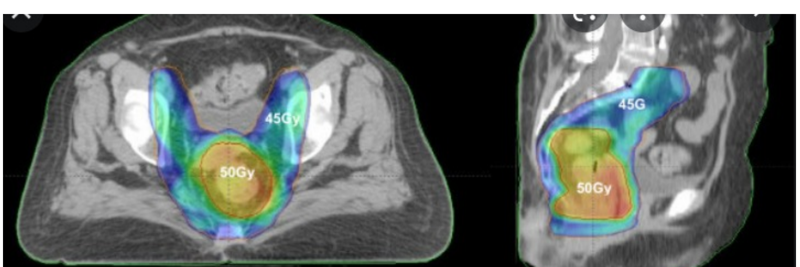


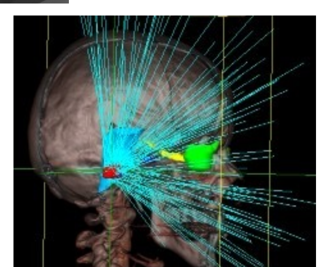
Beam shaping

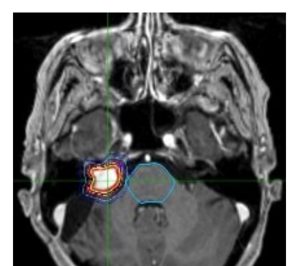
MLC

Leaf width – 1 cm to 1mm

Various designs







Beam modulation

IMRT

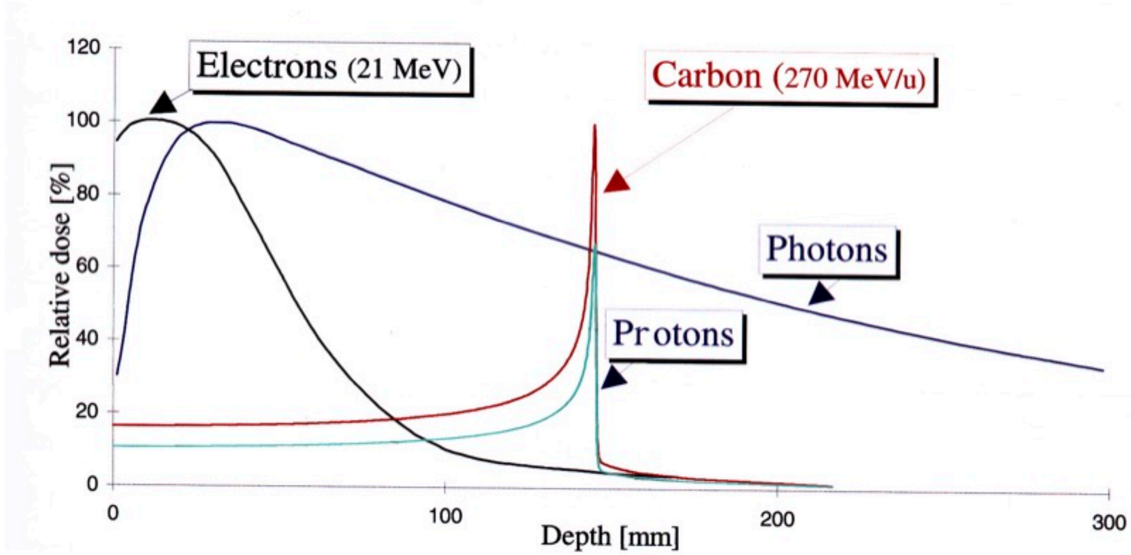
VMAT

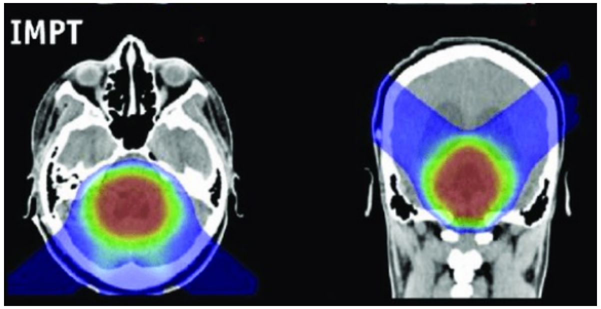
SRS/SBRT

(FFF technology)

Beam Energy and type

- Photons
  - Megavolt range – Higher penetration (4-18 MV)
- Electrons
  - Superficial treatment depending on energy (6-20 MeV)
- Particle therapy
  Protons
  Carbon ion and other heavy ions
- IMPT – modulation + Bragg peak advantage





Treatment verification systems (IGRT)

Non-radiation based

- Ultrasound-based (Clarity)
- Camera-based (SGRT, IR)
- Electromagnetic tracking
- **MRI-based**

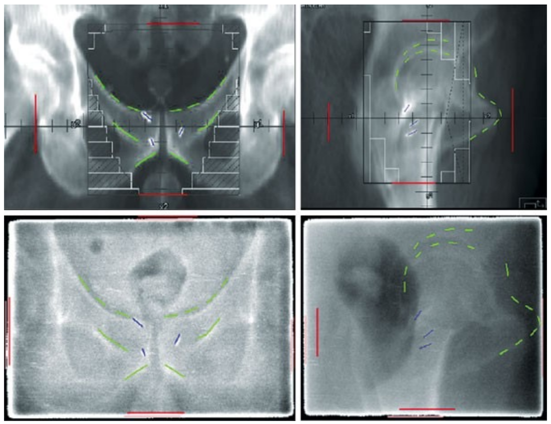
Radiation based

- EPID
- Cone beam CT – KV or MV
- Fan beam CT
  - KV – CT on rails
  - MV - Tomotherapy
- ExtacTrac 6D system
- Hybrid
  - 2D (Cyberknife)
  - RTRT
  - Vero

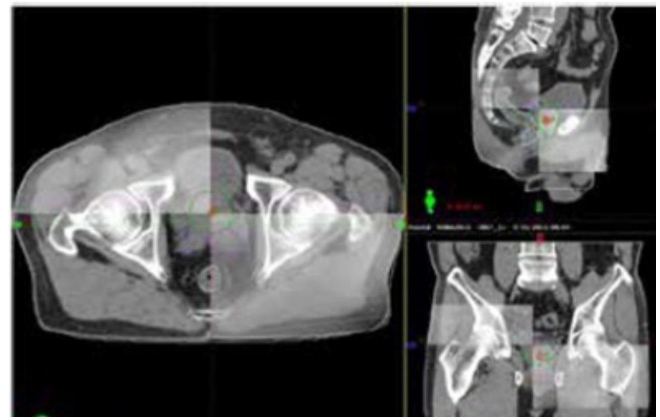
Conventional IGRT systems

- Use the planning CT data as reference
- The image/information acquired before treatment delivery tries to match the daily position at treatment to reference position of target
- However, we know that targets or adjacent OARs may
  - Move with respiration
  - Move with peristalsis
  - Change shape
  - Change position due to minor alterations in body positioning
- This may continue during the entire therapy duration
  - Within a fraction
  - Between fractions for multifraction regimes
- Hence, rigid matching may not give us a perfect correlation between planned and actual treatment
- Most systems rely on bony anatomy or radio-opaque fiducials
- Visualization of tumor outline and position is limited even with 3D imaging

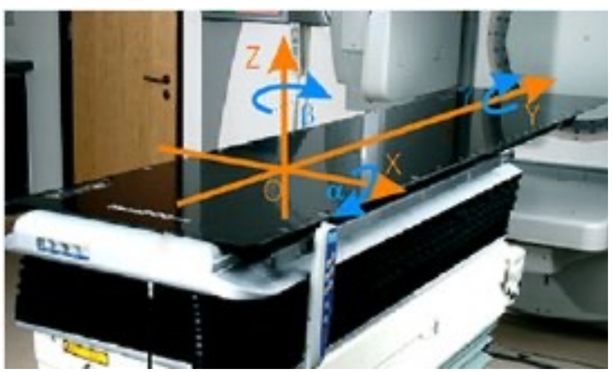
Treatment Verification and Delivery



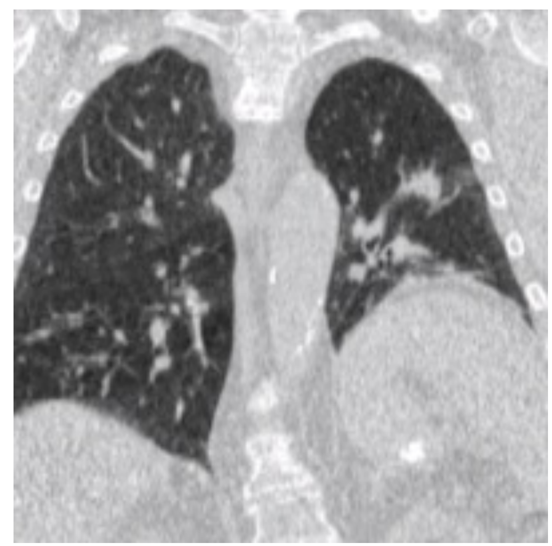
EPID



CBCT (KV, MV)



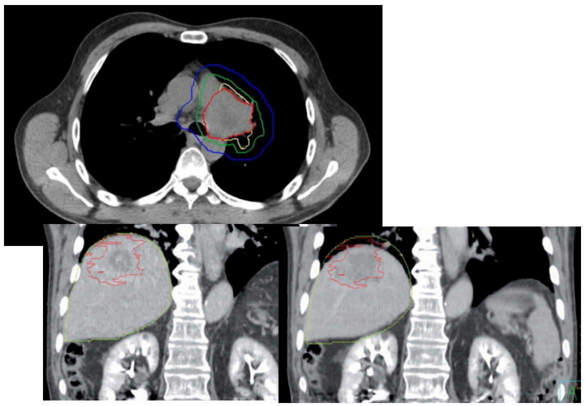
6-D positional correction on treatment couch



4D image acquisition & treatment

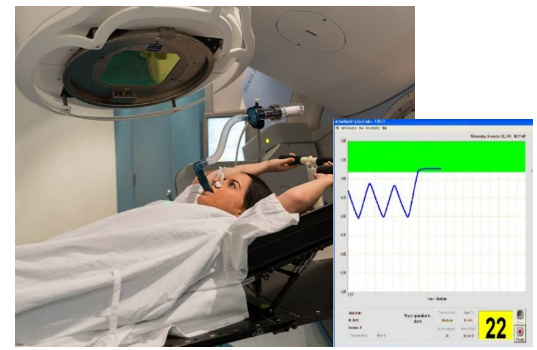
Respiratory motion management

Assess and encompass motion: ITV generation

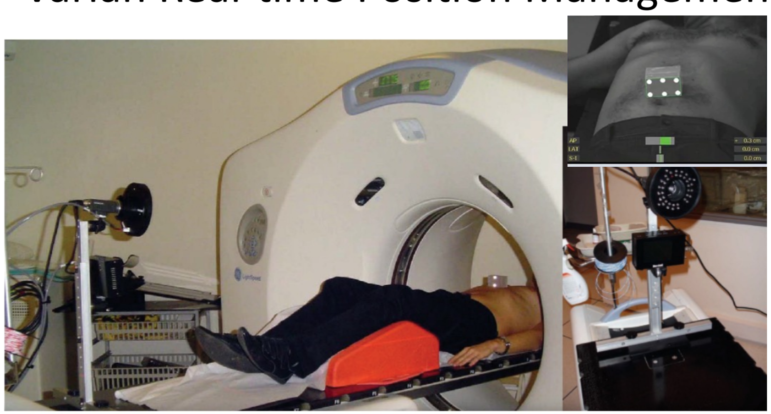


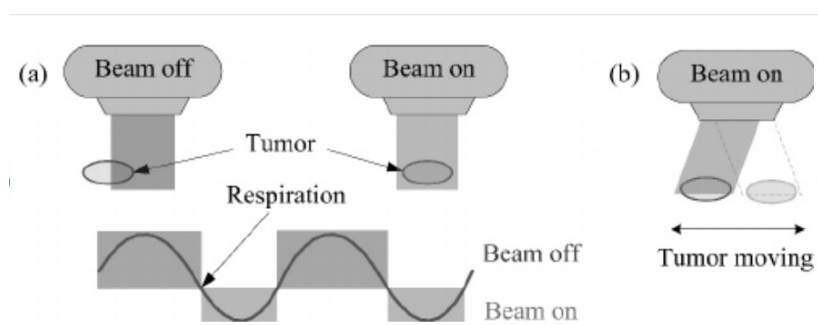
Suppress motion: Abdominal compression

Restrict motion: beam on during DIBH (ABC)



Beam on during a particular breathing phase : Gating
Varian Real-time Position Management (RPM)



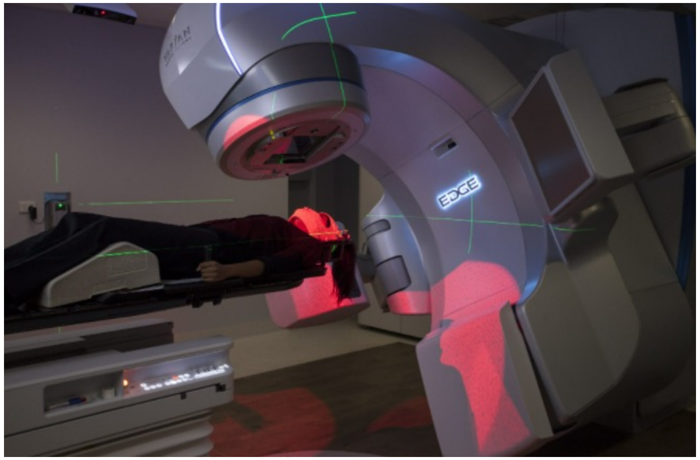


Mechanism of (a) respiratory-gated radiotherapy and (b) tumor tracking.

