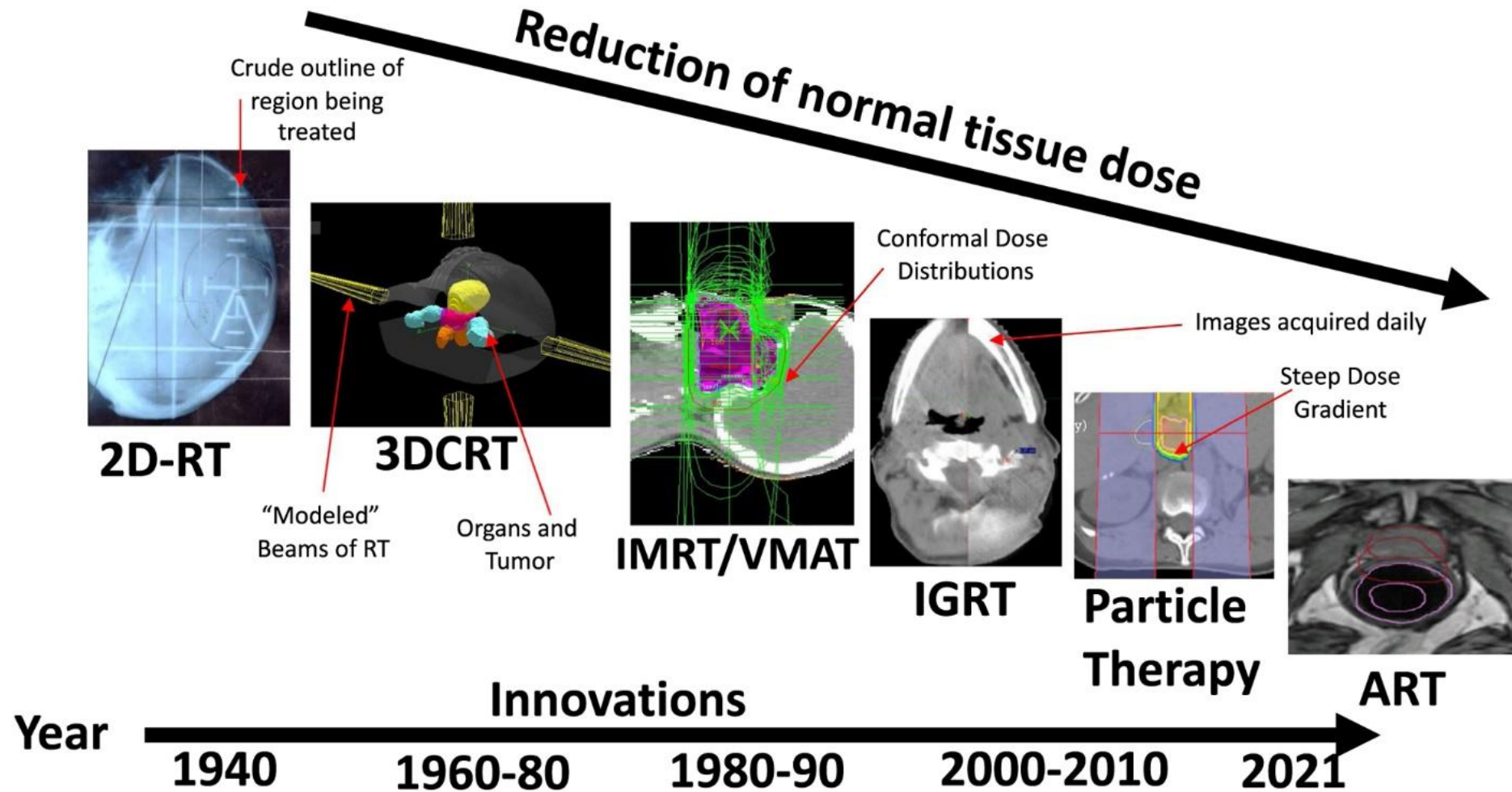


Redefining Lung Cancer Radiotherapy : From adaptive precision to particle beams

화순전남대병원
방사선종양학과 김용협



Evolution of RT Technology

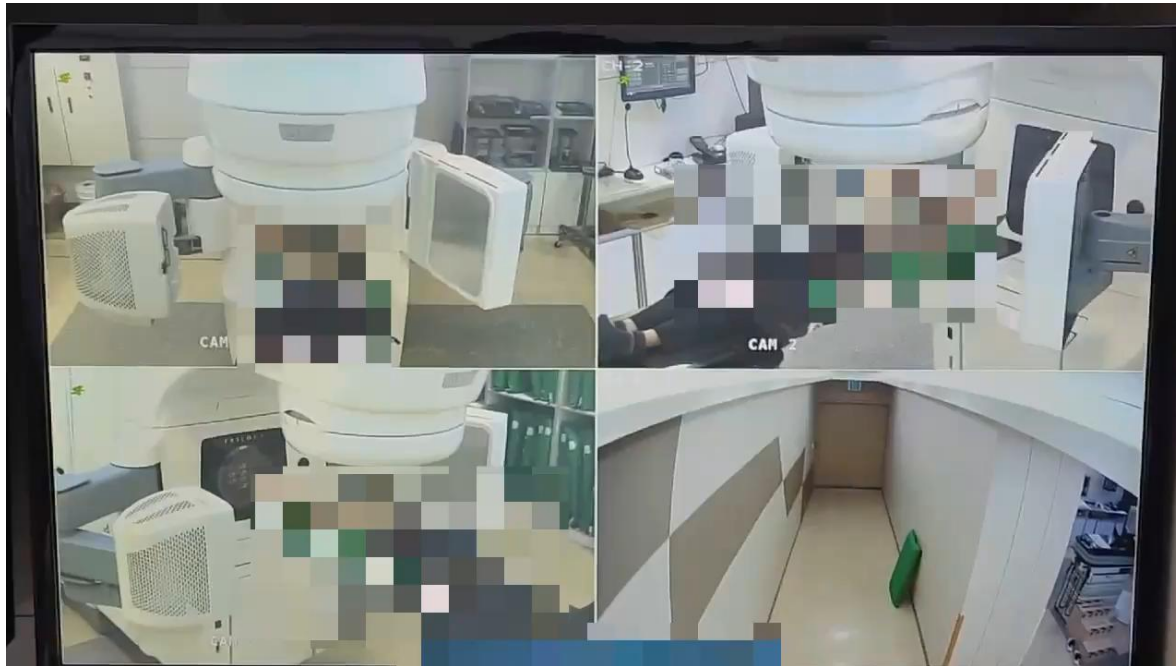


The Use of Image Guidance in RT

Image-Guided Radiotherapy (IGRT)

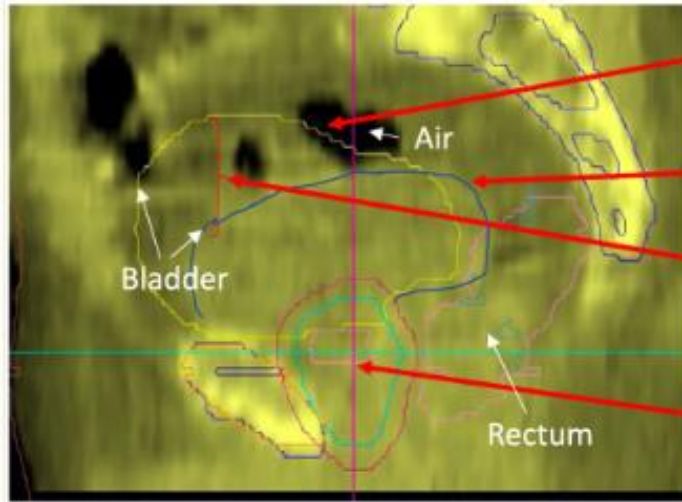
- Volumetric imaging via on-board 3D system before each radiation fraction
- Baseline (initial CT simulation) → Daily Verification → Alignment
- Daily anatomical variations (e.g., movement of the stomach),
ensuring accuracy in targeting while sparing surrounding healthy tissue.

The Use of Image Guidance in RT



Limitations of IGRT

Day 1, Daily Image Guidance MV CT (sagittal image) Treating the Prostate Gland



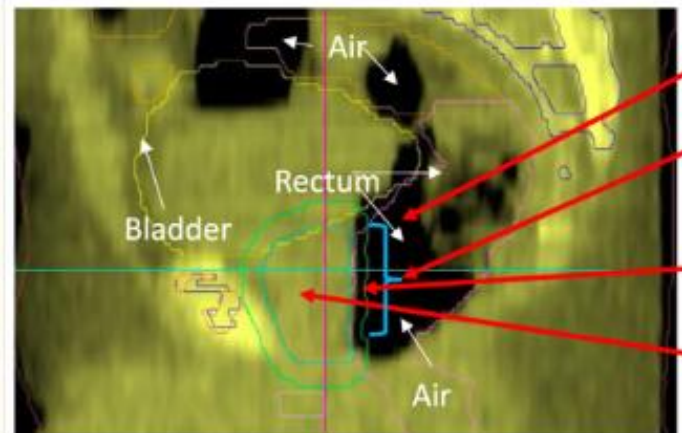
Bladder size (in yellow at the date of the original planning CT)

Actual bladder size day of treatment

Difference in the size of the bladder, the resulting RT dose change to the bladder is unknown

Prostate Gland, being treated with RT

Day 2, Daily Image Guidance MV CT (sagittal image)



Rectal air present

Impact of air on the RT dose to the rectum is unknown

High dose of RT surrounding the prostate gland

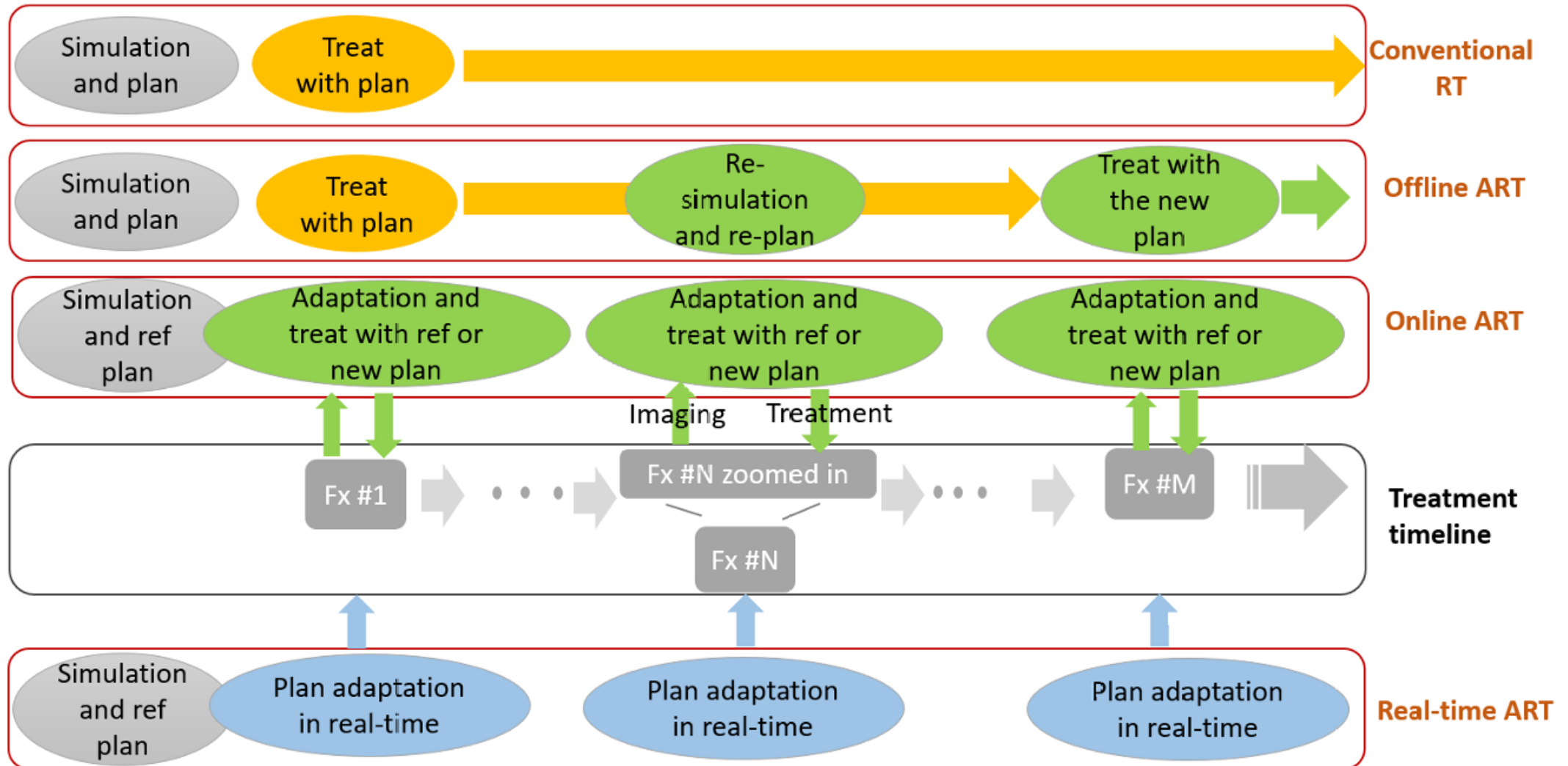
Prostate Gland

- Restricted to setup adjustments (positional shifts);
- No dose adaptation.
Anatomical Uncertainty: Vulnerable to physiological motion (peristalsis) and changes in organ shape/size.
- Inability to account for real-time volume changes or deformation of tumors and OARs.

