Swiss Institute for Translational and Entrepreneurial Medicine

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OncoRay
National Center for Radiation Research in Oncology Dresden

Interfractional Changes / Adaptive Radiotherapy

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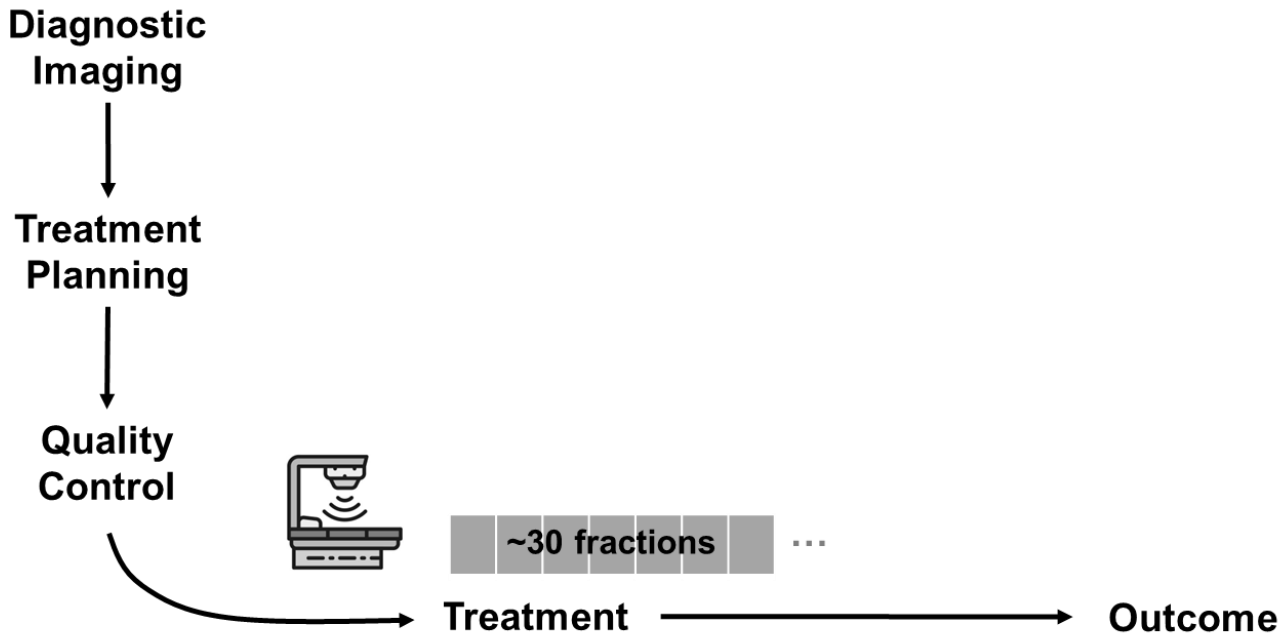
Professor for applied data sciences and decision support systems with a focus in radiation oncology

Academic lead of the sitem-insel School

Executive board member sitem-insel AG

Background

Adaptive Radiotherapy (ART)



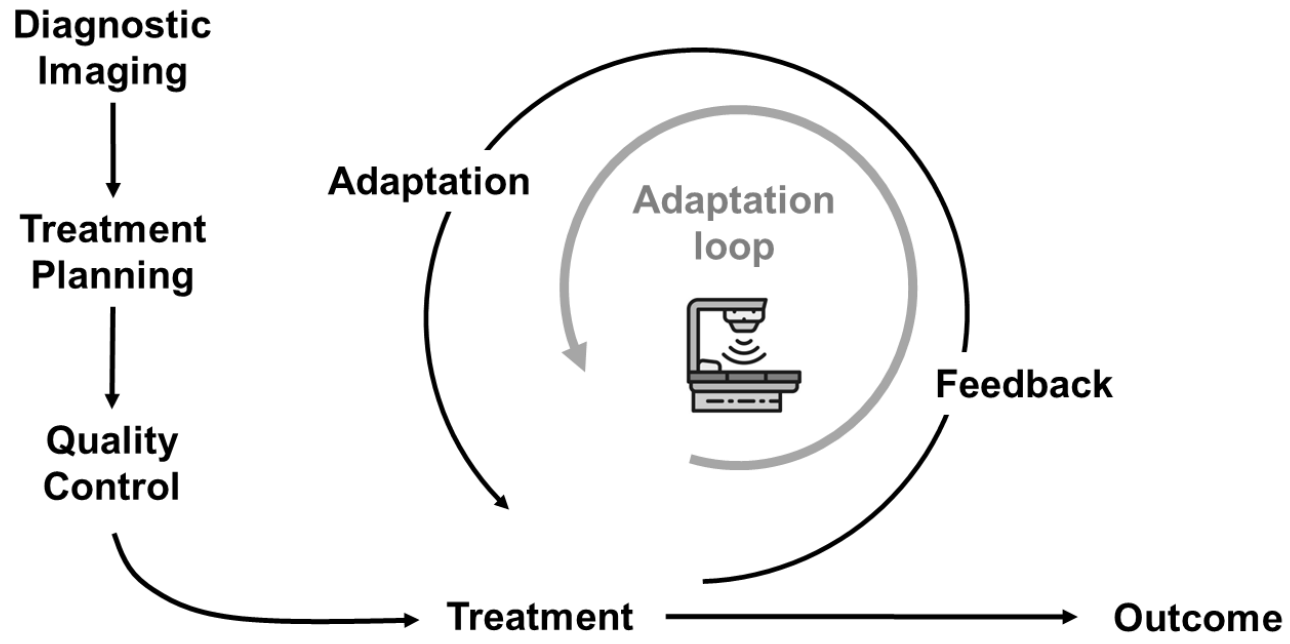
Concept

The concept of Adaptive Radiation Therapy (ART) was first defined by Di Yan. Yan envisioned the course of radiation therapy treatment as a closed circuit in which the treatment procedure and treatment plan are continuously adjusted based on patient-specific measurements and subsequent feedback.

Di Yan et al 1997 Phys. Med. Biol. 42 12

Background

Adaptive Radiotherapy (ART)



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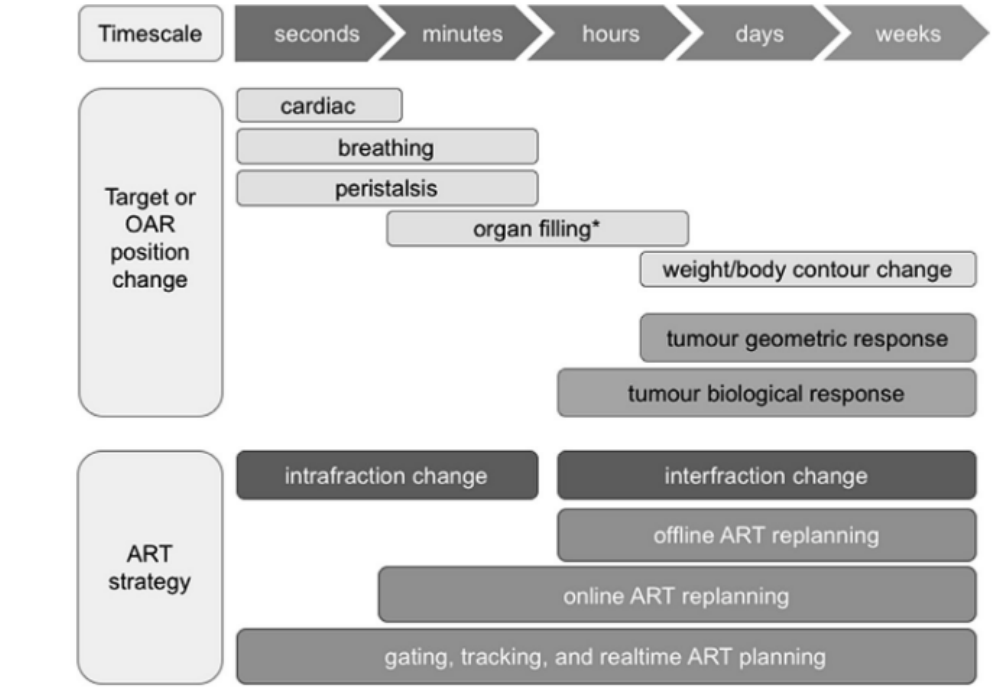
Background

Adaptive Radiotherapy

Time scales
Feedback can include organ movements, anatomy changes, but also biological changes in the tissue. Accordingly, ART can be divided into different time scales:

- **Real-time**: respond to rapid unpredictable modifications of the patient geometry
- **Online**: (periodic) intra-fractional movements
- **Offline**: long-term, inter-fractional changes
- **“Right-time”**



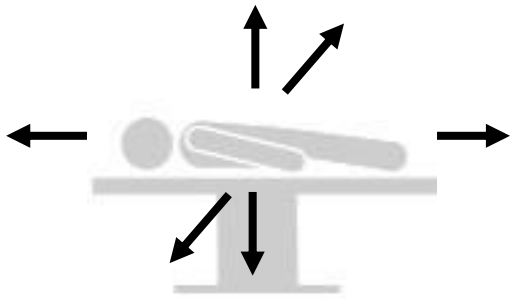
Hunt A, et al. **Adaptive Radiotherapy Enabled by MRI Guidance.** *Clin Oncol*. 2018;30(11):711-719.

Background

Adaptive Radiotherapy

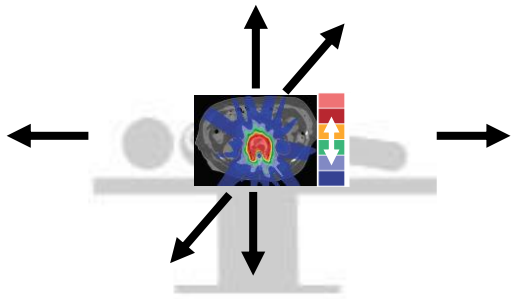
Distinction between ART and image guided radiotherapy (IGRT)
As ART has continued to evolve from the practical experience and increased use of IGRT, it is difficult to make a clear distinction between IGRT and ART.

IGRT focuses primarily on ensuring exact patient positioning and on the geometrically correct handling of patient or organ movements (usually assuming a rigid body).

