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Advanced imaging biomarker in Radiotherapy ~~Planning~~

What we can’t miss tomorrow

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Roma, Italy, 27.10.2025

Gemelli
Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore
GART
Advanced Radiation Therapy

Roadmap

- Why biomarkers in RT planning?
- Modalities & quantitative biomarkers (CT, MRI, PET)
- Radiomics & AI-derived biomarkers
- Adaptive RT & MR-Linac integration
- From biomarker → contouring → prescription (dose painting)
- Validation, standardization & QA
- Clinical ongoing project evidence
- Common pitfalls (and challanges)

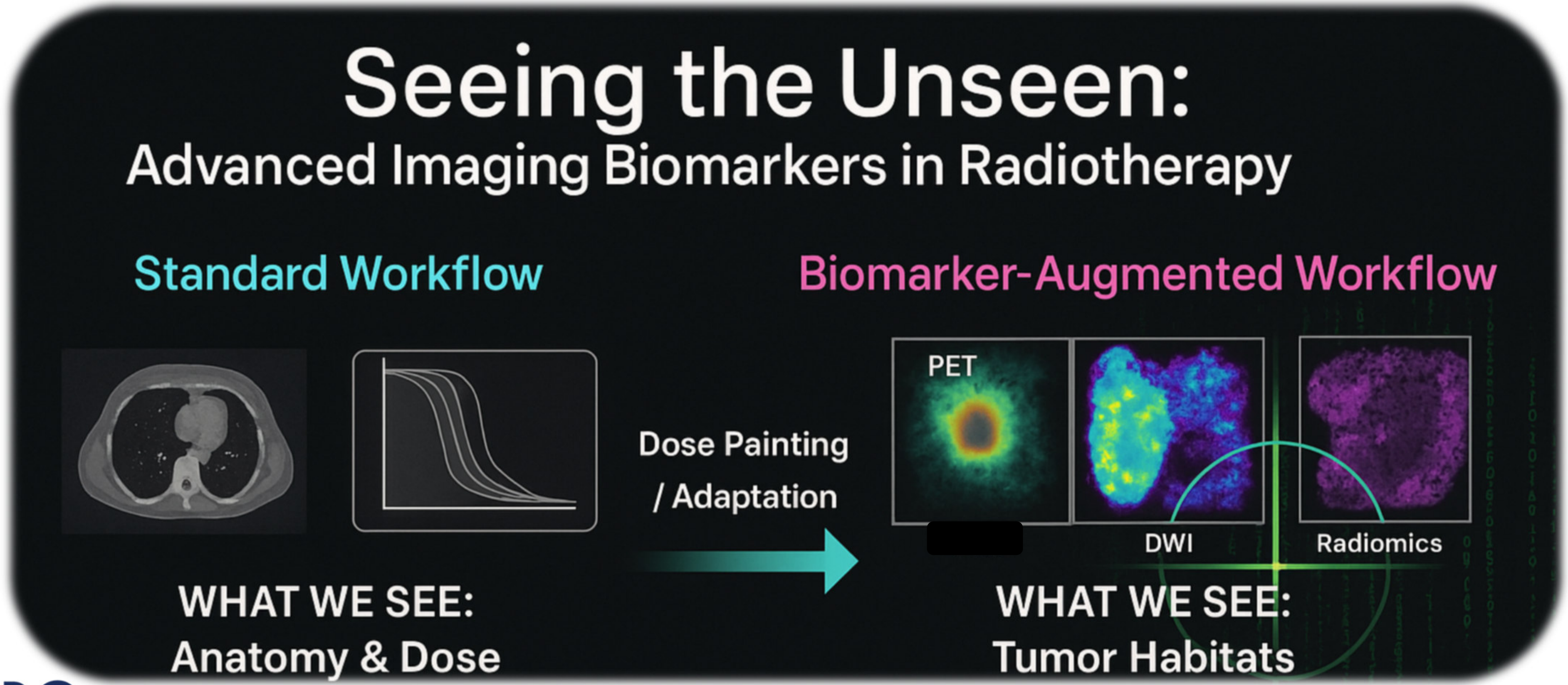
What is an imaging biomarker?

- A measurable image-derived indicator of normal or pathological processes or response to therapy.
- Should be quantitative, validated, and linked to a biological/clinical endpoint.

Why they matter in RT planning

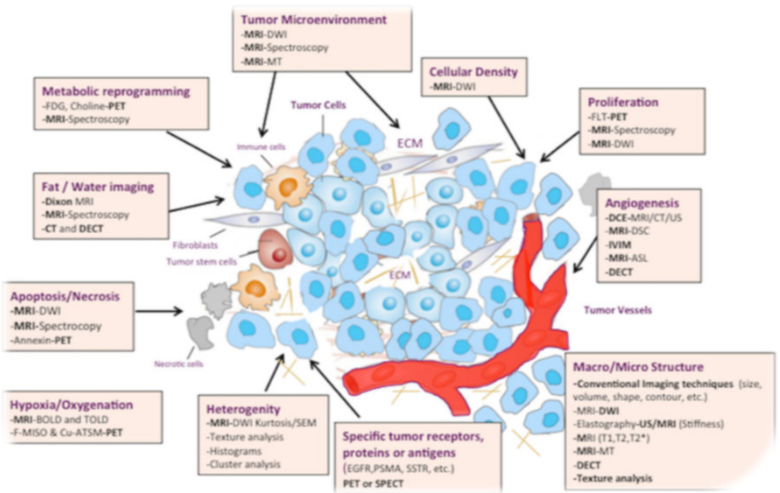
- Better target definition: integrate biology beyond anatomy.
- Predict/monitor response → personalize dose & adapt plans.
- Enable voxel-wise strategies (dose painting) while sparing OARs.
- ~~Bridge to radiogenomics & decision support.~~

Why they matter in RT planning



Modalities & exemplar biomarkers

- CT: electron density, dual-energy material maps; radiomics texture indices.
- MRI structural: T1/T2/FLAIR, tumor/edema delineation.
- MRI functional: DWI/ADC (cellularity), DCE/DSC perfusion (Ktrans, CBV), IVIM, ASL.
- Quantitative MRI: MR Fingerprinting (simultaneous T1/T2/PD, B1).
- Hybrid imaging: PET/CT, PET/MRI for co-registered biology.
- 4D imaging: motion-resolved CT/MRI; ventilation imaging.
- Multiparametric maps → composite 'habitats'.
- Quality frameworks: QIBA profiles, AAPM guidance.



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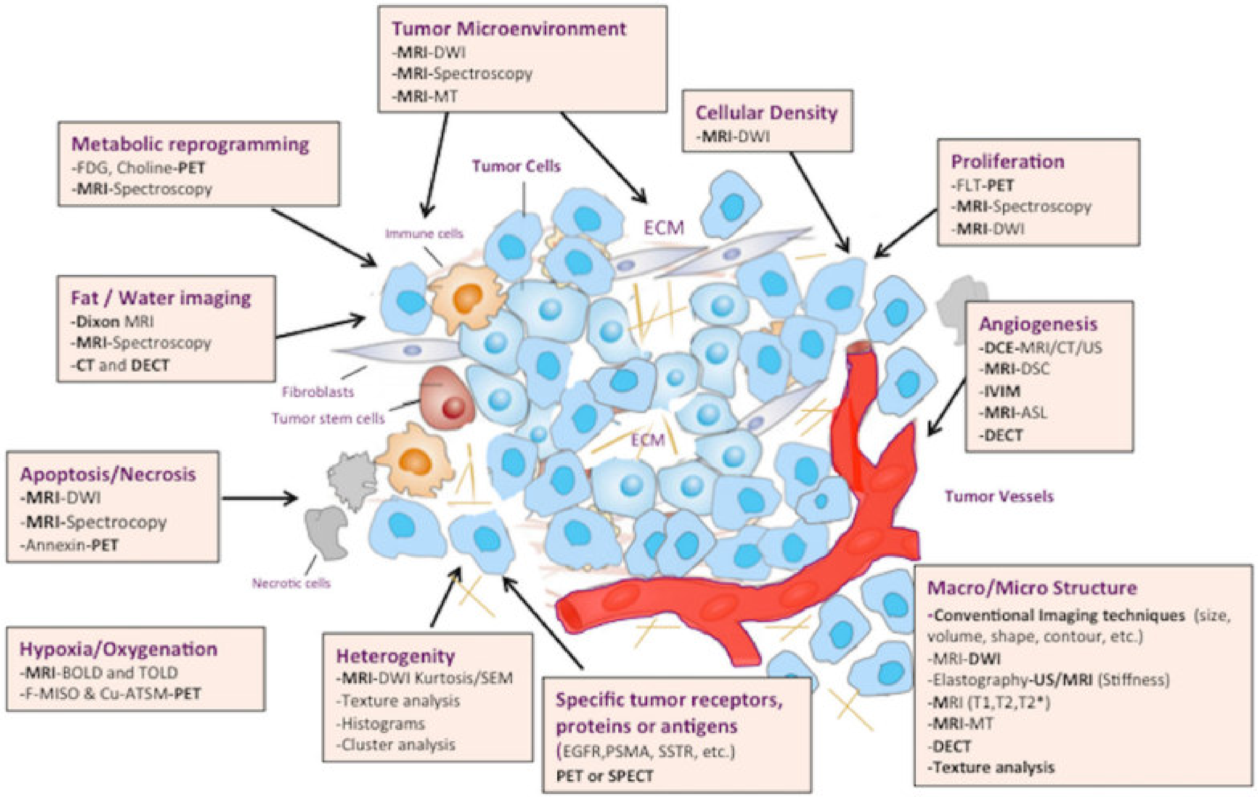
MRI biomarkers (highlight)

Quantitative MRI parameters reflect tumor biology

- **DWI/ADC: early response indicator; correlates with cellularity; hypoxia.**
- **Perfusion (DCE/DSC): vascular permeability; tumor aggressiveness.**
- **Spectroscopy: metabolic signatures (choline, citrate, lactate).**
- **MR Fingerprinting: fast multi-parametric quantitative maps with improved repeatability.**



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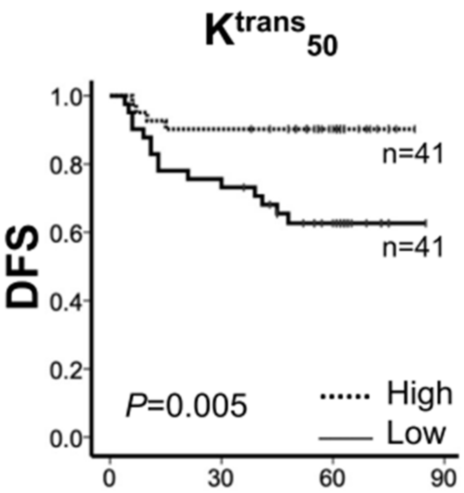
García-Figueiras et al. Insights into Imaging 2019

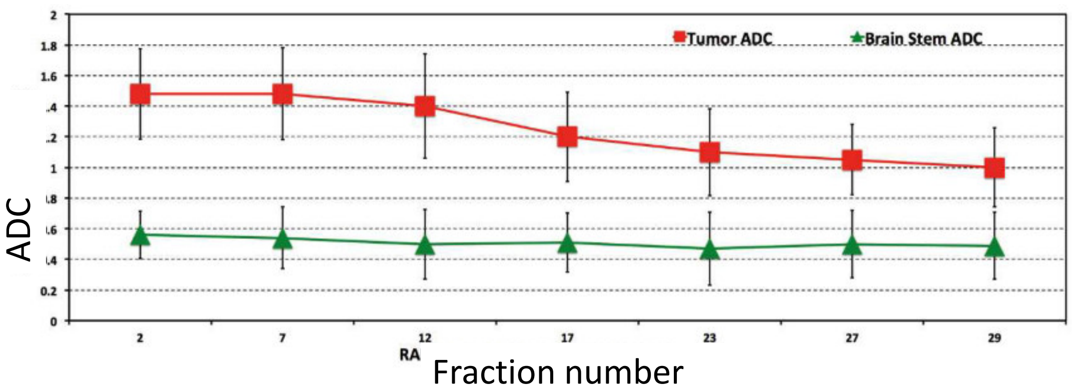
MR integrated in RT workflow

Potential for personalized radiotherapy with imaging biomarkers

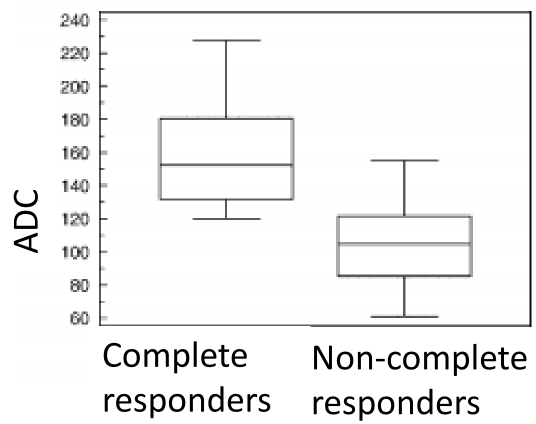
Pre-treatment	During treatment	Post-treatment
Outcome prediction	**Biological image-guided adaptive radiotherapy (BIGART)**	**Response assessment**
Patient selection and treatment stratification	Modify the dose and/or dose distribution based on changes seen during treatment	Determine next steps in treatment based