Adaptive Radiation Therapy (ART): Background

- **Definition** : Modifying RT dose delivery to account for temporal changes in tumor or OARs during treatment.
- **Key point for Adaptation**
Anatomic: Organ motion, size variation, weight flux, and daily setup variations.
Biologic: Progressive biological changes (e.g., PET-based treatment adjustment).
- **Clinical Benefits**
Personalization: Real-time correction of dose distributions.
Optimization: Dose escalation for tumor response vs. sparing normal organs.
- **Current Status**
Accelerated adoption driven by MR-guidance and technological innovations.

Adaptive Radiation Therapy (ART)

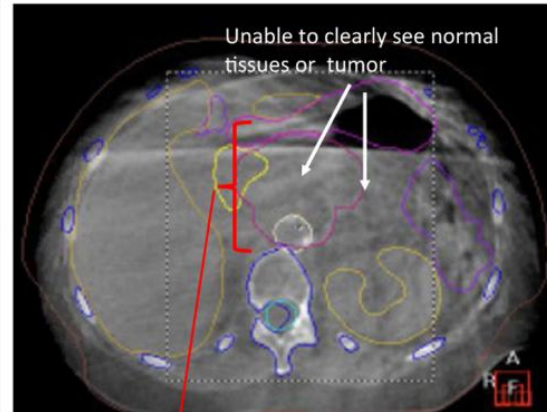


ART Imaging Modalities: CBCT vs. MRI

- **CBCT Limitations:** Poor soft tissue contrast and motion artifacts hinder precise boundary identification.
- **CT-on-rails:** Offers better contrast than CBCT but is rare, complicated, and time-consuming.
- **MRI Superiority**
 - : Provides exceptional soft tissue contrast for high-confidence daily adaptation.
 - : Clearer visualization of moving targets (e.g., pancreas) compared to blurry CBCT images.

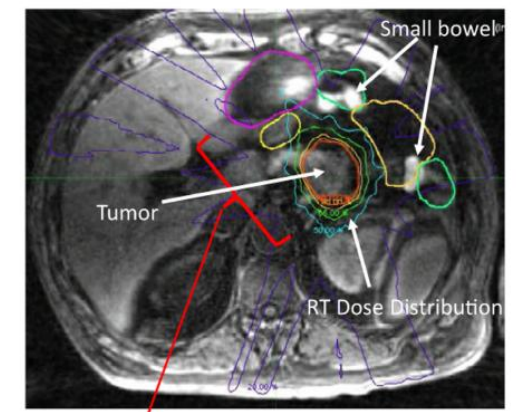


Cone beam CT acquired using modern linear accelerator



The locations of normal organs in proximity to the treatment volume is unknown, adaptive RT using this image is exceedingly difficult to nearly impossible

MR Imaging example



Improved visualization of organs in proximity of the tumor allows for relatively routine use of adaptive RT, normal organs can be seen, drawn, and their positions accurately accounted for

Advantages of MR-Guided Radiation Therapy

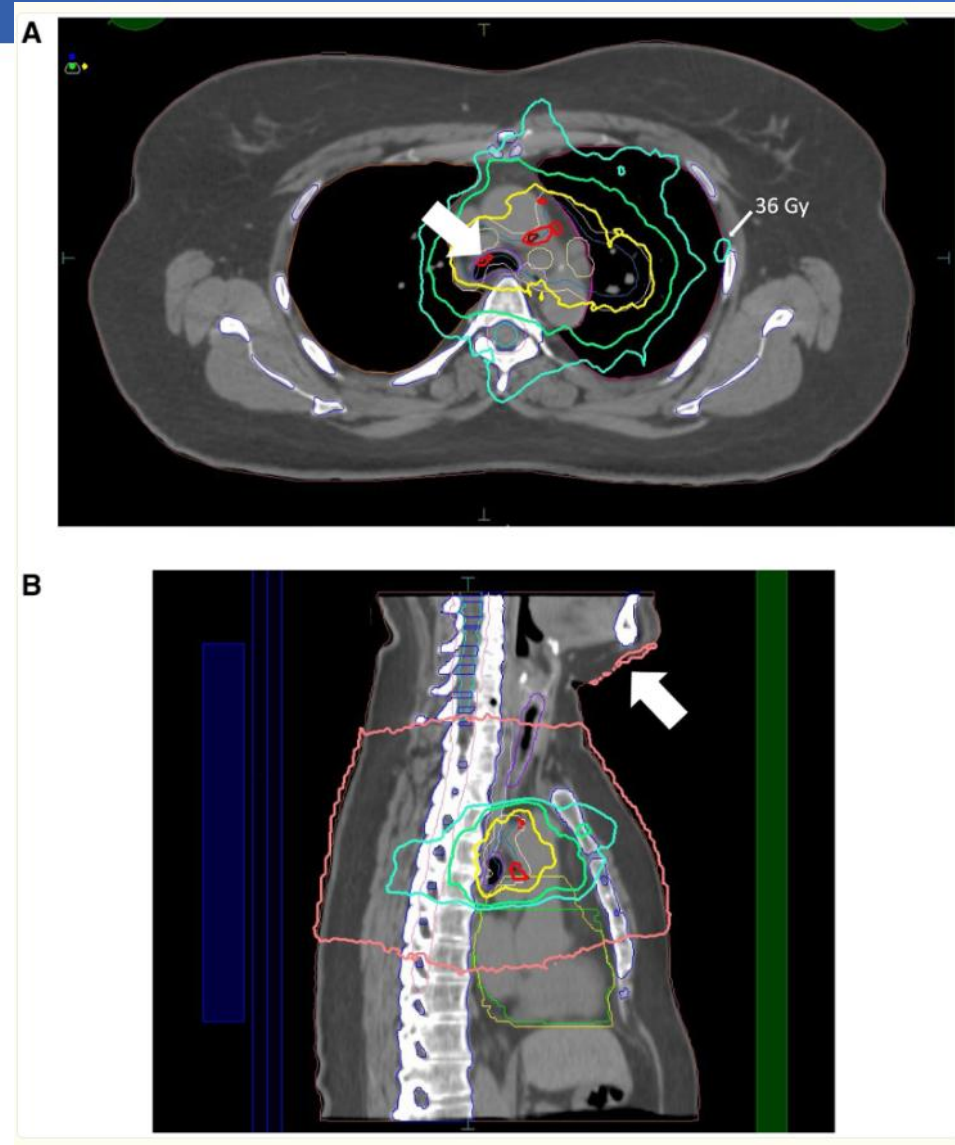
Advantages of MR-Guided Radiation Therapy

- Superior soft tissue contrast improves assessment of tumor invasion and target delineation.
- MR-linac provides tools to manage inter- and intra-fraction motion of lung targets and OARs.
- Smaller PTV margins, or even margin omission, may be possible, reducing normal tissue dose and enabling dose escalation and hypofractionation.
- Functional MRI may be integrated for disease assessment and post-treatment response evaluation, with correlation to FDG PET.
- MRI-only planning reduces the need for additional CT simulation, lowering cost, inconvenience, radiation exposure, and time.

Considerations of MR-Guided Radiation Therapy

Unique Physics and Dosimetric Considerations

- electron-return effect : complex dose calculations
- Lack of Advanced Capabilities: :
VMAT / Arc Therapy, Non-coplanar Beams



Practical Considerations in MR Guidance

1. Patient Selection (The Critical First Step):

- No contraindicated metallic implants or electronic devices.
- No significant claustrophobia.
- Must meet body habitus and size requirements.

2. **Clinical Expertise** : familiar with MR-based imaging used in the treatment delivery process.

3. **Artificial Intelligence and MR Guidance** : Key Areas for AI Partnership:

- Plan Quality Assurance (QA) review.
- Dosimetric tasks.
- Normal organ contouring.

Challenges of MRgRT in Lung Cancer

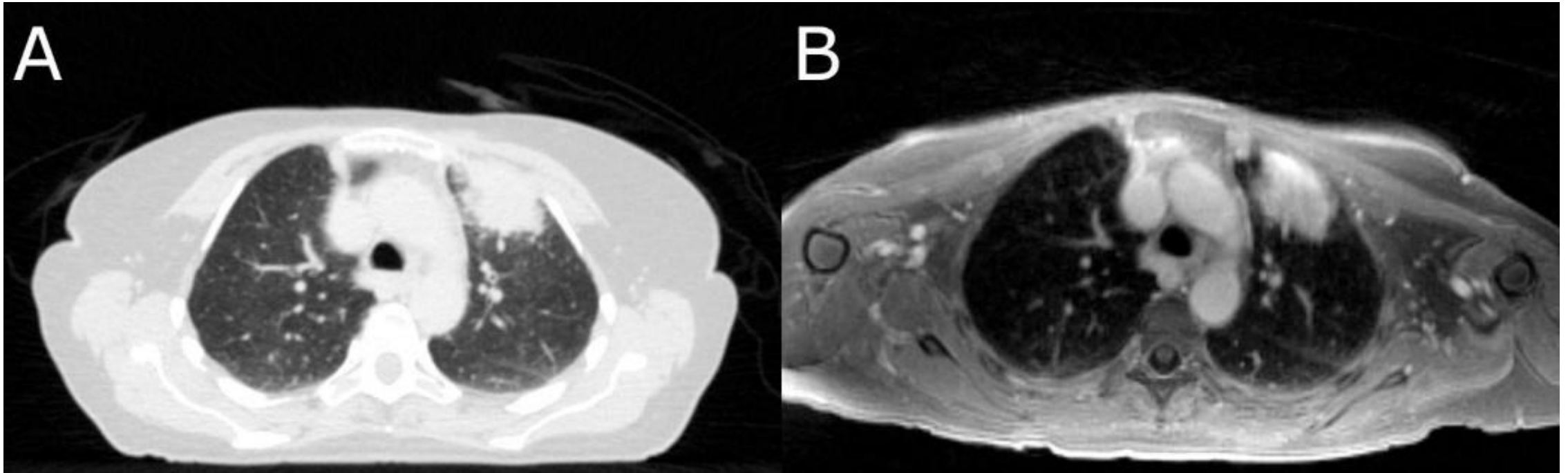
- Lung MR image quality is limited by respiratory motion, causing artifacts and blurring.
- Electron return effect at air–tissue interfaces can increase dose, especially at higher field strengths.
- MR tracking has difficulty identifying small tumors, particularly those 1 cm or less in size.
- VMAT is not currently available on MR-linacs, limiting rapid and highly conformal treatments.
- CT-based workup, restaging, and RT planning remain the cornerstone of lung cancer management.

