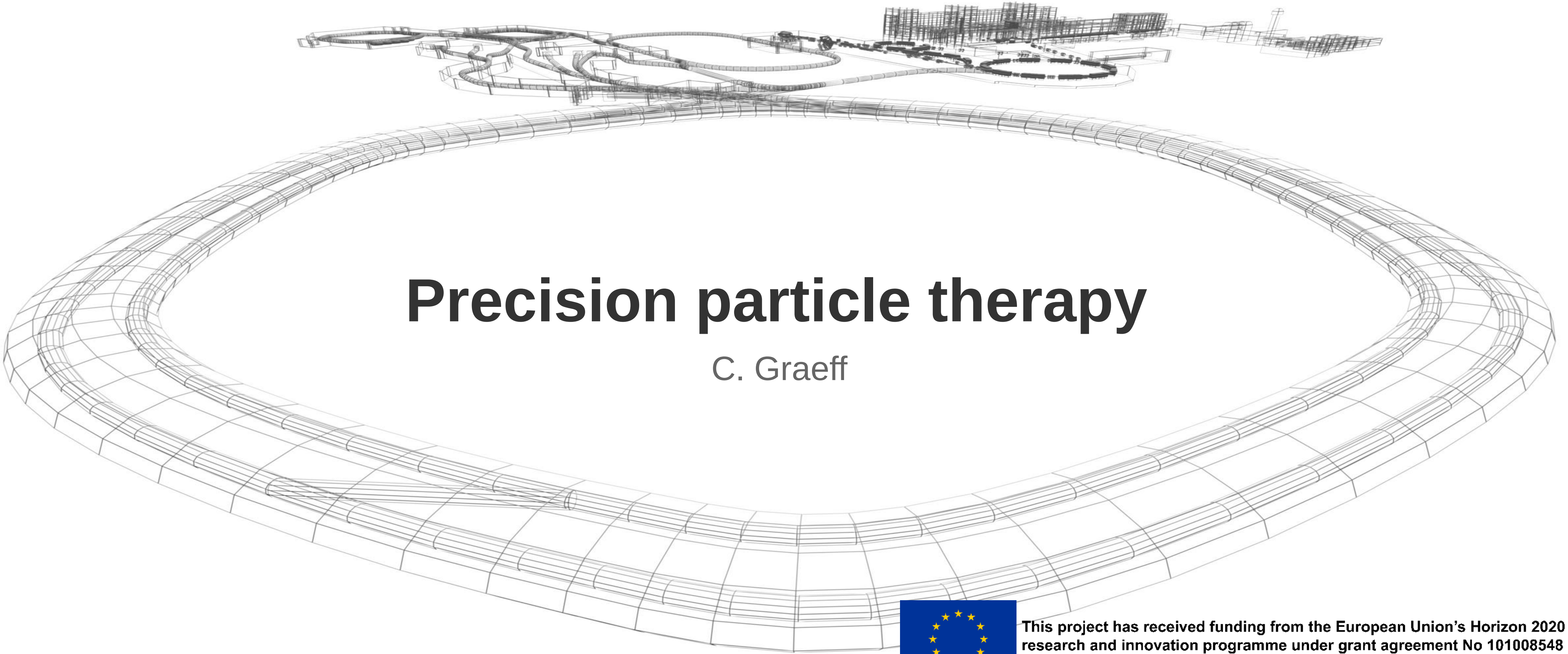


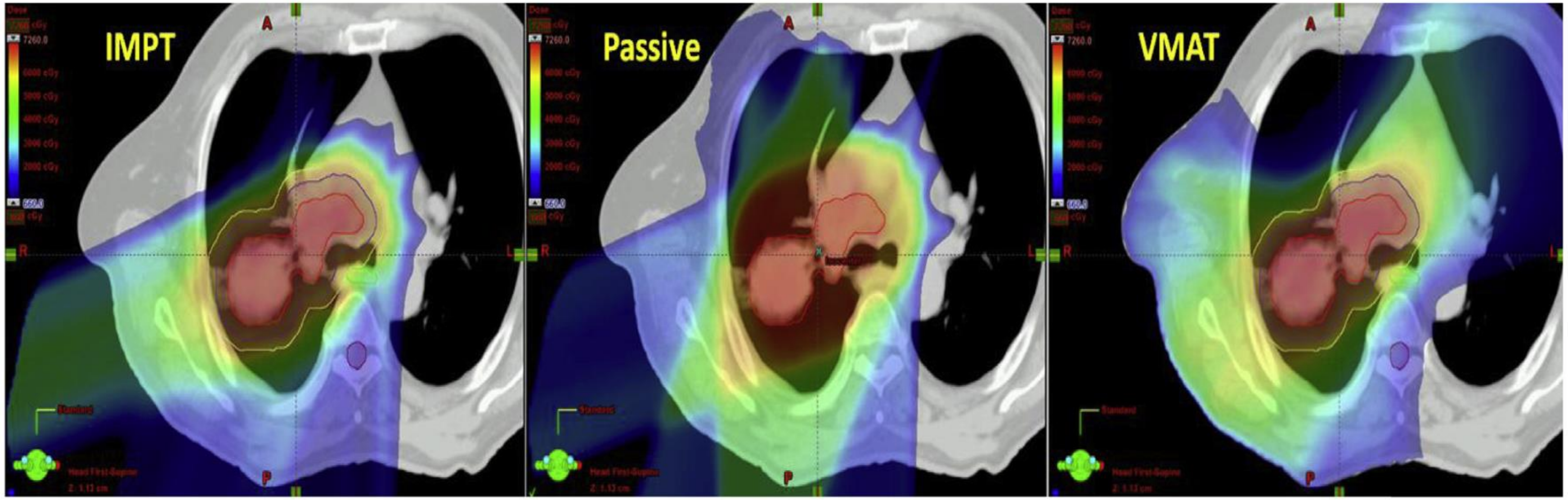
Precision particle therapy

C. Graeff

This project has received funding from the European Union’s Horizon 2020 research and innovation programme under grant agreement No 101008548

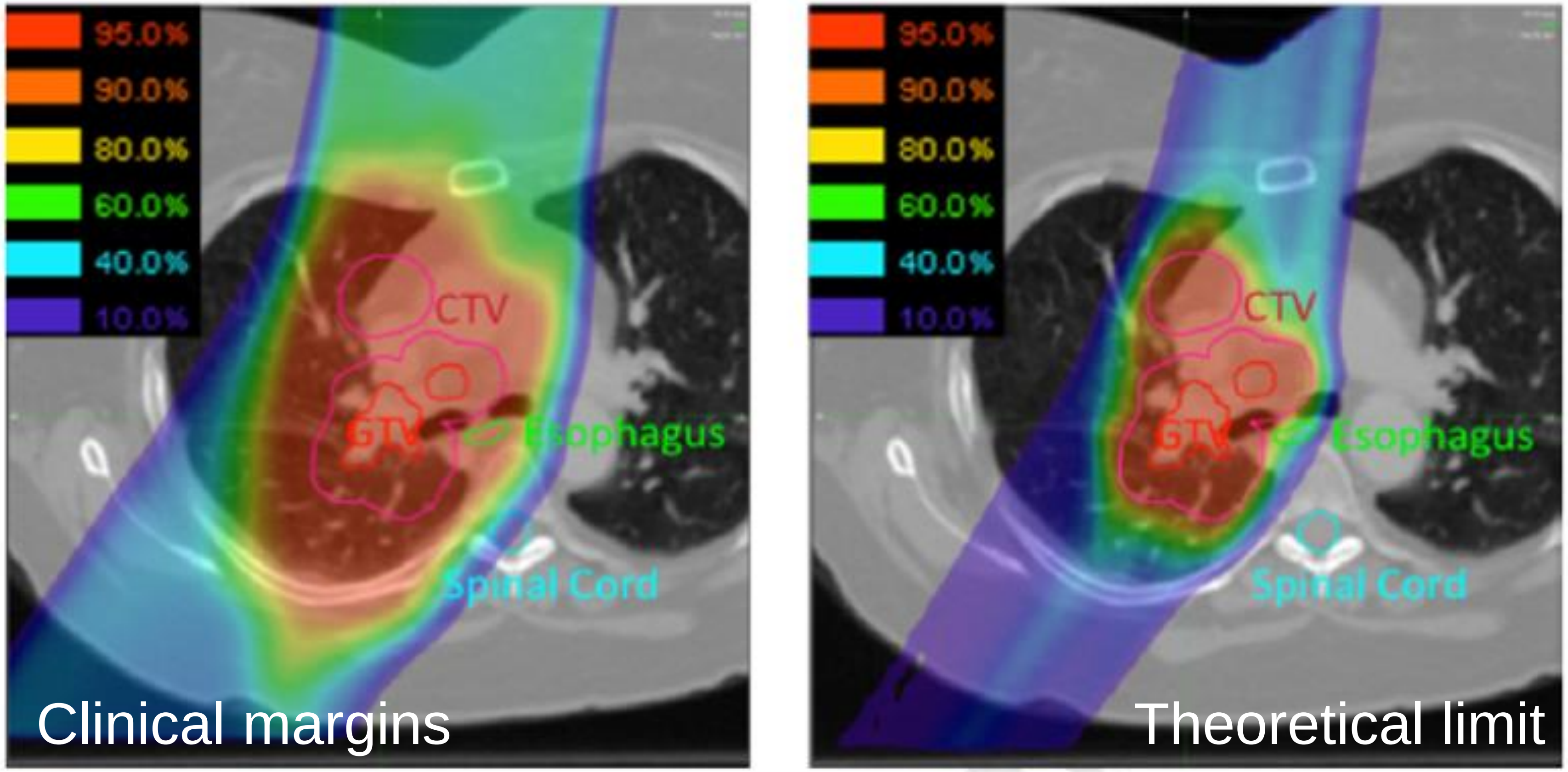
Rationale for precision therapy I

- The Bragg Peak is the primary reason for particle therapy
- In most cases, **TCP** for photons and particles is the same, but **NTCP** is supposed to be better
- In all other cases, photon **TCP** is limited by excessive **NTCP**, and better particle conformity should allow dose escalation



- Case in point: Active scanned delivery
- Much more conformal, and by now standard in every new facility

Rationale for precision II



- Particle conformity is limited by uncertainties **in the patient**, requiring significant margins that maintain **TCP** but increase **NTCP**

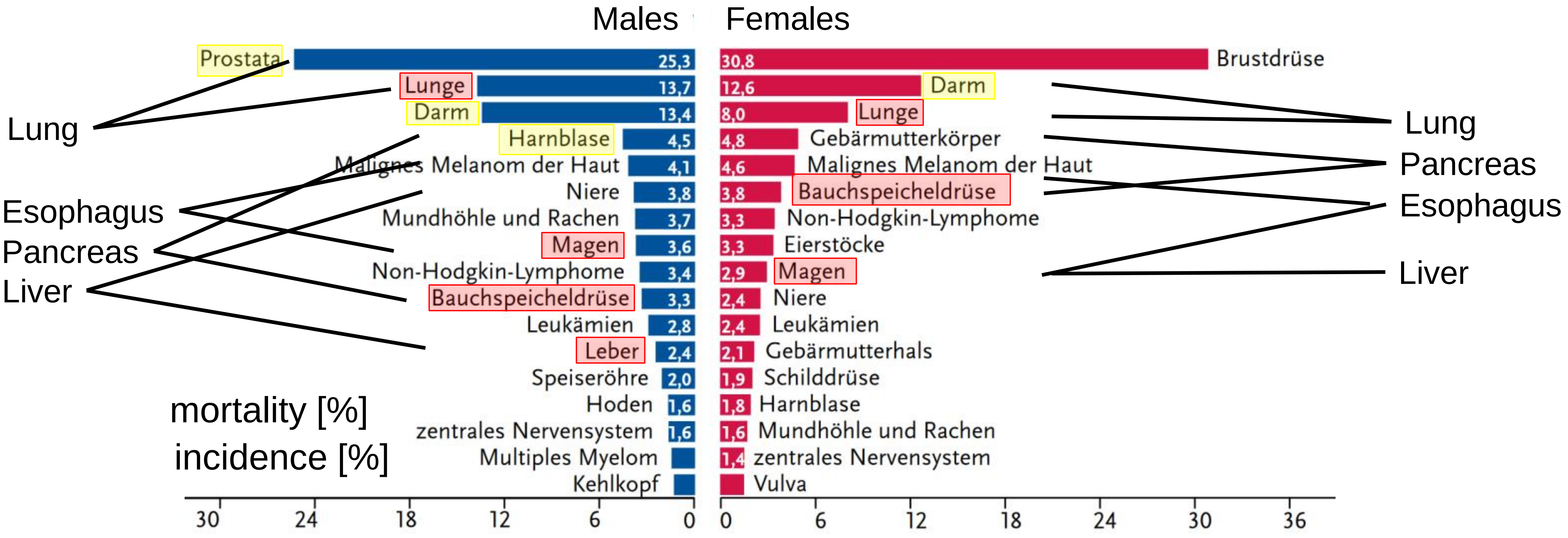
Agenda

- Selected topics on **beam delivery** aimed at increasing conformity and thereby improving NTCP
- As I am not working in a clinical facility,
  this is rather advanced research that will not be seen in a clinic tomorrow
  - Necessary for long-term perspective on what is possible!
- Three examples:
  - Treatment of **moving targets**, aiming at margin reduction
  - **FLASH**, potentially increasing NTCP through (yet unknown) radiobiology
  - **Particle arc therapy** for advanced dose shaping

Moving targets

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101008548

Cancer incidence and mortality



- Cancer of moving organs is common and in many cases has a bad prognosis

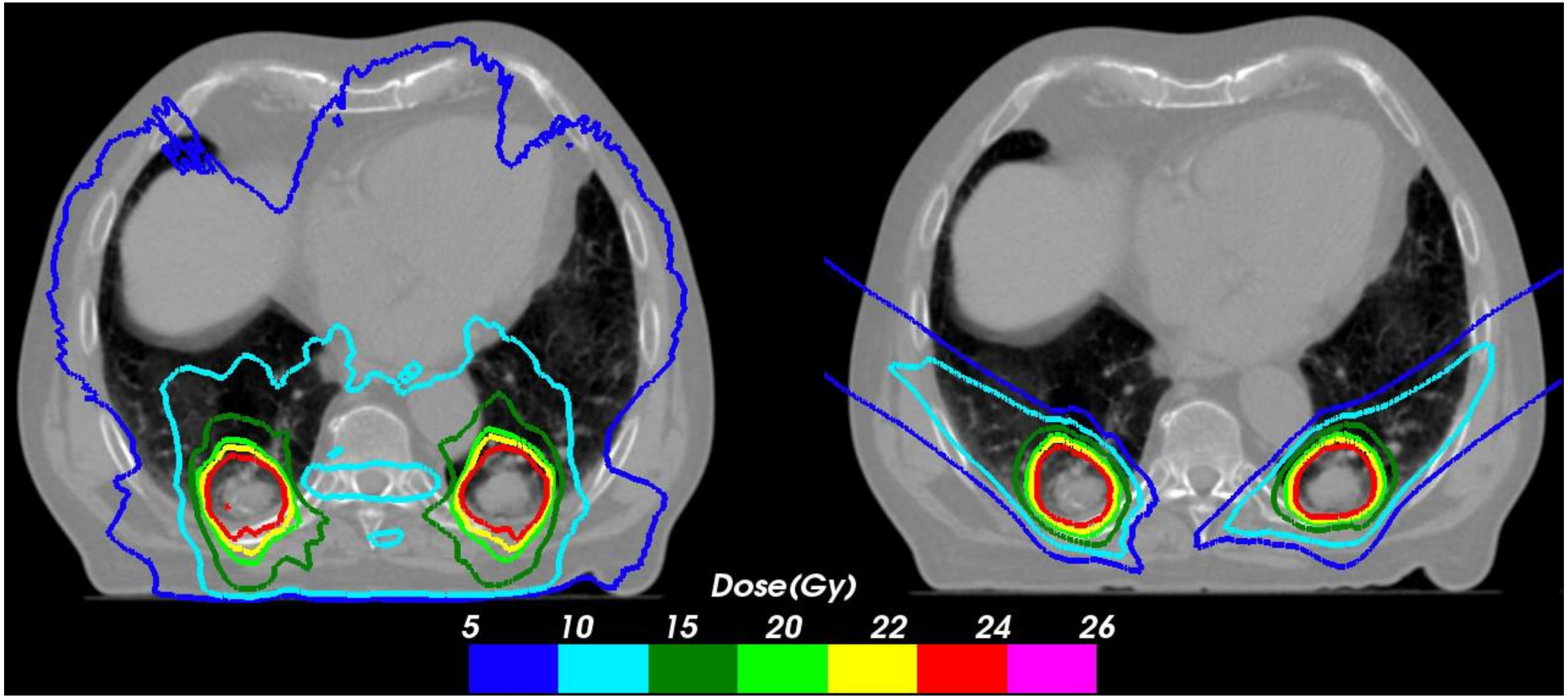
intrafractional motion

interfractional motion

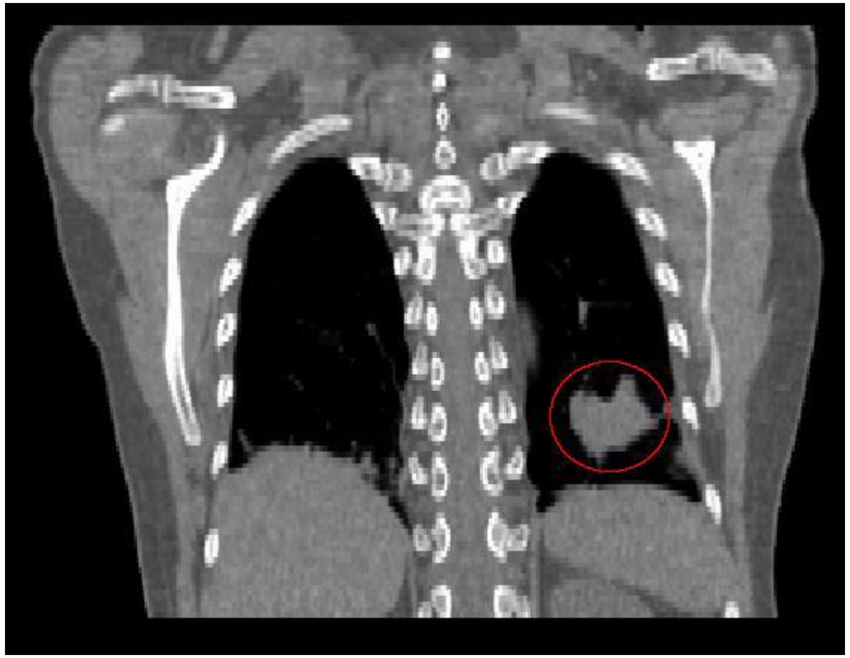
Robert Koch Institute 2015
Data from 2011

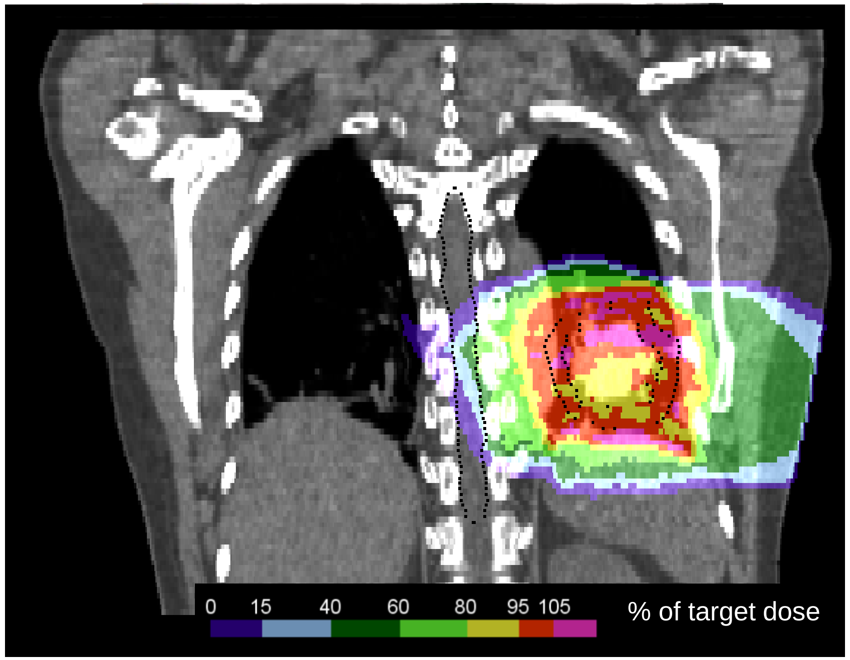
Rationale for 4D-treatment with ions

- Ions more conformal than photons



The problem of irradiating moving targets

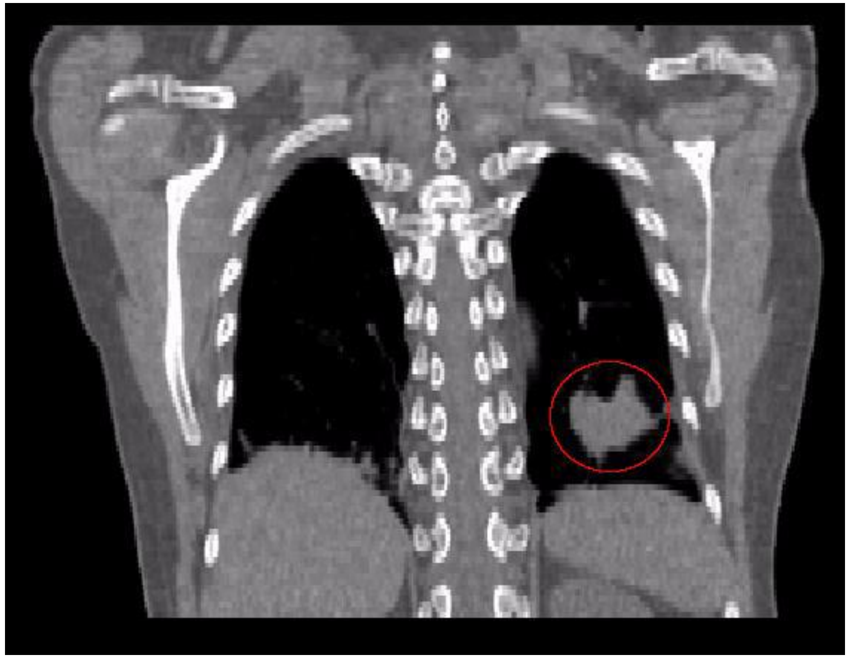


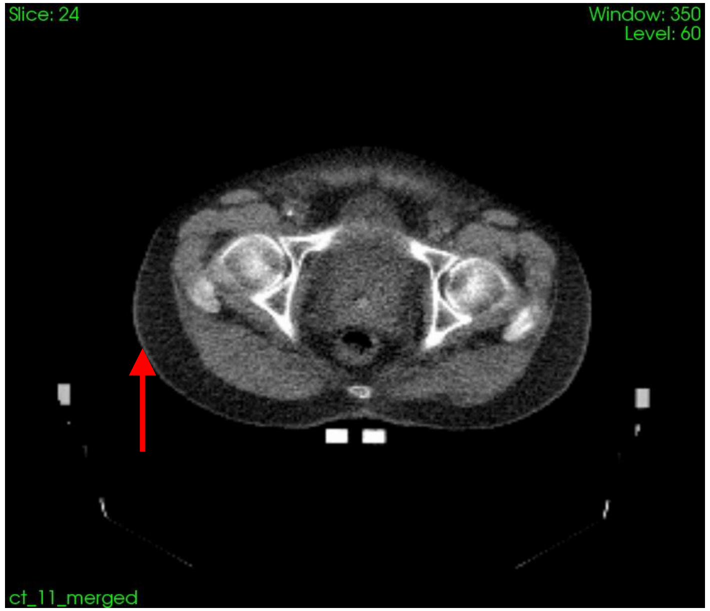


Courtesy M. Söhn, LMU

- **Motion**: Target miss
- **Range changes**: variable position of Bragg peaks
- **Interplay**: Interference between target and scanning motion

