Marco Esposito
Medical Physics ICTP

Offline and online Adaptive radiotherapy

Joint ICTP-IAEA Workshop on Radiation Protection in Image-Guided Radiotherapy (IGRT)

Outline

- **Introduction**
- **Imaging modality and technology for adaptive radiotherapy**
- **Anatomical changes requiring adaptation**
- **Offline Adaptive radiotherapy**
- **Online Adaptive radiotherapy**
- **Managing Uncertainties**

Principles of adaptive radiotherapy

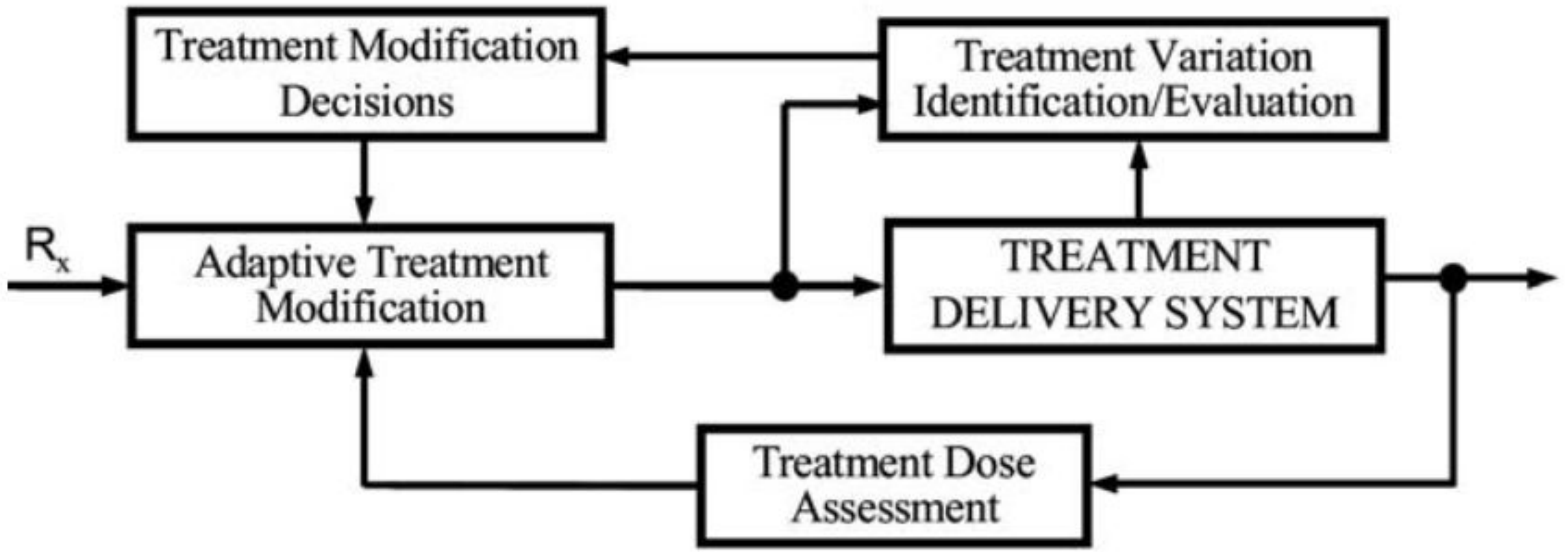


Figure 1 Flow chart of Model Identification Adaptive Control based radiotherapy system.

Adaptive radiotherapy workflow

- On board 3D imaging for anatomy monitoring
- Contour adaptation from planning CT to current anatomy
- Recomputation of the treatment plan based on the current anatomy
- Re-optimizing the treatment plan
- Plan-specific quality assurance
- Delivery of the adapted treatment plan

On board 3D imaging for anatomy monitoring

CT-on-rails

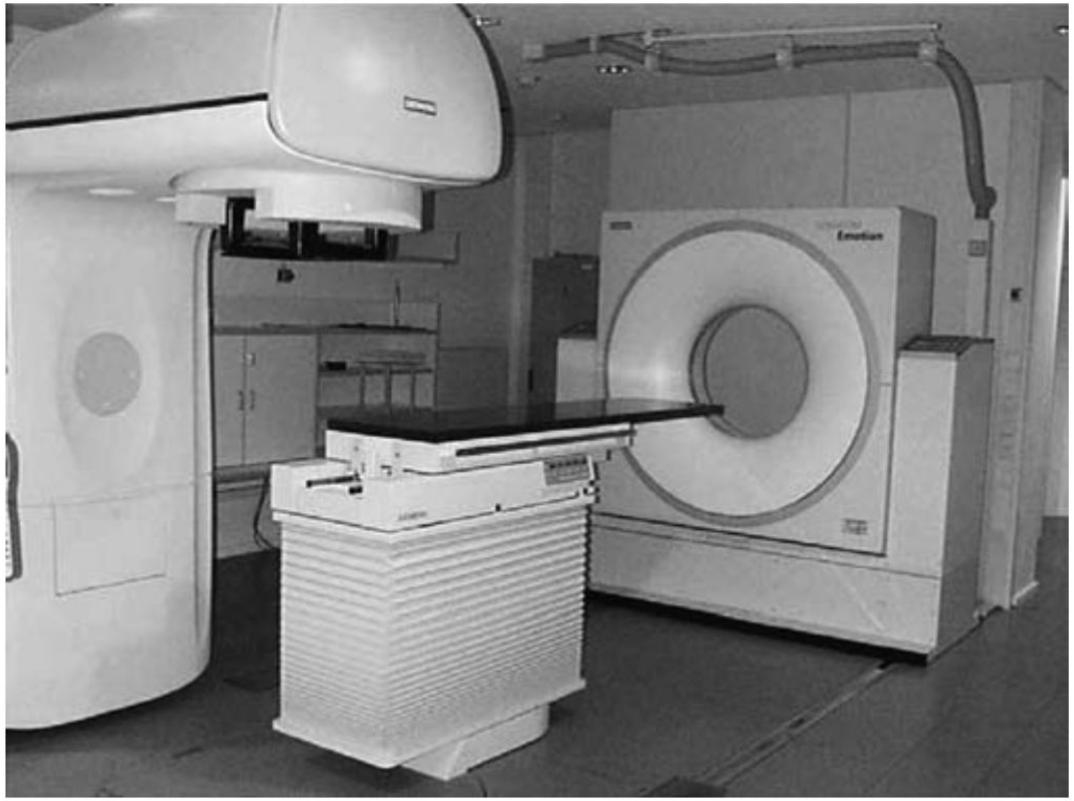


FIGURE 9.7 Example for CT-on-rails: SIEMENS CTVision with a PRIMUS accelerator (90° geometry).

CT-on-rails technology was first developed in Japan (Uematsu et al. 1996; Uematsu et al. 1999) and was commercially available from three different vendors.

In-room CT solution for volumetric imaging provodes the best image quality achievable compared to all other CT-based IGRT techniques .

The calibration between Hounsfield units and relative electron densities as required for dose calculations is well-established.

On board 3D imaging for anatomy monitoring

CT-on-rails: cons

1) Need additional bunker space

2) Requires additional movements of the patient couch, increasing setup time compared to linac-integrated CT solutions.

3) Additional uncertainties related to isocenter shift

4) Does not allow for monitoring of the patient during the treatment.

On board 3D imaging for anatomy monitoring
X-rays cone beam ct

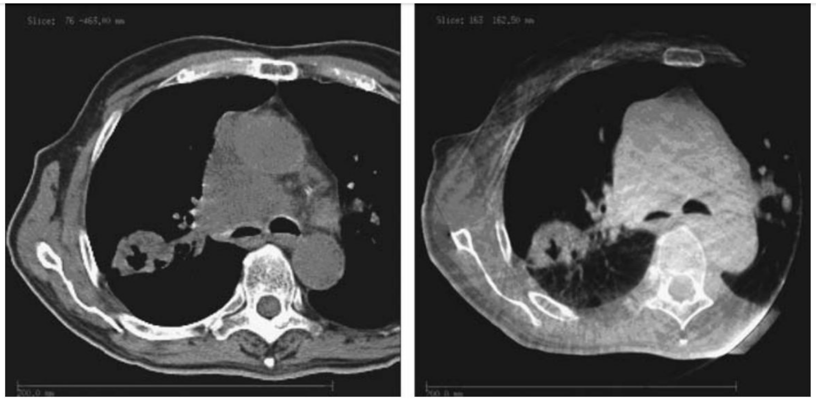
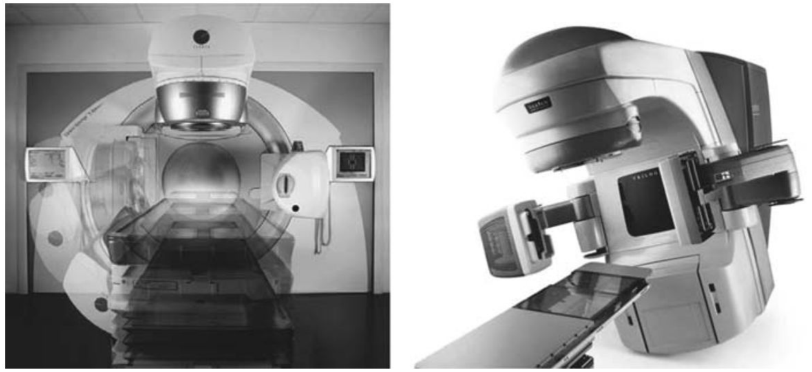


FIGURE 9.10 4D diagnostic CT in comparison to a 4D CBCT.



(a) (b)

FIGURE 9.11 (a) Synergy system of ELEKTA (Courtesy of Elekta). (b) Trilogy system of VARIAN (Courtesy of Varian).

David Jaffray group pioneered the design and construction of kV CBCTs (Jaffray et al. 1999, 2002)

Allows acquisition of patient anatomy in treatment position, without repositioning

Enables monitoring of patient anatomy during therapy

On board 3D imaging for anatomy monitoring

CBCT: cons

1. Low image quality (scatter correction needed);

2. Contouring is difficult

3. Discrepancy in HU between planning CT and daily CBCT

On board 3D imaging for anatomy monitoring

MRI-linac

On board 3D imagnig for anatomical monitoring

MRI-linac

- Superior soft tissue contrast compared to CT and CBCT
- Continuous intra-fraction MR imaging
- Online adaptive MRIgRT that incorporates real-time anatomical changes such soft-tissue deformity, volume changes, and changes in OAR positioning
- Incorporation of MRIgRT-based functional imaging has the potential of detecting biochemical changes that precede anatomical changes

On board 3D imagnig for anatomical monitoring

MRI-linac: cons

1) MRI scans do not readily provide the electron density distributions needed for dose calculations, so strategies for generating synthetic CT scans are needed.

2) Long delivery times, high cost

3) High magnetic fields MRI, introduces addition safety risk for staff and patients

4) Low magnetic fields MRI have limitation in image quality and functional acquisitions

Contour adaptation for anatomical changes

1. Deformable registration of old contours onto the new anatomy
2. Atlas-based auto contouring
3. Deep learning based auto contouring (through convolutional neural network CNN)

Adaptation for Anatomical changes

- Anatomical changes can occur in any region of the body but the pattern of change is region-specific
- Affect both tumor and healty organs
- Three types of anatomical changes can occur:

Day by day anatomic changes

1) Systematic changes

2) Random changes

3) Changes induced by the irradiation

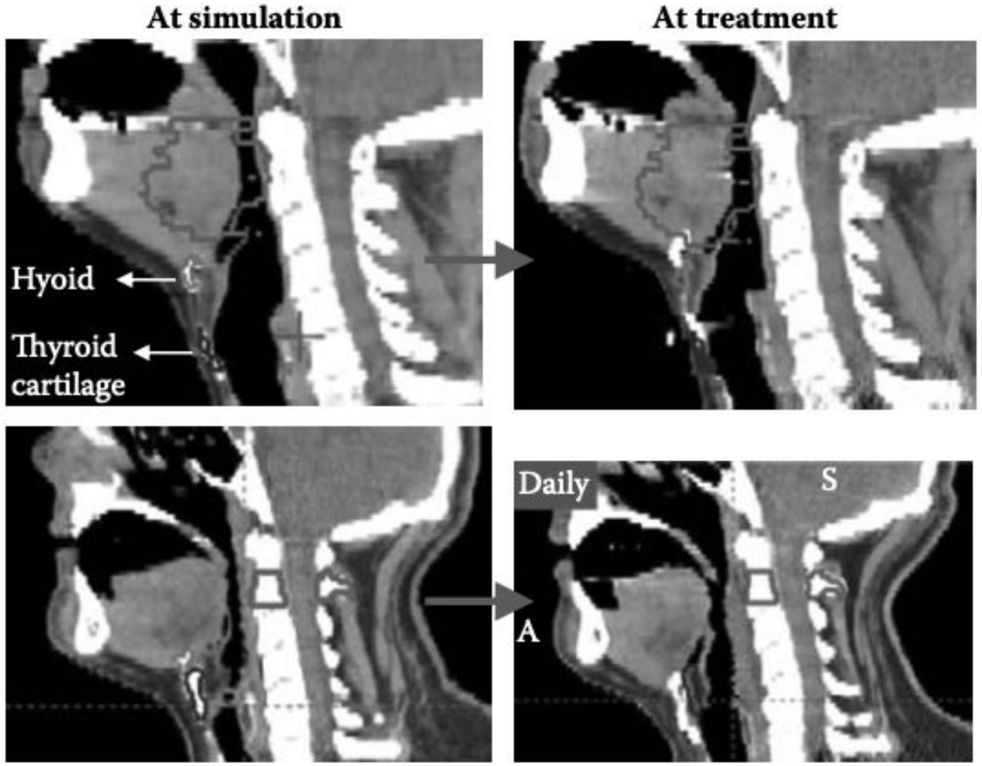


FIGURE 17.3 Positions of the hyoid bone and the thyroid cartilage at various computed tomography (CT) scanning times. The positions can change noticeably during the simulation or during the course of treatment. Because the swallowing action is usually infrequent and is of short duration, its intrafractional dosimetric effect is much less than its systematic effect. The simulation CT could be biased toward an infrequent anatomical pose as a consequence of swallowing. If the hyoid or cartilage is captured at the most inferior position (top row), the larynx may receive a higher dose during treatment. In the opposite situation, if the hyoid and cartilage are captured at the most superior position during CT simulation (bottom row), a primary target near the base of tongue could be underdosed during treatment.