The Use of Image Guidance in RT

Challenges and Solutions for MRgRT in the Lung

Challenge	Potential Solutions
Blurring and artifacts from lung motion	4D/5D MRI, respiratory gating, fast MRI sequences using breath hold, motion-robust reconstruction
Magnetic susceptibility artifacts in lung	Distortion corrections, lower field strengths, ultra-short echo time sequences
Low signal-to-noise ratio due to low tissue density	Signal averaging, use of surface coils, optimized sequences specifically for MR-linac
MRI tracking for small tumors and/or irregular breathing	3D cine capabilities, more robust tracking models, tracking using functional imaging/tracers
Lack of conformal dosimetry	VMAT capabilities
Workflow challenges	Clear protocols, staff training, faster online dose calculation, parallel workflows

Comparison of CT and MR Images in lung cancer



Bones and lung tissue are better recognizable on the CT image,
Soft-tissue contrast of the MR image is superior, especially with respect to the mediastinum

SBRT Toxicity, Timmerman et al., 2006

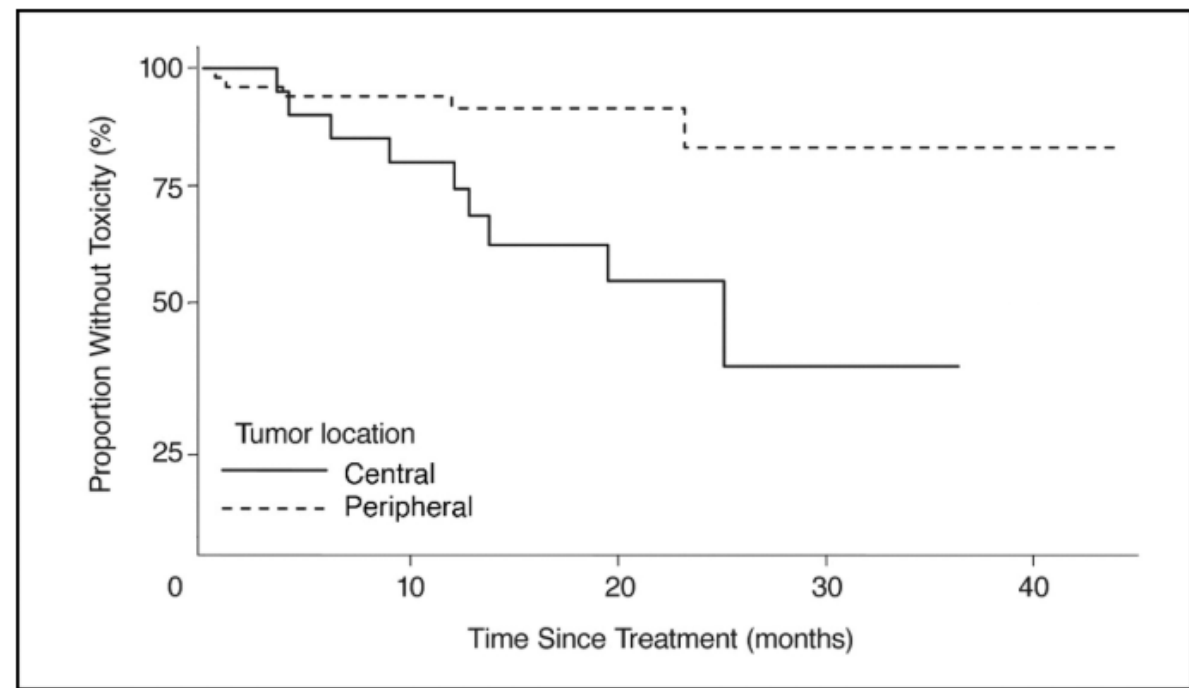
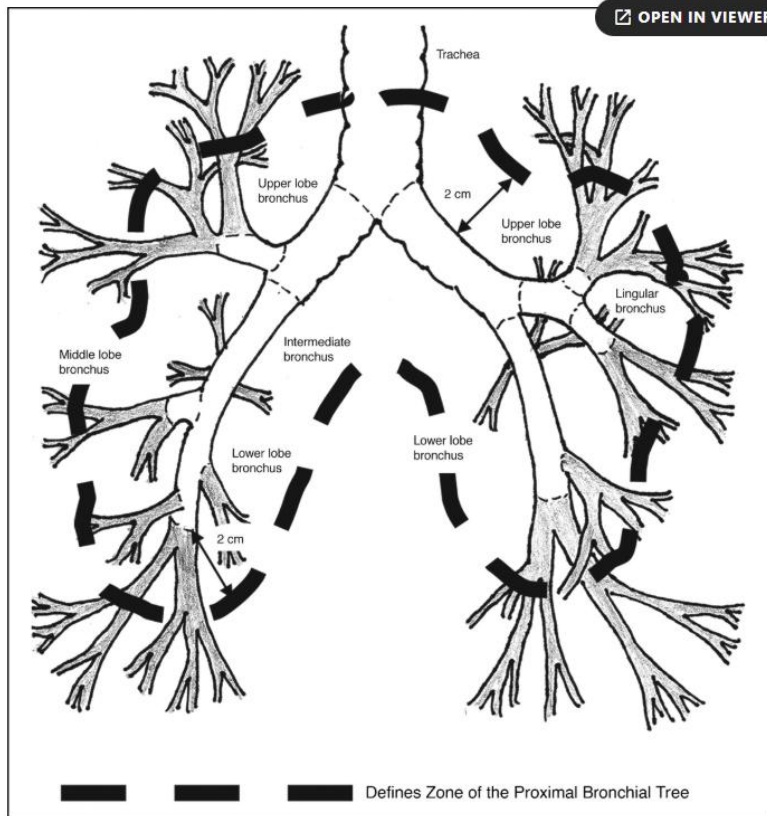


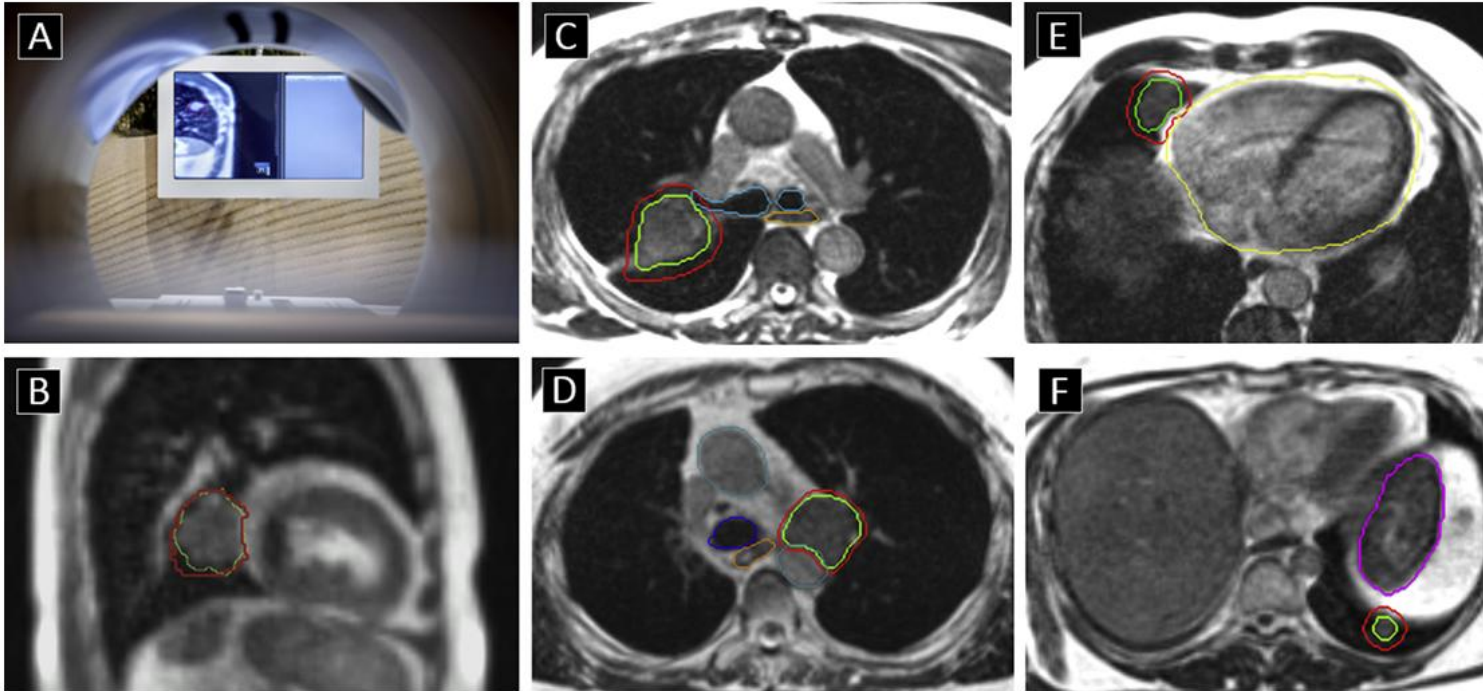
Fig 4. Kaplan-Meier plot of time from treatment until grade 3 to 5 treatment related toxicity comparing patients with tumors in the central (perihilar and central mediastinal) regions from those with more peripheral tumors.

2-year freedom from severe toxicity
83% (perihilar) vs 54% (central)

Grade 5: Fatal Complications

Bacterial Pneumonia (4 pts), Pericardial effusion (1 pt) and massive hemoptysis (1 pt)

Stereotactic MR-Guided Adaptive Radiation



Local control rate at 12 mo (95.6%)
OS rates at 12 mo (88.0%)

Grade 2 toxicity (30%), Grade 3 (8%)
No Grade 4 or 5 Toxicity

ART in the Era of Immunotherapy

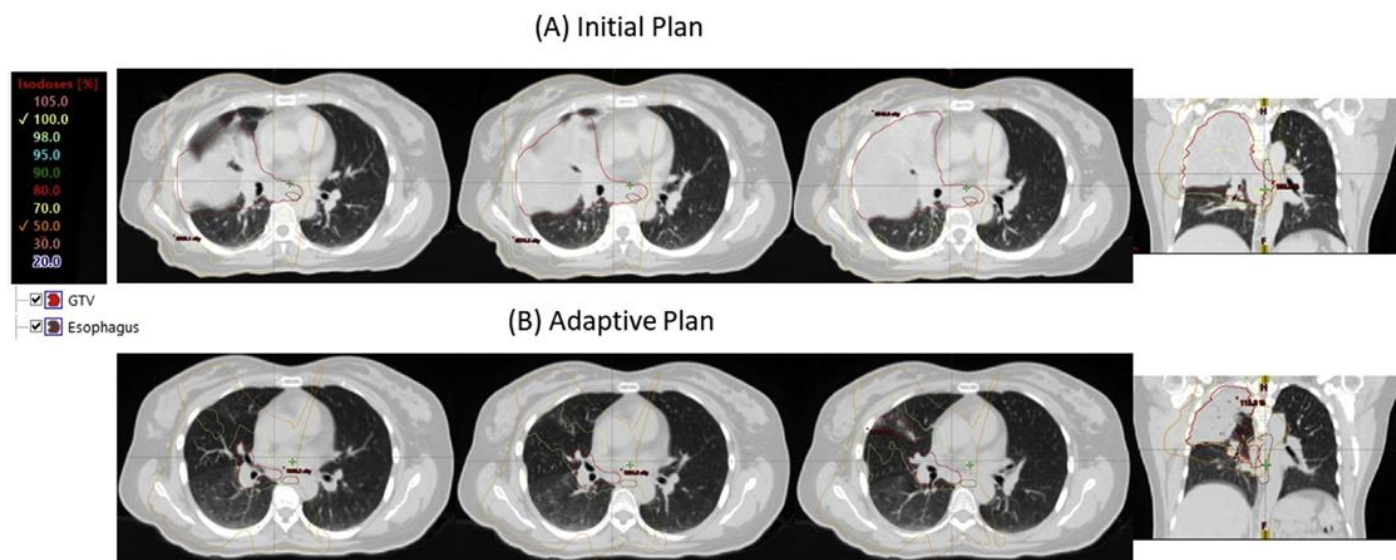
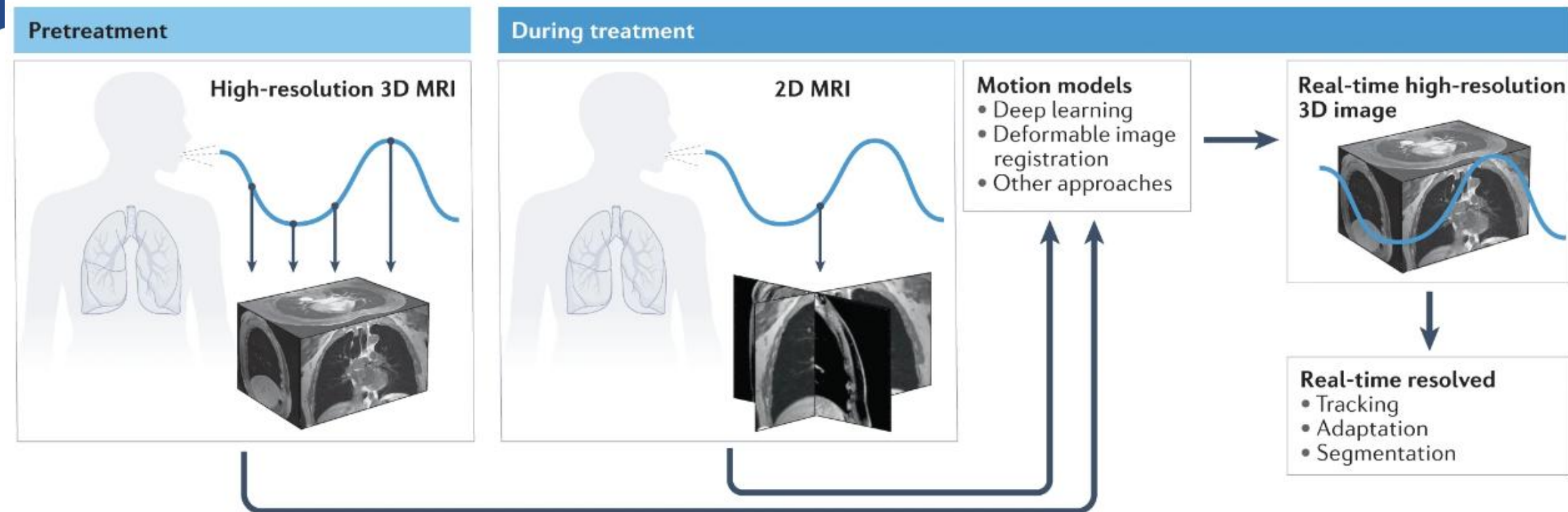