Types of motion



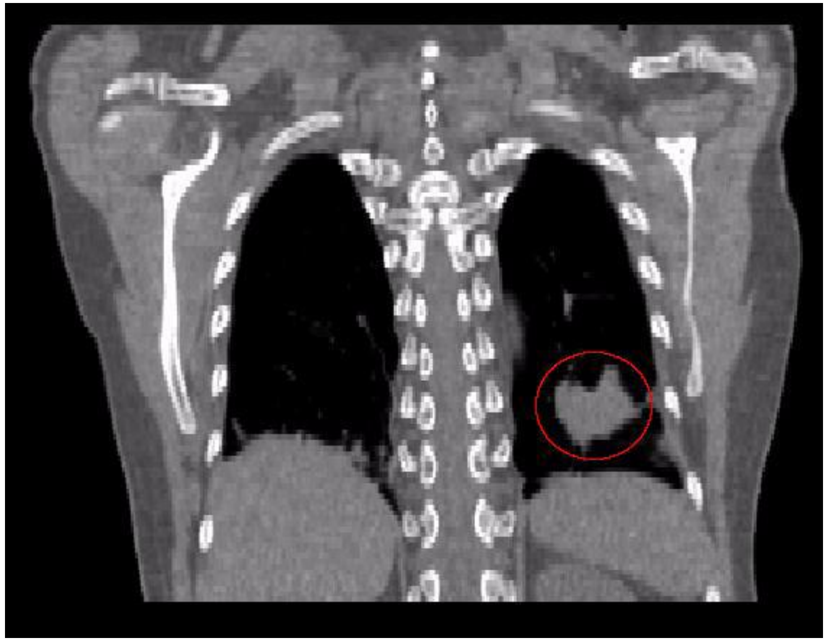


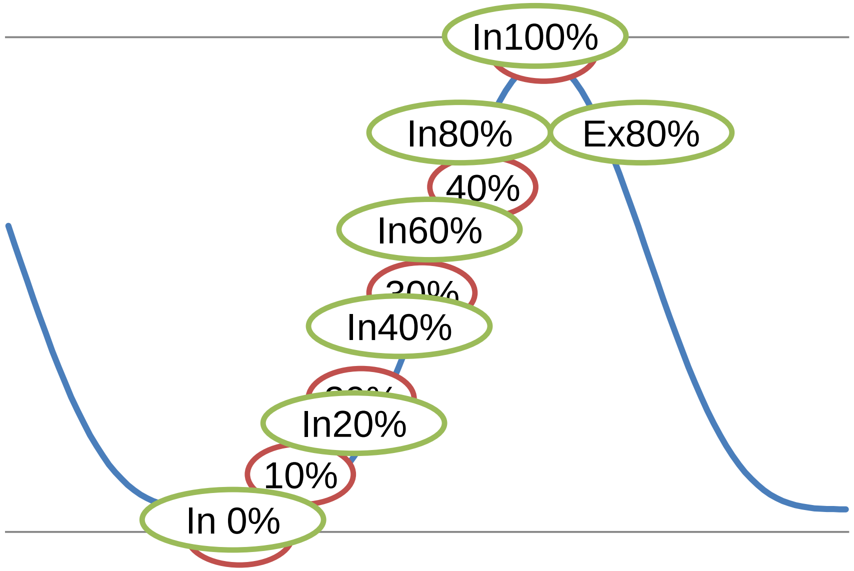
Courtesy A. Rucinski

- Intrafractional motion
  - regular: respiration, heartbeat
  - irregular: peristalsis
- Interfractional motion: Peristalsis, anatomy, positioning

Work horse: 4DCT

- Time-resolved, quasi-static CT
  - long acquisition with motion surrogate (Anzai belt, RPM, ...)
  - projections sorted according to motion signal
  - reconstruction of ~10 CTs representing motion phases

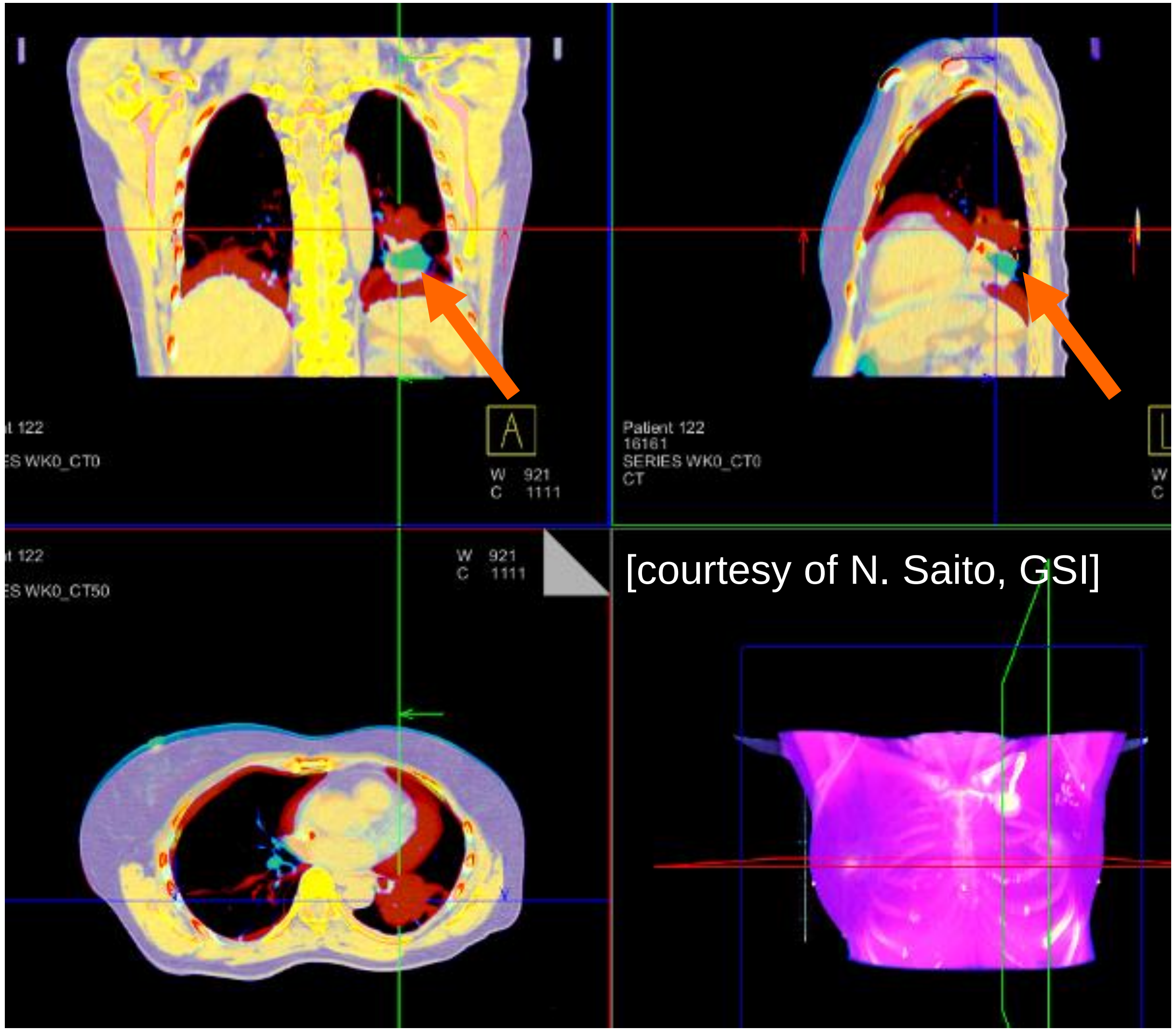




- phase-based: same duration, different amplitude
- amplitude-based: different duration, same amplitude

4D CT + Transformation Maps

- Deformable image registration (DIR)
- Determines geometric movement of each CT voxel
- Results in vector field
- Allows
  - motion estimation
  - dose summation
  - 4D planning
  - contour propagation



[courtesy of N. Saito, GSI]

4D CT + Transformation Maps

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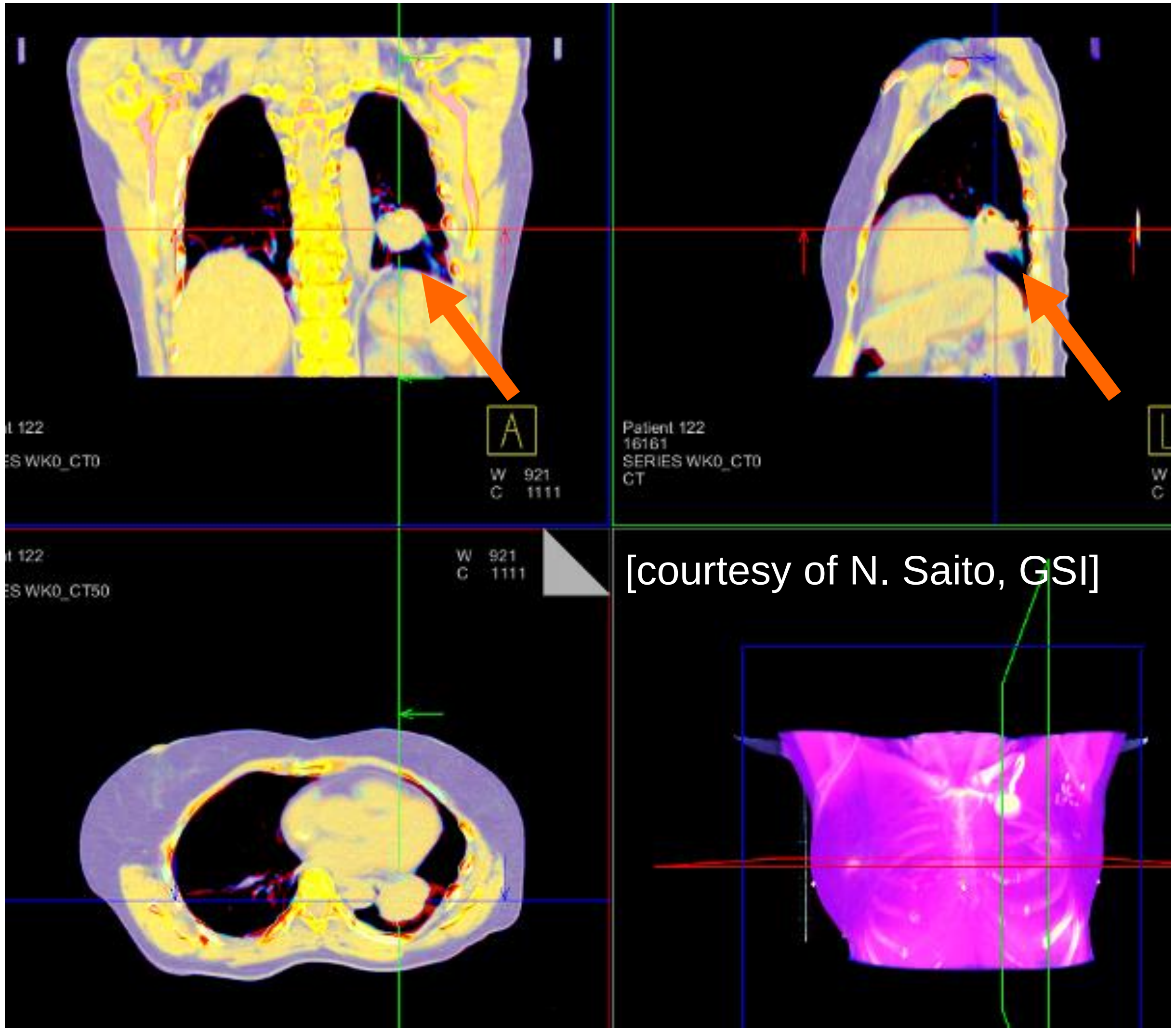
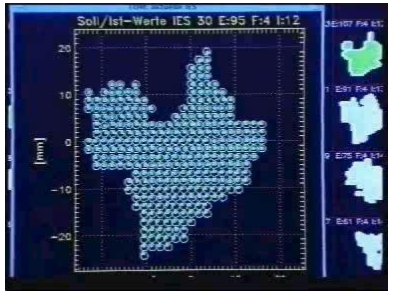
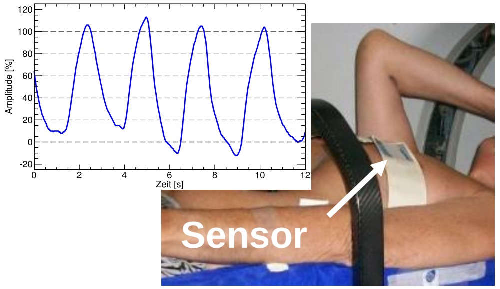
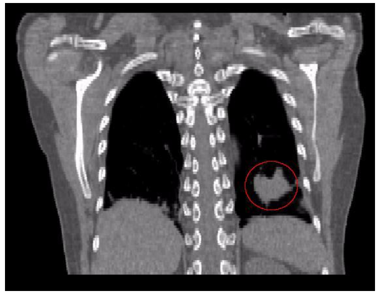


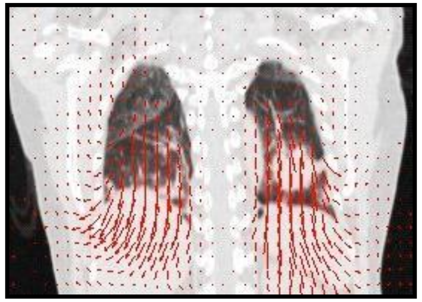
[courtesy of N. Saito, GSI]

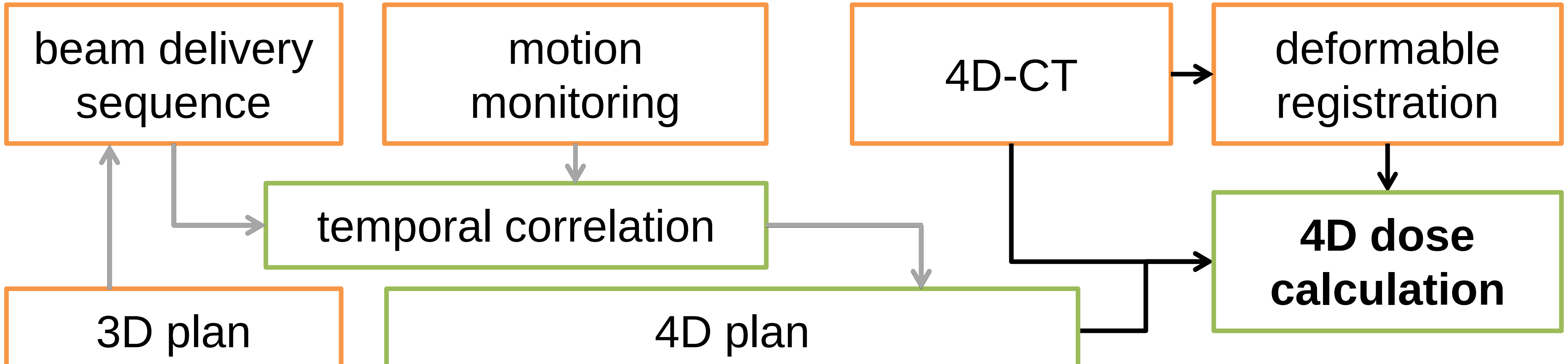
4D-dose calculation / treatment simulation