Respiratory motion management

Tracking motion of surrogates (e.g. fiducials, internal anatomy) or tumor

- Surface guided radiotherapy (Align RT)
- Calypso
- CyberKnife
- RTRT
- ExacTrac
- MRI-LINAC



Real time tracking

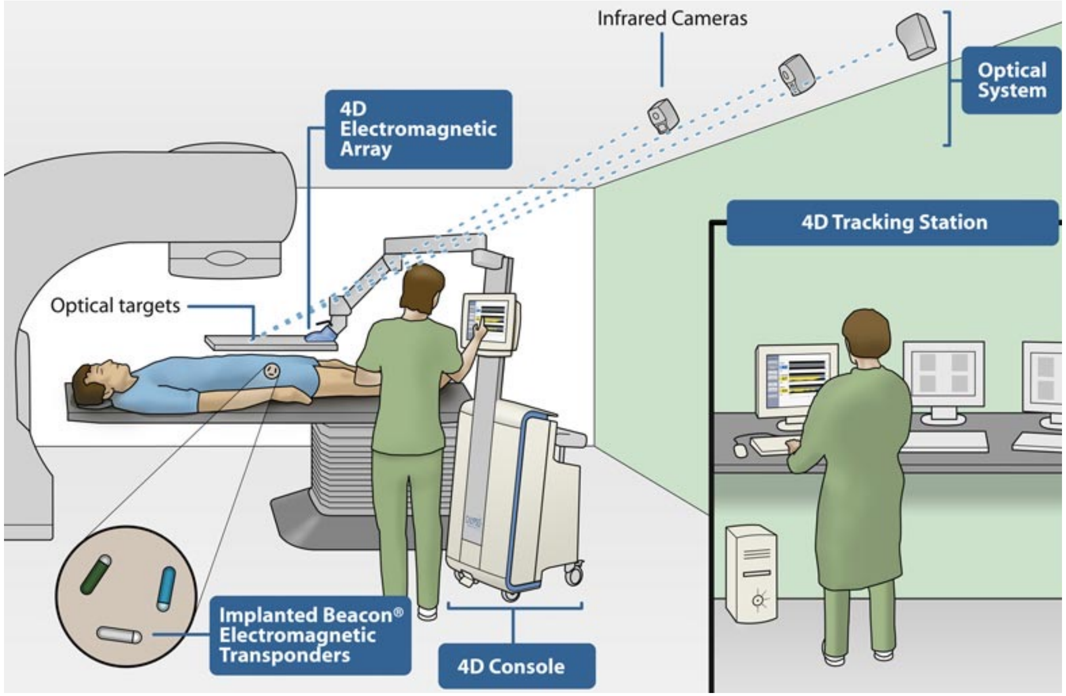
Calypso

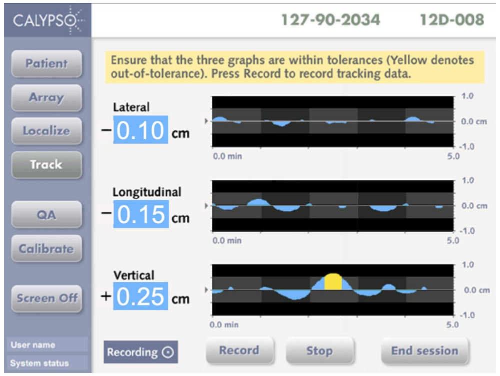
Electromagnetic transponders implanted into tumor/tissue

Tracked via optical system and infra-red array

Initial experience – prostate

Now expanding into other sites such as lung SBRT

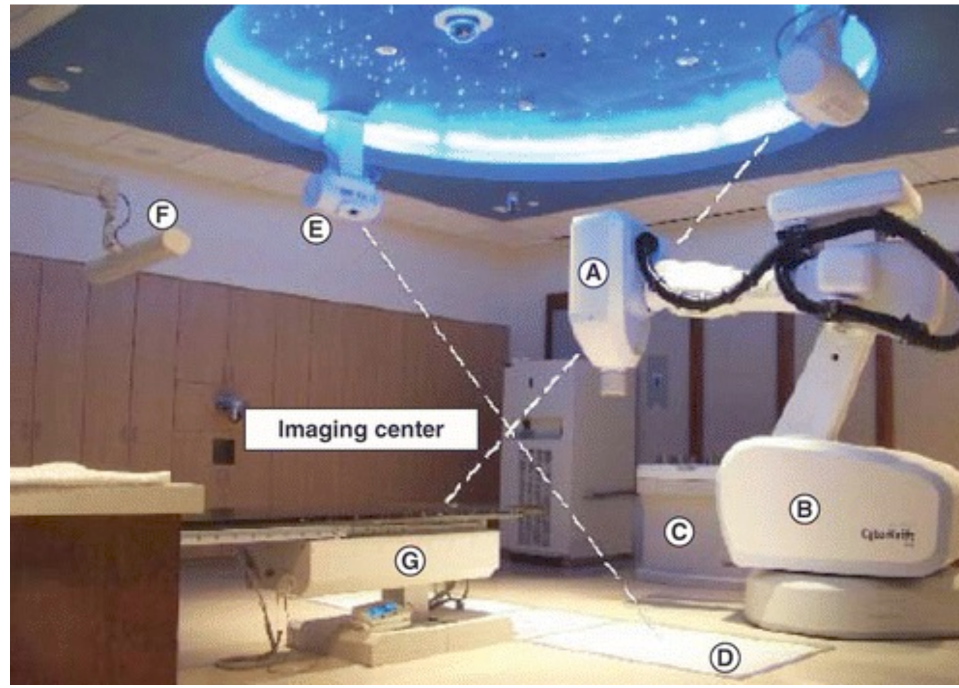


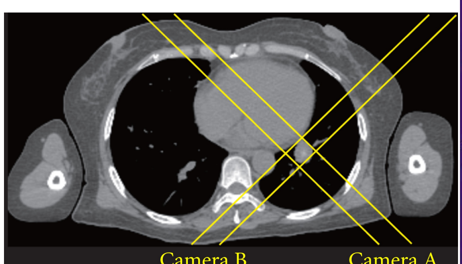


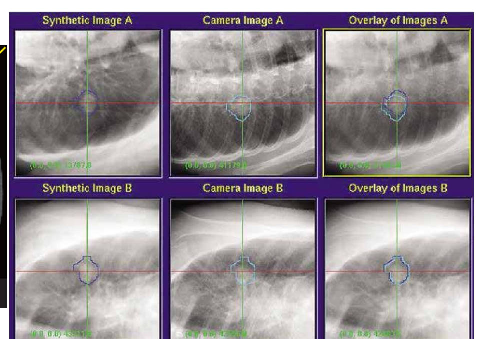
Real time tracking

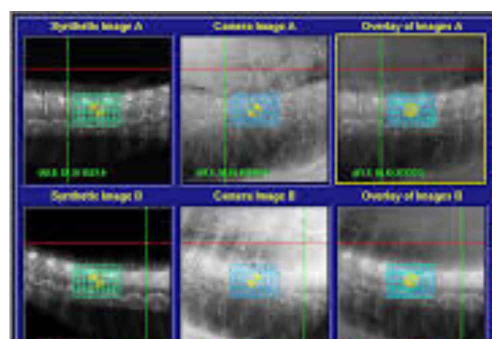
CyberKnife
X-ray based
Acquired images compared with a library of DRR pairs to calculate shifts and rotation
Not really “real time” Several modules

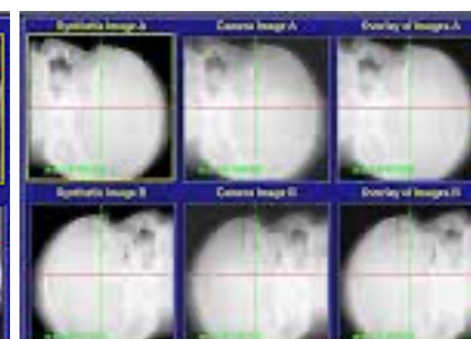
- Fiducial tracking
- Xsight Lung
- Synchrony
- Spine tracking
- Skull tracking







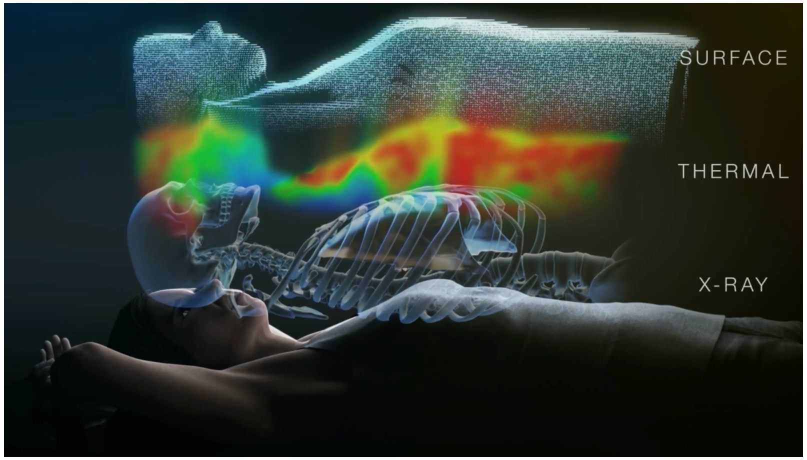




Real time tracking

Brainlab ExacTrac

- In-room X-Ray based monitoring system
- Complements LINAC on-board verification
- Detects intra-fractional tumor motion during treatment delivery
    - Internal anatomy
    - FIducials
- Independent of couch or gantry position
- 6D fusion
- Room based setup
    - Two KV X-Ray units
    - Independent verification tool
- Newer models (ExacTrac Dynamic)
    - Additional surface guidance and thermal guidance for setup



Real time tracking

Real time tracking radiotherapy (RTRT) system

2 sets of fluoroscopes

x-ray tubes on floor, image intensifiers on ceiling (capable of changing position by rotation)

Tracks radioopaque fiducials

Intra-fraction movement can be tracked

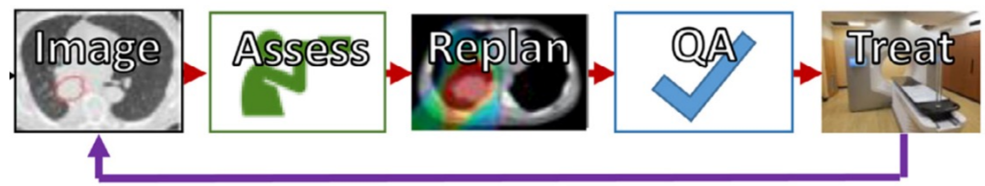
Adaptive radiotherapy in LINAC

- “Adaptare” - Latin for “to fit”
- Adaptive radiotherapy - Adapt plan to patient-specific changes that are unaccounted for in the initial plan
  - Treatment plan is modified using systematic feedback of measurements
  - Customization of treatment margins and dose
  - Most commonly, variations in target position and shape are incorporated into the treatment optimization plan
  - Goal: to improve treatment delivery accuracy and efficacy