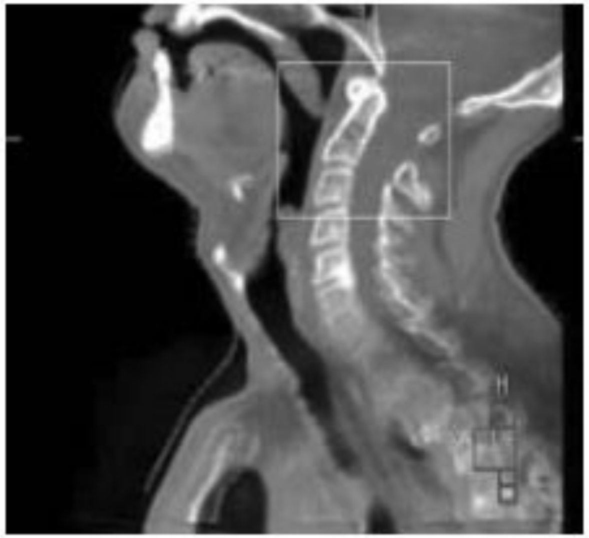


FIGURE 11.2 Local rigid alignment. Spinal positioning to provide tumor coverage and avoid cord overdose for a head and neck patient. A “clipbox” (white square) describes the region in which rigid alignment is performed to optimize the match between subregions of the treatment planning and cone-beam CT scans. Matched intensities are visible as grayscale values from mixing the overlaid colors. More distant anatomy is less accurately aligned, as can be seen by the color separation in the lower region of the spine. (Courtesy of Jan-Jakob Sonke, Netherlands Cancer Institute.)

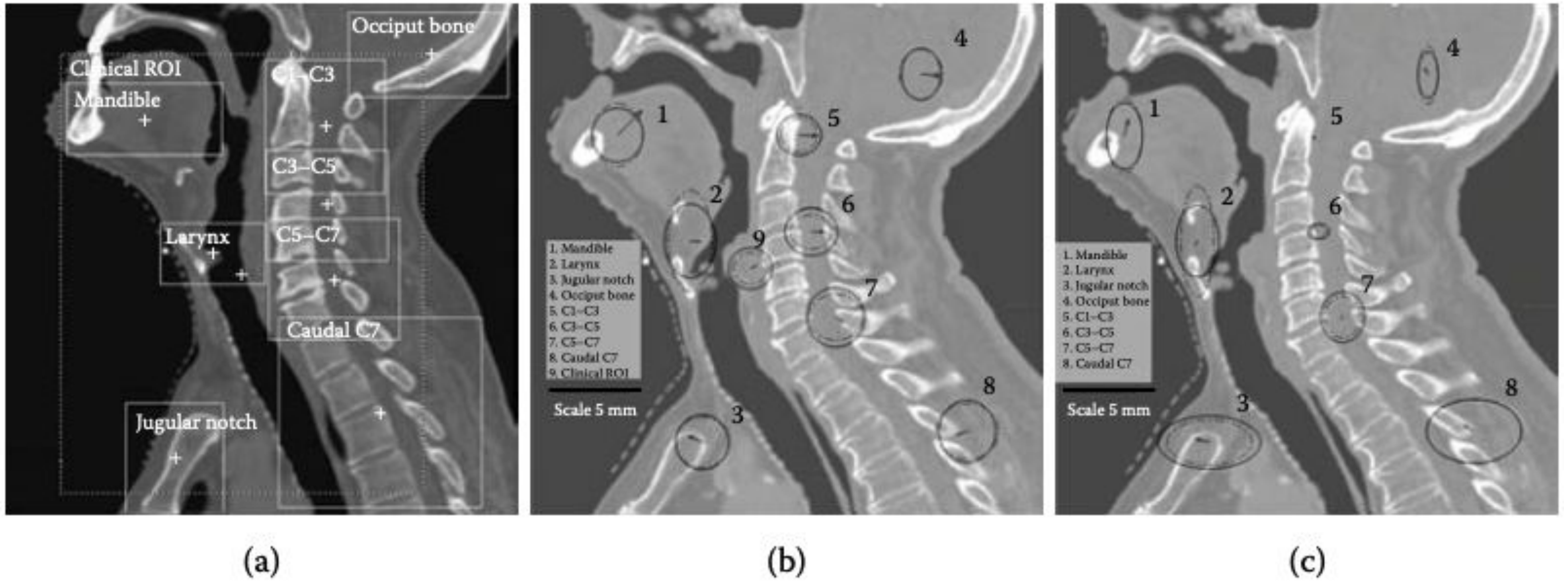


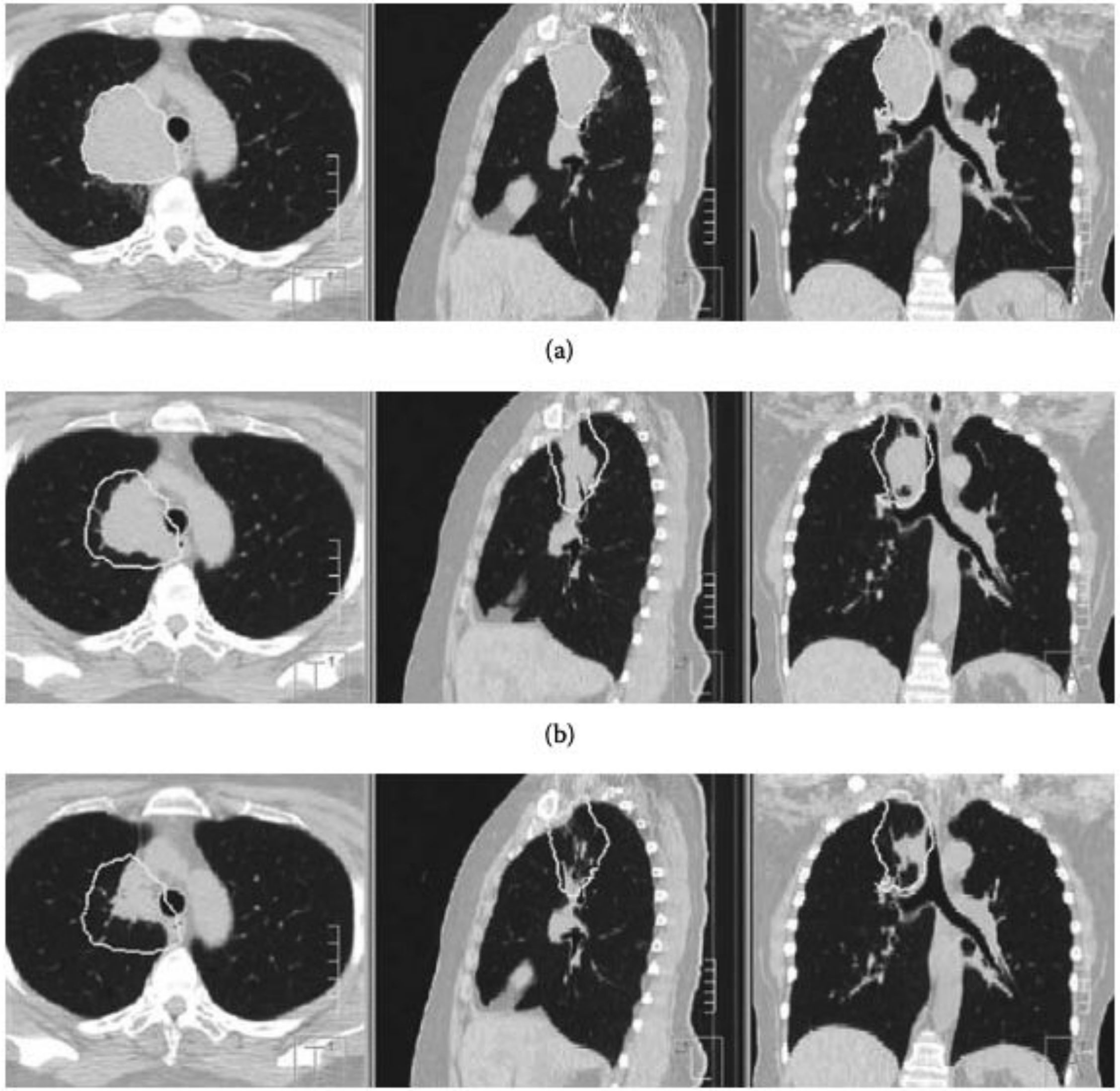
FIGURE 17.2 The eight subregions in the head and neck site chosen to study relative setup variations in 38 patients. (a) The large dotted box represents the clinically used region of interest (ROI) for patient positioning. (b) The residual setup uncertainties in local regions if the single large ROI was chosen as the reference ROI for patient setup. The systematic and random errors are plotted as dotted and solid ellipses, respectively, with the length of the major axes corresponding to one standard deviation. (c) The residual setup uncertainties if the vertebrae C1–C3 were chosen as the reference for patient setup. Note increase in uncertainty with longer distances from the reference ROI. (Reprinted from van Kranen, S., et al. 2009. *Int J Radiat Oncol Biol Phys* 73:1566–73. With permission.)

Table II. Residual setup errors (RSE) for different bony structures in HNC radiotherapy; with and without daily IG.

	No IG								
	μ (mm)			Σ (mm)			σ (mm)		
	LR	AP	SI	LR	AP	SI	LR	AP	SI
Maxilla	0.4	−0.9	1.4	1.6	1.9	1.9	1.9	1.4	1.8
Mandible	0.3	−0.6	1.0	2.2	3.1	2.3	1.8	2.2	2.1
C1	N/A	−0.8	1.9	N/A	1.8	1.5	N/A	1.4	1.7
C2	N/A	−1.1	1.7	N/A	2.2	1.3	N/A	1.6	1.7
C4	−0.1	−1.3	1.8	1.7	2.9	1.4	1.9	2.3	1.8
C5	−0.3	−1.1	1.8	1.8	3.0	1.5	1.9	2.4	1.8
	Residual errors with daily IG								
	μ (mm)			Σ (mm)			σ (mm)		
	LR	AP	SI	LR	AP	SI	LR	AP	SI
Maxilla	−0.5	−0.3	−0.2	1.6	1.9	1.3	1.6	1.5	1.3
Mandible	−0.6	−0.3	−0.6	1.1	2.3	2.1	1.5	1.7	1.5
C1	N/A	−0.3	−0.5	N/A	1.6	0.8	N/A	1.4	1.1
C2	N/A	−0.2	−0.3	N/A	0.7	0.6	N/A	1.1	1.0
C4	0.0	−0.5	−0.4	0.7	1.2	0.7	1.2	1.5	1.0
C5	0.2	−0.4	−0.4	0.7	1.5	0.7	1.2	1.6	1.0

AP, anterior-posterior; LR, left-right; SI, superior-inferior; μ, mean systematic error; Σ, SD of systematic errors; σ, root-mean square of random errors. The image registrations were based on reference structures outlined in DRR images; including the cervical vertebrae C1 to C3 and the angle of the mandible.