beam delivery sequence

motion monitoring

4D-CT

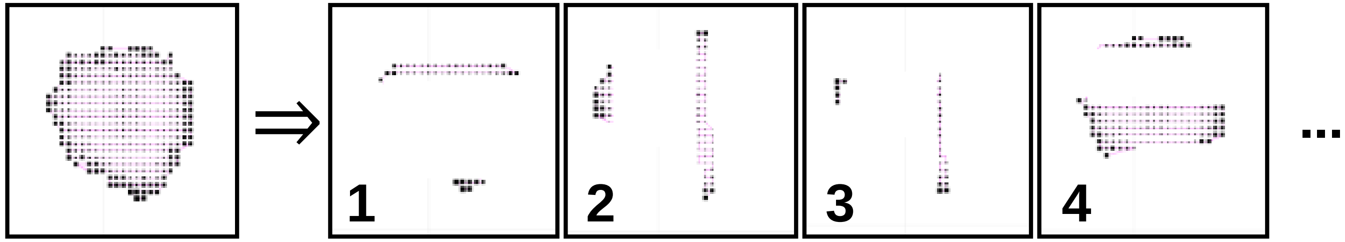
deformable registration

temporal correlation

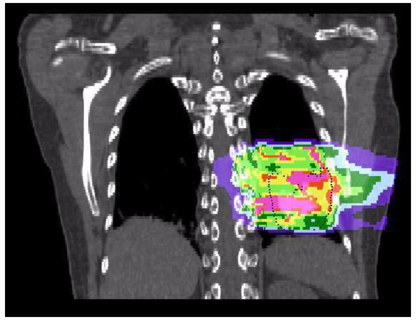
4D dose calculation

3D plan

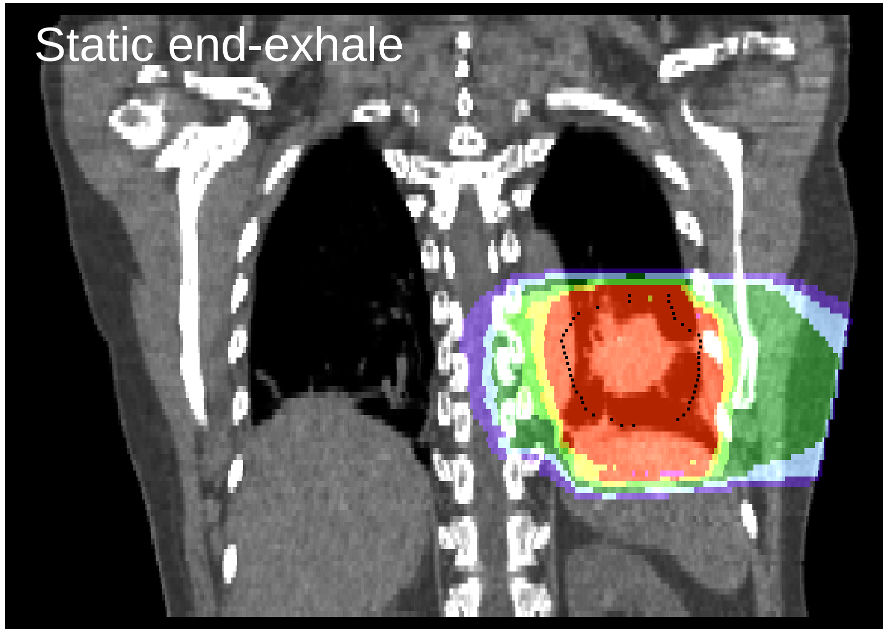
4D plan

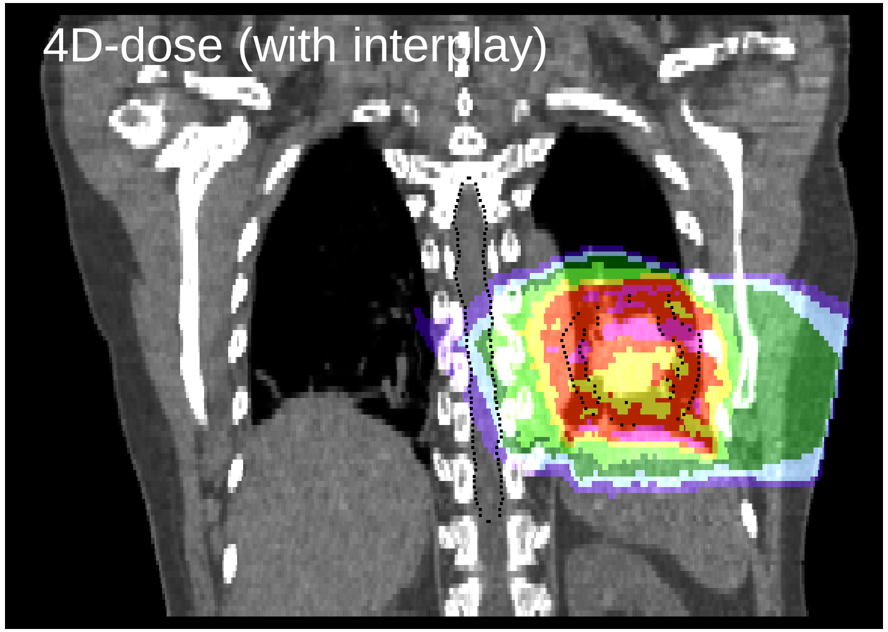


motion phases

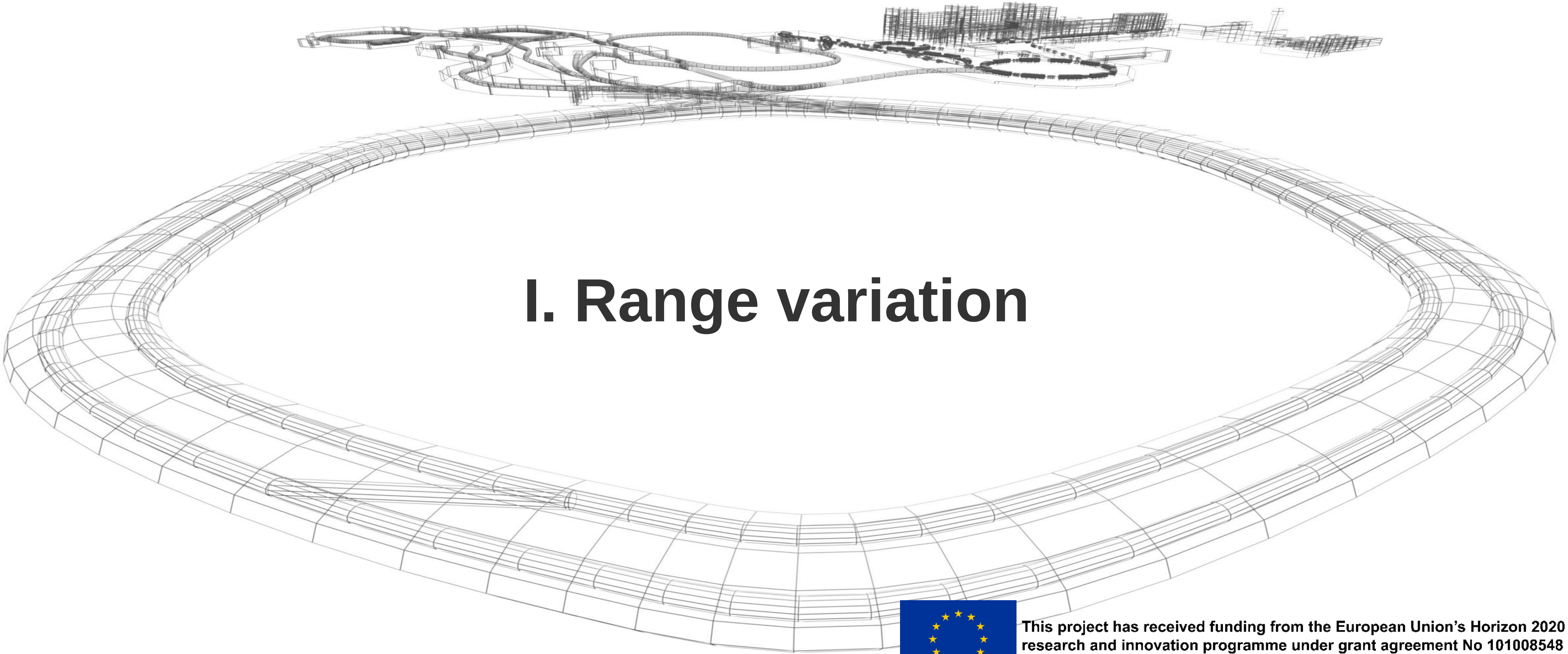


Static vs. dynamic dose calculation





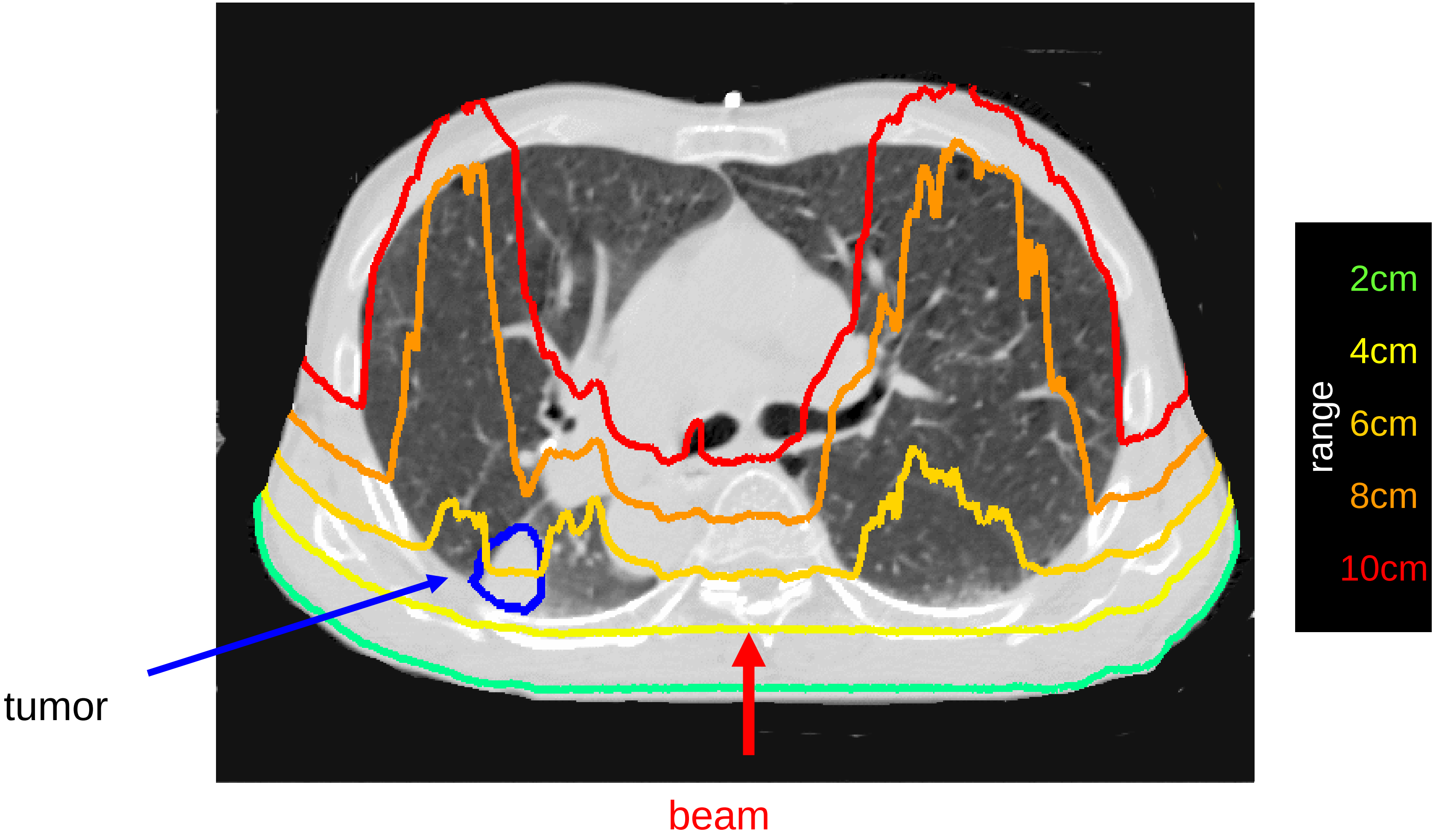
- 4D-dose calculation not available in (most) commercial TPS
- Interplay calculation not available in any commercial TPS
  - ➢ You don’t know how much worse it can get
  - ➢ You also don’t know if you’re mitigation actually helps...



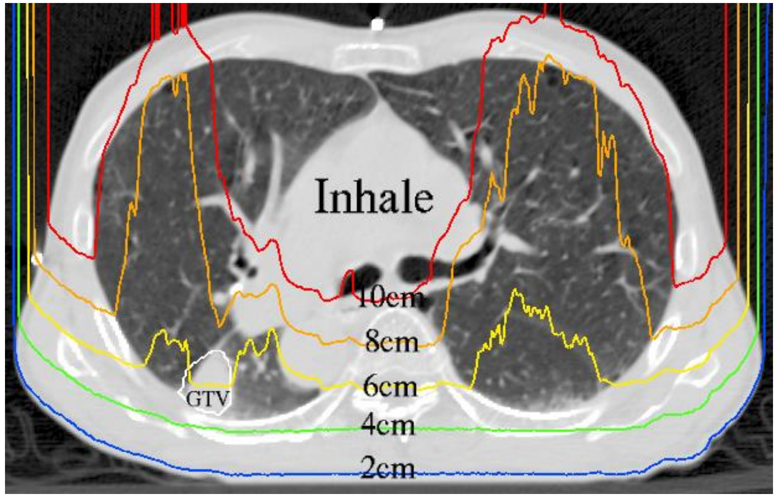
I. Range variation

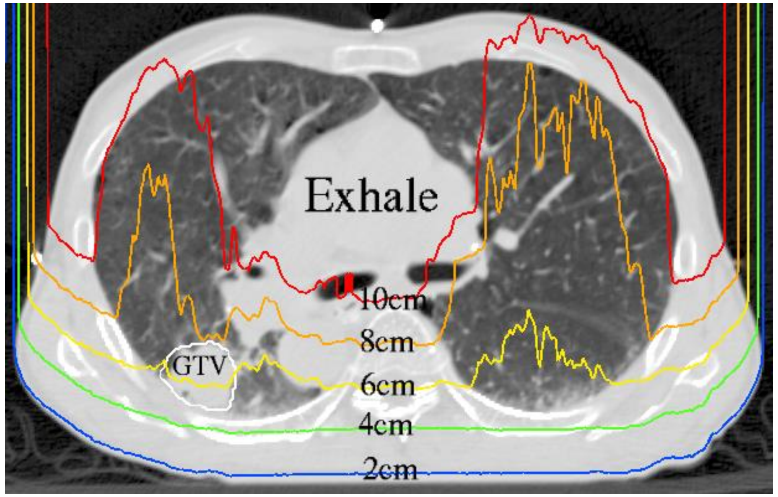
This project has received funding from the European Union’s Horizon 2020 research and innovation programme under grant agreement No 101008548

Respiratory motion - beam range

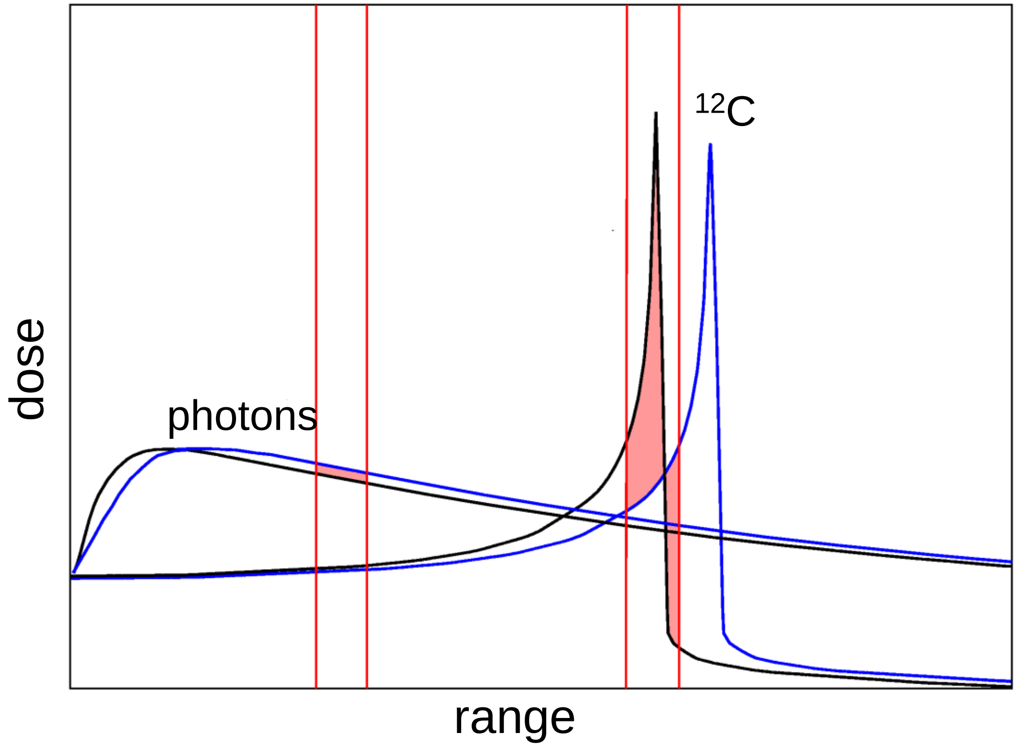


Respiratory motion - beam range





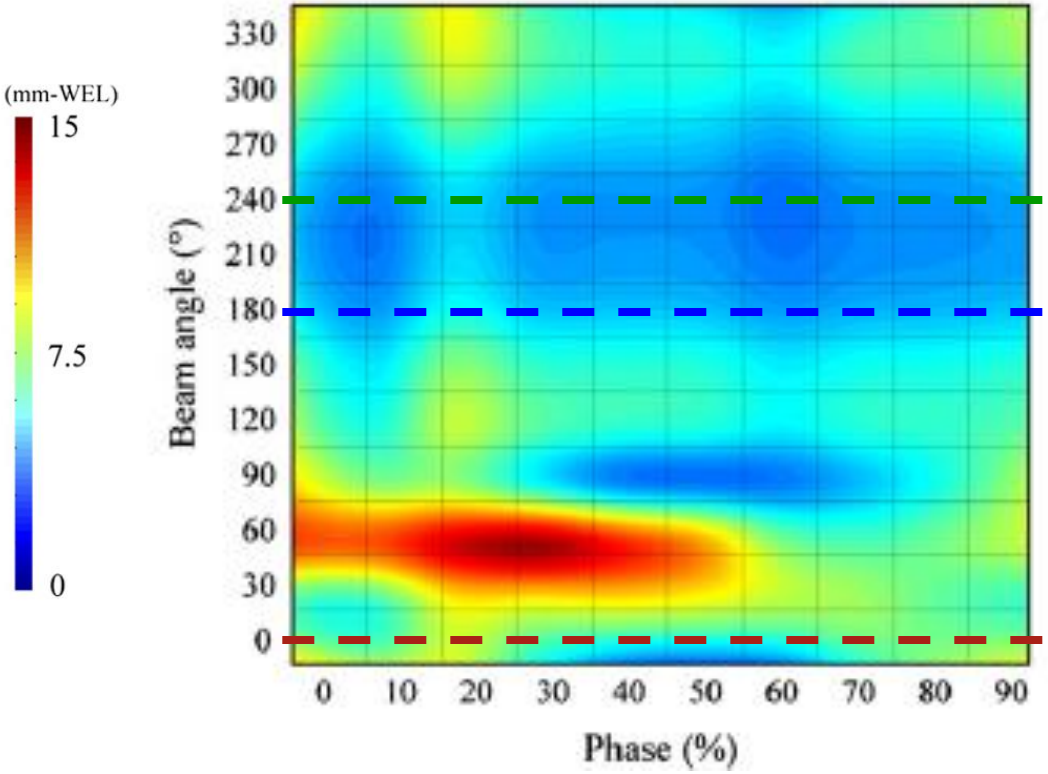
[S.O. Grözinger, GSI]

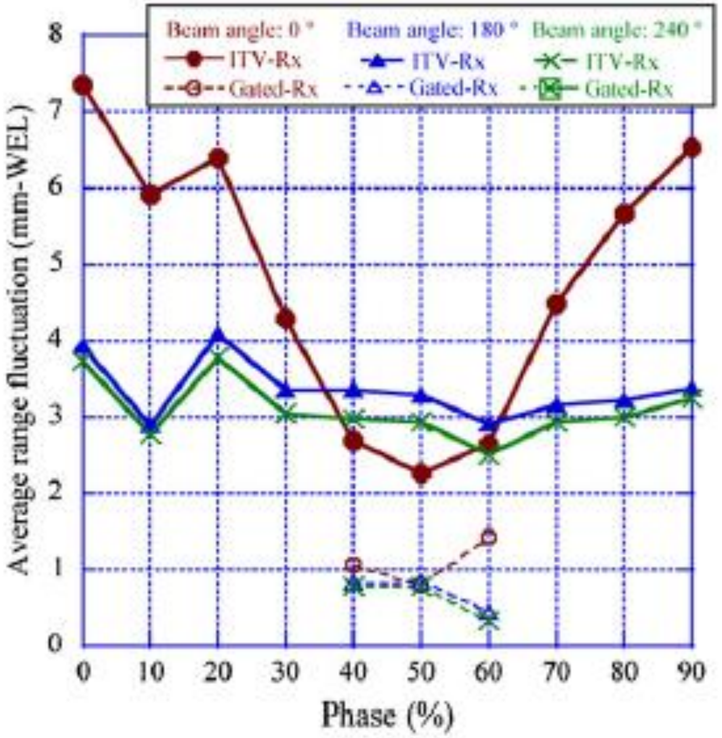


⇒ mitigation of range/longitudinal changes required

Lung cancer patient case

- average range fluctuations from phase to phase in ITV



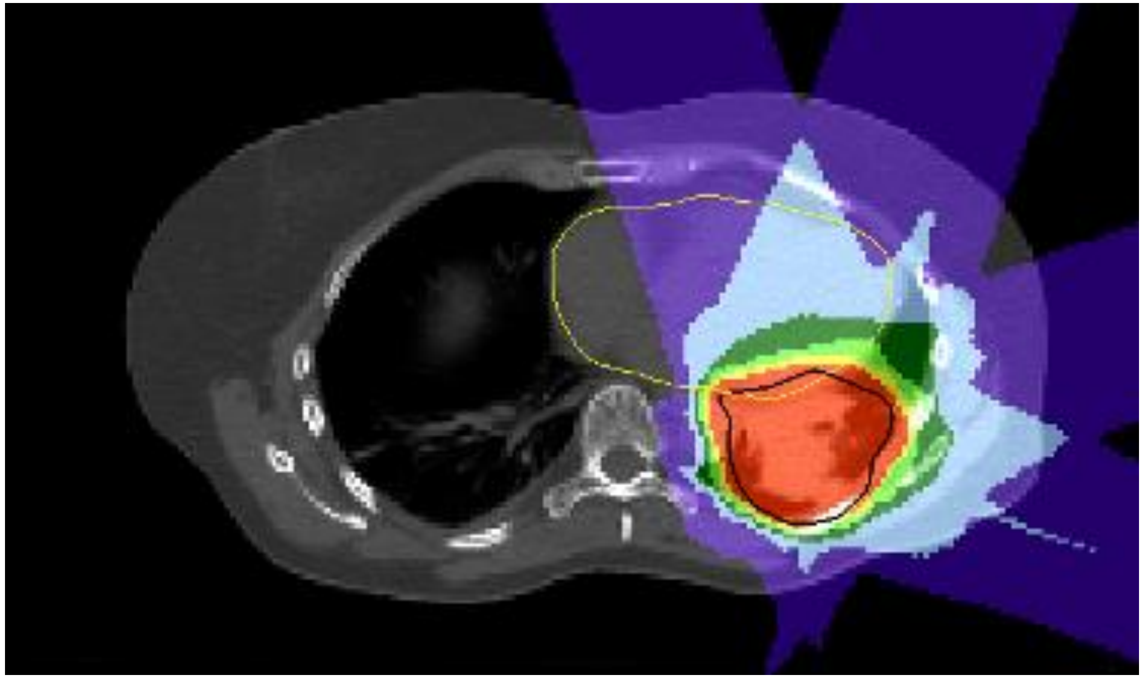


[Mori et al., IJROBP 70(1) 2008]

Internal target volumes (ITV)

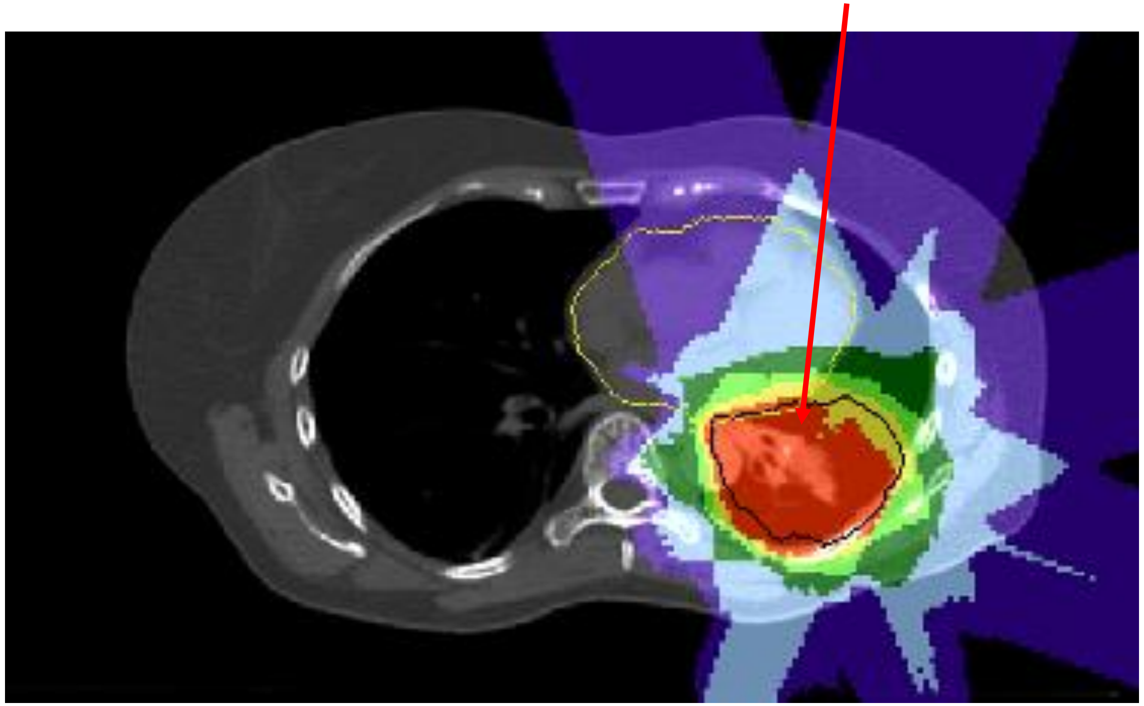
- The ITV should protect the CTV from motion-induced dose errors
- Increased high dose volume – intended to preserve target coverage
- Can be constructed in different ways
    1. Manually contoured on an average CT, possibly with fused MRI / PET
    2. Contoured on a Maximum Intensity Projection from 4D-CT phases
    3. Contour a reference phase, propagate to all 4D-CT phases with DIR
the ITV can be defined as the union of all CTVs in all motion phases
- The above is sufficient in photon therapy, but neglects range changes!
- Especially in the lung, leads to severe dose errors
    - Density Replacement – for planning, the ITV is filled with an average tumor density
    - Explicit calculation of beam ranges in the 4DCT,
use the union of range-space in water of all phases as range-ITV