Conventional Planning

Offline ART

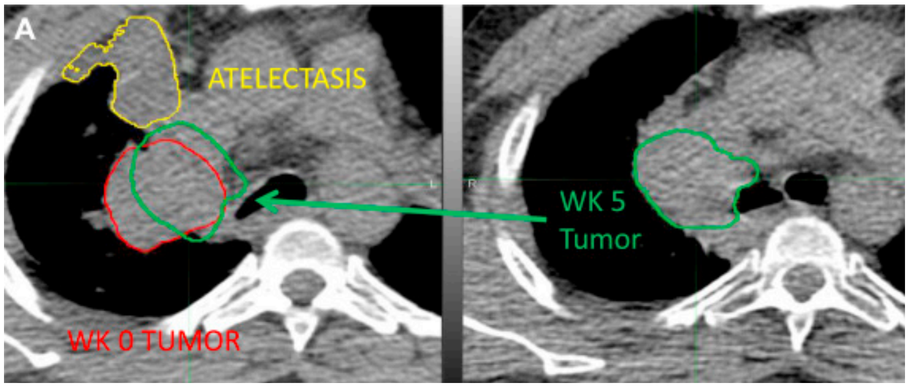
Online ART

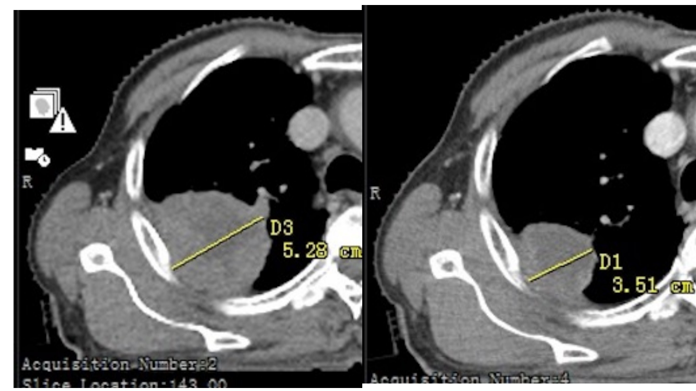


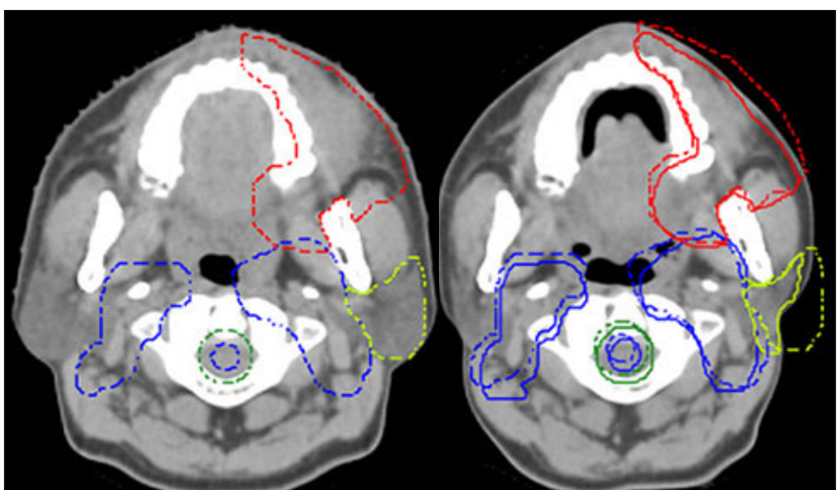
- To address progressive (systematic) changes
    - Weight change
    - Tumor response
- Timing
    - Between fractions

- To address random changes (Target/OAR)
    - Positional variation
    - Deformation
- Timing
    - Before each fraction
    - Intra-fraction – inline or real time

Offline adaptation - examples

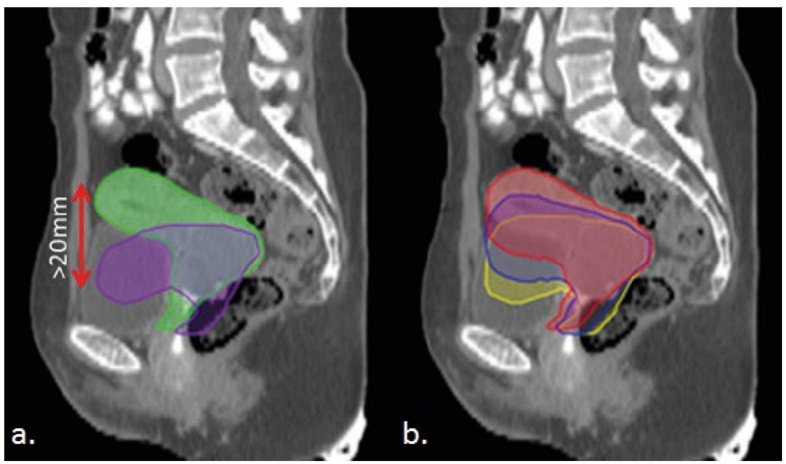


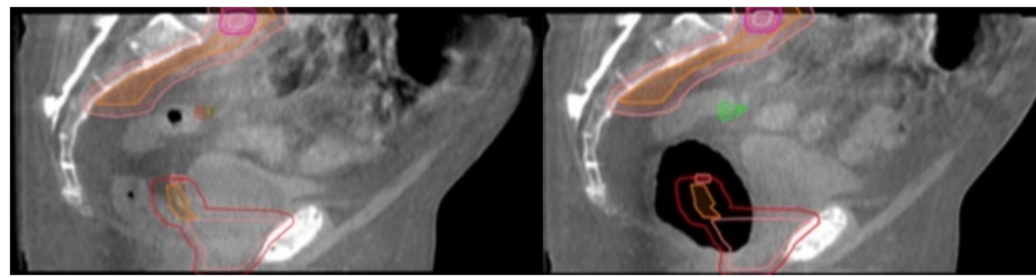




Online adaptation

- If frequency of anatomical change is high – changes occur within a fraction or frequently between fractions, e.g.,
  - volume change due to filling of hollow organs (stomach, bladder)
  - peristaltic movements with gaseous distension





- Need to rapidly respond to the change
  - Replanning and QA integrated while patient is in treatment position
  - “Plan of the day”

Benefits and problems with adaptation

Benefits

- Better accuracy of delivery
- Dose escalation is possible with customization of margins

Problems

- Time consuming
- Adaptation to large changes such as increase in bladder volume or peristalsis and replanning while the patient is still on couch may not necessarily add to accuracy
- Patient-specific QA cannot be performed
- Real-time adaptation: only small, predictable, measurable, anatomical changes can be adapted

Clinical threshold of necessity for adaptation *needs to be clearly defined* – not all adaptation will produce clinically meaningful dosimetric change

Utility of MRI in Radiotherapy

- MRI co-registration helps better delineation of target and organs at risk, e.g., prostate, brain, H&N
  - May still have errors of 1-2 mm due to different position and signal distortion
- MR-Sim
  - Diagnostic MRI (akin to CT sim) - hybrid of MR and CT
  - Helps in contouring targets and OARs for RT planning using electron density allocation
  - May or may not be used for planning purpose with a MR Linac
- MR-LINAC
  - MRI capability within the radiation delivery unit
  - For verification of treatment delivery accuracy
- Combined use of MR Sim and MR LINAC holds promise for better delineation and accurate delivery

MR Sim - Characteristics

- Coil bridges to prevent deformation of the patient's body contour
- Rigid flat table top
- Wider bore
- LASER positioning system
- MRI compatible immobilization devices to minimize patient movement
- Patient imaged in treatment (as opposed to imaging) position
- Dedicated scan protocols

Appropriate candidates for MR-based treatment

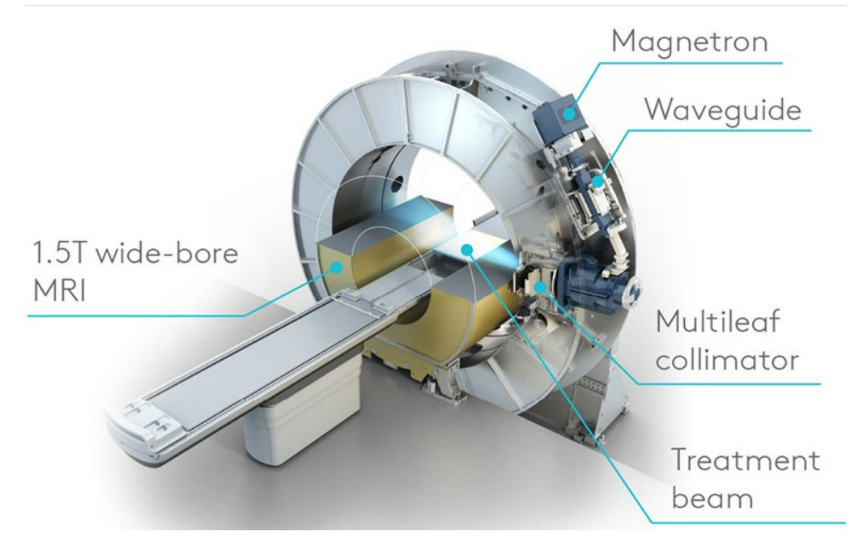
- **Two main criteria**
  1. Patient characteristics
     - Expected clinical benefit – disease site and prognosis, additional gain with MR
     - Feasibility – elderly, frail, obese, cachectic – artefacts, patient heating, bore size <70 cm
     - Compatibility
       - Fully compatible
       - Borderline compatible (mild claustrophobia) - psychological intervention, anesthesia, pharmacotherapy, music or aromatherapy
       - Clinically incompatible (severe psychiatric disorder/ claustrophobia/ inability to follow instructions)
       - Physically incompatible (non-MRI conditional pacemaker - interaction with magnetic fields)
  2. Target volume characteristics & surrounding normal tissues
     - Benefit of additional soft tissue contrast
       - Ideal site – CT density is homogeneous – MRI discriminates better (i.e. head&neck, upper abdomen, pelvis)
       - Moving targets, especially if close to sensitive OAR (lung, pancreas, liver, H&N, prostate, breast, pelvic nodes, kidney, adrenal)
       - Reirradiation settings when margin limitations exist
       - Other situations - shrinkage of tumor, early toxicity onset, radiomics applications
- Treatment slots for full online adaptive treatments ~ 60 min

MRI/LINAC integration for IGRT

- Direct visualization of tumor and adjacent tissue anatomy
- Excellent soft-tissue contrast
- Capability for identification of movements, function and physiology
- Real-time characterization and tracking of anatomical motion
- Respiratory gating – margin reduction, accuracy of delivery - enables SBRT in mobile targets
- Sites most benefitted with MR-guided gating
  - Thoracic tumors (lung, mediastinum)
  - Breast
  - Abdomen (liver, pancreas)
  - Pelvis (prostate, cervix)
- Real-time plan adaptation – further potential of reducing OAR dose, allows physicians to optimize dose escalation strategies

MR LINAC → MR guided radiotherapy [MRgRT]

- Hybrid device
  - LINAC to deliver radiotherapy
  - MRI scanner for verification of treatment delivery
- Allows for online real time MR imaging for customization and high-precision ART
- Offer real-time tumor tracking and beam gating
- First MR based treatment – Co-60 based MRIdian (Siteman Cancer Centre, Cleveland, 2014)
- First MR LINAC based treatment - Henry Ford Cancer Institute, Detroit, 2017
  - MRIdian - MR Linac of Viewray
- Two main models available for clinical practice
  - Unity by Elekta
  - MRIdian by Viewray
  - Several others in development



Clinically validated equipment

MRIdian (Viewray)

- Two models
  - Co60 [MRIdian]
  - 6 MV linac [MRIdian Linac]
- 0.35 Tesla MRI with split magnets and field aligned along craniocaudal axis of patient
- The beam does not pass between magnetic field

Unity (Elekta)

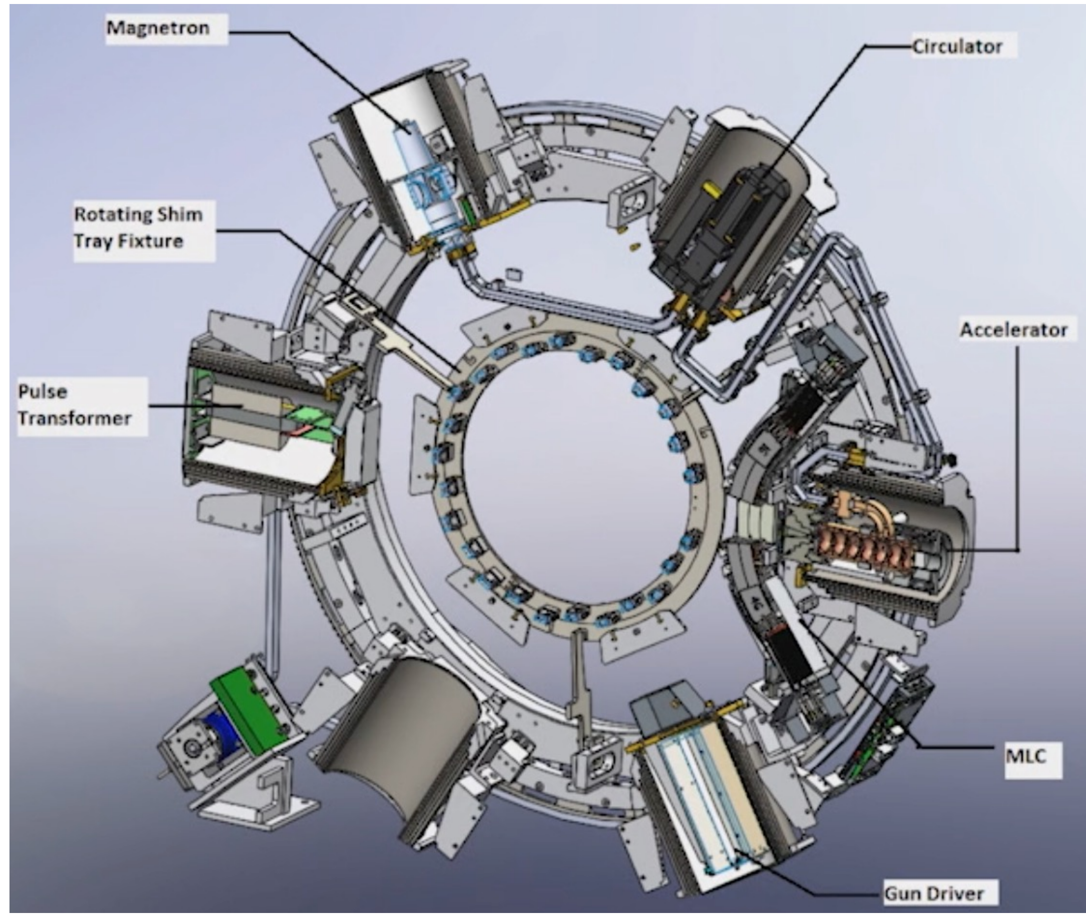
- 7 MV FFF LINAC
- 6 RPM gantry speed
- 1.5 Tesla MRI - magnetic axis along craniocaudal axis of patient
- Active magnetic shielding - to ‘decouple’ the MR and LINAC for independent functioning