Djordjevic, M., et al *Acta Oncologica*, *53*(5), 646–653. https://doi.org/10.3109/0284186X.2013.862593



(a) (b) (c)

FIGURE 19.1 Reduction of lung tumor gross tumor volume (GTV). Computed tomography images were acquired (a) pre-RT with initial GTV (b) at 30 Gy, with initial contour displayed, showing 42% volume reduction, and (c) at 50 Gy, with initial contour displayed, showing 71% volume reduction. (Reprinted from Fox, J., et al. 2009. *Int J Radiat Oncol Biol Phys* 74(2):341–8. With permission.)

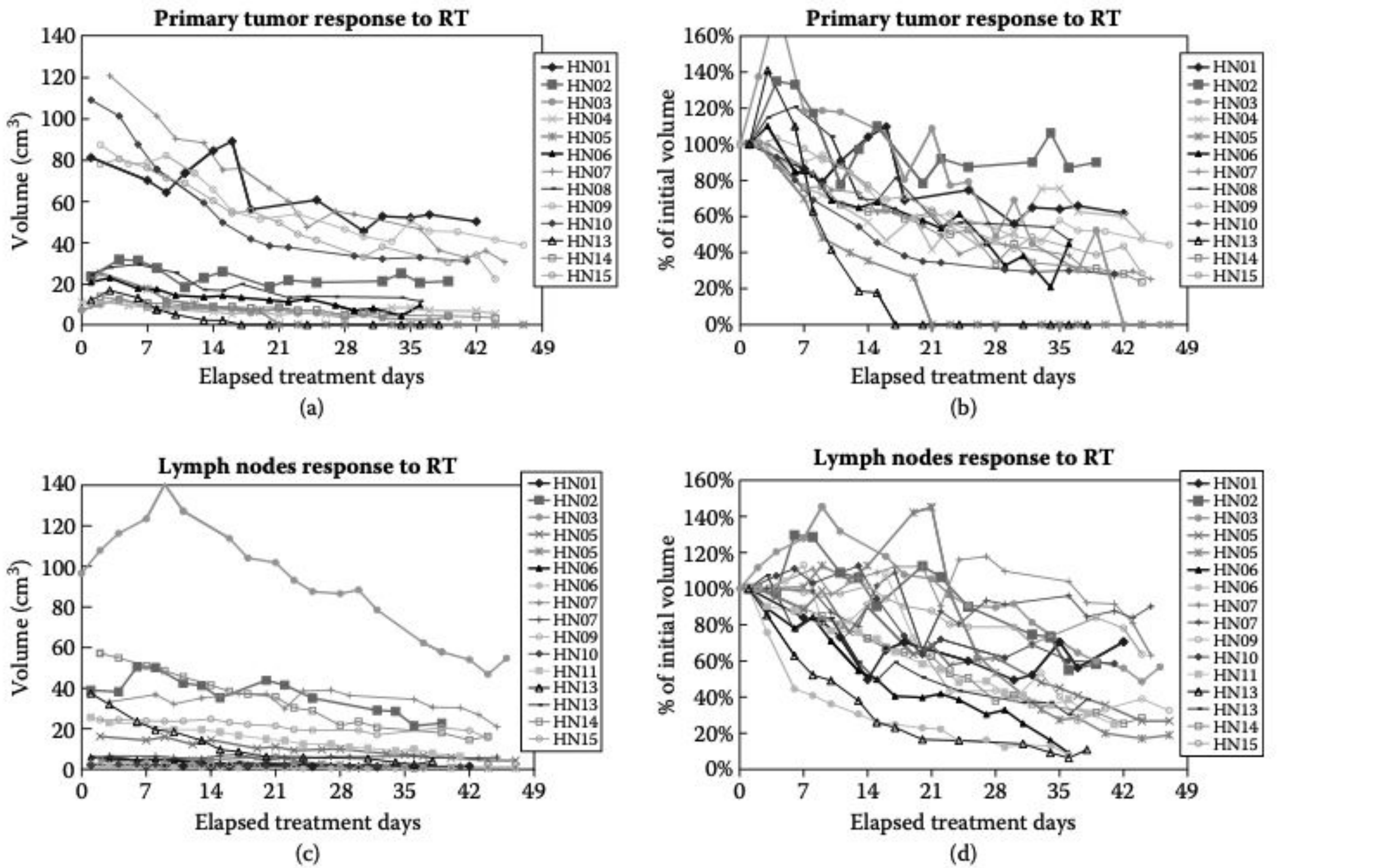


FIGURE 17.5 Gross tumor volume (GTV) changes over time among patients with head and neck cancers: Both primary tumor ((a) and (b)), and lymph nodes greater than 2 cm³ of volume ((c) and (d)) show similar trends. The GTVs decreased at a median rate of 0.2 cm³ or 1.8% of initial volume per treatment day. (Reprinted from Barker Jr., J. L., et al. 2004. *Int J Radiat Oncol Biol Phys* 59:960–70. With permission.)

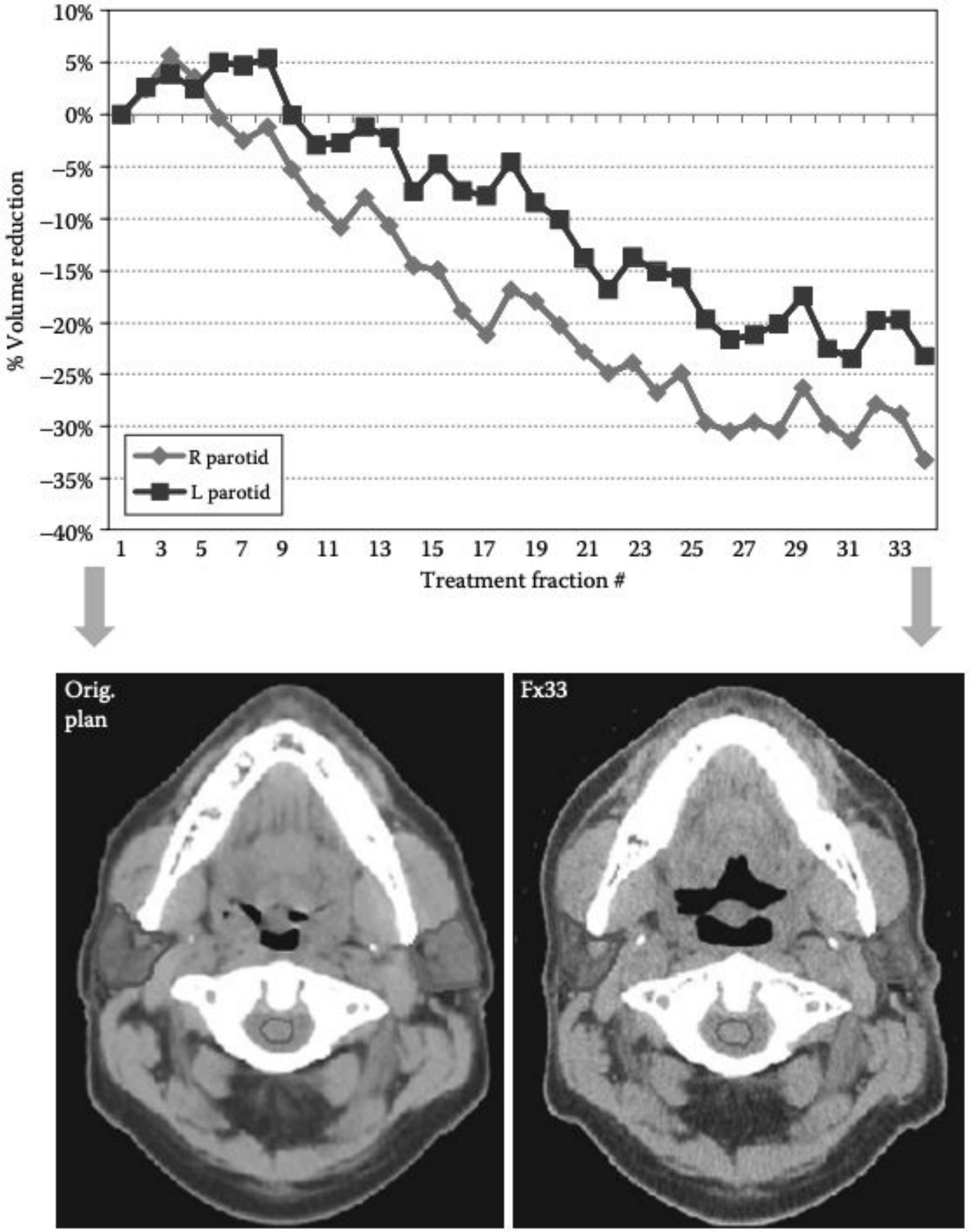


FIGURE 17.7 Example of volume change in parotid gland during a 33-fraction intensity-modulated radiation therapy treatment. The top figure shows the percent of volume change for each parotid as a function of treatment fraction. The bottom pictures show an axial computed tomography slice of the parotid before radiotherapy (RT; bottom left) and after 33 fractions of RT (bottom right).

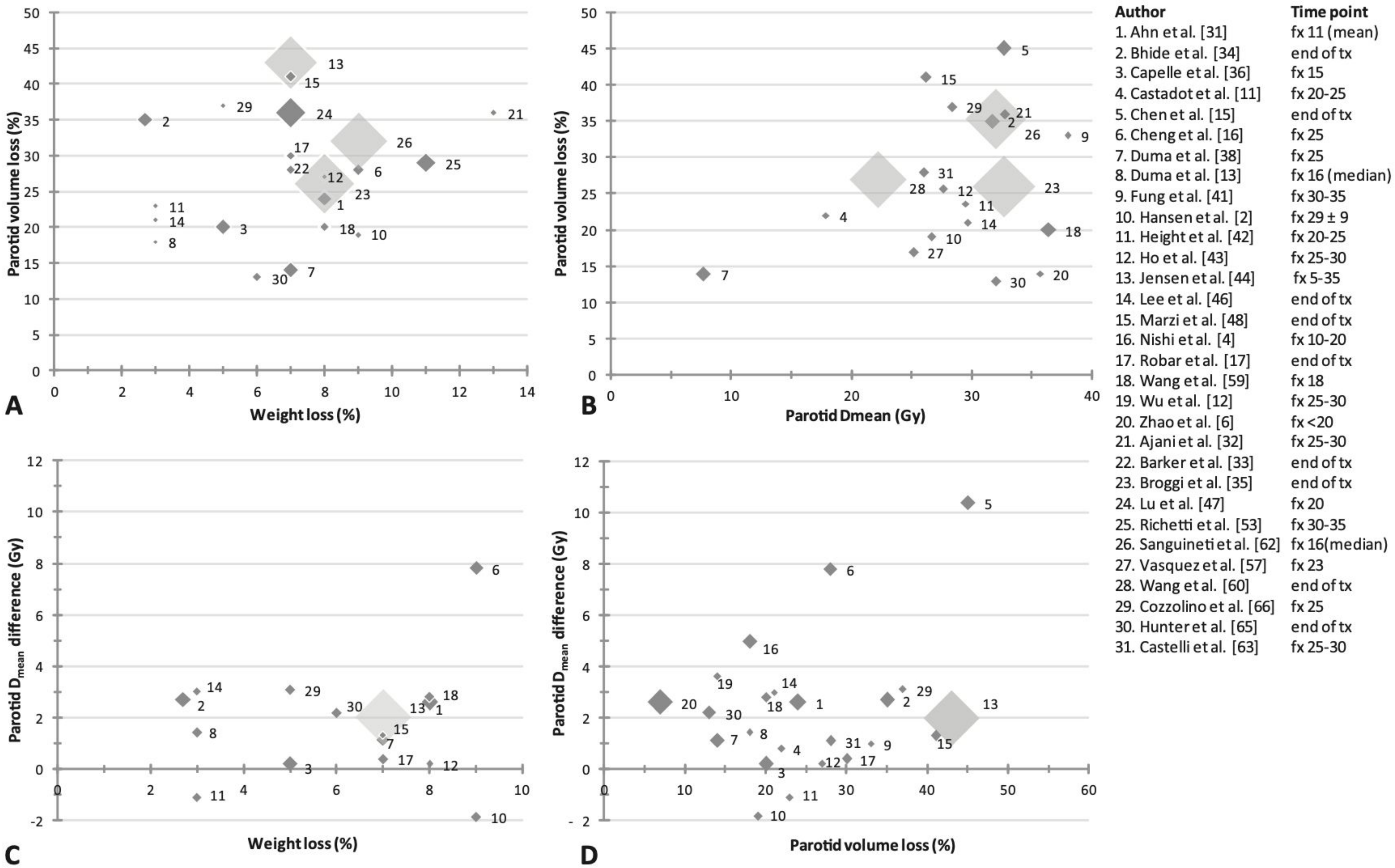


Fig. 2. (A) Parotid volume loss vs. patient's weight loss (22 studies), (B) parotid volume loss vs. planned parotid mean dose (20 studies), (C) parotid mean dose increase (repeat CT – plan CT) vs. weight loss (16 studies), and (D) parotid mean dose increase (repeat CT – plan CT) vs. parotid volume loss (23 studies) during radiotherapy. The size of the data points is proportional to the number of patients included in the study (minimum 10, maximum 87 patients). fx = fraction, tx = treatment. Time point: time of the repeat scan analysed.