Skipar et al. Radiother Oncol 2022



Yang et al. Med Phys 2016



Kim et al. Radiology 2009

Courtesy of Petra van Houdt

Radiotherapy and Oncology 146 (2020) 66–75
Contents lists available at ScienceDirect
Radiotherapy and Oncology
journal homepage: www.thegreenjournal.com

Review Article

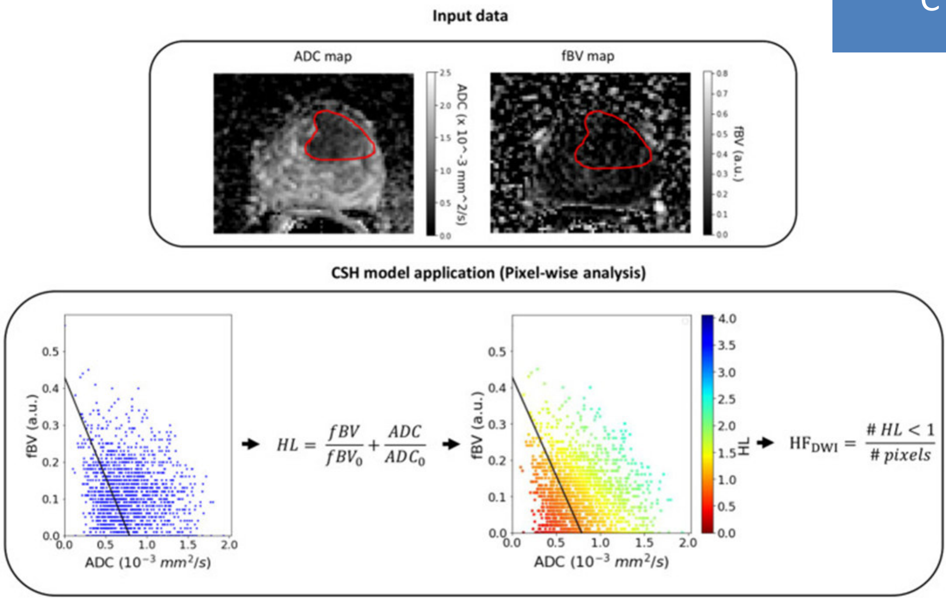
Quantitative imaging for radiotherapy purposes

Oliver J. Gurney-Champion [a,*], Faisal Mahmood [b,c], Marcel van Schie [d], Robert Julian [e], Ben George [f], Marielle E.P. Philippens [g], Uulke A. van der Heide [d], Daniela Thorwarth [h], Kathrine R. Redalen [i]

MR integrated in RT workflow

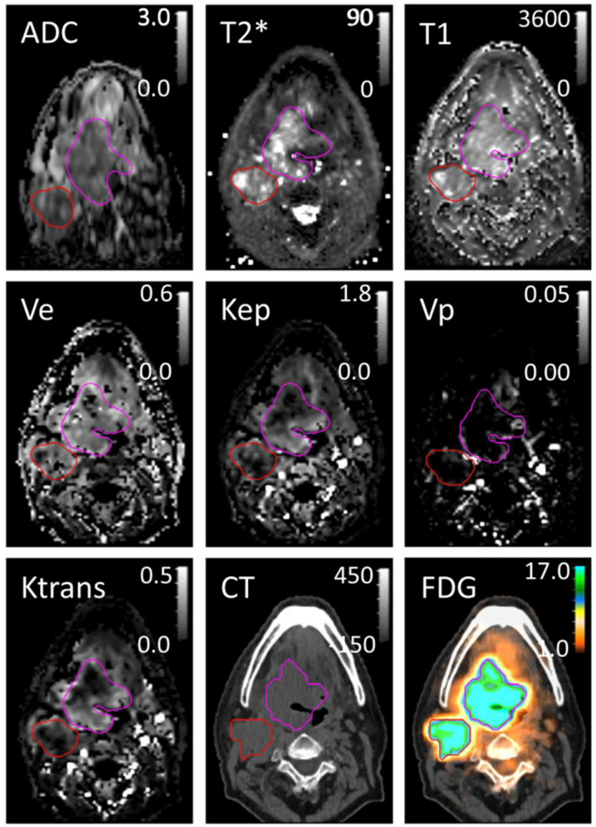
Quantitative imaging approaches

- CT
- PET
- MRI
  - DWI
  - MRI Relaxometry
  - DCE
  - MR Fingerprinting



Salamanca M et al. (2024) A DWI-based hypoxia model shows robustness in an external prostatectomy cohort Front. Oncol.

From qualitative to quantitative MRI



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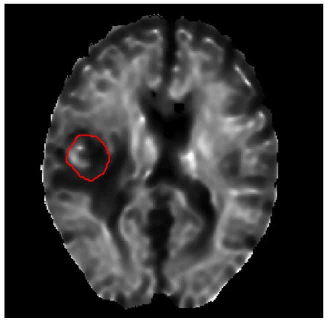
The Consumption and Supply based Hypoxia model exhibited sufficient robustness in the external cohort, suggesting a plausible reflection of true hypoxia and enabling the use of the HF_{DWI} metric for further research into prostate cancer and hypoxia.

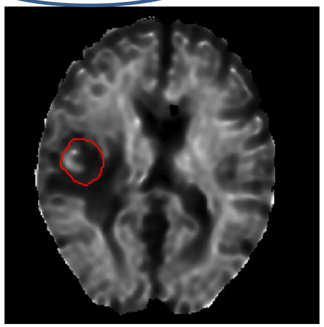
MR integrated in RT workflow

Time-dependent diffusion MRI as a potential quantitative imaging biomarker for radiotherapy

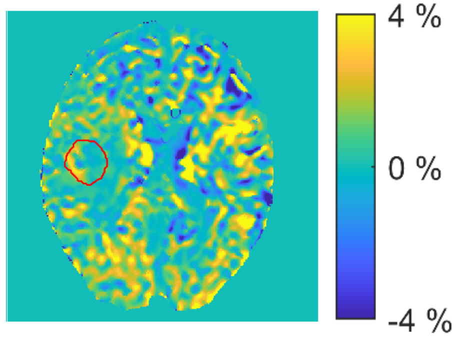
DWI 1:
b = 2500 s/mm2
t_d = 44 ms



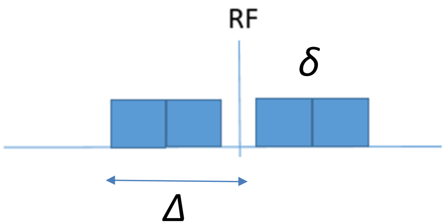
DWI 2:
b = 2500 s/mm2
t_d = 26 ms

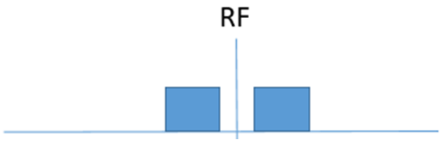


TDD contrast map
(= time-dependent diffusion contrast map)



Diffusion gradients:





$$t_d = \Delta - \frac{\delta}{3}$$

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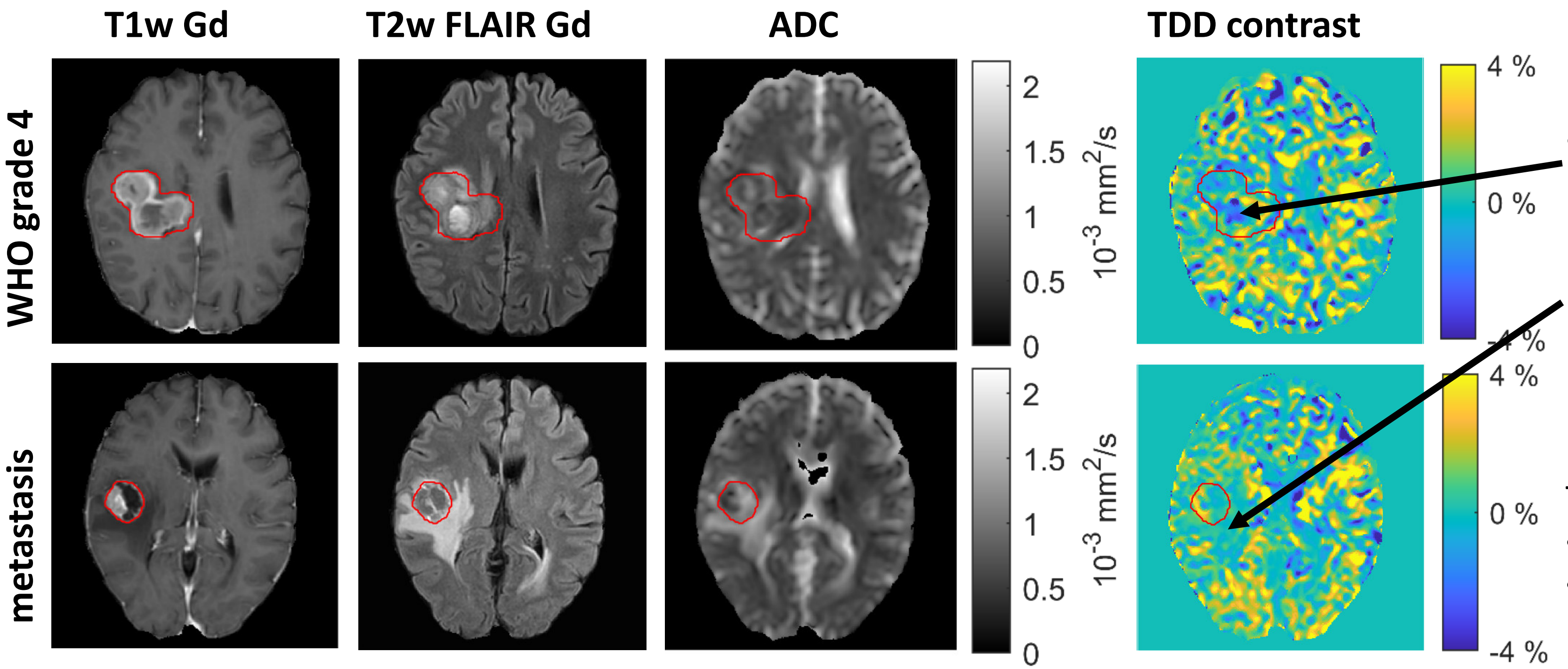
Courtesy of Minea Jokivuolle

MR integrated in RT workflow

Time-dependent diffusion MRI as a potential quantitative imaging biomarker for radiotherapy

= gross tumor volume (GTV)



Tumor rim:
Positive ↔ restriction

Tumor core:
Negative ↔ exchange

Edema:
No contrast ↔ free diffusion

Thermal noise:

- GTV: 0.38 +- 0.09%
- White matter: 0.69 +- 0.002%

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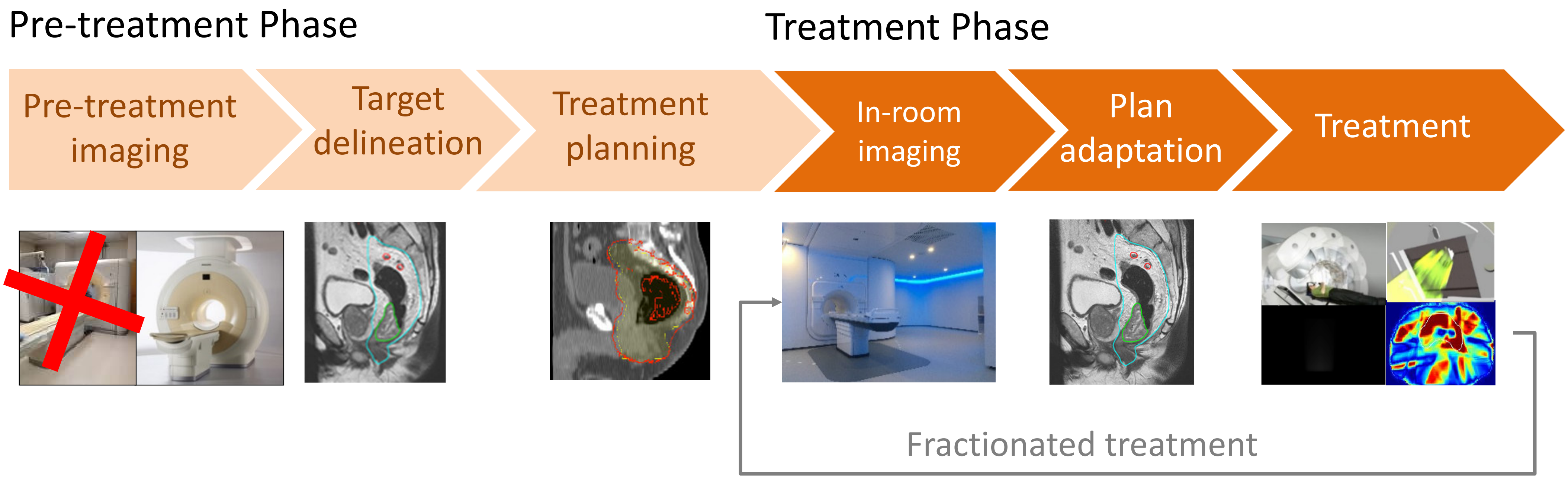
Courtesy of Minea Jokivuolle

MR integrated in RT workflow



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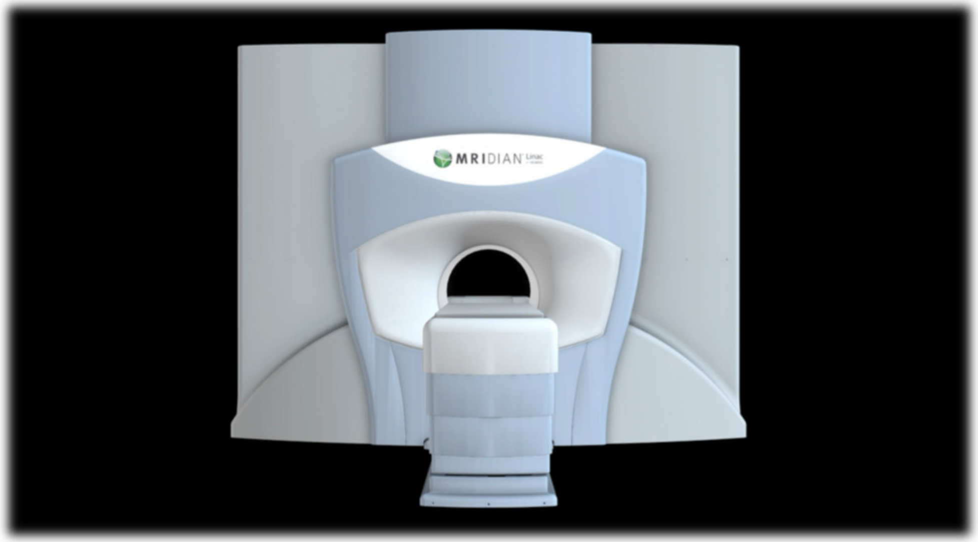
Courtesy of Petra van Houdt

Adaptive RT & MR-Linac: a catalyst

- On-table imaging enables biology-informed adaptation (daily/weekly).
- qMRI on MR-Linac (ADC, T1/T2, DCE, potentially MRF) → response monitoring.
- Biomarker trajectories → adapt margins, dose, or targets.
- Infrastructure: fast QA, robust registration, automated pipelines.



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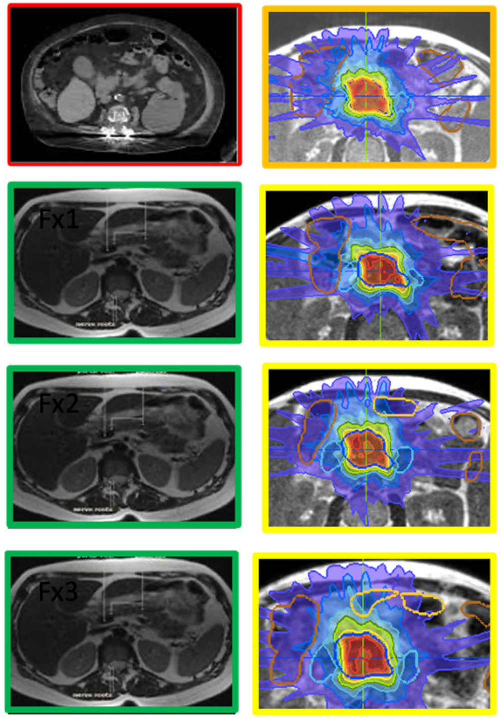
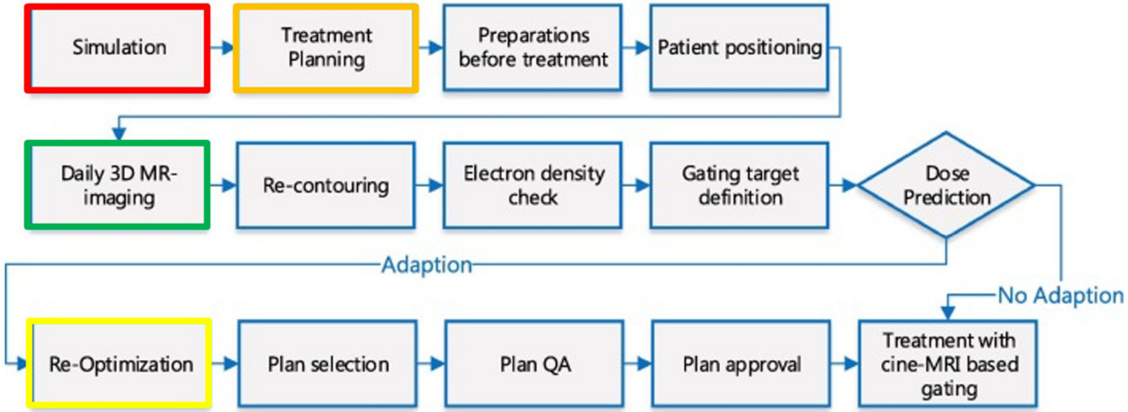
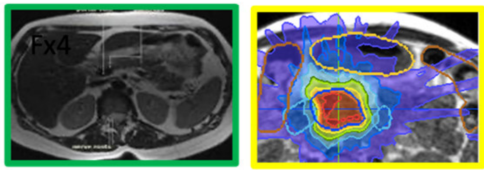
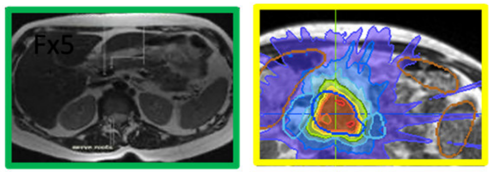
Adaptive RT & MR-Linac: a catalyst



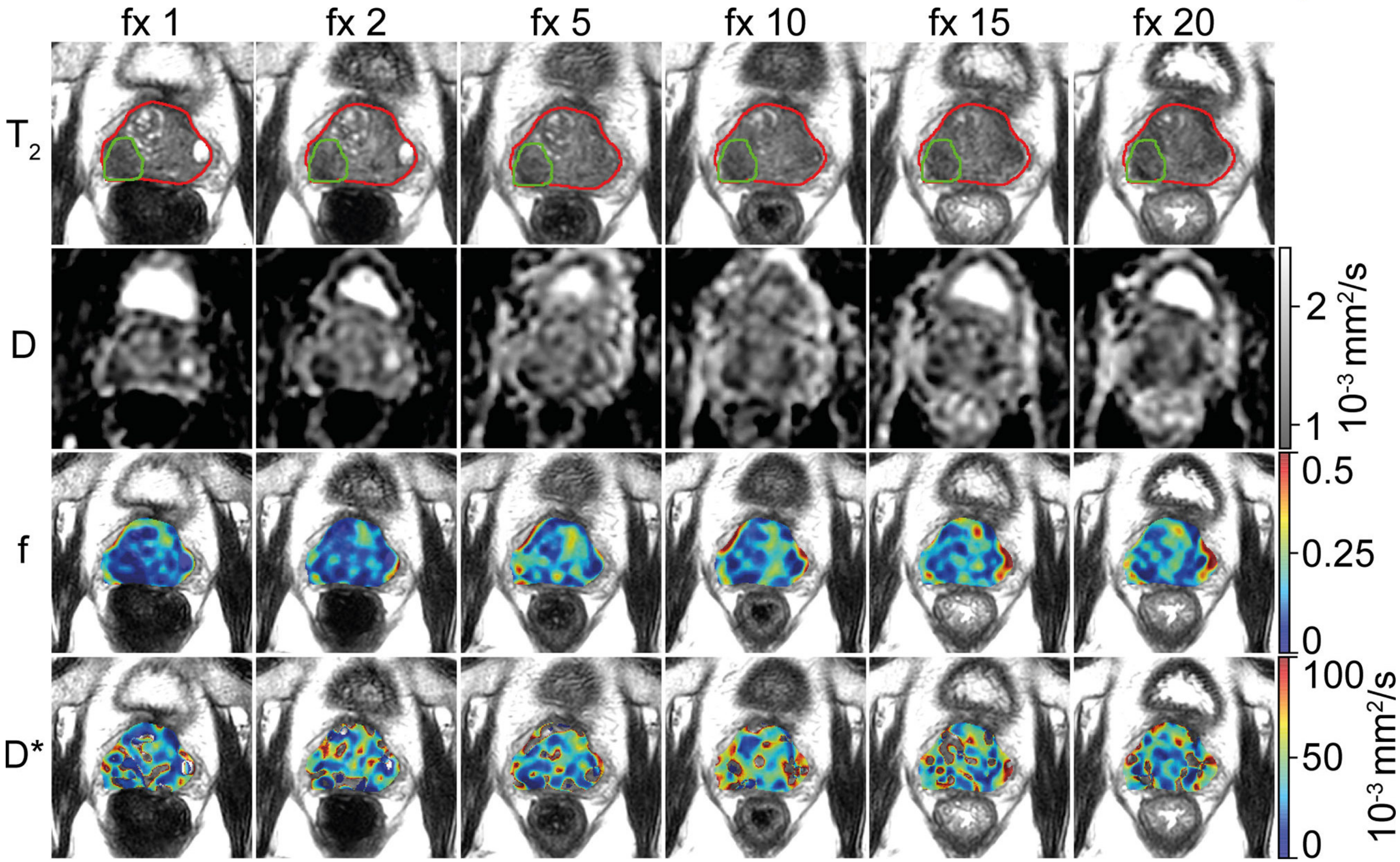


Klüter S. Technical design and concept of a 0.35 T MR-Linac. Clin Transl Radiat Oncol. 2019 Apr 8;18:98-101. doi: 10.1016/j.ctro.2019.04.007. PMID: 31341983; PMCID: PMC6630153.