Simulated Static Dose: Geometric ITV



End-Exhale (reference phase)

underdose due to range change

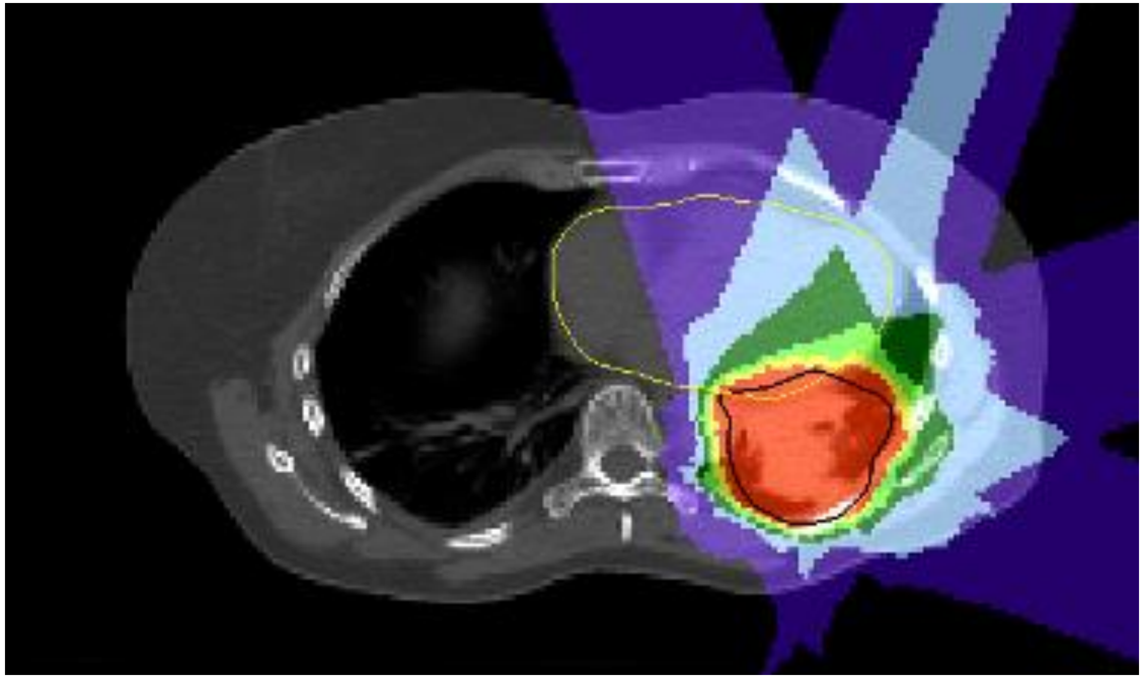


End-Inhale

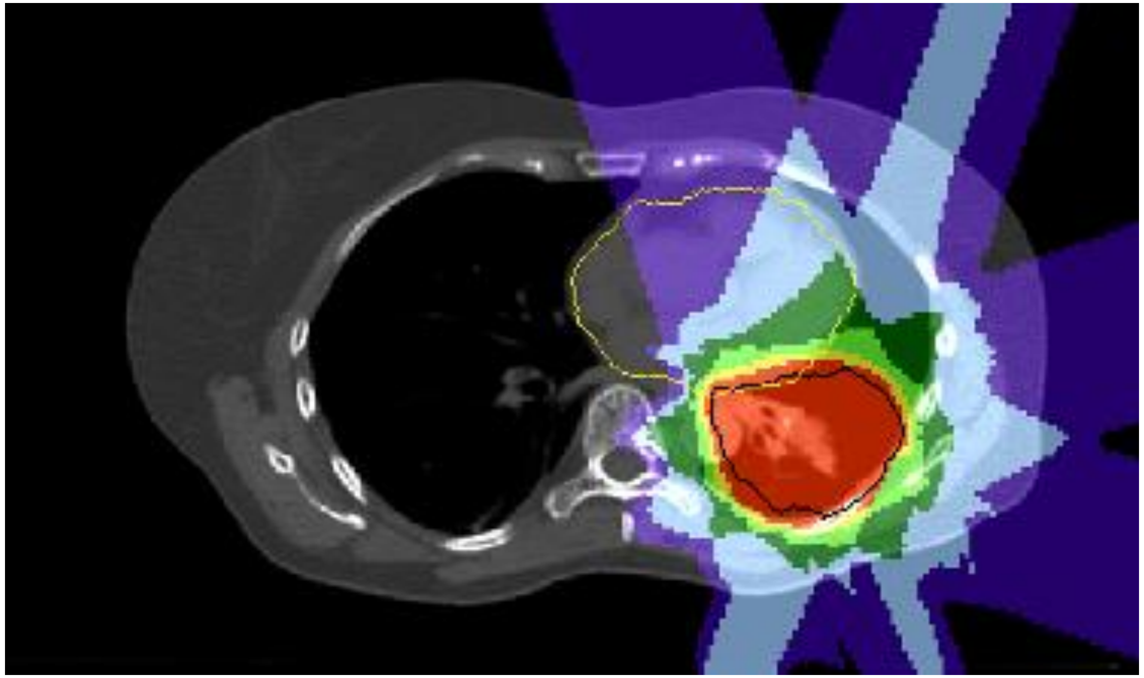
25 mm motion

Graeff et al. Med Phys 2012

Simulated Static Dose: Range-ITV



End-Exhale (reference phase)

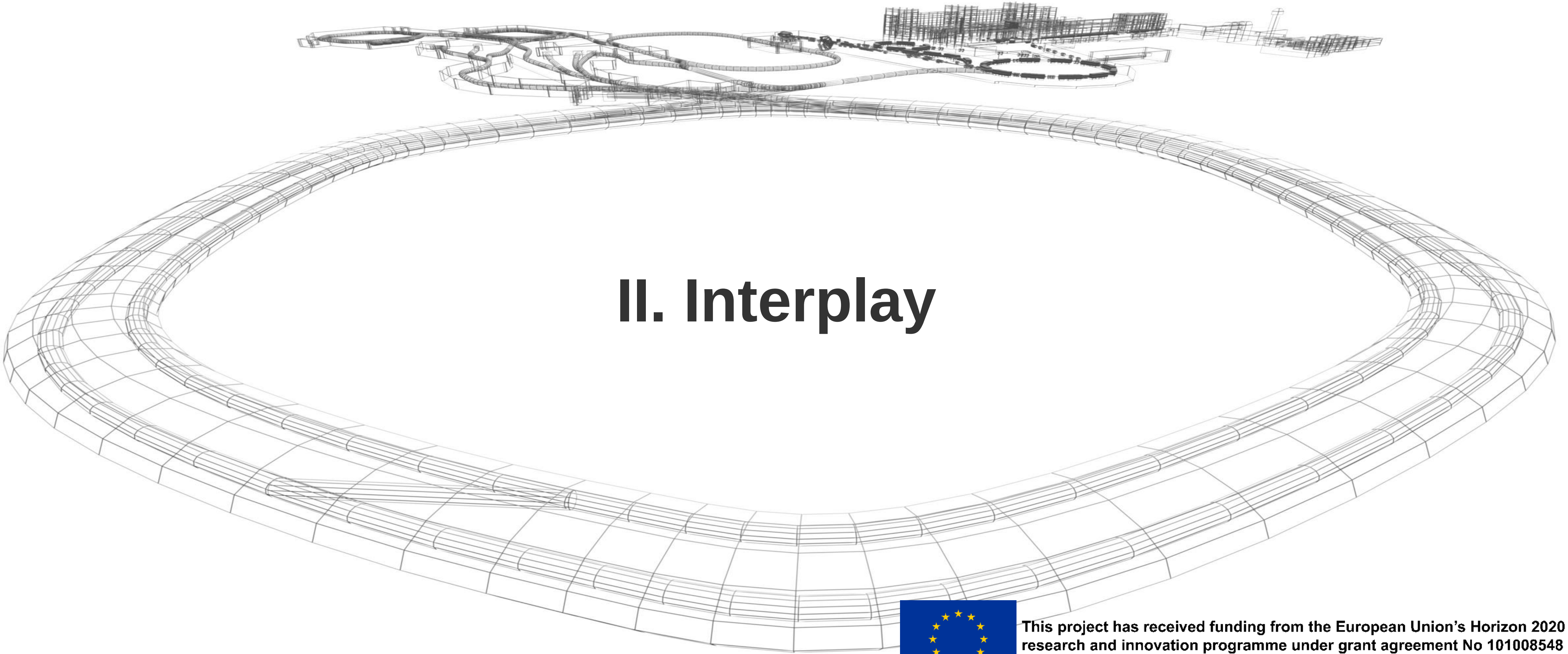


End-Inhale

25 mm motion

Graeff et al. Med Phys 2012

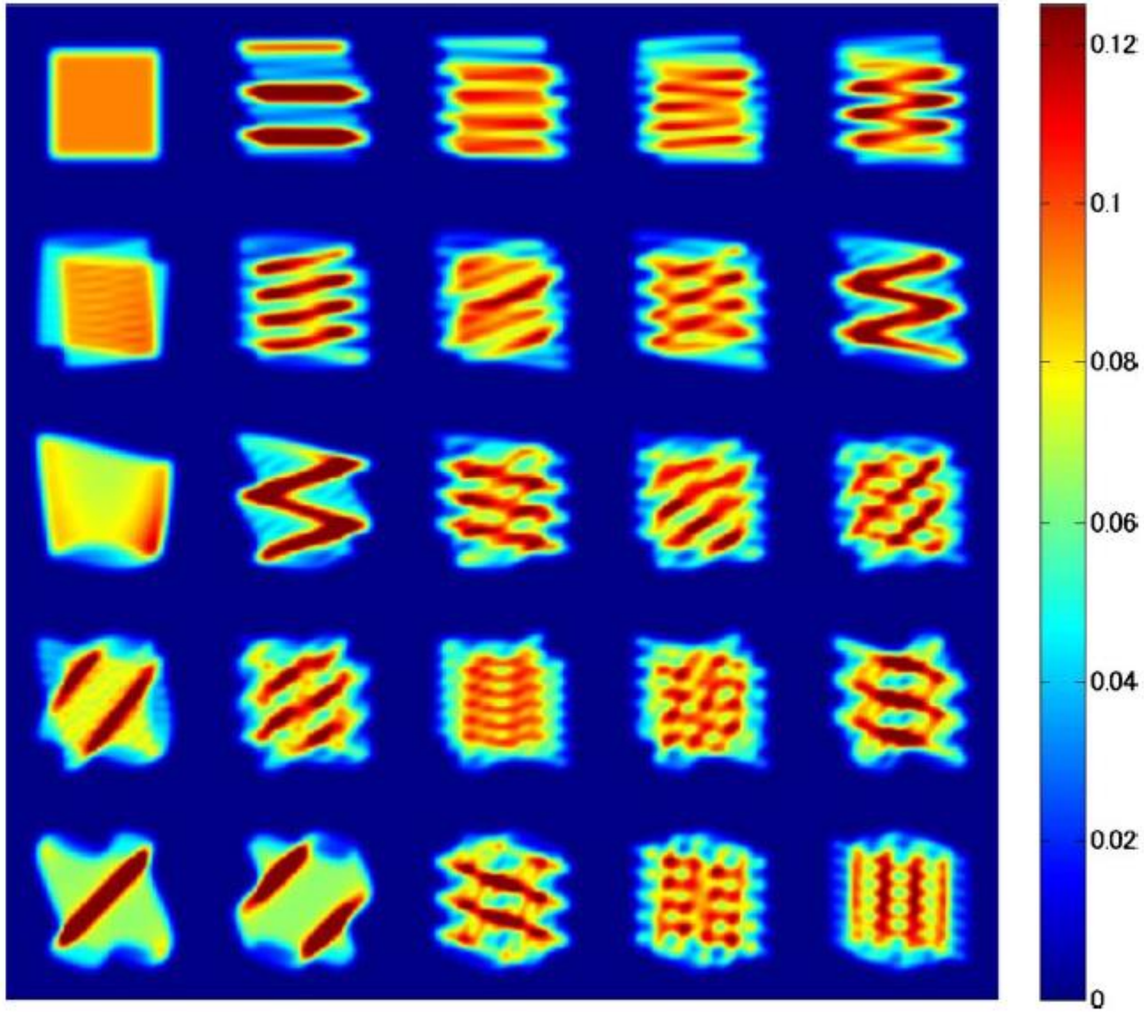
Heavy Ion Therapy Research Integration



II. Interplay

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101008548

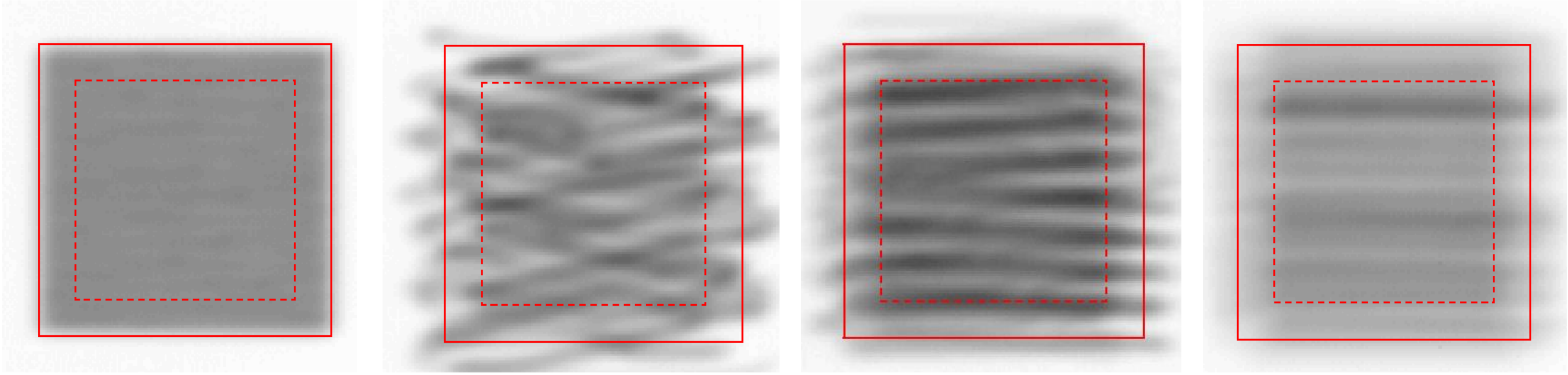
Interplay



Furukawa et al. Med Phys 2010

Rescanning

S. Grözinger, PhD thesis, 2004



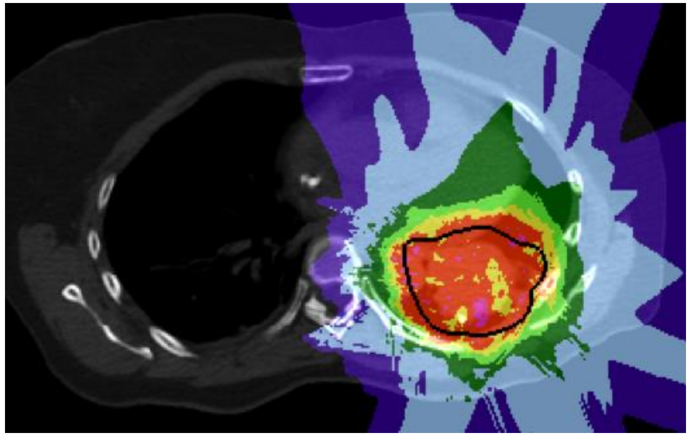
Static

1 scan

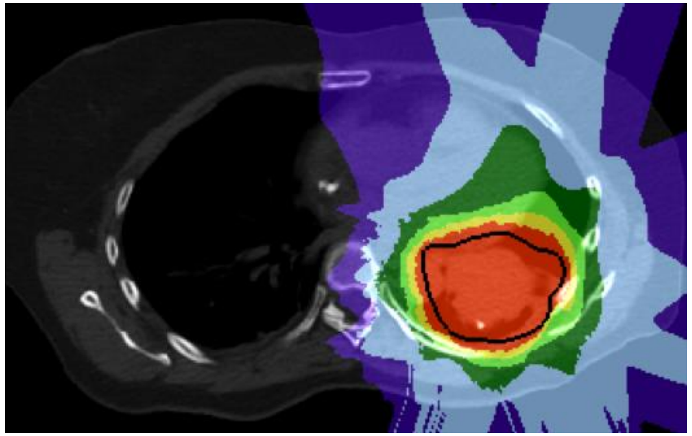
2 scans

10 scans

D. Müssig, PhD thesis, 2013

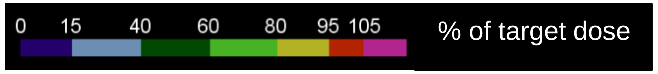


Interplay



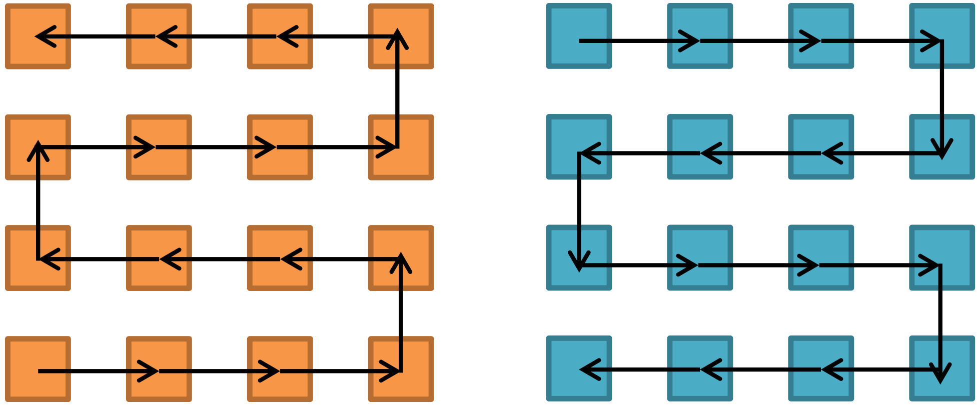
9 x Phase-controlled rescanning

Slice-by-slice rescanning



Rescanning flavors

- Slice-by-slice:
  - Divide spot weight by cycle count N, deliver N times
  - Typically, scan path is inverted for each second cycle

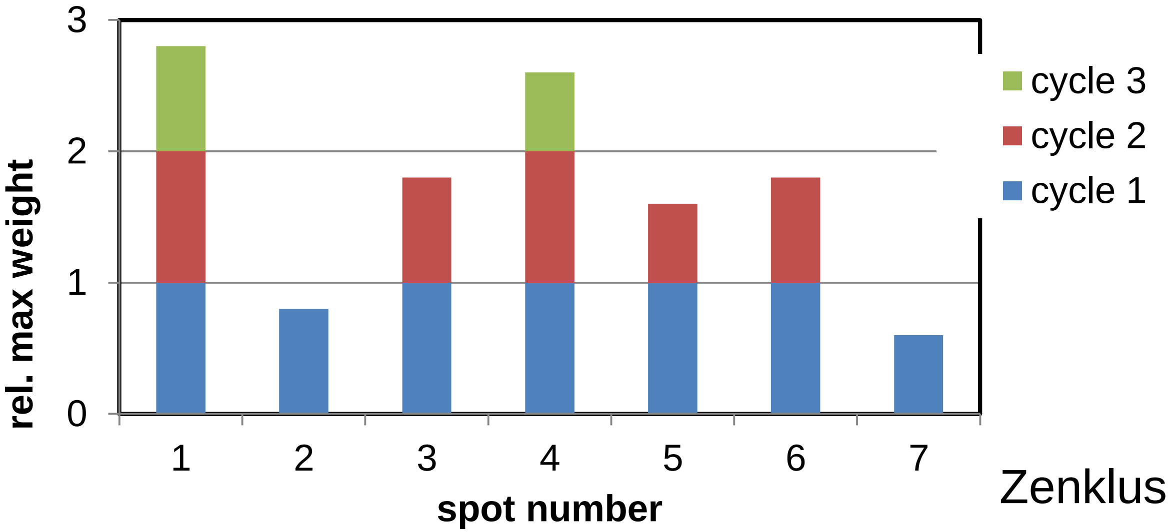


cycle m   cycle m+1

- Volumetric:
  - Divide spot weight and deliver entire plan N times
  - Not practical for too long energy switching times

Iso-layered rescanning

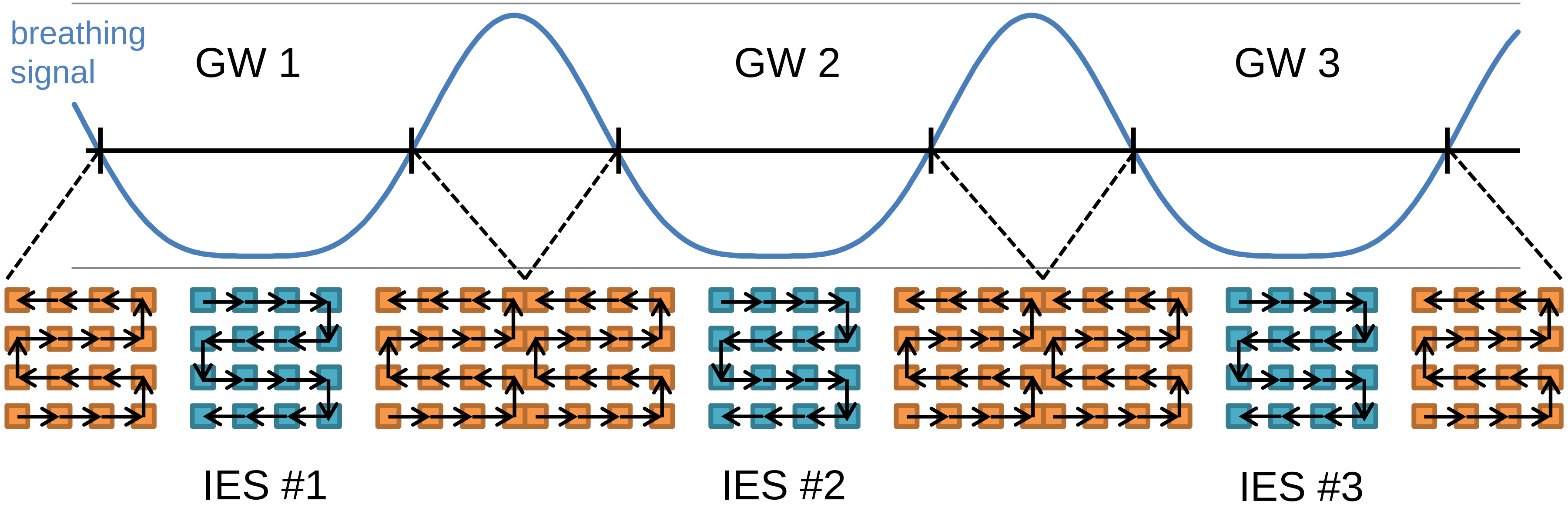
- All spots are irradiated multiple times with a fixed maximum beam weight
- Large spots are rescanned more often than small ones
- Scan path has to be modified – better for spot scanning
- Scan speed often limited by smallest spot weight - fast scanning possible



Zenklusen et al. 2010

Phase-controlled rescanning

- Similar to slice-by-slice rescanning
- Idea: deliver entire rescanning cycle in one breathing period or gating window
- effective de-correlation of rescanning / motion