Offline adaptive radiotherapy
Average anatomy volume

An average anatomical model can be estimated by:

- **Performing deformable registration of the planning scan to the scans of the initial fractions,**
- **Calculating the average deformation vector field,**
- **Deforming the planning scan and corresponding structures to create a synthetic scan representing the average anatomical configuration**

A new treatment plan can subsequently be optimized on the average anatomy model.

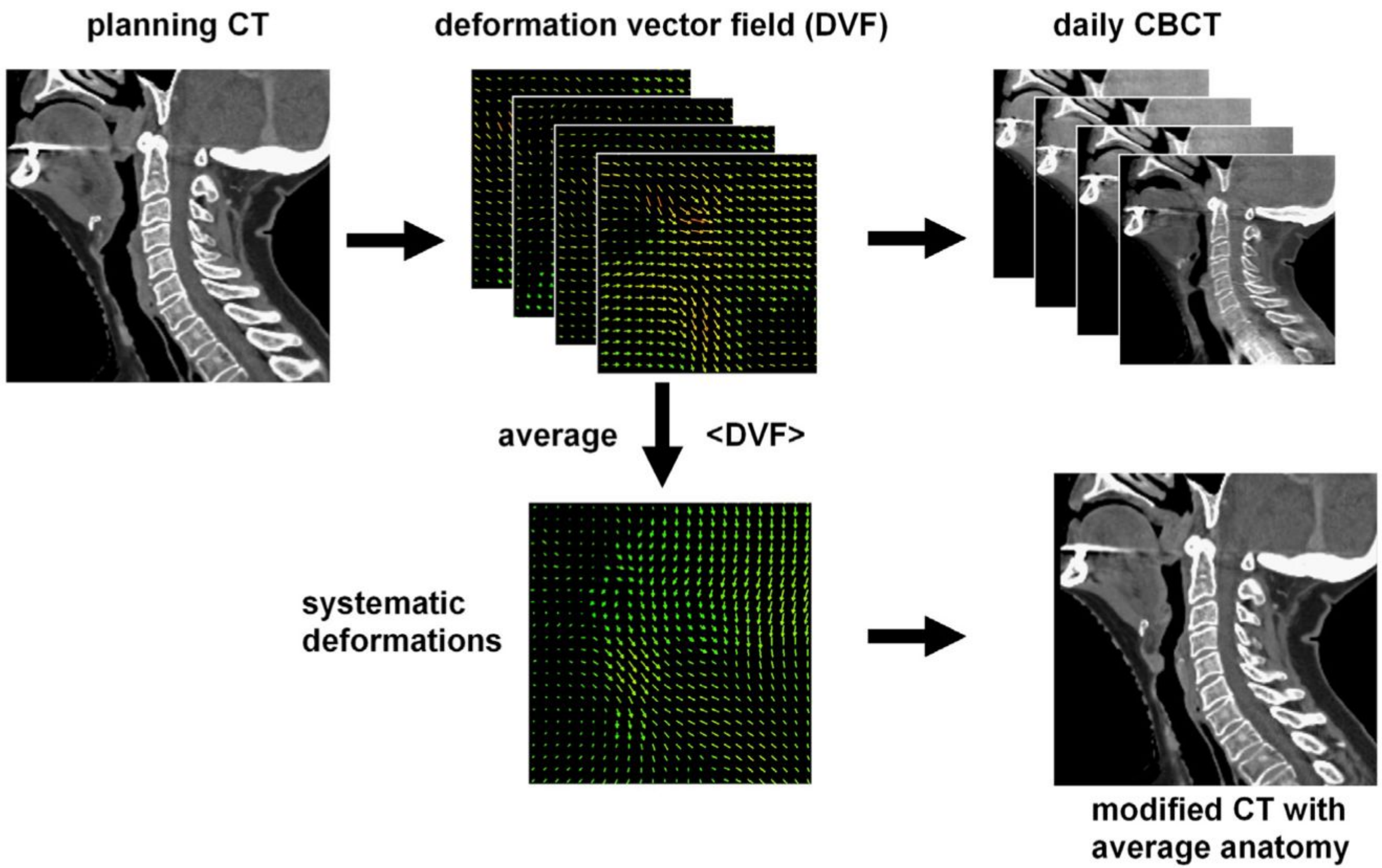


Fig. 1. Adaptive intervention with an average anatomy model. Daily deformations are calculated with non-rigid registration of CBCT scans to the planning CT. Systematic deformations are estimated with the average over a series of deformation vector fields. Application of the average deformations to the planning CT results in a modified CT for plan adaptation.

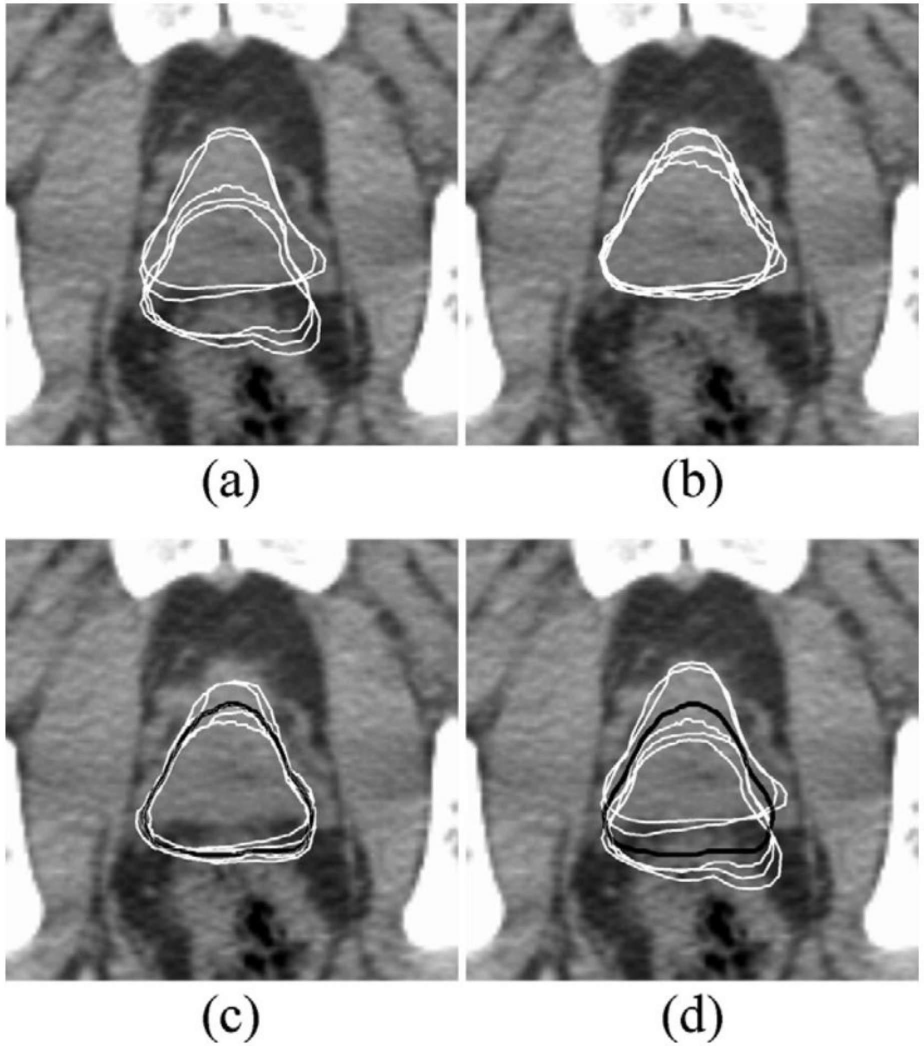


Fig. 1. Construction of the average prostate shape and position (planning computed tomography [pCT] scan, axial view). (a) Prostates of the *first 5 scans* resampled on the planning CT scan after bone matching; (b) prostates matched to the prostate of the planning CT scan; (c) prostates moved to the average position and calculated average prostate shape (black line); (d) prostates of the *first 5 scans* after bone matching, and average prostate (black line).

Nuver TT, et al Int J Radiat Oncol Biol Phys 67:1559-1567, 2007

Offline adaptive radiotherapy

Triggered adaptation

Triggered adaptation refers to the process of adapting the treatment plan when exceeding a certain "threshold," for example, when the patient experienced considerable anatomical changes such as weight loss.

ORIGINAL ARTICLE

Local Control and Toxicity of Adaptive Radiotherapy Using Weekly CT Imaging: Results from the LARTIA Trial in Stage III NSCLC

Sara Ramella, MD,[a,*] Michele Fiore, MD,[a] Sonia Silipigni, MD,[a] Maria Cristina Zappa, MD,[b] Massimo Jaus, MD,[c] Antonio Maria Alberti, MD,[d] Paolo Matteucci, MD,[a] Elisabetta Molfese, MD,[a] Patrizia Cornacchione,[a] Carlo Greco, MD,[a] Lucio Trodella, MD,[a] Edy Ippolito, MD,[a] Rolando Maria D'Angelillo, MD[a]

[a]*Radiation Oncology, Campus Bio-Medico University of Rome, Rome, Italy*
[b]*Pneumology, Sandro Pertini Hospital, Rome, Italy*
[c]*Thoracic Surgery, Sandro Pertini Hospital, Rome, Italy*
[d]*Medical Oncology, Sandro Pertini Hospital, Rome, Italy*

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Available online - 17 April 2017

Weekly chest CT visualized by two radiation oncologists independently.

For all CT simulations, each physician was able to judge whether reduction was

(1) present and clinically significant

(2) present and clinically nonsignificant,

(3) absent.

In the case of physician agreement for the first category, a Contrast-enhanced CT was performed, a new target volume was delineated, and a new treatment plan (replanning study) was performed.