Adaptive RT & MR-Linac: a catalyst

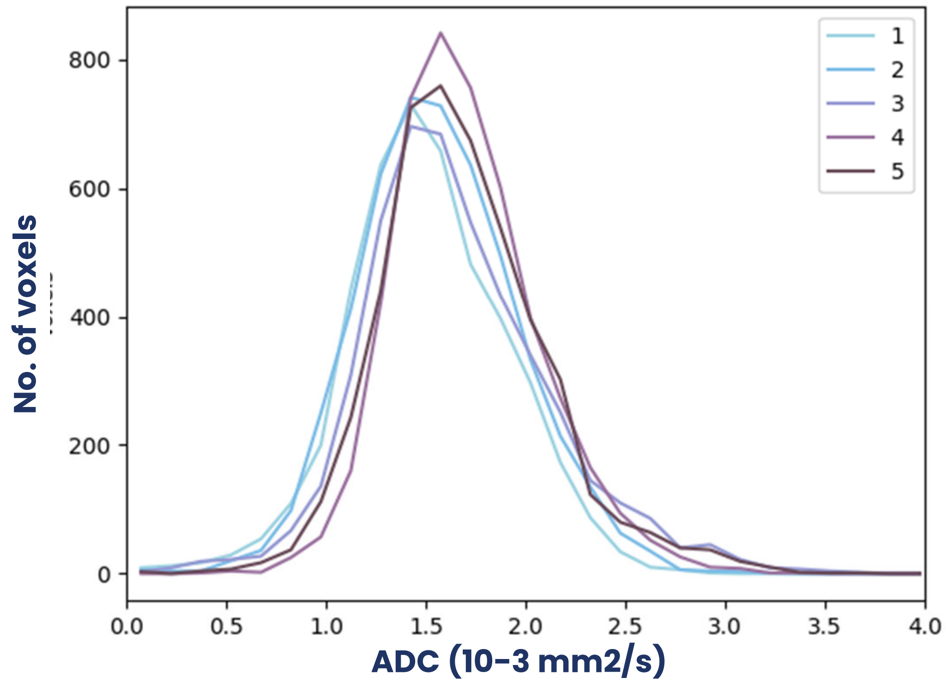


Kooreman ES et al. (2021) Daily Intravoxel Incoherent Motion (IVIM) in Prostate Cancer Patients During MR-Guided Radiotherapy—A Multicenter Study. Front. Oncol. 11:705964. doi: 10.3389/fonc.2021.705964

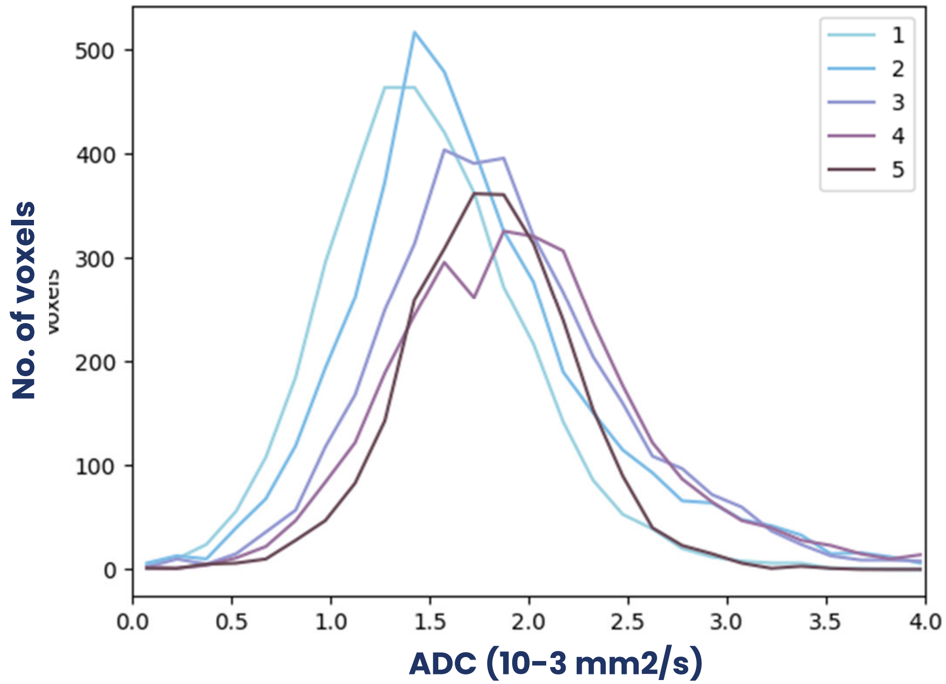
Adaptive RT & MR-Linac: a catalyst

Is there a potential for qMRI in hypofractionated treatments?

Patient 1: Minimal change



Patient 2: shift towards higher ADC values

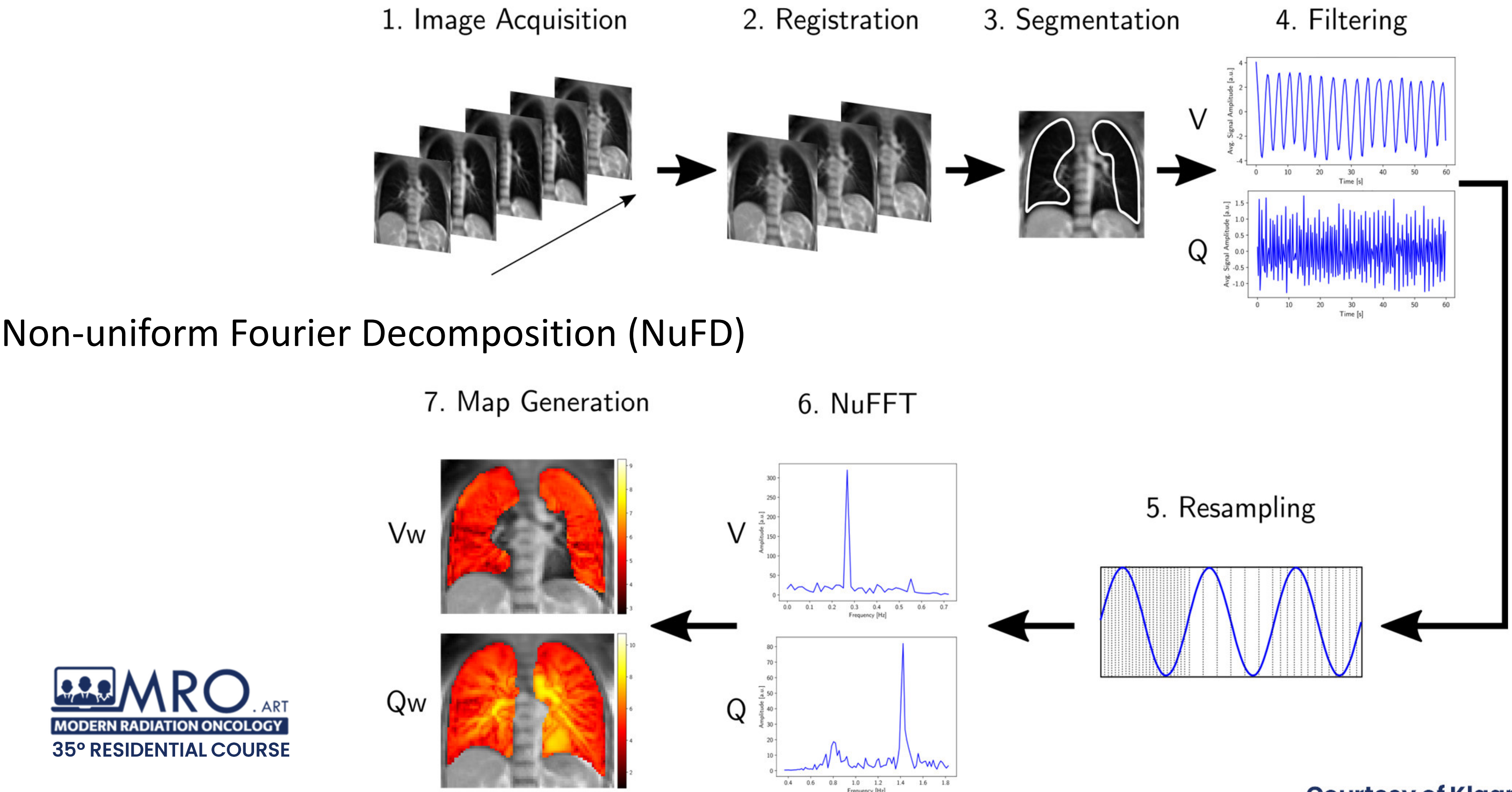


Example from rectal cancer

Courtesy of Petra van Houdt In collaboration with Anne Bisgaard and Faisal Mahmood (Odense)

Adaptive RT & MR-Linac: a catalyst

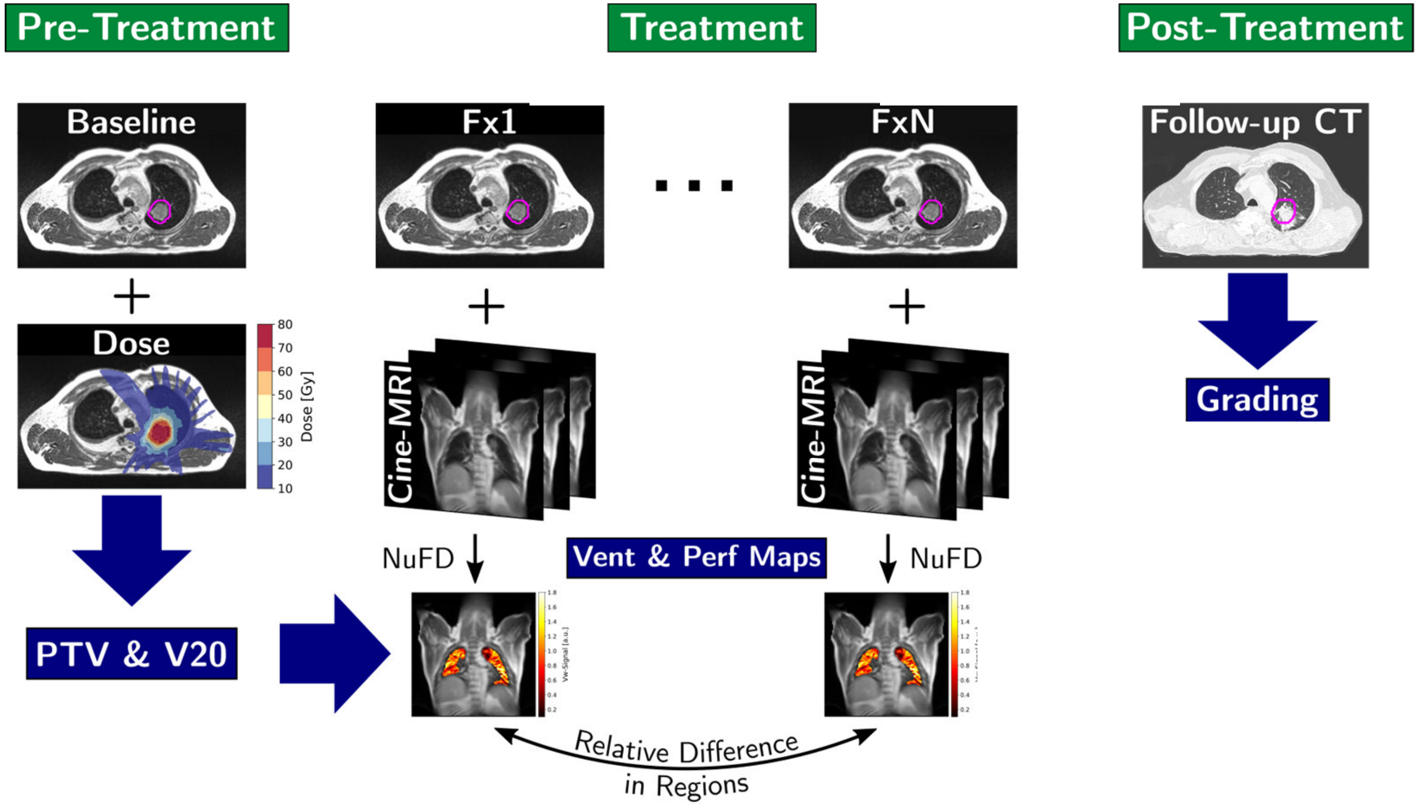
Ventilation and Perfusion Parameters Predictive of Radiation-Induced Pneumonitis



Courtesy of Klaar et al. Radiat Oncol (2023)

Adaptive RT & MR-Linac: a catalyst

Ventilation and Perfusion Parameters Predictive of Radiation-Induced Pneumonitis



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Courtesy of Klaar et al. Radiat Oncol (2023)