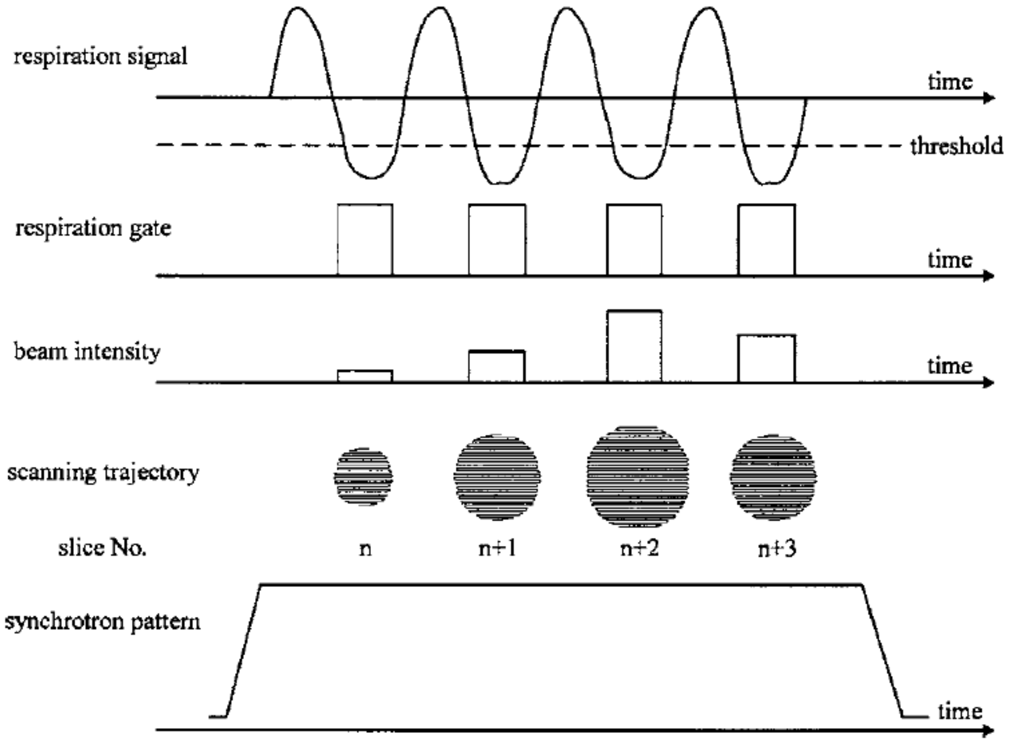


GW: gating window

Furukawa et al. 2007

Phase-controlled rescanning II

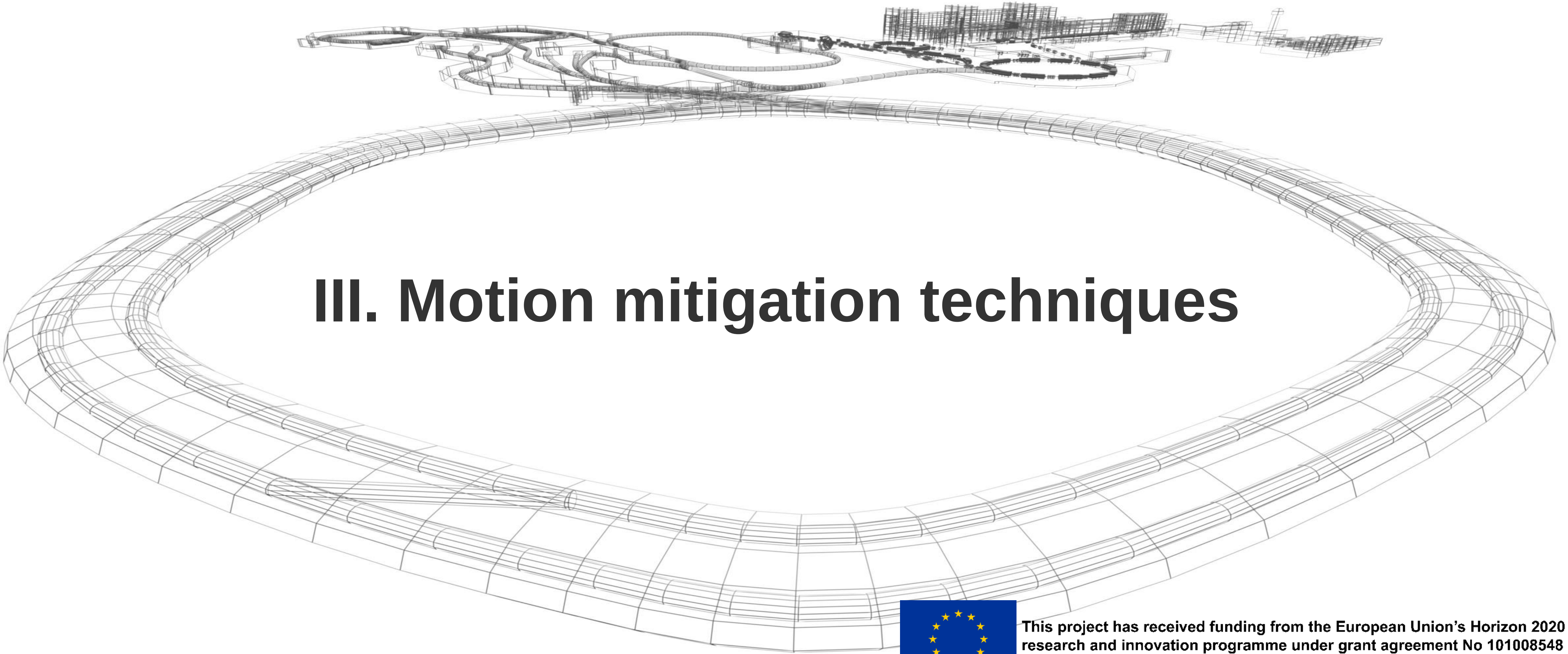
- requires adjustment of delivery speed to treatment plan and breathing frequency
- technically demanding but highly effective



Furukawa et al. 2007

Summary Motion I

- **Interplay** is the interference between target motion and the motion of the scanned beam
  - Can be compensated by rescanning in different forms
- **Range changes** are induced by patient motion and lead to misplacement of the Bragg Peak
  - Can be compensated by ITVs with an explicit consideration of beam range
  - Range changes are field-specific, simple isotropic margins are not ideal
- Range-considering ITVs plus rescanning are a valid form of motion mitigation, and are in use in clinical practice
  - No standardized strategy is available, most clinics use their own flavor depending on experience and clinical capabilities of their machine and TPS
  - Drawback is an increase irradiation volume to cover the tumor amplitude



III. Motion mitigation techniques

This project has received funding from the European Union’s Horizon 2020 research and innovation programme under grant agreement No 101008548

Motion reduction

- Rigid masks and/or abdominal compression can reduce the motion amplitude, and force the patient to use thoracic breathing
- This can be effective especially for (otherwise) large breathing amplitudes in tumors in the liver or the lower lung
- Motion is reduced but not eliminated!

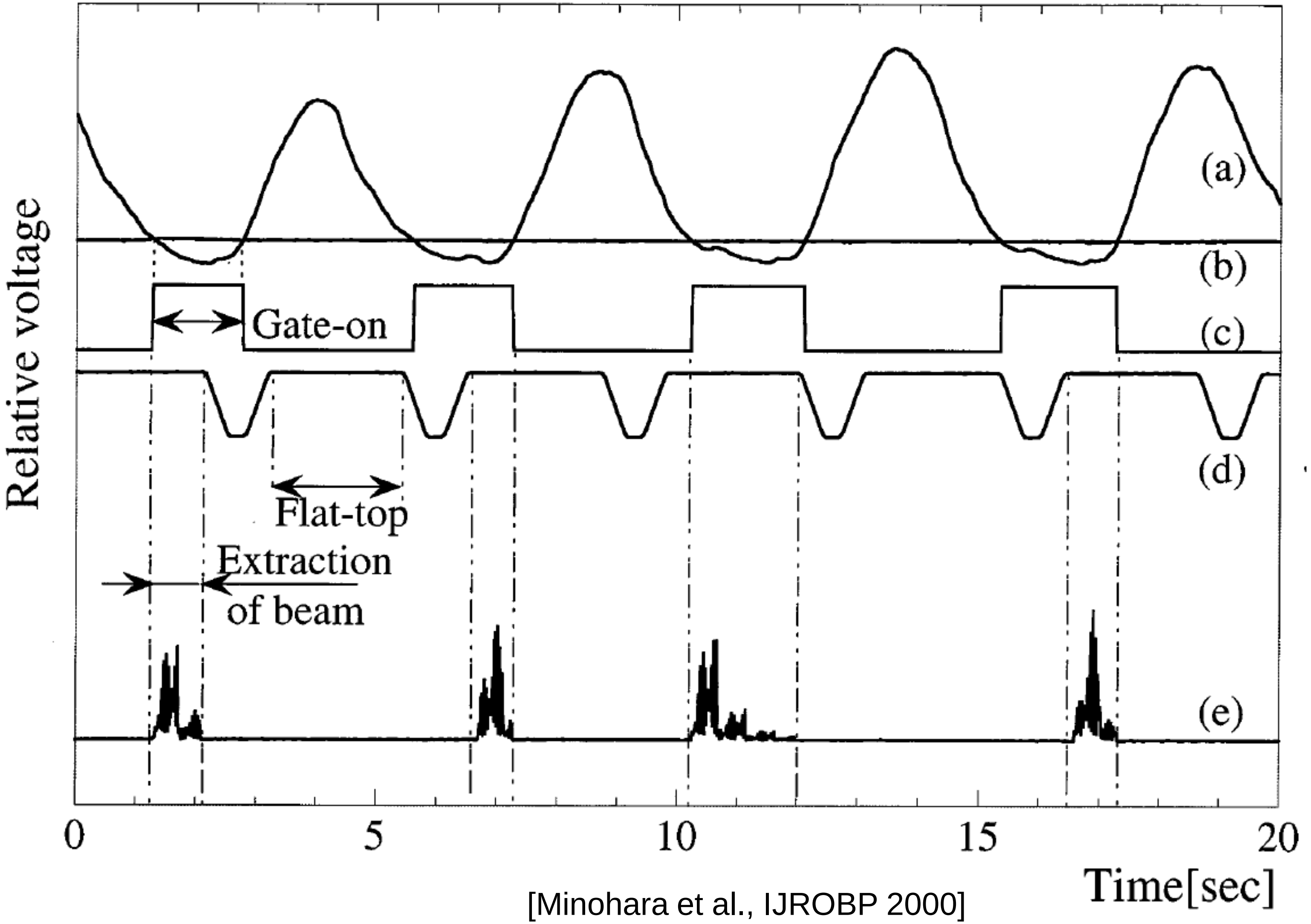
- Patient tolerance and reproducibility are an issue
  - Different papers report mixed results, in some patient cohorts, amplitudes were even increased
  - Likely depends on tumor location and experience of personnel

Courtesy HIT

Beam Gating

- Beam delivered only in pre-defined ‘window’
- Window can be defined by phase or amplitude
- Increases delivery time
- Trade-off of precision vs. delivery time
- Irregular motion is an issue

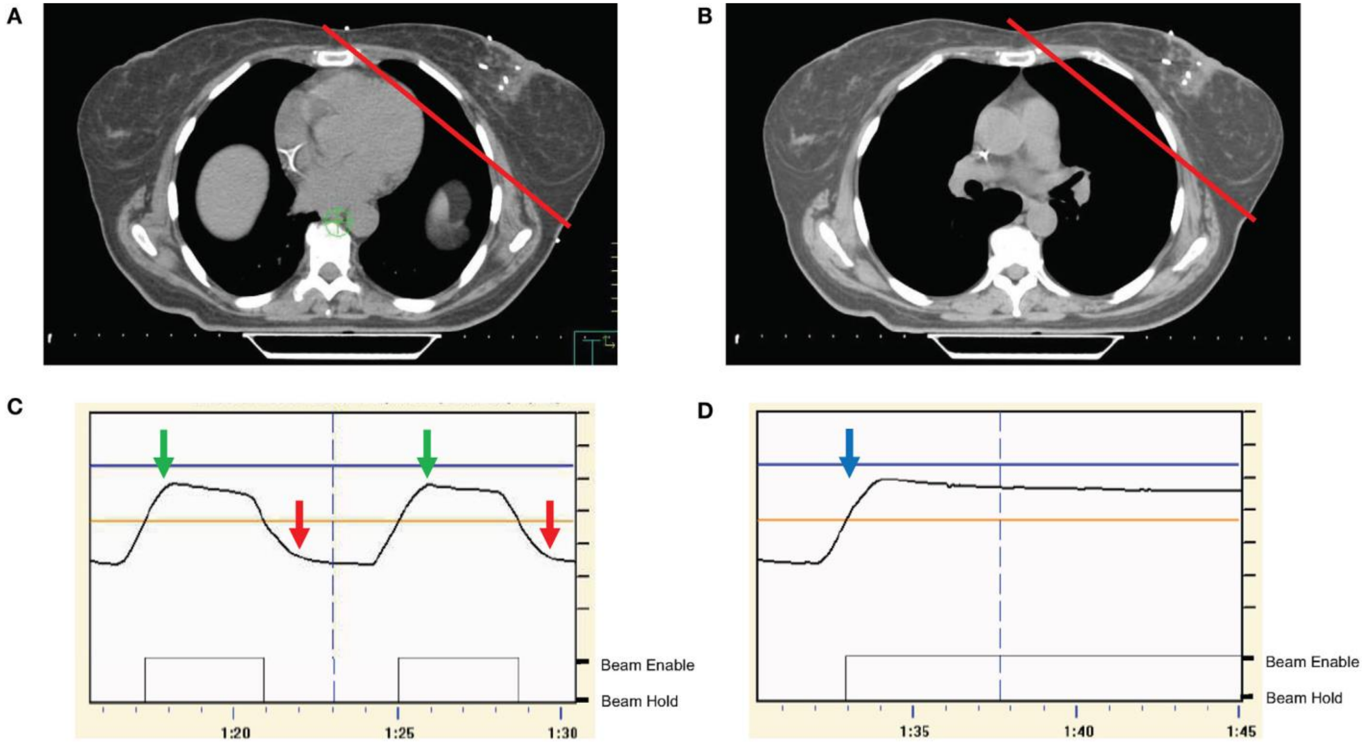
- Much more efficient in cyclotrons and modern synchrotrons



[Minohara et al., IJROBP 2000]

Deep-inspiration breath hold DIBH

- Patients are coached to hold breath at ~80% of maximum tidal volume
  - 30s or more are possible
- Volume or chest position is monitored and beam is turned on in a DIBH gating window
- Patient compliance and reproducibility are an issue, especially in lung cancer

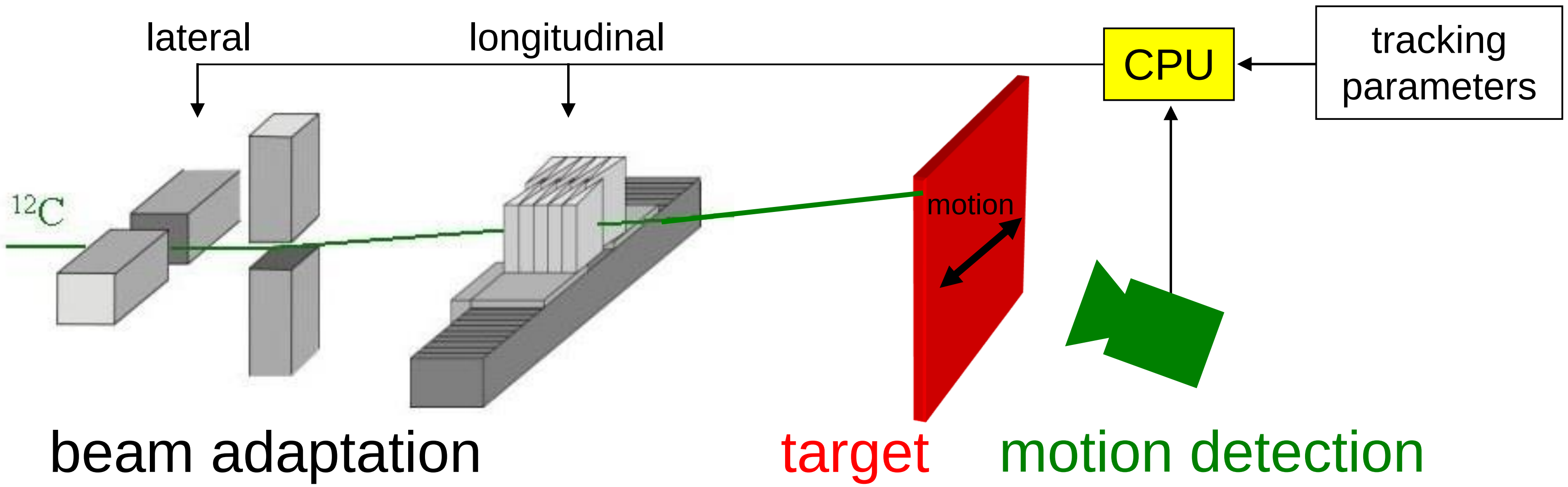


[CC-BY Bergom et al, Front Oncol 2018]

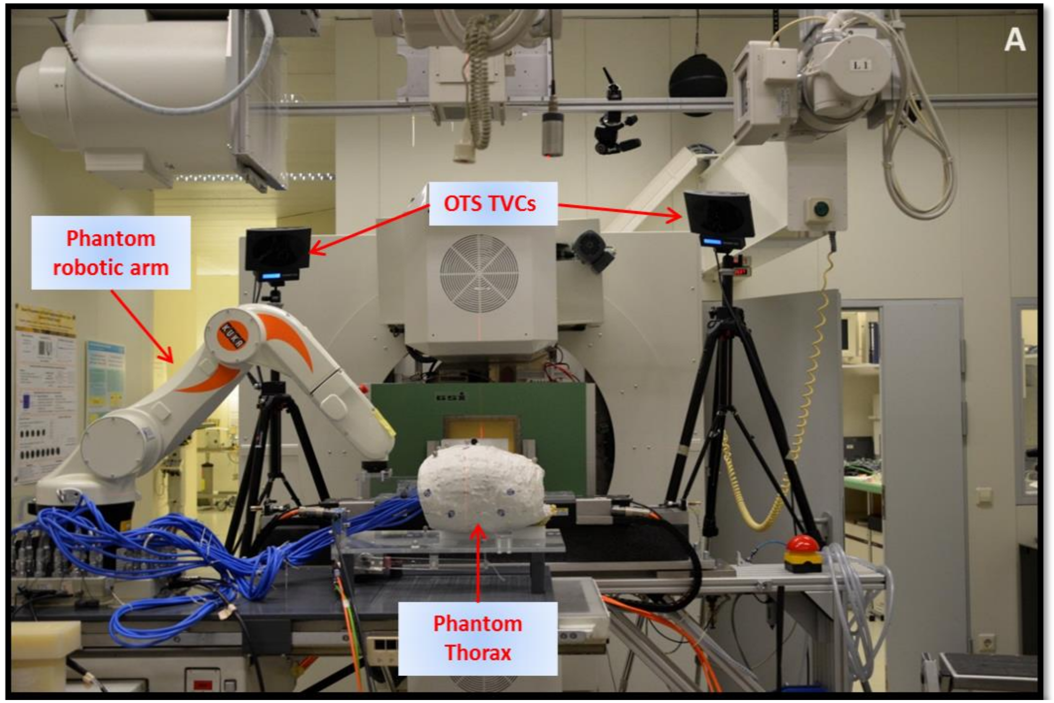
- More frequently used in breast cancer, where patients are younger, have better lung function. Also increases distance between breast and heart

Beam tracking

- For scanned particle beams, this is a ‘natural’ form of motion compensation
- The beam is moving already, much faster than respiration, so it can also follow the tumor motion
- Requires accurate knowledge of the tumor location

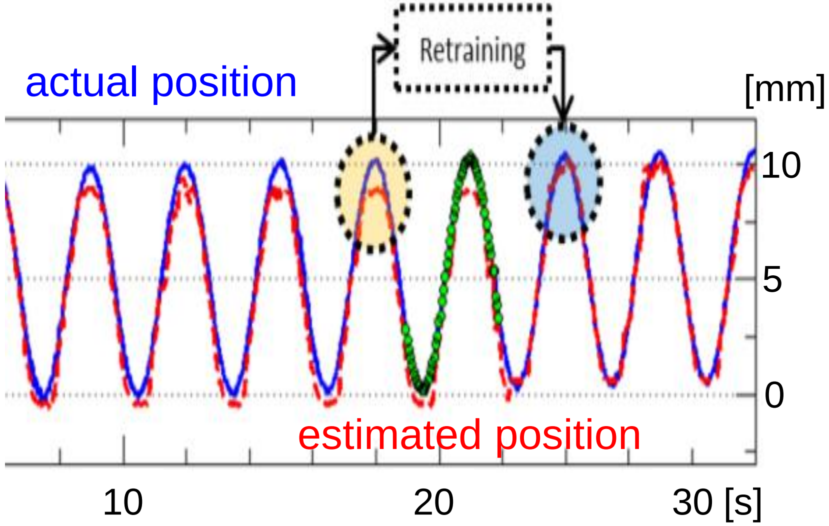


Beam tracking at Cave M



- 3D target motion (10 mm)
- breathing phantom
- optical monitoring plus model prediction
- dose error reduced from 24% to 3%