Table 3 Toxicities

Toxicity	Number of patients	
	Adapted, no. (%)	Control, no. (%)
Esophagitis		
Grade 1	3 (30)	5 (33)
Grade 2	4 (40)	7 (47)
Pneumonitis		
Grade 1	1 (10)	1 (6)
Grade 2	0	2 (13)
Grade 3	1 (10)	0

MRI-guided Radiotherapy



An important advance with MRI-guided radiotherapy is the possibility of developing methods to improve the spatial and temporal resolution of anatomical and functional imaging. The goal is to have a full picture of the totality of the tumour and non-malignant tissue in the path of the beam at all times, and to use this information to optimize treatment delivery. An example approach to creating real-time high-resolution images is shown.

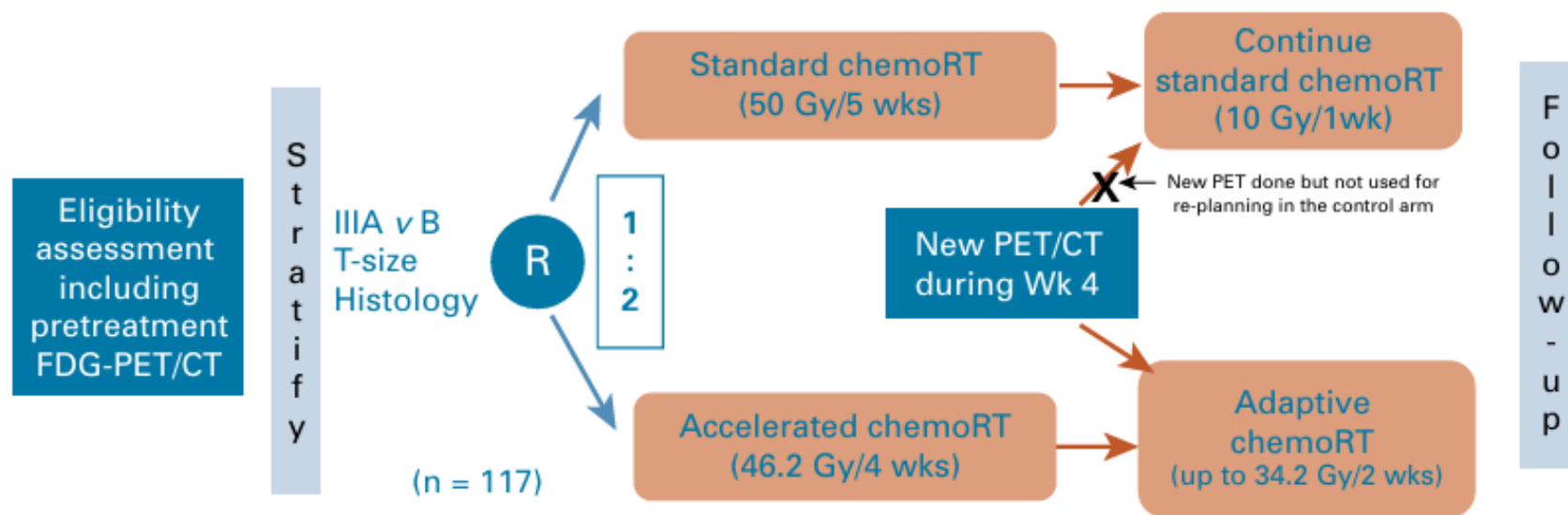


Elekta Unity

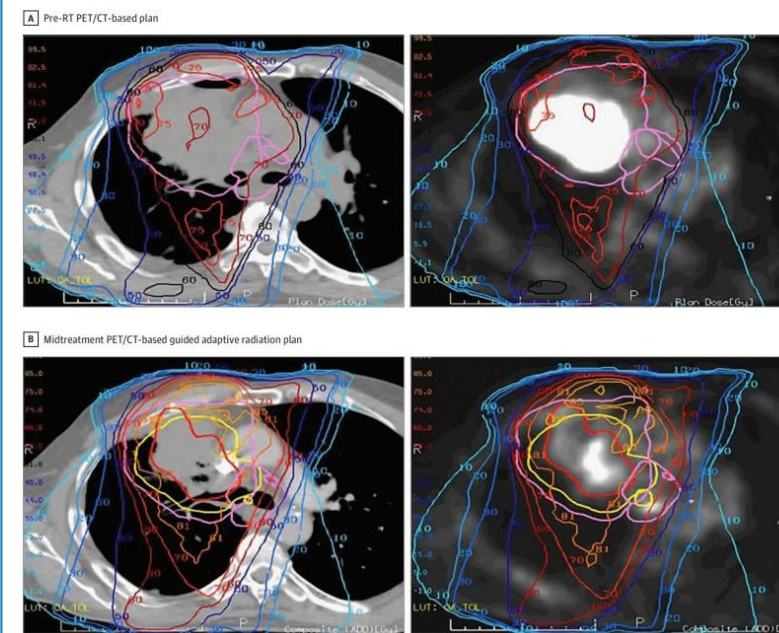
with Comprehensive Motion Management

NRG-RTOG1106, Phase 2

NRG-RTOG 1106 / ECOG-ACRIN 6697 Study of Adaptive, Dose-Dense Chemo-RT: General Design

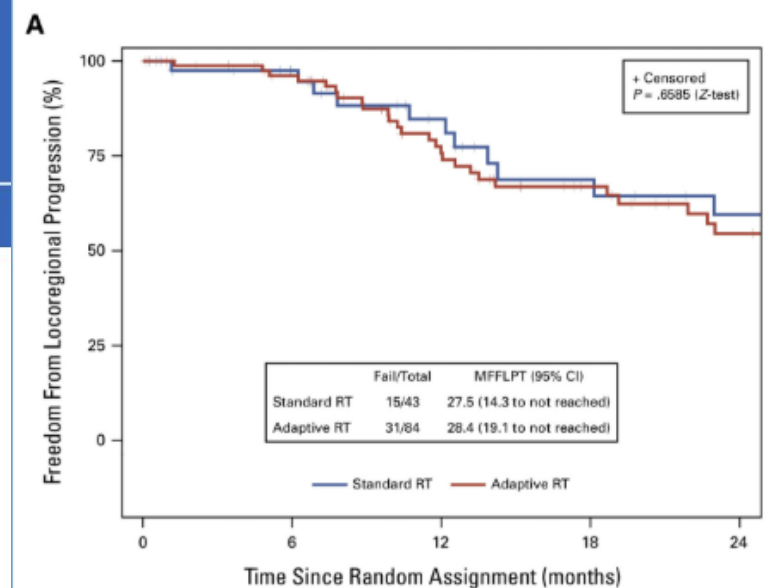


Primary end point (therapeutic): freedom from locoregional progression
Primary end point (diagnostic): $\Delta\text{SUV}_{\text{peak}}$ as a prognostic factor



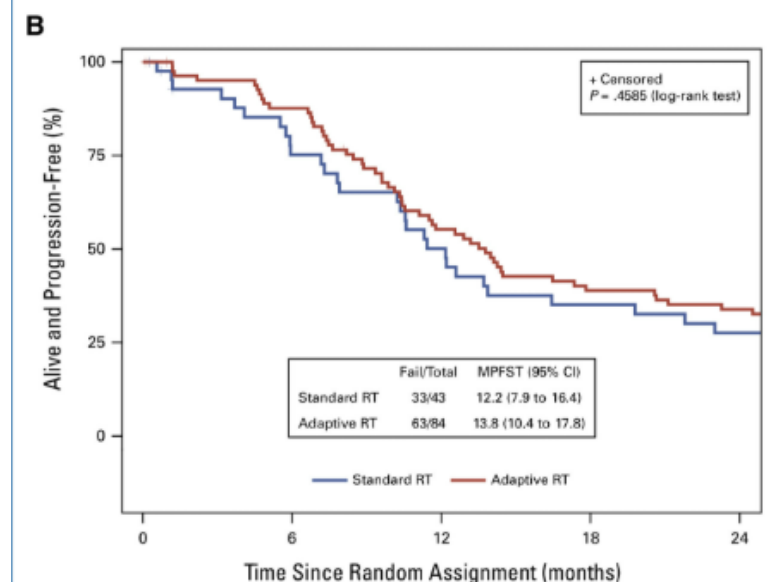
Efficacy	Standard RT (n = 43)		Adaptive RT (n = 84)		HR (95% CI)	P^a
	Fail, No.	3 Years, % (95% CI)	Fail, No.	3 Years, % (95% CI)		
Overall survival	26	49.1 (32.9 to 63.5)	51	47.5 (36.2 to 57.9)	1.06 (0.66 to 1.71)	0.80 _c
Median survival time, months	35.5 (21.8-49.0)		31.2 (21.5-46.8)			
Lung cancer-specific survival	24	45.9 (29.6 to 60.7)	42	42.6 (31.5 to 53.2)	0.89 (0.55 to 1.46)	0.65 _d

Toxicity	n = 42 _e	n = 80 _e	P^a
Toxicity: grade 3 or greater, No. (%)			
Protocol-specified grade 3+ RT-induced lung toxicity	2/38 (5.3)	5/72 (6.9)	1.00 _f
Grade 3+ esophagitis	3/42 (7.1)	3/80 (3.8)	.41 _f
Grade 3+ cardiac disorders	1/42 (2.4)	1/80 (1.3)	1.00 _f
Grade 3+ hematologic toxicity _g	18/42 (42.8)	36/80 (45.0)	.82 _h
Any toxicity grade 3 or higher	23/42 (54.8)	60/80 (75.0)	.023 _h