MRIdian (0.35 T)

- Localization accuracy of 1+/-0.1 mm
- 6 MV Beam, FFF, SAD 90 cm
- Small bore of 70 cm
  - Lateral shift at high couch position is +/-7 cm
  - Lesser for lower couch position
- Double focused stacked MLC [5.5 cm each, so 11 mm total height]
- Total 138 leaves
- Leaf width at isocentre 8.3 mm
- Field size
  - Smallest – 0.2 x 0.415 cm^2
  - Largest – 27.4 x 24.2 cm^2
- Beam passes only through a 5 mm thick fibre glass between the split magnets, NOT through the magnetic field due to split magnets

Gantry subsystem

- Designed to mount 6 magnetically shielded compartments
- Equal spacing – symmetric magnetic environment around MRI FOV to facilitate shimming required for field homogeneity
- Shielded compartments contain LINAC components:
  - Pulse transformer
  - Magnetron (3.1 MW)
  - Port circulator
  - LINAC
  - Gun driver



Radiotherapy system

6 MV FFF LINAC

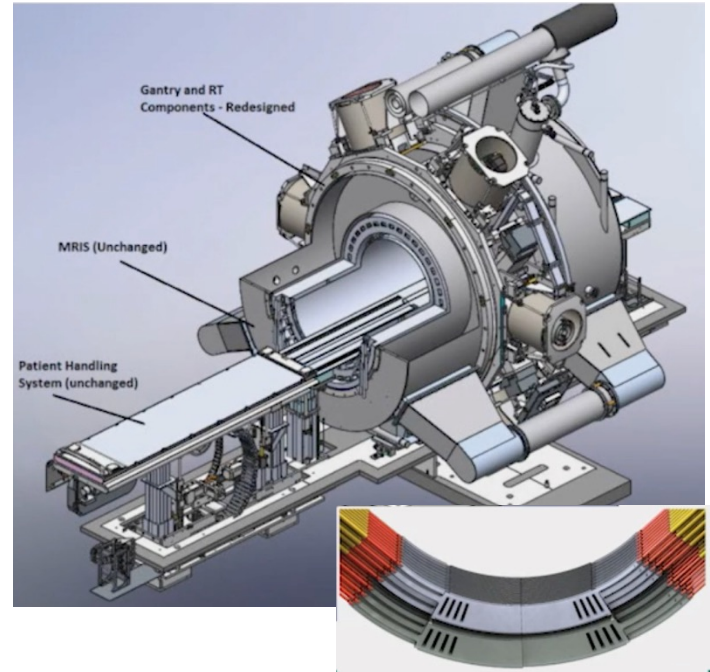
Dose rate 600-650 cGy/min

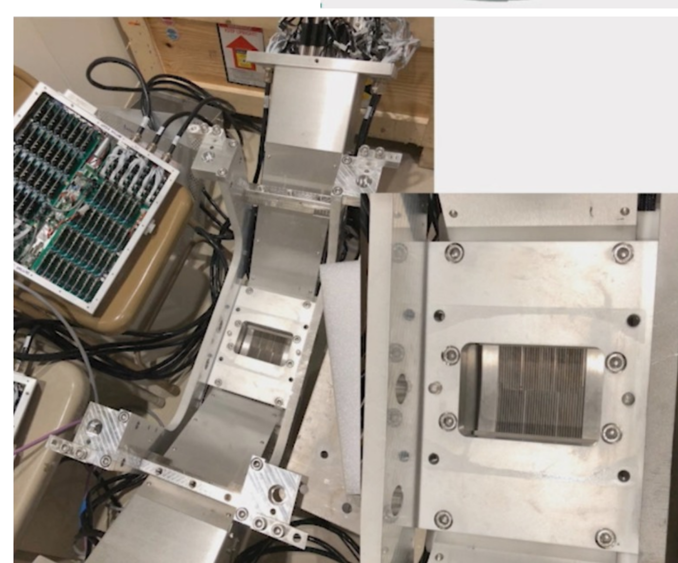
90 cm isocenter, matched to isocenter of magnet

Double stack, double focused MLCs

Full over-travel and interdigitation

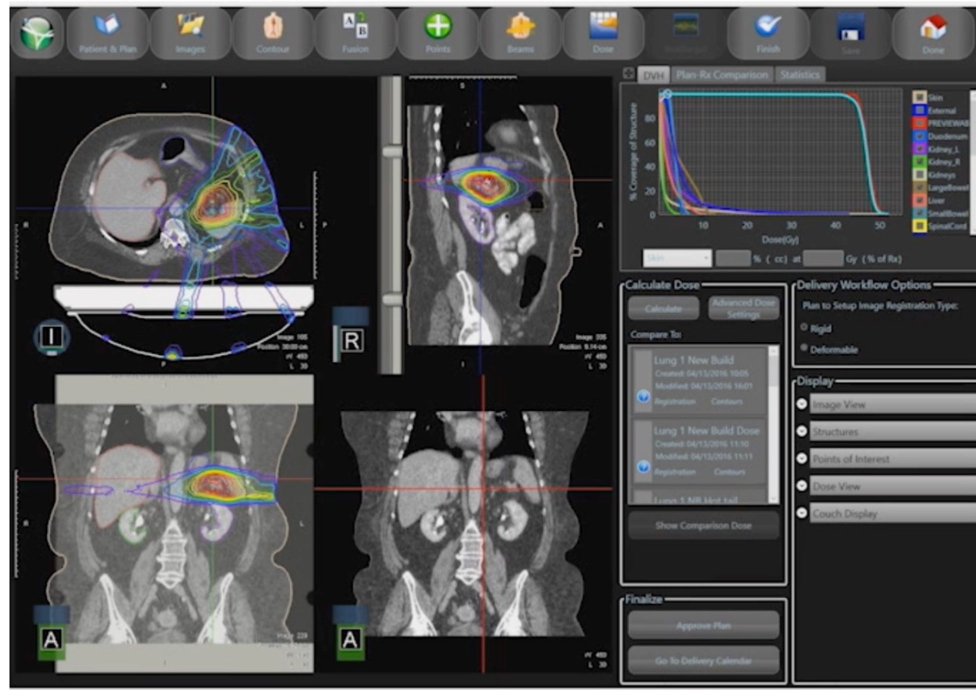
3D correction treatment couch

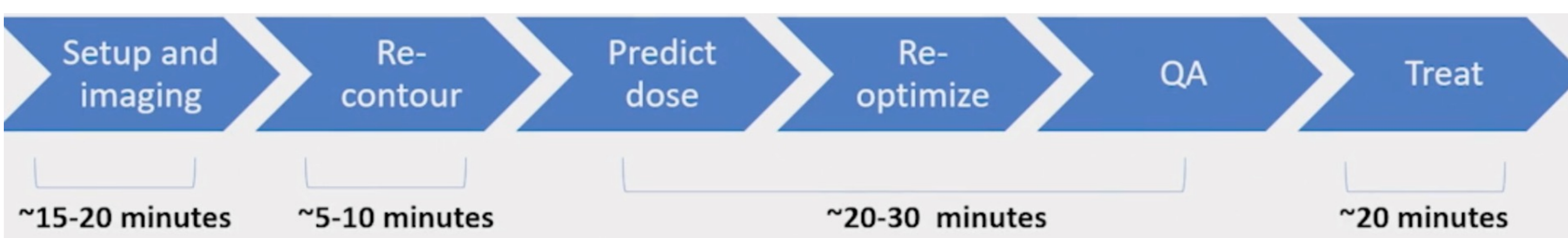




Treatment planning

- Integrated treatment planning and delivery software (planning, delivery QA)
- Contour and fusion capabilities
- Delivery techniques
  - 3DCRT
  - Fixed field IMRT
- Full Monte Carlo calculations
- Max field length: 36 cm @ isocentre
- Typical treatment schedule
  - 9-10 cases/day (10-hour shift)
  - 30-90 min per case (longer for adaptive)
  - SBRT and breath hold for most cases
  - 2-3 adaptive cases





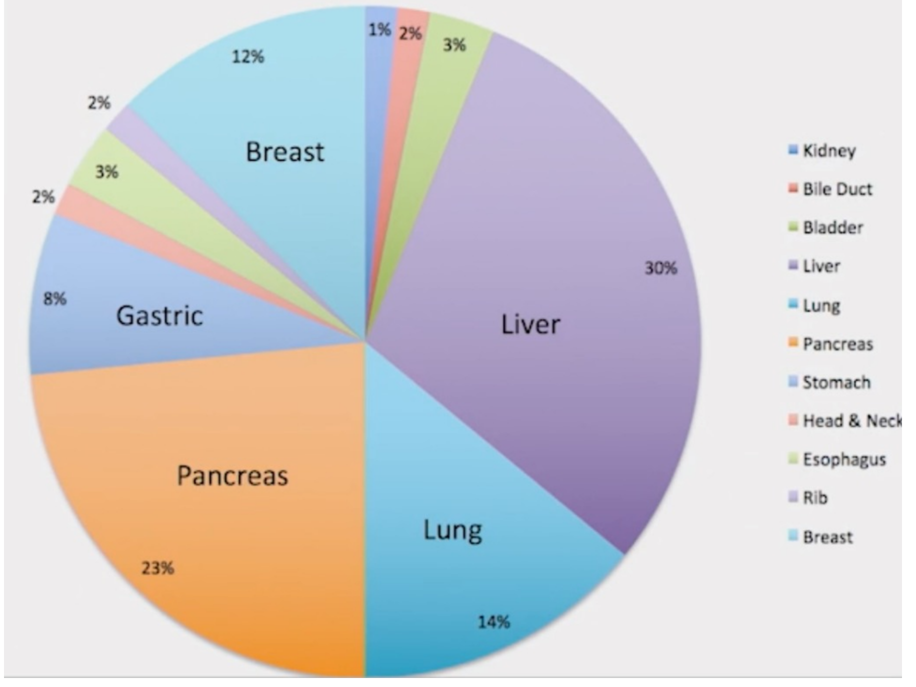
Average time ~ 75 minutes

MR imaging system

- MRIdian has Siemens MR
- Split bore magnet with 28 cm gap
- 0.35T
- 3D TrueFISP images (fast volumetric multi-planar imaging)
- Acquisition as fast as 17 seconds
- Real-time single plane treatment delivery imaging at 4-8 frames/s

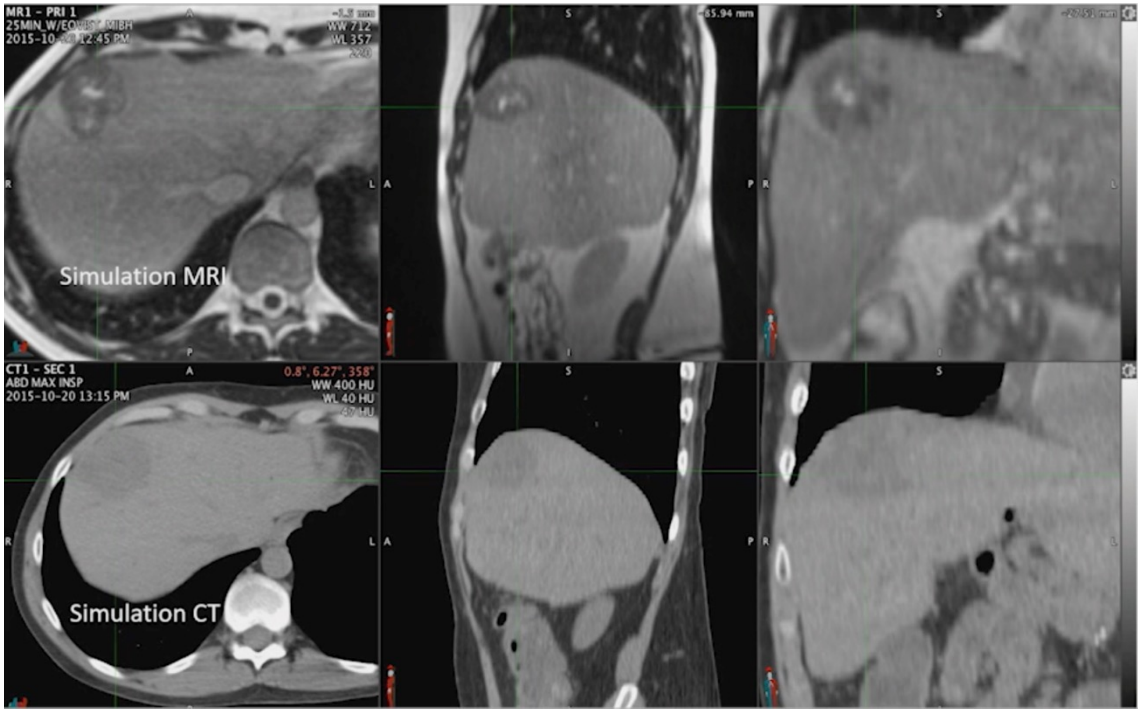
Clinical advantages of MRgRT

- Soft tissue target delineation and alignment
- Motion management
- Simulation and treatment
- Response assessment
- Adapting to changes in anatomy
- Same day RT