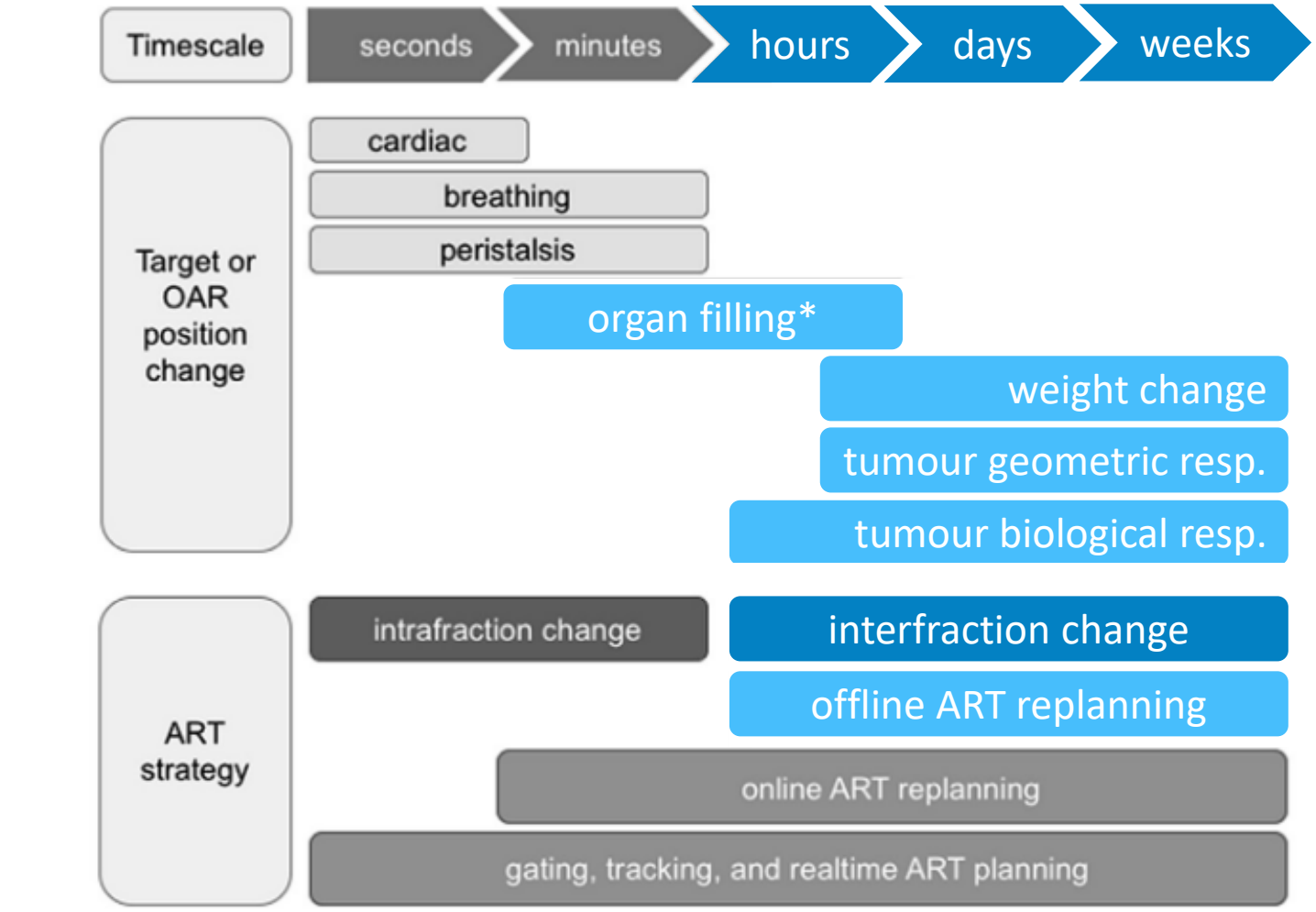


evolution

ART also includes a dosimetric adaptation of the radiation plan. This way it becomes possible to also react to deformations (e.g. of the tumor volume or a risk organ).



Scope of this lecture



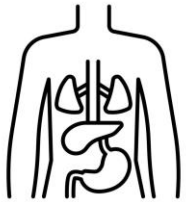
* Organs subject to filling and deformation including bladder, rectum, cervix, and stomach etc

Hunt A, et al. **Adaptive Radiotherapy Enabled by MRI Guidance.** *Clin Oncol*. 2018;30(11):711-719.

Inter-fractional changes

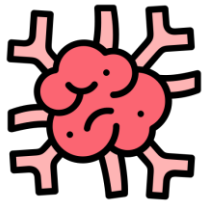
organ filling

weight /
body contour

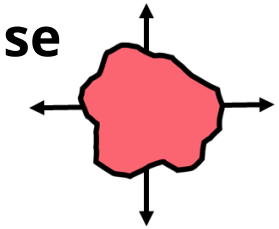


organ relation

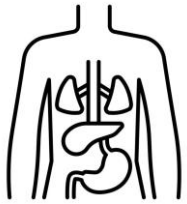
biological tumor
response

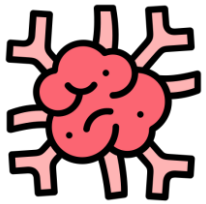


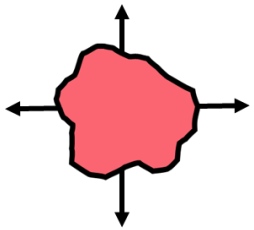
geometric tumor
response



Inter-fractional changes

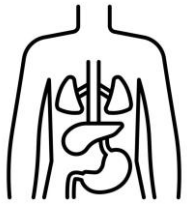


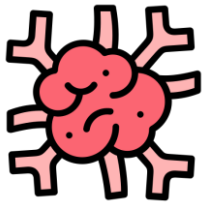


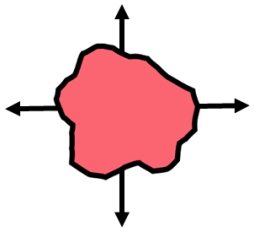


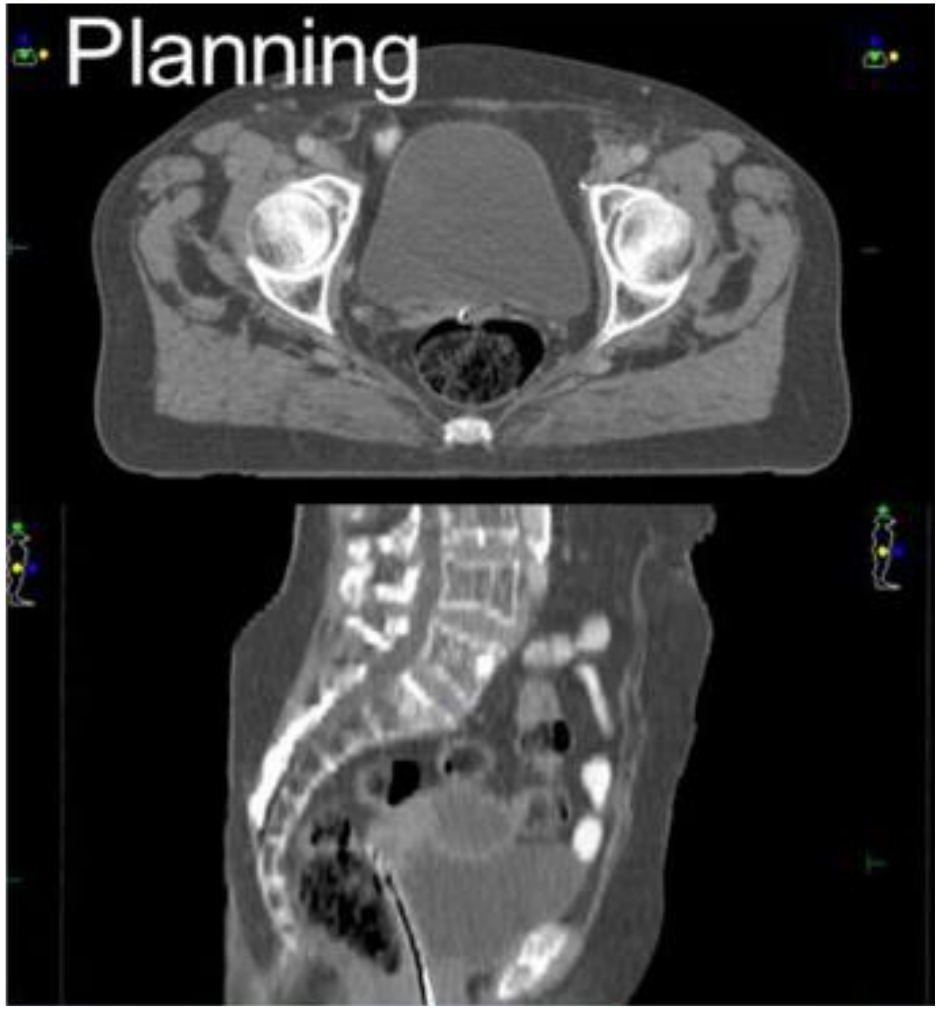
QUIZ I

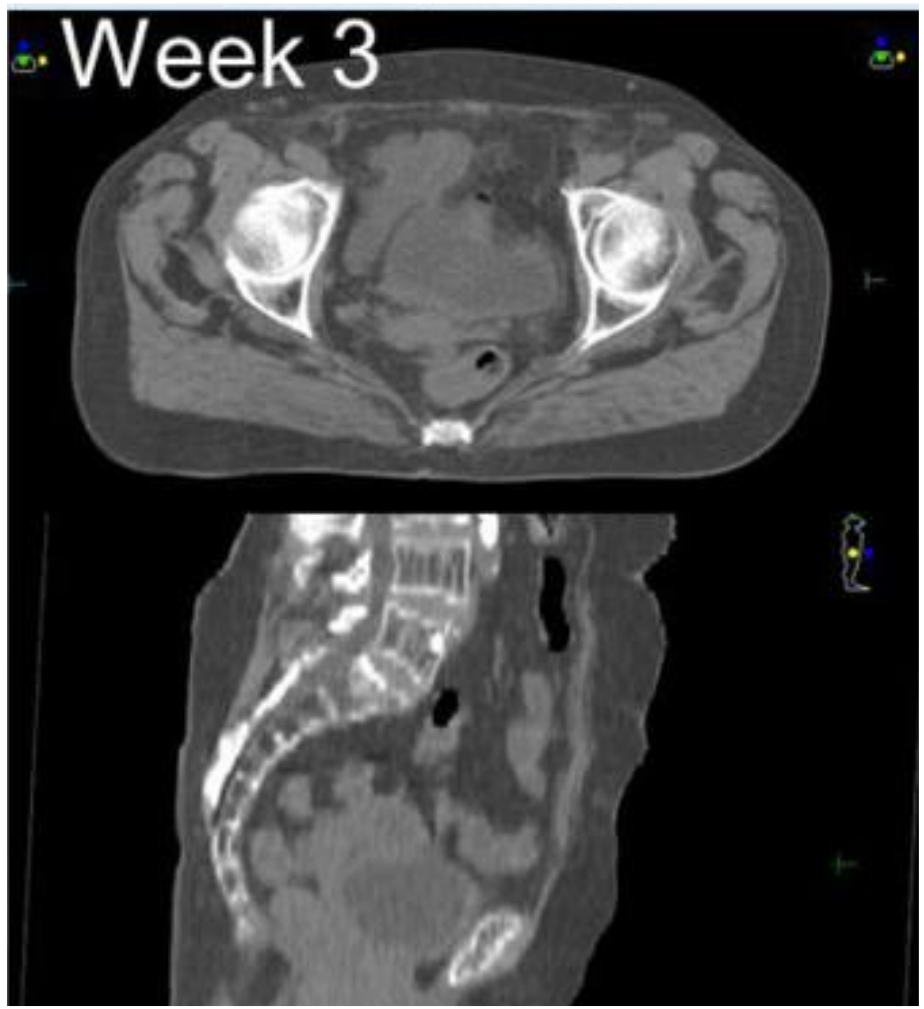
Inter-fractional changes











Herrmann H, Seppenwoolde Y, Georg D, Widder J. **Image guidance: past and future of radiotherapy**. Radiologe. 2019 Dec;59(Suppl 1):21-27. doi: 10.1007/s00117-019-0573-y. PMID: 31346650; PMCID: PMC6914710.