Number at risk

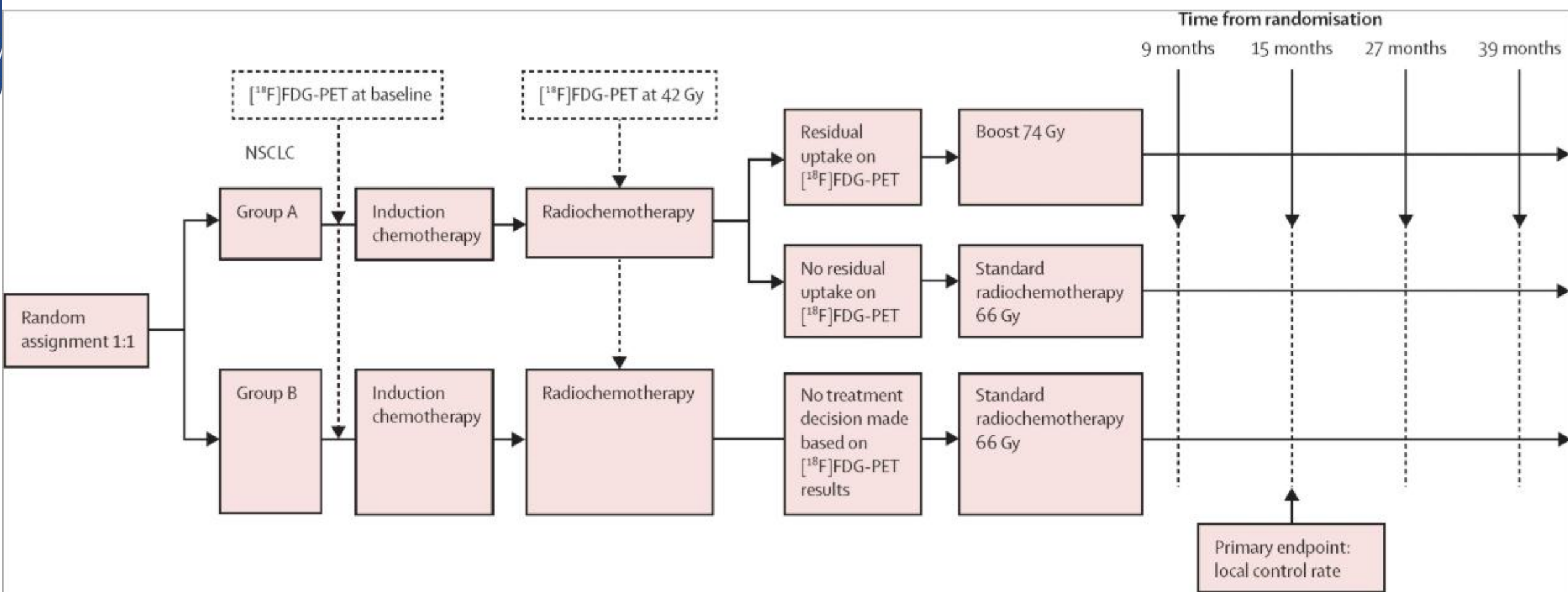
Standard RT	43	33	23	16	12
Adaptive RT	84	71	44	30	21



Number at risk

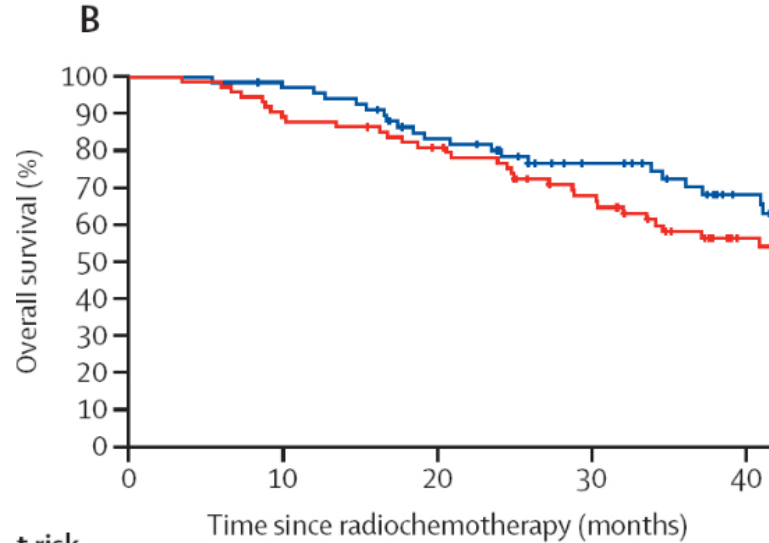
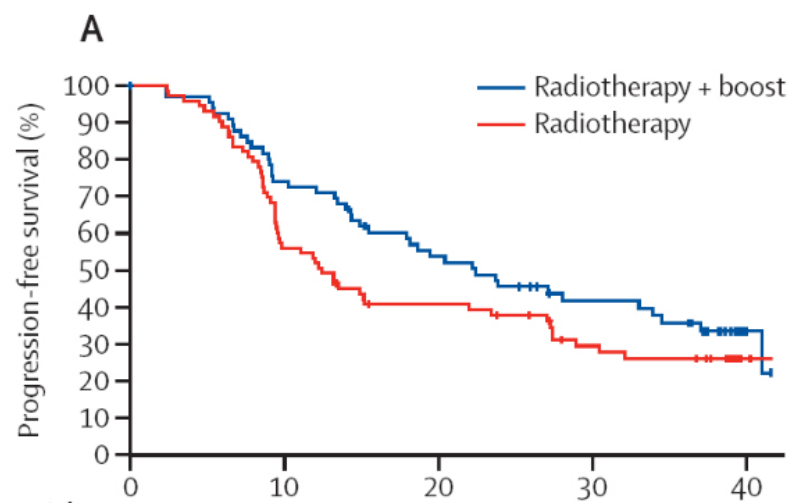
Standard RT	43	30	20	14	11
Adaptive RT	84	71	44	31	27

RTEP7-IFCT-1402, Phase 2



Durvalumab use was allowed.

RTEP7-IFCT-1402, Phase 2



	Boost	Std
mPFS	22.3 mo	12.3 mo
mOS	NR	43.3 mo

Number at risk
(number censored)

Radiotherapy + boost	67 (1)	49 (1)	33 (4)	21 (9)	3 (23)
Radiotherapy	73 (0)	41 (0)	28 (2)	17 (6)	3 (18)

Number at risk
(number censored)

Radiotherapy + boost	67 (0)	64 (1)	52 (4)	39 (13)	26 (22)
Radiotherapy	73 (0)	65 (0)	57 (2)	43 (7)	25 (18)

15-month LC 77.6 vs 71.2% (Boost vs Std dose)

- No durvalumab subgroup: 71.4 vs 61.1%
- Durvalumab subgroup: 82.1 vs 81.1%

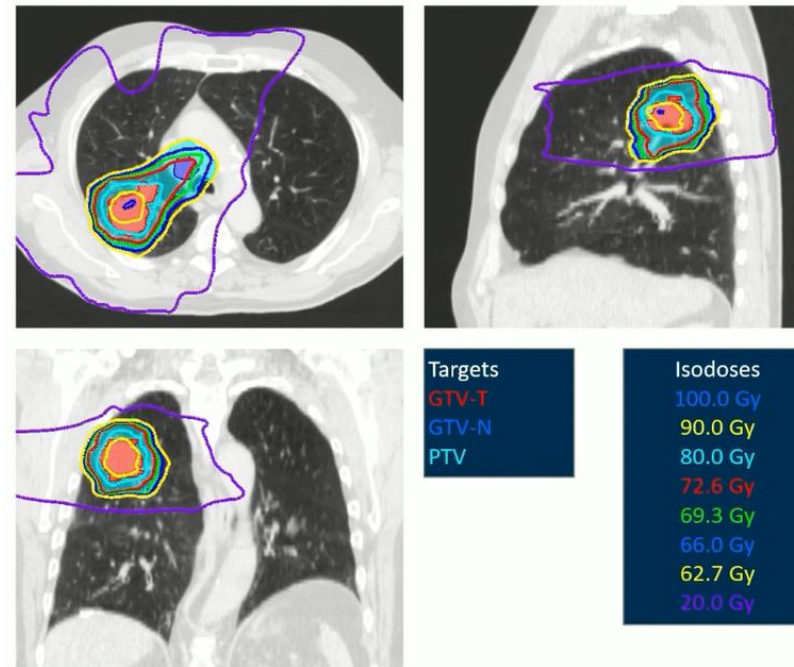
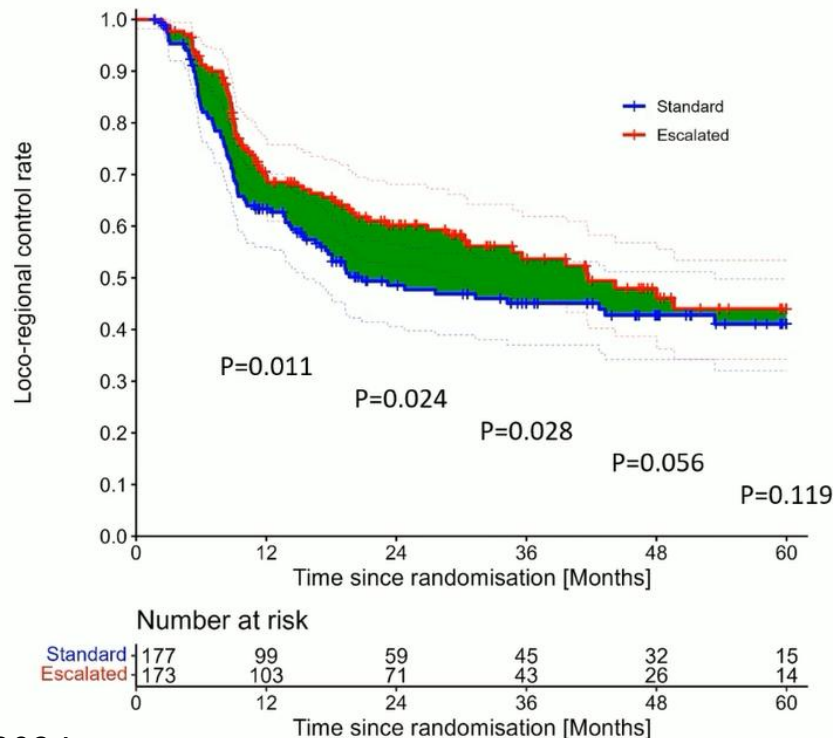
Grade 3–4 AEs: A (29%) vs B (45%)

Serious AEs (SAEs): A (7%) vs B (14%)

Late G3+ AEs: A (7%) vs B (5%)

NARLAL2 trial, randomized phase III trial

- Age > 18, IIB-III B
- 66Gy/33 fx vs. 95/33 GTVp and 74/33 GTVn to PET+
- Primary : Loco-regional control rate
- Secondary : Toxicity, OS, DFS, dose-response effect
- OS (standard : 35.8m, escalated : 56.1m, $p=0.36$).. 2024 ASCO Annual Meeting



ART: Challenges and Future Outlook

Current Status

Routine implementation remains limited despite established concepts.
Requires more prospective trials to become "Standard of Care."

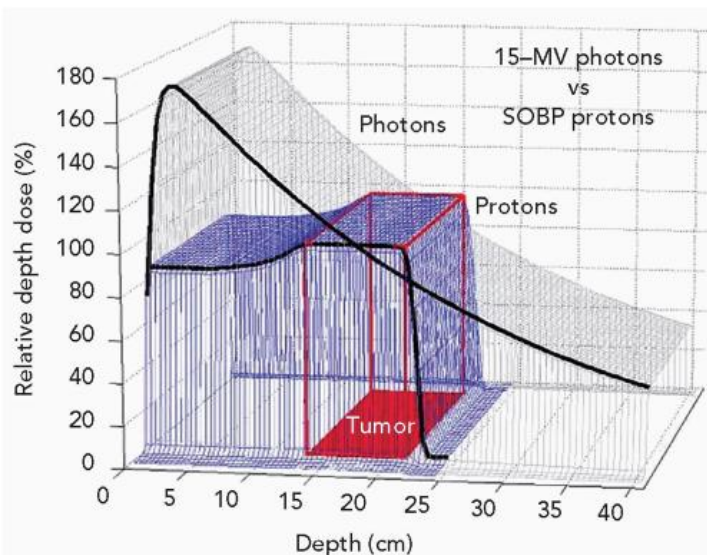
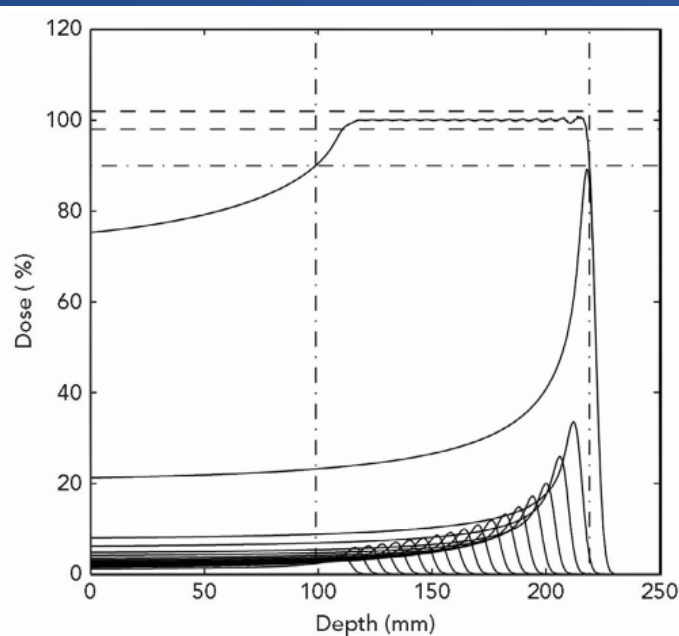
Main Barriers

High Workload: Extremely labor-intensive and time-consuming (daily re-contouring).
Economic Issues: Limited reimbursement for the high clinical effort required.
Accessibility: Technical complexity restricts use mostly to large centers.