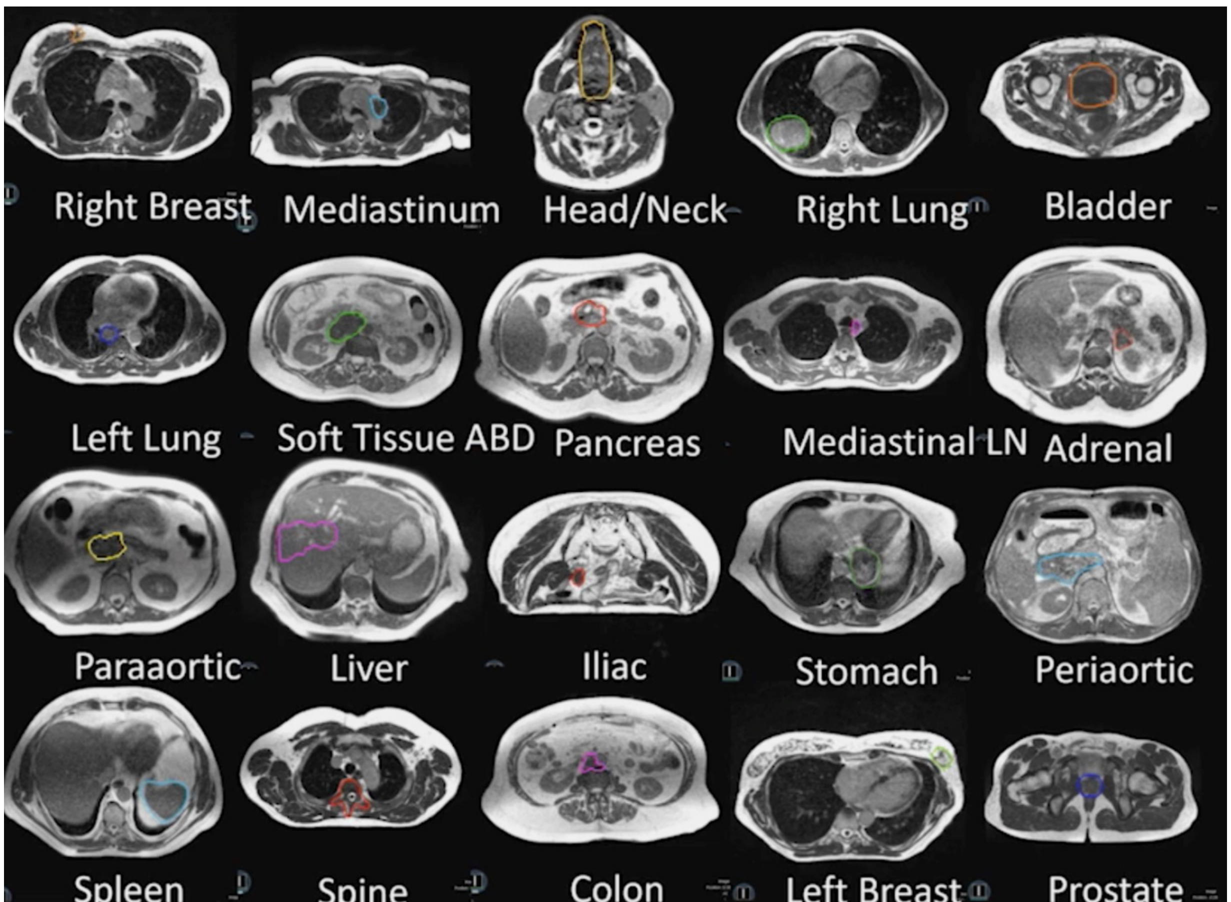
MR LINAC - Advantages

- Superior soft tissue imaging quality – target and OAR



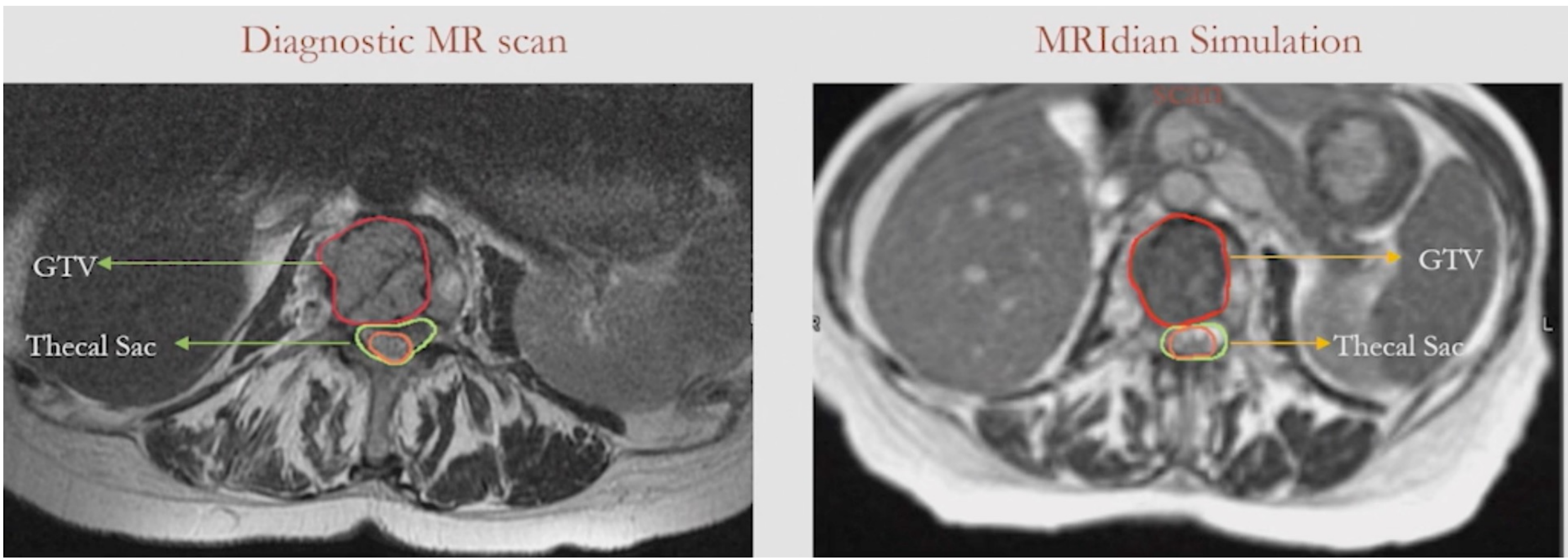
MR LINAC - Advantages

- Improved target volume delineation



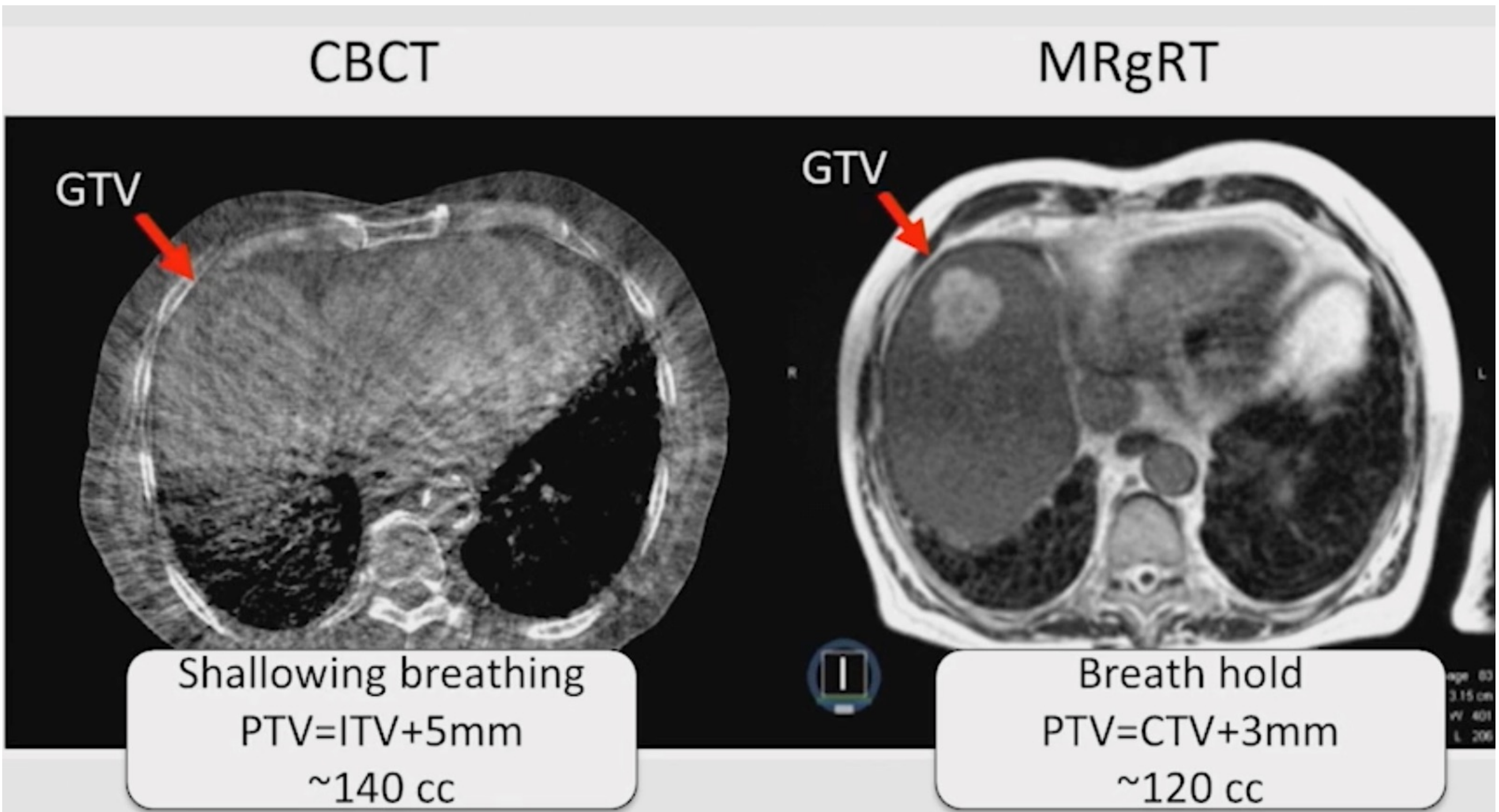
MR LINAC - Advantages

- Better OAR delineation – less distortion compared to diagnostic scans



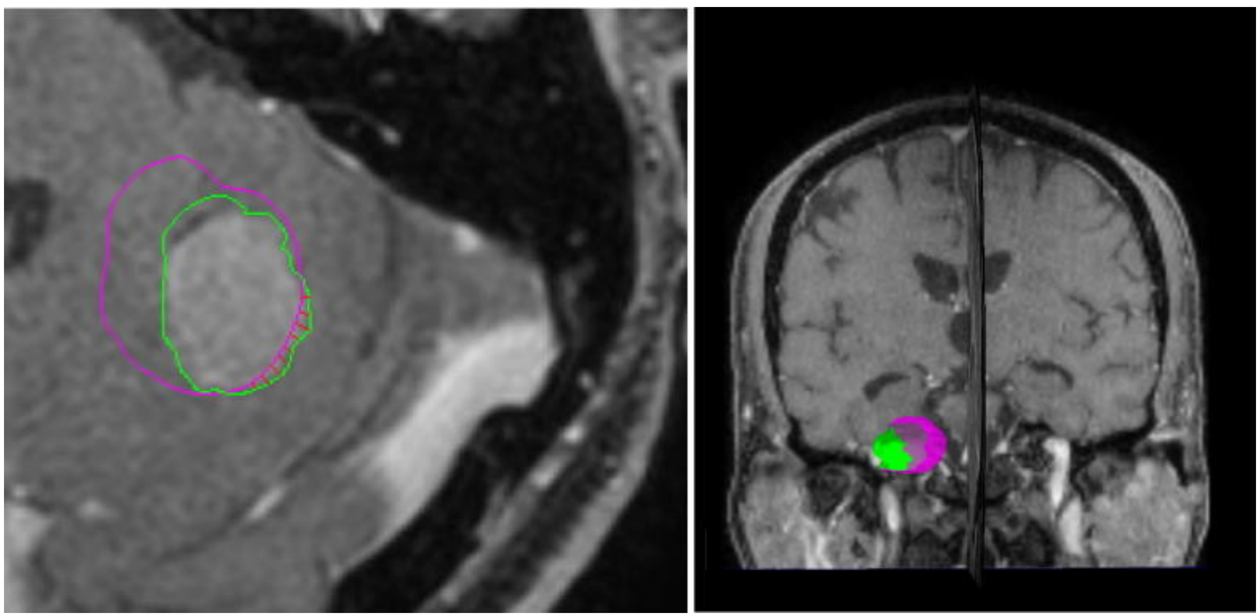
MR LINAC - Advantages

- Better discrimination of target compared to CBCT



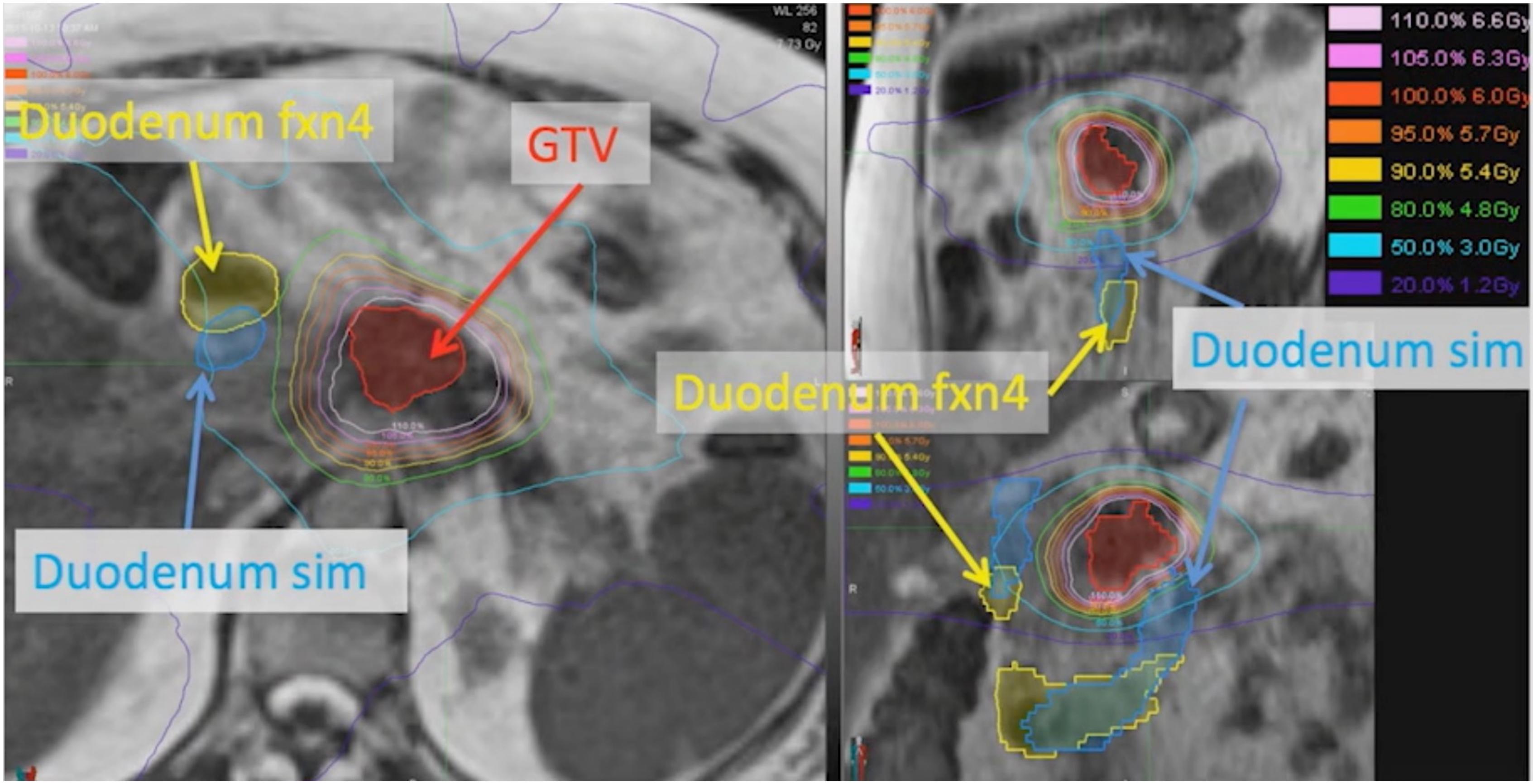