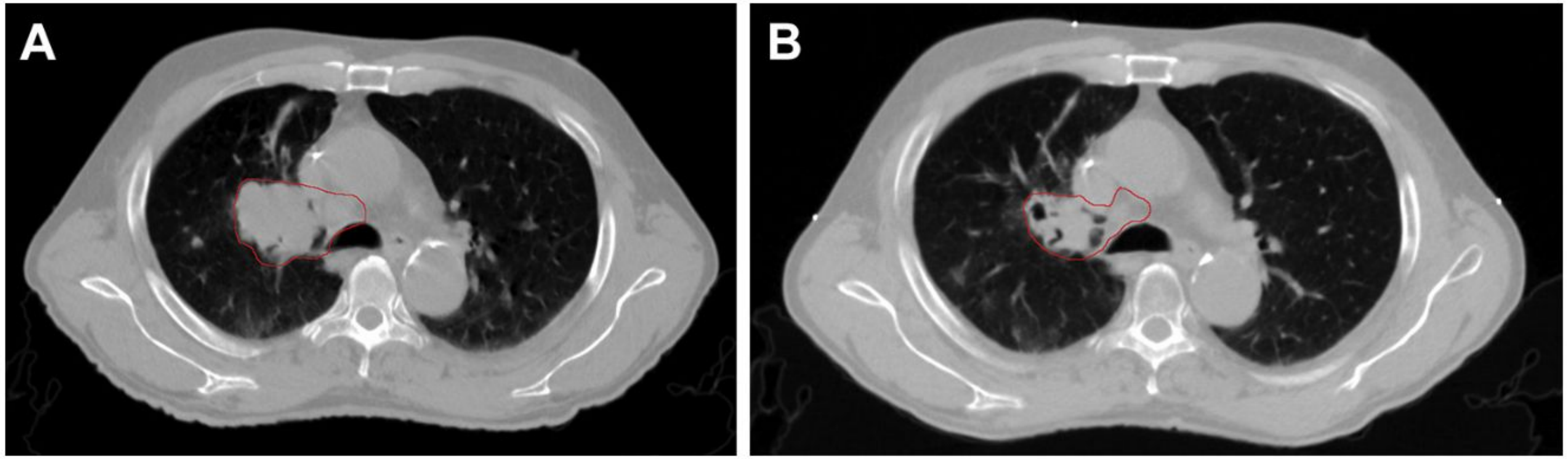
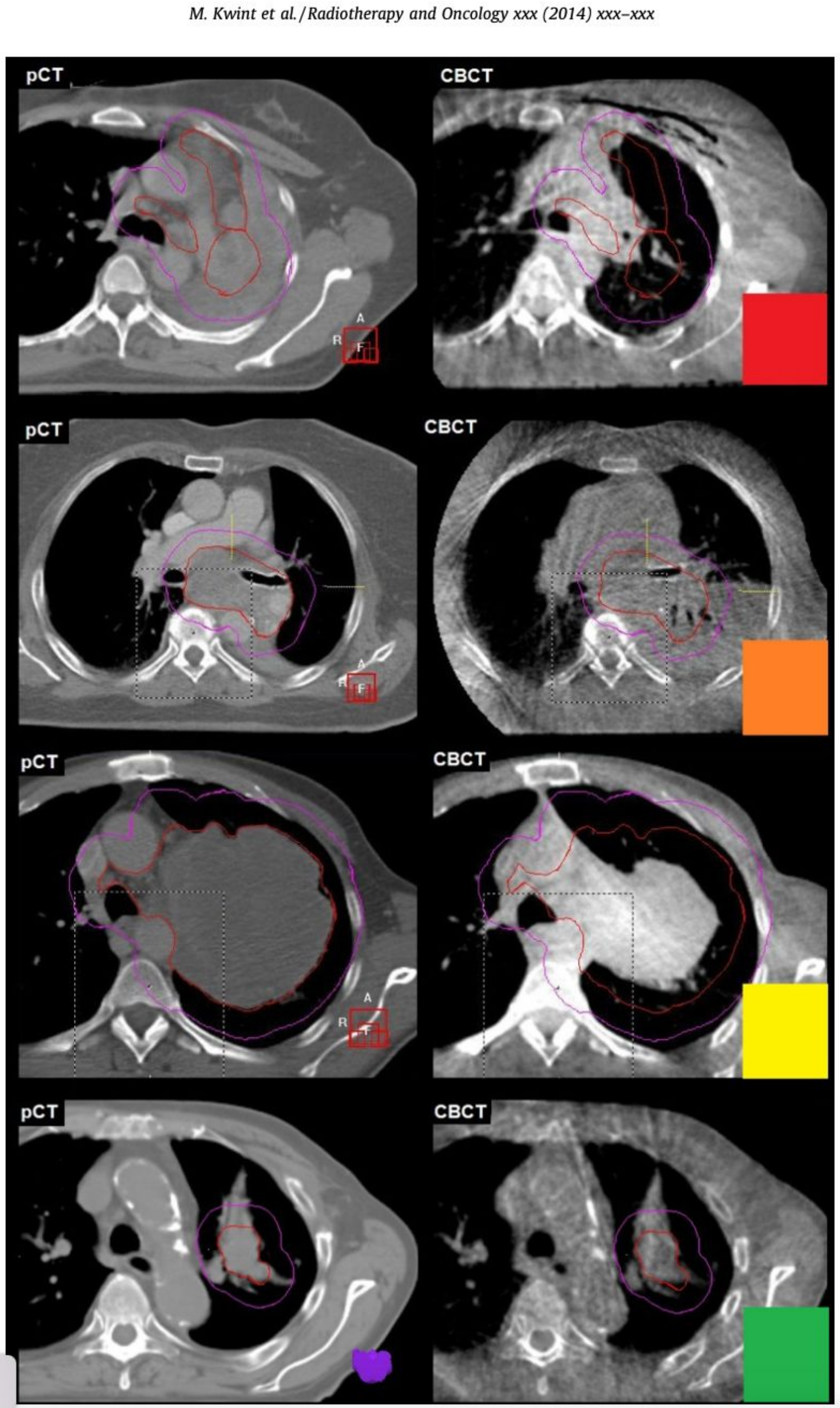


Figure 1. (*A*) Tumor volume delineation at first computed tomography simulation. (*B*) Reduced target volume at replanning computed tomography scan.



Action level red: The GTV is outside the PTV. The radiation oncologist is called immediately and treatment is only given when approved by the radiation oncologist.

Action level orange: The GTV is just inside the PTV. The radiation oncologist is notified by email and has to respond before the next fraction. Further diagnostics are.

Action level yellow: There is an ITAC visible but the GTV is well inside the PTV. The radiation oncologist is notified by email about the ITAC but no response is necessary and treat- ment may continue.

Action level green: No change visible. No action needed.

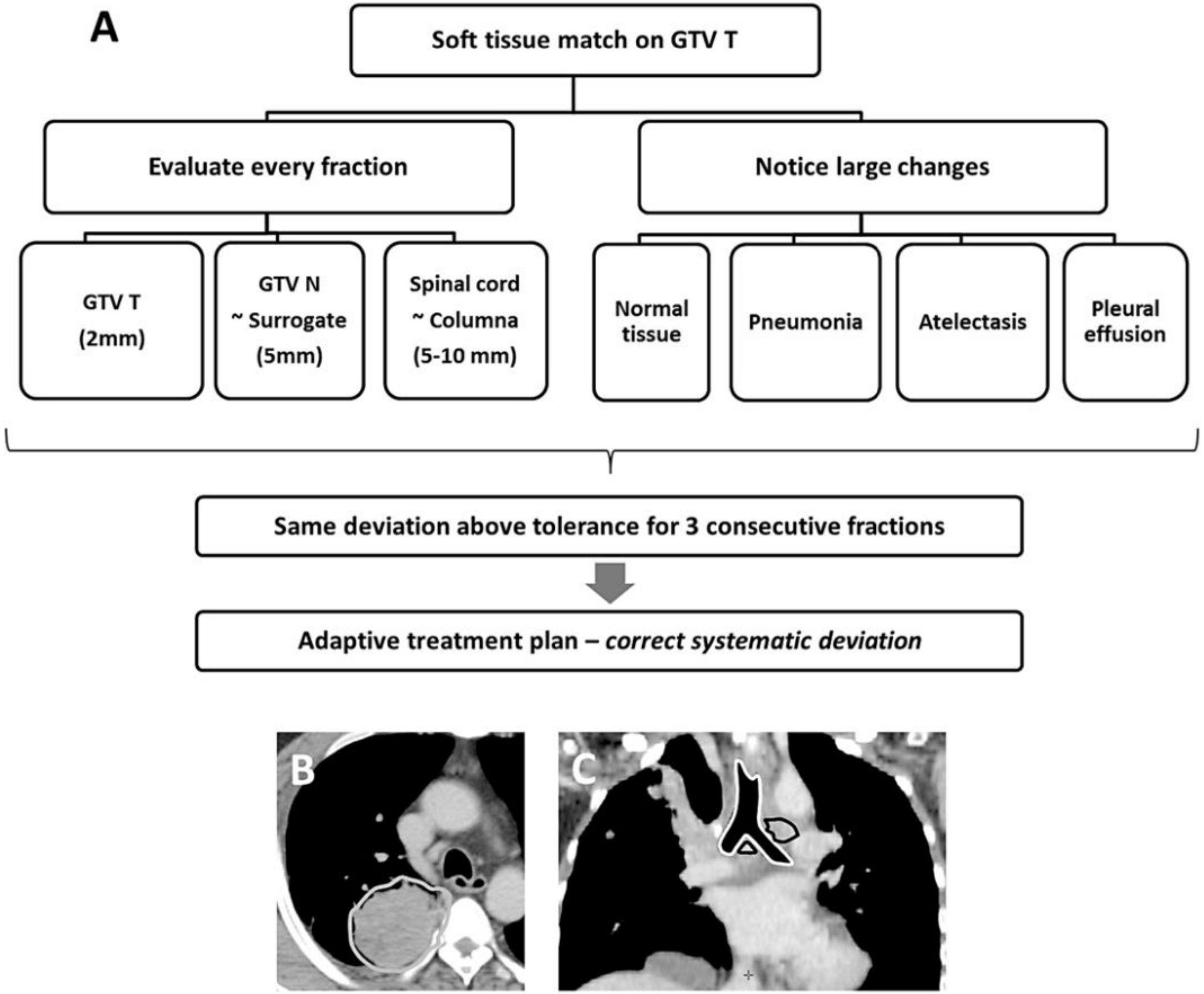


Fig. 1. (A) Flowchart for online adaptive evaluation. (B) Evaluation of primary tumor. A structure (gray) consisting of the GTV-T with a 2 mm isotropic margin is delineated and the primary tumor has to stay within this structure at the daily treatments. (C) The lymph nodes (black) are not easily visible on CBCT and are therefore evaluated via surrogate structures (white) with a 5 mm tolerance.

Please cite this article in press as: Møller DS et al. Adaptive radiotherapy for advanced lung cancer ensures target coverage and decreases lung dose. Radiother Oncol (2016), http://dx.doi.org/10.1016/j.radonc.2016.08.019