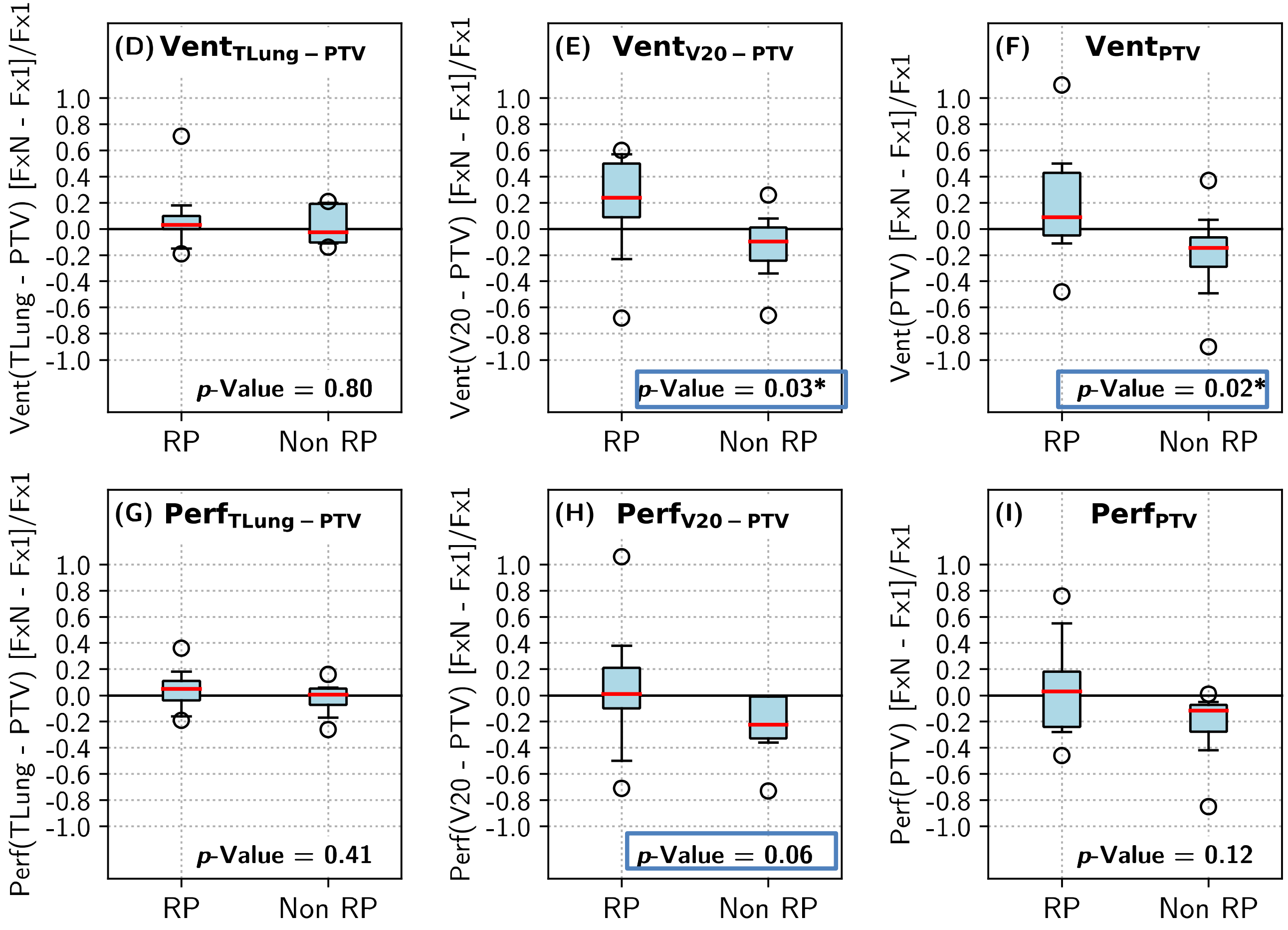
Adaptive RT & MR-Linac: a catalyst

Ventilation and Perfusion Parameters Predictive of Radiation-Induced Pneumonitis

Ventilation

- **Fast and easy extraction of functional changes over treatment course**
- **Ventilation and perfusion in high-dose region predictive**
- **Closer follow-up for identified patients at risk**
- **Acquisition of validation cohort ongoing**

Perfusion



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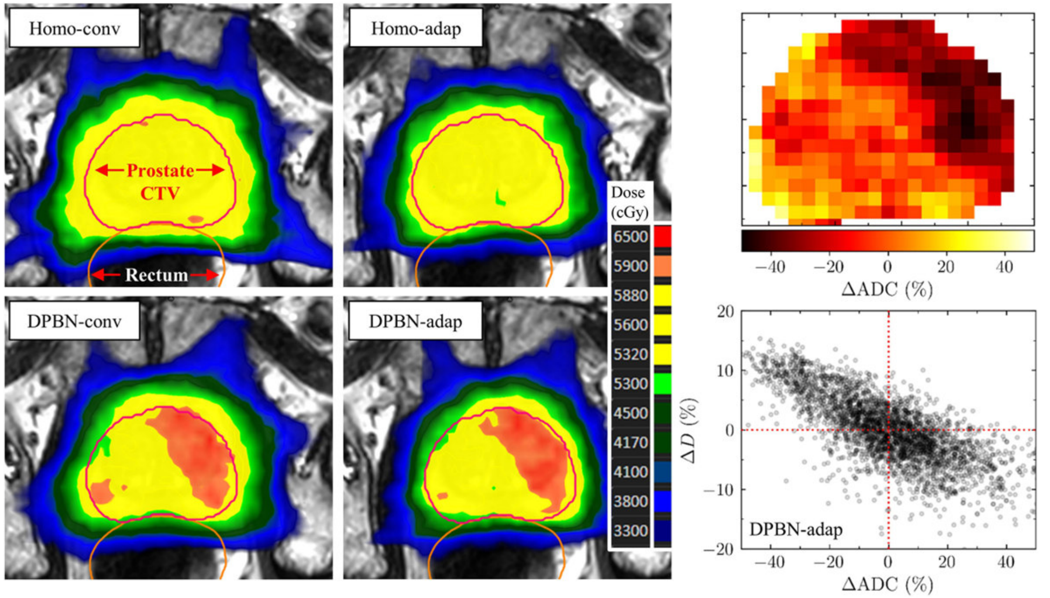
Courtesy of Klaar et al. Radiat Oncol (2023)

From biomarker to dose: Dose Painting

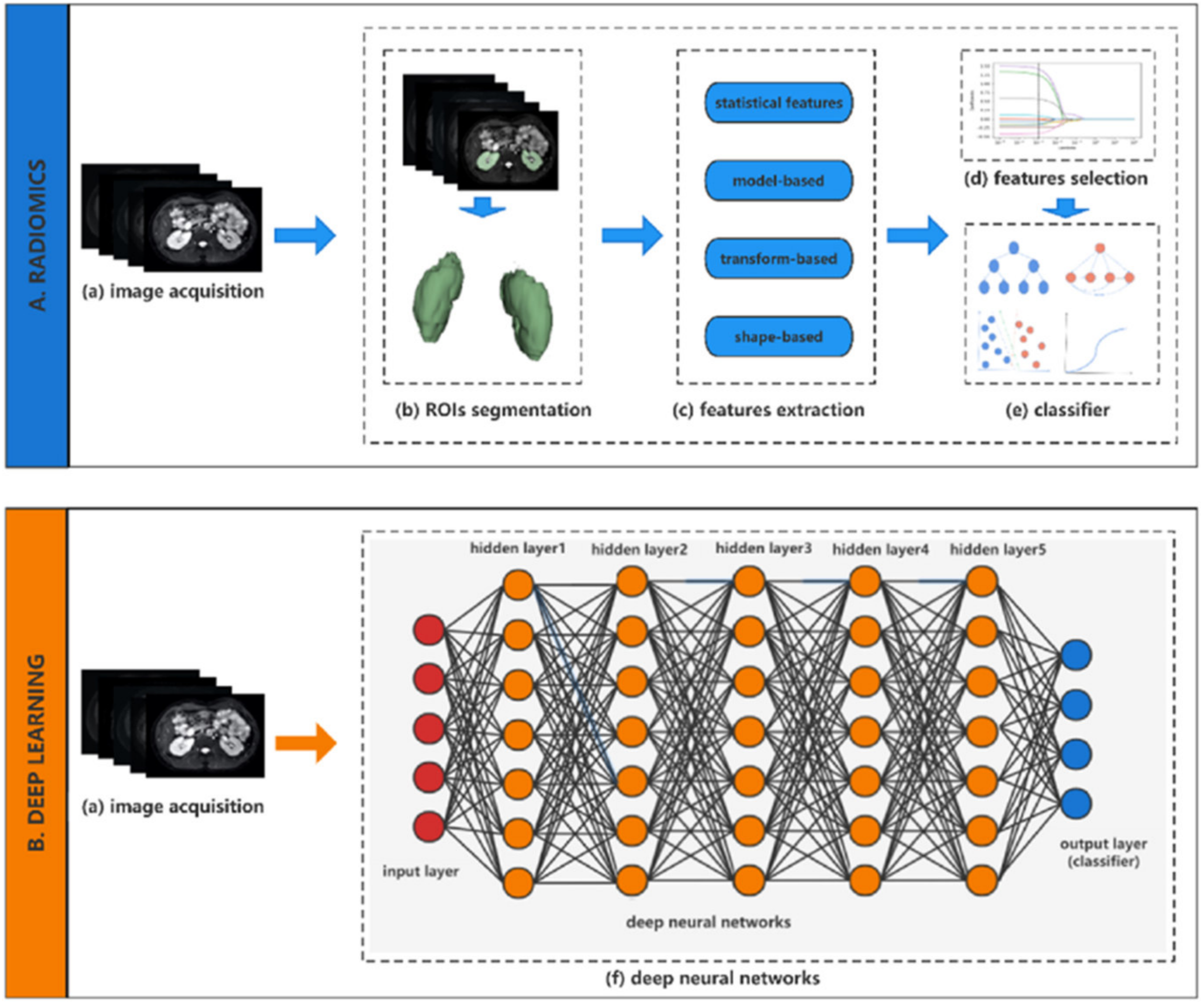
- ‘target within target’: boost based on thresholded maps (e.g., hypoxia).
- voxel-wise prescription proportional to biomarker intensity.
- requires quantitative maps, co-registration, and physics-constrained optimization.
- potential benefits: escalate resistant subvolumes; de-escalate less aggressive areas.
- challenges: biological validity of surrogates, uncertainties, delivery complexity.



. Frede´n E, Tilly D and Ahnesjö A (2022) Adaptive dose painting for prostate cancer. Front. Oncol 12:973067. doi: 10.3389/fonc.2022.973067

Radiomics & AI-derived biomarkers

- **Engineered texture/shape features (first/second/higher order).**
- **Deep features from CNNs; multi-omics integration.**



Zaho et al., Current Progress in Artificial Intelligence-assisted Medical Image Analysis for Chronic Kidney Disease: A Literature Review, Computational and Structural Biotechnology Journal 21 (2023) 3315–3326