MR LINAC - Advantages

Even in stable sites such as brain - Online MRI imaging picks up steroid-induced change in position and shape of brain metastases during FSRT – Adaptation during treatment



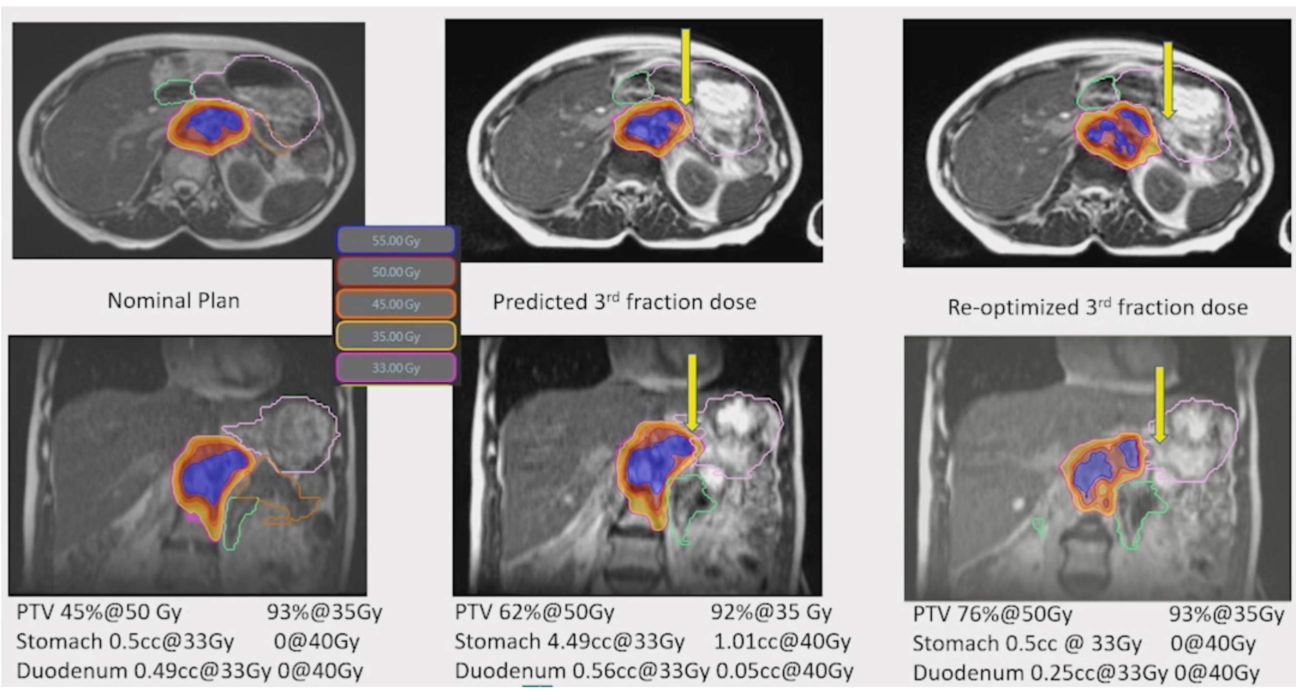
MR LINAC - Advantages

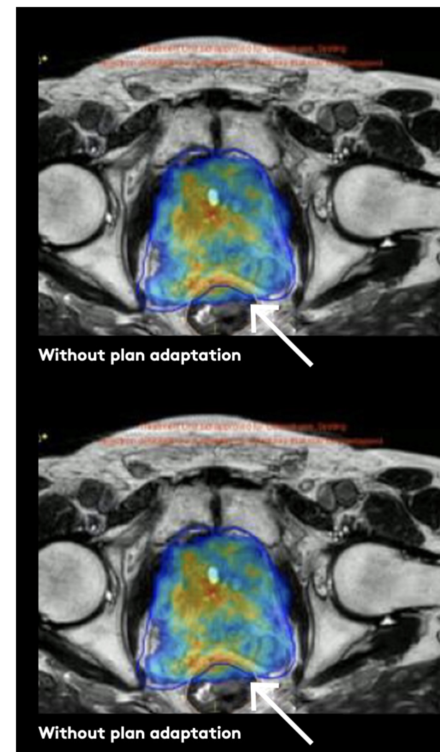
- Online adaptation to changes in target/OAR shape and position



MR LINAC - Advantages

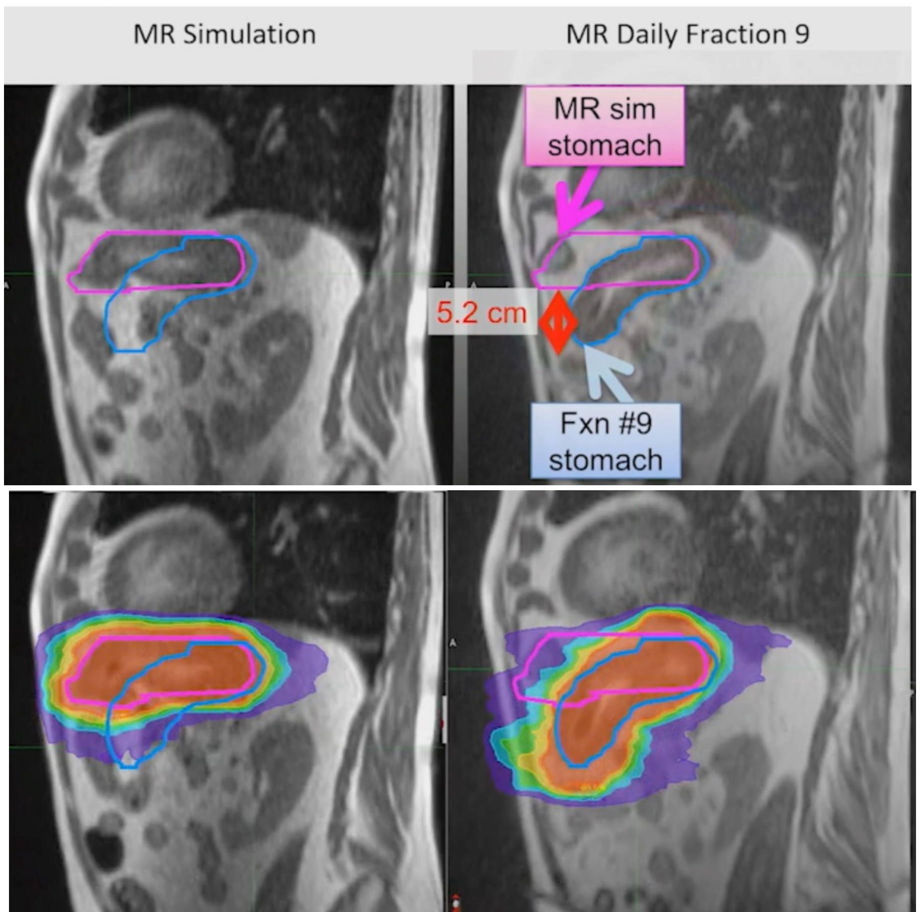
- Online adaptation to changes in target/OAR shape and position