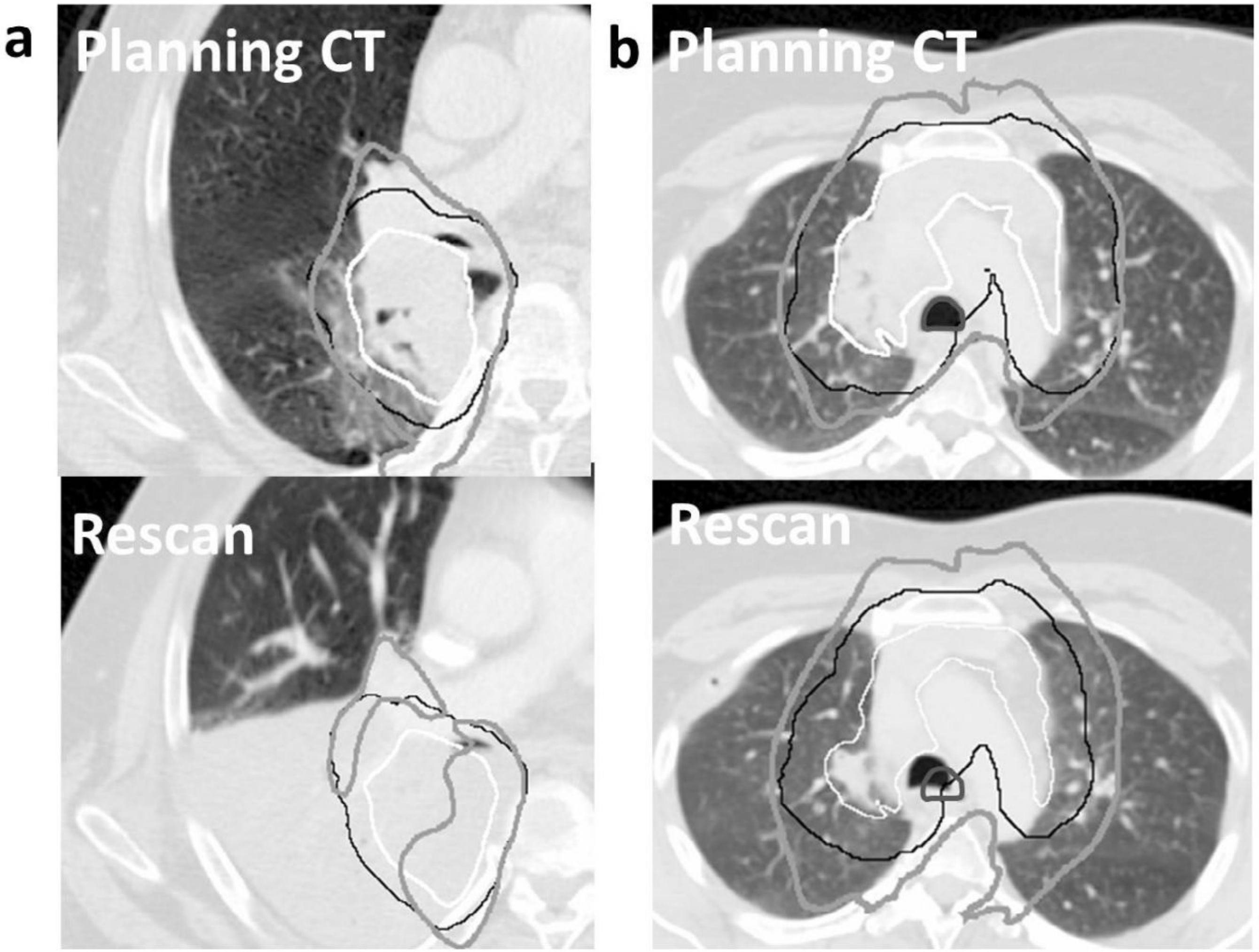
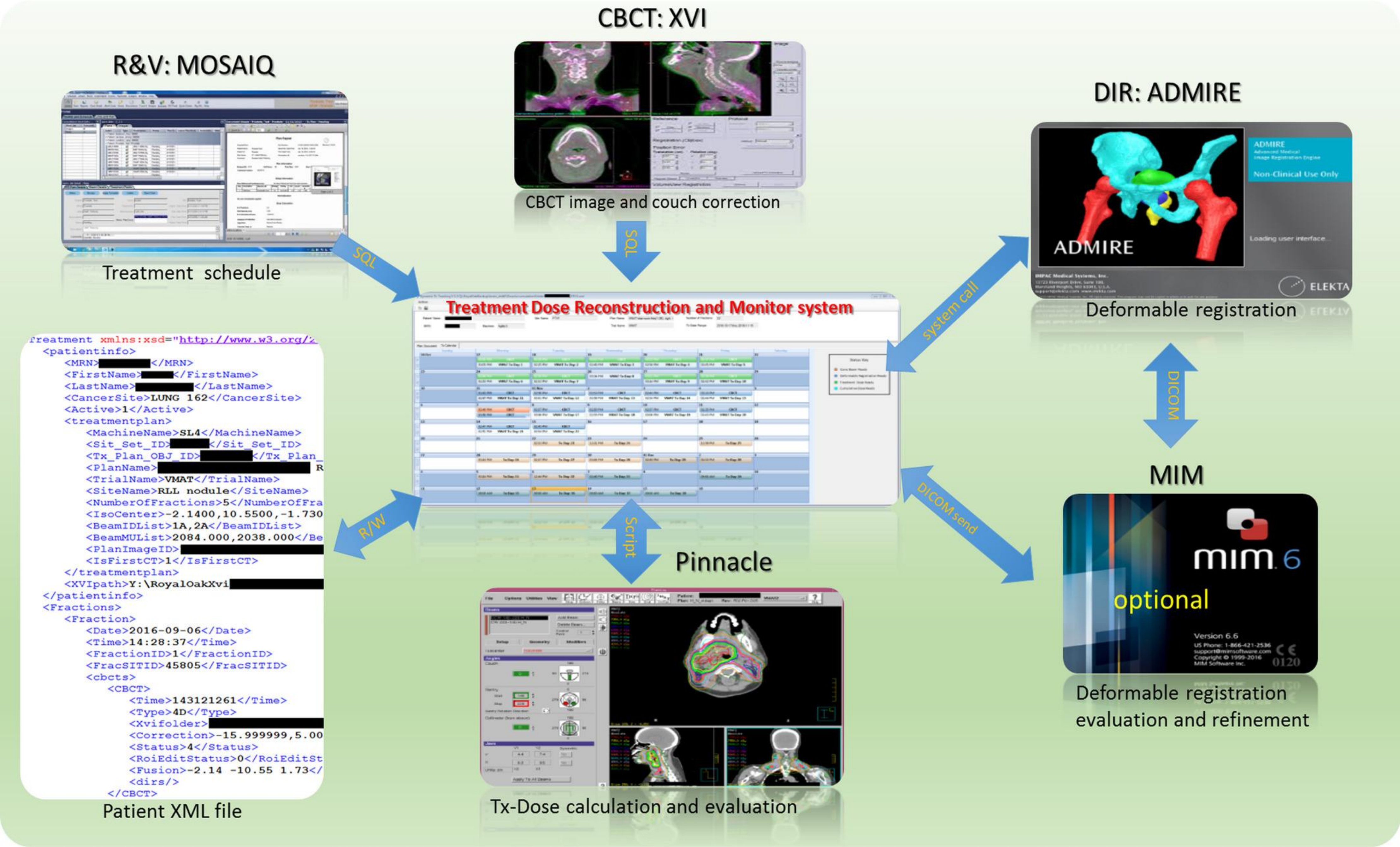
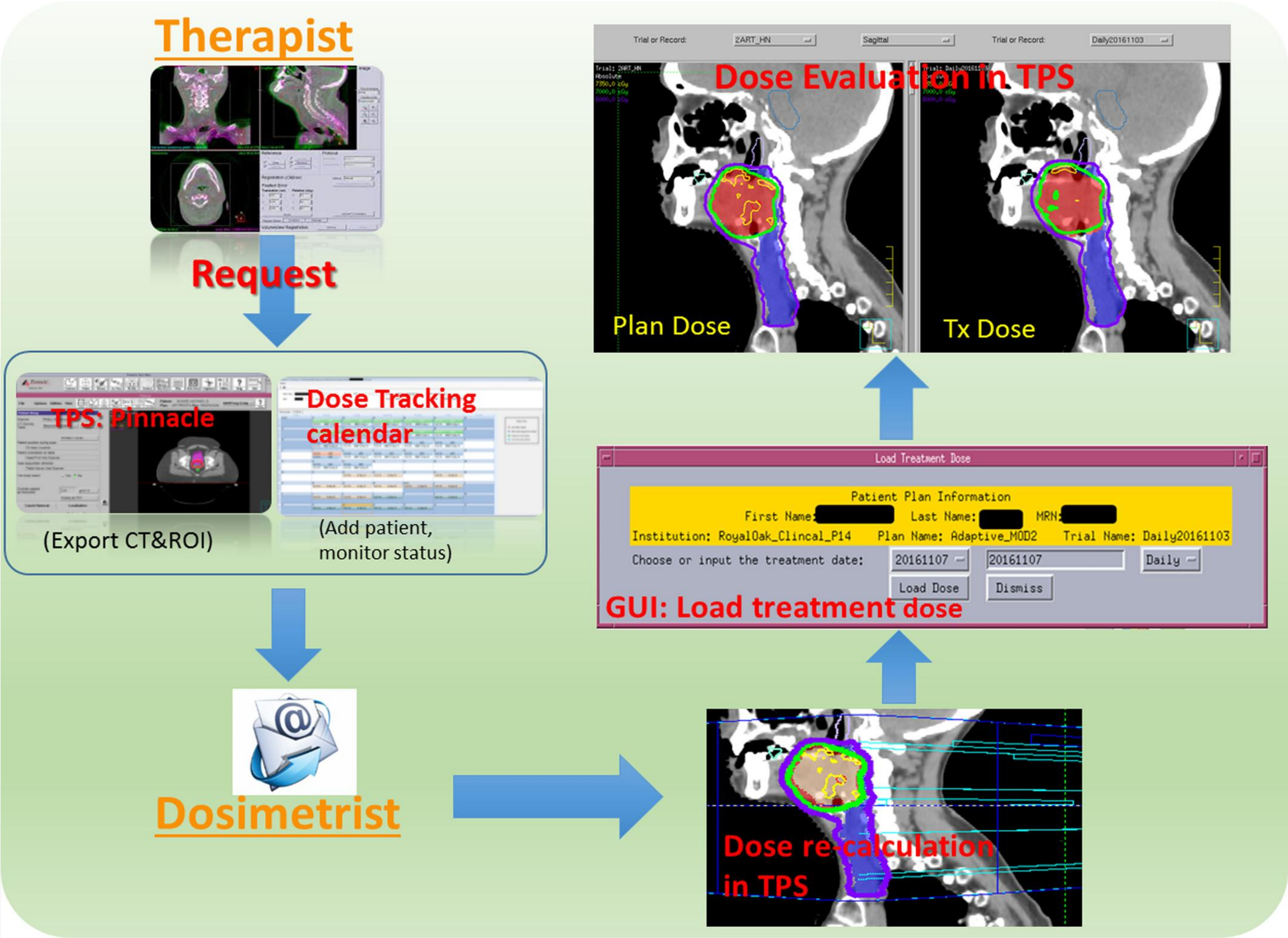


Fig. 2. Comparison of targets and dose coverage for two patient examples. Tumor or lymph node GTV (white), PTV (black) and 95% isodose line (gray) are shown for the plan on the planning CT in the upper panel and re-delineations and recalculation of the plan on the re-scan in the lower panel. a) shows a patient where an atelectasis occurs during the course and under dosage of the target is seen. b) shows a patient where a deformation and shrinkage of the mediastinum gives a deviation on the surrogate (dark gray), but no under dosage of the target is seen. The surrogate is shown on the re-scan as a rigid transfer to illustrate the deviation, whereas GTV, PTV are re-delineations and the isodose line is recalculated.

Møller DS, et al Radiother Oncol. 2016 Oct;121(1):32-38. doi: 10.1016/j.radonc.2016.08.019. Epub 2016 Sep 16. PMID: 27647459.



J Applied Clin Med Phys, Volume: 19, Issue: 6, Pages: 166-176, First published: 10 October 2018, DOI: (10.1002/acm2.12474)


Therapist
Request
TPS: Pinnacle
(Export CT&ROI)
Dose Tracking calendar
(Add patient, monitor status)
Dosimetrist
Dose re-calculation in TPS
Load Treatment Dose
Patient Plan Information
First Name: [redacted] Last Name: [redacted] MRN: [redacted]
Institution: RoyalOak_Clincal_P14 Plan Name: Adaptive_MOD2 Trial Name: Daily20161103
Choose or input the treatment date: 20161107 20161107 Daily
Load Dose
Dismiss
GUI: Load treatment dose
Trial or Record: 2ART_HN
Sagittal
Trial or Record: Daily20161103
Dose Evaluation in TPS
Plan Dose
Tx Dose

Scheduled adaptation

Triggered adaptation has the disadvantage of being unpredictable: arrangements for re-scanning/replanning can only be made once a change has been observed.

Rescanning can occur once (eg, halfway through the treatment course) or several times (eg, weekly during the treatment course)

To limit required resources, the original treatment plan can then be transferred and recalculated on the new anatomy to judge if it is still fulfilling the clinical objectives of tumor coverage and OAR sparing

Online Adaptive Radiotherapy
Library of plans

- Online approaches are required to account for the anatomical changes observed on each particular day.

- The approach most easily to implement consists of a library of treatment plans, created “a priori”, to account for expected anatomical changes such as variations in bladder volume.

The different plans are typically made on a single CT scan (eg an “empty bladder” scan) with interpolated and possibly even extrapolated contours obtained from additional scan(s) (eg a “full bladder” scan) and deformable registration.

Alternatively, a library of plans can be made on different CT scans (eg a “full bladder” scan followed by an “empty bladder” scan or using multiple CBCTs of the first few fractions.

Instead of creating a library based on patient specific variations, one can also design a library based on population statistics to generate different CTVs or PTVs.

For each treatment fraction, the best plan from the library is subsequently selected, typically using visual comparison of the daily in-room scan with the contours of the library plans. For practical reasons, only libraries containing a limited number of plans (2-5) can be generated.