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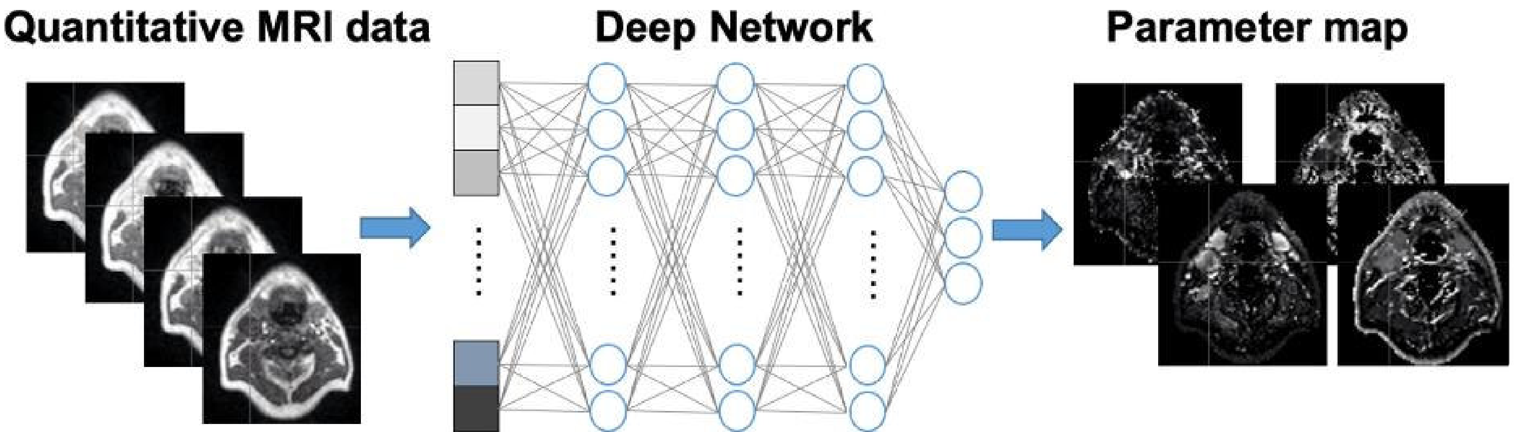
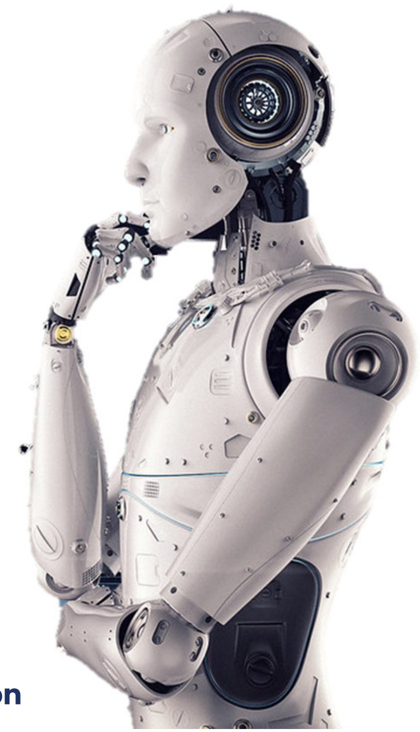
Radiomics & AI-derived biomarkers

- DL for faster imaging and reconstruction
- DL for advanced DWI models
- DL for parameter estimation
  - PINN (Physics-Informed Neural Networks)

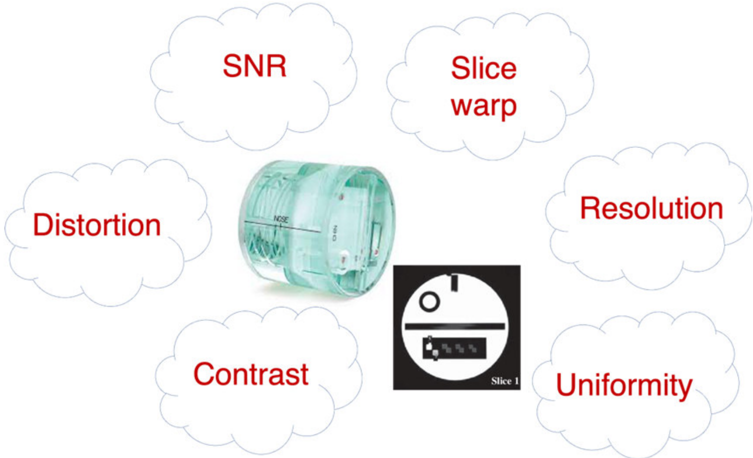




Courtesy of Oliver Gurney-Champion

Validation, standardization & QA

Dedicated qMRI QA



These control address the general performance of the scanner. No information on quantitative data can be drawn….

In qMRI ?

Review > Med Phys. 2022 Apr;49(4):2820-2835. doi: 10.1002/mp.15195. Epub 2021 Sep 29.

Challenges in ensuring the generalizability of image quantitation methods for MRI

Kathryn E Keenan [1], Jana G Delfino [2], Kalina V Jordanova [1], Megan E Poorman [1], Prathyush Chirra [3], Akshay S Chaudhari [4, 5], Bettina Baessler [6], Jessica Winfield [7, 8], Satish E Viswanath [3], Nandita M deSouza [7, 8]

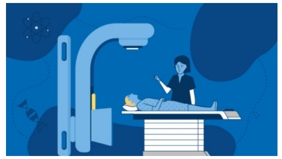
REVIEW ARTICLE

Clinical quantitative MRI and the need for metrology

[1]MATT T CASHMORE, PhD, [2]AARON J MCCANN, PhD, [3]STEPHEN J WASTLING, PhD, [2]CORMAC MCGRATH, PhD, [3]JOHN THORNTON, PhD and [1]MATT G HALL, PhD

Standardization of Quantitative DCE-MRI Parameters Measurement: An Urgent Need for Breast Cancer Imaging

Valeria Romeo, MD, PhD



Calibration → Dosimetry → Therapy

QA in quantitative MRI

- Identifying the specific **sources of error** of the quantitative technique
- Defining **procedures** for Quality Assurance of quantitative data.
- Evaluating clinical parameters
- Considering both hardware software components

Validation, standardization & QA

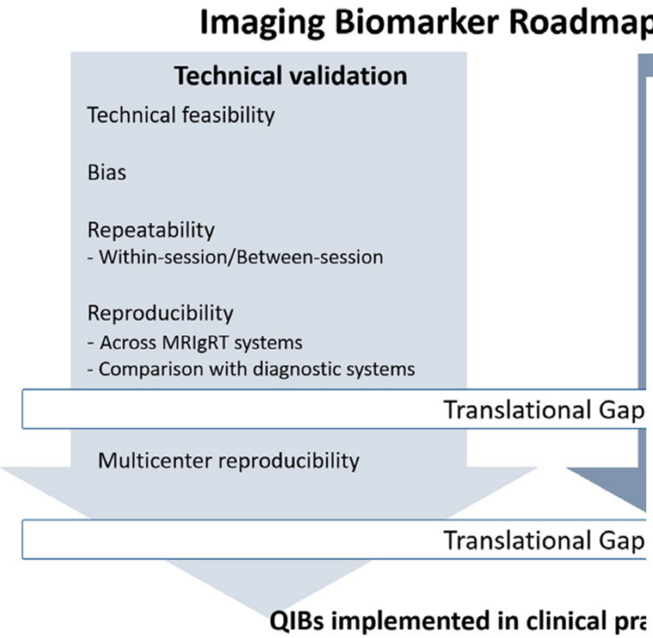


Table 2 Overview of Studies Investigating Clinical Validation of qMRI for BIGART on MRI-Guided Radiotherapy Systems

Tumor site	Reference	No. of subjects	Treatment Schedule	System	qMRI Parameters	No. of qMRI Measurements Per Subject	Link to clinical parameters	Clinical Validation Phase
Prostate	Kooreman et al. 2021[59]	43	20×3Gy	1.5T	D, f, D*	20	ISUP, ADT	Establish changes during treatment
	Kooreman et al. 2022[51]	20	20×3Gy	1.5T	D, f, D*, K^{trans}, k_{ep}, v_e	20 for IVIM, 5 for DCE	none	Establish changes during treatment
Rectum	Shaverdian et al. 2017[64]	3	50.4-54Gy (1.8 Gy fraction per day)	0.35T	ADC	4, 6, and 7	FDG-PET	Feasibility of repeated measurements
	Ingle et al. 2022[65]	9	Phase 1: 5×1.8Gy to GTV; Phase 2: 25×1.8Gy to GTV, mesorectum, pelvic nodes	1.5T	ADC	10 (daily in phase 1, weekly in phase 2)	TRG response	Establish changes during treatment
	Kooreman et al. 2022[50]	12	5×5Gy	1.5T	T1rho	5	complete and incomplete response	Establish changes during treatment
Brain	Nejad-Davarani et al. 2020[46]	4	25-30×2Gy	0.35T	T1, PD, and R2*	7-8 (pretreatment, once a week during RT, and post-treatment)	none	Feasibility of repeated measurements
	Lawrence et al. 2021[43]	59	30×2Gy/15×2.67 Gy/5×5.5Gy	1.5T	ADC	daily	none	Establish changes during treatment
	Chan et al. 2021[61]	54	30×2Gy/15×2.67Gy	1.5T	MTR_{amide}, MTR_{NOE} and asymmetry	5-6 (once a week)	tumor type and grade	Establish changes during treatment
	Tseng et al 2022[66]	10	30×2Gy	1.5T	ADC, T1, T2, CEST assymetry	daily (each time a different technique)	relation to the location of tumor recurrence	Establish changes during treatment
Abdominal	Hall et al. 2020[63]	10	6×5Gy/5×6.6 Gy/ 5×10Gy/5×15Gy/ 3×20Gy	1.5T	ADC, T2		none	Feasibility of repeated measurements
Head-and-neck	Yang et al. 2016[23]	3		0.35T	ADC	4-7	none	Feasibility of repeated measurements
Sarcoma	Yang et al. 2016[23]	3		0.35T	ADC	4-7	none	Feasibility of repeated measurements
	Gao et al 2020[20]	30	5×6Gy	0.35T	ADC	3	none	test prognostic value for outcome
	Gao et al 2021[67]	30	5×6Gy	0.35T	ADC	3 (15000 synthetic)	TE score	Test prognostic value for outcome

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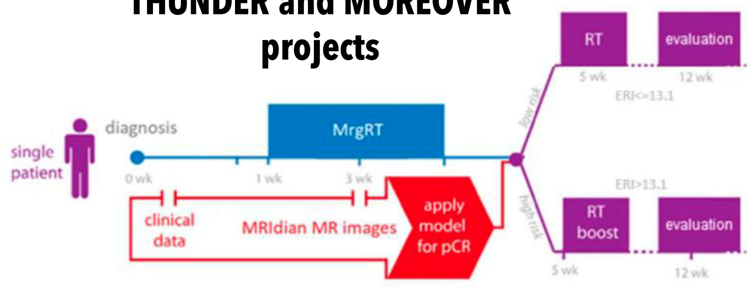
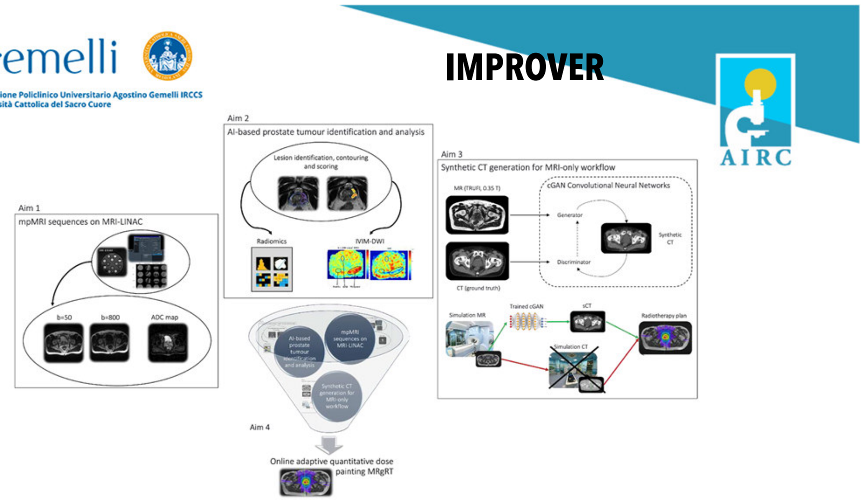
Clinical ongoing project evidence: in-house snapshots

THUNDER and MOREOVER projects





Doctoral Networks call schedule

- The call is **open**.
- This call will close on **25 November 2025**.