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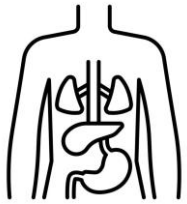

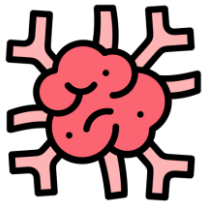

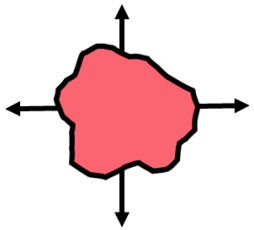

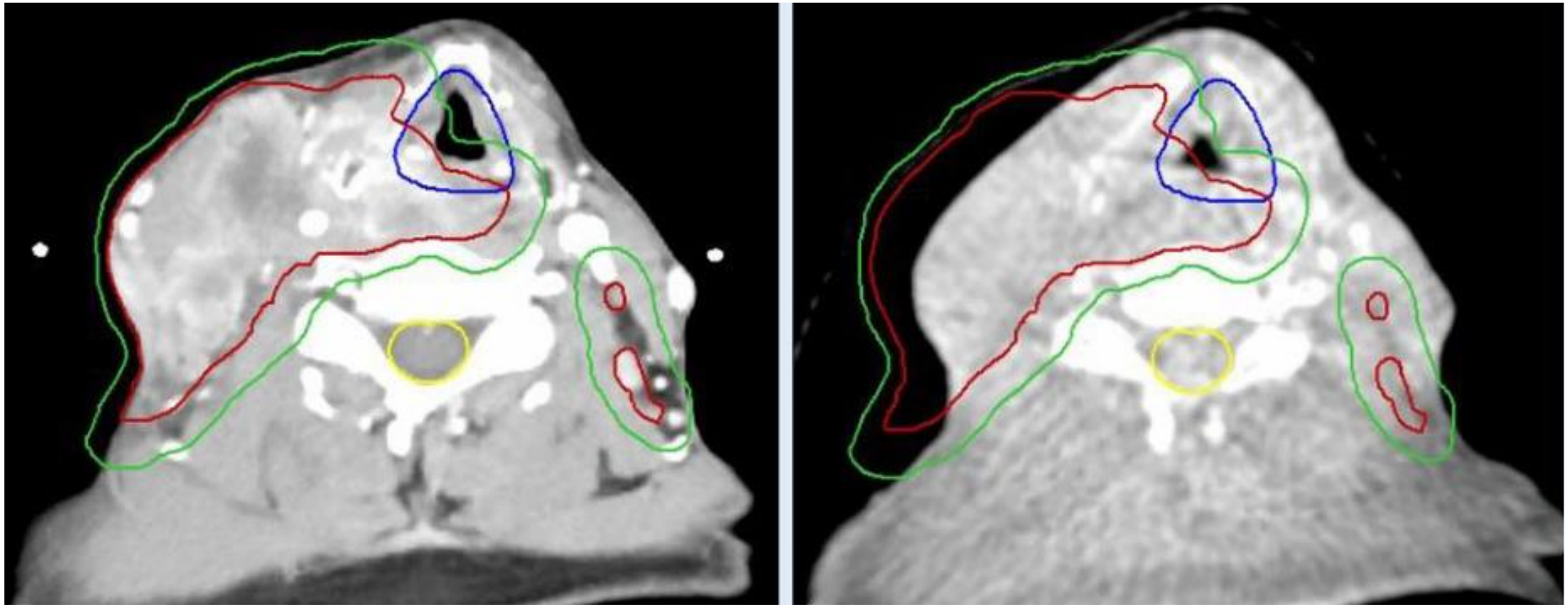

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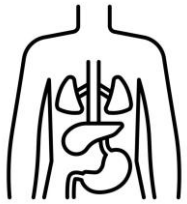

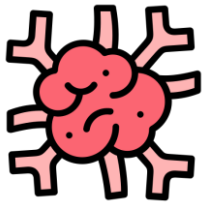

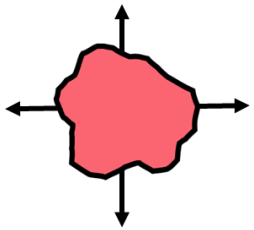

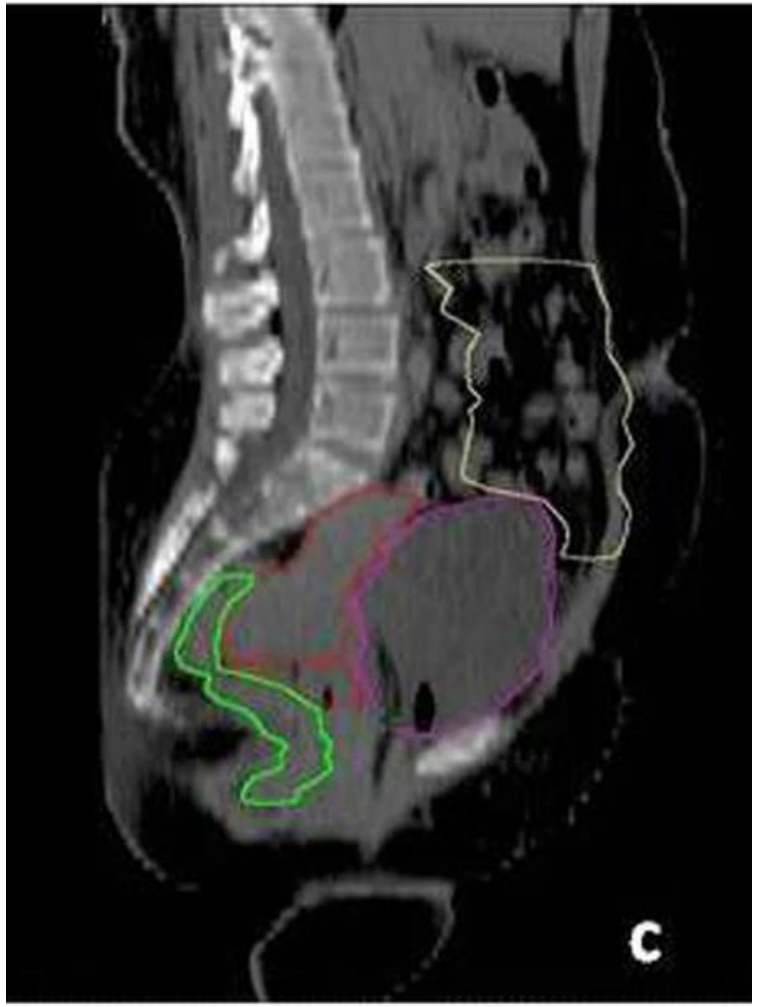

Dutta S, Dewan A, Mitra S, Sharma MK, Aggarwal S, Barik S, Mahammood Suhail M, Bhushan M, Sharma A, Wahi IK, Dobriyal K, Mukhee J. **Dosimetric impact of variable bladder filling on IMRT planning for locally advanced carcinoma cervix.** J Egypt Natl Canc Inst. 2020 Jul 31;32(1):31. doi: 10.1186/s43046-020-00033-5. PMID: 32734431.

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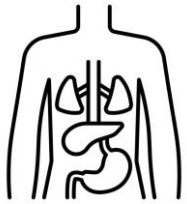

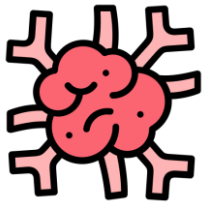

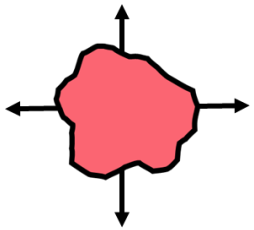

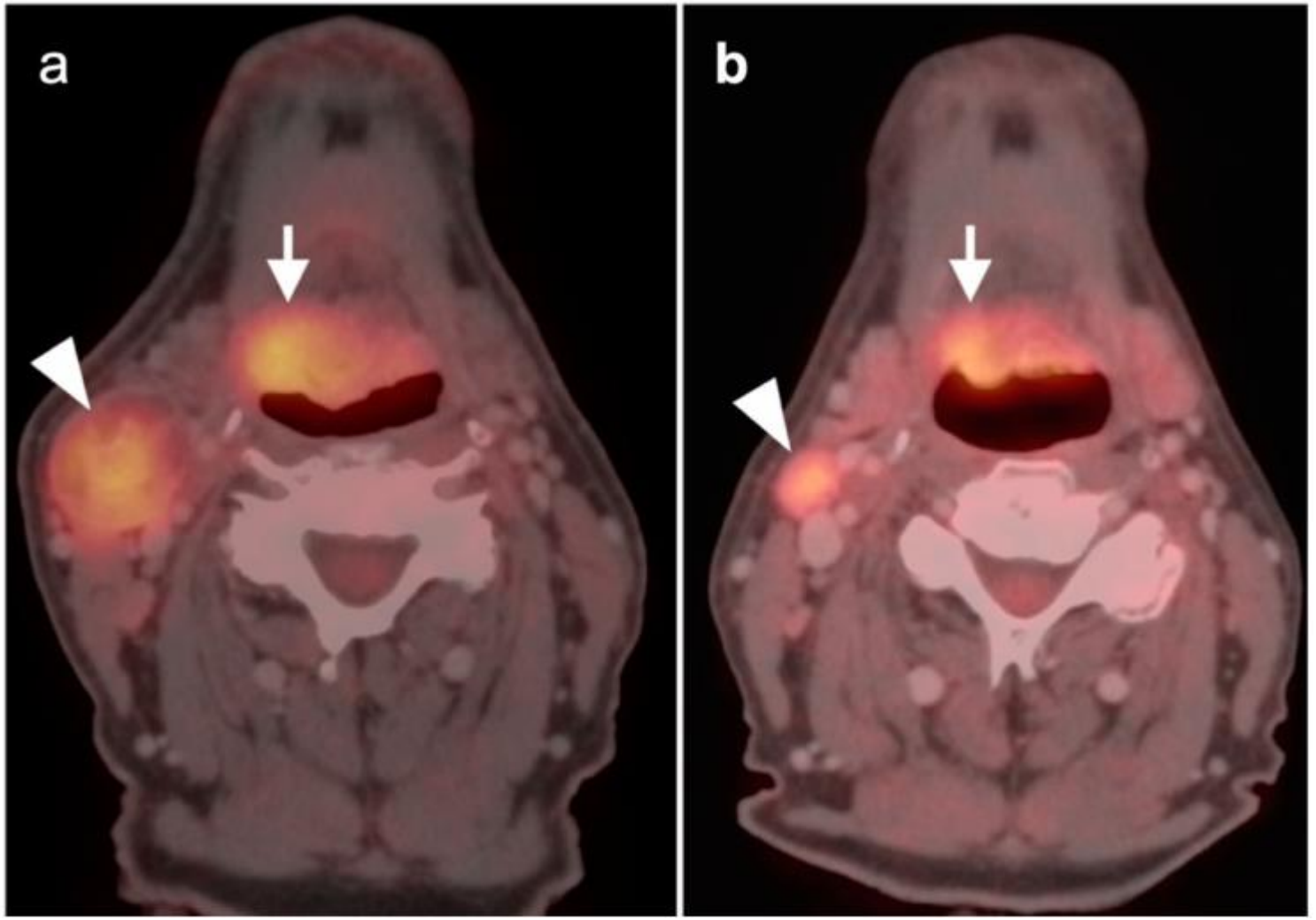

Wiggins RH, Hoffman JM, Fine GC, Covington MF, Salem AE, Koppula BR, Morton KA. **PET-CT in Clinical Adult Oncology-V. Head and Neck and Neuro Oncology**. Cancers (Basel). 2022 May 31;14(11):2726. doi: 10.3390/cancers14112726. PMID: 35681709; PMCID: PMC9179458.