- full 3D beam tracking



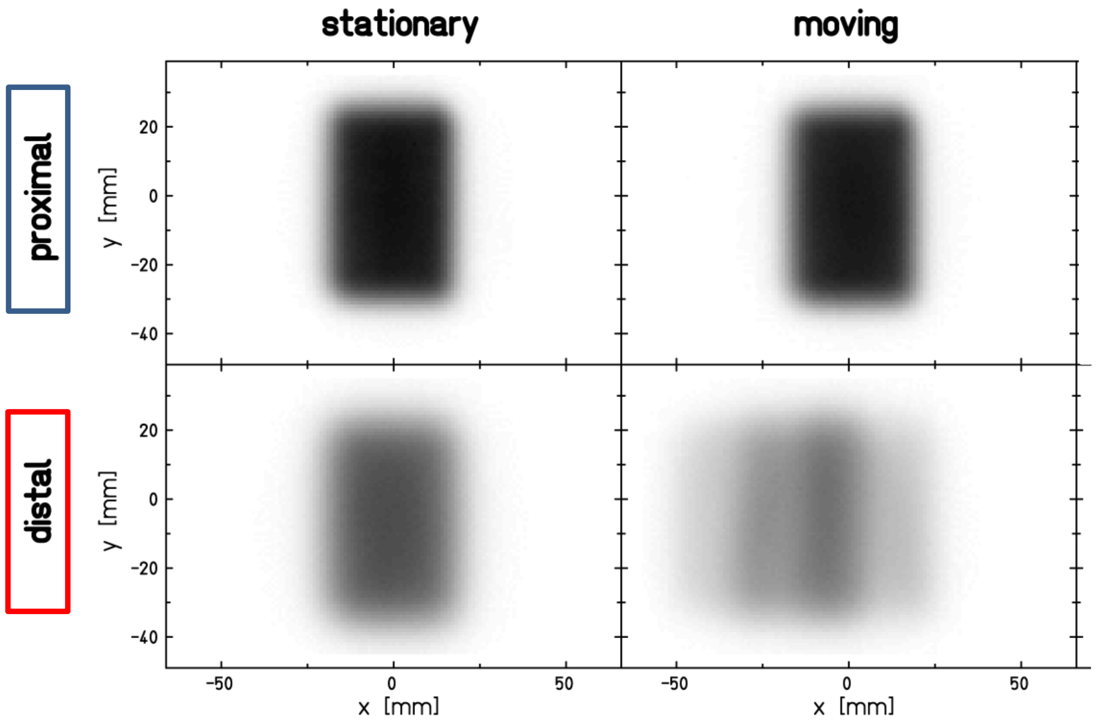
Fattori et al. Med Phys 2014

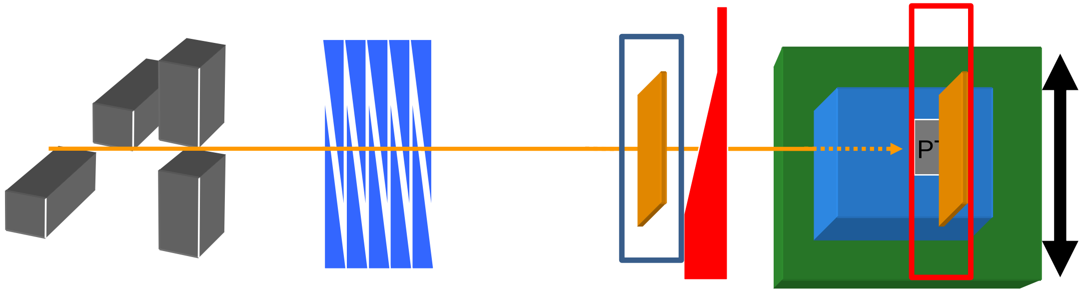
Tracking issues I: inverse interplay

tracking

static film

moving film

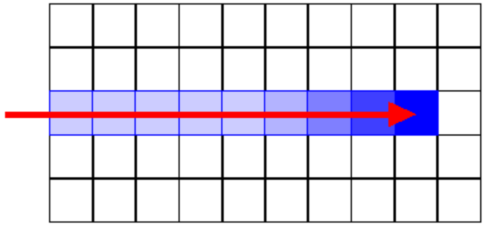




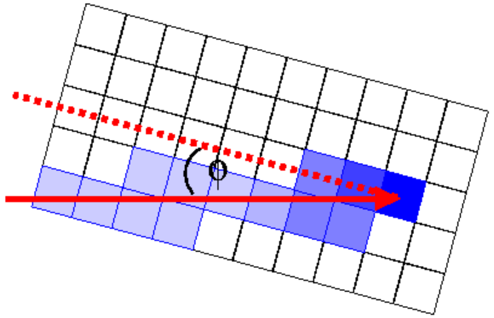
Bert et al Rad. Oncol 2010

Tracking issues II: complex motion

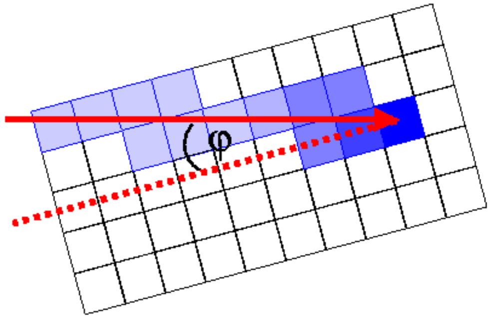
- Beam tracking compensates translation only
- Preplanned entry channel doses may be wrong!



Motion State Reference



Motion State k



Motion State i

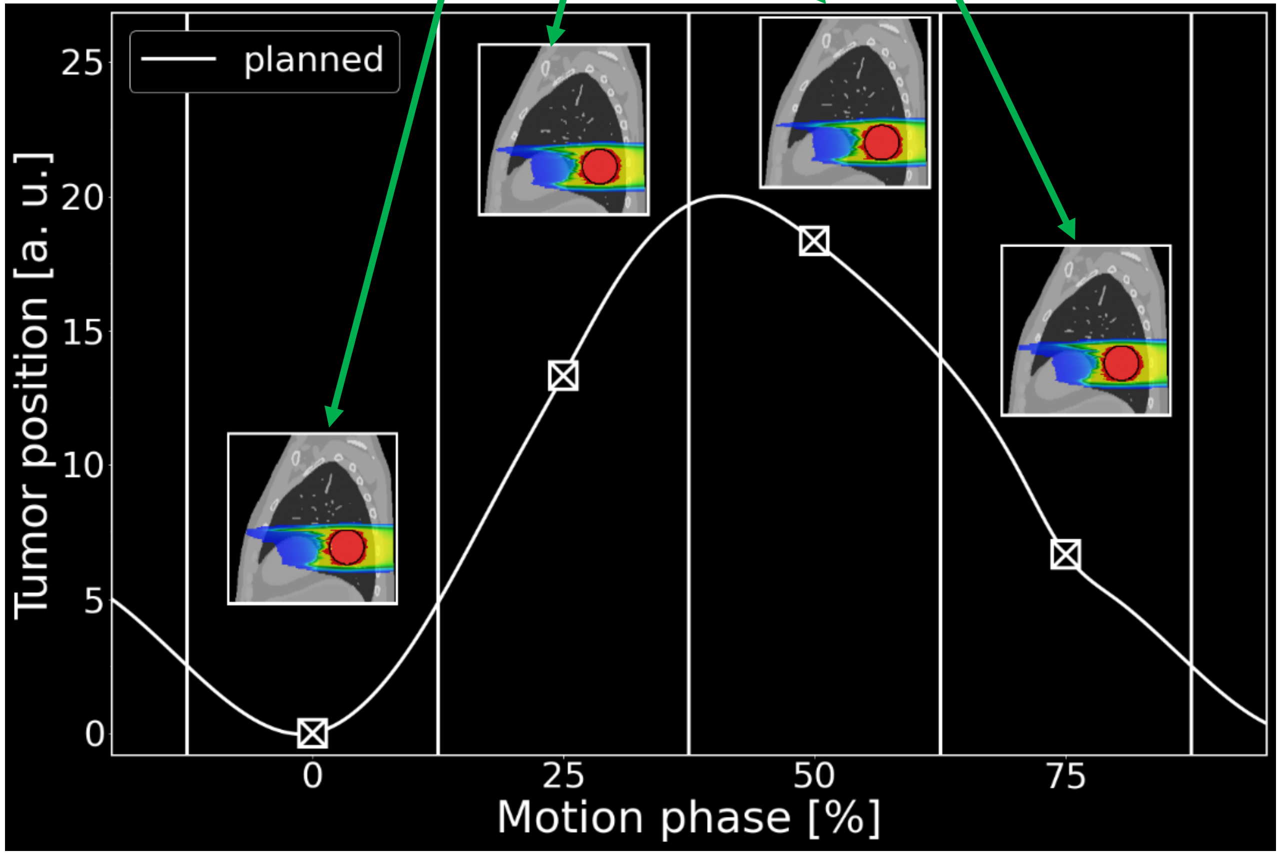
courtesy of Robert Lüchtenborg

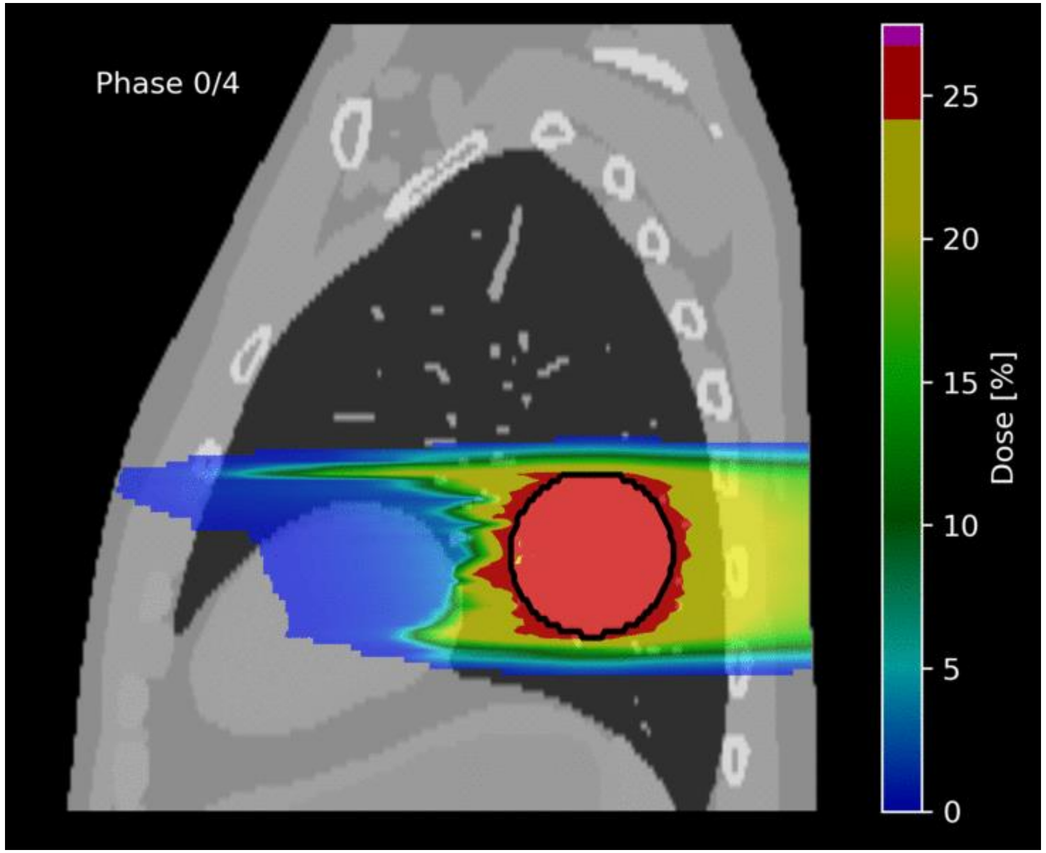
Motion compensation: Multiphase plan libraries (MP4D)

Phase specific treatment plans

Online plan switching

Synchronized, conformal delivery

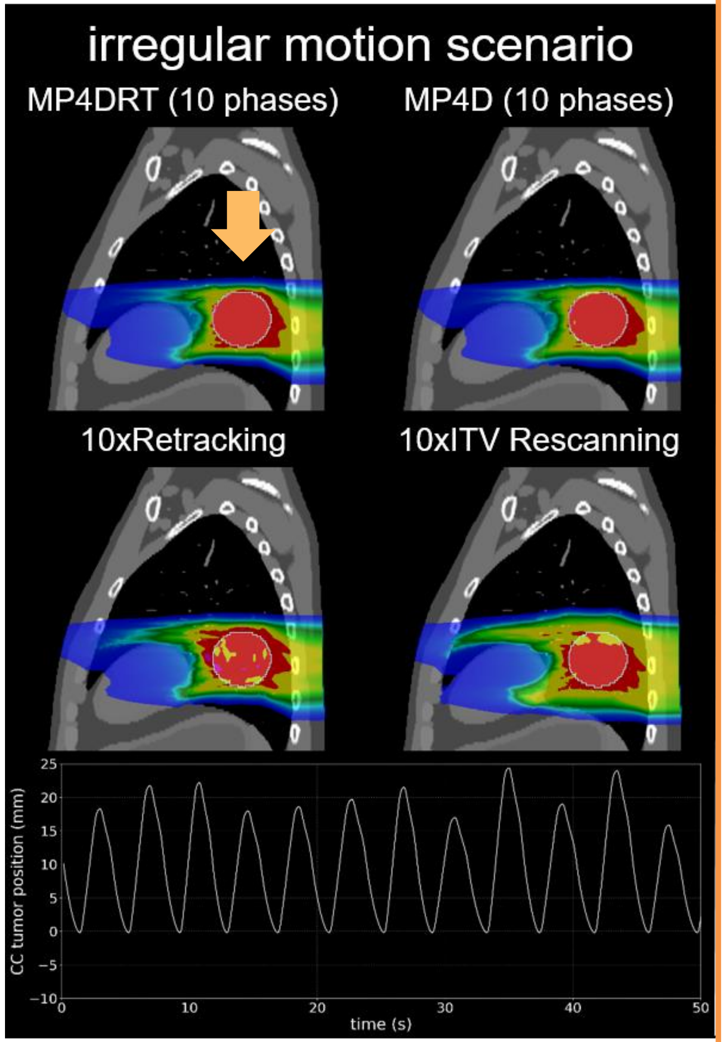




courtesy of Timo Steinsberger

Experimental validation of MP4D @ CNAO

- Treatment plans on the XCAT phantom
- Delivered to a moving detector performing irregular motion patterns
- Dose reconstruction
  - verified by detector
  - evaluated on XCAT geometry
- MP4DRT: Residual tracking compensates irregular motion



- Plans on XCAT phantom:
  - 10 phase MP4D
  - MP4DRT: same plan plus tracking
  - Lateral beam tracking with 10 rescans
  - Range ITV with 10 rescans
- MP4D + MP4DRT
  - more conformal
  - lower lung dose
  - robust against amplitude variation

Steinsberger et al. submitted to IJROBP

Summary motion mitigation

- Several techniques exist and can be combined
- Motion reduction (technically simple)
  - Gating, DIBH, abdominal compression
  - issues: residual motion, reproducibility, treatment time
  - should be combined with rescanning & range ITV
- Conformal motion compensation (technically complex)
  - Beam tracking, uses the fast scanning of the pencil beam for online adaption
  - 4D-optimization of plan libraries, exploits prior knowledge of 4DCT
  - A combination of both (MP4DRT) could be a conformal, robust solution also for irregular motion

Arc therapy

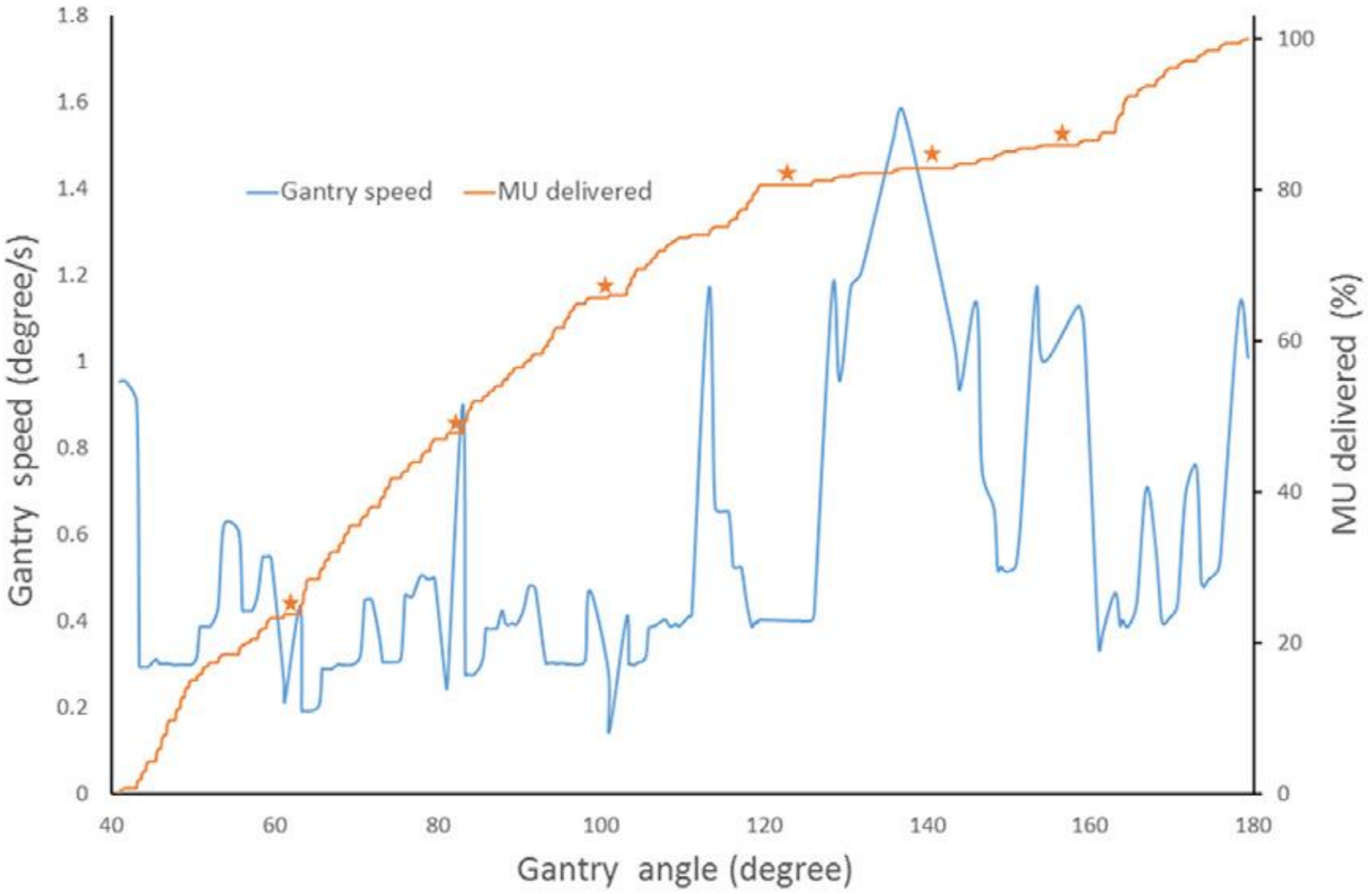
This project has received funding from the European Union’s Horizon 2020 research and innovation programme under grant agreement No 101008548

Particle arc therapy

- Arc therapy is clinical state-of-the-art in photon delivery
  - Continuous rotation of the gantry combined with continuous DMLC movement
  - Improved dose shaping capability
  - Lower treatment times than “step-and-shoot” delivery
- Can this be transferred to particle delivery?
  - Is it actually worthwhile, given the conformal fields of active scanning?
  - Can we deliver it to the patient, with the existing much heavier gantries?
  - Is there a feasible delivery scheme for active scanning with multiple energy layers and long switching times?

Spot-scanning Proton Arc therapy (SPArc)

- H&N SPArc plan delivered to phantom
  - Comparable or better plan quality to 3-field IMPT
  - Dose accuracy of γ(1mm,1%) 98.3%
- Delivered on an IBA cyclotron/gantry
- 50 control points and 97 energies
- Strategy: avoid up-switching of energy (5s), compared to down-switching (0.6s)
- ➢ Faster delivery (4 min vs. 11 min)

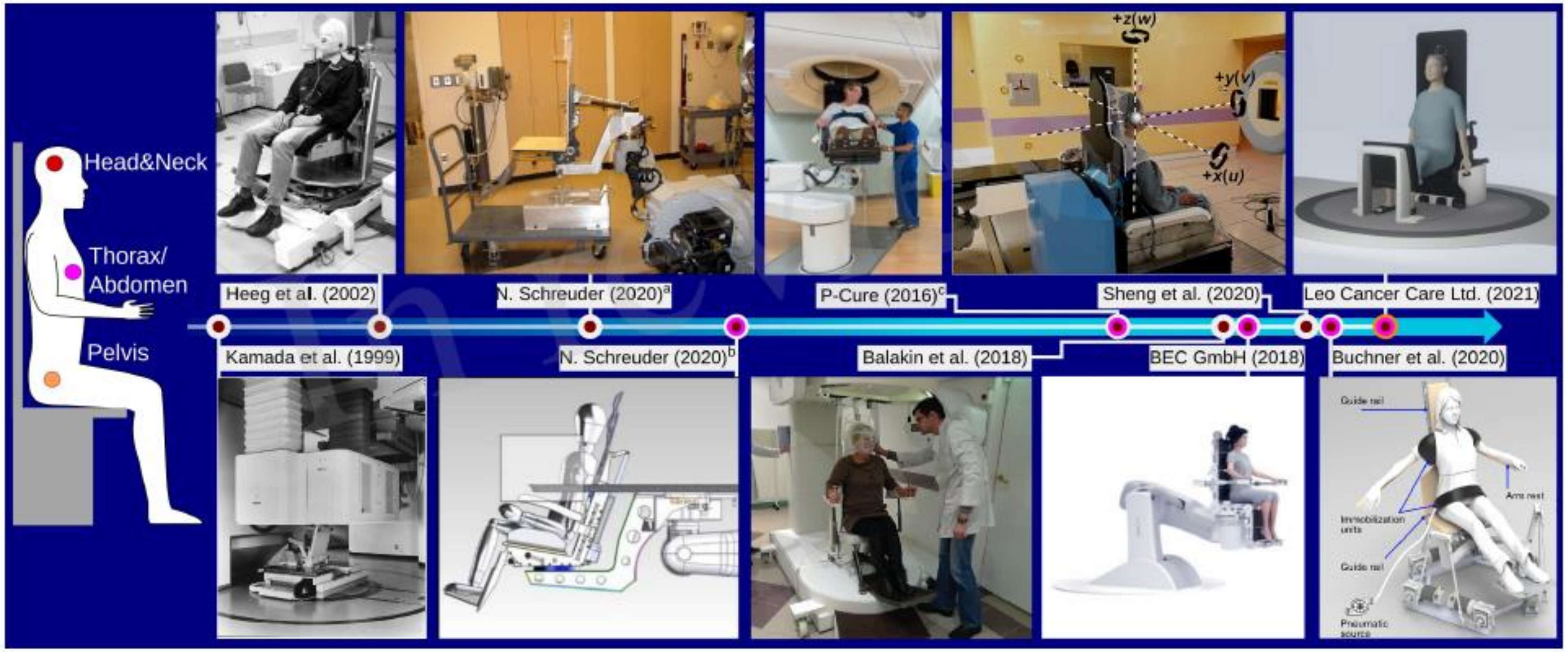


Li et al. Green Journal (2019)

Gantryless systems

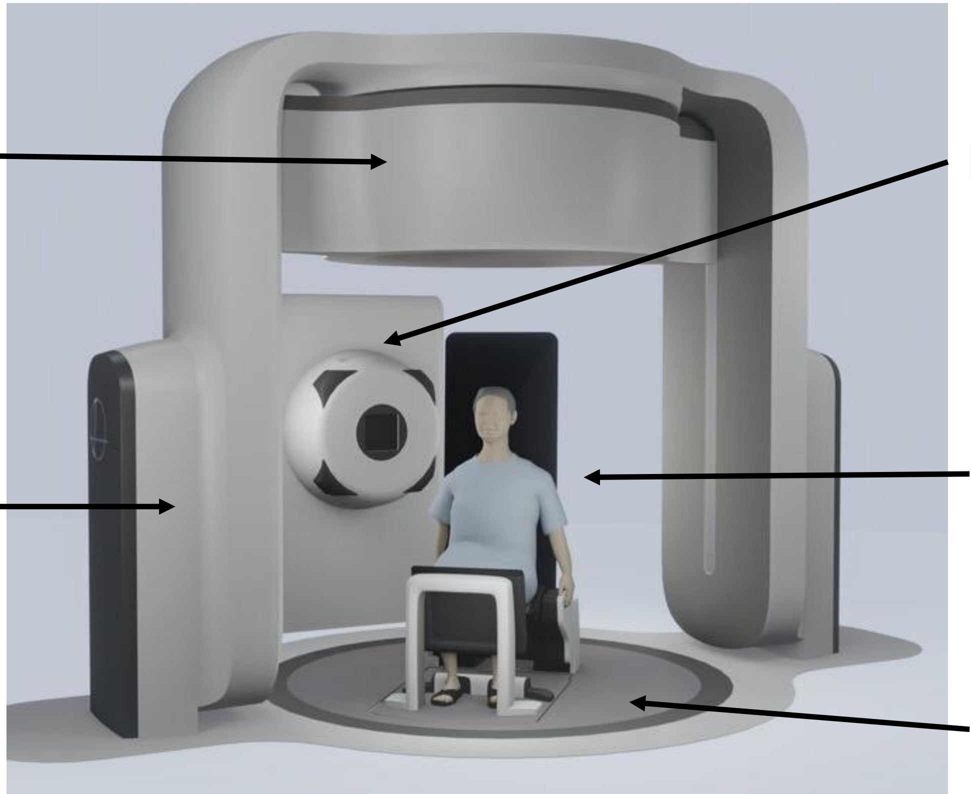
- Gantries are big and expensive, especially for heavier ions
- Gantries are also a strong clinical demand
  - HIT treats >50% of patients at the gantry, rest in 2 fixed beam rooms
- Can rotating an upright patient solve part of the issue?