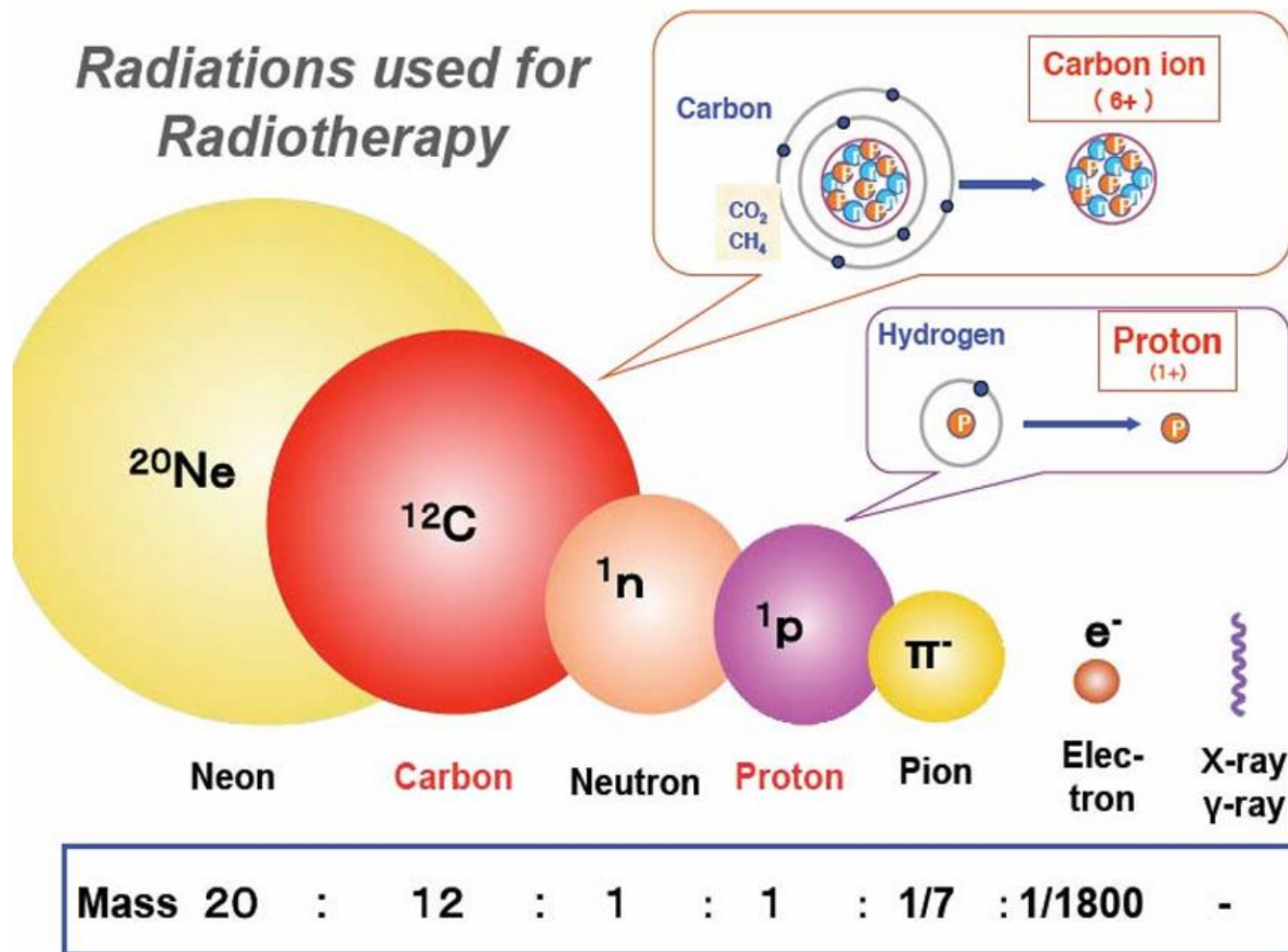
The Path Forward

New Platforms: Improving accessibility.
MR-Guidance: Offers a highly feasible and precise platform for adaptation.
Value: High technical complexity is balanced by significant clinical benefits.

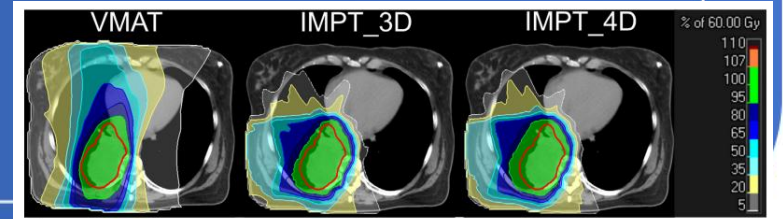
Charged Particle Radiotherapy



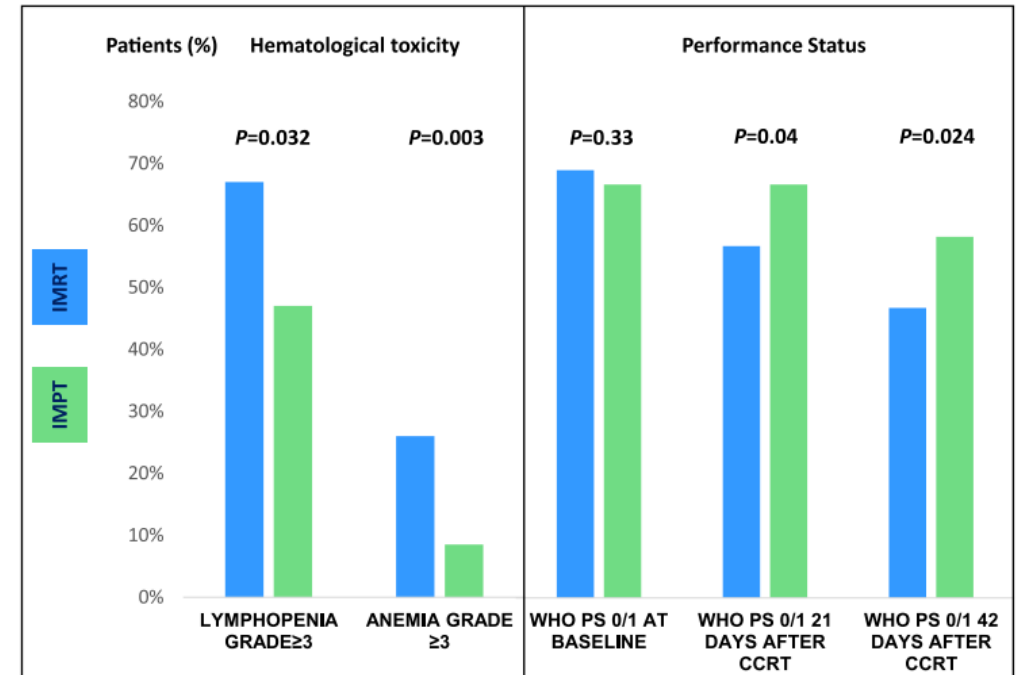
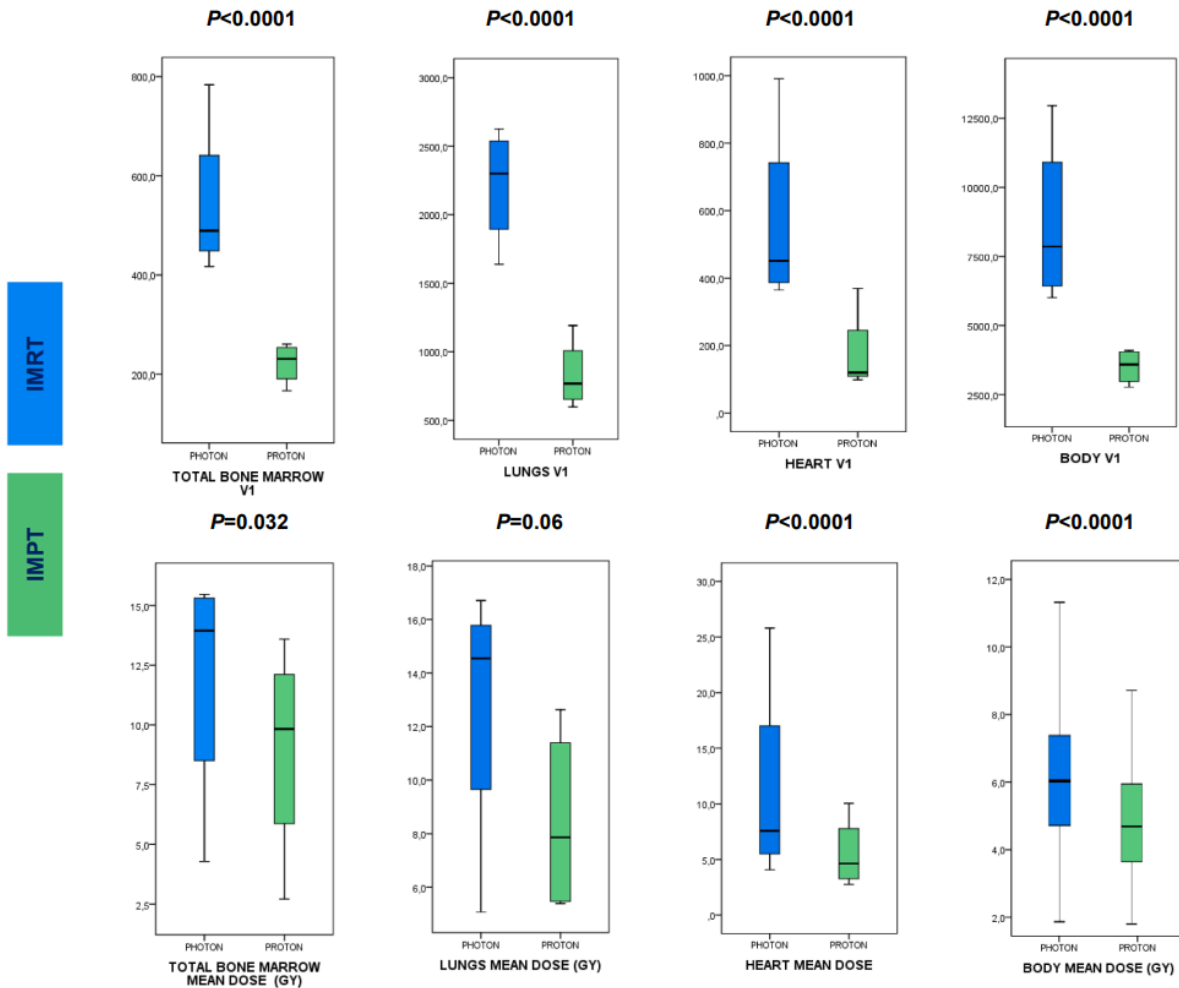
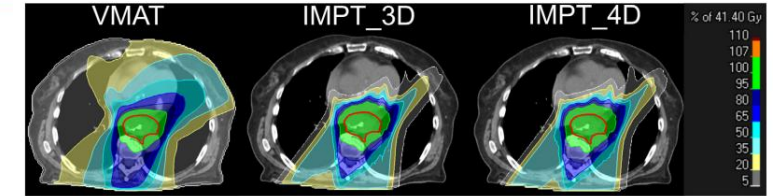
Radiations used for Radiotherapy



Proton and photon radiotherapy in stage III NSCLC: Effects on hematological toxicity and adjuvant immune therapy



A



Receiving durvalumab within 42 days
IMPT (72%) vs. IMRT (51%) $p = 0.015$

Outcomes of proton therapy for non-small cell lung cancer in patients with interstitial pneumonia