Doctoral Networks quick application guide →

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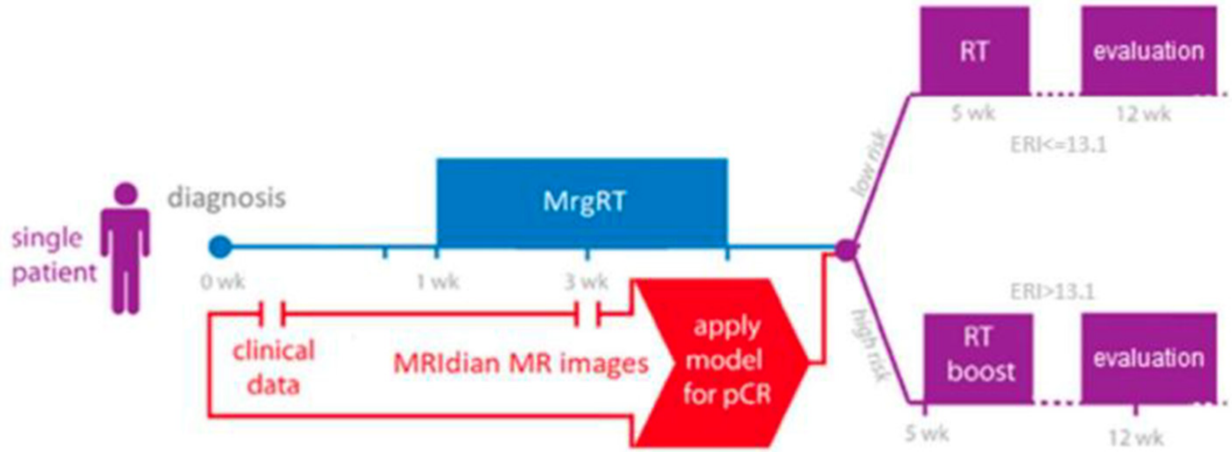
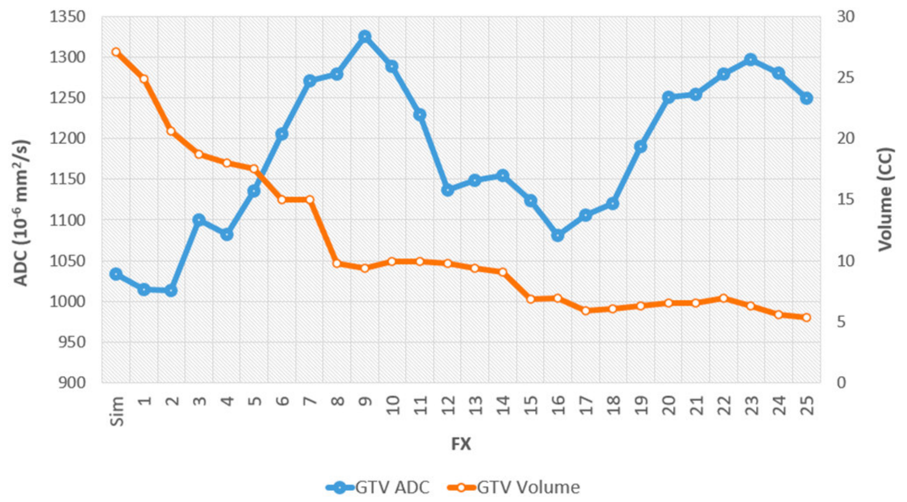
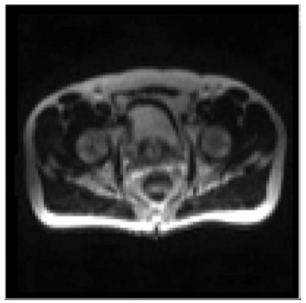
THUNDER and MOREOVER projects

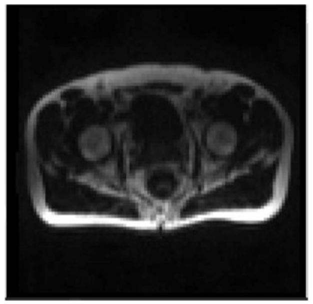




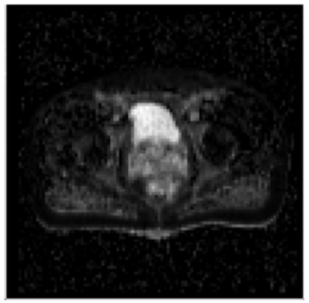
b = 50



b = 800



ADC MAP



Clinical ongoing project evidence: in-house snapshots

IMPROVER

Quant**I**tative **M**RI for **PR**ostate **O**nline Adapti**V**e Dos**E** Painting MRg**R**T

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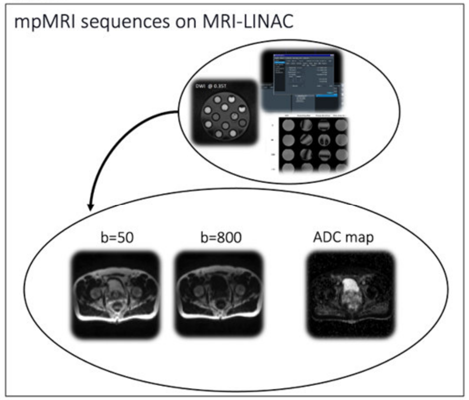
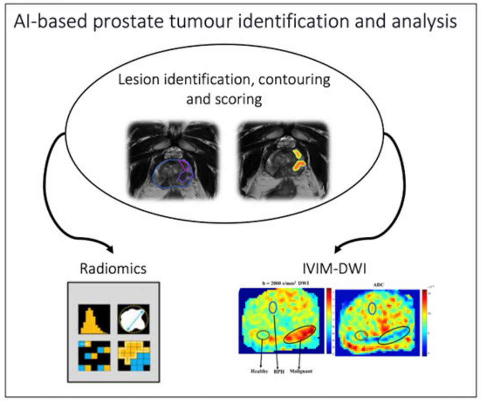
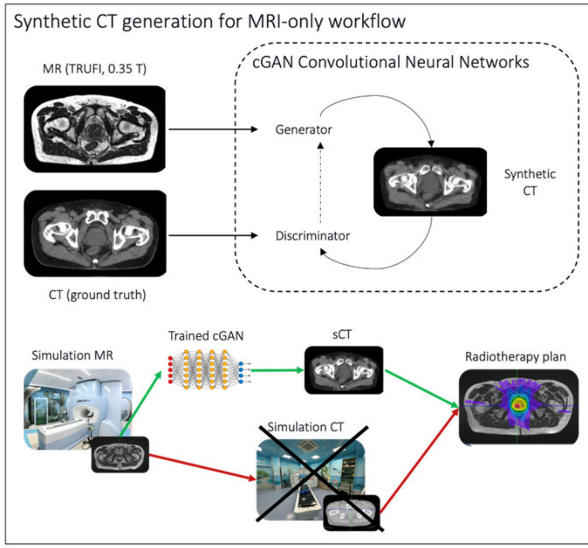
Aim 1

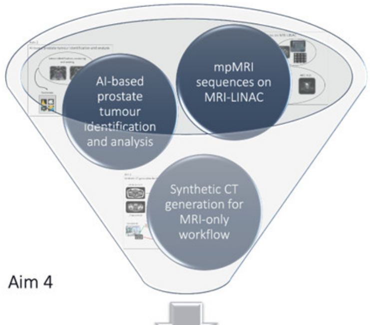


Aim 2



Aim 3





Aim 4

Online adaptive quantitative dose painting MRgRT

Clinical ongoing project evidence: in-house snapshots

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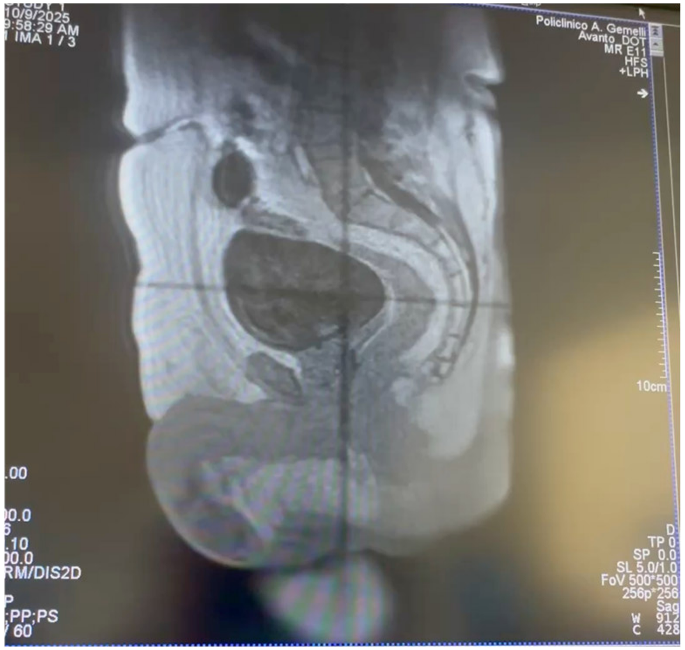
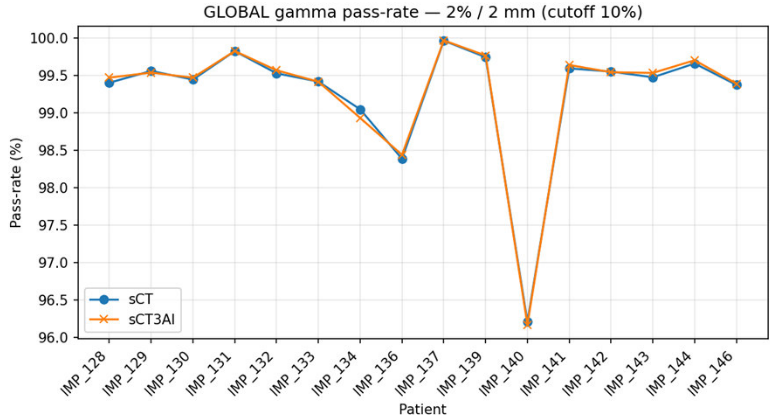
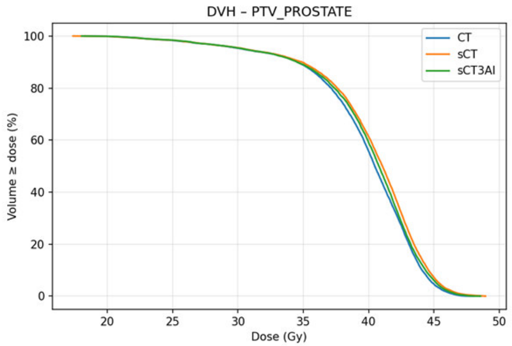
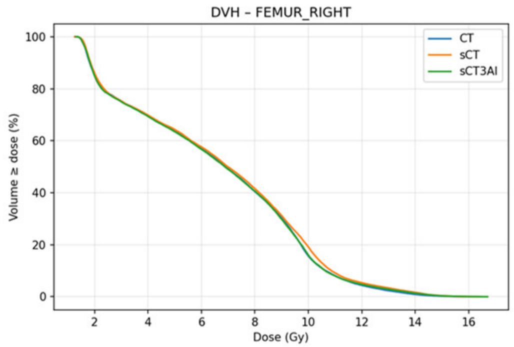
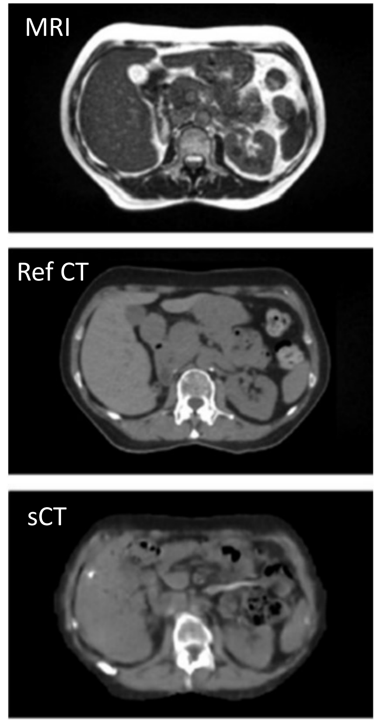
QuantItative MRI for PRostate Online AdaptiVe DosE Painting MRgRT











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Clinical ongoing project evidence: in-house snapshots

20 ESTRO Physics
24 Workshop

18-19 October 2024
Krakow, Poland

TEMPO DN Project

- Marie Skłodowska-Curie Action opens 608 million call for Doctoral Networks (DN)

Imaging biomarkers to monitor and predict response to radiation therapies

Tiziana Rancati, Claudio Fiorino, Robert Jeraj+ 36 other (super active) participants