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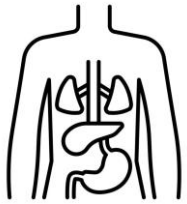
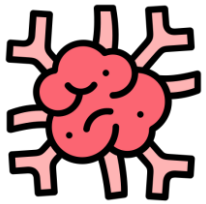
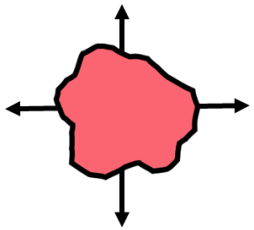
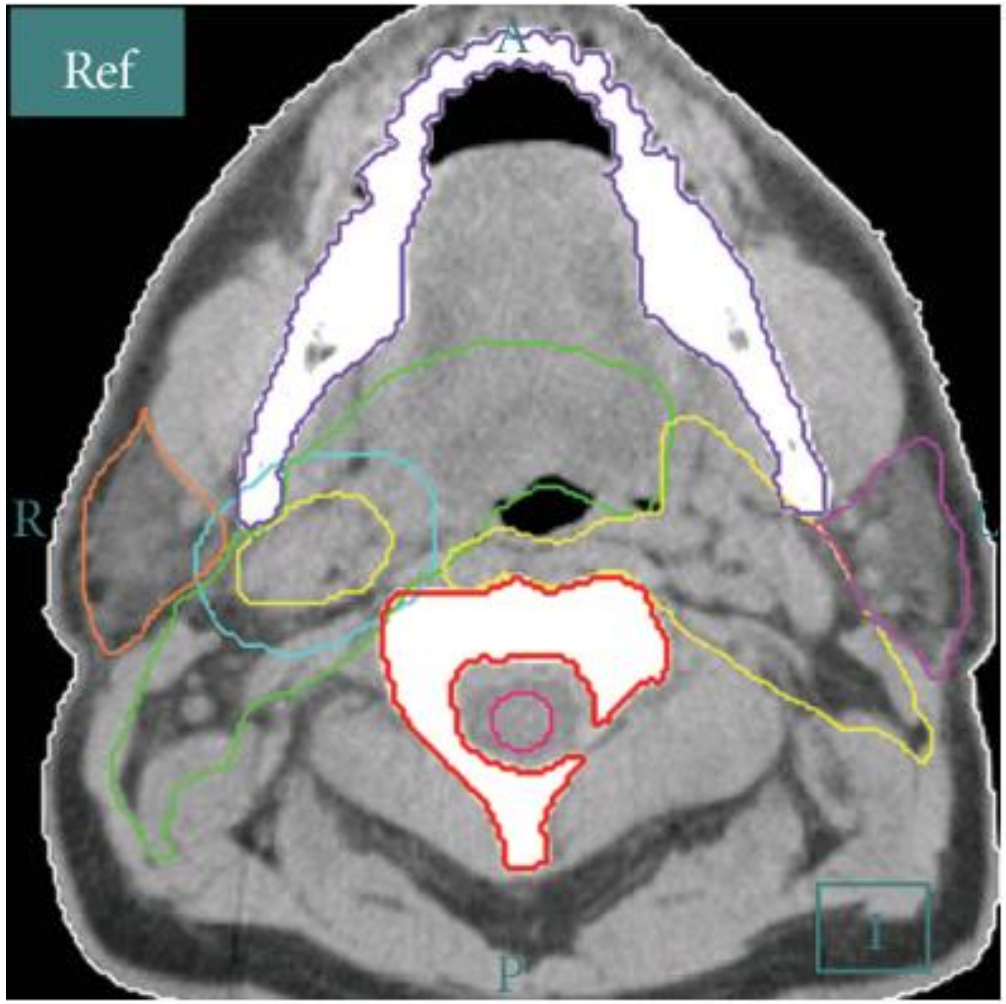
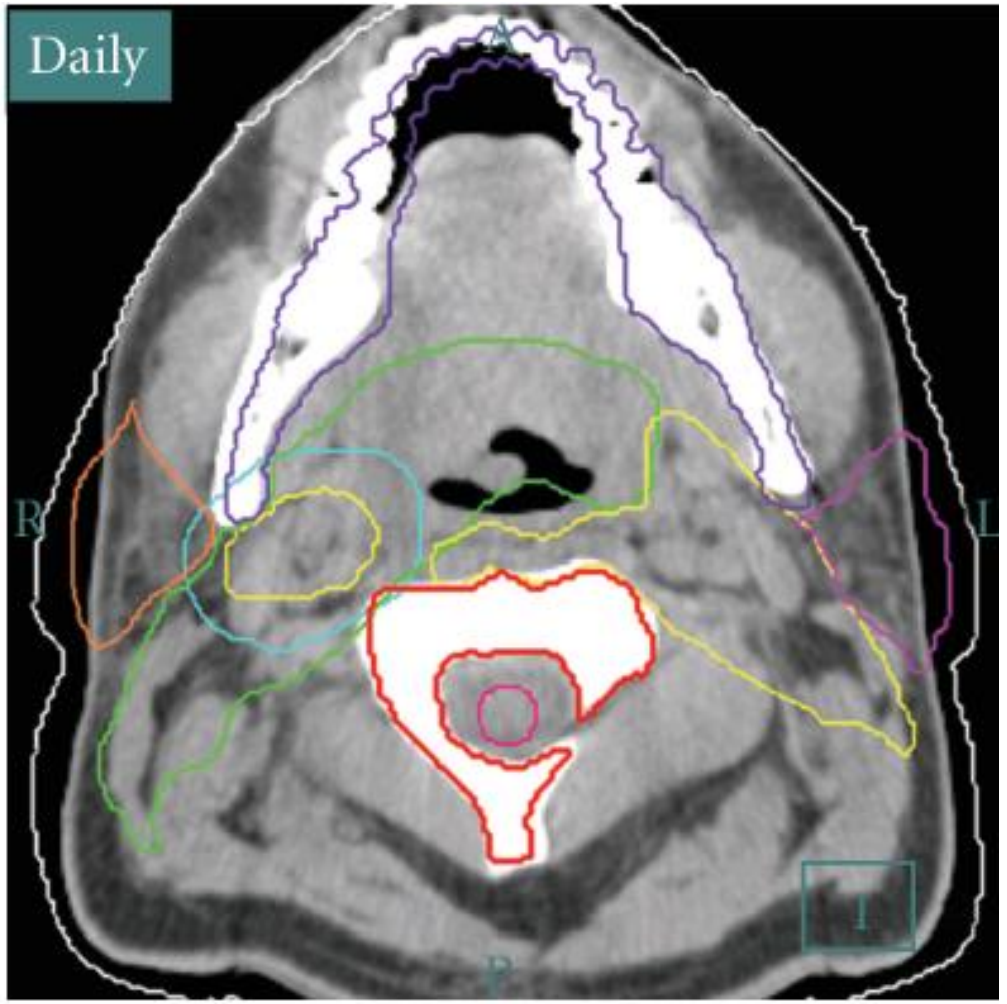




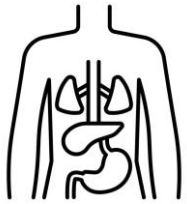


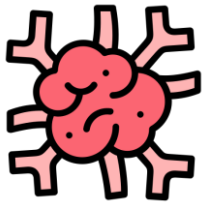


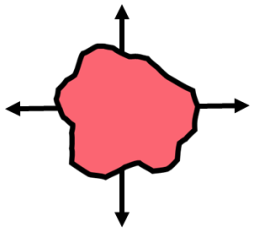


Schwartz DL, Dong L. **Adaptive radiation therapy for head and neck cancer-can an old goal evolve into a new standard?** J Oncol. 2011;2011:690595. doi: 10.1155/2011/690595. Epub 2010 Aug 18. PMID: 20847944; PMCID: PMC2933914.

Inter-fractional changes







How can we monitor these changes?

Via Imaging

- Visual
- X-Ray: kV/MV
- Magnetic resonance (MR)
- Surface imaging
- Ultra-sound
- PET/SPECT
- 2D/3D/4D
- Morphological / functional
- …

What do we do with the images?

We can

- Try to reproduce the reference situation → **IGRT**
- Compensate for the present situation → **ART**

ART Systems

Core components

An **ideal ART system** should have the following core components:

1. An **integrated imaging modality(s)** capable of collecting anatomical and perhaps functional information about the patient
2. (Automatic) **evaluation routines**, such as auto-segmentation algorithms, and clearly defined "action levels" at which it is necessary to intervene in the course of therapy
3. A **planning software** that allows frequent repetition of planning, in particular optimization
4. (Automatic) procedures for **quality assurance** to guarantee the safety of patient treatment

Adaptive workflows can also be performed with non integrated imaging modalities (in-room or next door imaging). However, that will add to the complexity of adaptive workflows and the resources needed.

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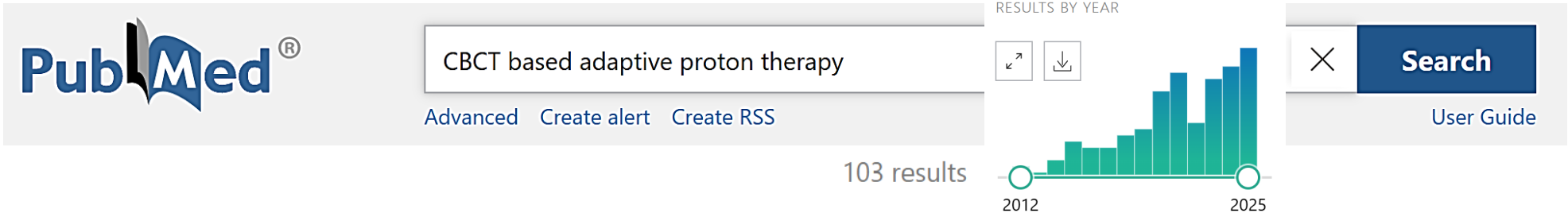
ART Systems – imaging

CBCT-based RT

Originally, CBCT was intended for accurate **patient positioning**.

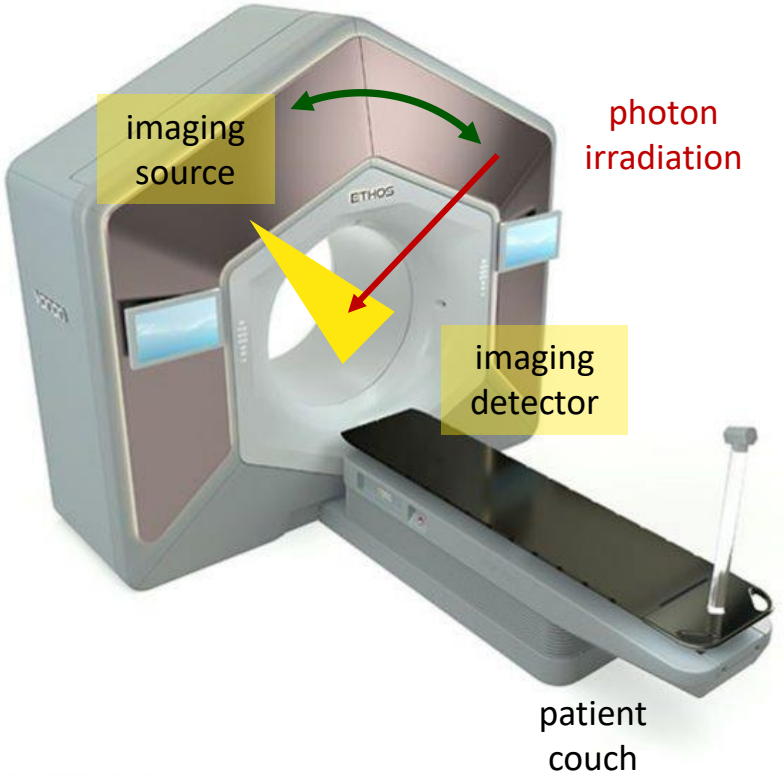
- In **conventional radiotherapy**, CBCT-based adaptive workflows have been clinically integrated.

- In **proton therapy**, the feasibility of CBCT-based adaptive workflows is investigated.