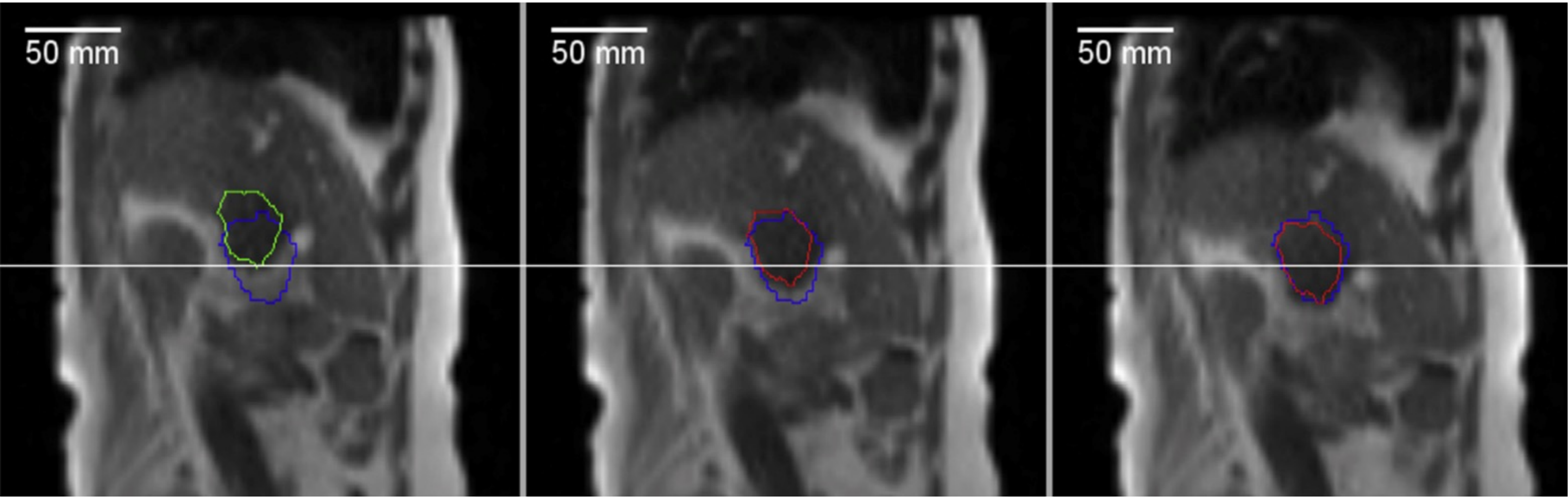
MR LINAC - Advantages

- Online adaptation to avoid missing target coverage



MR LINAC - Advantages

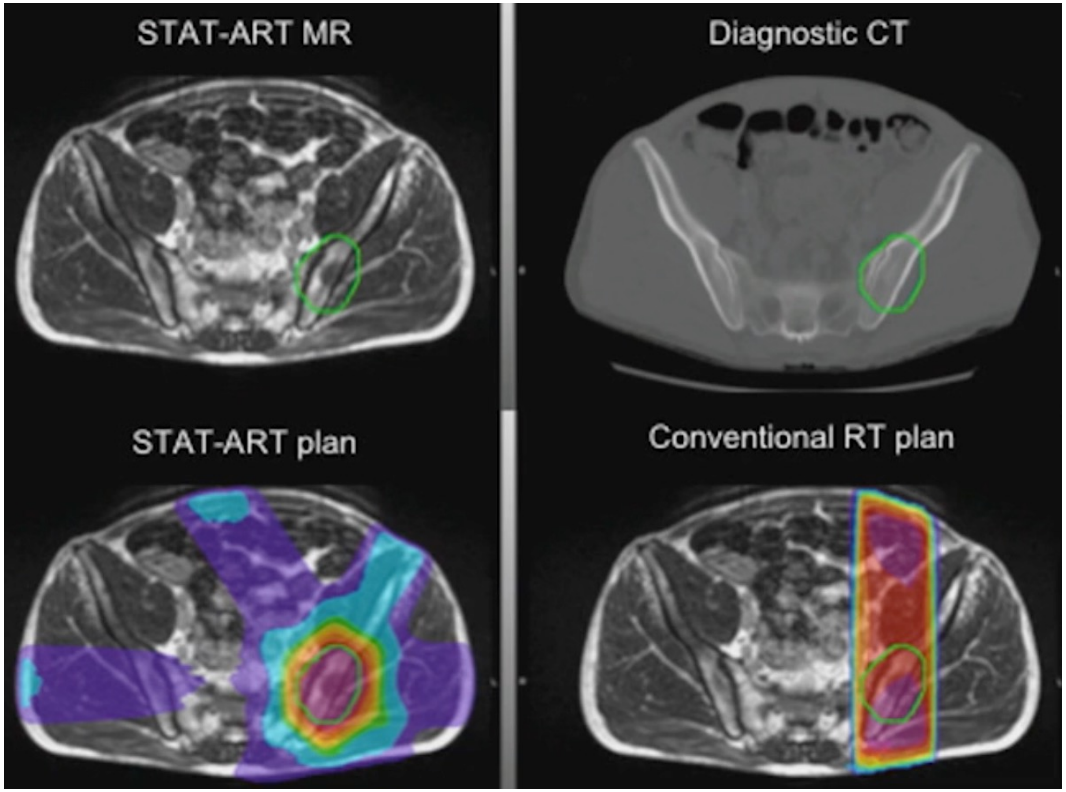
- Real time tracking and gating feasible



Real-time MR cine tracking of adrenal tumor in DIBH. PTV in blue. The tracked GTV appears green if excursion is <u>outside</u> the PTV threshold ROI%(left) and remains red if the excursion is <u>within</u> threshold-ROI% (middle) or entirely within PTV (right)

MR LINAC - Advantages

- Same day treatment for urgent palliative cases – no need for separate CT Simulation (STAT-ART)



MR LINAC - Advantages

- Precise contouring - margin reduction → dose escalation → better control
- No additional radiation exposure even when multiple images are acquired
- Regular imaging - useful to assess response, need of plan adaptation or change of treatment objective
- Differential response within target - assess genomics-related biological aspects like hypoxia and resistance

Plan adaptation in MR LINAC

- Predefine adaptation threshold – “Traffic light system”
  - Clarity on OAR dose constraints and target coverage
  - Time frame for online contouring and optimization
- Adaptations range from simple MLC position shifts to full reoptimization
- If minimal margins/SBRT: anatomic changes of OAR or target may mandate replanning
- Tracking
  - Treatment stops if target moves out of range
  - Action threshold for intervention in the event of target movement outside of the high dose area, which is dependent on PTV margins
    - MRIdian: DIBH, Cine-MRI upto 8 frames/sec in one plane
    - Unity: Tracks in all 3 planes, several sequences can be acquired
- Future: Deformable dose accumulation (based on actual delivered dose)

Clinical MRgRT workflow

Patient Positioning	3D MR-imaging	Image Registration	Re-contour	Dose prediction/ Plan	Plan QA	MRI Reimaging	Treatment Delivery
RTT	RTT, RadOnc	RTT, RadOnc	RTT, RadOnc, MedPh	RTT, RadOnc, MedPh	RTT, MedPh	RTT, RadOnc	RTT
Coils placement Check setup comments Avoid pitch/roll	Aquire daily 3D MRI Image registration with primary image of Baseplan on GTV (Rigid)	Deformable or rigid registration of GTV and OARs Start with Baseplan	If needed, contour correction or re-contouring	Check constraints and target coverage of dose prediction If needed, optimize plan with same optimization objectives Plan approval	Evaluation criteria: MU/FR/ γ-values, statistics Verification of accuracy of dose calculation and class-solution	3D MRI or cine MRI Is a table or dose shift required?	On-line cine MR imaging during treatment Adjusting for intrafractional changes in anatomy: shifting/gating

Image acquisition	3 min
Target and OAR contour review	15 min
Import initial plan on contour set of the day	5 min
Re-optimize when needed	5 min
QA with Monte Carlo calculation	5 min
Treatment delivery on LINAC	5 min
Total time	
No re-optimization	**28 min**
With re-optimization	**38 min**

Combining MR with RT

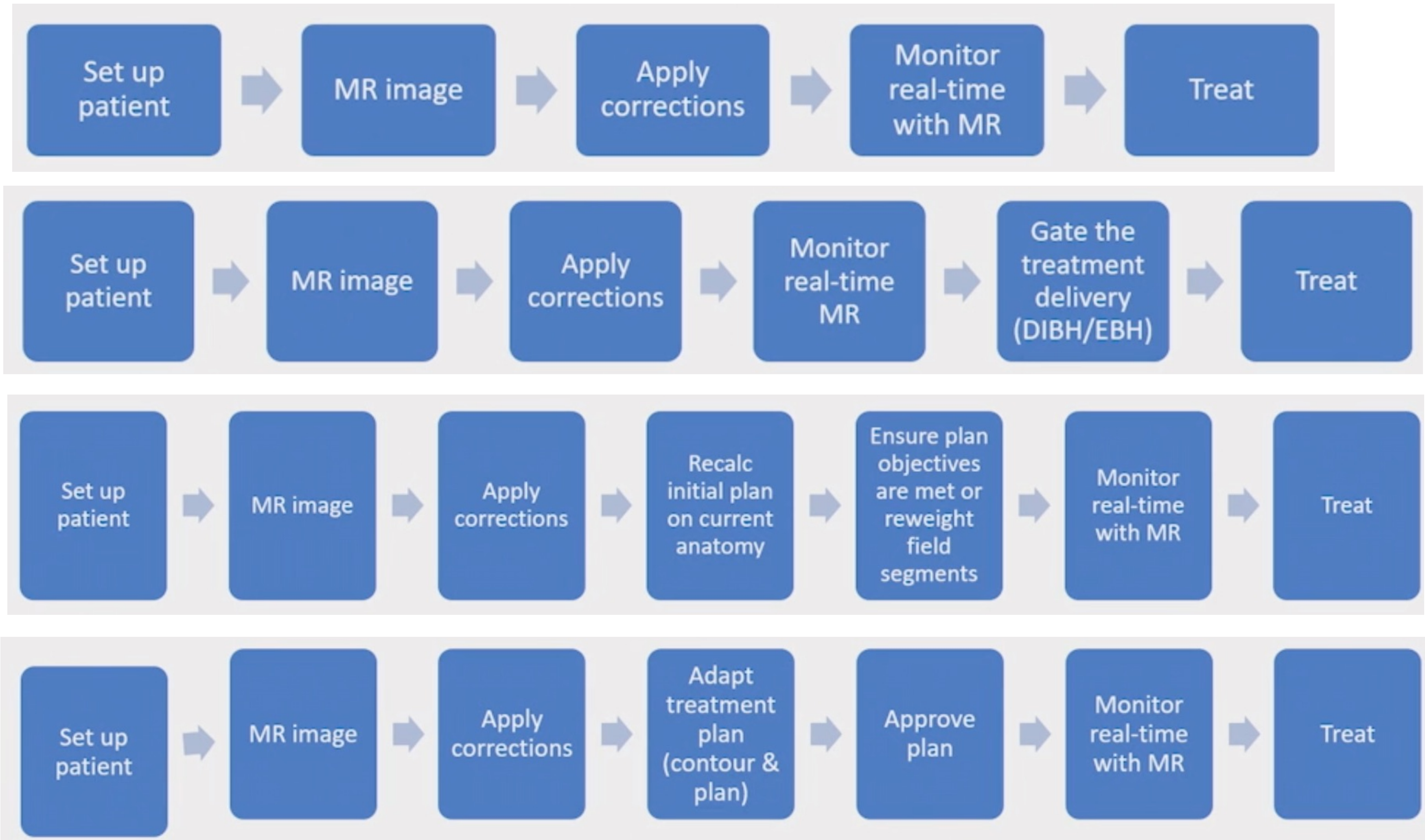
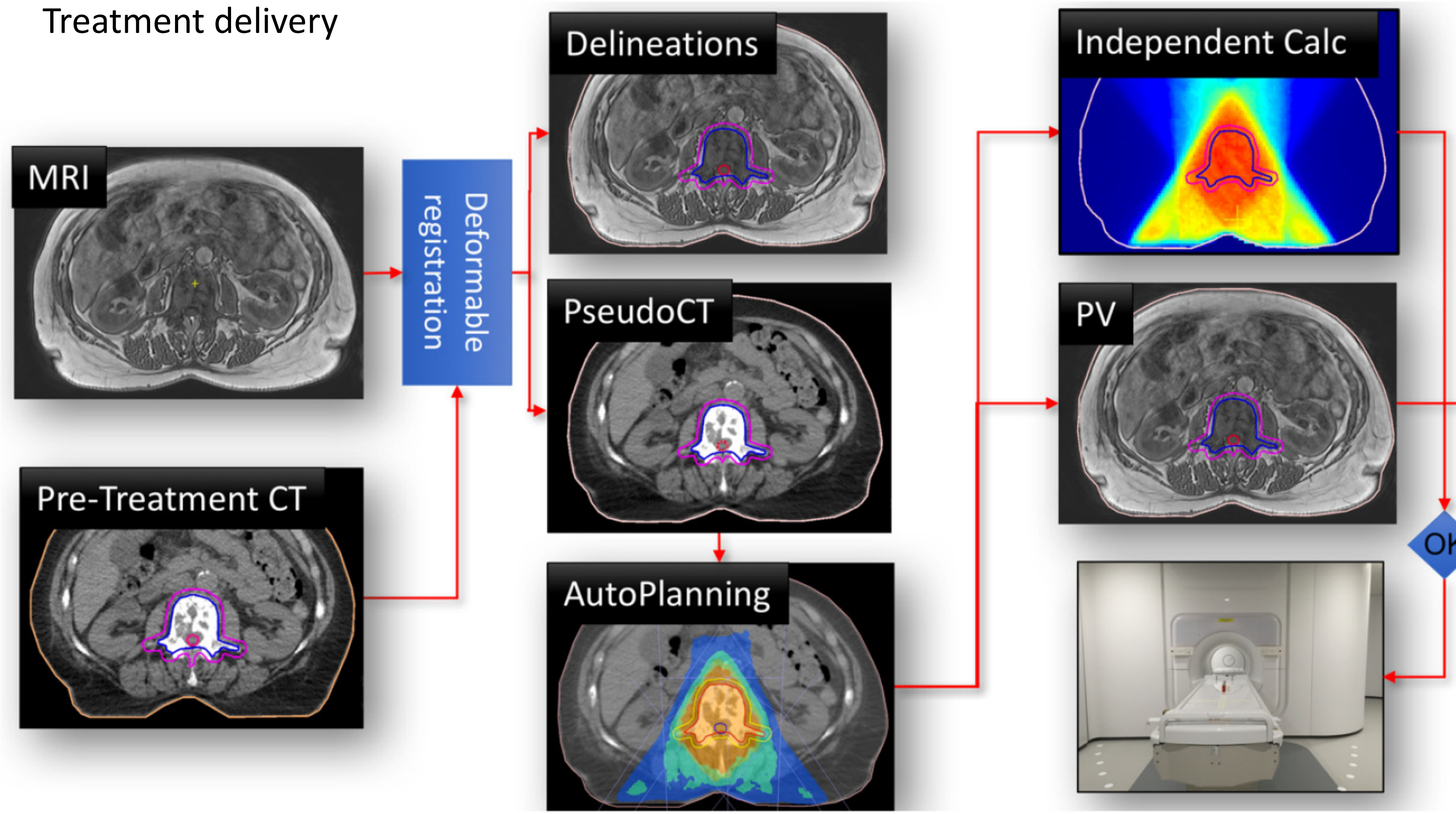