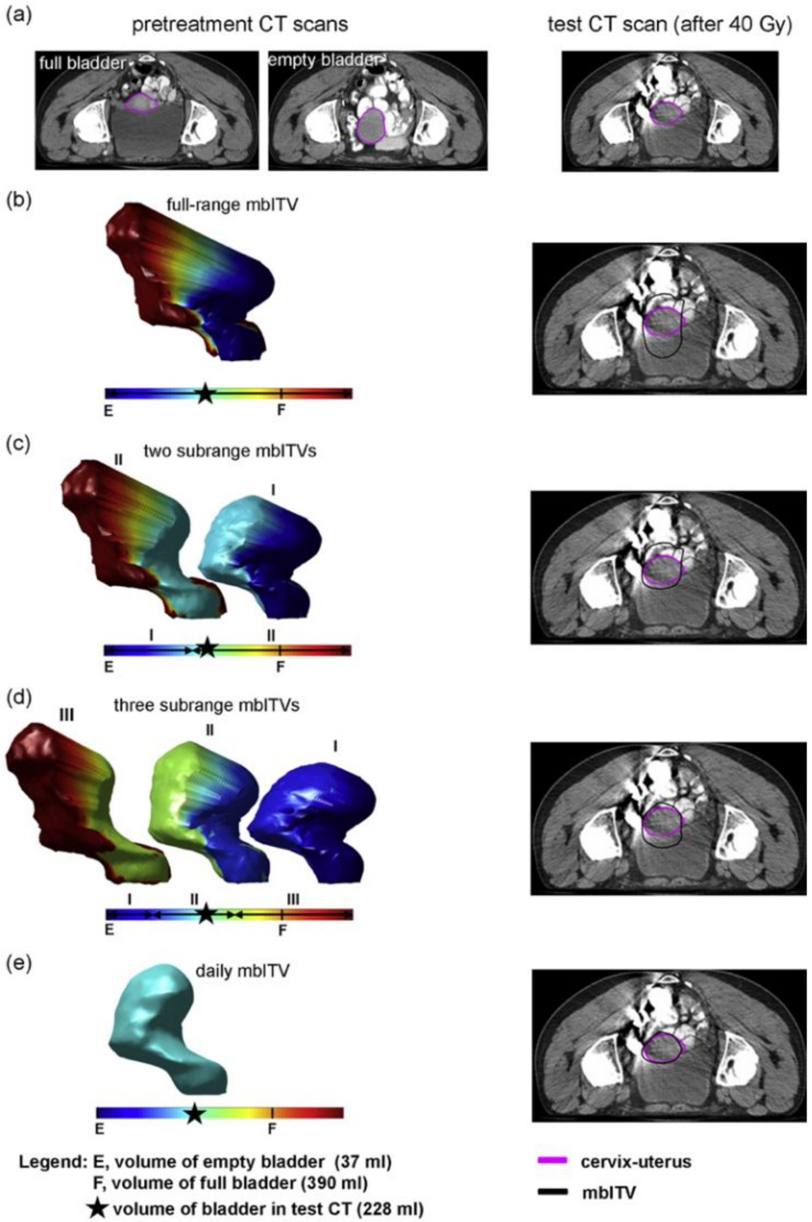
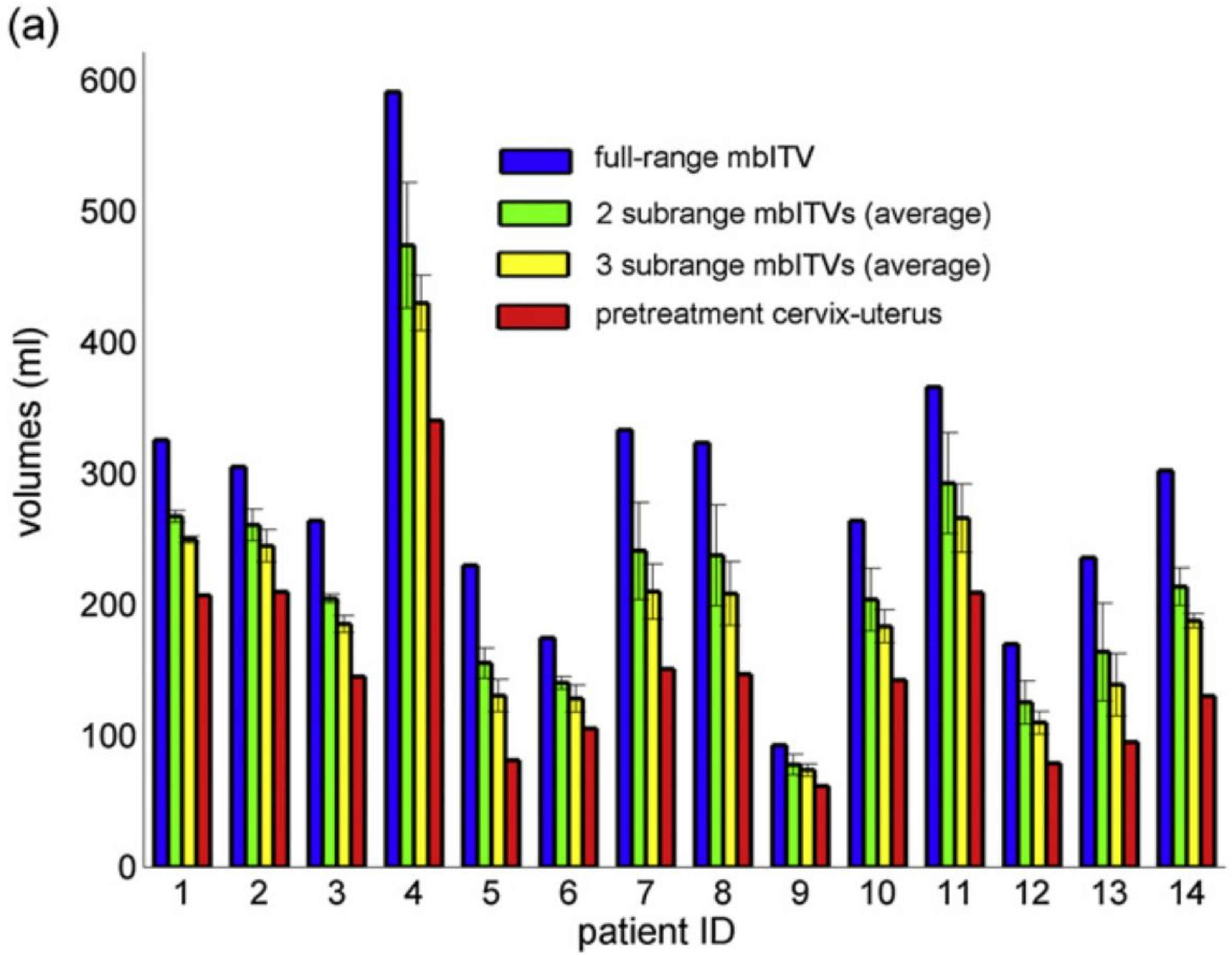


Fig. 2. Left column. (a) Examples for 1 patient of full and empty bladder pretreatment computed tomography (CT) scans. (b–e) Model-based target volumes constructed by using the two CT scans. Right column: example of test computed tomography (CT) scan. Black contour: model-based internal target volume (mbITV) corresponding to the bladder volume in the test CT scan. (b–d). Arrows indicate volume ranges used to construct mbITVs.



Bondar ML, et al Int J Radiat Oncol Biol Phys. 2012 Aug 1;83(5):1617-23. doi: 10.1016/j.ijrobp.2011.10.011. Epub 2012 Jan 21. PMID: 22270164.

Two planning CT scans with a full and empty bladder were acquired in supine position.

Bladder and GTV structures as delineated on the full bladder CT were registered to the bladder and GTV structures from the empty bladder CT

To represent different filling states, the following scale factors were used: 0%, 33%, 67%, 100% and 133%, with 0% and 100% structures corresponding to the empty and full bladder, respectively.

L.J. Lutkenhaus et al./Radiotherapy and Oncology 116 (2015) 51–56

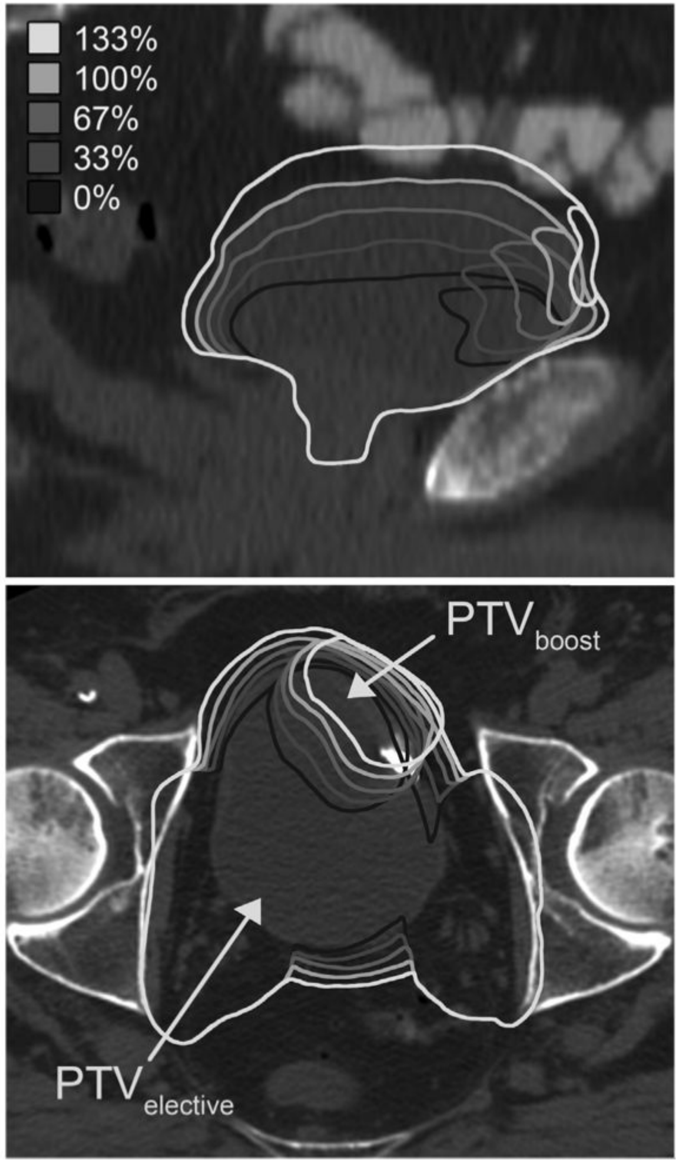


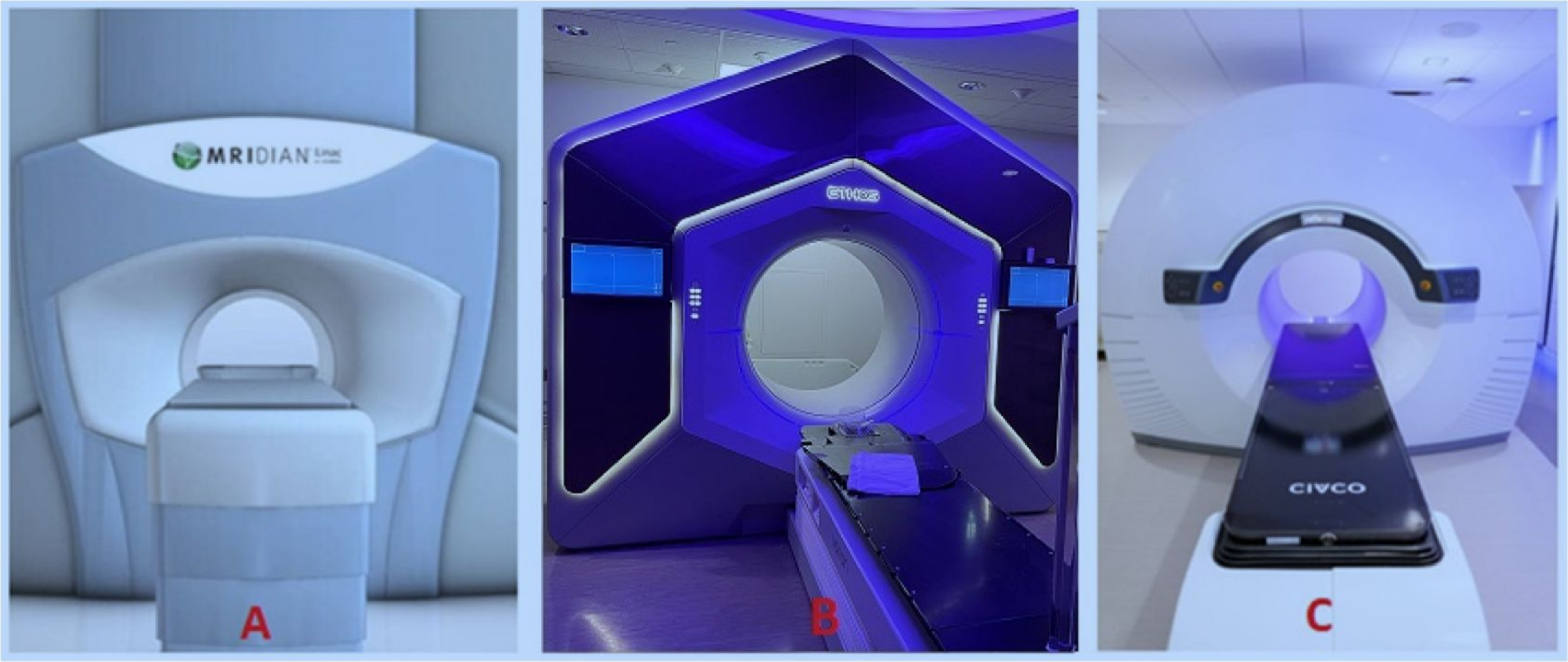
Fig. 1. Target delineations and interpolations. Top: sagittal view of CT scan of full bladder, with projections of bladder and tumor for all interpolations, i.e. 0%, 33%, 67%, 100% and 133%. The tumor volume stays stable, but appears to decrease for larger bladder volumes. This is caused by stretching and moving of the tumor due to bladder filling, resulting in sampling of different cross sections of the tumor in the same image. Bottom: transversal view of CT scan of full bladder with PTVs, i.e. PTV_{boost} and $PTV_{elective}$, for all interpolations.

Online adaptive radiotherapy
Daily online replanning

To account for both systematic and random complex anatomical changes as well as time trends, daily online replanning can be considered. With such an approach the plan is reoptimized every treatment fraction

The challenge is to condense the time of scanning and treatment planning traditionally spanning a few days to a few weeks, to a few minutes.

Online adaptive radiotherapy
Commercial solutions



Doma Lemus *et al*
Cancers **2024**, *16*, 1206

Example MR-based (**A**), CBCT-based (**B**), and PET-based (**C**) online ART systems, featuring the integration of corresponding imaging system with a 6MV FFF LINAC, installed at University of California Los Angeles, University of Rochester, and University of Texas Southwestern Medical Center, respectively.