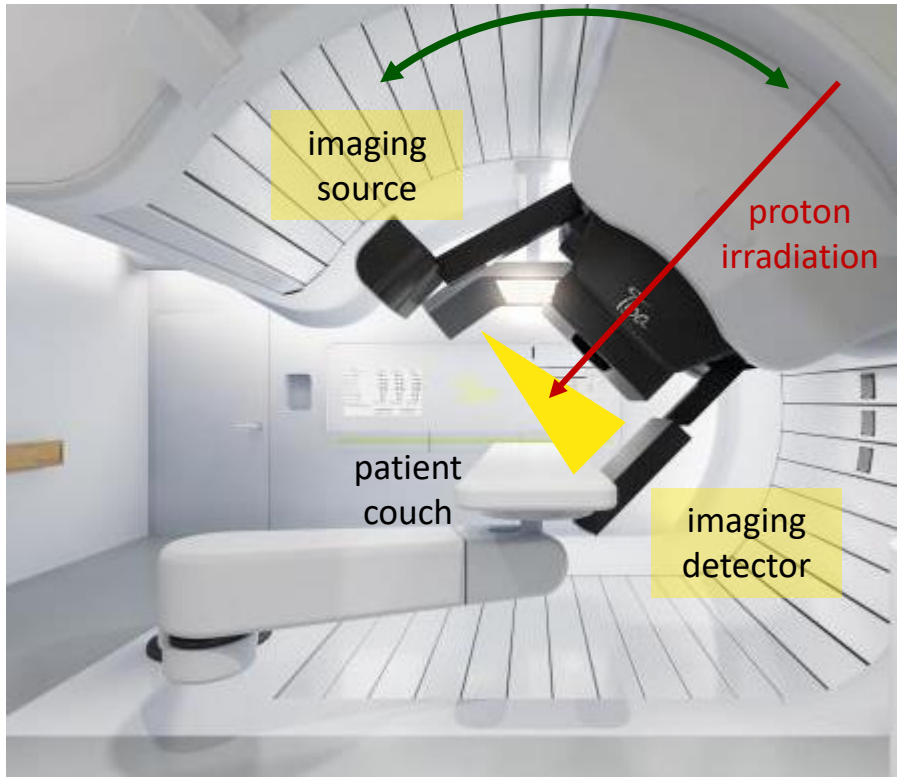


ART Systems – imaging

CBCT-based RT



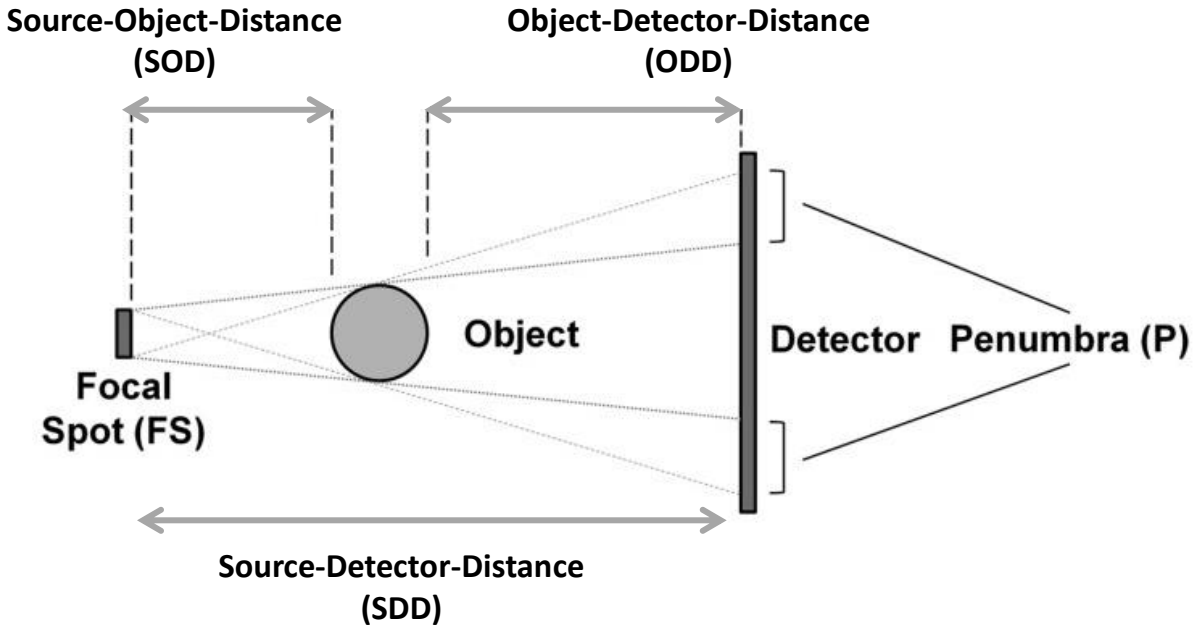
Ethos™, Varian

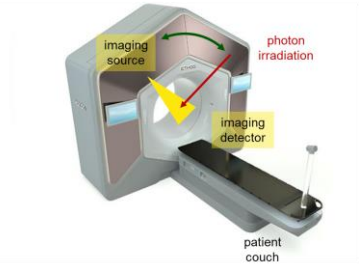


Proteus® One, IBA

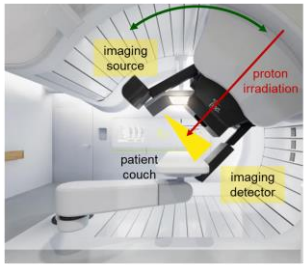
ART Systems – imaging

CBCT-based PT





Ethos™, Varian



Proteus® Plus, IBA

$SOD_{Protons} > SOD_{Photons}$

$SDD_{Protons} > SDD_{Photons}$

The CBCT image quality is lower for proton systems than for photon systems.

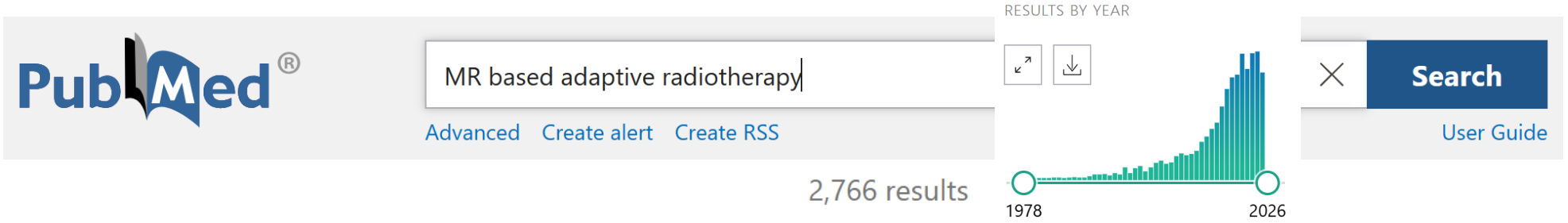
To be used for adaptive workflow,
the requirements on CBCT images are however higher in proton than in photon therapy.

ART Systems – imaging

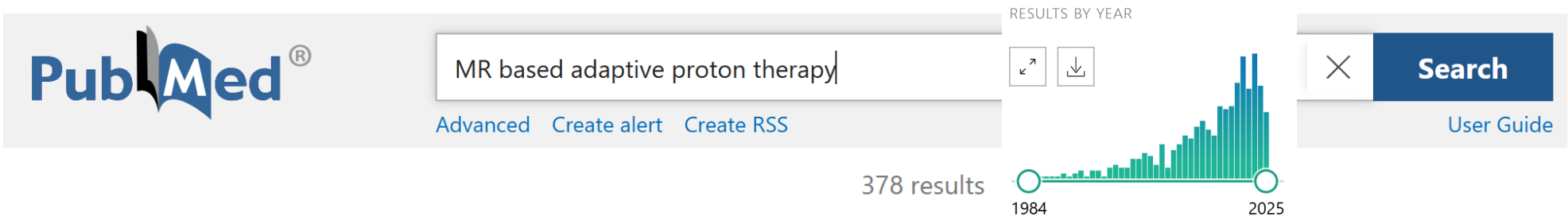
MR-based RT

The integration of MR equipment into a radiotherapy machine is **very challenging**.

- In **conventional radiotherapy**, MR-based adaptive workflows have been clinically integrated.



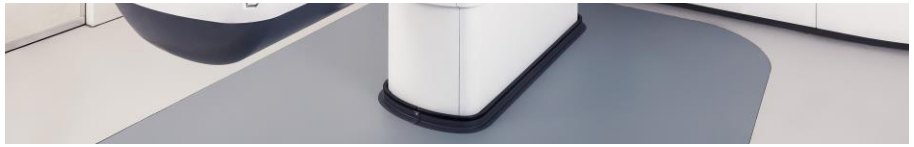
- In **proton therapy**, MR-based adaptive workflows are still a research topic.



ART Systems – imaging

MR-based RT

QUIZ II :Why are MR based adaptive workflows in proton therapy not as widely adopted in clinics as in conventional photon radiotherapy?



Elekta Unity, Elekta

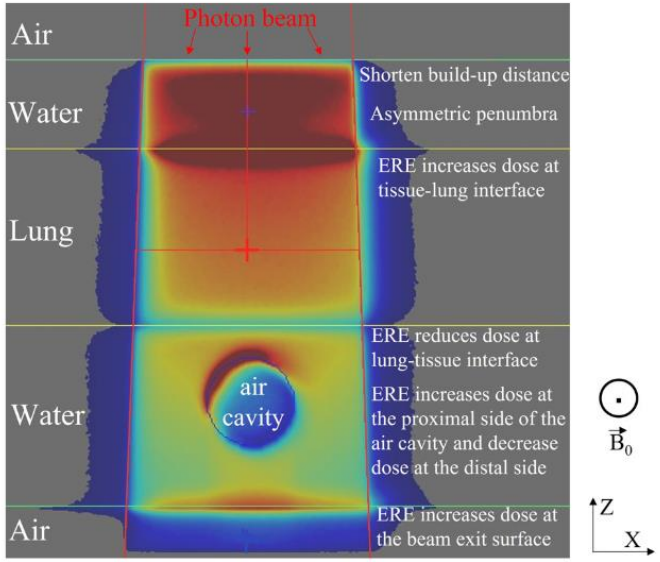
Research collaboration Dresden's HZDR center, Canadian startup MagnetTx, IBA...

ART Systems – imaging / delivery

MR-based RT

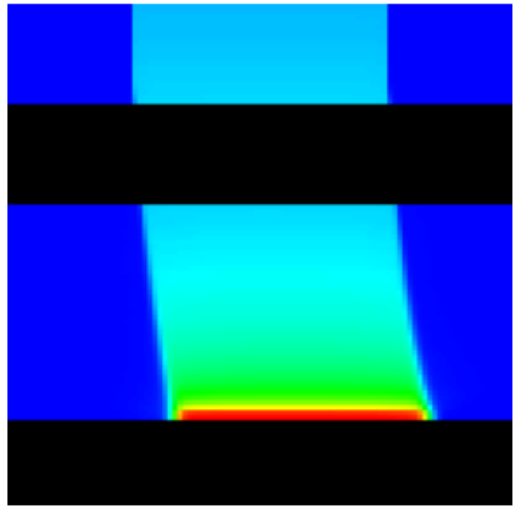
1. Irradiation within magnetic fields results in dosimetric effects.

photons



Huang CY et al.. **Magnetic field induced dose effects in radiation therapy using MR-linacs**. Med Phys. 2023 Jun;50(6):3623-3636. doi: 10.1002/mp.16397. Epub 2023 Apr 6. PMID: 36975016.

protons



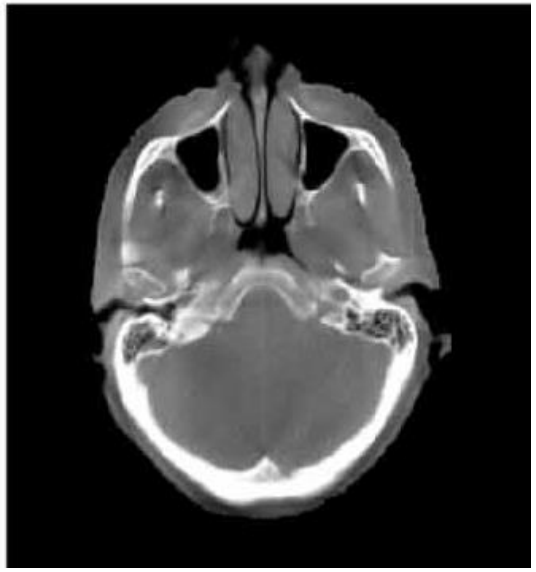
Raaymakers BW et al.. **Feasibility of MRI guided proton therapy: magnetic field dose effects**. Phys Med Biol. 2008 Oct 21;53(20):5615-22. doi: 10.1088/0031-9155/53/20/003. Epub 2008 Sep 17. PMID: 18799829.

2. MR images don’t provide information on electron density or proton stopping power and thus can’t be used directly for dose calculation.