Research | [Open access](#) | Published: 21 March 2022

Volume 17, article number 56 (2022) [Cite this article](#)



[Radiation Oncology](#)

From: Outcomes of proton therapy for non-small cell lung cancer in patients with interstitial pneumonia

References	Treatment	Number of patients	Median total dose (Gy)	Dose per fraction (Gy)	Pneumonitis	
					Grade 3	Grade 4/5
Lee et al. [8]	3D-CRT	15	56.9	1.8–2.0	6 (40%)	5 (33%)
Yamashita et al. [9]	SBRT	13	48	12	N/A	7 (54%)
Tsurugai et al. [36]	SBRT	42	40–60	8–22	4 (9.5%)	1 (2.4%)
Ono et al. [37]	PT	16	80 (RBE)	3.2 (RBE)	1 (6.3%)	1 (6.3%)
Present study	PT	29	66–74 (RBE)	6.6–2.0 (RBE)	2 (6.9%)	0 (0%)

3D-CRT 3D conformal radiotherapy, SBRT stereotactic body radiotherapy, PT proton therapy, RBE relative biological effectiveness, N/A not applicable

Proton Versus Photon Radiotherapy for NSCLC

RTOG-1308

Closed to Accrual

[Return to Protocol Table](#)

[Details](#)

[Documents & Materials](#)

[For Patients](#)

Phase III Randomized Trial Comparing Overall Survival After Photon Versus Proton Chemoradiotherapy for Inoperable Stage II-IIIB NSCLC

Principal Investigator [Zhongxing Liao, MD](#) 70 Gy (RBE), at 2 Gy once daily plus platinum based doublet chemotherapy

Status

Closed to Accrual

Date Opened To Accrual

February 03 2014

Date Closed to Accrual

September 26 2023

Read-out of the primary endpoint in December 2026

Flash radiation therapy

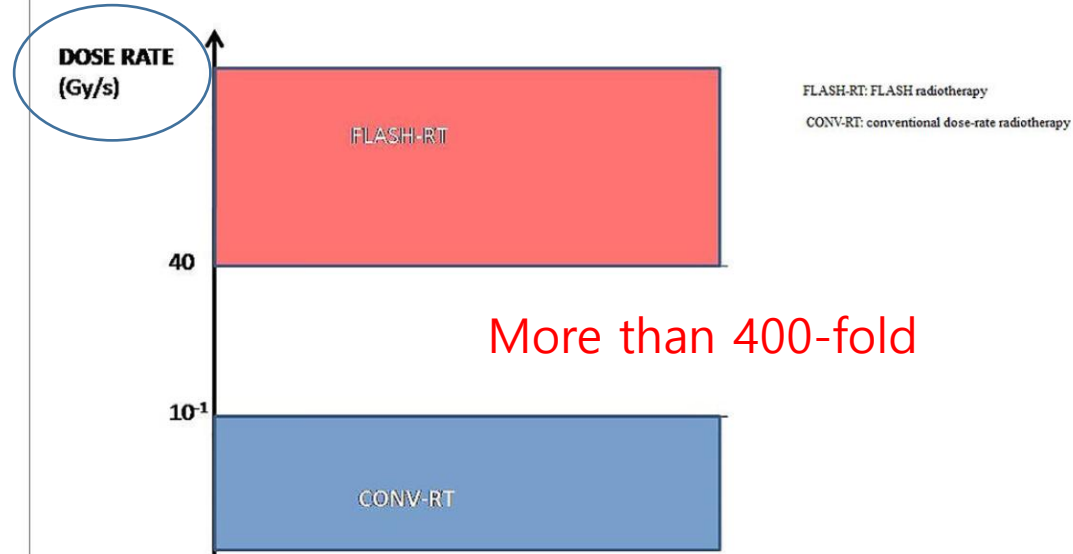
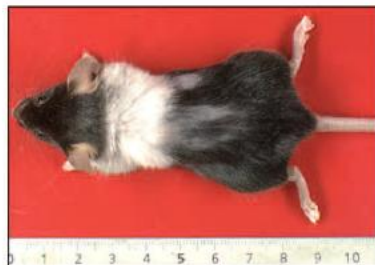
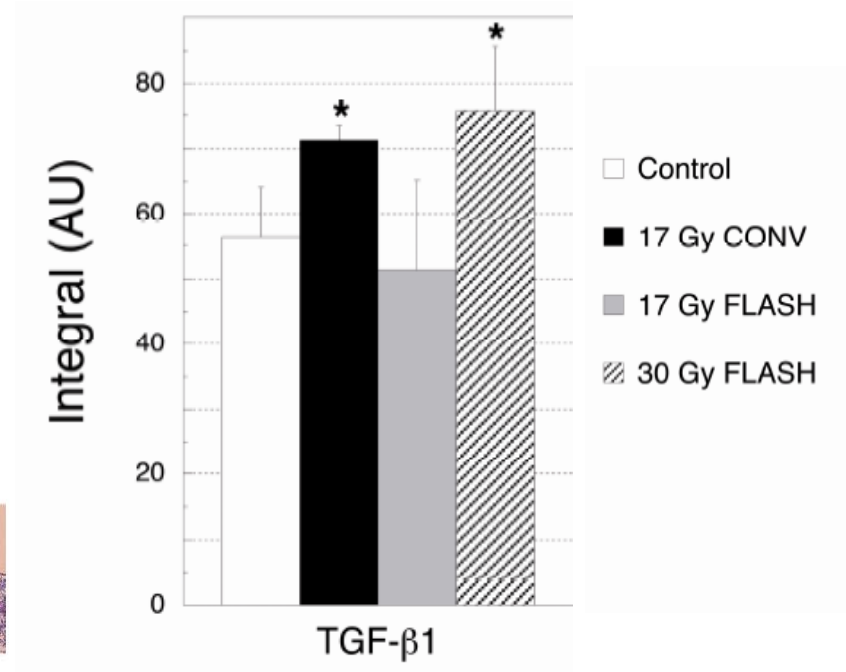
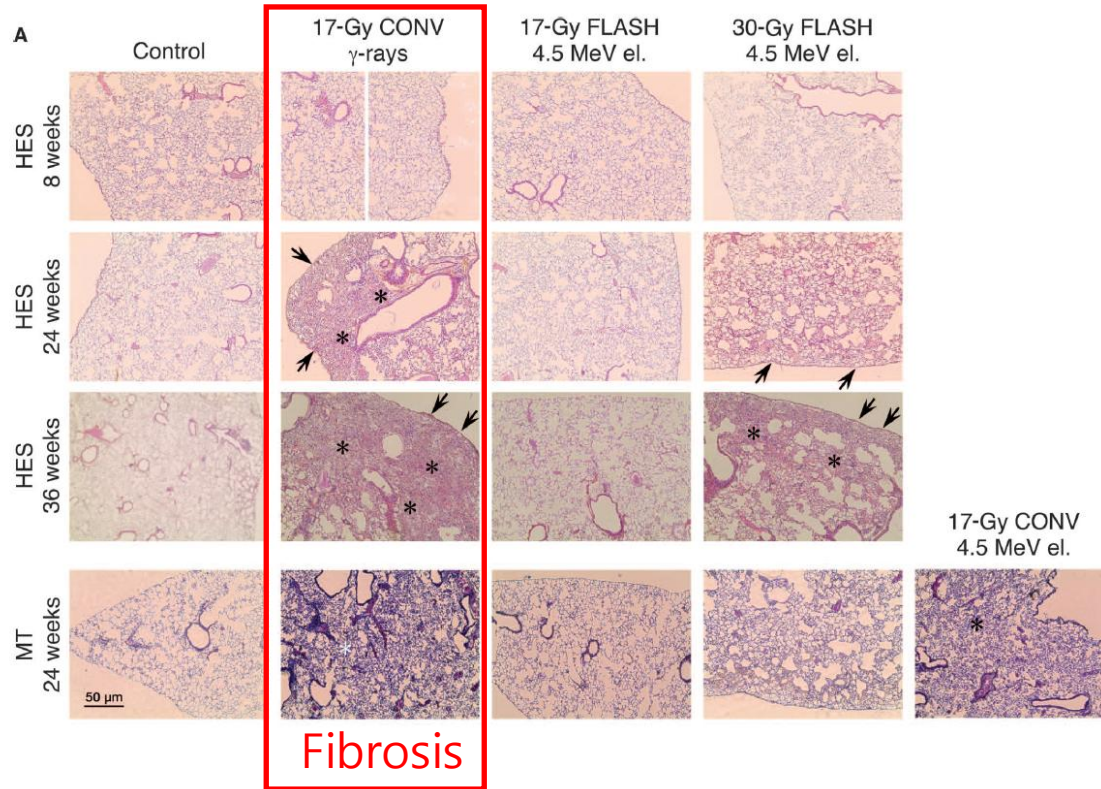
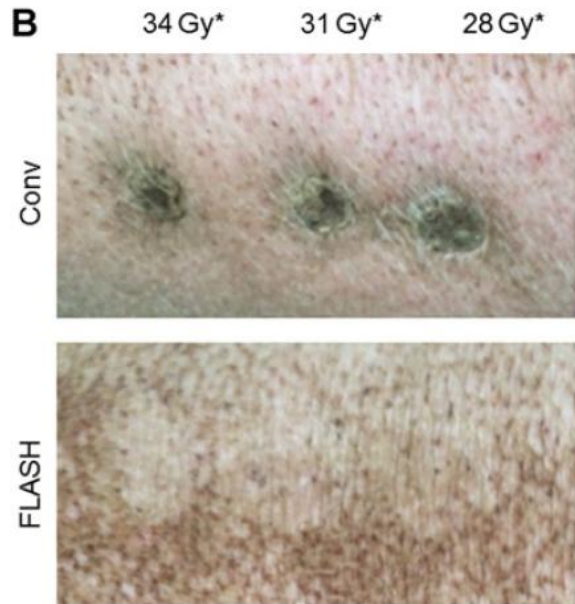


FIGURE 1 | The dose-rate of FLASH-RT and conventional irradiation.

The FLASH Effect is a biological phenomenon that consists in a remarkable **sparing of normal tissues** while the **killing effect on tumors is maintained**

Ultrahigh dose-rate FLASH irradiation increases the differential response between normal and tumor tissue in mice





- No erythema or moist desquamation
- No fibronecrosis
- No dermal remodeling

Treatment of a first patient with FLASH-radiotherapy

- 75y, multiresistant CD30+ T-cell cutaneous lymphoma
- Previously localized skin RT over 110 times
- 15 Gy, 5.6-MeV, in 90 ms
- Healthy tissues : no decrease of the thickness of the epidermis, no disruption at the basal membrane, limited increase of the vascularization
- Tumor : rapid, complete, durable