Image verification in MR LINAC

- Online MRI registered to pre-treatment CT to generate a warped CT and to propagate the pre-treatment contours
- IMRT plan generated and validated via independent dose calculations
- Additional MRI for position verification
- Treatment delivery

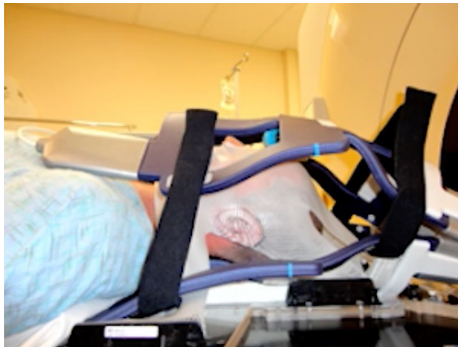


Issues and Concerns

- Safety issues related to magnetic field - projectile capabilities of metallic objects
  - Screen patients for magnetic implants (aneurysm clips, sutures, some heart valves, embedded wires, stimulators, batteries, implanted electrodes, shunts, pumps, pacemakers, some penile implants)
  - Non-magnetic implants may also cause artefacts - signal loss/accumulation, distortion
  - Handheld metal detector, dedicated gowns - minimize inadvertent carrying
- Loud knocking noise - ear protection, may cause peripheral nerve stimulation
- Thermal effects of radiofrequency - heating of body in thin patients
- Longer on-couch time –inconvenient, demands good compliance

Issues and Concerns

- Higher cost of equipment and installation (8-10 million dollars)*
- Special training and dedicated staff necessary
- Emergency training necessary – use of magnetic quench and evacuation procedure
- Accessories and QA equipment need to be MR-specific
- Safe handling and proper usage of magnetic coil - for minimal image deterioration and dose attenuation



*60-75 crore INR

Current available outcome data

Installation to clinical use time: 3-4 months

Long term outcomes awaited – recent technique, learning curve

Multiple studies are ongoing for technical feasibility and assessment of outcomes for different sites using MRgRT

- No increase in lung toxicity

CADTH rapid response report: summary with critical appraisal). Ottawa (ON): CADTH; 2019

- Improved OS in pancreatic cancer - Stereotactic MRI-guided On-table Adaptive Radiation Therapy (SMART) study

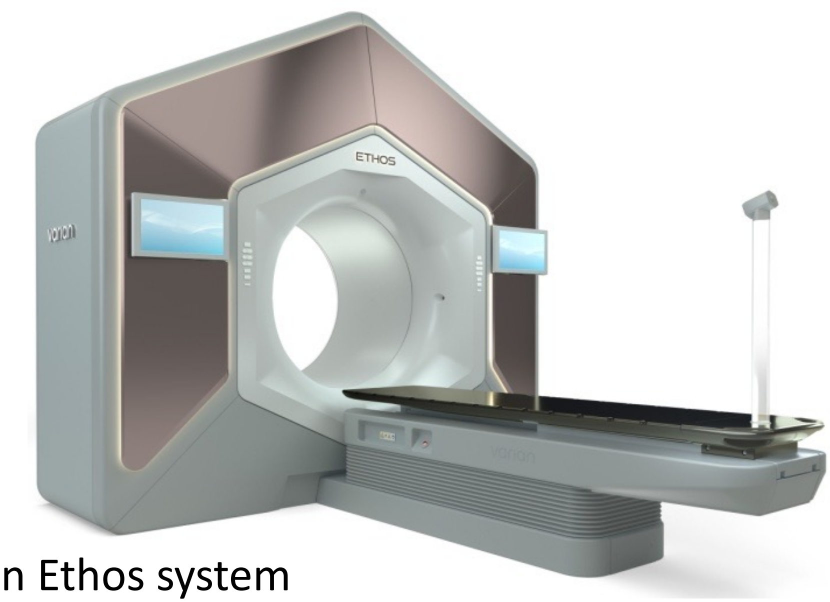
Physics Imaging Rad Oncol. 2019;9.

- MR-LINAC feasible and well-tolerated in prostate cancer

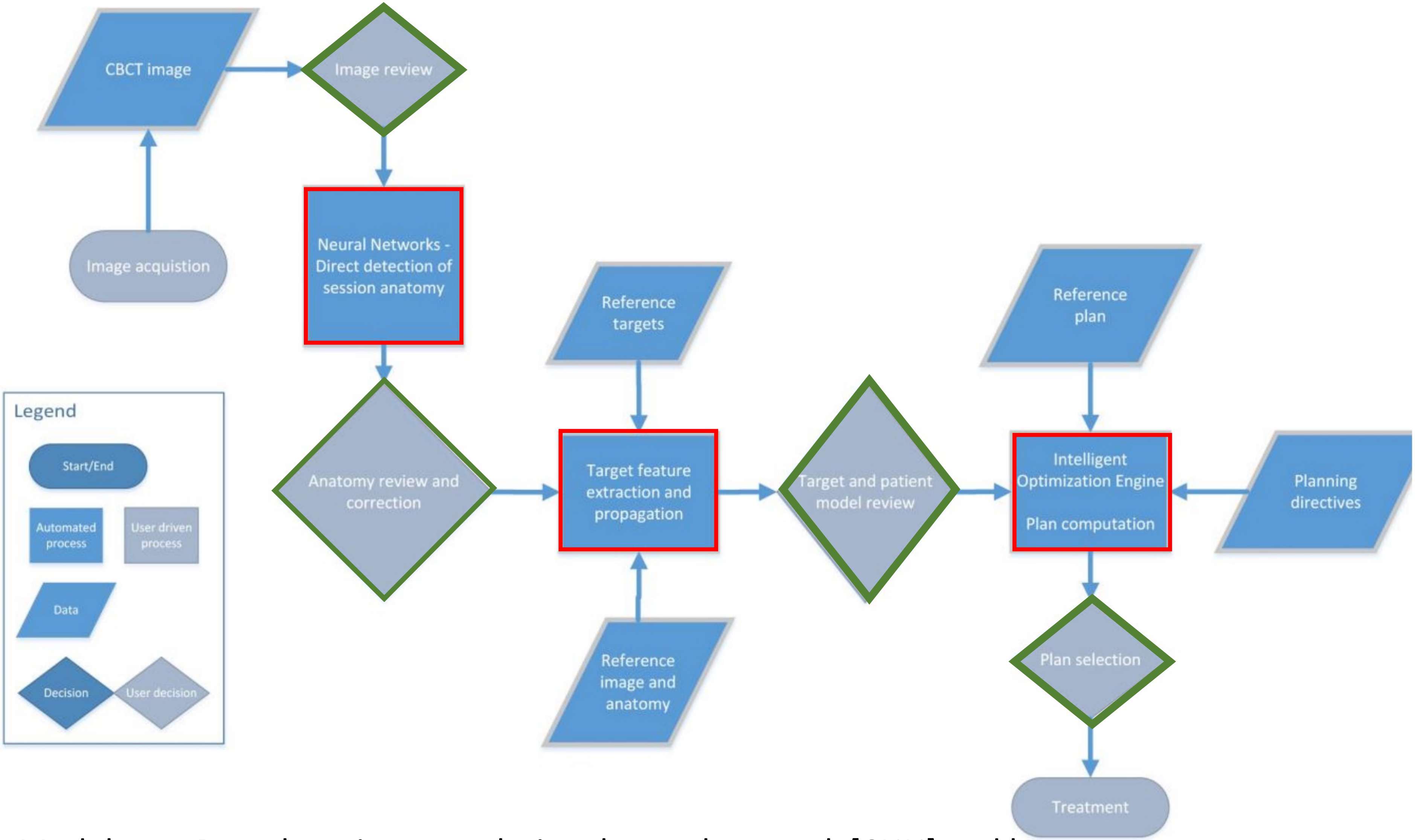
Cancer Med. 2019;8(5).

Artificial Intelligence based Online Adaptive Radiotherapy

- Replanning workflow - well-defined and predictable clinical decision points in order to lower the cognitive load of the clinician
  - Accepting the image
  - Assessing and modifying ‘influencer’ structures or OARs
  - Assessing and modifying target organs – creating the session model
  - Selecting the plan – scheduled or adapted



Varian Ethos system

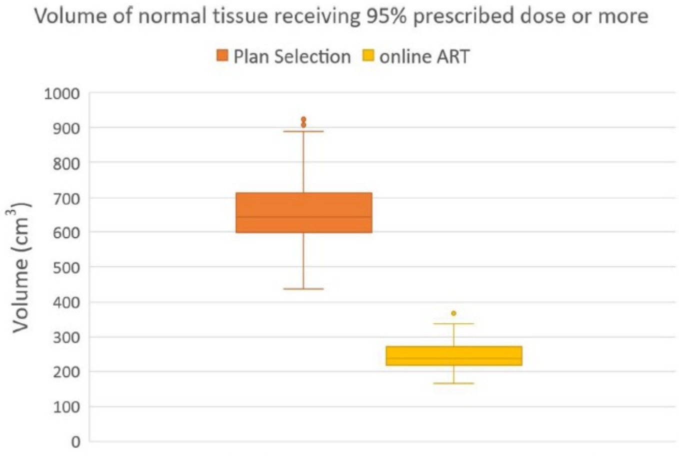


Models use Deep learning convolutional neural network [CNN] and hyperparameters
Acquired 3D iCBCT serves as input to the neural network
Output can be assessed and adapted by clinician

- After image approval, the system used deformable registration to make an image S-CBCT that conforms with the CBCT
- IOE (Intelligent optimization engine) generates IMRT/VMAT plans with
  - ➢ high degree of dose conformity
  - ➢ due significance to OAR doses
  - ➢ intelligent trade off clinically
- The IOE works by having pre-defined Q-functions [quality functions] for the planning purpose
  - ➢ Target upper dose [TUD] goal
  - ➢ Target lower dose [TUD] goal
  - ➢ Organ upper dose [OUD] goal
- Automated dose accumulation is calculated. This
  - Demonstrates the intended dose is delivered
  - Provides understanding and documentation of the process
  - Identifying need to resimulation
- Artificial intelligence makes multiple plans to choose from
- Clinician approval for treatment after review of plans

AI-driven CBCT guided oAT

- Preclinical studies (pelvis)
- Minimal editing or no editing needed in 75%
- Adaptive plans
  - Similar or better PTV coverage than original plan (IMRT > VMAT)
  - Reduced dose to bowel bag
  - MUs were occasionally higher
  - Satisfactory QA criteria
- Time from CBCT approval to starting treatment – 17.6 min
- Adaptive plan generation - superior to plan library approach



Sibolt P et al. PhIRO 2021
De Jong R et al. Radiation Oncol 2020

CT-based oART vs MRgRT

PROS

- Lesser training requirements on CT based oART
- On couch time is similar
- Easier logistics and financial superiority of CT based systems

CONS

- Delineation for soft tissue inferior to MR-based systems
- Automated influencer contour generation might not be possible in certain clinical situations [post prostatectomy, urinary catheter in situ etc]
- Do not yet incorporate the intrafraction imaging [like 3D cine MRI in the MR based systems]

Summary

- MR LINAC
  - High contrast soft tissue imaging
  - On table dose prediction and re-optimization
  - Continuous MRI-guided targeting

  →Better accuracy
- AI–based Online adaptive strategies
  - May reduce planner/physician input and time
- Newer LINAC technologies
  - Better precision → Better therapeutic ratio
  - Ultimate therapy customization
  - Longer time, fewer patients per machine, specialized training
  - Incremental cost - prohibitive
  - Suitable for research settings and tertiary centres with many machines
  - No utility at present as a stand-alone unit or for large scale use

Ongoing Projects

- UMBRELLA-II
  - Technical feasibility of MR – LINAC (Elekta, Netherlands)
  - Started in 2019 and plans accrual of 140 patients to test multiple new techniques and software
- MOMENTUM (Multi-OutcoMe EvaluatioN of radiation Therapy Using the MR-linac)
  - International Registry for Evidence-Based Introduction of MR-Guided Adaptive Therapy
  - Started within the MR-LINAC Consortium in 2019