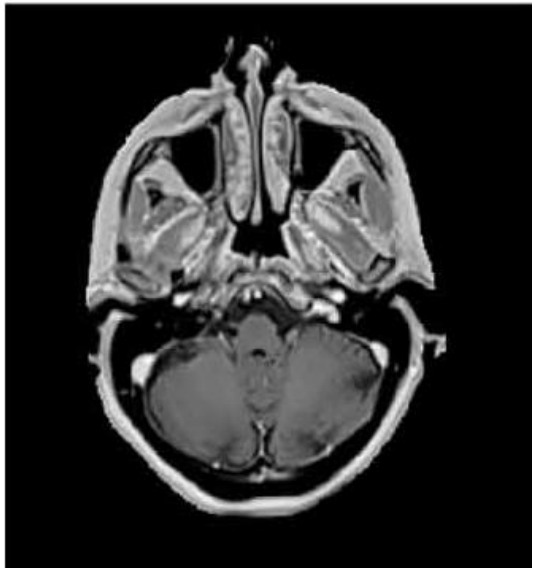
ART Systems – imaging

Synthetic images

CBCT



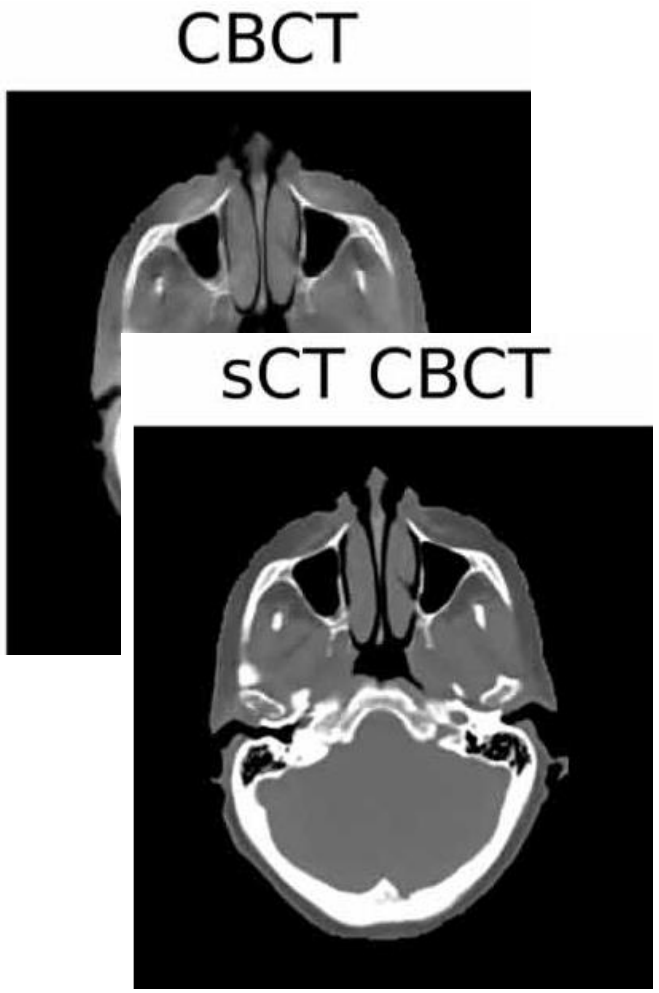
MRI

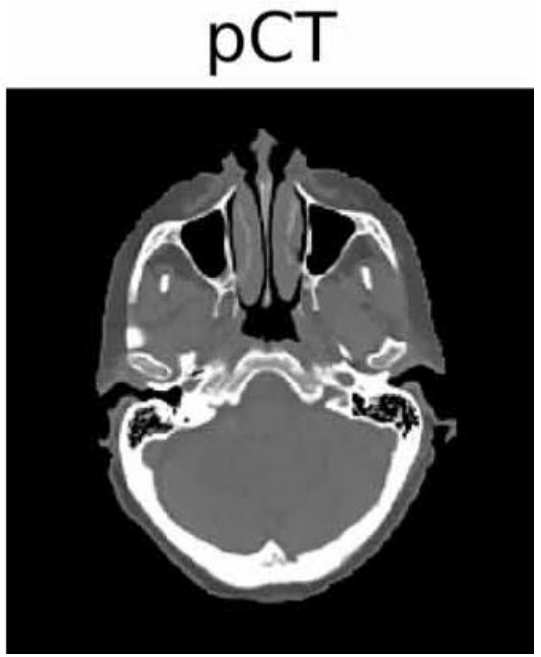


pCT

ART Systems – imaging

Synthetic images

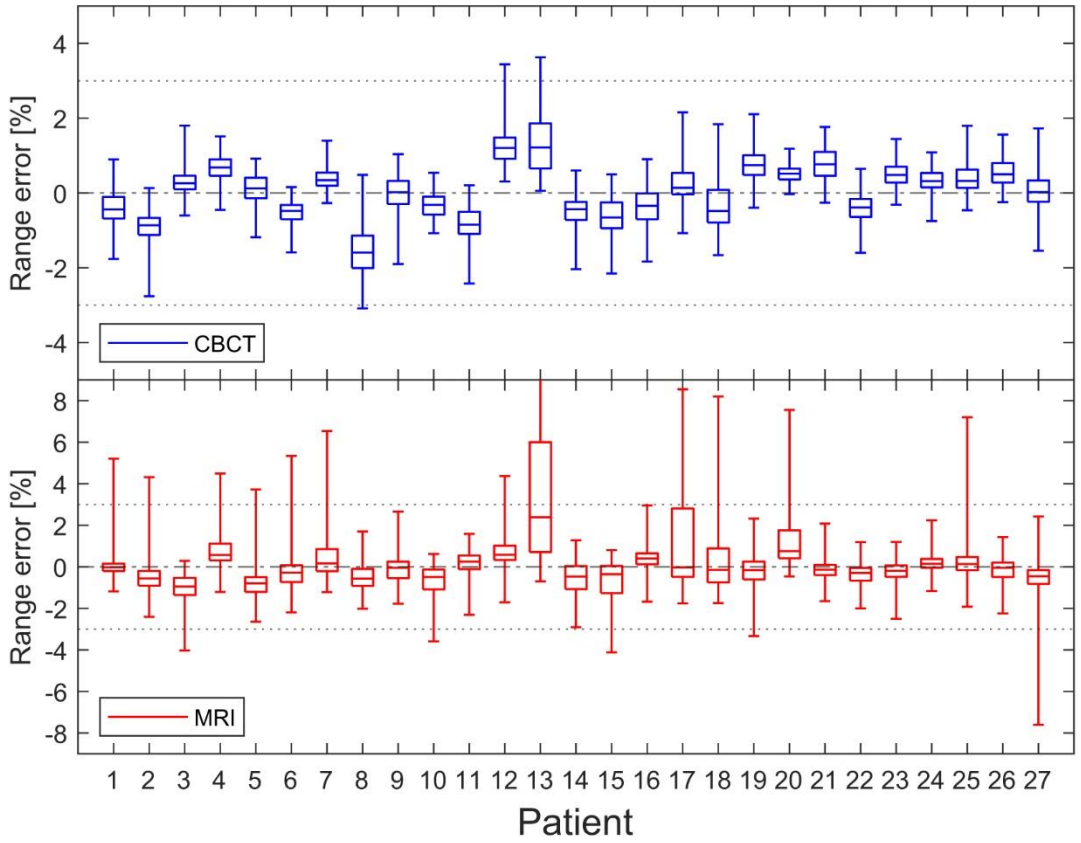




Thummerer A et al.. **Comparison of the suitability of CBCT- and MR-based synthetic CTs for daily adaptive proton therapy in head and neck patient**s. Phys Med Biol. 2020 Dec 5;65(23):235036. doi: 10.1088/1361-6560/abb1d6. PMID: 33179874.

ART Systems – imaging

Synthetic images



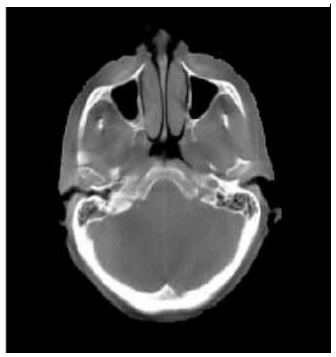
Range shifts for sCT_{CBCT} (top) and sCT_{MR} (bottom) calculated using the single beam plans. The dotted line indicates ± 3% range error.

Thummerer A et al.. **Comparison of the suitability of CBCT- and MR-based synthetic CTs for daily adaptive proton therapy in head and neck patients**. Phys Med Biol. 2020 Dec 5;65(23):235036. doi: 10.1088/1361-6560/abb1d6. PMID: 33179874.

ART Systems – imaging

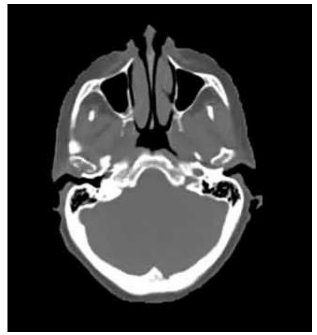
Synthetic images

CBCT



translate

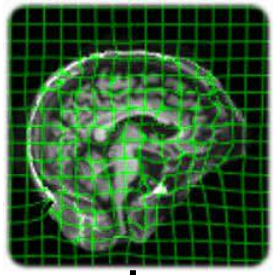
sCT



deep convolutional neural network

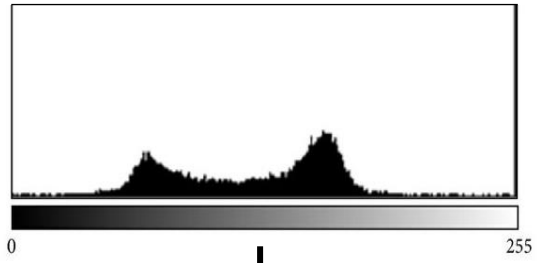
sCT_{NN}

deformable image registration



sCT_{DIR}

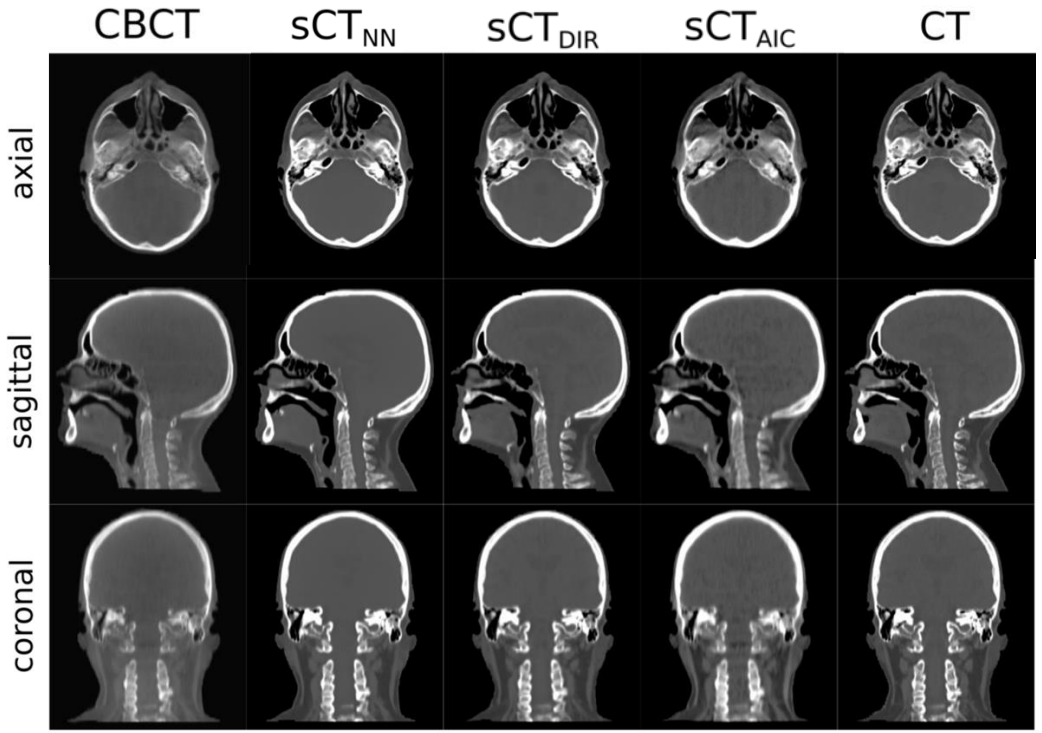
analytical image-based correction method