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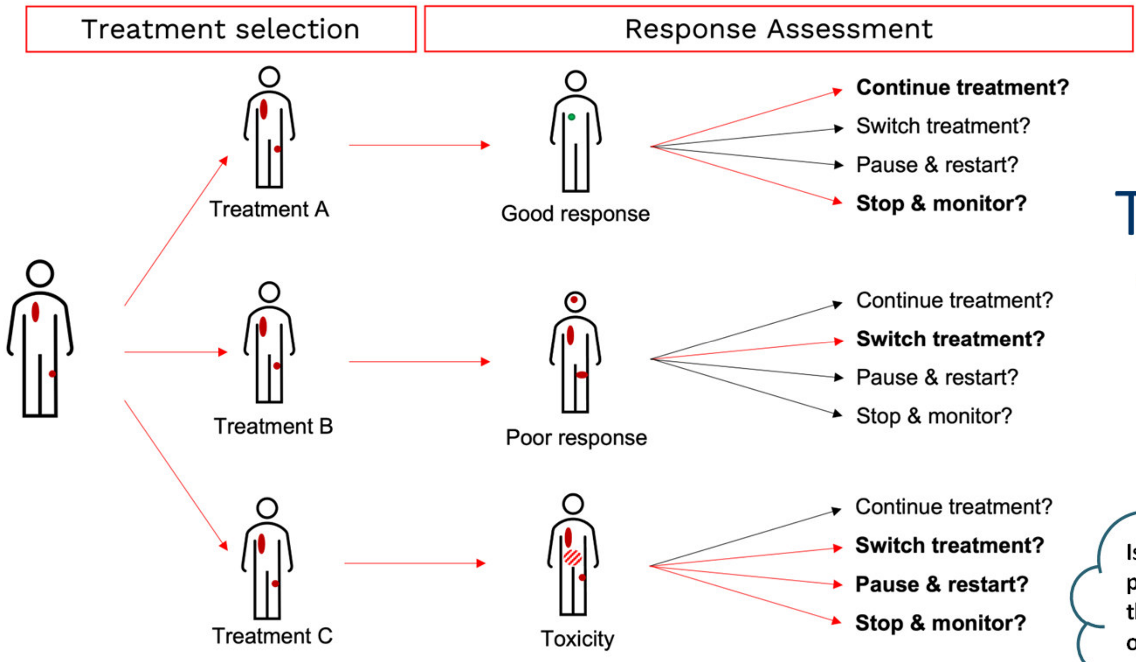
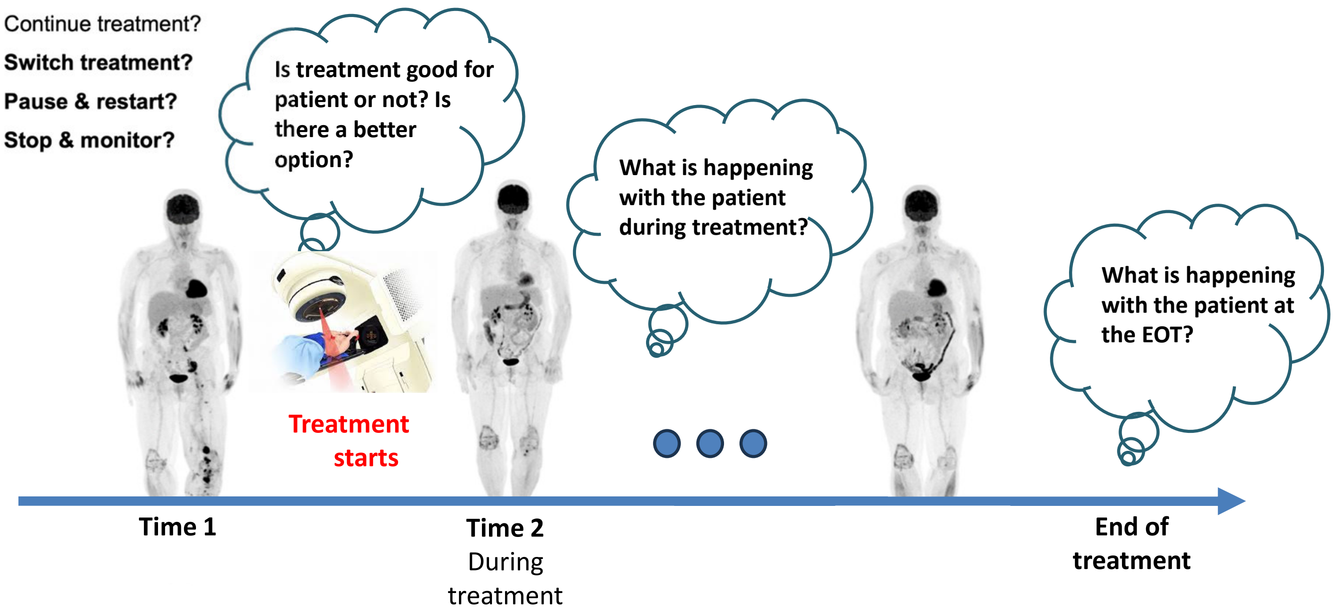
Clinical ongoing project evidence: in-house snapshots



TEMPO DN Project Overview

- Marie Skłodowska-Curie Action opens 608 million call for Doctoral Networks (DN)



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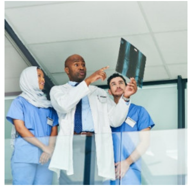
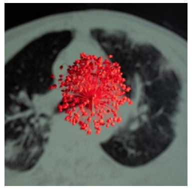
Clinical ongoing project evidence: in-house snapshots



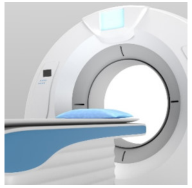
TEMPO Network Scope

TEMPO unites 15 PhD projects across Europe to advance research in imaging biomarkers for radiation therapies.



Imaging Biomarkers for Therapy

The network focuses on developing imaging biomarkers to personalize and improve radiation therapy outcomes.



Adaptive Radiotherapy Framework

TEMPO integrates biological, technical, predictive, and clinical data to enhance adaptive radiotherapy approaches.

TEMPO Work Packages

WP1 Biological Validation

Focuses on validating imaging biomarkers biologically and interpreting their physiological roles in cancer biology.

WP2 Technical Validation

Ensures imaging biomarkers are technically reliable and reproducible across multiple imaging platforms.

WP3 Predictive Integration

Integrates validated biomarkers into predictive models and adaptive frameworks for clinical decision support.

WP4 Clinical Translation

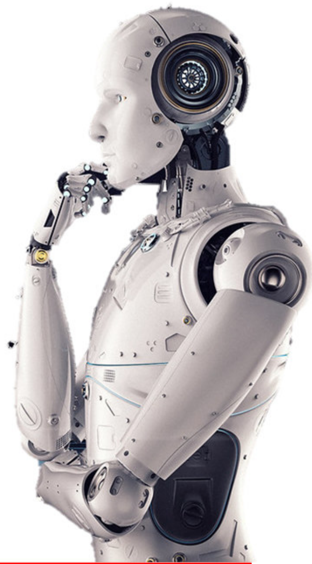
Focuses on adapting imaging protocols to clinical workflows and developing regulatory approval roadmaps.

Clinical ongoing project evidence: in-house snapshots

WP	Primary Supervisor	Original title
1	Tord Hompland - The Norwegian Radium Hospital	Early Response Assessment of proton therapy in soft tissue sarcoma
1	Faisal Mahmood - Odense University Hospital	Spatial correlation of diffusion weighted MRI and local response for tailored radiotherapy of pancreatic cancer
1	Marielle Philippens – University of Utrecht	Prediction of neuro-cognitive decline of brain metastases RT (fMRI)
2	Lars Olsson - Lund University	Validation of the CSH imaging biomarker for hypoxia assessment - technical validationtion
2	Oliver Gurney-Champion – Amsterdam University	Vendor-neutral qMRI sequences
2	Andreas Wetscherek – Institute of Cancer Research	Advanced diffusion-weighted MRI for biologically adaptive MR-guided radiotherapy
2	Marta Lazzeroni – Stockholm University	Early Response Assessment Through Robust Imaging Biomarker Definition in the Presence of Uncertainties
3	Azadeh Abravan- University of Manchester/university of Edimburgh	Improving early prediction of treatment response and complications in head & neck cancer using imaging biomarkers
3	Peter van Luijk – University of Groeningen	Changes in imaging to predict late cardiopulmonary toxicity
3	Tiziana Rancati – National Cancer Institute	Integration of dynamic microenvironmental signals into predictive models for adaptive radiotherapy in oropharyngeal cancer.
3	Laia Humbert-Vidan -VHIO	Imaging biomarkers for early detection of fibrosis and respiratory dysfunction in early-stage non-small cell lung cancer treated with radiation therapy
4	**Lorenzo Placidi & Matteo Galetto – Policlinico Gemelli**	**mpMRI for prostate on-line adaptive dose painting**
4	Daniela Thorwarth – University of Tübingen	Early response assessment using sequential MR-based hypoxia imaging during HNC RT
4	Robert Jeraj – University of Ljubljana	Targeting treatment resistance using individual lesion characteristics
4	Claudio Fiorino – San Raffaele Scientific Institute	Exploiting the MRI-based early regression index (ERI) in treatment personalization of neo-adjuvant radio-chemotherapy of rectal cancer

Common pitfalls (and challanges)

- Overfitting radiomics models; lack of external validation.
- Ignoring motion/partial-volume effects in MRI.
- Mixing scanners/protocols without harmonization.
- Biological misinterpretation of surrogates.
- Poor image quality
- Large day-to-day variation (functional change, image noise, fitting)
- Predominantly "group level effects"
- Slow acquisition and slow processing



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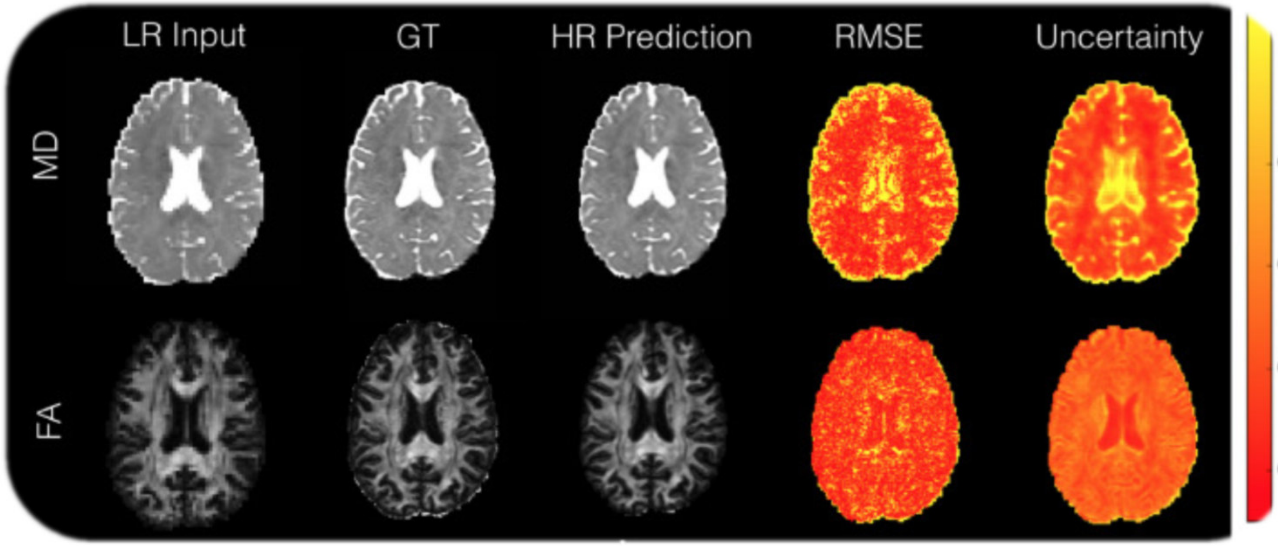
Consequently, no routine clinical usage yet

Common pitfalls (and challanges)

Word of caution: is better better?

- **Deep learning learns prior information on how DWI looks**
- **Hence, deep learnt images LOOK like DWI images**
- **<u>Need for uncertainty estimates</u>**



Tanno, et al. Uncertainty modelling in deep learning for safer neuroimage enhancement: demonstration in diffusion MRI. *NeuroImage* 225 (2021): 117366.

Key takeaways

- **Quantitative, validated imaging biomarkers can improve where and how much we treat.**
- **Start simple, standardize hard, validate locally, and scale thoughtfully.**
- **Adaptive RT and MR-Linac accelerate biomarker-driven personalization.**
- **Dose painting is promising—but demands rigorous biology & physics (supported by AI).**
- **… with these pieces in place, we can discuss, validate, and clinically translate to biological image-guided online radiotherapy: See you at MRO36! (?)**

Acknowledgements

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ESTRO
European SocieTy for
Radiotherapy & Oncology

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Thank you

email: lorenzo.placidi@policlinicogemelli.it

MRO.35: Equity and research in oncology. The subtle balance between personalized medicine and accessibility to care

26-27-28 OCTOBER 2025 - Fondazione Policlinico Universitario A. Gemelli IRCCS