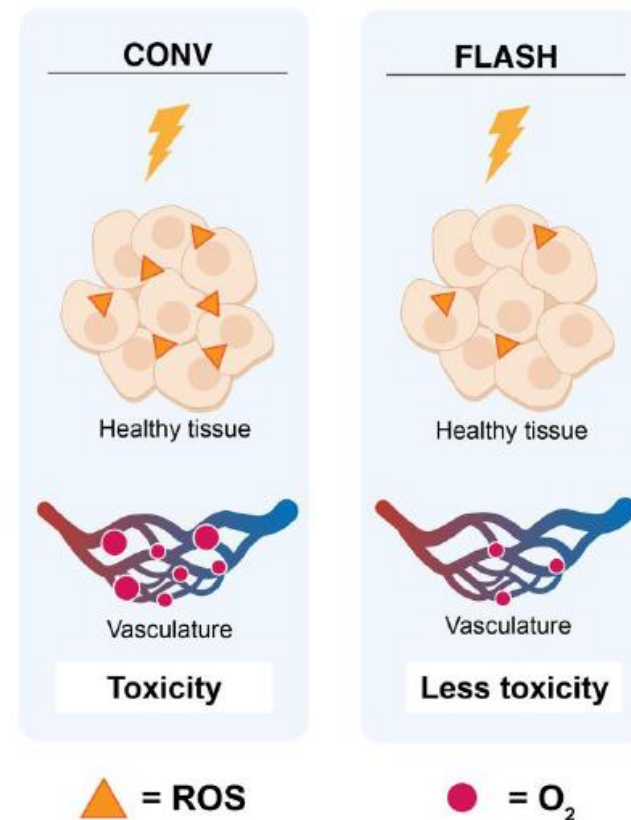
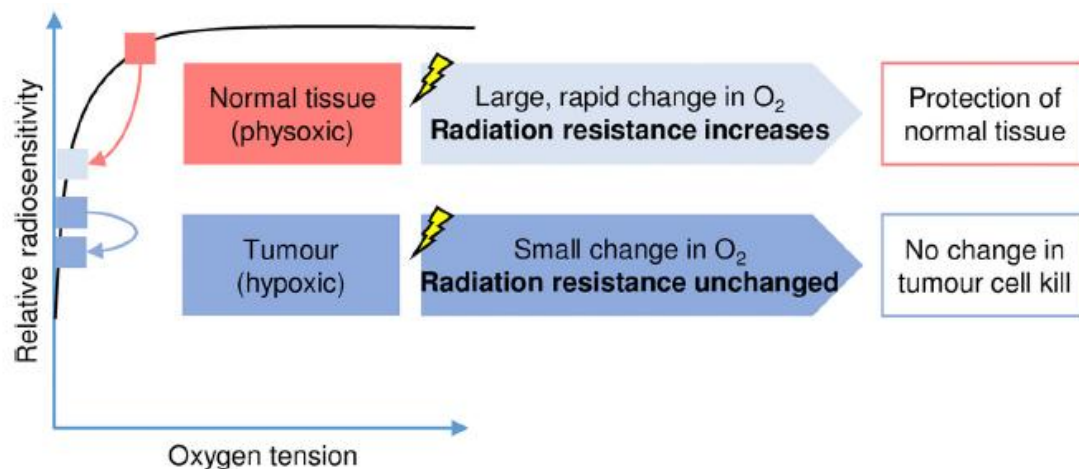
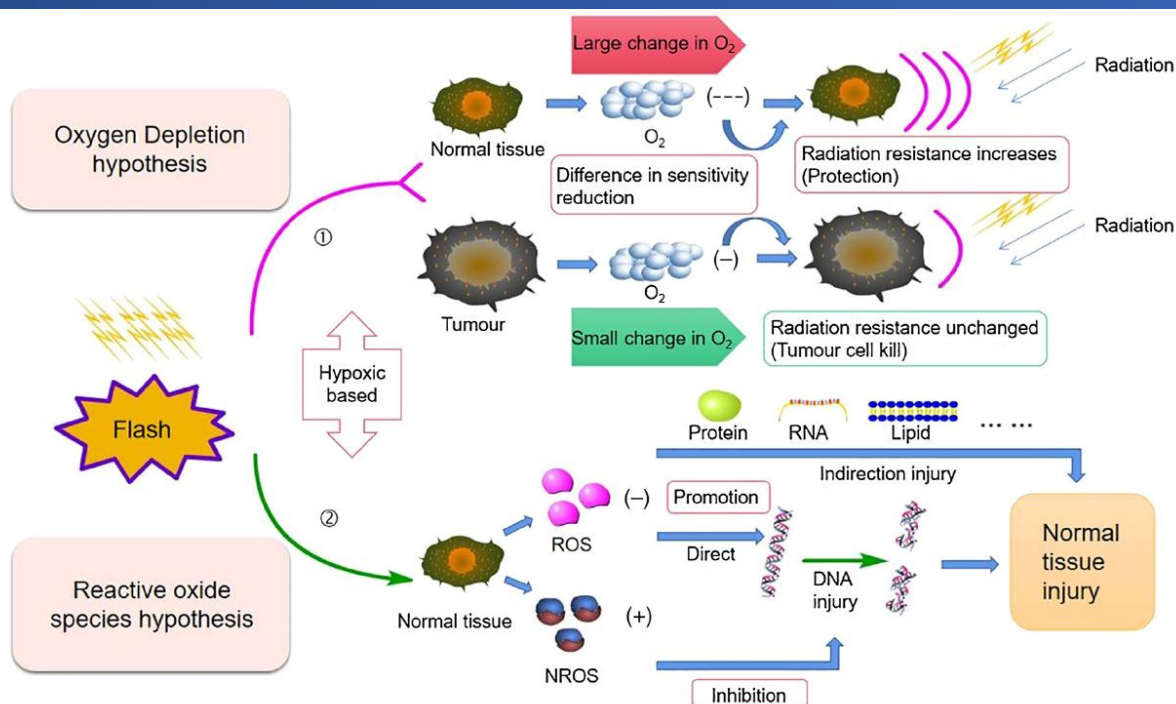
Fig. 1. Temporal evolution of the treated lesion: (a) before treatment; the limits of the PTV are delineated in black; (b) at 3 weeks, at the peak of skin reactions (grade 1 epithelitis NCI-CTCAE v 5.0); (c) at 5 months.

FLASH-RT biological mechanism

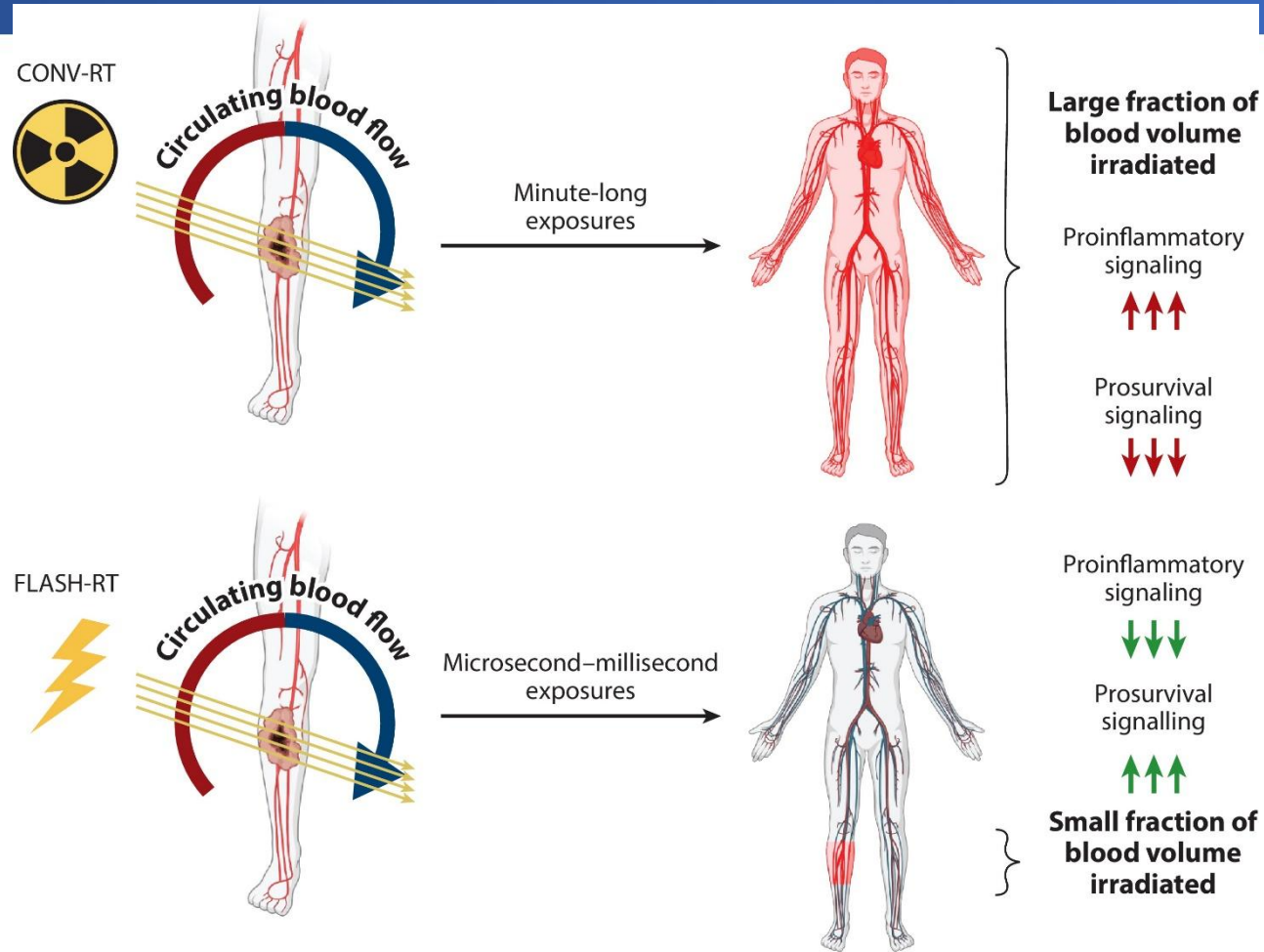
FLASH-RT biological mechanism

- Oxygen consumption hypothesis
- Immune and inflammatory hypothesis
- DNA damage, senescence and fibrosis - remains unclear

Oxygen Depletion Hypothesis



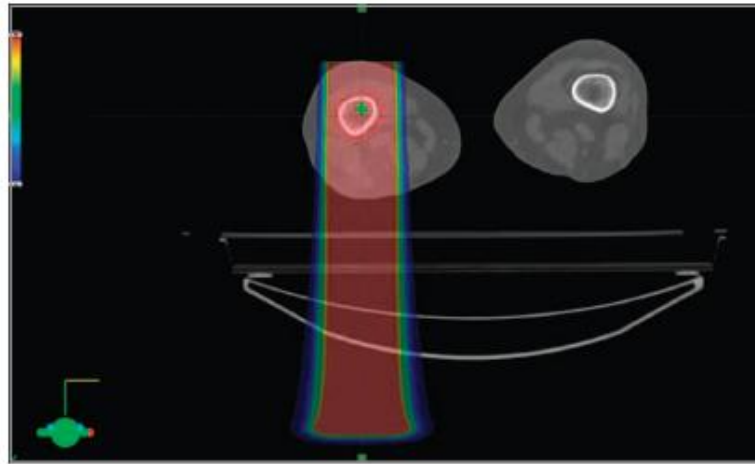
Immune and inflammatory hypothesis



AR Limoli CL, Vozenin M-C. 2023
Annu. Rev. Cancer Biol. 7:1–21

Proton FLASH Radiotherapy for the Treatment of Symptomatic Bone Metastases The FAST-O1 Nonrandomized Trial

- First-in-human clinical trial of proton FLASH therapy



C Radiation dose as a function of depth of penetration

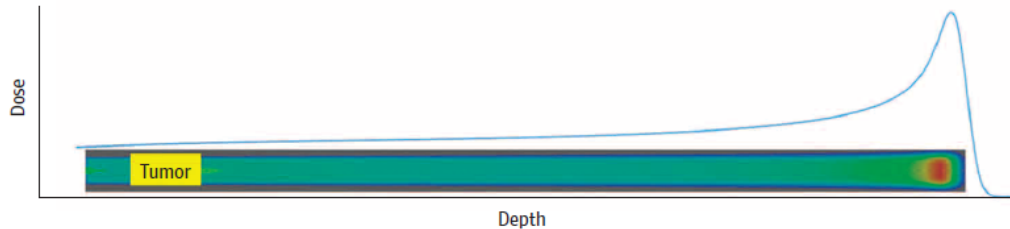


Table 2. Adverse Events (Possibly, Probably, or Definitely) Attributed to FLASH Treatment (N = 10)

Adverse events ^a	Patient, No. (%)
Acute (≤3 mo posttreatment)	
Edema, limb (grade 1)	1 (10)
Erythema (grade 1)	1 (10)
Extremity pain (grade 2)	1 (10)
Fatigue (grade 1)	1 (10)
Pruritus (grade 1)	2 (20)
Skin hyperpigmentation (grade 1)	4 (40)
Long term (>3 mo posttreatment)	
Skin discoloration (grade 1)	1 (10)

^a Adverse events were graded using the Common Terminology Criteria of Adverse Events, version 5.0.

Take home message

- MRgART
: Clinical Advantages: biologic targeting and response-mediated dosing, potentially reducing toxicity and improving survival outcomes.
: Future Requirements: To justify the high cost and resource-intensive nature of MRgART, high-quality prospective data from randomized trials are essential.
- Particle therapy minimizes severe radiation-induced lymphopenia and ILD-related pneumonitis, enhancing treatment tolerability and offering major synergistic potential for subsequent immunotherapy
- FLASH radiotherapy is a promising modality that spares normal tissue while effectively treating tumors, though its clinical adoption is currently limited by unclear biological mechanisms