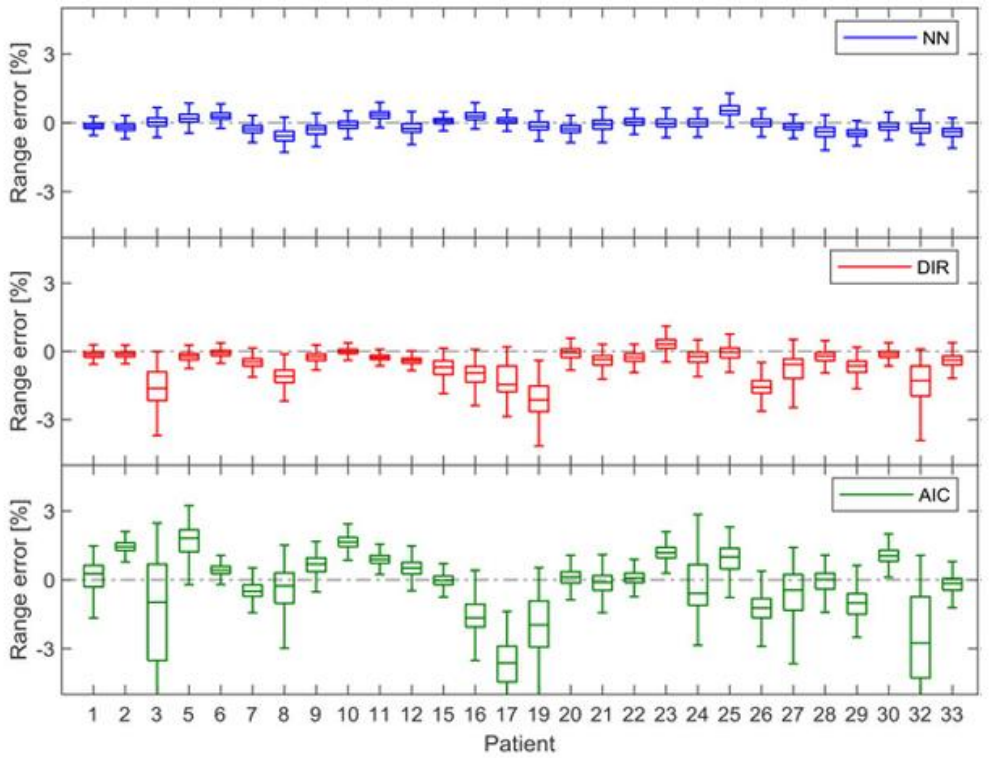


sCT_{AIC}

ART Systems – imaging

Synthetic images

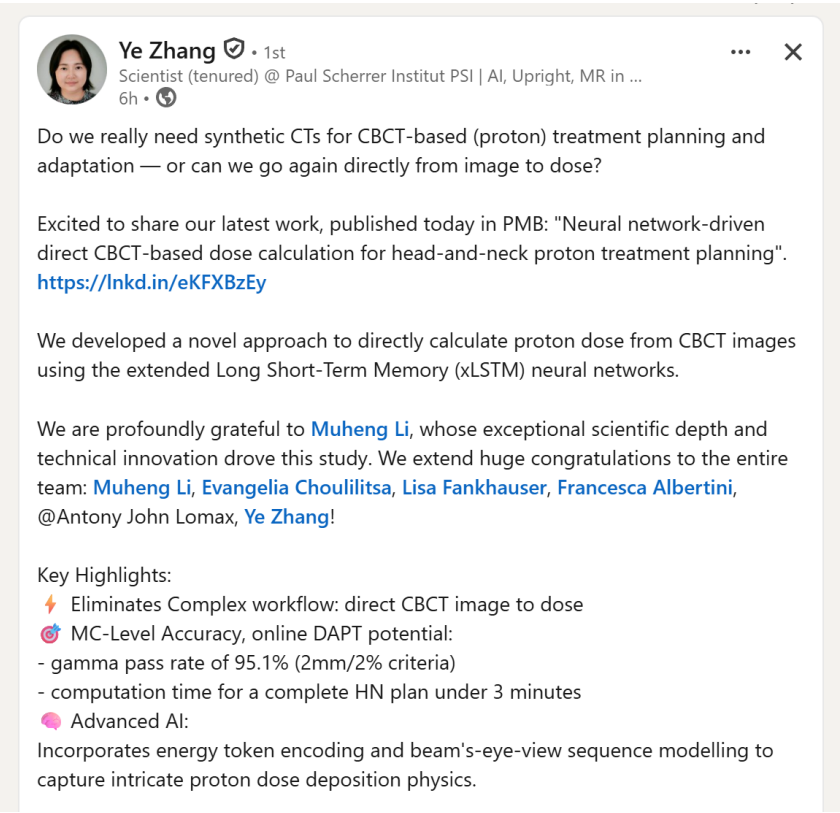




Thummerer A et al. **Comparison of CBCT based synthetic CT methods suitable for proton dose calculations in adaptive proton therapy**. Phys Med Biol. 2020 Apr 28;65(9):095002. doi: 10.1088/1361-6560/ab7d54. PMID: 32143207.

ART Systems – imaging

Synthetic images



Ye Zhang • 1st
Scientist (tenured) @ Paul Scherrer Institut PSI | AI, Upright, MR in ...
6h •

Do we really need synthetic CTs for CBCT-based (proton) treatment planning and adaptation — or can we go again directly from image to dose?

Excited to share our latest work, published today in PMB: "Neural network-driven direct CBCT-based dose calculation for head-and-neck proton treatment planning". https://lnkd.in/eKFXBzEy

We developed a novel approach to directly calculate proton dose from CBCT images using the extended Long Short-Term Memory (xLSTM) neural networks.

We are profoundly grateful to Muheng Li, whose exceptional scientific depth and technical innovation drove this study. We extend huge congratulations to the entire team: Muheng Li, Evangelia Choulilitsa, Lisa Fankhauser, Francesca Albertini, @Antony John Lomax, Ye Zhang!

Key Highlights:
⚡ Eliminates Complex workflow: direct CBCT image to dose
🎯 MC-Level Accuracy, online DAPT potential:
- gamma pass rate of 95.1% (2mm/2% criteria)
- computation time for a complete HN plan under 3 minutes
🧠 Advanced AI:
Incorporates energy token encoding and beam's-eye-view sequence modelling to capture intricate proton dose deposition physics.

ACCEPTED MANUSCRIPT • OPEN ACCESS

Neural network-driven direct CBCT-based dose calculation for head-and-neck proton treatment planning

Muheng Li, Evangelia Choulilitsa, Lisa Stefanie Fankhauser, Francesca Albertini, Antony John Lomax and Ye Zhang

Accepted Manuscript online 20 November 2025 • © 2025 The Author(s). Published on behalf of Institute of Physics and Engineering in Medicine by IOP Publishing Ltd

For AI-based synthetic CT generation or dose calculation the challenge remains how to assure and monitor performance in clinical practice.

Li M, Choulilitsa E, Fankhauser LS, Albertini F, Lomax AJ, Zhang Y. Neural network-driven direct CBCT-based dose calculation for head-and-neck proton treatment planning. Phys Med Biol. 2025 Nov 20. doi: 10.1088/1361-6560/ae222a. Epub ahead of print. PMID: 41265034.

ART Systems

Core components

An **ideal ART system** should have the following core components:

1. An **integrated imaging modality(s)** capable of collecting anatomical and perhaps functional information about the patient
2. (Automatic) **evaluation routines**, such as auto-segmentation algorithms, and clearly defined "action levels" at which it is necessary to intervene in the course of therapy
3. A **planning software** that allows frequent repetition of planning, in particular optimization
4. (Automatic) procedures for **quality assurance** to guarantee the safety of patient treatment

ART Systems – evaluation / planning / quality

There remain quite some open questions / challanges and opportunities to improve

- Should we only **adapt when necessary or adapt by default**?

Discussion

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ART Systems – evaluation / planning / quality

There remain quite some open questions / challanges and opportunities to improve

- Should we only **adapt when necessary or adapt by default**?
  - Do we know when it is necessary to adapt? → **action level**
  - Do we have the tools to adapt by default? → **automation (segmentation, planning, QA)**
  - Do we have the **resources** to adapt by default?
- Should we **consider the prior treatment** course in the adaptation?
  - Can we trust our **dose accumulation** algorithm for prior treatment course consideration and correct benefit assessment?
- …

Clinical Perspective

Does adaptive matter

Clinical Perspective

Does adaptive matter - dosimetric perspective

A study by Simone et al. compares IMRT, adaptive IMRT, IMPT (Intensity-Modulated Proton Therapy) and adaptive IMPT for tumors in the head and neck region.

Target

Comparison[†] of the mean dose to target volumes and conformity indexes[*] for IMRT, adaptive IMRT, IMPT, and adaptive IMPT.

	Volume of PTV receiving 100% of the prescribed dose			Conformity index		
	PTV_{50}	PTV_{64}	PTV_{70}	PTV_{50}	PTV_{64}	PTV_{70}
IMRT	99.9% (±0.2%)	99.1% (±0.3%)	98.6% (±0.7%)	1.97 (±0.48)	1.59 (±0.28)	1.49 (±0.26)
Adaptive IMRT	99.8% (±0.4%)	99.0% (±0.5%)	99.0% (±0.8%)	2.06 (±0.56)	1.53 (±0.39)	1.75 (±0.69)
IMPT	99.9% (±0.1%)	99.5% (±0.5%)	99.0% (±0.7%)	1.52 (±0.31)	1.30 (±0.18)	1.23 (±0.11)
Adaptive IMPT	99.9% (±0.1%)	99.5% (±0.5%)	99.4% (±0.7%)	1.64 (±0.38)	1.40 (±0.19)	1.54 (±0.46)

[†] Values listed for PTV volumes and conformity indexes are the mean values for the study population. The standard deviations for each comparison are listed in brackets.
[*] Conformity index was calculated as the ratio of the reference isodose–volume to the volume of each planning target volume being assessed, with the 95% isodose line of each PTV selected as the reference isodose–volume in accordance with ICRU 50 guidelines.

OAR

Comparison of the average maximum or mean doses to normal tissues between IMRT, adaptive IMRT, IMPT, and adaptive IMPT.

	Spinal cord	Left parotid		Right parotid		Ipsilateral parotid		Contralateral parotid		Glottic larynx	Brainstem	Mandible		
	Max[†] (Gy)	Mean (Gy)	V20[*] (%)	Mean (Gy)	V20[*] (%)	Mean (Gy)	V20[*] (%)	Mean (Gy)	V20[*] (%)	Mean (Gy)	Max[†] (Gy)	Max[†] (Gy)	V60[*] (%)	V70[*] (%)
IMRT	42.1	37.8	60.4	32.0	55.5	43.1	68.4	26.8	47.5	45.4	44.8	75.1	34.2	15.0
Adaptive IMRT	41.7	32.8	54.0	31.6	54.8	39.0	63.6	25.3	45.2	41.8	42.2	73.0	25.3	6.7
IMPT	30.5	27.2	47.9	25.3	45.8	32.9	54.5	19.5	39.2	35.3	31.3	73.8	22.8	8.9
Adaptive IMPT	28.4	25.0	43.3	23.1	43.5	29.8	51.3	18.3	35.7	31.0	29.0	71.1	19.5	5.2

[†] Max = average maximum point dose.
[*] V20/60/70 = volume receiving 20/60/70 Gy.