- Progress in vertical CT systems might lead to breakthrough



Volz *et al.*, *Front. Oncol*. 2022

Example: Patient chair and CT from Leo Cancer Care



CT ring

Gantry for CT

Fixed beam for radiotherapy

chair system
- 6 DOF
- carbon-fibre back
- knee-rest for stable position

360° rotating base plate

- Comparable system could be used to deliver arc therapy at lower cost and less technical complexity than gantries

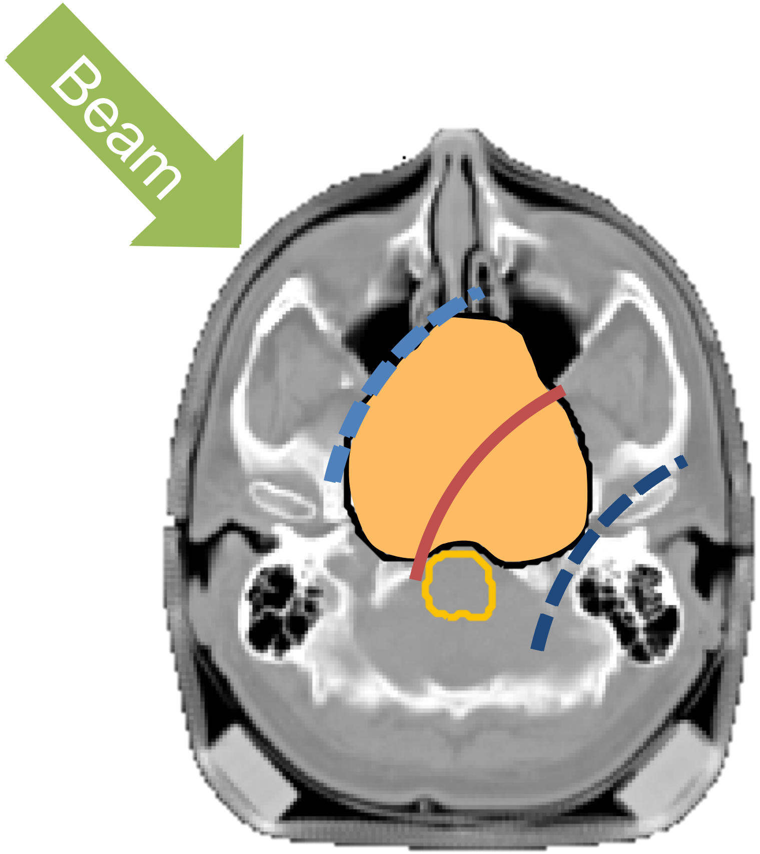
Leo Cancer Care

Arc therapy with synchrotrons

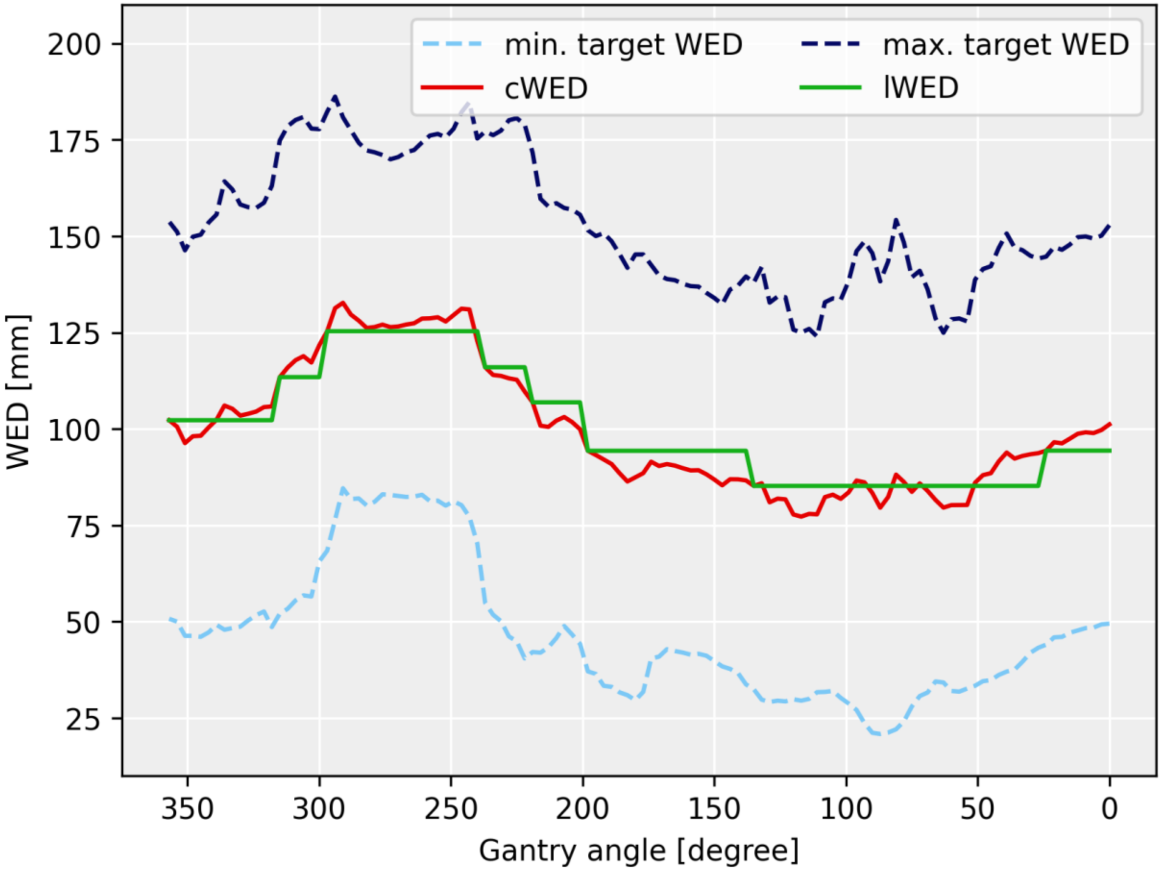
- Synchrotrons offer less flexible delivery timing
  - non-continuous delivery with spill pauses
  - Spill pauses are often longer than energy switching times in cyclotrons
- Even fewer energy changes are desirable

- Up until now only simulations, no delivery performed yet
- Timing is even more unclear
- But: Carbon arc might offer a unique advantage: increasing RBE in the target

A-priori energy selection[1]



- cWED: geom. middle WED
- pWED: most frequent WED
- lWED: piecewise monoenergetic arc segments



Courtesy Lennart Volz

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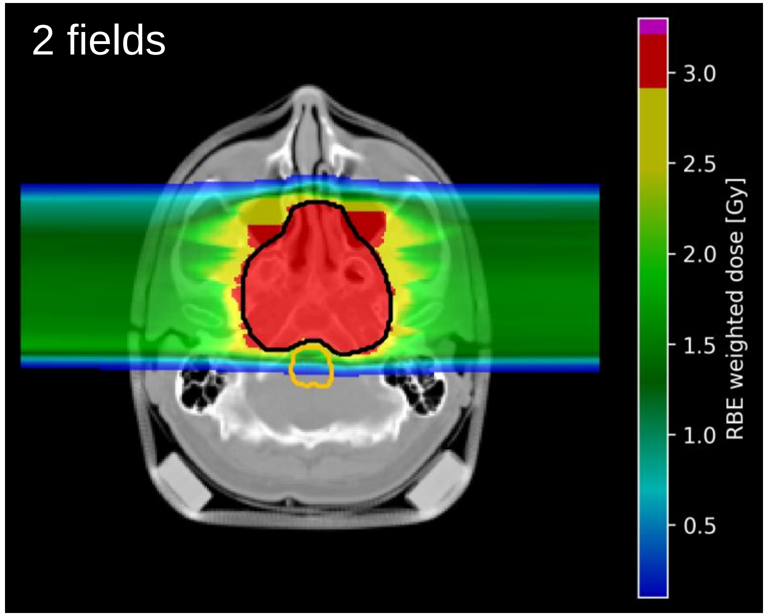
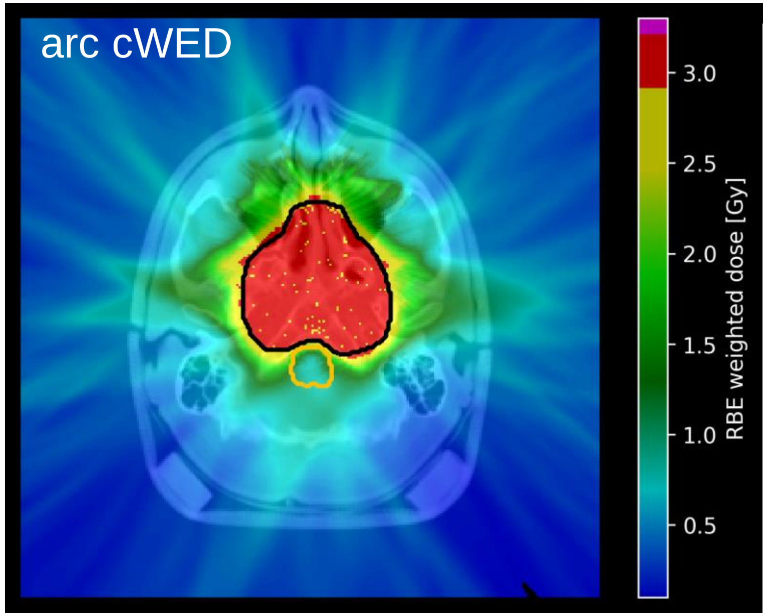
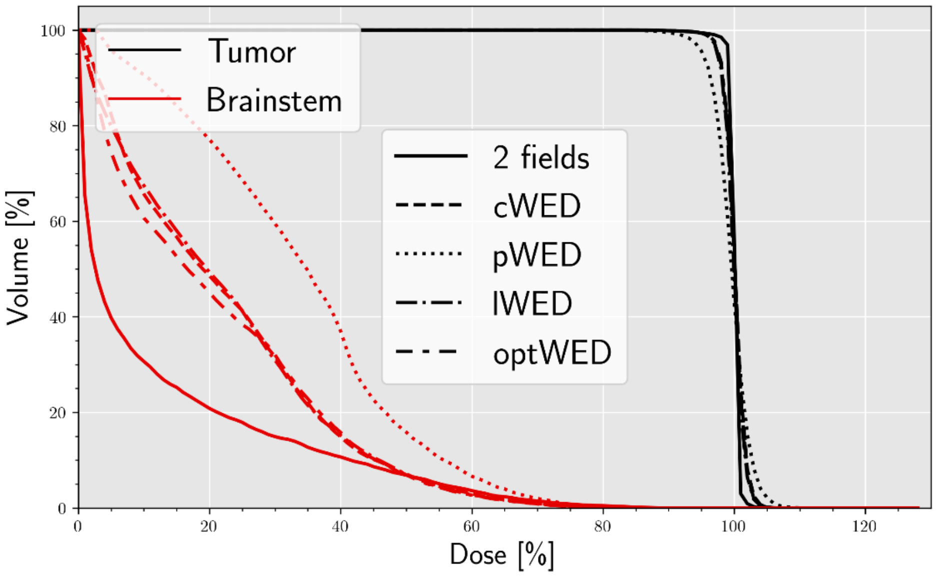
[1] Bertolet and Carabe (2020) Phys. Med. Biol. 65(16)

Carbon arc dose distribution



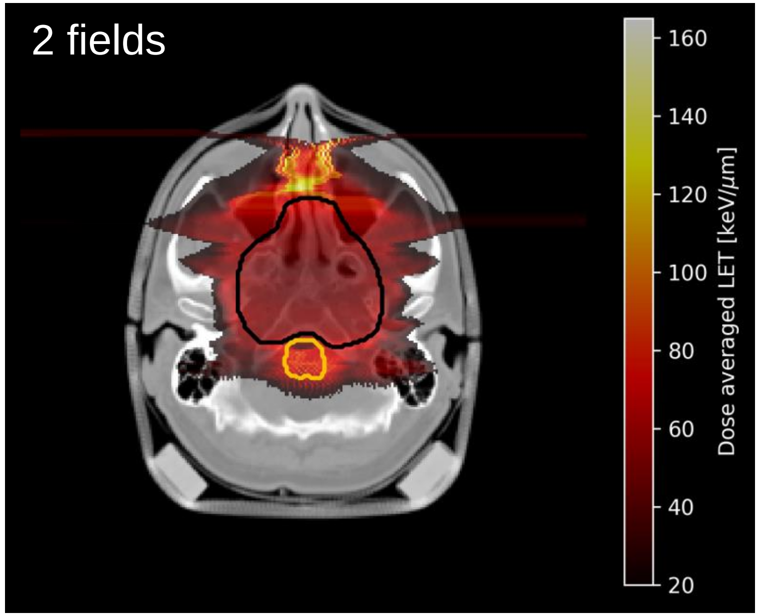


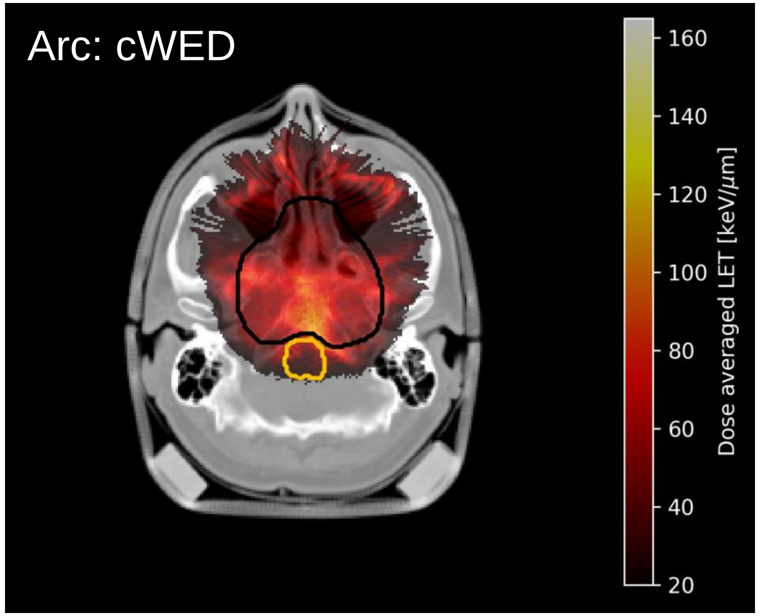


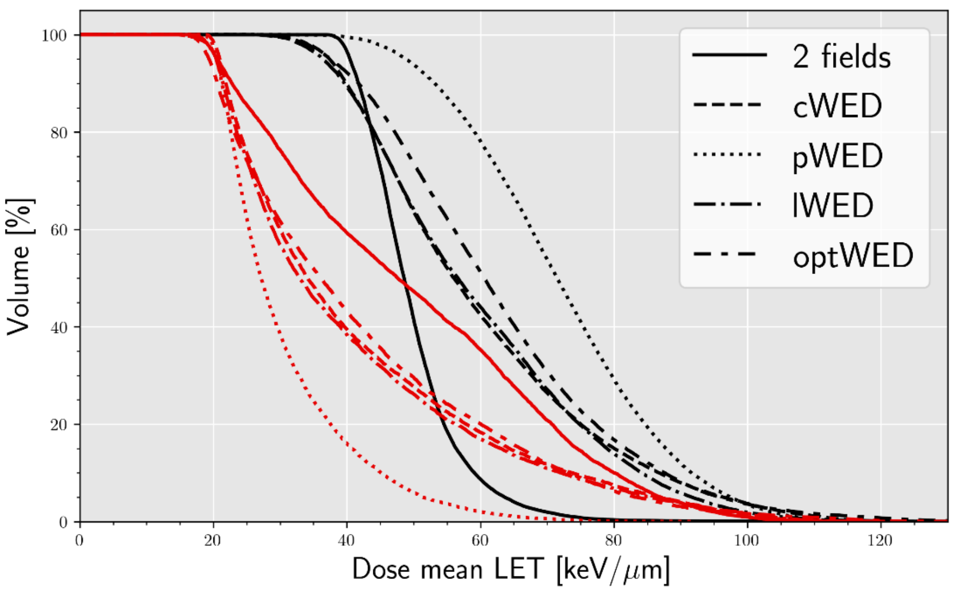
- 360° arc with one energy per angle (120 control points)
- As expected, larger low dose volume but lower max dose e.g. in brainstem

Courtesy Lennart Volz

Particle arc therapy: LET distribution







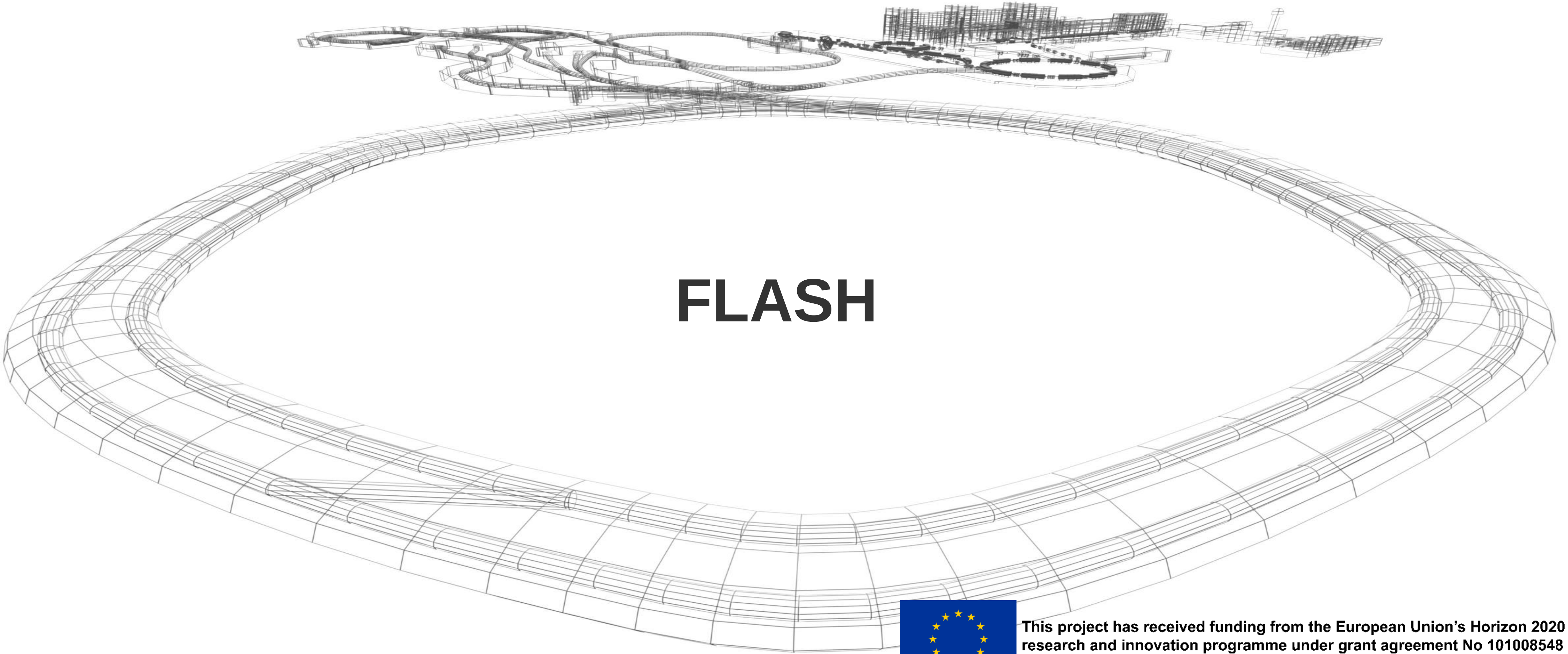
- Arcs shift high LET from OARS into the target
- Up to 100 keV/µm possible, which might have better effect against hypoxia

Courtesy Lennart Volz

Arc summary

- Particle arc delivery is a technically challenging new delivery option
- Comparable to photon arcs, permits more flexible dose shaping
    - higher low dose volumes, but lower volume of mid-to-high dose
- SParc strategy in clinical testing with commercial support
- Patient chair systems might make delivery simpler
    - especially for carbon ion centers, fixed beam lines could greatly profit from chairs

- Single energy Carbon ion arcs result in very high LET in the target, with potential radiobiological benefits for OARs and hypoxic tumors