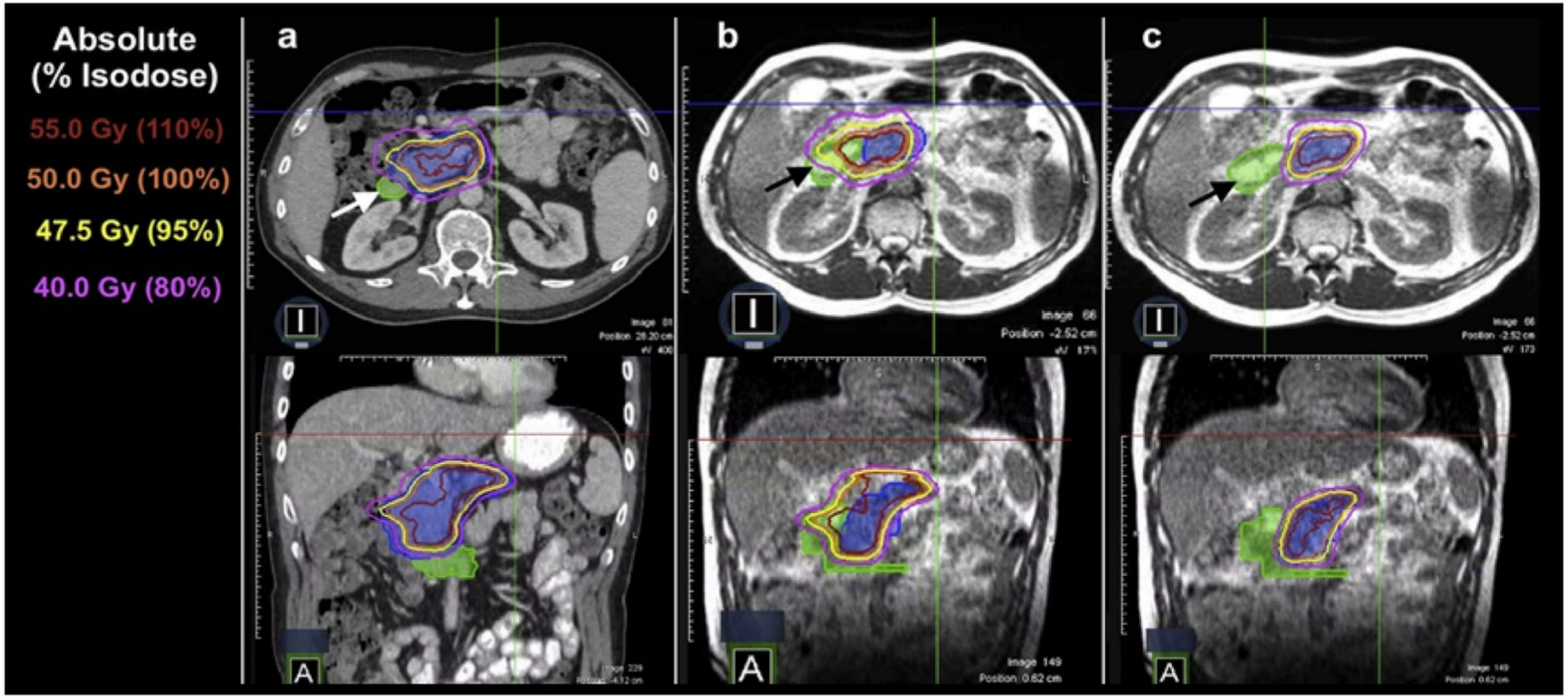


Figure 4. (**a**) Initial plan met all organ-at-risk constraints for a patient with a pancreatic tumor (blue color wash) based on the anatomy from the initial CT simulation. (**b**) Application of the plan to the daily MRI set resulted in a violation of hard duodenal (green color wash) constraints. (**c**) Daily adaptive planning achieved the resolution of the OAR constraint violation to the duodenum (marked with arrows) while preserving target volume coverage. Reprinted/adapted with permission from "Simulated Online Adaptive Magnetic Resonance–Guided Stereotactic Body Radiation Therapy for the Treatment of Oligometastatic Disease of the Abdomen and Central Thorax: Characterization of Potential Advantages" by Henke et al. 2016, International Journal of Radiation Oncology* Biology* Physics, 96(5), Copyright 2016 by Elsevier [23].

MRI based online adaptive RT

Two commercial MR-LINAC systems provide the necessary capabilities for online MR-guided planning adaptation. While the technological implementation and specifications of these systems may differ, their online adaptation mostly depends on anatomic MRI guidance.

	MRI
Current systems	Elekta Unity 1.5 T MRI with a 7MV FFF LINAC ViewRay MRIdian (legacy system) 6MV FFF 0.35 T MRI
ART workflow	Unity: Adapt to position (ATP) and adapt to shape (ATS). MRIdian: Choice between scheduled vs. adaptive plans.

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MRI based online adaptive RT

Elekta Unity

Adapt to position: isocenter shift is determined by performing rigid registration of daily MR images with the reference images. Subsequently, the initial treatment plan is adjusted to achieve the desired target coverage by modifying the shape and/or weighting of the MLC segments.

Adapt to shape: process of re-optimization, taking into account the actual anatomy and adjusted shapes. The ATS procedure directly performs dose re-optimization after making contour alterations.

MRI based online adaptive RT
MRIdian

Initial treatment plan reassessed using the daily MR images and adjusted contours to determine if the original plan is still suitable for the current daily anatomy.

If a dosimetric assessment, using the projected dose, determines that adaptive planning is required, the initial treatment plan will be re-optimized.

CBCT based online adaptive

The first CBCT-based ART system, Varian Ethos, was introduced in 2020 (Varian Medical Systems, Palo Alto, CA, USA).

1. Improved CBCT image quality
2. CNN for contour segmentation,
3. Machine learning-enhanced treatment planning system,
4. Intelligent optimization engine (IOE), for adaptive plan generation

Online adaptive plans created within a typical timeframe of 15–25 min

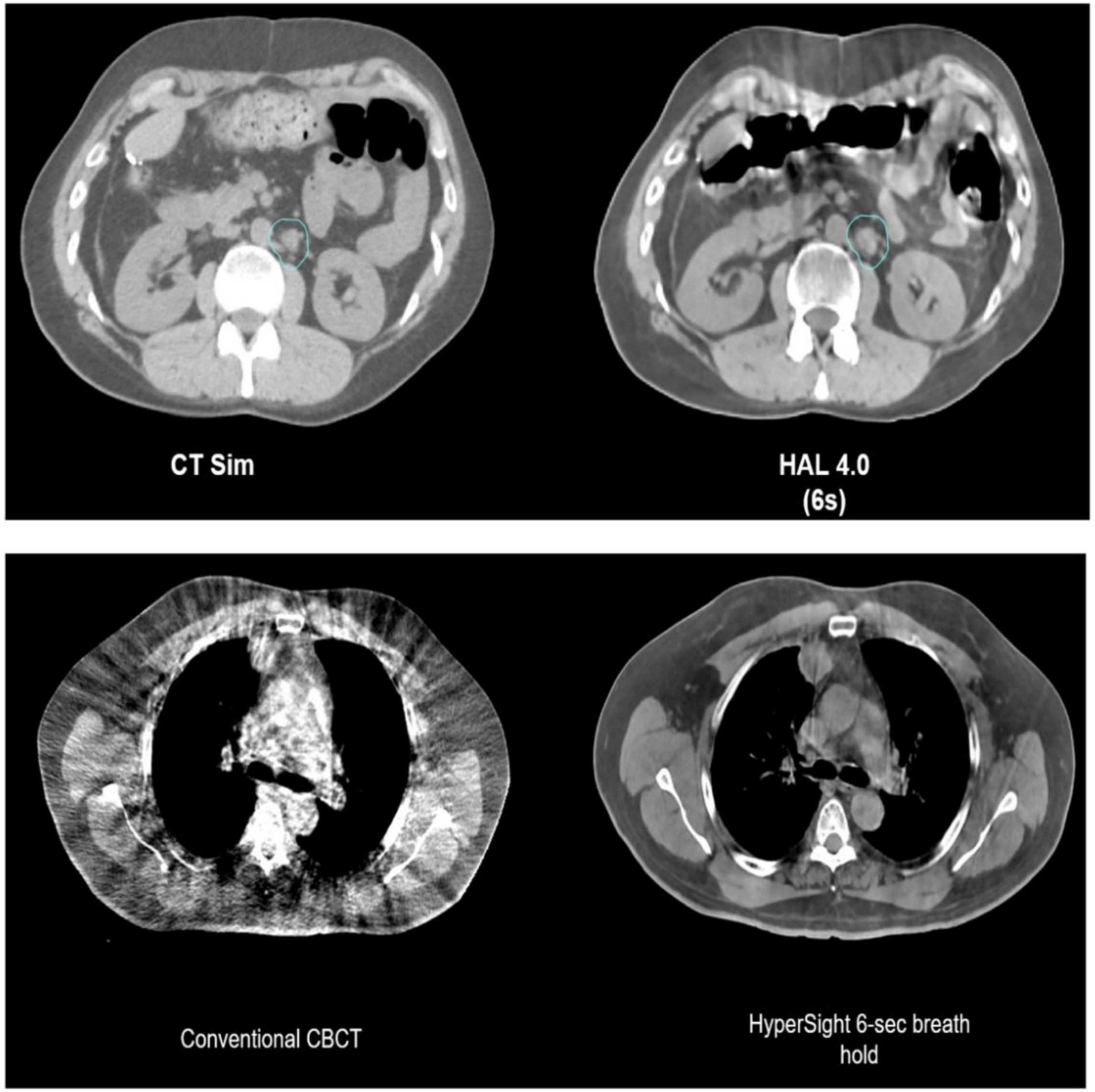

Figure 5. HyperSight CBCTs. The upper panel compares a simulation CT vs. a HyperSight CBCT (HAL 4.0 with a 6 s acquisition) of the abdomen. HyperSight CBCT shows comparable image contrast as the simulation CT and minimal streaking artifacts from gas pockets and breathing motion. The lower panel compares a conventional CBCT vs. a HyperSight CBCT (breath hold with a 6 s acquisition) of the thorax. The HyperSight CBCT shows much better image contrast and mitigated streaking artifacts and noise. Used with permission from Varian Medical Systems (https://medicalaffairs.varian.com/hypersight, accessed on 31 January 2024).

	Offline ART	Online ART
Frequency	Offline ART involves evaluation/adjustments to the treatment plan in between treatment sessions, with the patient off the table. Plan adjustments are based on anatomy imaged at a certain timepoint and applied for later sessions. It is often applied in lower frequency such as mid-treatment, biweekly, or weekly.	Online ART involves evaluations/adjustments based on the session anatomy, while the patient stays on the treatment table, and is applied for the treatment of the same session. It is currently more often applied in each treatment session.
Complexity	When performed less frequently, it is generally less resource-intensive compared to online ART. At the same time, it could still be staff-time-demanding if offline ART has a less streamlined or automated workflow than available in online ART.	Online ART can be more complex and resource-intensive compared to offline ART because it requires specialized equipment and software and may be carried out more frequently.
Treatment planning	Offline ART is not conducted on patient images obtained in the session the adaptive plan is intended to be applied. Instead, planning is conducted offline on previously obtained images to apply in future sessions.	It allows for a highly individualized and precise treatment plan for each session, taking into account the new anatomy in each treatment session. The adaptive plan is made based on the session image and applied to the same session.
Clinical Applications	It is suitable for patients with tumors, OARs, and body habitus that are less likely to experience rapid anatomical changes and when the tumor is relatively distant from critical structures. It is commonly employed in situations such as head and neck cancers. Patient setup changes could also trigger the need for offline adaptation.	Used for cases where anatomical changes are expected on a daily basis. It is commonly employed in situations such as abdominal and pelvic malignancies. Based on the optimal trade-off between clinical benefits and required resources, the online ART platform may also be used for various disease sites to apply daily, weekly, or on-demand plan adaptation.

Doma Lemus *et al Cancers* **2024**, *16*, 1206

Residual uncertainties

Table 1 Overview of Residual Uncertainties in Adaptive Radiotherapy

Type of Uncertainty	Range of Uncertainty	References
Limited number of observations	1/√N of the systematic error, with N the number of observations	69
Limited number of plans in library	1/P of the initial motion with P the number of plans in the library	80
Intra-fraction motion	2-5 mm	81,83
Respiratory motion	Peak-to-peak amplitude 0-50 mm	85
Imaging ISOC calibrations	±0.3 mm	75
Imaging distortions	CT: <1 mm	75
	MRI: <2 mm	89
Registration	Rigid: <0.5 voxel dimension	78
	Deformable: 95% <2 mm	
Contouring	4mm (1 SD)	90
Delivery inaccuracies	0.2-2 mm	72

Sonke JJ, Aznar M, Rasch C. Adaptive Radiotherapy for Anatomical Changes. Semin Radiat Oncol. 2019 Jul;29(3):245-257. doi: 10.1016/j.semradonc.2019.02.007. PMID: 31027642.