Dosimetrically

→ adap. is better than non-adap
→ adap. PT is better than adap RT

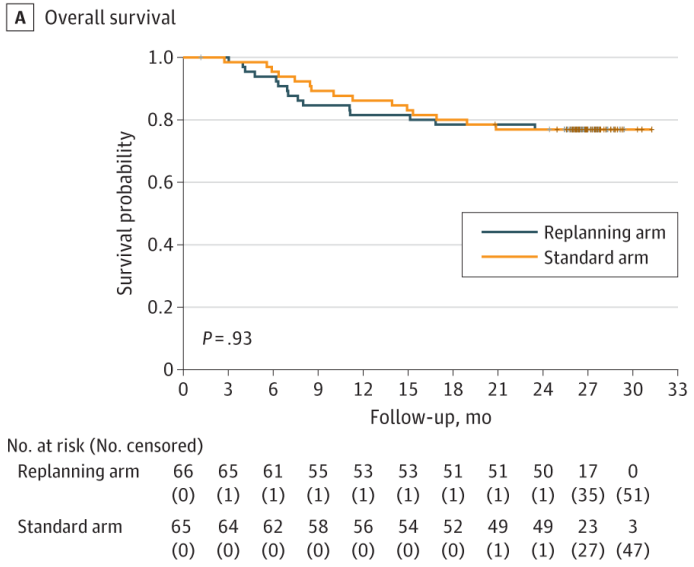
Does this matter **clinically**?

Simone CB et al. (2011) **Comparison of intensity-modulated radiotherapy, adaptive radiotherapy, proton radiotherapy, and adaptive proton radiotherapy for treatment of locally advanced head and neck cancer**. Radiother Oncol 101(3):376–382.

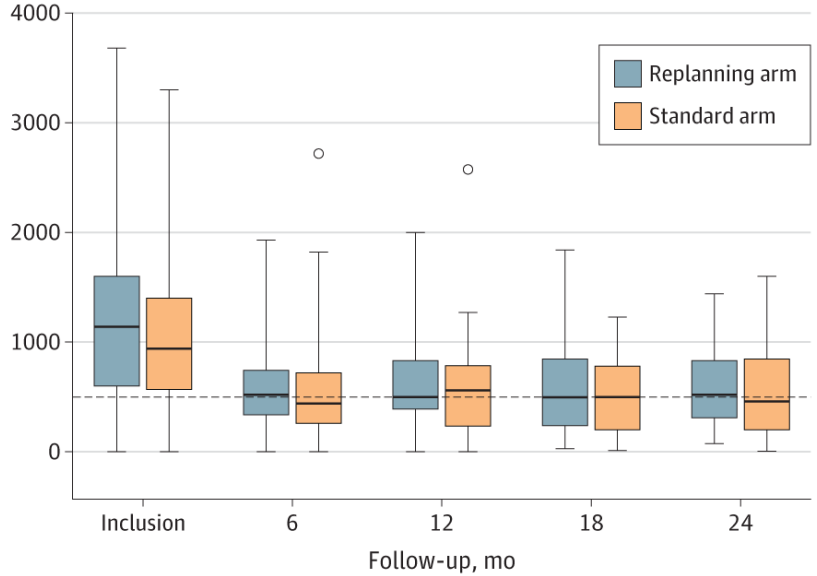
Clinical Perspective

Does adaptive matter – clinical perspective

Dosimetric comparisons suggest that offline adaptive radiotherapy could help reduce the risk of xerostomia by sparing the parotid glands. However, the first randomized clinical trial assessing the role of adaptive radiotherapy on salivary function showed **no clinical benefit of systematic weekly replanning compared with standard intensity-modulated radiotherapy** in this purpose.



Overall survival



Changes in Salivary Flow After Stimulation by Paraffin in the Intent-to-Treat Population

dosimetric benefit ≠clinical benefit

Lapierre A, Blanchard P. **Adaptive radiotherapy, promises and pitfalls. Cancer Radiother.** 2025 Sep-Oct;29(5-6):104677. doi: 10.1016/j.canrad.2025.104677. Epub 2025 Jul 19. PMID: 40684683..

Castelli J, Thariat J, Benezery K, Hasbini A, Gery B, Berger A, Liem X, Guihard S, Chapet S, Thureau S, Auberdiac P, Pommier P, Ruffier A, Perrier L, Devillers A, Campillo-Gimenez B, de Crevoisier R**. Weekly Adaptive Radiotherapy vs Standard Intensity-Modulated Radiotherapy for Improving Salivary Function in Patients With Head and Neck Cancer: A Phase 3 Randomized Clinical Trial.** JAMA Oncol. 2023 Aug 1;9(8):1056-1064. doi: 10.1001/jamaoncol.2023.1352. PMID: 37261806; PMCID: PMC10236337.

Summary

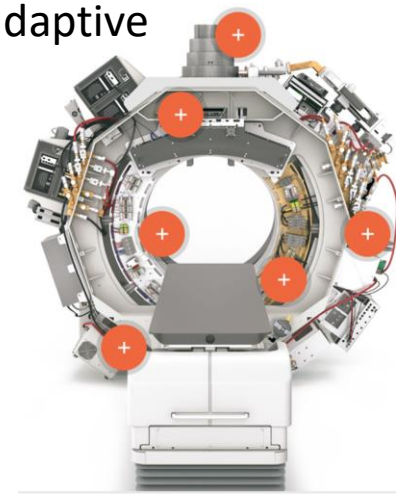
- There is no question that **the patient anatomy changes / varies throughout a fractionated treatment course**.
- Offline (and online) **adaptive** radiotherapy is **clinical reality for photon radiotherapy**.
- **Adaptive** workflows are **close to clinical implementation in protons therapy**
- There are still some **challenges that need to be address** (sCT quality control) for adaptive proton therapy and **room for improvement** (when needed versus default, automation, resource optimization) in conventional adaptive radiotherapy.
- A dosimetric benefit does not necessarily translate into a clinical benefit. To assess the **full clinical benefit** of adaptive workflows **more data** is required.

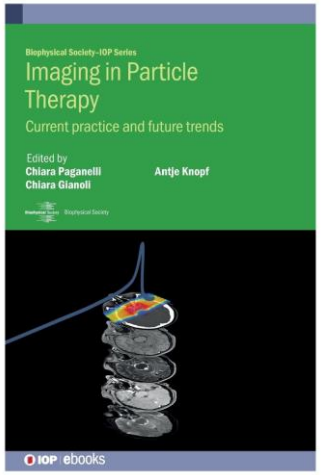
What is next?

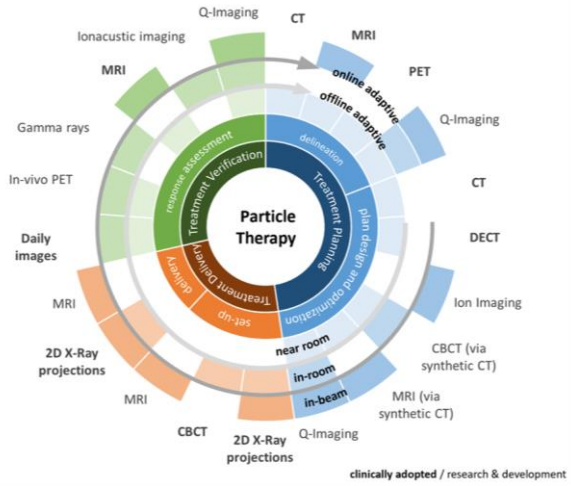
Outlook

A vision for the future of radiation therapy is **biology-based adaptive radiation therapy**, in which a better understanding of **radiation biology** and an increased use of **functional imaging** ensure that therapy can be better tailored to the individual patient and therapy success can be better predicted.

PET/CT guided adaptive radiotherapy







[Our Technology - RefleXion]

It remains to be seen whether this vision is technologically and financially feasible.

Outlook

RAPTOR (real-time) → **RAPTOR+** (right time)

RAPTOR

Realtime Adaptive Particle Therapy Of canceR consortium

European Commission

Marie Skłodowska-Curie Actions

RAPTOR 15 PhDs
RAPTOR+ 18 PhDs

RAPTOR+

Right-time Adaptive Particle Therapy Of canceR

What are the opportunities in terms of upright / adaptive treatments?

Swiss Institute for Translational and Entrepreneurial Medicine

sitem-insel

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DEPARTMENT DIGITAL MEDICINE

INSELSPITAL
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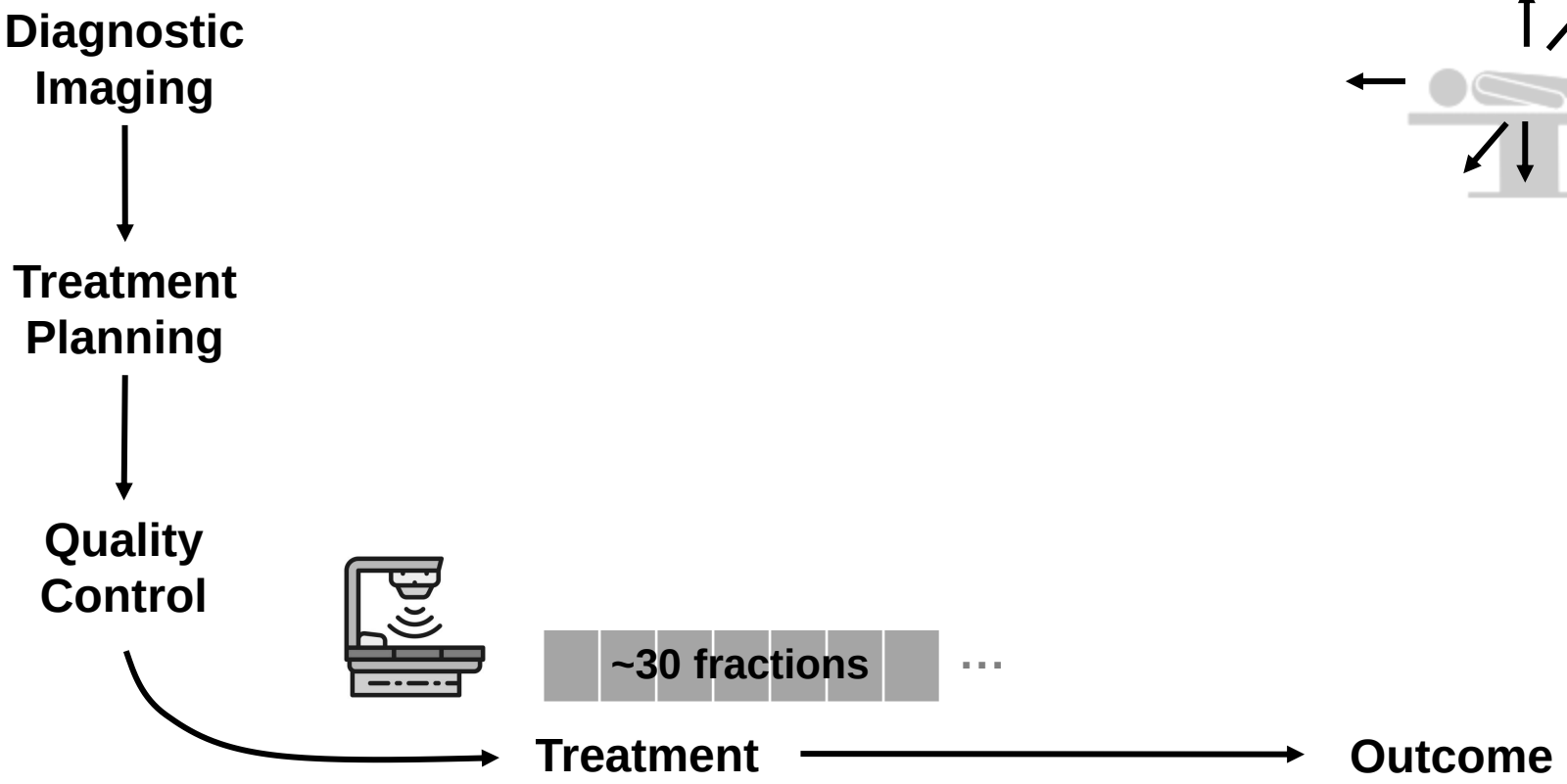
UKRO
UNIVERSITÄTSKLINIK FÜR RADIO-ONKOLOGIE

CAIRO

OncoRay
National Center for Radiation Research in Oncology Dresden

Thank you very much for you participation! Comments / Questions?

Adaptive radiotherapy



Adaptive radiotherapy