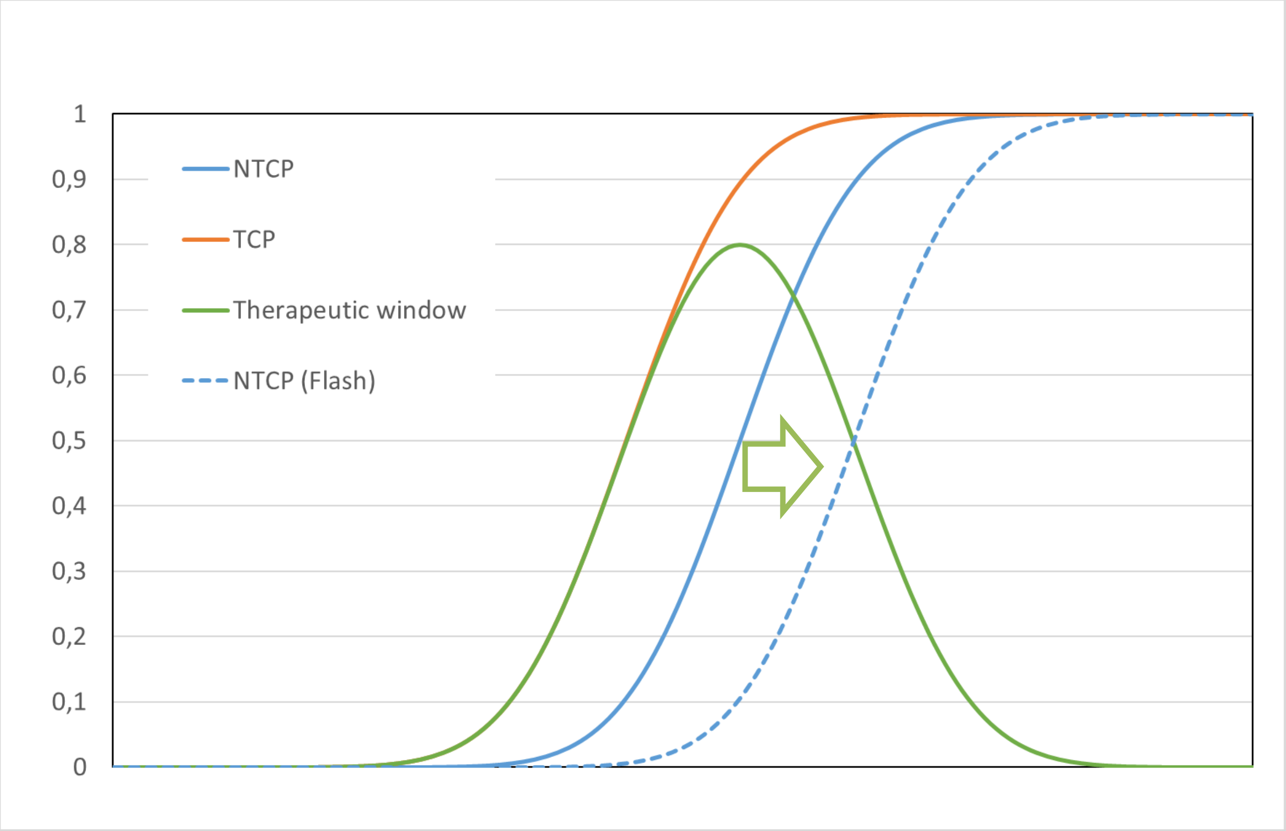


FLASH

This project has received funding from the European Union’s Horizon 2020 research and innovation programme under grant agreement No 101008548

The Flash-Effect

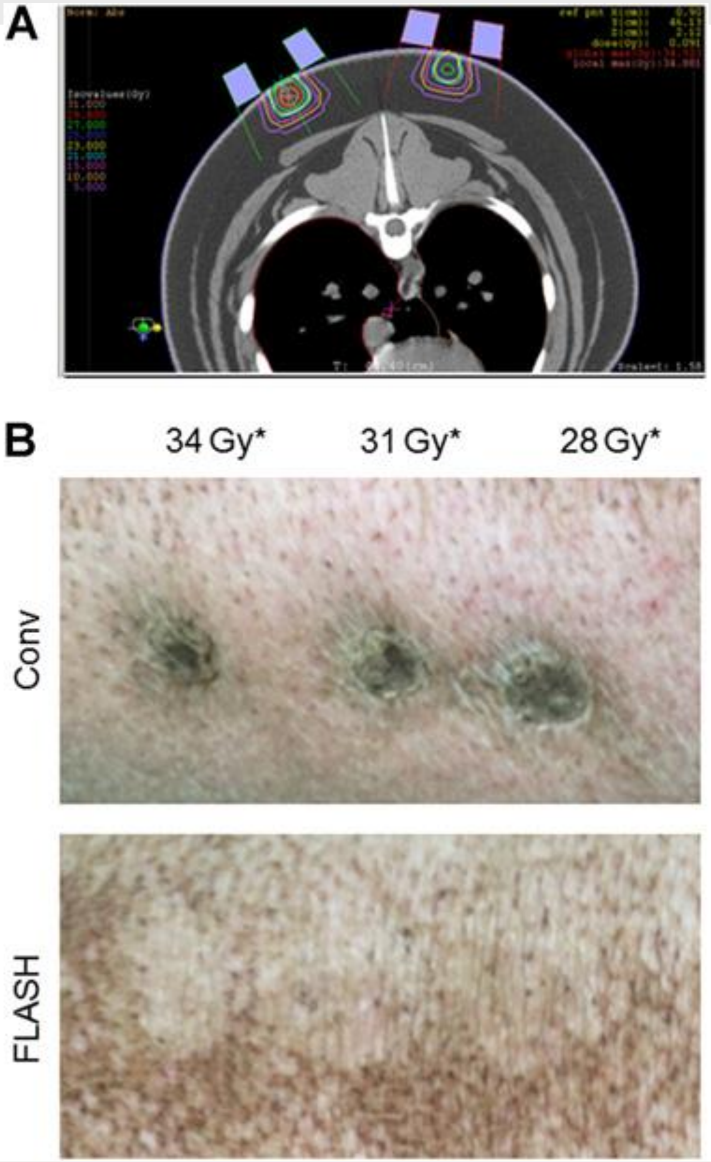
- Reduced NTCP through higher dose tolerance of normal tissue at ultra-high dose rates



What is FLASH?

- Deliver treatment at extreme dose rates: >100x faster than clinical standard
- Preclinical research shows greatly reduced side-effects but same tumor control
- Mechanism is not really understood – likely connected to oxygen depletion

- Thresholds for effect:
  at least 40 Gy/s, at least 5 - 8 Gy/fraction
  - standard treatment is 2-3 Gy per fraction in 3-5 min…
- Huge technical challenge – how to deliver >5 Gy in less than 150 ms safely?



Vozenin et al, Clin Cancer Res 2019

Technical FLASH boundary conditions

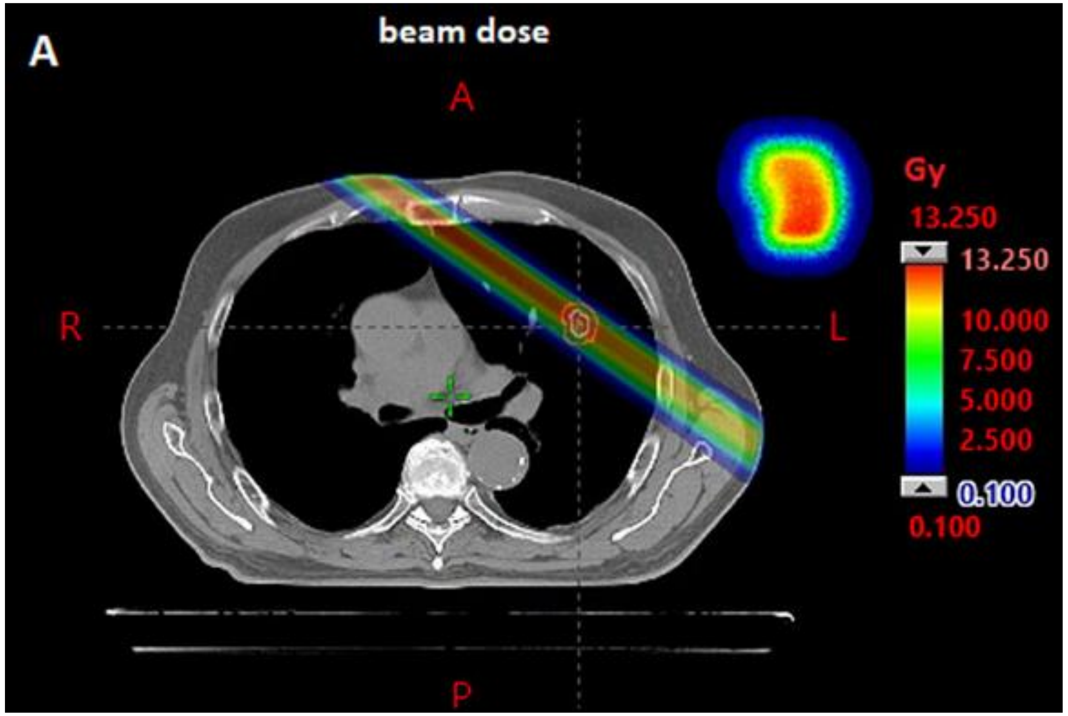
- Capacity of the accelerator – provide enough intensity for dose rate & dose
  - Proton cyclotrons designed for passive degradation to lowest energy
  - Synchrotrons are limited by spill structure – acceleration pause is too long
- Speed of delivery system
  - Active components of delivery – fully active scanning too slow
  - Passive range modulation or shoot-through investigated for particles
- Speed of dose monitoring
  - standard detector: parallel plate ionization chamber
  - recombination at high dose rates threatens linearity
- Safety – abort mechanisms and radioprotection designed for Gy/min

Dosimetric considerations

- How to define ‘dose rate’ in pencil beam scanning?

$$DADR(\vec{x}) = \sum_i \frac{dr_i(\vec{x}) \cdot D_i(\vec{x})}{D_{Tot}(\vec{x})}$$

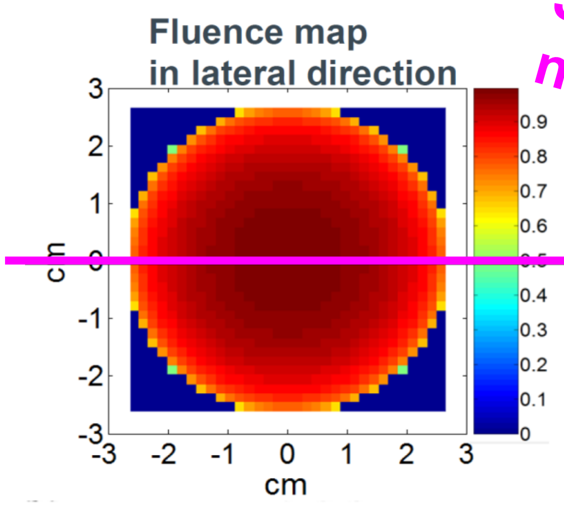
  - count very small contributions from far away pencil beams?
  - What about multiple fields? Fractions?
- Comparison studies of IMPT vs. shoot-through FLASH permit study of necessary “FLASH-factors”



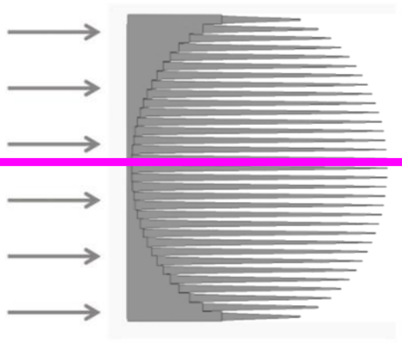
- Answer is patient and organ-specific, usually not clear cut for expected factors (of ~1.5) and realistic machine parameters

van Marlen et al, Adv Rad Onc 2022

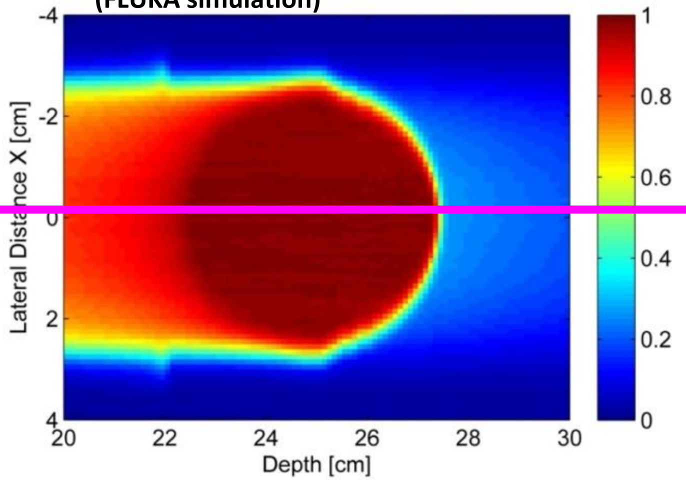
Beam application with 3D Range Modulators: Single-energy Irradiation



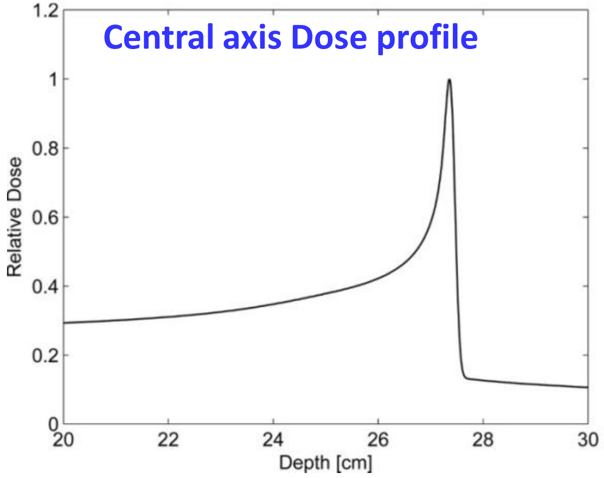
Scanning needed

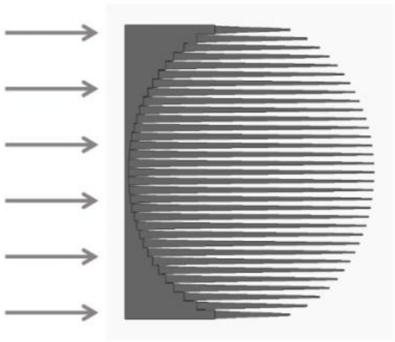


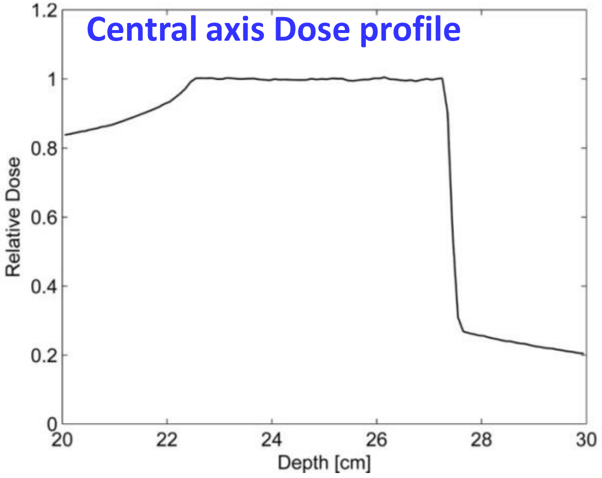
(FLUKA simulation)



Example for a spherical target volume, 5cm diameter, ^{12}C, E=400 MeV/u



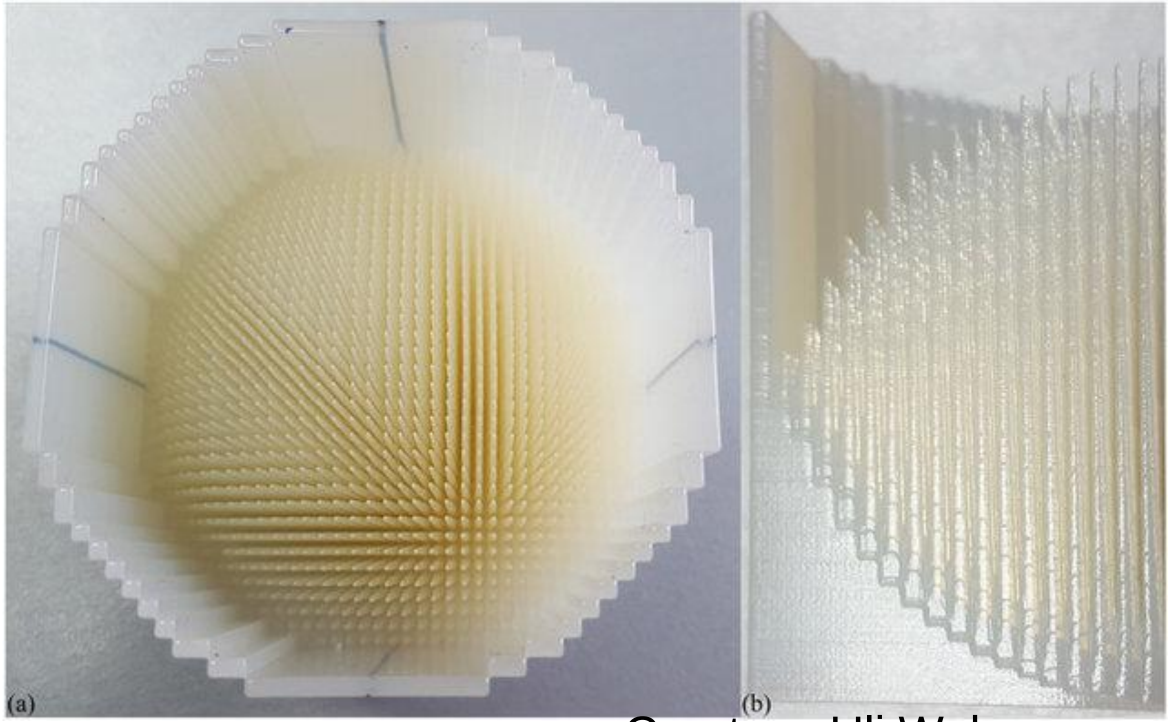




Courtesy Uli Weber

FLASH with 3D-range modulators

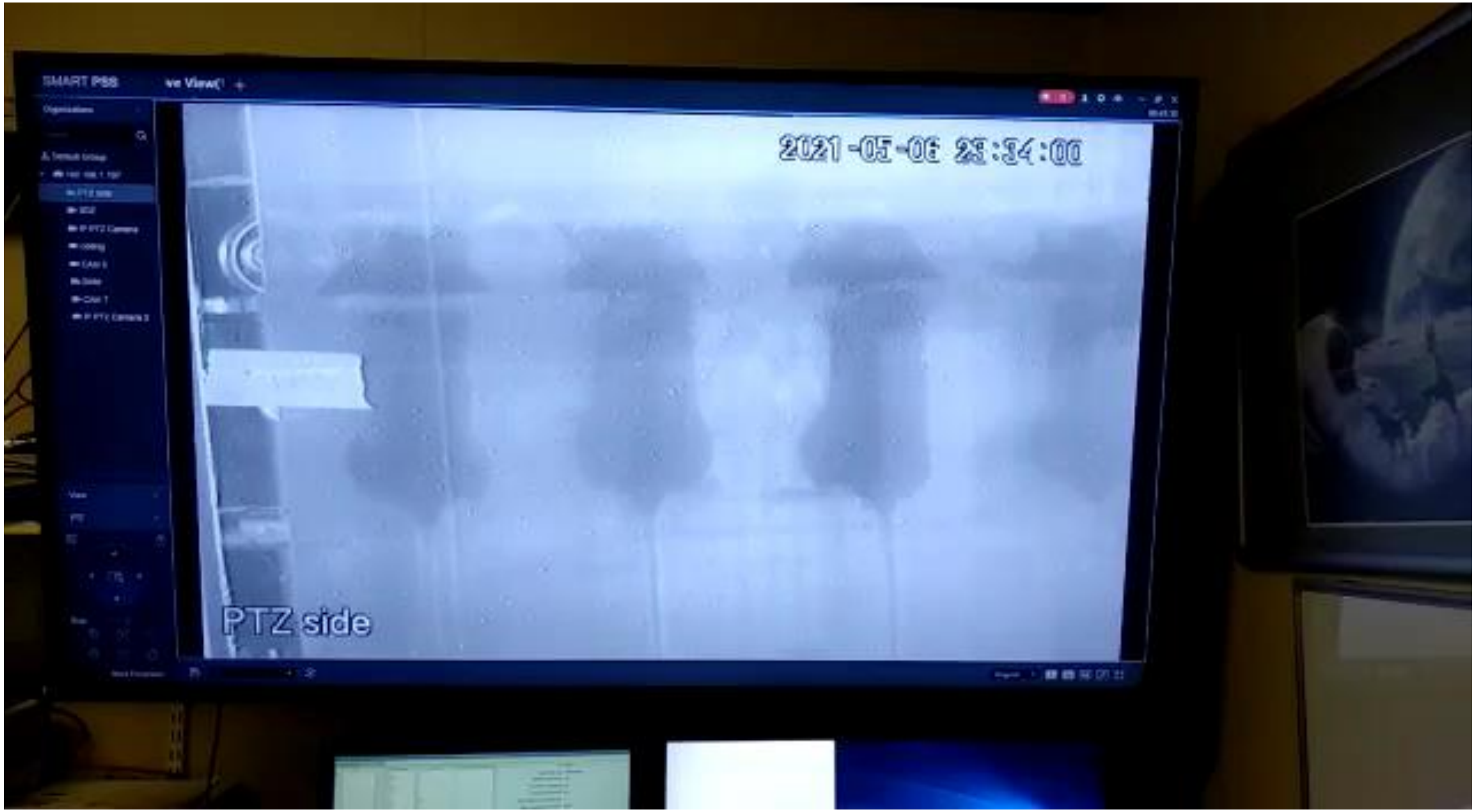
- Advantages:
  - permits to use the Bragg Peak at Flash dose rates => better conformity
  - potentially single fields possible => reduced uncertainty of Flash effect
  - use of Bragg Peak results in higher doses per delivered MU => easier to achieve
  - For carbon, keeps high LET
- Disadvantages
  - Patient-specific hardware is back,
    device printed for each field individually
  - QA of this hardware is unclear –
    deviation of shape leads to dosimetric errors



Courtesy Uli Weber

Research example: Carbon ion Flash delivery

- Carbon ion SOBP with range modulator
- 12, 15, 18 Gy to 20 x 16 mm² in < 200 ms
- dose rate around 100 Gy/s



Courtesy Uli Weber

Flash summary

- Flash is the delivery at ultrahigh dose rates, defined as >40 Gy/s for doses higher than 5-8 Gy
- Proton facilities are suited for Flash, and clinical trials are underway
  - cyclotron layout for energy degradation with losses of >95%
- 3D-printed range modulators offer conformal Flash with a single energy
  - Experimentally validated at GSI also for synchrotrons
- Cause and size of the Flash effect is not really clear
  - Requires drastic hypofractionation, with min dose requirement in the normal tissue(!)
  - Impact of multiple fields, fractionation etc. are unclear
- Technological development for much faster delivery will benefit the whole field in any case
  - Moving targets could be reduced to reliable targeting of a single breath hold

Final summary

- Particle therapy's unique advantage is its conformity and precision
- Advanced delivery techniques are required to fulfill this promise, for better patient benefit in terms of NTCP and dose escalation

GSI Biophysics 2022 (without masks!)

Thanks for your attention!